

Orphazyme

Sector: Biotech

Bull story below Bear price

Redeye revisits the Orphazyme case in light of exceptional news flow in the first half of 2021. We reiterate our positive fundamental view while raising fair value. Although the stock is now trading below our Bear Case, we see no intrinsic reason for its underperformance and expect the attractive pipeline-in-a-product – which holds blockbuster potential – to lift it.

Pipeline picking up momentum

- **NPC** - We present our arguments for approval in Q1'21
- **ALS** - Phase 3 results are due in H1 21; this update explains what would qualify as good results
- **sIBM** - Phase 2/3 results expected in H1 21 too
- **Gaucher** – Potential to move into the pivotal stage in the next year

Sentiment soured by overhang

The stock has underperformed due to an ongoing overhang from some of the larger shareholders. After investigating in depth, we find no fundamental justification for this weakness and affirm our view of the case.

Realizing upside

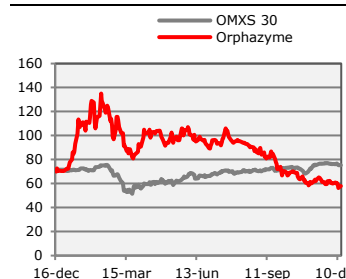
After reviewing our estimates, we raise our Base Case to DKK 145 per share (130). Valuation is supported by peer analysis too. The coming rich news flow should help realize the more than 100% upside that the stock now offers. Note that our Bear and Bull Cases, based on possible pipeline outcomes in the next year, are now DKK 70 and DKK 200 per share, respectively.

KEY FINANCIALS (DKKm)	2018	2019	2020E	2021E	2022E	2023E
Net sales	0	0	0	82	260	679
EBITDA	-232	-335	-624	-471	-265	117
EBIT	-232	-335	-627	-484	-279	103
EPS (adj.)	-11.5	-16.9	-18.1	3.9	-8.1	3.0
EV/Sales	N/A	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	N/A	N/A	N/A	N/A	N/A	N/A
EV/EBIT	N/A	N/A	N/A	N/A	N/A	N/A
P/E	N/A	N/A	N/A	N/A	N/A	N/A

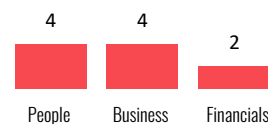
FAIR VALUE RANGE

BEAR	BASE	BULL
70.0	145.0	200.0

ORPHA.CO VERSUS OMXS30



REDEYE RATING



KEY STATS

Ticker	ORPHA.CO
Market	Mid cap
Share Price (DKK)	60.0
Market Cap (MDKK)	2082
Net Debt 20E (MDKK)	-635
Free Float	49 %
Avg. daily volume (000)	381

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Investment Case

- The stock in itself a catalyst
- Orphan case on the verge of commercialization
- Well-funded
- M&A target

In contrast to the continuing progress in its pipeline, Orphazyme's stock has gone backward. Selling pressure appears to have been fairly constant this year, though it seems to have stabilized somewhat in the last couple of months. With a rich news flow ahead, we see multiple opportunities for the valuation gap to our Base Case to close.

Orphazyme is a 100% orphan biopharma case with two programs (possibly three programs by the next year) in the late-stage development and one in the very last filing stage before potential approval in 2021. Its lead project, arimoclomol, addresses an attractive commercial opportunity and could come to market in four rare disease indications (ALS/Gaucher/NPC/sIBM) by 2024:

- we estimate combined peak sales above USD 1bn (blockbuster potential)
- we assign launch probabilities from 95% (NPC US) to 30% (Gaucher)

With its ambitious pipeline-in-a-product built around arimoclomol, Orphazyme has the prospect of strong news flow in the coming 12 months where essentially all four indications should play out.

As part of a dual listing in the US in September, Orphazyme raised USD 84m (DKK 534m). It should have over DKK 700m of cash at hand by yearend. Moreover, as NPC is a rare pediatric disease, Orphazyme could be entitled to a priority review voucher (PRV). Under US law, it could be expedited for another drug review, which would speed up the process by more than four months. As PRVs are also transferable to third parties and have been sold for around USD 100m lately, this represents a significant non-dilutive cash opportunity. Thus, our main message to investors is that we acknowledge the financial risk has come down in the case.

Priority review vouchers: Selling Price			
Seller	Buyer	Year	(USDm)
Lumos Pharma	Merck	2020	100
Argenx	Bayer	2020	98
Bavarian Nordic	N/A	2020	95
SOBI	AstraZeneca	2019	95
GW Pharmaceuticals	N/A	2019	105

* A selection of the most recent PRV sales

Source: Redeye Research

With its orphan franchise, together with the successful development in its pipeline in recent years, we argue that Orphazyme remains an acquisition target. We see clear evidence that larger pharma companies are seeking attractive assets in the orphan space. It also includes M&A's in the indications that Orphazyme addresses.

Relevant M&A						
Target	Buyer	Time	Assets	Stage	Purchase price (\$mn)	Comment
Sucampo Ph.	Mallinckrodt	Dec 2017	Amitiza, Rescula, VTS-270	Market, Ph 2/3	1200	VTS-270 (adobetadex) at that time in phase 2/3 development for NPC
Wilson Therapeutics	Alexion Ph.	Apr 2018	WTX101	Ph 3	855	WTX101 was in phase 3 development for Wilson's disease.
Calporta Therapeutics	Merck	Nov 2019	TRPML1 agonists	Preclinical	576	TRPML1 agonism presents a way to treat lysosomal storage disorders (LSD). Merck will pursue neurodegenerative disorders as well.
AskBio	Bayer	Oct 2020	Cell- and Gene Therapy	Preclinical- and early clinical	2000 + 2000*	Cell- and gene therapy approach for the treatment of, among others, LSD and neuromuscular disorders
Prevail Therapeutics	Eli Lilly	Dec 2020	Gene Therapy	Ph 1/2	880 + 160**	One of the lead programs, PR001, in development for neuropathic GD and GBA1-Parkinson's Disease

* USD 2 bn in upfront, USD 2 bn in additional milestones

** USD 880 mn at closing of the agreement, 160 contingent on first regulatory product approval

Source: Redeye Research

Counter-thesis

Development risk

Orphazyme targets rare and even ultra-rare disease areas. Data for these are often complex to analyze, and the regulatory pathway is often new territory.

Commercialization risk

Orphazyme is transforming itself from research and development-driven biotech into a commercial biopharma company. This requires industry professionals that have undergone this journey before and understand how to harvest commercial potential fully.

Follow-Up on CEO Resignation

The last week's news on CEO Stratton's resignation, following a dialogue initiated by the Board of Directors, was unexpected. There have been some related articles in the Danish financial press after this news, where board members have expressed themselves. We argue that this is good, as news like this tends to lead to all sorts of speculation.

From our side, we don't have anything new to comment on. We have been in regular contact with the management team during the last week, and our understanding is that it is 'business as usual.' The news per se is not material in our view. Our main concern is that they may lose speed, not particularly in the development or regulatory stage but rather in building the US's commercial organization. The good thing here is that Orphazyme has already appointed a US president, Molly Painter, and has begun to build commercial competencies. Regardless, we will closely follow up on corporate governance and want to see that the Board moves rapidly but thoughtfully appointing a new CEO.

Project Overview and General Estimates

How we model pricing for arimoclomol

The number of targeted patients is the strongest variable we can use to model the pricing of arimoclomol. We foresee an inverse relationship between the price and the number of targeted patients. As Orphazyme potentially targets more indications and a broader population base, we predict a gradual decline in price. But for 2021-2022, we expect that arimoclomol will only target the NPC indication. This is an indication that numbers hundreds in terms of prevalence on the major markets. We raise the initial price of arimoclomol based on some recent pricing for ultra-rare indications. We assume a wholesaler price of around USD 475 thousand and apply a standard 15% discount.

The illustration below shows the US market and the active cases that could be eligible for pharmacological treatment. We forecast European pricing at about 80% of the US market pricing.

Arimoclomol: Pricing Model (Applied on the US market)



Source: Redeye Research

Lysosomal Storage Disorders – Strengthening the Rationale

Neurological Gaucher's Disease (GD)

Arimoclomol status

After presenting top-line phase 2 results from the blinded part in Q2'20, the trial has now moved into an open-label (OLE) phase for a further six months. We expect readout from this phase at the end of this year or at the beginning of 2021.

We stand by our initial view that the phase 2 top-line results merit further development. We hope that our stance will be reinforced by the OLE data. Specifically, we will look for the following in the OLE dataset:

- **An ongoing favorable safety profile**

Data at the six months point showed that arimoclomol was generally safe and well-tolerated, with a slight overweight of adverse and severe events in the arimoclomol arms. The rationale behind running extension studies is to collect data on safety and tolerability over a longer treatment period. It is especially relevant for CNS-acting drugs with intended long treatment duration. Hence, it is important to see an ongoing good safety profile in the OLE study.

- **Neurological scores outcome**

The phase 2 trial enrolled both GD type 1 (GD1) and GD type 3 (GD3) patients (see further about the GD types in the Appendix section). Since the progression of neurological symptoms in GD1 is quite slow, the neurological symptoms were set to be measured at 6 + 6 months. Given this, and because Orphazyme targets neurological GD, the data should be more important than average OLE readouts.

For the neurological symptoms, Orphazyme uses the modified Severity Scoring Tool (mSST). It was originally established in 2007. It is a 11-domain score tool that encompasses, for instance; horizontal gaze palsy, epilepsy, ataxia/gait, cerebellar signs/ataxia, speech, and ophthalmology. The mSST is deemed to be sensitive enough to capture a change in GD1 and GD3. (Davies et al., 2011)

As the mSST endpoint is not controlled/randomized in Orphazyme's phase 2 trial, we are unlikely to draw any major implications from the results. On a high level, we want to see a trend in neurological benefit that merits further development with arimoclomol into a pivotal program. It could also be interesting to see if there is a separation effect between GD1 and GD3, since the two progress differently.

In the OLE readout, we will also monitor arimoclomol's efficacy on the underlying disease pathology. At the six months point, we were especially encouraged by the reductions in spleen and liver size.

Given a good OLE readout, together with productive interactions with experts in the field, we believe arimoclomol could move into the pivotal stage in the coming year. The study design and the primary endpoints used at such a stage yet are to be determined, and we will not discuss them further at this point.

We are also interested to learn about other efforts in related indications, such as Gcase-Parkinson's Disease (Gcase-PD). We believe such news could be presented in H1 21.

Additional Analysis – Gcase-PD

About 5-7% of GD1 patients develop Parkinsonism (Parkinson-related symptoms) before the age of 70. There is also a genetic link between GD and PD. GD is caused by mutations in the GBA1 gene, which encodes for glucocerebrosidase (GCase). Mutations in the GBA1 gene are also one of the best-known genetic risk factors for developing Parkinson's disease. An estimated 7-12% of patients with Parkinson's disease carry a GBA1 mutation. This corresponds to some 80,000 patients in the US and 100,000 patients on the major markets in the EU. It also highlights why we are attracted by the idea of Orphazyme potentially pursuing Gcase-PD:

- a genetically well-defined subpopulation
- Potential for Orphazyme to target Gcase-PD without necessarily compromising its orphan franchise.

Competitive landscape

Current market

Gaucher is an unusual rare disorder in the sense that there are several approved drugs, in two major drug classes: Substrate Reduction Therapy (SRT) and Enzyme Replacement Therapy (ERT). ERT and SRT have changed the prospects for many patients living with lysosomal storage disorders. We believe they will remain the mainstay treatments for the foreseeable future.

Approved ERT treatments include cerezyme/imiglucerase (Sanofi), with sales estimated at USD 718m for the current year, and vpriv/velaglucerase alfa (Shire), with sales estimated at USD 180m. Two oral SRTs are approved for Gaucher: zavesca/miglustat (J&J) and cerdelga/eliglustat tartrate (Sanofi), with combined annual sales of around USD 350m (although this figure also factors in miglustat sales in NPC (ex-US)).

ERT and SRT are approved for GD1. They have proven advantageous in stabilizing hematological and visceral symptoms. We believe there is an unmet medical need for the neurological symptoms in Gaucher. The neurological symptoms primarily relate to GD2 (an acute form with poor outcomes) and GD3. However, it is nowadays believed that approximately 30% of GD1 patients (where GD1 represents 90% of total Gaucher cases) develop neurological symptoms in the later stages of disease progression. This discovery could be due to the advent of ERT and SRT therapies, which have allowed GD1 patients to live longer and thereby develop neurological symptoms.

Pipeline

We consider arimoclomol to be attractively positioned in the pipeline. It is a small molecule with a novel mechanism of action, targeting the neurological symptoms of Gaucher. Pipeline peers are typically gene therapy candidates. Recent news flow in the Gaucher pipeline includes:

- Prevail Therapeutic's (acquired by Eli Lilly a few days ago) PR001, which aims to target neuronopathic Gaucher disease (GD2 and GD3), recently received fast track designation from the FDA. Prevail Therapeutics is currently recruiting neuronopathic Gaucher patients in its phase 1/2 study.

- Avrobio recently reported the first clinical data in GD1 from the first patient. This early data demonstrated reductions in GD biomarkers compared to the baseline when the patient was on ERT.
- Avrobio also reported in November that it would broaden its pipeline to GD3 as well.
- Phase 2/3 results from an SRT/ERT therapy combination (GZ/SAR 402671) in GD3 are expected by next year. Based on the targeted patients and what the study aims to study, it could potentially be positioned similarly to arimoclomol (Note that while ERT are unable to penetrate the blood-brain barrier, SRTs are CNS-penetrant)

Additional Analysis – Gene Therapy Candidates

Some general remarks are worth emphasizing about the competitive landscape in lysosomal storage disorders (LSDs). We see an increasing scope for gene (and cell) therapy candidates in development, including in Gaucher and NPC. There are several attributes that make gene therapies suitable to explore in LSDs. For instance, each LSD is a single gene edit recessive disorder, with a largely understood molecular pathology. We find the gene candidates in CNS disorders taking an interesting approach, but we also see some challenges, such as in the route of administration. In Gaucher and NPC specifically, we have identified the following drug candidates, all in preclinical or early clinical stage:

- **PR001 (Prevail Therapeutics)** – AAV* based Gene Therapy – **Phase 1/2** – Gaucher
- **AVR-RD-02 (AVROBIO)** – Lentiviral Gene Therapy – **Phase 1/2** – Gaucher
- **FLT200/201 (Freeline Therapeutics)** – AAV based Gene Therapy – **IND** – non-neurogenetic GD
- **Preclinical program (Amicus/Penn)** – AAV based Gene Therapy - **Preclinical** – NPC

*AAV – a gene therapy approach where Adeno-Associated Virus (AAV) are used as vectors to directly target the damaged genes

Gaucher Disease: Competitive Landscape*							
Drug Name	Lead Company Name	Drug Classification	MoA**/Target	Route of Administration	Current Phase	Next Event	Redeye Comment
Cerdelga	Sanofi	Small Molecule	Glucosylceramide Synthase	Oral (PO)	Approved		SRT therapy
Cerezyme	Sanofi	Protein	Glucocerebrosidase (glucosylceramide)	Intravenous (IV)	Approved		ERT therapy
Elieyso	Pfizer Inc.	Protein	Glucocerebrosidase (glucosylceramide)	Intravenous (IV)	Approved		ERT therapy
Vpriv	Takeda Pharmaceutical Co. Ltd.	Protein	Glucocerebrosidase (glucosylceramide)	Intravenous (IV)	Approved		ERT therapy
Zavesca	Johnson & Johnson	Small Molecule	Glucosylceramide Synthase	Oral (PO)	Approved		SRT therapy
Venglustat/Cerezyme	Sanofi	Small Molecule	Glucosylceramide Synthase	Oral (PO)	Ph 2/3	Top-line results from ph 2 expected in 2021	SRT and ERT combination therapy for GD3
Arimoclomol	Orphazyme A/S	Small Molecule	Heat Shock Protein (HSP-) amplifier	Oral (PO)	Ph 2	OLE data, progress into pivotal stage	
AVR-RD-02	AVROBIO, Inc.	Cellular	Stem Cells/Other Cell Therapies	Intravenous (IV)	Ph 1/2	We expect updated results from the ongoing ph 1/2 study in 2021	Targets GD1
PR001	Prevail Therapeutics Inc.	Viral Gene Therapy	GBA1 (lysosomal acid β-glucosidase acid 1)	Intracerebral/cerebroventricular	Ph 1/2		Targets neuronopathic GD (GD2 and GD3)
AVR-RD-06	AVROBIO, Inc.	Cellular	Stem Cells/Other Cell Therapies		Preclinical		Targets GD3
Small Molecule Program (Evotec/Centogene)	Evotec SE	Small Molecule/Stem Cell Therapy	GBA1 (lysosomal acid β-glucosidase acid 1), GBA2 (extralysosomal glucocerebrosidase)		Preclinical		Preclinical collaboration program with Centogene and Evotec to develop a treatment for Gaucher disease
FLT201	Freeline Therapeutics Holdings PLC	Viral Gene Therapy			Preclinical		

* The pipeline does not claim to comprehend all drug candidates in development

** Mechanism of Action

Source: Company pages, clinicaltrials.gov, Biomedtracker, Redeye Research

Estimates

Until we know more about the Company's interactions with experts and regulators in the field and have seen the OLE data, we can only fine-tune our project valuation for arimoclomol in Gaucher's disease:

- Market launch in 2024
- Peak sales of in the range USD 200-250 million

- Probability (likelihood of approval/LoA) to reach the market set at 30%
 - If the interactions with experts and regulators are fruitful, the OLE readouts positive, the pivotal study design is established and the patient recruitment is ongoing we see reason to raise our LoA to around 50%.

NPC

Arimoclomol status

Orphazyme filed a New Drug Application (NDA) for arimoclomol in Q2'20. Following the 60-day filing period, the FDA accepted the NDA with priority review and has set the target action date (PDUFA date) to March 17 2021.

In November, Orphazyme submitted a marketing authorisation application (MAA) with the European Medical Agency (EMA). We believe potential approval here could be given in Q4'21. This would put the European market 6-9 months behind the US for this indication.

A potential approval with arimoclomol in NPC in either or both key markets would mark a milestone for Orphazyme. In the Estimates section, we present the arguments for approval and the remaining risk factors. We currently apply a 95% probability for approval in the US and a slightly lower level in Europe.

Competitive landscape

Current market and potential

There are no approved drug therapies for this indication in the US. However, two cyclodextrin agents are part of an expanded access program. The proposed mechanism of cyclodextrin is the release of cholesterol from the cells, thereby normalizing cell function.

Trappsol cyclo (Cyclo Therapeutics) is a hydroxypropyl beta-cyclodextrin (HPβCD) with intravenous administration. It has been in compassionate use, a form of expanded access program, in Brazil and in the US since 2009. Some other countries later followed suit. Trappsol cyclo has received orphan drug designation (from the EMA and the FDA) and fast track designation in the US.

Adrabetadex/VTS-270 (Mallinckrodt) is another cyclodextrin used in the US today as part of an expanded access program (EAP). Administration of adrabetadex – directly into the spinal canal – is not favorable. Reported side effects include hearing loss. It should be noted that this side effect comes in an already severe patient group.

SRT therapy miglustat/zavesca is approved in Europe for NPC and in the EU and the US for Gaucher's disease. It was developed in the US for NPC and received favorable voting by the FDA Advisory Committee but subsequently received a complete response letter from the FDA, requiring more preclinical and clinical information. This was more than ten years ago, and today, it is only prescribed off-label to NPC patients.

NPC is a devastating, progressive, and eventually fatal disorder. NPC patients typically do not survive beyond their 20s. Given the lack of treatment options, there is an unmet need to improve the neurological symptoms associated with the disease, to improve quality of life, and to slow disease progression. However, NPC is also an ultra-rare disorder with patients numbering only in the hundreds in each region (the US and the EU). This limits the market potential, although this is partly offset by the potential for a high orphan-like price. Based on this, we assess the full market potential for the indication at some USD 300m on an annual basis.

Pipeline

Recent news flow in the NPC pipeline includes:

- Cyclo Therapeutics has advanced trappsol cyclo to a pivotal phase 3 trial for which enrollment has begun.
- Adrabetadex/VTS-270 is part of an expanded access program in the US (as mentioned above). However, its phase 2/3 trials showed mixed outcomes. To top things off, Mallinckrodt recently filed for bankruptcy in the wake of its involvement in the US's ongoing opioid crisis.
- IntraBio recently completed a phase 2 trial with its drug candidate IB1001 in NPC, which demonstrated a statistically and clinically meaningful improvement in symptoms after six weeks.

Cyclo Therapeutics' phase 3 is a global, double-blind, randomized, placebo-controlled, parallel-group, multicenter study that aims to evaluate safety, tolerability, and efficacy of intravenous trappsol cyclo compared to placebo and standard of care in patients with NPC. The information on the study design is relatively scarce at present. We do not know the primary endpoint or the number of enrolled patients yet. Based on the proposed timeline by Cyclo Therapeutics, we assess that trappsol cyclo is a few years behind arimoclomol in development.

The data from the compassionate use programs has paved the way for Cyclo Therapeutics to launch clinical trials with trappsol cyclo. According to Cyclo Therapeutics, earlier trials from phase 1 and phase 1/2 have reported a safety profile consistent with the compassionate use program, target engagement, and trends in efficacy outcomes. We note the small dataset, however, with 12 patients each in phase 1 and phase 1/2 trial.

According to Mallinckrodt, it will continue to supply products as normal, despite filing for bankruptcy. As far as we understand, this includes products serving the NPC community (i.e. adrabetadex/VTS-270) as well.

IB1001 is an orally administered drug candidate with a believed mechanism of action to normalize neuronal membrane via calcium channels. IntraBio claims that IB1001 has both symptomatic and disease-modifying potential in NPC. IB1001 has received orphan drug designation from the EMA and the FDA and fast track designation in the US.

Intrabio's phase 2 trial in NPC is divided into two parts: the first is a six-week treatment duration to assess efficacy and safety on NPC symptoms. Here, Intrabio reported that: 'IB1001 demonstrated a statistically significant and clear clinically meaningful improvement in symptoms, functioning, and quality of life for pediatric and adult patients with NPC.' The drug was further reported as safe and well-tolerated.

The study is now moving into an extension phase to evaluate its potential neuroprotective effects. Meanwhile, IntraBio will engage with regulatory agencies on an accelerated approval path. We find it unlikely that it could file an NDA based on the first part of the trial alone; it assessed symptoms after six weeks, which is a short duration. The phase 2 trial is not placebo-controlled either.

In summary, we believe arimoclomol is attractively positioned in the competitive landscape. We emphasize that arimoclomol could potentially benefit in the US from being first approved-on-the-market.

NPC: Competitive Landscape*							
Drug Name	Lead Company Name	Drug Classification	MoA**/Target	Route of Administration	Current Phase	Next Event	Redeye Comment
Zavesca (miglustat)	Johnson & Johnson	Small Molecule	Glucosylceramide Synthase	Oral (PO)	Approved in Europe		
Arimoclomol	Orphazyme A/S	Small Molecule	Heat Shock Protein (HSP-) amplifier	Oral (PO)	NDA	PDUFA on 17 March, 2021	
Trappsol Cyclo	Cyclo Therapeutics, Inc.	Small Molecule	Fatty acids	Intravenous (IV)	Ph 3	Ph 3 interim analysis (H1'22)	Just began enrollment in phase 3 (US)
IB1001	IntraBio Inc.	Small Molecule	Calcium channels	Oral (PO)	Ph 2	Extension phase in ph 2	Recently reported phase 2 results from the first part (symptomatic evaluation)
ESB1609	E-Scape Bio	Small Molecule	Sphingosine 1-Phosphate Receptor (S1P-R)		Ph 1		
Niemann-Pick Disease AAV Gene Therapy (Amicus/Penn)	Amicus Therapeutics, Inc.	Viral Gene Therapy	Gene Therapy	N/A	Preclinical		
VTS-270 (adrbetadex)	Mallinckrodt plc	Small Molecule	Fatty acids	Intracerebral/cerebroventricular, Intrathecal	Unknown		Part of an expanded access program in the US. Mallinckrodt recently filed for bankruptcy

* The pipeline does not claim to comprehend all drug candidates in development

** Mechanism of Action

Source: Company pages, clinicaltrials.gov, Biomedtracker, Redeye Research

Estimates

As arimoclomol in NPC nears the market, with potential approval in the coming year, we review our estimates. We have been in dialogue with patient community leaders and are looking to expand our contacts to KOLs and caregivers eventually.

The most important factors for investors to consider at this point are:

- **The probability for approval**, i.e., what lies behind our probability of 95% in the US and some 90% in Europe?
- **The commercial potential**, driven by variables such as prevalence, market uptake, market penetration, and pricing of arimoclomol (already discussed in 'How we model pricing for arimoclomol' in this report).

Probability rate

As stated above, the FDA will announce its approval decision by March 17, 2021 (PDUFA date). As an approval decision in the US draws nearer, investors will inarguably focus on questions such as:

- What is the probability for approval?
- What are the main arguments for approval?
- What are the remaining hurdles/risks?

According to Pharmapremia, the aggregated probability for the disease group 'Inborn error of Metabolism' is more than 90% at the NDA stage. We have also assigned a premium of few percent in the US. In the end, there will be some type of go or no-go decision by the FDA. Either decision could mean a number of things; neither necessarily stipulates a binary outcome. We will elaborate further on this in this section under our main arguments.

Even though it is relevant for investors to understand aggregated probability rates at different drug development stages, our applied probability rate mostly relates to how we risk-adjust future cash flow streams. We thus find it more relevant to discuss the two latter topics.

Our main arguments for approval are the:

- Lack of approved drug therapies for NPC in the US
- Efficacy data
- Safety data
- Regulatory milestones (e.g., early access program/EAP)

In our outlines of the respective arguments below, we incorporate some of the FDA review issues. These were presented in the F1 amendment in conjunction with the US IPO process. We believe they might have raised investors' pulse rates. We want to emphasize that the NDA filing is an extensive process, and review issues always come up. There is simply no scenario in which a company can take a drug through an NDA process without a single point being raised.

No approved drug therapies for NPC in the US

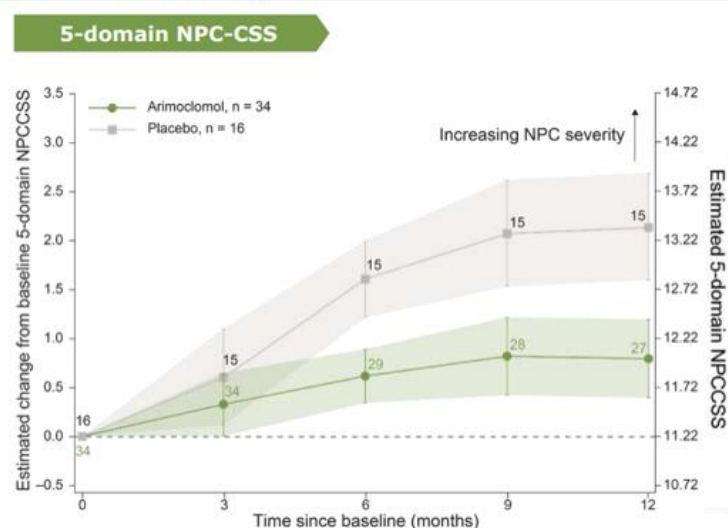
There are no drug therapies approved in the US. This is a compelling argument that speaks for itself. Besides, there is an urgent medical need for this devastating condition, which has been reinforced by our contacts with patient community leaders. Our understanding is that the NPC families seek treatment alternatives and want to make use of combination therapies to, by a minimum stabilize or improve symptoms.

Efficacy data

The efficacy data has been evolving progress, with the benefit profile of arimoclomol being reinforced along the way. When Orphazyme announced top-line results in September 2018, it missed the primary endpoint ($p = 0.0716$) – the five-domain NPC-CSS (ambulation, speech, fine motor skills, cognition, swallowing). There was a directional benefit with arimoclomol treatment, though, based on NPC-CSS. In agreement with the FDA, the Clinical Global Impression of Improvement (CGI-I) was included as a co-primary endpoint. There was no treatment response observed on the CGI-I scale, which, according to Orphazyme, was due to the slow progression in the placebo arm. When considering rapid progressors during the trial, only 10.7% of the arimoclomol-treated patients got 'much worse' or 'very much worse,' compared to 26.7% in placebo.

In January 2019, the full dataset showed a -1.34 point treatment effect in favor of arimoclomol based on 5-domain NPC-CSS, with borderline for statistical significance ($p = 0.0537$). A one-point change is regarded as meaningful.

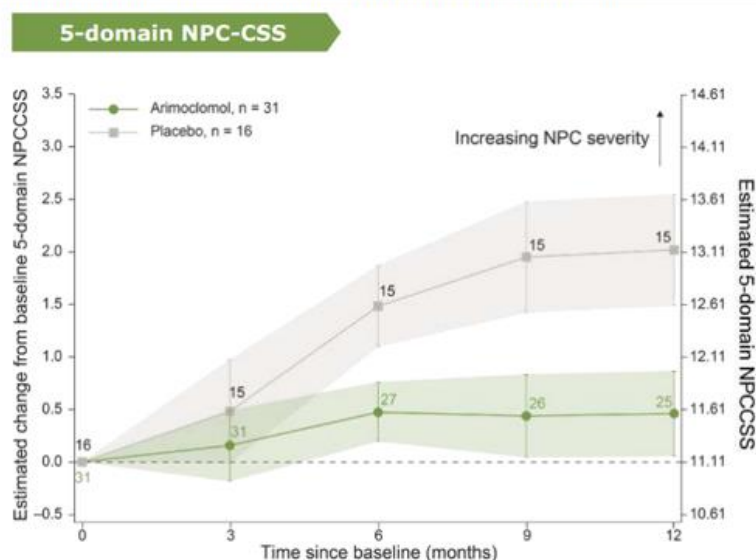
Arimoclomol Ph 2/3: Full Dataset



Source: Orphazyme

A genetic subgroup analysis indicated that the homozygous functional null mutation ($n=3$) was a factor in not meeting the primary endpoint with statistical significance. The null mutation patients tend to suffer from an earlier onset and a more rapid progression. In this trial, all three patients were under the age of four, and all received arimoclomol.

Arimoclomol Ph 2/3: Excluding Functional Null Mutations



Source: Orphazyme

Although the results excluding functional null mutations were reported in a post-hoc analysis, it was encouraged by the FDA. Could it potentially have implications in FDA's decision on March 17? That it was in fact a post-hoc analysis speaks against it. However, if the FDA concludes that patients with homozygous functional null mutations are less likely to respond to arimoclomol treatment, it could entail that the company gets a well-defined label, still addressing most of the total NPC population.

A highly statistically significant treatment difference was observed in another subgroup that compared arimoclomol to placebo control in patients receiving miglustat as part of routine clinical care ($p=0.0071$).

Moreover, the biomarker set reported from phase 2/3 both confirms target engagement and impact on disease biology. This was statistically significant.

Eventually, we also learned about 12+12 month OLE data, suggesting a sustained effect in reducing disease progression. 41 patients who completed the double-blinded part continued into the OLE part. Arimoclomol was safe and well-tolerated at 24 months.

Of FDA's review issues, three of them are related to efficacy:

- the proposed primary hypothetical treatment effect used in the Phase 2/3 trial in NPC to estimate the treatment benefit effect
- the meaningfulness of one metric utilized to evaluate patient progress in the Phase 2/3 trial of NPC
- The effect of the high degree of concomitant miglustat use in the Phase 2/3 trial in 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

We analyze the bullets backward and start with the last one. 39 of 50 patients in Orphazyme's phase 2/3 trial were on background miglustat treatment. This was stratified for in the study design to mitigate confounding data.

As we mentioned above, we don't see the PDUFA date as binary. It is especially relevant regarding the concomitant use of miglustat. As explicitly outlined in this review issue, it could instead have implications for the labeling and post-marketing studies. Two remarks are relevant to highlight with regards to potential labeling and post-marketing studies in the US:

- **Labeling** - Even though miglustat is not approved for NPC in the US, it is prescribed off-label. We cannot be any more specific than that. We don't know how many patients use miglustat in the US. But there might be that the strong subgroup results with miglustat as background treatment (n=39) is hence incorporated in the label. We won't speculate any further on the exact potential labeling, other than if arimoclomol gets approved, it will be the standard of care
- **Post-Marketing studies** – if arimoclomol gets approved, we predict that there will be studies conducted (post-approval) to increase the scope of data with arimoclomol as monotherapy in NPC

We interpret the second review issue related to filing based on the NPC-CSS metric and not CGI-I, which was used as a co-primary endpoint. We acknowledge that there is an explanation for the lack of treatment benefit based on CGI-I. But Orphazyme has to provide answers to the FDA why it is not a relevant endpoint in this context.

We interpret the first review issue related to if the outcome measures in phase 2/3 were the right way to estimate the treatment benefit effect. We can only reiterate that we think Orphazyme has conducted a thorough phase 2/3 trial study, with prespecified- and posthoc analysis in dialogue with regulatory agencies.

Safety data

It is relevant to elaborate on the safety and tolerability profile, particularly after the review issues disclosed in the F1 amendment. One of them related to a potential safety signal.

Arimoclomol has been extensively evaluated in more than 500 patients to date, among various patient groups, dosing regimens, and treatment durations. We have read through the clinical publications with arimoclomol again. The overall message has been that arimoclomol is safe and well-tolerated. It is also crucial to separate the adverse events (AEs) and the safety profile of a drug. A treatment can have many AEs reported but still be regarded as safe and tolerable. The severity of the AE, whether the AE is transient, whether it actually relates to the study drug, and, naturally, the overall benefit/risk profile are additional factors for regulators to weigh up.

One of the review issues regarded the timing of submission of the QTc (a measurement of the heart's electrical activity) and other study reports to the FDA, considering evidence that suggested a potential QT safety signal. The phrasing 'evidence of a potential QTc signal' only tells us that something needs to be investigated further. A QTc trial is currently being conducted with arimoclomol to assess any potential change in the QT interval. This trial is delayed due to Covid-19. We hope to receive further updates this quarter.

Regulatory Milestones (Early Access Program/EAP)

At the beginning of 2020, arimoclomol became available in the US through an early access program.

The EAP provides 'a pathway for patients with serious, life-threatening diseases or conditions who lack therapeutic alternatives to gain access to investigational drugs before they are approved'. As of September 2020, eight patients were on arimoclomol treatment as part of

the EAP. We argue that the EAP sends a signal value. By a minimum, it emphasizes the urgent medical need for NPC.

Moreover, the FDA does not plan to organize an advisory committee of independent experts to discuss the application. It might be a bit speculative from our side, but could it possibly imply that the FDA has already made its decision? At least, all else equal, it speeds up the process.

Remaining risk factors

- Orphazyme provides answers to the review issues that do not appeal to the FDA.
- The NDA package overall is an extensive dataset that leaves no stone unturned. We see another risk factor as something additional coming up during this review process, such as unexpected data from the QTc clinical trial.

Sales model

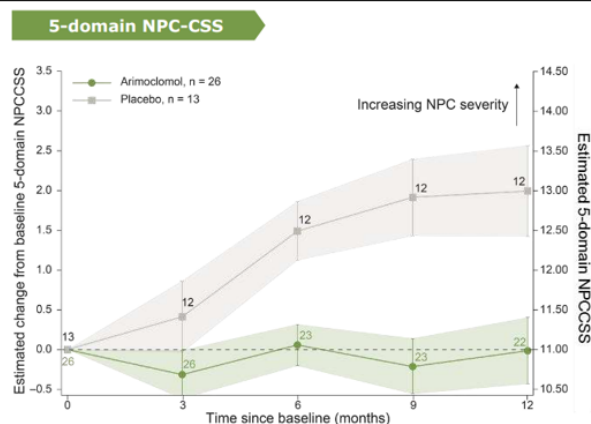
Our high-level estimate of the **diagnosed cases** that arimoclomol could target stands at some 400 patients in the US and around 800 patients in Europe. Our assessment is based on secondary data, cross-checked with patient organizations, and with information from Orphazyme.

We believe there are hidden numbers in both the US and Europe. Many NPC cases are probably mis- or undiagnosed. We can only assume low awareness among general practitioners owing to NPC's extremely rare profile. With the advent of new drug agents, such as arimoclomol, we believe we could see an increase in diagnosed cases. We therefore pencil in a steady increase in above-average population growth in the coming years.

We estimate a **market penetration** at more than half of the diagnosed cases at its peak. Our proposed market penetration comes on the back of, among others, being first-on-the-market, its favorable administration, and the urgent medical need

In Europe, miglustat is approved and Orphazyme cannot benefit from being first on the market. Interestingly though, we propose the same market penetration as in the US. We rather see miglustat as complimentary to arimoclomol as SRT therapies work mechanistically differently and later in the protein-misfolding pathway. Miglustat have truly opened up the NPC market for followers, in our view. About 80% of the NPC patients in Europe currently receive miglustat. Moreover, we are intrigued by the subgroup analysis from the phase 2/3 trial with arimoclomol. When miglustat was used as background treatment (n=39), this combo showed to be highly efficacious in halting disease progression:

Arimoclomol with Miglustat as Background Treatment



* In the predefined subgroup analysis in patients with miglustat as background treatment, arimoclomol halted disease progression at 12 months of treatment. This effect was statistically significant (p=0.0074)
Source: Orphazyme

We propose a strong US **market uptake**, taking off significantly a few years after launch, and with peak sales reached after 6-7 years. Our main arguments for the rapid uptake and high market penetration are:

- Arimoclomol's EAP and early commercialization efforts
- The urgent medical need
- Early commercialization efforts by Orphazyme
- Patients treated at specialized centers.

On the downside, only a handful of patients are part of the EAP today. It is also important to note that Orphazyme comes from a research-driven organization and has not made this journey before. It is crucial for the Company to have the right competencies to transition successfully into a commercially driven organization.

As mentioned above, even though there are no drug therapies approved in the US, NPC patients can receive treatment with the off-label miglustat and early access program agents. We believe arimoclomol has a favorable administration compared with those, which implies low switching barriers. It is worth to emphasize again that, if arimoclomol gets approved, it will be the standard of care.

Typically, market penetration for prescribed drugs goes slower in the EU markets compared to the US. We have factored this to some degree. However, again thanks to miglustat, the pace does not have to be that much slower in the EU.

NPC sales model

	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Active Cases										
US	471	481	490	505	520	536	549	563	577	591
Europe	828	845	862	888	914	942	965	989	1014	1039
arimoclomol, market share										
US penetration	6%	11%	23%	36%	45%	54%	60%	60%	60%	30%
Europe penetration	1%	8%	17%	24%	33%	45%	51%	57%	60%	60%
arimoclomol, patients treated										
US patients treated	28	52	112	182	234	289	329	338	346	177
Europe patients treated	7	71	142	213	302	424	492	564	608	624
arimoclomol sales (\$m)										
US	11	21	36	49	54	64	70	70	71	36
Europe	2	23	36	46	56	74	84	94	100	100
total sales	14	43	72	96	110	138	154	165	170	136

Source: Redeye Research

Neuromuscular Disorders – Previewing Ph 3 Data

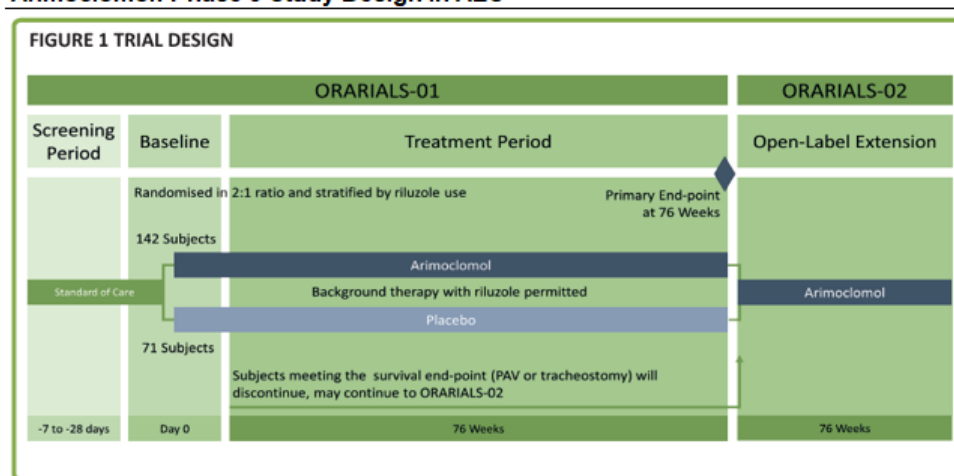
ALS

Arimoclomol status

In 2018, Orphazyme initiated ORARIALS-01, a phase 3 trial being conducted in the US, Canada, and Europe. ORARIALS-01 is a randomized, double-blind, placebo-controlled, parallel group trial that could serve as marketing registration in ALS. 245 ALS patients were randomized 2:1 in favor of arimoclomol treatment. Patients in the active arm are treated with 400 mg arimoclomol three times a day (1,200 mg/day).

In July 2019, Orphazyme reported the last patient in. Given the treatment duration of 18 months, followed by data collection, we anticipate top-line results in mid-Q1 (2021) at earliest.

Arimoclomol: Phase 3 Study Design in ALS



Source: Orphazyme

The primary aim of the study is to evaluate the safety and efficacy of arimoclomol in ALS patients. In terms of effectiveness, ORARIALS-01 uses the Combined Assessment of Functional and Survival (CAFS) as the primary endpoint at 18 months compared to placebo. The CAFS endpoint is a joint rank analysis of survival and function (ALSFRS-R), or essentially ALSFRS-R adjusted for mortality. In the ranking, survival is of most clinical importance. ORARIALS-1 is 90% powered to detect a statistically significant difference, assuming an effect size of 0.48 on CAFS between arimoclomol and placebo at 18 months.

ALSFRS-R

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 legible	Normal
Dressing & Hygiene	Total dependence	Needs attendant for self-care	Intermittent assistance 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 needed	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

Source: Cedarbaum JM et al. J Neurol Sci. 1999;169:13–21., Redeye Research

Our expectations

ALS is a notoriously hard field in which to succeed and conduct clinical trials, owing to factors such as the rapid progression of the disease course, the lack of an established biomarker, limited understanding of disease pathophysiology, and patient heterogeneity. Despite the statistics not being in favor of a positive outcome, we see two key factors to be optimistic about:

1. Preclinical and clinical data presented so far

Preclinical data

Arimoclomol has been studied in a transgenic mouse model overexpressing human mutant SOD1. SOD1 is the mutation in approximately 20% of familial ALS cases and in 2% of all ALS cases. The SOD1 transgenic mouse is regarded as the most appropriate animal model in ALS. Still, the mouse does not develop ALS but rather a phenotype similar to the disease.

Arimoclomol has been examined in SOD1 mice to see if daily treatment with at 10 mg/kg (HED: 45 mg daily) could prevent the loss of motoneurons and muscle function, as measured in a particular muscle (extensor digitorum longus). The results showed that arimoclomol-treated mice demonstrated a significant delay in disease progression, even after symptom onset. Treatment with arimoclomol also prolonged survival by 22% compared to untreated mice. The results also saw an increase in HSP70 and HSP90 in the spinal cord due to the prolonged activation of stress-induced Hsf-1, strengthening arimoclomol's mechanism of action.

Clinical data

In phase 2 data with 84 ALS patients, arimoclomol was evaluated for safety, tolerability, and pharmacokinetics. The treatment period was only 12 weeks, but patients who completed this could enroll in an open-label phase for another 6 months. Arimoclomol up to 300mg/day was found to be safe and tolerable, and arimoclomol levels in the cerebrospinal fluid (CSF) increased with dose (Cudkowicz et al., 2008).

The other phase 2 study was randomized (1:1) and placebo-controlled, evaluating arimoclomol up to 600 mg/daily up to 12 months. This study was more efficacy-related than Cudkowicz et al., 2008.

We have read through this publication (Benatar et al., 2018) again ahead of the phase 3 data and can conclude that the study showed consistency in efficacy parameters:

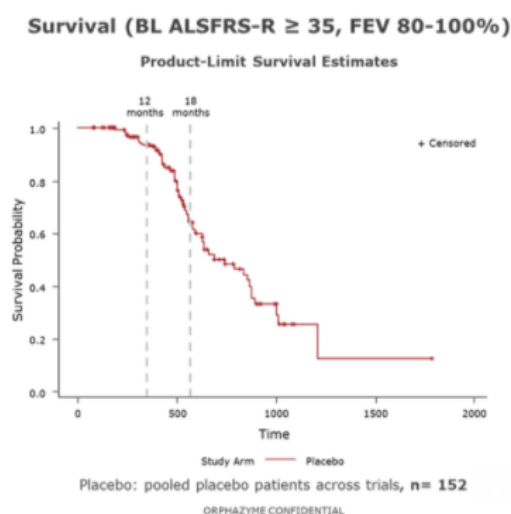
- A treatment difference of 0.5 points per month between active arm and placebo based on ALSFRS-R (function)
- Separations between arms in survival at 12 months
- FEV6 (a measure of lung capacity) declined at a slower rate of 1.24% predicted per month
- CAFS favored arimoclomol treatment, with a CAFS score of 20.9 in the arimoclomol arm, versus 16.3 in placebo (the higher, the better).

There are limitations with this data. The study only enrolled 36 SOD1-ALS patients and was not powered for efficacy. The authors also concluded that they do not interpret the data as showing effectiveness. Moreover, none of the efficacy domains yielded statistical significance. It is the consistency in efficacy trend that encourages us. It will be highly interesting to see the results from arimoclomol at twofold dosing, over an 18-month treatment duration, and in a larger patient group.

2. Phase 3 study design

We mentioned above that ALS is a heterogeneous disease. As Orphazyme is targeting the whole ALS population this time, rather than SOD1 patients as in phase 2, it has been crucial to enroll the most homogenous population possible from the broad ALS population. Therefore, inclusion criteria have been set based on analysis of the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT), helping Orphazyme to enroll patients with relatively homogenous disease progression over 12-18 months. The observations from PRO-ACT have shown that the disease often progresses relentlessly at the 12-18-month mark. This is consequently where treatment intervention could make a real difference. The primary endpoint in ORARIALS-01 has thus been set at 18 months. Many other phase 3 trials have a cut-off at 12 months or even earlier for primary endpoint.

ALS Progression Pattern



Source: Orphazyme

Conclusion

What can we expect? And what are 'good results' in concrete terms? These are more difficult questions to answer than they appear. We have to weigh up factors such as:

- The basis on which the current therapies have been approved
- What agencies mean represents a clinically meaningful effect
- The current medical need.

The last aspect is the easiest to discuss: the medical need is urgent. There is a strong rationale for evaluating the whole dataset and engaging with experts and regulators, even if the top-line results are borderline or initially disappointing. We expect this it will happen in the current case of Brainstorm Cell Therapeutics (more on that below).

The current drug therapies on the market are (both with different mechanism of actions than arimoclomol):

- Riluzole, approved in 1995 for ALS
- Radicava, approved in 2001 in Japan for acute ischemic stroke, and given FDA approval for ALS in 2017.

As both have been on the market for many years, we regard them as generally safe and tolerable.

Riluzole was approved 25 years ago. This was on the basis of a functional scale that is now outdated. Riluzole is regarded to prolong survival by a few months.

Edaravone (Mitsubishi Tanabe) has reported functional benefits in a well-defined subgroup of early ALS patients. Based on ALSFRS-R and after a 24-week treatment duration, phase 3 results showed that the change in ALSFRS-R score was -5.01 in the edaravone group compared to -7.5 in the placebo group. The difference was reported as statistically significant.

The literature on what constitutes a clinically meaningful change in absolute terms in the ALSFRS-R is scarce. The absolute change difference for edaravone must then be some baseline for what can be regarded as clinically meaningful, we judge.

A research survey among clinicians and researchers demonstrated that the vast majority regarded a 20% change in the slope of the ALSFRS-R as clinically meaningful. It is to be noted though, as stated above, that ORARIALS-01 uses CAFS as primary endpoint. CAFS is a joint rank analysis where survival benefit weighs heavier. A challenge with CAFS is that it is a non-parametric rank analysis and cannot be directly compared across trials. Hence, the best guidance we can give is that:

- A 2.5-point drop in absolute terms, and a 20% change in slope should be regarded as clinically meaningful (ALSFRS-R)
- As mortality dominates function in CAFS, a survival benefit needs to be demonstrated in ORARIALS-01. To put it simply, survival should firstly take place in the active arm, secondly with a longer duration.

We also want to see supportive outcomes on secondary measures, which include respiratory function (slow vital capacity), quality of life, and biomarkers supporting mechanism of action and target engagement. Last, but not least, the benefit/risk profile is always crucial. Any

clinical effect should outweigh possible adverse events, and the compound should be safe and well-tolerated overall.

Competitive landscape

Current market and Potential

Riluzole was approved in the US in 1995 and is today a widely used generic. Radicava received FDA approval in 2017 and has reported no data on survival. Together, we assess that this market dynamics is equivalent to some USD 100m in annual sales to date.

There is an urgent need for more efficacious drug therapies targeting ALS. Based on the number of cases, priced at orphan standards, an effective treatment could reach sales of USD 500-1,000m on the major markets. This estimate is strengthened by some 'street' analysis of other late-stage pipeline drugs.

Pipeline and news flow

Arimoclomol is among the furthest advanced compounds in a clinical pipeline of small molecules, biologics, cell/gene therapy, antisense, and non-NME (New Molecular Entities). Unfortunately for the patients, the pipeline has become thinner over the years, with few success stories and many failures.

Some recent news has come from **Simdax (Orion)** and **Nurown (Brainstorm Cell Therapeutics)**, neither of whose respective phase 3 trials met prespecified endpoints, along with positive phase 2 results for **AMX0035 (Amylyx Pharmaceuticals)**.

Simdax is an oral levosimendan that is approved in Europe for acute heart failure. The rationale to test it in ALS was to see if it improved slow vital capacity, a respiratory endpoint. The phase 3 study failed to meet the primary endpoint or ALSFRS-R, which served as a secondary endpoint.

Nurown is a therapeutic approach where a specific type of stem cells, MSC-NTF, is expanded and differentiated outside the body before it is delivered directly to the damaged site in the body to elicit biologic response of neurotrophic factors. Even though it is a completely different molecule to Orphazyme's arimoclomol, it is in late-stage development, making it relevant to discuss.

In November, Brainstorm Cell Therapeutics reported results from its phase 3 study, a randomized, multicenter, placebo-controlled, double-blind trial designed to evaluate the safety and efficacy of Nurown on 189 ALS patients. Patients were randomized 1:1 to receive three intrathecal injections with Nurown or placebo every eight weeks.

The primary efficacy measure was the rate of decline in ALSFRS-R at 28 weeks following the first treatment. The results showed a numerical improvement in primary and efficacy endpoints compared to placebo but did not reach statistical significance. The Brainstorm stock took a hefty beating on the results, dropping by some 70% the day the results were announced.

The study was powered to show a 35% treatment response in the active arm versus 15% in the placebo arm (ALSFRS-R). That was achieved in 34.7% of the Nurown patients, versus 27.7% in placebo. The placebo response was thus higher than anticipated. In a predefined subgroup of ALS patients with a higher score than 35 at baseline, the study reported clinically meaningful improvements, although it did not reach statistical significance. Nurown was generally well-tolerated.

AMX0035 is a small molecule in development by Amylyx in ALS and other CNS disorders. It is a proprietary combination of tauroursodeoxycholic acid and sodium phenylbutyrate. It acts by simultaneously blocking mitochondrial and endoplasmic reticulum (ER) stress.

Amylyx Pharmaceuticals recently announced the publication of results from its pivotal phase 2/3 trial (CENTAUR). The study enrolled 137 ALS patients, and the primary outcome was the rate of decline based on ALSFRS-R. After 24 weeks, patients treated with AMX0035 scored, on average, 2.32 points better than those on placebo ($p=0.03$). The publication also reported on numerical benefits on secondary outcomes.

The authors in the publication conclude that 'sodium phenylbutyrate-taurursodiol resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks' and that 'longer and larger trials are necessary to evaluate the efficacy and safety of sodium phenylbutyrate-taurursodiol in persons with ALS.'

In a sister publication, Amylyx Pharmaceuticals also announced data on survival with AMX0035. This analysis compared time to death (all-cause mortality) between those originally randomized to placebo and those originally randomized to active arm. The survival analysis encompassed all participants before randomization, including those who did not enter the open-label extension phase, discontinued in the study or were lost to follow-up. The analysis showed that the patients who received AMX0035 at baseline had a 44% risk reduction for death over the course of the follow-up period ($p=0.023$). The longest follow-up reported was 35 months. The group who originally received active drug had a median overall survival that was 6.5 months longer (25 versus 18.5 months) than those originally assigned to placebo.

The phase 2 results with AMX0035 are indeed encouraging for the patient community. We believe that a likely path forward for AMX0035 is to initiate one phase 3 trial with a single outcome score that combines survival and function. Meanwhile, Amylyx Pharmaceuticals will likely work closely with the agencies to get regulatory designations and analyze further the dataset from CENTAUR. For now, we regard AMX0035 as a few years behind relatively arimoclomol in development.

Bearing in mind the most recent pipeline news, we see those in the table below as the most relevant to compare with arimoclomol. Our short conclusion on Nurown is that its trial failed but the analysis will likely continue. We include it in our peer cohort for now, pending further information.

ALS: Closest Competitors*							
Drug Name	Lead Company Name	Drug Classification	MoA**/Target	Route of Administration	Current Phase	Next Event	Redeye Comment
<u>Approved Drugs</u>							
Riluzole	Generic	Small Molecule	Glutamate	Sublingual (SL)/Oral Transmucosal, Oral (PO)	Approved		
Radicava	Mitsubishi Tanabe	Small Molecule	Reduce oxidative stress	Intravenous (IV)	Approved	Phase 3 results for oral formulation (2021)	
<u>Pipeline Drugs</u>							
Arimoclomol	Orphazyme A/S	Small Molecule	Heat Shock Protein (HSP-) amplifier	Oral (PO)	Ph 3	Ph 3 Top-line results (H1'21)	
IONIS-SOD1Rx	Biogen, Inc.	Antisense	Antisense oligonucleotides	Intrathecal	Ph 3	Phase 3 top-line results (H2'21)	Targets SOD1-ALS patients, constitutes 2% of all ALS cases
Ultomiris	Alexion Pharmaceuticals Inc.	Biologic (Monoclonal antibody)	C5a Receptor	Intravenous (IV), Subcutaneous (SQ)	Ph 3	Ph 3 Top-line results (H2'22)	
Masitinib	AB Science S.A.	Small Molecule	Fibroblast Growth Factor Receptor (FGFR), KIT/c-KIT, Platelet-derived growth factor receptor (PDGFR)	Oral (PO)	Ph 3	We expect ph 3 top-line results in 2022 at earliest	
Cu(II)ATSM	Collaborative Medicinal Development, LLC	Small Molecule	Mitochondrial Electron Transport Chain	Oral (PO)	Ph 2/3	We expect Ph 2/3 top-line results in H1'21	
AMX0035	Amylyx Pharmaceuticals, Inc.	Small Molecule	Mitochondria	Oral (PO)	Ph 2 (Completed)	We expect progress update from Amylyx in Q4'20/Q1'21	
NSI-566	Seneca Biopharma Inc.	Biologic	Stem Cells/Other Cell Therapies	Intracerebral/cerebroventricular, Intrathecal	Ph 2	We believe a phase 3 trial could potentially start in 2021	
<u>Watchlist</u>							
NurOwn	BrainStorm Cell Therapeutics Inc.	Biologic	Stem Cells/Other Cell Therapies	Intravenous (IV), Intrathecal	Ph 3	Further analysis on phase 3 results	Recently reported that its phase 3 study did not meet the primary endpoint. We include it for now, pending further information.

* The pipeline does not claim to comprehend all drug candidates in development

** Mechanism of Action

Source: Company pages, clinicaltrials.gov, Biomedtracker, Redeye Research

Estimates

- We've added some margin of safety in our proposed launch, to 2023 (2022)
- We adjust the peak sales potential upwards in the range USD 500-1,000m to reflect the commercial potential of a drug therapy that could prolong survival and also provide a functional benefit
- We are unwilling to adjust our probability rate before phase 3 readout, as we acknowledge that this is a notoriously difficult indication in which to succeed.

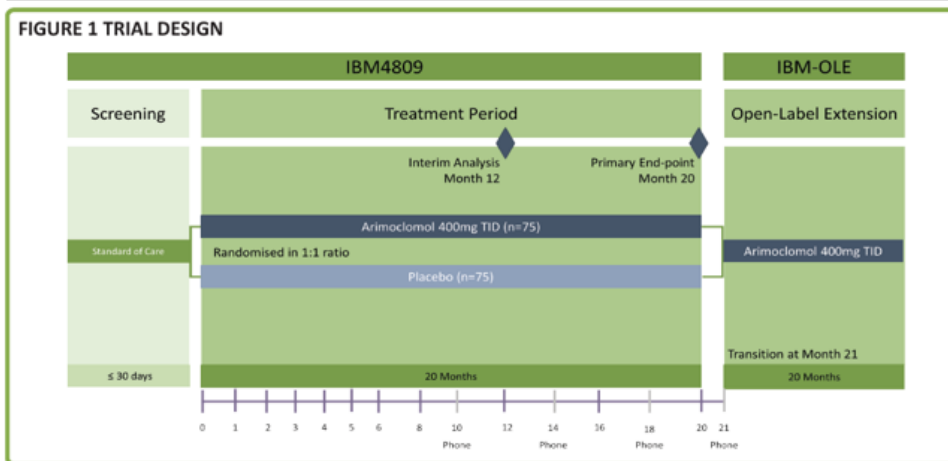
sIBM

Arimoclomol status

Orphazyme initiated a phase 2/3 trial in sIBM in 2017, conducted in the US and UK. This pivotal double-blind trial enrolled a total of 150 patients. Patients were randomized 1:1 to 400 mg t.i.d. (1,200mg/day) arimoclomol or placebo.

The last patient-in was reported in April 2019. Given a treatment duration of 20 months, followed by data collection, we anticipate top-line results in mid-Q1 (2021) at earliest (in other words, same as for ALS).

Arimoclomol: Phase 3 Study Design in sIBM



Source: Orphazyme

The primary endpoint is defined as a change from baseline to month 12 based on the validated IBMFRS total score (IBMFRS is derived from the ALSFRS-R score). The study is 80% powered to detect a mean response of 1.4 points on IBMFRS between the active arm and placebo. This is based on findings in the phase 2 trial (Ahmed et al., 2016), which we go through below.

IBMFRS

Domain \ Score	0	1	2	3	4
Swallowing	Needs tube feeding	Frequent choking	Dietary consistency changes	Early eating problems-occasional choking	Normal
Handwriting (dominant hand)	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 (Velcro snaps, shirts without buttons etc.)	Independent but with increased effort or decreased efficiency	Normal
Hygiene (bathing and toileting)	Completely dependent	Requires occasional assistance from caregiver	Independent but requires use of assistive devices (shower chair, raised toilet seat, etc)	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 (leaning forward, rocking) but without use of arms	Independent (without use of arms)
Walking	Wheelchair dependent	Dependent on assistive device	Intermittent use of an assistive device (e.g., walker)	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

Source: Amato & Barohn J. Neurol. Neurosurg. Psychiatry 2009;80:1186-1193, Redeye Research

Our expectations

This indication has some similarities to ALS, such as no effective therapies available and a progressive state. But the major similarities end here. sIBM has a slower disease progression and is not considered fatal. There could be indirect causes of death related to the disease, such as falls, respiratory failure, or infection.

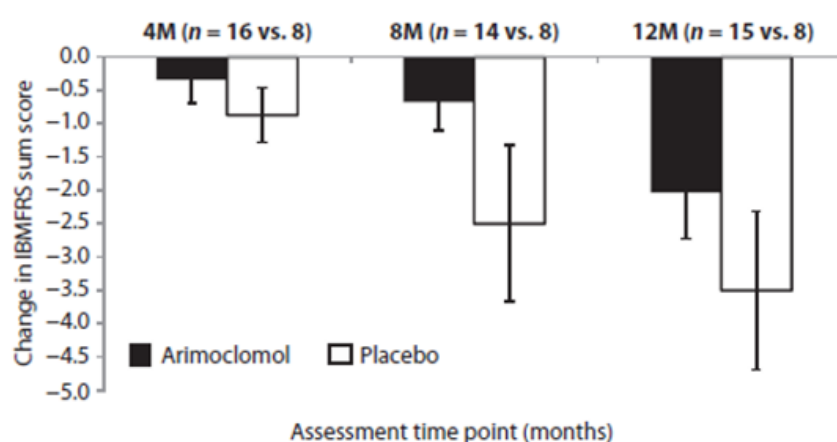
An sIBM patient has usually lost their full mobility and is dependent on a wheelchair after 15 years. On sIBMFRS, a patient averages a 2.0-2.5-point decline per eight months. This provides a well-defined benchmark for disease-modifying drug candidates, such as arimoclomol.

The full etiology of the disease remains uncertain. Muscle biopsies from sIBM patients typically show inflammatory, degenerative, and protein aggregation features. The disease is classified under the idiopathic inflammatory myopathies, a class of autoimmune conditions.

Therapeutic efforts have primarily been targeted towards the inflammatory aspects of the disease and appear to have had a unanimous lack of success. As a consequence, Ahmed et al. (2016) decided to test the effects of targeting protein homeostasis by initiating a phase 2 trial with arimoclomol.

This phase 2 trial was a randomized and placebo-controlled, double-blind, first proof-of-concept trial in 24 subjects. This trial is one of our primary arguments for a positive outcome in phase 3. Although not powered for efficacy, there were trends in favor of arimoclomol. At a p-value of 0.055, the arimoclomol-treated arm (100 mg t.i.d.) showed a reduction in score of 0.68 based on IBMFRS, versus 2.50 in placebo after eight months.

Arimoclomol: Phase 2 Efficacy Results in sIBM



Although not statistically significant, the phase 2 results saw a clear trend in efficacy measure based on IBMFRS.

Source: Ahmed et al 2016, Science Translation Medicine; Vol 8 Issue 331.

The phase 2/3 trial is designed based on observations in the phase 2. Hence, if we are not completely off in our thinking, if the placebo arm follows the standard deterioration pattern for sIBM patients, it is sufficient for this efficacy-powered trial to replicate the trends in efficacy seen with arimoclomol in the previous study. Besides, if arimoclomol works in this indication, the 20-month study duration should arguably show a more apparent separation effect as well, compared with 8 or 12 months as the change in IBMFRS is expected to not diminish over time for sIBM patients.

A few words about inclusion criteria: a participant in the phase 2/3 trial has to meet any of the sIBM categories defined by 2011 European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria, which includes both clinical and pathological features. The 2011 research diagnostic criteria are, as far as we know, the most up-to-date in the diagnosis of sIBM. Other inclusion criteria are:

- Demonstrate being able to rise from a chair without support from another person or device
- Ability to ambulate at least 20 ft/6 meters with or without an assistive device. Once up from the chair, the participant may use any walking device, e.g., crutches. They

cannot be supported by another person and cannot use furniture or a wall for support.

This is clearly about enrolling early sIBM patients, which is often highly relevant for therapies that claim to have disease-modifying potential in progressive conditions.

Conclusion

We look forward to learning about this study's results, as it is powered for efficacy. Given the failure of drug agents targeting the inflammatory drive, we lean toward interfering with the protein aggregation pathway. A phase 2 study with arimoclomol supports our probability prognosis of a good phase 3 readout. Lastly, we believe it is good to have a relatively clear view of the pace at which sIBM patients deteriorate. This provides a benchmark for what we can expect from the placebo group.

Competitive landscape

There are currently no drug agents that have shown efficacy on progressive disease course and so no drugs are approved for sIBM. We regard the pipeline as thin, even thinner than when we initiated coverage of Orphazyme in 2018. Back then, we identified a gene therapy candidate, AAV1-FS344 (Milo Technology), as the only direct peer in active development. However, there has been no news flow on this over the past year, and Biomedtracker has labeled it as 'Suspended' in the pipeline, pending further information. There are some immunology drug candidates in clinical development in other idiopathic inflammatory myopathies. These are in adjacent disorders and is only on our radar for now. In sIBM specifically, we cannot identify any direct peer to arimoclomol.

Estimates

We have only fine-tuned our estimates upon phase 3 results. Given that this is the most common muscle-wasting disorder among those above the age of 50, with no effective therapies that can affect the disease course, and slow disease progression, we see this as an attractive commercial opportunity. It equals the combined potential in NPC and neurological GD.

Financials

Financial Position

Following the US IPO and the concurrent private placement, we acknowledge Orphazyme as well-funded. The financial risk in Orphazyme is mitigated, and we foresee a cash position of above DKK 700m by yearend, in line with corporate communication.

P&L Interpretation

Orphazyme is amid a possible transition, from a project-driven biotech to also become a biopharma company with a full-fledged commercial organization. It makes our P&L estimates and our overall Financials & Valuation somewhat difficult to interpret. This is our main message though.

- We continue to value each project with no terminal value in a Sum-of-the-Parts-model
- It means that we still make use of risk-adjusted, future cash flows as well as on the cost side

Having said that, we could potentially transition into a more standard DCF within a couple of years, if we continue to see a successful transformation of the business.

To get a glimpse of, not least, the commercial potential, we also present some figures below that are non-risk adjusted. It appears from respective figure below if the numbers behind are risk- or non-risk adjusted.

P&L Estimate Changes

Based on Orphazyme's guidance from October, we raise our forecast for opex for the current year, which drives change for the current year. There's a slight Fx headwind in our P&L estimates as the result of a strengthened Danish krona against the US dollar.

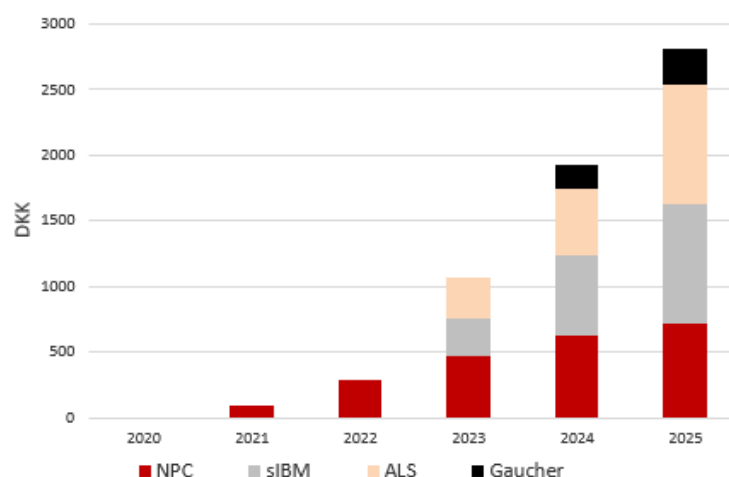
The lowered sales estimate in the coming years should be seen in the light of a small postponement, where we add some margin of safety. It is not related to a lowered commercial potential.

Orphazyme: P&L estimate changes*									
	2020E			2021E**			2022E		
	New	Old	Absolute change	New	Old	Absolute change	New	Old	Absolute change
Revenues	0	0	0	82	122	-40	260	303	-43
OPEX	-621	-511	-110	-529	-538	9	-470	-474	4
EBIT	-627	-515	-112	-484	-461	-23	-279	-242	-37
Earnings	-628	-517	-111	134	145	-11	-281	-248	-33

* Risk-adjusted from 2021

** A sell of a PRV with updated risk-adjustment is incorporated in earnings for 2021

Source: Redeye Research

Orphazyme: Sales Potential 2020-2025*

* Non-risk adjusted

Source: Redeye Research

Valuation

Key Parameters

We highlight changes in our key parameters:

- Lower financial and development risk enables a lower WACC, down from 12%
- Per share valuation based on 34.7m outstanding shares
- Some Fx headwind (Previously USD/DKK: 6.8)

	Generic	Base	Bull	Bear
Key model parameters				
tax rate	22%			
shares outstanding	34.7			
USD/DKK	6.5			
EUR/DKK	7.5			
WACC	11%			
Initial price, US (\$'000)	400			
Initial price Europe (\$'000)	320			
Risk-free interest rate	1%			
Probabilities				
NPC		90%/95%	100%	100%
sIBM		50%	87%	0%
ALS		35%	35%	0%
Gaucher		30%	45%	30%
Rare pediatric voucher		95%	100%	100%
Market share				
NPC		60%	60%	50%
sIBM		45%	50%	0%
ALS (non-SOD1)		40%	40%	0%
ALS (SOD1)		35%	35%	0%

Source: Redeye Research

Scenario Analysis

In view of Orphazyme's strong likely news flow in the coming months, it is important to consider all three of our scenarios the stock: Bear, Base and Bull Case. Below we show in terms of the projects in NPC, ALS, and sIBM:

NPC

- We value arimoclomol-NPC at around DKK 40 per share
- As a result of the high likelihood of market approval, the unadjusted value is not much higher at around DKK 45 per share
- As arimoclomol potentially transitions into a commercial asset by next year, other factors (pricing, market uptake, market penetration, etc.) will drive value
- A worst-case scenario is that arimoclomol fails at this late stage for some reason. As we see this as unlikely, it is not embedded in our Bear Case

sIBM

- We value arimoclomol-sIBM at around DKK 40 per share
- Our unadjusted value in this indication is around DKK 85 per share.
- The phase 2/3 readout in H1 21 is a key catalyst and embedded in our scenario modeling

ALS

- We value arimoclomol-ALS at around DKK 30 per share.
- Our unadjusted value in this indication is around DKK 100 per share
- The phase 3 readout in H1 21 is a key catalyst and embedded in our scenario modeling

Orphazyme: Sum-of-the-parts valuation								
Project	Indication	Phase	Launch	Peak sales (\$m)	Value, unadj. DKKm	Probability	Value, adj. DKKm	Per share
arimoclomol	NPC	NDA	2021	170	1,563	90%/95%	1,438	41
arimoclomol	sIBM	II/III	2023	340	2,886	50%	1,385	40
arimoclomol	ALS	III	2023	660	3,413	35%	950	27
arimoclomol	Gaucher	II	2024	240	1,554	30%	338	10
NMEs	n.a.	n.a.	n.a.	n.a.	0	0%	0	0
Total projects							4,110	119
Priority review voucher							550	16
Other costs							(300)	-9
Net cash							649	19
Total							5,008	145
Shares outstanding (m)							34.7	
Value per share							145	

Source: Redeye Research

Bear Case 70 (70) DKK

- Arimoclomol gains approval for NPC but we lower the commercial potential somewhat and also factor in a lower sale of the PRV (USD 90 mn)
- We factor in negative results in both ALS and sIBM

Base Case 145 (130) DKK

- See our SOTP-model above

Bull Case 200 (175) DKK

- This scenario factors in a positive readout in sIBM phase 3, and treats it as an NDA asset
- It also factors in borderline results in ALS that are subject to further interpretation. This raises LoA slightly but postpones launch in a zero-sum game
- Arimoclomol gains approval for NPC and we maintain our commercial assumptions
- Orphazyme starts enrollment of Gaucher patients in the pivotal stage

Orphazyme: Summary of scenarioanalysis

	Bear	Base	Bull
SEK per share	70	145	200
Potential / Risk*	17%	142%	233%

* Based on closing price 16 Dec 2020: DKK 60.0 per share
Source: Redeye Research

Stock performance – looking ahead after weakness

While the company has reported continuing positive news in 2020, the stock has performed negatively. We have sought to understand if anything fundamental explains this puzzle. Analyzing its performance is also crucial to having conviction over its likely direction from current levels.

We break the stock's 2020 performance into five periods:

- Period 1: Momentum (January to mid-February)
- Period 2: The corona crisis (Mid-February to March)
- Period 3: Selling pressure (April to the half year-end)
- Period 4: Sustained selling pressure (July to October)
- Period 5: Stabilizing at depressed levels (Nov to mid-December)

Period 1 and **Period 2** are fairly self-explanatory. At the beginning of the year Orphazyme reported positive results from the OLE part in NPC (12+12 months). The results showed a

sustained effect, with a genetic sub-group analysis (post-hoc analysis encouraged by the FDA) reinforcing the efficacy results. The company also raised USD 110m in a successful private placement to international investors.

When the pandemic's magnitude became apparent to investors, the stock was affected, inevitably.

In **Period 3** we link the weak performance to sales by Novo Holding (Novo). Holdings analysis shows that this investor sold 1.6m shares in H1. At the end of May it still had 1.3m shares. This is the last Holdings data for Novo's stake in Orphazyme.

Period 4 saw an unprecedented, continuing decline in the stock without any material or negative news in this period. Indeed, the opposite is true as Orphazyme reported progress at the NDA filing stage in NPC.

We reckon from the broker statistics during this period that there are a few brokers selling rather large volumes. This suggests that it could be the result of a continuing overhang from a couple of the larger shareholders. We assume that Novo continued to sell in H2 and may have shed its entire stake (Novo is no longer listed as one of the larger shareholders on Orphazyme's web page). We also learned about a second major holder, Consonance Capital, who decreased its holdings. According to the Holdings database, it became a holder in February 2020 with 1.9m shares. It had sold roughly a quarter of its stake by the beginning of October, leaving it with 1,339,909 shares.

While Scandinavian retail buyers soaked up the shares sold, this could only dampen the decline.

Broker Stats Activity: July-Oct				
Broker Code	Broker Name	Buy Volume	Sell Volume	Net Volume
Top-10 Net Buyers				
DDB	Danske Bank A/S	1,685,655	919,516	766,139
NON	NordNet AB	2,019,762	1,435,840	583,922
SYD	Sydbank A/S	614,201	290,584	323,617
NRD	Nordea Bank AB	573,026	302,526	270,500
AVA	Avanza Bank AB	383,587	125,346	258,241
SNB	Spar Nord Bank A/S	227,591	59,183	168,408
SAX	Saxo Bank A/S	382,516	218,860	163,656
SHD	Svenska Handelsbanken AB	177,660	17,389	160,271
KRO	Sparekassen Kronjylland	274,088	132,216	141,872
JYB	Jyske Bank A/S	257,540	125,585	131,955
Top-10 Net Sellers				
PAS	Pareto Securities AS	1,122,882	1,583,624	-460,742
MSE	Morgan Stanley Europe	908,839	1,258,604	-349,765
ENS	Skandinaviska Enskilda Banken AB	1,293,312	1,565,761	-272,449
SGL	Societe Generale SA	17,915	207,000	-189,085
VFB	VIRTU FINANCIAL IRELAND	3,045	180,998	-177,953
GSI	Goldman Sachs International	134,711	290,230	-155,519
BRC	Barclays Capital Securities Limited Plc	198,100	329,478	-131,378
CSV	Credit Suisse Sociedad de Valores S.A.	161,153	267,125	-105,972
INT	Instinet Europe Limited	450,537	515,538	-65,001
CAR	Carnegie Investment Bank AB	72,441	121,964	-49,523

Source: Bloomberg

ORPH (US) 's first day of trading occurred at the end of September. The first US banks initiated research coverage about a month later. So far, we have seen no significant interest

among US investors - the stock is trading well below its IPO price and trading volumes are relatively low. We expect interest to lift eventually as potential commercialization nears.

Along with the US listing, FDA review issues became public (also known as the Day 74 letter). We believe this was a concern for investors as disclosing this kind of information is uncommon. We refer to our 'Probably rate' in the NPC section above for a thorough review. The overall timeline stands, though, with the PDUFA date on March 17, 2021.

Period 5 has seen the stock trade sideways and stabilized at around DKK 60. The news on CEO Stratton's resignation moved the stock temporarily below the SEK 60.

Analysis

Novo's and Consonance selling are clear explanations for the pressure on the stock in both H1 and H2. Much of this selling appears to have gone through the open market as there are no material block trades reported, especially not in H2 (Holdings).

We have not researched Novo and Consonance's selling in depth. Still, we do not view it as necessarily alarming. It could well be driven by policy decisions rather than fundamentals. Note that Novo was a long-term investor in Orphazyme, first becoming an owner back in 2010.

Consonance became an owner when the stock was trading far above its present level. Accordingly, we speculate whether some stop-loss policy triggered its sale.

We also want to emphasize that some of the other larger shareowners have protected their ownership or maintained the same number of shares in 2020. It includes the current top three holders; Lsp V Coöperatieve, Sunstone Capital, and Coöperatieve Aescap Venture.

Orphazyme: Top Stockholders and Change in 2020

Owner	Holdings	Capital	Country	Verified	Absolute Change
Lsp V Coöperatieve U.a	2,710,829	7.8%	Netherlands	2020-10-01	0
Sunstone Capital	1,803,450	5.2%	Denmark	2020-10-01	-11,050
Coöperatieve Aescap Venture i U.a	1,765,600	5.1%	Netherlands	2020-10-01	-9,021
Consonance Capital Management L	1,339,909	3.9%	USA	2020-10-05	1,339,909
Islet Management LP	1,331,395	3.8%	USA	2020-09-30	1,331,395
PFA Pension A/S	795,064	2.9%	Denmark	2020-06-30	214,954
Handelsbanken Fonder	741,483	2.1%	Sweden	2020-09-30	730,646
Fjärde AP-fonden	534,285	2.0%	Sweden	2020-06-30	534,285
Danske Invest (DK)	571,212	1.6%	Denmark	2020-09-30	71,560
PFA	502,899	1.4%	Denmark	2020-09-30	258,394
Novo Holdings A/S*	1,349,541	5.0%	Denmark	2020-05-29	

* As per Holdings, not updated since May

Source: Holdings, Orphazyme, Redeye Research

In retrospect, it is debatable whether the dual listing's timing was right. Orphazyme would probably have raised the same (or more) funding through a private placement. It could have then benefitted from a dual listing at a later and potentially already commercial stage. US investors' interest would probably have been higher then than currently.

Although the stock had started to plummet previously, the disclosure of the FDA review issues may well have created some concern among investors. We can understand this reaction, it might hold back investors until we know the FDA's response next year.

We see no selling pattern among insiders that would change our fundamental view of the case. Indeed, management and the board trading has been rather favorable.

Orphazyme: Insider Holding and Change in 2020

Insider	Position	# of Shares	Absolute Change	
			Capital	in 2020
Bo Jesper Hansen	Board Member	143,234	0.5%	42,689
Anders Vadsholt	CFO	135,556	0.5%	2,961
Georges Gemayel	Chairman of the Board	100,809	0.4%	3,451
Martin Bonde	Board Member	47,936	0.2%	1,927
Anders Hedegaard	Board Member	15,677	0.1%	1,927
Catherine Moukheibir	Board Member	7,980	0.0%	0

Source: Holdings

Final remarks

While there are some clear explanations for the stock's weakness, these are not clearly related to the case's fundamentals. Orphazyme's business has developed well during the year and the company is now entering a defining moment.

We believe the recent flat performance at levels around DKK 60 per share over the past month represents something of a floor, albeit at very depressed levels. We expect sentiment around the stock to improve as we move nearer to the key period at the end of Q1 21/beginning of Q2 21. Orphazyme will then readout two phase 3 studies and may get approval for arimoclomol in the US in NPC.

Accordingly, it is time for investors to look ahead.

Peer valuation

Our peer analysis, based on Enterprise Value (EV), underscores our view that Orphazyme is fundamentally undervalued – although this has no direct impact on our scenario-based fair values. Criteria for inclusion in our peer cohort are the same as before: orphan profile, late-stage (beyond phase 3), well-funded, and Scandinavia-listed.

Should Orphazyme trade at an EV discount to our identified peers? Possibly. It targets indications with an often complex dataset. It can also be argued that a couple of its peers operate in areas of greater commercial potential, such as oncology (Oncopeptides) and IgA nephropathy (Calliditas Therapeutics). But should it trade at an EV less than a quarter to the cohort? Unquestionably not, in our view.

Peer Valuation Analysis

Company	Market cap (\$m)	Net cash (\$m)	EV (\$m)	Stage
Hansa Biopharma	1144	159	985	Pivotal
Oncopeptides	1235	135	1101	Pivotal
Calliditas Therapeutics	765	150	615	Pivotal
Mean	1048	148	900	
Median	1144	150	985	
Orphazyme	320	100	220	Pivotal

SEK/USD 9.5, DKK/USD 6.7

Source: Company reports, Redeye Research

Catalysts

Gaucher

12-month upside potential: ~ DKK 15 per share

12-month downside risk: ~ DKK 10 per share

Pivotal Stage Advancement in GD

Given a good OLE readout, together with productive interactions with experts in the field, we believe arimoclomol could move into the pivotal stage and start patient recruitment in 2021.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Moderate	Unlikely	Moderate	Possible	Mid

Development efforts in related indications

We are interested to learn about other efforts in Gaucher-related indications, such as Gcase-Parkinson's Disease (Gcase-PD). This could be presented in 2021.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Moderate	Unlikely	Moderate	Possible	Mid

NPC

12-month upside potential: ~ DKK 10 per share

12-month downside risk: Unknown (depends on regulatory outcome)

Potential US approval by FDA

The PDUFA date is set for March 17, 2021.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Major	Unlikely	Major	Highly likely	Short

Potential EU approval by EMA

We judge that arimoclomol is some 6-9 months behind in development in Europe versus the US.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Major	Unlikely	Major	Highly likely	Mid

ALS

12-month upside potential: ~ DKK 70 per share (on positive/home-run ph 3)

12-month downside risk: ~ DKK 30 per share (on negative ph 3)

ALS: Phase 3 results

Top-line phase 3 results are expected in H1 21.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Major	Possible	Major	Possible	Short

sIBM

12-month upside potential: ~ DKK 45 per share (on positive/home-run ph 3)

12-month downside risk: ~ DKK 40 per share (on negative ph 3)

sIBM: Phase 2/3 results

As in ALS, top-line phase 3 results are expected in H1 21.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Major	Possible	Major	Possible	Short

Corporate

Sale of PRV to a third party

If arimoclomol in NPC gains approval, the Company could be handled a priority review voucher (PRV). These can be sold to third parties, typically for around USD 100m. As noted, this represents a major non-dilutive cash opportunity, which we include in our financials for 2021.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Moderate	Possible	Major	Possible	Mid

M&A Target

Orphazyme is an appealing acquisition target, in our view. Recent M&A in the orphan space suggests that pharma is prepared to pay a premium for de-risked assets. Inevitably, the timing of any acquisition is hard to predict.

IMPACT

Downside		Upside		Time Frame
<u>Significance</u>	<u>Likelihood</u>	<u>Significance</u>	<u>Likelihood</u>	
Moderate	Possible	Major	Possible	-

Appendix – Arimoclomol and the Addressed Indications

Orphazyme's lead asset is arimoclomol; a first-in-class oral compound acquired from US biotech company Cytrx in 2011. The drug came with a range of pre-clinical and clinical data in ALS. Orphazyme is developing the drug more broadly, addressing three additional indications (besides ALS) to explore its full potential: Niemann Pick Disease Type C (NPC), sporadic Inclusion Body Myositis (sIBM), and Gaucher disease (GD).

Arimoclomol acts as a heat-shock protein (HSP) amplifier. HSPs are the body's natural response to cellular stress. The production of HSPs is regulated by a transcription factor, heat shock factor 1 (HSF1). HSF1 is inactive under normal conditions, but cellular stress, such as through protein misfolding, can trigger activation. Arimoclomol amplifies and prolongs the activation of HSF1, which leads to increased production of HSPs and thereby promotes the correct folding and disaggregation of proteins.

Arimoclomol is a small molecule that crosses the blood-brain barrier. It is intended as oral administration. It has a favourable safety profile, as demonstrated in over 500 patients and healthy volunteers so far.

Lysosomal Storage Disorders (LSD)

Niemann-Pick disease Type C (NPC)

NPC is a neurodegenerative disorder with early-onset and fatal outcome. When diagnosed in childhood, the patient is unlikely to survive beyond the teenage years. The disease occurs through a genetic mutation in NPC1 (95% of cases) or NPC2 (5% of cases), which results in the accumulation of lipids in liver-, spleen, and brain cells.

NPC manifests in symptoms such as loss of motor function, coordination, speech, and cognition. Due to the incredibly rare nature of the disease and lack of good treatment options, there is little awareness of NPC among physicians. Accordingly, the disease is often mis- and/or underdiagnosed. Various sources have pointed towards an incidence of approximately 1 in 100,000-120,000 (npuk.org, orpha.net). The current prevalence in the US and the EU is estimated at approximately between 1,000-2,000.

The lack of good treatment options makes the medical need significant. In the US, no drug therapies are approved for NPC. In Europe, only one drug is approved: Zavesca (miglustat). This is a substrate reduction therapy (SRT) that works by inhibiting the first step in the production of complex fats.

Neurological Gaucher disease (nGD)

Gaucher disease is a lysosomal storage disorder caused by an inherited deficiency in the lysosomal enzyme acid beta-glucocerebrosidase (Gcase). The mutation causes an accumulation of waste lipids, particularly in macrophages called Gaucher cells, leading to organ and tissue damage. Typical symptoms are enlarged organs (liver and spleen), damage to bone marrow that results in significant bone destruction, anemia, and thrombocytopenia.

It is a more common lysosomal storage disease than NPC but still with a clear orphan profile. The estimated prevalence is 10,000-17,000 individuals in the US and the EU. Gaucher is sorted under three types (I-III) based on the manifestation of neurological symptoms:

- Gaucher disease type 1 (GD1) – representing 90% of the total cases. It is characterized by the absence of early-onset neurological symptoms
- Gaucher disease type 2 (GD2) – is an acute neuronopathic form that usually leads to death by age 2 years
- Gaucher disease type 2 (GD3) – is a chronic neuronopathic form, with a slightly later onset of neurological symptoms than GD2, and with a slower progression

The I-III sorting has come under challenge, as it is now widely regarded that around 30% of GD1 patients eventually develops neurological symptoms.

There are good treatment options for type 1 Gaucher disease patients in the form of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). ERT treatment infuses recombinant enzymes to compensate for the metabolic defects in Gaucher patients. A certain mannose receptor transports the enzymes to the lysosomes, where they perform catalytic activity.

SRTs were proposed as a therapeutic approach in Gaucher many decades ago. Its principle is to inhibit the first enzyme in the pathway for glycosylating sphingolipids, thereby reducing the lysosomal accumulation.

Together these therapies constitute a billion-dollar sales market, despite having been approved for decades in a couple of cases. Neither has a good effect on neurological symptoms though, leaving a true medical need to treat neurological Gaucher disease.

Neuromuscular disorders

Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurological disorder characterized by the degeneration of both upper and lower motor neurons. Motor neurons control muscles throughout the body. When these cells die, the brain can no longer control muscle movement. Gradually, the patient loses their ability to move, speak, eat, and breathe, leading to severe disability, paralysis, and death. The average life expectancy after the onset of symptoms is two to five years.

There are two different types of ALS: sporadic (SALS) and familial (FALS). The most common form is SALS, accounting for 90-95% of cases. As it does not have a genetic component, it can affect anyone anywhere. The average age for onset of symptoms for SALS is around 55-65 years of age.

FALS constitutes the remaining 5-10% of cases and is the inherited form of the disease. It has an earlier onset (45-55 years of age) and more rapid progression than SALS.

According to Datamonitor, the incidence of ALS in Europe and North America was slightly above 10,000 in 2019. Due to the short life expectancy, the estimated prevalence might only be two to five times that of the annual incidence.

The main management of the disease is a multidisciplinary approach with neurologists, psychologists, nutritionists, pulmonologists, physical therapists, speech therapists, and specialized nurses. More than 50 drugs have been tested for modifying disease progression but only two have reached the market. Neither of these can halt or reverse the disease pattern to a great extent. Another true medical need in ALS is a more accurate and early diagnosis of the disease. As an example, there is no established biomarker.

Sporadic Inclusion Body Myositis (sIBM)

Sporadic Inclusion Body Myositis (sIBM) is a slowly but relentlessly progressing muscle-wasting disorder, especially those in the arms and legs. It usually presents with weakness in the proximal leg and distal arm.

Although not considered a direct fatal disease, the patient usually loses their entire mobility in the 10-15 years after diagnosis. There is no established disease cause to date, but degenerative factors such as misfolded proteins (i.e., inclusion bodies) play a significant role.

sIBM is the most common muscle-wasting disorder among the elderly population, but it is still a rare condition. The estimated prevalence in the US and Europe is some 30,000 individuals.

There is no approved drug therapy for sIBM. Available treatment options are supportive and focus on physical, speech, and occupational therapy.

Summary Redeye Rating

The rating consists of three valuation keys, each constituting an overall assessment of several factors that are rated on a scale of 0 to 1 points. The maximum score for a valuation key is 5 points.

Rating changes in the report: Financials (+1)

People: 4

The resignation of Stratton comes in a critical stage in the company's development. Redeye prefers consistency in the management team. Our biggest concern is that the company might lose speed at this crucial stage. We want to see that the Board moves rapidly but thoughtfully in appointing a new CEO.

Business: 4

Orphazyme is a late-stage biotech company but has no track record of recurring revenues. Arimoclomol represents a large commercial opportunity in diseases with little direct competition. A potential first approval could come soon, though there are still some hurdles to clear before sales and earnings materialize.

Financials: 2

Orphazyme is a non-profitable company and runs an ambitious pipeline agenda. However, for a biotech company, Orphazyme should be regarded as well-funded. The cash position should be above DKK 700 million at yearend 20/21.

INCOME STATEMENT	2018	2019	2020E	2021E	2022E
Net sales	0	0	0	82	260
Total operating costs	-232	-335	-624	-553	-525
EBITDA	-232	-335	-624	-471	-265
Depreciation	0	0	-2	-2	-2
Amortization	0	0	-2	-12	-12
Impairment charges	0	0	0	0	0
EBIT	-232	-335	-627	-484	-279
Share in profits	0	0	0	0	0
Net financial items	-3	-7	-7	-5	-2
Exchange rate dif.	0	0	0	0	0
Pre-tax profit	-235	-342	-634	-489	-281
Tax	6	6	6	6	0
Net earnings	-230	-337	-628	134	-281

BALANCE SHEET	2018	2019	2020E	2021E	2022E
Assets					
<i>Current assets</i>					
Cash in banks	393	124	704	761	446
Receivables	0	0	0	12	38
Inventories	0	0	0	10	24
Other current assets	23	19	24	29	39
Current assets	416	143	729	813	547
<i>Fixed assets</i>					
Tangible assets	2	4	6	7	8
Associated comp.	1	0	0	0	0
Investments	0	0	0	0	0
Goodwill	0	0	0	0	0
Cap. exp. for dev.	0	0	0	0	0
Intangible rights	11	11	11	59	49
Non-current assets	3	2	2	2	2
Total fixed assets	16	30	33	78	66
Deferred tax assets	8	8	8	8	0
Total (assets)	441	181	770	899	614
Liabilities					
<i>Current liabilities</i>					
Short-term debt	0	13	13	13	4
Accounts payable	41	32	50	62	69
Other current liabilities	11	21	31	45	61
Current liabilities	52	66	94	120	135
Long-term debt	0	52	43	16	0
Other long-term liabilities	1	0	0	0	0
Convertibles	0	0	0	0	0
Total Liabilities	53	118	137	136	135
Deferred tax liab	0	0	0	0	0
Provisions	0	0	0	0	0
Shareholders' equity	388	53	619	753	472
Minority interest (BS)	0	0	0	0	0
Minority & equity	388	53	619	753	472
Total liab & SE	441	181	770	899	614

FREE CASH FLOW	2018	2019	2020E	2021E	2022E
Net sales	0	0	0	82	260
Total operating costs	-232	-335	-624	-553	-525
Depreciations total	0	0	-3	-13	-14
EBIT	-232	-335	-627	-484	-279
Taxes on EBIT	5	5	5	6	0
NOPLAT	-226	-330	-621	-479	-279
Depreciation	0	0	3	13	14
Gross cash flow	-226	-330	-618	-465	-265
Change in WC	-8	5	23	-2	-26
Gross CAPEX	-3	-1	-6	-62	-5
Free cash flow	-237	-325	-601	-529	-297

CAPITAL STRUCTURE	2018	2019	2020E	2021E	2022E
Equity ratio	88%	29%	80%	84%	77%
Debt/equity ratio	0%	140%	11%	5%	2%
Net debt	-393	-49	-635	-722	-435
Capital employed	-6	-6	-30	21	30
Capital turnover rate	0.0	0.0	0.0	0.1	0.4

GROWTH	2018	2019	2020E	2021E	2022E
Sales growth	0%	0%	0%	2,046.5	217%
EPS growth (adj)	82%	47%	7%	-121%	-310%

DCF VALUATION		
WACC (%)	11.0 %	

PROFITABILITY	2018	2019	2020E	2021E	2022E

DATA PER SHARE	2018	2019	2020E	2021E	2022E
EPS	-11.52	-16.89	-18.13	3.87	-8.11
EPS adj	-11.52	-16.89	-18.13	3.87	-8.11
Dividend	0.00	0.00	0.00	0.00	0.00
Net debt	-19.73	-2.48	-18.33	-20.84	-12.56
Total shares	19.93	19.93	34.66	34.66	34.66

VALUATION	2018	2019	2020E	2021E	2022E
EV			1,486.0	1,398.8	1,685.7

SHARE PERFORMANCE		GROWTH/YEAR	18/20E
1 month	-6.1 %	Net sales	0.0 %
3 month	-29.5 %	Operating profit adj	64.5 %
12 month	-14.0 %	EPS, just	25.4 %
Since start of the year	-15.5 %	Equity	26.3 %

SHAREHOLDER STRUCTURE %	CAPITAL	VOTES
Lso V Coöperatieve U.A.	7.8 %	7.8 %
Sunstone Capital	5.2 %	5.2 %
Coöperatieve Aescap Venture I U.A.	5.1 %	5.1 %
Consonance Capital Management LP	3.9 %	3.9 %
Islet Management LP	3.8 %	3.8 %

SHARE INFORMATION	
Reuters code	ORPHA.CO
List	Mid cap
Share price	60.0
Total shares, million	34.7
Market Cap, MDKK	2082

MANAGEMENT & BOARD	
CEO	Anders Vadsholt (Acting)
CFO	Anders Vadsholt
IR	
Chairman	Georges Gemayel

FINANCIAL INFORMATION	
AR 2020	March 2, 2021
H1 2021	August 24, 2021

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Redeye Rating and Background Definitions

Company Quality

Company Quality is based on a set of quality checks across three categories; PEOPLE, BUSINESS, FINANCE. These are the building blocks that enable a company to deliver sustained operational outperformance and attractive long-term earnings growth.

Each category is grouped into multiple sub-categories assessed by five checks. These are based on widely accepted and tested investment criteria and used by demonstrably successful investors and investment firms. Each sub-category may also include a complementary check that provides additional information to assist with investment decision-making.

If a check is successful, it is assigned a score of one point; the total successful checks are added to give a score for each sub-category. The overall score for a category is the average of all sub-category scores, based on a scale that ranges from 0 to 5 rounded up to the nearest whole number. The overall score for each category is then used to generate the size of the bar in the Company Quality graphic.

People

At the end of the day, people drive profits. Not numbers. Understanding the motivations of people behind a business is a significant part of understanding the long-term drive of the company. It all comes down to doing business with people you trust, or at least avoiding dealing with people of questionable character.

The People rating is based on quantitative scores in seven categories:

- Passion, Execution, Capital Allocation, Communication, Compensation, Ownership, and Board.

Business

If you don't understand the competitive environment and don't have a clear sense of how the business will engage customers, create value and consistently deliver that value at a profit, you won't succeed as an investor. Knowing the business model inside out will provide you some level of certainty and reduce the risk when you buy a stock.

The Business rating is based on quantitative scores grouped into five sub-categories:

- Business Scalability, Market Structure, Value Proposition, Economic Moat, and Operational Risks.

Financials

Investing is part art, part science. Financial ratios make up most of the science. Ratios are used to evaluate the financial soundness of a business. Also, these ratios are key factors that will impact a company's financial performance and valuation. However, you only need a few to determine whether a company is financially strong or weak.

The Financial rating is based on quantitative scores that are grouped into five separate categories:

- Earnings Power, Profit Margin, Growth Rate, Financial Health, and Earnings Quality.

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Disclaimer

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Redeye AB ("Redeye" or "the Company") is a specialist financial advisory boutique that focuses on small and mid-cap growth companies in the Nordic region. We focus on the technology and life science sectors. We provide services within Corporate Broking, Corporate Finance, equity research and investor relations. Our strengths are our award-winning research department, experienced advisers, a unique investor network, and the powerful distribution channel redeye.se. Redeye was founded in 1999 and since 2007 has been subject to the supervision of the Swedish Financial Supervisory Authority.

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Redeye Rating (2020-12-16)

Rating	People	Business	Financials
5p	21	16	3
3p - 4p	107	89	38
0p - 2p	5	28	92
Company N	133	133	133

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CONFLICT OF INTERESTS

Anders Hedlund owns shares in the company : No

Ludvig Svensson owns shares in the company : No

Redeye performs/have performed services for the Company and receives/have received compensation from the Company in connection with this.