Safety and Tolerability of Ecopipam in Tourette Syndrome With Psychiatric Comorbidities

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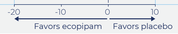
BACKGROUND

- Patients with Tourette syndrome (TS) commonly have comorbid psychiatric conditions (eg, anxiety disorders [ANX], attention-deficit/hyperactivity disorder [ADHD], depression, and obsessive-compulsive disorder [OCD])[1-2] that may influence TS-related treatment decisions
- Ecopipam is a first-in-class, potent, selective human dopamine D1 receptor antagonist being investigated for the treatment of TS[3]
- In a phase 2b trial (D1AMOND), ecopipam tablets (2 mg/kg/day) improved the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) by 30% from baseline at Week 12 in patients with TS, with significance versus placebo (P=0.01)[3]
  - In a subset of the 149 (62.4%) patients who had a medical history of ADHD, ANX, or OCD, these comorbid conditions did not impact the efficacy of ecopipam for TS tic reduction (ie, improvement from baseline in YGTSS-TTS at Week 12) versus placebo (**Figure 1**)[4]

Figure 1. Efficacy of Ecopipam Versus Placebo in Patients With and Without Psychiatric Comorbidities[4]

POPULATION	LSM DIFFERENCE IN YGTSS-TTS* (95% CI)	*P* VALUE
Total (n=149)	-3.44 (-6.09, -0.79)	**0.01**
Comorbid ANX (n=51)	-4.15 (-8.56, +0.26)	0.06
No comorbid ANX (n=98)	-3.41 (-6.96, +0.14)	0.06
Comorbid ADHD (n=68)	-4.40 (-8.78, -0.03)	**0.048**
No comorbid ADHD (n=81)	-2.18 (-5.59, +1.23)	0.21
Comorbid OCD (n=26)	-7.84 (-17.86, +2.19)	0.13
No comorbid OCD (n=123)	-3.42 (-6.38, -0.46)	**0.02**
Comorbid ANX, ADHD, or OCD (n=93)	-3.88 (-7.23, -0.52)	**0.02**
No comorbid ANX, ADHD, or OCD (n=56)	-2.66 (-7.49, +2.17)	0.28



*Ecopipam minus placebo (Week 12). Comorbid identification based on case report form information under medical history.
ADHD = attention-deficit/hyperactivity disorder; ANX = anxiety disorders; LSM = least-squares mean; OCD = obsessive-compulsive disorder; YGTSS-TTS = Yale Global Tic Severity Scale-Total Tic Score.

- However, data are lacking on the potential impact of ecopipam in patients with these comorbidities

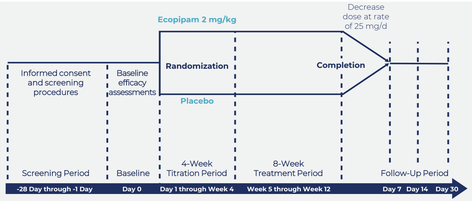
OBJECTIVE

- To assess if ecopipam effects measures of psychiatric comorbidities (ADHD, ANX, depression, and OCD) over the course of the trial

METHODS

- Post hoc subgroup analysis included patients from the phase 2b, randomized, double-blind, placebo-controlled D1AMOND trial aged ≥6 to <18 years with confirmed TS and YGTSS-TTS ≥20 at screening[2]
  - ANX, ADHD, antidepressant, and OCD medications were permitted if dosage was stable for ≥4 weeks before screening and not specifically prescribed for neurologic symptoms of TS
  - Patients were randomly assigned to ecopipam or placebo for a 4-week titration period, an 8-week maintenance period, and a taper period (**Figure 2**)

Figure 2. Study Design



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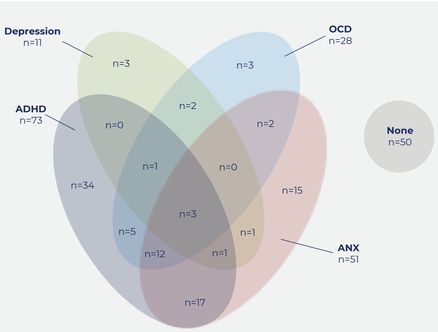
- Psychiatric comorbidities were assessed by the Swanson, Nolan, and Pelham questionnaire (SNAP-IV); SNAP-IV Connor Index Questionnaire; Pediatric Anxiety Rating Scale (PARS); Children's Depression Rating Scale-Revised (CDRS-R); and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores at baseline and Weeks 4, 6, 8, and 12
- In the current analysis, patients were subgrouped post hoc by presence or absence of baseline psychiatric comorbidities (ie, ANX [generalized or social anxiety, elective/selective mutism, and anxiety disorders not otherwise specified], ADHD, depression, and OCD [both single and multiple diagnoses])
  - Psychiatric comorbidities were identified based on investigator-completed case report forms of medical history and psychiatric history (which asked specifically about ADHD and OCD)
- Changes from baseline with ecopipam versus placebo were compared using a mixed model for repeated measures analysis of covariance model with an unstructured covariance matrix that included the following terms: baseline value, region, age group (6-11 y and 12-17 y), visit, treatment group, and visit-by-treatment interaction

RESULTS

- 149 patients were included in the analysis, with the majority (66.4%) of patients having ≥1 comorbid condition of ADHD, ANX, depression, and OCD (**Figure 3**)
  - The most common psychiatric comorbidities were ADHD (49.0%) and ANX (34.2%)

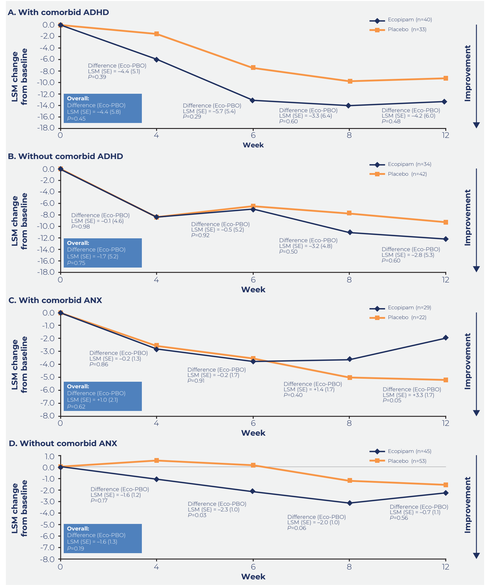
Figure 3. Patients With Psychiatric Comorbidities



ADHD = attention-deficit/hyperactivity disorder; ANX = anxiety disorders; OCD = obsessive-compulsive disorder.

- Serial assessment showed that 12 weeks of ecopipam did not significantly negatively impact measures of ANX, ADHD, depression, or OCD versus placebo in patients with TS with or without the comorbid condition of interest (**Figures 4A-D** and **5A-D**)
  - No significant differences from baseline were observed between ecopipam and placebo for all subscales of SNAP-IV in patients with or without comorbid ADHD (data not shown)
  - In addition, no significant negative impact was observed with ecopipam versus placebo across the 12 weeks versus baseline for SNAP-IV Connor Index Questionnaire score in patients with (difference ecopipam – placebo LSM [SE] = –0.1 [0.1]; P=0.43) or without (LSM [SE] = 0.0 [0.1]; P=0.84) comorbid ADHD

Figure 4. Change in SNAP-IV Scale Score in Patients With (A) or Without (B) Comorbid ADHD and Change in PARS Score in Patients With (C) or Without (D) Comorbid Anxiety



ADHD = attention-deficit/hyperactivity disorder; ANX = anxiety disorders; Eco = ecopipam; LSM = least-squares mean; PARS = Pediatric Anxiety Rating Scale; PBO = placebo; SNAP-IV = The Swanson, Nolan, and Pelham questionnaire.

Figure 5. Change in CDRS-R Scale Score in Patients With (A) or Without (B) Comorbid Depression and Change in CY-BOCS Score in Patients With (C) or Without (D) Comorbid OCD

CDRS-R = Children's Depression Rating Scale-Revised; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; Eco = ecopipam; LSM = least-squares mean; NC = not calculated; OCD = obsessive-compulsive disorder; PBO = placebo.

CONCLUSIONS

- Ecopipam has previously been shown to significantly improve symptoms of TS[3]
- Compared to placebo, ecopipam was not associated with worsening of ADHD, ANX, depression, or OCD comorbidities during the trial
- A phase 3 trial of ecopipam focused on the treatment of TS in pediatric patients aged ≥6 to <18 years is ongoing (NCT05615220)

REFERENCES: 1. Johnson KA, et al. *Lancet Neurol*. 2023;22(2):147-158. **2.** Hirschtritt ME, et al. *JAMA Psychiatry*. 2015;72(4):325-333. **3.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574. **4.** Atkinson SD, et al. Presented at American Psychiatric Association Annual Meeting; May 20-24, 2023; San Francisco, CA.

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DISCLOSURES: DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc., and PTC Therapeutics. SDA, GBK, and FEM are employees of Emalex Biosciences, Inc. SPW and TMC are employees of Paragon Biosciences, LLC, a company that founded Emalex Biosciences, Inc.

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