Soticlestat vs Placebo as Adjunctive Therapy for Lennox-gastaut Syndrome: Results from the Phase 3, Randomized SKYWAY Clinical Trial

Abstract number : 1.489
Submission category : 7. Anti-seizure Medications / 7B. Clinical Trials
Year : 2024
Submission ID : 1423
Source : www.aesnet.org
Presentation date : 12/7/2024 12:00:00 AM
Published date :

Authors :
Presenting Author: Stéphane Auvin, MD, PhD, FAES – Paris-Cité University & Robert-Debré University Hospital, Paris, France

Author: Renzo Guerrini, MD, FRCP, FAES – Meyer Children's Hospital IRCCS, and University of Florence

Cecil Hahn, MD – The Hospital for Sick Children, Toronto, Ontario, Canada
Jimmy Schiemann, MD – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Yasir Khan, MD, MPH, BCMAS – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Pranab Mitra, PhD – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Samuel Hsiao, PhD – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Sarah I. Sheikh, BM BCh – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Philipp von Rosenstiel, MD – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Mahnaz Asgharnejad, PharmD – Takeda Development Center Americas, Inc., Cambridge, MA, USA
Dennis Dlugos, MD – The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA, USA
Venkatesha Murthy, MD – Takeda Development Center Americas, Inc., Cambridge, MA, USA

Rationale: Soticlestat (TAK-935) is a first-in-class potent, selective inhibitor of cholesterol 24-hydroxylase, a brain-specific enzyme that catabolizes cholesterol to 24*S*-hydroxycholesterol resulting in reduced glutamatergic hyperexcitability. The phase 2 ELEKTRA study showed numerically favorable effects in the LGS population with a favorable safety and tolerability profile. SKYWAY investigated the efficacy, safety, and tolerability of soticlestat as adjunctive therapy in children and adults with LGS.

Methods: SKYWAY (NCT04938427) was a phase 3, randomized, double-blind, placebo-controlled trial. The primary endpoint was percent change from baseline in major motor drop (MMD) seizure frequency per 28 days during the full treatment period. Key secondary endpoints were the proportion of participants with ≥ 50% reduction in MMD seizures from baseline; Caregiver Global Impression of Improvement; Clinical Global Impression of Improvement (CGI-I); CGI-I Non-seizure Symptoms; Quality of Life Inventory-Disability; and CGI-I Seizure Intensity and Duration. Participants aged 2–55 years were enrolled and randomized 1:1 to either soticlestat or matching placebo. The diagnosis of LGS was

independently adjudicated by the Epilepsy Study Consortium. On study completion, participants could enroll in an ongoing open-label extension study, ENDYMION 2 (NCT05163314).

Results: SKYWAY enrolled 270 participants (134 soticlestat; 136 placebo) with a mean (SD) age of 12.9 (8.1) years; 163 (60.4%) were male and 190 participants (70.4%) were on 3 antiseizure medications. The median (range) MMD seizure frequency per 28 days at baseline was 53.33 (6.3 to 2128.8) and 66.18 (11.5 to 2794.6) for soticlestat and placebo, respectively. Median change from baseline in MMD seizure frequency per 28 days over the full treatment period was −6.11% with soticlestat (n=134) and −6.69% with placebo (n=136), a difference of −1.17% (p=0.785). No meaningful difference was observed between soticlestat and placebo for most of the key secondary endpoints. The proportion of participants showing any improvement on CGI-I Seizure Intensity and Duration was higher with soticlestat (49.2% [n=122]) than placebo (35.1% [n=131]; odds ratio 1.67; nominal p value=0.029). The most commonly reported treatment-emergent adverse events considered related to the study drug were somnolence (13.4% vs 5.9%) and change in seizure presentation (11.2% vs 4.4%) in the soticlestat and placebo groups, respectively.

Conclusions: In the SKYWAY study of individuals with LGS, soticlestat did not demonstrate efficacy vs placebo on the primary or multiple secondary endpoints. Soticlestat was well tolerated with a safety profile that was consistent with previous studies.

Funding: Takeda Development Center Americas, Inc.

Anti-seizure Medications