# A Multicenter, Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial to Determine the Efficacy and Safety of Ganaxolone as Adjunctive Therapy for Adults with Drug-Resistant Focal-Onset Seizures

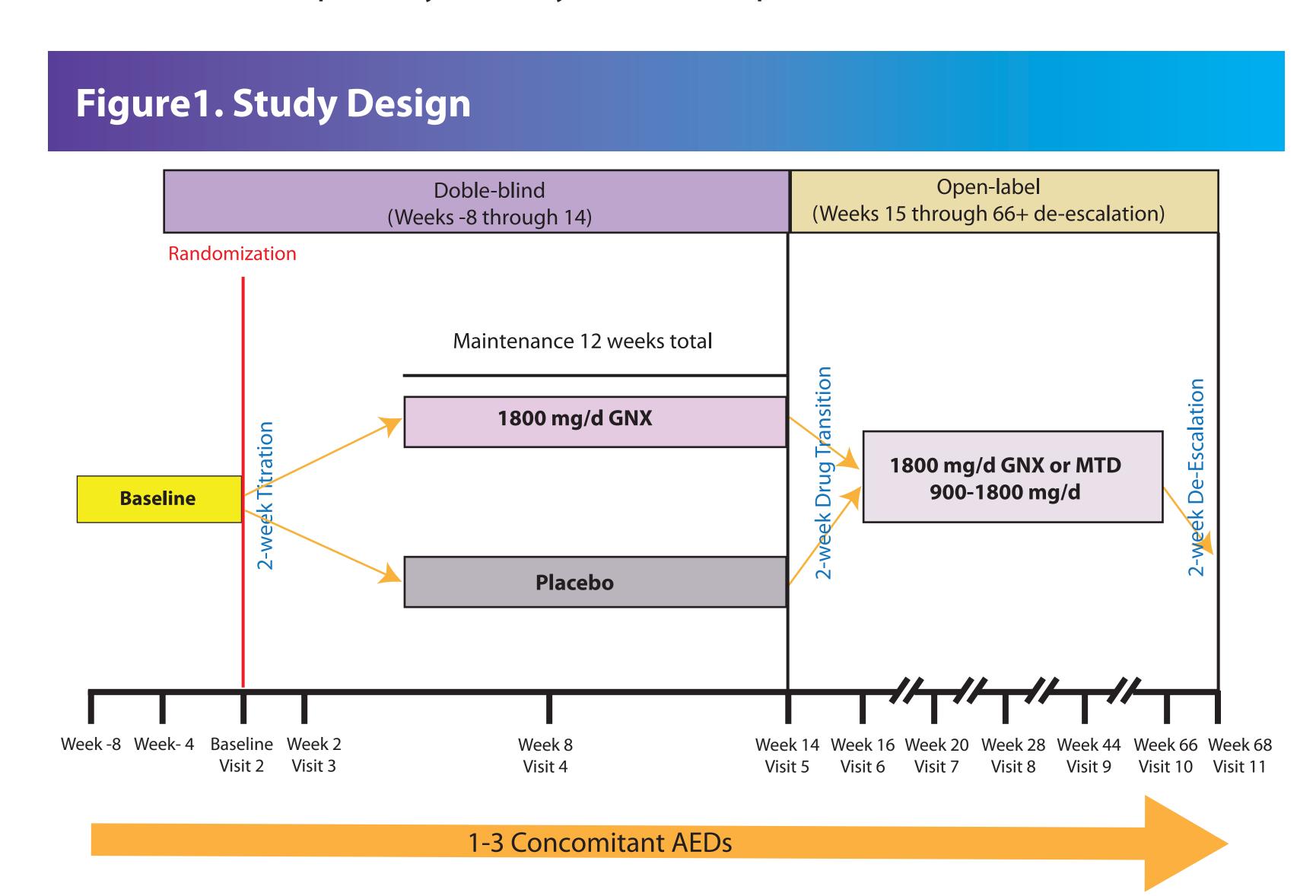
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# BACKGROUND

Ganaxolone (GNX) a synthetic analog of allopregnanolone, is in development for treatment of various neurological and psychiatric conditions. Ganaxolone is a positive allosteric modulator of GABA<sub>A</sub> receptors and has anxiolytic and anticonvulsant effects. The goal of this study was to assess the efficacy and safety of ganaxolone as adjunctive therapy in adult patients with drug-resistant focal-onset seizures.

# Design

This was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study conducted at 61 sites in the United States, Germany, Poland, Australia, Bulgaria, and Russia. In the primary efficacy cohort, following a baseline period and randomization to receive either ganaxolone (1800 mg/day) or placebo, the subjects entered a 14-week double-blind treatment phase consisting of a 2-week titration phase and 12 weeks of maintenance treatment. After the double-blind phase the patients could enroll in a 52-week open-label extension phase. The primary efficacy end-point was percent change from baseline in the 28-day focal onset seizure frequency. Results from the primary efficacy cohort are presented below.



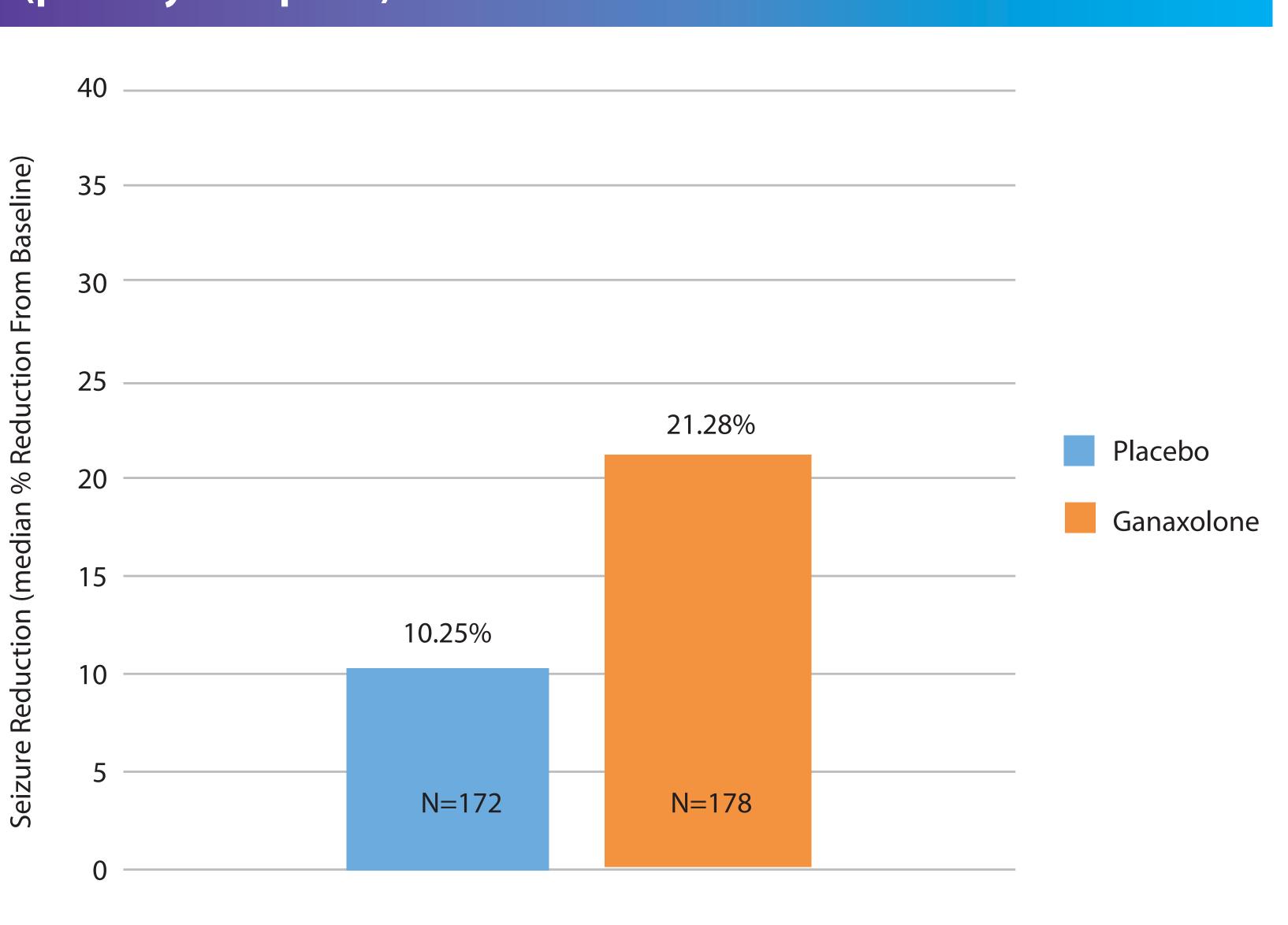
## Table 1. Subject Enrollment and Disposition

	Ganaxolone	Placebo			
Subjects randomized	179	180			
mITT population	178 (99.4%)	172 (95.6%)			
Subjects completed DB	135 (75.4%)	154 (85.6%)			
Subjects discontinued DB	44 (24.6%)	26 (14.4%)			
Reason for Discontinuation					
Adverse Event	30 (16.8%)	11 (6.1%)			
Withdrawal of consent	8 (4.5%)	9 (5.0%)			
Non-compliance	4 (2.2%)	0 (0%)			
Protocol violation	1 (0.6%)	3 (1.7%)			
Other reason	1 (0.6%)	1 (0.6%)			
Insuff. clinical response	0 (0%)	1 (0.6%)			
Lost to follow-up	0 (0%)	1 (0.6%)			

# Table 2. Key Demographic Characteristics (mITT population)

	Ganaxolone (n=178)	Placebo (n=172)	
Mean age	40.6	42.1	
Female	113 (63.5%)	97 (56.4%)	
White	168 (94.4%)	161 (93.6%)	
Mean BMI	26.8	27.3	
Years Since Epilepsy Diagnosis.	24.4	23.1	
VNS (past or current)	20 (11.2%)	22 (12.8%)	
≥ 2 concomitant AEDs	137 (77%)	128 (74%)	
Mean Baseline 28-day seizure frequency (Median)	15.01 (8.5)	15.26 (7.5)	

# Figure 2. Median Percent Reduction in 28-day Seizure Frequency (primary end-point)



rank ANCOVA p-value p=0.178, mITT

# Table 3. Summary of Responder Rates

	Ganaxolone (n=178)	Placebo (n=172)
≥ 80%	13 (7.3%)	4 (2.3%)
≥ 60%	37 (21.3%)	29 (16.9%)
≥ 40%	59 (33.7%)	51 (29.7%)
≥ 20%	92 (51.7%)	75 (43.6%)

All comparisons non-significant at p<0.05 level

#### Table 4. Overview of Adverse Events

	Ganaxolone (n=179)	Placebo (n=176)
Any TEAE	125 (69.8%)	92 (52.37%)
TEAE by highest severity		
Mild	60 (33%)	46 (26.1%)
Moderate	52 (29.1%)	41 (23.3%)
Severe	13 (7.8%)	5 (2.8%)
TEAEs leading to discont.	32 (17.9%)	11 (6.3%)
Treatment-related TEAE	99 (55.3%)	49 (27.8%)
Serious TEAE	9 (5%)	9 (5.1%)

## Table 5. Most Common Adverse Events (≥ 5%)

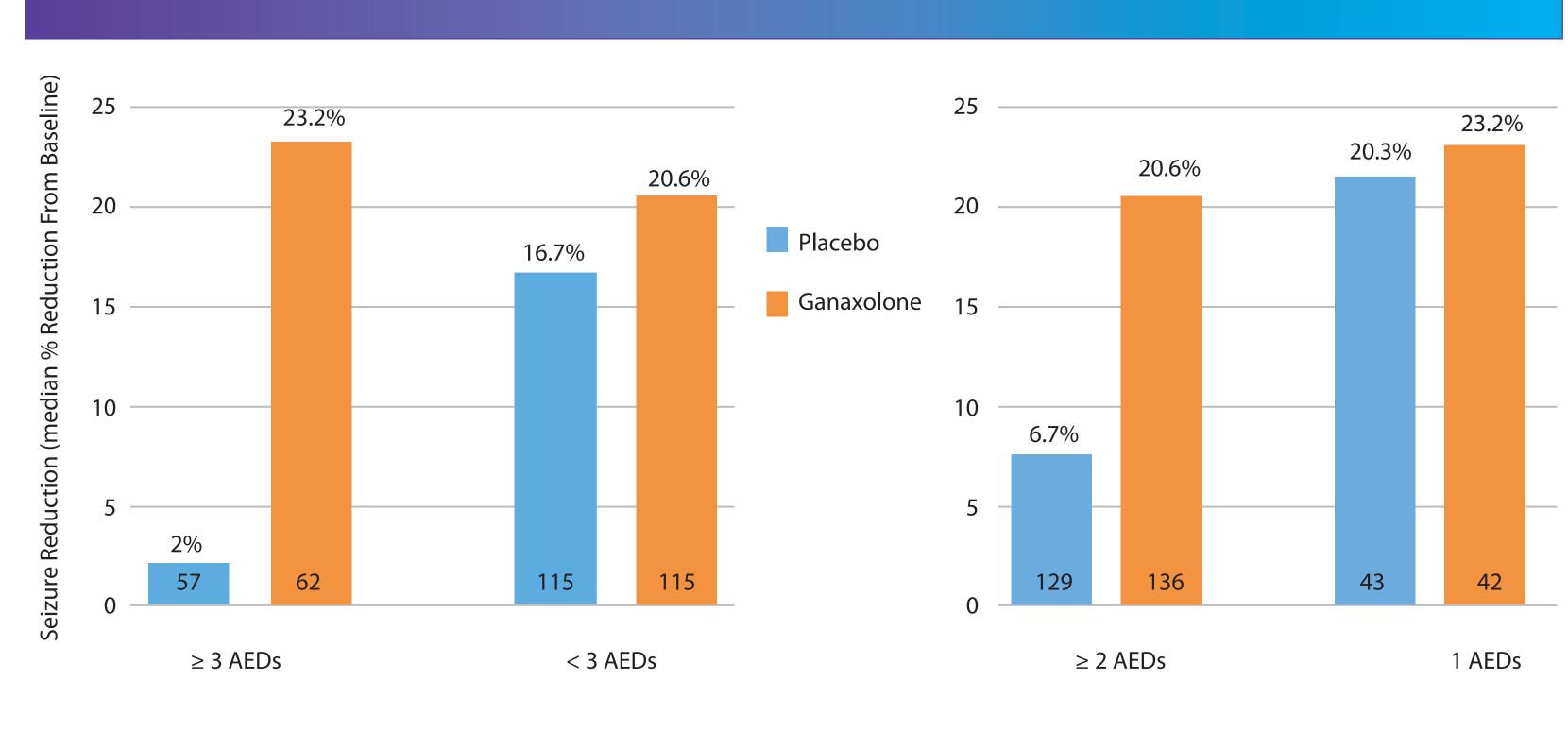
	Ganaxolone (n=179)	Placebo (n=176)					
Somnolence	42 (23.5%)	8 (4.5%)					
Dizziness	35 (19.6%)	8 (4.5%)					
Fatigue	21 (11.7%)	12 (6.8%)					
Headache	16 (8.9%)	15 (8.5%)					
Convulsion	7 (3.9%)	7 (4.0%)					
Nasopharyngitis	5 (2.8%)	9 (5.1%)					

#### Table 6. Other Safety Findings (Ganaxolone vs Placebo)

- No effects on weight
- No effects on blood pressure or pulse
- No effects on chemistry or hematology
- No effects on ECG parameters
- No increase in suicidal ideation or suicide attempts

A set of exploratory analyses were conducted after the main analyses were completed to understand whether the data set consisted of subgroups which showed more robust efficacy, or whether there were subgroups which could have deflated the response to ganaxolone. These analyses focused on refractoriness to treatment, presence of concomitant medications and geographic location of the study site. The results showed that there was a greater separation between placebo and ganaxolone in patients who were treated 2 or 3 concomitant AEDs (p-value = 0.024 GNX vs placebo in patients with ≥ 3 AEDs; Figure 3). In addition, large variations in response to drug and placebo were seen depending on the geographical region of the investigative site (Table 7).

#### Figure 3. The Effect of Number of Concomitant AEDs on Efficacy



Rank ANCOVA P-value = 0.024

# Table 7. Improvement in 28-day Seizure Frequency by Country

Australia Bulgaria		Germany		Poland		Russia		USA			
acebo n=22)	GNX (n=24)	Placebo (n=38	GNX (n=38)	Placebo (n=9)	GNX (n=8)	Placebo (n=21)	GNX (n=21)	Placebo (n=29)	GNX (n=30)	Placebo (n=53)	GNX (n=57)
2.3%	6.9%	50.1%	59.0%	17.2%	-3.8%	3.3%	18.0%	-3.6%	9.1%	6.7%	16.7%

#### CONCLUSIONS

- The study population consisted of subjects with drug-refractory focal onset seizures
- The primary efficacy end-point did not meet statistical significance (p=0.178)
- Reduction in seizures favoring ganaxolone over placebo was seen across different end-points
- Rates of sedation, dizziness, fatigue were observed at higher frequency in the ganaxolone treated group vs placebo
- Rates of serious adverse events were balanced between ganaxolone and placebo treated groups
- Ganaxolone was generally safe and tolerated
- Post hoc analyses suggest that ganaxolone may be efficacious in the most drug refractory patient population
- Variability across countries may have influenced the overall outcome of the study