(a public limited liability company incorporated in Denmark under registration (CVR) no. 32266355)

This listing prospectus (the "**Prospectus**") has been prepared for the sole purpose of the admission of 7,616,146 shares (the "**Listing Shares**") with a nominal value of DKK 1 each in Orphazyme A/S (the "**Company**" or "**Orphazyme**") for trading and official listing on Nasdaq Copenhagen A/S ("**Nasdaq Copenhagen**") (the "**Listing**"). As used herein, "**Shares**" shall refer to all outstanding shares of the Company at any given time.

The Listing Shares will be issued in connection with an initial public offering (the "**U.S. Offering**") in the United States of 3,966,146 American Depositary Shares ("**ADSs**") at a price of USD 11.00 per ADS. Each ADS represents one Listing Share. The Listing Shares are underlying the ADSs. The ADSs were listed and began trading on September 29, 2020 on Nasdaq Global Select Market in the United States ("**Nasdaq**") under symbol "ORPH". The price of USD 11.00 per ADS corresponds to a subscription price of DKK 70.1844 per Listing Share (using a DKK/USD exchange rate of 6.3804). The Bank of New York Mellon has been appointed as depositary (the "**Depositary**") for the ADSs and will be the holder of the Listing Shares underlying the ADSs upon issue.

Concurrently with the U.S. Offering, we have offered up to 3,650,000 ordinary shares in Europe (the "**European Offered Shares**") in a private placement (the "**EU Private Placement**") to qualified investors, as defined under the Regulation (EU) no. 2017/1129 of the European Parliament and the Council of June 14, 2017, as amended (the "**Prospectus Regulation**"). The term "Listing Shares" also includes the European Offered Shares.

The closings of the U.S. Offering and the EU Private Placement, which are together referred to as the "**Global Offering**", will occur substantially simultaneously.

Certain banks who have entered into the underwriting agreement (collectively, the "**Underwriters**") have, severally and not jointly, agreed to subscribe for and purchase 3,966,146 Listing Shares to be delivered in the form of ADSs in the U.S. Offering and subscribe for, on behalf of investors, 3,650,000 Listing Shares to be delivered as ordinary shares in connection with the EU Private Placement. Further, in connection with the Global Offering, the Company has granted an option to the Underwriters, exercisable for 30 days after the date of announcement of the pricing of the Global Offering, to subscribe for and purchase up to 1,142,421 additional ordinary shares (which may be in the form of ADSs) (collectively, the "**Additional Securities**") at the offering price offered in connection with the Global Offering, less the underwriting commission (the "**Overallotment Option**"). The Overallotment Option may be exercised in full or in part. The term "Listing Shares" does not include any Additional Securities that may be issued by the Company. Any such Additional Securities will be listed on Nasdaq Copenhagen in reliance on an exemption pursuant to the Regulation (EU) no. 2017/1129 of the European Parliament and the Council of June 14, 2017, as amended.

The Listing Shares will be issued without pre-emptive rights for the existing shareholders and pursuant to an authorization in article 3.1 of the articles of association of the Company (the "**Articles of Association**") granted to the board of directors of the Company (the "**Board of Directors**") at the extraordinary general meeting of the Company on September 21, 2020. To the extent any Additional Securities will be issued these will also be issued pursuant to this authorization as well.

Prior to the Global Offering, the Company had 27,081,557 outstanding shares with a nominal value of DKK 1 each (the "**Existing Shares**"). After completion of the Global Offering, the Company will have issued 34,697,703 shares, assuming the Overallotment Option is not exercised (or 35,840,124 shares assuming the Overallotment Option is exercised in full).

The Company's Existing Shares are admitted to trading and official listing on Nasdaq Copenhagen under the symbol "ORPHA" and in the ISIN code DK0060910917. The Listing Shares will be initially issued in an temporary ISIN code DK0061411378 on or around October 1, 2020 and will not be admitted to trading and official listing under such temporary ISIN. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities. An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen in the permanent ISIN code for the Existing Shares. Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares. It is expected that the listing of the Listing Shares on Nasdaq Copenhagen under the Company's existing symbol "ORPHA" and in the ISIN of the Existing Shares DK0060910917 will be effective on or around October 2, 2020, after registration of the capital increase related to the Listing Shares with the Danish Business Authority, expected on October 1, 2020.

The Listing Shares will be issued through VP Securities are expected to be registered with the Danish Business Authority on October 1, 2020 and will upon such registration rank *pari passu* in all respects with the Existing Shares. The ADSs will not carry the same rights as the Shares and the ADS holders will not have shareholder

rights. For a description of the rights pertaining to holders of the ADSs, see *"General Information—The Global Offering"* on page 71.

The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen. No issue or offering of shares is made by the Company or any other person in connection with the publication of the Prospectus. The Listing does not comprise an offer of, an invitation to purchase or subscribe for or a placement of Listing Shares in any jurisdiction and this Prospectus may not be used in connection with any offer of Shares or solicitation by anyone in any jurisdiction. No offer of Listing Shares or ADSs has been or will be made in the EU/EEA under this Prospectus and no offer of any securities has been or will be made under this Prospectus in the United States or to U.S. Persons (as such term is defined in Regulation S under the U.S. Securities Act of 1933, as amended). The EU Private Placement was carried out under applicable exemptions from the obligation to publish a prospectus pursuant to the Prospectus Regulation. Investors in ADSs or Shares may not rely on this Prospectus for any purpose. The Company accepts no liability for any violation of any such restrictions by any person. For a more detailed description of certain restrictions in connection with the Listing, see "*The Listing–Terms and Conditions of the Listing*".

Any person in whose possession this Prospectus may come, should be aware that an investment in the Shares involves a high degree of risk. See "*Risk factors*" for a description of the factors that should be considered before investing in the Shares.

This Prospectus has been prepared in accordance with Danish legislation and regulations, including the Consolidated Act No. 377 of April 2, 2020 on Capital Markets, as amended (the "Danish Capital Markets Act"), Prospectus Regulation, Commission Delegated Regulation (EU) 2019/980 of March 14, 2019 as well as Commission Delegated Regulation (EU) 2019/979 of March 14, 2019, and Nordic Main Market Rulebook for Issuers of Shares on Nasdaq Copenhagen of May 1 2020 ("Nasdaq Issuer Rules"). This Prospectus does not constitute an offer to sell or the solicitation of an offer to buy any of the Shares or ADSs in any jurisdiction.

This Prospectus will not be and may not be distributed or otherwise be made available in any jurisdiction (other than any publication of this Prospectus in accordance with Danish law, rules and regulations), and the Listing Shares may not be offered or sold, directly or indirectly, in the United States, Canada, Australia or Japan or in any other jurisdiction pursuant to this Prospectus. Persons into whose possession this Prospectus comes are required by the Company to inform themselves about and to observe such restrictions. For a description of certain restrictions on distribution of this document, see page 3 "Important Information".

The Company has filed a registration statement with the U.S. Securities and Exchange Commission (the "SEC") on form F-1 (the "U.S. Prospectus") in respect of the Listing Shares and the Depositary has filed a registration statement with the SEC on form F-6 in respect of the ADSs. The Listing Shares and the ADSs have not been approved, disapproved or recommended by the SEC, any state securities commission in the United States or any other U.S. regulatory authority, nor have any of the foregoing authorities passed upon or determined or endorsed the merits of the Listing or the adequacy or accuracy of the information contained in this Prospectus. Any representation to the contrary is a criminal offence in the United States.

This Prospectus is prepared for the sole purpose of satisfying applicable Danish securities legal and regulatory requirements in order to list the Listing Shares on Nasdaq Copenhagen. This Prospectus may not be relied upon for any other purposes, including with respect to the Global Offering by us or any other person. Neither the Company, its management team, its board of directors, its employees, its advisors, the Underwriters nor any other person accept any liability for any information contained (or not contained) in the U.S. Prospectus or for any inconsistencies between the U.S. Prospectus and the contents of this Prospectus.

The date of this Prospectus is September 30, 2020.

IMPORTANT INFORMATION

This Prospectus has been prepared solely for admission to trading and official listing of the Listing Shares on Nasdaq Copenhagen in compliance with Danish legislation and regulations, including the Danish Capital Markets Act, the Prospectus Regulation, Commission Delegated Regulation (EU) no. 2019/980 of March 14, 2019 as well as Commission Delegated Regulation (EU) 2019/979 of March 14, 2019, and Nasdaq Issuer Rules. This Prospectus has been prepared in accordance with Article 14 (Simplified disclosure regime for secondary issuances) of the Prospectus Regulation, Annex 3 (Registration document for secondary issuances of equity securities) and Annex 12 (Securities note for secondary issuances of equity securities or of units issued by collective investment undertakings of the closed-end type) to the Commission Delegated Regulation (EU) no. 2019/980 of March 14, 2019. The Company has elected to apply the aforementioned Annexes, as the proportionate disclosure regime has been specifically implemented to be used in secondary issuances and admissions to trading and official listing of securities from such issuances.

This Prospectus has been prepared in connection with the EU Private Placement of European Offered Shares and the U.S. Offering of ADSs in the United States as a result of which the Company has filed the U.S. Prospectus with the SEC. This Prospectus does not include all the information included in the U.S. Prospectus, as this Prospectus has been drawn up as part of a simplified prospectus in accordance with Article 14 of the Prospectus Regulation. Neither the Company, its management team, its board of directors, its employees, its advisors, the Underwriters nor any other person accept any liability for any information contained (or not contained) in the U.S. Prospectus or for any inconsistencies between the U.S. Prospectus and the contents of this Prospectus. The Underwriters have not been involved in the preparation of this Prospectus.

Neither the Company or its advisors have authorized anyone to provide you with information that is different from that contained in this Prospectus. The Company takes no responsibility for, and can provide no assurance as to the reliability of, any information that others may give you. The information contained in this Prospectus is accurate only as of the date on the front of this Prospectus.

The information contained herein is as at the Prospectus Date, unless stated otherwise. Any material changes in connection with the information in this Prospectus which may affect the evaluation of the Shares, which occurs or is ascertained between the time of approval of this Prospectus and the commencement of trading on Nasdaq Copenhagen of the Listing Shares, will be published as a supplement to this Prospectus pursuant to applicable rules and legislation in Denmark.

Unless the context otherwise requires, references in this Prospectus to the “Company,” “Orphazyme”, "we," "us" and "our" refer to Orphazyme A/S and “Group” refer to Orphazyme A/S and its subsidiaries. Certain technical terms, abbreviations and defined terms have the meaning given to it in “Glossary”.

The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen. No issue or offering of shares is made by the Company or any other person in connection with the publication of the Prospectus. The Listing does not comprise an offer of, an invitation to purchase or subscribe for or a placement of Listing Shares sold, directly or indirectly, in the United States, Canada, Australia or Japan or in any other jurisdiction pursuant to this Prospectus and this Prospectus may not be used in connection with any offer of Shares or solicitation by anyone in any jurisdiction. No offer of Listing Shares or ADSs has been or will be made in the EU/EEA under this Prospectus and no offer of any securities has been or will be made under this Prospectus in the United States or to U.S. Persons (as such term is defined in Regulation S under the U.S. Securities Act of 1933, as amended). Investors in ADSs may not rely on this Prospectus for any purpose. The Company accepts no liability for any violation of any such restrictions by any person. This Prospectus will not be and may not be distributed or otherwise be made available in any jurisdiction (other than any publication of this Prospectus in accordance with Danish law, rules and regulations). Persons into whose possession this Prospectus comes are required by the Company to inform themselves about and to observe such restrictions.

The Company makes no offer or solicitation to any person under any circumstances that may be unlawful.

Notice to Investors in the United States

The Company has filed a registration statement with the U.S. Securities and Exchange Commission (the “**SEC**”) on form F-1 (the “**U.S. Prospectus**”) in respect of the Listing Shares and the Depositary

has filed a registration statement with the SEC on form F-6 in respect of the ADSs. The Listing Shares and the ADSs have not been approved, disapproved or recommended by the U.S. Securities and Exchange Commission, any state securities commission in the United States or any other U.S. regulatory authority, nor have any of the foregoing authorities passed upon or determined or endorsed the merits of the Listing or the adequacy or accuracy of the information contained in this Prospectus. Any representation to the contrary is a criminal offence in the United States.

This Prospectus is personal to each reader and does not constitute an invitation to purchase or subscribe for or a placement of Listing Shares. No offer to the public of Listing Shares is being or will be made in the United States pursuant to this Prospectus. This Prospectus has been prepared for the sole purpose of the Listing and on the basis that no offer to the public of the Listing Shares will be made in that connection.

Any reproduction or distribution of this Prospectus in the United States, in whole or in part, and any disclosure of its contents to any other person, is prohibited. Any person in the United States that obtains a copy of this Prospectus or any pre-printed issue statement or application form is required to disregard them.

Notice to Investors in the European Economic Area

This Prospectus has been prepared for the purpose of the Listing. In relation to each member state of the European Economic Area where the Prospectus Regulation applies (each a "**Relevant Member State**"), no offering of Listing Shares will be made to the public in any Relevant Member State (including Denmark).

Accordingly, any person making or intending to make any offer within the EEA of Listing Shares should only do so in circumstances in which no obligation arises for the Company to produce a prospectus for such offer. The Company has not authorized, nor do the Company authorize, the making of any offer of the Listing Shares through any financial intermediary.

Notice to Investors in the UK

This Prospectus has been prepared for the purpose of the Listing. This Prospectus is not being distributed in the UK.

Notice to Investors in Canada, Australia and Japan

The Listing Shares have not been approved, disapproved or recommended by any foreign regulatory authorities, nor have any of such authorities passed upon or endorsed the merits of the Listing or the accuracy or adequacy of this Prospectus.

This Prospectus may not be distributed or otherwise made available, the Listing Shares may not be offered, sold or subscribed for, directly or indirectly, in Canada, Australia or Japan or in any other jurisdiction pursuant to this Prospectus.

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SUMMARY

Section A – Introduction and warnings

Warnings	This summary should be read as an introduction to this Prospectus. Any decision to invest in the Shares should be based on a consideration of the Prospectus as a whole by the investor. Prospective investors in the Shares could lose all or part of the invested capital. Where a claim relating to the information contained in the Prospectus is brought before a court, the plaintiff investor might, under national law, have to bear the costs of translating this Prospectus before the legal proceedings are initiated. Civil liability attaches only to those persons who have tabled the summary, including any translation thereof, but only where the summary is misleading, inaccurate or inconsistent, when read together with the other parts of the Prospectus, or where it does not provide, when read together with the other parts of the Prospectus, key information in order to aid investors when considering whether to invest in the Shares. Investors in ADSs may not rely on this Prospectus for any purpose.
Share information	The Nasdaq Copenhagen symbol for the Shares is "ORPHA". On Nasdaq the symbol for the ADSs is "ORPH". The ISIN code for the Existing Shares is DK0060910917. The temporary ISIN code for the Listing Shares is DK0061411378, which will not be admitted to trading and official listing on Nasdaq Copenhagen. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities. Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares. An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen. It is expected that the listing of the Listing Shares on Nasdaq Copenhagen under the Company's existing symbol "ORPHA" and in the ISIN of the Existing Shares DK0060910917 will be effective on or around October 2, 2020, after registration of the capital increase related to the Listing Shares with the Danish Business Authority, expected on October 1, 2020.
Issuer information	The issuer of the Listing Shares is Orphazyme A/S (the "**Company**" , "**Orphazyme**", "**we**", "**ours**" or "**our**"). The address and other contact details of the Company are Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark, telephone number (+45) 39 17 82 72 and email contact@orphazyme.com. The Company has the legal entity identifier (LEI) 54930025OZD2GGSQ7L42 and has registration (CVR) no. 32266355.
Competent authority	This Prospectus has been approved on September 30, 2020 by the Danish Financial Supervisory Authority as competent authority under the Prospectus Regulation. The address and other contact details of the Danish Financial Supervisory Authority are Århusgade 110, DK-2100 Copenhagen OE, Denmark, telephone number +45 33 55 82 82, email finanstilsynet@ftnet.dk and fax +45 33 55 82 00.

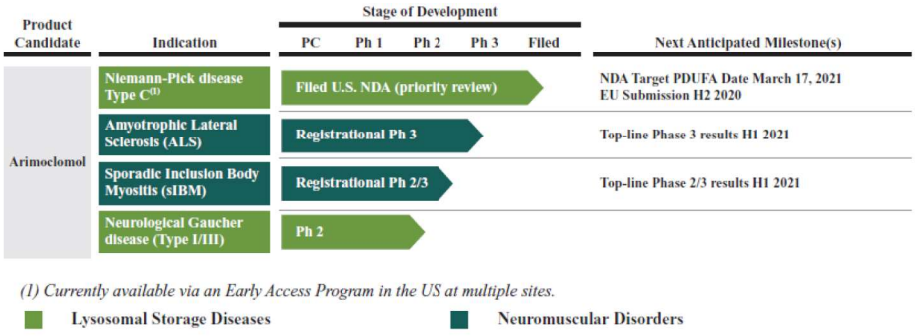
Section B – Key information on the issuer

Who is the issuer of the securities?	The Company has its registered office at Ole Maaløes Vej 3, DK-2200 Copenhagen N in the municipality of Copenhagen, Denmark and is incorporated in Denmark as a Danish public limited liability company under the laws of Denmark. The Company has the legal entity identifier (LEI) 54930025OZD2GGSQ7L42 and has registration (CVR) no. 32266355.
Principal activities	We are a late-stage biopharmaceutical company harnessing the amplification of Heat Shock Proteins ("**HSPs**") in order to develop and commercialize novel therapeutics for the treatment of neurodegenerative orphan diseases. In September 2020, the U.S. Food and Drug Administration ("**FDA**") accepted our new drug application ("**NDA**"), for our product candidate, arimoclomol, for Niemann-Pick disease Type C ("**NPC**"), with priority review. In the letter accepting the NDA, the FDA set a target action date of March 17, 2021 under the Prescription Drug User Fee Act ("**PDUFA**"), for completion of its review of our NDA. The FDA has also notified us that it has identified potential review issues that we need to address before obtaining FDA approval. We also intend to submit a marketing authorization application ("**MAA**"), to the European Medicines Agency ("**EMA**"), in the second half of 2020. Arimoclomol is also in registrational clinical trials for the treatment of Amyotrophic Lateral Sclerosis ("**ALS**"), and Sporadic Inclusion Body Myositis ("**sIBM**"), and we intend to advance into pivotal-stage clinical development in neurological Gaucher disease. Arimoclomol is an orally- or

naso/gastrically-administered small molecule that crosses the blood-brain barrier and is designed to selectively amplify the natural role of endogenous HSPs, which protect against cellular toxicity caused by protein misfolding, aggregation and lysosomal dysfunction. In our Phase 2/3 clinical trial of arimoclomol in NPC, we have observed evidence of slowing of disease progression, supporting our registration effort in the United States and Europe. Results observed in the Phase 2 clinical trials for ALS, sIBM and Gaucher disease demonstrated the potential of arimoclomol to slow the progression of such diseases, forming the basis of our ongoing registrational clinical trials in ALS and sIBM, as well as our intention to advance into pivotal-stage clinical development in neurological Gaucher disease. We also believe that arimoclomol has been well tolerated in clinical trials including more than 500 human subjects for various indications. We are committed to leveraging our deep scientific expertise in the field of HSPs and lysosomal biology, the unique benefits of arimoclomol and our commercial experience and infrastructure to dramatically transform the lives of underserved individuals living with devastating neurodegenerative orphan diseases.

Arimoclomol functions by upregulating HSPs, which are molecular chaperones that are critical in the natural cellular response to stress, protein misfolding, aggregation and lysosomal dysfunction. We believe that arimoclomol is the first clinical product candidate to harness this mechanism of action for the treatment of lysosomal storage diseases ("**LSDs**") and neuromuscular diseases affecting the central nervous system("**CNS**") and muscle. Arimoclomol is currently available to NPC patients in the United States through our early access program ("**EAP**"), with nine patients on treatment as of September 18, 2020 and we have established and may in the future establish early access programs or compassionate use programs for same and other indications and in other locations. We are conducting clinical trials for arimoclomol in three additional indications, including a Phase 3 registrational clinical trial in ALS, for which we expect top-line results in the first half of 2021, a Phase 2/3 registrational clinical trial in sIBM, for which we expect top-line results in the first half of 2021, and a Phase 2 clinical trial in Gaucher disease, for which we announced top-line results in June 2020. We believe that each of these indications has a significant unmet medical need today, given the limited availability of effective therapies for NPC, ALS and neurological Gaucher disease and the lack of any approved drugs for sIBM. Both the FDA and the EMA have granted arimoclomol orphan drug designation for NPC, ALS and sIBM. The FDA has also granted arimoclomol fast track designation in NPC, ALS and sIBM, has designated arimoclomol as a breakthrough therapy in NPC and has granted arimoclomol a rare pediatric disease designation in NPC, potentially entitling us to a priority review voucher if arimoclomol is approved in NPC.

The following table summarizes the indications we are pursuing with arimoclomol, for which we have retained our full, worldwide, exclusive marketing and distribution rights.



Major Shareholders

As of the Prospectus Date, the Company has received notifications of holdings of 5% or more of the share capital or voting rights from the shareholders below:

Shareholder(1)	Number of Shares as at latest announcement	Ownership interest as at latest announcement	Voting rights as at latest announcement
LSP V Coöperatieve U.A.	2,710,829	10.03%	10.03%
Sunstone Life Science Ventures Fund II K/S	1,804,405	9.10%	9.10%
Coöperative Aescap Venture I U.A.	1,765,605	8.90%	8.90%
Consonance Capital Master Account LP	1,900,000	7.0%	7.03%

(1) The ownership and voting rights percentages are shown as of the latest announcements received by the Company and assume no further trading by these respective major shareholders. Following completion of the Global Offering, and assuming no trading by these

respective major shareholders, these shareholdings will be diluted and each shareholder will notify the Company in the event its shareholdings fall below 5% and/or 10% threshold.

The Company is not aware of being owned or controlled, directly or indirectly, by others.

Key managing directors

A the Prospectus Date, the Board of Directors consists of Georges Gemayel (Chairman), Bo Jesper Hansen (Deputy Chairman), Anders Hedegaard, Catherine Moukheibir, Martijn Kleijwegt, Martin Bonde, Rémi Droller, Sten Verland and Carrolee Barlow, and the Executive Management consists of Kim Stratton, CEO, and Anders Vadsholt, CFO (the "**Executive Management**").

The Executive Management is supported by the Key Employees. The Key Employees consists of Thomas Blaettler, CMO and Thomas Kirkegaard Jensen, CSO.

Statutory auditors

The statutory auditors of the Company is EY Godkendt Revisionspartnerselskab (formerly named Ernst & Young Godkendt Revisionspartnerselskab). The independent auditors' report included in the Annual Report for 2019, which includes the consolidated financial statements and the parent company financial statements for the financial year January 1 – December 31, 2019 were signed by State Authorised Public Accountant, Christian Schwenn Johansen and State Authorised Public Accountant, Rasmus Bloch Jespersen.

What is the key financial information regarding the issuer?

The key financial information shown below has been derived from the FY2019 Group Financial Statements prepared in accordance with IFRS as adopted by the EU and additional disclosure requirements of the Danish Financial Statements Act and the H1 2020 Interim Financial Statements prepared in accordance with IAS 34 Interim Financial Reporting as adopted by EU

The Company's consolidated financial statements are prepared and presented in accordance with IFRS. Our historical results are not necessarily indicative of results expected for future periods.

Since the end of the period covered by the H1 2020 Interim Financial Statements, no significant change to the financial position of the Group has occurred.

Selected Consolidated Statements of Profit or Loss and Other Comprehensive Income Data:

	Six Months Ended June 30,			Years Ended December 31,		
(In thousands, except per share data)	2020		2019	2019		2018
	$(1)	DKK	DKK	$(1)	DKK	DKK
Research and development expenses	(25,179)	(166,980)	(141,710)	(43,037)	(285,413)	(196,525)
General and administrative expenses	(11,848)	(78,575)	(23,345)	(7,621)	(50,541)	(35,127)
Operating loss	(37,027)	(245,555)	(165,055)	(50,658)	(335,954)	(231,652)
Financial income	19	126	152	48	316	5
Financial expenses	(1,201)	(7,967)	(1,500)	(1,110)	(7,359)	(3,453)
Loss before tax	(38,209)	(253,396)	(166,403)	(51,720)	(342,997)	(235,100)
Income tax benefit	299	1,981	2,495	829	5,500	5,500
Net loss for the period	(37,911)	(251,415)	(163,908)	(50,891)	(337,497)	(229,600)
Exchange difference from translation of foreign operation, net of tax DKK 0	(20)	(135)	(19)	10	67	42
Total comprehensive loss	(37,930)	(251,550)	(163,927)	(50,881)	(337,430)	(229,558)
Loss per share (2)						
Basic loss per share	(1.49)	(9.88)	(8.20)	(2.54)	(16.87)	(11.49)
Diluted loss per share	(1.49)	(9.88)	(8.20)	(2.54)	(16.87)	(11.49)

(1) Translated solely for convenience into U.S. dollars at an assumed exchange rate of DKK 6.6318 per $1.00, which was the rounded official exchange rate of such currencies as of June 30, 2020.

(2) See Note 4.3 to our audited consolidated financial statements which are publicly available for further details regarding the calculation of basic and diluted loss per share.

Selected Consolidated Statements of Financial Position:

			As of December 31,		
(in thousands)	As of June 30, 2020		2019		2018
	$(1)	DKK	$(1)	DKK	DKK
Cash	92,049	610,448	$18,636	123,588	394,706
Working capital(2)	77,865	516,384	12,400	82,237	370,389
Total assets	101,987	676,360	27,256	180,754	441,349
Share Capital	4,078	27,045	3,013	19,984	19,939
Total equity	76,319	506,135	7,987	52,969	388,249

(1) Translated solely for convenience into U.S. dollars at an assumed exchange rate of DKK 6.6318 per $1.00, which was the rounded official exchange rate of such currencies as of June 30, 2020.
(2) We define working capital as current assets less current liabilities.

Cash flow statement	Six Months Ended June 30,		Year ended December 31,	
	2020 (DKK thousand)	2019	2019	2018
Cash flow from operating activities	(204,169)	(166,597)	(326,818)	(234,764)
Cash flow from investing activities	(1,760)	(1,225)	(3,285)	(2,346)
Cash flow from financing activities	692,944	(1,061)	58,939	-
Net cash flows	487,015	(168,883)	(271,164)	(237,110)
Cash	610,448	225,560	123,588	394,706

What are the key risks that are specific to the issuer?

The main risks that are specific to the Company's business and industry are:

- We have not received approval for any product candidate for commercial sale and, as a result, we have never generated any revenue and have incurred significant financial losses, and expect to continue to incur significant financial losses in the future, which makes it difficult to assess our future viability.
- Even if the Global Offering is successful, we will require additional capital in the future, which may not be available to us on commercially favorable terms, or at all.
- Our business, operations and clinical development plans and timelines could be adversely affected by the effects of health epidemics, including the recent COVID-19 pandemic, on the manufacturing, clinical trial and other business activities performed by us or by third parties with whom we conduct business, including our contract manufacturers, CROs, shippers and others.
- Our indebtedness may limit our flexibility in operating our business and could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.
- Clinical trials being conducted to test our product candidate, arimoclomol, may not obtain the desired safety and efficacy results or may be delayed or more costly than anticipated.
- As we have focused our efforts on the development of arimoclomol, we are currently highly dependent on obtaining and maintaining regulatory approval for arimoclomol and the potential success of this one product candidate.
- We are highly dependent on obtaining and maintaining required regulatory approvals and may not receive such approvals.
- Because we are developing arimoclomol for the treatment of diseases in which there is little clinical experience, the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to predict or provide clinically meaningful results.
- Arimoclomol may be shown to cause undesirable side effects or other adverse events that could delay or prevent its regulatory approval, limit its commercial profile or result in significant negative consequences following regulatory approval, if such approval is granted.
- If we are unable to obtain or maintain orphan drug designation or if we are unable to benefit from orphan drug exclusivity for arimoclomol, it will have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.
- Fast track and orphan drug designation by the FDA and EMA may not actually lead to a faster development or regulatory review or approval process, and does not assure FDA or EMA approval of arimoclomol.
- A breakthrough therapy designation by the FDA for arimoclomol may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidate will receive marketing approval.
- We and our CROs have conducted and intend to conduct additional clinical trials at sites outside the United States, and the FDA may not accept data from trials conducted in such locations due to the study design and conduct, trial population or for other reasons, or may require additional U.S.-based trials.

Section C – Key information on the securities

What are the main features of the

The Listing comprises up to 7,616,146 Listing Shares. The Shares are ordinary shares and are not divided into share classes. The ISIN code for the Existing Shares is DK0060910917..

The Listing Shares will initially be issued in an temporary ISIN code, which will not be admitted to trading and official listing on Nasdaq Copenhagen. Upon completion of the Listing, the temporary ISIN

securities ?	code will be merge with the ISIN code for the Existing Shares, and the Listing Shares will be admitted to trading and official listing under the perminant ISIN code for the Existing Shares DK0060910917. The Shares are denominated in DKK. Prior to the Global Offering, the Company had 27,081,557 outstanding shares with a nominal value of DKK 1 each (the "**Existing Shares**") each or multiples thereof, which are all issued and fully paid up. After completion of the Global Offering, the Company will have issued 34,697,703 shares, assuming the Overallotment Option is not exercised (or 35,840,124 shares assuming the Overallotment Option is exercised in full).
Rights attached to the Listing Shares	The Listing Shares will be registered with the Danish Business Authority and have the same rights as the Existing Shares, including with respect to eligibility for any dividends. Any dividends will be paid in DKK to the shareholder's account with VP Securities. No restrictions on dividends or special procedures apply to holders of Listing Shares who are not residing in Denmark. All Shares in the Company will rank pari passu, including with respect to voting rights and pre-emption rights. All Shares will then carry one vote per Share of a nominal value of DKK 1. A person registered as a holder of shares of the Company in VP Securities A/S and acting in a professional capacity on behalf of other natural or legal persons, including holders of ADS representing shares of the Company, may exercise voting rights attached to any such shares in a manner that is not identical to the exercise of the voting rights attached to other shares of the Company held by such person. In case of the dissolution or winding-up of the Company, the Listing Shares will be entitled to a proportionate part of the Company's assets after payment of the Company's creditors. The Articles of Association do not contain any provisions on redemption or exchange of Shares. None of the Shares carry any redemption or conversion rights or any other special rights, but the Shares may be subject to compulsory redemption pursuant to the Danish Companies Act.
Restrictions	The Listing Shares are negotiable instruments and no restrictions under the Company's Articles of Association or Danish law apply to the transferability of the Listing Shares. The Shares are subject to transfer and reselling restrictions in certain jurisdictions. Any acquirer of Shares must comply with all applicable laws and regulations in force in any country or region in which it acquires or resells Shares or possesses or distributes this Prospectus and must obtain any consent, approval or permission required for acquiring Shares. This Prospectus may not be distributed or otherwise made available, and Shares may not be offered or sold, directly or indirectly, in the United States, Canada, Australia or Japan or in any other jurisdiction pursuant to this Prospectus. The Shares have not been approved, disapproved or recommended by any foreign regulatory authorities, nor have any of such authorities passed upon or endorsed the merits of the Listing or the accuracy or adequacy of this Prospectus.
Dividend policy	The Company has not declared or made any dividend payments for the last financial year. Currently, the Company intends to use all available financial resources as well as revenue, if any, for purposes of the Company's current and future business. As of the date hereof, the Company does not expect to make dividend payments within the foreseeable future.
Where will the securities be traded?	The Listing Shares will be registered with the Danish Business Authority on or around October 1, 2020 and issued through VP Securities the same day. The Listing Shares will initially be issued in an temporary ISIN code, which will not be admitted to trading and official listing on Nasdaq Copenhagen. Upon completion of the Listing, the temporary ISIN code will be merge with the ISIN code for the Existing Shares, and the Listing Shares will be admitted to trading and official listing under the perminant ISIN code for the Existing Shares DK0060910917. The Listing Shares will be issued in connection with the EU Private Placement and the U.S. Offering of 3,966,146 ADSs at a price of USD 11.00 per ADS (using a USD/DKK exchange rate of 6.3804). Each ADS represents one Listing Share. The Listing Shares are underlying the ADSs. The ADSs are listed and began trading on Nasdaq on September 29, 2020 under symbol "ORPH".
What are the key risks that are specific to the securities ?	The trading price of our equity securities may be volatile due to factors beyond our control, and purchasers of the Shares could incur substantial losses. We have broad discretion over the use of the net proceeds from the Global Offering and may use them in ways with which you do not agree and in ways that may not enhance our operating results or the price of the Shares

Section D – Key information on the offer and admission to trading

Under which	This Prospectus is a listing prospectus in which there is no public offering of Listing Shares in Denmark, the EEA, the United States or in any other jurisdiction. The Listing Shares will in their entirety be

conditions and timetable can I invest in this security?

Terms and conditions of the offering

subscribed for by the Underwriters (or their respective affiliates), severally and not jointly, on behalf of themselves or on behalf of the investors, as applicable, who, with respect to the U.S. Offering, have instructed the Company to deliver such Listing Shares underlying ADSs to the Depositary, The Bank of New York Mellon. The Depositary will then be allowed to deliver the number of ADSs which are subject to the U.S. Offering. The Prospectus is solely prepared for the purposed of having the Listing Shares, which (i) were offered as the European Offered Shares in connection with the EU Private Placement and (ii) which are underlying ADSs that were offered in the Unites States in connection with the U.S. Offering and are listed and traded on Nasdaq. The Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen, subject to completion and settlement of the U.S. Offering and the EU Private Placement and the approval and publication of this Prospectus. Investors in ADSs or Shares may not rely on this Prospectus for any purpose. The Listing Shares will initially be issued under a temporary ISIN code and will not be admitted to trading and official listing under such temporary ISIN code. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities. Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares. The Listing Shares are expected to be registered with the Danish Business Authority, issued in VP Securities and on or around October 1, 2020. The Listing Shares offered in connection with the U.S. Offering will be delivered to the Depositary through Danske Bank A/S on or around October 1, 2020. The expected timetable is as follows:

Date of launch of the Global Offering and publication of the preliminary U.S. prospectus for the offering in the United States	September 21, 2020
Pricing of the U.S. Offering and EU Private Placement	September 29, 2020 (CET)/ September 28, 2020 (ET)
ADSs started trading on Nasdaq	September 29, 2020
Date of publication in the United States of the final U.S. prospectus	September 30, 2020 (CET)
Publication of this Prospectus	September 30, 2020
Completion of the U.S. Offering and the EU Private Placement (expected)	October 1, 2020
Registration of the Listing Shares with the Danish Business Authority (expected)	October 1, 2020
First day of trading of the Listing Shares on Nasdaq Copenhagen	October 2, 2020

The timetable above is subject to change. Any such changes will be announced as company announcements.

Admittance to trading

The Existing Shares are admitted to trading and official listing on Nasdaq Copenhagen under the symbol "OPRHA" and in the ISIN code DK0060910917. An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen. The Listing Shares are expected to be admitted to trading and official listing on Nasdaq Copenhagen on or around September 30, 2020 under the existing ISIN code DK0060910917 and under the Company's existing symbol "ORPHA". The Listing Shares will be issued in connection with the EU Private Placement and the U.S. Offering of 3,966,146 ADSs at a price of USD 11.00 per ADS (using a USD/DKK exchange rate of 6.3804). Each ADS represents one Listing Share. The Listing Shares are underlying the ADSs. The ADSs were listed and began trading on Nasdaq on September 29, 2020 under the symbol "ORPII".

Plan for distribution

Not applicable since there is no offering of securities for sale or subscription pursuant to this Prospectus. The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen. Investors in ADSs or Shares may not rely on this Prospectus for any purpose.

Dilution

Not applicable since the Listing of the Listing Shares on Nasdaq Copenhagen will not result in any dilution. As a result of the Global Offering, the Existing Shares at the date of this Prospectus will be diluted by the issue of 7,616,146 Listing Shares, corresponding to a nominal value of DKK 7,616,146. If the Overallotment Option is exercised in full, the Existing Shares will be diluted by 8,758,567 Shares, corresponding to a nominal value of DKK 8,758,567, including the Listing Shares and such Shares issued under the Overallotment Option. Following the completion of the Global Offering, the Existing Shares will represent 78% of the Company's share capital if the Overallotment Option is not exercised, and 75.6% if the Overallotment Option is exercised in full.

Estimated expenses

Expenses, after deducting the underwriting commissions and offering expenses, are expected to be approximately DKK 16.6 (or USD 2.6 million using a U.S. Dollar/DKK exchange rate of 6.3804) and are payable by the Company. The Company has agreed to reimburse the Underwriters for certain expenses as set forth in the Underwriting Agreement. The total underwriting commission is approx. DKK 37.4 million (or USD 5.9 million), and approx. DKK 42.7 million (or USD 6.7 million) if the Overallotment Option is exercised in full, in each case using a U.S. Dollar/DKK exchange rate of 6.3804.

Why is this prospectus being produced?	The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen and there is no offering of securities for sale or subscription in connection with this Prospectus. The Listing Shares are being issued in connection with the Global Offering.
Net amounts and use of proceeds	Since the purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen and there is no offering of securities for sale or subscription in connection with this Prospectus, there are, in turn, no net proceeds as a result of the Listing as such. Investors in ADSs may not rely on this Prospectus for any purpose. We intend to use the net proceeds from the global offering, together with our existing cash, to continue the regulatory approval process for and fund the commercial launch, if approved, of arimoclomol for the treatment of NPC, advance the clinical development of arimoclomol for the treatment of ALS, sIBM and neurological Gaucher disease and for working capital and general corporate purposes, including to fund the development of our next generation of HSP amplifiers. We estimate that the net proceeds to us from the Global Offering, after deducting the underwriting commissions and estimated offering expenses payable by us, to be approximately DKK 480 milion (75.3 million), or DKK 555 million ($87.0 million) if the underwriters exercise their option in full to purchase Additional Securities, based on the initial offering price of DKK 70.1844 ($11.00 per ADS),), using a U.S. Dollar/DKK exchange rate of 6.3804.
Underwriting	Not applicable since there is no offering of securities for sale or subscription. The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen.
Material conflicts of interest	No material conflicts of interest pertaining to the Listing or the admission to trading exist.
Recent Developments	In September 2020, the FDA accepted our NDA for arimoclomol for NPC with priority review. In the letter accepting the NDA, the FDA set a target action date of March 17, 2021 under the PDUFA for completion of its review of our NDA. On September 24, 2020, we received a filing communication from the FDA in connection with our NDA for arimoclomol for the treatment of NPC in which the FDA summarized six potential review issues, four of which we have previously discussed with the FDA, including the FDA's continuing evaluation of the integrity of data from our Phase 2/3 trial for NPC; the effect of the high degree of concomitant miglustat use in our Phase 2/3 trial for NPC on its ability to determine the safety and efficacy of arimoclomol, which could have potential implications for labeling/recommended dosing and post-marketing studies; the proposed primary hypothetical treatment effect used in our Phase 2/3 trial for NPC to estimate the treatment benefit effect; the meaningfulness of one metric utilized to evaluate patient progress in our Phase 2/3 trial of NPC; the timing of submission of the QTc and other study reports to the FDA, including in light of evidence suggesting a potential QT safety signal; and differences among the formulations of arimoclomol used in our Phase 2/3 trial of NPC as compared to the formulation of arimoclomol to be marketed. The FDA has requested that we submit reports from the QTc clinical trial by October 1, 2020 and that, given the priority review timeline and both nonclinical and clinical evidence suggesting a potential QT safety signal, submission of these reports after that date may not allow the FDA sufficient time to review. In a preclinical study, we observed a potential QT signal in dogs at a level of arimoclomol exposure that is 28 times higher than the level of exposure in humans in our Phase 2/3 trial in NPC. To date, we are not aware of any clinical evidence of a potential QT signal related to arimoclomol.We do not anticipate being able to submit the reports by October 1, 2020, which may negatively impact our development timeline. The filing communication constitutes preliminary notice from the FDA of potential review issues as part of its ordinary course review of our NDA and is not necessarily indicative of deficiencies that may be identified during the review. We intend to discuss the filing communication with the FDA. The receipt of the filing communication does not impact the FDA's acceptance of the NDA for arimoclomol, the target PDUFA date or the priority review determination. However, we cannot assure you that such issues will not result in a delay of any potential approval of arimoclomol for the treatment of NPC by the FDA or a determination by the FDA not to approve the product candidate for marketing in the United States.

RISK FACTORS

Prospective investors should carefully consider all information in this Prospectus (including any information or material incorporated by reference), including the risks described below, before they decide to subscribe to invest in the Shares. This section addresses both general risks associated with the industry and market in which the Company operates and the specific risks associated with its business and its intellectual property rights. If such risks were to materialize, the Company's business, results of operations, cash flows, financial condition, and/or prospects could be materially and adversely affected. With respect to forward-looking statements that involve risks and uncertainties, see "*General Information–Forward-looking statements*".

The risks and uncertainties discussed below are those that the Company's management currently views as material, but these risks and uncertainties are not the only ones that it faces. Additional risks and uncertainties, including risks that are not known to the Company at present or that its management currently deems immaterial, may also arise or become material in the future and could, individually or in the aggregate, have a material adverse effect on the Company's business, results of operations, cash flows, financial condition, and/or prospects. The most material risks, as currently assessed by the Company, taking into account the expected magnitude of their negative impact on the Company and the Company's business and the probability of their occurrence are set out first in each category of risk factors below.

Risks Related to our Financial Position and Capital Needs

We have not received approval for any product candidate for commercial sale and, as a result, we have never generated any revenue and have incurred significant financial losses, and expect to continue to incur significant financial losses in the future, which makes it difficult to assess our future viability.

We have not had any product candidates approved for commercial sale. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk, including risks related to the regulatory approval process for arimoclomol. To date, we have focused on research and development activities on developing arimoclomol, as described in "*Company Information—Business*" Since our inception in 2009, we have incurred significant losses, which have substantially resulted from costs related to our research and development programs and general and administrative activities. Our net loss for the year ended December 31, 2019 was DKK 337.5 million ($50.9 million) and for the six months ended June 30, 2020 was DKK251.4 million ($37.9 million). Going forward, we expect to continue to incur significant losses from our operations.

We anticipate that our expenses will increase substantially if, and as, we, for instance:

- continue the ongoing and planned development of arimoclomol for multiple indications;
- initiate, conduct and complete ongoing, anticipated or future preclinical studies and clinical trials for our current and future product candidates;
- seek marketing approvals for product candidates that successfully complete clinical trials;
- pay milestone and royalty fees to CytRx Corporation ("**CytRx**") and other third parties from whom we have licensed intellectual property in accordance with the terms of the applicable license agreement;
- establish a sales, marketing and distribution infrastructure to commercialize products for which we may obtain marketing approval;
- continue to build a portfolio of product candidates through the acquisition or in-license of product candidates or technologies;

- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and

- incur additional legal, accounting and other expenses associated with operating as a dual-listed public company.

If annual operating expenses increase significantly over the next several years and we are not able to commercialize our product candidate, we will have less financial resources available for our other business prospects, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Even if the Global Offering is successful, we will require additional capital in the future, which may not be available to us on commercially favorable terms, or at all.

We expect to incur significant expenses and operating losses over the next several years and we will need to raise additional capital in the future. We have so far been financed by funds provided by debt providers or invested by our shareholders. Based on the current operating plan and the existing capital resources together with the anticipated net proceeds from the Global Offering, we expect to be able to fund our operating plan for at least the next 24 months. However, the operating plan may change as a result of many factors currently unknown, and it may be necessary to seek additional funds sooner than anticipated. The future funding requirements will depend on many factors, including the progress, timing, scope, results and costs of our preclinical studies and clinical trials, including the ability to enroll patients in a timely manner for clinical trials as well as the time and cost necessary to obtain regulatory approvals for arimoclomol and any future product candidates. For example, we will require additional capital in the future in order to obtain regulatory approval for arimoclomol in ALS and sIBM. In addition, funding requirements will also depend on the progress in commercialization and promotion of arimoclomol as well as the manufacturing, selling and marketing costs associated with arimoclomol, including the cost and timing of building sales and marketing capabilities. This extends to the sales price and the availability of adequate third-party coverage and reimbursement for our products, the number and scope of preclinical and discovery programs that we may decide to pursue or initiate, the time and cost necessary to respond to technological and market developments and the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights, including litigation costs and the outcome of such litigation. We may also engage in future acquisitions or strategic partnerships, which may increase our capital requirements, dilute our shareholders if we issue equity securities, cause us to incur debt or assume contingent liabilities, divert management's attention and subject us to other risks.

We may seek to raise new capital in the future through public or private debt or equity financings by issuing additional ordinary shares or ADSs, debt or equity securities convertible into shares, or rights to acquire these securities.

Any additional financing that we could seek may not be available on favorable terms or at all. For example, while the potential impact and duration of the COVID-19 pandemic on the global economy and our business in particular may be difficult to assess or predict, the pandemic has resulted in, and may continue to result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. If we are unable to obtain adequate financing or financing on terms satisfactory to us when we require it, our future plans and our ability to execute our strategy could be adversely affected, which in turn could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Our business, operations and clinical development plans and timelines could be adversely affected by the effects of health epidemics, including the recent COVID-19 pandemic, on the manufacturing, clinical trial and other business activities performed by us or by third parties with whom we conduct business, including our contract manufacturers, CROs, shippers and others.

Our business has been and could be further adversely affected by health epidemics wherever we have clinical trial sites or other business operations. In addition, health epidemics could cause significant disruption in the operations of third-party manufacturers, CROs and other third parties upon whom we

rely. For example, in December 2019, a novel strain of coronavirus, SARS-CoV-2, causing a disease referred to as COVID-19, was reported to have surfaced in Wuhan, China. Since then, COVID-19 has spread to multiple countries worldwide, including the United States. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, and the U.S. government ordered the closure of all non-essential businesses, imposed social distancing measures, "shelter-in-place" orders and restrictions on travel between the United States, Europe and certain other countries. The global pandemic and government measures taken in response have also had a significant impact on businesses and commerce worldwide, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended across a variety of industries; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. On March 18, 2020 the FDA issued updated industry guidance for conducting clinical trials during the COVID-19 pandemic, which requires clinical trial sponsors to consider the need to delay or cease patient recruitment, change protocol regarding patient monitoring and assessment that minimizes in-person visits, alternative administration of certain investigational products due to compromised clinical sites and to put in place new processes or modify existing processes in consultation with the FDA that would ensure the safety of clinical trial participants. In connection with COVID-19, we temporarily closed our executive offices and implemented optional work-from-home policies for most employees. The effects of government orders and our work-from-home policies may negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course.

We depend on a global supply chain to manufacture product candidates used in our preclinical studies and clinical trials. Quarantines, "shelter-in-place" and similar government orders, or the expectation that such orders, shutdowns or other restrictions could occur, whether related to COVID-19 or other infectious diseases, could impact personnel at third-party manufacturing facilities in the United States and other countries, or the availability or cost of materials, which could disrupt our supply chain.

If our relationships with our suppliers or other vendors are terminated or scaled back as a result of the COVID-19 pandemic or other health epidemics, we may not be able to enter into arrangements with alternative suppliers or vendors or do so on commercially reasonable terms or in a timely manner. Switching or adding additional suppliers or vendors involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new supplier or vendor commences work. As a result, delays may occur, which could adversely impact our ability to meet our desired clinical development and any future commercialization timelines. Although we carefully manage our relationships with our suppliers and vendors, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not harm our business.

In addition, our preclinical studies and clinical trials have been and may continue to be affected by the COVID-19 pandemic. Clinical site initiation, patient enrollment and activities that require visits to clinical sites, including data monitoring, have been and may continue to be delayed due to prioritization of hospital resources toward the COVID-19 pandemic or concerns among patients about participating in clinical trials during a pandemic. Some patients may have difficulty following certain aspects of clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. For example, some patients, including patients in our Phase 3 registrational clinical trial in ALS, may not be able to attend follow-ups and comply with trial protocols. These challenges have and in the future may continue to also increase the costs of completing our clinical trials. Similarly, if we are unable to successfully recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 or experience additional restrictions by their institutions, city or state, our clinical trial operations could be adversely impacted. In addition, access to arimoclomol as a treatment for NPC, which was announced in January 2020 to be available through the EAP, in the United States, was delayed due to the COVID-19 pandemic. Furthermore, the QTc clinical trial required to support our NDA for NPC has been delayed due to COVID-19. The FDA has requested that we submit reports from the QTc clinical trial by October 1, 2020 and that, given the priority review timeline and both nonclinical and clinical evidence suggesting a potential QT safety signal, submission of these reports after that date may not allow the FDA sufficient time to review. We do not anticipate being able to submit the reports by October 1, 2020, which may delay the timing of FDA approval for NPC. Additionally, we cannot assure you that the potential QT safety signal (individually or together with other factors) will not prevent us from obtaining FDA approval for NPC.

The spread of COVID-19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by, and the duration of, COVID-19 may be difficult to assess or predict, a widespread pandemic has resulted in significant disruption of global financial markets, resulting in an economic downturn that could continue to significantly impact our business and operations and may reduce our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and the value of the ordinary shares and ADSs.

Further, we may experience additional disruptions that could severely impact our business and clinical trials, including:

- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;

- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;

- limitations on employee resources that would otherwise be focused on the conduct of our preclinical studies and clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people;

- risk that participants enrolled in our clinical trials will acquire COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events; and

- refusal of the FDA to accept data from clinical trials in these affected geographies.

These and similar, and perhaps more severe, disruptions in our operations could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

The global pandemic of COVID-19 continues to evolve rapidly. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we continue to monitor the COVID-19 situation closely. To the extent the COVID-19 pandemic adversely affects our business, results of operations, cash flows, financial condition and/or prospects, it may also have the effect of heightening many of the other risks described in this "Risk Factors" section.

Our indebtedness may limit our flexibility in operating our business and could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

As of June 30, 2020, we had €9.0 million of principal balance (the "**Term Loan**"), outstanding under the loan facility agreement (the "**Loan Agreement**"), with Kreos Capital VI (UK) Limited("**Kreos**"). We are required to repay the Term Loan over 42 months with the first 12 months requiring interest only payments at a nominal annual fixed interest rate of 9.75% and the remaining 30 months requiring equal installments comprising principal and interest. Early repayment of the borrowed amounts may be made in whole but not in part, with the repayment amount being equal to the principal outstanding plus the sum of all the interest repayments that would have been paid throughout the remainder of the loan discounted at an annual rate of 4.0%. The Loan Agreement also provides that we will pay Kreos a facilitation fee upon the request of Kreos, which request may be made in its sole discretion at any time prior to the earlier to occur of August 27, 2024 and the date of delisting of our shares, including ADSs representing our ordinary shares, from a securities exchange. The facility fee is equal to the greater of (i) €0.9 million and (ii) the percentage increase in our share price between the 30-day volume-weighted average share price on the date of the Loan Agreement and the closing share price on the day immediately preceding the date of the notification applied to the aggregate amount borrowed. We have also agreed to pay Kreos an end of loan payment in an amount equal to 3% of the amount drawn under the first tranche. The amounts due under the Loan Agreement are secured by certain of our assets, including our intellectual property rights, pursuant to a floating charge agreement registered with the

Danish personal register in the initial principal amount of €9.0 million, our patents registered in Germany, the United Kingdom and the United States, and our shares in our U.S. subsidiary. Our obligations under the Loan Agreement are guaranteed by our U.S. subsidiary.

In order to service this indebtedness and any additional indebtedness we may incur in the future, we need to generate cash. Our ability to generate cash is subject, in part, to our ability to successfully execute our business strategy, as well as general economic, financial, competitive, regulatory and other factors beyond our control. It cannot be guaranteed that our business will be able to generate sufficient cash flow or that future borrowings or other financings will be available to us in an amount sufficient to enable us to service our indebtedness and fund our other liquidity needs. To the extent we are required to use cash from operations or the proceeds of any future financing to service our indebtedness instead of funding working capital, capital expenditures or other general corporate purposes, we will be less able to plan for, or react to, changes in our business, industry and in the economy generally. This will place us at a competitive disadvantage compared to our competitors that have less indebtedness.

In addition, the Loan Agreement contains, and any agreements evidencing or governing other future indebtedness may contain, certain covenants that limit our ability to engage in certain transactions that may be in our long-term best interests. Subject to certain limited exceptions, these covenants limit our ability to, among other things:

- sell, lease, convey, transfer, assign, license or otherwise of or deal with all or any material part of our property, assets or undertaking;
- sell, assign transfer or otherwise dispose of any assets that are subjects to liens under the Loan Agreement, any of our material assets or any share therein
- incur or allow to remain outstanding any indebtedness
- create or permit to subsist any liens; and
- declare and/or make or agree to make any distribution by way of dividend or otherwise, without the written consent of Kreos.

While we have not previously breached and are not currently in breach of these or any of the other covenants contained in the Loan Agreement, there can be no guarantee that we will not breach these covenants in the future. Our ability to comply with these covenants may be affected by events and factors beyond our control. In the event that we breach one or more covenants, our lender may choose to declare an event of default and require that we immediately repay all amounts outstanding, terminate any commitment to extend further credit and foreclose on the collateral granted to it to collateralize such indebtedness. The occurrence of any of these events could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Risks Related to Development of Our Product Candidates

Clinical trials being conducted to test our product candidate, arimoclomol, may not obtain the desired safety and efficacy results or may be delayed or more costly than anticipated.

Prior to launching a pharmaceutical product into the market, its safety and efficacy for treatment of patients must be ascertained through execution of certain preclinical studies and clinical trials conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the FDA, the EMA, and other applicable regulatory authorities' legal requirements, regulations and guidelines, including good laboratory practices, an international standard meant to harmonize the conduct and quality of non-clinical studies and the reporting of findings, as well as good clinical practices ("**GCP**") an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Conducting such trials is complex, costly and time-consuming, and neither the results nor the timing can be predicted with any certainty. Some of the clinical trials that we currently sponsor relate to pediatric diseases for which there are additional regulatory requirements.

The performance of clinical trials is associated with risks. We may experience numerous unforeseen events prior to, during or as a result of clinical trials that could delay or prevent our ability to receive marketing approval or commercialize arimoclomol, including:

- effects of the ongoing COVID-19 pandemic, including delays in clinical trial enrollment, patient treatment and data processing, as well as complications with commercial suppliers, clinical testing sites and/or CROs;
- the FDA, the EMA or other comparable regulatory authority may disagree as to the number, design or implementation of our clinical trials, or may not interpret the results from clinical trials as we do;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may not reach agreement on acceptable terms with prospective clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- clinical trials of arimoclomol may produce negative or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of arimoclomol may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, participants may drop out of these clinical trials at a higher rate than we anticipate or we may fail to recruit eligible patients to participate in a trial;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators may issue a clinical hold, or regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of arimoclomol may be greater than we anticipate;
- the supply or quality of arimoclomol or other materials necessary to conduct clinical trials of arimoclomol may be insufficient or inadequate;
- arimoclomol may have undesirable side effects or other unexpected characteristics causing us or our investigators, regulators or institutional review boards to suspend or terminate the clinical trials; and
- the approval policies or regulations of the FDA, the EMA or other comparable regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

There is a risk that the clinical trials that we currently sponsor will not confirm previous results or will not demonstrate sufficient evidence of safety and efficacy to receive requisite regulatory approvals. This risk is compounded by the fact that, thus far, we have only conducted relatively small Phase 2/3 and Phase 2 clinical trials, only one of which was designed to measure efficacy. Such clinical trials may not lead to pharmaceutical products that can be effectively commercialized. Adverse or inconclusive results may, despite initially promising results, result in arimoclomol not receiving requisite approvals for marketing and sale, and there is a risk that additional clinical trials will be required to obtain such approvals or that our clinical development program will be required to be altered, which would result in increased costs, significant delays to filing with regulatory authorities, filing for a narrower indication

than previously anticipated or the abandonment of efforts to commercialization of arimoclomol. For example, even though we did not meet the primary endpoint in our Phase 2 clinical trial for Gaucher disease, based on other results in this clinical trial, including the statistically significant dose-dependent reduction in liver size dose-dependent reduction in spleen size, we intend to advance arimoclomol into pivotal-stage clinical development in neurological Gaucher disease. However, it is possible that the FDA may require us to conduct further clinical trials. Further, even though we believe chitotriosidase is of limited value moving forward and we no longer intend to use chitotriosidase as a key endpoint in our clinical trials in Gaucher disease, it is possible that the FDA may require us to alter our intended design for the Phase 3 trial for Gaucher disease.

In addition, the FDA, the EMA or other regulatory authorities may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a product.

All of our current clinical trials are studying the same chemical compound, arimoclomol, but for different indications. There is a risk, therefore, that any unexpected findings, including serious adverse events, in one clinical trial may have a "spill-over" effect on other trials, in particular if the finding is related to the compound's safety and tolerability. An adverse or inconclusive finding in one trial, therefore, may halt or significantly delay our entire clinical development portfolio. If our ongoing clinical trials are unsuccessful, we may be unable to expand our development of arimoclomol to other indications.

Designing and conducting clinical trials for orphan drugs involves additional risks because, for instance, the relevant indications are not well characterized and experience with treatment of orphan diseases is limited. In addition, patients in our clinical trials may have a clinically relevant medical condition that may make conducting the clinical trial difficult and/or confound an assessment of the effects of the experimental therapy and its adverse events. Such risks may also include delays and increased costs.

As clinical product development can be affected by unforeseen delays, increased costs, unexpected adverse events, unforeseen suspensions and unfavorable results, these circumstances could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

In addition, we depend on our ability to enter into agreements with CROs, conducting clinical trials with respect to arimoclomol. Through our CROs, we are in a close, ongoing dialogue with physicians, who are relevant as investigators. However, if we are not able, through our CROs, to enter into the necessary agreements with respect to clinical trials, it may have a material adverse effect on our ability to complete such clinical trials. Further, if the counterparties to our sponsored clinical trial agreements do not carry out their obligations or do so within the agreed deadlines, the clinical trials may be delayed, terminated or deemed unsuccessful, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Most of our clinical trials conducted have been small, each with less than 100 persons, and have advanced through Phase 1 and Phase 2. Our later-phase clinical trials are being conducted with larger patient populations, such as our recently-enrolled Phase 3 clinical trial evaluating arimoclomol for the treatment of ALS, which has enrolled 245 patients. In these trials, additional risks, including previously unidentified low incidence safety risks, safety risks associated with high-dose long-term treatment or lack of efficacy may materialize.

If the above risks were to materialize, it could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

As we have focused our efforts on the development of arimoclomol, we are currently highly dependent on obtaining and maintaining regulatory approval for arimoclomol and the potential success of this one product candidate.

To date, we have focused substantially all of our efforts on the development of arimoclomol.We are currently conducting preclinical studies and clinical trials based on the arimoclomol molecule. In September 2020, the FDA sent us a letter in which it accepted our NDA for arimoclomol for NPC with priority review and set a target

action date of March 17, 2021 under the PDUFA to complete its review of our NDA. On September 24, 2020, we received a filing communication from the FDA in connection with our NDA for arimoclomol for the treatment of NPC in which the FDA summarized six potential review issues, including the FDA's continuing evaluation of the integrity of data from our Phase 2/3 trial for NPC; the effect of the high degree of concomitant miglustat use in our Phase 2/3 trial for NPC on its ability to determine the of safety and efficacy of arimoclomol which could have potential implications for labeling/recommended dosing and post-marketing studies; the proposed primary hypothetical treatment effect used in our Phase 2/3 trial for NPC to estimate the treatment benefit effect; the meaningfulness of one metric utilized to evaluate patient progress in our Phase 2/3 trial for NPC; the timing of submission of the QTc and other study reports to the FDA, including in light of evidence suggesting a potential QT safety signal; and differences among the formulations of arimoclomol used in our Phase 2/3 trial of NPC as compared to the formulation of arimoclomol to be marketed. The filing communication constitutes preliminary notice from the FDA of potential review issues as part of its ordinary course review of our NDA and is not necessarily indicative of deficiencies that may be identified during the review.We cannot assure you that such issues will not result in a delay of any potential approval of arimoclomol for the treatment of NPC by the FDA or a determination by the FDA not to approve the product candidate for marketing in the United States. Further, as part of its review process, the FDA may request additional information and data, require us to make modifications to ongoing NPC-related clinical trials, manufacturing or other processes, run additional studies or clinical trials or incur significant additional expenditures in order to obtain such approval. If arimoclomol does not obtain approval for the indications we are currently exploring, we will have spent substantial time and financial resources without receiving a return on investment. As a result, if arimoclomol does not become a success, this will have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We are highly dependent on obtaining and maintaining required regulatory approvals and may not receive such approvals.

Before we can start commercializing arimoclomol, a number of regulatory registrations and approvals must be obtained. For instance, approvals from the authorities and ethical committees as well as consents from patients participating in our clinical trials are required before initiating preclinical studies and clinical trials, and marketing authorizations must be obtained from the relevant regulatory authorities. Biopharmaceutical development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials. For example, in connection with the transfer of manufacturing for arimoclomol to a different facility, our CMO informed us that a component of arimoclomol may deflagrate during the drying process if not manufactured with specialized equipment. Our CMO will install and obtain approval for such equipment, which may result in a delay in approval by the EMA of arimoclomol in NPC.

The success in the development of arimoclomol and any future product candidates will depend on many factors, including:

- completing preclinical studies and receiving regulatory approvals or clearance for conducting clinical trials for our preclinical-stage programs;
- obtaining positive results in our clinical trials demonstrating efficacy, safety and durability of effect of arimoclomol and any future product candidates;
- receiving approvals for commercialization of arimoclomol and any future product candidates from regulatory authorities;
- manufacturing of arimoclomol and any future product candidates at an acceptable quality and cost; and
- maintaining and growing an organization of scientists, medical professionals and business people who can develop and commercialize our products and technology.

If required regulatory registrations or approvals are delayed, denied or withdrawn or if the regulatory authorities question the efficacy of arimoclomol as a treatment, it is likely to have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Because we are developing arimoclomol for the treatment of diseases in which there is little clinical experience, the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to predict or provide clinically meaningful results.

There are currently either no or limited approved therapies in the orphan disease indications we are targeting and there may be no therapies approved to treat other diseases that we will target in the future. As a result, the design and conduct of clinical trials of arimoclomol or any future product candidate may take longer, be more costly or be less effective as a result of the novelty of development in these diseases. In some cases, we may use endpoints or methodologies that regulatory authorities may not consider to be clinically meaningful and that we may not continue to use in clinical trials or that we may determine after the initiation of the trial to no longer be an appropriate endpoint or methodology. Any such regulatory authority may require evaluation of additional or different clinical endpoints in our clinical trials or ultimately determine that these clinical endpoints do not support marketing approval. In addition, if we are required to use additional or different clinical endpoints by regulatory authorities, arimoclomol may not achieve or meet such clinical endpoints in our clinical trials. Even if a regulatory authority finds our clinical trial success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance in any pivotal or other clinical trials we may conduct for our product candidate. Further, even if we do achieve the pre-specified criteria, our trials may produce results that are unpredictable or inconsistent with the results of other efficacy endpoints in the trial. Regulatory authorities also could give overriding weight to other efficacy endpoints over a primary endpoint even if we achieve statistically significant results on that primary endpoint, if we do not do so on our secondary efficacy endpoints. Regulatory authorities also weigh the benefits of a product against its risks and may view the efficacy results in the context of safety as not being supportive of approval.

Arimoclomol may be shown to cause undesirable side effects or other adverse events that could delay or prevent its regulatory approval, limit its commercial profile or result in significant negative consequences following regulatory approval, if such approval is granted.

We or regulatory authorities may suspend clinical trials at any time if it is believed that patients who participate in such clinical trials are being exposed to unacceptable health risks resulting in an unfavorable risk-benefit assessment or other adverse events. Undesirable side effects caused by arimoclomol could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive use permitted by such regulatory authorities or the delay or denial of approval by such regulatory authorities. In the event that the data from clinical trials suggest an unacceptable severity and prevalence of adverse side effects, such clinical trials could be suspended or terminated, and regulatory authorities could order us to cease further development of, or deny approval of, arimoclomol for any or all targeted indications. Treatment-related side effects could affect patient recruitment or the ability of enrolled patients to complete a clinical trial or result in potential product liability claims. In addition, if adverse effects occur during clinical testing or during our EAP or any other early access program or compassionate use program that we have established or may in the future establish, we may also have to conduct additional testing, which will cause delays in our development program and result in increased costs, or may ultimately lead to the abandonment of the development of arimoclomol for any specific indication or for all indications. For example, there was one death that was deemed possibly related to treatment by the investigator during the initial six month assessment period in our Phase 2 clinical trial for Gaucher disease and there were two additional deaths during the extension portion of this trial (where prior placebo patients were randomized to one of 3 arimoclomol doses), one of which was deemed probably related, and the other of which was deemed possibly related, to treatment by the investigator. In addition, there were two deaths that were deemed possibly related to treatment by the blinded investigator in our ongoing Phase 3 clinical trial in ALS. In addition, in our clinical trials of ALS and sIBM, we have observed increased transaminases in a minority of patients. Currently the association of increased transaminases to arimoclomol is undetermined but all cases are considered possibly related to arimoclomol until further data becomes available. If the increased transaminases are considered related to arimoclomol, it could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could lead to the delay or denial of approval by such regulatory authorities.

Even after receiving approval, the products may later exhibit adverse effects that could prevent their widespread use or necessitate their withdrawal from the market. If adverse events occur once the

product is on the market, there is a risk that we may have to recall and destroy products, and ultimately there is a risk of fines, suspension or withdrawal of regulatory approvals and potential litigation.

Any of these events could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

If we are unable to obtain or maintain orphan drug designation or if we are unable to benefit from orphan drug exclusivity for arimoclomol, it will have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We are dependent on obtaining and maintaining orphan drug designations for NPC, ALS and sIBM. Further, we are dependent on the future grant of orphan drug exclusivity for arimoclomol for the treatment of NPC, ALS and sIBM after marketing approval, as such exclusivity is important in light of the fact that our general patent protection for the composition-of-matter of arimoclomol expired in 2020. The method of use patent protection for treatment of lysosomal diseases, including NPC and Gaucher disease, is anticipated to expire in 2029, with possible extensions to 2032 in the United States and 2034 in the European Union based on method of use patents, and we do not currently have patent protection for the treatment of sIBM. The method of use patent protection for ALS is anticipated to expire in 2024.

Even if we obtain orphan drug exclusivity for arimoclomol for NPC or other orphan designated indications, the exclusivity may not effectively protect the product from competition, because exclusivity can be broken under certain circumstances. In the United States, even after an orphan drug is approved, the FDA can subsequently approve an application for the same drug for the same orphan indication if the FDA concludes that such subsequent applicant's version of the drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, orphan drug exclusivity will not prevent a marketing authorization being granted for a similar medicinal product in the same indication if the new product is safer, more effective or otherwise clinically superior to the first product or if the marketing authorization holder of the first product is unable to supply sufficient quantities of the product. If an orphan drug designation or other designations are revoked or if the market exclusivity granted in connection with the orphan drug designation period is suspended, shortened or revoked, it could have a material adverse impact on our business, results of operations, cash flows, financial condition and/or prospects. Additionally, obtaining orphan drug exclusivity for arimoclomol for NPC would not necessarily ensure that we would obtain orphan drug exclusivity for other indications and would therefore not preclude generic competition for other non-orphan approved uses of arimoclomol, such as sIBM, ALS or any other indications. If we are not able to obtain or maintain orphan drug status for NPC, ALS and sIBM or for other diseases or disorders, or if we are unable to benefit from the associated marketing exclusivity, it could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Fast track and orphan drug designation by the FDA and EMA may not actually lead to a faster development or regulatory review or approval process, and does not assure FDA or EMA approval of arimoclomol.

If a product candidate is intended for the treatment of a serious or life threatening condition and the product candidate demonstrates the potential to address unmet medical need for this condition, the sponsor may apply for FDA or EMA fast track designation. In addition, orphan drug designation can be granted for product candidates intended to treat a rare disease or condition. However, neither a fast track designation nor an orphan drug designation ensures that the product candidate will receive marketing approval or that approval will be granted within any particular timeframe. As a result, while we received fast track designation for arimoclomol for NPC, ALS and sIBM as well as orphan drug designation for arimoclomol for NPC, ALS and sIBM from both the FDA and EMA, we may not experience a faster development process, review or approval compared to conventional FDA or EMA procedures. In addition, the FDA or EMA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. In addition, the FDA or EMA may withdraw orphan drug designation. Fast track and orphan drug designation alone does not guarantee qualification for the FDA's or EMA's priority review procedures.

A breakthrough therapy designation by the FDA for arimoclomol may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidate will receive marketing approval.

A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

The FDA designated arimoclomol as a breakthrough therapy for NPC and in the future it may designate it as such for other indications. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our current or future product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. The receipt of such designation for arimoclomol for a particular indication may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even though the FDA granted arimoclomol breakthrough therapy for NPC and even if it decides to grant such designation for another indication, the FDA may later decide that arimoclomol no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

We and our CROs have conducted and intend to conduct additional clinical trials at sites outside the United States, and the FDA may not accept data from trials conducted in such locations due to the study design and conduct, trial population or for other reasons, or may require additional U.S.-based trials.

We and our CROs have conducted, currently are conducting and intend in the future to conduct, clinical trials outside the United States, particularly in the European Union where we are headquartered. We also conducted a Phase 2 clinical trial for neurological Gaucher disease in India, with respect to which we announced top-line results in June 2020 and are currently conducting an open label extension of the same trial. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted by qualified investigators in accordance with current good manufacturing practices ("**cGMP**") including review and approval by an independent ethics committee and receipt of informed consent from trial patients. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical trial conducted outside of the United States must be representative of the population for which we intend to seek approval in the United States. In addition, while these clinical trials are subject to applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also comply with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from any clinical trials that we or our CROs conduct outside the United States, it would likely result in the need for additional clinical trials, which would be costly and time-consuming and delay or permanently halt our ability to develop and market arimoclomol for the proposed indications in the United States.

In addition, there are risks inherent in conducting clinical trials in multiple jurisdictions, inside and outside of the United States, such as:

- regulatory and administrative requirements of the jurisdiction where the trial is conducted that could burden or limit our and our CROs' ability to conduct clinical trials;

- foreign exchange fluctuations;

- manufacturing, customs, shipment and storage requirements;
- cultural differences in medical practice and clinical research; and
- the risk that the patient populations in such trials are not considered representative as compared to the patient population in the target markets where approval is being sought.

We have limited long-term data regarding the safety and effectiveness of arimoclomol and results in preclinical studies or clinical trials of our current and future product candidates may not be indicative of results in future clinical trials, and does not assure FDA or EMA approval of arimoclomol.

Results from preclinical studies are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. While we have received some positive data in clinical trials of arimoclomol in ALS and sIBM, we are still conducting additional clinical trials in such indications and intend to conduct additional clinical trials in other indications in order to seek regulatory approvals. We do not know whether these clinical trials will establish sufficient efficacy and safety in order to receive regulatory approval.

Further, although we believe that we have demonstrated the safety, effectiveness and clinical advantages of arimoclomol in approximately 35 patients with NPC for two years, the long-term effects of arimoclomol in a large number of patients have not been studied and the existing data do not necessarily predict long-term clinical benefits or reveal long-term adverse effects. This failure to establish sufficient efficacy and safety could cause us to abandon clinical development of arimoclomol and any other current or future product candidates entirely or for specific indications.

Our molecules in preclinical development may also fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies.

We may never obtain approval with respect to arimoclomol for NPC or for any of the indications we intend to seek approval for, which would limit our ability to realize our full market potential.

If we obtain regulatory approval for arimoclomol for the treatment of NPC, we intend to follow with data to support use in other indications such as ALS, sIBM and neuropathic Gaucher disease. If we are successful, the indication for use of arimoclomol could potentially be broadened beyond the treatment of NPC to include such additional indications. However, there can be no assurance that, even if we obtain approval for one or more of these indications, we will obtain approval for any other or all of these additional indications, or for a broadened indication beyond the treatment of NPC. If we fail to obtain and maintain required approvals for these additional or broadened indications, or if regulatory approvals are delayed, we will not realize the full market potential of arimoclomol.

Obtaining and maintaining regulatory approval of arimoclomol in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of arimoclomol in other jurisdictions.

Obtaining and maintaining regulatory approval of arimoclomol in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in other jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining non-U.S. regulatory approvals and compliance with non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of arimoclomol will be harmed.

All the above risks, individually or in the aggregate, could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

The fact that we have received rare pediatric disease designation for arimoclomol as a treatment for NPC is not an indication that we will receive a rare pediatric disease priority review voucher.

As further described under "*Company Information—Business*," the FDA has granted a rare pediatric disease designation to arimoclomol as a treatment for NPC, and we may seek rare pediatric disease designations for any future product candidates. Under the FDA's rare pediatric disease priority review voucher program, upon the approval of a new drug application ("**NDA**)", for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent new drug application. However, receiving a rare pediatric disease designation for arimoclomol as a treatment for NPC does not automatically mean that we will receive a priority review voucher as a priority review voucher is only awarded following approval by the FDA of arimoclomol as a treatment for NPC.

If a priority review voucher is granted, we may use the voucher for our own FDA approval processes or decide to sell the voucher to other biotech or pharmaceutical companies. The market for priority review vouchers has a limited history and disclosed sales prices may not be indicative of the current value of vouchers, which may also fluctuate significantly. Congress has only authorized the Rare Pediatric Disease Priority Review Voucher program until September 30, 2020. However, if a drug candidate receives Rare Pediatric Disease Designation before October 1, 2020, it is eligible to receive a voucher if it is approved before October 1, 2022. Hence, it may be unavailable to us even if we meet all of the requirements. Further, the potential award of a voucher would trigger an obligation to market the relevant rare pediatric disease product within one year from FDA approval or the FDA may revoke the voucher. Finally, a voucher award subjects us to post-marketing reporting obligations to the FDA.

We may not be able to recruit enough patients for clinical trials to research new molecular entities or for agreements with investigators and hospitals and this may have a material adverse impact on our business.

The diseases for which arimoclomol is currently being developed are rare and, consequently, patient groups relevant for testing arimoclomol are limited in size and located across many jurisdictions. Therefore, even though we, through our CROs, cooperate closely with relevant physicians treating such patient groups, finding and recruiting the appropriate number of patients for the clinical trials, as well as patients with a profile appropriate for such clinical trials, may be challenging. Should clinical trials in indications similar to arimoclomol be initiated, it could negatively affect the possibility that we will be able to recruit patients. Failure to find and recruit the necessary number of appropriate patients to complete our clinical trials may have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Interim, "top-line" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publish interim, "top-line" or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or "top-line" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our ordinary shares and ADSs to fluctuate significantly, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We might not be able to identify, acquire, in-license and develop additional product candidates and, even if we are able to develop additional product candidates, such development might expose us to additional and new risks.

Efforts to identify, acquire or in-license, and then develop product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our efforts may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development, approved products or commercial revenues for many reasons, including the following:

- the methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render any product candidates we develop obsolete;
- any product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by physicians, patients, the medical community or third-party payors.

We have limited financial and personnel resources and, as a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater market potential. Our resource allocation decisions may cause it to fail to capitalize on viable commercial drugs or profitable market opportunities. If we do not accurately evaluate the commercial potential or target market for a particular product, we may relinquish valuable rights to that product through collaboration, licensing or other royalty arrangements in circumstances under which it would have been more advantageous for us to retain sole development and commercialization rights to such product. If we are unsuccessful in identifying and developing additional product candidates or are unable to do so, our business, results of operations, cash flows, financial condition and/or prospects may be materially and adversely affected.

Risks Related to Commercialization of Our Product Candidates

Even if arimoclomol receives marketing approval, we may not be successful in our commercialization efforts and arimoclomol may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Even if arimoclomol receives marketing approval, we may not be successful in our commercialization efforts and market acceptance by physicians, patients, third-party payors and others in the medical community may be less than estimated. Market acceptance will require us to build and maintain strong relationships with healthcare professionals involved in the treatment of orphan diseases, including nationally-recognized as well as community physicians, in addition to nurses and other allied health professionals. The number of healthcare professionals within orphan diseases and treatment centers that address NPC is limited. A failure to build or maintain these important relationships with these healthcare professionals and treatment centers could result in lower market acceptance. Our efforts to educate physicians, patients, third-party payors and others in the medical community on the benefits of arimoclomol may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of arimoclomol. The degree of market acceptance of, for instance, arimoclomol, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy of arimoclomol;
- the convenience and ease of administration as an oral capsule, sprinkled in food/beverage or via a feeding tube compared to alternative treatments and therapies;
- limitations or warnings or any restrictions on the use of arimoclomol together with other medications and the prevalence and severity of any side effects;
- the efficacy and potential advantages compared to alternative treatments and therapies;
- the cost-effectiveness of arimoclomol compared to alternative therapies and the ability to offer such drug for sale at competitive prices;
- changes in the standard of care for the targeted indications for our product candidate;
- the effectiveness of sales and marketing efforts and the strength of marketing and distribution support;
- availability and amount of coverage and reimbursement from government payors, managed care plans and other third-party payors;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; and
- the timing of competitive product introductions and other actions by competitors in the marketplace.

The market opportunities for arimoclomol may be limited because we are targeting patients suffering from orphan diseases with relatively small populations and these populations may be smaller than expected.

Our estimates of the annual total addressable markets for arimoclomol under development is based on our beliefs and estimates regarding the incidence or prevalence of certain types of lysosomal and neuromuscular degenerative orphan diseases that may be addressable by arimoclomol, which is derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations or market research. While we believe our assumptions and the data underlying our estimates are reasonable, these assumptions and estimates may not be correct and the conditions supporting our assumptions or estimates may change at any time, thereby reducing the predictive accuracy of these underlying factors and therefore the accuracy of these estimates.

We base our development activities and commercial strategy on estimates of the number of patients who may benefit from and who may be medically eligible for a particular treatment. In addition to the number of patients, the ultimate pricing of arimoclomol, if approved, may be affected by the burden of disease, the extent of unmet need and clinical efficacy. Even if the number of medically eligible patients is correctly estimated, the number of patients who will ultimately receive a particular treatment may be greatly reduced if governmental authorities decide to change reimbursement policies. These estimates are subject to significant uncertainty and may prove to be inaccurate and we may not generate significant drug revenue and may not become profitable. Even if we obtain significant market share for arimoclomol, because the initial target populations for NPC, ALS and sIBM are relatively small, we may never achieve profitability without obtaining regulatory approval for additional and broader indications.

To date, we have not commercialized a drug and currently have a limited commercial infrastructure. We may not be successful in commercializing arimoclomol if it is approved unless, among other factors, we are able to identify patients, expand sales and marketing capabilities or enter into agreements with third parties to sell and market arimoclomol.

Even if arimoclomol receives marketing approval, whether commercialization will be successful and whether we will ultimately be profitable, will depend on factors such as our ability to successfully execute our business strategy and attract and build-up the internal resources necessary to effectively market our products.

To achieve commercial success for any approved drug, among other factors, we must either develop and expand our sales and marketing organization or outsource these functions to strategic collaborators and other third parties. We currently have limited in-house capabilities for sales, marketing and distribution but intend to expand such capabilities in order to market arimoclomol, if approved, directly through our own sales and marketing force in selected geographic areas, including the United States and Europe. In order to implement this strategy of commercializing in-house, we must expand our sales and marketing organization and establish distribution capabilities. This entails recruiting additional managerial, operational, financial and other employees, which is expensive and time-consuming and could delay product launches. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

In addition, to achieve commercial success for any approved drug we must be able to identify patients. The diseases for which we are currently developing our product candidate have a limited number of patients and for which, in many cases, there are limited diagnostics tools. The lack of diagnostic tools, coupled with the fact that there is frequently limited awareness among certain health care providers concerning the rare diseases we treat, often means that a proper diagnosis can, and frequently does, take years to identify (or an appropriate diagnosis may never be made for certain patients). As a result, we may not be able to grow our revenues if our product candidate is approved.

Factors that may inhibit our efforts to commercialize our drugs on our own after obtaining any regulatory approval to gain market acceptance include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or educate adequate numbers of physicians on the benefits of prescribing any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization;
- inability to maintain or develop additional relationships with medical centers or patient advocacy groups;
- inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies; and
- inability to identify patients and improve diagnosis rates particularly in orphan populations in which no effective therapies exist.

We are not currently a party to a strategic collaboration that provides us with access to a collaborator's resources in selling or marketing drugs. If we enter into arrangements with third parties to perform sales and marketing services, our revenues from the sale of drugs or the profitability of these revenues

to us are likely to be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market arimoclomol or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish further sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing arimoclomol.

If we are unable to achieve and maintain adequate levels of coverage or reimbursement for arimoclomol, if commercialized, or any future product candidates we may seek to commercialize, or if patients are left with significant out-of-pocket costs, our commercial success may be severely hindered.

Our product candidate, arimoclomol, may be significantly more expensive than traditional drug treatments and we expect that many patients will require governmental payors, such as Medicare and Medicaid in the United States or other country specific government organizations in foreign countries and/or private third-party payors to pay all or a portion of the cost of arimoclomol. Even if arimoclomol is approved for sale by the appropriate regulatory authorities, market acceptance and sales will depend on reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will reimburse and establish payment levels and, in some cases, utilization management strategies, such as tiered formularies and prior authorization. There is also a significant trend in the health care industry by public and private payors to contain or reduce their costs. As a result, payors may (i) decrease the portion of costs they will cover, (ii) cease providing adequate payment for arimoclomol or (iii) not cover arimoclomol at all. Any of the foregoing may have an adverse impact on our revenue and results of operations. We cannot be certain that reimbursement will be available for any products that we develop or that the reimbursement level will be adequate to allow us to operate profitably. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products. If reimbursement is not available or is available on a limited basis, or if the reimbursement amount is inadequate, we may not be able to successfully commercialize any products, if approved.

We anticipate that we will derive substantially all of our revenue from the sale of our products to hospitals and specialized medical centers. Hospitals typically bill various third-party payors to cover all or a portion of the costs and fees associated with the treatments in which arimoclomol will be used and bill patients for any deductibles or co-payments.

The Centers for Medicare & Medicaid Services ("**CMS**"), have established guidelines for the coverage and reimbursement of certain products and treatments by Medicare. In general, in order to be reimbursed by Medicare, a treatment furnished to a Medicare beneficiary must be reasonable and necessary for the diagnosis or treatment of an illness or injury, or to improve the functioning of a malformed body part. The methodology for determining coverage status and the amount of Medicare reimbursement varies based upon, among other factors, the setting in which a Medicare beneficiary received healthcare products and services. Any changes in federal legislation, regulations and policy affecting CMS coverage and reimbursement relative to the treatment using our products could have a material effect on our performance.

Physicians that perform treatments using our products, or the hospitals or specialized medical centers for which they work, may be subject to reimbursement claim denials upon submission of the claim. Physicians or hospitals may also be subject to recovery of overpayments if a payor makes payment for the claim and subsequently determines that the payor's coding, billing or coverage policies were not followed. Some physicians and hospitals may be unwilling to adopt our products in light of any additional associated cost. Further, any decline in the amount payors are willing to reimburse physicians and hospitals could make it difficult for existing physicians and hospitals to continue using or to adopt our products and could create additional pricing pressure for us. If we are forced to lower the price we charge for our products, our gross margins will decrease, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Outside of the United States, reimbursement levels vary significantly by country and by patient. Reimbursement is obtained from a variety of sources, including government sponsors, hospital budgets,

or private health insurance plans, or combinations thereof. In the European Union, changes to pricing and reimbursement of medicinal products, are almost exclusively a matter for national, and not EU, law and policy, which have generally resulted in restrictions on the pricing and reimbursement of medicines due to healthcare budgetary constraints in most EU member states. Even if we succeed in bringing our products to market in additional foreign countries, uncertainties regarding future healthcare policy, legislation and regulation, as well as private market practices, could affect our ability to sell our products in commercially acceptable quantities at acceptable prices.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs and it is unlikely there will be a uniform policy of coverage and reimbursement for treatments using our products. Therefore, coverage and reimbursement for treatments using our products can differ significantly from payor to payor. Payors continually review new and existing technologies for possible coverage and can, without notice, deny or reverse coverage for new or existing products and treatments. There can be no assurance that third-party payor policies will provide coverage for treatments in which our products are used. Further, we believe that future coverage and reimbursement may be subject to increased restrictions, such as additional prior authorization requirements, both in the United States and in international markets. Third-party coverage and reimbursement for treatments using arimoclomol, if approved, may not be available or adequate in either the United States or international markets, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We are operating in a field with substantial global competition and swift technological advances which could mean that our competitors may develop other treatments for similar or the same diseases as those targeted by arimoclomol and may be able to commercialize them more successfully.

The biopharmaceutical industry is subject to substantial global competition and swift technological advances. Certain companies are currently developing, or may initiate development of, competing product candidates targeting the same diseases as those targeted by us. For instance, we are aware of several pharmaceutical and biopharmaceutical companies that have successfully commercialized products or have commenced clinical trials of product candidates addressing indications that we target with arimoclomol.

With respect to NPC, we consider our most direct competitor to be Zavesca (miglustat), which was originally developed by Actelion Pharmaceuticals and is now owned by Johnson & Johnson, which is also available as a generic product in several countries and is currently approved for the treatment of NPC. Miglustat has not been approved by the FDA for treatment of NPC, but it is approved for the treatment of Gaucher Type I disease in the United States. For the treatment of NPC, it is approved only in Europe, Canada, Australia, New Zealand, and several countries in Asia and South America as Zavesca and in Japan as Brazaves. We are also aware of several pharmaceutical and biopharmaceutical companies that have commenced clinical trials of product candidates for NPC, including: adrabetadex (VTS-270), being developed by Mallinckrodt for NPC; trappsol, being developed by Cyclo Therapeutics for NPC; IB1001, being developed by IntraBio for NPC; and ESB1609, being evaluated by E-scape Bio for NPC.

With respect to ALS, we consider our most direct competitors to be Sanofi and Mitsubishi Tanabe Pharma America, which have the pharmaceutical products Rilutek (riluzole) and Radivaca (edaravone). In addition to the current treatment options for ALS, a number of pharmaceutical product candidates are being developed to treat ALS, including: levosimendan (Orion Pharma); (ii) NurOwn (Brainstorm Therapeutic); and (iii) BIIB067/tofersen (Biogen); Masitinib (AB Science); and reldesemtiv (Cytokinetics).

There are currently no treatments for neurological symptoms of Gaucher disease. However, there are two types of treatment currently available for patients with Gaucher Type 1 disease: ERT, such as Cerezyme (Sanofi), Elelyso (Pfizer) and Vpriv (Shire); and SRT using Zavesca or Cerdelga (Sanofi). There are a few other advanced clinical programs for the treatment of Gaucher disease, including: Genzyme is currently evaluating the combined use of two agents for Gaucher disease Type 3; Tottori University Hospital and Shire are evaluating ambroxol hydrochloride for neuronopathic Gaucher disease; and AVROBIO Inc. is evaluating a product candidate for Gaucher disease Type 1.

We may also face heightened competition from gene therapy, alternative treatment forms and generics, after expiry of patent protection and loss of any market exclusivity for our products.

Any product candidates that we are able to commercialize in the United States and the EU may be subject to competition from lower priced imports of those same products, leading to reduced revenues and lower sales margins, as well as lower priced imports of competing products from countries with government price controls or other market dynamics that, in each case, reduce prices of products. The ability of patients and other customers to obtain these lower priced imports has grown significantly. Some of these foreign imports are illegal under current law. However, the volume of imports is now significant, due in part to the limited enforcement resources and the pressure in the current political environment to permit the imports as a mechanism for expanding access to lower priced medicines. Parallel importation or importation of foreign products could adversely affect our future profitability. This impact potentially could become even greater if there is a further change in relevant protective legislation or if state or local governments take further steps to import products from abroad.

Further, these competitors may have greater resources than us, develop more effective or affordable product candidates than us or develop their product candidates faster or more efficiently than us and thereby achieve commercialization of their products earlier or more effectively than us.

If we are unable to respond effectively to competition, arimoclomol may be rendered obsolete and our ability to generate revenue may be limited, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Product liability and other claims or litigation may have material adverse effects on our business.

Companies in the life sciences industry, such as us, are generally subject to risks related to product liability litigation and other claims or litigation.

Product liability risks are inherent in developing, marketing and sale of pharmaceutical products. Even though we are not currently subject to any product liability claims, such claims could arise at a later date. Litigation would be time-consuming for our management and lead to significant costs and losses, which would adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

In addition, we may from time to time become involved in various litigation matters and governmental or regulatory investigations, prosecutions or similar matters arising out of our current or future business. We cannot accurately anticipate how the liabilities from any claims asserted against us, regardless of merit or eventual outcome, may harm our reputation. There is no guarantee that we will be successful in defending against future litigation or similar matters brought under various laws.

Even though we have obtained product liability insurance in respect of all clinical trials we have performed and are performing with respect to arimoclomol and for the EAP and any other early access program or compassionate use program that we have established or may in the future establish, there can be no assurance that such insurance coverage or any future insurance coverage for commercialization of arimoclomol will be available on reasonable commercial terms or that it will prove adequate. If sufficient insurance coverage is not obtained covering, for instance, product liability, or if such future litigation or investigation exceeds our insurance coverage, we could be subject to significant liabilities, which could have material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Our insurance policies protect us only from some business risks, which leaves us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. Although we have product liability and clinical study liability insurance that we believe is appropriate, this insurance is subject to deductibles and coverage limitations. Our current product liability insurance may not continue to be available to us on acceptable terms, if at all, and, if available, coverage may not be adequate to protect us against any future product liability claims. If we are unable to obtain insurance at an acceptable cost or on acceptable terms or otherwise protect against potential product liability

claims, we could be exposed to significant liabilities. A product liability claim or other claim with respect to uninsured liabilities or for amounts in excess of insured liabilities could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. We do not carry specific hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended. Additionally, we do not carry cyber security insurance, which may expose us to certain potential losses for damages or result in penalization with fines in an amount exceeding our resources.

We also expect that operating as a public company in the United States will make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, on our board committees or as executive officers. We do not know, however, if we will be able to maintain existing insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Risks Related to Our Dependence on Third Parties

Data provided by collaborators and others upon which we rely that has not been independently verified could turn out to be false, misleading or incomplete.

We rely on third-party vendors, such as CROs and other collaborators to provide us with significant data and other information related to our projects, preclinical studies or clinical trials and our business. If such third parties provide inaccurate, misleading or incomplete data, our business, results of operations, cash flows, financial condition and/or prospects could be materially adversely affected. In addition, our CROs in the past have been and will be subject to regular inspections by regulatory authorities. Any findings of deficiencies, data integrity issues or noncompliance with applicable rules and regulations in such inspections may lead to delay or suspension of preclinical studies or clinical trials, implementation of additional internal controls and policies required by the authorities, refusal by the FDA or EMA to accept results of our preclinical studies or clinical trials as a result of compromised data integrity and control processes and termination of our agreement with such CROs. If our existing or future CROs are not in compliance with applicable rules and regulations in conducting our preclinical studies or clinical trials or otherwise fail to fulfil their contractual and regulatory obligations, this could adversely affect our business, results of operations, cash flows, financial condition and/or prospects. In addition, any delays in providing data or providing inaccurate, misleading or incomplete data would adversely affect our preclinical studies and human clinical trials, including timing for obtaining marketing approval, which could adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

We are currently dependent on third parties for manufacturing arimoclomol. If such third-party manufacturers do not deliver their manufactured products in time, this could have a material adverse effect on our business.

Manufacturing includes the production, formulation and stability testing of an active pharmaceutical ingredient and its formulation into pharmaceutical products, such as capsules or tablets. We do not have our own manufacturing facility and currently we do not intend to develop any such manufacturing capacity. We are therefore dependent on third parties for manufacturing our products and if any of those third parties terminates the agreements or moves their facilities to a different location, this could have a material adverse effect on our ability obtain such manufactured products. We currently depend on one manufacturer for arimoclomol and were our relationship with that manufacturer to deteriorate or the contract with such supplier be terminated then that could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. If we had to replace our manufacturer for arimoclomol, this could entail significant costs, delay, disruption of management attention and inventory shortage.

We may be required in the future to enter into agreements with other third parties to manufacture arimoclomol at a larger scale to increase supply for potential marketing and sale of its drug (if

arimoclomol as a treatment for any of the indications targeted by us receives approval in any jurisdiction). We can provide no assurance that we will be able to make the transition from the current scale of production to a larger scale of production of arimoclomol or from laboratory-scale production to development-scale production of new molecules. We may need to enter into additional collaborative arrangements with other parties who have established manufacturing capabilities, or have other third parties manufacture our products on a contractual basis. We may not have access to the substantial financing on acceptable terms that would be required to scale-up production and develop effective commercial manufacturing processes and technologies. We may not be able to enter into collaborative or contracting arrangements on acceptable terms with parties that will meet our requirements for quality, quantity and timeliness.

Any manufacturing of pharmaceutical products is subject to a number of regulatory requirements, for instance quality control and documentation. We are dependent on our contract manufacturing partners appropriately handling arimoclomol in accordance with good manufacturing practices and the costs of compliance may be high. Manufacturing facilities must be approved by the authorities and will be subject to regular inspections by the authorities. Such inspections may lead to suspension of manufacturing and interfere with product supply and distribution. If our existing or future contract manufacturing partners do not manufacture arimoclomol properly and otherwise fulfil their contractual and regulatory obligations to deliver agreed quantities of arimoclomol in a timely manner and of sufficient quality, this could adversely affect our business, results of operations, cash flows, financial condition and/or prospects. In addition, any delays in production would delay our preclinical studies and human clinical trials, which could adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

We are dependent on third-party vendors to provide certain licenses, products and services and our business and operations, including clinical trials, could be disrupted by any problems with our significant third-party vendors.

We engage a number of third-party suppliers and service providers to supply critical goods and services, such as contract research services, contract manufacturing services and IT services. Disruptions to the business, financial stability or operations of these suppliers and service providers, including due to strikes, labor disputes or other disruptions to the workforce, for instance, if, as a result of COVID-19, employees are not able to come to work, or to their willingness and ability to produce or deliver such products or provide such services in a manner that satisfies the requirements put forth by the authorities, or in a manner that satisfies our own requirements, could affect our ability to develop and market arimoclomol on a timely basis. If these suppliers and service providers were unable or unwilling to continue to provide their products or services in the manner expected, or at all, we could encounter difficulty finding alternative suppliers. Even if we are able to secure appropriate alternative suppliers in a timely manner, costs for such products or services could increase significantly. Any of these events could adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

Specifically, we depend on agreements with external parties that carry out the clinical trials sponsored by us. If these external parties do not carry out their obligations under these agreements, or do not meet expected deadlines, if the parties need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised, ongoing and planned clinical trials may be extended, delayed or terminated which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

In the future we may seek to enter into collaborations with third parties for the development and commercialization of arimoclomol. If such collaborations are not successful, we may not be able to capitalize on the market potential of arimoclomol.

In the future we may enter into collaboration agreements with third-party collaborators, such as by introducing a license right or a distribution agreement, for development and commercialization of existing or other products to address market opportunities that require large development investments and/or special expertise in selected geographic areas, as well as to share the financial risks involved in drug development and commercialization of arimoclomol.

We have no significant experience in entering into major collaboration or license agreements. We may be unable to attract partners for collaboration agreements or the terms of those collaboration agreements that we choose to enter into may not be favorable to us. This may be a result of factors such as general market demand for particular products or products within specific therapeutic areas, results of clinical trials relating to the product candidates or market competition.

If we are not successful in efforts to enter into future partnership agreements, our business, results of operations, cash flows, financial condition and/or prospects may be negatively affected. Even if we are successful in entering into collaboration agreements, such agreements may not lead to development or commercialization of the products in the most efficient manner or at all.

With any future collaboration agreements, we expect to have limited control over the amount and timing of resources that such collaborators dedicate to the development or commercialization of the products. The ability to generate revenue from these arrangements will depend on such collaborators' abilities to successfully perform the functions assigned to them in these arrangements. Our potential partners may have significant discretion in determining how to pursue planned activities and we may have limited control over the quality and nature of the efforts and resources that such a partner applies to the collaboration as well as the branding and marketing of us and our products. We cannot be certain that any collaborations will be scientifically or commercially successful or that we will receive revenues from any collaboration agreements.

Should any of the risks associated with the entering into collaborations with third parties for the development and commercialization of arimoclomol materialize, these could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Our employees, third-party contractors and other commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements.

We are exposed to the risk that our employees, consultants, and other commercial partners and business associates may engage in fraudulent or illegal activity. Misconduct by these parties could include intentional, reckless or negligent conduct or other unauthorized activities that violate the regulations of the FDA, the EMA and non-U.S. regulators, including those laws requiring the reporting of true, complete and accurate information to such regulators, manufacturing standards, healthcare fraud and abuse laws and regulations in the United States and internationally or laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. It is not always possible to identify and deter misconduct by our employees, third-party contractors and other commercial partners, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could result in the imposition of significant fines or other sanctions, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of operations, any of which could adversely affect our ability to operate our business and our results of operations. Whether or not we are successful in defending against such actions or investigations, we could incur substantial costs, including legal fees and reputational harm, and divert the attention of management in defending ourselves against any of these claims or investigations.

Risks Related to Legal and Regulatory Compliance Matters

Our business operations and current and future relationships with healthcare professionals, principal investigators, consultants, customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, physician payment transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to substantial penalties.

Healthcare providers, physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors may expose us to broadly applicable healthcare laws, including, without limitation, the U.S. federal Anti-Kickback Statute and the U.S. federal False Claims Act, that may constrain the business or financial arrangements and relationships through which we sell, market and distribute any product candidates for which we obtain marketing approval. In addition, we may be subject to physician payment transparency laws and privacy and security regulation by the U.S. federal government and by the states and non-U.S. jurisdictions in which we conduct our business. The applicable federal, state and non-U.S. healthcare laws that may affect our ability to operate include the following:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under federal and state healthcare programs such as Medicare and Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other hand. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration that are alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the federal Anti-Kickback Statute has been violated;

- U.S. federal civil and criminal false claims laws, including the federal False Claims Act, which can be enforced through civil whistleblower or qui tam actions, and civil monetary penalty laws, which, among other things, impose criminal and civil penalties, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Further, pharmaceutical manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. Criminal prosecution is also possible for making or presenting a false, fictitious or fraudulent claim to the federal government;

- Health Insurance Portability and Accountability Act of 1996 ("**HIPAA**"), which contains new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of whether the payor is public or private, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("**HITECH**"), and their respective implementing regulations, which impose obligations on "covered entities," including certain healthcare providers, health plans, and healthcare clearinghouses, as well as their respective "business associates" that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Additionally, HITECH also contains four new tiers of civil monetary penalties; amends HIPAA to make civil and criminal penalties directly applicable to business associates and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and to seek attorneys' fees and costs associated with pursuing federal civil actions;

- the U.S. federal Food, Drug and Cosmetic Act, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- the EU General Data Protection Regulation ("**GDPR**"), and other EU member state data protection legislation as well as that of the United Kingdom, which requires data controllers and processors, to adopt administrative, physical, and technical safeguards designed to protect personal data, including health-related data, including mandatory contractual terms with third-party providers, requirements for establishing an appropriate legal basis for processing personal data, transparency requirements related to communications with data subjects regarding the processing of their personal data, standards for obtaining consent from individuals to process their personal data, notification requirements to individuals about the processing of their personal data, an individual data rights regime, mandatory data breach notifications, limitations on the retention of personal data, increased requirements pertaining to health data, and strict rules and restrictions on the transfer of personal data outside of the EU, including to the United States;

- the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively the "**ACA**"), and its implementing regulations, created annual reporting requirements for certain manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions), to report information related for certain payments and "transfers of value" provided to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse-midwives; and

- analogous state laws and regulations and non-U.S. laws, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; state and non-U.S. laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or to adopt compliance programs as prescribed by state laws and regulations, or that otherwise restrict payments that may be made to healthcare providers; state and non-U.S. laws that require

drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing; state and local laws that require the registration of pharmaceutical sales representatives; and state and non-U.S. laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Further, the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute and certain criminal statutes governing healthcare fraud. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the ACA provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Because of the breadth of these laws and the narrowness of their exceptions and safe harbors, it is possible that our business activities can be subject to challenge under one or more of such laws. The full scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform. Federal and state enforcement bodies have continued to increase their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry.

Efforts to ensure that our internal operations and future business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, including, without limitation, damages, monetary fines, imprisonment, disgorgement of profits, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting or oversight obligations if we become subject to a corporate integrity agreement or other agreement to resolve allegations of noncompliance with the law and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and pursue our strategy. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including future collaborators, are found not to be in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also affect our business.

Nearly all aspects of our activities are subject to substantial regulation and compliance and staying up-to-date with such regulation is time-consuming and expensive.

Our business activities are subject to a wide range of laws as well as regulations, including those promulgated by the FDA and EMA, and other regulatory authorities, regulating matters such as orphan drug designations, clinical trials, use of data, animal testing, approval processes, requirements for production, marketing, sales, pricing, pharmacovigilance and intellectual property rights. Compliance with such laws is time-consuming and expensive. In addition, the FDA, the EMA or comparable regulatory authorities may change their policies, adopt additional regulations or revise existing regulations or take other actions, which may prevent or delay approval of arimoclomol. Changes to the prevailing legal or regulatory regime, may cause us to incur significant costs, revise, delay or discontinue all or part of our development program or adopt new processes and procedures in order to comply with new laws or regulations, which may negatively impact how we develop, attest, produce, market or sell our products, if approved, for instance, by making it more costly and demanding to develop or obtain approval for arimoclomol and this may materially and adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

Even if we obtain regulatory approval for arimoclomol, it will remain subject to ongoing regulatory oversight.

Even if we obtain regulatory approvals for arimoclomol, such approvals will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for arimoclomol may also be subject to a risk evaluation and mitigation strategy limitations on the approved indicated uses for which the drug may be marketed or to the conditions of

approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 trials, and surveillance to monitor the quality, safety and efficacy of the drug. For instance, the FDA has notified us that since approximately 80% of patients enrolled in our Phase 2/3 NPC trial received miglustat as a concomitant medication, it may limit their ability to determine efficacy and safety and will therefore be a significant review issue. This may have implications for labeling and recommended dosing and may lead to a need for post-marketing trials. Such regulatory requirements may differ from country to country depending on where we have received regulatory approval.

In addition, drug manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the NDA or non-U.S. marketing application. If we, or a regulatory authority, discover previously unknown problems with a drug, such as adverse events of unanticipated severity or frequency, or problems with the facility where the drug is manufactured or if a regulatory authority disagrees with the promotion, marketing or labeling of that drug, a regulatory authority may impose restrictions relative to that drug, the manufacturing facility or us, including requesting a recall or requiring withdrawal of the drug from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of arimoclomol, a regulatory authority may:

- issue an untitled letter or warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA, MAA, or comparable non-U.S. marketing application or any supplements thereto submitted by us or our partners;
- restrict the marketing or manufacturing of the drug;
- seize or detain the drug or otherwise require the withdrawal of the drug from the market;
- refuse to permit the import or export of arimoclomol; or
- refuse to allow us to enter into supply contracts, including government contracts.

Moreover, the FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products.

If we are unable to comply with applicable regulatory requirements, we may be subject to fines, withdrawal of regulatory approvals, recall of products, suspension of manufacturing or other operational restrictions, as well as criminal sanctions and damage claims. Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize arimoclomol and harm our business, results of operations, cash flows, financial condition and/or prospects.

We are subject to anti-corruption laws and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete

in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, and the rules and regulations thereunder, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and any other domestic or foreign anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties to sell our products outside the United States, to conduct clinical trials, and/ or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

We, our employees and third-party contractors are subject to safety requirements and any failure to comply with such requirements could result in liability or reputational damage.

Due to the chemical ingredients of pharmaceutical products and the nature of the research and development and manufacturing process, we, our employees and third-party contractors are subject to safety reporting requirements, environmental regulations and, going forward, additional requirements following potential receipt of marketing approval. If we fail to comply with applicable rules and regulations, we could be subject to criminal sanctions and substantial liability or could be required to suspend or modify our operations. Further, if any of our employees or third-party contractors perform acts or omissions that are considered unethical, criminal or otherwise contrary to applicable laws and regulations or internal guidelines, our reputation may be harmed, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Compliance with environmental laws and regulations could be expensive, and the failure to comply with these laws and regulations could subject us to significant liability.

Our research, development and manufacturing operations involve the use of hazardous substances, and we are subject to a variety of federal, state, local and foreign environmental laws and regulations relating to the storage, use, handling, generation, manufacture, treatment, discharge and disposal of hazardous substances. Our products may also contain hazardous substances, and they are subject laws and regulations relating to labeling requirements and to their sale, collection, recycling, treatment, storage and disposal. Hazardous materials are also used by us in our research and development, such as Rotenone. We cannot completely eliminate the risk of accidental contamination or injury from the use, storage, handling or disposal of these materials. We may be held liable for any accident or injury that occurs as a result of this risk, the costs of which may exceed any insurance coverage that we currently have, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. Compliance with these laws and regulations may be expensive and noncompliance could result in substantial fines and penalties. Environmental laws and regulations also impose liability for the remediation of releases of hazardous substances into the environment and for personal injuries resulting from exposure to hazardous substances, and they can give rise to substantial remediation costs and to third-party claims, including for property damage and personal injury. Liability under environmental laws and regulations can be joint and several and without regard to fault or negligence, and they tend to become more stringent over time, imposing greater compliance costs and increased risks and penalties associated with violations. We cannot assure you that violations of these laws and regulations, or releases of or exposure to hazardous substances, will not occur in the future or have not occurred in the past, including as a result of human error, accidents, equipment failure or other causes. The costs of complying with environmental laws and regulations, and liabilities that may be imposed for violating them, or for remediation obligations or responding to third-party

claims, could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Although we believe that we hold all permits required for our use of hazardous materials, any failure to comply with applicable laws and regulations could result in fines, suspension of permits or authorizations or claims for damages, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We are subject to risks related to data privacy concerns, cyber security breaches and failure to comply with laws, regulations, standards, and contracts relating to data privacy and security.

We are subject to evolving data protection laws, privacy and security requirements and other regulatory restrictions in the various jurisdictions in which we operate. These laws are subject to differing interpretations and may be inconsistent among jurisdictions, and guidance on implementation and compliance practices are often updated or otherwise revised, which adds to the complexity of processing personal information. During the course of our business, we come in the possession of sensitive personal data, including information from clinical trials, and health data obtained in connection with reporting of adverse events and may store or process such information outside the country in which it was collected. This information needs to be handled by us in compliance with such obligations. These and other obligations could require us or our partners to incur additional costs to achieve compliance, limit our competitiveness, necessitate the acceptance of more onerous obligations in our contracts, restrict our ability to use, store, transfer, and process data, impact our or our partners' ability to process or use data in order to support the provision of our products or services, affect our or our partners' ability to offer our products and services or operate in certain locations, cause regulators to reject, limit, or disrupt our clinical trial activities, result in increased expenses, reduce overall demand for our products and services and make it more difficult to meet expectations of or commitments to customers or collaborators

Furthermore, our failure to keep apprised of, and comply with, privacy, data use and security laws, standards and regulations, including, for instance, unauthorized disclosure of, or access to, data, could result in the suspension or revocation of our approvals or registrations, the limitation, suspension or termination of services or the imposition of administrative, civil or criminal penalties, including fines. For example, under the EU General Data Protection Regulation that entered into force in May 25, 2018, fines may be as high as 20 million Euros or 4% of the annual worldwide revenue, whichever is higher, for certain infringements. Laws such as the GDPR and EU member state laws may also apply to health-related and other personal information that we process. These laws impose strict obligations on the ability to process health-related and other personal information of data subjects in the European Union and the United Kingdom, including, among other things, standards relating to the privacy and security of personal data, which require the adoption of administrative, physical and technical safeguards designed to protect such information. These laws may affect our use, collection, analysis, and transfer (including cross-border transfer) of such personal information. These laws include several requirements relating to transparency requirements related to communications with data subjects regarding the processing of their personal data, obtaining the consent of the individuals to whom the personal data relates, limitations on data processing, establishing a legal basis for processing, notification of data processing obligations or security incidents to appropriate data protection authorities or data subjects, the security and confidentiality of the personal data and various rights that data subjects may exercise. The GDPR prohibits the transfer, without an appropriate legal basis, of personal data to countries outside of the European Economic Area ("**EEA**"), such as the United States, which are not considered by the European Commission to provide an adequate level of data protection. Switzerland has adopted similar restrictions. Although there are legal mechanisms to allow for the transfer of personal data from the EEA and Switzerland to the United States, uncertainty about compliance with EU data protection laws remains and such mechanisms may not be available or applicable with respect to the personal data processing activities necessary to research, develop, and market our products and services. For example, ongoing legal challenges in Europe to the mechanisms allowing companies to transfer personal data from the EEA to the United States could result in further limitations on the ability to transfer personal data across borders, particularly if governments are unable or unwilling to reach new or maintain existing agreements that support cross-border data transfers, such as the EU-U.S. and Swiss-U.S. Privacy Shield Frameworks. Additionally, other countries have passed or are considering passing laws requiring local data residency and/or restricting the

international transfer of data. Further, the UK's decision to leave the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, while the Data Protection Act of 2018, that "implements" and complements the GDPR achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. During the period of "transition" (i.e., until December 31, 2020), EU law will continue to apply in the United Kingdom, including the GDPR, after which the GDPR will be converted into UK law. Beginning in 2021, the UK will be a "third country" under the GDPR. We may, however, incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act ("**CCPA**"), it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provides consumers with new data privacy rights, imposes new operational requirements for covered businesses, creates a statutory damages framework, and allows for a new cause of action for data breaches. Although there are limited exemptions for clinical trial data, the CCPA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

In addition, we may obtain health information from third parties in the United States (including research institutions from which we may obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. Additionally, HITECH created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce HIPAA and seek attorneys' fees and costs associated with pursuing federal civil actions. Depending on the facts and circumstances, we could be subject to criminal penalties, including if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity or business associate in a manner that is not authorized or permitted by HIPAA. In addition, such failure or non-compliance may cause existing or potential partners, including hospitals, physicians and patients to cease interacting with us, and could damage our reputation and brand. In addition, to the extent more restrictive laws, rules or security requirements relating to business and personal data are adopted in the future in the various jurisdictions in which we operate, such changes could have an adverse impact on our business by increasing our costs or imposing restrictions on our business processes.

Any failure by our vendors to comply with applicable law, regulations or contractual obligations related to data privacy and security could result in proceedings against us by governmental entities or others.

We publish privacy policies, self-certifications, and other documentation regarding our collection, processing, use and disclosure of personal information and/or other confidential information. Although we endeavor to comply with our published policies, certifications, and documentation, we may at times fail to do so or may be perceived to have failed to do so. Moreover, despite our efforts, we may not be successful in achieving compliance if our employees or vendors to comply with our published policies, certifications, and documentation. Such failures can subject us to potential international, local, state and federal action if they are found to be deceptive, unfair, or misrepresentative of our actual practices. Moreover, patients or subjects about whom we or our partners obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information. Claims that we have violated individuals' privacy rights or failed to comply with data protection laws or applicable privacy notices even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

Because of the breadth of these laws, it is possible that some of our current or future business activities could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that a healthcare company may fail to comply fully with one or more of these requirements. If our operations are alleged to be or are found to be in violation of any of the privacy or data security

laws or regulations described above that are applicable to us, or any other laws that apply to us, we may be subject to government investigations and enforcement actions, private litigation, penalties, including potentially significant criminal, civil, and administrative penalties, damages, fines, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements, and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that arimoclomol, once approved, is sold in a foreign country, we may be subject to similar foreign laws. Accordingly, our failure to keep apprised of, and comply with, privacy, data use and security laws, standards and regulations could have a material adverse effect on our reputation and negatively affect our business, results of operations, cash flows, financial condition and/or prospects.

Cyber security attacks on our servers, information systems and databases, or the third-party servers, information systems and databases on which our information is stored or processed, could compromise the security, availability, or integrity of our data or could cause interruptions in the operations of our business. We cannot guarantee that our security measures will be sufficient to protect against unauthorized access to or other compromise of the personal or confidential information we process. The techniques used to sabotage or to obtain unauthorized access to our systems, networks and/or physical facilities in which data is stored or through which data is transmitted change frequently, and we may be unable to implement adequate preventative measures or stop security breaches. The recovery systems, security protocols, network protection mechanisms and other security measures that we have integrated into our platform, systems, networks and physical facilities, which are designed to protect against, detect and minimize security breaches, may not be adequate to prevent or detect service interruption, system failure or data loss. Notwithstanding safeguards, cyber security breaches, internal security breaches, physical security breaches or other unauthorized or accidental access to our servers, other information systems or databases could result in tampering with, or the theft or publication of, sensitive information or the deletion or modification of data, or could otherwise cause interruptions in our operations, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

The tampering with, disruption to, or the theft or publication of, sensitive information or the deletion or modification of records held either in our systems or the systems of others to which we have access, could subject us to increased costs and exposure to litigation. We have contractual and legal obligations to notify relevant stakeholders of security breaches. Most jurisdictions have enacted laws requiring companies to notify individuals, regulatory authorities, and others of security breaches involving certain types of data. In addition, our agreements with certain partners may require us to notify them in the event of a security breach. The loss of confidential information could result in the payment of damages and reputational harm and could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Despite the implementation of security measures, our internal computer systems and those of our third-party CMOs, CROs and other contractors and consultants are vulnerable to damage from computer viruses, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. For example, the loss of pre-clinical studies or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any such disruption results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidate, or inappropriate disclosure or theft of confidential or proprietary information, we could incur liabilities, our competitive position could be harmed and the further development of our product candidates could be delayed.

The financial exposure from the items referenced above could either not be insured against or not fully covered through any insurance that we maintain and could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. In addition, we cannot be sure that our existing insurance coverage and coverage for errors and omissions will continue to be available on acceptable terms or that our insurers will not deny coverage as to any future claim. There can be no assurance that the limitations of liability in our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages.

Risks Related to Intellectual Property Rights

If we are unable to obtain and maintain our marketing and distribution rights for arimoclomol, as well as patent protection for our technology and current or future product candidates, or if the scope of the marketing and distribution rights or patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our development programs and product candidate. Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our current and future product candidates. We have sought to protect our proprietary position by filing and in-licensing patent applications in the United States and abroad related to our development programs and product candidate. The patent prosecution process is expensive and time-consuming, and we or our licensors may not be able to file, maintain or prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions. We currently do not have composition of matter patents that cover our product candidate nor any patent that covers the formulation of our product candidate. We rely on method of use patents for protection of our product candidate, which protect methods of treating the current indications that we are targeting other than sIBM (the treatment of which is not currently covered by patent protection).

It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we have licensed from third parties. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our current and future product candidates in the United States or in other foreign countries. Our patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless, and until, a patent issues from such applications, and then only to the extent the issued claims cover the technology.

If the patent applications we hold or have in-licensed with respect to our development programs and product candidate fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our current and future product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, products. Any such outcome could have a negative effect on our business.

The patent position of biopharmaceutical companies is generally highly uncertain, involves complex legal, scientific and factual questions for which important legal principles remain unresolved and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights may be uncertain. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, patent laws in various jurisdictions, including significant commercial markets such as Europe, restrict the patentability of methods of treatment of the human body more than U.S. law does. In addition, many countries, including certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties (for example, the patent owner has failed to "work" the invention in that country, or the third party has patented improvements). In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patent and other intellectual property protection, which makes it difficult to stop infringement. Publications of discoveries in scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions remain confidential for a period of time after filing, and some remain so until issued. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, and such prior art could potentially

invalidate a one or more of our patents or prevent a patent from issuing from a one or more of our pending patent applications. There is also no assurance that there is not prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim in our patents and patent applications, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. Even if patents do successfully issue and even if such patents cover our current and future product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed, invalidated or held unenforceable, which could allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our current or future product candidates, prevent others from designing around our claims or provide us with a competitive advantage. Any of these outcomes could impair our ability to prevent competition from third parties.

We have filed several patent applications covering various aspects of our current or future product candidates. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent, or whether any issued patents will be found invalid and unenforceable or will be challenged by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

Our current intellectual property portfolio may not prove to be sufficient to protect the exclusivity of arimoclomol for our indications. Additional competitors could enter the market, including with generic versions of our products, and sales of affected products may decline materially.

We do not own any patents covering the composition of matter or the current formulation for arimoclomol. Composition of matter patents are generally believed to offer the strongest patent protection. It is therefore possible for any third party to make arimoclomol for another unpatented indication, and for such third party product to have the same formulation as ours. Such third party may also offer its version of arimoclomol at a lower cost.

Our patent portfolio has a strategic scope of protection consisting of method of use patents. While many countries such as the United States permit method of use patents relating to the use of drug products, in some countries the law relating to patentability of such use claims is evolving and may be unfavorably interpreted to prevent us from patenting some or all of our pending patent applications. There are some countries that currently do not allow such method of use patents, or that significantly limit the types of uses that are patentable.

Since our composition of matter patent for arimoclomol has expired, a competitor could, at any time, submit an ANDA for a generic version of arimoclomol and request immediate approval. The ANDA process is confidential, so there may be other arimoclomol ANDAs pending. As a result, it is possible that we could face competition from third party products that have arimoclomol as the active pharmaceutical ingredient. If a third party were to obtain FDA approval in the United States for the use of arimoclomol, or regulatory approval in another jurisdiction, for an indication before we did, such third party would be first to market and could establish the price for arimoclomol in these jurisdictions. This could adversely impact our ability to implement our pricing strategy for the product and may limit our ability to maximize the commercial potential of arimoclomol in the United States and elsewhere. The presence of a lower priced competitive product with the same active pharmaceutical ingredients as our product could lead to use of the competitive product for our indications, including on an off-label basis. Such uses may be made by physicians or other third parties that are too small for us to pursue patent claims against. This could lead to pricing pressure for arimoclomol, which would adversely affect our ability to generate revenue from the sale of arimoclomol.

Our rights to develop and commercialize product candidates may be subject, in part, to the terms and conditions of licenses granted to us by others, and, if we fail to comply with our obligations under these arrangements, we could lose such intellectual property rights or owe damages to the licensor of such intellectual property.

We license know-how and technology related to our product candidate and certain other intellectual property rights from third parties, and in the future may be party to other material license or collaboration agreements. These agreements typically impose numerous obligations on a licensee, including payment obligations. If we fail to comply with our obligations under these agreements, our licensors may have the right to terminate our licenses, in which event we might not be able to develop, manufacture or market any product that is covered by the intellectual property we in-license from such licensors and may face other penalties. In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed or will license in the future prevent or impair our ability to maintain our current or future licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected technology and product candidates, which could have a material adverse effect on our business, financial conditions, results of operations and prospects. In addition to the above risks, intellectual property rights that we license in the future may include sublicenses under intellectual property owned by third parties, in some cases through multiple tiers. The actions of our licensors may therefore affect our rights to use our sublicensed intellectual property, even if we are in compliance with all of the obligations under our license agreements. Should our licensors or any of the upstream licensors fail to comply with their obligations under the agreements pursuant to which they obtain the rights that are sublicensed to us, or should such agreements be terminated or amended, our ability to develop and commercialize our product candidates may be materially harmed.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent which might adversely affect our ability to develop and market our current or future product candidates.

We cannot guarantee that any of our or our licensors' patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our current or future product candidates in any jurisdiction. Even if we diligently search third-party patents for potential infringement by our products or current or future product candidates, we may not successfully find patents our products or current or future product candidates may infringe. For example, U.S. applications filed before November 29, 2000 and certain U.S. applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Because patent applications in the United States, Europe and many other jurisdictions are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date, patent applications covering our current or future product candidates could have been filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our current or future product candidates or the use of such product candidates. The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our current or future product candidates. We may incorrectly determine that our current or future product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our current or future product candidates. Our failure to identify and correctly interpret relevant

patents may negatively impact our ability to develop and market our current or future product candidates.

If we fail to identify and correctly interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay damages, we may be temporarily or permanently prohibited from commercializing any of our current or future product candidates that are held to be infringing and/or harm our reputation and financial results. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products, in the case of claims concerning registered trademarks, rename our current or future product candidates, or obtain one or more licenses from third parties, which may require substantial time and monetary expenditure, and which might be impossible or technically infeasible. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

Patent terms may be inadequate to protect our competitive position on our current or future product candidates for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our current or future product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive medications, including biosimilar or generic medications. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours. Depending upon the timing, duration and conditions of FDA marketing approval of our current or future product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and similar legislation in the EU. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office ("**USPTO**"), reviews and approves the application for any patent term extension in consultation with the FDA. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

Intellectual property rights do not necessarily address all potential threats to our business.

While we seek broad coverage under our existing patent applications, there is always a risk that an alteration to products or processes may provide sufficient basis for a competitor to avoid infringing our patent claims. In addition, patents, if granted, expire and we cannot provide any assurance that any potentially issued patents will adequately protect our current or future product candidates. Once granted, patents may remain open to opposition, interference, re-examination, post-grant review, inter partes review, nullification or derivation action in court or before patent offices or similar proceedings for a given period after allowance or grant, during which time third parties can raise objections against

such grant. In the course of such proceedings, which may continue for a protracted period of time, the patent owner may be compelled to limit the scope of the allowed or granted claims thus attacked, or may lose the allowed or granted claims altogether.

In addition, the degree of future protection afforded by our intellectual property rights is uncertain because even granted intellectual property rights have limitations and may not adequately protect our business. The following examples are illustrative:

- others may be able to make compounds, or formulations that are similar to our current or future product candidate formulations but that are not covered by the claims of the patents that we own or control;
- the patents of third parties may have an adverse effect on our business;
- we or our licensors or any future strategic partners might not have been the first to conceive or reduce to practice the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we or our licensors or any future strategic partners might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our owned or in-licensed pending patent applications will not lead to issued patents;
- issued patents that we own or have exclusively licensed may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- third parties performing manufacturing or testing for us using our current or future product candidates or technologies could use the intellectual property of others without obtaining a proper license;
- we cannot ensure that any of our patents, or any of our pending patent applications, if issued, or those of our licensors, will include claims having a scope sufficient to protect our current or future product candidates;
- we cannot ensure that any patents issued to us or our licensors will provide a basis for an exclusive market for our current or future commercially viable product candidates or will provide us with any competitive advantages;
- the Supreme Court of the United States, other U.S. federal courts, Congress, the USPTO or similar foreign authorities may change the standards of patentability and any such changes could narrow or invalidate, or change the scope of, our or our licensors' patents;
- patent terms may be inadequate to protect our competitive position on our current or future product candidates for an adequate amount of time;
- we cannot ensure that our commercial activities or current or future product candidates will not infringe upon the patents of others;

- we cannot ensure that we will be able to successfully commercialize our current or future product candidates on a substantial scale, if approved, before the relevant patents that we own or license expire;

- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property;

- we may not develop additional proprietary technologies that are patentable; and

- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, results of operations, cash flows, financial condition and/or prospects.

Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our current and future product candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological complexity and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. In addition, the America Invents Act (the "**AIA**"), which was signed into law on September 16, 2011, includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art, may affect patent litigation, and changed the U.S. patent system from a "first-to-invent" system to a "first-to-file" system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention prior to such third party. While this will require us to be cognizant of the time that passes from creating an invention to filing a patent application on such invention, circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

In the last few years, the USPTO has developed regulations and procedures to govern administration of the AIA, and many of the substantive changes to patent law associated with the AIA, and, in particular, the first-to-file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' or collaboration partners' patent applications and the enforcement or defense of our or our licensors' or collaboration partners' issued patents, all of which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

In addition, patent reform legislation may pass in the future that could lead to additional uncertainties and increased costs surrounding the prosecution, enforcement and defense of our patents and pending patent applications. The U.S. Supreme Court has ruled on several patent cases in recent years, such as Association for Molecular Pathology v. Myriad Genetics, Inc., Mayo Collaborative Services v. Prometheus Laboratories, Inc., and Alice Corporation Pty. Ltd. v. CLS Bank International, which together have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Similarly, the complexity and uncertainty of European patent laws has also increased in recent years. For example, the April 2010 amendment of the European Patent Convention, which limited the time permitted for filing divisional applications, was subsequently abrogated. This amendment and subsequent abrogation illustrates the uncertainty involved in the prosecution of European patent laws. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution. These changes could limit our ability to obtain new patents in the future that may be important for our business.

Furthermore, the United States federal government retains certain rights in inventions produced with its financial assistance under the Bayh-Dole Act. The federal government retains a "nonexclusive, nontransferable, irrevocable, paid-up license" for its own benefit. The Bayh-Dole Act also provides federal agencies with "march-in rights". March-in rights allow the government, in specified circumstances, to require the contractor or successors in title to the patent to grant a "nonexclusive, partially exclusive, or exclusive license" to a "responsible applicant or applicants." If the patent owner refuses to do so, the government may grant the license itself. We cannot be sure that any co-developed intellectual property will be free from government rights pursuant to the Bayh-Dole Act. For instance, we have license agreements with the University of Miami and the University of Kansas pursuant to which we have in-licensed specified data, know-how, inventions and patent rights generated from clinical trials. As the University of Miami and University of Kansas have obtained federal grants, such license agreements may be subject to the Bayh-Dole Act. If, in the future, we co-own or license in technology which is critical to our business that is developed in whole or in part with federal funds subject to the Bayh-Dole Act, our ability to enforce or otherwise exploit patents covering such technology may be adversely affected.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a negative impact on the success of our business.

Our commercial success depends, in part, upon our ability, and the ability of any future collaborators, to develop, manufacture, market and sell our current and future product candidates, if approved, and use our proprietary technologies without alleged or actual infringement, misappropriation or other violation of the patents and intellectual property and proprietary rights of third parties. There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and re-examination proceedings before the USPTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our current or future product candidates may be subject to claims of infringement of the intellectual property rights of third parties.

We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to arimoclomol and any future product candidates and technology, including interference or derivation proceedings, post grant review and inter partes review before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. Similarly, we may initiate such proceedings or litigation against third parties, including to challenge the

validity or scope of intellectual property rights controlled by third parties. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which may result in such patents being narrowed, invalidated or held unenforceable, which could allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent right, unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, or methods of treatment, prevention or use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our current or future product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In such an event, we would be unable to further practice our technologies or develop and commercialize any of our current or future product candidates at issue, which could harm our business significantly.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our current and future product candidates and/or harm our reputation and financial results. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. Third parties making such claims may have the ability to dedicate substantially greater resources to these legal actions than we or our licensors or collaborators can. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products, in the case of claims concerning registered trademarks, rename our current or future product candidates, or obtain one or more licenses from third parties, which may be impossible, technically infeasible or require substantial time and monetary expenditure. Furthermore, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us, or include terms that impede or destroy our ability to compete successfully in the commercial marketplace.

We may become involved in lawsuits to protect or enforce our patents, the patents of our licensors or our other intellectual property rights, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe or otherwise violate our or our licensors' patents or misappropriate or otherwise violate our or our licensor's other intellectual property rights. To counter infringement or unauthorized use, we may be required to file legal claims on a country-by-country basis, which can be expensive, time-consuming and divert the time and attention of our management and scientific personnel. Our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. There can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded.

In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could limit our ability to assert those patents against those parties or other competitors and curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the trademarks we

have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks, which could materially harm our business and negatively affect our position in the marketplace.

The initiation of a claim against a third party may also cause the third party to bring counter claims against us such as claims asserting that our patents are invalid or unenforceable or claims challenging the scope of the intellectual property rights we own or control. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or lack of statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the USPTO, or made a materially misleading statement, during prosecution. Third parties may also raise similar validity claims before the USPTO in post-grant proceedings such as ex parte re-examinations, inter partes review, or post-grant review, or oppositions or similar proceedings outside the United States, in parallel with litigation or even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. We cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of any future patent protection on our current or future product candidates. Such a loss of patent protection could harm our business. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

We may not be able to prevent, alone or with our licensors, infringement or misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. Our business could be harmed if in litigation the prevailing party does not offer us a license on commercially reasonable terms. Any litigation or other proceedings to enforce our intellectual property rights may fail, and even if successful, may result in substantial costs and distract our management and other employees.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during the course of litigation. There could also be public announcements regarding the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of the ordinary shares and ADSs. Any of the foregoing could allow third parties to develop and commercialize competing technologies and products and have a material adverse impact on our business, financial condition, results of operations and/or prospects.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

While we seek to protect the trademarks we use in the United States and in other countries, we may be unsuccessful in obtaining registrations and/or otherwise protecting these trademarks. If that were to happen, we may be prevented from using our names, brands and trademarks unless we enter into appropriate royalty, license or coexistence agreements, which may not be available or may not be available on commercially reasonable terms. Over the long term, if we are unable to establish name recognition based on our trademarks, trade names, service marks and domain names, then we may not be able to compete effectively, resulting in a material adverse effect on our business. Our registered or unregistered trademarks or trade names may be challenged, infringed, diluted or declared generic, or determined to be infringing on other third-party trademarks. In addition to registrations, we also rely on common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trademarks and trade names similar to ours, thereby impeding our ability to build brand

identity and possibly leading to market confusion. In addition, there could be potential trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks. Over the long term, if we are unable to establish name recognition based on our trademarks, then we may not be able to compete effectively and our business may be adversely affected. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Effective trademark protection may not be available or may not be sought in every country in which our products are made available. Any name we propose to use for our products in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed product names, we may be required to expend significant additional resources in an effort to identify a usable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

We may not have enough financial resources to successfully enforce and defend our intellectual property rights.

The enforcement and defense of our intellectual property rights, including patent rights, through legal or administrative proceedings may be costly and time-consuming, may divert our personnel from their usual responsibilities and may provide our competitors and others with insights into our proprietary rights. Moreover, there can be no assurance that we will have sufficient financial or other resources to conduct such enforcement or defense actions. An adverse determination in any litigation or other proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our pending patent applications at risk of not being issued. The occurrence of any of the above could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers. The majority of our employees and consultants were previously employed at universities or biopharmaceutical or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have, inadvertently or otherwise, used or disclosed intellectual property, trade secrets or other proprietary information of their former employers or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, we may have to pay substantial monetary damages and, lose valuable intellectual property rights or personnel, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and may not be able to adequately enforce our intellectual property rights even in the jurisdictions where protection is sought.

Filing, prosecuting and defending patents on the products in all countries and jurisdictions throughout the world would be prohibitively expensive, and the intellectual property rights in some countries could be less extensive than those in the European Union or the United States, assuming that rights are obtained in the European Union and the United States. Competitors may use our technologies in such jurisdictions to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the European Union or the United States.

In addition, the laws of some countries do not protect intellectual property rights to the same extent as in the European Union and the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biopharmaceuticals or biotechnologies. This could make it difficult to stop the infringement of our patents, if obtained, or the misappropriation of other intellectual property rights. For example, many countries have compulsory licensing laws under which a patent owner under certain conditions must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes.

Such lack of patent protection may lead to material costs for us, or we may be unable to protect or use our intellectual property rights, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. While it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. For example, the assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, or we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our current or future product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time-consuming and is likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Our inability to protect our confidential information and trade secrets would harm our business and competitive position.

In addition to seeking patents for some of our technology and products, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. We cannot guarantee that our trade secrets and other proprietary and confidential information will not be disclosed or that competitors will not otherwise gain access to our trade secrets. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts both within and outside the United States may be less willing or unwilling to protect trade secrets. If a competitor lawfully obtained or independently developed any of our trade secrets, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position.

Trade secrets and know-how can be difficult to protect as trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles, and the movement of personnel skilled in the art from company to company or academic to industry scientific positions. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position. If we are unable to prevent material disclosure of the intellectual property related to our technologies to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. Even if we are able to adequately protect our trade secrets and proprietary information, our trade secrets could otherwise become known or could be independently discovered by our competitors. Competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, in the absence of patent protection, we would have no right to prevent them, or those to whom they communicate, from using that technology or information to compete with us.

We may not be able to prevent misappropriation of our intellectual property, trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable

rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our products, our competitors might be able to enter the market, which would harm our business.

We may not be successful in obtaining necessary intellectual property rights to future products through acquisitions and in-licenses.

Although we intend to develop products and technology through our own internal research, we may also seek to acquire or in-license technologies to grow our product offerings and technology portfolio. However, we may be unable to acquire or in-license intellectual property rights relating to, or necessary for, any such products or technology from third parties on commercially reasonable terms or at all. In that event, we may be unable to develop or commercialize such products or technology. We may also be unable to identify products or technology that we believe are an appropriate strategic fit for our company and protect intellectual property relating to, or necessary for, such products and technology.

The in-licensing and acquisition of third-party intellectual property rights for product candidates is a competitive area, and a number of more established companies are also pursuing strategies to in-license or acquire third-party intellectual property rights for products that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. Furthermore, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. If we are unable to successfully obtain rights to additional technologies or products, our business, financial condition, results of operations and/or prospects for growth could suffer.

In addition, if competition for the in-licensing or acquisition of third-party intellectual property rights for products and technologies that are attractive to us increases in the future, there may be fewer suitable opportunities for us as well as higher acquisition or licensing costs. We may be unable to in-license or acquire the third-party intellectual property rights for products or technology on terms that would allow us to make an appropriate return on our investment.

Risks Related to Employee Matters and Managing Our Growth

We may not be able to attract, integrate, manage and retain qualified personnel or key employees or our employees may not be able to come to work as a result of COVID-19.

The success of our business depends on our ability to successfully develop and commercialize arimoclomol. Since our organization currently consists of a limited number of employees with additional personnel hires planned for the years to come, our ability to successfully develop and commercialize arimoclomol will depend on recruiting a range of specialist personnel, particularly in the areas of development of new products, planning and managing clinical programs and commercialization of pharmaceutical products, and also requires that we retain and develop the necessary qualified personnel who can provide the needed expertise to support our business and operations. The market for qualified personnel is competitive and we may not succeed in recruiting personnel to, for instance, commercialize arimoclomol as currently envisaged, or we may fail to effectively replace current personnel who depart with qualified or effective successors. Our effort to retain and develop personnel may also result in significant additional expenses, which could adversely affect our profitability. We can make no assurances that key personnel, including our senior management such as our Chief Executive Officer, Chief Financial Officer, Chief Medical Officer, or Chief Scientific Officer, will continue to be employed or that we will be able to attract and retain qualified personnel in the future. Failure to retain or attract key personnel could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects. In addition, if, as a result of COVID-19, our employees are not able to come to work, then this could also have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our third-party collaborators, CROs, CMOs, suppliers, manufacturers and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, protests, strikes, civil unrest, revolutions, rebellions, terrorist activities, and other natural or man-made disasters or business interruptions. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We currently rely on one third-party manufacturer to produce and process arimoclomol. Our ability to obtain clinical supplies of arimoclomol could be disrupted if the operations of this manufacturer are affected by a man-made or natural disaster or other business interruption. Damage or extended periods of interruption to our third-party collaborators' facilities due to fire, natural disaster, power loss, communications failure, unauthorized entry or other events could cause us to cease or delay development of arimoclomol. Although we intend to maintain property damage and business interruption insurance coverage on these facilities, our insurance might not cover all losses under such circumstances and our business may be seriously harmed by such delays and interruption.

We are increasing and expect to continue increasing the size of our organization. If we are unable to effectively manage the anticipated growth, our business, results of operations, cash flows, financial condition and/or prospects will be negatively affected.

Any growth that we experience in the future will require us to expand our sales personnel, manufacturing operations and general and administrative infrastructure. As a dual listed public company, we will need additional managerial, operational, financial and other resources. In addition to the need to scale our organization, future growth will impose significant added responsibilities on management, including the need to identify, recruit, train and integrate additional employees. Rapid expansion of personnel could mean that less experienced people manufacture, market and sell arimoclomol if approved, which could result in inefficiencies and unanticipated costs, reduced quality and disruptions to our operations. In addition, rapid and significant growth may strain our administrative and operational infrastructure. Our ability to manage our business and growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. If we are unable to manage our growth effectively, it may be difficult for us to execute our business strategy and could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

If and when demand for arimoclomol or any of our future product candidates increases, we will need to continue to scale our capacity, expand customer service, billing and systems processes and enhance our internal quality assurance program. We cannot assure you that any increases in scale, related improvements and quality assurance will be successfully implemented or that appropriate personnel will be available to facilitate the growth of our business. Failure to implement necessary procedures, transition to new processes or hire the necessary personnel could result in higher costs of processing data or inability to meet increased demand. If we encounter difficulty meeting market demand, quality standards or physician expectations, our reputation will be harmed and negatively affect our business, results of operations, cash flows, financial condition and/or prospects.

Our operations as a global company subject us to various risks, and our failure to manage these risks could adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

We face significant operational risks as a result of doing business globally, such as:

- fluctuations in currency exchange rates (in particular, U.S. dollars, Euros and Danish kroner);
- potentially adverse tax consequences, including the complexities of foreign value-added tax systems, tax inefficiencies related to our corporate structure, and restrictions on the repatriation of earnings;
- reduced or varied protection for intellectual property rights in some countries;

- export restrictions, trade regulations and foreign tax laws;
- foreign certification and regulatory clearance or approval requirements;
- difficulties in developing effective marketing campaigns in unfamiliar foreign countries;
- customs clearance and shipping delays;
- political, social, and economic instability abroad, global health epidemics or other contagious diseases, terrorist attacks and security concerns in general;
- differing payment and reimbursement regimes;
- the burdens of complying with a wide variety of foreign laws and different legal standards; and
- increased financial accounting and reporting burdens and complexities.

If one or more of these risks are realized, it could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Global economic uncertainty and other global economic or political and regulatory developments could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Growth in the global pharmaceutical market has become increasingly tied to (i) global economic growth as an economic downturn may, for example as the result of COVID-19 paralyzing economic activities, reduce the amount of funding for the pharmaceutical sector as a whole or certain diseases targeted by us and (ii) political conditions, tension and uncertainty which could, for instance, impact the regulations applicable to us. The successful commercialization of arimoclomol will depend in part on the extent to which governmental authorities and health insurers are willing or able to establish coverage, and adequate reimbursement levels, as well as pricing policies.

Uncertain political and geopolitical conditions currently exist in various parts of the world, including barriers to free trade and free movement of people in the European Union following the United Kingdom's exit from the EU on January 31, 2020 and transition period that is set to end on December 31, 2020. The full effects of the United Kingdom's exit from the EU are impossible to predict but may result in significant market volatility and dislocation, and adversely affect the United Kingdom, European and global economy. In addition, as part of Brexit, the EMA has formally relocated to Amsterdam on March 30, 2019. This relocation might interrupt current administrative routines and occupy resources, which may cause delays in EMA's handling of our applications or otherwise adversely affect our dealings with the EMA. In addition, the United Kingdom will no longer be covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of medical products, including arimoclomol, will be required in the United Kingdom, the potential process for which is currently unclear. Brexit may, therefore, adversely affect and delay our ability to commercialize, market and sell arimoclomol in the United Kingdom. Brexit may also result in a reduction of funding to the EMA if the United Kingdom no longer makes financial contributions to European institutions, such as the EMA. If the United Kingdom funding is reduced, it could create delays in EMA issuing regulatory approvals for arimoclomol.

Future legal or regulatory changes in jurisdictions where we currently operate, or in such jurisdictions in which we may choose to operate in the future, could materially and adversely affect our business, results of operations, cash flows, financial condition and/or prospects, including by imposing regulatory and operational restrictions and compliance obligations on our business, reducing our revenue or increasing our expenses. For instance, changes in applicable laws in the following areas may have an impact on our operations: orphan drugs; clinical trials; use of data; animal testing; regulatory approval processes; requirements to production; marketing, sales and pricing of pharmaceutical products; pharmacovigilance and other regulatory requirements; and intellectual property rights.

In the United States, in particular, and in the other principal markets in which we may in the future sell arimoclomol, if approved, there is continued economic, regulatory and political pressure to promote changes in healthcare systems that would limit healthcare costs and expand access to healthcare. This uncertainty is further heightened in light of the impeding 2020 presidential elections. Legislation that has been enacted in the United States, at both the federal and state levels, has introduced cost-reduction measures and other provisions that could decrease the coverage and compensation that we may receive for arimoclomol, if approved. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, the ACA was passed, which is a sweeping law intended to broaden access to health insurance, improve quality, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare (under the Physician Payments Sunshine Act) and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. In the years since enactment of the ACA, there have been, and continue to be, significant developments in, and continued executive, judicial and legislative activity around attempts to repeal or repeal and replace the ACA. On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case, and has allotted one hour for oral arguments, which are expected to occur in the fall. It is unclear how such litigation and other efforts to repeal and replace the ACA will impact the ACA and our business. Due to these efforts, there is significant uncertainty regarding the future of the ACA, and its impact on our business and operations.

Additionally, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the current presidential administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the current presidential administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the current presidential administration previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contained proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. The Department of Health and Human Services ("**HHS**") has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019.

There have also been legislative changes in response to the COVID-19 pandemic. For example, the Coronavirus Aid, Relief and Economic Security Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare payment reduction sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. It is possible that additional governmental action is taken in response to the COVID-19 pandemic. In addition, changes to the political landscape in the United States (including as a result of the 2020 presidential elections) may impact the market sentiment surrounding the pharmaceutical industry.

In the EU, changes to healthcare systems, including the establishment and operation of health services and the pricing and reimbursement of medicinal products, are almost exclusively a matter for national, and not EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that

context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines, and such measures are expected to continue, which could affect our ability to commercialize any product candidate for which we obtain marketing approval.

The above circumstances, individually or in the aggregate, could have a material adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Risks Related to the Shares

The dual listing of our Shares and the ADSs following the U.S. offering may adversely affect the liquidity and value of the Shares and our ADSs.

Following the U.S. offering and after the ADSs begin trading on the Nasdaq Global Select Market, our ordinary shares will continue to be listed on Nasdaq Copenhagen. Trading of the ordinary shares or ADSs, as applicable, in these markets will take place in different currencies (U.S. dollars on the Nasdaq Global Select Market and DKK on Nasdaq Copenhagen), and at different times (resulting from different time zones, different trading days and different public holidays in the United States and Denmark). The trading prices of our ordinary shares or ADSs, as applicable, on these two markets may differ due to these and other factors. Any decrease in the price of our ordinary shares on Nasdaq Copenhagen could cause a decrease in the trading price of the ADSs on the Nasdaq Global Select Market. Investors could seek to sell or buy our ordinary shares or ADSs to take advantage of any price differences between the markets through a practice referred to as arbitrage. Any arbitrage activity could create unexpected volatility in both the trading prices on one exchange and the ordinary shares or ADSs available for trading on the other exchange. In addition, holders of ADSs will not be immediately able to surrender their ADSs and withdraw the underlying ordinary shares for trading on the other market without effecting necessary procedures with the depositary. This could result in time delays and additional cost for holders of ADSs. We cannot predict the effect of this dual listing on the value of the ordinary shares and the ADSs. However, the dual listing of the ordinary shares and the ADSs may reduce the liquidity of these securities in one or both markets and may adversely affect the development of an active trading market for the ADSs in the United States or our ordiary shares in Denmark.

The trading price of our equity securities may be volatile due to factors beyond our control, and purchasers of the Shares could incur substantial losses.

The market prices of the Shares may be volatile. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their Shares at or above the price originally paid for the security. The market price for the Shares may be influenced by many factors, including:

- actual or anticipated fluctuations in our financial condition and operating results;
- the release of new data from the clinical trials of arimoclomol;
- actual or anticipated changes in our growth rate relative to our competitors;
- competition from existing products or new products that may emerge;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- issuance of new or updated research or reports by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;

- currency fluctuations;
- ordinary share price and volume fluctuations attributable to inconsistent trading volume levels of the ADSs and the Shares;
- additions or departures of key management or scientific personnel;
- disputes or other developments related to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- changes to coverage policies or reimbursement levels by commercial third party payors and government payors and any announcements relating to coverage policies or reimbursement levels;
- announcement or expectation of additional debt or equity financing efforts;
- uncertainty caused by and the unprecedented nature of the current COVID-19 pandemic;
- issuances or sales of our ordinary shares or ADSs by us, our insiders or our other shareholders; and
- general economic and market conditions.

These and other market and industry factors may cause the market price and demand for the Shares to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their Shares and may otherwise negatively affect the liquidity of the trading market for Shares.

We have broad discretion over the use of the net proceeds from the Global Offering and may use them in ways with which you do not agree and in ways that may not enhance our operating results or the price of the Shares.

Our Board of Directors and management will have broad discretion over the application of the net proceeds that we receive from the Global Offering. We may spend or invest these proceeds in ways with which our Shareholders disagree or that do not yield a favorable return, if at all. We intend to use the net proceeds from the Global Offering, together with our existing cash resources as described in "*The Listing—Use of Proceeds of the* Global Offering." However, our use of these proceeds may differ substantially from our current plans. For instance, if we do not use the proceeds to obtain regulatory approval and fund a potential commercial launch of arimoclomol for the treatment of NPC, we will continue to not generate any revenue in the near future. Failure by our management to apply these funds effectively could harm our business, results of operations, cash flows, financial condition and/or prospects. Pending their use, we may invest the net proceeds from the Global Offering in a manner that does not produce income or that loses value.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, the price of the Shares and their trading volume could decline.

The trading market for the Shares depends in part on the research and reports that securities or industry analysts publish about us or our business. If no or only limited securities or industry analysts cover the Company, the trading price for the Shares could be negatively impacted. If one or more of the analysts who covers us downgrades our equity securities or publishes inaccurate or unfavorable research about our business, the price of our Shares would likely decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, or downgrades our securities, demand for Shares could decrease, which could cause the price of the Shares or their trading volume to decline.

We intend to retain all available funds and any future earnings and, consequently, the Shareholders' ability to achieve a return on their investment will depend on appreciation in the price of the Shares.

We have never declared or paid any cash dividends on our shares, and we intend to retain all available funds and any future earnings to fund the development and expansion of our business. Therefore, Shareholders are not likely to receive any dividends on their Shares for the foreseeable future and the success of an investment in Shares will depend upon any future appreciation in their value. Consequently, investors may need to sell all or part of their holdings of Shares after price appreciation, which may never occur, as the only way to realize any future gains on their investment. There is no guarantee that the Shares will appreciate in value or even maintain the price at which our investors have purchased them. Investors seeking cash dividends should not purchase the Shares.

In addition, if we choose to pay dividends in the future, exchange rate fluctuations may affect the amount of Danish kroner that we are able to distribute, and the amount in U.S. dollars that our Shareholders receive upon the payment of cash dividends or other distributions we declare and pay in Danish kroner, if any. Any dividends will generally be subject to Danish withholding tax. See the section of this prospectus titled "*The Listing—information concerning the Listing Shares—Taxation*" for a more detailed description of Danish taxes on dividends. These factors could harm the value of the Shares

Future sales, or the perception of future sales, of a substantial number of our Shares could adversely affect the price of the Shares, and actual sales of our equity will dilute Shareholders.

Future sales of a substantial number of our Shares, or the perception that such sales will occur, could cause a decline in the market price of the Shares. Following the completion of the Global Offering, based on the number of shares outstanding as of June 30, 2020, we will have 34,661,075 shares outstanding (assuming no exercise of the Overallotment Option). This includes the shares underlying the ADSs offered in the U.S. Offering, which may be resold in the public market immediately without restriction, unless purchased by our "affiliates" as that term is defined in Rule 144 under the Securities Act, which may be resold only if registered under the Securities Act or in accordance with the requirements of Rule 144 or another applicable exemption from the registration requirements of the Securities Act. Shares held by our directors, officers and certain shareholders will be subject to the lock-up agreements, see "*Board of Directors, Executive Management and Key Employees-Restrictions on securities trading*". If, after the period during which such lock-up agreements restrict sales of the Shares or if BofA Securities, Inc. and Cowen and Company, LLC waive the restrictions set forth therein (which may occur at any time), one or more of these Shareholders sell substantial amounts of Shares in the public market, or the market perceives that such sales may occur, the market price of the Shares and our ability to raise capital through an issue of equity securities in the future could be adversely affected.

If we issue shares in future financings, shareholders may experience dilution and, as a result, our ordinary share price may decline.

We may from time to time issue additional ordinary shares at a discount from the trading price of our Shares. As a result, our Shareholders would experience immediate dilution upon the issuance of any of our Shares at such discount. In addition, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt securities, preference shares or shares. If we issue ordinary shares or securities convertible into ordinary shares of our share capital, our Shareholders would experience additional dilution and, as a result, our ordinary share price may decline.

U.S. Holders and other non-Danish holders may not be able to exercise the pre-emptive subscription rights related to the ordinary shares, and may suffer dilution of their equity holding in the event of future issuances of our Shares.

Under the Danish Companies Act ("**Danish Company Act**"), our Shareholders benefit from a pre-emptive subscription right on the issuance of ordinary shares for cash consideration only and not in the event of issuance of shares against non-cash contribution or debt conversion. Shareholders' pre-emptive subscription rights, in the event of issuances of ordinary shares against cash payment, may be disapplied by a resolution of the Shareholders at a general meeting of our shareholders and/or the

ordinary shares may be issued on the basis of an authorization granted to the Board of Directors pursuant to which the board may disapply the shareholders' pre-emptive subscription rights. Our Shareholders have authorized our Board of Directors to issue securities, including in connection with issues of new ordinary shares without pre-emptive rights for our existing shareholders at or above market price against cash payment, issues of new ordinary shares without pre-emptive rights to members of our board of directors, our executives and/or our employees and to certain specific third-parties which may be below the market price against cash payment or, for certain third-parties, by issuance of bonus shares as well as issues of new ordinary shares with pre-emptive rights for our existing shareholders against cash payment or conversion of debt which may be below the market price. Ordinary shares may be issued at or above the market price or below the market price, as such term is construed under Danish law, in the case of rights issues or pursuant to a resolution of the shareholders. The absence of pre-emptive rights for existing equity holders may cause dilution to such holders.

It may be difficult or impossible for the Company's shareholders and investors outside Denmark to enforce judgments from their home jurisdictions against the Company.

The Company is incorporated, and a majority of its assets and operations are held and conducted in, Denmark. As such, it may be difficult or impossible for shareholders and investors outside of Denmark to enforce judgments obtained in courts of such shareholder's and investor's home jurisdictions against the Company.

In the future, we may lose our foreign private issuer status in the U.S., which could result in significant additional costs and expenses.

As a foreign private issuer in the United States, we are not required to comply with all the periodic disclosure and current reporting requirements of the U.S. Securities Exchange Act of 1934 (the "**Exchange Act**") and related rules and regulations. Following the consummation of the Global Offering, the determination of foreign private issuer status in the United States will be made annually on the last business day of our most recently completed second fiscal quarter. Accordingly, we will next make a determination with respect to our foreign private issuer status on June 30, 2021. There is a risk that, in the future, we will lose our foreign private issuer status in the United States.

We would lose our foreign private issuer status in the United States if, for instance more than 50% of our Shares are owned by U.S. residents or persons and more than 50% of our assets are located in the United States and we continue to fail to meet additional requirements necessary to maintain our foreign private issuer status. The regulatory and compliance costs to us under U.S. securities laws as a U.S. domestic issuer may be significantly greater than the costs we incur as a foreign private issuer in the United States. If we are not a foreign private issuer in the United States, we will be required to file periodic reports and registration statements on U.S. domestic issuer forms with the SEC, which are more detailed and extensive in certain respects than the forms available to a foreign private issuer. We would be required under current SEC rules to prepare our financial statements in accordance with U.S. GAAP and modify certain of our policies to comply with corporate governance practices associated with U.S. domestic issuers. Such conversion and modifications would involve additional costs. In addition, we may lose our ability to rely upon exemptions from certain corporate governance requirements on U.S. stock exchanges that are available to foreign private issuers in the United States, which could also increase our costs.

The intended tax effects of our corporate structure depend on the application of the tax laws of various jurisdictions and on how we operate our business.

During the ordinary course of business, there are many transactions and calculations for which the ultimate tax determination is uncertain. For example, our effective tax rates could be adversely affected by changes in foreign currency exchange rates or by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations. As we intend to operate in numerous countries and tax jurisdictions, the application of tax laws can be subject to diverging and sometimes conflicting interpretations by tax authorities of these jurisdictions. It is not uncommon for tax authorities in different countries to have conflicting views, for instance, with respect to, among other things, the manner in which the arm's length standard is applied for transfer pricing purposes, or with respect to the valuation of intellectual property. In addition, it is uncertain whether we will be able to fully utilize our net operating losses as an income tax benefit for future periods. To the extent that our ability to use

our net operating losses is restricted, this may result in us paying more tax and could therefore reduce our post-tax profits. In addition, tax laws are subject to change as new laws are passed and new interpretations of the law are promulgated by taxing authorities or sustained by judicial bodies. We are unable to predict what tax law changes may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and increase the complexity, burden and cost of tax compliance.

We are exposed to changes in foreign currency exchange rates and interest rates.

Substantially all of our income is expected to be in U.S. dollars and Euros, while part of our operating costs are currently denominated in Danish kroner, although in the future such Danish kroner denominated operating costs are likely to constitute a smaller percentage of our total operating costs. We do not currently have in place hedging contracts to cover our currency risks and, accordingly, fluctuations in Danish kroner against, in particular U.S. dollars, could have an adverse effect on our business, results of operations, cash flows, financial condition and/or prospects.

Our interest rate risk mainly derives from the fact that we hold a large cash position. Significant negative changes in interest rates could affect the value of our funds and any placement thereof and may thereby adversely affect our business, results of operations, cash flows, financial condition and/or prospects.

Shareholders outside Denmark may be subject to exchange rate risk.

The Shares are denominated in Danish kroner. Accordingly, an investment in the Shares by an investor whose principal currency is not Danish kroner may expose such investor to foreign currency exchange rate risk. Any depreciation of Danish kroner against such foreign currency would reduce the value of the investment in the Shares in terms of such foreign currency.

We will incur significant increased costs as a result of operating as a company that is publicly listed on both Nasdaq in the United States and Nasdaq Copenhagen in Denmark, and our management will be required to devote substantial time to new compliance initiatives.

As a U.S. public company listed on Nasdaq, we will incur legal, accounting, and other expenses that we did not previously incur. We will be subject to the reporting requirements of the Securities Exchange Act of 1934 (the "**Exchange Act**"), the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the Nasdaq listing requirements and other applicable securities rules and regulations. Compliance with these rules and regulations will increase our legal and financial compliance costs, make some activities more difficult, time consuming or costly and increase demand on our systems and resources, particularly after we are no longer an "emerging growth company" and/or a foreign private issuer. The Exchange Act would require that, as a public company, we file annual, semi-annual and current reports with respect to our business, financial condition and result of operations. However, as a foreign private issuer in the United States, we are not required to file quarterly and current reports with respect to our business and results. We currently make annual and semiannual reporting with respect to our listing on Nasdaq Copenhagen.

Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified senior management personnel or members for our board of directors.

However, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Further, being a U.S. listed company and a Danish public company with ordinary shares admitted to trading on Nasdaq Copenhagen impacts the disclosure of information and requires compliance with

two sets of applicable rules. From time to time, this may result in uncertainty regarding compliance matters and result in higher costs necessitated by legal analysis of dual legal regimes, ongoing revisions to disclosure and adherence to heightened governance practices. As a result of the enhanced disclosure requirements of the U.S. securities laws, business and financial information that we report is broadly disseminated and highly visible to investors, which we believe may increase the likelihood of threatened or actual litigation, including by competitors and other third parties, which could, even if unsuccessful, divert financial resources and the attention of our management from our operations.

As a result of becoming a U.S. public company, we will become subject to additional regulatory compliance requirements, including Section 404, and if we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results or prevent fraud.

Pursuant to Section 404, our management will be required to assess and attest to the effectiveness of our internal control over financial reporting in connection with issuing our consolidated financial statements as of and for the year ending December 31, 2021. Section 404 also requires an attestation report on the effectiveness of internal control over financial reporting be provided by our independent registered public accounting firm beginning with our annual report following the date on which we are no longer an "emerging growth company" in the United States, which may be up to five fiscal years following the date of the U.S. Offering.

The cost of complying with Section 404 will significantly increase and management's attention may be diverted from other business concerns, which could adversely affect our results. We may need to hire more employees in the future or engage outside consultants to comply with these requirements, which will further increase expenses. If we fail to comply with the requirements of Section 404 in the required timeframe, we may be subject to sanctions or investigations by regulatory authorities, including the SEC and Nasdaq. Furthermore, if we are unable to attest to the effectiveness of our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, and the market price of our ordinary shares could decline. Failure to implement or maintain effective internal control over financial reporting could also restrict our future access to the capital markets and subject each of us, our directors and our officers to both significant monetary and criminal liability. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure are creating uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. These laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expense and a diversion of management's time and attention from revenue generating activities to compliance activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to their application and practice, regulatory authorities may initiate legal proceedings against us and our business, financial position, results and prospects may be adversely affected.

We may be subject to securities litigation, which is expensive and could divert management's attention.

The market price of the Shares may be volatile and, in the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

RESPONSIBILITY STATEMENT

The Company's Responsibility

The Company is responsible for this Prospectus in accordance with Danish law.

The Company's Statement

We hereby declare that we, as the persons responsible for this Prospectus on behalf of the Company, have taken all reasonable care to ensure that, to the best of our knowledge, the information contained in this Prospectus is in accordance with the facts and makes no omission likely to affect its import.

We furthermore declare that this Prospectus has been approved by the Danish Financial Supervisory Authority as competent authority under the Prospectus Regulation. The Danish Financial Supervisory Authority only approves this Prospectus as meeting the standards of completeness, comprehensibility and consistency imposed by the Prospectus Regulation. Such approval should not be considered as an endorsement of the Company that is the subject of this Prospectus. The Prospectus has been drawn up as part of a simplified prospectus in accordance with Article 14 of the Prospectus Regulation.

Copenhagen, September 30, 2020.

Orphazyme A/S

Board of Directors

Georges Gemayel *Chairman*	Bo Jesper Hansen *Deputy Chairman*
Martijn Kleijwegt *Board Member*	Martin Bondc *Board Member*
Sten Verland *Board Member*	Anders Hedegaard *Board Member*
Catherine Moukheibir *Board Member*	Rémi Droller *Board Member*
Carrolee Barlow *Board member*	

Georges Gemayel: Professional board member
Bo Jesper Hansen: Professional board member
Martijn Kleijwegt: Founder and Managing Partner at LSP
Martin Bonde: Professional board member
Sten Verland: Partner and co-founder at Sunstone Life Science Ventures

Anders Hedegaard: Chief Executive Officer of Rodenstock GmbH
Catherine Moukheibir: Professional board member
Rémi Droller: Managing Partner at Kurma Partners
Carrolee Barlow: Professional board member

Executive Management

Kim Stratton *CEO*	Anders Vadsholt *CFO*

GENERAL INFORMATION

This Prospectus has been prepared in compliance with Danish law, including the Danish Capital Markets Act, the Prospectus Regulation, Commission Delegated Regulation (EU) no. 2019/980 of March 14, 2019 as well as Commission Delegated Regulation (EU) 2019/979 of March 14, 2019, and Nasdaq Issuer Rules. This Prospectus is governed by Danish law. The U.S. Offering of ADSs in the Unites States has, however, been made in accordance to U.S. law. The EU Private Placement has been made in accordance with EU law and Danish law.

References in this Prospectus to the "Company", "Orphazyme", "we", "our" or "ours" are references to Orphazyme A/S, and references to the "Group" are references to Orphazyme A/S together with its subsidiaries unless the context requires otherwise. See "*Glossary*" for a list of terms and definitions frequently used in this Prospectus.

This Prospectus is not intended to provide the basis of any credit or any other evaluation and should not be considered as a recommendation or invitation by the Company that any recipient of this Prospectus should acquire any Shares. Any person who comes into the possession of this Prospectus should determine for itself the relevance of the information contained in this Prospectus, and any acquisition of Shares should be based upon such information as it deems necessary.

The information contained in this Prospectus has been provided by the Company and by other sources identified herein.

The information contained herein is as at the Prospectus Date, unless stated otherwise. Any material changes in connection with the information in this Prospectus which may affect the evaluation of the Shares, which occurs or is ascertained between the time of approval of this Prospectus and the commencement of trading on Nasdaq Copenhagen of the Listing Shares, will be published as a supplement to this Prospectus pursuant to applicable rules and legislation in Denmark.

Further, no person has been authorized to give any information or to make any representation concerning the Group or the Shares other than contained in this Prospectus, and, if given or made, any such information or representation should not be relied upon as having been authorized by the Company. The Company accepts no liability for any such information or representation.

The Prospectus may not be forwarded, reproduced or otherwise redistributed, in whole or in part, by anyone but the Company. Investors may not disclose any of the contents of this Prospectus or use any information herein.

The Company or any of its representatives will not make any representation to any subsequent purchaser of the Shares.

Prospective investors of Shares must comply with all applicable rules and legislation in countries or territories in which they offer or sell Shares or possess or distribute this Prospectus and must obtain consent, approval or permission, as required, for the acquisition of Shares. Any person into whose possession this Prospectus may come is required by the Company to inform themselves about such restrictions and to observe such restrictions. Neither the Company nor the Company's auditors accepts any liability for any violation of these restrictions by any person, irrespective of whether such person is an existing shareholder or a potential purchaser of Shares.

Enforceability of judgments

The Shares have been issued in accordance with Danish law. The U.S. Offering, however, has been made in accordance with U.S. law. The Prospectus has been prepared in compliance with the standard and requirements of Danish law, including the rules issued by Nasdaq Copenhagen. Any disputes that may arise as a result of the Listing is subject to exclusive jurisdiction of the Danish Courts.

The Company is organized under the laws of Denmark, with a domicile in the municipality of Copenhagen, Denmark. Substantially all of our assets are located outside the United States. The majority of our board members and employees reside outside the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce against them or us in U.S. courts, including judgments predicated upon the civil liability provisions of the U.S. securities laws.

The United States and Denmark currently do not have a treaty providing for the reciprocal recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a U.S. court, whether or not predicated solely upon U.S. securities laws, would not be enforceable in Denmark.

In order to obtain a judgment that is enforceable in Denmark, the party in whose favor a final and conclusive judgment of the U.S. court has been rendered will be required to file its claim again with a court of competent jurisdiction in Denmark. The Danish court will not be bound by the judgment by the U.S. court, but the judgment may be submitted as evidence. It is up to the Danish court to assess the judgment by the U.S. court and decide if and to what extent the judgment should be followed. Danish courts are likely to deny claims for punitive damages and may grant a reduced amount of damages compared to U.S. courts.

Based on the lack of a treaty as described above, U.S. investors may not be able to enforce against the Company or members of the Board of Directors or our Executive Management, or certain experts named herein who are residents of Denmark or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

Third-party information

Unless otherwise indicated, information contained in this Prospectus concerning our industry and the markets in which we operate, including our general expectations and market opportunity, is based on information from the Company's own management estimates and research, as well as from industry and general publications, research, surveys and studies conducted by third parties, including market studies that the Company commissioned from the Centers for Disease Control and Precention, Grand View Research, the ALS Association, Aptis Partners, as well as, more generally, the U.S. Food and Drug Administration and the European Medicines Agency. Management estimates are derived from publicly available information, the Company's knowledge of its industry and assumptions based on such information and knowledge, which the Company believes to be reasonable. The industry publications and third-party studies generally state that the information that they contain has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Market data and statistics are inherently predictive and subject to uncertainty and not necessarily reflective of actual market conditions. Such statistics are based on market research, which itself is based on sampling and subjective judgements by both the researchers and the respondents. While the Company can confirm that information from external sources has been accurately reproduced, the Company has not independently verified and cannot give any assurances as to the accuracy of market data as presented in this Prospectus that was extracted or derived from these external sources. As far as the Company is aware and able to ascertain from this information, no facts have been omitted which would render the information provided inaccurate or misleading.

The Company makes no representation as to the accuracy of such information that was extracted or derived from these external sources. Thus, any development in the Group's activities may deviate from the market developments stated in the Prospectus. The Company does not assume any obligation to update such information.

As a result, persons who come into the possession of this Prospectus should be aware that statistics, data, statements and other information relating to markets, market sizes, market shares, market positions and other industry data in this Prospectus (and projections, assumptions and estimates based on such information) may not be reliable indicators of the Company's future performance and the future performance of the industry in which it operates. Such indicators are necessarily subject to a high degree

of uncertainty and risk due to the limitations described above and to a variety of other factors. Other forecasts and forward-looking information obtained from these sources are subject to the same qualifications and uncertainties as the other forward-looking statements in this Prospectus. See "*General Information—Forward-Looking Statements*." These forecasts and forward-looking information are subject to uncertainty and risk due to a variety of factors, including those described under "Risk Factors." These and other factors could cause results to differ materially from those expressed in the Company's forecasts or estimates or those of independent third parties. While the Company believes its internal research is reliable and the definition of its market and industry are appropriate, neither such research nor these definitions have been verified by any independent source.

Presentation of financial statements and other information

This Prospectus includes financial information which has been derived from the Company's (i) audited consolidated financial statements as of and for the years ended December 31, 2019 with comparative figures as of and for the year ended December 31, 2018 and the related notes (the "**FY 2019 Group Financial Statements**") and (ii) unaudited interim consolidated financial statements as of and for the six months ended June 30, 2020 with comparative figures as of and for the year ended December 31, 2019 and the related notes (the "**H1 2020 Interim Financial Statements**"), which are both incorporated by reference.

The Company maintains its books and records in Danish kroner and it prepares its audited consolidated financial statements in accordance with International Financial Reporting Standards ("**IFRS**"), as issued by the International Accounting Standards Board ("**IASB**"). None of the consolidated financial statements in this Prospectus were prepared in accordance with accounting principles generally accepted in the United States ("**U.S. GAAP**").

All references in this Prospectus to "$" are to U.S. dollars, to "DKK" are to Danish kroner and to "€" are to the Euro. Except with respect to U.S. dollar amounts presented as contractual terms, amounts denominated in U.S. dollars when received or paid and unless otherwise indicated, certain Danish kroner amounts contained in this Prospectus have been translated into U.S. dollars at the rate of $1.00 to DKK 6.6554, which was the noon buying rate of the Federal Reserve Bank of New York on December 31, 2019, the last business day of the Company's fiscal year ended December 31, 2019. In addition, certain Danish kroner amounts contained in this Prospectus that are derived from our Interim Financial Statements have been translated into U.S. dollars at the rate of $1.00 to DKK 6.6318, which was the noon buying rate of the Federal Reserve Bank of New York on June 30, 2020. These translations should not be considered representations that any such amounts have been, could have been or could be converted into U.S. dollars or Danish kroner at that or any other exchange rate as of that or any other rate.

Certain accounting and statistical figures in this Prospectus have been subject to rounding adjustments. Accordingly, the sum of these figures is not necessarily equivalent to the total amounts stated. In addition, certain percentage figures reflect calculations based on the underlying information prior to rounding up and, accordingly, the percentage figures may not necessarily be exactly equivalent to the figures that would be derived if the relevant calculations were based upon the rounded numbers.

Forward-looking statements

This Prospectus contains forward-looking statements that reflect our current expectations and views of future events. The forward-looking statements are contained principally in the sections entitled "*Summary*", "*Risk Factors*", and "*Company Information—Business*." Known and unknown risks, uncertainties and other factors, including those listed under "*Risk Factors*", may cause our actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements.

You can identify some of these forward-looking statements by words or phrases, such as "may," "will," "expect," "anticipate," "aim," "estimate," "intend," "plan," "believe," "is/are likely to," "potential," "continue" or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events that we believe may affect our financial

condition, results of operations, business strategy and financial needs. These forward-looking statements include statements relating to:

- the ability of our clinical trials to demonstrate acceptable safety and efficacy of our product candidate, and other positive results;
- the timing, progress and results of clinical trials for our product candidate, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our research and development programs;
- the timing, scope and likelihood of regulatory filings, NDA submissions and approvals, including the NDA process for arimoclomol for the treatment of NPC and final regulatory approval of arimoclomol;
- our ability to obtain marketing approvals of our product candidate and to meet existing or future regulatory standards or comply with post-approval requirements;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash, cash equivalents and short-term investments and net proceeds of the Global Offering;
- our payments of future milestone payments to our licensing partners, and the expected timing of such payments;
- our expectations regarding the potential market size and the size of the patient populations for our product candidate, if approved for commercial use;
- our expectations regarding the potential advantages of our product candidate over existing therapies;
- the impact of COVID-19 on our business and operations;
- our potential to enter into new collaborations;
- our expectations with regard to our ability to develop additional product candidates or product candidates for other indications our ability to identify additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- our expectations with regard to the willingness and ability of our current and future licensing and collaboration partners to pursue the development of our product candidate;
- our ability to develop, acquire and advance additional product candidates into, and successfully complete, clinical trials;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- the commercialization and market acceptance of our product candidate;
- our marketing and manufacturing capabilities;
- the pricing of and reimbursement for our product candidate;
- the implementation of our business model and strategic plans for our business and product candidate;

- our ability to operate our businesses without infringing the intellectual property rights and proprietary technology of third parties;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidate;
- our analysis of our actual or potential patent infringement claims and the rights of our collaboration partners with respect to such claims;
- estimates of our expenses, future revenue, capital requirements, our needs for additional financing and our ability to obtain additional capital;
- regulatory development in the United States, Europe and other jurisdictions;
- our exposure to additional scrutiny as a U.S. public company;
- our ability to effectively manage our anticipated growth;
- our ability to attract and retain qualified employees and key personnel;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;
- our use of proceeds from the Global Offering;
- our financial performance;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act and qualify as a foreign private issuer; and
- developments and projections relating to our competitors and our industry, including competing therapies.

These forward-looking statements involve various risks and uncertainties. Although we believe that our expectations expressed in these forward-looking statements are reasonable, our expectations may later be found to be incorrect. Our actual results could be materially different from our expectations. Important risks and factors that could cause our actual results to be materially different from our expectations are generally set forth in "Prospectus Summary," "Risk Factors," "Business," and other sections in this Prospectus. You should read thoroughly this Prospectus and the documents that we refer to with the understanding that our actual future results may be materially different from and worse than what we expect. We qualify all of our forward-looking statements by these cautionary statements.

The forward-looking statements made in this Prospectus relate only to events or information as of the date on which the statements are made in this Prospectus. Except as required by law, we undertake no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise, after the date on which the statements are made or to reflect the occurrence of unanticipated events. You should read this Prospectus and other publicly available information, completely and with the understanding that our actual future results may be materially different from what we expect.

The Global Offering

The Global Offering comprises 7,616,146 ordinary shares offered by us, consisting of 3,966,146 ordinary shares in the form of ADSs offered in the U.S. Offering and 3,650,000 ordinary shares offered in the EU Private Placement as the European Offered Shares. The closings of the U.S. Offering and the EU Private Placement are expected to occur substantially simultaneously.

The U.S. Offering was an initial public offering in the United States of 3,966,146 American Depositary Shares ("**ADSs**") at a price of USD 11.00 per ADS (using a USD/DKK exchange rate of 6.3804). Each ADS represents one Listing Share. 3,966,146 of the Listing Shares are underlying the ADSs.

The U.S. Offering is made pursuant to a registration statement on Form F-1 (No. 333-248607) that was declared effective on September 28, 2020. The final U.S. Prospectus including the subscription price for the ADSs will be published in the United States on or before September 30, 2020. Pricing of the Global Offering took place on September 29, 2020 (CET) and after market close in the United States on September 28, 2020, and the price per ADS was fixed at USD 11.00, corresponding to DKK 70.1844 (using a USD/DKK exchange rate of 6.3804). The price for the ADSs corresponds to a subscription price of DKK 70.1844 per Listing Share. Completion and settlement of the U.S. Offering and EU Private Placement is expected to take place substantially simultaneous on October 1, 2020.

The ADSs were listed and began trading on September 29, 2020 on the Nasdaq Global Select Market in the United States (NASDAQ) under the symbol "ORPH".

The Bank of New York Mellon has been appointed as depositary for the ADSs and will issue and register the ADSs to the holders thereof and be the holder of such Listing Shares underlying ADSs upon issue.

No offer of Listing Shares or ADSs has been or will be made in the EU/EEA under this Prospectus and no offer of any securities has been or will be made under this Prospectus in the United States or to U.S. Persons (as such term is defined in Regulation S under the U.S. Securities Act of 1933, as amended). The EU Private Placement was carried out under applicable exemptions from the obligation to publish a prospectus pursuant to the Prospectus Regulation. Investors in ADSs or Shares may not rely on this Prospectus for any purpose.

Concurrently with the U.S. Offering. we have offered 3,650,000 ordinary shares, being the European Offered Shares, in an international private placement to qualified investors in Europe, as defined under the Prospectus Regulation (the "**EU Private Placement**"). The term "Listing Shares" will also include the European Offered Shares.

The Underwriters, have, subject to the terms and conditions of an underwriting agreement dated September 28, 2020 (due to the time difference between Denmark and the United States) among the Company and BofA Securities, Inc., Cowen and Company, LLC, Guggenheim Securities, LLC, as representatives of the several Underwriters, in relation to the Global Offering (the "**Underwriting Agreement**"), severally and not jointly, agreed to subscribe for 7,616,146 Listing Shares (with respect to the European Offered Shares, such subscription taking place on behalf of investors in the EU Private Placement). In connection with the U.S. Offering, the Listing Shares will be delivered in the form of ADSs.

The Company has granted an option to the Underwriters, exercisable for 30 days after the date of announcement of the pricing of the Global Offering, to subscribe for and purchase, for themselves or on behalf of investors, up to 1,142,421 additional ordinary shares (which may be in the form of ADSs) (collectively, the "**Additional Securities**") at the offering price in connection with the Global Offering, less the underwriting commission (the "**Overallotment Option**"). The Overallotment Option may be exercised in full or in part. The term "Listing Shares" does not include any Additional Securities that may be issued by the Company. Any such Additional Securities will be listed on Nasdaq Copenhagen in reliance on an exemption pursuant to the Regulation (EU) no. 2017/1129 of the European Parliament and the Council of June 14, 2017, as amended.

As used herein, "Shares" shall refer to all outstanding shares of the Company at any given time.

As used herein, the term "**Underwriters**" refers to with respect to the EU Private Placement, the underwriters (or their respective affiliates) subscribing, on behalf of certain investors, for ordinary shares issued by the Company in the EU Private Placement and with respect to the U.S. Offering, the underwriters subscribing for the ordinary shares issued by the Company and underlying the ADSs in the U.S. offering, in each case, in accordance with the Underwriting Agreement. The underwriters in

the U.S. offering and the underwriters in the EU Private Placement are collectively referred to herein as the "Underwriters."

When the board of directors of the Company resolved to issue the Listing Shares on September 28, 2020, the board of directors also resolved to issue up to 1,142,421 Additional Securities.

The Underwriting Agreement provides that the obligations of the Underwriters to pay for and accept delivery of the ADSs offered in the U.S. Offering and Shares in connection with the EU Private Placement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The Underwriters are obligated to take and pay for (i) all of the ADSs offered in the U.S. Offering if any such ADSs are taken and (ii) all of the ordinary shares offered in the EU Private Placement. However, the Underwriters are not required to take or pay for the Additional Securities covered by the Overallotment Option, unless they decide to exercise the Overallotment Option.

The Underwriters have not been involved in the preparation of this Prospectus.

Stabilization

Until the distribution of the ADSs and/or the Shares, as applicable, is completed, SEC rules and Danish law may limit underwriters and selling group members from bidding for and purchasing the Shares and ADSs. However, the Underwriters may engage in transactions that stabilize, maintain or otherwise effect the price of the Shares and ADSs, such as bids or purchases to peg, fix or maintain that price for 30 days from the date of announcement of the pricing of the Global Offering (the "Stabilization Period"). Stabilization, if any, will not occur at a price higher than the public offering price. However, such stabilization may not necessarily occur during the Stabilization Period and may cease at any time. Any stabilization action must be conducted by the Underwriters (or person(s) acting on their behalf) in accordance with applicable laws and rules. In connection with the Global Offering, the Underwriters (or persons acting on their behalf) may overallot Shares in the and ADSs or effect transactions with a view to supporting the market price of the Shares and ADSs during the Stabilization Period at a level higher than that which might otherwise prevail. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the Underwriters of a greater number of Shares and ADSs than they are required to purchase in the Global Offering. "Covered" short sales are sales made in an amount not greater than the Overallotment Option. The Underwriters may close out any covered short position by either exercising their option to subscribe for and purchase Additional Securities or by purchasing Shares or ADSs in the open market. In determining the source of Shares or ADSs to close out the covered short position, the Underwriters will consider, among other things, the price of Shares and ADSs available for purchase in the open market as compared to the price at which they may purchase Shares and ADSs through the option granted to them. "Naked" short sales are sales in excess of such option. The Underwriters must close out any naked short position by purchasing Shares or ADSs in the open market. A naked short position is more likely to be created if the Underwriters are concerned that there may be downward pressure on the price of the Shares and ADSs in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of the Shares and ADSs made by the Underwriters in the open market prior to the end of the Stabilization Period. The Underwriters may also impose a penalty bid. This occurs when a particular Underwriter repays to the Underwriters a portion of the underwriting commission received by it because the representatives have repurchased Shares or ADSs sold by or for the account of such Underwriter in stabilizing or short covering transactions. Similar to other purchase transactions, the Underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of the Shares and ADSs or preventing or retarding a decline in the market price of the Shares and ADSs. As a result, the price of the Shares and ADSs may be higher than the price that might otherwise exist in the open market. However, the Underwriters are not required to engage in such activities and may end such activities at any time Any stabilization action or over allotment must be conducted by the relevant underwriter (or persons acting on their behalf) in accordance with all applicable laws and rules and in any event in accordance with the principles and procedures set forth herein as well as in compliance with Regulation (EU) No 596/2014 on market abuse, including delegated Regulation (EU) No. 1052/2016 of March 8, 2016, and will be undertaken in the U.S.

securities markets, including on the Nasdaq Global Select Market, in the over-the-counter market or otherwise, on the Nasdaq Copenhagen or at the offices of the relevant underwriter (or persons acting on their behalf).

ADSs (American depositary shares)

General

An ADS represents equity shares of a foreign issuer and is available for purchase on a stock exchange in the United States. The ADSs are delivered by a depositary bank in the United States under an agreement with a foreign issuer.

An ADS may be held either (a) directly (i) through an American Depositary Receipt ("**ADR**") which is a certificate evidencing a specific number of ADSs, registered in the name of the holder, or (ii) by having uncertificated ADSs registered in the holder's name, or (b) indirectly by holding a security entitlement in ADSs through a broker or other financial institution that is a direct or indirect participant in the Depository Trust Company. If a person holds ADSs directly, such a person is registered as an ADS holder ("**ADS Holder**"). The below description relates to ADS Holders. If a person holds the ADSs indirectly, such person must rely on the procedures of its broker or other financial institution to assert the rights of ADS holders described below.

ADSs in terms of the U.S. Offering

In the U.S. Offering, each ADS represents one Share. The Bank of New York Mellon (the "**Depositary**") acts as depositary and will register and deliver the ADSs. The Depositary will hold the Listing Shares which are deposited with the Copenhagen office of Danske Bank A/S, whose business address is Holmens Kanal 2-12, 1060 Copenhagen K, Denmark, as custodian for the Depositary in Denmark. An ADS Holder will not be treated as a Shareholder and will not have shareholder rights. Danish law governs shareholder rights. The Depositary will be the holder of the Listing Shares underlying the ADSs and a registered holder of ADSs will have ADS holder rights. A deposit agreement among the Company, the depositary, ADS holders and all other persons indirectly or beneficially holding ADSs (the "**Deposit Agreement**") sets out ADS holder rights as well as the rights and obligations of the Depositary. New York law governs the Deposit Agreement and the ADSs.

Deposit Agreement

Below is an extract of some of the material terms of the Deposit Agreement:

Dividend and Other Distributions

The Depositary has agreed to pay or distribute to ADS holders the cash dividends or other distributions it or the custodian receives on the Listing Shares or other deposited securities. Distributions to the ADS Holders will be in proportion to the number of shares the ADSs represent. The Depositary may distribute additional ADSs representing any Shares we distribute as a dividend or free distribution.

Listing Shares

If we offer holders of our Shares any rights to subscribe for additional Shares or any other rights, the Depositary may (i) exercise those rights on behalf of ADS Holders, (ii) distribute those rights to ADS Holders or (iii) sell those rights and distribute the net proceeds to ADS Holders.

Withdrawal

The ADS Holder may with few limitations choose to surrender its ADSs for the purpose of withdrawal at the Depositary's office. Upon payment of its fees and expenses, the Depositary will deliver the Shares and any other deposited securities underlying the ADSs to the ADS holder or a person the ADS holder designates at the office of the custodian or at its office, if feasible.

Voting Rights

ADS Holders may instruct the Depositary how to vote the number of deposited Shares their ADSs represent. The Company can choose to request the Depositary to solicit the ADS Holder's voting instructions. If the Company so requests, the Depositary will notify of a general meeting and send or make voting materials available to the ADS Holders. Those materials will describe the matters to be voted on and explain how ADS holders may instruct the depositary how to vote.

If it solicited voting instructions, the Depositary will try, as far as practical, subject to the laws of Denmark and the provisions of the Articles of Association, to vote or to have its agents vote the Shares as instructed by ADS holders. The Articles of Association allow for differentiated voting. This means the depositary may vote the shares registered in its name that underlie the ADSs in a manner that is not identical. As a result, the depositary will be able to vote such shares in a manner to reflect the preferences of the ADS holders, thereby effectively permitting pass-through voting by ADS holders who indicate their preference to the depositary in accordance with and subject to the depositary's procedures. If the Company does not request the Depositary to solicit the ADS Holder's voting instructions, the ADS Holder can still send voting instructions, and, in that case, the Depositary may try to vote as instructed, but it is not required to do so.

Tender and Exchange Offers; Redemption, Replacement or Cancellation of Deposited Securities

The Depositary will not tender deposited Shares or other securities in any voluntary tender or exchange offer unless instructed to do so by an ADS Holder surrendering ADSs and subject to any conditions or procedures the Depositary may establish. If deposited Shares or other securities are redeemed for cash in a transaction that is mandatory for the Depositary as a holder of deposited securities, the Depositary will call for surrender of a corresponding number of ADSs and distribute the net redemption money to the holders of called ADSs upon surrender of those ADSs. If there is any change in the deposited Shares or other securities such as a subdivision, combination or other reclassification, or any merger, consolidation, recapitalization or reorganization affecting the Company of deposited Shares or other securities in which the Depositary receives new Shares or other securities in exchange for or in lieu of the old deposited Shares or other securities, the Depositary will, if lawful and practical, hold those replacement Shares or other securities as deposited Shares or other securities under the Deposit Agreement.

If there are no deposited Shares or other securities underlying ADSs, including if the deposited Shares or other securities are cancelled, or if the deposited Shares or other securities underlying ADSs have become apparently worthless, the Depositary may call for the surrender of those ADSs or cancel those ADSs upon notice to the ADS holders.

Amendment and Termination

The Company may agree with the Depositary to amend the Deposit Agreement without the ADS Holders' consent for any reason. Such amendments will apply to ADS Holders. The Deposit Agreement can be terminated by the instruction of the Company and under certain circumstances, the Depositary can terminate the agreement.

COMPANY INFORMATION

1 PERSONS RESPONSIBLE, THIRD PARTY INFORMATION, EXPERTS' REPORTS AND COMPETENT AUTHORITY APPROVAL

1.1 Persons responsible and approval from competent authority

See "*Responsibility statement*" for more details.

1.2 Experts' reports and third party information

This Prospectus does not contain any expert statements or expert reports.

For details on information sourced from third parties, see *"General information–Third party information"*.

2 AUDITORS

The Company's independent auditors are:

EY Godkendt Revisionspartnerselskab (formerly named Ernst & Young Godkendt Revisionspartnerselskab)CVR no. 30700228

c/o Postboks 250

Dirch Passers Allé 36

Denmark

EY Godkendt Revisionspartnerselskab (formerly named Ernst & Young Godkendt Revisionspartnerselskab) is represented by Christian Schwenn Johansen, State Authorized Public Accountant and Rasmus Bloch Jespersen, State Authorized Public Accountant, both members of FSR – Danish Auditors, the Danish association for state-authorized public accountants, (FSR – Danske Revisorer).

The audited consolidated financial statements of the Group as at and for the year ended December 31, 2019 with comparative figures as at and for the yeas ended 2018, which have been audited by the Group's independent auditors, EY Godkendt Revisionspartnerselskab, have been incorporated by reference in this Prospectus.

3 RISK FACTORS

See "*Risk Factors*" for more details.

4 COMPANY INFORMATION

4.1 Name and registered office

Orphazyme A/S
CVR no. 32 26 63 55
Ole Maaløes Vej 3
DK-2200 Copenhagen N
Denmark

Legal Entity Identifier (LEI): 54930025OZD2GGSQ7L42

Telephone: (+45) 39 17 82 72
E-mail: contact@orphazyme.com
Website: www.orphazyme.com

The information on the website does not form part of the Prospectus unless that information is incorporated by reference into the Prospectus.

4.2 Country of incorporation and governing law

The Company is a limited liability company incorporated in Denmark and is subject to Danish law.

5 REGULATION

Government authorities in the United States, at the federal, state and local levels, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products, such as those we are developing. The processes for obtaining regulatory approvals in the United States and other countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act ("**FDCA**") and its implementing regulations and guidance. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and non-U.S. statutes, regulations and guidance requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the drug development process, including preclinical and clinical testing, the approval process or post-approval process, may subject an applicant to delays in conducting the preclinical study or clinical trial, regulatory review, approval, a variety of administrative or judicial sanctions, such as the FDA's refusal to approve a pending NDA, other applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, civil or criminal investigations brought by the FDA, the DOJ and other government entities, including state agencies and associated civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice regulations;
- completion of the manufacture, under cGMP conditions, of the drug substance and drug product that the sponsor intends to use in clinical trials along with required analytical and stability testing;
- submission to the FDA of an investigational new drug ("**IND**") application for clinical trials, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board ("**IRB**"), at each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled clinical trials, in accordance with good clinical practice ("**GCP**") requirements to establish the safety, potency, purity and efficacy of the proposed drug for each proposed indication;
- payment of user fees;

- preparation and submission to the FDA of an NDA requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labelling;

- satisfactory completion of an FDA advisory committee review, if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties at which the product, or components thereof, are produced to assess compliance with cGMP requirements, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;

- satisfactory completion of an FDA inspection of selected clinical sites to assure compliance with GCPs and the integrity of the clinical data;

- FDA review and approval of the NDA; and

- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy ("**REMS**") and any post-approval studies or other post-marketing commitments required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin.

As a result, submission of an IND may not result in the FDA allowing clinical trials to commence. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND process, it may choose to impose a partial or complete clinical hold. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, preclinical, and/ or chemistry, manufacturing, and controls. This order issued by the FDA would delay either a proposed clinical trial or cause suspension of an ongoing trial, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed. This could cause significant delays or difficulties in completing our planned clinical trial or future clinical trials in a timely manner.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational products for patients who may benefit from investigational therapies. FDA regulations allow access to investigational products under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the investigational product under a treatment protocol or treatment IND application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 clinical trial; or 15 days after the investigational drug receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a manufacturer to make its investigational products available to eligible patients as a result of the Right to Try Act.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects, including healthy volunteers or patients with the disease or condition to be treated, under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the clinical trial as support for an IND or application for marketing approval. Specifically, the FDA requires that such clinical trials be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from participants. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for clinical trials in the United States.

In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. An IRB must operate in compliance with FDA regulations. The FDA, the IRB, or the clinical trial sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or that the participants are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Information about certain

clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. Additional studies may be required after approval.

- Phase 1: The drug is initially introduced into a limited number of healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness.

- Phase 2: The drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 2 clinical trials. Once Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile, it proceeds to Phase 3 clinical trials.

- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the safety and efficacy of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug; such Phase 3 studies are referred to as "pivotal."

- Phase 4: In some cases, the FDA may conditionally approve an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post-approval to gain more information about the drug. Such post-approval trials are typically referred to as Phase 4 clinical trials.

Progress reports detailing the results of the clinical trials must be submitted, at least annually, to the FDA, and more frequently if serious adverse events ("**SAEs**") occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements, or if the drug has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Compliance with cGMP Requirements

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The Public Health Service Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their

initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the PDUFA guidelines that are currently in effect, the FDA has a goal of ten months to review and act on a standard NDA and six months to review and act on a priority NDA, measured from the date of "filing" of a standard NDA for a NME. This review typically takes eight months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act of 2003, as amended an reauthorized, certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For products intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-the Phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a REMS plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP requirements.

The FDA generally accepts data from foreign clinical trials in support of an NDA if the trials were conducted under an IND. If a foreign clinical trial is not conducted under an IND, the FDA nevertheless may accept the data in support of an NDA if the study was conducted in accordance with GCP requirements and the FDA is able to validate the data through an on-site inspection, if deemed necessary. Although the FDA generally requests that marketing applications be supported by some data from domestic clinical studies, the FDA may accept foreign data as the sole basis for marketing approval if the foreign data are applicable to the U.S.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and takes several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing, manufacturing or formulation modifications or other changes in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

The Hatch-Waxman Amendments

As an alternative path to FDA approval for modifications to formulations or uses of drugs previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments. A Section 505(b)(2) NDA is an application that contains full reports of investigations of safety and effectiveness, but where at least some of the information required for approval comes from studies not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This type of application permits reliance for such approvals on literature or on an FDA finding of safety, effectiveness or both for an approved drug product. As such, under Section 505(b)(2), the FDA may rely, for approval of an NDA, on data not developed by the applicant. Therefore, if we can satisfy the conditions required for a Section 505(b)(2) NDA submission, it may eliminate the need for us to conduct some of the preclinical studies or clinical

trials for a product candidate that might otherwise have been required, although the review time is not shortened. The FDA may then approve the new product candidate for the new indication sought by the 505(b)(2) applicant.

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, known as the Orange Book. Any applicant who files an Abbreviated New Drug Application (ANDA) seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must certify, for each patent listed in the Orange Book for the referenced drug, to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA, (2) such patent has expired, (3) the date on which such patent expires or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. The fourth certification described above is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers. The applicant may also elect to submit a "section viii" statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. This section viii statement does not require notice to the patent holder or NDA owner. There might also be no relevant patent certification.

If the reference NDA holder and patent owners assert a patent challenge directed to one of the Orange Book listed patents within 45 days of the receipt of the paragraph IV certification notice, the FDA is prohibited from approving the application until the earlier of 30 months from the receipt of the paragraph IV certification expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the applicant. Even if the 45 days expire, a patent infringement lawsuit can be brought and could delay market entry, but it would not extend the FDA-related 30-month stay of approval.

The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired. Specifically, the holder of the NDA for the listed drug may be entitled to a period of non-patent exclusivity, during which the FDA cannot approve an ANDA or 505(b)(2) application that relies on the listed drug. For example, a pharmaceutical manufacturer may obtain five years of non-patent exclusivity upon NDA approval of an NCE, which is a drug that contains an active moiety that has not been approved by FDA in any other NDA. An "active moiety" is defined as the molecule or ion responsible for the drug substance's physiological or pharmacologic action. During the five-year exclusivity period, the FDA cannot accept for filing any ANDA seeking approval of a generic version of that drug or any 505(b)(2) NDA for the same active moiety and that relies on the FDA's findings regarding that drug, except that FDA may accept an application for filing after four years if the follow-on applicant makes a paragraph IV certification. This exclusivity period may be extended by an additional six months if certain requirements are met to qualify the product for pediatric exclusivity, including the receipt of a written request from the FDA that the NDA holder conduct certain pediatric studies, the submission of studyreports from such studies to the FDA after receipt of the written request and satisfaction of the conditions specified in the written request.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000, there is no reasonable expectation that sales of the drug in the United States will be sufficient to offset the costs of developing and making the drug available in the United States. Orphan drug designation must be requested before submitting an NDA. A product becomes an orphan when it receives orphan drug designation from the Office of Orphan Products Development at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process like any other product.

Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. If the FDA approves a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which it was designated, the sponsor is eligible for tax credits and a seven-year period of marketing exclusivity, during which the FDA may not approve another sponsor's marketing application for a drug with the same active moiety and intended for the same use or indication as the approved orphan drug, except in limited circumstances, such as if a subsequent sponsor demonstrates its product is clinically superior. During a sponsor's orphan drug exclusivity period, competitors, however, may receive approval for drugs with different active moieties for the same indication as the approved orphan drug, or for drugs with the same active moiety as the approved orphan drug, but for different indications. Orphan drug exclusivity could block the approval of one of our products for seven years if a competitor obtains approval for a drug with the same active moiety intended for the same indication before we do, unless we are able to demonstrate that grounds for withdrawal of the orphan drug exclusivity exist, or that our product is clinically superior. Further, if a designated orphan drug receives marketing approval for an indication broader than the rare disease or condition for which it received orphan drug designation, it may not be entitled to exclusivity.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. The FDA cannot, however, approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval, priority review, and breakthrough therapy designation, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures. To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The FDA may review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted. If the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

The FDA may give a priority review designation to drugs that are designed to treat serious conditions, and if approved, would provide a significant improvement in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six and ten month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation may be considered appropriate to receive a priority review.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability

or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

Breakthrough therapy designation is for a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. We may explore some of these opportunities for our product candidate as appropriate.

Rare pediatric disease designation by FDA enables priority review voucher eligibility upon U.S. market approval of a designated drug for rare pediatric diseases. The rare pediatric disease-priority review voucher program is intended to encourage development of therapies to prevent and treat rare pediatric diseases. The voucher, which is awarded upon NDA approval to the sponsor of a designated rare pediatric disease can be sold or transferred to another entity and used by the holder to receive priority review for a future NDA submission, which reduces the FDA review time of such future submission from ten to six months.

Post-approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA and other government authorities, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications, manufacturing changes or other labeling claims, are subject to further testing requirements and prior FDA review and approval. There also are continuing annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as application fees for supplemental applications with clinical data. Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events, or adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label, although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (**"PDMA"**) which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws may impact, among other things, our current and future business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain the business or financial arrangements and relationships with healthcare providers and other parties through which we market, sell and distribute our products for which we obtain marketing approval. These laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations, including, without limitation, those laws described below.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

Federal false claims laws, including the federal civil False Claims Act, prohibits any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996 ("**HIPAA**") created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("**HITECH**") and their respective implementing regulations, imposes specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act ("**CCPA**") it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. The CCPA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services("**CMS**") information related to payments or other transfers of value made to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be

required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse-midwives.

We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, as well as state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing. In addition, we may be subject to state and local laws that require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to significant penalties, including criminal, civil and administrative penalties, damages, fines, imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Patent Term Restoration and Extension

In the United States, a patent claiming a new drug product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent extension of up to five years for patent term lost during product development and FDA regulatory review. Assuming grant of the patent for which the extension is sought, the restoration period for a patent covering a product is typically one-half the time between the effective date of the investigational new drug application ("**IND**") involving human beings and the submission date of the NDA, plus the time between the submission date of the NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension in consultation with the FDA.

Coverage and Reimbursement

The future commercial success of our product candidate or any of our collaborators' ability to commercialize any approved product candidate successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide coverage for and establish adequate reimbursement levels for our product candidate. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government, through the Medicare or Medicaid programs, provides reimbursement for such treatments. In the United States, the European Union("**EU**") and other potentially significant markets for our product candidate, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product

sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidate may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidate or exclusion of our product candidate from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third-party coverage or adequate reimbursement for our product candidate in whole or in part.

Impact of Healthcare Reform on our Business

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidate profitably, if approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

There have been several U.S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidate. If third-party payors do not consider our product candidate to be cost-effective compared to other available therapies, they may not cover our product candidate, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our product on a profitable basis.

The ACA became law in March 2010 and substantially changed the way healthcare is financed by both governmental and private insurers. Among other measures that may have an impact on our business, the ACA established an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, the ACA extended manufacturers' Medicaid rebate liability, expanded eligibility criteria for Medicaid programs, and expanded entities eligible for discounts under the Public Health Service pharmaceutical pricing program. There have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the current presidential administration to repeal or replace certain aspects of the ACA, and we expect such challenges and amendments to continue. Since January 2017, President Trump has signed Executive Orders designed to delay the implementation of any certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directed federal agencies with

authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminated the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. In December 2018, CMS published a new final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal court litigation regarding the method CMS uses to determine this risk adjustment. On April 27, 2020, the U.S. Supreme Court reversed the Federal Circuit decision that previously upheld Congress' denial of $12 billion in ACA risk corridor payments to certain ACA qualified health plans and health insurance issuers. The full effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. While Congress has not passed comprehensive repeal legislation, bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017 ("**TCJA**") includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The current presidential administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The current presidential administration recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On March 2, 2020, the U.S. Supreme Court granted the petitions for writs of certiorari to review this case, and has allotted one hour for oral arguments, which are expected to occur in the fall. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018 (the "**BBA**"), among other things, amended the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole."

In addition, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the current presidential administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. The current presidential administration previously released a blueprint for action, the administration indicated that the Department of Health and Human Services ("**HHS**") will take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase

transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. HHS has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. On March 10, 2020, the current presidential administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. In addition, on December 23, 2019, the current presidential administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products). While some of these and other proposed measures will require additional authorization to become effective, Congress and the current presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

As a result of the ACA, Medicare payments are increasingly tied to quality of care and value measures, and reporting of related data by providers such as physicians and hospitals. So called "value based reimbursement" measures may present challenges as well as potential opportunities for biopharmaceutical manufacturers. Medicare incentives for providers meeting certain quality measures may ultimately prove beneficial for manufacturers that are able to establish that their products may help providers to meet such measures. However, manufacturers' ability to market their drug products based on quality or value is highly regulated and not always permissible. In addition, potentially decreased Medicare reimbursement to those providers that fail to adequately comply with quality reporting requirements could translate to decreased resources available to purchase products and may negatively impact marketing or utilization of our product candidate if it is approved for marketing. We cannot predict at this time what impact, if any, the longer-term shift towards value based reimbursement will have on our product candidate in either the Medicare program, or in any other third-party payor programs that may similarly tie payment to provider quality.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011 was enacted, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which began in 2013 and, following passage of subsequent legislation, including the BBA, will continue through 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief, and Economic Security Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. In January 2013, the American Taxpayer Relief Act of 2012 was enacted and, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding. For example, it is possible that additional governmental action is taken to address the COVID-19 pandemic.

There have been, and likely will continue to be, additional legislative and regulatory proposals at the foreign, federal, and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from

product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

European Economic Area regulation

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety, and efficacy, and governing, among other things, clinical trials, marketing authorization, commercial sales, and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions.

Clinical Trial Approval

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on GCP, in order to undertake a clinical trial in a European Union member state, an applicant must obtain approval from the competent national authority of the European Union member state in which the clinical trial is to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. Furthermore, the applicant may only start a clinical trial at a specific site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by an IMP dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the member states and further detailed in applicable guidance documents.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, but it is not yet applicable in the European Union. The new legislation, which will be directly applicable in all European Union member states, aims to streamline the approval of clinical trials in the European Union by applying consistent rules and harmonising the approvals process throughout the European Union. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single-entry point facilitating a harmonized assessment across multiple member states. The timing of implementation of the new Clinical Trials Regulation will be dependent on the development and launch of a fully functional clinical trials portal and database, which would be confirmed by an independent audit. The new legislation will come into effect six months after the European Commission publishes a confirmation of full functionality of the clinical trials information system. The website indicated that the audit was expected to commence in December 2020.

Parties conducting certain clinical trials in the European Union must, as in the United States, post clinical trial information at the EudraCT website: https://eudract.ema.europa.eu.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines ("**PRIME**") scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products that may offer a major therapeutic advantage over existing treatments or benefit patients without treatment options, reviewed under the centralized procedure. Products from small and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Human Medicinal Products ("**CHMP**") or Committee for Advanced Therapies are appointed early in the PRIME scheme. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product in the European Union, an applicant must submit a marketing authorization ("**MA**") either through the centralized procedure administered by the EMA or one of the procedures administered by the competent authorities in European Union Member States. A marketing authorization may be granted only to an applicant established in the European Union. An MA may be granted in one of three ways:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use ("**CHMP**") of the EMA, and which is valid throughout the entire territory of the European Economic Area ("**EEA**"). Pursuant to Regulation (EC) No. 726/2004, the Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases. The Centralized Procedure is also optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union.

Under the centralized procedure, the CHMP established at the EMA is responsible for conducting an initial scientific assessment of a product. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MA is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that it is no longer appropriate to conduct an accelerated assessment.

- Under the Decentralized Procedure("**DCP**") MAs are available for medicinal products not falling within the mandatory scope of the Centralized Procedure. An identical dossier, including a draft summary of the product characteristics ("**SmPC**") and draft labeling and package leaflet, is submitted to the competent authorities of each of the member states of the EEA in which the MA is sought, one of which is selected by the applicant as the reference member state ("**RMS**"). The competent authority of the RMS prepares a draft assessment report, including any proposed revisions to the draft SmPC, draft labeling and package leaflet, which is sent to the other member states (referred to as the concerned member states ("**CMS**")) for their approval. If the CMSs raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or package leaflet proposed by the RMS, the product is subsequently granted a national MA in each of the involved member states (i.e., in the RMS and the selected CMS).

- National Procedure MAs, which are issued by a single competent authority of the member states of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National Procedure MA can also be recognized in other member states through the Mutual Recognition Procedure to enable recognition of the national MA in other selected EEA member states. Similarly to the DCP, if the CMSs raise no objections, based on a potential serious risk to public health, to the assessment of the RMS, the product is subsequently granted a national MA in each of the involved CMSs.

Manufacturers must demonstrate the quality, safety, and efficacy of their products to the EMA, which provides an opinion regarding the MA. The European Commission grants or refuses the MA in light of the opinion delivered by the EMA.

Orphan Drug Designation and Exclusivity

In the European Union, Orphan Drug designation was introduced to stimulate the development of orphan drugs in the European Union. In the European Union, the Committee for Orphan Medicinal Products is responsible for the scientific examination of applications leading to the designation of an

Orphan Medicinal Product. Such designation is reassessed at the time a marketing authorization is granted. In the European Union, a medicinal product may be designated as an Orphan Medicinal Product if its sponsor can establish that the prevalence of the condition in the European Union is not more than five in 10,000 or that it is unlikely that marketing the medicinal product in the European Union, without incentives, would generate sufficient return to justify the necessary investment needed for its development. In the European Union there is a further requirement that the drug is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition for which there exists no satisfactory method of diagnosis, prevention or treatment or, if such method exists, that the drug will be of significant benefit as compared to existing treatments to those affected by the condition. An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized European Union marketing authorization. If a product is granted Orphan Medical Product status, it is eligible for a 10-year exclusive marketing period in the European Union. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for the same therapeutic indication in respect of a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The period can be reduced to six years in the European Union if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. In the European Union, orphan exclusivity may also be extended for an additional two years (for a maximum of 12 years of orphan exclusivity), if the product is approved on the basis of a dossier that includes pediatric clinical trial data generated in accordance with an approved pediatric investigation plan.

Regulatory Data Protection in the European Union

In the European Union, new drugs approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic MA can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period may be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new drug so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained a marketing authorization based on an MA which does not reference the existing MA holder's data.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Patent Term Extensions in the European Union and Other Jurisdictions

The European Union also provides for patent term extension through SPCs. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of overall marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

Regulatory Requirements after Marketing Authorization

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include compliance with the European Union's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's good manufacturing practice requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities, and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. Finally, the marketing and promotion of authorized products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union under Directive 2001/83EC, as amended.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020, which is extendable up to two years. During the Brexit transitional period, the United Kingdom will continue to be subject to the laws and obligations applicable to all European Union member states. However, future regulations that will apply in the United Kingdom following the transitional period (including financial laws and regulations, tax and free trade agreements, intellectual property rights, data protection laws, supply chain logistics, environmental, health and safety laws and regulations, medicine licensing and regulations, immigration laws and employment laws), have yet to be addressed. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic disruption.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may result in a restriction or delay in our ability to seek regulatory approval in the United Kingdom for our product candidate, which could significantly and materially harm our business.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. During the period of "transition" (i.e., until December 31, 2020), EU law will continue to apply in the United Kingdom, including the GDPR, after which the GDPR will be converted into UK law. Beginning in 2021, the UK will be a "third country" under the GDPR. We may, however, incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

Other Healthcare Laws

Outside the United States and the EEA, our ability to market a product is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing market authorization, pricing and reimbursement vary widely from country to country. In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our product candidate. Whether or not we obtain marketing approval for a drug in the United States or EEA, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain approval in the United States or EEA. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

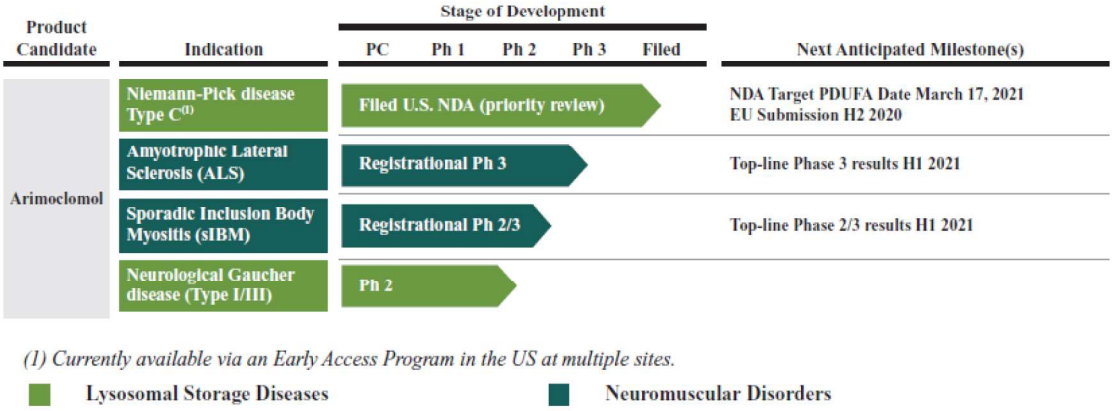
6 BUSINESS

Overview

We are a late-stage biopharmaceutical company harnessing the amplification of Heat Shock Proteins ("**HSPs**") in order to develop and commercialize novel therapeutics for the treatment of neurodegenerative orphan diseases. In September 2020, the U.S. Food and Drug Administration ("**FDA**") accepted our a new drug application ("**NDA**"), for our product candidate, arimoclomol, for Niemann-Pick disease Type C ("**NPC**"), with priority review. In the letter accepting the NDA, the FDA set a target action date of March 17, 2021 under the Prescription Drug User Fee Act ("**PDUFA**"), for completion of its review of our NDA. The FDA has also notified us that it has identified potential review issues that we may need to address before obtaining FDA approval, as discussed in *"—Recent Developments*." We also intend to submit a marketing authorization application ("**MAA**"), to the European Medicines Agency ("**EMA**"), in the second half of 2020. Arimoclomol is also in registrational clinical trials for the treatment of Amyotrophic Lateral Sclerosis ("**ALS**"), and Sporadic Inclusion Body Myositis ("**sIBM**"), and we intend to advance into pivotal-stage clinical development in neurological Gaucher disease. Arimoclomol is an orally- or naso/gastrically-administered small molecule that crosses the blood-brain barrier and is designed to selectively amplify the natural role of endogenous HSPs, which protect against cellular toxicity caused by protein misfolding, aggregation and lysosomal dysfunction. In our Phase 2/3 clinical trial of arimoclomol in NPC, we have observed evidence of slowing of disease progression, supporting our registration effort in the United States and Europe. Results observed in the Phase 2 clinical trials for ALS, sIBM and Gaucher disease demonstrated the potential of arimoclomol to slow the progression of such diseases, forming the basis of our ongoing registrational clinical trials in ALS and sIBM, as well as our intention to advance into pivotal-stage clinical development in neurological Gaucher disease. We also believe that arimoclomol has been well tolerated in clinical trials including more than 500 human subjects for various indications. We are committed to leveraging our deep scientific expertise in the field of HSPs and lysosomal biology, the unique benefits of arimoclomol and our commercial experience and infrastructure to dramatically transform the lives of underserved individuals living with devastating neurodegenerative orphan diseases.

Arimoclomol functions by upregulating HSPs, which are molecular chaperones that are critical in the natural cellular response to stress, protein misfolding, aggregation and lysosomal dysfunction. We believe that arimoclomol is the first clinical product candidate to harness this mechanism of action for the treatment of lysosomal storage diseases ("**LSDs**") and neuromuscular diseases affecting the central nervous system("**CNS**") and muscle. Arimoclomol is currently available to NPC patients in the United States through our early access program ("**EAP**"), with nine patients on treatment as of September 18, 2020 and we have established and may in the future establish early access programs or compassionate use programs for same and other indications and in other locations. We are conducting clinical trials for arimoclomol in three additional indications, including a Phase 3 registrational clinical trial in ALS, for which we expect top-line results in the first half of 2021, a Phase 2/3 registrational clinical trial in sIBM, for which we expect top-line results in the first half of 2021, and a Phase 2 clinical trial in Gaucher disease, for which we announced top-line results in June 2020. We believe that each of these indications has a significant unmet medical need today, given the limited availability of effective therapies for NPC, ALS and neurological Gaucher disease and the lack of any approved drugs for sIBM. Both the FDA and the EMA have granted arimoclomol orphan drug designation for NPC, ALS and sIBM. The FDA has also granted arimoclomol fast track designation in NPC, ALS and sIBM, has designated arimoclomol as a breakthrough therapy in NPC and has granted arimoclomol a rare pediatric disease designation in NPC, potentially entitling us to a priority review voucher if arimoclomol is approved in NPC.

The following table summarizes the indications we are pursuing with arimoclomol, for which we have retained our full, worldwide, exclusive marketing and distribution rights.



Our Product Candidate – Arimoclomol

Our most advanced program is for the treatment of NPC, a LSD. NPC is a rare, genetic and progressive disease that impairs the ability of the body to recycle cholesterol and other types of lipids, resulting in damage to the body's tissues, including the brain. Symptoms of NPC usually occur during mid to late childhood, and include difficulties in swallowing, loss of speech and cognition, motor coordination and ambulation. In more aggressive forms, NPC is frequently fatal by the time patients reach their twenties. We estimate the incidence of NPC to be one in 100,000 live births. Based on these incidence rates, the number of NPC patients in the United States and in Europe is estimated to be approximately 1,800 individuals. Of these, we estimate that approximately 1,100 individuals have been diagnosed, of which approximately 300 are in the United States and approximately 800 are in Europe. However, diagnostic challenges may affect the number of potential patients, and we believe that the availability of treatment options could increase awareness of the disease and assist in identifying more cases. We believe that there is a significant unmet need for new treatments for NPC due to the side effects, limited availability and efficacy of the existing treatment options. In our registrational Phase 2/3 clinical trial for NPC, arimoclomol was observed to be well-tolerated and demonstrated a benefit over placebo and routine clinical care using the 5-domain NPC clinical severity score ("**NPCCSS**") the key primary endpoint, corresponding to a 63% relative reduction in disease progression (p=0.0537). The 5-domain NPCCSS is a disease-specific and validated measure of disease progression refined by us with disease opinion leaders, consisting of the five clinically most relevant domains to patients with NPC, caregivers and physicians. Arimoclomol demonstrated a statistically significant benefit over placebo using the 5-domain NPCCSS score when excluding three patients with double functional null mutations, corresponding to a 77% relative reduction in disease progression (p=0.0242); in patients aged ≥ 4 years, corresponding to an 80% relative reduction in disease progression (p=0.0189); and in patients also

receiving miglustat (corresponding to a 101% reduction in disease progression over routine care including miglustat (p=0.0074)). We are also developing arimoclomol for the treatment of ALS. ALS, commonly referred to as Lou Gehrig's disease, is a rapidly progressing neurological disease with the onset of symptoms typically occurring between 40 to 70 years of age, with patient mortality occurring in most patients within three to five years of disease onset. ALS attacks neurons responsible for controlling voluntary muscles, resulting in muscle weakness in limbs, and impacts speaking, chewing, swallowing and breathing, leading to progressive disability and eventually death, typically from respiratory failure and aspiration pneumonia. In addition, up to 50% of ALS patients develop cognitive impairment associated with frontotemporal dementia. According to the ALS Association, the incidence of ALS in the United States is estimated to be two per 100,000 within the general population and prevalence is estimated to be between five and seven cases within a population of 100,000, equating to approximately 20,000 patients in the United States and 30,000 patients in Europe. 5,000 new ALS patients are diagnosed each year in the United States. ALS affects men to women at a ratio of 3:2. There are currently a limited number of treatments available for ALS, with disease management predominantly focused on treatment of symptoms and supportive care. Riluzole, developed by Sanofi, was the first drug to be approved by the FDA for the treatment of ALS more than 20 years ago, but has been shown to prolong survival by just two to three months. In May 2017, the FDA approved Edaravone, which has been shown to slow functional decline in ALS patients, but is administered through a burdensome intravenous regimen. Non-invasive ventilation has also been shown to support against respiratory failure, improve quality of life, and potentially increase survival by around seven months. We believe there is a significant unmet need for new effective treatments for patients suffering from ALS in order to improve the clinical course of their disease and extend their survival. In a Phase 2 clinical trial of arimoclomol for the treatment of ALS and in a Phase 2/3 clinical trial for the treatment of superoxide dismutase 1 ("**SOD1**"), ALS, arimoclomol was observed to be well tolerated, and showed positive trends across clinical endpoints, including a 30% and 28% slowing of disease progression, respectively, as measured by the ALS Functional Rating Scale ("**ALSFRS-R**"), from baseline, when compared to a historical control group. The ALSFRS-R is an instrument for evaluating the functional status of patients with ALS, including respiratory function. Based on these results, we are conducting a Phase 3 registrational trial of arimoclomol for ALS, for which we expect to report top-line results in the first half of 2021.

In addition, we are developing arimoclomol for the treatment of sIBM. sIBM is an acquired, rare and slowly progressive muscle disorder. The onset of symptoms occurs on average after age 50, with up to three of every four cases occurring in men. Many patients with sIBM will suffer loss of fine motor skills such as writing, grooming and the ability to eat unaided, and it is associated with significant morbidity including a propensity to fall, difficulty swallowing and severe disability. Patients with sIBM may also require use of a walking stick as early as five years after symptom onset and become wheelchair dependent and severely disabled within 10 to 15 years. In a recent systematic review, the prevalence of sIBM has been estimated to be 4.6 per 100,000 people, equating to an estimated 40,000 individuals living with sIBM in the United States and Europe combined. sIBM is distinct in its presentation, most commonly affecting muscles of the thigh and forearm, and immunosuppressive treatments have not been shown to be effective, despite evidence of inflammatory pathology. There is a prominent degenerative element to the disease and muscle biopsies reveal the presence of myotoxic protein aggregates (inclusions). There are currently no effective or approved treatments for sIBM. In a Phase 2 clinical trial of arimoclomol for the treatment of sIBM, arimoclomol was observed to be well tolerated and demonstrated a slowing in the rate of disease progression as measured on the Inclusion Body Myositis functional rating scale ("**IBMFRS**") with a 60% reduction in progression at four months when compared to placebo. This was shown to persist for several months beyond the 4 month treatment period (72.8% reduction at 8-months, p=0.055). Typically, sIBM patients progress by losing up to 2.0 to 2.5 points on the IBMFRS score per eight months. Based on these results, we are conducting a Phase 2/3 registrational trial in sIBM, for which we expect top-line results in the first half of 2021.

We are also developing arimoclomol for the treatment of neurological manifestations of Gaucher disease. Gaucher disease is a rare, inherited metabolic disorder causing certain sugar containing fats to abnormally accumulate in the lysosomes of cells, especially within cells of the blood system and nerve cells, thereby affecting organs such as the brain, bone marrow, spleen and liver. The typical systemic symptoms of Gaucher disease, which can appear at any age, include an abnormally enlarged liver and/or spleen and low levels of circulating red blood cells and platelets. These systemic symptoms are generally treated by existing enzyme replacement therapy ("**ERT**") and substrate reduction therapy, ("**SRT**"). The neurological symptoms, although heterogeneous, may include muscle rigidity, loss of movement, seizures, cognitive impairment and vision problems and are insufficiently treated by these therapies, given their limited ability to cross the blood-brain barrier. Gaucher disease is the most common LSD,

with an estimated incidence of one in 50,000, and affects up to an estimated 15,000 individuals in the United States and Europe combined. Gaucher disease has three subtypes, which are, in part, distinguished by the presence or absence of neurological symptoms. Type 1 Gaucher disease is the most common form of the disease, can occur at any age and initially do not present with neurological symptoms. It is now estimated that up to 30% of patients diagnosed with Gaucher Type 1 develop neurological symptoms later in life, including 5% to 7% showing Parkinsonism symptoms. We believe this is due to individuals with Gaucher Type 1 living much longer as a result of availability of ERT and SRT therapy. Patients with Gaucher disease Type 2 or Type 3 present with acute neurological symptoms (Type 2) or develop chronic neurological disease (Type 3). Results of preclinical studies demonstrated an increase in HSP70, a key member of the HSP family, and refolding, maturation and correct intracellular localization of GCase, an enzyme responsible for breaking down certain lipids and for which reduced activity causes Gaucher disease. Based on these results, we initiated a randomized, double-blinded, dose-ranging Phase 2 clinical trial of arimoclomol for the treatment of neurological Gaucher disease in June 2018, which completed enrollment in August 2019. We reported top-line Phase 2 results in June 2020, in which arimoclomol was observed to be well-tolerated and demonstrated a relative reduction in serum chitotriosidase activity from baseline to six months, the primary endpoint, across all dosages compared to placebo ranging from -12% to -29%, although statistical significance was not achieved ($p=0.4$). However, we observed a statistically significant dose-dependent reduction in liver size ranging from -15% to -20% relative to placebo (dose trend analysis $p<0.05$). Based on these results, we intend to advance into pivotal-stage clinical development for arimoclomol in neurological Gaucher disease.

If we are successful in our initial indications of NPC, ALS, sIBM and neurological Gaucher disease, we estimate that arimoclomol could benefit up to approximately 100,000 patients in the United States and Europe. However, based on the significant data we have generated to date, we believe that arimoclomol's unique mechanism of action has potential therapeutic application across a broader range of lysosomal and neurodegenerative orphan diseases, several of which address significantly larger patient populations and target markets than those we are currently pursuing in our clinical development programs. Beyond the registrational clinical trials in ALS and sIBM, we are undertaking preclinical studies to explore and inform us on the opportunity to address additional indications, including GCase-deficient Parkinson's disease among others. If we are also successful in the GCase-deficient Parkinson's disease indication in addition to the other 4 initial indications, we estimate that arimoclomol could benefit up to approximately 500,000 patients in the United States and Europe.

We are currently building a highly specialized commercial sales organization in anticipation of a potential launch of arimoclomol for the treatment of NPC in the United States and Europe. Our plans include having a commercial infrastructure that is supported by high-touch patient support initiatives and established relationships with the concentrated number of treatment centers that address NPC in advance of a potential launch in the United States. We have had significant and positive engagement with payors, physicians and patient advocacy organizations. We have already successfully established our EAP for NPC patients, which continues to provide us with significant insights to enhance our broader commercial readiness plans. In NPC, there are approximately 25 to 50 highly specialized centers in the United States and Europe that cover the vast majority of patients, and we believe this market can be effectively addressed with our own targeted commercial field force of approximately 20 to 30 representatives. If arimoclomol is approved for additional diseases, we plan to leverage our core orphan disease commercial infrastructure and expertise to efficiently address the relevant patient populations. We are also actively engaging with key ALS, sIBM and Gaucher disease patient advocacy groups.

We were founded in 2009 based on a scientific discovery published in *Nature* on the function of HSPs co-authored by Dr. Thomas Kirkegaard Jensen, who serves as our Chief Scientific Officer. We are led by our Chief Executive Officer, Kim Stratton, our Chief Financial Officer, Anders Vadsholt, our Chief Medical Officer, Dr. Thomas Blaettler, and Dr. Jensen. Each member of our management team has extensive experience in the global biopharmaceutical industry. Our management team's experience in clinical drug development, manufacture and commercialization, particularly in the rare disease drug space, provide us with valuable insights that we believe will help us maximize the value of arimoclomol and our foundational expertise in HSPs. Our management team has a highly successful track record of launching and commercializing products in more than fifteen rare diseases across the United States and international markets at leading global pharmaceutical firms such as Shire Pharmaceuticals, Novartis, Roche and Bristol-Myers Squibb. We are supported by leading global life sciences investors, including Consonance Capital, Coöperative Aescap Ventures, Sunstone Life Science Ventures and, through a joint investment vehicle Orpha Pooling N.V., Life Science Partners and the ALS Investment Fund. Our board of directors also includes industry experts with experience at companies focused on rare diseases,

including Genzyme and Swedish Orphan Biovitrum. We completed the initial public offering of our ordinary shares in Denmark in November 2017. Our ordinary shares currently trade on Nasdaq Copenhagen under the symbol "ORPHA." Our initial public offering in Denmark raised gross proceeds of DKK 600 million ($90 million). In February 2020, we also raised gross proceeds of DKK 745 million ($112 million) in a directed issue and private placement in Europe and the United States. Our Competitive StrengthsWe believe we have the potential to transform the lives of underserved individuals living with devastating neurodegenerative orphan diseases. Our key competitive strengths include:

- **Deep scientific expertise and discovery capabilities in the field of Heat Shock Proteins and lysosomal biology:** Orphazyme was founded on pioneering discoveries made in the biology of HSPs, which are the body's natural response to cellular stress, and their role in lysosomal function. We are the first to successfully apply this foundational expertise to pursue registrational development of novel therapeutic candidates for the treatment of lysosomal and neurodegenerative orphan diseases.

- **Our product candidate, arimoclomol, which has exhibited compelling results in clinical trials of neurodegenerative orphan diseases**: In clinical trials to date, arimoclomol has exhibited compelling results on slowing of disease progression in NPC and results observed in our clinical trials in ALS, sIBM and Gaucher disease also demonstrated the potential of arimoclomol to slow the progression of such diseases. We also believe that arimoclomol has been well tolerated in clinical trials including more than 500 human subjects for various indications.

- **Potential near-term approval of arimoclomol in our first targeted ultra-orphan indication of NPC:** If approved, arimoclomol could be the first product approved by the FDA for the treatment of NPC. In September 2020, the FDA accepted our NDA for arimoclomol for the treatment of NPC with priority review and we plan to submit an MAA in Europe in the second half of 2020.

- **Arimoclomol's pipeline-in-a-product potential, with registrational clinical trials ongoing in two additional orphan indications and our intention to advance into pivotal-stage clinical development in a third:** We believe arimoclomol's novel mechanism of action has potential in a range of increasingly more widespread orphan diseases. Registrational clinical trials are ongoing in ALS and sIBM and we reported positive data from a Phase 2 clinical trial in Gaucher disease in June 2020, which may support the ability of arimoclomol to address a larger group of LSDs. If arimoclomol is approved for the treatment of NPC, ALS, sIBM and neurological Gaucher disease, we estimate the total addressable patient pool would be approximately 100,000 patients in the United States and Europe.

- **A highly experienced, rare disease focused management team:** Our organization is built around a scientific, development, medical and commercial team with extensive expertise in the pharmaceutical and biotechnology industry and rare diseases. This includes experience in patient advocacy, education, diagnosis, EAPs, engaging with specialty pharmacies and the supply chain to support patient access and adherence.

- **Multiple regulatory designations that support the importance of arimoclomol and potentially provide accelerated approval pathways:** Arimoclomol has been granted orphan drug designation in the United States and Europe for NPC, ALS and sIBM. Arimoclomol has also been granted fast track designation by FDA for NPC, ALS and sIBM and has received breakthrough therapy designation for NPC. Furthermore, arimoclomol has received rare pediatric disease designation from FDA, potentially entitling the sponsor to a priority review voucher should the product be approved in NPC.

- **Exclusive worldwide marketing and distribution rights, supported by intellectual property protections and additional regulatory exclusivity protections:** We have retained our exclusive worldwide marketing and distribution rights for arimoclomol. Furthermore, our patent portfolio provides us with protection for the treatment of NPC and Gaucher disease until 2029, with possible extensions to 2032 in the

United States and 2034 in the European Union based on method of use patents, and for the treatment of ALS until 2024, as well as orphan drug exclusivity, if approved, for seven years in the United States and ten years in the European Union for NPC, ALS and sIBM.

Our Strategy

Our goal is to leverage our deep scientific expertise in the field of HSPs and lysosomal biology, the unique benefits of arimoclomol and our commercial experience and infrastructure to dramatically transform the lives of underserved individuals living with devastating neurodegenerative orphan diseases. The key pillars of our business strategy include:

Secure regulatory approvals in the United States and European Union for arimoclomol in NPC

We believe arimoclomol has the potential to become the first FDA-approved therapy for the treatment of NPC. Based on the data observed in the registrational Phase 2/3 clinical trial, the FDA accepted our NDA for arimoclomol in NPC in September 2020 with priority review, and we expect to submit an MAA in Europe in the second half of 2020. Arimoclomol is available in the United States through our EAP, which provides access to arimoclomol to NPC patients before the drug is approved by the FDA and we are exploring similar initiatives for early access in Europe.

Maximize the commercial potential of arimoclomol in NPC and beyond

We are building an efficient, highly specialized commercial organization in anticipation of a potential launch of arimoclomol for the treatment of NPC in the United States and Europe. Our management's expertise in rare disease drug commercialization has informed our commercial readiness plans in the United States and Europe, where we intend to deploy a targeted field force of 20 to 30 representatives, alongside various high-touch patient support initiatives and make use of our already established relationships with the 25 to 50 specialized treatment centers that address NPC. We also plan to build on the significant engagement we have fostered with payors, physicians and the patient advocacy community. We are harnessing many of these efforts in our EAP for NPC patients in the United States while also using this program to further inform our commercial strategy. If arimoclomol is approved for additional diseases, we plan to leverage our rare disease commercial infrastructure and expertise to efficiently address those patient populations. We may also opportunistically seek strategic collaborations in disease areas or geographies that we believe could benefit from the resources of either larger biopharmaceutical companies or those specialized in a particular area of relevance.

Complete registrational studies and obtain regulatory approval of arimoclomol for ALS and sIBM and advance into pivotal-stage clinical development in Gaucher disease

Based on the compelling results from our Phase 2/3 clinical trial in NPC and investigator and CytRx Corporation ("**CytRx**"), sponsored clinical trials, we believe there is significant potential for arimoclomol in the treatment of other protein misfolding and aggregation disorders. Arimoclomol has demonstrated clinical proof-of-concept in ALS and sIBM, with Phase 2 clinical trials in both indications having shown trends in pre-defined efficacy endpoints. We are currently conducting registrational clinical trials of arimoclomol for ALS and sIBM, and we expect top-line results in both indications in the first half of 2021. We intend to advance arimoclomol into pivotal-stage clinical development in neurological Gaucher disease following compelling results reported in our Phase 2 clinical trial in June 2020, in which we achieved clinical proof-of-concept.

Actively expand and advance our pipeline, including developing arimoclomol for additional indications and discovering additional NMEs

Based on our expertise in HSPs' mechanism and lysosomal biology, we believe arimoclomol has the potential to be an effective treatment for additional protein misfolding and aggregation diseases, as well as diseases characterized by lysosomal dysfunction. Furthermore, we are actively evaluating opportunities in disorders such as GCase-deficient Parkinson's disease and other LSDs. We are also actively developing a proprietary suite of next generation HSP amplifiers and lysosome biology-targeting compounds and intend to select protein misfolding diseases for these new molecular entities ("**NMEs**"), based on genetic and mechanistic insights. For our new indications and molecule

development, we plan to continue to closely collaborate with academic experts and patient organizations, and we intend to leverage our learnings to inform a selection of additional indications involving related biological mechanisms.

Heat Shock Proteins and the Heat Shock Response

We are pioneering the use of a natural cellular defense system, the heat shock response, or Heat Shock Protein response, for the treatment of neurodegenerative orphan diseases, based around our investigational drug arimoclomol.

HSPs are a family of molecular chaperone proteins present in all cells throughout the body, characterized by their cell protective properties and whose levels are amplified by cells in response to exposure to a wide variety of stressful conditions, including thermal, oxidative, mechanical, chemical and pathophysiological stresses. This amplification of HSP production in times of stress is described as the Heat Shock Response. The HSPs form a natural cellular defense system that helps other proteins work correctly and guards against the toxicity arising from misfolded proteins, protein aggregation and dysfunctional cellular recycling systems (lysosomes), essentially acting as cellular lifeguards.

In particular, HSPs promote the survival of stressed cells by re-folding misfolded proteins into their correct conformation, or by directing terminally misfolded proteins to be broken down. They also protect cells by stabilizing lysosomes and thereby allow cells to clear away waste, prevent lysosome-associated cell death and return to their healthy status.

There are several different types of HSPs which work in conjunction. A key member of the HSP family is HSP70, which has been shown to protect against the formation of protein aggregates that are the defining characteristic of a number of neurodegenerative diseases including ALS and sIBM. HSP70 has also been identified to be a co-factor for lysosomal sphingolipid breakdown: a necessary step in the metabolism of stored lipids, which otherwise cause toxicity if accumulated in the lysosome and whose deficiencies give rise to a group of lysosomal storage disorders known as the sphingolipidoses.

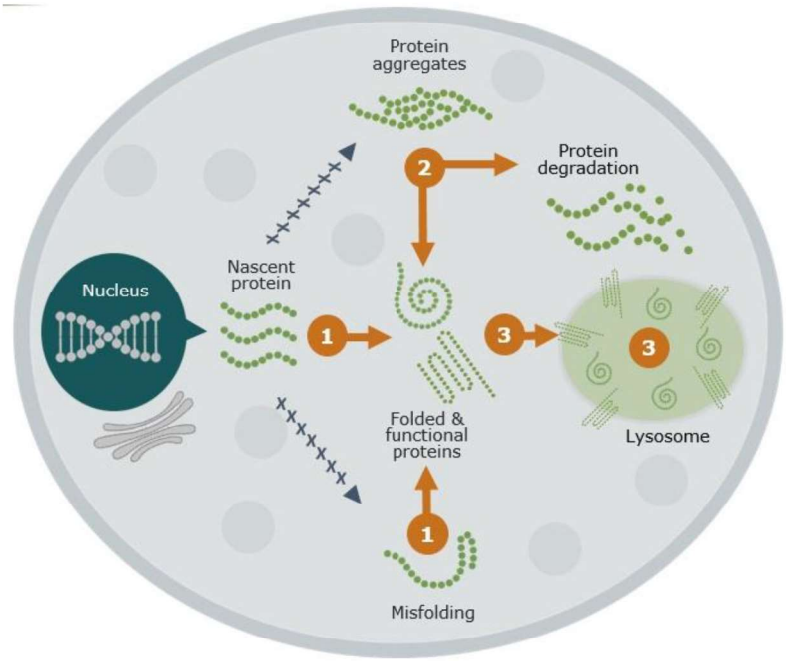
When protein misfolding occurs gradually as a consequence of an inherited mutation or as part of a disease progression, this can lead to a slow but steady aggregation of misfolded proteins occurring under the threshold for the cells to activate the production of HSPs. This sub-threshold accumulation and aggregation can lead to cellular dysfunction and eventually, in time, cell death, leading to loss of brain, nerve, muscle and other affected cells. These events can contribute to a wide range of diseases, including ALS, sIBM, GCase-deficient Parkinson's disease and others.

Protein misfolding, aggregation and lysosomal dysfunction

If a protein does not fold properly or if it gets mislocalized in the wrong part of the cell, it can clump together with other proteins, creating accumulations or aggregates. Both the mislocalization and formation of aggregates can cause cell stress and toxicity, which are major components of the pathology in many neurodegenerative and other progressive diseases. HSP70 and other HSPs chaperone nascent proteins and misfolded proteins, ensuring their correct folding, function and cellular localization. HSP70 is also involved in dissolving aggregates and is part of a system that guides unsalvageable proteins to be degraded by the cells' recycling systems.

Lysosomes are essential compartments of cells and contain enzymes which act like molecular scissors to digest cellular waste products for recycling. If, as a result of a genetic mutation, one of these digestive enzymes does not function properly, the waste product will accumulate inside the lysosome and eventually become toxic to cells. The digestive enzymes are proteins, and their dysfunction can be the result of a failure to fold into the correct shape (misfolding) or because they are incomplete. In some cases, cells do not produce a specific digestive enzyme at all. The extent of the digestive enzyme dysfunction depends on the genetic mutations. These mutations are inherited from both parents who are carriers of the mutation. HSP70 promote lysosomal function by facilitating the function of these lysosomal digestive enzymes both through its effect on the enzymes' folding, as well as acting directly in the lysosomes, thereby increasing lipid metabolism and removal, which leads to stabilization of lysosomal membranes and prevention of cell death.

As exemplified in the figure below, the way HSPs target protein misfolding, aggregation and lysosomal function can be summarized as follows:



1. HSPs chaperone nascent proteins and misfolded proteins, ensuring their correct folding and function;

2. HSPs can dissolve protein aggregates, potentially restore folded and functional proteins, or ensure their removal by facilitating degradation; and

3. HSPs promote lysosomal function by chaperoning lysosomal proteins to the lysosome, thereby increasing lipid metabolism and removal. In addition, intra-lysosomal HSP70 also enhances lipid metabolism thereby stabilizing lysosomal membranes and preventing cell death.

Our research focuses on the beneficial effects of HSP70. In NPC and Gaucher disease, as well as several other LSDs, we aim to target both protein misfolding and lysosomal function. In ALS and sIBM our goal is to target protein mislocalization, misfolding and aggregation. It has also been our ambition since our foundation that this beneficial impact on lysosomal biology might be translated to a treatment that could benefit many LSDs. We furthermore use HSP70 as a key parameter to measure activity of our drug candidates in both preclinical studies and clinical trials.

Our Product Candidate – Arimoclomol

Summary of Arimoclomol

Arimoclomol is an orally or naso/gastrically-administered small molecule that crosses the blood-brain-barrier and is designed to selectively amplify the natural role of endogenous HSPs, which protect against cellular toxicity caused by protein misfolding, aggregation and lysosomal dysfunction. In our Phase 2/3 clinical trial in NPC, we have observed evidence of slowing of disease progression, which supports our registration effort in the United States and Europe. Results observed in the Phase 2 clinical trials for ALS, sIBM and Gaucher disease demonstrated the potential of arimoclomol to slow the progression of such diseases, forming the basis of our ongoing registrational clinical trials in ALS and sIBM, as well as our intention to advance into pivotal-stage clinical development in neurological Gaucher disease. We also believe that arimoclomol has been well tolerated in clinical trials including more than 500 human subjects for various indications. We are committed to leveraging our deep scientific expertise in the field of HSPs and lysosomal biology, the unique benefits of arimoclomol and our commercial expertise and infrastructure to dramatically transform the lives of underserved individuals living with devastating neurodegenerative orphan diseases.

Arimoclomol functions by upregulating HSPs, which are molecular chaperones that are critical in the natural cellular response to stress, protein misfolding, aggregation and lysosomal dysfunction. We believe that arimoclomol is the first clinical product candidate to harness this mechanism of action targeting lysosomal storage diseases and neuromuscular diseases affecting the CNS and muscle. The FDA accepted our NDA for arimoclimol in September 2020 for the treatment of NPC with priority review. The FDA has set a target action date of March 17, 2021 under the PDUFA for completion of its review of our NDA. We also intend to submit an MAA to the EMA in the second half of 2020. Arimoclomol is already available to NPC patients in the United States through our EAP, with nine patients on treatment as of September 18, 2020 and we have established early access programs or compassionate use programs for same and other indications and in other locations. We are also conducting additional clinical trials for arimoclomol including a Phase 3 registrational clinical trial for ALS, for which we expect top-line results in the first half of 2021, a Phase 2/3 registrational clinical trial in sIBM, for which we expect top-line results in the first half of 2021, and a Phase 2 clinical trial in Gaucher disease, for which we announced top-line results in June 2020. We believe that each of these indications has a significant unmet medical need today, given the limited availability of effective therapies for NPC, ALS and neurological Gaucher disease and the lack of any approved drugs for sIBM. Both the FDA and the EMA have granted arimoclomol orphan drug designation for NPC, ALS and sIBM. The FDA has also granted arimoclomol fast track designation for NPC, ALS and sIBM, has designated arimoclomol as a breakthrough therapy for NPC and has granted arimoclomol a rare pediatric disease designation in NPC, potentially entitling us to a priority review voucher if arimoclomol is approved in NPC.

Arimoclomol Mechanism of Action

The production of HSPs is regulated by a transcription factor, heat shock factor 1 ("**HSF1**"). A transcription factor is a protein that regulates production of other proteins in the cell. Activation of HSF1 starts the production of the HSP70 chaperone along with other HSP-chaperones. Under normal cellular conditions, HSF1 is inactive. However, the transcription factor can be activated by an initial cellular stress, such as protein misfolding, and become fully activated under a sustained stress signal.

Arimoclomol has been shown to amplify and prolong the activated, HSP-producing state of HSF1. This is believed to lead to an increase in the production of cell protective HSPs, but only in physiologically stressed cells.

This increase in the production of naturally occurring HSPs inside the cells, which reduce protein misfolding and aggregation and improve lysosomal function (the cells' recycling system), selectively targets cells that are under stress. Accordingly, it is believed that increasing production of HSPs enhances the natural biological mechanisms that reduce protein misfolding and aggregation and improve lysosomal function.

Our Program for the Treatment of Lysosomal Storage Diseases

LSDs are inherited metabolic disorders in which enzyme and protein deficiencies result in an accumulation of toxic materials in the lysosomes, the cells' recycling centers. This leads to lysosomal dysfunction and cell death and consequently organ dysfunction. The enzyme and protein deficiencies are often caused by genetic mutations leading to misfolding and degradation of the enzymes. Lysosomes are membrane-bound compartments located in the body's cells, used to break down fats, proteins and other large molecules into their respective building blocks. Loss of lysosomal enzyme activity due to enzyme misfolding and dysfunction prohibits the lysosomes from performing their normal function and results in accumulation of metabolites in the lysosomes, which is why these diseases are referred to as LSDs.

LSDs include more than 50 different diseases, that may affect different parts of the body, including the brain, CNS, spleen, liver, skeleton, skin and heart.

The two LSDs that we are initially focused on are NPC and neurological Gaucher disease.

Arimoclomol for the Treatment of Niemann-Pick Disease Type-C

Our most advanced indication with arimoclomol is for the treatment of NPC. In January 2019, we reported results from a Phase 2/3 clinical trial of arimoclomol in NPC and we reported additional results from the open-label extension clinical trial in January 2020. In the trial, including the extension, we observed that arimoclomol was well-tolerated and demonstrated evidence of slowing the disease

progression in NPC over two years. Based on the data from our Phase 2/3 clinical trial, the FDA accepted our NDA in the United States in September of 2020 with priority review and we plan to submit an MAA in the EMA in the second half of 2020 for arimoclomol as a treatment for NPC. If approved, we intend to launch arimoclomol for NPC in the United States and Europe.

Overview of NPC

NPC is a rare, genetic and progressive disease that impairs the ability of the body to recycle cholesterol and other types of lipids, resulting in damage to the body's tissues, including the brain. The symptoms upon onset of NPC vary from fatality during the first months after birth to a progressive disorder not diagnosed until adulthood. The disease affects the brain as well as various internal organs. Symptoms of NPC usually occur during mid to late childhood, including difficulties in swallowing, loss of speech and cognition, motor coordination and ambulation. In more aggressive forms, NPC is frequently fatal by the time patients reach their twenties. During this period, affected individuals may also develop impairment of intellectual ability, psychiatric disturbances and progressive loss of memory. Symptoms include enlargement of the liver and/or spleen and lung diseases, epileptic seizures and dystonia. Systemic symptoms of NPC are more common in infancy or childhood and the rate of progression is usually much slower in individuals with onset of symptoms during adulthood. In more aggressive forms, NPC is frequently fatal by the time patients reach their twenties. However, approximately half of NPC patients are adults with a less aggressive form of the disease that progresses more slowly, and is frequently initially misdiagnosed, as these patients are more likely to present with dementia, psychiatric symptoms and other symptoms.

NPC is caused by mutations in one of two genes, NPC1 or NPC2, which prevent cells from properly processing waste lipids and lead to an accumulation of lipids in the lysosomes, resulting in cell toxicity and loss of cell function. In the CNS, it results in progressive motor and brain impairment. Approximately 95% of people with the disease have mutations in NPC1. Genetic diseases are determined by the combination of the pair of genes for a particular trait received from the father and the mother. NPC is an autosomal recessive disorder, *i.e.* two copies of an abnormal gene must be present in order for the disease or trait to develop. Although uncertainty exists about the function of the NPC1 and NPC2 protein products, they are known to be involved in the trafficking (transportation) of large molecules inside human cells. Hence, a mutated gene may lead to insufficient protein production and, as a consequence, an abnormal accumulation, *e.g.* cholesterol and/or other fatty materials and sugars in the organs most commonly affected, such as the liver, spleen and brain.

Many cases of NPC go misdiagnosed or undiagnosed. NPC is often initially misdiagnosed as a learning disability, mild retardation, and delayed development of fine motor skills and it is common to spend several years seeking a diagnosis before NPC is identified. The diagnosis of NPC is made upon the characteristic symptoms, as described above, obtained from clinical evaluations and tests to evaluate a protein's function or the presence of accumulated byproducts (biochemical tests) and to evaluate if the NPC1 or NPC2 gene is mutated (gene sequencing). However, physicians' limited experience with NPC often results in delayed diagnosis. According to Aptis Partners, an estimated 40-70% of all NPC patients are diagnosed depending on the country. We estimate the incidence of NPC to be one in 100,000 live births. Based on these incidence rates, the number of NPC patients in the United States and in Europe is estimated to be approximately 1,800 individuals. Of these, we estimate that approximately 1,100 individuals have been diagnosed, of which approximately 300 are in the United States and approximately 800 are in Europe. However, diagnostic challenges may affect the number of potential patients, and we believe that the availability of treatment options could increase awareness of the disease and assist in identifying more cases.

Treatment Options for NPC and Unmet Need

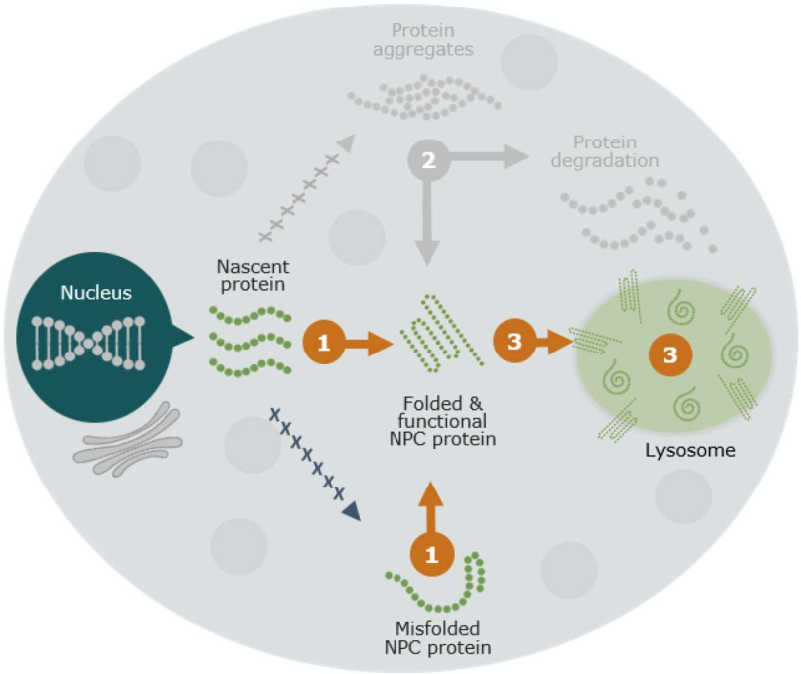
The majority of current treatment options are directed towards the specific symptoms apparent in each individual. These include, for example, referral to a therapist to optimize the swallowing function, prescription of anti-seizure medications to prevent seizures and prescription of melatonin to treat insomnia and other sleep problems caused by the disease, and may require the coordinated efforts of a team of specialists.

Zavesca (miglustat), which was originally developed by Actelion Pharmaceuticals and is now owned by Johnson & Johnson and is also now available as a generic product in several countries, is currently the only approved treatment for NPC. It is approved only in Europe, Canada, Australia, New Zealand and several countries in Asia and in South America as Zavesca and in Japan as Brazaves. In Europe, miglustat is indicated for the treatment of progressive neurological manifestations in adult patients and pediatric patients with NPC disease. The FDA declined to approve miglustat for NPC in 2010 and requested more data be provided. A range of side effects are known to be associated with miglustat, including weight loss, decreased appetite, diarrhea, nausea and thrombocytopenia. While miglustat has not been approved by the FDA for the treatment of NPC, it has been approved by the FDA for the treatment of Gaucher Type I disease. In addition, studies are currently being performed to test the safety and efficacy of other treatment options, which are discussed in more detail below under "— Competition."

Due to the limited availability, efficacy and side effects of existing treatment options, we believe that a significant unmet need for treatment of NPC continues to exist.

Our Solution – Arimoclomol for NPC

To date in our clinical trials, we have observed that arimoclomol amplifies and sustains levels of HSP70 which, as shown in the figure below:



- Prevents and corrects NPC protein misfolding, specifically improving NPC1 folding and maturation across genotypes (as indicated by (1) in the figure below); and

- Promotes lysosomal function by chaperoning NPC protein to the lysosome, thereby increasing lipid metabolism and removal. In addition, intra-lysosomal HSP70 also

enhances lipid metabolism thereby stabilizing lysosomal membranes and preventing cell death (as indicated by (3) in the figure below).

Clinical Trials of Arimoclomol for the Treatment of NPC

We initiated a Phase 2/3, randomized placebo-controlled clinical trial in July 2016, after receiving regulatory advice from the EMA and the FDA. The aim of the Phase 2/3 clinical trial was to investigate the safety and efficacy of arimoclomol. The multi-center trial completed enrollment in May 2017, with 50 patients recruited at sites across Europe and the United States, and was completed in the second half of 2018. In January 2019, we announced clinical trial results of the Phase 2/3 clinical trial of arimoclomol in NPC and, in November 2019, we received breakthrough therapy designation for arimoclomol in NPC from the FDA.

Trial design. A total of 50 patients were enrolled with patients randomized 2:1 to arimoclomol and placebo (34 patients in the arimoclomol group and 16 patients in the placebo group), respectively, and assessed for a total of 12 months of randomized treatment, followed by open-label treatment of up to 48 months. The purpose of the clinical trial was to assess the efficacy and safety of arimoclomol citrate 200 mg, weight adjusted, three times-a-day when administered in addition to patient's current prescribed routine clinical care, which included miglustat for 39 of the patients. Patients included in the trial were: aged 2–18 years, had a minimum 1 neurological symptom, had the ability to walk with assistance and, if on miglustat, were stable on treatment for at least six months. Patients who participated in other trials, had epilepsy or liver/renal insufficiency were excluded from the clinical trial.

The primary endpoint was disease severity as measured by the 5-domain NPCCSS. The 5-domain NPCCSS is a disease-specific and validated measure of disease progression refined by us with disease opinion leaders, consisting of the five clinically most relevant domains to patients with NPC, caregivers and physicians. The score ranges from 0 – 25, a higher score corresponds to more severe clinical impairment. A change of 1 point or greater on the scale has been assessed to be a clinically meaningful change based on a survey with NPC clinicians, individuals with NPC and caregivers. The overall estimated mean 5-domain NPCCSS score at baseline was 11.2 (SD=6.8). The mean baseline 5-domain NPCCSS score was higher in the group of patients randomized to arimoclomol (n=34: mean 12.1 (SD=6.9)) than the placebo group (n=16; mean 9.4 (SD=6.4)).

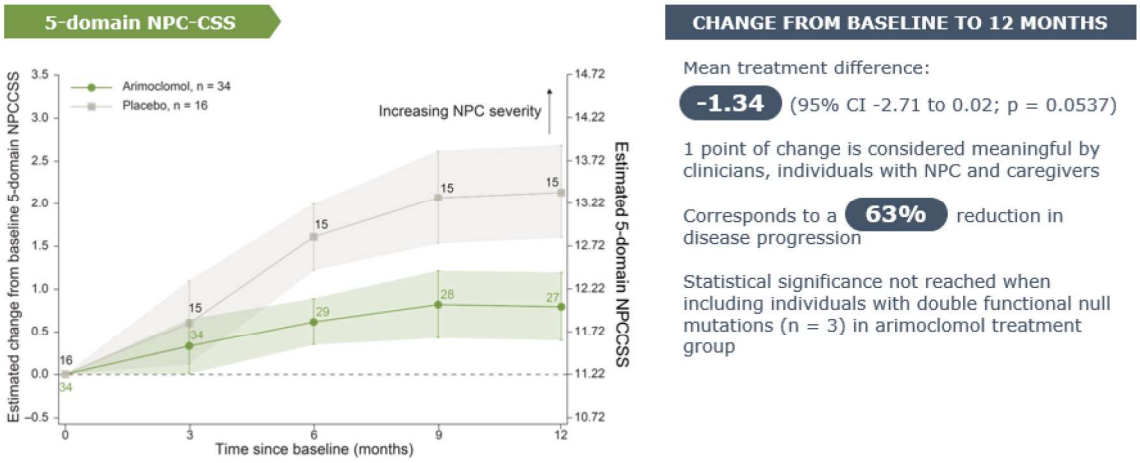
5 domain NPC-CSS

Score / Domain	0	1	2	3	4	5
1 Ambulation	Normal	Clumsy, bangs into things	Ataxic, gait wider, poor balance		Assisted ambulation – only walk short distance indoor	Wheelchair dependent
2 Fine motor skills	Normal	Slight dysfunction but able to handle cutlery	Mild dystonia Require little assistance, able to feed without help		Limited skills, unable to use pencil or eat independently	Unable to use hands. Assistance needed for all activities
3 Swallow	Normal	Cough while eating	Intermittent problems with drink or food	Constant and intermittent feeding problems	Constant feeding problems or use of tube	Dependent feeding by tube
4 Cognition	Normal	Mild learning delay, still in normal class		Moderate learning delay – need special support in school and kindergarten	Severe delay – Constant supervision, not able to learn new skills	Loss of cognitive function Unable to understand day-to-day events
5 Speech	Normal	Mild slurring / slower speech	Severe dysarthria Very slow, difficult to understand	Non-verbal communication, Uses simple signs / pictures		Absence of communication

In agreement with the FDA, treatment response defined as no change or improved on the Clinical Global Impression of Improvement scale ("**CGI-I**"), was included as a co-primary endpoint after the clinical trial had already been initiated.

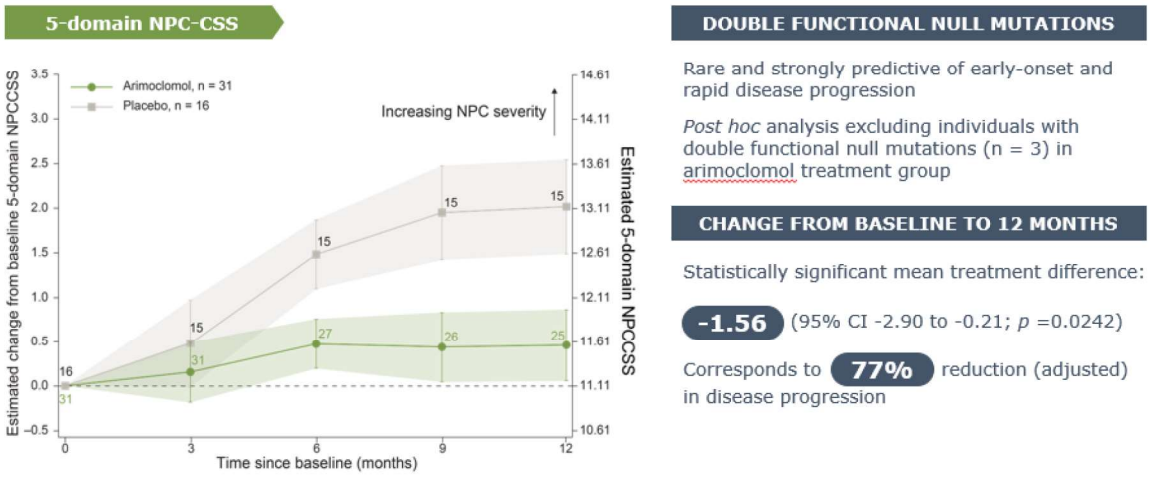
Efficacy results. In January 2019, we announced clinical trial results of our Phase 2/3 clinical trial of arimoclomol in NPC. As shown in the figure below, a benefit of arimoclomol over placebo was established on the 5-domain NPCCSS score at 12-months, the primary endpoint, corresponding to a 63% relative reduction in disease progression (mean treatment difference of -1.34, 95% CI: -2.71 to 0.02; p=0.0537). A result is considered to be statistically significant when the probability of the result occurring by random chance, rather than from the efficacy of the treatment, is sufficiently low. The conventional method for determining the statistical significance of a result is known as the "p-value," which represents the probability that random chance caused the result (e.g., a p=0.01 means that there is a 1% probability that the difference between the control group and the treatment group is purely due to random chance). Generally, a p-value less than 0.05 is considered statistically significant.

5-domain NPCCSS (P=0.0537), corresponding to a 63% relative reduction in disease progression



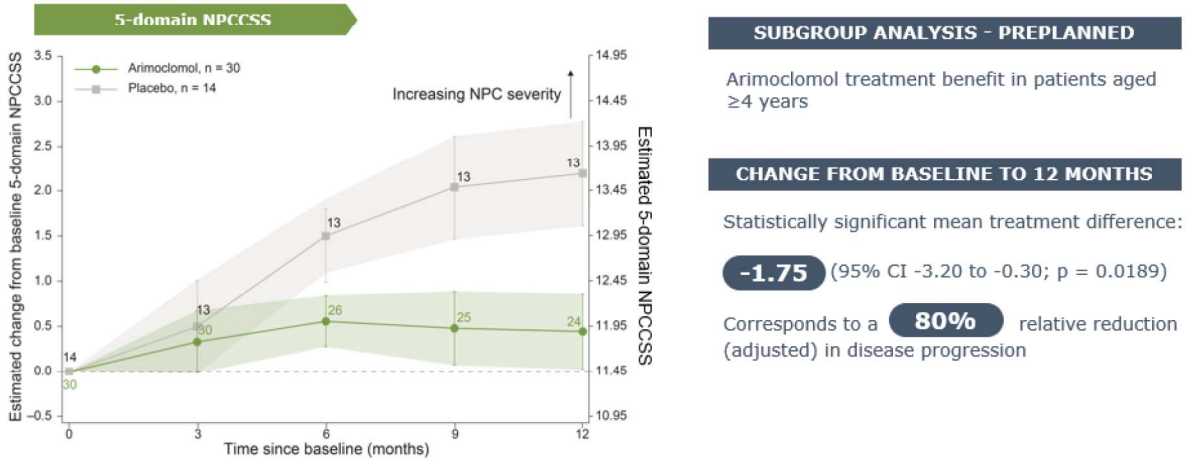
In agreement with the FDA, a post-hoc analysis was conducted to exclude three patients with double functional null mutations (do not express NPC protein and predictive of early-onset, rapid disease progression). All excluded patients had been randomized to the arimoclomol arm. After this exclusion, the results showed a statistically significant benefit of arimoclomol over placebo on the 5-domain NPCCSS score, corresponding to a 77% relative reduction in disease progression (mean treatment difference of −1.56: 95% CI −2.90 to −0.21, p=0.0242), as shown in the figure below.

5-domain NPCCSS (P=0.0242), corresponding to a 77% relative reduction in disease progression, when excluding patients with double functional null mutations

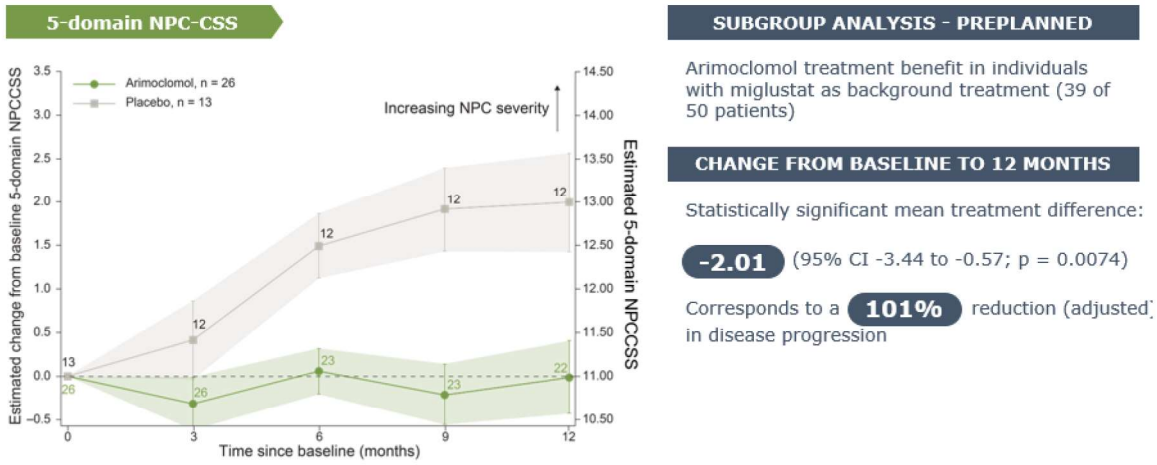


Two preplanned subgroup analyses were also conducted which also showed a statistically significant and benefit of arimoclomol over placebo on the 5-domain NPCCSS score: patients aged ≥ 4 years, corresponding to an 80% relative reduction in disease progression (mean treatment difference of −1.75: 95% CI −3.20, −0.30; p=0.0189) and in patients receiving miglustat (corresponding to a 101% reduction in disease progression over routine care + miglustat; treatment difference of −2.01, 95% CI −3.44, −0.57; p=0.0074).

5-domain NPCCSS (P=0.0189), corresponding to an 80% relative reduction in disease progression, in patients aged ≥4 years



5-domain NPCCSS (P=0.0074), corresponding to a 101% relative reduction in disease progression, in patients receiving miglustat



Because the FDA requested we add CGI-I as a co-primary endpoint only after the clinical trial had already been initiated, only eight patients had a formal baseline assessment for CGI-I – for the remaining patients such data had to be reconstructed afterwards. A responder rate of more than 50% in CGI-I in the placebo control group impeded the ability to show an overall effect on this endpoint and therefore was not statistically significant. However, when considering patients who severely progressed during the clinical trial based on clinician assessment, only 10.7% of the arimoclomol-treated patients got 'much worse' or 'very much worse' compared to 26.7% in the placebo control group.

Several exploratory biomarkers were measured during the clinical trial, demonstrating a clear biological effect of arimoclomol in support of the clinical results. The biomarker data showed a biological response to arimoclomol on key characteristics of its mechanism of action and the disease biology of NPC. This includes the important rescue protein HSP70 and accumulating lipids involved in the disease pathology. HSP70 levels in peripheral blood mononuclear cells ("**PMBCs**"), showed a statistically significant increase in patients treated with arimoclomol (p=0.0010) demonstrating target engagement. The accumulation of un-esterified cholesterol in PBMCs was less in the arimoclomol group as compared to the placebo group (p=0.0959) and the change in the cholestane-triol levels in serum declined more in the arimoclomol group as compared to the placebo group (p=0.2251). Furthermore, a reduction of the cholesterol metabolite oxysterol was also observed (p=0.0613). We believe these results support our hypothesis that arimoclomol may correct the underlying pathology of NPC based on observed biomarker response that it is in line with preclinical data, such as increased levels of HSP70, reduced lipid burden and improved measurable manifestations of ataxia.

Safety results. Arimoclomol was well-tolerated with a similar incidence of adverse events("**adverse events**"), for arimoclomol (88%) and placebo control (75%). Common adverse events that occurred in at least 8% of patients with NPC treated with arimoclomol and more frequently than in patients receiving placebo were: decreased weight (transient), tremor, urticaria, and decreased appetite (see table below).

Safety results: Common adverse events reported in Phase 2/3 clinical trial occurring in at least 8% of patients treated with arimoclomol than in patients receiving placebo

Adverse Reaction	Arimoclomol (N=34) n (%)	Placebo (N=16) N (%)
Weight decrease*	5 (14.7)	0
Tremor	3 (8.8)	0
Urticaria	3 (8.8)	0
Decreased appetite	3 (8.8)	0

*For the majority of the patients the weight decrease was temporary.

Three patients (9%) withdrew because of adverse events, all in the arimoclomol group (2 urticaria/angiodema and one patient with a two-fold increase in serum creatinine from baseline) (see table below). Serious adverse events ("**SAEs**") occurred less frequently in the arimoclomol group (15%) compared to placebo control (31%). All SAEs, except 2 events of urticaria and angioedema in the arimoclomol group, were assessed as not related to arimoclomol and were in line with the expected adverse event profile in NPC patients. One patient died due to cardiorespiratory arrest. The event was assessed as related to the underlying NPC disease and not related to arimoclomol.

Summary of Adverse Events: Double-Blind Phase

	Arimoclomol 372 mg[1] weight-adjusted N (%) E	Placebo N (%) E
Safety set (N,%)	34 (100.0)	16 (100.0)
TEAEs	30 (88.2) 278	12 (75.0) 87
Serious TEAEs	5 (14.7) 9	5 (31.3) 8
Non-serious TEAEs	30 (88.2) 269	12 (75.0) 79
TEAEs leading to withdrawal from IMP	3 (8.8) 4	
AEs with fatal outcome	1 (2.9) 1	
Severity of TEAEs		
Mild	27 (79.4) 148	12 (75.0) 48
Moderate	26 (76.5) 120	9 (56.3) 34
Severe	4 (11.8) 10	3 (18.8) 5
Relationship of TEAEs		
Probably related	5 (14.7) 12	
Possibly related	12 (35.3) 26	3 (18.8) 3
Not related	30 (88.2) 240	12 (75.0) 84
Relationship of serious TEAEs		
Probably related	2 (5.9) 3	
Not related	3 (8.8) 6	5 (31.3) 8

(1) Arimoclomol citrate 200 mg three times a day weight-adjusted.

The safety results reported during the 12-month open label extension is detailed in the table below which provides an overview of adverse events and SAEs during the open-label extension portion of the trial. Similar to the doubled-blinded portion of the trial, a total of 87.8% of the patients reported at least one treatment emergent adverse event. A slightly higher proportion of patients (24.4%) reported at least 1 SAE in the open-label portion of the trial than in the arimoclomol group during the double-blinded phase (14.7%), while the proportion was lower than in the placebo group of the double-blinded phase (31.3%). One out of the 19 SAEs were assessed as probably related to arimoclomol (an event of proteinuria which did not resolve, although the arimoclomol dosing continued unchanged). The proteinuria did not have clinical symptoms. One patient died during the first 12 months of the open-label portion of the trial due to lower respiratory tract infection, which was deemed to be unrelated to treatment by the investigator.

Summary of Adverse Events: Open-Label Phase

	Arimoclomol 372 mg[1] weight-adjusted/ Arimoclomol 372 mg[1] weight-adjusted N (%) E	Placebo/ Arimoclomol 372 mg[1] weight-adjusted N (%) E	Arimoclomol Total N (%) E
Safety set (N,%)	26 (100.0)	15 (100.0)	41 (100.0)
TEAEs	24 (92.3) 114	12 (80.0) 48	36 (87.8) 162
Serious TEAEs	8 (30.8) 17	2 (13.3) 2	10 (24.4) 19
Non-serious TEAEs	24 (92.3) 97	12 (80.0) 46	36 (87.8) 143
TEAEs leading to withdrawal from IMP	2 (7.7) 3	1 (6.7) 2	3 (7.3) 5
AEs with fatal outcome	1 (3.8) 1		1 (2.4) 1
Severity of TEAEs			
Mild	20 (76.9) 54	9 (60.0) 27	29 (70.7) 81
Moderate	17 (65.4) 44	5 (33.3) 21	22 (53.7) 65
Severe	9 (34.6) 16		9 (22.0) 16
Relationship of TEAEs			
Probably related	1 (3.8) 1	1 (6.7) 1	2 (4.9) 2
Possibly related	2 (7.7) 2	3 (20.0) 4	5 (12.2) 6
Not related	24 (92.3) 111	11 (73.3) 43	35 (85.4) 154
Relationship of serious TEAEs			
Probably related	1 (3.8) 1		1 (2.4) 1
Not related	8 (30.8) 16	2 (13.3) 2	10 (24.4) 18

(1) Arimoclomol citrate 200 mg three times a day weight-adjusted.

Trial extension. We also conducted an open-label Phase 2/3 extension clinical trial in NPC following 41 patients and reported interim results in January 2020. This 12-month interim data from the open-label extension trial showed sustained effect in reducing disease progression over two years and further demonstrated the potential of arimoclomol in NPC. Arimoclomol was well-tolerated and no new safety signals were detected during the first 12 months of the open-label extension trial. We will continue to follow the patients on an open-label basis for 24-months from the completion of the Phase 2/3 clinical trial.

QTc trial. A thorough QT trial with arimoclomol is currently being conducted to assess potential effects of arimoclomol on ventricular repolarization and arrhythmia risk by assessing the potential presence of a small change in the corrected QT ("QTc") interval. The QTc clinical trial has been delayed due to COVID-19. The FDA has requested that we submit reports from the QTc clinical trial by October 1, 2020 and that, given the priority review timeline and both nonclinical and clinical evidence suggesting a potential QT safety signal, submission of these reports after that date may not allow the FDA sufficient time to review. We do not anticipate being able to submit the reports by October 1, 2020, which may delay the timing of FDA approval for NPC.

Regulatory Pathway

In September 2020, the FDA accepted our NDA with priority review. The FDA has set a target action date of March 17, 2021 under the PDUFA for completion of its review of our NDA. We also intend to submit an MAA with the EMA in the second half of 2020.

Arimoclomol for the Treatment of Neurological Gaucher Disease

We initiated a randomized, double-blinded, dose-ranging Phase 2 clinical trial of arimoclomol in Gaucher disease in June 2018, which completed enrollment in August 2019. We reported top-line results from this Phase 2 clinical trial in June 2020.

Overview of Gaucher disease

Gaucher disease is a rare, inherited metabolic disorder causing certain sugar containing fats to abnormally accumulate in the lysosomes of cells, especially within cells of the blood system and nerve cells, thereby affecting organs such as the brain, bone marrow, spleen and liver, due to the lack of a certain enzyme (glucocerebrosidase). The symptoms vary greatly from patient to patient with some patients having few or no symptoms while others may experience significant complications. The typical systemic symptoms of Gaucher disease, which can appear at any age, include an abnormally enlarged liver and/or spleen (hepatosplenomegaly), low levels of circulating red blood cells (anemia) and blood cells promoting clotting (thrombocytopenia) and skeletal abnormalities. Gaucher disease is an autosomal recessive disorder where the lack of glucocerebrosidase activity is caused by mutations in the glucocerebrosidase ("**GBA**"), gene encoding the enzyme.

Three distinct forms of Gaucher disease have been identified to date based on the absence or presence of neurological manifestations and the extent of such complications. Gaucher Type 1 is at the outset characterized by a lack of neurological manifestations and usually results in a low level of blood clotting cells (thrombocytopenia) and a low level of red blood cells in circulation (anemia) causing easy bruising and chronic fatigue, respectively. In addition, affected individuals may experience an abnormally enlarged liver and/or spleen (hepatosplenomegaly) and skeletal anomalies. Gaucher Type 1 is most prevalent in Western countries, accounting for an estimated 95% of the 15,000 patients diagnosed with Gaucher disease across the United States and European Union. The remaining 5% of patients with Gaucher disease in these regions suffer from Gaucher Type 3. Gaucher Type 2 is rare. It is estimated that up to 30% of patients diagnosed with Gaucher Type 1 develop neurological symptoms later in life, including 5-7% showing Parkinsonism symptoms. Gaucher Type 2 (so-called acute neuronopathic Gaucher disease) is characterized by onset in the early months of life and entails neurological manifestations arising from the accumulation of a certain lipid (glucocerebroside) in the brain. The symptoms include enlargement of the spleen (splenomegaly), loss of motor skills, involuntary muscle spasms (spasticity), decreased muscle tone (hypotonia) and dysphagia. Gaucher Type 2 usually results in fatality by three years of age. Finally, patients with Gaucher Type 3 (so-called chronic neuronopathic Gaucher disease) may experience the same blood and bone anomalies as Gaucher Type 2, however, with the neurological manifestations usually progressing at a slower rate. Gaucher Type 3 usually onsets during the first decade of life and patients may live into their teens, early 20s and some even longer. Gaucher Type 3 has a higher reported prevalence in China, Japan and India. As the presence of

neurologic symptoms are not confined to a single type of Gaucher disease, and with no approved treatments for the neurological manifestations of the disease, we are focused on investigating arimoclomol in all Gaucher disease patients.

The diagnosis of Gaucher disease is made upon characteristic symptoms, as described above, especially in conjunction with enlargements of the spleen and/or liver and fractures. The diagnosis can be confirmed by clinical evaluations and numerous tests measuring the activity in, for example, white blood cells or skin cells along with an analysis of potentially mutated genes.

Gaucher disease is the most common LSD, with an estimated incidence of one in 50,000 individuals in the general population with an exceptionally high prevalence in the Ashkenazi Jewish population, up to one per 850 individuals, and affects up to an estimated 15,000 individuals in the United States and Europe combined. According to Grand View Research, in 2017, global sales of products for treatment of Gaucher disease was $1.55 billion.

Treatment Options for Gaucher Disease and Unmet Need

Two types of treatment are currently available for patients with Gaucher disease: ERT, such as Cerezyme (Sanofi), Elelyso (Pfizer) and Vpriv (Shire), and SRT, using Zavesca or Cerdelga (Sanofi). These treatments were approved based on their ability to improve the systemic peripheral features of Gaucher disease, but not the neurological manifestations of the disease, and none of them are approved for treatment of Gaucher disease Type 2 and 3. In addition to ERT and SRT, there are few other advanced programs, which are discussed in more detail below under "*—Competition*."

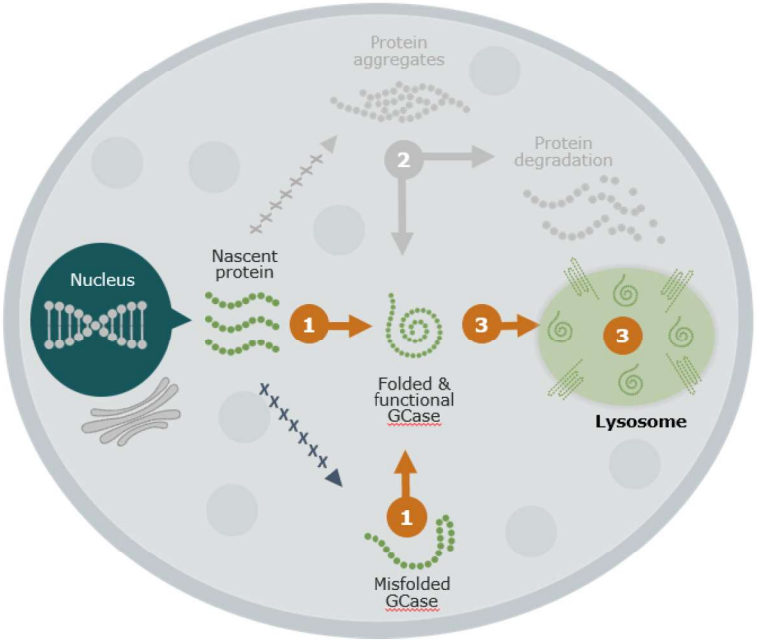
As currently available therapies do not treat the pathology of the CNS, a significant unmet need for treatment of Gaucher disease continues to exist, especially for Gaucher Type 2 and Type 3 and Gaucher Type 1 patients developing neurological symptoms at a later disease stage.

Our Solution – Arimoclomol for Neurological Gaucher Disease

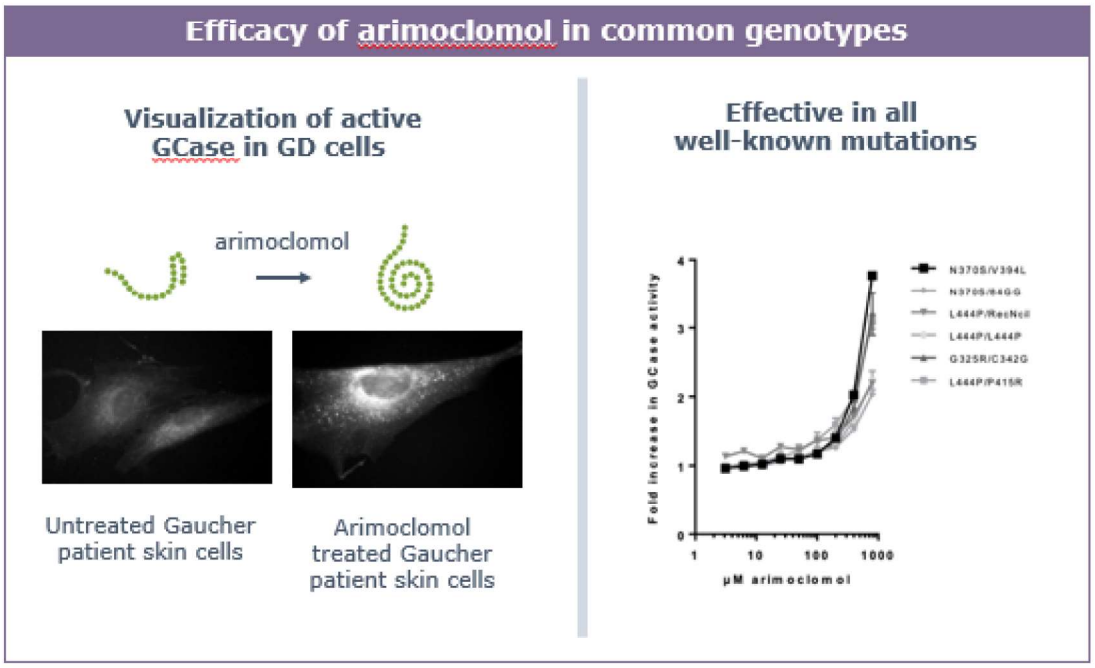
With Gaucher disease, mutations in the GBA gene encoding the lysosomal enzyme glucocerebrosidase ("**GCase**") lead to enzyme misfolding and loss of activity. This leads to accumulation of lipids in the lysosomes which causes lysosomal and cellular dysfunction. HSP70 is a key protein in Gaucher disease and has been shown to directly bind to and chaperone GCase. To date in our clinical trials, we have observed that arimoclomol amplifies and sustains levels of HSP70 which, as shown in the figure below:

- Prevents and corrects misfolded, dysfunctional GCase, specifically improves GCase refolding, maturation and lysosomal activity across genotypes (as indicated by (1) in the figure below); and

- Improves lysosomal function by chaperoning GCase into lysosome, thereby increasing lipid metabolism and removal. In addition, intra-lysosomal HSP70 also enhances lipid metabolism thereby stabilizing lysosomal membranes and preventing cell death (as indicated by (3) in the figure below).



The increase in GCase activity from arimoclomol has been confirmed in a complementary neurological Gaucher disease stem cell model and marked effects were observed across common genotypes, including L444P, as shown in the figure below.



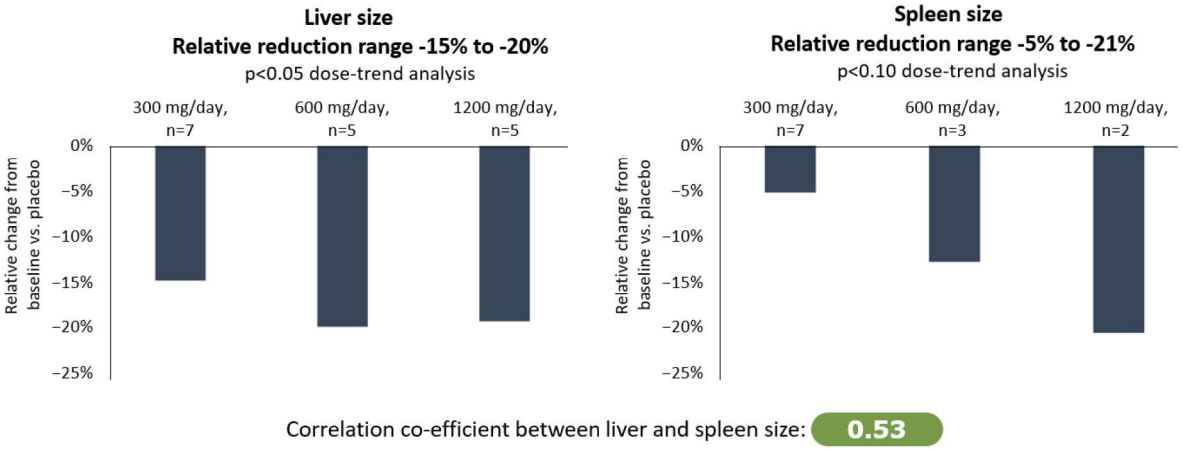
Clinical Trials of Arimoclomol for the Treatment of Gaucher Disease

In June 2020, we reported top-line 6-month data from a multicenter, randomized, double-blinded, placebo-controlled, dose-ranging Phase 2 clinical trial. The trial enrolled 39 patients who have been diagnosed with either Gaucher disease Type 1 or Type 3 who are naive to any treatment for Gaucher disease. The trial was conducted at seven clinical sites in India where access to SRT and ERT was limited. This allowed for direct assessment of the effect of arimoclomol treatment on pharmacodynamic biomarkers in blood and other tissues, as ERT treatment may obscure the effect of arimoclomol on peripheral symptoms and biomarkers. In addition, performing the clinical trial in India provided patients (aged between 4 and 60 years) suffering from this rare disease with the opportunity to receive a potential treatment.

Trial design. Patients were randomized 1:1:1:1 into four treatment arms – active treatment three times per day at three different doses (arimoclomol citrate 1200 mg, 600 mg or 300 mg daily, weight-adjusted) and placebo, and assessed for six months. Following the placebo-controlled period, the placebo group has been re-randomized into one of the three active treatment groups for a long-term extension with the next data readout at six months. Overall, data from 37 patients were analyzed, of which 21 were Gaucher disease Type 1 and 16 were Gaucher disease Type 3. Two patients were excluded from the analysis due to negative confirmatory Gaucher disease genotype. The mean age of the 37 patients was 11.8 years.

The primary endpoint in this clinical trial is the reduction of chitotriosidase activity levels in blood from baseline to six months. Chitotriosidase was deemed to be the most suitable biomarker of Gaucher disease at the time of the trial design, because it is found in high levels in patients whose immune cells have accumulated an excess lipid burden. However, there can be large inter-subject variability in chitotriosidase, different chito-genotypes determine enzyme activity and chitotriosidase is not directly linked to the arimoclomol mechanism of action. Because of these limitations, we believe chitotriosidase is of limited value moving forward and we no longer intend to use chitotriosidase as a key endpoint in our clinical trials in Gaucher disease. Secondary endpoints include growth and maturation endpoints, such as change in weight and age at pubertal onset, imaging endpoints such as longitudinal change in size of the liver and spleen, and other biomarker endpoints in the blood and CSF. *Efficacy results*. Arimoclomol demonstrated a relative reduction in serum chitotriosidase activity from baseline to six months, the primary endpoint, across all dosages compared to placebo ranging from -12% to -29%, although statistical significance was not achieved ($p=0.4$). However, we observed a statistically significant dose-dependent reduction in liver size ranging from -15% to -20% relative to placebo (dose trend analysis $p<0.05$). In addition, we observed a dose-dependent reduction in spleen size ranging from -5 to -21% relative to placebo was observed, although statistical significance was not achieved, likely due to the small sample size (dose trend analysis $p<0.10$). A non-significant directional dose-dependent reduction in the Gaucher Type 1 severity score outcome, a validated tool to monitor adult Gaucher Type 1 patients that tracks hematological, visceral and bone domains, was also observed across treatment groups. A post-hoc calculation of the correlation between liver and spleen size was conducted, which supports consistency of effect (correlation coefficient: 0.53). Patients anemic at baseline showed a time-dependent increase in hemoglobin in the highest dose group ($p<0.05$). Consistent with arimoclomol's proposed mechanism of action, we observed a dose-dependent increase in the exploratory biomarker, glycosylsphingosine (lyso-Gb1), possibly indicating release out of the cells of affected organs into the blood.

Efficacy results: Dose Dependent Reduction in liver and spleen size



Safety results. Arimoclomol was well tolerated with a slightly higher incidence of adverse events (70% placebo; 83% arimoclomol all doses) and serious adverse events (SAEs: none in placebo group; 21% arimoclomol all doses) in the arimoclomol groups compared to the placebo group. The most common adverse events are shown in the table below. One patient who had elevated bilirubin at baseline

discontinued treatment due to an increase in transaminases (levels of liver function enzymes) which was assessed as probably related to arimoclomol by the investigator. The transaminases normalized a few weeks after stopping the treatment. All SAEs, except an event of hepatic encephalopathy described below and the event of abnormal liver function tests were assessed as not related to arimoclomol by the investigator.

Safety results: Overall incidence of TEAEs (treatment-emergent adverse events) with arimoclomol was 83% (n=24/29) and with placebo was 70% (n=7/10)

	Placebo N = 10 N (%)	Arimoclomol 300 mg/ day N = 10 N (%)	Arimoclomol 600 mg/ day N = 9 N (%)	Arimoclomol 1200 mg/day N = 10 N (%)
Patients with Any TEAE in Double-Blinded Phase	7 (70.0)	9 (90.0)	7 (77.8)	8 (80.0)
Pyrexia	1 (10.0)	3 (30.0)	1 (11.1)	3 (30.0)
Cough	2 (20.0)	4 (40.0)	1 (11.1)	1 (10.0)
Epistaxis	1 (10.0)	1 (10.0)	2 (22.2)	3 (30.0)
Vomiting	1 (10.0)	1 (10.0)	2 (22.2)	3 (30.0)
Abdominal pain	0	2 (20.0)	2 (22.2)	1 (10.0)
Upper respiratory tract infection	2 (20.0)	2 (20.0)	2 (22.2)	0
Viral upper respiratory tract infection	0	4 (40.0)	0	0
Diarrhoea	2 (20.0)	0	0	0

Three deaths occurred during the blinded phase of the trial, one of which was deemed possibly related to treatment by the investigator and two of which were deemed unrelated to treatment by the investigator. One of those deaths was due to an event of hepatic encephalopathy, which was assessed by the investigator as possibly related to arimoclomol.

During the ongoing extension portion of the trial, as of July 30, 2020, nine patients have had SAEs including four patients who died. One patient died due to upper gastrointestinal bleeding with pneumonia, which was deemed to be probably related to arimoclomol by the investigator. In addition, one patient died after episodes of vomiting followed by cough and difficulty breathing, which was deemed to be possibly related to arimoclomol by the investigator. The two other deaths were deemed to be unrelated to arimoclomol by the investigator. One non-fatal SAE of abnormal liver function tests has also been assessed as possibly related to arimoclomol by the investigator. The patient recovered after treatment using arimoclomol was halted.

These findings have been shared with the health authorities and ethics committees who have not provided any feedback or highlighted any concerns with the safety results to date and the Independent Data Monitoring Committee has recommended that the extension portion of the trial continue as planned. We believe that these data support using weight-adjusted dosing regimens in future clinical trials.

Trial extension. Following the placebo-controlled period, the placebo group has been re-randomized into one of the three active treatment groups for a long-term extension with the next data readout at six months. We will continue to evaluate clinical outcomes, monitor safety, and further explore relevant biomarkers.

Clinical Development Plan

Based on the top-line results of the Phase 2 trial, we intend to proceed with pivotal-stage clinical development in neurological Gaucher disease. We intend to discuss these data, along with results from the extension portion of the trial, with Gaucher disease experts and regulators.

Our Program for the Treatment of Neuromuscular Disorders

Neuromuscular disorders encompass a range of conditions affecting a part of the neuromuscular system and impairing the functioning of the muscles, thereby causing muscle weakness. In particular, the disorders affect the nerve cells that send messages to control the voluntary muscles (*i.e.* muscles one can control, such as arms and legs) and the muscles themselves. As the disorders manifest, the neurons become unhealthy or die, resulting in a loss of communication between the nervous system and the

muscles. Weakening of the muscles may lead to aches, pains, movement problems and may affect the heart function and ability to breathe, speak and swallow. The causes of neuromuscular disorders vary by type, but the diseases targeted by us are characterized by protein misfolding and aggregation, prohibiting proper recycling. Protein aggregation can cause cell stress and eventually cell death.

The two neuromuscular disorders that we are currently targeting are ALS and sIBM.

Arimoclomol for the Treatment of Amyotrophic Lateral Sclerosis

Based on investigator-initiated preclinical studies and clinical proof-of-concept observed in two Phase 2 clinical trials of arimoclomol in ALS, we are currently conducting a Phase 3 clinical trial assessing efficacy and safety of arimoclomol. The clinical trial is intended to support a marketing authorization in the broad ALS population. We expect to announce top-line results from the clinical trial in the first half of 2021.

Overview of ALS

ALS, which is also commonly referred to as Lou Gehrig's disease, is a rapidly progressing neurological disease with the onset typically occurring between 40 to 70 years of age, with patient mortality occurring in most patients within three to five years of disease onset. ALS attacks neurons responsible for controlling voluntary muscles, resulting in muscle weakness in limbs, and impacts speaking, chewing, swallowing and breathing, leading to progressive disability and eventually death, typically from respiratory failure and aspiration pneumonia. In addition, up to 50% of patients with ALS develop cognitive impairment associated with frontotemporal dementia. The cause of damage to the neurons is unknown, but several theories have been proposed, including glutamate toxicity, protein misfolding and oxidative stress.

About 10% of ALS cases are inherited and are associated with pathogenic mutations, which are commonly referred to as "familial ALS," and the remaining 90% have a sporadic onset of ALS, or ALS without any identified genetic component. Both familial and sporadic ALS is characterized by the presence of inclusions of aggregated proteins in motor neurons. Although many different proteins are known to form aggregates in ALS, the most common is TDP-43 which is found to be mislocalized and aggregated in up to 97% of all ALS patients. Mutations in TDP-43 are associated with familial ALS (5-10% of cases), but it belongs to a group of several RNA binding proteins that are found in aggregates in ALS, also in the their normal form without any mutation. In about 20% of the cases of familial ALS, which accounts for 2% of the total ALS population, mutations in the gene coding for the copper-zinc SOD1 enzyme have been found. SOD1 is an enzyme with antioxidant properties important in the protection against free radicals, a highly reactive oxygen species that can damage cellular components via oxidative stress. Defects in SOD1 may cause ALS via two mechanisms: inhibition of SOD1 enzymatic activity and the formation of toxic SOD1 protein aggregates.

In Western countries, the rate of diagnosis is high, but initial symptoms of ALS can be subtle at first, and it may take 12 to 14 months to be accurately diagnosed. Early symptoms of ALS may resemble those of other diseases and therefore other diseases must be excluded before the diagnosis of ALS can be made. For that, certain diagnostic procedures, such as magnetic resonance imaging or a test to detect electrical activity in muscles (electromyography) may be utilized. ALS is characterized by degeneration of both the upper and lower motor neurons. Some patients with ALS may initially present only with findings due to degeneration of the upper motor neurons. Lower motor neuron degeneration usually appears within three to five years in these patients.

Despite being classified as a rare disease, ALS is considered one of the more common neurodegenerative diseases worldwide. The Centers for Disease Control and Prevention estimates that there are approximately 16,000 cases of ALS in the United States and that approximately 5,000 new cases are diagnosed each year. The number of total cases for the largest five markets in Europe (Germany, France, Italy, Spain and the United Kingdom) is estimated to be slightly higher and for the broader European geography the estimate is approximately 30,000 cases. Therefore, we estimate the market for the United States and Europe is approximately 50,000 patients. ALS affects men to women at a ratio of 3:2.

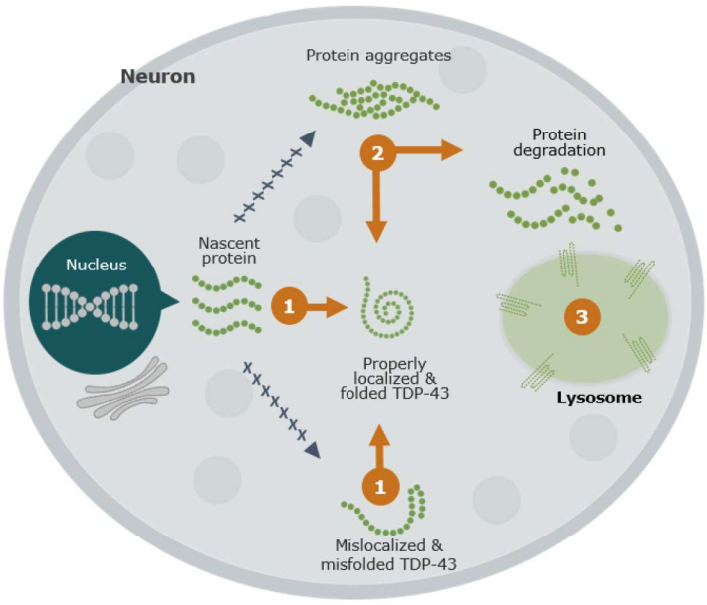
Treatment Options for ALS and Unmet Need

There are currently a limited number of available treatments for ALS and these only impart a modest effect. Currently available treatments have been shown to only provide symptomatic management of patients with mild to moderate disease and easing intervention in patients with severe or terminal disease. Patients are often managed by specialized multidisciplinary care sites, of which there are approximately 200 in the United States, or by community practices and clinics. Until recently, the only approved pharmaceutical drug used for slowing disease progression in ALS was Rilutek (riluzole). It was the first drug to be approved by the FDA for the treatment of ALS more than 20 years ago and is now available in oral generic tablets as well as branded liquid and film formulations. In May 2017, the FDA approved Radicava (edaravone), which is administered through chronic cycles of 14-days of intravenous infusions followed by a two-week treatment-free period. In recent years, the FDA approved two new formulations of riluzole that address the need for an improved route of administration in patients who suffer mobility and swallowing complications. In September 2018, the FDA approved Tiglutik, an oral suspension administered via syringe. In November 2019, Exservan, a new soluble oral formulation which dissolves on the tongue, was approved. In Europe, the only approved pharmaceutical drug to extend the patient's life or to delay the need for mechanical ventilation in ALS is riluzole. With the current treatment options there is still a major need for new effective treatments for patients with ALS in order to improve the disease course and to further extend survival.

Our Solution – Arimoclomol for ALS

The pathological processes in motor neurons include protein misfolding, mislocalization and aggregation, with the presence of misfolded and aggregated proteins, as well as ubiquitin-positive inclusions (aggregates) containing RNA-binding proteins, such as the signature protein, TDP-43. Misfolding and aggregation of TDP-43 is associated with cell dysfunction and cell death and motor neuron cells are highly vulnerable as they are not replaced and cannot regenerate. To date in our clinical trials, we have observed that arimoclomol amplifies and sustains levels of HSP70 which, as shown in the figure below:

- Prevents the misfolding and mislocalization of TDP-43 (as indicated by (1) in the figure below);
- Prevents inclusion formation, including aggregation of ubiquitin and TDP-43 in the cytoplasm (as indicated by (2) in the figure below); and
- HSP70 improves lysosomal function which is thought to facilitate protein degradation and clearance of aggregates (as indicated by (3) in the figure below).



Completed Clinical Trials of Arimoclomol for the Treatment of ALS

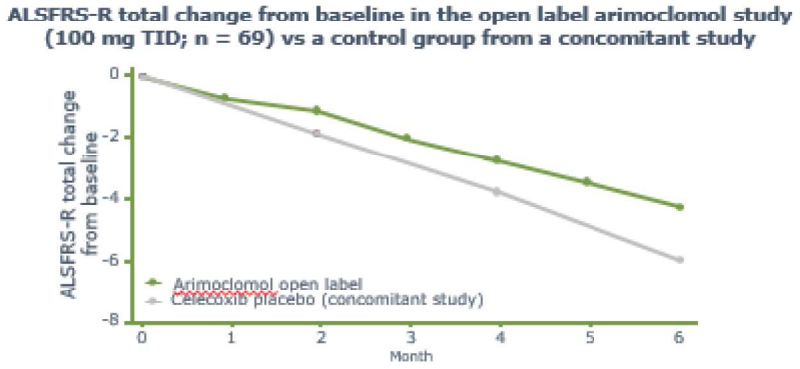
Arimoclomol has so far been tested in two Phase 2 ALS trials, one dose-ranging trial with open-label extension in ALS, Trial AALS-001, and one trial in rapidly progressive ALS caused by SOD1 mutations, Trial 20100758.

Trial AALS-001

Trial design. A CytRx-sponsored 12 week dose-ranging clinical trial in ALS patients was performed with the objective to assess the safety, tolerability and pharmacokinetics of arimoclomol in ALS. A total of 84 patients with ALS received arimoclomol citrate at one of three oral doses (25, 50 or 100 mg three times daily) or placebo. The primary outcome measure was safety and tolerability.

Trial results. Arimoclomol citrate at doses up to 300 mg/day was observed to be well tolerated. Arimoclomol resulted in dose-linear pharmacologic exposures and the half-life did not change with continued treatment. Arimoclomol CSF levels increased with dose and reached a CSF-to-serum ratio of 1 at steady state and equilibrium indicating that arimoclomol crosses the blood-brain-barrier. 77 patients completed the 12 weeks of treatment, of which 69 patients enrolled in a six-month open-label trial at the highest dose (arimoclomol citrate 100 mg three times daily). In the open label clinical trial, the rate of decline of ALSFRS-R was slower in the arimoclomol-treated group than in a historical placebo control group, controlling for baseline ALSFRS-R (p=0.034).

Efficacy results: Arimoclomol slowed disease progression by 30%



A total of nine SAEs were reported in seven patients in the arimoclomol group, including pulmonary embolus, myasthenia/ALS progression, apnea and respiratory disorder, but all SAEs were determined not to be treatment-related. During the open-label trial, a total of 13 patients experienced 16 SAEs including ALS progression, respiratory failure, deep vein thrombosis and gastrostomy. These SAEs were considered not related or unlikely related to the treatment other than the event of pulmonary embolism, which was considered to be possibly related to the treatment.

Trial 20100758

Results from an investigator-led randomized, double-blinded, placebo-controlled Phase 2/3 clinical trial conducted in patients with SOD1 ALS were published in 2018. The Phase 2/3 clinical trial was conducted in collaboration with University of Miami, Emory University and Massachusetts General Hospital and Harvard University. The primary objective of the trial was to investigate the safety and efficacy of arimoclomol in ALS patients with pathogenic mutations in the SOD1 gene. Although the clinical trial was not powered for efficacy, the results revealed a consistent trend across all efficacy endpoints. A key aspect of this clinical trial was the selection of a trial patient population with pathogenic SOD1 mutation and rapid disease progression which allowed for signal detection despite the small size of the clinical trial.

Trial design. A total of 36 patients were randomized 1:1 into two treatment arms, arimoclomol citrate (200 mg three times daily) and placebo, with 13 patients in each treatment arm with the A4V mutation, and assessed for a total of 12 months. The primary endpoints were safety and tolerability. The secondary efficacy endpoints included survival, the revised ALSFRS-R and forced expiratory volume in six

seconds, or FEV6%, a measurement of lung function. In addition, the combined assessment of survival and function ("**CAFS**"), a composite score of survival and ALSFRS-R, which is detailed in the figure below, was included.

12-domain ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale

Domain \ Score	0	1	2	3	4
Speech	Loss of useful speech	Speech combined with non-verbal communication	Intelligible with repeating	Detectable speech disturbance	Normal
Salivation	Marked drooling, requires constant tissue	Marked excess of saliva with some drooling	Moderately excessive saliva, may have minimal drooling	Slight but definitive excess of saliva; may have night-time drooling	Normal
Swallowing	Exclusively parenteral or enteral feeding	Needs supplemental tube feeding	Dietary consistency changes	Early eating problems – occasional choking	Normal
Handwriting	Unable to grip pen	Able to grip pen but unable to write	Not all words are legible	Slow or sloppy; all words are legible	Normal
Dressing & Hygiene	Total dependence	Needs attendant for self-care	Intermittent assitance or substitute methods	Independent and complete self-care with effort or decreased efficiency	Normal
Cutting food and handling utensils	Needs to be fed	Food must be cut by someone, but can still feed slowly	Can cut most foods, although clumsy and slow; some help neede	Somewhat slow and clumsy, but no help needed	Normal
Turning in bed and adjusting covers	Helpless	Can initiate, but not turn or adjust sheets alone	Can turn alone or adjust sheets, but with great difficulty	Somewhat slow and clumsy but no help needed	Normal
Walking	No purposeful leg movement	Non-ambulatory functional movement	Walks with assistance	Early ambulation difficulties	Normal
Climbing stairs	Cannot do	Needs assistance	Mild unsteadiness or fatigue	Slow	Normal
Dyspnea	Significant difficulty, considering using mechanical support	Occurs at rest	Occurs with one or more of the following: eating, bathing, dressing	Occurs when walking	None
Orthopnea	Unable to sleep	Can only sleep sitting up	Needs extra pillows in order to sleep	Some difficulty sleeping at night due to shortness of breath	None
Respiratory insufficiency	Invasive mechanical ventilation by intubation or tracheostomy	Continuous use of BiPAP during night and day	Continuous use of BiPAP during night	Intermittent use of BiPAP	None

Baseline clinical and demographic characteristics were similar between groups with the exception of pulmonary function and SOD1 mutations other than the A4V mutation. Of the SOD1-ALS subpopulation, the mutation known as A4V is the most commonly detected mutation in the SOD1 gene in the United States, and it is associated with a very aggressive disease course. The most frequent mutation was the A4V mutation, accounting for 72% of patients enrolled. A4V patients were well balanced across the two treatment arms (given the large proportion, sub-analyses were pre-defined for patients with this mutation). Patients with the common A4V mutation were balanced between the treatment and placebo group.

Trial results. The primary endpoints of safety and tolerability were met. The clinical trial results indicated a consistent benefit of arimoclomol over placebo on all pre-defined clinical endpoints, survival, ALSFRS-R and pulmonary function (FEV6). ALSFRS-R declined more slowly in the arimoclomol group, with treatment differences of 0.5 point/month. Survival estimates (defined as permanent assisted ventilation and tracheostomy-free survival) also favored arimoclomol compared to placebo, with an unadjusted hazard ratio of 0.67 (p=0.33). This indicates that patients treated with arimoclomol had 0.67 times the likelihood of experiencing death over 12 months compared to the placebo group patients, corresponding to a 33% reduction in probability of death during the observation period. CAFS, a score combining functionality and mortality, also indicated that arimoclomol was superior to placebo (20.9 for arimoclomol versus 16.3 for placebo, where a lower rank score indicates a worse outcome, indicating a 28% improvement with arimoclomol). Other mutations were either only in the treated group or in the placebo group. An efficacy analysis of the A4V subpopulation was therefore predefined in the protocol.

In the A4V patient population, the clinical trial demonstrated a reduction of the progression rate on the

ALSFRS-R scale by up to 28%, including a treatment difference of 0.98 point/month. On the survival endpoint, hazard ratios of 0.60 were in favor of arimoclomol, which indicates that patients treated with arimoclomol had a 40% reduction in probability of death during the observation period. In line with a functional and survival benefit there was also a reduction in the decline of pulmonary function by up to 33%. CAFS for the A4V patient population was also higher in arimoclomol compared to placebo (20.5 for arimoclomol versus 14.5 for placebo, indicating a 41% improvement with arimoclomol). Sensitivity analyses correcting for baseline imbalances confirmed the effects observed in the primary analyses.

The clinical trial results demonstrated that 200 mg of arimoclomol citrate administered three times per day for 12 months was well tolerated. The clinical trial also demonstrated that patients treated with arimoclomol showed positive trends across all clinical endpoints when compared to placebo treatment. The clinical trial was not powered to demonstrate efficacy. However, pre-defined analyses revealed consistent trends in favor of the arimoclomol-treated group across all pre-defined clinical endpoints. We believe that results observed in preclinical studies also support our hypothesis that arimoclomol may slow the rate of disease progression. This clinical trial is intended to support submission of an NDA and MAA for ALS.

Ongoing Clinical Trial of Arimoclomol for the Treatment of ALS

In August 2018, we initiated a 2:1 randomized, double blinded, placebo-controlled Phase 3 clinical trial assessing efficacy and safety of arimoclomol citrate 400 mg three times per day in patients with ALS. The clinical trial completed enrollment in July 2019 with 245 patients, across 29 centers in the United States, Europe and Canada. We expect to announce top-line results from the clinical trial in the first half of 2021.

Trial design. The primary endpoint is CAFS in arimoclomol versus placebo. Secondary endpoints include survival, function as measured by ALSFRS-R and pulmonary function as measured by slow vital capacity. The clinical trial design includes clinical enrichment strategies to ensure homogeneous disease progression in the clinical trial.

Interim safety results. In this clinical trial, increased transaminases (>3x upper limit of normal) have been observed in a minority of patients and patients' treatment allocation between arimoclomol and placebo remain blinded. For the majority of these affected patients, the elevations were asymptomatic although for some patients a concomitant rash was observed. The elevations have most commonly been observed within the first three months of treatment and values have normalized either after withdrawal or during continued treatment. Currently the association of increased transaminases to arimoclomol is undetermined but all cases are considered at least possibly related to arimoclomol until further data becomes available. The transaminase elevations were not accompanied by elevations of alkaline phosphatase.

There have also been two deaths as of June 30, 2020 that were deemed possibly related to treatment by the blinded investigator.

Arimoclomol for the Treatment of Sporadic Inclusion Body Myositis

Based on preclinical studies and clinical proof-of-concept observed in a Phase 2 clinical trial of arimoclomol in sIBM, we are currently conducting a Phase 2/3 clinical trial assessing efficacy and safety of arimoclomol in patients with sIBM in the United States and Europe. We expect to report top-line results from the Phase 2/3 clinical trial in the first half of 2021. If the results of the trial are positive, we believe the trial has the potential to form the basis for regulatory submissions.

Overview of sIBM

sIBM is an acquired, rare and a slowly progressive muscle disorder. The onset of symptoms occurs on average after age 50, with up to three of every four cases occurring in men. Among individuals older than 50 years it is the most common muscle wasting disorder. The disease is generally characterized by progressive weakness and degeneration, or atrophy, of the muscles, especially those of the arms and legs, particularly the quadriceps. sIBM typically affects the ability to grab or manipulate objects, causes trouble walking or rising and can progress to cause severe disability. Many patients with sIBM will suffer loss of fine motor skills such as writing, grooming and the ability to eat unaided, and it is associated with significant morbidity including a propensity to fall, difficulty swallowing and severe disability. Patients with sIBM may also require use of a walking stick as early as five years after symptom onset

and become wheelchair dependent and severely disabled within 10 to 15 years. In addition, difficulty swallowing (dysphagia) due to weakness of throat muscles may occur.

The cause of sIBM is unknown. It is possible that multiple immunological, genetic and environmental factors and age-related factors (degenerative factors) are all involved in the development of the disorder. Two distinct processes have been identified in individuals with sIBM – one autoimmune, or immunologic, and one degenerative – and it is possible that these processes are related. Autoimmune disorders occur when the body's immune system mistakenly attacks healthy tissue. Numerous factors support that sIBM likely may be an autoimmune disorder, including the presence of certain inflammatory white blood cells in the muscle tissue of affected individuals, which has led sIBM to be classified as an autoimmune inflammatory muscle disease. However, sIBM does not respond to conventional therapies used to treat autoimmune disorders, such as corticosteroids or immunosuppressive drugs, suggesting that other factors play a critical role in development of sIBM. In addition to inflammatory signs, muscle tissue of individuals with sIBM shows degenerative changes. Specifically, the muscle tissue of affected individuals contains compartments containing abnormal clumps of a wide range of different proteins. These clumps (or protein aggregates), called 'inclusion bodies', give the disorder its name. The significant degenerative component suggests that sIBM is primarily a degenerative muscle disorder, making protein misfolding and aggregation a prominent target for therapy.

In a recent systematic review, the prevalence of sIBM has been estimated to be 4.6 per 100,000 people, equating to an estimated 40,000 individuals living with sIBM in the United States and Europe combined. However, diagnosis of sIBM can be challenging as a result of the slow progression of the disease and patient assumption that initial weakness is due to aging, which can lead to a diagnostic delay in many cases of five to eight years from onset of the disease, in particular when patients do not consult neuromuscular experts. Today, the diagnosis of sIBM is made based on thorough clinical evaluation, careful patient history review and a variety of specialized tests, such as muscle biopsy.

This challenge in diagnosing sIBM is one of the confounding factors to the unknown prevalence of sIBM. sIBM is commonly misdiagnosed as polymyositis because the immunologic hallmarks are similar, particularly early in the disease course. The insidious onset and slow progression of the disease process accounts, in part, for the misdiagnosis. In a long-term observation study of sIBM conducted in two research centers, it was discovered that 30% of patients initially received an incorrect diagnosis. We believe that awareness of the disease would increase and patients may be diagnosed at an earlier stage of disease progression. This may in turn lead to an increase in the prevalence of sIBM through the identification of patients who are currently not diagnosed or misdiagnosed.

Treatment Options for sIBM and Unmet Need

There are currently no effective treatments for sIBM. To date, no therapeutic agent has shown efficacy in preventing, halting or reversing the progression of sIBM and therefore, no drugs have been approved for the indication. In particular, the disorder has not shown to respond to conventional therapies for autoimmune disorders, such as corticosteroids or immunosuppressive drugs. Therefore, the standard treatment option for sIBM consists only of supportive therapy such as physical, speech and occupational therapy. In addition, there are a limited number of investigational therapies currently in development for patients with sIBM.

As there are currently no effective treatments for sIBM, there is a significant unmet need for safe and efficacious treatment options. Although life expectancy for sIBM patients is similar to that of the general population, quality of life is severely affected. 10 to 15 years post-symptom onset, most patients will require assistance with basic daily activities, and some become wheelchair bound or bedridden. There is no evidence that any course of treatment slows progression. The disease can be an indirect cause of death due to respiratory failure (aspiration, dysphagia or cachexia) or infection, particularly those of the respiratory tract. In the terminal phase of illness, some patients have requested euthanasia due to unbearable suffering or terminal deep sedation has been applied due to dysphagia and cachexia.

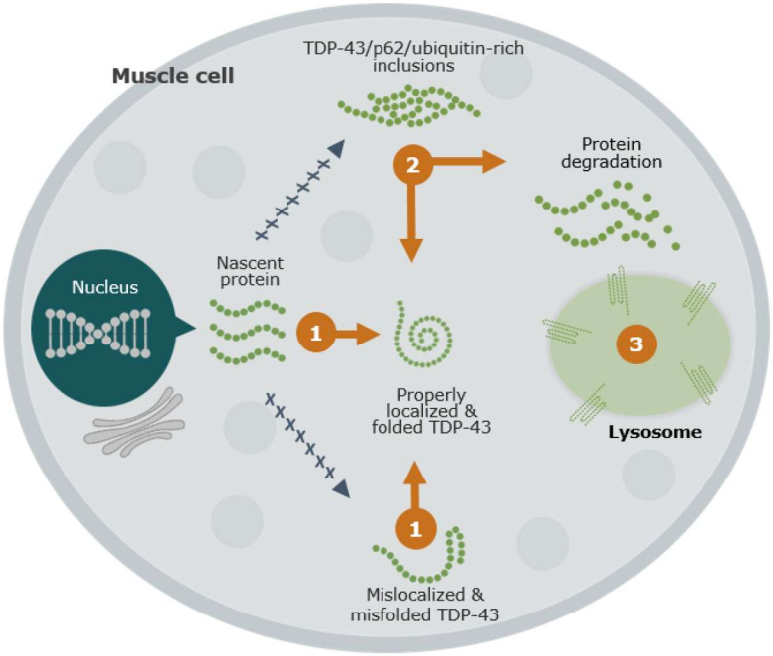
Our Solution – Arimoclomol for sIBM

As protein misfolding, mislocalization and aggregation is a key feature of sIBM, arimoclomol's effect of the HSPs presents a novel disease-modifying therapeutic strategy. To date in our clinical trials, we have observed that arimoclomol amplifies and sustains levels of HSP70 which, as shown in the figure below:

- Prevents the misfolding and mislocalization of TDP-43, a key molecule associated with dysfunctional muscle cells in the disease (as indicated by (1) in the figure below);

- Mitigates formation of TDP-43/p62/ubiquitin-rich protein inclusion bodies, i.e. aggregates, and ensures their removal by facilitating degradation (as indicated by (2) in the figure below); and

- HSP70 improves lysosomal function which is thought to facilitate protein degradation and clearance of aggregates (as indicated by (3) in the figure below).



Completed Clinical Trials of Arimoclomol for sIBM

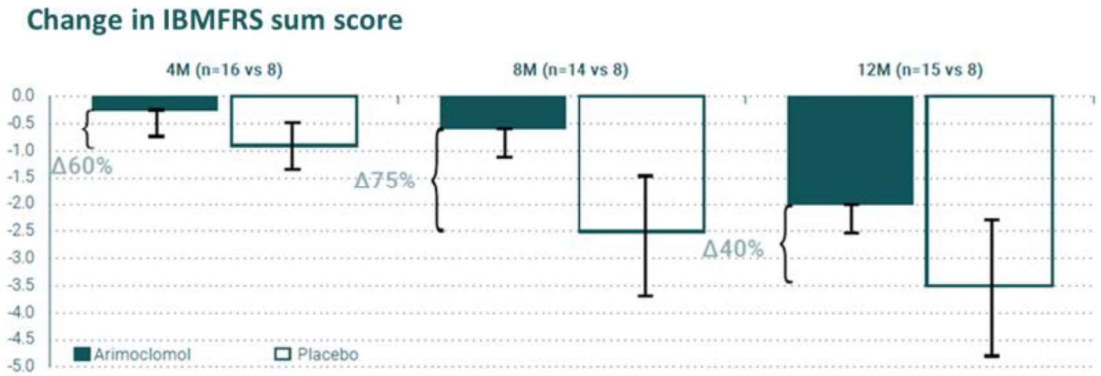
Results from an investigator-initiated, randomized, double blinded, placebo-controlled Phase 2 clinical trial in sIBM were published in 2016. The primary endpoint of the clinical trial was safety and tolerability of arimoclomol. Secondary endpoints included clinically relevant efficacy data, such as measurement of physical function and muscle strength, but these were not statistically powered. Post-hoc responder analysis indicated a consistent treatment response.

Trial design. A total of 24 patients were randomized 2:1 to arimoclomol (16 patients in the arimoclomol group and 8 patients in the placebo group), receiving arimoclomol citrate 100 mg three times per day versus placebo treatment, respectively, and treated for four months. Baseline clinical and demographic characteristics were similar between the groups. Efficacy assessments continued beyond the randomized treatment period for eight months such that efficacy was assessed for a total of 12 months. The primary endpoint was safety and tolerability. Efficacy endpoints were secondary and statistically not powered for. These secondary endpoints included IBMFRS, manual muscle testing ("**MMT**"), and the maximum voluntary isometric contraction testing ("**MVICT**"). IBMFRS is a ten-domain functional rating scale with a total score range 0 to 4 (within each domain, 0 ascribed to no function and 4 ascribed to normal function) which assesses a patient's ability to complete a range of tasks relevant in daily living, including writing, swallowing and climbing stairs, as detailed in the figure below.

The Inclusion Body Myositis Functional Rating Scale

Domain \ Score	0	1	2	3	4
Swallowing	Needs tube feeding	Frequent choking	Dietary consistency changes	Early eating problems— occasional choking	Normal
Handwriting	Unable to grip pen	Able to grip pen but unable to write	Not all words are legible	Slow or sloppy; all words are legible	Normal
Cutting food	Needs to be fed	Food must be cut by someone, but can still feed slowly	Can cut most foods, although clumsy and slow; some help needed	Somewhat slow and clumsy, but no help needed	Normal
Fine motor tasks	Unable	Frequently requires assistance from caregiver	Independent but requires modified techniques or assistive devices	Slow or clumsy in completing task	Independent
Dressing	Total dependence	Requires assistance from caregiver for some clothing items	Independent but requires assistive devices or modified techniques	Independent but with increased effort or decreased efficiency	Normal
Hygiene	Completely dependent	Requires occasional assistance from caregiver	Independent but requires use of assistive devices	Independent but with increased effort or decreased activity	Normal
Turning in bed and adjusting covers	Unable or requires total assistance	Can initiate, but not turn or adjust sheets alone	Can turn alone or adjust sheets, but with great difficulty	Somewhat slow and clumsy but no help needed	Normal
Sit to stand	Unable to stand	Requires assistance from a device or person	Requires use of arms	Performs with substitute motions but without use of arms	Independent (without use of arms)
Walking	Wheelchair dependent	Dependent on assistive device	Intermittent use of an assistive device	Slow or mild unsteadiness	Normal
Climbing stairs	Cannot climb stairs	Dependent on hand rail and additional support	Dependent on hand rail	Slow with hesitation or increased effort; uses hand rail intermittently	Normal

Trial results. Arimoclomol was observed to be well tolerated. After four months of treatment the arimoclomol group demonstrated 60% reduction in progression on the IBMFRS sum score from the baseline compared to placebo. The effect of arimoclomol on the change in IBMFRS sum score was maintained beyond the four-months treatment period. Compared to the placebo group, the decline in IBMFRS sum score was reduced by 72.8% and 40% at eight months and at 12 months, respectively. Although not powered for efficacy, there was a trend in favor of arimoclomol on the IBMFRS (p=0.055) at eight months. Similar effects were observed for the two other efficacy endpoints, MMT and the MVICT.



Change in IBMFRS score (disease progression) among patients receiving either arimoclomol (filled bar) or placebo (white bar). The figure illustrates that the progression was faster among patients receiving placebo compared to patients receiving arimoclomol. N value indicates the number of patients receiving arimoclomol who attended each clinic visit (not all patients were able to attend the

eight and 12 month follow up visits). The trial was not powered for efficacy, and results were not statistically significant. Source: Ahmed et. al.

In a post-hoc analysis, the assessment of disease progression showed that, irrespective of responder definition, patients on arimoclomol treatment fared better than those on placebo treatment, as illustrated in the figure below. Typically, sIBM patients progress by losing up to 2.0 to 2.5 points per eight months.

There were no significant differences between treatment groups regarding the rate, type, and severity of adverse events. There were eight adverse events in the placebo group and 14 in the arimoclomol group, the most common being gastrointestinal. In the arimoclomol group, one serious adverse event was reported as a result of persistent high blood pressure which was subsequently normalized after adjustment of the patient's anti-hypertensive medication.

The clinical trial results demonstrated that 100 mg arimoclomol citrate administered three times per day for four months was well tolerated and associated with benefits when comparing with placebo treatment and these benefits persisted for several months beyond treatment period. The clinical trial was not powered to demonstrate efficacy. However, a responder analysis revealed consistent positive trends in favor of the arimoclomol-treated group. We believe that results observed in preclinical studies also support our hypothesis that arimoclomol may slow the rate of disease progression as well as support arimoclomol's potential for disease modification.

Ongoing Clinical Trial of Arimoclomol for sIBM

We are currently conducting a multicenter randomized 1:1, double blinded, placebo-controlled Phase 2/3 clinical trial for assessing efficacy and safety of arimoclomol citrate 400 mg three times per day in patients with sIBM in 12 centers across the United States and the United Kingdom. The clinical trial was initiated in August 2017 and fully enrolled 152 patients meeting any of the European Neuromuscular Centre IBM research diagnostic criteria from the 2011 categories in April 2019. We are conducting the clinical trial in collaboration with the University of Kansas and the University College London. This trial started as an investigator-initiated trial led by the KUMC and UCL, and the sponsorship of the trial was transferred to us in December 2017. We expect top-line results from the Phase 2/3 clinical trial to be available in the first half of 2021. If successful, the trial has the potential to serve as a registrational clinical trial in support of our NDA for sIBM. In November 2017, the FDA granted an orphan drug designation to arimoclomol for the treatment of sIBM. In addition, in December 2019 we received fast track designation from the FDA for arimoclomol as a treatment for sIBM.

Trial design. The primary endpoint is the IBMFRS. Secondary endpoints include MMT, isometric contraction testing of bilateral quadriceps muscle, 6-mins walking test, modified time up and go and grip strength. Patients included in the trial were: able to rise from a chair without support from another person or device, able to ambulate at least 20 feet or six meters with or without assistive device and had disease onset over the age of 45.

Interim safety results. In this ongoing trial, increased transaminases (>3x upper limit of normal) have been observed in a minority of patients and patients' treatment allocation between arimoclomol and placebo remain blinded. For the majority of these affected patients, the elevations were asymptomatic although for some patients a concomitant rash was observed. The elevations have most commonly been observed within the first three months of treatment and values have normalized either after withdrawal or during continued treatment. The transaminase elevations were not accompanied by elevations of alkaline phosphatase. Currently the association of increased transaminases to arimoclomol is undetermined but all cases are considered at least possibly related to arimoclomol until further data becomes available. One patient in the arimoclomol group (arimoclomol citrate 1200mg per day) experienced severe tubulointerstitial nephritis with acute tubular injury and tubular necrosis. Due to the strong temporal relationship with investigational medicinal product ("**IMP**"), initiation without other more likely explanations for the event, a possible causal relation of the event to IMP cannot be excluded.

Supplemental Nonclinical Safety Data

A comprehensive nonclinical program covering pharmacology, pharmacokinetics, drug metabolism, safety pharmacology, single- and repeat-dose toxicity, genotoxicity, reproductive and developmental

toxicity, juvenile toxicity, local tolerance and interaction studies has been conducted in arimoclomol. Carcinogenicity studies are ongoing.

The nonclinical safety studies to date have revealed adverse findings after oral administration of arimoclomol. These findings included mortality and clinical signs (primarily neuro-behavioral and gastrointestinal) at high doses, direct or indirect (via stress) effects on the immune system, slight effects on the CNS (increased activity), kidney toxicity (of no human relevance or of uncertain toxicological significance), changes in the liver (mainly adaptive changes; sporadic adverse changes at high doses), gastrointestinal tract effects (short term, but no long term effects), increased density of the lens of the eye (at high doses in a single study), reduced male and female fertility, embryo-fetal mortality and structural abnormalities and reduced offspring body weight.

We believe the existing safety pharmacology and toxicology data support oral administration of arimoclomol at the anticipated human doses of up to 400 mg three times daily, except in pregnant women who should not be treated with arimoclomol.

New Molecular Entity Programs

We are developing our next generation of HSP amplifiers based on our expertise and know-how of the role of HSPs and lysosomal biology across our targeted disease areas. We have developed an expansive library of potential product candidates and are in the process of assessing these candidates across a range of parameters including: HSP potency, GCase activity and capacity to cross the blood-brain-barrier. These molecules are currently in lead optimization and we expect to select top candidates to move forward into preclinical assessment in the first half of 2021.

Sales and Marketing

We are building an efficient, highly specialized commercial organization in anticipation of a potential launch of arimoclomol for the treatment of NPC in the United States and Europe. Our plans include having a commercial infrastructure that is supported by high-touch patient support initiatives and established relationships with the concentrated number of treatment centers that address NPC in advance of a potential launch in the United States. We have had significant and positive engagement with payors, physicians and patient advocacy organizations. We have already successfully established our EAP for NPC patients, which continues to provide us with significant insights to enhance our broader commercial readiness plans. We have also established a U.S. steering committee with key stakeholders to guide our preparedness for a commercial launch of NPC, if approved. In NPC, there are approximately 25 to 50 highly specialized centers in the United States and Europe that cover the vast majority of patients, and we believe this market can be effectively addressed with our own targeted commercial field force of approximately 20 to 30 representatives, alongside various high-touch patient support initiatives. In NPC, we expect to enter into an agreement with a third-party logistics firm for commercial outsourcing and related services, including customer service, warehousing and distribution, and accounting services. We expect to enter into agreements with the specialty pharmacy for patient hub and data services and for the purchase of commercial product from us upon launch of arimoclomol, if approved. We have also developed a market access plan for Europe, which includes us having begun to interact with payors in Germany and the United Kingdom. In ALS and sIBM, we intend to expand our footprint to cover key orphan disease centers and to leverage our experience gained with our EAP in NPC. We are also harnessing our EAP for NPC patients in the United States to further inform our commercial strategy. If arimoclomol is approved for additional diseases, we plan to leverage our rare disease commercial infrastructure and expertise to efficiently address those patient populations. We may also opportunistically seek strategic collaborations in disease areas or geographies that we believe could benefit from the resources of either larger biopharmaceutical companies or those specialized in a particular area of relevance, including for NPC in Japan, China, Central and Eastern Europe, the Middle East and Africa, Canada and Latin America. In determining our pricing strategy for arimoclomol, we will consider pricing for other orphan or ultra-orphan indications, as applicable, among other factors.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We use contract manufacturing organizations ("**CMOs**") for the manufacture of the arimoclomol citrate

active ingredient and the arimoclomol capsule drug product. Manufacturing clinical products is subject to various regulations that impose procedural and documentation requirements that govern record-keeping, manufacturing processes and controls, personnel, quality control and quality assurance. Our vendors are required to comply with current good manufacturing practices ("**cGMP**"), regulations, which are regulatory requirements enforced by the FDA, EMA and other regulatory bodies to assure proper design, monitoring and control of manufacturing processes. All facilities have good inspection histories, including by the FDA and local EU authorities. We have assembled a team of experienced employees and consultants to provide the necessary technical, quality and regulatory oversight of our CMOs. The manufacturing is performed under a Quick-to-Care™ program with Patheon, by Thermo Fisher Scientific. In addition, in connection with the transfer of manufacturing for arimoclomol to a different facility, our CMO informed us that a component of arimoclomol may deflagrate during the drying process if not manufactured with specialized equipment. Our CMO is expected to install and obtain approval for such equipment by the end of 2020 and, while we do not expect this to delay our planned submission of a MAA to the EMA in the second half of 2020, it may result in a delay in approval by the EMA of arimoclomol in NPC. We currently have no plans to build our own clinical or commercial-scale manufacturing capabilities.

The arimoclomol citrate active ingredient has to date been manufactured by Patheon API Manufacturing, Inc., which has developed the process through an internal study and confirmed the robustness of the process through validation of the process at two different manufacturing batch scales.

The arimoclomol capsules are manufactured by Patheon France S.A.S. in Bourgoin-Jallieu (France). They developed the manufacturing process through an internal study, and the validation of the manufacturing process has been successfully completed. Patheon France is responsible for the manufacturing, quality control, labeling and packaging of the product, and release for commercial distribution.

We may elect to pursue additional CMOs for manufacturing supplies of drug substance and finished drug product in the future. We believe that our standardized manufacturing process can be transferred to a number of other CMOs for the production of clinical and commercial supplies of our product candidate in the ordinary course of business.

Catalent Germany Schorndorf GmbH in Schorndorf (Germany) is under contract for the storage, labeling and worldwide distribution of product for the Orphazyme clinical trials.

Intellectual Property

Although we do not have a composition of matter patent (which are generally believed to provide the strongest patent protection) protecting arimoclomol or a patent covering the current formulation of our arimoclomol product candidate, our patent portfolio has a strategic scope of protection mainly consisting of method of use patents and patent applications issued or filed in various geographic territories. Arimoclomol is covered by a number of second medical use patents and pending patent applications. These cover or claim the medical use of arimoclomol – as well as other inducers of HSPs - in the treatment of relevant medical indications. These include LSDs, specifically NPC and Gaucher disease, as well as neuromuscular/neurodegenerative disorders, such as ALS and GCase-deficient Parkinson's disease and frontotemporal disorders such as frontotemporal dementia ("**FTD**"), and ALS-FTD. We do not currently have patent protection covering the use of arimoclomol in the treatment of sIBM, but we continuously explore the opportunity for additional patent coverage of arimoclomol including for use in the treatment of new indications including specific protein aggregation diseases, as well as additional coverage for specific aspects of arimoclomol in the treatment of indications in our clinical development programs.

We strive to further identify and develop novel small molecule inducers of HSPs through our NME program. We continuously evaluate potential compounds with the ultimate aim to obtain patent protection for the NME compounds, preferably as composition-of-matter.

As of September 1, 2020, we hold the rights to 10 patent families, each with a number of granted patents (approximately 113 in total) and pending patent applications (approximately 43 in total). Of these, approximately 10 pending patent applications are jointly owned with UCL Business Ltd, including in the United States, Europe, Canada and Japan.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries in which we file, including the United States, the patent term is generally 20 years from the earliest filing date of a non-provisional patent application. In certain countries, the term of a patent that covers a pharmaceutical product may also be eligible for patent term extension when regulatory approval is granted, provided the legal requirements are met. In the United States, the Hatch-Waxman Act permits patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the pharmaceutical product is under regulatory review. The remaining term of a patent cannot extend beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and certain other jurisdictions to extend the term of a patent that covers an approved pharmaceutical product. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we will seek to extend the exclusivity period for pharmaceutical products up to five years via Supplementary Protection Certificate ("**SPC**") available in most European countries, and via patent term extension in the United States. We believe that it is possible to obtain at least one SPC/PTE per pharmaceutical product.

We estimate that arimoclomol for treatment of the LDSs, NPC and Gaucher disease is covered by basic patent coverage until approximately June 2029, with the possibility of up to three and five year extensions in the United States and Europe, respectively. Other countries offer similar extensions, including Japan and Canada.

Patent family	*Type*	*Expiration*	*Regions*	*Status*
Use of HSP70 as a regulator of enzymatic activity (PCT/DK2009/050151)	*Second medical use directed to hydroxylamine derivative type small molecule inducers of the HSP, including arimoclomol, and HSP70 protein, for treatment of LSDs, including NPC and Gaucher disease*	*– Projected patent expiry date (for granted patents): 26JUN 2029*	*AU, BR, CA, CN, EP, HK, IL, JP, RU, US*	*Granted and maintained in: AU, BR, CA, CN, EP (AT, BE, CH/LI, CZ, DE, DK, ES, FI, FR, GB, GR, HU, IE, IT, NL, NO, PL, PT, RO, SE, TR), HK, IL, JP, RU, US* *Pending in: BR, CA, EP, US*
Methods for increasing intracellular activity of HSP70 (PCT/DK2011/050444)	*Second medical use directed to hydroxylamine derivative type small molecule inducers of the HSP, including arimoclomol, and HSP7022 protein, for treatment of additional LSDs, such as NCL*	*–Projected patent expiry date (for granted patents): NOV2031*	*EP, US*	*Granted and maintained in: EP (AT, BE, CII/LI, CZ, DE, DK, ES, FI, FR, GB, GR, HU, IE, IT, NL, NO, PL, PT, RO, SE, TR), US* *Pending in: EP, US*
Arimoclomol formulation (PCT/DK2015/050275)	*Formulation: Extended-release formulation of arimoclomol*	*Projected patent expiry date (for granted patents): 15 SEP2035*	*AU, BR, CA, CN, EP, IL, IN, JP, KR, RU, US*	*Granted and maintained in: JP, US* *Pending in: AU, BR, CA, CN, EP, IL, IN, KR, RU, US*

Patent family	Type	Expiration	Regions	Status
Heat Shock Proteins and Cholesterol Homeostasis (PCT/DK2017/050114)	Second medical use directed to hydroxylamine derivative type small molecule inducers of the HSPs, including arimoclomol, and HSP7010 protein, for treatment of diseases associated with dysregulation of cholesterol homeostasis	–Projected patent expiry date (for granted patents): APR2037	EP, US	Pending in: EP, US
Arimoclomol for treating glucocerebrosidase associated disorders (PCT/EP2017/060205)	Second medical use directed to arimoclomol for treatment of glucocerebrosidase (GBA)-associated disorders, including GBA-associated Parkinson's disease, which includes approximately 5 to 25% of patients with Parkinson's disease who have a GBA-mutation (which is the greatest risk factor for Parkinson's disease discovered to date)	–Projected patent expiry date (for granted patents): 28 APR2037	AU, CA, CN, EP, IL, JP, KR, RU, US	BR, Pending in: AU, BR, CA, CN, EP, IL, JP, KR, RU, US
Heat shock protein inducers and frontotemporal disorders (PCT/EP2018/063662)	Second medical use directed to hydroxylamine derivative type small molecule inducers of the heat shock proteins, including arimoclomol, and HSP70 protein, for treatment of frontotemporal disorders including frontotemporal dementia FTD and ALS-FTD	–Projected patent expiry date (for granted patents): 24 MAY2038	AU, CA, CN, EP, IL, JP, MX, RU, US	BR, Pending in: AU, BR, CA, CN, EP, IL, JP, MX, RU, US
HSP70 as a biomarker (PCT/EP2019/063854)	Biomarker - directed to the correlation of reduced HSP70 protein levels observed in peripheral blood mononuclear cell (PBMC) samples and	Projected patent expiry date (for granted patents):	PCT	Pending - PCT

Patent family	Type	Expiration	Regions	Status
	certain diseases; such as LSDs and neurodegenerative diseases, neuromuscular disorders.	28 MAY 2039		
A pyridine-1-oxide derivative, and process for its transformation into pharmaceutically effective compounds (PCT/HU01/00046)	Manufacture - directed to an arimoclomol intermediate compound and its use in the preparation of arimoclomol	Projected patent expiry date: 17 APR 2021	AU, CA, CN, EP, IL, JP, US	BR, Granted and maintained in: AU, BR, CA, CN, EP (DE, DK, FR, GB), IL, JP, US
Use of a hydroximic acid halide derivative in the treatment of neurodegenerative diseases (PCT/HU04/00098)	Second medical use – directed to arimoclomol for treatment of neurodegenerative diseases, including ALS and Parkinson's disease	Projected patent expiry date (for granted patents): 25 OCT 2024	AU, CA, EP, JP, UA, ZA	BR, Granted and maintained in: RU, AU, CA, EP (AT, BE, DE, DK, ES, FR, GB, GR, HU, IT, NL, PL, PT, SE, TR), JP, RU, UA, US, ZA Pending in: US Under appeal in: BR
Arimoclomol for treating Gaucher disease (Unpublished)	Second medical use – directed to arimoclomol for treatment of aspects of Gaucher disease	Projected patent expiry date (for granted patents): by 24 JUNE 2041 (assuming regular filing will be made by 24 June 2021)	EP (priority founding)	Filed as a priority founding application; a regular patent application will be filed no later than 24 June 2021 claiming this priority

As of June 30, 2020, our trademark portfolio contained approximately 11 trademark registrations and approximately 12 trademark applications, including one U.S. trademark registration, five EU trademark registrations, one trademark registration in each of China, Israel, India, Japan and Russia, eight pending U.S. trademark applications and four pending EU trademark applications. We have registered "ORPHAZYME" as a word mark in relevant trademark classes and jurisdictions (in the European Union and International Madrid Protocol designating the United States, Canada, Israel, India, Japan and Russia).

Furthermore, we rely upon trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality and invention assignment agreements with our commercial partners, collaborators, employees, and consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with an employee or a third party.

Partnerships and Academic Collaborations

We strive to further develop our expertise within our therapeutic areas of interest through close collaborations with academic experts and patient organizations. Through these partnerships, we support the advancement of molecular and clinical understandings and perform preclinical evaluations in biological models of relevant diseases. Our academic partners include academic professors and clinicians from institutions such as the University of Oxford, University College London and the University of Kansas. Through these collaborations, we have conducted a number of preclinical studies that have provided insights into the potential of HSP amplifying therapeutic strategies for LSDs and neuromuscular diseases. Further, our collaborations with the patient community have enabled patient-relevant outcomes to be assessed in scientific models and subsequently published in peer-reviewed scientific journals.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly changing technologies, competition and a strong emphasis on intellectual property. We are aware of several large and specialty pharmaceutical and biopharmaceutical companies that have developed or are focused on developing treatments for NPC, ALS, sIBM and neurological Gaucher disease. We may also face competition from government agencies, academic research institutions and public and private research institutions with a variety of therapeutic approaches to NPC, ALS, sIBM and neurological Gaucher disease.

Many of our potential competitors may have significantly greater financial resources, a more established presence in the market, and more expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These potential competitors may also compete with us in recruiting and retaining top qualified scientific, sales, marketing and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of arimoclomol are likely to be its efficacy, safety, convenience, price, commercialization capabilities, the level of generic competition and the availability of reimbursement from government and other third-party payors.

A number of large pharmaceutical and biotechnology companies that currently market and sell drugs are pursuing the development of therapies in the fields in which we are interested. Our commercial opportunity for our product candidate could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, less expensive, more convenient or easier to administer, or have fewer or less severe side effects, than any products that we may develop. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

Treatment Options for NPC

The majority of current treatment options for NPC are only directed towards the specific symptoms apparent in each individual.

We consider our most direct competitor with respect to NPC to be Zavesca (miglustat), which was originally developed by Actelion Pharmaceuticals and is now owned by Johnson & Johnson, which is also available as a generic product in several countries and is currently approved for the treatment of NPC. Miglustat has not been approved by the FDA for treatment of NPC, but it is approved for the treatment of Gaucher Type I disease in the United States. For the treatment of NPC, it is approved only in Europe, Canada, Australia, New Zealand, and several countries in Asia and South America as Zavesca and in Japan as Brazaves.

Studies are currently being performed to test the safety and efficacy of other treatment options, including the following:

- Adrabetadex (VTS-270), which has been evaluated in a Phase 2b/3 clinical trial by Mallinckrodt Pharmaceuticals. In June 2019, Mallinckrodt Pharmaceuticals communicated that the Phase 2/3 top-line results did not meet statistical significance (p=0.55). This product candidate has received orphan drug designation by both the FDA and EMA.

- Trappsol is being evaluated in a Phase 1/2a clinical trial by Cyclo Therapeutics. This product candidate has received orphan drug designation by both the FDA and EMA.

- IB1001 is being evaluated in a Phase 2 clinical trial by IntraBio. This product candidate has received orphan drug designation by both the FDA and EMA and fast track designation by the FDA.

- ESB1609 is being evaluated in a Phase 1 clinical trial by E-scape Bio.

Treatment Options for ALS

We consider our most direct competing products with respect to ALS to be Rilutek (riluzole) and Radicava (edaravone). Until recently, the only pharmaceutical product used for modifying ALS was Rilutek, developed by Sanofi, which was the first drug to be approved by the FDA for the treatment of ALS more than 20 years ago and is now available in oral generic tablets as well as branded liquid and film formulations. In May 2017, the FDA approved Radicava, developed by Mitsubishi Tanabe Pharma America, which is administered through chronic cycles of 14-days of intravenous infusions. Clinical trial data have demonstrated that patients receiving Radicava for six months experienced significantly less decline in physical function compared to placebo. A clinical trial of oral Radicava has recently been initiated. Radicava has an indicated cost of $1,000 for each infusion, and the ALS Association has estimated an annual treatment cost of $146,000. A MAA for Radicava was filed by Mitsubishi Tanabe in Europe in 2018, but was subsequently withdrawn in May 2019.

In addition to the current treatment options for ALS, a number of pharmaceutical product candidates are being developed to treat ALS, including (i) levosimendan (Orion Pharma), a calcium channel sensitizer approved in many countries outside of the United States for treatment of acutely decompensated heart failure, (ii) NurOwn (Brainstorm Therapeutic), a mesenchymal stem cell treatment, (iii) BIIB067/tofersen (Biogen), an antisense oligonucleotide therapy of SOD1-ALS. Each of these product candidates are currently undergoing Phase 3 clinical development, (iv) oral edaravone (Mitsubishi Tanabe), an oral version of currently approved IV formulation, and (v) Ultomiris (ravulizumab; Alexion), a long-acting C5 inhibitor. In addition, there are planned Phase 3 clinical trials for (i) Masitinib (AB Science), a tyrosine kinase inhibitor used for mast cell tumors and (ii) reldesemtiv (Cytokinetics), a fast skeletal muscle troponin activator. The Phase 2 trial of reldesemtiv did not achieve statistical significance for its primary efficacy endpoint.

Treatment Options for sIBM

We are not aware of any therapeutic agent that has shown efficacy in preventing, halting or reversing the progression of sIBM and therefore, no drugs have been approved for sIBM. In particular, the disorder has not shown to respond to conventional therapies for autoimmune disorders, such as

corticosteroids or immunosuppressive drugs. Therefore, the standard treatment option for sIBM consists only of supportive therapy such as physical, speech and occupational therapy. We also do not expect any therapies to be approved for sIBM in the near future.

Treatment Options for Gaucher Disease

There are currently no treatments for neurological symptoms of Gaucher disease. There are treatments for Gaucher Type 1 and these have been approved based on their ability to improve the systemic features of Gaucher disease. None of them are approved for treatment of Gaucher disease type 2 and 3. The two types of treatment currently available for patients with Gaucher Type 1 disease include: ERT, such as Cerezyme (Sanofi), Elelyso (Pfizer) and Vpriv (Shire); and SRT using Zavesca or Cerdelga (Sanofi).

In addition to ERT and SRT, there are a few other advanced clinical programs for the treatment of Gaucher disease, including:

- Genzyme (a Sanofi subsidiary) is currently evaluating the combined use of two agents in an ongoing open-label Phase 2 clinical trial with a target enrollment of 10 patients with Gaucher disease Type 3. The patients received combination treatment with GZ/SAR 402671 (venglustat, Sanofi), a SRT in combination with the marketed ERT Cerezyme (imiglucerase, Genzyme).

- Tottori University Hospital and Shire (a Takeda subsidiary) have registered an open-label, Phase 2/3 clinical trial in the Japan clinical trial registry, evaluating the efficacy and safety of ambroxol hydrochloride, an over-the-counter antitussive first registered in 1978, in patients with neuronopathic Gaucher disease.

- AVROBIO Inc. is sponsoring an ongoing open-label, non-randomised Phase 1/2 clinical trial Lentiviral Vector Gene Therapy AVR-RD-02 for subjects with Gaucher disease Type 1.

Organization and Employees

We are located at Copenhagen Bio Science Park, Ole Maaløes Vej 3, 2200 Copenhagen N, Denmark. Our office in Copenhagen serves as our headquarters and focuses on coordination and execution of the drug development process and on the conduct of preclinical and clinical trials and administration. We have a wholly-owned subsidiary, Orphazyme US, Inc., with offices at 180 N. LaSalle Street, Suite 3475, Chicago, IL 60601. Our office in Illinois serves as the headquarters for our U.S. operations. As of June 30, 2020, we had 114 employees, most of whom are engaged in the development of strategies, design, planning, procurement and project management and execution of clinical trials and preclinical studies and regulatory matters.

Our History and Development

We were founded in 2009 with the objectives to develop new therapies for patients suffering from protein misfolding diseases with no or limited treatment options available. At inception, we were based on a scientific discovery on the function of HSPs by Thomas Kirkegaard Jensen, who currently serves as our Chief Scientific Officer, and Professor Marja Jäättelä, which was published in *Nature*. Since inception, we have translated certain of our scientific discoveries into a late stage clinical development program. A brief historical overview of the key milestones in our development is presented below:

2009 ***We were founded to pursue the opportunity of developing new therapies based on the cell protective function of HSPs***

2010 ***Our current Chief Scientific Officer and co-authors published scientific foundation of our company in Nature***

We raised DKK 22 million (approximately $4 million at the rate of $1.00 to DKK 5.6183, which was the noon buying rate of the Federal Reserve Bank of New York on December 30, 2010) in a seed financing round (share issue) initiated in 2010. Novo Holdings and Sunstone Capital become shareholders

2011	***We acquired arimoclomol and a portfolio of other molecules from the United States based biopharmaceutical company CytRx***
	We raised DKK 104 million (approximately $18 million at the rate of $1.00 to DKK 5.7303, which was the noon buying rate of the Federal Reserve Bank of New York on December 30, 2011) in a series A financing round initiated in 2011. Aescap Venture becomes shareholder
2013	***EMA granted orphan drug designation to HSP70 for the treatment of NPC***
2014	***EMA granted orphan drug designation to arimoclomol for the treatment of NPC***
	We were awarded the Wellcome Trust Pathfinder Award in collaboration with Oxford University for the project "Regulation of the Heat Shock Response as a Treatment for Niemann-Pick Type C disease"
	We received the EY Entrepreneur of the Year award in the Life Science category
2015	***We raised DKK 150 million (approximately $21 million at the rate of $1.00 to DKK 6.8723, which was the noon buying rate of the Federal Reserve Bank of New York on December 31, 2015) in a series B financing round (share issue) initiated in 2015. Kurma Partners and Idinvest Partners become shareholders***
	FDA granted orphan drug designation to arimoclomol for the treatment of NPC
	We initiated observational trial in NPC
2016	***University College London and University of Kansas invested DKK 1.3 million as part of the sIBM collaboration***
	Preclinical and Phase 2 clinical data with arimoclomol as a potential for the treatment for sIBM was published
	EMA granted orphan drug designation to arimoclomol for the treatment of sIBM
	We and University of Miami announced successful Phase 2 trial of arimoclomol in SOD1-ALS patients. Data presented at the 27th International Symposium on ALS/MND in Dublin
	Our current Chief Scientific Officer and co-authors published preclinical data demonstrating the potential of HSP70 and arimoclomol as a treatment for multiple LSDs, including NPC and Gaucher disease, in Science Translational Medicine
	FDA granted a fast track designation for the Phase 2/3 clinical trial with arimoclomol for the treatment of NPC
	Dosing began in our Phase 2/3 clinical trial with arimoclomol for the treatment of NPC
2017	***We raised DKK 109 million (approximately $18 million at the rate of $1.00 to DKK 6.1933, which was the noon buying rate of the Federal Reserve Bank of New York on December 29, 2017) as an extension to the series B financing round (share issue). LSP and the ALS Investment Fund (through ALS Invest 2 B.V.) became shareholders***

We completed enrollment into the clinical Phase 2/3 trial with arimoclomol for the treatment of NPC

FDA granted orphan drug designation to arimoclomol for the treatment of sIBM

Dosing began in our Phase 2/3 clinical trial with arimoclomol for the treatment of sIBM

End of Phase 2 meeting with FDA regarding arimoclomol for ALS

We assumed sponsorship of the Phase 2/3 arimoclomol trial for sIBM from University of Kansas Medical Center and UCL

We completed our initial public offering and listing on Nasdaq Copenhagen, raising gross proceeds of DKK 600 million ($90 million)

2018 ***We were granted rare pediatric disease designation from the FDA for arimoclomol for the treatment of NPC, enabling eligibility for a priority review voucher***

We established our U.S. subsidiary with offices in Newton, Massachusetts

We enrolled the first patients in a Phase 2 clinical trial for arimoclomol for the treatment of Gaucher disease and Phase 3 clinical trial for arimoclomol for the treatment of ALS

Our current Chief Scientific Officer and co-authors published preclinical proof-of-concept for arimoclomol in Gaucher disease

2019 ***We announced top-line data from our clinical Phase 2/3 clinical trial in NPC***

We confirmed preparation of filings for arimoclomol in NPC with the FDA and the EMA

We completed enrollment of clinical Phase 2/3 clinical trial in sIBM

Kim Stratton joined as our Chief Executive Officer

We completed enrollment of clinical Phase 3 clinical trial for ALS

We completed enrollment of clinical Phase 2 clinical trial in Gaucher

We borrowed €9 million under loan with Kreos Capital VI (UK) Limited

Arimoclomol for the treatment of NPC received Breakthrough Therapy Designation from the FDA

Arimoclomol for the treatment of sIBM received fast track designation in the United States

2020

We reported positive data from our open-label Phase 2/3 extension in NPC

Initiated U.S. EAP for arimoclomol as a treatment for NPC

We incorporated a subsidiary in Switzerland

We raised DKK 745 million ($112 million) through a private placement

Arimoclomol for the treatment of ALS received fast track designation in the United States

We reported data from our Phase 2 clinical trial in Gaucher disease

NDA submission accepted by the FDA for NPC with priority review

Legal Proceedings

From time to time, we may be a party to governmental, litigation, administrative or arbitration proceedings arising in the ordinary course of our business. As of the date of this prospectus, we are not party to any such proceedings. Regardless of the outcome, any future governmental, litigation, administrative or arbitration proceedings could have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors, which impact may be material.

Property

We lease office and laboratory space from COBIS A/S on Ole Maaløes Vej 3, 2200 Copenhagen N, Denmark, with a current total gross area of approximately 1,590 square meters. The lease agreement expires on September 1, 2024. COBIS A/S is entitled to relocate us to another leasehold in the same building with the same size and standard and on the same terms, against payment of reasonable costs associated with the relocation. We also lease an office in Chicago, Illinois for our wholly-owned U.S. subsidiary with a current total gross area of approximately 3,089 square feet. We intend to add new facilities as we add employees, and we believe that suitable additional or substitute space will be available as needed to accommodate any such expansion of our operations.

Recent Developments

In September 2020, the FDA accepted our NDA for arimoclomol for NPC with priority review. In the letter accepting the NDA, the FDA set a target action date of March 17, 2021 under the PDUFA for completion of its review of our NDA. On September 24, 2020, we received a filing communication from the FDA in connection with our NDA for arimoclomol for the treatment of NPC in which the FDA summarized six potential review issues, four of which we have previously discussed with the FDA, including the FDA's continuing evaluation of the integrity of data from our Phase 2/3 trial for NPC; the effect of the high degree of concomitant miglustat use in our Phase 2/3 trial for NPC on its ability to determine the safety and efficacy of arimoclomol, which could have potential implications for labeling/recommended dosing and post-marketing studies; the proposed primary hypothetical treatment effect used in our Phase 2/3 trial for NPC to estimate the treatment benefit effect; the meaningfulness of one metric utilized to evaluate patient progress in our Phase 2/3 trial of NPC; the timing of submission of the QTc and other study reports to the FDA, including in light of evidence suggesting a potential QT safety signal; and differences among the formulations of arimoclomol used in our Phase 2/3 trial of NPC as compared to the formulation of arimoclomol to be marketed. The FDA has requested that we submit reports from the QTc clinical trial by October 1, 2020 and that, given the priority review timeline and both nonclinical and clinical evidence suggesting a potential QT safety signal, submission of these reports after that date may not allow the FDA sufficient time to review. In a preclinical study, we observed a potential QT signal in dogs at a level of arimoclomol exposure that is 28 times higher than the level of exposure in humans in our Phase 2/3 trial in NPC. To date, we are not aware of any clinical evidence of a potential QT signal related to arimoclomol.We do not anticipate being able to submit the reports by October 1, 2020, which may negatively impact our development timeline.

The filing communication constitutes preliminary notice from the FDA of potential review issues as part of its ordinary course review of our NDA and is not necessarily indicative of deficiencies that may be identified during the review. We intend to discuss the filing communication with the FDA. The receipt of the filing communication does not impact the FDA's acceptance of the NDA for arimoclomol, the

target PDUFA date or the priority review determination. However, we cannot assure you that such issues will not result in a delay of any potential approval of arimoclomol for the treatment of NPC by the FDA or a determination by the FDA not to approve the product candidate for marketing in the United States.

Significant change in the operations and principal activities

There has been no significant change to the operations and principal activities of the Group since the end of the period covered by the FY2019 Group Financial Statements.

6.1 Investments

Since the end of the period covered by the H1 2020 Interim Financial Statements, the Company has not made any material investments, is not in progress of making any material investments and/or has no firm commitments to make any material investments.

7 TREND INFORMATION

Most significant recent trends

There has been no significant trends in production, sales and inventory, and costs and selling prices since the end of the period covered by the FY2019 Group Financial Statements.

Significant change in the financial performance

There has been no significant change to the financial performance of the Group since the end of the period covered by the H1 2020 Interim Financial Statements.

Known trends, uncertainties, demands, commitments or events

There have been no known trends, uncertainties, demands, commitments or events that are reasonably likely to have a material effect on the Company's prospects for at least the current financial year.

8 PROSPECTIVE FINANCIAL INFORMATION

8.1 Statement by Management on prospective financial information for the Group for the financial year 2020

Management's prospective consolidated financial information for the financial year 2020 is presented below (the "**Prospective Financial Information**").

We have prepared and presented the Prospective Financial Information, including the key assumptions set out in "*–Methodology and assumptions*". The Prospective Financial Information has been compiled and prepared on a basis which is both comparable with the financial information in the annual report for the financial year 2019 ("**FY2019 Annual Report**") and consistent with the accounting policies applied in the consolidated financial statements for year ended December 31, 2019 ("**FY2019 Group Financial Statements**") as well as the interim consolidated financial statements as of and for the six months ended June 30, 2020 and the related notes ("**H1 2020 Interim Financial Statements**").

The Prospective Financial Information has been prepared for the purpose of this Prospectus.

The Prospective Financial Information is based on a number of factors, including certain estimates and assumptions. The material assumptions on which the Prospective Financial Information is based are described in "*–Methodology and assumptions*".

The Prospective Financial Information represents the best estimates of Management at the Prospectus Date. Actual results are likely to be different from the Prospective Financial Information since anticipated events may not occur as expected, or may materially differ from the forecast provided. The Prospective Financial Information in this section should be read in conjunction with "*Risk factors*" and "*General Information–Forward-looking statements*" included elsewhere in this Prospectus.

Board of Directors

Georges Gemayel
Chairman

Bo Jesper Hansen
Deputy Chairman

Martijn Kleijwegt
Board Member

Martin Bonde
Board Member

Sten Verland
Board Member

Anders Hedegaard
Board Member

Catherine Moukheibir
Board Member

Rémi Droller
Board Member

Carrolee Barlow
Board member

Executive Management

Kim Stratton *CEO*	Anders Vadsholt *CFO*

8.2 Prospective Financial Information

Introduction

The Company prepared the Prospective Financial Information for the FY2020, which is included in this Prospectus, in accordance with applicable laws, rules and regulations.

The Prospective Financial Information was not prepared with a view towards compliance with published guidelines of the U.S. Securities and Exchange Commission and the American Institute of Certified Public Accountants (the "**AICPA**"), for preparation and presentation of prospective financial information. Accordingly, this information does not include disclosure of all information required by the AICPA guidelines on prospective financial information.

While this Prospective Financial Information is presented with numerical specificity, this information is based upon a number of assumptions and estimates, which the Company considers reasonable. As a result, this Prospective Financial Information is inherently subject to significant business, operational, economic and competitive uncertainties and contingencies, and based upon future business decisions that are subject to change.

Therefore, the Company's expectations presented in the Prospective Financial Information as to future developments may deviate substantially from actual developments, and the Group's actual results of operations are likely to be different from the Prospective Financial Information since anticipated events may not occur as expected, or may materially differ from the forecast provided. Accordingly, potential investors should treat this information with caution and not place undue reliance on the expectations set forth below.

Management's Responsibility

The Management is responsible for the proper compilation of the Prospective Financial Information on the basis stated and for accounting policies used for the Prospective Financial Information and their consistency with the accounting policies of the Company and for such internal control as the Management determines is necessary to enable the preparation of Prospective Financial Information on the basis stated.

Furthermore, the Management is responsible for the assumptions underlying the Prospective Financial Information.

Methodology and assumptions

The Prospective Financial Information has been prepared in accordance with the accounting policies presented in the FY2019 Group Financial Statements, which have been prepared in accordance with IFRS as issued by the IASB and in accordance with IFRS as adopted by the EU.

The Prospective Financial Information is prepared for the purpose of this Prospectus.

The Prospective Financial Information has been based on Management's budget for 2020 prepared in accordance with the Company's forecasting and budgeting procedures and on a basis comparable to the FY2019 Group Financial Statements.

The Prospective Financial Information is based on a number of factors, including certain estimates and assumptions. The key assumptions concerning the future, and other key sources of estimation uncertainty at the date of the Prospective Financial Information that have a significant risk of causing a material adjustment to the prospective amounts of expenses, and change to assets and liabilities during the year ending December 31, 2020, are listed below. The Company based its assumptions and estimates on information available when the Prospective Financial Information was prepared.

Certain assumptions, uncertainties and contingencies relating to the Prospective Financial Information are wholly or partly within the control of the Company, while others are outside or substantially outside the control of the Company.

While the Company has presented the key assumptions on which the prospective financial information is based below, it is likely that one or more of the assumptions that the Company has relied upon will not prove to be accurate in whole or in part.

The Group's results of operations could deviate materially from its forecasts as a result of other factors, including but not limited to those described in "*General Information–Forward-looking statements*" and "*Risk Factors*".

For the purpose of preparing the Prospective Financial Information, the Company has applied the key assumptions below:

Currency

The Prospective Financial Information is presented in the Company's reporting currency DKK. Many of the expected costs for the year are denominated in foreign currencies. While many of the large cost drivers within research and development costs are denominated in EUR, which is pegged to the DKK within a narrow fluctuation band, many of the pre-commercial and launch costs anticipated will be incurred in the U.S. in USD. Accordingly, future changes in the exchange rates between the DKK and the USD will impact the Company's actual expenses and expose the Company to currency gains or losses that will impact the expected amounts of assets and liabilities, income and expenses and the impact could be material. The currency assumptions applied for purposes of the Prospective Financial Information are outside the control of the Company.

For the time being, the Company has decided not to utilize foreign currency forward contracts or other derivative instruments to mitigate cash flow or market value risks associated with foreign-currency-denominated transactions.

Research and development expenses

Research and development expenses include costs arising from research and clinical development activities, including employee costs for research and development personnel (i.e. salaries, bonuses, employer contributions to pension schemes, share-based compensation), legal expenses related to the protection, defines and enforcement of the Company's intellectual property, as well as depreciation on right-of-use assets associated with facilities and equipment used for research and development purposes.

The Company's research and development expenses vary from period to period depending on the phase of development of its product candidates. For the financial year ending December 31, 2019, research and development expenses were mainly affected by the full costs of the s-IBM phase 2/3 trial and the ALS phase 3 trial, as they both completed recruitment during the year. In addition, open-label extensions of both trials were initiated during 2019 and pre-clinical activities increased in preparation for the regulatory filings.

For the financial year ending December 31 2020, the Company expects to continue to incur substantial costs associated with clinical trials. Clinical trial costs are a significant component of research and development expenses. The Company's clinical trials activities are performed by third-party Clinical Research Organizations (CROs) and in order to estimate the amount of costs to charge to expense, Management has developed expense models for each clinical trial based on specific estimates and assumptions related to that particular clinical trial (see additional information in note 2.1 of the FY 2019 Group Financial Statements). The majority of the assumptions associated with estimating research and development costs are considered substantially outside the Company's control.

Another significant component of research and development activities are costs related to the manufacturing of our drug candidate, arimoclomol, which the Company expects to increase in 2020. In addition, costs have increased as expected as a result of preparations done in connection with the filing of the NDA earlier in 2020.

General and administrative expenses

General and administrative expenses include salaries for administrative employees and Executive Management, remuneration to the Board of Directors, share-based compensation costs, depreciation on right-of-use assets associated with facilities not used for research and development purposes, and investor relations. In addition, the Company includes pre-commercial activities in general and administrative expenses, such as the costs associated with the Early Access Program for NPC, tradename costs, market and pricing studies, and launch preparation activities. The majority of the assumptions associated with estimating general and administrative expenses are substantially within the Company's control.

The Company's general and administrative expenses are expected to significantly increase in 2020, both in number of FTEs as well as costs of activities, as it prepares for commercial launch by building up the U.S. organization and prepares to expand the global reach. In addition, the support functions such as finance, legal and IT are also expected to increase both in FTEs and costs in order to effectively support the organization. Lastly, the Company also anticipates increased investor relations activities.

Income tax benefit

Consistent with prior years, the Company has included an estimated income tax benefit in the Prospective Financial Information resulting from the anticipated tax credit for research and development expenses at the applicable tax rate under the Danish Corporate Income Tax Act. No capitalization of deferred tax assets is included.

Expectations for the net result for the financial year ending December 31, 2020

Based on the assumptions and methodology as set out above, the Company confirms the expectations for the net result for the financial year ending December 31, 2020, as set out in the FY2019 Group Financial Statements, and accordingly expects a net loss for the financial year 2020 in the range of DKK 500 million - DKK 550 million. At December 31, 2020 the Company anticipates a cash position greater than DKK 300 million.

The Company's result of operations for the financial year 2020 could deviate materially from this forecast as a result of other factors, including, but not limited to, those described in "*General Information–Forward-looking statements*" and "*Risk Factors*".

9 BOARD OF DIRECTORS, EXECUTIVE MANAGEMENT AND KEY EMPLOYEES

9.1 Overview

The Company has a two-tier governance structure consisting of the Board of Directors and the Executive Management. The two bodies are separate and have no overlapping members. The Executive Management is supported by the Company's key employees (the "**Key Employees**").

The business address of the Board of Directors, Executive Management and the Key Employees is Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark.

For a description of the remuneration of the Board of Directors, Executive Management and Key Employees, including ownership of Shares and holding of Share related instruments granted under the Company's current incentive schemes, also see the FY2019 Group Financial Statements.

Board of Directors

The Board of Directors is responsible for the overall and strategic management and proper organization of the Company's business and operations and supervises the Company's activities, management and organization. The Board of Directors appoints and dismisses the members of the Executive Management, who are responsible for the day-to-day management of the Company.

In accordance with article 8.1 of the Articles of Association, the general meeting of the Company shall elect not less than six and not more than nine members to the Board of Directors. The Board of Directors elects a chairman (the "**Chairman**") and, if so decided, a deputy chairman ("**Deputy Chairman**") of the Board of Directors among its members. See article 8.3 of the Articles of Association.

The members of the Board of Directors elected by the general meeting are elected for a term of one year. Members of the Board of Directors may be re-elected. See article 8.2 of the Articles of Association.

At the date of this Prospectus, the Board of Directors comprises of nine members elected by the general meeting comprising the Chairman, the Deputy Chairman and seven board members.

The following table presents an overview of the current composition of the Board of Directors:

Name	Position	Independent(1)	Year of first appointment	Expiration of term
Georges Gemayel(4)	Chairman	Independent	2012	2021
Bo Jesper Hansen(3)	Deputy Chairman	Independent	2010	2021
Anders Hedegaard(3)	Member	Independent	2017	2021
Catherine Moukheibir(2)	Member	Independent	2017	2021
Martijn Kleijwegt (2)	Member	Independent	2017	2021
Martin Bonde(4)	Member	Independent	2010	2021
Rémi Droller(3)	Member	Independent	2015	2021
Sten Verland(2)(4)	Member	Independent	2010	2021
Carrolee Barlow	Member	Independent	2020	2021

(1) The Company has based its assessment of independence on the basis of the criteria set out in the current Corporate Governance Recommendations.
(2) Member of the Audit Committee.
(3) Member of the Remuneration Committee.
(4) Member of the Nomination Committee.

All members of the Board of Directors are considered by the Company to be independent under the current Corporate Governance Recommendations.

Biographies

Other than as presented below, none of the members of the Board of Directors have been a member of the administrative, management or supervisory bodies of a company or a partnership or been a partner in a partnership outside the Company within the past five years.

Georges Gemayel (born 1960, American nationality) has served as a member of our board of directors since November 2012 and as Chairman of our board of directors since September 2014. Mr. Gemayel is currently chairman of the board of directors of Dynacure SAS, Enterome SA and OxThera AB and a member of the board of directors of Momenta Pharmaceuticals Inc. and Supernus Pharmaceuticals Inc. Mr. Gemayel has been a partner in Gemayel Investment LLC since 2012, as well as a director of the non-governmental organization, St. Andrew's School in Ngong Inc. and a trustee of the Gemayel Family

Foundation. In the past five years, Mr. Gemayel was chairman of the board of directors of Dimension Therapeutics Inc., Epitherapeutics ApS and Vascular Magnetics Inc., a member of the board of directors of NPS Pharmaceuticals Inc. and Raptor Pharmaceuticals Corp., a consultant for Novo Ventures 1 A/S, Fidelity Ventures and Noveome Biotherapeutics Inc. as well as a director of the nongovernmental organization, International Institute of New England. Mr. Gemayel holds a Master's degree and a PhD degree in Pharmacology from Paris-Sud University and a Docteur d' Exercice en Pharmacie from the St. Joseph University.

Bo Jesper Hansen (born 1958, Danish nationality) has served as a member of our board of directors since December 2010 and as Deputy Chairman since October 2017. Dr. Hansen is currently chairman of the board of directors of Laborie Inc., Innoventa Medica ApS and Karo Pharma AB, as well as a member of the board of directors of Ascelia Pharma AB. Dr. Hansen is also a venture partner at Wellington Partners Life Science Fund LP and an advisory consultant for Aescap 2.0, Nordic Capital, EQT AB and Broad Street Principal Investments Europe Ltd. and senior business advisor for HBM Ventures Ltd. In the past five years, Dr. Hansen was chairman of the board of directors and a member of the executive management of Swedish Orphan Biovitrum AB, chairman of the board of directors of Ablynx NV, Karolinska Development AB and a member of the board of directors of Newron Pharmaceuticals SpA, CMC Sweden AB, Hyperion Therapeutics Inc., Azanta A/S (which was acquired by Norgine B.V. in 2020) and Inspyr Inc. Dr. Hansen holds an M.D. and Ph.D. degree in Medicine from the University of Copenhagen.

Anders Hedegaard (born 1960, Danish nationality) has served as a member of our board of directors since November 2017. Mr. Hedegaard has been Chief Executive Officer of Rodenstock Group since 2019 and serves on the board of directors of certain Rodenstock Group companies. Mr. Hedegaard has been the chairman of the board of directors of ALK-Abelló A/S since March 2020. In the past five years, Mr. Hedegaard was chairman of the board of directors of Natus Medical Denmark ApS, chief executive officer of GN Store Nord A/S and GN Hearing A/S, a member of the executive management and a member of the board of directors of GN Advanced Hearing Protection A/S as well as a member of the board of directors of the Confederation of Danish Enterprise, Hearing Instrument Manufacturers Software Association A/S and HIMSA II A/S. Mr. Hedegaard holds a Master of Science in Chemical Engineering from the Technical University of Denmark.

Catherine Moukheibir (born 1959, American, Lebanese and British nationality) has served as a member of our board of directors since November 2017. Ms. Moukheibir is currently chairman of the board of directors and chief executive officer of MedDay Pharmaceuticals SA, as well as a member of the board of directors of Genkyotex SA, Ironwood Pharmaceuticals, Inc. and Kymab Ltd. In the past five years, Ms. Moukheibir has been a member of the executive management and a consultant for Innate Pharma Inc., chairman of the board of directors of Creabilis Therapeutics SRL, a member of the board of directors of Zealand Pharma A/S, Ablynx NV and Cerenis Therapeutics SA, member of the international advisory board of Imperial College Business School and a member of the international advisory board of the Yale School of Management. Ms. Moukheibir holds a Master in Economics and an MBA degree, both from Yale University.

Martijn Kleijwegt (born 1955, Dutch nationality) has served as a member of our board of directors since January 2017. Mr. Kleijwegt is currently founder and managing partner at LSP Management Group BV and a member of the board of directors of the following portfolio companies of LSP: Kiadis Pharma N.V., Pharvaris BV., OxThera AB, Eloxx Pharmaceuticals Ltd., Arvelle Therapeutics B.V., AM Pharma BV and Vico Therapeutics Holding B.V. In the past five years, Mr. Kleijwegt was also a member of the board of directors of Prosensa N.V. Mr. Kleijwegt holds a Master's degree in Economics from the University of Amsterdam.

Martin Bonde (born 1963, Danish nationality) has served as a member of our board of directors since June 2010 and was chairman of our board of directors until September 2014. Mr. Bonde is currently the Chief Executive Officer at Inthera Bioscience, a biotechnology company, a position he has held since June 2020. Mr. Bonde was previously an Entrepreneur-in-Residence at BiOrigin ApS, a Novo Seeds company. Mr. Bonde is also a member of board of directors of Visiopharm A/S, chief executive officer of Bohrs Tower ApS as well as a member of the board of directors and the executive management of Biotopix ApS. Mr. Bonde was chairman of the board of directors of the trade organization Dansk Biotek,

chief executive officer of Vaccibody AS and Epitherapeutics ApS. Mr. Bonde holds a Graduate Diploma in Business Administration (HD i Udenrigshandel) from Copenhagen Business School, a Master of Science and a Ph.D. in Chemical Engineering from the Technical University of Denmark.

Rémi Droller (full name: Rémi Pascal Louis Droller, born 1975, French nationality) has served as a member of our board of directors since January 2015. Rémi Droller is currently managing partner of Kurma Partners SA and is a member of the board of directors of Dynacure SAS, ImCheck Therapeutics SAS, OxThera AB, AM Pharma BV, Flamingo Therapeutics BV, Vico Therapeutics BV and Pharvaris BV. In the past five years, Mr. Droller was chairman of the board of directors of Step Pharma SAS and a member of the board of directors of STAT Dx (sold to Qiagen). Mr. Droller holds a Master's degree in Molecular Biology from Pierre and Marie Curie University in Paris and a Master's degree in Finance and Management of Innovation from AgroParisTech.

Sten Verland (born 1957, Danish nationality) has served as a member of our board of directors since December 2010. Mr. Verland is currently co-founder and a member of the board of directors of Sunstone Capital A/S, a member of the board of directors and general partner at Sunstone Life Science Ventures A/S, a member of the board of directors of STipe Therapeutics ApS, Anergis SA, MinervaX ApS, OxThera AB, as well as a member of the board of directors and executive management in certain companies in, or associated with, the Sunstone group. Mr. Verland is also currently a member of the executive management of Verland Capital ApS, Verland Holding ApS, Verland Holding II ApS and Genobiotix ApS. In the past five years, Mr. Verland was a member of the board of directors of F2G Ltd., Vaximm AG, Rigontec GmbH, the Danish Venture Capital and Private Equity Association (DVCA), Selskabet af 9. september 2015 A/S and Selskabet af 23. september 2015 ApS, a member of the board of directors and chief executive officer of VetVerland ApS, as well as a general partner and a member of the board of directors and executive management in certain companies in or associated with the Sunstone group. Mr. Verland holds a Master's degree in Biology and a PhD in Immunology, both from the University of Copenhagen.

Carrolee Barlow (born 1963, nationality U.S. citizen) has served on our board of directors since September 2020. Dr. Barlow is the Chief Medical Officer of E-Scape Bio Inc. since January 2019. In the past five years, Dr. Barlow has served as chief executive officer and a member of the board of directors of the Parkinson's Institute and Clinical Center and as a member of the scientific and/or clinical advisory board for multiple companies focused on neurodegenerative and brain disorders. Dr. Barlow is currently a member of the board of directors of Supernus Pharmaceuticals and is a member of the scientific and/or clinical advisory boards of Neurametrix Inc., Kainos Medicine and the Silverstein Foundation. Dr. Barlow holds a Bachelor's degree in English from the University of Utah, an M.D. from the University of Utah School of Medicine and a Ph.D. in Molecular and Development Biology from the Karolinska Medical Nobel Institute.

Executive Management

According to article 9.1 of the Articles of Association, the Board of Directors appoints an Executive Management consisting of one to three members. The primary task of the Executive Management is to carry out the day-to-day management of the Company with the support of the Key Employees.

The following table presents an overview of the current members of the Executive Management:

Name	Position	Year of first appointment	Year of appointment to current position
Kim Stratton	Chief Executive Officer	2019	2019
Anders Vadsholt	Chief Financial Officer	2016	2016

Biographies

Other than as presented below, none of the members of the Executive Management have been members of the administrative, management or supervisory bodies of a company or a partnership or a partner in a partnership outside the Company within the past five years.

Kim Stratton (full name: Kim Narelle Stratton, born 1962, Australian nationality) has served as our Chief Executive Officer since October 2019. Ms. Stratton has been a member of the board of directors of Novozymes A/S since February 2017 and Vifor Pharma AG since May 2019. Ms. Stratton was Head of International Commercial for all ex-U.S. Business across Specialty and Rare Diseases at Shire from August 2013 to October 2019. Previously, Ms. Stratton held several global and local positions with Novartis in the United Kingdom, United States, Switzerland and Europe. Ms. Stratton is a Registered Nurse and received her certification at Royal North Shore Hospital (Australia).

Anders Vadsholt (full name: Anders Fink Vadsholt, born 1969, Danish nationality) has served as our Chief Financial Officer since May 2016 and is registered as part of executive management with the Danish Business Authority. Mr. Vadsholt has been a member of the board of directors of Oxthera AB since February 2019 and the owner and a member of the executive management of Alpha Healthcare Investments ApS since 2015, as well as a partner at Obton Solenergi Sinope Komplementaranpartsselskab since 2015. Mr. Vadsholt was a member of the executive management of Lakeside Invest ApS from 2015 to 2018 and Copenhagen Innovation Capital Management ApS from 2015 to 2018. Mr. Vadsholt holds an MBA in Finance and Strategy from the University of Melbourne and a Master of Science in Corporate Law and Economics from Copenhagen Business School.

Key Employees

The Key Employees are employed by the Company with responsibility for their functional areas.

The following table presents an overview of the Company's current Key Employees:

Name	Position	Year of first appointment	Year of appointment to current position
Thomas Blaettler	Chief Medical Officer	2016	2016
Thomas Kirkegaard Jensen	Chief Scientific Officer	2009[1]	2010

(1) Thomas Kirkegaard Jensen joined the Company as CEO in 2009 and was made CSO in 2010.

Biographies

Other than as presented below, none of the Key Employees have been members of the administrative, management or supervisory bodies of a company or a partnership or a partner in a partnership outside the Company within the past five years.

Thomas Blaettler (born 1967, Danish and Swiss nationalities) has served as our Chief Medical Officer since November 2016. Mr. Blaettler was PD Neuroscience Group Medical Director at F. Hoffmann-La Roche Ltd. from 2009 to October 2016. Mr. Blaettler holds a Doctorate in Medicine from the University of Zürich and a Medical School Certificate Swiss State Examination from the Medical School of the University of Zürich and is a board certified neurologist by the Swiss Medical Association (the Foederation Medicorum Helveticorum).

Thomas Kirkegaard Jensen (born 1977, Danish nationality) has served as our Chief Scientific Officer since March 2010 and previously served as our Chief Executive Officer from June 2009 to March 2010. Mr. Kirkegaard Jensen has been a member of the executive management of Dare to Dream ApS since September 2017, an expert reviewer for the European Research Council since 2015 and a member of the advisory board for the Rare Disease Report since 2014. Mr. Kirkegaard Jensen was a member of the board of directors and executive management of OZ Holding ApS from 2009 to 2017 and vice-chairman of the national Orphan Disease Council from 2014 to 2016. Mr. Kirkegaard holds a Bachelor of Science in Biochemistry, a Master of Science in Human Biology and a PhD in Medicine from the University of Copenhagen.

Statement of kinship

There are no family ties among the members of the Board of Directors, the Executive Management or any of the Key Employees.

Statement on past records

During the past five years, none of the members of the Board of Directors, the Executive Management or any of the Key Employees have been (i) convicted of fraudulent offenses; (ii) directors or officers of companies that have entered into bankruptcy, receivership, liquidation or companies put into administration, except as set out immediately below; or (iii) subject to any official public incrimination and/or sanctions by statutory or regulatory authorities (including designated professional bodies), and have not been disqualified by a court from acting as a member of an issuer's board of directors, executive management or supervisory body or from acting in the management or conduct of the affairs of any issuer.

Georges Gemayel was chairman of Epitherapeutics ApS until 2015, when the company went into voluntary liquidation (which is currently still ongoing). Georges Gemayel was a member of the board of directors of NPS Pharmaceuticals Inc. until 2015, when the company was dissolved following merger; Prosensa N.V. until 2015, when it was dissolved following merger; and Raptor Pharmaceuticals Corp. until 2016, when the company was dissolved following merger.

Bo Jesper Hansen was a member of the board of directors of Hyperion Therapeutics Inc. until 2015, when the company was dissolved following acquisition.

Anders Hedegaard was chairman of the board of directors of Scanning Technology A/S until 2015, when the company was dissolved following merger.

Martijn Kleijwegt was a member of the board of directors of Prosensa N.V. until 2015, when the company was dissolved following merger.

Martin Bonde was a member of the executive management of Epitherapeutics ApS, when it was dissolved following merger in 2015.

Sten Verland was a member of the board of directors of P/S Sunstone Biomedicinsk Venture III, which is currently undergoing voluntary liquidation and NsGene A/S, when it was dissolved by voluntary liquidation in May 2017. Sten Verland was a member of the executive management of Sunstone LSV Partners Holding III ApS, when it was dissolved following declaration of payments in January 2015 and Sunstone LSV Partners & Co. Holding III ApS, when it was dissolved following declaration of payments in January 2015.

Anders Vadsholt was a member of the executive management of Lakeside Invest ApS, when it was dissolved by voluntary liquidation in 2018 and Copenhagen Innovation Capital Management ApS, when it was dissolved by voluntary liquidation in 2018.

9.2 Conflict of interest

Statement on conflicts of interest

No actual or potential conflicts of interest exist between any of the duties of the members of the Board of Directors, the Executive Management and the Key Employees and their private interests or other duties.

None of the members of the Board of Directors, or the Executive Management or any other Key Employees have conflicts of interest with respect to their duties as members of the Board of Directors, or the Executive Management or as Key Employees except for the members of the Board of Directors, Martin Kleijwegt, Rémi Droller and Sten Verland, for the reasons set out in the paragraph above.

None of the members of the Board of Directors, the Executive Management or the Key Employees have positions in other companies which could result in a conflict of interest vis-à-vis such companies, either because the Company has an equity interest in such company or because the Company and the company concerned have an ongoing business relationship. However, the Company may do business in the

ordinary course with companies in which members of the Board of Directors, or the Executive Management, or the Key Employees may hold positions as directors or officers.

With the exception of the members of the Board of Directors, Martin Kleijwegt, Rémi Droller and Sten Verland, the Company is not aware of any member of the Board of Directors, or the Executive Management or any of the Key Employees having been appointed to their current position pursuant to an agreement or understanding with Major Shareholders, customers, suppliers or others.

It follows from the Rules of Procedure of the Company's Board of Directors and the Danish Companies Act that a member of the Board of Directors or the Executive Management shall not participate in the preparation, discussions or the decision-making process concerning an agreement between the Company and the member in question or concerning legal proceedings between the member in question and the Company or an agreement between the Company and any third party or legal proceedings brought against any third party if the member in question has a significant interest therein that may conflict with its interests.

Restrictions on securities trading

In connection with the Global Offering, each of the members of the Board of Directors, the Executive Management and the Key Employees of the Company and certain of its existing shareholders have agreed, subject to limited exceptions, not to offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the ADSs, ordinary shares or such securities convertible or exercisable into ADS or ordinary shares for a period of 90 days after the date of the U.S. Prospectus, or publicly disclose the intention to do any of the foregoing, without the prior written consent of BofA Securities Inc. and Cowen and Company, LLC.

Committees of our Board of Directors

Our board of directors has three standing committees: an audit committee, a remuneration committee and a nomination committee.

Audit Committee

The audit committee consists of Catherine Moukheibir, Martijn Kleijwegt and Sten Verland, and assists the board of directors in overseeing our accounting and financial reporting processes. Ms. Moukheibir serves as chairman of the audit committee.

The audit committee's responsibilities following the Global Offering will include, among other things:

- recommending and supervising our external auditors;
- pre-approve all non-audit services to be provided by any external auditors exceeding a cap determined by our board of directors;
- providing our board of directors with advice regarding the proposed external auditors from time to time as well as evaluate the quality of work being performed by the external auditors;
- ensuring that appropriate policies with regard to hiring employees from our external auditors are in place;
- reviewing and monitoring the independence and quality of work being performed by our external auditors, especially the appropriateness of the provision of non-audit services us;
- evaluating the information contained in our external financial reporting;

- reviewing our annual and quarterly financial statements prior to publication and/or filing (or submission, as the case may be) with the SEC;

- informing our board of directors of the result of the statutory audit, including the financial reporting process;

- monitoring the financial reporting process and submit recommendations or proposals to ensure its integrity;

- evaluating the "going-concern" principle, including any special assumptions, qualifications and/or uncertainties related thereto;

- evaluating the main accounting policies and principles applied including to make recommendations to our board of directors regarding whether these should be amended;

- evaluating significant accounting estimates and judgments made and changes hereto;

- reviewing and evaluating transactions with related parties;

- evaluating relevant risks and uncertainties for the relevant year, e.g. in relation to the outlook in the financial reporting;

- evaluating the overall presentation of our financial reporting in order to ensure that it provides a true and fair view of the financial position as well as our development and performance;

- evaluating our compliance with relevant audit and accounting related laws and regulations;

- supervising our internal audit program;

- such other matters that are specifically delegated to our audit committee by our board of directors from time to time; and

- meeting separately, periodically, with management, internal auditors and the independent auditor.

Remuneration Committee

The remuneration committee consists of Bo Jesper Hansen, Rémi Droller and Anders Hedegaard. Mr. Jesper Hansen serves as chairman of the remuneration committee.

The remuneration committee's responsibilities include, among other things:

- continuously ensuring that the remuneration of the members of our board of directors and our executive management is in accordance with our remuneration policy and is consistent with the performance of the relevant member;

- annually reviewing and, if relevant, making recommendations for amendment of the remuneration policy for the members of our board of directors and our executive management;

- annually reviewing the compensation level of our executive management and comparing it to the market level of management compensation among comparable companies;

- ensuring that agreements with the members of our executive management entitle us under special circumstances to reclaim in full or in part variable remuneration that is paid on the basis of information, which subsequently proves to be manifestly misstated ("claw-back")

and that termination/severance payments shall not exceed the aggregate remuneration for the last two years;

- reviewing any proposals and make recommendations to our board of directors regarding any change to the remuneration or contract terms of our executive management;

- reviewing any proposals and make recommendations to our board of directors regarding any severance payment to our executive management;

- making recommendations to our board of directors regarding the remuneration of the members of our board of directors, including components and levels thereof.

- monitoring that the information in the annual report regarding the remuneration of our board of directors and our executive management is correct, sufficient, and gives a true and fair view;

- ensuring that key compensation terms are disclosed accurately in connection with our annual reporting;

- making recommendations regarding the criteria for assessing the annual incentive and performance pay for our executive management;

- making recommendations to our board of directors at the start of each financial year regarding the criteria for determining the size of our incentive and performance pay for all employees for the present year and at the conclusion of each financial year, review and make recommendations to our board of directors regarding the size and allocation of the incentive and performance pay; and

- such other matters that are specifically delegated to the remuneration committee by our board of directors from time to time.

Nomination Committee

The nomination committee consists of Georges Gemayel, Martin Bonde and Sten Verland. Mr. Gemayel serves as chairman of the nomination committee.

The nomination committee's responsibilities include, among other things:

- assisting the chairman of our board of directors with the annual evaluation of the effectiveness, achievements and competencies of our board of directors and executive management;

- annually reviewing developments in respect of independence criteria for our board of directors and executive management and review the composition of our board of directors and executive management in relation to independence;

- ensuring a formal, thorough and transparent process for selection and nomination of candidates to our board of directors taking into consideration the need for diversity as well as recommending that the majority of the members of our board of directors elected by the general meeting be independent as defined in the Danish Recommendations on Corporate Governance (as amended from time to time);

- reviewing and recommending to our board of directors the target figures and policy for the gender composition of our board of directors and other managerial positions;

- considering proposals for candidates to our board of directors and executive management submitted by relevant persons, including shareholders and members of our board of directors and executive management;

- recommending to our board of directors candidates and any changes to our board of directors and executive management, which shall include a review and assessment of potential candidates for our board of directors and executive management, including their qualifications, experience and other competences as well as any possible conflicts of interests such candidates may have;

- ensuring that recommendations for the nomination and/or replacement of members of our board of directors and executive management shall be prepared on the basis of the qualifications and competences deemed to be required by the Nomination Committee;

- ensuring that recommendations for the nomination and/or replacement of members of our board of directors and executive management shall be prepared in accordance with the target figures and policy for the gender composition of our board of directors and other managerial positions as set out by our board of directors;

- prepare descriptions of nominated candidates' qualifications, including information on other executive functions (e.g. memberships of management boards, boards of directors, supervisory boards, board committees etc.) in Danish and foreign companies as well as any demanding positions and tasks in organizations;

- annually make suggestions for appointment of members to the committees established by our board of directors; and

- such other matters that are specifically delegated to the nominating committee by our board of directors from time to time.

Code of Business Conduct

In connection with the Global Offering, we intend to adopt a code of business conduct and ethics, or code of conduct, which outlines the principles of legal and ethical business conduct under which we do business. The code of conduct applies to all of our board members and employees. The full text of the code of conduct will be made available on our website at www.orphazyme.com. The information on, or that can be accessed through, our website is not part of and is not incorporated by reference into this Prospectus. We have included our website address as an inactive textual reference only. Any amendments to the provisions of the code of conduct will be made only after approval by our Board of Directors or committees thereof and will be disclosed on our website promptly following the date of such amendment or waiver. Any waivers from the provisions of the code of conduct for the benefit of a director or an executive officer will be made only after approval by our Board of Directors or committee thereof and will be disclosed in accordance with applicable securities laws and any waiver from the provisions of the code of conduct for other employees may be made by our compliance officer or by our Board of Directors or committee thereof.

Compensation of Executive Management, Key Employees and Directors

Our executive management consist of our Chief Executive Officer and Chief Financial Officer (the "**Executive Management**"). The members of our Executive Management are eligible to receive an annual performance-based cash bonus subject to certain predefined corporate and individual goals as determined by our Board of Directors on an annual basis. A cash bonus received under the short-term incentive program may not exceed 100% of the annual fixed salary of the participants. The members of our Executive Management are also eligible to receive an extraordinary bonus at the discretion of our Board of Directors.

The following table presents employee compensation, including remuneration to our Board of Directors, for the years ended December 31, 2019 and 2018. Remuneration to our Executive Management includes

remuneration to Kim Stratton for the period from October 1, 2019 to December 31, 2019, to Anders Vadsholt for the full year and to Anders Hinsby for the full year, as he received salary and benefits for the full year of 2019.

	Years Ended December 31,	
(in thousands of DKK)	**2019**	**2018**
Anders Hinsby (former CEO)		
Salary	2,424	1,917
Bonus	1,038	723
Share-based compensation	294	676
Other employee benefits	270	215
Total	4,026	3,531
Kim Stratton (current CEO since Oct 1, 2019)		
Salary	962	—
Bonus	1,025	—
Share-based compensation	—	—
Other employee benefits	215	—
Total	2,202	—
Anders Vadsholt (CFO)		
Salary	1,803	1,411
Bonus	1,250	450
Share-based compensation	406	463
Other employee benefits	260	161
Total	3,719	2,485
Total remuneration to the Executive Management	9,947	6,016

The following table lists aggregate remuneration to our execute officers and Board of Directors for the years ended December 31, 2019 and 2018:

(in thousands of DKK)	Years Ended December 31, 2019	2018
Employee costs, excluding Executive Management and Board		
Salaries	63,530	38,915
Cash bonus	5,394	3,410
Share-based compensation	1,705	1,006
Pensions	4,972	2,686
Other social security contributions	815	322
Other staff costs	766	966
Total employee costs, excluding Executive Management and Board	77,182	47,305
Executive Management remuneration		
Salaries	5,189	3,328
Cash bonus	3,313	1,173
Share-based compensation	700	1,139
Pensions	589	372
Other social security contributions	60	4
Other staff costs	96	—
Total Executive Management remuneration	9,947	6,016
Board of Directors remuneration		
Board and committee fees	2,594	2,584
Travel allowance	294	179
Share-based compensation	145	—
Total Board of Directors remuneration	3,033	2,763
Total employee costs	90,162	56,084
Recognized as follows in the Statement of Profit or Loss:		
Research and development expenses	64,167	40,281
General and administrative expenses	25,995	15,803
Total employee costs	90,162	56,084
Average number of full-time employees	74	46
Year-end number of full-time employees	86	57

The following table lists remuneration to our Board of Directors for the years ended December 31, 2019 and 2018:

(in thousands of DKK)	Years Ended December 31, 2019	2018
Georges Gemayel (Chairman of the Board)		
Board and committee fees	470	468
Travel allowance	64	47
Share-based compensation	28	—
Total	562	515
Bo Jesper Hansen (Deputy Chairman of the Board)		
Board and committee fees	395	394
Travel allowance	46	33
Share-based compensation	21	—
Total	462	427
Martin Bonde		
Board and committee fees	259	258
Travel allowance	—	—
Share-based compensation	16	—
Total	275	258
Martijn Kleijwegt		
Board and committee fees	285	284
Travel allowance	46	33
Share-based compensation	16	—
Total	347	317
Rémi Droller		
Board and committee fees	270	269
Travel allowance	46	33
Share-based compensation	16	—
Total	332	302
Sten Verland		
Board and committee fees	309	307
Travel allowance	—	—
Share-based compensation	16	—
Total	325	307
Anders Hedegaard		
Board and committee fees	270	269
Travel allowance	46	—
Share-based compensation	16	—
Total	332	269
Catherine Moukheibir		
Board and committee fees	336	335
Travel allowance	46	33
Share-based compensation	16	—
Total	398	368
Carrolee Barlow[(1)]	—	—
Total remuneration to the Board of Directors	3,033	2,763

(1) Carrolee Barlow joined the board of directors in September 2020.

No member of the Board of Directors is entitled to any kind of remuneration upon retirement from his or her position as a member of the Board of Directors. We have not allocated funds for any pension benefits, severance schemes or similar measures, or undertaken any other obligations to do so on behalf of the Board of Directors, and we have no obligation to do so.

We previously adopted a Remuneration Policy for the Board of Directors and executive management in accordance with Sections 139 and 139(a) of the Danish Companies Act ("**DCA**").

Executive Management Agreements

Kim Stratton

We entered into a service agreement with Kim Stratton in July 2019 with an effective date of October 1, 2019. Pursuant to the service agreement, Ms. Stratton is entitled to (i) an annual base salary of DKK 3.5 million, which is subject to review on an annual basis, (ii) a sign-on bonus of DKK 675,000 and (iii) standard benefits (such as a mileage allowance, insurance coverage and a company-paid computer). Ms. Stratton is also eligible to participate in our incentive schemes, including for an annual maximum cash bonus of 50% of her annual gross salary. In addition, under the LTIP, Ms. Stratton is eligible to purchase Investment Shares (as defined below) for a total amount of up to 25% of Ms. Stratton's annual gross salary and, subject to the LTIP, is eligible to receive one Matching Share (as defined below) per Investment Share. Additionally, subject to the terms of the LTIP, Ms. Stratton will be eligible to receive six Performance Shares (as defined below) per Investment Share, provided that our share price increased between 20-80%. For further details on the terms and conditions of the LTIP, see "*Related Party Transactions—Equity Plans*." and "*Additional Information—Equity Incentive Plans—Long term Incentive Programs*."

Ms. Stratton also received an additional sign-on bonus in the form of a special CEO share grant. As a prerequisite to such bonus, Ms. Stratton was required to invest DKK 675,000 in shares to be acquired through the public markets. Pursuant to this grant, Ms. Stratton was eligible to receive up to 58,000 shares, provided that our share price increased to 125 DKK per share within three years from the date of employment, consisting of (i) 6,000 shares, provided that our share price increased to 75 DKK per share, (ii) 12,000 shares, provided that our share price increased to 100 DKK per share, and (iii) 40,000 shares, provided that our share price increased to 125 DKK per share.

Ms. Stratton may terminate her employment with us by giving nine months' notice and we can terminate her employment with us by giving 12 months' notice.

The service agreement with Ms. Stratton provides for the payment of a takeover retention bonus equaling 12 months' base salary if Ms. Stratton is still employed by us and not under notice on the first anniversary of completion of certain transactions resulting in a change of control. Ms. Stratton will still be entitled to this bonus if she is under notice on the first anniversary, if we terminate her employment without a reasonably justifiable cause or if she gives the notice due to a gross breach by us.

The service agreement with Ms. Stratton also provides for the payment of post-employment compensation to her dependents in the event of her death. If Ms. Stratton's employment with us ends due to her dismissal by us without the dismissal being due to her circumstances, she is entitled to severance equal to 24 months of her base salary.

Ms. Stratton is subject to a non-competition clause and a non-solicitation of customers clause applicable during her employment and for a period of 12 months following expiry of her employment. Ms. Stratton is not entitled to any separate compensation under her non-competition and non-solicitation clauses. Pursuant to mandatory Danish law, Ms. Stratton's non-competition clause lapses if her employment is terminated by the Company for a reason that is not attributable to her.

Anders Vadsholt

We entered into a service agreement with Anders Vadsholt in October 2017 with an effective date of November 1, 2017, which was later amended to adjust for, among other things, annual salary increases. Pursuant to the service agreement, as amended, Mr. Vadsholt is entitled to (i) an annual base salary of approximately DKK 2.3 million, (ii) participate in our incentive schemes and (iii) standard benefits (such as a mileage allowance, insurance coverage and a company-paid computer).

Mr. Vadsholt may terminate his employment with us by giving six months' notice and we can terminate his employment with us by giving 12 months' notice.

The service agreement with Mr. Vadsholt provides for the payment of a takeover retention bonus equalling 12 months' base salary if Mr. Vadsholt is still employed by us and not under notice on the first anniversary of completion of certain transactions resulting in a change of control. Mr. Vadsholt will still be entitled to this bonus if he is under notice on the first anniversary, if we terminate his employment without a reasonably justifiable cause or if he gives the notice due to a gross breach by us. The service

agreement with Mr. Vadsholt also provides for the payment of post-employment compensation to his dependents in the event of his death.

Mr. Vadsholt is subject to a non-competition clause and a non-solicitation of customers clause applicable during his employment and for a period of 12 months following expiry of his employment. Mr. Vadsholt is entitled to separate compensation under his non-competition and non-solicitation clauses. Pursuant to mandatory Danish law, Mr. Vadsholt's non-competition clause lapses if his employment is terminated by the Company for a reason that is not attributable to him.

9.3 Indemnification of the member of the Board of Directors, Executive Management and Employees

According to the Danish Company Act, the general meeting is permitted to discharge our board members and members of our executive management from liability for any particular financial year based on a resolution relating to the period covered by the financial statements for the previous financial year. This discharge means that the general meeting will relieve such board members and members of our executive management from liability to us. However, the general meeting cannot discharge any claims by individual shareholders or other third parties. In addition, the discharge can be set aside in case the general meeting prior to its decision to discharge was not presented with all reasonable information necessary for the general meeting to assess the matter at hand.

Additionally, at the extraordinary general meeting held on September 21, 2020 the Company's shareholders authorized the Company to indemnify the Board of Directors in relation to certain claims related to the offer, sale and listing of the Company's securities in the United States and in respect of the Company's reports filed with or furnished to the U.S. Securities and Exchange Commission thereafter. The Company's indemnification covers claims and reasonable legal costs arising from the offer, sale and listing of the Company in the United States and/or the Company's subsequent status as a listed company in the United States, including in respect of the Company's reports filed with or furnished to the U.S. Securities and Exchange Commission thereafter. The indemnification is limited to a maximum amount per claim per person equivalent to the gross proceeds obtained by the Company in connection with the offering of American Depositary Shares in the United States.

At that same extraordinary general meeting, the shareholders authorized the Board of Directors to extend the same indemnity to members of the Company's Executive Management and employees of the Company and its subsidiaries, which authorization was inserted as a new article 9.2 in the Company's Articles of Association. At the board meeting held on September 21, 2020, the Board of Directors resolved to exercise this authorization to let the Company indemnify members of the Executive Management and certain employees of the Company for certain claims against these individuals in connection with their services to the Company. The Company's indemnification covers claims and reasonable legal costs arising from the offer, sale and listing of the Company's securities in the United States and/or the Company's subsequent status as a listed company in the United States, including in respect of the Company's reports filed with or furnished to the U.S. Securities and Exchange Commission thereafter. The indemnification is limited to a maximum amount per claim per person equivalent to the gross proceeds obtained by the Company in connection with the offering of American Depositary Shares in the United States.

The Company will not, however, indemnify the member of our Board of Directors, Executive Management and employees, in respect of:

- claims against a person pursuant to Danish law raised before the Danish Courts, except claims arising from the offer, sale and listing of the Company's securities in the United States and/or the Company's subsequent status as a listed company in the United States, including in respect of the Company's reports filed with or furnished to the U.S. Securities and Exchange Commission thereafter;
- claims against a person for damages and legal costs related to criminal and/or grossly negligent or willful acts or omissions committed by the indemnified person;

- claims against an indemnified person, which is attributable to the gaining or purported gaining of any profit or advantage to which the indemnified person or any related natural or legal person was not legally entitled;
- claims covered by insurance. To the extent the insurer refuses to provide cover for other reasons than those referenced in items (i) and (ii) above, the Company's indemnification will cover such claims, provided, however, that the Company shall in such event be entitled at any time to represent the insured in respect of the insurer and shall automatically by subrogation enter into any and all rights under said insurance policy;
- claims brought against the indemnified person by the Company or any subsidiary of the Company; orany sum payable to a regulatory authority by way of a penalty in respect of the indemnified person's personal non-compliance with any requirement of a regulatory nature howsoever arising.

The indemnification shall remain in force for a period of five years after the resignation of the indemnified person from the Company or its subsidiaries, if the claims made within such period are related to such person's services to the Company.

There is a risk that such indemnification will be deemed void under Danish law, either because the indemnification is deemed contrary to the rules on discharge of liability in the Danish Company Act as set forth above, because the indemnification is deemed contrary to sections 19 and 23 of the Danish Liability and Compensation Act, which contain mandatory provisions on recourse claims between an employee (including members of our executive management) and the company, or because the indemnification is deemed contrary to the general provisions of the Danish Contracts Act.

In addition, we provide our board members and executive management with directors' and officers' liability insurance.

10 MAJOR SHAREHOLDERS

Pursuant to section 38 of the Danish Capital Markets Act and section 55 of the Danish Companies Act, the Company has received notifications of holdings of 5% or more of the share capital or voting rights from the shareholders below.

At the Prospectus Date, the Company has received notifications of holdings of 5% or more of the share capital or voting rights from the shareholders below:

Shareholder[a]	Number of Shares as at latest announcement	Ownership interest as at latest announcement	Voting rights as at latest announcement
LSP V Coöperatieve U.A.[1]	2,710,829	10.03%	10.03%
Sunstone Life Science Ventures Fund II K/S[2]	1,804,405	9.10%%	9.10%
Coöperative Aescap Venture I U.A.[3]	1,765,605	8.90%	8.90%
Consonance Capital Master Account LP[4]	1,900,000	7.03%	7.03%

[a] The ownership and voting rights percentages are shown as of the latest announcements received by the Company and assume no further trading by these respective major shareholders. Following completion of the Global Offering, and assuming no trading by these respective major shareholders, these shareholdings will be diluted and each shareholder will notify the Company in the event its shareholdings fall below 5% and/or 10% threshold.

[1] Includes a direct holding of 279,157 shares and an indirect holding of 2,431,672 shares through Orpha Pooling B.V. which is an investment vehicle 88.2% owned by LSP V Coöperatieve U.A. and 11.8% owned by ALS Invest 2 B.V. LSP Management B.V. is the director of LSP V Coöperatieve U.A and the director of Orpha Pooling B.V. and exercises voting rights on behalf of Orpha Pooling B.V.

Martijn Kleijwegt is a director of LSP Management B.V. The address for LSP V Coöperatieve U.A., Orpha Pooling B.V., LSP Management B.V. and Martijn Kleijwegt is Johannes Vermeerplein 9, 1071 DV Amsterdam, the Netherlands.

(2) Sunstone Life Science Ventures Fund II K/S is managed by Sunstone Life Science Ventures A/S (CVR no. 33 85 91 98). The address for Sunstone Life Science Ventures Fund II K/S and Sunstone Life Science Ventures A/S is Store Strandstræde 18, DK-1255 Copenhagen, Denmark.

(3) Coöperative Aescap Venture I U.A. is managed by Aescap Venture Management B.V. Patrick Krol is the manager of Aescap Venture Management B.V. The address for Coöperative Aescap Venture I U.A.Aescap Venture Management B.V. and Patrick Krol is Barbara Strozzilaan 101, 1083 HN Amsterdam, the Nethderlands.

(4) Consists of ordinary shares held by Consonance Capital Master Account LP ("**Consonance Master**"), Consonance Capital Opportunity Master Fund LP ("**Consonance Opportunity**"), and P Consonance Opportunities Ltd. ("**P Consonance**"). Consonance Capital Management LP (the "**Adviser**") is the investment adviser of Consonance Master and Consonance Opportunity, and pursuant to an investment advisory agreement, the Adviser exercises voting and investment power over our ordinary shares held by Consonance Master. Consonance Capital Opportunity Fund Management LP (the "**Capital Opportunity Adviser**") is the investment adviser of P Consonance, and pursuant to an investment advisory agreement, the Capital Opportunity Adviser exercises voting and investment power over the ordinary shares held by P Consonance. Consonance Capman GP LLC ("**Capman**") is the general partner of the Adviser and the Capital Opportunity Advisor and Mitchell Blutt, as the Manager & Member of Capman and Chief Executive Officer of the Adviser and the Capital Opportunity Advisor, may be deemed to control Capman, the Adviser and the Capital Opportunity Advisor. Capman is also the general partner of Consonance Opportunity and Mr. Blutt, as the Manager & Member of Capman, may be deemed to control Capman and Consonance Opportunity. Each of Capman and Mr. Blutt may be deemed to beneficially own these ordinary shares. The address for Consonance Master, Consonance Opportunity, the Adviser, the Capital Opportunity Advisor, Capman and Mr. Blutt is 1370 Avenue of the America, Floor 33, New York, New York 10019.

The percentage of voting rights described above is based on the entire registered share capital of the Company as at the Prospectus Date.

The Company is not authorized to issue company announcements regarding major shareholdings unless the Company has received a prior notice to that effect from a shareholder. Thus, the number of shares and voting rights of major shareholders stated in the specification above may have changed.

The Major Shareholders do not have different voting rights. All Shares in the Company will rank *pari passu*, including with respect to voting rights. All Shares will carry one vote per share of a nominal value of DKK 1. A person registered as a holder of shares of the Company in VP Securities A/S and acting in a professional capacity on behalf of other natural or legal persons, including holders of ADS representing shares of the Company, may exercise voting rights attached to any such shares in a manner that is not identical to the exercise of the voting rights attached to other shares of the Company held by such person.

The Company is not aware of being owned or controlled, directly or indirectly, by others, and the Company is not aware of any agreements that could later result in others taking over the control of the Company.

11 RELATED PARTY TRANSACTIONS

11.1 General

The Company refers to its FY2019 Financial Statements for a description of any related party transaction. Since the FY2019 Financial Statements, the Company entered into the related party transactions described below.

11.2 Share Lending and Subscription Agreement

We entered into a Stock Lending and Subscription Agreement on February 6, 2020 with Danske Bank A/S, Orpha Pooling B.V. and Novo Holdings A/S (the "**Lending Shareholders**"), pursuant to which the Company borrowed 3,071,673 existing ordinary shares (the "**Lending Shares**"), from the Lending Shareholders through Danske Bank A/S as settlement agent in order for the Company to place such ordinary shares in a private placement. The Lending Shares were borrowed subject to an obligation for the Company to issue new ordinary shares of an equivalent number as the Lending Shares placed in this private placement and for Danske Bank A/S to use the proceeds from the sale of Lending Shares in the private placement to subscribe for the new shares and deliver those new shares to the Lending Shareholders. Those new shares were issued and delivered to the Lending Shareholders on February 11, 2020.

11.3 Equity Plans

As of the Prospectus Date, there were 43,951 RSUs (as defined below) outstanding and not exercised, of which (i) 5,781 were granted in July 2019 and vested following our annual meeting on March 26, 2020 and are now exercisable until 12 months following such annual meeting and (ii) 15,177 were granted in March 2020 and will vest following our annual general meeting in 2021 and will be exercisable for a period of 12 months following such annual general meeting in 2021. In addition, 22,993 RSUs were granted in September 2020 and will vest following our annual general meeting in 2021 and will be exercisable for a period of 12 months following such annual general meeting in 2021, such exercise being contingent on the RSU holder not exercising the RSUs granted to him or her in March 2020, and the RSUs granted in March 2020 will subsequently lapse and no longer be exercisable.

As of the Prospectus Date, there were 148,538 Matching Shares that were granted and unvested, which will vest on January 1, 2021. In addition, there were up to 760,594 Performance Shares granted, of which up to (i) 86,700 will vest on November 16, 2021; up to (ii) 125,000 will vest on July 29, 2023; and up to (iii) 548,984 will vest on January 1, 2024, respectively, in each case the total number of Performance Shares being allocated upon vesting is dependent on certain performance criteria. The Company may deliver Matching Shares and Performance Shares under its LTIP by a variety of means, including by way of delivering treasury shares or directed issues of shares and/or bonus shares.

12 INFORMATION ON ASSETS AND LIABILITIES, FINANCIAL POSITION, RESULTS AND DIVIDENDS

12.1 Financial Statements

The information explicitly listed in the table below has been incorporated by reference into this Prospectus pursuant to Article 19 of the Prospectus Regulation. Non-incorporated parts of the documents incorporated by reference are either not relevant for the investor or covered elsewhere in this Prospectus. Direct and indirect references in the documents included in the table below to other documents or websites are not incorporated by reference and do not form part of this Prospectus. The documents speak only for the period in which they are in effect and have not been updated for purposes of this Prospectus. Potential investors should assume that the information in this Prospectus as well as the information incorporated by reference herein is accurate only in the period in which they are in effect.

The information incorporated by reference into this Prospectus is exclusively set out in the cross reference table below, and is available on the Group's website www.Orphazyme.com.

Document/information:

Annual Report 2019
Published at February 28, 2020
FY2019 Group Financial Statements
Management statement, page 88
Independent auditor's report, pages 89-92
Consolidated financial statement including notes, pages 41-76
Interim Report First Half 2020
Published at August 28, 2020
H1 2020 Interim Financial Statements

The tables set out below comprise key financial information pertaining to the Group and has been derived from the FY2019 Group Financial Statements and the H1 2020 Interim Financial Statements prepared in accordance with IFRS as adopted by the EU and additional disclosure requirements of the Danish Financial Statements Act and the H1 2020 Interim Financial Statements prepared in accordance with IAS 34 Interim Financial Reporting as adopted by the EU:

Selected Consolidated Statements of Profit or Loss and Other Comprehensive Income Data:

(In thousands, except per share data)	Six Months Ended June 30,			Years Ended December 31,		
	2020		2019	2019		2018
	$(1)	DKK	DKK	$(1)	DKK	DKK
Research and development expenses	(25,179)	(166,980)	(141,710)	(43,037)	(285,413)	(196,525)
General and administrative expenses	(11,848)	(78,575)	(23,345)	(7.621)	(50,541)	(35,127)
Operating loss	(37,027)	(245,555)	(165,055)	(50,658)	(335,954)	(231,652)
Financial income	19	126	152	48	316	5
Financial expenses	(1,201)	(7,967)	(1,500)	(1,110)	(7,359)	(3,453)
Loss before tax	(38,209)	(253,396)	(166,403)	(51,720)	(342,997)	(235,100)
Income tax benefit	299	1,981	2,495	829	5,500	5,500
Net loss for the period	(37,911)	(251,415)	(163,908)	(50,891)	(337,497)	(229,600)
Exchange difference from translation of foreign operation, net of tax DKK 0	(20)	(135)	(19)	10	67	42
Total comprehensive loss	(37,930)	(251,550)	(163,927)	(50,881)	(337,430)	(229,558)
Loss per share (2)						
Basic loss per share	(1.49)	(9.88)	(8.20)	(2.54)	(16.87)	(11.49)
Diluted loss per share	(1.49)	(9.88)	(8.20)	(2.54)	(16.87)	(11.49)

(1) Translated solely for convenience into U.S. dollars at an assumed exchange rate of DKK 6.6318 per $1.00, which was the rounded official exchange rate of such currencies as of June 30, 2020.

(2) See Note 4.3 to our audited consolidated financial statements which are publicly available for further details regarding the calculation of basic and diluted loss per share.

Selected Consolidated Statements of Financial Position:

(in thousands)	As of June 30, 2020		As of December 31, 2019		2018
	$(1)	DKK	$(1)	DKK	DKK
Cash	92,049	610,448	$18,636	123,588	394,706
Working capital(2)	77,865	516,384	12,400	82,237	370,389
Total assets	101,987	676,360	27,256	180,754	441,349
Share Capital	4,078	27,045	3,013	19,984	19,939
Total equity	76,319	506,135	7,987	52,969	388,249

(1) Translated solely for convenience into U.S. dollars at an assumed exchange rate of DKK 6.6318 per $1.00, which was the rounded official exchange rate of such currencies as of June 30, 2020.

(2) We define working capital as current assets less current liabilities.

Cash flow statement	Six Months Ended June 30,		Year ended December 31,	
	2020 (DKK thousand)	2019	2019	2018
Cash flow from operating activities	(204,169)	(166,597)	(326,818)	(234,764)
Cash flow from investing activities	(1,760)	(1,225)	(3,285)	(2,346)
Cash flow from financing activities	692,944	(1,061)	58,939	-
Net cash flows	487,015	(168,883)	(271,164)	(237,110)
Cash	610,448	225,560	123,588	394,706

12.2 Auditing of financial statement

The audit report for the FY2019 Group Financial Statements is included in this Prospectus by reference.

See "*–Financial statement*".

12.3 Legal and arbitration proceedings

As at the Prospectus Date, the Company is not involved in any governmental, legal or arbitration proceedings, and Management is not aware of any such proceedings being threatened that could have a significant effect on the Company's or the Group's financial position or profitability, nor has the Company or the Group been involved in any such governmental, legal or arbitration proceedings during the previous 12 months as at the Prospectus Date.

12.4 Significant change to the Group's financial position

Since the end of the period covered by the H1 2020 Financial Statements, no significant change to the financial position of the Group has occurred.

12.5 Pro forma financial information

No pro forma financial information has been included in this Prospectus.

12.6 Dividend policy

We have never declared or paid any cash dividends on our ordinary shares and we do not anticipate paying any cash dividends on our shares in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. In addition, the Loan Agreement prohibits us to agree, make or agree to make any distribution by way of dividend or otherwise without the written consent of the lender thereunder.

Any future determination related to our dividend policy and the declaration of any dividends will be made at the discretion of our Board of Directors and will depend on a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors our Board of Directors deems relevant. There can be no assurances that the Group's performance will facilitate dividend payments, and, in particular, the Company's ability to pay dividends may be impaired if any of the risks described in this Prospectus were to occur. See "*Risk factors*".

If we pay any dividends on our ordinary shares, we will pay those dividends, which are payable in respect of the Listing Shares underlying the ADSs to the Depositary, as the registered holder of such Listing Shares, and the Depositary then will pay such amounts to our ADS holders in proportion to the ordinary shares underlying the ADSs held by such ADS holders, subject to the terms of the Deposit Agreement, including the fees and expenses payable thereunder. Cash dividends on our ordinary shares, if any, will be paid in U.S. dollars.

12.6.1 Legal and Regulatory Requirements

In accordance with the Danish Company Act, dividends, if any, are declared with respect to a financial year at the annual general meeting of shareholders in the following year, where the statutory annual report (which includes the audited consolidated financial statements) for that financial year is approved. Any resolution to distribute interim dividends within six months of the date of the statement of financial position as set out in our latest adopted annual report must be accompanied by the statement of financial position from our latest annual report or an interim statement of financial position which must be reviewed by our auditor. If the decision to distribute interim dividends is passed more than six months after the date of the statement of financial position as set out in our latest adopted annual report, an interim statement of financial position must be prepared and reviewed by our auditor. The statement of financial position or the interim statement of financial position, as applicable, must show that sufficient funds are available for distribution. Dividends may not exceed the amount recommended by the Board of Directors for approval by the general meeting of shareholders. Moreover, dividends and interim dividends may only be made out of distributable reserves and may not exceed what is considered sound and adequate with regard to our financial condition or be to the detriment of our creditors and such other factors as the Board of Directors may deem relevant. The Board of Directors is not authorized to distribute interim dividends.

In accordance with the Danish Company Act, share buybacks, if any, may only be carried out by the Board of Directors using funds that could have been distributed as dividends at the latest annual general meeting of shareholders. Any share buyback must be conducted in accordance with an authorization to our Board of Directors to purchase our Shares granted at a general meeting of our shareholders. The authorization must be granted for a defined period of time not exceeding five years. In addition, the authorization must specify the maximum permitted value of treasury shares as well as the minimum and maximum amount that we may pay as consideration for such Shares. A decision by our Board of Directors to engage in share buybacks, if any, will be made in accordance with the factors applicable to dividend payments set forth above. At the annual general meeting of the shareholders held on March 26, 2020, the Board of Directors was authorized until March 26, 2025 to, on behalf of the Company, acquire our own shares for a total nominal value of up to 20% of our share capital for the time being, so long as the company's holding of treasury shares after such acquisition does not exceed 20% of the Company's share capital. The price paid for such shares may not deviate by more than 10% from the share price quoted on Nasdaq Copenhagen at the time of acquisition.

13 ADDITIONAL INFORMATION

13.1 Share capital before and after the Listing

Prior to the Global Offering, we had 27,081,557 Existing Shares with a nominal value of DKK 1 each. Following completion of the Global Offering and the Listing, the Company will have a share capital of 34,697,703 shares, assuming the Overallotment Option is not exercised (or 35,840,124 shares assuming the Overallotment Option is exercised in full) with a nominal value of DKK 1 each or multiples thereof as determined by the Board of Directors. All Shares are issued and fully paid up.

13.2 Equity Incentive Plans

13.2.1 Restricted Share Units

The Board of Directors may be granted share-based incentives in the form of restricted share units ("**RSUs**") under the Board Incentive Program outlined in the Remuneration Policy. Each RSU grants a right to the participants to be allocated one share in the Company. The RSUs will have a vesting period from the date of grant and until the approval of the annual report at the annual general meeting in the following calendar year and is therefore aligned with the one-year election period for the members of the Board of Directors. Following vesting, participants may be allocated a number of shares equivalent to the number of RSUs vested at a maximum price per RSU equal to the par value of the Company's shares and may be exercised within a period of 12 months following vesting.

In general, according to the Company's Remuneration Policy, our Board of Directors may at the time of grant decide to make the vesting or exercise of the RSUs conditional upon certain criteria, including as

continued board membership through the applicable vesting date and, in connection with the September 2020 grant letters, the successful initiation or completion of the Global Offering. To ensure the Board of Directors' independence and supervisory function, such conditions will not be related to financial performance criteria.

Board members are eligible to receive one annual grant with a value corresponding to up to 50% of their fixed annual base fee, such base fee to include additional base fees to the chairman and deputy chairman but excluding any additional fees for committee membership. New board members are eligible to receive one on-boarding grant in connection with their election to the Board of Directors with a value corresponding up to 100% of their fixed annual base fee, such base fee to include additional base fees to the Chairman and Deputy Chairman but excluding any additional fees for committee membership. The value of a grant will be calculated on the basis of a recognized valuation model as determined by the Board of Directors.

In cases where the Board of Directors assesses that the issue or transfer of shares would have a materially adverse effect on us and/or the board member, the Board of Directors may decide to settle the RSUs in cash.

Incentives granted under a share-based incentive program are subject to recovery or "claw-back" in case they have been granted, vested, or exercised on a basis subsequently substantiated as being incorrect.

Our Board of Directors may in its sole discretion resolve to accelerate vesting or amend the terms of the Board Incentive Program or grants thereunder under special circumstances, e.g., in connection with a merger, demerger or delisting or in connection with a public takeover bid for our shares.

13.2.2 Long-term Incentive Programs

The Orphazyme A/S long-term incentive program ("**LTIP**"), was initially established in connection with our admission to trading and official listing on Nasdaq Copenhagen. The LTIP is a matching and performance share program under which the executive management and certain other key employees may be offered to acquire or subscribe for our shares (the "**Investment Shares**"), as determined by the Board of Directors from time to time in connection with each grant. Our Board of Directors may decide to offer other of our or our subsidiaries' current or new employees to participate in the LTIP.

Under the LTIP, the participants may be allocated a number of our shares (the "**Performance Shares**") in proportion to the number of Investment Shares held by the participants, at a maximum price per Performance Share equal to the par value of our shares at the end of a vesting period covering at least three financial years. The number of Performance Shares allocated upon vesting shall be proportional to a potential increase in share price will be calculated as the volume weighted average share price as quoted on Nasdaq Copenhagen during the 10 trading days preceding the relevant vesting date and a reference date to be determined by the Board of Directors. Performance Shares will be allocated on a linear scale with maximum allocation triggered by an 80% increase in share price at the time of vesting, whereas no Performance Shares will be allocated, if the share price has increased 20% or less at the time of vesting. Additionally, vesting is inter alia subject to the participants having maintained ownership of their Investment Shares (as outlined in individual grant letters) and continued employment at the time of vesting. The maximum allocation of Performance Shares will be up to six times the number of Investment Shares subscribed for or held by the participants. The value of Performance Shares shall be calculated using a recognized valuation model as determined by the Board of Directors. The value shall not exceed 200% of the member of the executive management's annual fixed salary at the time of grant.

In order to also promote a short-term share-based incentive for the participants to retain their employment with the company, they may be allocated a number of company shares, or Matching Shares, at a maximum price per Matching Share of DKK 1 with a vesting period shorter than two years to be determined by the Board of Directors. The number of Matching Shares shall at least be equal to the number of Investment Shares subscribed for or held at the time of grant as determined by the Board of Directors and vesting will be subject to the participants having maintained ownership of their Investment Shares and continued employment at the time of vesting. The value of Matching Shares shall

be calculated using a recognized valuation model as determined by our Board of Directors. The value may not exceed 50% of the executive management's annual fixed salary at the time of grant.

The Matching Shares and Performance Shares will vest on an accelerated basis in connection with a public takeover bid for our shares (subject to the vesting conditions of the LTIP being satisfied at such time). Furthermore, our Board of Directors may in its sole discretion decide to accelerate vesting under other special circumstances, e.g. in connection with a merger, demerger or delisting. The number of Matching Shares and Performance Shares may be adjusted in connection with certain changes to our capital structure which may have unintended effects on the value of the Matching Shares or Performance Shares, e.g. capital increases below market value (subject to certain exceptions, including capital increases made in connection with share-based incentive programs).

Incentives granted under a share-based incentive program are subject to recovery or "claw-back" in case they have been granted, vested or exercised on a basis subsequently substantiated as being incorrect.

Our obligation to deliver Matching Shares and Performance Shares under the LTIP may be covered by a variety of means in our discretion, including shares held in treasury by us accumulated through share buy-backs or directed issues of shares and/or bonus shares.

13.2.3 IPO cash bonuses

In connection with the U.S. Offering, Orphazyme has granted its Executive Management, its Key Employees and other employees a cash bonus of six months base salary for Executive Management, four months for Key Employees and up to one month for other employees. This cash bonus will be payable if the U.S. Offering is completed in accordance with specified terms set forth in the individual grant letters. Executive Management may invest one third of such cash bonus in our ordinary shares and the Key Employees may invest one fourth of such cash bonus in our Shares, in each case in accordance with Orphazyme's LTIP.

13.2.4 Shareholding Requirements

Our executive management are at all times required to hold a minimum amount of our shares with a value equal to each of their respective annual fixed salaries at the time of acquisition of the shares. The required shareholding may be built up over a specified period.

14 REGULATORY DISCLOSURES

During the last 12 months, the Company has announced the following inside information in accordance with Regulation (EU) No 596/2014 on market abuse ("**Market Abuse Regulation**"):

- Its announcement of the commencement of a global offering, consisting of initial public offering of ADSs in the U.S. and concurrent private placement of ordinary shares in Europe; subsequent postponement of such offering; (See company announcement no. 52/2020, dated September 21, 2020 and company announcement no. 54/2020, dated September 25, 2020); pricing of its global offering and announcement that the stabilization period has begun (see company announcement no. 55/2020 and no. 56/2020, both dated September 29, 2020);

- its U.S. FDA acceptance and Priority Review of New Drug Application for arimoclomol for NPC (See company announcement no. 50/2020, dated September 16, 2020);

- Its confidential submission of a draft registration statement for a potential registered public offering in the United States (See company announcement no. 37/2020, dated July 1, 2020);

- Its phase II study of arimoclomol in Gaucher disease, which demonstrated marked improvements in key clinical markers (See company announcement no. 36/2020, dated June 24, 2020);

- Its initiation of rolling submission of a new drug application for arimoclomol with US FDA in NPC (See company announcement no 34/2020, dated May 29, 2020);

- Its directed issue and private placement of shares (See company announcement no. 08/2020 and no. 12/2020, dated February 6, 2020 and February 7, 2020);

- Preliminary results for 2019 and financial outlook for 2020 (See company announcement no. 07/2020, dated February 4, 2020);

- Its receipt of US Fast Track designation for arimoclomol in sporadic Inclusion Body Myositis (sIBM) and amyotrophic Lateral Sclerosis ALS (See company announcement no. 31/2019 and 33/2020, dated December 18, 2019 and May 22, 2020);

- (a) Its positive results from its open-label Phase II/III extension in NPC (See company announcement no. 01/2020, dated January 3, 2020); (b) receipt of Breakthrough Therapy Designation for arimoclomol in NPC (See company announcement no. 29/2019, dated November 19, 2019) and (c) the availability of an Early Access Program in the United States for its investigational drug arimoclomol for the treatment of NPC (See company announcement no. 03/2020, dated January 6, 2020).

In addition, the Company disclosed certain transactions with persons discharging managerial responsibilities in the Company in accordance with Article 19 of Market Abuse Regulation, including (i) grants of restricted share-units and vesting of Matching Shares under the Company's LTIP and Board Incentive Program, (ii) acquisitions of shares by a closely associated person to a person discharging managerial responsibilities in the Company and (iii) acquisitions of shares by a person discharging managerial responsibility.

15 MATERIAL CONTRACTS

Material agreements

This section contains brief summaries of (i) material agreements, other than agreements entered into in the ordinary course of business, to which the Company or a company of the Group is a party, for the two years immediately preceding publication of this Prospectus and of (ii) other agreements (not being agreements entered into in the ordinary course of business) entered into by a company of the Group which contain provisions under which a company of the Group has an obligation or entitlement which is material to the Group as at the Prospectus Date.

Asset Purchase Agreement with CytRx

In May 2011, we entered into an Asset Purchase Agreement with the biopharmaceutical company CytRx. Pursuant to this agreement, CytRx sold and transferred certain preclinical and clinical data, patents and other intellectual property rights, and other assets, including contractual rights and obligations relating to a portfolio of chemical compounds, including arimoclomol, to us.

Under the terms of the Asset Purchase Agreement, we made an up-front cash payment of $150,000 and further agreed to make future payments to CytRx contingent upon the achievement of specified clinical/regulatory and sales milestones as well as royalty payments based on a specified percentage of any eventual net sales of products containing one of the purchased compounds, as summarized further below. As of June 30, 2020, we have paid CytRx an aggregate of $500,000 under the Asset Purchase Agreement, which includes the up-front cash payment of $150,000.

Clinical/Regulatory Milestone payment obligations (non-ALS or stroke products)

We have agreed to pay CytRx clinical and regulatory milestone payments for the first two products being developed or labelled for indications other than for the treatment or prevention of amyotrophic lateral sclerosis or stroke (non-ALS or stroke products). Payments are triggered upon achieving certain key

clinical or regulatory milestones. The maximum aggregate amount of milestone payments that may be triggered is $12.1 million for the first non-ALS or stroke product and $10.3 million for the second non-ALS or stroke product developed assuming (for both products) approval in the European Union (or certain major European markets), United States and Japan. A second non-ALS or stroke product is not considered a second product (and does not trigger milestone payments) unless it contains a different compound than the first non-ALS or stroke product. In 2016, we paid CytRx $0.1 million for achievement of a clinical milestone for the first product.

Clinical/Regulatory Milestone payment obligations (ALS or stroke products)

We have also agreed to pay CytRx clinical and regulatory milestone payments (payable one time only) for each product developed that is being developed or labelled for the treatment or prevention of ALS or stroke (ALS or stroke products). Payments are triggered upon achieving certain key clinical or regulatory milestones. The maximum aggregate amount of milestone payments that may be triggered per ALS or stroke product is $23.8 million assuming approval in the European Union (or certain major European markets), the United States and Japan. The milestone obligations are payable only once per ALS or stroke product. A subsequent ALS or stroke product may achieve a milestone and trigger a payment obligation, only if it contains a different compound than an ALS or stroke product previously achieving the same milestone, or if it contains the same compound as another ALS or stroke product previously achieving same milestone but is for a different indication. Under the terms of the Asset Purchase Agreement, we were assigned and became party to a royalty agreement with the ALS Charitable Remainder Trust pursuant to which we are obliged to pay a 1% royalty to the ALS Charitable Remainder Trust on global net sales of products to treat ALS.

Sales milestones. We also agreed to pay CytRx milestone payments upon reaching certain aggregated annual global net sales of all products developed by us containing any of the compounds purchased from CytRx. The first milestone payment is triggered on aggregated annual global net sales exceeding $100 million. The aggregate milestone payment obligations may be up to $50 million assuming aggregated annual global net sales in excess of $1 billion.

Royalties. We have agreed to pay CytRx a low teens double-digit royalty on net sales of all products developed by us, our affiliates or licensees which are labeled or prescribed for the treatment or prevention of ALS or stroke and a mid-single digit royalty on net sales of all other products developed by us or our affiliates or licensees containing any of the compounds purchased from CytRx. Royalties accrue on a country-by-country and product-by-product basis until the latest of expiration of relevant patent claims in the country covering such product, expiry of regulatory exclusivity in the country for such product or ten years from the date of the approval of the product in the country. The royalty rates are subject to reductions for patent expiration, lack of regulatory exclusivity, third party payments and generic competition.

We have no contractual obligations to CytRx to develop or commercialize any products under the terms of the Asset Purchase Agreement and we cannot be held liable towards CytRx for our failure to do so.

Exclusive License Agreement with University of Miami

In September 2019, we entered into an exclusive license agreement with the University of Miami on behalf of itself, Emory University and Massachusetts General Hospital. Pursuant to the exclusive license agreement, we have been granted a global royalty-bearing, exclusive license to all data, know-how, inventions and technology generated by the aforementioned institutions in a Phase 2 clinical trial of arimoclomol in ALS with the A4V SOD1 mutation to research, develop, make, use or sell certain pharmaceutical products or processes containing arimoclomol. Under the license agreement, we are required to use commercially reasonable efforts to develop and commercialize the licensed product. The license is subject to rights of the U.S. federal government.

Under the terms of the exclusive license agreement, we made an up-front cash payment of $75,000 and further agreed to make certain future payments, including (i) a development milestone payment of $1,150,000 upon receiving regulatory approval for a pharmaceutical product containing arimoclomol for which the intended indication is ALS if the institution's Phase 2 clinical trial results were used in

support of such regulatory approval, (ii) annual license fees from 2023 until the earlier of 2033 or termination of the agreement for a maximum aggregate amount of $570,000, and, (iii) beginning on the date of first commercial sale by us, our affiliates or sublicensees of a licensed product or licensed process in a country, a low single-digit royalty on net sales of licensed products or licensed processes on a product-by-product and country-by-country basis for a period of ten (10) years thereafter unless the agreement is terminated earlier. Any annual license fees will be creditable against other payments due in the same calendar year. As of June 30, 2020, we have made payments of an aggregate of $75,000 under the license agreement.

This license agreement will continue on a country-by-country basis until ten (10) years after the first commercial sale of a licensed product or licensed process in such country. This license agreement may be earlier terminated by us for convenience, by either party for the other party's uncured material breach, including for our failure to meet milestone schedules, or by University of Miami for our bankruptcy.

License Agreement with University of Kansas and UCL Business PLC

In October 2017, we entered into a license agreement with the University of Kansas, KU Center for Technology Commercialization Inc., Kansas Life Sciences Development Company Inc. and UCL Business PLC (a wholly-owned subsidiary of University College London which subsequently has been converted into a Ltd). The license agreement grants us the global, royalty bearing exclusive license to all data, know-how, inventions and patent rights generated in the course of the ongoing Phase 2/3 clinical trial for testing arimoclomol in sIBM and other relevant data to research, develop, make, sell and otherwise commercialize pharmaceutical products containing arimoclomol for any purpose. Such license grant is subject to rights held by the U.S. government. The trial was initiated in August 2017 with the University of Kansas as sponsor and supported by an FDA grant. Sponsorship of the trial was transferred to us in December 2017.

Under the terms of the license agreement, we are obliged to pay an aggregate royalty of a low single-digit percentage of net sales of licensed products sold for the treatment, diagnosis, palliation or prevention in humans of sIBM for a period of 10 years in each country from the first commercial sale of a licensed product in such country. We are required to use commercially diligent efforts to develop and commercialize such products and to perform the development plan for the aforementioned clinical trial. As of June 30, 2020, we have not made any cash payments under the license agreement. The license agreement also provides that, in consideration of the license, we are obliged to issue bonus shares in favor of the Kansas Life Sciences Development Company Inc. (for the University of Kansas) and UCL Business Ltd, for up to an aggregate value of $2.5 million depending on the amount of the FDA grant the universities spent the preceding calendar year (with a price per share calculated based on the average closing price of the shares on Nasdaq Copenhagen for the 30 days immediately prior to the date of issuance). The shares are required to be issued or delivered on a yearly basis subject to certain reporting requirements. As of June 30, 2020, 58,090 bonus shares had been issued.

We are also responsible for the enforcement, prosecution and maintenance of licensed patents and all associated costs, subject to the consultation rights of the University of Kansas and UCL Business Ltd. If we choose to abandon or not to maintain any licensed patent, such patent will no longer be licensed to us under the agreement.

This license agreement will continue on a country-by-country basis until ten (10) years after the first commercial sale of the licensed product in such country. This license agreement may be terminated earlier by either party for the other party's uncured material breach or bankruptcy. Following the delivery of the final clinical report for the clinical trial, we may terminate this license agreement if the clinical trial fails to achieve primary endpoints, if a regulatory authority does not approve the licensed product or if the licensed product is approved with a so called "Black-Box Warning". University of Kansas or UCL Business Ltd may terminate the agreement if the aforementioned shares cannot be issued or delivered without any costs to such parties.

Other Agreements Related to Clinical Trials of Arimoclomol

In 2013, we entered into a master service agreement with a UK-based contract research organization ("**CRO**"). Under the terms of the master service agreement, the CRO agreed to provide various services to support our clinical testing of arimoclomol for the treatment of NPC. Contracted services comprise trial set-up and monitoring, trial and data management, statistical analytical work as well as preparation of final study report. As part of the study set-up, we are co-signing as sponsor on the clinical trial agreements entered into with the individual trial sites. Under the terms of the master service agreement, all intellectual property rights pertaining to arimoclomol, including possible patents based on data provided from inventions made during the clinical trial, are owned by us. We have agreed to indemnify the CRO for third-party claims arising from the performance of the clinical trial or from the use of arimoclomol.

We have subsequently entered into similar master service agreements for clinical trial services with three additional CROs, to support our dose-ranging Phase 2 clinical trial of arimoclomol in Gaucher disease, our Phase 3 clinical trial of arimoclomol in ALS and our Phase 2/3 clinical trial of arimoclomol in sIBM.

Loan facility agreement with Kreos Capital VI (UK) Limited

In August 2019, we entered into a structured debt facility (the "**Loan Agreement**"), with Kreos, which consisted of two tranches of €9.0 million (DKK 67.2 million) each. We borrowed €9.0 million from the first tranche (the "**Term Loan**"), but did not draw on the second tranche prior to the expiration date on January 1, 2020. We are required to repay the Term Loan over 42 months with the first 12 months requiring interest only payments at a nominal annual fixed interest rate of 9.75% and the remaining 30 months requiring equal installments comprising principal and interest. Early prepayment of the borrowed amounts may be made in whole but not in part, with the repayment amount being equal to the principal outstanding plus the sum of all the interest repayments that would have been paid throughout the remainder of the loan discounted at an annual rate of 4.0%. The Loan Agreement also provides that we will pay Kreos a facilitation fee upon the request of Kreos, which request may be made in its sole discretion at any time prior to the earlier to occur of August 27, 2024 and the date of delisting of our shares, including ADSs, from a securities exchange. The facilitation fee is equal to the greater of (i) €0.9 million and (ii) the percentage increase in our share price between the 30-day volume-weighted average share price on the date of the Loan Agreement and the closing share price on the day immediately preceding the date of the notification applied to the aggregate amount of amounts borrowed. We have also agreed to pay Kreos an end of loan payment in an amount equal to 3% of the amount drawn under the first tranche on the date the Term Loan is repaid in full. The amounts due under the Loan Agreement are secured by certain of our assets, including our intellectual property rights, pursuant to a floating charge agreement registered with the Danish personal register in the initial principal amount of €9.0 million, our patents registered in Germany, the United Kingdom and the United States, and our shares in our U.S. subsidiary. Our obligations under the Loan Agreement are guaranteed by our U.S. subsidiary. The Loan Agreement includes certain covenants that, subject to certain limited exceptions, limit our ability to, among other things:

- sell, lease, convey, transfer, assign, license or otherwise of or deal with all or any material part of our property, assets or undertaking;
- sell, assign transfer or otherwise dispose of any assets that are subjects to liens under the Loan Agreement, any of our material assets or any share therein;
- incur or allow to remain outstanding any indebtedness;
- create or permit to subsist any liens; and
- declare and/or make or agree to make any distribution by way of dividend or otherwise, without the written consent of Kreos.

While we have not previously breached and are not currently in breach of these or any of the other covenants contained in the Loan Agreement, there can be no guarantee that we will not breach these covenants in the future.

Deposit Agreement

See "*General Information—The Global Offering—Deposit Agreement*" on page 74.

Underwriting Agreement

The Company has entered into an underwriting agreement (the "**Underwriting Agreement**") with BofA Securities, Inc., Cowen and Company, LLC and Guggenheim Securities, LLC, acting as representatives of each of the several underwriters named therein, in relation to the Global Offering . For more information, see "*General Information—The Global Offering*" on page 71. The Underwriters have not been involved in the preparation of this Prospectus.

Other agreements

Save as disclosed above, there are no agreements (other than entered into in the ordinary course of business) to which the Company is a party which (i) are, or may be, material to the Company and which have been entered into in the two years immediately preceding the date of this Prospectus; or (ii) contain any obligations or entitlements which are, or may be, material to the Company as of the date of this Prospectus.

16 DOCUMENTS AVAILABLE

For the term of this Prospectus, the following documents are available for inspection at the Company's head office:

- The Company's Memorandum of Association and Articles of Association.
- The FY2019 Group Financial Statements.
- H1 2020 Interim Financial Statements
- The Prospectus related to the Listing.

Any request for copies of the Prospectus may be made to:

Orphazyme A/S, CVR-no. 32 26 63 55

Ole Maaløes Vej 3

DK-2200 Copenhagen

Tel: (+45) 39 17 82 72

E-mail: contact@orphazyme.com

Subject to certain exceptions, the Memorandum of Association, Articles of Association, the FY2019 Group Financial Statements, the H1 2020 Interim Financial Statements and the Prospectus can also be downloaded from the Company's website: www.orphazyme.com. Except for the information incorporated herein by reference, the contents of the website do not form part of the Prospectus.

The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen. No issue or offering of Shares is made by the Company in connection with the publication of the Prospectus. Investors in ADSs may not rely on this Prospectus for any purpose. This Prospectus will not be and may not be distributed or otherwise made available in any jurisdiction (other than any publication of this Prospectus in accordance with Danish law, rules and regulations) and the Shares may not be offered or sold, directly or indirectly, in the United States, Canada, Australia or Japan or in any other jurisdiction pursuant to this Prospectus. The Company makes no offer or solicitation to

any person under any circumstances that may be unlawful. Persons into whose possession this Prospectus may come are required to inform themselves about and to observe such restrictions.

THE LISTING

1 PERSONS RESPONSIBLE, THIRD PARTY INFORMATION, EXPERTS' REPORTS AND COMPETENT AUTHORITY APPROVAL

1.1 Persons responsible and approval from competent authority

See "*Responsibility statement*" for more details.

1.2 Experts' reports and third party information

This Prospectus does not contain any expert statements or expert reports.

For details on information sourced from third parties, see "*General information–Third party information*".

2 RISK FACTORS RELATED TO THE LISTING

See "*Risk Factors*" for more details.

3 KEY INFORMATION ON CAPITALIZATION AND BACKGROUND OF THE LISTING

3.1 Interest of natural and legal persons involved in the Listing

Some of the Underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates. They have received, or may in the future receive, customary fees and commissions for these transactions. For example, Guggenheim Securities, LLC, an Underwriter in the Global Offering, acted as a placement agent and Danske Bank A/S, an underwriter in the EU Private Placement, acted as a placement agent, lending shareholder and settlement agent in connection with our February 2020 directed issue and private placement and in connection therewith received customary fees and commissions. In addition, Danske Bank A/S and certain of its affiliates are also shareholders of the Company.

In addition, in the ordinary course of their business activities, the Underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The Underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

The Underwriters have not been involved in the preparation of this Prospectus.

Additionally, certain members of the Board of Directors, Executive Management and certain of the Key Employees participate in our equity plans and may therefore have an economic interest in the Global Offering.

Except for this, the Company is not aware of any interests, including conflicting ones, which are material to the Listing.

3.2 Background for the Listing

The purpose of this Prospectus is to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen.

The Listing Shares will be issued through VP Securities and registered with the Danish Business Authority on or around October 1, 2020.

The Listing Shares will be issued in connection with the Global Offering, consisting of the EU Private Placement and the U.S. Offering. 3,966,146 of the Listing Shares are underlying ADSs. The ADSs were listed and began trading on September 29, 2020 on Nasdaq under symbol "ORPH". The price of USD 11.00 per ADS corresponds to a subscription price of DKK 70.1844 per Listing Share (using a USD/DKK exchange rate of 6.3804).

The Bank of New York Mellon has been appointed as Depositary for the ADSs and will be the holder of such Listing Shares underlying ADSs upon issue. The Listing Shares issued in connection with the Global Offering will initially be issued under the temporary ISIN code DK0061411378, and will not be admitted to trading and official listing on Nasdaq Copenhagen under such temporary ISIN. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities.

Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares.

An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen. It is expected that the listing of the Listing Shares on Nasdaq Copenhagen under the Company's existing symbol "ORPHA" and in the ISIN of the Existing Shares DK0060910917 will be effective on or around October 2, 2020, after registration of the capital increase related to the Listing Shares with the Danish Business Authority, expected on October 1, 2020.

3.3 Use of Proceeds of the Global Offering

Since the purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen and there is no offering of securities for sale or subscription in connection with this Prospectus, there are, in turn, no net proceeds as a result of the Listing as such.

However, the Listing Shares are being issued in connection with the EU Private Placement and the U.S. Offering of 3,966,146 ADSs at a price of USD 11.00 per ADS (using a USD/DKK exchange rate of 6.3804). The Company's reason for the EU Private Placement and the U.S. Offering in the United States is to access the U.S. and European capital markets in order to raise funds to support its business.

We estimate that the net proceeds to us from the Global Offering, after deducting the underwriting commissions and estimated offering expenses payable by us, to be approximately DKK 480 milion (USD 75.3 million), or DKK 555 million (USD 87.0 million) if the underwriters exercise their option in full to purchase Additional Securities, based on the initial offering price of DKK 70.1844 (USD 11.00 per ADS), using a U.S. Dollar/DKK exchange rate of 6.3804.

Expenses, after deducting the underwriting commissions and offering expenses, are expected to be approximately DKK 16.6 million (or USD 2.6 million using a U.S. Dollar/DKK exchange rate of 6.3804) and are payable by the Company. The Company has agreed to reimburse the Underwriters for certain expenses as set forth in the Underwriting Agreement. The total underwriting commission is approx. DKK 37.4 million (or USD 5.9 million), and approx. DKK 42.7 million (or USD 6.7 million) if the Overallotment Option is exercised in full, in each case using a U.S. Dollar/DKK exchange rate of 6.3804.

The principal purposes of the Global Offering are to obtain additional capital to support our operations, establish a public market for the ADSs and facilitate our future access to the public capital markets.

We expect to use the net proceeds from the Global Offering, together with our existing cash, as follows:

- approximately USD 35 million to USD 40 million to continue the regulatory approval process for and fund the commercial launch, if approved, of arimoclomol for the treatment of NPC;
- approximately USD 10 million to USD 15 million to advance the clinical development of arimoclomol for the treatment of ALS;
- approximately USD 8 million to USD 12 million to advance the clinical development of arimoclomol for the treatment of sIBM;

- approximately USD 2 million to USD 3 million to advance the clinical development of arimoclomol for the treatment of neurological Gaucher disease; and

- the remaining amounts for working capital and general corporate purposes, including to fund the development of our next generation of HSP amplifiers.

Based on our current operating plan, we believe that the net proceeds from the Global Offering, together with our existing cash, will enable us to fund our planned operating expenses and capital expenditures through the next 24 months. The net proceeds from the Global Offering, together with our existing cash, may be insufficient to fund our product candidate through regulatory approval for one or more indications. We anticipate these funds will be sufficient to fund the commercial launch, if approved, of arimoclomol for the treatment of NPC. We also anticipate these funds will be sufficient to fund the completion of our Phase 3 trial of arimoclomol for the treatment of ALS, completion of our Phase 2/3 trial of arimoclomol for the treatment of sIBM and the initiation of pivotal-stage clinical development of arimoclomol for the treatment of neurological Gaucher disease. We anticipate that we will need additional funds to obtain regulatory approval of arimoclomol for the treatment of ALS, obtain regulatory approval of arimoclomol for the treatment of sIBM and complete the pivotal-stage clinical development of arimoclomol for the treatment of neurological Gaucher disease. It is difficult to predict the cost and timing required to complete development and obtain regulatory approval of, and commercialize, our product candidate due to, among other factors, the relatively short history of our experience with initiating, conducting and completing clinical trials, obtaining regulatory approval and commercializing our product candidate, the rate of subject enrolment in our clinical trials, filing requirements with various regulatory agencies, clinical trial results and the actual costs of manufacturing and supplying our product candidate.

Our expected use of the net proceeds from the Global Offering represents our intentions based upon our current plans and business conditions. As of the date of the Global Offering, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of the Global Offering or the amounts that we will actually spend on the uses set forth above. We believe that opportunities may exist from time to time to expand our current business through licenses with or acquisitions of, or investments in, complementary businesses, products or technologies. While we have no current agreements, commitments or understandings for any specific licenses, acquisitions or investments at this time, we may use a portion of the net proceeds for these purposes.

Our management will have broad discretion over the use of the net proceeds from the Global Offering. The amounts and timing of our expenditures will depend upon numerous factors, including the results of our research and development efforts, the timing, cost and success of preclinical studies and ongoing clinical trials or clinical trials we may commence in the future, the timing of regulatory submissions, our ability to obtain additional financing, the amount of cash obtained through our existing collaborations and future collaborations, if any, and any unforeseen cash needs.

Pending any use described above, we intend to invest the net proceeds of the Global Offering in short- and intermediate-term interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

3.4 Working capital statement

In the opinion of the Company, the working capital available, including the net proceeds of the Global Offering, as of the date of this Prospectus is sufficient for its present working capital needs for the 12 months following the date of this Prospectus.

3.5 Capitalization and indebtedness

The following table sets forth the capitalization, indebtedness (distinguishing between guaranteed and unguaranteed, secured and unsecured) and cash, cash equivalents, and securities of the Company as of June 30, 2020 on an actual basis reflecting the carrying amounts on the balance sheet of the Company and on an as adjusted basis to give effect to the Global Offering (assuming no exercise of the Overallotment Option and after deducting the underwriting commissions and estimated offering expenses payable by the Company). The as adjusted information set forth below is unaudited and for illustrative purposes only.

See "*—Information concerning the Listing Shares*" for information relating to the Company's issued share capital and number of outstanding Shares. You should read this table in conjunction with the Company's FY2019 Group Financial Statements and the H1 2020 Interim Financial Statements.

DKK thousand	**As of June 30, 2020**	**Adjusted for the Global Offering as of June 30, 2020[1]**
Cash	610,448	1,091,194
Total cash	**610,448**	**1,091,194**
Current borrowings	29,954	29,954
Lease liabilities	3,183	3,183
Trade payables and accruals	58,769	58,769
Tax payable	665	665
Other liabilities	29,235	29,235
Total current liabilities	**121,806**	**121,806**
Of which is secured	29,954	29,954
Of which is guaranteed	-	-
Of which is unsecured/unguaranteed	91,852	91,852
Borrowings	36,827	36,827
Lease liabilities	10,976	10,976
Other non-current liabilities	616	616
Non-current liabilities	**48,419**	**48,419**
Of which is secured	36,827	36,827
Of which is guaranteed	-	-
Of which is unsecured/unguaranteed	11,592	11,592
Total financial indebtedness	**170,225**	**170,225**
Net financial indebtedness	**440,223**	**920,969**
Share capital	27,045	34,661
Share premium	1,611,630	2,084,760
Other reserves	5,753	5,753
Accumulated deficit	(1,138,293)	(1,138,293)
Total equity	**506,135**	**986,881**
Total capitalization	**572,916**	**1,053,662**

(1) Assuming a USD/DKK exchange rate of DKK 6.6318 per 1 USD, which was the rounded exchange rate as of June 30, 2020.

Other than as specifically set out above, all of the Company's interest-bearing liabilities are unsecured and unguaranteed.

The Company may need additional capital in the future and may seek to obtain further financing through raising new equity capital or debt financing.

The Company has no reason to believe that there has been any material change to its actual capitalization or indebtedness position since June 30, 2020, other than changes as a result of the Global Offering (as indicated above) and in the ordinary course of business.

4 INFORMATION CONCERNING THE LISTING SHARES

4.1 Type of security and ISIN codes

The Company's Existing Shares are admitted to trading and official listing on Nasdaq Copenhagen under ISIN code DK0060910917. The Company has only one share class.

The Listing Shares will initially be issued under the temporary ISIN code DK0061411378. The Listing Shares will not be admitted to trading and official listing on Nasdaq Copenhagen under the temporary ISIN code. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities.

An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen in the permanent ISIN code for the Existing Shares. Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares. It is expected that the listing of the Listing Shares on Nasdaq Copenhagen under the Company's existing symbol "ORPHA" and in the ISIN of the Existing Shares DK0060910917 will be effective on or around October 2, 2020, after registration of the capital increase related to the Listing Shares with the Danish Business Authority, expected on October 1, 2020.

4.2 Applicable law and jurisdiction

The Listing Shares will be issued in accordance with Danish law. The U.S. Offering has, however, been made in accordance with U.S. law. The EU Private Placement has been made in accordance with EU law and Danish law.

This Prospectus has been prepared in accordance with Danish legislation and regulations applicable in Denmark, including the Danish Capital Markets Act, the Prospectus Regulation, Commission Delegated Regulation (EU) no. 2019/980 of March 14, 2019 as well as Commission Delegated Regulation (EU) 2019/979 of March 14, 2019, and the Nasdaq Issuer Rules. Any dispute which may arise as a result of the Listing is subject to the exclusive jurisdiction of the Danish courts.

4.3 Registration

The Listing Shares will be electronically registered with the Danish Business Authority and issued in book-entry form in VP Securities.

The Company's shareholders' register is kept by Computershare A/S, company registration number (CVR-number) 32266355.

4.4 Currency

The Listing Shares will be denominated in DKK and paid for in United States. When calculating the subscription price for the Listing Shares underlying ADSs in DKK, a USD/DKK exchange rate of 6.3804 has been applied, which was the USD/DKK exchange rate as of September 28, 2020 as published by the Danish Central Bank.

4.5 Rights attached to the Listing Shares

The Listing Shares are registered with the Danish Business Authority and have the same rights as the Existing Shares.

Dividend rights

The Listing Shares have the same rights as the Existing Shares, including with respect to eligibility for any dividends. Each Listing Share entitles its holder to receive distributed dividends and will confer on the holder the right to receive dividends declared after the registration of the Listing Shares with the Danish Business Authority.

Any dividends will be paid in DKK to the shareholder's account with VP Securities. No restrictions on dividends or special procedures apply to holders of Listing Shares who are not residing in Denmark. See "*The Listing–Information regarding the Listing Shares–Taxation*" for a description of the treatment of dividends under Danish tax law. Our dividend policy is described in "*Company Information—Information on assets and liabilities, financial position, results and dividends—Dividend Policy*".

Dividends which have not been claimed by shareholders within three years from the time they are payable will be forfeited and will accrue to the Company.The Articles of Association do not contain provisions on cumulative payments of dividends.

Voting rights

All Shares in the Company will rank *pari passu*, including with respect to voting rights and pre-emption rights. All Shares will then carry one vote per Share of a nominal value of DKK 1. A person registered as a holder of shares of the Company in VP Securities A/S and acting in a professional capacity on behalf of other natural or legal persons, including holders of ADS linked to shares of the Company, may exercise voting rights attached to any such shares in a manner that is not identical to the exercise of the voting rights attached to other shares of the Company held by such person.

The right of a shareholder to attend a general meeting and to vote is determined by the shares held by the shareholder at the record date. The record date is one week before the general meeting is held. The shares held by each shareholder are determined at the record date based on the number of shares held by that shareholder as registered in our register of shareholders and any notification of ownership received by us for the purpose of registration in our register of shareholders, but which have not yet been registered.

Pre-emption rights

If the shareholders of the Company at a general meeting resolve to increase the share capital of the Company by a cash contribution, section 162 of the DCA will apply. Under that section, shareholders have a pre-emptive right to subscribe for new shares in proportion to their existing shareholdings. However, the pre-emptive right may be derogated from by a majority comprising at least two-thirds of the votes cast, as well as at least two-thirds of the share capital represented at the general meeting, provided the share capital increase takes place at market price or nine-tenths of the votes cast, as well as at least nine-tenths of the share capital represented at the general meeting if the share capital increase takes place below market price, unless (i) such capital increase is directed at certain but not all shareholders (in which case all shareholders must consent); or (ii) such capital increase is directed at our employees whereby a majority comprising at least two-thirds of the votes cast, as well as at least two-thirds of the share capital represented at the general meeting is required. Further, the pre-emptive rights may be derogated from by an exercise of the board of directors of a valid authorization in our Articles of Association, provided that the share capital increase takes place at or above market price.

Liquidation rights

In case of the dissolution or winding-up of the Company, the Listing Shares will be entitled to a proportionate part of the Company's assets after payment of the Company's creditors. The Articles of Association do not contain any provisions on redemption or exchange of Shares.

Other Rights

None of the Listing Shares carry any redemption or conversion rights or any other special rights, but the Listing Shares may be subject to compulsory redemption pursuant to the Danish Companies Act, see *"—Danish legislation concerning tender offers, redemption of shares and disclosure of shareholdings*" below.

4.6 Resolutions, authorizations and approvals

The issuance of the Listing Shares took place pursuant to an authorization granted to the Board of Directors at the Company's extraordinary general meeting on September 21, 2020. At the extraordinary general meeting, the Board of Directors was authorized to increase the Company's share capital in one or more issues of new shares without pre-emption rights for the Company's existing shareholders by up to a nominal amount of DKK 10,815,000 from the date of the meeting until March 26, 2025.

The Listing Shares issued in connection with the completion of the Global Offering is expected to be admitted to trading and official listing on Nasdaq Copenhagen under the existing ISIN code on or around September 30, 2020.

4.7 Issue Date of the Listing Shares

The Listing Shares will be issued in the temporary ISIN code DK0061411378, expected on or around October 1, 2020, and will be admitted to trading and official listing on Nasdaq Copenhagen in the permanent ISIN code for the Company's Existing Shares, DK0060910917, and under the existing symbol "ORPHA", expected on or around October 1, 2020.

The Listing Shares will be registered with the Danish Business Authority on or around October 1, 2020 and issued through VP Securities the same day.

4.8 Negotiability and transferability of Listing Shares

The Listing Shares are negotiable instruments under Danish law and there are no restrictions with respect to the transferability of the Listing Shares. General transfer restrictions in connection with the Listing Shares are described in *"—Terms and conditions of the Listing"*. The Articles of Association of the Company do not contain obligations on shareholders to have their shares redeemed.

4.9 Taxation

Introduction

The following is a summary of certain Danish income tax considerations relating to the New Shares. The below is a summary of certain Danish key tax aspects for Danish and foreign investors in relation to acquisition, ownership and disposal of Shares in the Company. The purpose and focus of this summary is solely to outline general information and, as such, the summary should not in any way serve as – and does not purport to constitute – tax or legal advice.

The summary is not an exhaustive description of all tax matters and aspects that may be relevant in relation to the acquisition, ownership or disposal of Shares in the Company. It is specifically noted that the summary does not address all possible tax consequences relating to the Shares.

The summary only includes a description of the Danish taxation of dividends and gains and losses on shares admitted to trading on a regulated market. It is assumed that the relevant shareholder is the beneficial owner of the Shares, and in respect of non-Danish shareholders that the Shares are not attributed to a Danish permanent establishment of the non-Danish shareholder.

The tax legislation applicable to investors may impact the income received from the Shares, investors should take advice from their own tax advisers in relation to identifying the tax consequences of a potential acquisition, ownership or disposal of Shares in the Company based on their specific conditions, including the consequences of state, local or other national tax legislation, if any.

This summary does not include a description of the tax consequences for investors who qualify as traders in securities for tax purposes or for professional investors, such as pension companies etc. Further, the summary does not address situations where Shares are acquired on the basis of subscription rights granted as part of an employment. This summary is based on current legislation, judicial decisions and rulings in Denmark as at the Prospectus Date, all of which may be amended, in some cases with retroactive effect.

Taxation of shareholders resident in Denmark for tax purposes

Individuals who are resident in Denmark for tax purposes, and companies etc. registered in Denmark, or whose effective seat of management is in Denmark, are normally fully liable to pay tax in Denmark. In case the individual or company is also fully liable to pay tax in another country, specific rules not mentioned in this summary may apply.

Taxation of dividends

Individuals, in general

For individuals, dividends are taxed as share income. In the income year 2020, a tax rate of 27% must be paid on the annual share income up to DKK 55,300 (DKK 110,600 for married couples cohabiting at the end of the income year) and 42% of the annual share income exceeding DKK 55,300 (DKK 110,600 for married couples cohabiting at the end of the income year).

The thresholds are adjusted annually and include all share income of the individual / couple concerned during the year.

In case of dividend payments, 27% dividend tax is normally withheld by the company.

Special rules apply to individuals' investment of pension savings. See "*—Capital gains taxation*" for a description of the tax treatment of investment of pension savings.

Companies etc.

In general, a company holding shares in another company admitted to trading on a regulated market is liable for tax on dividends received on the shares. The dividends are taxable at a tax rate of 22%, which is withheld by the company distributing the dividends in connection with the payment of dividends.

Regardless of ownership period, companies may receive tax-exempt dividends in case the shares are subsidiary shares or group company shares. See "*—Capital gains taxation*" regarding the definition of subsidiary shares and group company shares.

Capital gains taxation

Individuals, in general

Capital gains realized on shares are taxed as share income. In the income year 2020, 27% tax must be paid on the annual share income up to DKK 55,300 (DKK 110,600 for married couples cohabiting at the end of the income year) and 42% of the annual share income exceeding DKK 55,300 (DKK 110,600 for married couples cohabiting at the end of the income year). The maximum amounts allowed are adjusted annually and include all share income of the individual/couple concerned during the year.

In case of loss on shares admitted to trading on a regulated market, the loss may be offset against taxable income (capital gains and dividends) from other shares admitted to trading on a regulated market. If the individual is married and the total loss on shares admitted to trading on a regulated market exceeds the individual's capital gains and dividends realized on other shares admitted to trading on a regulated market, the remaining loss is offset against the spouse's share income pursuant to similar rules provided that the spouses are cohabiting at the end of the income year. In case there are still unutilized losses, these may be carried forward indefinitely to be offset against future income from similar shares.

It is a condition for offsetting losses on shares admitted to trading on a regulated market that the Danish tax authorities have received information on the identity of the shares, the quantity, the acquisition date, and the acquisition price before expiry of the deadline for filing the tax return for the income year in which the shares were acquired. The information is generally provided to the Danish tax authorities automatically when the shares are placed in a custody account with a Danish financial institution.

Capital gains and losses are calculated pursuant to the average cost formula according to which the acquisition price of each specific share is calculated as a proportionate part of the total acquisition price for the shareholder's total number of shares in the issuing company.

Individuals, investment of pension savings

Within certain limits, investors have the possibility of placing pension savings in shares having the effect that the net profit will be subject to the Danish Pension Returns Tax Act. The net profit is calculated as the annual realized and unrealized capital gains and losses and added any other profits (such as dividend etc.). The annual net profit is taxed at a rate of 15.3%. Pension return tax is normally settled by the pension company. A transfer from a pension savings custody account to the individual's ordinary custody account is considered a disposal and must be made at market value.

Companies etc.

Irrespective of the period of ownership, companies are liable for tax on capital gains and losses on shares admitted to trading on a regulated market except in case of subsidiary shares and group company shares. The annual realized and unrealized capital gains are taxed pursuant to the mark-to-market principle and is included in the statement of taxable income. Losses calculated pursuant to the mark-to-market principle may be deducted in the statement of taxable income, including in other corporate income. The taxable income is taxed at a rate of 22%.

Capital gains and losses incurred in connection with the sale of group company shares and subsidiary shares are not included in the statement of taxable income of companies. "Subsidiary shares" is generally defined as shares owned by a company holding at least 10% of the share capital of the company issuing the shares. "Group company shares" is generally defined as shares owned by a company, which is jointly taxed (pursuant to section 31 of the Danish Corporation Tax Act) with the company in which shares are owned or which may be internationally jointly taxed (pursuant to section 31 of the Danish Corporation Tax Act) with the company in which shares are owned.

For tax purposes, the transition from subsidiary share status and group company share status to portfolio share status and vice versa is treated as a disposal of shares and acquisition at market value at the time of the transition of status.

Special anti-avoidance rules may apply to prevent, e.g., that shareholdings are pooled in an intermediary holding company in order to avoid taxation of dividends and capital gains. These rules are not further described in this summary.

Danish taxation of investors not fully liable to pay tax in Denmark

Taxation of dividends

Individuals

As a main rule, individuals who are not Danish tax residents are subject to a 27% withholding tax on dividends from Danish companies.

However, it is possible to apply for partial reimbursement of Danish withholding tax if the individual (i) is entitled to a reduction of the tax under a double taxation treaty concluded between Denmark and the tax jurisdiction in which the shareholder is resident; or (ii) holds less than 10% of the Danish company and the competent authority in the state, or in Greenland or in the Faroe Islands, where the person is resident is required to exchange information with the Danish tax authorities according to a double taxation treaty, another international agreement or an administrative agreement of assistance in tax issues. If the shareholder is resident in a country outside the EU, it is also a condition that the shareholder, together with related parties, holds less than 10% of the Danish company. The amount of the reimbursement in question (i) depends on the provisions of the specific double taxation treaty whereas the final withholding tax rate (which also determines the amount of reimbursement) and in situation (ii) constitutes 15%.

Regardless of whether the (final) taxation is reduced as described above, the Danish dividend-distributing company is, as a main rule, obliged to withhold 27% dividend tax. Consequently, the said foreign shareholders subject to a reduced taxation need to file an online application to the Danish tax authorities for the repayment of the excess amount of withholding tax.

Companies etc.

As a main rule, companies who are not Danish tax residents are subject to a 27% withholding tax on dividends from Danish companies.

In general, a foreign company may, however, always apply for partial reimbursement of Danish withholding tax down to 22%.

Moreover, companies may apply for reimbursement if the shareholder (i) is entitled to a reduction of tax under the double taxation treaty concluded between Denmark and the tax jurisdiction in which the shareholder is resident; or (ii) holds less than 10% of the Danish company and the competent authority in the state, or in Greenland or in the Faroe Islands, where the person is resident is required to exchange information with the Danish tax authorities according to a double taxation treaty, another international agreement or an administrative agreement of assistance in tax issues. If the shareholder is resident in a country outside the EU, it is also a condition that the shareholder, together with related parties, holds less than 10% of the Danish company. The amount of the reimbursement in question (i) depends on the provisions of the specific double taxation treaty whereas the final withholding tax rate (which also determines the amount of reimbursement) and in situation (ii) constitutes 15%.

Regardless of whether the (final) taxation is reduced as described above, the Danish dividend-distributing company is, as a main rule, obliged to withhold 27% dividend tax. Consequently, the said foreign shareholders subject to reduced taxation need to file an online application with the Danish tax authorities for the repayment of the excess amount of withholding tax.

A foreign company is exempt from withholding tax on dividends received from a Danish company if the foreign company:

a) receives dividends on shares in subsidiaries and may rely on either reduction or elimination of Danish dividend tax according to the EU Parent-Subsidiary Directive (Directive 2011/96/EU as amended) or according to a double taxation convention between the foreign company's tax jurisdiction and Denmark; or

b) receives dividends on shares in group companies, which are not shares in subsidiaries, when (i) the company receiving the dividends is resident in an EU/EEA member state; and (ii) the taxation of dividends should be waived or reduced according to the provisions of the EU Parent-Subsidiary Directive or a double taxation convention between the foreign company's tax jurisdiction and Denmark if the shares had qualified as shares in subsidiaries.

Accordingly, dividend tax will not be withheld in the two above cases.

Proposal for a Net-Withholding Mechanism

The Danish minister of taxation has published a proposal for a so-called 'net-withholding mechanism' for the handling of dividend withholding taxation of 1) non-resident individuals having shares admitted to trading on a regulated market in Danish companies; and 2) non-resident corporate entities having portfolio shares admitted to trading on a regulated market in Danish companies. It is expected that the proposal shall have legal effect from 1 July 2021.

The key point in the proposed mechanism is the elimination of the dividend tax reclaims, as dividend payments from Danish listed companies to non-resident shareholders will be distributed on a net basis and no longer on a gross basis.

From a technical perspective, this requires that non-resident shareholders must disclose certain key information to their respective custodian bank(s), including, inter alia, the characteristics of the entity, domicile state for tax purposes, a statement of beneficial ownership of the shares for Danish tax purposes and a power of attorney granted to the custodian.

Based on this information, the Danish Tax Authority then issues a unique taxpayer identification number, which grants a right to receive dividends net of the rate of withholding tax applicable in the relevant tax treaty, e.g. most often 15% (if applicable).

Non-resident shareholders eligible for a special tax treatment different from the general tax rate according the relevant tax treaty, e.g. pension funds with a right to 0% in Danish dividend withholding tax, must obtain an advance approval from the Danish Tax Authority to qualify for such special treatment.

Once the non-resident shareholders have submitted information and received a unique taxpayer identification number, they will receive dividends net of the applicable rate.

Non-resident shareholders encompassed by the new net-withholding mechanism will no longer be able to request a reclaim under the current procedure. Instead, there is a 45 days rectification period subsequent to a dividend decision. Furthermore, a relief mechanism in a tax treaty is still available for a non-resident shareholder.

Capital gains taxation

Individuals

As a main rule, individuals who are not Danish tax residents are not liable to pay tax in Denmark on capital gains on the sale of shares in Danish companies.

However, capital gains and losses on shares in Danish companies are taxable in Denmark pursuant to the same rules that apply to individuals resident in Denmark in case the shares are attributable to a permanent establishment in Denmark.

Special rules apply to distributions in connection with capital reductions or the resale of shares to the issuing company.

Companies etc.

As a main rule, companies which are not Danish tax residents are not liable to pay tax in Denmark on capital gains on the sale of shares in Danish companies.

Capital gains and losses on shares in Danish companies are taxable in Denmark pursuant to the same rules that apply to corporate investors resident in Denmark in case the shares are attributable to a permanent establishment in Denmark.

Special rules apply to distributions in connection with capital reductions or the resale of shares to the issuing company as well as sale of shares to a group company.

Share transfer duty

There is no share transfer duty in Denmark.

Tax treatment of ADSs under Danish law

It is currently not clear under Danish tax legislation or case law how ADSs will be treated for Danish tax purposes.

4.10 Danish legislation concerning tender offers, redemption of shares and disclosure of shareholdings

Mandatory takeover bids

The Danish Capital Markets Act (Part 8) and the Danish Executive Order on Takeover include rules concerning public offers for the acquisition of shares admitted to trading on a regulated market (including Nasdaq Copenhagen).

If a shareholding is transferred, directly or indirectly, in a company with one or more share classes admitted to trading on a regulated market, to an acquirer or to persons acting in concert with such acquirer, the acquirer and the persons acting in concert with such acquirer, if applicable, shall give all shareholders of the company the option to dispose of their shares on identical terms, if the acquirer or the persons acting in concert with such acquirer gains control over the company as a result of the transfer.

Control as mentioned above exists if the acquirer or persons acting in concert with such acquirer, directly or indirectly, holds at least one-third of the voting rights in the company, unless it can be clearly proven in special cases that such ownership does not constitute control. An acquirer or persons acting in concert with such acquirer who does not hold at least one-third of the voting rights in a company, nevertheless has control when the acquirer has or persons acting in concert with such acquirer have:

- the right to control at least one-third of the voting rights in the company according to an agreement with other investors; or

- the right to appoint or dismiss a majority of the members of the central governing body.

Voting rights attached to treasury shares shall be included in the calculation of voting rights.

The Danish Capital Markets Act contains specific exemptions from the obligation to submit a mandatory takeover offer, including transfers of shares by inheritance or transfer within the same group and as a result of a creditor's debt enforcement proceedings. Exemptions from the mandatory tender offer rules may be granted under special circumstances by the FSA.

Squeeze-out

Where a shareholder holds more than nine-tenths of the shares in a company and a corresponding proportion of the voting rights, such shareholder may, pursuant to the Danish Company Act, Section 70, demand that the other shareholders have their shares redeemed by that shareholder. In this case, the other shareholders must be requested, under the rules governing notices for general meeting, to transfer their shares to the shareholder within four weeks after the request to transfer their shares. In addition, the other shareholders shall through the Danish Business Authority's IT system be requested to transfer their shares within the same four-week period. Specific requirements apply to the contents of the notices to the other shareholders regarding the redemption. If the redemption price cannot be agreed upon, the redemption price must be determined by an independent expert appointed by the court in the jurisdiction of the company's registered office in accordance with the provisions of the Danish Company Act. However, the redemption price will be deemed fair under any circumstances, provided that (i) the redemption price is equal to the consideration paid by the bidder in connection with a voluntary tender offer by which the bidder obtained at least 90% of the voting rights or (ii) the redemption price is equal to the consideration paid by the bidder in connection with a mandatory tender offer. To the extent any minority shareholders have not transferred their shares to the acquiring shareholder before the expiry of the four-week period, the redeeming shareholder shall pay the redemption price to the remaining minority shareholders through the securities deposit. Upon such payment through the securities deposit, the minority shareholders will have been redeemed and the minority shareholders shall in such case through the Danish Business Authority's IT system be notified that the right to require determination of the redemption price by the independent expert expires at the end of a period, which cannot be less than three months pursuant to the Danish Company Act, Section 72.

Furthermore, where a shareholder holds more than nine-tenths of the shares in a company and a corresponding proportion of the voting rights, the other shareholders may require such shareholder to acquire their shares pursuant to Section 73 of the Danish Company Act. If the redemption price cannot be agreed upon, the redemption price must be determined by an independent expert appointed by the court in the jurisdiction of the company's registered office in accordance with the provisions of the Danish Company Act. Expenses relating to the determination of the redemption price must be paid by the shareholder requesting such determination. If the expert's valuation is higher than the price offered by the redeeming shareholder, the court may order the redeeming shareholder to pay the expenses relating to determination of the redemption price in full or in part.

Major shareholdings

Shareholders in Danish companies with shares admitted to trading and official listing on Nasdaq Copenhagen are, pursuant to Section 38 of the Danish Capital Markets Act, required to give simultaneous notice to the company and the Danish Financial Supervisory Authority (the "**FSA**"), of the shareholding in the company, when the shareholding reaches, exceeds or falls below thresholds of 5%, 10%, 15%, 20%, 25%, 50% or 90% and limits of one-third or two-thirds of the voting rights or nominal value of the total share capital.

A shareholder in a company means a natural or legal person who, directly or indirectly, holds: (i) shares in the company on behalf of itself and for its own account; (ii) shares in the company on behalf of itself, but for the account of another natural or legal person; or (iii) depository receipts, where such holder is considered a shareholder in relation to the underlying shares represented by the depository receipts.

The duty to notify set forth above further applies to natural and legal persons who are entitled to acquire, sell or exercise voting rights which are:

- held by a third party with whom that natural or legal person has concluded an agreement, which obliges them to adopt, by concerted exercise of the voting rights they hold, a lasting common policy towards the management of the issuer in question (common duty to inform for all parties to the agreement);

- held by a third party under an agreement concluded with that natural or legal person providing for the temporary transfer of the voting rights in question in return for consideration;

- attached to shares which are lodged as collateral for that natural or legal person, provided the person controls the voting rights and declares an intention of exercising them;

- attached to shares in which that natural or legal person has a lifelong right of disposal;

- held, or may be exercised within the meaning of (i) to (iv), by an undertaking controlled by that person or entity;

- attached to shares deposited with that natural or legal person and which the person can exercise at its own discretion in the absence of specific instructions from the shareholders;

- held by a third party in its own name on behalf of that person; or

- exercisable by that person through a proxy where that person may exercise the voting rights at its discretion in the absence of specific instructions of the shareholder.

The duty to notify set forth above also applies to anyone, who directly or indirectly holds (a) financial instruments that afford the holder either an unconditional right to acquire or the discretion as to its right to acquire existing shares (e.g., share options); and/or (b) financial instruments based on existing shares and with an economic effect equal to that of the financial instruments mentioned in (a), regardless of them not affording the right to purchase existing shares (e.g., the ADSs or, under the circumstances, cash-settled derivatives linked to the value of our Shares or ADSs representing our

shares). Holding these kinds of financial instruments counts towards the thresholds mentioned above and may thus trigger a duty to notify by themselves or when accumulated with a holding of shares or ADSs. The FSA will in certain cases publish information concerning sanctions imposed, including, as a general rule, the name of the shareholder in question, as a consequence of non-compliance with the above rules.

The notification shall be made promptly, but not later than four weekdays after the shareholder was aware or should have become aware of the completion of the transaction, and in accordance with the provisions of Danish Executive Order on Major Shareholders. The shareholder is deemed to have become aware of the completion of the transaction no later than two weekdays after the completion of the transaction. The shareholder shall disclose the change in voting rights and shares, including the number of voting rights (and the division of voting rights between share classes, if applicable) and shares held directly or indirectly by the shareholder following the transaction. The notification shall further state the transaction date on which the threshold was reached or no longer reached and the identity of the shareholder as well as the identity of any natural or legal person with the right to vote on behalf of the shareholder and in the case of a group structure, the chain of controlled undertakings through which voting rights are effectively held. The information shall be notified to the company and simultaneously submitted electronically to the FSA. Failure to comply with the notification requirements is punishable by fine or suspension of voting rights in instances of gross or repeated non-compliance.

When an obligation to notify rests on more than one natural or legal person, the notification may be made through a joint notification. However, use of a joint notification does not exempt the individual shareholders or natural or legal persons from their responsibilities in connection with the obligation to notify or the contents of the notification.

After receipt of the notification, but not later than three weekdays thereafter, the company shall publish the contents of the notification.

Furthermore, the general duty of notification under Section 55 of the Danish Company Act in respect of notification of significant holdings (similar to the thresholds set out in the Danish Capital Markets Act Section 38) applies, including when the limit of 100% of the share capital's voting rights or nominal value of the company is reached or are no longer reached.

4.11 Public takeover bids for the Company

No takeover offers have been made by any third party in respect of our shares during the past or current financial year. Our Articles of Association do not contain provisions that are likely to have the effect of delaying, deferring or preventing a change in control of the Company.

5 TERMS AND CONDITIONS OF THE LISTING

5.1 Terms, expected timetable and restrictions

This Prospectus is a listing prospectus and no public offering of Listing Shares are made under this Prospectus in Denmark, the EEA or elsewhere. The Listing Shares will in their entirety be subscribed for by the Underwriters, severally and not jointly, on behalf of themselves or on behalf of the investors, as applicable, who, with respect to the U.S. Offering, have instructed the Company to deliver the Listing Shares to the Depositary through Danske Bank A/S, The Bank of New York Mellon whose business address is 101 Barclay Street, New York, New York 10286. The Depositary will then be allowed to deliver the number of ADSs which are subject to the U.S. Offering. The Company has entered into the Underwriting Agreement.

As used herein, the term "Underwriters" refers to with respect to the EU Private Placement, the underwriters (or their respective affiliates) subscribing, on behalf of certain investors, for the European Offered Shares issued by the Company in the EU Private Placement and with respect to the U.S. Offering, the underwriters subscribing for the ordinary shares issued by the Company and underlying the ADSs in the U.S. offering, in each case, in accordance with the Underwriting Agreement. The underwriters in

the U.S. offering and the underwriters in the EU Private Placement are collectively referred to herein as the "Underwriters."

The Underwriters have not been involved in the preparation of this Prospectus.

For more information on the ADSs and the Underwriting Agreement. See *"General Information—The Global Offering"*. The Underwriters have not been involved in the preparation of this Prospectus.

The time table below is for the Global Offering and subsequent Listing:

Date of launch of the EU Private Placement and the U.S. Offering in the United States and publication of the preliminary U.S. prospectus for the offering in the United States	September 21, 2020
Pricing of the U.S. Offering and the EU Private Placement	September 29, 2020 (CET)/ September 28, 2020 (ET)
ADSs started trading on Nasdaq	September 29, 2020
Date of publication in the United States of the final U.S. prospectus	September 30, 2020 (CET)
Publication of this Prospectus	September 30, 2020
Completion of the EU Private Placement and the U.S. Offering (expected)	October 1, 2020
Registration of the Listing Shares with the Danish Business Authority (expected)	October 1, 2020
First day of trading of the Listing Shares on Nasdaq Copenhagen	October 2, 2020

The timetable above is subject to change. Any such changes will be announced as company announcements.

5.2 Total amount

The Listing comprises a total of 7,616,146 Listing Shares, each with a nominal value of DKK 1.

The Company has granted BofA Securities, Inc., Cowen and Company, LLC and Guggenheim Securities, LLC, as representatives of the several Underwriters, an option to subscribe for and purchase up to 1,142,421 Additional Securities to cover the Overallotment Option. The Overallotment Option will expire 30 days after the date of announcement of the pricing of the Global Offering. The Overallotment Option may be exercised in full or in part. The term "Listing Shares" does not include any Additional Securities that may be issued by the Company. The Underwriters have not been involved in the preparation of this Prospectus.

We estimate that the net proceeds to us from the Global Offering, after deducting the underwriting commissions and estimated offering expenses payable by us, to be approximately DKK 480 milion (USD 75.3 million), or DKK 555 million (USD 87.0 million) if the underwriters exercise their option in full to purchase Additional Securities, based on the initial offering price of DKK 70.1844 (USD 11.00 per ADS), using a U.S. Dollar/DKK exchange rate of 6.3804.

5.3 Subscription ratio and allocation

The subscription price for the Listing Shares is DKK 70.1844 (the "**Subscription Price**") corresponding to a price of DKK 70.1844 per ADS (using a DKK/U.S. dollar exchange rate of 6.3804).

The Listing Shares are expected to be issued by us and the capital increase to be registered with the Danish Business Authority on October 1, 2020. The Listing Shares offered in connection with the U.S. Offering will be delivered to the Depositary through Danske Bank A/S on or around October 1, 2020.

5.4 Listing and proceeds

Since the purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen and there is no offering of securities for sale or subscription in connection with this Prospectus, there are, in turn, no net proceeds as a result of the Listing as such. Investors in ADSs may not rely on this Prospectus for any purpose.

However, the Listing Shares are being issued in connection with the EU Private Placement of Shares and the U.S. Offering of 3,966,146 ADSs at a price of USD 11.00 per ADS (using a DKK/U.S. dollar exchange rate of 6.3804). The Company's reason for the EU Private Placement and the U.S. Offering is to access the U.S. and European capital markets in order to raise funds to support its business. We estimate that the net proceeds to us from the Global Offering, after deducting the underwriting commissions and estimated offering expenses payable by us, to be approximately DKK 480 milion (USD 75.3 million), or DKK 555 million (USD 87.0 million) if the underwriters exercise their option in full to purchase Additional Securities, based on the initial offering price of DKK 70.1844 (USD 11.00 per ADS), using a U.S. Dollar/DKK exchange rate of 6.3804.

Plan of distribution

Not applicable since there is no offering of securities for sale or subscription. The purpose of this Prospectus is solely to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen.

In connection with the Global Offering, the Company entered into an underwriting agreement dated September 28, 2020 (due to the time difference between Denmark and the United States). See "*General Information—The Global Offering*." The Underwriters have not been involved in the preparation of this Prospectus.

6 ADMISSION TO TRADING AND OFFICIAL LISTING

6.1 Admission to trading and official listing

The Company has one share class. The Listing Shares will be initially issued in an temporary ISIN code DK0061411378 on or around October 1, 2020 and will not be admitted to trading and official listing under such temporary ISIN. The Listing Shares under the temporary ISIN code will solely be registered with VP Securities. Upon completion of the Listing, expected on or around October 2, 2020, the Listing Shares will be admitted to trading and official listing on Nasdaq Copenhagen under the permanent ISIN code for the Existing Shares and, subsequently on October 5, 2020, the temporary ISIN code will be merged with the ISIN code of the Existing Shares.

An application has been made for the Listing Shares to be admitted to trading and official listing on Nasdaq Copenhagen. It is expected that the listing of the Listing Shares on Nasdaq Copenhagen under the Company's existing symbol "ORPHA" and in the ISIN of the Existing Shares DK0060910917 will be effective on or around October 2, 2020, after registration of the capital increase related to the Listing Shares with the Danish Business Authority, expected on October 1, 2020.

The Listing Shares are issued in connection with the EU Private Placement of Shares and the U.S. Offering of 3,966,146 ADSs at a price of USD 11.00 per ADS (using a DKK/U.S. dollar exchange rate of 6.3804). Each ADS represents one Listing Share. The Listing Shares are underlying the ADSs. The ADSs were listed and began trading on September 29, 2020 on NASDAQ under the symbol "ORPH". The price

of USD 11.00 per ADS corresponds to a subscription price of DKK 70.1844 per Listing Share (using a DKK/U.S. dollar exchange rate of 6.3804).

The Bank of New York Mellon has been appointed as depositary for the ADSs and will be the holder of such Listing Shares underlying ADSs upon issue.

BofA Securities, Inc., Cowen and Company, LLC and Guggenheim Securities, LLC, whose business addresses are for BofA Securities, Inc. One Bryant Park, New York, New York 10036, for Cowen and Company, LLC 599 Lexington Avenue, New York, New York 10022 and for Guggenheim Securities, LLC is 330 Madison Ave, 15th Floor, New York, NY 10017, United States were the representatives of the Underwriters in connection with the Global Offering. The Underwriters have not been involved in the preparation of this Prospectus.

6.2 Market making

The Company has not entered into any market making agreement.

6.3 Stabilization

See "*General information–Stabilization*".

7 SELLING SHAREHOLDERS AND LOCK-UP

7.1 Shareholders who have indicated that they expect to sell their Shares

The Company has not received any indications from shareholders that they intend to sell their Shares. There is no offering of Shares for sale or subscription since the purpose of this Prospectus solely is to have the Listing Shares admitted to trading and official listing on Nasdaq Copenhagen.

7.2 Lock-up agreements with the Company

In connection with the Global Offering the Company has agreed, subject to limited exceptions, not to offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, or enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the ADSs, ordinary shares or such securities convertible or exercisable into ADS or ordinary shares for a period of 90 days after the date of the U.S. Prospectus, or publicly disclose the intention to do any of the foregoing, without the prior written consent of BofA Securities Inc. and Cowen and Company, LLC.

8 COSTS OF THE ADMISSION

We estimate that the net proceeds to us from the Global Offering, after deducting estimated underwriting commissions and estimated offering expenses payable by us, to be approximately USD 90.4 million, or USD 104.4 million if the Underwriters exercise their Overallotment Option in full. These estimates are based on an assumed initial public offering price of DKK 82.70 per ordinary share (USD 13.3 per ADSs), which was the last reported sale price of our ordinary shares on Nasdaq Copenhagen on September 17, 2020 (assuming a DKK/U.S. dollar exchange rate of 6.2967 per USD 1.00 as of September 17, 2020 and a ADS-to-ordinary share ratio of 1 to 1.

Expenses, after deducting the underwriting commissions and offering expenses, are expected to be approximately DKK 16.6 million (or USD 2.6 million using a U.S. Dollar/DKK exchange rate of 6.3804) and are payable by the Company. The Company has agreed to reimburse the Underwriters for certain expenses as set forth in the Underwriting Agreement. The total underwriting commission is approx. DKK 37.4 million (or USD 5.9 million), and approx. DKK 42.7 million (or USD 6.7 million) if the Overallotment Option is exercised in full, in each case using a U.S. Dollar/DKK exchange rate of 6.3804

9 DILUTION

As a result of the Global Offering, the Existing Shares at the date of this Prospectus will be diluted by the issue of 7,616,146 Listing Shares, corresponding to a nominal value of DKK 1. If the Overallotment Option is exercised in full, the Existing Shares will be diluted by 8,758,567 Shares, corresponding to a nominal value of DKK 1, including the Listing Shares and such Shares issued under the Overallotment Option. Following the completion of the Global Offering, the Existing Shares will represent 78% of the Company's share capital if the Overallotment Option is not exercised, and 75.6% if the Overallotment Option is exercised in full.

10 ADDITIONAL INFORMATION

10.1 Advisers

Legal adviser to the Company in connection with the Listing:

Gorrissen Federspiel Advokatpartnerselskab
Axeltorv 2
DK-1609 Copenhagen V
Denmark

U.S. legal adviser to the Company

Cooley LLP
55 Hudson Yards
New York, New York 10001
United States

Auditors to the Company:

ERNST & YOUNG Godkendt Revisionspartnerselskab
Osvald Helmuths Vej 4
DK-2000 Frederiksberg
Denmark

GLOSSARY

In the Prospectus, the following words and expressions have the meanings stated below, unless the context requires otherwise.

Additional Securities	Up to 1,142,421 additional ordinary shares (which may be in the form of ADSs), which may be purchased or subscribed for by the Underwriters pursuant to the Overallotment Option
ADR	American Depositary Receipt
ADS	American Depositary Share
ADS Holder	A person holding ADSs directly and registered as the ADS holder
ALS	Amyotrophic Lateral Sclerosis
ANDA	Abbreviated New Drug Application
Articles of Association	The Company's Articles of Association of September 21, 2020
Board Incentive Program	The board incentive program of the Company
Board of Directors	The board of directors of the Company
cGMP	Current good manufacturing practices
Chairman	The chairman of the Board of Directors
CMOs	Contract manufacturing organizations.
CMS	The Centers for Medicare & Medicaid Services
CNS	Central nervous system
Company	Orphazyme A/S, CVR no. 32 26 63 55

Corporate Governance Recommendations	The recommendations on corporate governance published by the Committee on Corporate Governance in November 2017 (as amended)
CRO	Contract research organization
CVR no.	The Danish Central Business Register number
CytRx	CytRx Corporation
Danish Business Authority	The Danish Business Authority (in Danish: "*Erhvervsstyrelsen*")
Danish Capital Markets Act	Consolidated Act no. 377 of April 2 2020 on Capital Markets, as amended
Danish Companies Act	Consolidated Act no. 763 of July 23, 2019 on limited liability companies, as amended
Danish Corporation Tax Act	The Danish Consolidated Act no. 1164 of September 6, 2016 on corporate income tax (in Danish: "*selskabsskatteloven*"), as amended
Danish Pension Returns Tax Act	The Danish Consolidated Act no. 1126 of October 10, 2014 on pension returns tax (in Danish: "*pensionsafkastbeskatningsloven*"), as amended
Deposit Agreement	Deposit agreement among the Company, the depositary, ADS holders and all other persons indirectly or beneficially holding ADSs
Depositary	The Bank of New York Mellon
Deputy Chairman	The deputy chairman of the Board of Directors
DKK	The official currency of the Kingdom of Denmark
EAP	Early access program for NPC patients in the United States
EEA	European Economic Area

EMA	The European Medicines Agency
EU Private Placement	Offering of up to 3,650,000 ordinary shares to qualified investors in Europe though a private placement
European Offered Shares	Ordinary shares offered in connection with the EU Private Placement
Exchange Act	U.S. Securities Exchange Act of 1934
Executive Management	The Executive Management of the Company as registered with the Danish Business Authority at the Prospectus Date
Existing Shares	The Company's share capital before the Global Offering consisting of 27,081,557 Shares with a nominal value of DKK 1 each
FDA	U.S. Food and Drug Administration
FSA	The Danish Financial Supervisory Authority
FY 2019 Group Financial Statements	The consolidated financial statement of the Company for the financial year ended December 31, 2019 with comparative figures as of and for the year ended December 31, 2018 and the related notes
GCP	Good clinical practices, an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
GDPR	EU General Data Protection Regulation
Global Offering	The U.S. Offering and the EU Private Placement
Group	The Company and its subsidiaries
H1 2020 Interim Financial Statements	Interim consolidated financial statements as of and for the six months ended June 30, 2020 with comparative figures as of and for the year ended December 31, 2019 and the related notes

HHS	The Department of Health and Human Services
HSPs	Heat shock proteins
IFRS	International Financial Reporting Standards as adopted by the EU
IND	An investigational new drug
IRB	An independent institutional review board
Key Employees	Thomas Kirkegaard Jensen and Thomas Blaettler
Kreos	Kreos Capital VI (UK) Limited
Listing	The admission for trading and official listing of the Listing Shares on Nasdaq Copenhagen
Listing Shares	7,616,146 shares with a nominal value of DKK 1 each in the Company
Loan Agreement	The loan facility agreement, dated August 27, 2019, between the Company Kreos Capital VI (UK) Limited
LSDs	Lysosomal storage diseases
LTIP	The long-term incentive program of the Company
MA	Marketing authorization
MAA	A marketing authorization application which can be submitted to the European Medicines Agency
Major Shareholders	Shareholders who have notified the Company that they hold more than 5% of the Company's registered share capital
Management	The Board of Directors and the Executive Management

Market Abuse Regulation	Regulation (EU) No. 596/2014 of April 16, 2014 on market abuse (market abuse regulation) and repealing Directive 2003/6/EC of the European Parliament and of the Council and Commission Directives 2003/124/EC, 2003/125/EC and 2004/72/EC
Nasdaq	Nasdaq Global Select Market in the United States
Nasdaq Copenhagen	Nasdaq Copenhagen A/S
Nasdaq Issuer Rules	Nordic Main Market Rulebook for Issuers of Shares on Nasdaq Copenhagen of May 1 2020
NDA	New drug application
NMEs	New molecular entities
NPC	Niemann-Pick disease Type C
Orphazyme	Orphazyme A/S, CVR-no. 32 26 63 55
Overallotment Option	An option granted to the Underwriters, exercisable for 30 days after the date of announcement of the pricing of the Global Offering, to subscribe for and purchase the Additional Securities at the offering price offered in connection with the Global Offering, less the underwriting commission
Prospective Financial Information	The prospective consolidated financial information for the financial year ended December 31, 2020
Prospectus	This Prospectus covering the listing of the Listing Shares
Prospectus Date	September 30, 2020
Prospectus Regulation	Regulation (EU) No. 2017/1129 of June 14, 2017 (as amended) on the prospectus to be published when securities are offered to the public or admitted to trading on a regulated market, and repealing Directive 2003/71/ECText with EEA relevance

Qualified Investors	As defined in the Prospectus Regulation
Regulation S	Regulation S under the U.S. Securities Act
Relevant Member State	Each member state of the European Economic Area, where the Prospectus Regulation apply
Relevant Persons	Persons who: (i) are investment professionals falling within Article 19(5); or (ii) fall within Article 49(2)(a) to (d) ("high net worth companies; unincorporated associations, etc."), of the UK Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 or other persons to whom such investment or investment activity may lawfully be made available
SEC	U.S. Securities and Exchange Commission
Shares	All outstanding shares of the Company at any given time
sIBM	Sporadic Inclusion Body Myositis
Stabilization Period	30 days from the date of announcement of the pricing of the Global Offering
Underwriters	Certain banks who have entered into the Underwriting Agreement
Underwriting Agreement	The underwriting agreement, dated September 28, 2020, among BofA Securities, Inc., Cowen and Company, LLC, Guggenheim Securities, LLC and the Company
U.S. GAAP	Accounting principles generally accepted in the United States
U.S. Offering	An initial public offering in the United States of 3,966,146 ADSs at a price of USD 11.00 per ADS, with each ADS represents one Listing Share
U.S. Prospectus	The registration statement filed by the Company, with the SEC on form F-1

U.S. Securities Act	Securities Act of 1933, enacted by the 73rd United States Congress, as amended
USPTO	The U.S. Patent and Trademark Office
United States	The United States of America
VP Securities	VP Securities A/S, CVR. no. 21599336