Design of Two Parallel, Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies to Evaluate the Safety and Efficacy of XEN1101 as Adjunctive Therapy in Patients with Partial-Onset Seizures

Emilio Perucca,¹ Jacqueline French,² Elinor Ben-Menachem,¹ David Goss,³ W. Curt LaFrance, Jr.⁴ Philippe Ryvlin,⁵ Mona Saggar,⁶ Manuel Toledo,⁷ Torbjörn Tomson,⁸ Eugen Trinka,⁹ Vicente Villanueva,¹⁰ Robert Wechsler,¹¹ Cynthia Harden,¹¹ Jenny Qian,¹¹ Constanza Luzon Rosenblut,¹¹ Christopher Kenney,¹¹ Gregory N. Beatch¹¹

¹Department of Neurology, University of Toronto and Hospital for Sick Children, Toronto, Canada; ²Epilepsy Center, University of California, Los Angeles, Los Angeles, CA, USA; ³Texas A&M University College of Medicine and M Matches IRIS, Longview, Texas; ⁴New England Epilepsy Research Institute of Connecticut, Newington, CT, USA; ⁵Department of Neurology, University of Gothenburg, Gothenburg, Sweden; ⁶Department of Neurology, Karolinska Institutet, Stockholm, Sweden; ⁷Department of Neurology, Karolinska University Hospital, Stockholm, Sweden; ⁸Department of Neurology, University of Göteborg, Göteborg, Sweden; ⁹Department of Neurology, University of Gothenburg, Gothenburg, Sweden; ¹⁰Hospital Universitari Vall d’Hebron, Barcelona, Spain; ¹¹Janssen Pharmaceuticals Inc., Parsippany, NJ, USA

INTRODUCTION

- XEN1101 is a novel, potent, selective KCNA2/3 (6.7/7.3) potassium channel opener being developed for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures, and major depressive disorder.
- The pharmacokinetic properties of XEN1101 support once-daily (QD) oral dosing without the need for titration at initiation of dosing or tapering at termination of dosing.

- XEN1101 demonstrates higher in vitro and in vivo potency compared to the first-generation K.7.2-7.5 opener, esagolin, and lacks the chemical properties that could form pigmentary dimers.
- XEN1101 has been evaluated in phase 1 clinical studies, including a companion pharmacodynamic crossover study using transcranial magnetic stimulation. These data demonstrated that dosing XEN1101 up to 25 mg QD was generally well tolerated and reduced cortical excitability, with a strong pharmacokinetic/pharmacodynamic relationship in healthy volunteers.

X-TOLE PHASE 2B STUDY

- X-TOLE (NCT03739692) is a phase 2b randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an optional 5-year open-label extension that evaluated clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in adults with FOS. All data presented are from the double-blind treatment period (DBP).
- XEN1101 showed a dose-dependent and highly statistically significant reduction (p<0.001 for 20 mg and 25 mg QD) in FOCS across endpoints in a patient population who had failed a median of 6 antiseizure medications (ASM); 50.8% of the population were on background ASMs.
- XEN1101 was generally well tolerated with a low incidence of serious adverse events (SAs) compared with the placebo group (2.6%), and there were no deaths in the DBP of the study.

- The most common treatment-emergent adverse events (TEAEs) leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysphoria (1.9%), and gastrointestinal disturbances (1.9%). There were no cardiovascular signals of concern in electrocardiograms or vital signs.
- Based on the strong topline results from the X-TOLE study, Xenon initiated its XEN1101 phase 3 development program, which includes 2 identical phase 3 clinical trials in FOS (X-TOLE2 and X-TOLE3) and a phase 3 trial in primary generalized tonic-clonic seizures (X-ACCT, NCT05657142).

X-TOLE2 AND X-TOLE3 PHASE 3 STUDIES

- X-TOLE2 (NCT05614063) and X-TOLE3 (NCT05716100) are identical phase 3, multicenter, randomized, double-blind, placebo-controlled studies to evaluate the clinical pharmacokinetics, safety, and efficacy of XEN1101 as adjunctive therapy in patients with FOS. Table 1 summarizes the primary and key secondary objectives and endpoints for XEN1101.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>To assess the effect of XEN1101 vs placebo on reducing FOCS frequency</td>
<td>Primary Efficacy Endpoint: Proportion of patients experiencing ≥50% reduction in FOCS frequency from baseline through the DBP</td>
</tr>
<tr>
<td>To assess the safety and tolerability of XEN1101 vs placebo on seizure impact</td>
<td>Secondary Endpoints: Proportion of patients experiencing at least one seizure event per week during the DBP</td>
</tr>
</tbody>
</table>

Table 1. X-TOLE2 and X-TOLE3 Primary and Key Secondary Objectives and Endpoints

ACKNOWLEDGMENTS

Medical writing support was provided by Foundry, LLC, for the Core Regulatory Group, LLC (Chesapeake, VA), and funded by Xenon Pharmaceuticals.

FUNDING

This work was supported by Xenon Pharmaceuticals.

DISCLOSURES

Emilio Perucca, MD, is a consultant to the following: Biogen, Baxalta, Cephalon, Cubist, Dompé, Eisai (adjunct), Eeon, Genentech (adjunct), Genzyme (adjunct), GlaxoSmithKline, Novartis, Pfizer, Quest, Sanoft, and Tocis. He has received numerous grants-in-aid from the following: Biogen, Eisai, and Novartis. He also serves on the board of directors of the following: Epilepsy International, International League Against Epilepsy, International Bureau of Epilepsy, and the International League Against Epilepsy European Region. He also serves as a member of the following: American Academy of Neurology, American Epilepsy Society, Neurology, and the American Epilepsy Society. He holds numerous leadership roles in the following: International League Against Epilepsy, American Epilepsy Society, and the American Epilepsy Society.

KEYWORDS

epilepsy, focal-onset seizures, partial-onset seizures, XEN1101, clinical trial, safety, efficacy, adjunctive therapy

REFERENCES


SUMMARY

- X-TOLE2 and X-TOLE3 will provide insight into the safety, tolerability, and efficacy of XEN1101 in FOS. These studies are designed to further evaluate the therapeutic potential of XEN1101 and support registration of XEN1101 as a novel ASM for the treatment of adults with FOS.
- XEN1101 has a novel mechanism of voltage-gated potassium channel opening and would be the only-in-class, K.7.2/7.3 opener ASM, if approved.

Poster No. 38 | American Society for Experimental Neurotherapeutics Annual Meeting (Virtual) | March 13–15, 2023