The pivotal Phase 3 NEPTUNE trial investigating OV101 (gaboxadol) in Angelman syndrome: study overview and rationale

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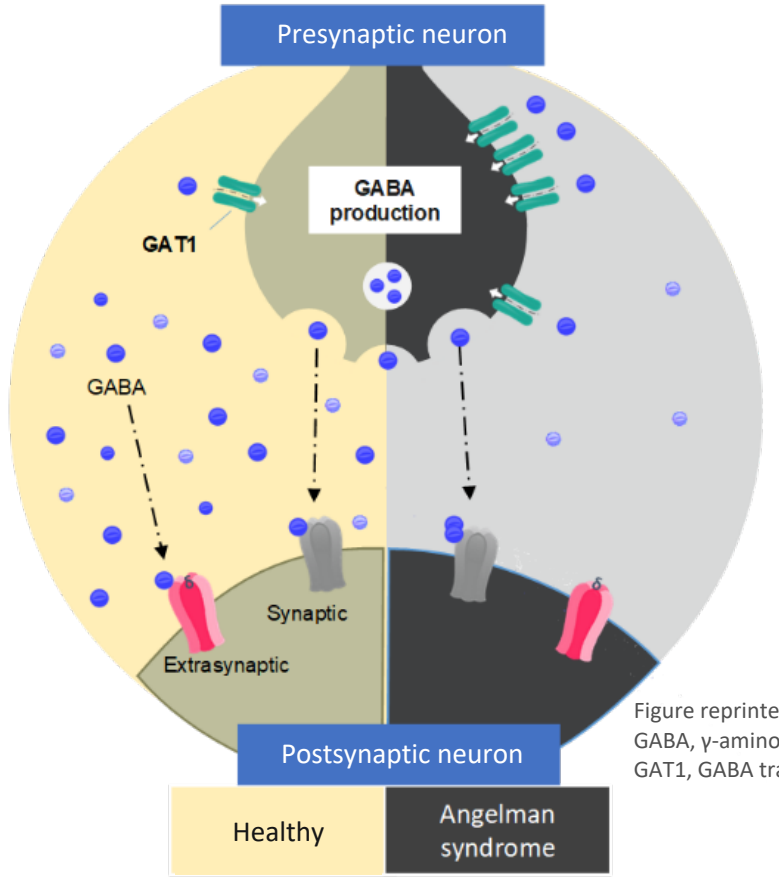
INTRODUCTION: Angelman Syndrome

Angelman Syndrome

- Angelman syndrome (AS) is a rare, genetic neurodevelopmental condition characterized by severe impairments in behavior, motor function, communication, and sleep, as well as intellectual disability, seizures, and ataxia[1]
- AS is most commonly caused by a deletion or loss-of-function mutation in the maternal gene coding for ubiquitin-protein ligase E3A (*UBE3A*)[2]
  - No functional UBE3A enzyme is produced in AS neurons[3]
- Studies in a mouse model of AS have observed excessive accumulation of the synaptic γ-aminobutyric acid (GABA) transporter type 1 (GAT1),[4] which has been associated with a loss of tonic inhibition, presumably owing to low ambient GABA concentrations[4–7] (Figure 1)
  - Reduced GABA concentration and loss of normal levels of tonic inhibition may theoretically play an important role in the underlying neuropathophysiology of AS

Figure 1. GABAergic Transmission in Physiological Conditions and in Angelman Syndrome



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GABA, γ-aminobutyric acid;
GAT1, GABA transporter type 1.

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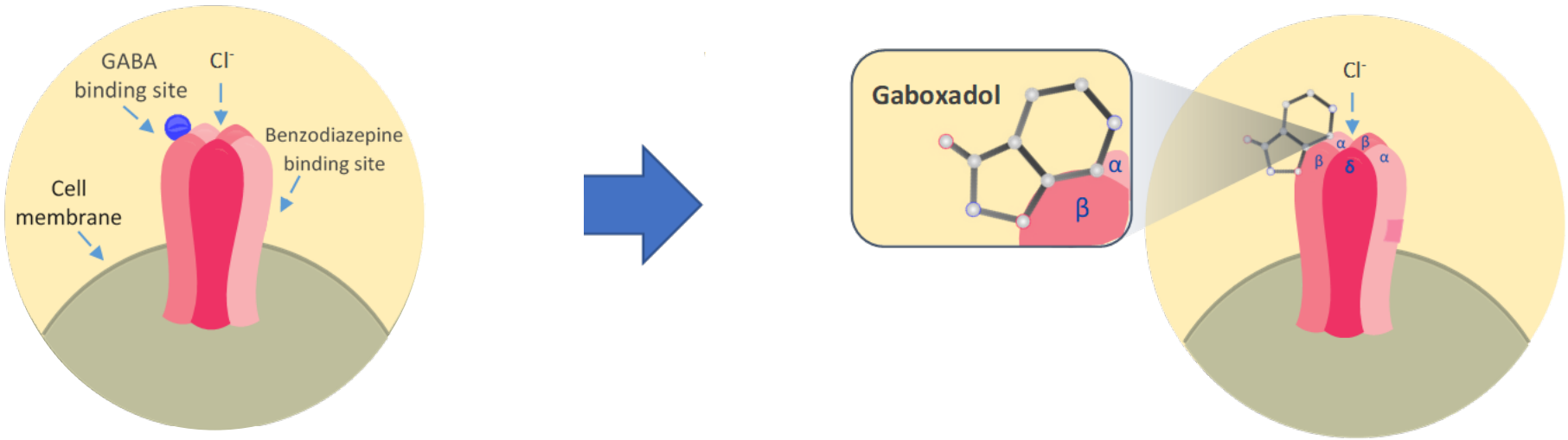
INTRODUCTION: OV101 (gaboxadol)

OV101 (gaboxadol)

- Preclinical studies suggest gaboxadol, which is a δ subunit–selective extrasynaptic GABA type A ($GABA_A$) receptor agonist (Figure 2), mediates tonic inhibition in cerebellar neurons and may partially restore cerebellar motor dysfunction in a mouse model of AS[1,2]
- When administered to mice with disrupted *Ube3a* expression, gaboxadol has restored deficits in tonic inhibition[1,3–5]

Figure 2. Gaboxadol Site of Action



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

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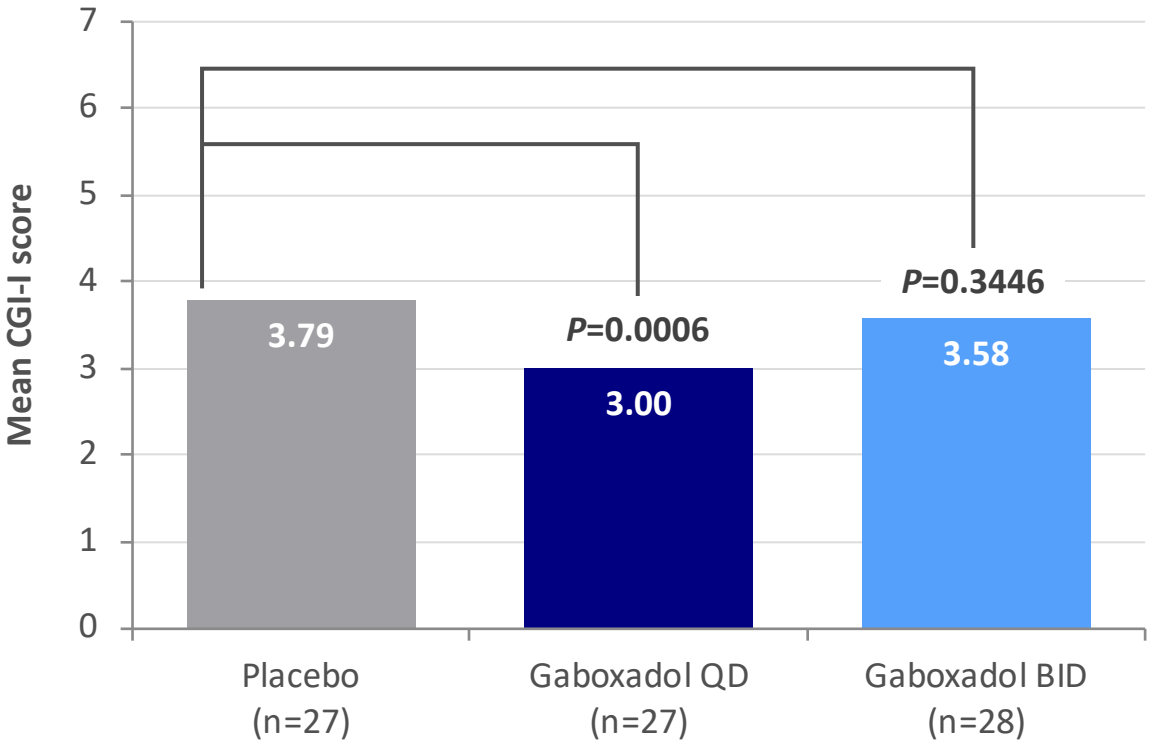
INTRODUCTION: Clinical Global Impressions Rating Scales

Clinical Global Impressions Rating Scales

- In STARS, a Phase 2 trial that investigated gaboxadol in adolescents and adults with AS, a statistically significant improvement in overall global functioning was observed in the gaboxadol 15-mg group versus placebo at Week 12, as demonstrated by the Clinical Global Impressions–Improvement (CGI-I) scale[1] (Figure 3)
- The current Phase 3 trial (NEPTUNE; ClinicalTrials.gov identifier NCT04106557) will use the CGI-I adapted specifically for AS, the CGI-I Angelman Syndrome (CGI-I-AS) scale, as the primary endpoint to evaluate the efficacy of gaboxadol versus placebo in pediatric individuals with AS at 12 weeks of treatment
  - The CGI scales have utility for assessing rare neurodevelopmental disorders, including AS[2–4]
  - The CGI-I was used as a co-primary endpoint in a clinical trial involving children and adolescents with Fragile X syndrome,[4] and disease-specific adaptations of the CGI have been previously made for rare neurodevelopmental disorders[5,6]
  - The CGI-I-AS provides an assessment of meaningful change in symptom severity unique to key features of AS

Figure 3. STARS Trial Mean CGI-I at Week 12 (MMRM)*[1]



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*LS mean difference (95% CI) for drug versus placebo was −0.78 (−1.22, −0.35) with gaboxadol QD and −0.21 (−0.64, 0.22) with gaboxadol BID.
BID, twice daily; CGI-I, Clinical Global Impressions–Improvement; LS, least squares; MMRM, mixed model for repeated measures; QD, once daily.

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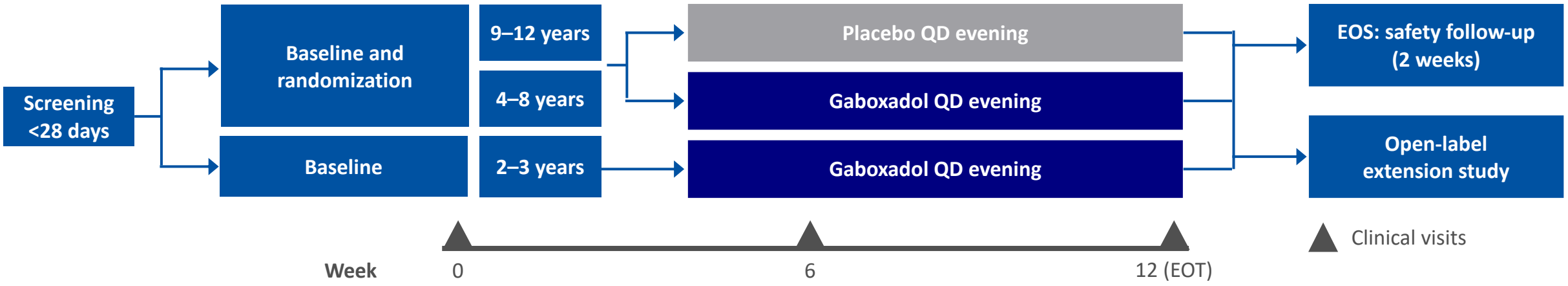
STUDY STATUS: Study Design and Enrollment

Study Design and Enrollment Status

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group study (Figure 4)
  - Eligible individuals (Table 1) are enrolled at study sites in the United States, Israel, Australia, and/or Europe
  - Enrollment: ≈90 participants aged 4–12 years (at ≤15 study sites) and up to 5 participants aged 2–3 years (for safety assessment only)
- Allocation (1:1) to gaboxadol or matching placebo for 12 weeks; stratified by age group (9–12 years [inclusive]/4–8 years [inclusive]), with ≥24 individuals in each treatment arm
- Participants aged 2–3 years (inclusive) assigned to gaboxadol; no participants in this age group randomized to placebo

Figure 4. Study Design



EOS, end of study; EOT, end of treatment; QD, once daily.
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STUDY STATUS: Key Inclusion and Exclusion Criteria

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Aged 2–12 years, inclusive • Individuals with a diagnosis of AS confirmed by genetic testing • Clinical Global Impressions–Severity (CGI-S) score ≥3 • Meets age-appropriate body weight criterion: aged 2–3 years, ≥9 kg; aged ≥4 years, 17–64 kg (inclusive) • Caregiver is capable of providing informed consent, overseeing study drug administration, attending scheduled study visits, and providing feedback • Concomitant medications and special diet regimens are stable for ≥4 weeks prior to randomization and are maintained throughout the study • Able to take oral study drug (as capsule or with capsule contents mixed with low-fat, semiliquid food) • Female participants of child-bearing potential agree to use contraception during the study and for 30 days following the last dose of study treatment	• Concomitant gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease or condition that would limit participation in the study • Poorly controlled seizures (weekly seizures of any frequency with duration >3 minutes, weekly seizures occurring >3 times/week and with frequency of <3 minutes, or as assessed by investigator) • Clinically significant laboratory abnormalities at screening • Regular use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep or minocycline or levodopa within 4 weeks prior to day 1 or during the study; benzodiazepines administered as needed for situational anxiety or for seizure control are permitted • Inability to wear actigraphy for ≥7 consecutive days (including 2 consecutive weekend days) during the 28-day screening period • Is at risk of harming self and/or others • Recent enrollment in any clinical study or use of any investigational agent, device, or procedure (within 30 days of screening) • Has a sibling enrolled in the study

AS, Angelman syndrome.
Data on file, Ovid Therapeutics Inc.

MATERIAL & METHODS: Study Objectives

Study Objectives

- **Primary objective:** to evaluate the efficacy of gaboxadol versus placebo on global functioning in pediatric individuals aged 4–12 years with AS, as assessed by the CGI-I-AS score at Week 12
- **Secondary/tertiary objectives**:
  - To evaluate the efficacy of gaboxadol versus placebo in pediatric individuals aged 4–12 years with AS, as assessed by the proportion of subjects who experience any meaningful improvement on study treatment (defined as CGI-I-AS score of 1, 2, or 3 at Week 12)
  - To evaluate the efficacy of gaboxadol versus placebo in pediatric individuals aged 4–12 years with AS, as assessed by the proportion of subjects who experience a response of much improved or very much improved (defined as CGI-I-AS score of 1 or 2 at Week 12)
  - To evaluate the safety and tolerability of gaboxadol versus placebo in pediatric individuals aged 2–12 years with AS
  - To assess effects of gaboxadol on sleep and on relevant domains of behavior, motor function, and communication at Week 12 from actigraphy and the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), respectively, in pediatric individuals aged 4–12 years with AS
- **Pharmacokinetic (PK) objective**: to estimate systemic plasma exposure to gaboxadol (maximum plasma concentration and area under the concentration-time curve) following a single oral dose using sparse sampling and a population PK approach for pediatric individuals aged 2–12 years with AS

MATERIAL & METHODS: Gaboxadol Weight-Based Dosing and Titration

Gaboxadol Weight-Based Dosing and Titration

- Starting dose administered for 5 days (Table 2) and increased to maintenance dose beginning on Day 6 in absence of tolerability concerns or study drug-related adverse events (down-titration permitted at Day 11 if tolerability issues are detected)
- All treatments administered ≈30 minutes prior to bedtime

Table 2. Daily Dosing and Titration

Weight, range (kg)*	Starting dose (mg)	Maintenance dose (mg)	Maintenance dose, range (mg/kg)
45–64	6	10	0.222–0.156
35–44	4	8	0.23–0.19
25–34	2	6	0.24–0.176
17–24	2	4	0.23–0.16
9–16†	1	2	0.23–0.125

*Weight at screening; †Younger than 4 years of age at screening.
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MATERIAL & METHODS: Study Endpoints

Study Endpoints

- Safety, sleep, and global functioning/quality of life are being assessed (Table 3)

Table 3. Clinical Assessments

Domain	Assessments
Safety	• Incidence of adverse events and changes from baseline in clinical laboratory parameters • Vital signs, physical examination parameters, suicidality (Aberrant Behavior Checklist, irritability subscale), and seizure frequency (seizure diary)
Global functioning/ quality of life (all scores at Week 12, except where noted)	• CGI-S-AS/CGI-I-AS scores – CGI-I-AS score* – CGI-S-AS overall score change from baseline† – Relationship between CGI-S-AS overall score at baseline and CGI-I-AS† – Relationship between each of the CGI-S-AS domains at baseline and CGI-I-AS score† – Responder analyses of CGI-I-AS scores for responses ≤3 and responses ≤2†‡ • Vineland-3 standard scores, change from baseline† • PedsQL Cerebral Palsy, Multidimensional Fatigue, and Family Impact modules§
Sleep	• Actigraphy, change from baseline to Week 12† – Latency of sleep onset from beginning of rest period to start of sleep onset – Sleep efficiency: percentage of total sleep time out of duration of the rest period • Actigraphy, total sleep time, total activity, total daytime sleep, and duration of sleep time in the active interval§ • Caregiver-reported sleep diary data§ • Children's Sleep Habits Questionnaire§

*Primary efficacy endpoint; †Secondary efficacy endpoints; ‡Participants receiving a score of ≤3 are considered responders with "at least minimal improvement"; participants receiving a score of ≤2 are considered responders with "at least much improvement"; §Tertiary efficacy endpoints.
CGI-S-AS, Clinical Global Impressions–Severity–Angelman Syndrome; PedsQL, Pediatric Quality of Life Inventory; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.
Data on file, Ovid Therapeutics Inc.

CONCLUSIONS

- The pivotal NEPTUNE Phase 3 trial is designed to evaluate the efficacy, safety, and tolerability of gaboxadol in the treatment of pediatric individuals with AS
- Based on the positive results on the CGI-I from the Phase 2 STARS trial, which investigated gaboxadol in adolescents and adults with AS, the NEPTUNE trial is evaluating the effects of gaboxadol in pediatric individuals with AS using the CGI-I-AS
- The CGI-I-AS was adapted from the CGI-I for use in this trial as the primary efficacy endpoint to provide an assessment that can capture meaningful change across a diverse spectrum of symptom severity, addressing the lack of specific rating scales that capture the heterogeneity of impairment seen in AS
- Efficacy is being assessed from the CGI-I-AS for meaningful change in symptom severity unique to key features of AS in the context of treatment with gaboxadol