Efficacy, Safety, and Tolerability of Ecopipam in Tourette Syndrome With Psychiatric Comorbidities

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Sarah D. Atkinson, MD[1]; Donald L. Gilbert, MD, MS[2]; Jordon S. Dubow, MD[3]*; Timothy M. Cunniff, PharmD[3]; Atul R. Mahableshwarkar, MD[1]*

[1]Emalex Biosciences, Inc., Chicago, IL; [2]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH; [3]Paragon Biosciences, LLC, Chicago, IL

*At the time the study was conducted.

BACKGROUND

- The following information concerns a use that has not been approved by the US Food and Drug Administration
- Patients with Tourette syndrome (TS) commonly have comorbid psychiatric conditions (eg, anxiety disorders [ANX], attention-deficit/hyperactivity disorder [ADHD], and obsessive-compulsive disorder [OCD])[1]
  - Alpha-2 adrenergic agonists may be more effective in patients with TS and ADHD than in those with TS without comorbid ADHD[2]
  - Antipsychotics (eg, dopamine D_2 receptor antagonists) have an unfavorable safety profile that includes the risk of weight gain and development of metabolic abnormalities and movement disorders[2]
- Ecopipam is a first-in-class investigational agent that is being studied as a potential treatment for TS that blocks the actions of the neurotransmitter dopamine at the D_1 receptor
- The recently published phase 2b trial (N=153; patients aged 6 to <18 y) demonstrated a significant improvement from baseline in the Yale Global Tic Severity Score-Total Tic Score (YGTSS-TTS) at Week 12 (*P*=0.01) without the weight gain and development of metabolic or movement disorders associated with dopamine-2 antagonists[3]

OBJECTIVE

- Evaluate the efficacy of ecopipam in treating TS in children and adolescents with pre-existing psychiatric comorbidities of ANX, ADHD, or OCD

METHODS

- Data were analyzed from the phase 2b, randomized, double-blind, parallel-group, placebo-controlled trial that included patients aged 6 to <18 years with confirmed TS and a YGTSS-TTS ≥20 at screening[3]
  - ANX, ADHD, 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 1**)
  - **Primary endpoint:** mean change from baseline in the YGTSS-TTS at Week 12 in the modified intent-to-treat population (mITT: all randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline YGTSS-TTS assessment)
  - Results of the Pediatric Anxiety Rating Scale (ANX); the Swanson, Nolan, and Pelham questionnaire (ADHD); and the Children's Yale-Brown Obsessive Compulsive Scale (OCD) scores were assessed at baseline and Weeks 4, 6, 8, and 12
- In the current analyses, patients in the trial were stratified post hoc by presence or absence of baseline psychiatric comorbidities (ie, ANX, ADHD, and OCD [both single and multiple diagnoses]) in order to explore whether these comorbidities affect tic-suppressing efficacy of ecopipam
- Statistical analyses followed the original trial primary efficacy endpoint methodology—a mixed model for repeated measures (mITT population)[3]

FIGURE 1. STUDY DESIGN

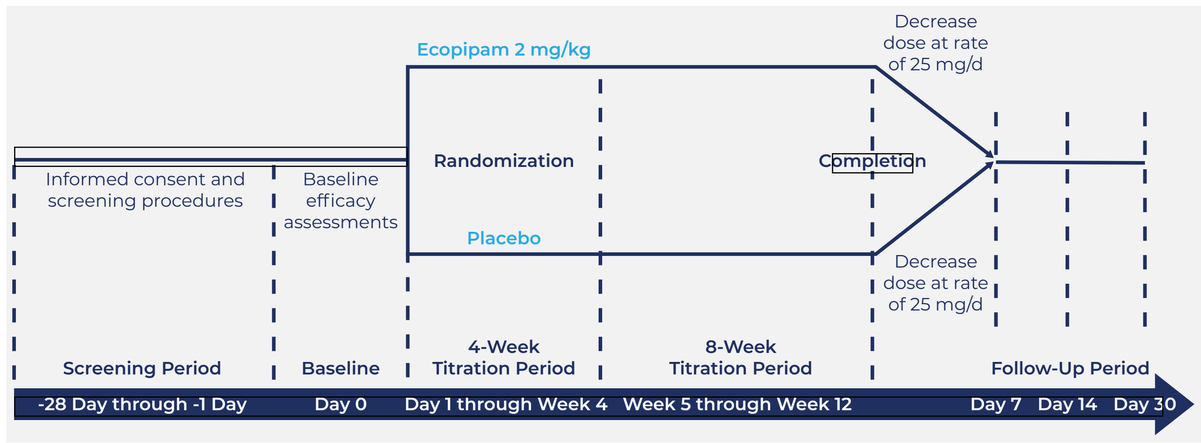
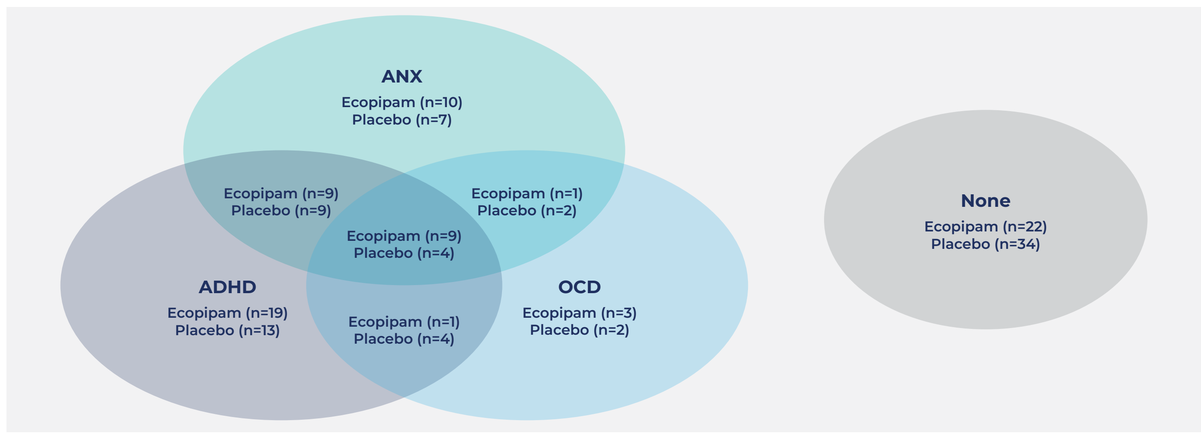


Figure reproduced from Gilbert DL, et al.[3]

RESULTS

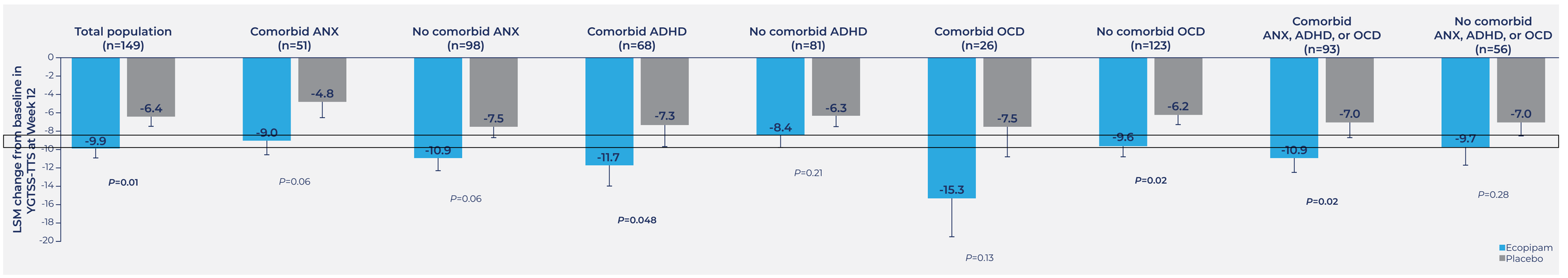
- 149 patients were included in the mITT population, with a majority (ecopipam [70.3%]; placebo [54.7%]) having comorbid ANX, ADHD, or OCD (**Figure 2**)
- Significant improvements (ie, decrease in YGTSS-TTS) with ecopipam versus placebo were observed at Week 12 in the overall population (*P*=0.01), the pooled subgroup with ANX, OCD, or ADHD (n=93; *P*=0.02), those with comorbid ADHD (n=68; *P*=0.048), and those without OCD (n=123; *P*=0.02) (**Figures 3** and **4**); all other subgroups showed numeric improvements favoring ecopipam
- Results from the 3 scales assessing ANX, ADHD, or OCD indicated no shifts from baseline in the total population or any of the subgroups during the 12-week trial (data not shown)
- To date, the safety profile of ecopipam appears favorable, with no substantial weight gain or metabolic (eg, diabetes, dyslipidemia, hyperglycemia, hyperprolactinemia) or movement disorders (eg, akathisia, dystonia, tardive dyskinesia, withdrawal-emergent dyskinesia) reported during the phase 2b trial[3]
  - For the overall phase 2b trial population, the most commonly reported adverse events were headache, insomnia, somnolence, fatigue, anxiety, nausea, and restlessness (**Table 1**)[3]

FIGURE 2. PATIENTS WITH TOURETTE SYNDROME AND PSYCHIATRIC COMORBIDITIES



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

FIGURE 3. LSM CHANGE FROM BASELINE IN YGTSS-TTS AT WEEK 12



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.

FIGURE 4. LSM DIFFERENCE IN YGTSS-TTS FOR ECOPIPAM VERSUS PLACEBO AT WEEK 12

POPULATION	LSM DIFFERENCE* (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.
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.

TABLE 1. SUMMARY OF ADVERSE EVENTS (OVERALL SAFETY POPULATION)

ADVERSE EVENTS	PATIENTS, N (%) PLACEBO (n=77)	PATIENTS, N (%) ECOPIPAM (n=76)
Any AE	38 (49.4)	47 (61.8)
Treatment-related AE*	16 (20.8)	26 (34.2)
AE leading to withdrawal	1 (1.3)†	4 (5.3)§
Serious AE	1 (1.3)‡	2 (2.6)¶
Most common AEs#		
Headache	7 (9.1)	12 (15.8)
Insomnia	2 (2.6)	10 (13.1)
Fatigue	0	6 (7.9)
Somnolence	2 (2.6)	6 (7.9)
Anxiety	0	4 (5.3)
Nausea	1 (1.3)	4 (5.3)
Restlessness	0	4 (5.3)

*Considered "possibly related" or "probably related" to treatment. †Suicidal ideation based on Columbia-Suicide Severity Rating Scale and defined as nonspecific suicidal thoughts or active suicidal ideation without intent to act. ‡Suicidal ideation. §4 patients with nausea, anxiety, depressed mood, self-injurious ideation, suicidal ideation, tic. ¶Coronavirus disease 2019 infection, vomiting. #≥5.0% incidence in ecopipam safety population.
Table reproduced from Gilbert DL, et al.[3]
AE = adverse event.

CONCLUSIONS

- In all comorbid subgroups (ie, ANX, ADHD, OCD, and combination), tic reduction (ie, improvement from baseline in YGTSS-TTS at Week 12) with ecopipam was greater compared with placebo
  - Although statistical differences were not observed in all subgroups, this is likely due to the analyses being underpowered to see an effect
- Based on treatment effect sizes (YGTSS-TTS), ecopipam may be more effective in patients with TS and comorbid ADHD or OCD than those with TS without these conditions
- A phase 3 trial of ecopipam for the treatment of TS in patients ≥6 years of age is ongoing (NCT05615220)

REFERENCES: 1. Hirschtritt ME, et al. *JAMA Psychiatry*. 2015;72(4):325-333. **2.** Weisman H, et al. *Neurosci Biobehav Rev*. 2013;37(6):1162-1171. **3.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574.

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DISCLOSURES: SDA is an employee at Emalex Biosciences, Inc. At the time of the study, she was an employee of Finger Lakes Clinical Research, Rochester, NY (now part of ERG Clinical). DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc., and PTC Therapeutics. JSD is a former employee of Paragon Biosciences, LLC, a company that founded Emalex Biosciences, Inc. TMC is an employee of Paragon Biosciences, LLC. ARM is a former employee at Emalex Biosciences, Inc.

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