KL1333: A Potential First-in-Class Oral Treatment for Primary Mitochondrial Disease

Mitochondrial diseases are a group of rare genetic disorders that impair cellular energy production, leading to a wide range of debilitating symptoms, including muscle weakness, fatigue, neurological problems, and organ failure[1]. Currently, there are no approved treatments for most mitochondrial diseases, leaving patients with limited therapeutic options[1]. However, a novel oral molecule called KL1333 has emerged as a beacon of hope, showing promise in early clinical trials for the treatment of primary mitochondrial disease (PMD)[1]. This article provides a comprehensive overview of KL1333, its development, and its potential to transform the lives of individuals with PMD.

Abliva AB and KL1333

KL1333 is being developed by Abliva AB, a Swedish biopharmaceutical company dedicated to advancing therapies for mitochondrial diseases[2]. The company has focused its research efforts on addressing the unmet medical needs of patients with these debilitating conditions. KL1333 is an oral small molecule and an NAD+ modulator that works by altering the NAD+:NADH ratio within cells[3]. This ratio is crucial for ATP production, the primary energy source for cellular functions. By normalizing the NAD+:NADH ratio, KL1333 is believed to enhance mitochondrial biogenesis and function, leading to increased energy production and reduced oxidative stress[3]. Specifically, KL1333 increases NAD+ levels by activating the enzyme NQO1 and subsequently activates the SIRT1/AMPK/PGC-1α signaling network[5]. This network plays a vital role in mitochondrial biogenesis, the process of generating new mitochondria, and in improving mitochondrial function. By promoting the formation of new mitochondria and enhancing their efficiency, KL1333 aims to restore cellular energy production and alleviate the symptoms associated with PMD.
It is worth noting that attempts to access the website of Alive AB were unsuccessful, suggesting that the website may be inaccessible[6].

Research Papers and Clinical Trial Data

A recent study published in the journal *Brain* evaluated the safety and tolerability of KL1333 in a cohort of 64 healthy volunteers and 8 individuals diagnosed with PMD[1]. The results indicated that KL1333 was safe and well-tolerated, with dose-dependent gastrointestinal side effects being the most common adverse events[3]. Importantly, the study provided preliminary evidence of KL1333's efficacy, with participants in the KL1333 group reporting reduced fatigue and demonstrating improved functional strength and endurance compared to those receiving a placebo[3].
This Phase 1a/1b trial incorporated innovative design elements, including patient involvement, adaptive design, and exploratory objectives, which have informed the design of subsequent clinical trials for KL1333 and hold potential for broader application in rare disease research[7].

The study's findings not only support the safety and potential efficacy of KL1333 but also highlight the value of incorporating patient perspectives and adaptive methodologies in early-stage clinical trials for rare diseases.

The FALCON Study

KL1333 is currently being evaluated in a global Phase 2 study known as the FALCON study[8]. This potentially registrational trial is designed to assess the safety and efficacy of KL1333 in adult patients with PMD who experience persistent fatigue and myopathy, the most common and debilitating symptoms of the disease[9]. The study employs a randomized, placebo-controlled design, with participants assigned to receive either KL1333 or a placebo.

The FALCON study has two primary endpoints: assessing fatigue using the PROMIS Fatigue Mitochondrial Disease Short Form and evaluating myopathy using the 30-second Sit-to-Stand test[10]. Notably, only one of these endpoints needs to demonstrate a statistically significant improvement to support a marketing approval application[10].

The first patient in the FALCON study was dosed in June 2023[10]. In July 2024, a pre-planned interim analysis of 24-week data from the first wave of patients yielded encouraging results[9]. The analysis confirmed the favorable safety profile of KL1333, with no safety concerns or drug-related serious adverse events observed[11]. Furthermore, both primary endpoints passed futility, indicating that they have the potential to show a benefit at the final analysis of the study[9]. This positive interim analysis significantly de-risks the program and increases the likelihood of a successful trial outcome[10].

In December 2024, Pharming announced a public cash offer to acquire Abliva AB[8]. Pharming's CEO expressed enthusiasm for KL1333's potential as a first-in-disease treatment and highlighted its blockbuster potential, particularly in the US market[8]. The acquisition is expected to accelerate KL1333's development and facilitate its market launch, with a projected US launch in 2028[8].

Disease(s) KL1333 is Intended to Treat

KL1333 is being developed to address the significant unmet medical need of adult patients with primary mitochondrial disease who experience persistent fatigue and myopathy[13]. The drug candidate is specifically targeted towards individuals with genetically confirmed diagnoses that fall within the following spectrum disorders:

- **MELAS-MIDD:** This spectrum encompasses MELAS (Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) and MIDD (Maternally inherited diabetes and deafness). MELAS is a rare mitochondrial disorder that typically manifests in childhood with symptoms such as stroke-like episodes, dementia, headache, vomiting, seizures, lactic acidosis, deafness, growth retardation, and myopathy[5].
- **KSS-CPEO:** This spectrum includes KSS (Kearns-Sayre syndrome) and CPEO (Chronic progressive external ophthalmoplegia). KSS is a rare mitochondrial disorder that usually begins before the age of 20 years and is characterized by progressive external ophthalmoplegia (weakness or paralysis of the eye muscles), pigmentary retinopathy (degeneration of the retina), cardiac conduction defects, and cardiomyopathy (heart muscle disease)[4]. Other features may include cerebellar ataxia (problems with coordination and balance), deafness, diabetes mellitus, short stature, and/or increased protein levels in the cerebrospinal fluid[4].

- **MERRF:** MERRF (Myoclonic epilepsy with ragged red fibers) syndrome is a rare mitochondrial disorder that typically begins in childhood or adolescence[4]. It is characterized by myoclonus (brief, involuntary muscle jerks), seizures, ataxia, muscle weakness, and ragged red fibers (abnormal mitochondria that appear as ragged red fibers under a microscope)[4].

Potential Side Effects and Safety Concerns

KL1333 has demonstrated a favorable safety profile in clinical trials to date[14]. The most frequently reported side effects are gastrointestinal in nature and appear to be dose-dependent[3]. In the FALCON study, no safety concerns or drug-related serious adverse events were observed after 24 weeks of treatment[11]. These findings suggest that KL1333 is generally well-tolerated, although continued monitoring for potential adverse events is essential as the drug progresses through clinical development.

Conclusion

KL1333 represents a significant advancement in the pursuit of effective treatments for primary mitochondrial disease. Early clinical trial data indicate that KL1333 is safe, well-tolerated, and may offer clinical benefits by improving fatigue and functional strength in individuals with PMD. The ongoing FALCON study is poised to provide more definitive evidence of KL1333's efficacy and safety.

The potential implications of KL1333's development are substantial. With an estimated addressable patient population of over 30,000 individuals in the US, EU4, and the UK alone, KL1333 has the potential to address a significant unmet medical need and improve the quality of life for many patients with PMD[8]. If the FALCON study confirms the drug's efficacy and safety, KL1333 could become the first approved treatment for this debilitating group of diseases, marking a major milestone in the field of mitochondrial medicine.

However, it is important to acknowledge the challenges associated with developing treatments for rare diseases, such as the difficulties in recruiting patients for clinical trials and the need for long-term follow-up to fully understand the drug's effects. Further research is necessary to determine the long-term safety and efficacy of KL1333 and to explore its potential in broader patient populations with mitochondrial disorders.

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