Safety and Efficacy of Intravenous Ganaxolone in Severe Postpartum Depression: Results from a Double-Blind, Placebo-Controlled Phase 2 Study

Maximos B[1], Riesenberg R[2], Johnson K[3], Gutierrez-Esteinou R[4], Aimetti A[4], Lappalainen J[5], Masuoka L[4]

[1]Maximos Ob/Gyn, League City, TX, [2]Atlanta Center for Medical Research, Atlanta, GA, [3]iResearch Atlanta, LLC, Atlanta, GA, [4]Marinus Pharmaceuticals, Radnor, PA, [5]Crozer Keystone Health System, Chester, PA

BACKGROUND

Disease

Postpartum depression (PPD) affects more than 400,000 women each year in the United States but effective treatment options are limited[1]. Common symptoms include feelings of extreme sadness, hopelessness, anxiety, fatigue and suicidal ideation. PPD is thought to be linked to disorders of the GABA system, possibly mediated by rapid fluctuations in the levels of reproductive hormones and allopregnanolone after childbirth. PPD can affect a mother's ability to care for her child and may negatively affect the child's development.

Ganaxolone

Ganaxolone is a synthetic analog of allopregnanolone, and acts as a positive allosteric modulator of $GABA_A$ receptors. Ganaxolone is being developed in intravenous and oral forms intended to meet the needs of patients experiencing PPD. Unlike benzodiazepines, ganaxolone exhibits anti-seizure and anti-anxiety activity via its effects on synaptic and extrasynaptic $GABA_A$ receptors. Ganaxolone has been studied in over 1600 subjects, both pediatric and adults for up to four years. In these studies, ganaxolone was generally safe and well tolerated. The most commonly reported adverse events were somnolence, dizziness and fatigue.

STUDY DESIGN

Objectives

- Safety: To assess the safety and tolerability of escalating doses of intravenously and orally administered ganaxolone as determined by adverse events and changes from baseline in laboratory and ECG measures, vital signs, Columbia Suicide Severity Rating Scale (CSSRS) and physical examination.
- Efficacy: To explore the efficacy of escalating doses of intravenously administered ganaxolone in the treatment of PPD with the Hamilton Depression Rating Scale 17-item version (HAM-D17) and Clinical Global Impression-Improvement (CGI-I) scale.

Key inclusion and exclusion criteria

- Women between the ages of 18 and 45 years diagnosed with postpartum depression (onset from the last trimester of pregnancy through the first four weeks postpartum) and within one year of delivery
- Hamilton Depression Rating Scale severity above 26 points total at screening and 22 at randomization
- May be receiving treatment with an antidepressant medication if started more than 21 days before screening
- No active suicidal ideation or suicide attempt within the past 3 years
- Must agree to stop breastfeeding and to use acceptable contraception

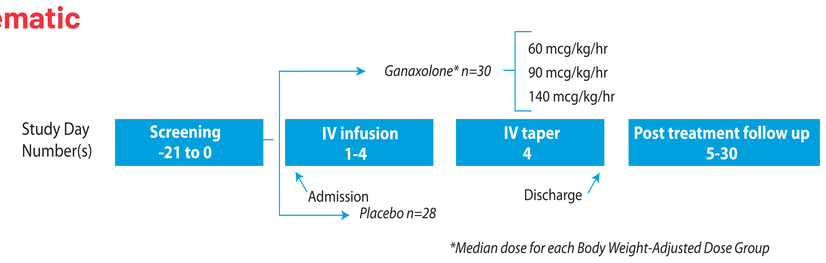
Design

Double blind, parallel group (1:1 randomization), placebo controlled, in 3 cohorts receiving 48 hrs of fixed doses of ganaxolone IV: 4 mg/hr; 8 mg/hr; or 12-mg bolus (given in 2 minutes) plus 12 mg/hr in 3 consecutive cohorts. Each cohort underwent a dose taper during hours 49-60 of IV treatment. Patients were followed for 30 days post treatment.

Analysis

- Weight-adjusted dose group assignment of patients receiving active ganaxolone treatment, divided into 3 groups identified by median dose: 40, 90, 140 mcg/hr/kg
- Efficacy: Descriptive analysis of HAM-D17 total scores and CGI-I scores over time
- Safety: Tabulation of incidence of adverse events by treatment group

Design Schematic



*Median dose for each Body Weight-Adjusted Dose Group

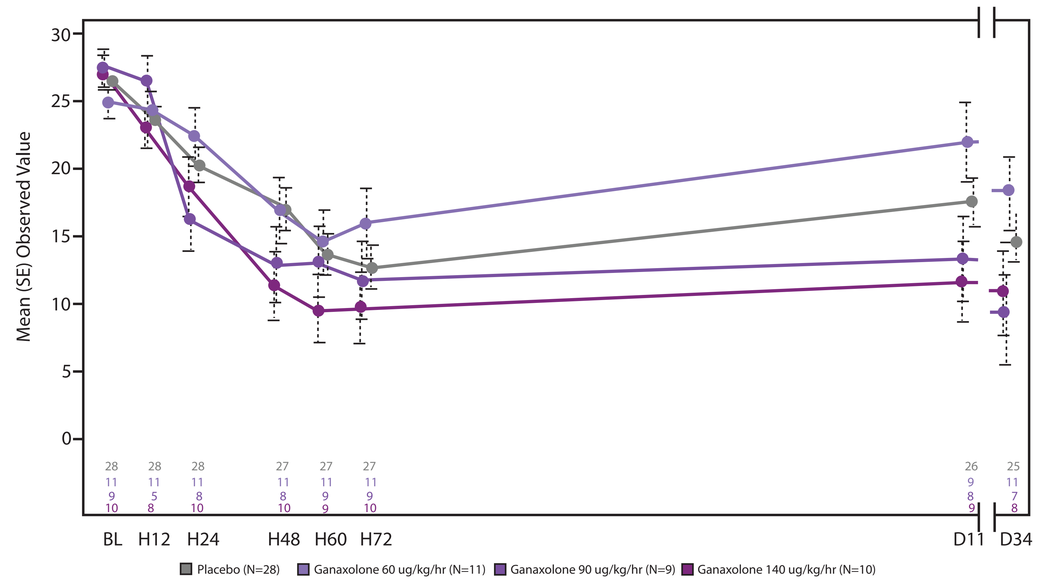
RESULTS

A dose response was observed with the highest ganaxolone dose (140 µg/kg/hr, n=10 at baseline) generally performing the best over placebo. Patients in this dose group experienced a 15.1, 16.9, and 15.7 point HAM-D17 reduction from baseline at 48 hrs, 60 hrs, and Day 34, respectively. These HAM-D17 reductions reflect clinically meaningful 5.6, 4.2, and 4.1 point improvements over placebo (n=28 at baseline) at the corresponding timepoints. Ganaxolone was safe and well-tolerated with the most common reported adverse events of mild sedation and dizziness. There were no reports of syncope or loss of consciousness.

	Placebo n=28	Ganaxolone 60 mcg/kg/hr n=11	Ganaxolone 90 mcg/kg/hr n=9	Ganaxolone 140 mcg/kg/hr n=10
Age (yrs)	26.2	25.6	27.6	24.7
Weight (kg)	90.8	91.4	84.7	66.3
Taking antidepressants	4	3	0	0
Baseline HAM-D17 total	26.5	24.9	27.4	27.1
EPDS total	20.9	18.6	21.3	22.0

Patient Disposition		
Screened	N=98	
	Placebo	Ganaxolone
Randomized	28	30
Completed	26	28

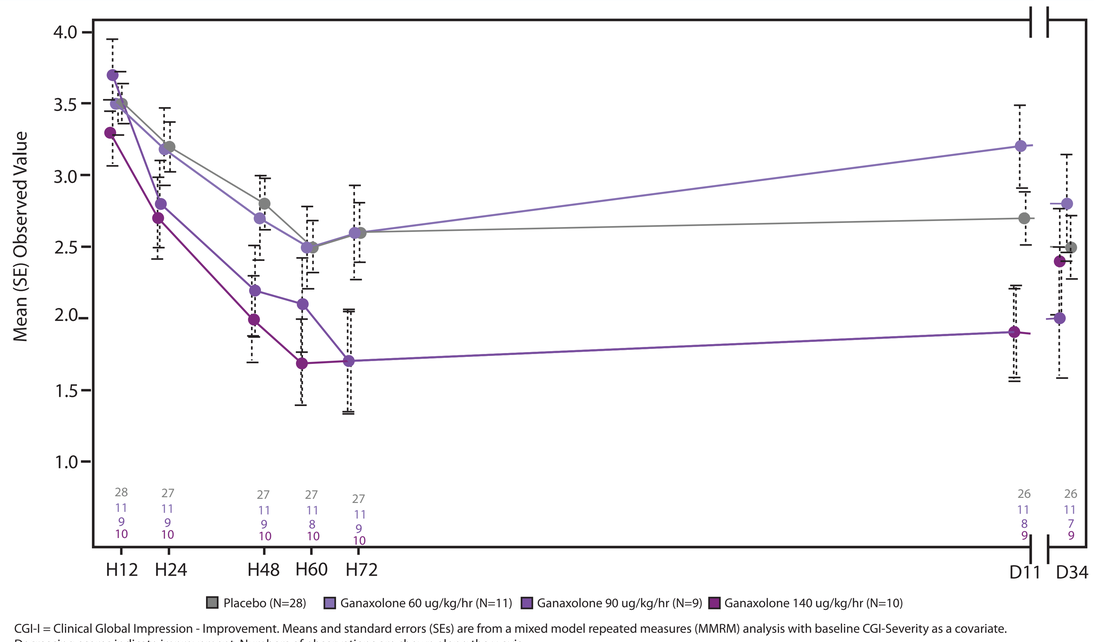
Figure 1: Mean (SE) HAM-D17 Total Score by Weight-Adjusted Dose (mITT Set).



HAM-D17 = Hamilton Depression Rating Scale. 17-item version. Post-baseline means and standard errors (SEs) are from a mixed model repeated measures (MMRM) analysis with baseline as a covariate. Decreasing scores indicate improvement. Numbers of observations are shown along the x-axis.

PROTOCOL 1042-PPD-2002 (MAGNOLIA)
SOURCE: ADRS

Figure 2: Mean (SE) CG-I by Weight Adjusted Dose (mITT Set).



CGI-I = Clinical Global Impression - Improvement. Means and standard errors (SEs) are from a mixed model repeated measures (MMRM) analysis with baseline CGI-Severity as a covariate. Decreasing scores indicate improvement. Numbers of observations are shown along the x-axis.

PROTOCOL 1042-PPD-2002 (MAGNOLIA)
SOURCE: ADQS

Safety (Adverse Events Reported in More Than One Subject).

Preferred Term	Placebo n=28	Ganaxolone 60 mcg/kg/hr n=11	Ganaxolone 90 mcg/kg/hr n=9	Ganaxolone 140 mcg/kg/hr n=10
Dizziness	1	2	1	2
Sedation	0	0	1	5
Headache	2	1	0	0
Pruritic rash	0	0	2	0
TSH elevated	0	0	2	0
No serious adverse events or discontinuations because of an adverse event.				

CONCLUSIONS

Ganaxolone IV in severe PPD demonstrates preliminary evidence of rapid and durable antidepressant action with a favorable safety profile. Although the 48-hr infusion followed by a 12-hr taper paradigm presents an encouraging treatment option, future ongoing studies plan to assess a short-course IV infusion followed by daily oral ganaxolone to provide a more convenient treatment paradigm while maintaining acute and durable antidepressant effects.

REFERENCES

1. Ko, J. Y., Rockhill, K. M., Tong, V. T., Morrow, B. & Farr, S. L. Trends in Postpartum Depressive Symptoms — 27 States, 2004, 2008, and 2012. *MMWR. Morb. Mortal. Wkly. Rep.* **66**, 153–158 (2017).