Efficacy and Safety of Ecopipam for Tourette Syndrome: Results From a Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Trial

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INTRODUCTION

- Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder[1] and when indicated, targeted behavior therapy is currently recommended as first-line therapy[2,3]
- When behavioral therapy is not available, effective, or preferred, pharmacologic treatment with alpha-2 adrenergic receptor agonists (eg, clonidine, guanfacine) or dopamine D2 receptor (D2R) modulators (eg, aripiprazole, haloperidol, risperidone) is recommended[1,2]
- Although D2R modulators are efficacious, a major barrier to their successful, prolonged use for tic reduction in TS is the risk of adverse events (AEs; eg, weight gain, dyslipidemia, hyperglycemia, QT prolongation, and drug-induced movement disorders)[2-4]
- Ecopipam is a first-in-class selective dopamine D1 receptor antagonist under investigation for the treatment of TS
  - In a phase 2b trial (n=153 participants aged 6 to <18 years with TS), ecopipam significantly improved Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) from baseline at Week 12 compared with placebo (*P*=0.01)[5]
  - Sustained improvement in YGTSS-TTS was also observed during 12 months of ecopipam treatment in the open-label extension trial[6]
  - The most commonly reported AEs (≥5.0%) in these studies included headache, insomnia, fatigue, somnolence, anxiety, depression, nausea, diarrhea, and restlessness[5,6]

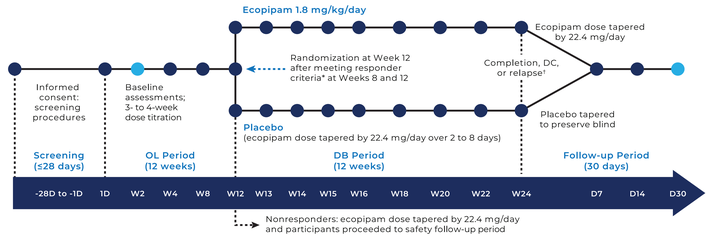
AIM

- To evaluate the durability of efficacy and the safety and tolerability of ecopipam as maintenance therapy in children, adolescents, and adults with TS

METHODS

- To address this objective, a randomized withdrawal trial design was selected
- Participants aged ≥6 years with TS, weight ≥18 kg, with motor and vocal tics causing impairment with normal routines, and YGTSS-TTS ≥20 at both the screening and baseline visits were eligible for this phase 3, randomized, double-blind, placebo-controlled, withdrawal trial (**Figure 1**)

Figure 1. Study Design



Light blue dot indicates phone visit.
*≥50% improvement from baseline (Day 1) in Yale Global Tic Severity Scale Total Tic Score at both Weeks 8 and 12.
†≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score previously observed from baseline to Week 12, initiation of additional treatment for Tourette syndrome symptoms, or hospitalization related to worsening symptoms.
D = Day; DB = double-blind; DC = discontinuation; OL = open-label; W = Week.

- Ecopipam was titrated over 3 to 4 weeks to a target dose of 1.8 mg/kg/day (administered as ecopipam HCl tablets 2 mg/kg/day) during a 12-week open-label period
- Participants with a clinically meaningful reduction (≥25%) in YGTSS-TTS at both Weeks 8 and 12 were randomly assigned to either ecopipam (1.8 mg/kg/day) or placebo during a 12-week double-blind period
- **Primary efficacy endpoint:** time from randomization to relapse (≥50% decrease in YGTSS-TTS improvement observed at open-label period Week 12, initiation of additional treatment for TS symptoms, or hospitalization related to worsening symptoms) in pediatric participants (6 to <18 years) receiving ecopipam compared with placebo
- **Secondary efficacy endpoint:** time from randomization to relapse in the overall population (any age) receiving ecopipam compared with placebo

RESULTS

Table 1. Demographic and Baseline Characteristics

Characteristic	Open-Label Period	Double-Blind Period	
	Ecopipam (n=216)	Ecopipam (n=51)	Placebo (n=53)
Age, y Mean (SD) Range	16.3 (8.8) 6-58	14.3 (5.5) 6-36	14.0 (5.8) 6-41
Age group, n (%) 6-11 years 12-17 years ≥18 years	56 (25.9) 111 (51.4) 49 (22.7)	15 (29.4) 28 (54.9) 8 (15.7)	16 (30.2) 31 (58.5) 6 (11.3)
Male, n (%)	146 (67.6)	37 (72.5)	35 (66.0)
Race, n (%) White Black Asian Other	196 (90.7) 7 (3.2) 3 (1.4) 10 (4.6)	46 (90.2) 1 (2.0) 0 4 (7.8)	50 (94.3) 2 (3.8) 1 (1.9) 0
Hispanic or Latino, n (%)	29 (13.4)	10 (19.6)	6 (11.3)
Weight, mean (SD), kg	61.7 (22.4)	61.4 (21.6)	60.2 (23.9)
YGTSS-TTS score, mean (SD)*	34.3 (6.0)	33.9 (5.8)	35.3 (5.8)

*Range from 0 ("none") to 50 ("severe").
YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

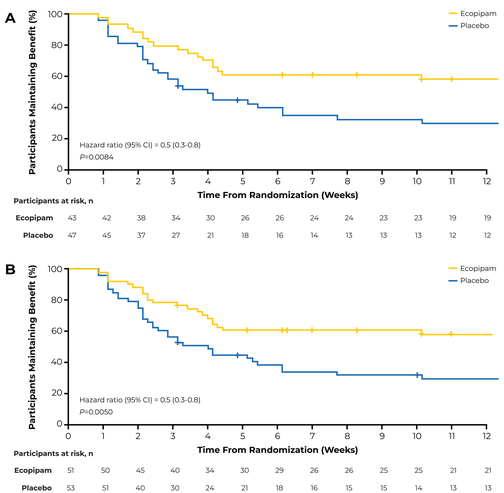
Table 2. Summary of Adverse Events

Characteristics	Open-Label Period	Double-Blind Period		All Periods
	Ecopipam (n=216)	Ecopipam (n=51)	Placebo (n=53)	Ecopipam (n=216)
Any AE	140 (64.8)	20 (39.2)	22 (41.5)	147 (68.1)
Treatment-related AE	90 (41.7)	7 (13.7)	8 (15.1)	92 (42.6)
Severe AE	12 (5.6)	0	2 (3.8)	12 (5.6)
Serious AE*	1 (0.5)	1 (2.0)	2 (3.8)	2 (0.9)
Discontinuation due to AE	34 (15.7)	0	1 (1.9)	34 (15.7)
Most frequently reported AEs‡				
Somnolence	24 (11.1)	0	0	24 (11.1)
Anxiety	20 (9.3)	1 (2.0)	1 (1.9)	21 (9.7)
Headache	19 (8.8)	2 (3.9)	3 (5.7)	21 (9.7)
Insomnia	16 (7.4)	3 (5.9)	5 (9.4)	19 (8.8)
Tic	15 (6.9)	2 (3.9)	1 (1.9)	17 (7.9)
Fatigue	14 (6.5)	0	0	14 (6.5)
AEs of special interest‡				
Depressed mood	8 (3.7)	0	1 (1.9)	8 (3.7)
Suicidal ideation	5 (2.3)	0	1 (1.9)	5 (2.3)
Nausea	6 (2.8)	1 (2.0)	0	7 (3.2)
Diarrhea	5 (2.3)	1 (2.0)	1 (1.9)	6 (2.8)
Vomiting	6 (2.8)	1 (2.0)	1 (1.9)	6 (2.8)

*Open-label ecopipam: 1 participant with acute kidney injury, blood creatine phosphokinase increased, and obsessive-compulsive disorder (all considered possibly or probably related to treatment); double-blind ecopipam: 1 participant with type 1 diabetes mellitus; double-blind placebo: suicidal ideation (considered possibly related to treatment) and Tourette syndrome in 1 participant each. †5.0% of ecopipam-treated participants. ‡≥2.0% of ecopipam-treated participants. Somnolence, anxiety, and fatigue (reported above) were also AEs of special interest.
AE = adverse event.

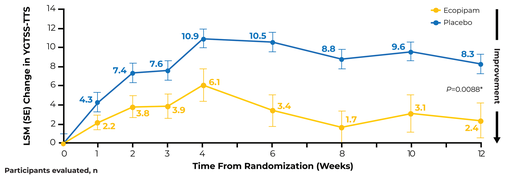
- 216 participants (167 pediatric) were enrolled in the 12-week open-label phase and 104 (90 pediatric) were randomly assigned to the 12-week double-blind period to continue ecopipam (n=51 [43 pediatric]) or switch to placebo (n=53 [47 pediatric]; **Table 1**)
- In the pediatric population (primary efficacy endpoint), there was a 50% risk reduction for time to relapse for ecopipam compared with placebo (hazard ratio [95% CI], 0.5 [0.3-0.8]; *P*=0.0084 [log-rank test]; **Figure 2A**)
  - Median time from randomization to relapse was 4.0 weeks (95% CI, 2.4-6.1 weeks) in the placebo group and not estimable in the ecopipam group (4.1 weeks-not estimable) because <50% of participants relapsed
- In the overall population (secondary efficacy endpoint), there was a 50% risk reduction for time to relapse for ecopipam compared with placebo (hazard ratio [95% CI], 0.5 [0.3-0.8]; *P*=0.0050 [log-rank test]; **Figure 2B**)
  - Median time from randomization to relapse was 4.0 weeks (95% CI, 2.4-6.1 weeks) for placebo and not estimable (4.1 weeks-not estimable) for ecopipam
- Treatment difference (ecopipam minus placebo) in least-squares mean change in YGTSS-TTS from randomization to end of treatment was −5.1 (95% CI, −8.8 to −1.4; *P*=0.0088; **Figure 3**)
- Ecopipam treatment for up to 24 weeks was well tolerated (**Table 2**)
  - The most commonly reported AEs in the ecopipam group during the 24-week trial were somnolence (11.1%), anxiety (9.7%), headache (9.7%), insomnia (8.8%), tic (7.9%), and fatigue (6.5%); there were no reports of weight gain
  - No notable changes in vital signs, physical examination, laboratory values (including lipids and glycated hemoglobin), or ECG measurements were observed

Figure 2. Time to Relapse in the (A) Pediatric Population and (B) Overall Population*



*From randomization (Week 12); plus (+) sign indicates censored data. All participants relapsed because of ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score previously observed from baseline to Week 12.

Figure 3. Change From Randomization in YGTSS-TTS in the Overall Population



*Ecopipam versus placebo. Based on a mixed model for repeated measures analysis of covariance with an unstructured covariance matrix including treatment, visit, treatment-by-visit interaction, region, age group (children [6-11 years]; adolescents [12-17 years]; adults [≥18 years]), and YGTSS-TTS at Week 12.
LSM = least-squares mean; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

CONCLUSIONS

- Time to relapse was significantly delayed in the ecopipam group versus placebo in both pediatric and overall populations during the 12-week withdrawal period
  - Risk reduction for both groups was 50% (ecopipam vs placebo)
  - Supports maintenance and durability of treatment effect
- Ecopipam safety observations
  - Most common (≥5.0%) AEs were somnolence, anxiety, headache, insomnia, tic, and fatigue
  - No drug-induced movement disorder AEs attributed to ecopipam
  - No signal of clinically relevant adverse metabolic effects or weight gain
- Based on these positive results, ecopipam has the potential to become a pharmacological treatment option for TS

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