Development of a new drug to treat mitochondrial disease and Parkinson's disease through enhancement of cellular bioenergetics

EnePharma Inc.
www.enepharma.com
c/o Adrian Rich, esq., Perkins Coie LLP
3150 Porter Drive, Palo Alto, CA 94304, USA
E-mail: info@enepharma.com
Management team
Nao Kamatani, CEO
Yoshi Shima, Secretary
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EnePharma Inc. was incorporated in the U.S. state of Delaware in June 2019 to develop a new therapeutic class of ATP enhancers that have application to indications characterized by cellular "energy shortages" such as **mitochondrial diseases** and CNS disorders including **Parkinson's disease** (PD), as well as have potential to impact the aging process. EnePharma's lead drug, [ATP enhancer], is a proprietary combination of febuxostat and inosine which has large market potential and that is patented in Japan, US and Russia. Early phase clinical trials of [ATP enhancer] demonstrated a positive safety profile and provided early evidence of a therapeutic effect.

Rationale: More than 10% of human genes are related to energy (ATP), and many diseases are thought to be caused by "energy deficiency". Energy crisis (EC) refers to the situation in which cellular ATP levels become reduced, and in such circumstances, it is known that hyperuricemia due to excessive purine degradation can occur. That situation is due to a vicious cycle whereby cells use all available means to maintain ATP levels, but that may nevertheless lead to ATP deficiency and reduced cellular purine stores. However, that vicious cycle can be broken by administering a xanthine oxidase inhibitor such as febuxostat that prevents the degradation of hypoxanthine. Animal experiments have shown that organ damage due to hypoxia associated with ischemia of the heart and kidney can be suppressed by febuxostat due to re-synthesis of ATP (Lee et al. 2011, Fujii et al. 2019), but while a mouse's high systemic metabolism degrades purines at a sufficient rate for hypoxanthine to be released from one tissue and salvaged into ATP in another, the purine degradation rate in humans is comparatively rather slow. To compensate for that, co-administration with inosine, which is a raw material of hypoxanthine, can generate a stronger ATP enhancing effect. Because of their key importance in human disease, ATP enhancement therapies such as [ATP enhancer] have the potential to treat a wide-variety of human maladies (Johnson et al. 2019).

Safety and efficacy supported by clinical data: [ATP enhancer] has been co-administered to 65 subjects (18 healthy subjects and 47 patients), and the data from these trials support its safety (Kamatani et al. 2017). ATP and hypoxanthine were markedly increased in healthy subjects by the co-administration of febuxostat and inosine for 2 weeks but not by administration of either compound alone. In patients with Parkinson's disease treated with our drug combination, significant improvement ($P = 0.0146$) of the MDS-UPDRS Part III score with more than a minimal clinically important difference (MCID = -3.25) was achieved in 26 patients treated for 8 weeks (Watanabe et al. 2020). Likewise, in two patients with mitochondrial disease, co-administration of febuxostat and inosine for 2 weeks dramatically improved a biomarker of cardiac failure (BNP) in a mitochondrial cardiomyopathy patient and a biomarker of diabetes (insulinogenic index) in a mitochondrial diabetes patient (Kamatani et al. 2019).

Clinical situation: Mitochondrial diseases are unequivocally caused by energy shortage, and about one in 4300 people carry related pathogenic mutations (Schaefer et al. 2019). Symptoms are wide-spread and involve the central nervous system, skeletal muscles, cardiovascular system, hearing loss, eye disorder, liver abnormality, renal disease, and/or diabetes. Treatment options are generally limited to symptomatic treatment (Parikh et al. 2017). PD has about 50,000 new cases annually in the US and is distinguished by a severe loss of pigmented dopaminergic neurons of the substantia nigra. PD treatments such as levodopa and dopamine agonists target symptoms, but no available treatments are able to modify the disease course. While alpha-synuclein deposition has been a center of drug research, mounting evidence suggests that PD is related to mitochondrial dysfunction and energy shortage (Vicario et al. 2018). As such, [ATP enhancer] represents a strong PD treatment candidate with a large market potential if successful.

Current development status: EnePharma is preparing for pre-IND meetings with the U.S. FDA for Parkinson's and mitochondrial diseases based on our preclinical and clinical data. It has assembled an outstanding scientific advisory board who bring state of the art expertise in metabolic diseases (including mitochondrial disease), personalized medicine, and broad clinical backgrounds to support development of the company's lead drug. EnePharma is seeking synergistic clinical development partners and investors in the pursuit of therapeutic solutions for these and other indications.

EnePharma Inc. is seeking additional capital to continue the clinical development of its promising febuxostat and inosine combination for the treatment of major market human diseases for patients with limited therapeutic options and dismal prognoses.

Slide-deck available under "About us" on http://enepharma.com

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