

Sponsored By:



## GANAXOLONE

Gail Farfel, PhD and Julia Tsai, PhD  
Marinus Pharmaceuticals, Inc., Branford CT USA

Ganaxolone (3 $\alpha$ -hydroxy-3 $\beta$ -methyl-5 $\alpha$ -pregnan-20-one) is the 3 $\beta$ -methyl analog of the progesterone metabolite allopregnanolone (3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one; 5 $\alpha$ ,3 $\alpha$ -P), currently in development for the treatment of seizures. As a centrally active neurosteroid, it is thought to exert its effects through positive allosteric modulation of both synaptic and extra-synaptic GABA A receptors via a site that is distinct from benzodiazepine and barbiturate binding. Unlike naturally occurring allopregnanolone, ganaxolone cannot be converted in the body to 3-keto intermediates with classical steroid hormone activity.

Ganaxolone 1500mg/day has been shown as safe and effective for the treatment of epilepsy in a 10-week, double-blind (DB), placebo (PBO)-controlled study of adjunctive therapy in adult outpatients with uncontrolled partial onset seizures (POS)(Tsai, J., Antiepileptic Drug Trials X, Coral Gables, FL, April 2009). A 2-year, open-label extension (OLE) to the double-blind study was conducted to assess the long-term safety and efficacy of ganaxolone.

Preliminary analysis shows ganaxolone to be safe and well tolerated for extended use. The most frequent (>10%) adverse events (AEs) in the OLE were fatigue, headache, dizziness, convulsion, fall, contusion, somnolence, and nasal congestion; most were mild or moderate in severity. SAEs were reported in 17 subjects; 7 were related to the disease being studied. There were no trends of changes in chemistry, vital signs or ECGs that would limit clinical use. No mean changes in weight were observed up to 18 mo; 4 subjects (3%) reported weight increase as an AE.

Preliminary analysis of OLE data shows subjects experienced a reduction in mean weekly seizure frequency from baseline to endpoint of 15.0%. The reduction in mean weekly seizure frequency measured at Wk 52 (observed cases) was 41.3%. Mean weekly seizure frequency decreased by 18.8% after 10 wks of open-label treatment for the group that received PBO in the DB study and began GNX in the OLE. This result is similar to the 17.6% decrease seen with GNX treatment in the DB study. DB GNX subjects who continued on GNX in the OLE maintained their response. The overall responder rate (defined as 50% improvement over DB baseline) in the OLE was 22.5%; the rate for observed cases at 52 wks was 45.0%.

In summary, ganaxolone, the first neurosteroid with positive Phase 2 data in adjunctive treatment of partial onset seizures, continued to demonstrate safety, tolerability and efficacy in long-term treatment of epilepsy in this open-label extension study. Ganaxolone investigations into PTSD and Fragile X are also under way.