1. SUMMARY OF EPI-743

1.1. EPI-743

EPI-743 is a member of the chemical class called benzoquinones. It is administered orally either in a hard-shell capsule or as a liquid (oil) mixed with an excipient. EPI-743 has a molecular weight of 440.66, and is manufactured through a semi-synthetic approach. Its biological activity is predicated on its redox properties. Results summarizing the pre-clinical and non-clinical properties of EPI-743 have been published.

As of September 15, 2012 EPI-743 has been dosed in ~130 subjects for an estimated 48,000 cumulative dosing days. No serious adverse events (SAEs) have been recorded that were definitively attributed to drug treatment, with one SAE possibly associated with drug treatment.

1.2. Stage of development

EPI-743 is in phase 2 clinical development for inherited respiratory chain diseases of the mitochondria. Four phase 2 clinical trials are ongoing or are in progress:

- Extension phase of single arm Leigh syndrome (Italy);
- Double-blind placebo-controlled Leigh syndrome (United States);
- Double-blind placebo-controlled Friedreich's ataxia (United States); and
- Double-blind placebo-controlled undiagnosed disorders of oxidation- reduction (United States).

Two compassionate use programs were set up by Edison that include:

- Expanded access for subjects with inherited mitochondrial disease within 90 days of end-of-life care; and
- Emergency use for subjects with actively converting with Leber's hereditary optic neuropathy.

Both compassionate use programs will be closed effective October 15, 2012 and have, per FDA guidance, been supplanted by prospective controlled clinical trials.

Patients in the US who do not meet eligibility criteria can gain access to EPI-743 through a physician-sponsored IND mechanism. Edison is in the process of setting up a named patient program in the EU for those patients who, likewise, do not meet clinical trial enrollment criteria.

1.3. Clinical indications

1.3.1. Leigh syndrome

Leigh syndrome is a fatal early-onset progressive neurodegenerative disorder exhibiting considerably variable clinical signs, symptoms, onset time, and disease course. Dr. Denis Leigh first described Leigh syndrome in 1951 as subacute necrotizing encephalomyopathy. The disease occurs in ~1:30,000 live births in the United States and Europe. Characteristic neuropathologic features of Leigh syndrome consist of spongiform necrosis, myelin degeneration, vascular proliferation, and gliosis in one or more areas of the central nervous system, including thalamus, basal ganglia, brainstem, and spinal cord. The clinical features include psychomotor retardation, lactic acidemia, abnormal respiration, nystagmus, ophthalmoparesis, ataxia, dystonia, and optic atrophy. The typical disease progression of Leigh syndrome results in patient death by respiratory failure by age five. Leigh syndrome is an inherited mitochondrial disease that can be maternally inherited due to mutations in the mitochondrial DNA (mtDNA) genes, sex-linked due to pyruvate dehydrogenase deficiency, or autosomal recessive due to mutations in nuclear encoded respiratory chain complex subunits or complex assembly genes.

1.3.2. Friedreich's ataxia

Friedreich's ataxia is an autosomal recessive, neurodegenerative disease that primarily affects the nervous system and heart. Nicolaus Friedreich first described the disease in the nineteenth century. The prevalence of Friedreich's ataxia is highest in Western Europe, with more than one case per 30,000 individuals. In the United States the prevalence is about one case per 50,000 individuals. Friedreich's ataxia is a severely debilitating disease that causes severe morbidity and mortality in affected patients. The condition is characterized by progressive gait and limb ataxia, dysarthria, lower-limb areflexia, muscular weakness in the legs, and vision loss as well as non-neurological signs including hypertrophic cardiomyopathy and diabetes mellitus. Nearly all patients become paraplegic and eventually require wheelchairs. Typical disease onset occurs during puberty; however both early-onset and late-onset variants exist and median age of death is 35 years. More than 95 percent of patients are homozygous for a large expansion (60–2,000) of a guanine-adenine-adenine (GAA) trinucleotide-repeat sequence located within the first intron of the gene for frataxin on chromosome 9q13. The mutation causes a defect in transcription of the frataxin protein, a 210-aminio acid protein found in the mitochondria.

1.3.3. Undiagnosed disorders of oxidation-reduction

Individuals with extremely rare or undiagnosed diseases often find it difficult to receive appropriate diagnoses and treatments. A subset of patients with undiagnosed diseases has clinical findings that suggest defective energy utilization or an abnormal reduction/ oxidation (redox) state within cells. These abnormalities are generally attributable to mitochondrial disorders, but they could also involve cytoplasmic defects. The diseases themselves are sometimes fatal in the first decade of life. Patients often present with significant neurological and/or muscular findings that can include growth failure, short stature, psychomotor retardation, abnormal respiration, nystagmus, ophthalmoparesis, ataxia, dystonia, optic atrophy, retinitis pigmentosa, hypotonia, myopathy, seizures, or Parkinsonism. Laboratory findings can include elevated lactate and pyruvate levels in plasma and/or cerebrospinal fluid, abnormal mitochondrial morphology on muscle, nerve, or liver biopsy, and the presence of mutations on sequencing of mitochondrial genes or nuclear genes encoding mitochondrial proteins. In addition, muscle biopsy can reveal abnormal electron transport chain enzymology, changes in mtDNA copy number, or muscle-specific coenzyme Q deficiency. To address the problem of diagnosing extremely rare and enigmatic diseases, the National Institutes of Health Undiagnosed Diseases Program (UDP) was established in 2008. The NIH UDP has received over 6,200 inquiries, reviewed over 2,200 medical records, and admitted about 500 patients to the NIH Clinical Center. Approximately 25 percent of patients have achieved diagnoses, some of which are amenable to conventional treatments. Most UDP patients, however, never reach a diagnosis or therapy, and many of them exhibit clinical findings suggesting a defect in energy balance or in oxidation/reduction status.

1.3.4. Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy is a mitochondrial disease affecting principally the retinal ganglion cells and results in persistent bilateral blindness. LHON is the most common mitochondrial optic neuropathy with a prevalence of one in 50,000. The peak age of onset in LHON is between the ages of 15–30 years and 95 percent of carriers who will experience visual failure will do so before the age of 50 years. Typically LHON presents with sudden unilateral, followed by bilateral, blindness. With the exception of rare cases of spontaneous partial and late recovery, the resulting visual impairment is permanent. LHON results from one of three pathogenic mitochondrial DNA mutations occurring at positions 11778/ND4, 3450/ND1 or 14486/ND6 of the NADH dehydrogenase gene leading to dysfunction of complex 1 of the mitochondrial respiratory chain.

2. EPI-743 PUBLICATIONS

Shrader, W.D., et al., α-Tocotrienol quinone modulates oxidative stress response and the biochemistry of aging. Bioorg. Med. Chem. Lett., 2011. 21,p. 3693-3698.

Enns, G.M., et al., Initial experience in the treatment of inherited mitochondrial disease with EPI-743. Molecular Genetics and Metabolism, 2012. 105: p. 91-102.

Sadun, A.A., et al., Effect of EPI-743 on the Clinical Course of the Mitochondrial Disease Leber Hereditary Optic Neuropathy. Arch Neurol, 2012. 69(3): p. 331-338.

Martinelli, D. et al., EPI-743 reverses the progression of the pediatric mitochondrial disease defined Leigh Syndrome. Accepted for publication to Mol. Genet. Metabol. (2012).

Blankenberg, F. et al. Brain uptake of Tc99m-HMPAO correlates with clinical response to the novel redox modulating agent EPI-743 in patients with mitochondrial disease. Accepted for publication to Mol. Genet. Metabol. (2012).