

Preliminary Report on Initial Subjects Diagnosed With Genetically Confirmed Mitochondrial Disease at End-Of-Life Treated With EPI-743 Under FDA-Approved Expanded Access Protocol EPI-2009-1

The United States EPI-743 Investigator Team¹ & Edison Pharmaceuticals²

¹ Gregory M. Enns, MB, ChB*; Francis G. Blankenberg, MD; Salvatore DiMauro, MD; Michio Hirano, MD; Stephen L. Kinsman, MD; Susan L. Perlman, MD; David Lynch, MD, PhD; Bruce H. Cohen, MD, FAAN; Russell P. Saneto, DO, PhD; Elwood W. Hopkins, MD; Jose E. Abdenur, MD

² Guy Miller, MD, PhD*; Martin Thoolen, PhD; William D. Shrader, PhD

Introduction

On January 11, 2010, the United States Food & Drug Administration authorized Edison Pharmaceuticals and its United States Investigator Team to provide treatment with the experimental therapeutic EPI-743 to patients that met two criteria: 1. Genetic confirmation of inherited mitochondrial disease; and 2. Acute illness at risk of death. At request of FDA, posting of this expanded access trial on clinicaltrials.gov was embargoed.

On June 22, 2010, the first patient was enrolled at Lucile Packard Children's Hospital, Stanford University Medical Center into the expanded access protocol entitled Emergency Use Protocol for EPI-743 in Acutely Ill Patients with Inherited Mitochondrial Respiratory Chain Disease Within 90 Days of End-of-Life Care (EPI-2009-1) under FDA IND #107,401.

FDA Expanded Access Program

The Expanded Access Program was established by FDA in 1987 and amended in 2009³ to provide physicians and patients access to experimental drugs in instances of medical need absent approved therapies. The intention of expanded access is to provide treatment to patients in need, not to serve as a substitute for controlled clinical trials.

³<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm>

EPI-743 United States Investigator Team

The Principal Investigator of Protocol EPI-2009-1 is Gregory M. Enns, MB, ChB, Lucile Packard Children's Hospital, Stanford University Medical Center. Other Co-Investigators on the protocol in the United States currently include:

Francis G. Blankenberg, MD	Associate Professor of Radiology & Pediatrics	Lucile Packard Children's Hospital, Stanford University Medical Center
Salvatore DiMauro, MD	Lucy G. Moses Professor of Neurology	Columbia University College of Physicians
Michio Hirano, MD	Professor of Neurology	Columbia University Medical Center
Stephen L. Kinsman, MD	Associate Professor of Neurosciences, Division of Pediatric Neurology	Medical University of South Carolina
Susan L. Perlman, MD	Clinical Professor of Neurology; Director, Ataxia Center and HD Center of Excellence	University of California, Los Angeles
David Lynch, MD, PhD	Professor	Children's Hospital of Philadelphia
Bruce H. Cohen, MD, FAAN	Director of Pediatric Neurology and Professor of Pediatrics	Akron Children's Hospital
Russell P. Saneto, DO, PhD	Associate Professor Neurology and Pediatrics	Seattle Children's Hospital, University of Washington
Elwood W. Hopkins, MD	Capt., US Navy	US Naval Hospital, Bremerton
Jose E. Abdenur, MD	Chief, Division of Metabolic Disorders	Children's Hospital of Orange County

EPI-743

EPI-743 is an orally absorbed small molecule that readily crosses into the central nervous system. It works by targeting the enzyme NADPH quinone oxidoreductase 1 (NQO1). Its mode of action is to synchronize energy generation in mitochondria with the countering of redox stress. A recent article detailing EPI-743's chemical, biological, and pharmacological properties has been published⁴.

Protocol Parameters

While the intention of the Expanded Access Program is treatment, this intention does not preclude the gathering of human subject data. FDA, Edison Pharmaceuticals, and the United States EPI-743 Investigator Team agreed upon a protocol (EPI-2009-1) where clinical, biochemical, non-invasive imaging, and quality-of-life outcome metrics are assessed.

Clinical Safety

As of June 1, 2011, EPI-743 has been dosed in 40 subjects worldwide for 7,436 cumulative patient dosing days. No significant drug-related adverse events have been recorded. One patient death occurred under IND #107,401 which was attributed to the natural history of disease and not deemed drug-related.

Pharmacology

EPI-743 has been extemporaneously formulated and administered orally or via gastrostomy tube at a maximal dose of 100 mg, three times per day. In each subject, EPI-743 blood concentrations were measured at predetermined time intervals. EPI-743 has an estimated C_{max} of 300 ng/mL. In one subject, prior to establishment of the expanded access protocol, cerebral spinal fluid levels of EPI-743 were determined at steady state at one time point. A value of 1.3 ng/mL was recorded.

⁴ *α-Tocotrienol quinone modulates oxidative stress response and the biochemistry of aging* **2011** *Bioorganic & Medicinal Chemistry Letters* 21(12) pp 3693-3698. William D. Shrader, Akiko Amagata, Adam Barnes, Gregory M. Enns, Andrew Hinman, Orion Jankowski, Viktoria Kheifets, Ryo Komatsuzaki, Edgar Lee, Paul Mollard, Katsuyuki Murase, Alfredo A. Sadun, Martin Thoolen, Kieron Wesson, Guy Miller.

Clinical Results

Analysis of clinical response was undertaken on seven subjects with the following diagnoses that are confirmed by known pathogenic changes in the gene: Leigh syndrome caused by SURF1 mutations; Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke caused by the A3243G mutation; Kearns–Sayre syndrome caused by the common large-scale deletion in the mtDNA; Friedreich’s ataxia due to mutations in frataxin; and Alpers disease due to mutations in the polymerase gamma-1 gene. Treatment response was measured through serial neurological examinations, quality-of-life assessments, and brain redox imaging using technetium-99m-hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomographic (SPECT) radionuclide imaging. All subjects treated more than 30 days have survived and all have exhibited improvement in certain specific functions. Disease progression has not been readily noted with one subject exhibiting partial relapse. Six of the seven subjects showed an improvement in quality-of-life scores. In six of the seven subjects, treatment response correlated with increased regional and whole brain HMPAO uptake.

Notes

Initial Clinical Data: While encouraging, we caution drawing any definitive conclusions on data obtained under this expanded access protocol. Data obtained under the expanded access protocol will be verified in prospective controlled studies.

Prospective Trials: Data obtained under this expanded access protocol is being further analyzed to guide future clinical trials. The EPI-743 Investigator Team and Edison Pharmaceuticals are working closely with FDA and EMA on the design of prospective controlled studies to further investigate the clinical properties of EPI-743.

Amended Enrollment Criteria for EPI-2009-1 Protocol: On May 23, 2011, FDA amended enrollment criteria to include mitochondrial patients at end-of-life absent a genetically confirmed diagnosis. In addition, FDA released its embargo on posting the expanded access trial on clinicaltrials.gov. Clinical eligibility can be found at clinicaltrials.gov or through the principal investigator of protocol EPI-2009-1, Dr. Enns at greg.enns@stanford.edu.

Additional data on EPI-743 obtained under IND #107,772 in Leber’s hereditary optic neuropathy: As of June 2, 2011, nine subjects diagnosed with Leber’s hereditary optic neuropathy have been treated with EPI-743 in the United States and Europe. An abstract reporting on the first four subjects treated with EPI-743 in Leber’s hereditary optic neuropathy entitled *EPI-743 alters the natural history of progression of Leber’s hereditary optic neuropathy* was presented at The American Ophthalmological Society meeting on May 22, 2011⁵. The principal investigator of this study is Alfredo A. Sadun, MD, PhD.

⁵ http://www.aosonline.org/annualmeeting/am_program.pdf, page 11