

Abliva

Company report

KL1333 ready for pivotal Phase II/III trial

Pharma & biotech

27 May 2021

Price **SEK0.7**
Market cap **SEK282m**

Net cash (SEKm) end-Q121 plus private placement proceeds (gross) 128.0
Shares in issue (post-private placement) 403m
Free float 80%
Code ABLI
Primary exchange Nasdaq Stockholm
Secondary exchange OTCQX

Share price performance



Business description

Abliva is a Swedish biotech with deep expertise in mitochondrial medicine. Its focus area is primary mitochondrial diseases with lead assets KL1333, an NAD+ modulator (Phase II/III ready), and NV354, a succinate prodrug (preclinical). The company plans to start a pivotal Phase II/III trial with KL1333 in selected PMDs later this year.

Next events

Patient data analysis from Phase Ia/b with KL1333 Q321
Completion of preclinical safety studies with NV354 2021
Q221 results 19 August 2020

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Just a few months in, Abliva's new CEO has already spearheaded a successful private placement (SEK80m gross in March 2021), which will now support the preparations for the pivotal KL1333 trial in primary mitochondrial diseases (PMDs). The R&D plan is focused on a single randomised, placebo-controlled Phase II/III trial with an adaptive design, which should start in H221. The newly released clinical dataset from the Phase Ia/b study also support such a strategy. The Phase II/III trial is envisioned undergo an interim futility analysis in H222 and the final results should be available by end-2023. Abliva's second lead asset NV354, a succinate prodrug for complex I disorders, should complete preclinical development this year. Our valuation is SEK1.21bn or SEK3.01 per share.

| Year end | Revenue (SEKm) | PBT* (SEKm) | EPS* (SEK) | DPS (SEK) | P/E (x) | Yield (%) |
|----------|----------------|-------------|------------|-----------|---------|-----------|
| 12/20 | 3.6 | (74.6) | (0.43) | 0.0 | N/A | N/A |
| 12/21 | 1.9 | (57.4) | (0.23) | 0.0 | N/A | N/A |
| 12/22e | 1.9 | (72.7) | (0.21) | 0.0 | N/A | N/A |
| 12/22e | 1.9 | (97.5) | (0.24) | 0.0 | N/A | N/A |

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

Positive KL1333 Phase Ia/b clinical results

As is typical, the main endpoints in the Phase Ia/b study were safety, tolerability and PK/PD, however, Part C of the study also recruited eight PMD patients (with mutations in the mitochondrial DNA). This was the first-time KL1333 was administered to patients. No new safety/tolerability issues were reported, while numerically the PMD patients improved better compared to placebo patients after only 10 days of dosing. In addition, patients with the highest exposure to KL1333 had the best effects. So, although the sample was small, the placebo-control, clear numerical difference and exposure/effect correlation all support Abliva's R&D strategy to move directly into the pivotal trial, in our view.

Flagship Phase II/III trial with KL1333 to start in H221

The initial details of the Phase II/III programme were first revealed in September 2020 after a positive pre-IND meeting with the FDA, which agreed that a single well-designed, placebo-controlled study would be sufficient for approval. PMDs are a group of conditions with the hallmark symptom of impaired energy production. At the core of the late-stage KL1333 development is the strategic choice to target two specific mitochondrial conditions: MIDD-MELAS and KSS-CPEO spectrum disorders. This will allow the investigators to evaluate the primary endpoint in a more homogenous patient population, which should improve the statistical analysis.

Valuation: SEK1.21bn or SEK3.01 per share

Following the recent R&D progress (Phase I clinical data and late-stage development plans introduced) and corporate updates (new CEO and the first strategic update in conjunction with the share issue), we took a fresh look at the investment case and are reinitiating with new forecasts and valuation. Our valuation of Abliva is SEK1.21bn or SEK3.01 per share, which is based on the two lead assets KL1333 and NV354. Existing cash is sufficient well into 2022, while the funding gap next year is SEK33m, according to our model.

New management; focused R&D pipeline

Abliva's new CEO Ellen Donnelly joined the company in early February and has already contributed by successfully supervising the private placement in March 2021. Dr Donnelly, a US national, has a PhD in pharmacology from Yale University. Her commercial knowledge comes from working in management consulting and drug development experience from almost a decade at Pfizer. More recently, Dr Donnelly gained C level experience as CEO of Modus Therapeutics (Stockholm, 2017–20) and CEO of the Division of Epigenetics at Juvenescence (US). We note that drug development experience at large pharma makes Dr Donnelly especially well-positioned to understand exactly what a potential partner would find interesting in Abliva's portfolio.

With the new CEO in place, Abliva now has a sharp focus on the two lead assets KL1333 and NV354. We note that Abliva also has several other compounds, but has made a decision to only invest in the two lead drug candidates. The company is working to secure licensing deals for its non-core assets. NeuroSTAT in particular is interesting, in our view, as it is ready for a Phase II trial and Abliva is in discussions with the US government-backed brain trauma physician network, which could lead the next trial as soon as the US Department of Defense approves the funding (details below).

Exhibit 1: Current status of the core assets

| Product | Stage | Indication | Current status and upcoming events |
|--|--------------------|-------------------------|---|
| KL1333 NAD+ modulator oral; chronic treatment | Phase II/III-ready | MIDD-MELAS and KSS-CPEO | In-licensed from Yungjin Pharm (South Korea) in May 2017. Phase I development finished. Phase II/III trial plan agreed with the FDA. The trial is expected to start in H221. Orphan drug designation. |
| NV354 succinate prodrug iv and oral alternative energy source | Preclinical | Complex I disorders | Preclinical development is expected to be completed in 2021 and the drug candidate could enter clinical development in 2022. |

Source: Edison Investment Research, Abliva

Phase Ia/b clinical data

The Phase Ia/b was a randomised, double-blind, parallel-group, placebo-controlled study. The main endpoints were safety, tolerability (primary), pharmacokinetics and pharmacodynamics (PK/PD, secondary). The exploratory endpoints included the analysis of blood biomarkers in healthy volunteers and PMD patients as well as outcome assessments in patients. The study was conducted in four parts:

- Part A. Single ascending dose (SAD) with food effect, 25mg once a day, healthy volunteers.
- Part B. Multiple ascending doses (MAD), 25, 50, 75, 150 and 250mg once a day, healthy volunteers.
- **Part C. 10 days dosing, 50mg once daily, PMD patients.**
- Part D. Split dosing, 75mg two times a day or 50mg three times a day, healthy volunteers.

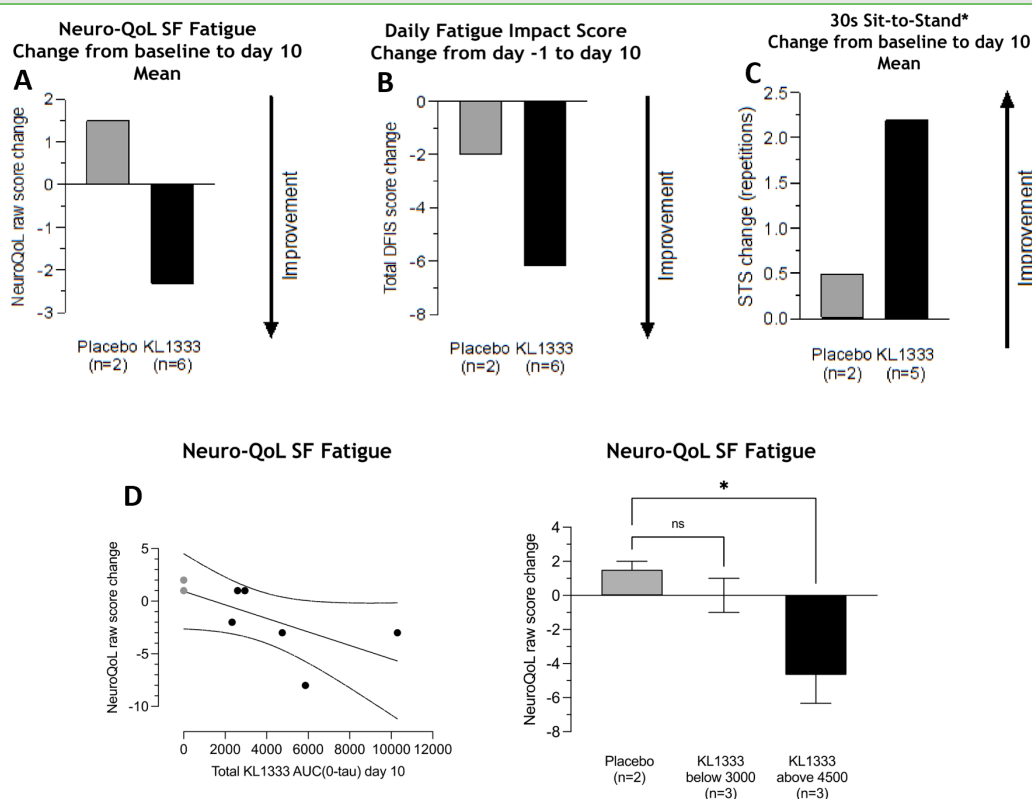
Parts A and B showed that KL1333 was generally safe and well tolerated. GI symptoms were observed in some cases, which improved when the daily dose was split (investigated in Part D).

The most interesting dataset came from Part C, which recruited eight PMD patients with mutations in the mitochondrial DNA. It was the first-time that patients received KL1333. Six patients received KL1333 and two received placebo. No new safety or tolerability issues were reported. The endpoints to assess the initial clinical efficacy included **two different patient-reported fatigue questionnaires** and a **functional endpoint, 30-second sit-to-stand**. The duration of dosing was 10 days. With the caveat that it was not designed to fully evaluate the efficacy and the dosing length was just 10 days, however, numerically the PMD patients showed greater improvement for

all three endpoints compared to placebo patients (Exhibit 2, charts A, B and C). In addition, patients with the highest exposure of KL1333 had the best effects (chart D).

One of the key questions for Abliva is which is the correct endpoint to evaluate KL1333's efficacy in the upcoming Phase II/III trial. Fatigue is a hallmark symptom of all PMD where muscles are affected and it will be the primary endpoint in the Phase II/III study. For this reason, the company is running complementary studies (as detailed below). We believe the new insights from the patients will be very valuable in this regard.

Exhibit 2: Exploratory efficacy data from Phase Ia/b PMD patients



Source: Abliva. One subject in the KL1333 group did not perform the sit-to-stand test and was excluded from analysis.

Flagship Phase II/III trial to start in H221

At the core of the late-stage KL1333 development is the strategic choice to target two specific mitochondrial conditions: **MIDD-MELAS** (encephalomyopathy, lactic acidosis and stroke-like episodes) and **KSS-CPEO** (progressive paralysis of certain eye muscles, pigmentary retinopathy and cardiomyopathy and/or arrhythmia) spectrum disorders. This will allow the investigators to evaluate the primary endpoint in a more homogenous patient population, which should improve the statistical analysis. However, we note that KL1333 theoretically could be beneficial in other PMD conditions as well; PMD is a group of diverse conditions and all are rare or ultrarare. So, if the efficacy is proven in MIDD-MELAS and KSS-CPEO, label expansion with bridging trials in other conditions is possible.

Enrolment criteria include:

- adults with genetically confirmed PMD, who also have chronic fatigue and systemic manifestations involving exercise intolerance; and
- underlying cause of PMD are MIDD-MELAS or KSS-CPEO syndromes.

In total, **120–180 patients** are expected to be enrolled, who will receive peroral treatment with KL1333 for a period of 12 months. The **study timeline plan** envisages:

- patient enrolment starts in H221;
- interim futility analysis is planned in H222; and
- data readout around end 2023.

To evaluate the efficacy of KL1333, Abliva plans to use improvement in fatigue as the **key primary efficacy endpoint**. Since PMDs by definition are very rare conditions with no effective treatment, that means that there are no standard measures to evaluate the efficacy of any potential new drugs. Of the many different symptoms PMD patients experience, Abliva identified fatigue as the most common and one that could be reliably quantifiable. The FDA also agreed that this symptom can be used for the primary endpoint. Currently Abliva is conducting a qualitative study focused on validating a patient reported outcome for fatigue that is sensitive to the PMD patient condition. We note that Abliva has a long history of working with PMD patient associations (eg [Mitochondria Day 2020](#) event), which, in our view, is key to understanding the day-to-day challenges PMD patients face. This, we believe, will ensure the informed selection of an appropriate endpoint for the Phase II/III trial.

The **next step** is the submission and approval of an IND that will enable Abliva to recruit patients in the US. Abliva has already received feedback from the European Medicines Agency (EMA) and from the UK's Medicines and Healthcare products Regulatory Agency (MHRA), which will be used to inform the design of the trial.

Complementary studies ongoing in preparation for Phase II/III

The Phase II/III development plan for KL1333 that was agreed with the FDA also includes several additional studies that are collecting complementary data that will provide inputs into the design. According to the latest update, these studies are either ongoing or being finalised. These include:

- **A qualitative study** to validate patient-reported outcome assessment as the primary endpoint for the efficacy study, as discussed above.
- **A patient registry study**, which involves the review of data from the UK patient registry study MitoCohort. The goal of this data review, like with the qualitative study, is to better understand the challenges and needs of the PMD patients.
- **A drug-drug interaction study** in healthy volunteers (completed). This study evaluated potential interactions between KL1333 and some standard of care drugs used for a variety of more common conditions.
- **Long-term toxicology studies** in animals are required for drugs that are intended to be used chronically. These studies can take many months, so the fact the FDA agreed that they can be run in parallel to the Phase III trial means there will be no delay to the initiation of the Phase II/III trial.

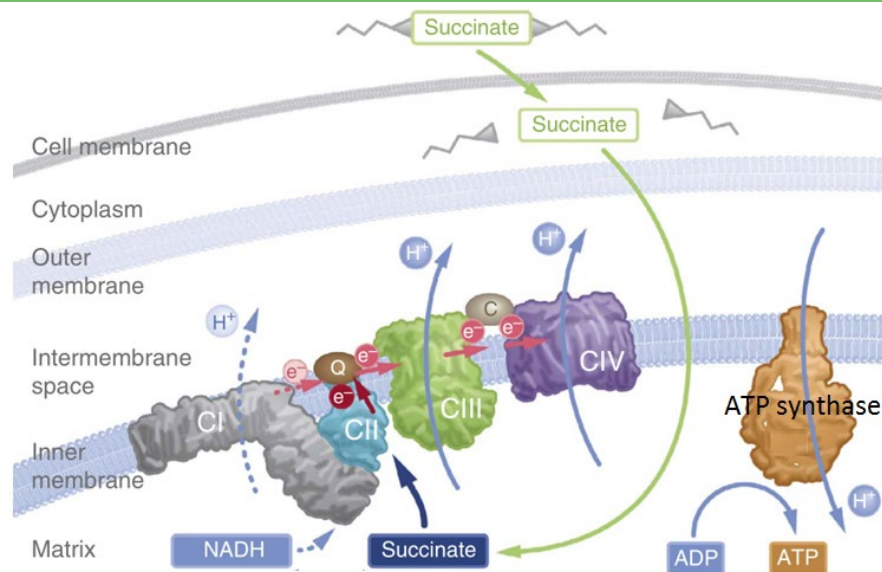
Biology 101

Mitochondria are cellular organelles found in large numbers in most cells and is responsible for the majority of energy production needed for cell survival. Strikingly, mitochondria have their own DNA, which codes genes essential for their function. One of the leading evolutionary theories is that mitochondria originated from bacteria, which were engulfed and assimilated by early eukaryotic organisms, which gave birth to advanced life. Normal cell metabolism is powered by the consumption of adenosine triphosphate (ATP), which is the main energy source. Once consumed, ATP is resynthesized from adenosine diphosphate (ADP), which is also called cellular respiration.

Impaired mitochondrial function results in impaired cellular respiration. Cellular respiration consists of complex metabolic pathways that can be classified into three main groups:

- **Glycolysis**, which occurs in the cytoplasm. It is the inefficient or anaerobic form of cellular respiration under physical strain, which produces lactic acid, for example the characteristic muscle pain after a workout.
- **The citric acid cycle**, also known as the Krebs cycle. It occurs inside of the mitochondria and is part of the aerobic cellular respiration and main ATP production pathway.
- **The electron transport chain**, which occurs in the inner membrane of the mitochondria. The process produces the majority of energy in the form of ATP. The electrons transfer their energy to certain proteins (complexes) in the inner membrane, which pump hydrogen ions across the membrane. This flow forms a gradient that allows an enzyme ATP synthase to produce ATP (Exhibit 3). Oxygen is the final electron acceptor (therefore this process is called cellular respiration), which is then combined with hydrogen to produce water.

Exhibit 3: Schematic representation of the electron transport chain in mitochondria



Source: Ehinger, J., Piel, S., Ford, R. *et al.* Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency. *Nat Commun* 7, 12317 (2016). Notes: CI to CIV – complex I to complex IV, H⁺ – hydrogen, e⁻ – electron flow, Q – coenzyme Q, C – cytochrome, ADP – adenosine diphosphate, ATP – adenosine triphosphate, NADH – nicotinamide adenine dinucleotide.

PMD: Complex diseases, complicated diagnosis, no effective drugs

Mitochondrial diseases are a group of conditions with the hallmark symptom of impaired energy production. Varying, often non-specific symptoms and the fact that the syndromes are rare make the diagnosis challenging. Mitochondrial disease is a relatively recent concept first introduced in 1962, when a group of Swedish researchers described a patient case with severe hyper-metabolism and a defect in mitochondrial function.¹ Overall, approximately 12.5 in 100,000 people suffer from mitochondrial diseases, which makes this a group of rare conditions.

The diseases may appear at any age and consist of a number of syndromes with clinical presentation varying widely. For example, Chi (2017) lists 78 separate mitochondrial disease entities (Exhibit 4, left-hand column).¹ Children have more acute onset, while adults have more slowly progressing presentations. Cells with high energy requirements, such as neurons, skeletal and cardiac muscles, are most susceptible to impaired energy metabolism; therefore,

¹ Ch. Chi. Diagnostic Approach in Infants and Children with Mitochondrial Diseases. *Pediatrics and Neonatology* (2015) 56, 7e18.

encephalopathy and myopathy are the most common features of the clinical picture, although other organs may also be affected (Exhibit 4, right-hand column). When it comes to treatment options, mainly supportive strategies are available and only to alleviate the symptoms.²

Exhibit 4: Selected mitochondrial diseases and symptoms

| Mitochondrial diseases | Affected organ system | N = 103 (%) |
|---|---------------------------|-------------|
| Defined syndromes | Central nervous system | 93 (90.3) |
| ■ Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) | Failure to thrive | 37 (35.9) |
| ■ Kearns-Sayre syndrome (KSS) | Hearing system | 20 (19.4) |
| ■ Chronic progressive external ophthalmoplegia (CPEO) | Endocrinologic system | 8 (7.8) |
| ■ Leigh syndrome | Ophthalmologic system | 37 (35.9) |
| ■ Leber's hereditary optic neuropathy (LHON) | Peripheral nervous system | 4 (3.9) |
| ■ Alpers' disease | Cardiovascular system | 26 (25.2) |
| ■ Lethal infantile mitochondrial disease (LIMM) | Gastrointestinal system | 23 (22.3) |
| ■ Pearson's syndrome | Muscular system | 22 (21.4) |
| ■ Myoclonic epilepsy with ragged-red fibres (MERF) | Hepatic system | 19 (18.4) |
| ■ Neuropathy, ataxia, and retinitis pigmentosa (NARP) | Short stature | 18 (17.5) |
| ■ Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) | Urologic system | 9 (8.7) |
| ■ Barth syndrome | Pancreas | 2 (1.9) |
| Non-categorised syndromes | Hematologic system | 1 (1.0) |
| ■ Patients who do not meet specific criteria of recognised syndromes | Psychic | 1 (1.0) |
| | Pulmonary oedema | 1 (1.0) |

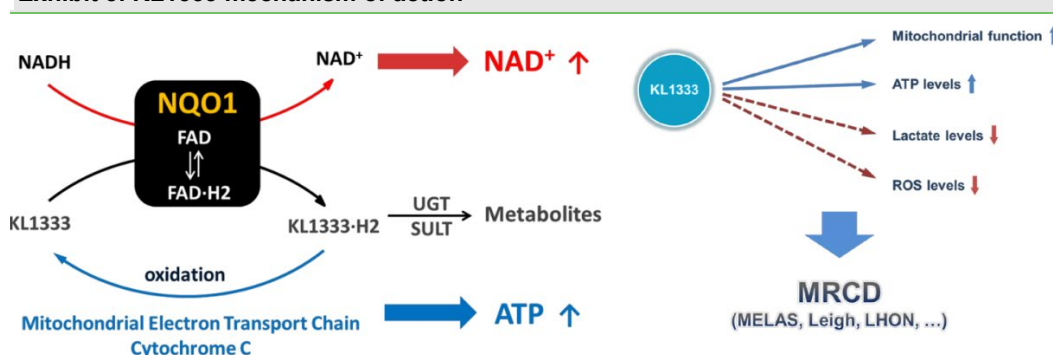
Source: Chi (2015). Note: Right-hand side column summarises frequency rates of organ system symptoms of 103 paediatric patients with various mitochondrial diseases as reported by Chi (2015).

KL1333: Boosting mitochondrial function

KL1333 was originally developed by KT&G Life Sciences, which was acquired by Yungjin in January 2017. Abliva in-licensed KL1333, from Yungjin Pharm (a diversified South Korean pharmaceutical company) as a Phase I-ready drug candidate In May 2017. The deal term included a total of \$12m in development milestone payments, \$42m for marketing authorisation and reimbursement approval plus sales-related milestone payments later and tiered single to low double-digit royalties on net sales. Yungjin retained rights to South Korea and Japan.

KL1333 is a novel, orally available, small organic molecule that interacts with NAD(P)H:quinone oxidoreductase 1 (NQO1). NQO1 is a cytosolic enzyme that oxidises NADH into NAD⁺, which is a coenzyme necessary for many cellular metabolism processes including mitochondrial function and production of ATP in the electron transport chain. KL1333 acts as a substrate to NQO1 and increases the NAD⁺/NADH ratio, which could improve mitochondrial function in various mitochondrial diseases.

Exhibit 5: KL1333 mechanism of action



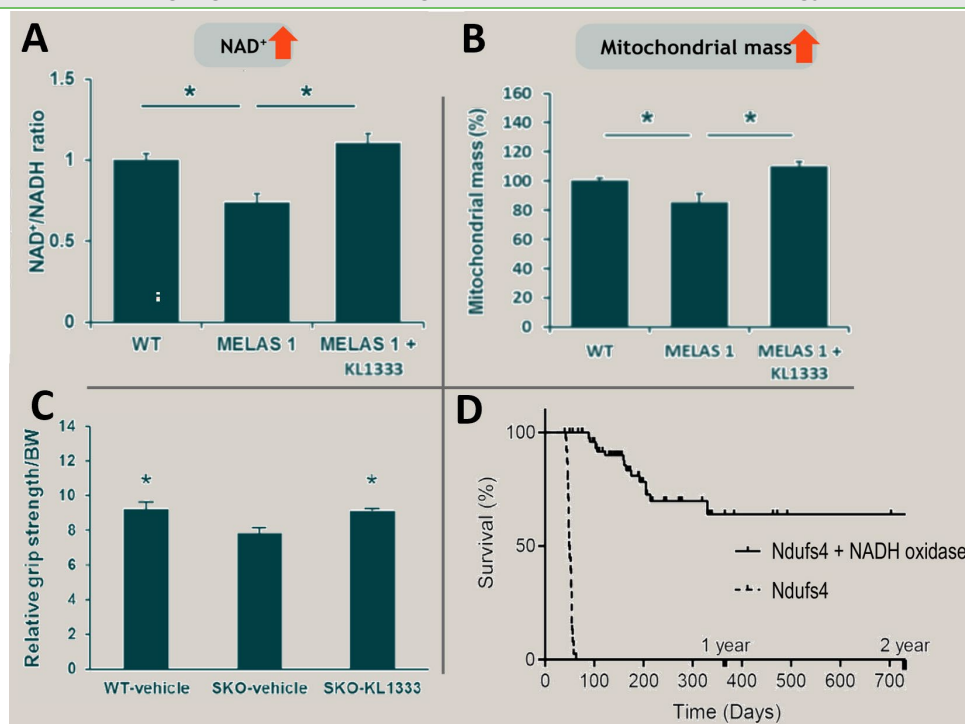
Source: Abliva. Note: MRCD – mitochondrial respiratory chain disorders (MRCD).

Data accumulated from various preclinical and clinical studies (Abliva, Yungjin and other third parties) show that KL1333 has a positive effect on energy metabolism. The highlights include:

² G. Pfeffer. Treatment for mitochondrial disorders. *Cochrane Database of Systematic Reviews* 2012, Issue 4.

- In an in vitro model of cell cultures taken from MELAS patients, KL1333 treatment increased NAD⁺ levels via the action of NQO1 (Exhibit 6A) and increased energy production and mitochondrial mass (Exhibit 6B) (Seo et al, 2018).
- In an in vivo mitochondrial disease model (Crif1 skeletal knock-out mice) KL1333 significantly increased grip strength and normalised muscle histology (Exhibit 6C).
- In another in vivo mitochondrial disease model (NDUFS4), artificial NADH oxidases raised NAD⁺ levels and increased the lifespan of mice (McElroy et al, 2020; Exhibit 6D).

Exhibit 6: Data highlights demonstrating KL1333's beneficial role in energy metabolism



Source: A and B – [Seo et al, 2018](#); C – [Hirano et al, 2016 \(NCT00887562\)](#); D – [McElroy et al, 2020](#); WT – 'wild type' or normal fibroblasts; MELAS 1 – mutant fibroblasts; FSS – Fatigue severity scale; SKO – skeletal knock-out mice.

NV354: Targeting complex I deficiency

Mitochondrial complex I deficiency is the most prevalent defect in the respiratory chain in paediatric mitochondrial diseases (around 50%) and clinically presents as a group of syndromes that can be caused by changes in either nuclear or mitochondrial genome.³ It is often a serious or even fatal syndrome. Abliva is focusing on Leigh syndrome, which is a fatal primary mitochondrial disease and children with this condition usually die before age five. Symptoms usually debut at one to two years of age. Symptoms include developmental delay, psychomotor regression and hypotonia. There are currently no approved medicines. With bridging studies NV354's label could later be potentially expanded to include MELAS in children and adolescents with neurological symptoms, and for the treatment of LHON, a disease affecting the optic nerve that can lead to blindness in both eyes.

Complex I is the entry point to the electron transport chain for energy carriers (NADH, Exhibit 3). In case of a complex I defect, the whole cellular respiratory process becomes disrupted. However, complex II also derives electrons from a substrate succinate (Exhibit 3). Abliva hypothesises that supplementation of succinate could replenish the electron transport chain with electrons, bypassing the complex I defect.

³ J. K. Ehinger et al. Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency. *Nat. Commun.* 7:12317, 2016.

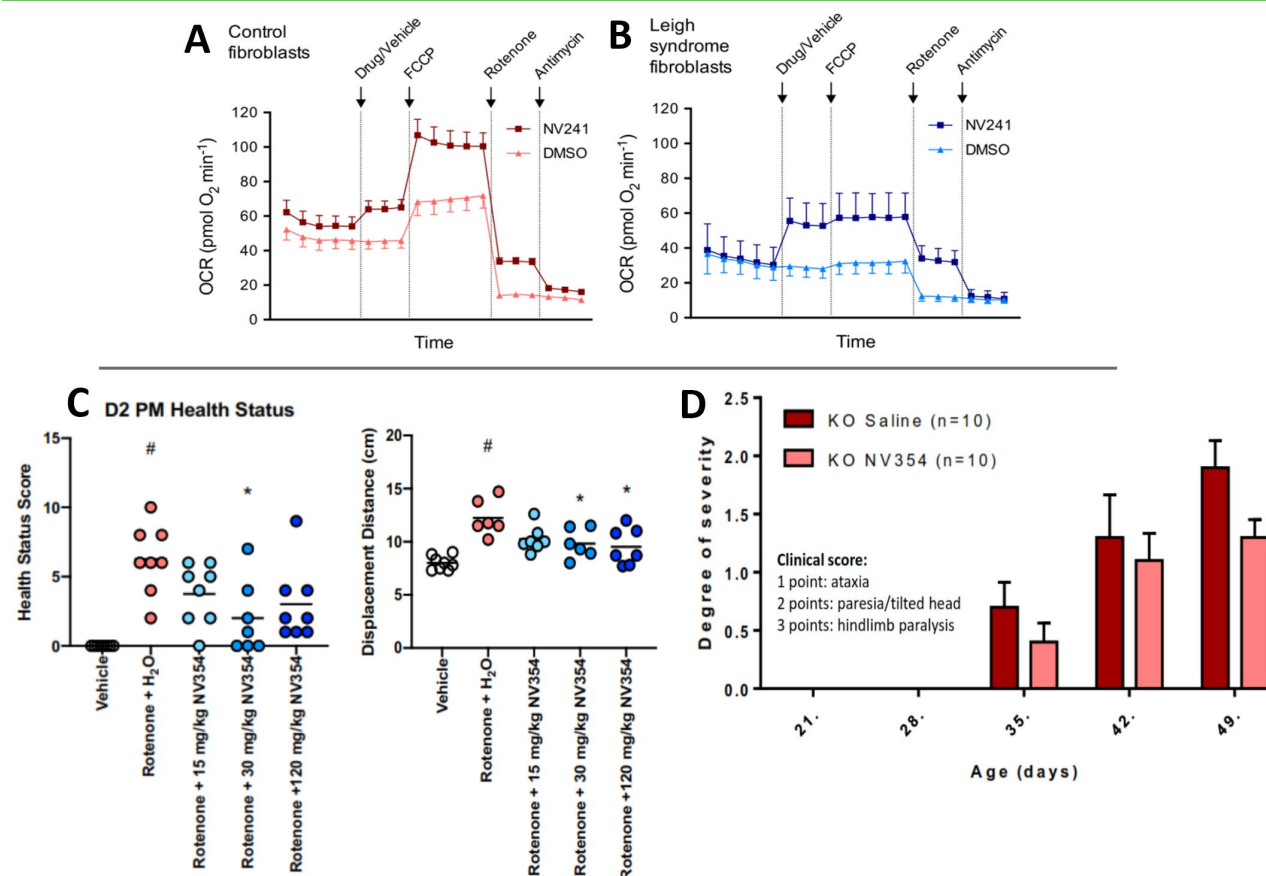
Succinate cannot easily pass through the cell's membrane and therefore biological availability is limited if supplemented externally. Abliva's NV354 is a programme that explores succinate prodrug that can pass through a cell's membrane and subsequently is metabolised to succinate, which in turn can be used by complex II.

In the discovery programme, Abliva designed a series of succinate prodrugs (a prodrug turns into a drug once metabolised) and evaluated their ability to pass through the cell membrane and aid mitochondrial respiration with defective complex I. The accumulated data was published in *Nature Communications*, one of the top science journals worldwide, in August 2016 (JK Ehinger et al). In preclinical in vitro proof-of-concept studies, the researchers evaluated the compounds using healthy human fibroblasts (the most common connective tissue cell) and in fibroblasts from patients with Leigh syndrome. Exhibit 7 shows the oxygen consumption rate (OCR) in healthy fibroblasts and Leigh syndrome fibroblasts and the dynamics under various conditions. Highlights included:

- Basal OCR was decreased in the Leigh syndrome patient cells compared to control (Exhibit 7, chart A versus chart B). The maximum respiration (achieved with the addition of FCCP, see notes in the chart) rate was decreased similarly.
- After the addition of Abliva's succinate prodrug, the OCR in Leigh syndrome patient fibroblasts increased to similar or higher levels compared to the untreated control cells.
- After inhibiting complex I with rotenone, the remaining respiratory activity was comparable between the cells and responded to succinate prodrug treatment. In Leigh syndrome patients, the OCR rebounded to basal OCR.
- NV354 has also been evaluated in preclinical proof-of-concept animal studies. NV354 was shown to be effective in a rat study in which complex I disease was modelled with the administration of rotenone (complex I inhibitor) (Exhibit 7, chart C) and in a genetic mouse model (NDUFS4) of complex I dysfunction (Exhibit 7, chart D).

Currently NV354 is in late preclinical studies and Abliva has in parallel started preparations for the clinical program. The remaining preclinical work (pharmacology and safety studies and regulatory documentation) is expected to be completed this year.

Exhibit 7: NV354 preclinical data highlights



Source: JK Ehinger et al, 2016, company data. Notes: FCCP – protonophore carbonyl cyanide, a so-called uncoupling agent that disrupts ATP synthesis, which results in an increased activity of electron transport chain or maximum respiration. Rotenone – inhibits complex I, ie mimics complex I diseases. Antimycin – complex III inhibitor. DMSO – vehicle used on fibroblast.

Potential upside from non-core assets

NeuroSTAT, an innovative formulation of ciclosporin, is the most advanced asset in the portfolio for out-licensing and partnering, and is positioned for the treatment of traumatic brain injury, where there is no neuroprotective treatment available yet. NeuroSTAT has accumulated some initial human efficacy data and has received IND approval from the FDA as well as Fast track designation. Abliva indicated that, while the drug candidate is promising, traumatic brain injury is not a focus area for Abliva anymore. The goal now is to look for partners to carry out a Phase II study.

One possibility is a collaboration with the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) network for a Phase II with NeuroSTAT under the Precision Medicine project, which would be funded by the US Department of Defense (DOD). TRACK-TBI Precision Medicine is a DOD-funded project run by the leading traumatic brain injury clinical trial network, TRACK-TBI, in the US. Abliva has had preliminary discussions with TRACK-TBI. If the Phase II trial is approved by the US DOD, it could start in 2022.

NeuroSTAT is meant to be administered during the acute phase of the brain injury (the first several weeks), when brain oedema and secondary injury are still developing and can further worsen the outcomes. Brain oedema is a particularly challenging condition, as the brain is encased in a close compartment (skull). Any more significant swelling of brain tissue can completely cut off the blood supply and lead to death. The only reliable intervention is urgent surgery (decompression, a procedure where a bone flap is removed to make space for brain tissue expansion). An effective non-invasive treatment to manage secondary injury during this acute phase is one of the highest unmet needs in neurotrauma and the likely cause of interest in this drug from the US DOD.

Valuation

Following the recent R&D progress and corporate updates, we have taken a fresh look at the investment case. Our valuation is SEK1.21bn or SEK3.01 per share underpinned by the two lead assets KL1333 and NV354. We do not value NeuroSTAT (a Phase IIb-ready asset), although there is a likelihood that Abliva will decide to carry on the project if the ongoing discussions regarding the Phase II trial are successful and the data are positive. We will review this asset when Abliva releases more information.

With regards to partnering strategy for KL1333 and NV354, Abliva's management has indicated that both options are on the table. The company could bring the assets all the way to the market itself or sign a deal if the right partner comes on board. In our model we assume that Abliva will commercialise both products itself. The assumptions for our rNPV model are summarised in Exhibit 10. Key inputs include:

- **Target patient populations.** Abliva is focusing on specific PMDs for both assets in order to evaluate the drug candidates in as homogenous patient population as possible, which improves the likelihood of quality data and statistical analysis. PMD epidemiology data are scarce, but using available sources we calculate respective target patient populations for KL1333 and NV354 of 40k and 18k in the United States and the top 15 wealthy European countries (top five, the Nordics, Benelux, Austria, Switzerland and Ireland).
- **Success probabilities.** For KL1333 we use a 25% probability to reach the market, which is in line with recent analysis published by [Wong and Siah \(2019\)](#), who found drug candidates in neurology in Phase II have probability within the range 20–24%; drug candidates for all indications excluding oncology had probabilities within the range 27–29%. For NV354 we use 5% while this asset is in the preclinical stage. As described above, it could move into Phase I as soon as next year.
- **Pricing and market penetration.** We assume a price tag of \$110,000 for KL1333 and \$130,000 for NV354 (50% discount in Europe applied) per patient per year. [EvaluatePharma's 2019 report](#) calculates that the average price per patient for an orphan drug (top 100 products) was \$151k in 2018, while the median was \$110k. For KL1333 we use the price equal to the median (2018 data available only), while for NV354 we assume a price closer to the average orphan drug pricing, as it is a smaller indication than that targeted by KL1333. The range is wide, however, and higher pricing could be secured depending on cost effectiveness. We assume 20% market penetration for KL1333 and 30% for NV354, as it targets a smaller indication. As there are no effective treatments available, there is no precedent for how to model the uptake of new drugs in PMDs. It could be argued that once an effective treatment is introduced, most patients would be willing to receive it, so market penetration could be well above 50%. For the time being we use a conservative approach, but in Exhibit 9 we have provided a sensitivity analysis of peak sales to price and market penetration.
- **R&D development costs.** We estimate the cost of Abliva's pivotal Phase II/III study of KL1333 at c \$30m and assume a similar development pathway for NV354. Assumed launch dates are 2025 for KL1333 and 2028 for NV354, with peak sales reached in six years (\$670m for KL1333 and \$320m for NV354).

Exhibit 8: Abliva sum-of-the parts valuation

| Product | Launch | Peak sales (\$m) | NPV (SEKm) | NPV/share (SEK) | Probability (%) | rNPV (SEKm) | rNPV/share (SEK) |
|---|--------|------------------|----------------|-----------------|-----------------|----------------|------------------|
| Core assets | | | | | | | |
| KL1333 | 2025 | 670 | 4,290.4 | 10.65 | 25% | 1,017.8 | 2.53 |
| NV354 | 2028 | 470 | 2,692.6 | 6.68 | 5% | 66.9 | 0.17 |
| Net cash, end-Q121 plus gross proceeds from the share issue | | | 128.0 | 0.32 | 100% | 128.0 | 0.32 |
| Valuation | | | 7,111.0 | 17.6 | | 1,212.7 | 3.01 |

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Exhibit 9: Peak sales sensitivity to market penetration and pricing

| KL1333 | | Market penetration | | | | | NV354 | | Market penetration | | | | |
|---------|---------|--------------------|------------|-------|-------|-------|---------|---------|--------------------|-----|------------|-------|-------|
| | | 10% | 20% | 40% | 60% | 80% | | | 10% | 20% | 30% | 60% | 80% |
| Pricing | 60,000 | 180 | 360 | 730 | 1,090 | 1,460 | Pricing | 80,000 | 100 | 190 | 290 | 580 | 780 |
| | 110,000 | 330 | 670 | 1,340 | 2,010 | 2,670 | | 130,000 | 160 | 320 | 470 | 950 | 1,260 |
| | 160,000 | 490 | 970 | 1,950 | 2,920 | 3,890 | | 180,000 | 220 | 440 | 660 | 1,310 | 1,750 |
| | | | | | | | | | | | | | |

Source: Edison Investment Research

Exhibit 10: Assumptions for R&D and commercial projects

| Product, stage, indication | Out-licensing assumptions | Comments |
|--|--|--|
| KL1333 NAD+ modulator ■ Phase II/III ready ■ MIDD-MELAS and KSS-CPEO | Develops standalone 5% COGS 30% S&M 10% royalty rate to Yungjin | <ul style="list-style-type: none"> ■ Target population: the number of MIDD-MELAS and KSS-CPEO patients is approximately 40k in Europe and the United States (Gorman et al, 2015). We assume 20% market penetration as Abliva has narrowed the focus to a specific target population for the upcoming trial. ■ Pricing: \$110,000 per patient, per year in the United States, 50% discount in Europe. Chronic oral use. EvaluatePharma's 2019 report calculates that the average price per patient for an orphan drug (top 100 products) was \$151k in 2018, while the median was \$110k. We use the price equal to the median (2018 data available only), but the range is wide and higher pricing could be secured depending on cost effectiveness. ■ R&D costs: \$30m for the Phase II/III study. ■ Launch: 2025; peak sales reached in six years. ■ Rights: In-licensed from Yungjin Pharm in May 2017, exclusive global rights to KL1333 excluding South Korea and Japan. Last patent expires or exclusivity until 2034. Orphan drug designation provides market exclusivity for seven years in the United States and 10 years in Europe top 15. |
| NV354 Succinate prodrug ■ Late preclinical ■ Leigh syndrome | Develops standalone 5% COGS 30% S&M | <ul style="list-style-type: none"> ■ Target population: 25 per 1,000,000 children are estimated to be born with Leigh syndrome, which translates into a c 18k target patient population in the United States and Europe. We assume 30% market penetration, as Abliva has narrowed its focus to a specific syndrome and the prevalence is rather low. ■ Pricing: \$130,000 per patient per year (closer to average orphan drug pricing, as it is a smaller indication than that targeted by KL1333; see KL1333 pricing). ■ R&D costs: \$1m to finish pre-clinical development, \$5m for Phase Ia/b, \$30m for Phase II/III (development path assumed to be similar to KL1333). ■ Launch: 2028; peak sales reached in six years. ■ Rights: Last patent expires or exclusivity until 2034. Could secure orphan drug designation (seven years in the United States and 10 years in Europe top 15). |

Source: Edison Investment Research, Abliva. For the calculation of target patient groups, we use the US population plus the top 15 wealthy European countries (top five, the Nordics, Benelux, Austria, Switzerland and Ireland).

Financials

In FY20 Abliva's operating loss of SEK60.1m was lower year-on-year (SEK77.1m in 2019) due to lower R&D spending ('other external expenses' of SEK46.4m in 2020 vs SEK63.5m in 2019) partly due to disruptions caused by the COVID-19 pandemic, and partly because of refocusing R&D activities on the two leading assets. Personnel costs decreased somewhat as well (to SEK13.3m from SEK14.9m). Abliva's Q121 operating loss was SEK21.5m and we forecast an FY21 operating loss of SEK75.3m.

At end-Q121, cash was SEK48.0m, although in Q121 Abliva has raised SEK80m gross (to be booked in Q221), which should now be sufficient well into 2022, according to our model. The funding gap next year is SEK33m, according to our model. Abliva carried out the directed issue in March 2021 with 106,666,666 shares sold to several Swedish and international qualified investors, including Hadean Ventures, virtually at the market price of SEK0.75 per share (vs the previous close of SEK0.76 per share) raising in total SEK80m (69% of this issue was contingent and successfully authorised at an EGM on 29 April 2021).

Exhibit 11: Financial summary

| | SEK'000s | 2019 | 2020 | 2021e | 2022e |
|---|----------|----------|----------|----------|----------|
| Year end 31 December | | IFRS | IFRS | IFRS | IFRS |
| PROFIT & LOSS | | | | | |
| Revenue | | 3,634 | 1,864 | 1,864 | 1,864 |
| Cost of Sales | | 0 | 0 | 0 | 0 |
| Gross Profit | | 3,634 | 1,864 | 1,864 | 1,864 |
| EBITDA | | (72,317) | (54,955) | (70,201) | (95,007) |
| Operating Profit (before amort. and except.) | | (74,696) | (57,513) | (72,736) | (97,544) |
| Intangible Amortisation | | 0 | 0 | 0 | 0 |
| Exceptionals | | (2,379) | (2,558) | (2,558) | 0 |
| Other | | 0 | 0 | 0 | 0 |
| Operating Profit | | (77,075) | (60,071) | (75,294) | (97,544) |
| Net Interest | | 75 | 77 | 0 | 0 |
| Profit Before Tax (norm) | | (74,621) | (57,436) | (72,736) | (97,544) |
| Profit Before Tax (reported) | | (77,000) | (59,994) | (75,294) | (97,544) |
| Tax | | 0 | 0 | 0 | 0 |
| Minority Interests | | (6) | (5) | (5) | (5) |
| Profit After Tax (norm) | | (74,621) | (57,436) | (72,736) | (97,544) |
| Profit After Tax (reported) | | (76,994) | (59,989) | (75,289) | (97,539) |
| Average Number of Shares Outstanding (m) | | 171.6 | 249.7 | 349.6 | 403.0 |
| EPS - normalised (SEK) | | (0.43) | (0.23) | (0.21) | (0.24) |
| EPS - normalised fully diluted (SEK) | | (0.43) | (0.23) | (0.21) | (0.24) |
| EPS - reported (SEK) | | (0.45) | (0.24) | (0.22) | (0.24) |
| Dividend per share (SEK) | | 0.0 | 0.0 | 0.0 | 0.0 |
| Gross Margin (%) | | 100.0 | 100.0 | 100.0 | 100.0 |
| EBITDA Margin (%) | | N/A | N/A | N/A | N/A |
| Operating Margin (before GW and except.) (%) | | N/A | N/A | N/A | N/A |
| BALANCE SHEET | | | | | |
| Fixed Assets | | 88,573 | 87,506 | 87,579 | 87,255 |
| Intangible Assets | | 74,686 | 74,021 | 74,094 | 73,770 |
| Tangible Assets | | 99 | 41 | 41 | 41 |
| Investments | | 13,788 | 13,444 | 13,444 | 13,444 |
| Current Assets | | 59,919 | 63,157 | 67,790 | 3,514 |
| Stocks | | 0 | 0 | 0 | 0 |
| Debtors | | 0 | 0 | 0 | 0 |
| Cash | | 58,319 | 61,643 | 66,276 | 2,000 |
| Other | | 1,600 | 1,514 | 1,514 | 1,514 |
| Current Liabilities | | (20,337) | (10,209) | (10,209) | (10,209) |
| Creditors | | (20,337) | (10,209) | (10,209) | (10,209) |
| Short term borrowings | | 0 | 0 | 0 | 0 |
| Long Term Liabilities | | (361) | (92) | (92) | (33,036) |
| Long term borrowings | | 0 | 0 | 0 | (32,944) |
| Other long term liabilities | | (361) | (92) | (92) | (92) |
| Net Assets to shareholders and minority interests | | 127,794 | 140,362 | 145,068 | 47,523 |
| CASH FLOW | | | | | |
| Operating Cash Flow | | (72,367) | (67,528) | (72,759) | (95,007) |
| Net Interest | | (46) | (30) | 0 | 0 |
| Tax | | 0 | 0 | 0 | 0 |
| Capex | | (69) | 0 | 0 | 0 |
| Acquisitions/disposals* | | 0 | 0 | 0 | 0 |
| Financing | | 107,780 | 72,564 | 80,000 | 0 |
| Other | | (2,930) | (1,682) | (2,608) | (2,214) |
| Dividends | | 0 | 0 | 0 | 0 |
| Net Cash Flow | | 32,368 | 3,324 | 4,633 | (97,220) |
| Opening net debt/(cash) | | (25,951) | (58,319) | (61,643) | (66,276) |
| HP finance leases initiated | | 0 | 0 | 0 | 0 |
| Other | | (0) | 0 | 0 | 0 |
| Closing net debt/(cash) | | (58,319) | (61,643) | (66,276) | 30,944 |

Source: Abliva accounts, Edison Investment Research

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