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Promising initial data in patients

Efficacy in patients with mitochondrial disease

Last week, Abliva reported the results of the first trial of the company's drug candidate KL1333 in patients with primary mitochondrial disease, or PMD. Six patients were treated for ten days with KL1333, and preliminary data from this part of a larger Phase 1 study indicates the compound had an effect on the patients' fatigue, a general condition that decreases the quality of life of patients with PMD.

The signal of therapeutic effect gains strength from the fact that the study included two PMD patients who received a placebo without displaying the same improvement as those treated with KL1333. Management expressed its continued confidence that a registrational Phase 2/3 study in certain types of PMD patients could be started as early as this year.

Alleviation of patients' experienced fatigue

The primary aim of the study was to investigate the safety and pharmacokinetic effects of KL1333. No serious side effects were reported from the study, but higher dosages of KL1333 gave rise to varying degrees of diarrhea, a side effect that was also noted in earlier studies. The company is considering reducing this by dividing the medication into repeated doses instead of one dose per day.

Fatigue was one of several exploratory endpoints that were included in the study. Two different scales for measuring fatigue – both based on patient self-evaluations – indicated positive signals in the first limited cohort. A third functional scale reported patient strength in standing up and sitting down repeatedly over 30 seconds.

Funding for Phase 2/3 still to be secured

Based on initial contacts with the drug authorities in the US and Europe, the company hopes to be able to initiate a registrational Phase 2/3 study in late 2021. This optimism is founded on factors including the substantial medical need among PMD patients for improved therapies. We feel that the results of the Phase 1b study support the possibility of securing funding for the next phase, retaining a justified value of SEK 1.6 per share.

Abliva

Analysis

Date	26 May, 2021
Analyst	Sten Westerberg

Basic facts

Industry	Drug development
Chairman	David Laskow-Pooley
CEO	Ellen K. Donnelly
Listing year	2013
Listing	Nasdaq Stockholm
Symbol	ABLI
Share price	SEK 0.75
Number of shares, mil.	403.0
Market cap., SEK	302 101
Website	www.abliva.com

Share price performance, preceding year

Source: Refinitiv

Forecast & performance indicators, SEK m.

	2019	2020	2021e	2022e
Net sales	0.1	0.2	0	0
Loss before tax	-77	-60	-96	-273
Net loss	-77	-60	-96	-273
Earnings per share	SEK -0.5	SEK -0.1	SEK -0.2	SEK -0.7
Operating margin	neg	neg	neg	neg
Cash and cash equivalents	58	62	404	224
New share issue	108	87	472	100
Dividend yield	0%	0%	0%	0%

Source: Company,

Investment thesis

Rare disorders need cures

Abliva conducts drug research in a field that is part of the group of primary mitochondrial diseases, or PMDs. Mitochondria are often called the "powerhouse of the cell" and the diseases originate in a metabolic disruption that can be linked to various congenital mutations and genetic alterations. The diseases often emerge early in life, are extremely troublesome and markedly lower the quality of life for the afflicted. In Abliva's case, it is a matter of two different spectra of primary mitochondrial diseases: MELAS-MIDD and KSS-CPEO, two conditions that afflict 35 and 15 people per 1,000,000, respectively. There is currently no approved therapy for these diseases, which creates a substantial underlying medical need for new drugs. Abliva's angle of approach is the development of a drug, KL1333, that strengthens the cell's energy production by increasing the levels of nicotinamide adenine dinucleotide, or NAD+.

Key study could begin next year

Abliva is working out a plan, in discussion with drug authorities, to move KL1333 forward to a key study on the basis of the limited clinical data the company has produced. This study could then begin without KL1333 having yet demonstrated proof of concept in a Phase 2a study. We feel that this accelerated development plan has been strengthened after the Phase 1 data that has now been presented:

- Indications of increased effect with higher exposure to KL1333;
- Positive findings in three different placebo-controlled outcome measures;
- Side effects that can be solved with a different dosage;
- Clear medical need in a small cohort of patients.

Sales potential over USD 1 billion per year

The company estimates the cost of conducting a registrational study of KL1333 at USD 30–40 million, which is money that remains to be raised. An investment in Abliva means the possibility of taking part in the unusually compressed development of a drug candidate that could be approved for sale as early as 2025. We have a conservative forecast of top sales for KL1333 of USD 1.1 billion in 2031, a forecast that we give a 23% chance of being fulfilled. The justified value of SEK 1.6 per share remains.

No serious side effects in Phase 1

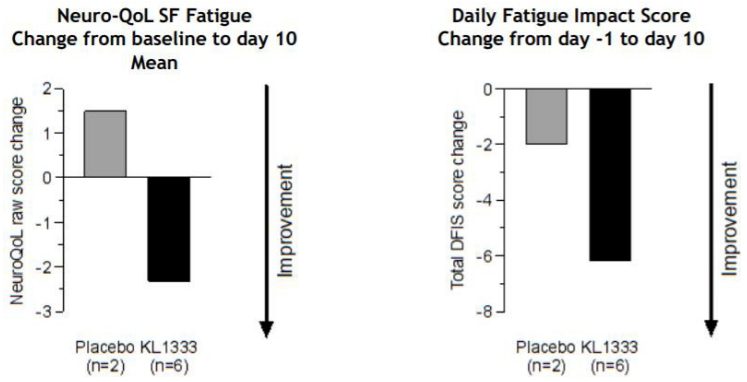
Abliva's initial study with drug candidate KL1333 in patients with various forms of primary mitochondrial disease, or PMD, reported its initial findings last week. The study was a Phase 1b study in eight patients, and was conducted after relatively exhaustive tests on healthy volunteers in an earlier Phase 1a portion. The primary aim of the study – KL1333 demonstrating an acceptable safety profile – was achieved, which allows the company to move on to testing KL1333 in larger patient cohorts in a Phase 2/3 study. The company's ambition is to begin this study late in the year, which can be considered optimistic but not unthinkable. In our primary scenario, the first patient in the Phase 2/3 study will be treated early next year, provided that the company has solved its funding issue by then.

In the Phase 1b part now being reported, KL1333 was tested at 50 mg per day in six PMD patients with some form of mitochondrial disease. The therapy was administered for ten days. To obtain better knowledge of the effect of the active compound, a further two patients received placebo. The company wrote in its press release that no serious side effects were seen. From previous studies in healthy volunteers with dosages up to 250 mg, it is known that KL1333 causes intestinal problems that correlate to dosage strength. Abliva intends to counteract this by dividing the dosage up into two or three occasions per day.

Decreased fatigue in focus

The encouraging news in the study was that during this brief period of therapy, KL1333 still succeeded in achieving signals of an alleviation of the patient's experience of fatigue on two different patient-reported scales. One scale, Neuro-QoL, will form the basis for the primary endpoint in the future registrational Phase 2/3 study, in which the therapy period will be considerably longer than ten days.

KL1333 demonstrates effect on fatigue in initial study



Source: Abliva

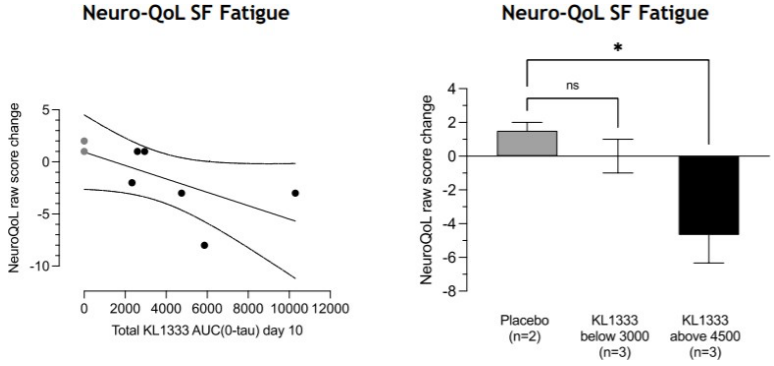
Quality of Life in Neurological Disorders Short Form, or Neuro-QoL SF, is a protocol where the patients themselves estimate various symptoms of fatigue in eight different questions on a scale of 1 to 5. The diagram on the preceding page shows that according to the scale, the two patients who did not receive KL1333 stated that they experienced somewhat increased symptoms of fatigue during the evaluation. On the other hand, the six patients who received KL1333 over ten days stated that their symptoms of fatigue decreased. The difference (delta) between the bars is just over 4 points. In its presentation, Abliva wrote that a difference between 2.5 and 5 is considered clinically meaningful among researchers, which thus indicates that the results in these six patients are clinically meaningful.

According to the Daily Fatigue Impact Score, another patient-reported scale, the two placebo patients also experienced an improvement during this brief period, presumably a traditional placebo effect. On the other hand, the six patients who were treated with KL1333 experienced a palpably greater effect, and the difference between the cohorts was approximately 4 points here as well, a signal of clinically meaningful improvement based on earlier evaluations, which was highlighted by Abliva.

Signal for dose response reinforces confidence in KL1333

Yet another interesting finding in the study is that the three patients with the best uptake of 50 mg KL1333 in their bloodstream were also those who showed the clearest outcome on the Neuro-QoL scale (right-hand diagram below). Below, it can be seen that two of the three black dots representing the patients with the worst uptake of KL1333 in their bloodstream did not present any clear changes on the scale whereas the three other patients, with an uptake of over 4,500ng/mL, had a clear outcome on the scale. We stress that this signal is uncertain and, like the other clinical observations, is based on data from too few observations to ensure that conclusions can be drawn.

Decreased fatigue follows exposure to KL1333



Source: Abliva

Yet another factor that reinforces our confidence that KL1333 could have potential in PMD therapy is the functional test that the patients performed during the study: a 30-second “sit to stand” test. Five of the patients demonstrated an improvement after ten days of therapy compared with the placebo in 2 repetitions on average during the 30-second duration of the test. This improvement may seem small for a healthy person, but for a PMD patient it can mean a big difference.

Abliva expects to release further findings from its study at the end of June in a digital meeting with the United Mitochondrial Disease Foundation (UMDF), a US interest group for people who are suffering from primary mitochondrial diseases.

Preparations ahead of a key Phase 3 study

Ahead of a registrational Phase 2/3 study, which the company hopes to set in motion before the end of the year, a number of preparations remain. Apart from ensuring funding for the study, either in one or several steps, the company will establish and optimize the criteria, known as inclusion criteria, that determine which PMD patients will be allowed into the study. The company intends to direct its study toward two different spectra of primary mitochondrial disease: MELAS-MIDD and KSS-CPEA, which can have different courses of development and heterogeneous backgrounds both between and within themselves.

The company will also, in collaboration with the drug authorities, establish the clinical endpoint that will primarily determine whether KL1333 has an effect on the patients. Abliva expects that an abbreviated Neuro-QoL form will be the basis of the patient-reported experiences that the US Food and Drug Administration will take a position on before approval can be granted.

Earlier studies in PMD patients have used a six-minute walk test (6MWT), which no company with drug projects in PMD have successfully demonstrated sufficient effect in. The hope is that a patient-reported outcome (PRO) will better identify reduced fatigue and how it impacts the patient’s normal daily activities after a longer period of therapy. Since no PMD studies have previously used the Neuro-QoL, interviews are being conducted with patients and their physicians to confirm the details.

We expect that the study will recruit its first patient in early 2022, that all 150 patients will be recruited after 9 to 12 months and that the therapy of the patients will continue for 12 months. In parallel with the study, the company will also conduct a toxicology study over a longer period than the 15 days that the initial study reported.

The hope is to be able to include clinics in both the US and Europe in the same study, which presumes that the authorities in both areas will not impose entirely different requirements on the design of the study. Our basic belief is that the lack of therapeutic alternatives for this small patient cohort provides the conditions for the drug authorities to go far towards allowing a study to begin without having to

demonstrate a previous proof of concept. The first part of the study will be directed towards finding an individually optimal dose based on the maximum tolerated dose within a predetermined interval. This abbreviated and accelerated development plan for a drug can be viewed in light of the existing substantial medical need for patients suffering from these rare disorders.

Funding remains a key area of focus

Abliva announced in January that the company had appointed Dr. Ellen Donnelly as the new CEO after Erik Kinnman, who left the company in February. Dr. Donnelly comes most recently from a brief stint as CEO for both the Division of Epigenetics of Juvenescence Ltd and for Juvenescence's portfolio company Souvien Bio, which is in the early development phase of drugs for neurodegeneration. Prior to that. Dr. Donnelly was CEO of Modus Therapeutics from 2017 to 2020, and also has a history of directorial positions in Pfizer's CNS research. We feel that the recruitment of Dr. Donnelly is a step on the way toward creating a company that has firmer roots in the US market ahead of both the capital-raising process and clinical trials.

Dr. Donnelly's major task going forward will be securing funding to conduct the new study. The company has estimated the cost at USD 30–40 million, or SEK 250–350 million. This is a limited investment, if the investors take into account that it could be enough to take the company all the way to an application for approval of KL1333, but on the other hand it is a major investment in relation to the company's current market value of SEK 300 million.

Financial discussion and evaluation

In our evaluation of Abliva, we assumed that the company issues shares for a further SEK 250 million this year and SEK 100 million next year. We have set the issue price at SEK 0.70. In total, the company would then need to issue just over 500 million new shares, a major dilution from the current total of 403 million shares. Considering the uncertainty around an impending major new share issue, we are treating Abliva in a calculation of present value with a relatively high yield requirement: 15%, which can be lowered once the first step in a new share issue to fund the Phase 2/3 study has been completed.

In a long-term evaluation of KL1333, an additional major new share issue should be expected in order to reflect market investments in launch and manufacturing in the US and the EU, which we roughly estimate at just over SEK 1 billion. More likely is that the company will sell the rights to KL1333 after a successful Phase 3 study, but we expect that the value of such a transaction will be based on the alternate cost for Abliva's shareholders of building up their own organization in the US and the EU (see table on page 8).

Assumptions in calculation of sales forecast

In our evaluation of the Abliva share, we start from a conservative scenario for KL1333 and its chances of reaching the market. We start from the population of 12,000 patients with primary mitochondrial disease in MELAS-MIDD and KSS-CPEO, who the company describes as most seriously ill. With prevalence figures of 3.5 and 1.5 per 100,000 respectively, the total population among both of these genetic diseases is 42,000 in the US and Europe, but at present we do not have enough information to take a position on whether a large portion of this population will be medicated. In our forecasts, we have therefore set the company's target group as 28% of these 42,000.

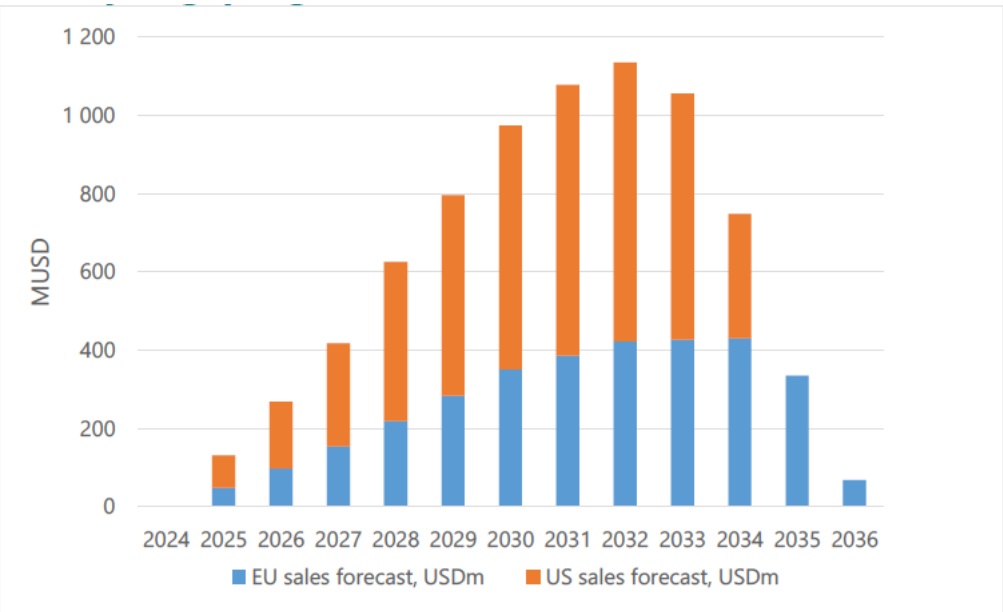
Pricing of drugs for rare disorders (orphan drugs) is difficult to assess. Prices upwards of USD 500,000 per patient and year can be noted for gene therapy-based treatments. Some enzyme inhibitors sell for up to USD 250,000 per patient and year. In a study published in 2019, the average price for orphan drugs in the US in 2017 was USD 123,000 per patient and year[1]. In its compilation for 2018, Evaluate Pharm concluded that the average price for an orphan drug in the US totaled USD 150,000 per patient and year. Owing to extreme values, the median price stood at USD 110,000 per patient and year.

In our calculation, we have assumed a sale price for KL1333 in the US of USD 150,000 per patient and year, somewhat higher than the median price for orphan drugs in the US. In Europe, we estimate a price of USD 85,000 per year, on a par with remuneration for other orphan drugs. Moreover, we expect that by 2032 the company will reach approximately 70% of the seriously ill portion of its patient cohort, which means top sales in 2031–32 of USD 1.1 billion. To achieve these sales numbers, we have assumed that the company will build up its own sales organization in the US and the EU, but it is also possible that the company will license its preparation to a company with previously established sales channels. In the forecasts below, we start from the assumption that KL1333 will obtain seven years of market exclusivity in the US and ten years of market exclusivity in the EU.

Our evaluation of the company's other assets, primarily NV354 and NeuroSTAT, is marked by the absence of funding and limited clinical data. We would regard positive developments in funding or sales of these for projects as a pure upside for the share.

[1] The Rise of Orphan Drugs, America's Health Insurer Plans, September 2019

Sales forecast for KL1333



Source: Analysguiden forecasts

Assumptions in calculating present value of KL1333

SEK M (unless otherwise indicated)	**2020**	**2021e**	**2022e**	**2023e**	**2024e**	**2025e**	**2026e**	**2030e**	**2031e**	**2034e**
Costs, development of KL1333	-41	-30	-189	-50	0	0	0			
Milestones to Yungjin Pharma	0	-10	-40	-34	0	-253	-100	0		
Calculation for the US market										
Number of patients in target group	5	per	100,000 inhabitants, total			19,321	US citizens			
Num of potential patients for trx	28% of target group					5,455	5,565	6,023	6,144	6,392
Sale price, USD/patient-year						151,500	153,015	159,228	160,820	165,693
Proportion of seriously ill who receive therapy						*10%*	*20%*	*65%*	*70%*	*30%*
US sales, USD m						83	170	623	692	318
Calculation for the European market										
Number of patients in target group	5	per	100,000 inhabitants, total			25,000	25,000	25,000	25,000	25,000
Num of potential patients for trx	28% of target group					7,059	7,059	7,059	7,059	7,059
Sale price, USD/patient-year						85,850	86,709	90,229	91,132	93,893
Proportion of seriously ill who receive therapy						*5%*	*10%*	*55%*	*60%*	*65%*
EU sales, USD m						30	61	350	386	431
Total sales, USD m						**113**	**231**	**974**	**1,078**	**749**
EBIT, SEK m	-60	-87	-243	-257	-588	-477	871	6,416	6,938	5,438
Net earnings, SEK m	-60	-87	-243	-257	-588	-477	871	5,133	5,551	4,350
Risk adjustment factor			***1.00***	***0.40***	***0.26***	***0.23***	***0.23***	***0.23***	***0.23***	***0.23***
Present value of KL1333, SEK m	2,035			-78	-101	-64	101	341	321	165

Outcome per share	SEK 2.2	after new share issue 1 at subscription price of SEK 0.70	Total no. of shares, mil.	914
	SEK 1.7	after new share issue 2 at subscription price of SEK 4.00	Total no. of shares, mil.	1,180

SEK/USD	8.4
Discount factor	15%
Tax rate	20%
Positive Phase 1	100%
Successful Phase 2/3	26%
Successful application	90%
Accumulated probability	23%

Overview of target group for KL1333

Researchers estimate that primary mitochondrial diseases (PMD) occur in approximately 125 persons per million. PMD is caused primarily by mutations in the mitochondrial gene pool, which is inherited from the mother, and affecting the mitochondria – the powerhouse of the cell – ceasing to function in the desired manner. The disease can also be caused by changes in the DNA of the cell nucleus.

One of the most common mutations, m.3243A>G, will cause illness in approximately 3.5 births per 100,000. In a population of 10 million, that would mean that 350 people have a disease caused by this mitochondrial mutation, which gives rise to conditions such as the MELAS-MIDD spectrum of rare disorders. According to the Swedish National Board of Health and Welfare, MELAS affects approximately 1 or 2 Swedes per 100,000 and there are some 30 mutations that could give rise to the mitochondrial dysfunction MELAS, but the m.3243A>G mutation is believed to be the most common source of the disease.

Abliva intends to treat the MELAS-MIDD spectrum of diseases with the NAD modulator KL1333. MELAS is an abbreviation for Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes Syndrome. MIDD stands for Maternally Inherited Diabetes and Deafness. Ablivas's focus is on patients on the MELAS-MIDD spectrum with pronounced exhaustion, muscle weakness, and diabetes as the main symptoms.

MELAS-MIDD can be an extremely serious disease with continual degradation of status that primarily affects musculature and metabolism, which leads to pronounced exhaustion, muscle weakness and severe mitochondrial diabetes. In 5–10% of the patients with MELAS-MIDD, severe symptoms exist in the central nervous system, with stroke-like episodes and loss of critical brain functions as a result. The majority of the patients have peripheral symptoms such as muscle exhaustion. The disease is chronic, coming and going periodically, and the first symptoms usually occur between the ages of 5 and 15, and nearly always before the age of 40. Common symptoms in children are severe headaches and vomiting. Epilepsy is a frequent consequence of the disease, which ultimately transitions into unconsciousness and severe neurological conditions. Attacks can last from a few hours up to two or three days.

Kearns-Sayres syndrome (KSS), another of the genetic diseases that Abliva intends to treat with KL1333, is stated to effect some 20 Swedes, and is thus an extremely rare disorder (one case per half million people). The initial symptoms in Kearns-Sayres syndrome usually manifest between the ages of 5 and 20 and then become progressive. Illness later in life up to age 60 can occur but is extremely rare. When the symptoms manifest early in childhood, this usually

results in a more severe course of development for the disease.

CPEO is a mitochondrial disease related to KSS that Abliva also intends to treat. CPEO stands for chronic progressive external ophthalmoplegia, two serious neuromuscular eye diseases that debut before the age of 20. According to the Swedish National Board of Health and Welfare, the actual prevalence is not known but is estimated to be 1 to 2 people per 100,000 inhabitants. KSS-CPEO is believed to be caused by a deletion (loss of genetic material) in different sequence of mtDNA than with MELAS-MIDD. According to Abliva, deletions that lead to diseases on the KSS-CPEO spectrum affect approximately 15 children per million.

Mitochondrial diseases distinguish themselves through high intracellular levels of free reactive oxygen species (ROS) and a reduction in the levels of the molecule adenosine triphosphate (ATP), which actually fuels the cell. The most important task of the mitochondria is freeing energy from glucose and fat in the form of ATP, which is consumed in the various tasks of the cell. Additionally, the mitochondria are involved in the production of free ROS, high levels of which can damage the cell. The mitochondria also affect other signaling systems in the cell, cell death and the cell's own metabolism. As we reported above, mitochondria has its own DNA that comes exclusively from the child's mother and thus differs from the DNA of the chromosomes in the cell nucleus.

Introduction and description of KL1333

KL1333 was developed by the South Korean company KT&G (Korean Tobacco & Ginseng Company). In 2017, Abliva signed an agreement with Yungjin Pharmaceutical, a subsidiary of KT&G, for the right to the development of KL1333 against primary mitochondrial diseases.

The KL1333 molecule is a derivative of a known family of molecules called β-lapachones. This class of molecules was discovered in studies of the health-giving properties of the bark of the pau d'arco tree, which grows in Central and South America. Several attempts have been made to show that the substance has an anti-cancer effect, but currently the bark is sold only as a health supplement. Various molecules in this class have been shown to have an effect, apart from cancer, on cell metabolism and energy regulation.

KL1333 is an oral preparation that modulates the levels of intracellular nicotinamide adenine dinucleotide, or NAD+, an enzyme that is central to the energy metabolism of mitochondria and cells. In preclinical studies, the compound has been shown to increase mitochondrial energy production, reduce lactate accumulation, prevent the formation of free oxygen radicals, and have long-lasting positive effects on energy metabolism.

NAD+ and its reduced form, NADH, are regulators of intracellular redox homeostasis, energy metabolism and several other signaling paths in the cell. NAD+ can be produced by the cell *de novo* or via

salvage pathways when the cell consumes large amounts of energy. NAD+ can also be generated through transforming NADH via various enzymes or substrates such as NQO1. It is through this latter enzyme, NQO1, that the NAD modulator KL1333 operates. KL1333 increases the levels of NAD+ through oxidation of the reduced basic form, NADH. The intracellular quotient of NAD+/NADH is thereby positively impacted, which increases the cell's energy production and stimulates the production of new mitochondria. Owing to dysfunctional mitochondria, the quotient of NAD+/NADH is low in patients with primary mitochondrial diseases.

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Responsible analyst:

Sten Westerberg