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Ecopipam Reduces Tics and Does Not Negatively Impact Measures of Anxiety or Depression in Patients With Tourette Syndrome: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Trial

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BACKGROUND

- Tourette syndrome (TS) frequently coexists with psychiatric disorders (eg, anxiety, depression) that confound management[1]
- TS treatment options include targeted behavioral therapy and pharmacologic treatment with alpha-2 adrenergic receptor agonists or dopamine D2 receptor modulators[2-4]
- Current pharmacotherapy is limited by potential adverse events (AEs; eg, weight gain, sedation)[3-5] and treatment discontinuation rates are high[6]
- Ecopipam, a first-in-class selective dopamine D1 receptor antagonist, improved Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) in children and adolescents with TS
  - In a phase 2b trial (n=153 participants aged 6 to <18 years with TS), ecopipam significantly improved YGTSS-TTS from baseline at Week 12 (P=0.01 vs placebo)[7]
  - Sustained improvement in YGTSS-TTS was also observed at 12 months of ecopipam treatment (P<0.0001 vs baseline) in an open-label extension of the phase 2b trial[8]
  - The most commonly reported AEs (≥5.0%) in these studies included headache, insomnia, fatigue, somnolence, anxiety, depression, nausea, diarrhea, and restlessness[7,8]

OBJECTIVE

- To evaluate the maintenance of efficacy and the safety and tolerability of ecopipam for up to 24 weeks of treatment in children, adolescents, and adults with TS

METHODS

- This was a phase 3, double-blind, placebo-controlled, randomized withdrawal trial in individuals aged ≥6 years with TS (**Figure 1**)
  - Ecopipam was titrated over 3 to 4 weeks (target dose, 1.8 mg/kg/day [active moiety], administered as ecopipam HCl tablets, 2 mg/kg/day) during a 12-week open-label period
  - Participants with clinically meaningful (≥25%) reduction from baseline in YGTSS-TTS at both Weeks 8 and 12 were randomly assigned to continue ecopipam (1.8 mg/kg/day) or taper to placebo during a 12-week double-blind period
- **Primary efficacy endpoint:** time from randomization to relapse (≥50% loss of open-label period YGTSS-TTS improvement, initiation of additional treatment for TS symptoms, or hospitalization related to worsening TS symptoms) in the pediatric (6 to <18 years) population receiving ecopipam versus placebo
- **Secondary efficacy endpoint:** time from randomization to relapse in the overall (≥6 years) population receiving ecopipam versus placebo
- Additional outcomes included change from randomization in YGTSS-TTS (exploratory efficacy endpoint) in the overall population, mean Extrapyramidal Symptom Rating Scale (ESRS; safety assessment) in the overall population over time, and mean Pediatric Anxiety Rating Scale (PARS) and Children's Depression Rating Scale Revised (CDRS-R; safety assessments) in pediatric participants over time

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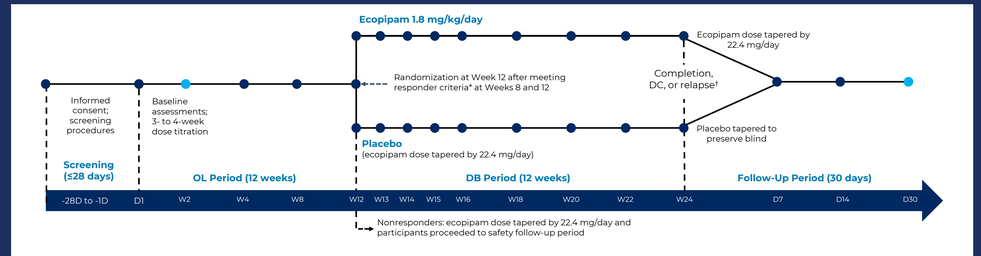
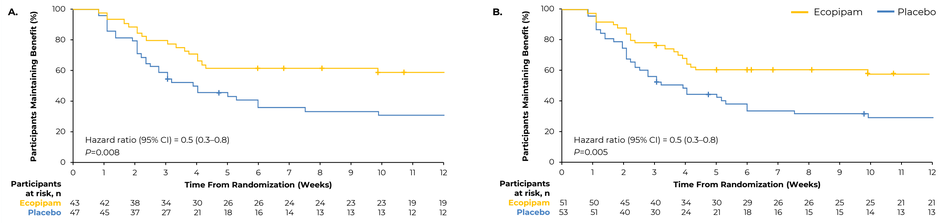
Figure 1. Study Design



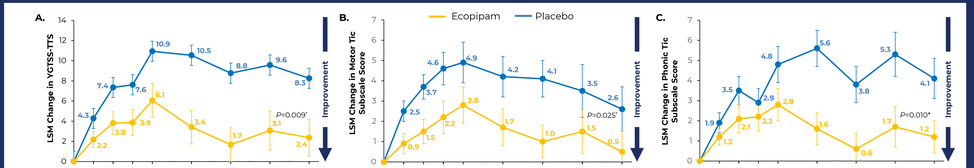
Light blue dot indicates phone visit. *≥25% improvement from baseline (D1) in YGTSS-TTS at both Weeks 8 and 12. †≥50% loss of open-label period YGTSS-TTS improvement, initiation of additional treatment for TS symptoms, or hospitalization related to worsening symptoms. D = Day; DC = discontinuation; DB = double-blind; OL = open-label; W = Week.

Figure 2. Time From Randomization to Relapse in the (A) Pediatric and (B) Overall Populations



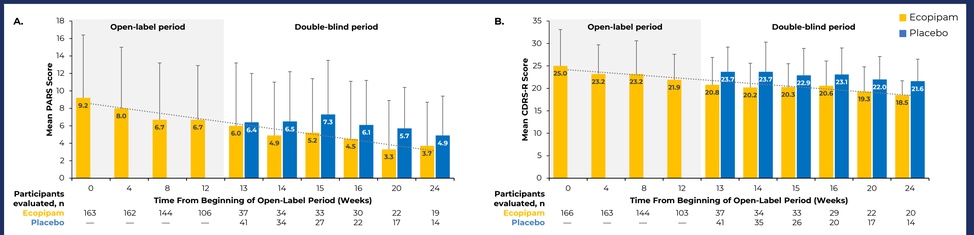
Plus (+) sign indicates censored data. P values determined using log-rank test. All participants relapsed because of ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score previously observed from baseline to Week 12.

Figure 3. Change From Randomization in (A) YGTSS-TTS and the (B) Motor and (C) Phonic Subscale Scores in the Overall Population*



*LSM change (SE); 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 score at time of randomization. Interpretation may be complicated because statistical modeling did not adjust for missing data due to relapse or dropout (censoring) that might be due to treatment or disease. LSM = least-squares mean; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

Figure 4. Mean (A) PARS and (B) CDRS-R Scores Over Time in Pediatric Participants*



*Lower scores indicate less severity; data are mean (SD). Interpretation may be complicated because descriptive statistics were not adjusted for missing data due to relapse or dropout (censoring) that might be due to treatment or disease. CDRS-R = Children's Depression Rating Scale Revised; PARS = Pediatric Anxiety Rating Scale.

DISCLOSURES

DLG is a clinical trial site investigator for Emalex Biosciences, Inc., Quince Therapeutics, and PTC Therapeutics; and received consulting fees and/or travel support from Emalex Biosciences, Inc., PTC Therapeutics, and Vima Therapeutics. SDA, DJBK, MMM, PMR, JAF, GBK, and FEM are employees of and have personal equity interest in Emalex Biosciences, Inc. AC and RTK are interns with Emalex Biosciences, Inc. SPW and TMC are employees of Paragon Biosciences, which has controlling equity interest in Emalex Biosciences, Inc., and have personal equity interest in Emalex Biosciences, Inc. KKT is a clinical trial site investigator for Emalex Biosciences, Inc.; received travel support from Emalex Biosciences, Inc.; and received consulting fees from Jazz Pharmaceuticals.

RESULTS

- 216 participants (167 pediatric) were enrolled in the 12-week open-label period and 104 (90 pediatric) were randomly assigned to ecopipam (n=51 [43 pediatric]) or placebo (n=53 [47 pediatric]) during the 12-week double-blind period
  - For the overall randomized population (n=104), baseline characteristics were similar in the ecopipam versus placebo treatment groups; the majority were male (72.5% vs 66.0%), aged 12 to 17 years (54.9% vs 58.5%), and not Hispanic or Latino (80.4% vs 88.7%), respectively
- In pediatric participants, there was a 50% risk reduction for time to relapse with ecopipam versus placebo (**Figure 2A**)
  - Median time from randomization to relapse was 4.0 weeks (95% CI, 2.4–6.1 weeks) for placebo and not estimable for ecopipam (95% CI, 4.1 weeks–not estimable) because >50% of participants in this group maintained improvement at Week 24
- In the overall population, there was a 50% risk reduction for time to relapse with ecopipam versus placebo (**Figure 2B**)
  - Median time from randomization to relapse was 4.0 weeks (95% CI, 2.4–6.1 weeks) for placebo and not estimable (95% CI, 4.1 weeks–not estimable) for ecopipam
- In the overall population, the treatment difference (ecopipam minus placebo) in least-squares mean change from randomization in YGTSS-TTS and its motor and phonic subscales favored ecopipam (P<0.05 for all; **Figure 3A-3C**)
- Ecopipam treatment for up to 24 weeks was well tolerated (**Table**)
  - The most commonly reported AEs during ecopipam treatment (n=216) were somnolence (11.1%), anxiety (9.7%), and headache (9.7%)
  - Body mass index remained stable over the study duration and there were no notable changes in vital signs, physical examination, laboratory values (including prolactin, total cholesterol, triglycerides, and glycated hemoglobin), or electrocardiogram measurements

Table. Summary of Adverse Events

	Open-Label Period	Double-Blind Period		All Periods
Participants With an AE, n (%)	**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)
Select AEs of special interest				
Anxiety-related	20 (9.3)	1 (2.0)	1 (1.9)	21 (9.7)
Depression-related	14 (6.5)	0	2 (3.8)	14 (6.5)
Suicidal ideation	5 (2.3)	0	1 (1.9)	5 (2.3)
EPS-like (movement related)	0‡	0	0	0‡

*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. ‡Tremor and dystonia were reported in 1 participant each during the open-label period and were determined to be unrelated to ecopipam by a masked clinical adjudication committee. AE = adverse event; EPS = extrapyramidal symptom.

- In the overall population, no change in drug-induced movement disorders (based on ESRS) was observed
- In pediatric participants, PARS and CDRS-R scores decreased (improved) during open-label ecopipam treatment; during the double-blind period, scores transiently increased (worsened) in the placebo group, but slightly decreased in the ecopipam group (**Figure 4A and 4B**)

CONCLUSIONS

- Ecopipam maintained tic suppression efficacy, as assessed by the YGTSS-TTS, for up to 24 weeks of treatment in children, adolescents, and adults with TS
- No signal for clinically relevant weight gain, adverse metabolic effects, or drug-induced movement disorders was observed
- In pediatric participants, scales assessing depression and anxiety showed slight improvement with ecopipam throughout the trial, suggesting treatment did not worsen these psychiatric symptoms
- An ongoing open-label extension study will provide additional insights into the long-term safety, tolerability, and durability of effect of ecopipam for TS