Summary - EPI-743 Leighs Syndrome Trial Update
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Introduction: The EPI-743 clinical trials currently being conducted by Edison Pharmaceuticals are laying the foundation for exciting developments in the care of patients with mitochondrial disease, with the goal of developing a first treatment for Mitochondrial Disease. Dr. Guy Miller and Dr. Matt Kline, both from Edison Pharmaceuticals, will share up-to-date information drug trials being conducted at this time, including EPI-589, the second-generation drug which is coming through phase one clinical development currently. The status of all trials can be tracked at www.clinicaltrials.gov.

Casting a wide net over a broad array of mitochondrial diseases, EPI-743 was developed and was tested in about 100 patients worldwide, with three questions in mind: Is the drug absorbed, safe, and have hints of efficacy? Due to the diverse presentation of Mitochondrial Diseases, a natural history of the disease needs to be established so that efficacy can be proven. These diseases are not only very diverse, but are beginning to get genetically and biochemically characterized, as well as clinically characterized which will help to evaluate efficacy. An entire array of Phase 2A trials have been launched for Leighs Syndrome, Retts Syndrome (Japan), MELAS, Friedreichs Ataxia, and others, with the hope of reproducibility of results as well as meeting clinically and statically significant endpoints.

Leighs Syndrome and EPI-743

Leighs Syndrome is an inherited, lethal, predominately pediatric neuromuscular disease for which no approved treatments exist. First described by Dr. Leigh in 1951, this disease is characterized by bilateral necrosis (death) of certain areas of the brain. The necrotic areas in the brain bring about terrible consequences for the patient, such a loss of respiratory function, ability to walk or talk, etc., and often causing death by early school age (5-6 years of age). Leighs Disease is complex, arising from a number of different mutations, occurring in the nuclear genome or mitochondria genome or DNA. Patients can present at different ages, can have different presentations, but commonly share the death in certain parts of the brain and ultimate early demise. EPI-743 is being studied in Leighs syndrome in term of absorption, safety, and learning about the effects of the drug on the signs and symptoms of the disease, knowing that the disease course may differ significantly between different patients.

Leighs Syndrome is a rare disease, often known as an orphan disease. Edison has recently received FDA orphan designation for EPI-743 for the treatment of Leighs Syndrome. FDA established the orphan designation program in 1983 with the goal of providing incentives for drug research for rare diseases, such as Leighs and other mito diseases. Drug companies do not flock to develop drugs for rare diseases as compared to common conditions such as high blood pressure and diabetes. The challenges to get a drug approved for a rare drug are very high, while the patient numbers are strikingly low, thus the FDA developed **Orphan Designation for rare diseases**:

- Rare disease - defined as fewer than 200,000 people in the United States having the disease, with Leighs disease considered to be “ultra orphan.”
- Awarded by FDA to drugs developed explicitly for serious and life threatening rare diseases, for which there is no treatment.
- Awarded to drugs that have shown promise of being effective to treat these diseases.
- Does not mean that EPI-743 has been approved by the FDA, nor that doctors can prescribe it at this time. EPI-743 remains in clinical trial phase of development.
- Incentives awarded to help get the drug through the FDA approval process.
- Additional incentives gained once drug has FDA approval, again to encourage companies to help develop drugs for rare diseases.

EPI-743 has obtained orphan designation, meaning that it has shown promise in treating mitochondrial disease in early trials. Edison Pharma, MitoAction, and UMDF have pioneered enrollment for the now completed placebo control trial. The response of the patient community has been excellent and health professionals have collaborated with enthusiasm. Data is being analyzed to gleam key factors that will guide phase two trials (clinical approval trials), such as:

- optimal dose (two different doses have were studied in the trial)
- genetic defects responding best
- optimal treatment duration
- how to best quantify, or measure, patient improvement. Tremendous patient heterogeneity, or variability, renders this quantification challenging as presentations vary vastly from patient to patient. Improvement in day to life will need to be proven to the regulatory committee in a measurable format.

Currently, EPI-743 trials include patients with a genetic diagnosis of mitochondrial disease, but the hope is to expand use of EPI-743 to eventually treat all with a genetic and/or clinical diagnosis of many of the mitochondrial diseases, including LHON. No compassionate use of EPI-743 exists at this time. Rigorous study of new drugs in this step-wise fashion has the benefit of studying drug safety and drug efficacy before release to a wider population. Learning exactly who is good responder to EPI-743 and how that response compares to the specific genetic profile is one example of data that needs to be analyzed before drug release.

EPI-743’s molecular action for Mitochondrial Disease:

- Redox (how nature moves electrons) co-factor of cellular targets:

1. enhancement in glutathione pool of cell (critical antioxidant pool of the cell)
2. diminution of a key signaling molecules within the cell involved in electron transport and cellular respiration
3. altering intracellular redox ratios at pivotal enzymatic sites
4. alteration of antioxidant response factors - combat defects in electron handling

- Remit (goal) is to devise an entire set of pharmacological tools to treat mitochondrial disease via redox chemistry.

Next Steps!

1. Analyze data from current clinical trials to gain a clear understanding of natural history of disease, gain understanding of who responds, and what that response may look like in terms of being clinically meaningful. EPI -743 is currently in this step.
2. Determination as to whether any response patterns are consistent with a safe treatment effect.
3. Working with regulators, if required, to design subsequent clinical trials that are necessary for the approval process. Accelerated approval process is possible.

Predicting a timeline of when EPI-743 could be widely available is nearly impossible. Mitochondrial patients need to exercise patience in the EPI-743 drug approval process. Patients should “stay visible” so that when new trials come down the road, patients can be contacted and enrolled. www.edisonpharma.com