# MIT-E Trial: PTC743 Mitochondrial Epilepsy Trial

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# EPI-743 is now….PTC743

- BioElectron's assets were acquired by PTC Therapeutics in October 2019
- The BioE team and drug candidates—including EPI-743—are now part of the PTC family
- PTC is a rare disease-focused, global commercial biotechnology company
- PTC brings added muscle and experience to the development of EPI-743 and other compounds for patients with mitochondrial disease

# Multiplatform, Diversified Pipeline Built Through Internal Innovation & Strategic Business Development

## SCIENTIFIC PLATFORMS & RESEARCH

| | Deflazacort | LatAm Commercial | Nonsense Mutation | Splicing | Gene Therapy | Bio-e | Metabolic | Oncology |
|---|---|---|---|---|---|---|---|---|
| Commercial | Emflaza® | Tegsedi™ (inotersen) injection 284 mg/1.5 mL<br>waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL | translarna™ ataluren | | | | | |
| Clinical | | | US Dystrophin | SMA | AADC | PTC743 Mito Epilepsy<br>PTC743 FA | PTC923 PKU | PTC596 DIPG<br>PTC596 LMS<br>PTC299 AML |
| Research | | | | PTC518 HD<br>Undisclosed | FA<br>Angelman<br>IRDs | PTC857 GBA-PD<br>Undisclosed | | |
| | Potential registrational studies | | | | | | | |

# MIT-E Trial: PTC743 Mitochondrial Epilepsy Trial


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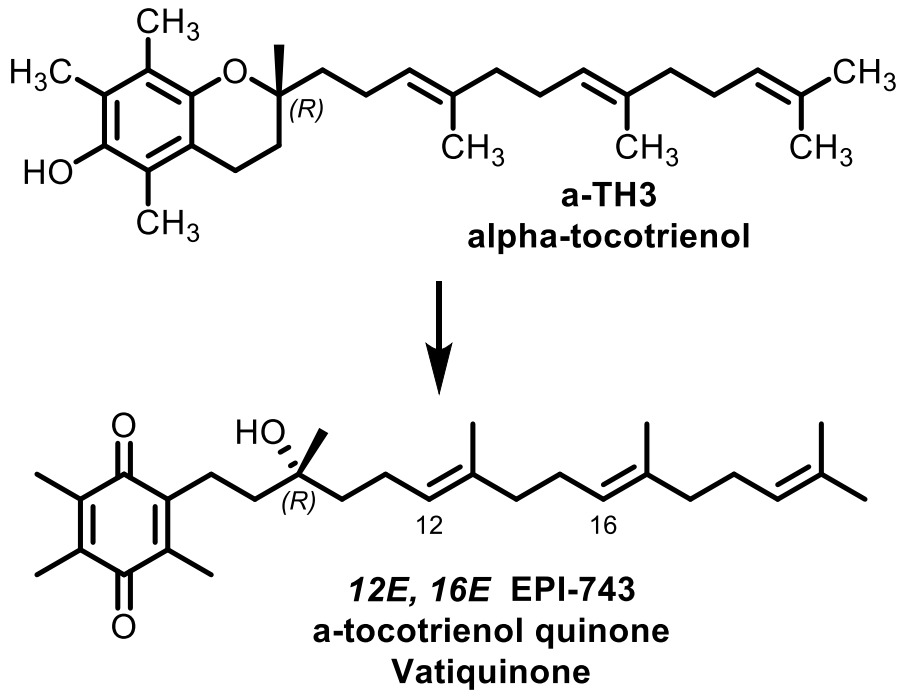
# PTC-743

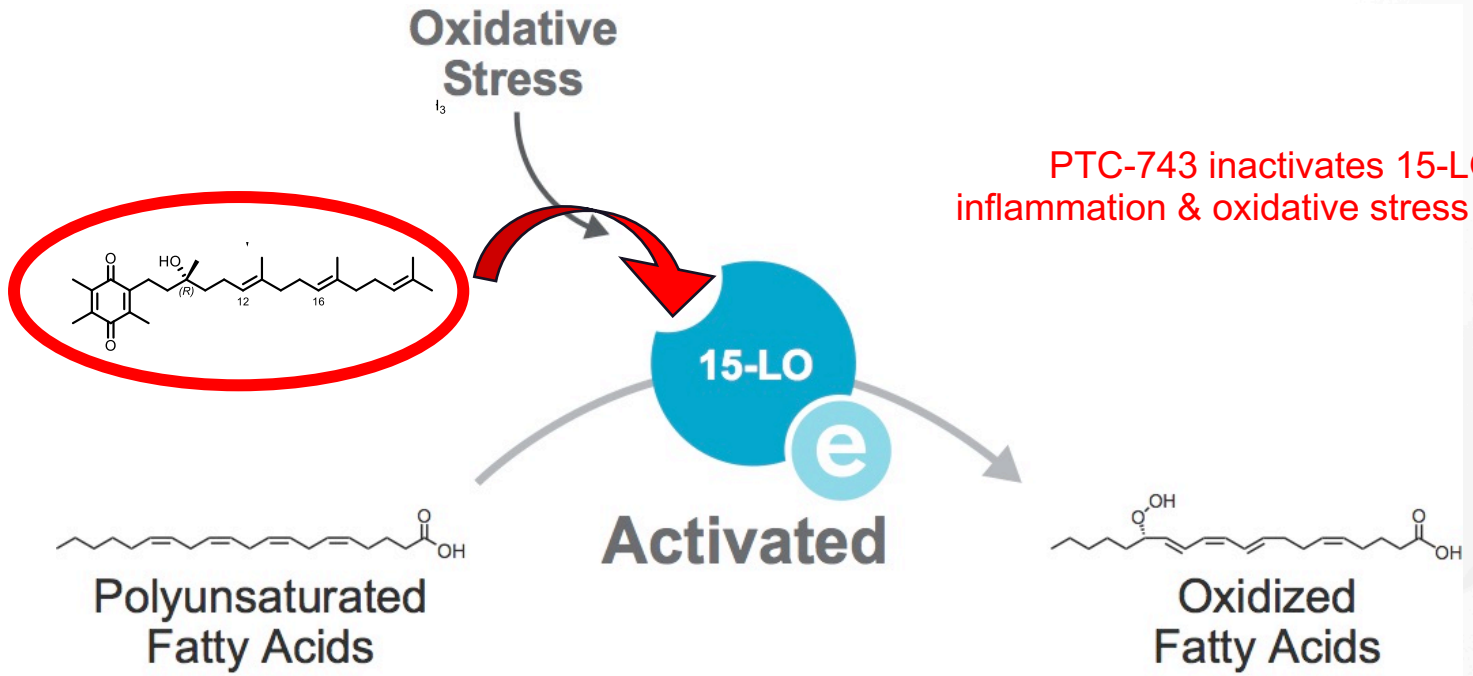



PTC-743 (INN: vatiquinone – previously known as EPI-743) is the oxidation product of alpha tocotrienol, one of the E vitamers

# PTC-743 Target and Mechanism-of-Action

PTC-743 targets the enzyme 15-lipoxygenase, a key regulator of oxidative stress and inflammation in all tissues

Oxidative stress activates 15-LO resulting in increased inflammation & oxidative stress and decreased cellular viability




PTC-743 inactivates 15-LO resulting in decreased inflammation & oxidative stress and improved cellular viability

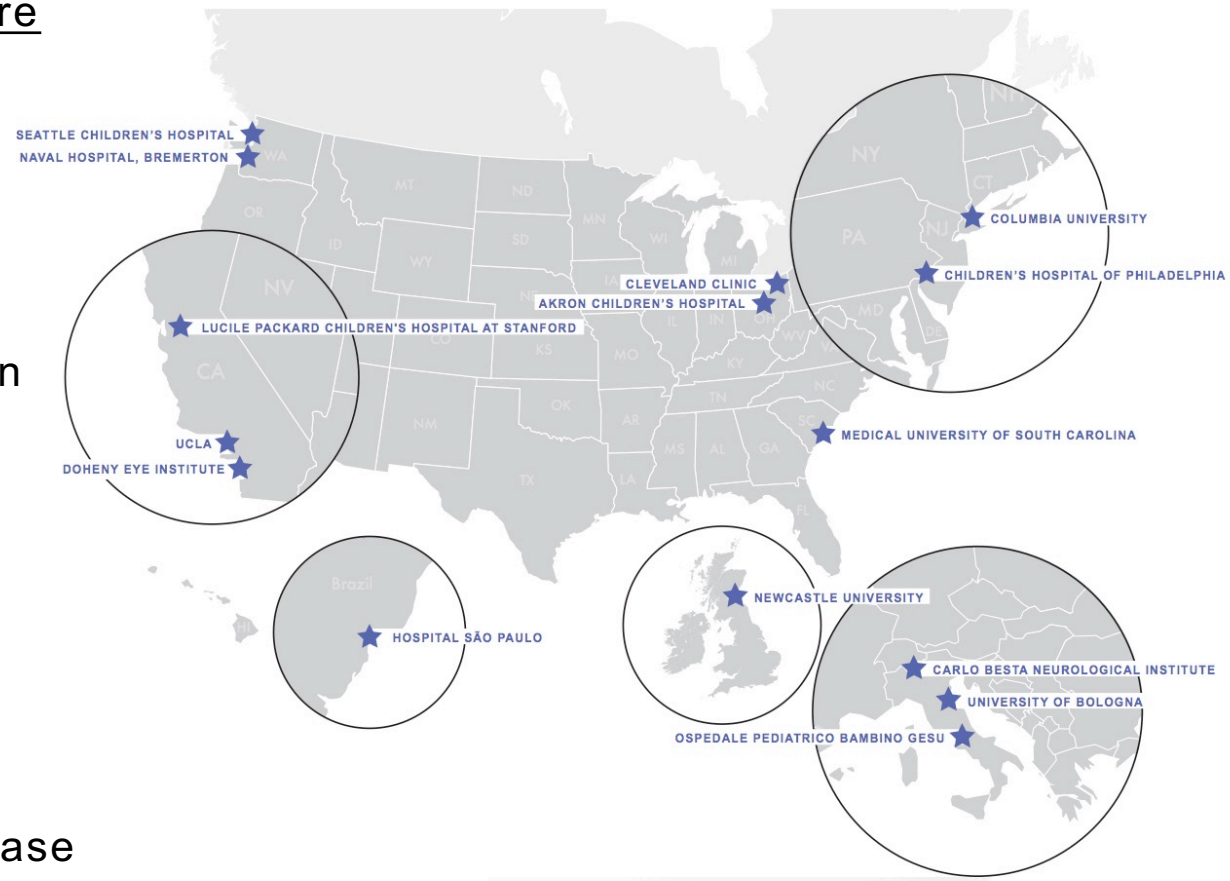
# Initial PTC-743 Clinical Study: Expanded Access Program

**Study Overview**

- Between 2009 and 2012, enrolled patients with inherited mitochondrial disease within 90 days of end-of-life care
- Initial treatment of 13 weeks with long-term extension phase
- Measured mortality, drug safety & pharmacokinetics

**Study Results**

- 94 patients enrolled; 42 patients currently alive and on treatment
- Mean survival of over 4 years
- PTC-743 was safe and well-tolerated
- Clinical efficacy findings including reduced seizures, improved neurological and neuromuscular function, decreased transfusion requirements, improved liver function
- Improved CNS biomarker signals across multiple disease subtypes



# PTC-743 Refractory Mitochondrial Epilepsy: Treatment Data

- Expanded Access Case Examples
  - Alpers/POLG1: Decreased seizure frequency and improved myoclonus, decreased disease-related hospitalizations from 201 days over previous 18 months, to 20 during first six months on EPI-743
  - Alpers/POLG1: Resolution of refractory status, discharged home with better seizure control
  - Complex III mitochondrial mutation: resolution of refractory status epilepticus, fewer illnesses, faster recovery, no clinical seizures in 6 months
  - Alpers: Decrease seizures, easier to control breakthrough seizures, weight gain, improved neuromuscular function
  - MELAS: resolution of seizures, restored ability to ambulate independently
  - MELAS: decreased seizure frequency, increased strength, speech fluency
  - mtDNA mutation: decreased seizures, slight motor skills improvement

# EPI-743 Mitochondrial Epilepsy: Leigh syndrome

| Study | Mutation | Age | Seizure Frequency * | |
|---|---|---|---|---|
| | | | Baseline | EPI-743 |
| Italy Phase 2 | ND1 (Complex 1) | 9 years | **Mild** | **None** |
| Italy Phase 2 | ETHE1 | 1 years | **Moderate** | **Mild** |
| US Phase 2 | ND3 (Complex 1) | 7 years | **Moderate** | **None** |
| US Phase 2 | ND6 (Complex 1) | 1.5 years | **Moderate** | **Mild** |
| US Phase 2 | ND6 (Complex 1) | 9 years | **Moderate** | **Mild** |
| US Phase 2 | None | 8 years | **Moderate** | **None** |
| US Phase 2 | mtATPase (Complex 5) | 1 year | **Moderate** | **None** |

*based on Newcastle survey seizure frequency item

# PTC743-MIT-001-EP

# PTC-743: Refractory Mitochondrial Epilepsy

**Description:** Over 40% of all patients with mitochondrial disease have associated epilepsy which is refractory to traditional anti-epileptic medications

**Rationale (Scientific):** PTC743 target pathway has been linked to refractory epilepsy syndromes in both *in vitro* and *in vivo* models

**Rationale (Clinical):** In our clinical studies, PTC743 has disrupted refractory status epilepticus, decreased seizure frequency, and decreased seizure-related morbidity in patients with mitochondrial disease and associated refractory epilepsy

# Study Endpoints

## Primary Efficacy Endpoint

- The primary efficacy endpoint of the study is the percent change from baseline in frequency of observable motor seizures per 28 days during the placebo-controlled phase

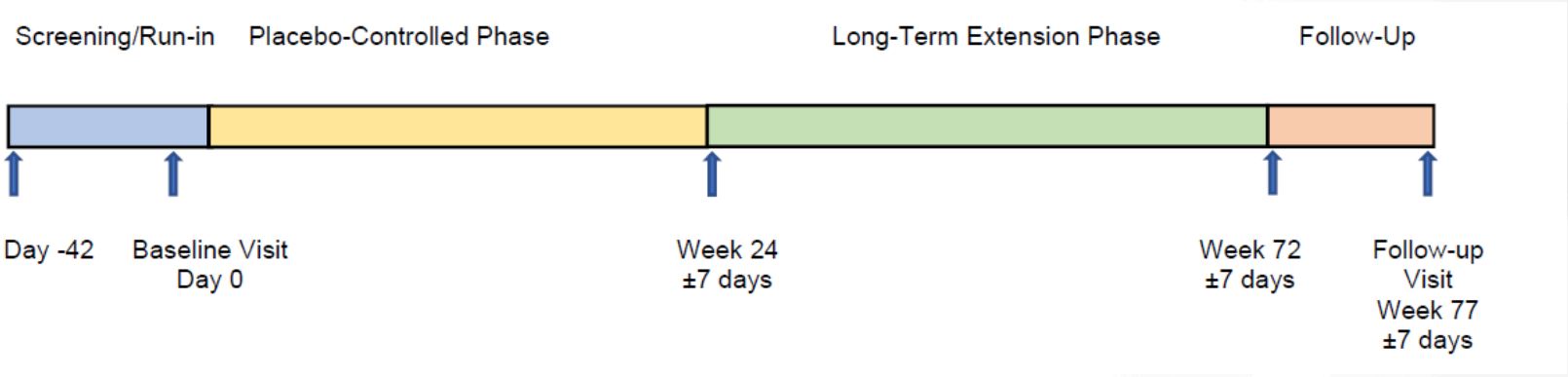
## Key Secondary Efficacy Endpoints

- Number of disease-related hospital days
- Occurrence or recurrence of status epilepticus

## Evaluation of Safety

# Study Design

- This study will be a parallel-arm, double-blind, placebo-controlled trial, with a screening phase that includes a 28-day Run-in phase to establish baseline seizure frequency.
- The 28 days immediately prior to the Baseline Visit will be considered the Run-in phase.
- Screening is followed by a 24-week randomized placebo-controlled phase during which subjects will have been randomized to receive either vatiquinone at a dose of 15 mg/kg, up to a maximum dose of 200 mg 3 times daily (TID) or placebo TID.
- Following completion of the randomized placebo-controlled phase, all subjects will be offered entry into a long-term extension phase (48 weeks) during which they will receive open-label treatment with vatiquinone and then a safety follow-up as needed.



# Inclusion Criteria

- Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial.
- Age <18 years at time of randomization
- Subject or parent/legal guardian is able and willing to complete seizure diaries for the duration of the study
- Genetic confirmation of inherited mitochondrial disease with associated epilepsy phenotype (Alpers/POLG, Leigh syndrome, MELAS, or other genetically confirmed mitochondrial disease secondary to mitochondrial mutation)
- Despite ongoing treatment with at least 2 AEDs:
  - have ≥6 observed motor seizures occurring during the 28 days prior to the Baseline Visit
  - have ≥2 observed motor seizures in the first 14 days and ≥2 in the second 14 days of the Run-in period
  - Do not have a consecutive 20-day seizure free period, and
  - have at least 80% of seizure diary data
- Documented medical history of epilepsy associated with mitochondrial disease for at least 6 months prior to screening
- Consent to abstain from non-approved therapies for 30 days prior to the Baseline Visit and for the duration of the study

# Inclusion Criteria (Cont...)

- Stable dose regimen of antiepileptic therapies 60 days prior to the Baseline Visit
- Stable regimen of dietary supplements 30 days prior and, if on a ketogenic diet, stable ketogenic diet 90 days prior to the Baseline Visit and for duration of the study
- Electroencephalogram (EEG) at screening or historical EEG for diagnostic confirmation of seizures

# Seizure Diaries

- During the first part of Screening subjects will be instructed on how to complete the seizure diaries. To ensure the accuracy of diary entries during the study, subjects must complete at least 5 days of diary entries that will be reviewed prior to the Run-in period. Following diary review, at the discretion of the investigator a further diary entry training period can be implemented. Diary entries during this period are for training purposes and will not be included in the seizure count.

- Subjects will be eligible to participate in the study if they:
  - have ≥6 observed motor seizures occurring during the 28 days prior to the Baseline Visit
  - have ≥2 observed motor seizures in each half of the 28-day Run-in period
  - do not have a consecutive 20-day seizure free period, and
  - have at least 80% of seizure diary data

# Randomization

- Randomization will be 1:1 vatiquinone to placebo and will be stratified by disease subtype including: 1) Alpers/POLG (DNA polymerase subunit gamma); 2) Leigh syndrome; 3) MELAS, and 4) Other genetically confirmed mitochondrial disease secondary to genetic mutation.

- A minimum of 6 subjects will be allocated to category 1), 2), and 3), respectively

# Study duration and number of sites

## Study Duration

- The maximum duration of subject treatment will be approximately 72 weeks (including placebo-controlled phase and extension phase) from baseline visit. The overall study duration will be a maximum of approximately 83 weeks per subject from screening visit.

## Number of sites

- Approximately 12 sites globally.
- Approximately 60 subjects will be enrolled.
- Additional sites and investigators may be added as needed to complete the study.