The Impact of Disease Severity on Responder Rates in a Phase 2b Study of XEN1101, a Potent, Selective Potassium Channel Opener, in Adults With Focal Epilepsy (X-TOLE)

Roger Porter,1 Jacqueline French,2 Emilio Perucca,3 Martin Brodie,4 Cynthia Harden,5 Constanza Luxon Rosenblut,6 Jenny Qian,7 Christopher Kenney,8 Gregory N. Beatch9

1University of Pennsylvania, Philadelphia, PA; 2New York University-Grossman School of Medicine and NYU Langone Health, New York, NY; 3Manassas University, Melbourne, Victoria, Australia; and 4University of Melbourne (Austin Health), Heidelberg, Australia; 5University of Georgia Department of Medicine and Therapeutics, Athens, Georgia; 6Sangamo Therapeutics Inc., Vancouver, BC, Canada

INTRODUCTION

XEN1101 is a novel, potent, 1a/1b potassium channel opener in development for the treatment of focal-onset seizures (FOS), primary generalized tonic-clonic seizures, and major depressive disorder.1 X-TOLE is a completed Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 5-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of XEN1101 administered as add-on therapy for adults with FOS.2

XEN1101 was generally well-tolerated, with adverse events consistent with commonly prescribed antiseizure medications (ASMs).3 Compared to other recent adult FOS clinical studies (Table 1), X-TOLE included a substantially lower patient population given the baseline seizure burden, number of tried and stopped ASMs, and number of comitant ASMs during the study.4

RESULTS

• A prior post hoc analysis of X-TOLE suggested that the efficacy of XEN1101 25 mg QD with food, measured by the median percentage change (MPC) in monthly FOS frequency, may be most pronounced in patients with less-severe disease.5

• Another widely used efficacy endpoint for evaluating ASM efficacy is the percentage of patients with ≥50% reduction in seizure frequency during a given treatment period compared with baseline, known as the responder rate (RR50).6

• We sought to evaluate the long-term potential impact of baseline disease severity on the RR50 in patients treated with XEN1101 25 mg QD in X-TOLE.

METHODS

• Key eligibility criteria: aged 18–75 years with a diagnosis of focal epilepsy per International League Against Epilepsy (ILAE) criteria (22 years).7–24 Countable focal seizures per month during a planned 8-week baseline period, and receiving stable treatment with 1 to 3 ASMs.

• A total of 125 patients were randomized to an 8-week double-blind period (DBP) and treated across 3 active treatment groups or placebo in a 2:1:1:2 ratio (25 mg: 10 mg: placebo: QD: food).

Efficacy Results: Baseline Disease Severity Impact on RR50 in the 25 mg Group

Baseline Seizure Sub-Group Analysis

• RR50 was achieved by 65.5% of patients with ≤8.5 seizures per month at baseline and 50.0% with >8.5 seizures per month; with placebo treatment, RR50 was higher (20.0% vs. 13.1%) in the ≤8.5 vs >8.5 seizure per month sub-group (Figure 2).

• Number of Tried and Stopped ASMs Sub-Group Analysis

• RR50 was achieved by 64.2% of patients with ≤2 tried and stopped ASMs and 40.0% with >6 ASMs; with placebo treatment, RR50 was higher (19.4% vs 8.5%) in the ≤2 vs >6 tried and stopped ASMs sub-group (Figure 3).

Concomitant ASMs Sub-Group Analysis

• RR50 was achieved by 56.9% of patients treated with XEN1101 25 mg QD and 40.0% with >6 ASMs; with placebo treatment, RR50 was higher (64.2% vs 13.1%) in the ≤6 ASMs at DBP baseline: 49.1% were taking 3 concomitant ASMs (Table 2) (Figure 4).

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