ENDYMION 2: Phase 3, Open-label Extension Study Assessing Long-term Safety, Tolerability and Secondary Outcomes of Adjunctive Soticlestat in Individuals with Dravet Syndrome or Lennox-gastaut Syndrome

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Rationale:

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare, treatment-resistant developmental and epileptic encephalopathies. Soticlestat (TAK-935) has a novel mechanism of action and was investigated for the treatment of seizures in DS and LGS. ENDYMION 2 (NCT05163314) is an ongoing, open-label extension study aiming to assess the long-term safety and tolerability of soticlestat in individuals who participated in the phase 3 trials SKYLINE (DS; NCT04940624) and SKYWAY (LGS; NCT04938427).

Methods:

Individuals were enrolled in ENDYMION 2 on completion of SKYLINE or SKYWAY and are receiving their standard antiseizure therapy plus soticlestat ≤ 300 mg twice daily (weight-based in < 45 kg participants). Primary endpoints focus on long-term safety, including the incidence of treatment-emergent adverse events (TEAEs). Percentage change from baseline in seizure frequency per 28 days and effects on health outcomes (Caregiver and Clinical Global Impression of Improvement [GI-I]) are secondary endpoints. Data are collected at scheduled visits every ~12 weeks for the first 2 years and every 6 months thereafter.

Results:

ENDYMION 2 began in March 2022 and is ongoing in 17 countries. At the interim analysis (data cut: April 12, 2024), 121 participants with DS and 231 with LGS had enrolled, of which 93 (76.9%, DS) and 136 (58.9%, LGS) were ongoing. Mean (SD) ages at baseline (core study) were 10.0 (4.96) and 13.0 (8.16) years, respectively; 64 (52.9%, DS) and 137 (59.3%, LGS) were male. 91 (75.2%) participants with DS and 185 (80.1%) with LGS reported any TEAE; most were mild (DS: 36 [29.8%]; LGS: 66 [28.6%]) or moderate (41 [33.9%]; 89 [38.5%]). Frequent TEAEs are reported in Table 1. Drug-related TEAEs occurred in 44 (36.4%) and 77 (33.3%) participants with DS or LGS, respectively, and serious TEAEs leading to study drug discontinuation in 2 (1.7%) and 5 (2.2%). There was a decrease in the median percent change from baseline in seizure frequency (Figure 1). Percentages with improvements (very much, much, or minimally improved) in Caregiver GI-I measures at 26, 52, and 78 weeks were 74.1% (n=58), 72.4% (n=29), and 92.9% (n=14) for DS and 58.4% (n=161), 77.7% (n=94), and 63.4% (n=41) for LGS. Improvements in Clinical GI-I at 26, 52, and 78 weeks were 72.4% (n=58), 65.5% (n=29), and 92.9% (n=14) for DS, and 60.0% (n=160), 73.4% (n=94), and 68.3% (n=41) for LGS.

Conclusions:

In the ENDYMION 2 study, soticlestat was well tolerated with a safety profile consistent with previous studies in DS and LGS. A sustained reduction in convulsive seizure frequency and improvements in Caregiver and Clinical GI-I measures were reported for participants with DS who remained in the study, though we acknowledge the absence of a control group, and potential for adjustments to background antiseizure therapies and selection bias. LGS data must be considered with caution as the double-blind, placebo-controlled SKYWAY study did not demonstrate efficacy in this population.

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Anti-seizure Medications