The Phase 2a ROCKET trial investigating OV101 (gaboxadol) in adolescents and young adults with Fragile X syndrome

Dejan Budimirovic[1], Anna Lee[2*], Kelli C. Dominick[3], Nicole Tartaglia[4], Elizabeth Berry-Kravis[5]

[1]Kennedy Krieger Institute, Johns Hopkins University, Baltimore, MD, USA; [2]Ovid Therapeutics Inc., New York, NY, USA; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [4]University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, USA; [5]Rush University Medical Center, Chicago, IL, USA

*Was an employee at Ovid Therapeutics Inc. at the time of abstract submission.

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INTRODUCTION: Fragile X Syndrome Prevalence, Mechanism of Disease, Symptomatology, and Treatment

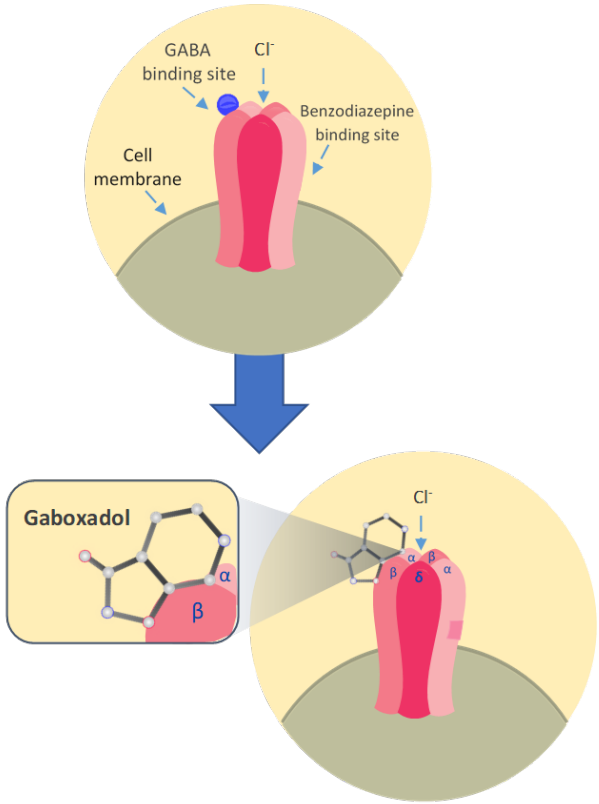
Fragile X Syndrome

- Fragile X syndrome (FXS) is the leading genetic cause of inherited intellectual disability and autism spectrum disorder, with a prevalence of up to 1 in 2500 males and 1 in 6000 females[1,2]
- FXS is caused by a mutation of the fragile X mental retardation 1 (*FMR1)* gene, resulting in a deficit or absence of fragile X mental retardation protein (FMRP)[3]
- Individuals with FXS present with a broad range of neurocognitive and neurobehavioral limitations, such as intellectual disability, language impairment, attentional network symptoms, autism spectrum disorder, social withdrawal and avoidance, anxiety symptoms, repetitive and stereotyped behaviors, perseverative speech, as well as aggressive and/or self-injurious behaviors[3,4]
  - Symptoms vary widely in severity, although they tend to be more severe in males than in females, and may depend on the magnitude of the FMRP deficit[5]
- Current treatments for FXS consist of a combination of non-pharmacological interventions and symptom-based use of pharmacological agents[6]

OV101 (gaboxadol)

- OV101 (gaboxadol) is a δ-subunit–selective extrasynaptic γ-aminobutyric acid (GABA) type A ($GABA_A$) receptor agonist (Figure 1)[7]

Figure 1. Gaboxadol Site of Action



Cl-, chloride ion; GABA, γ-aminobutyric acid.

1. Schneider A, et al. *Dev Disabil Res Rev.* 2013;18(1):68–74; 2. Li Y, et al. *Nat Commun.* 2018;9(1):2494; 3. Bagni C, et al. *J Clin Invest.* 2012;122(12):4314–4322; 4. Bagni C, et al. *Neuron.* 2019;101(6):1070–1088; 5. Hagerman RJ. The physical and behavior phenotype. In: Hagerman RJ, Hagerman PJ, eds. *Fragile X syndrome: diagnosis, treatment, and research*. 3rd ed. Johns Hopkins University Press; 2002:3–109; 6. Berry-Kravis EM, et al. *Nat Rev Drug Discov.* 2018;17(4):280–299; 7. Olmos-Serrano JL, et al. *Dev Neurosci.* 2011;33(5):395–403.

INTRODUCTION: ROCKET Trial Rationale and Objectives

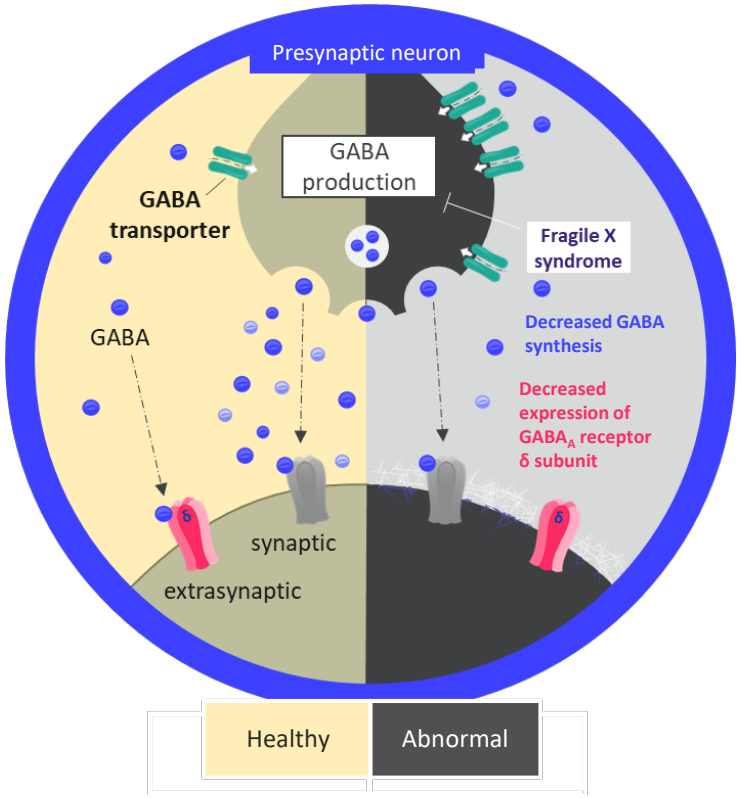
Study Rationale

- Evidence from *Fmr1* knockout (KO) mice supports the role of GABA, the primary inhibitory neurotransmitter in the brain, in mediating symptoms of FXS[1,2]
  - *Fmr1* KO mice have decreased $GABA_A$ receptor δ subunit expression, decreased GABA synthesis, and decreased levels of GABA, resulting in decreased tonic inhibition (Figure 2)[1,3]
  - Gaboxadol restored tonic inhibition in the amygdala, reduced sensory hypersensitivity and motor hyperactivity, and improved pre-pulse inhibition in *Fmr1* KO mice[1]
  - Gaboxadol normalized hyperactivity as well as repetitive, social, and anxiety-like behavior in *Fmr1* KO2 mice, another murine model of FXS[4]
- The present signal-finding Phase 2a ROCKET trial (ClinicalTrials.gov identifier: NCT03697161) explored effects of multiple dosing regimens of gaboxadol in males aged 13 to 22 years with FXS

Study Objectives

- **Primary:** evaluate safety and tolerability of gaboxadol in males aged 13 to 22 years with FXS over 12 weeks of treatment across different daily dosing regimens
- **Secondary:** evaluate the effect of gaboxadol on changes in behavior in males aged 13 to 22 years with FXS over 12 weeks of treatment across different daily dosing regimens
- **Exploratory:** evaluate other efficacy outcomes (eg, changes in sleep, adaptive functioning, quality of life) in males aged 13 to 22 years with FXS across different daily dosing regimens and explore associations between factors (eg, gaboxadol plasma levels, metabolomic biomarkers, clinical presentation, evoked resting potential [ERP], microbiomes); perform population pharmacokinetic (PK) and PK-pharmacodynamic (PD) analysis and evaluate possible acute rebound phenomena (eg, sleep disruption or behavioral problems) following discontinuation of treatment

Figure 2. Potential Mechanisms of Decreased Tonic Inhibition in FXS



FXS, Fragile X syndrome; GABA, γ-aminobutyric acid; $GABA_A$, GABA type A.

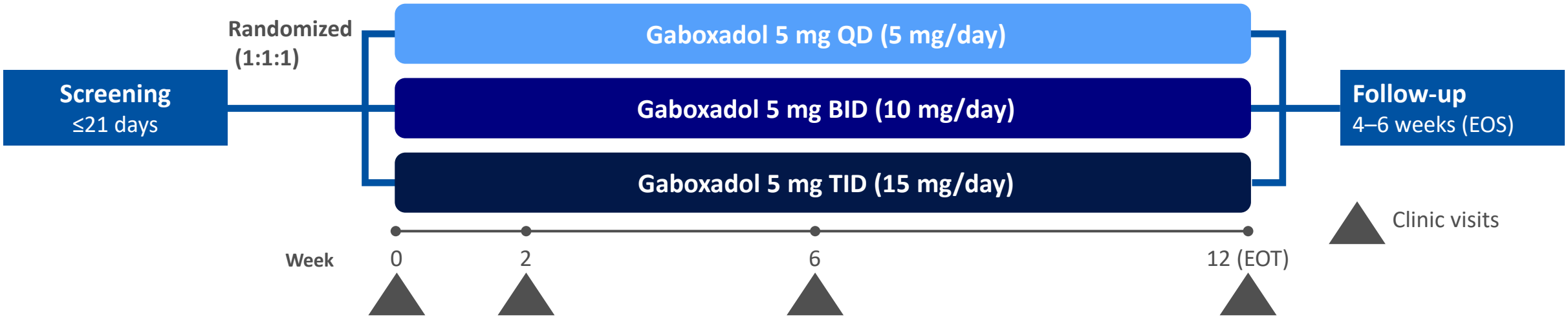
1. Olmos-Serrano JL, et al. *Dev Neurosci.* 2011;33(5):395–403; 2. Zafarullah M, et al. *Brain Sci.* 2019;9(5):96; 3. Olmos-Serrano JL, et al. *J Neurosci.* 2010;30(29):9929–9938;
4. Cogram P, et al. *Front Behav Neurosci.* 2019;13:141.

METHODS: Design of ROCKET Phase 2a Trial in Fragile X Syndrome

Study Design

- Phase 2a, randomized, double-blind, parallel-group study (Figure 3)
  - Eligible males aged 13 to 22 years with FXS were enrolled at 8 sites in the United States and 1 site in Israel (Table 1)
  - Target enrollment: ≤36 participants
- Allocation 1:1:1 of gaboxadol 5 mg once daily, 5 mg twice daily, or 5 mg thrice daily for 12 weeks; stratified by age group (adolescents, aged 13 to 17 years; adults, aged 18 to 22 years; 1:1 allocation)
  - All participants received study drug thrice daily: gaboxadol in the morning, and gaboxadol or placebo in the afternoon and evening

Figure 3. Study Design



BID, twice daily; EOS, end of study; EOT, end of treatment; QD, once daily; TID, thrice daily.

METHODS: ROCKET Trial Key Inclusion and Exclusion Criteria

Table 1. Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Male, aged 13–22 years, inclusive • Diagnosis of FXS with *FMR1* full mutation (>200 CGG repeats) confirmed prior to participant randomization • CGI-S score of 4 (moderately ill) or more at screening • Intelligence quotient <75 as measured by the Stanford-Binet-5 at screening • Currently receiving ≤3 antiepileptic and/or psychoactive medications; medications stable for ≥4 weeks prior to randomization and maintained throughout the study duration • Able to take oral study drug • Caregiver capable of providing informed consent, overseeing study drug administration, attending scheduled study visits, and providing feedback • Willing to remain sexually abstinent from first day of screening through 30 days after last dose of study treatment • Caregiver agrees to refrain from posting any of the participant's personal medical data related to the study on any website or social media platform until conclusion of the study	• Concomitant gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease or condition of a degree that would limit participation in the study • Clinically significant laboratory abnormalities or vital signs at screening • Regularly uses GABAergic agent • Cannabinoid derivative use • History of uncontrollable seizure disorder or seizure episodes with 6 months of screening or change in anticonvulsant pharmacotherapy within 3 months of screening • History of suicidal behavior or at high risk of suicide • Participation in any clinical trial or use of any investigational agent, device, and/or procedure within 30 days of screening • Unable to comply with study requirements • Family member of investigator or study site personnel

CGG, cytosine-guanine-guanine; CGI-S, Clinical Global Impressions–Severity; FMR1, fragile X mental retardation 1; FXS, Fragile X syndrome; GABA, γ-aminobutyric acid.

METHODS: Study Endpoints for Safety, Tolerability, and Efficacy

Study Endpoints

Primary Safety and Tolerability Endpoints

- Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, TEAEs leading to study discontinuation, and serious adverse events (SAEs)

Secondary Efficacy Endpoints

- Changes from baseline in Aberrant Behavior Checklist–Community (ABC-C) total and subscale scores; ABC-C factor score for FXS (ABC-C_{FXS}); Clinical Global Impressions (CGI)–Severity (CGI-S) and CGI–Improvement (CGI-I) scores; Anxiety, Depression, and Mood Scales (ADAMS) subscale scores; Repetitive Behavior Scale–Revised (RBS-R) total and subscale scores; Conners 3rd Edition subscale scores; and Short Sensory Profile 2 total and subscale scores

Exploratory Efficacy Endpoints

- **Direct participant assessment:** actigraphy parameters for sleep, including sleep onset latency (SOL), wake time after sleep onset (WASO), sleep fragmentation, number of nocturnal awakenings, total sleep time (TST), sleep efficiency, and daily activity level; mean change from baseline in Test of Attentional Performance for Children (KiTAP) subtest scores; mean change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) subtest scores
- **Caregiver completed:** change from baseline in Behavior Assessment System for Children, 3rd Edition, Parenting Relationship Questionnaire (BASC-3 PRQ) subscale scores; Parent Global Impressions (PGI)–Severity (PGI-S) and PGI–Improvement (PGI-I) scores; Pediatric Quality of Life Inventory (PedsQL) total and subscale scores; Children's Sleep Habits Questionnaire (CHSQ) total and subscale scores; sleep diary parameters, including SOL, WASO, TST, and daytime sleepiness, defined as duration of napping in the daytime
- **Clinician completed:** change from baseline in top 3 concerns visual analog scale; Vineland Adaptive Behavior Scale, 3rd Edition (VABS-3), overall composite and subscale scores; Pediatric Sleep CGI-S and Pediatric Sleep CGI-I scores
- **Other Exploratory Endpoints**: mean change from baseline in ERP response; change from baseline in microbiomes and biomarkers**;** plasma gaboxadol concentrations at sampling time points

METHODS: Statistical Analysis

Statistical Analysis

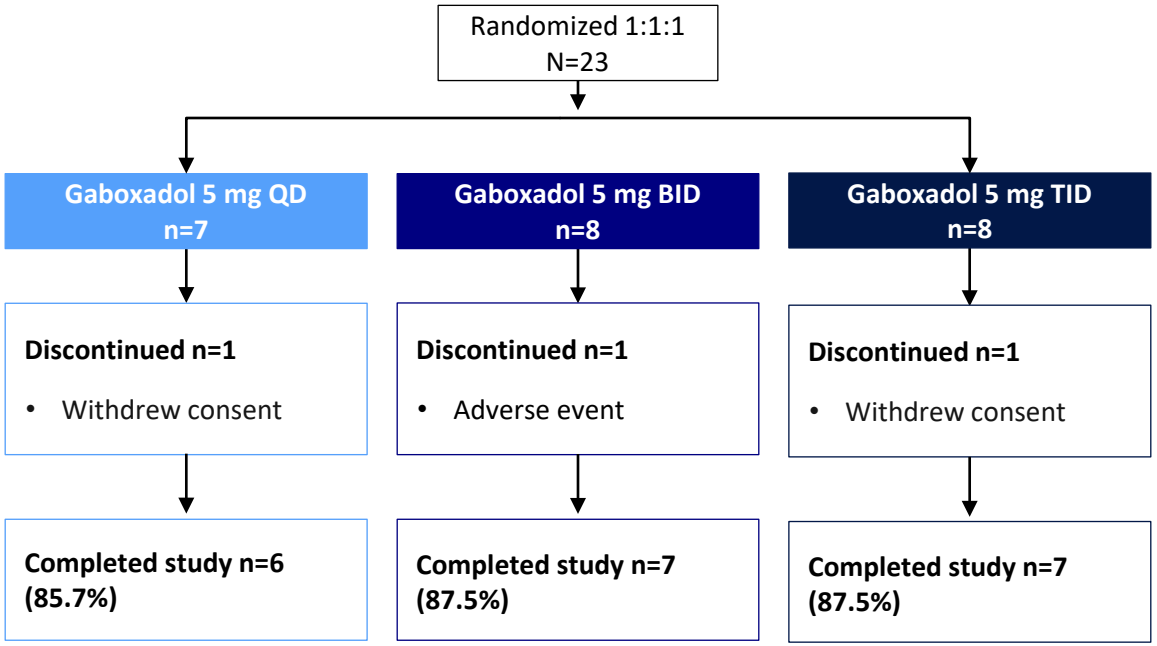
- Summaries of subject disposition, demographics, and other baseline characteristics are described from the randomized analysis set, which comprised all randomly assigned subjects
- All safety data analyses were conducted on the safety set, which included all subjects who received ≥1 dose of study drug
- Efficacy analyses were performed from the full-analysis set (FAS), which comprised all randomly assigned subjects who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment

RESULTS: Demographics and Baseline Clinical Characteristics

Demographics and Baseline Clinical Characteristics

- Twenty-three (23) patients were randomized in the study (Figure 4)
- Demographic and baseline clinical characteristics are summarized in Table 2

Figure 4. Study Flow of Patients



BID, twice daily; QD, once daily; TID, three times daily.

Table 2. Demographic and Baseline Clinical Characteristics by Treatment (Randomized Patients)

Characteristic	Gaboxadol 5 mg QD	Gaboxadol 5 mg BID	Gaboxadol 5 mg TID	Total
Number (male participants), n	7	8	8	23
Adolescents, n*	4	5	4	13
Adults, n†	3	3	4	10
Age, years	17.0 (3.46)	16.5 (2.93)	17.5 (3.34)	17.0 (3.12)
Race, Black or African-American, n (%)	0 (0.0)	1 (12.5)	0 (0.0)	1 (4.3)
Race, Native Hawaiian or Other Pacific Islander, n (%)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.3)
Race, White, n (%)	7 (100)	7 (87.5)	6 (75.0)	20 (87.0)
Race, Other, n (%)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.3)
Baseline weight, kg	85.10 (25.03)	76.89 (31.86)	84.16 (35.02)	81.92 (29.97)
Baseline height, cm	171.77 (6.30)	170.39 (10.46)	168.43 (12.72)	170.05 (10.09)
Patient IQ score in percentiles	41.7 (4.11)	40.5 (0.93	42.3 (4.10)	41.5 (3.29)
DSM-5 autism spectrum disorder criteria, n (%)	7 (100)	6 (75.0)	6 (75.0)	19 (82.6)

Data presented as mean (SD) unless otherwise specified.
*Ages 13–17 years, inclusive; †Ages 18–22 years, inclusive.
BID, twice daily; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IQ, intelligence quotient; QD, once daily; SD, standard deviation; TID, three times daily.

RESULTS: Safety Assessed From Adverse Events

Safety

- TEAEs were reported in 16 (69.6%) of gaboxadol-treated patients (Table 3)
- TEAEs occurring in ≥2 patients included diarrhea, irritability, headache, and upper respiratory tract infection

Table 3. TEAEs, Treatment-related TEAEs, TEAEs Leading to Study Discontinuation, and SAEs From Baseline to Week 12 by Treatment (Safety Set)

Event, n (%)	Gaboxadol 5 mg QD n=7	Gaboxadol 5 mg BID n=8	Gaboxadol 5 mg TID n=8	Total N=23
Patients with any TEAE	2 (28.6)	8 (100)	6 (75.0)	16 (69.6)
Severity of TEAE				
Mild	2 (28.6)	7 (87.5)	6 (75.0)	15 (65.2)
Moderate	0 (0.0)	1 (12.5)	0 (0.0)	1 (4.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs occurring in ≥2 patients				
Diarrhea	0 (0.0)	0 (0.0)	2 (25.0)	2 (8.7)
Irritability	0 (0.0)	1 (12.5)	1 (12.5)	2 (8.7)
Headache	0 (0.0)	3 (37.5)	0 (0.0)	3 (13.0)
Upper respiratory tract infection	0 (0.0)	3 (37.5)	1 (12.5)	4 (17.5)
Patients with any treatment-related TEAE	1 (14.3)	5 (62.5)	2 (25.0)	8 (34.0)
Patients with any AE leading to study discontinuation	0 (0.0)	1 (12.5)	0 (0.0)	1 (4.3)
Patients with any SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE, adverse event; BID, twice daily; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TID, three times daily.

RESULTS: Across Gaboxadol Dosing Groups, Significant Improvements Were Observed in ABC-C_{FXS} and ADAMS Total Scores

Efficacy: ABC-C_{FXS} and ADAMS

- Across dosing groups, significant improvement was observed from baseline to Week 12 in ABC-C_{FXS} total score (Figure 5; *P*=0.0017) and ADAMS total score (Figure 6; *P*=0.0039)
  - In ABC-C_{FXS} subscales, patients showed significant improvements from baseline to Week 12 in lethargy/social withdrawal, hyperactivity, stereotypic behavior, and irritability, but not social avoidance or inappropriate speech subscales
  - In ADAMS subscales, patients also showed statistically significant mean improvements from baseline to Week 12 in manic/hyperactive behavior, social avoidance and general anxiety, but not compulsive behavior or depressed mood subscales

Figure 5. Change From Baseline to Week 12 in ABC-C_{FXS} Total Score

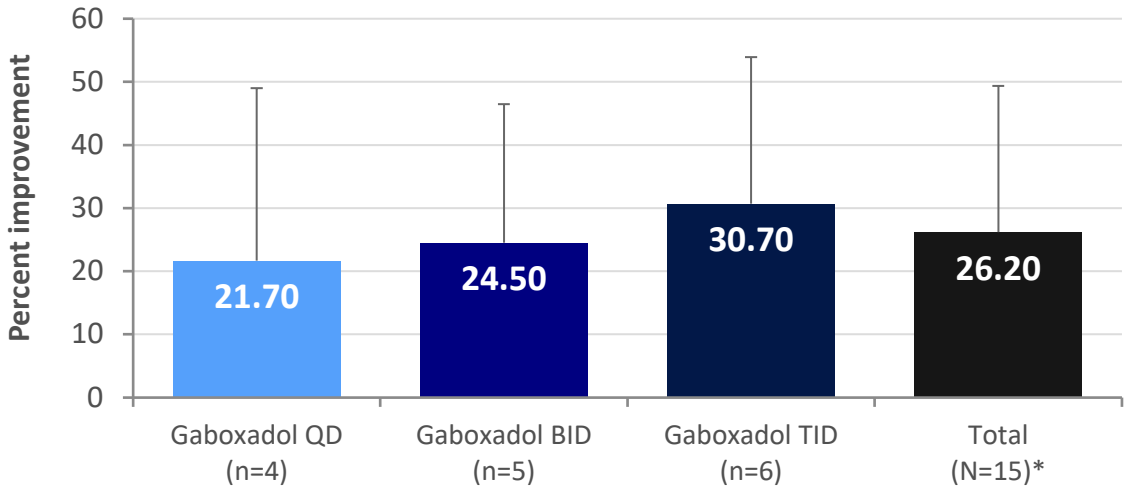
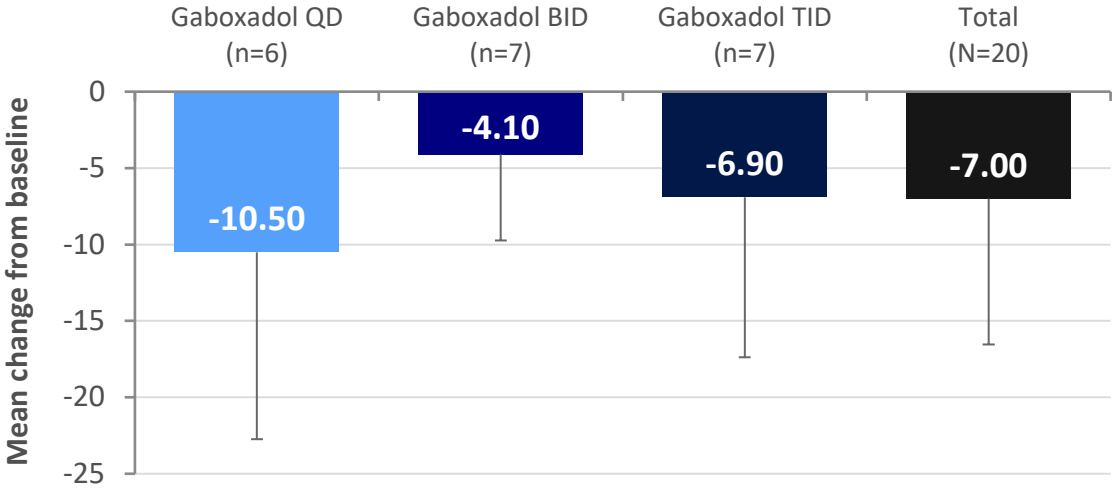


Figure 6. Change From Baseline to Week 12 in ADAMS Total Score



Data presented as mean change (SD) unless otherwise specified; sample sizes (n) were different in the study population due to patients who discontinued later in the study.
*Individuals with minimal behavior symptoms as measured by the ABC-C scale (defined as baseline ABC-C total score ≤16) were prespecified to be excluded from this planned analysis. Six individuals from the total cohort of 23 patients met this exclusion criteria.
ABC-C_{FXS}, Aberrant Behavior Checklist–Community for Fragile X syndrome; BID, twice daily; ADAMS, Anxiety, Depression, and Mood Scales; QD, once daily; SD, standard deviation; TID, three times daily.

RESULTS: Across Gaboxadol Dosing Groups, Significant Improvement Was Observed in CGI-S, and 60% of Participants Were Identified as CGI-I Responders

Efficacy: CGI-S and CGI-I

- Across dosing groups, statistically significant improvement was observed from baseline to Week 12 in CGI-S total score (Figure 7; *P*=0.002)
  - In CGI-S subscales, statistically significant mean improvements were observed from baseline to Week 12 in communication, anxiety, attention deficit hyperactivity disorder, and activities of daily living domains, but not disruptive behavior and repetitive or restrictive behaviors domains
- Compared to baseline measurements, 60% of participants who received gaboxadol were identified as CGI-I responders at Week 12 (Figure 8; defined as improvement in CGI-I by a response of "2-Much Improved" [40%], or "3-Minimally Improved" [20%])

Figure 7. Change From Baseline to Week 12 in CGI-S Total Score

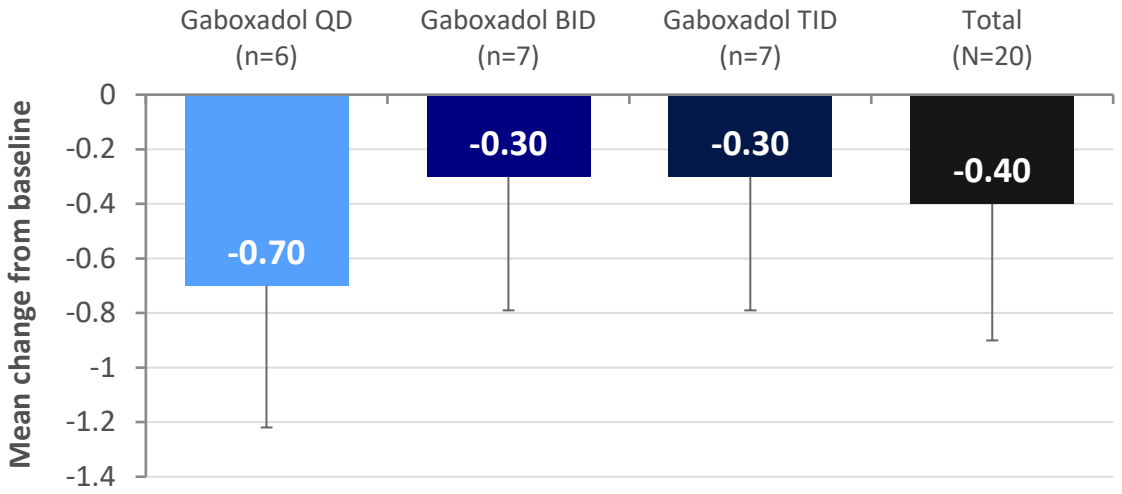
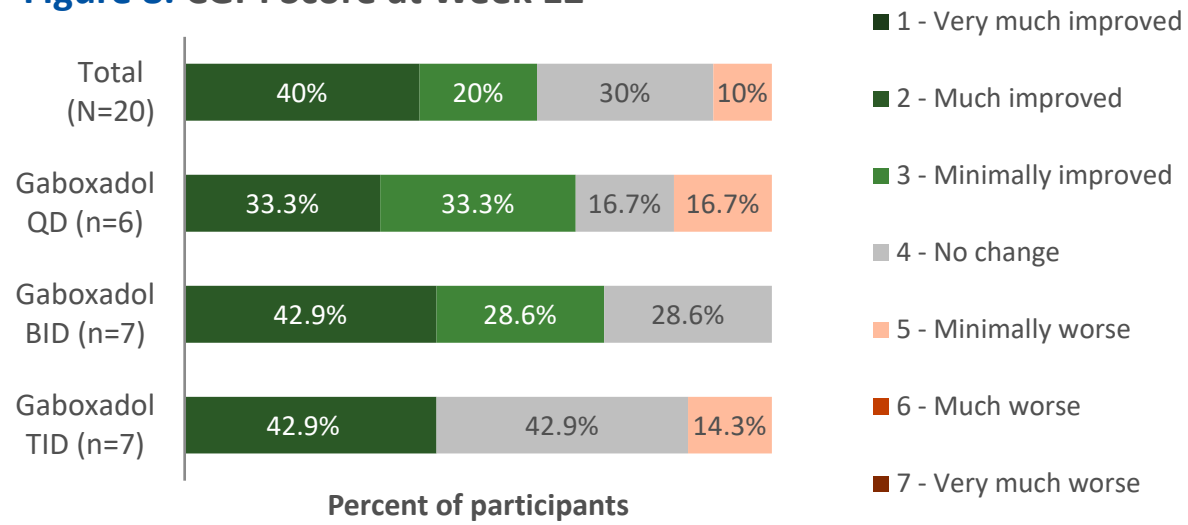


Figure 8. CGI-I Score at Week 12



Data presented as mean change (SD) unless otherwise specified; sample sizes (n) were different in the study population due to patients who discontinued later in the study.
BID, twice daily; CGI-I, Clinical Global Impressions–Improvement; Clinical Global Impressions–Severity; QD, once daily; TID, three times daily.

CONCLUSIONS

- The ROCKET Phase 2a clinical trial investigated gaboxadol in adolescents and young adult males with FXS
- The trial met its primary endpoint of safety and tolerability
  - Gaboxadol appeared to be well tolerated over 12 weeks of treatment across all 3 dosing regimens
- Improvements from baseline to end of treatment were observed from several efficacy endpoints when examined across dosing groups
  - Across dosing groups, significant improvements were observed from baseline to Week 12 in ABC-C_{FXS}, ADAMS, and CGI-S total scores, and 60% of participants were identified as CGI-I responders
- Additional analyses are ongoing
- A limitation to extrapolating these results was the absence of a placebo group and the potential for placebo effects on behavioral measures, as large placebo effects have been observed in FXS patients from previous trials[1]
  - Larger placebo effects have been observed in open-label studies than in placebo-controlled trials in patients with intellectual disability
- The results suggest that gaboxadol holds potential to be a therapeutic option for individuals with FXS, and they may help inform future placebo-controlled trials of gaboxadol for FXS

1. Berry-Kravis EM, et al. *Nat Rev Drug Discov.* 2018;17(4):280–299.