Long-Term Safety and Durability of Effect of Ecopipam in Pediatric Patients With Tourette Syndrome: Results of a 12-Month Open-Label Extension Study

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BACKGROUND

- Tourette syndrome (TS) is a childhood-onset movement disorder characterized by motor and phonic tics that can disrupt function and affect mental and physical health[1]
- Medications currently prescribed for TS include dopamine D_2 receptor antagonists, which have a safety profile that includes risk of weight gain and development of metabolic abnormalities and movement disorders[2-3]
- Ecopipam is a first-in-class D_1 receptor antagonist under investigation as a potential treatment for TS[4]
- In a previously published phase 2b, randomized, double-blind, parallel-group, placebo-controlled trial (ecopipam [n=76]; placebo [n=77]), ecopipam tablets (2 mg/kg/day for 12 weeks) reduced the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) by 30% from baseline, which was significant compared with placebo (p=0.01)[4]
  - Weight gain, metabolic syndrome, and drug-induced dyskinesias associated with antipsychotic agents were not observed in this study of up to 12 weeks duration

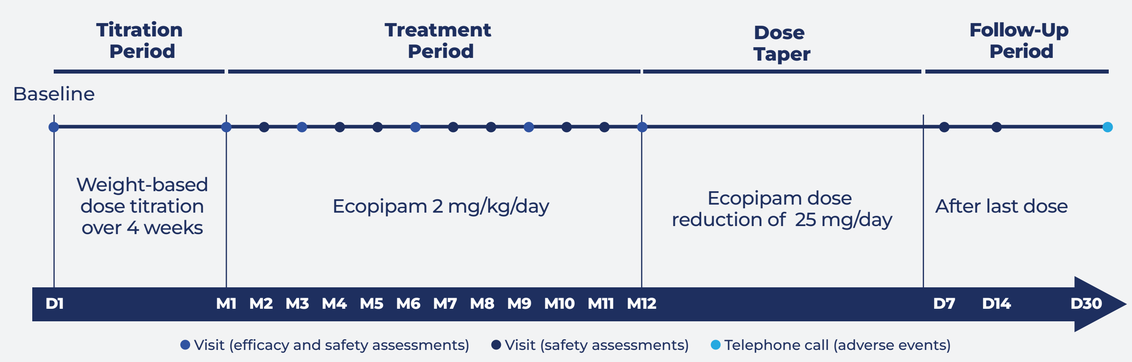
OBJECTIVE

- To evaluate the safety and tolerability of ecopipam in TS, and to inform the durability of effect for up to 12 months in pediatric patients with TS who completed the phase 2b, placebo-controlled trial

METHODS

- Patients aged 6 to ≤18 years with confirmed TS who completed the phase 2b placebo-controlled trial[4] were eligible for this long-term, open-label extension (OLE) trial (NCT04114539)
- All patients in the OLE trial were titrated over a 4-week period to an oral dose of ecopipam 2 mg/kg/day; dosing was adjusted by weight over the 12-month study
- Patients completed study visits every month for 1 year; follow-up visits were conducted 7 and 14 days after patients received the last dose of ecopipam and a follow-up phone call was conducted 30 days after the last dose of ecopipam (Figure 1)
- To evaluate the long-term safety and tolerability of ecopipam in pediatric patients with TS the following were completed:
  - Vital signs including orthostatic blood pressure, physical exam, electrocardiogram, and laboratory tests with monitoring of adverse events (AEs); and
  - The Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Children's Depression Rating Scale-Revised (CDRS-R), and the Columbia–Suicide Severity Rating Scale (C-SSRS)
- To inform the durability of effect of ecopipam, the following were completed:
  - YGTSS-TTS, YGTSS-TTS motor and vocal subscales, YGTSS Impairment (YGTSS-I), Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S), and the Gilles de la Tourette Syndrome, Quality of Life Scale for Children and Adolescents (C&A-GTS-QoL) based on change from baseline at Months 1, 3, 6, 9, and 12 (or early termination)

Figure 1. Study Design



RESULTS

- Of the 124 patients enrolled in the OLE trial: 121 received ecopipam (Table 1), 80 (66.1%) completed the study

Table 1. Patient Baseline Demographic and Disease Characteristics

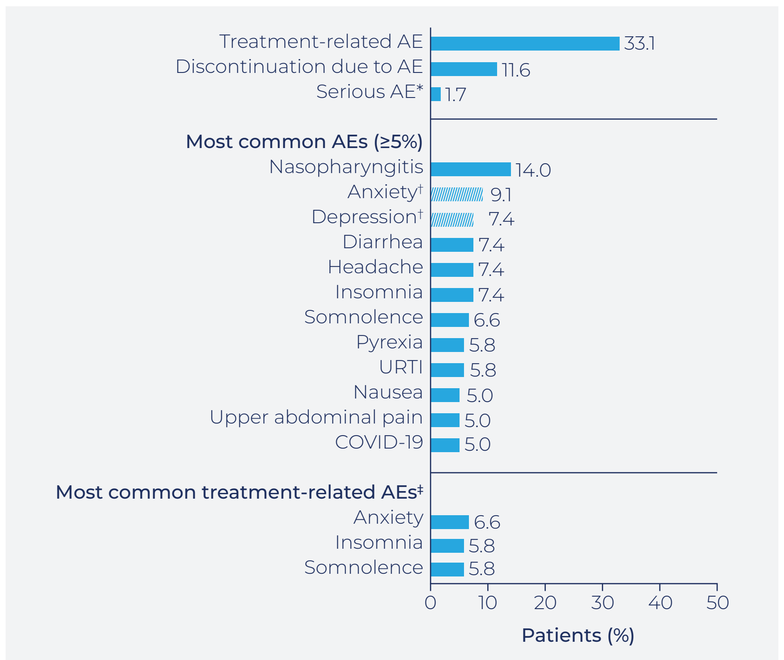
Characteristic	Patients (n=121)
Age	
Mean (SD)	12.8 (2.8)
Range	6-18
Male, n (%)	89 (73.6)
Race*	
White	110 (90.9)
Black	7 (5.8)
Asian	3 (2.5)
Other	1 (0.8)
Weight, kg	
Mean (SD)	56.7 (21.5)
Range	21.8-152.6
YGTSS-TTS†	
Mean (SD)	29.6 (8.2)
Median	30.0
YGTSS-GS, mean (SD)‡	56.7 (16.3)
YGTSS-I score, mean (SD)†	27.1 (9.9)
CGI-TS-S, mean (SD)§	4.3 (0.9)
C&A-GTS-QoL total score, mean (SD)‡¶	26.6 (16.5)

*Hispanic/Latino ethnicity was reported for 14 patients (11.6%). †Range from 0 (none) to 50 (severe). ‡Range from 0 to 100 (worse). §Range from 1 ("normal, not ill at all") to 7 ("extremely ill"). ¶n=120.
C&A-GTS-QoL = Gilles de la Tourette Syndrome, Quality of Life Scale for Children and Adolescents; CGI-TS-S = Clinical Global Impression of Tourette Syndrome Severity; YGTSS-GS = Yale Global Tic Severity Scale, Global Score; YGTSS-I = Yale Global Tic Severity Scale, Impairment; YGTSS-TTS = Yale Global Tic Severity Scale, Total Tic Score.

Safety and Tolerability

- Ecopipam was generally well tolerated, with 69.4% (84/121) of patients reporting any AE and 11.6% (14/121) of patients discontinuing due to an AE (Figure 2)
  - Treatment-related AEs were reported in 33.1% (40/121) of patients
  - Most AEs (64.4%) were mild or moderate in severity
  - The most commonly reported AEs (>7%) were nasopharyngitis (14.0%), anxiety (9.1%), depression (including depression, depressed mood, major depression, and depressive symptoms; 7.4%), diarrhea (7.4%), headache (7.4%), and insomnia (7.4%)
  - A total of 14 patients (11.6%) experienced AEs leading to treatment termination; the most commonly reported AEs leading to treatment termination (reported in ≥2 patients) included anxiety and depression (n=2 patients each [1.7%]); all other AEs leading to treatment termination occurred in 1 patient each (0.8%) and included abdominal discomfort, aggression, akathisia, decreased appetite, depressed mood, depressive symptom, diarrhea, headache, insomnia, joint lock, mental disorder, migraine, obsessive thoughts, somnolence, and upper abdominal pain
  - Most patients who experienced AEs leading to treatment termination experienced mild (n=3 patients [2.5%]) or moderate (n=8 patients [6.6%]) AEs; 3 patients (2.5%) experienced severe AEs leading to treatment termination: abdominal discomfort, anxiety, and diarrhea
  - AEs of special interest included:
    - Extrapyramidal side effect-related events including akathisia, joint lock, and tremor (n=4, 3.3%)
    - Adverse movement-related events including balance disorders, bruxism, and tongue biting (n=2, 1.7%)
    - Suicidal ideation (n=3, 2.5%)

Figure 2. Adverse Event Profile



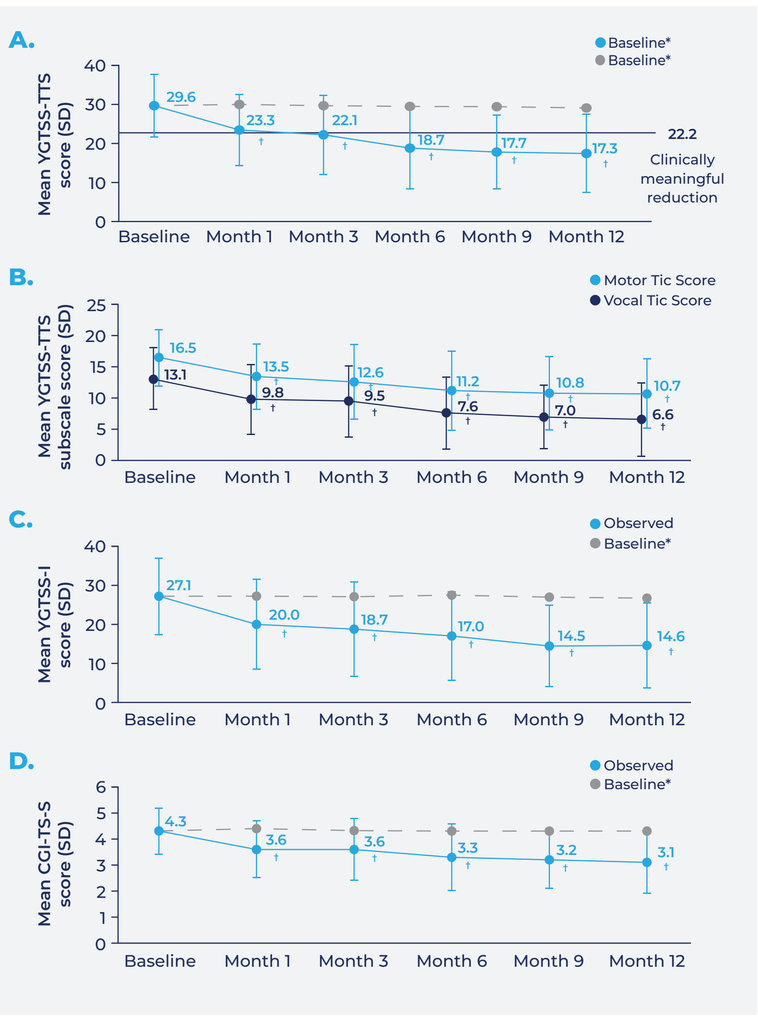
*Obsessive thoughts, possibly related to treatment and resulting in drug withdrawal (1 patient), and serious accidental injury AEs, not related to drug (1 patient). †Anxiety and depression are also AEs of special interest. Depression includes depression, depressed mood, major depression, and depressive symptoms. ‡Possibly/probably related or relationship missing in ≥5.0% of patients.
AE = adverse event; URTI = upper respiratory tract infection.

- During the 12-month study period, z-scores for height, weight, and body mass index showed no apparent clinically significant change
- No clinically significant changes from baseline were observed in vital signs including orthostatic blood pressure, physical exam, laboratory values including HbA1c and lipid profile, or electrocardiogram measurements
- Safety assessments, including AIMS, BARS, CDRS-R, C-SSRS, or Pediatric Anxiety Rating Scale (PARS) showed no apparent clinically significant change

Durability of Effect

- While this open-label study does not allow a formal assessment of efficacy, measures of TS severity and quality of life were obtained at baseline, and after Months 1, 3, 6, 9, and 12 of treatment
- Mean YGTSS-TTS (Figure 3A), YGTSS-TTS motor and vocal tic subscales (Figure 3B), and YGTSS-I (Figure 3C) scores were significantly improved from baseline at all timepoints (all p<0.0001 vs baseline)
- CGI-TS-S (Figure 3D) was significantly improved from baseline at all timepoints (all p<0.0001 vs baseline)
- C&A-GTS-QoL total score was significantly improved from baseline at all timepoints (p<0.001 vs baseline; Figure 4)

Figure 3. Mean Score by Timepoint in (A) YGTSS-TTS, (B) YGTSS-TTS Motor and Vocal Subscales, (C) YGTSS-I, and (D) CGI-TS-S



*Defined as patients' baseline for those with data at each visit. †p<0.0001 vs baseline.
CGI-TS-S = Clinical Global Impression of Tourette Syndrome Severity; SD = standard deviation; YGTSS-I = Yale Global Tic Severity Scale, Impairment; YGTSS-TTS = Yale Global Tic Severity Scale, Total Tic Score.

Figure 4. Mean Score by Timepoint for C&A-GTS-QoL Total Score

*Defined as patients' baseline for those with data at each visit. †p<0.001 vs baseline. ‡p<0.0001 vs baseline.
C&A-GTS-QoL = Gilles de la Tourette Syndrome, Quality of Life Scale for Children and Adolescents; SD = standard deviation.

CONCLUSIONS

- Ecopipam had an acceptable safety and tolerability profile over this 12-month study
  - AEs were experienced by approximately two-thirds of patients, with most mild or moderate in severity
  - SAEs were reported in 2 patients (obsessive thoughts, accidental injury)
  - The rate of AE-related study discontinuations was 11.6%
  - No notable changes observed in laboratory assessments, vital signs, ECG results, physical examination, C-SSRS, PARS, AIMS, BARS, or CDRS-R
  - Significant improvements in measures of TS severity from baseline were noted in YGTSS-TTS, and in both motor and vocal subscales, in YGTSS-I, and CGI-TS-S
  - C&A-GTS-QoL significantly improved at all timepoints compared with baseline
- In conclusion, ecopipam appears to be both well-tolerated and safe over this 12-month study of 121 patients; additionally, there was no evidence to suggest tachyphylaxis of treatment effect[4]
- A phase 3 trial of ecopipam for the treatment of TS (patients aged ≥6 years) is ongoing (NCT05615220)

REFERENCES: **1.** Johnson KA, et al. *Lancet Neurol*. 2023;22(2):147-158. **2.** Weisman H, et al. *Neurosci Biobehav Rev*. 2013;37(6):1162-1171. **3.** Pringsheim T, et al. *Neurology*. 2019;92(19):896-906. **4.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574.

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DISCLOSURES: DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc., and PTC Therapeutics. DJBK, MMM, 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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