Differential pharmacodynamics of once vs. twice daily OV101 (gaboxadol) administration: Evidence of pharmacodynamic tolerance with twice daily gaboxadol dosing in individuals with Angelman syndrome

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**INTRODUCTION: Background of Angelman Syndrome**

**Objective**

- To evaluate evidence from the STARS Phase 2 trial in individuals with Angelman syndrome (AS) for emergence of pharmacodynamic tolerance or desensitization with multiple daily doses of gaboxadol (4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridin-3-ol [THIP]; OV101)

**Background**

- AS is a rare, genetic neurodevelopmental condition with an estimated prevalence of 1/12,000 to 1/20,000\(^1\)
- It is primarily caused by deletion or loss of function of the maternally inherited \textit{UBE3A} gene, which codes for ubiquitin-protein ligase E3A
- Loss of maternal \textit{UBE3A} gene function in the background of a normally silenced paternal \textit{UBE3A} allele leads to loss of \textit{UBE3A} expression in neurons within the central nervous system (CNS)
- Symptoms of AS are phenotypically heterogeneous; clinical manifestations include severe impairments in behavior, motor function, communication, and sleep, as well as intellectual disability, seizures, ataxia, and dysmorphic features
  - No currently approved therapy targets the underlying pathophysiology of AS

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INTRODUCTION: Disruption in UBE3A Gene Is Associated With Decreased Tonic Inhibition

GABAergic Signaling

• Tonic inhibition mediated by extrasynaptic, δ-subunit–containing GABA type A (GABA_{A}) receptors is a key contributor to the excitability of individual neurons and neuronal networks\(^1\)

• γ-aminobutyric acid (GABA) signaling regulates excitatory/inhibitory balance, which optimizes information processing within neuronal circuits (Figure 1)\(^1\)

• Disrupted UBE3A gene expression is associated with accumulation of GABA transporter type 1 (GAT1)\(^1\)

• Increased GAT1 activity leads to decreased ambient GABA concentrations, resulting in functional disruption of GABA neurotransmission and decreased tonic inhibition\(^1,2\)
  
  • Deficient tonic inhibitory signaling induces excessive neuronal firing and an elevated rate of network activity

Figure 1. Impaired Tonic Inhibition Induces Neuronal Hyperactivity

E/I, excitatory/inhibitory; GABA, γ-aminobutyric acid.

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INTRODUCTION: Gaboxadol Is a GABA<sub>A</sub> Receptor Agonist

**Gaboxadol**
- Gaboxadol preferentially activates extrasynaptic, δ-subunit–containing GABA<sub>A</sub> receptors at therapeutic concentrations (Figure 2)
  - Gaboxadol binds to δ-subunit–containing GABA<sub>A</sub> receptors (predominantly α4βδ, but also α6βδ and α1βδ) with an affinity 1 to 3 orders of magnitude greater than GABA<sup>1–3</sup>
  - At supratherapeutic concentrations, gaboxadol binds to all GABA<sub>A</sub> receptors
- Activation of δ-subunit–containing GABA<sub>A</sub> receptors by GABA (a partial agonist) or gaboxadol (a full agonist with respect to GABA) produces sustained or tonic increase in conductance of chloride (Cl<sup>−</sup>) ions; this sustained increase in Cl<sup>−</sup> conductance is inhibitory to the neuron and generates tonic inhibition in most areas of the developed brain<sup>4,5</sup>
  - This tonic inhibition is a sustained, low-amplitude, inhibitory current compared with the phasic current resulting from synaptically released GABA
- Recent studies suggest that δ-containing GABA<sub>A</sub> receptors also contribute to the phasic current, though to a lesser degree than to the tonic current<sup>6</sup>

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**Dose-dependent Effects of Gaboxadol**

- Functional desensitization to gaboxadol in mice has been observed over time and across dose levels (Figure 3)\(^1,2\)
- Rotarod performance over time following a single daily dose of gaboxadol in wild-type mice suggested a loss of pharmacologic effect over time (Figure 3A)\(^2\)
- Systemic administration of gaboxadol in \textit{Ube3a}\(^{-/-}\)-deficient mice, an AS model, has been found to improve multiple behavioral and motor deficits\(^1\)
  - Rotarod performance in AS mice (\textit{Ube3a}\(^{m-/p^+}\)) over increasing concentrations suggested a loss of pharmacologic effect at the highest dose of gaboxadol evaluated in both wild-type and \textit{Ube3a}\(^{m-/p^+}\) mice (Figure 3B)
  - The amount of time on a rotarod 30 minutes after an injection was normalized to the time before the injection

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**Figure 3. Preclinical Desensitization Effects of Higher Doses of Gaboxadol**

- *Significantly different (\(P<0.05\)) from starting value (1-way ANOVA); **significantly different from untreated (2-way repeated-measures ANOVA). For both plots, data are means ± SEM.

ANOVA, analysis of variance; s, seconds; SEM, standard error of the mean; WT, wild type.

Figure 3A is reprinted from the European Journal of Pharmacology, volume 482, by Voss J et al. Rotarod studies in the rat of the GABA\(_A\) receptor agonist gaboxadol: lack of ethanol potentiation and benzodiazepine cross-tolerance, pages 215–222, copyright 2003, with permission from Elsevier.

Figure 3B is used with permission of the American Association for the Advancement of Science, from Science Translational Medicine, Decreased tonic inhibition in cerebellar granule cells causes motor dysfunction in a mouse model of Angelman syndrome, by Egawa K et al, volume 4, issue 163, copyright 2012; permission conveyed through Copyright Clearance Center, Inc.

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**Design of STARS Phase 2 Trial in Angelman Syndrome**

**STARS Clinical Trial Design (NCT02996305) (Figure 4)**

- Eighty-eight (88) individuals with AS (aged 13–45 years) completed the study
  - Inclusion criteria: AS diagnosis confirmed by genetic testing and a stable regimen of concomitant medications for ≥4 weeks prior to baseline
  - Treatment schedule: participants were randomized (1:1:1) to placebo twice daily (BID), placebo morning and gaboxadol once daily (QD), or gaboxadol BID for 12 weeks
- The Clinical Global Impressions–Improvement (CGI-I) scale is a well-validated clinician-rated method commonly used in CNS drug development trials to assess outcome in heterogeneous populations and to measure global changes and treatment effects that are clinically meaningful
  - In the STARS trial, CGI-I change (overall and in 9 prespecified clinical domains) was assessed at Week 12 using a modified CGI-I scale
- Additional assessments occurred at screening, baseline, and Weeks 6 and 12; actigraphy measurements were taken at Weeks 1, 2, 4, 6, and 12

**Figure 4. Overall Design of STARS Trial**

Data on file, Ovid Therapeutics Inc.
RESULTS: Gaboxadol QD Had a Significant Effect on CGI-I at Week 12 Versus Placebo

**Gaboxadol Appears to Promote Improvements on CGI-I (Figure 5/Table 1)**

- Mixed-effect model repeated measures (MMRM) analysis of the CGI-I score at Week 12 showed significant improvement in the gaboxadol QD group versus placebo (Table 1; Figure 5A; \( P=0.0006 \))

- However, MMRM analysis did not show significant difference between the gaboxadol BID group and placebo (Figure 5A; \( P=0.3446 \))

- Responder analysis of CGI-I showed statistically significant improvement in the combined gaboxadol group (QD and BID) at Week 12 versus placebo (Figure 5B: 66.7% and +39.3% respectively; \( P=0.0206 \))

- Responders exhibiting minimal (CGI-I=3) or much (CGI-I=2) improvement in CGI-I (Figure 5C) were as follows:
  - 66.6% of individuals in the gaboxadol QD treatment group
  - 42.8% of individuals in the BID group
  - 22.2% of individuals in the placebo-treated group

### Table 1. MMRM Analysis of CGI-I

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Gaboxadol QD</th>
<th>Gaboxadol BID</th>
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<tbody>
<tr>
<td>CGI-I score at Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>LSM (SE)</td>
<td>3.79 (0.161)</td>
<td>3.00 (0.163)</td>
<td>3.58 (0.161)</td>
</tr>
<tr>
<td>Gaboxadol-placebo</td>
<td>---</td>
<td>-0.78 (0.218)</td>
<td>-0.21 (0.216)</td>
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<tr>
<td>LSM difference (SE)</td>
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</tr>
<tr>
<td>( P ) value</td>
<td>0.0006</td>
<td>0.3446</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as LSM or LSM difference. SE indicates the standard error associated with the parameter.

BID, twice daily; CGI-I, Clinical Global Impressions–Improvement; LSM, least squares mean; MMRM, mixed-effect model repeated measures; QD, once daily.

Data on file, Ovid Therapeutics Inc.
RESULTS: Compared to Baseline, 67% of Individuals on Gaboxadol QD Were Identified as CGI-I Responders Versus 43% on BID and 22% on Placebo

Figure 5. Effects of Gaboxadol on CGI-I

(A) Mean CGI-I score in placebo, gaboxadol QD, and gaboxadol BID treatment groups. (B) Percentage of responders in CGI-I and 9 clinical domains with OV101 (QD and BID) versus placebo. (C) Percentage of individuals in each CGI-I score category at Week 12 of the study.

BID, twice daily; CGI-I, Clinical Global Impressions–Improvement; QD, once daily.

Data on file, Ovid Therapeutics Inc.
RESULTS: Gaboxadol QD, but Not Gaboxadol BID, Produced Progressive Improvement in Sleep Onset Latency Over Time

Sleep Onset Latency (Figure 6)

- Dosing with gaboxadol QD was found to produce progressive improvement (reduction) in sleep onset latency over time, with sustained improvement from Weeks 4 to 12
- No effect was observed with QD dosing at Week 1
- Dosing with BID was found to produce rapid (though transient) improvement in sleep onset latency at Week 1
  - The observed effect with BID dosing was lost from Weeks 4 to 12
- Whereas significant sustained improvement was observed with QD dosing, the lack of sustained improvement with BID dosing suggests emergence of tolerance or desensitization produced by more frequent daily gaboxadol treatment

Figure 6. Effects of Gaboxadol Versus Placebo on Sleep Onset Latency

Data are expressed as mean change in sleep onset latency from baseline in minutes at study intervals of 1, 2, 4, 6, and 12 weeks.

BID, twice daily; min, minutes; QD, once daily.

Data on file, Ovid Therapeutics Inc.
CONCLUSIONS: Differences in QD and BID Regimens on Behavior May Result From Tolerance or Desensitization

CONCLUSIONS

• In the STARS trial, QD administration of gaboxadol resulted in significant improvement in CGI-I and sleep onset latency in adults and adolescents with AS
  • BID administration, by contrast, had no significant effect on these endpoints
• Differences in CGI-I and sleep onset latency outcomes between QD and BID gaboxadol dosing regimens in people with AS may result from receptor overstimulation–induced pharmacodynamic tolerance or desensitization
• Extrasynaptic GABA_A receptor desensitization and tolerance in response to GABAergic stimulation have been demonstrated with gaboxadol¹ and other agonists,²,³ including positive allosteric modulators,⁴ and are related to both dose level and duration of drug exposure¹-⁴
• Supratherapeutic doses and excessive temporal exposure to GABA_A agonists are commonly associated with the emergence of pharmacodynamic tolerance²

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