Ecopipam Does Not Adversely Affect Metabolic Parameters in Pediatric Patients With Tourette Syndrome: Results From a Phase 2b Randomized, Placebo-Controlled Trial With a 12-Month Open-Label Extension

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BACKGROUND

- Tourette syndrome (TS) is a childhood-onset movement disorder characterized by motor and phonic tics that can negatively affect function and mental and physical health[1]
- Dopamine-2 receptor antagonists are prescribed for TS, but their use is limited due to risk of increased weight gain and prolactin levels, dyslipidemia, and hyperglycemia, including diabetes[2-4]
- Ecopipam is a first-in-class selective dopamine-1 receptor antagonist under investigation as a treatment for TS[5]
- In a phase 2b, double-blind, randomized, placebo-controlled trial (RCT) of children aged 6 to <18 years with confirmed TS, treatment with ecopipam for 12 weeks significantly improved the mean Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) by 30% from baseline (P=0.01 vs placebo)[5]
- During a 12-month open-label extension (OLE) study, ecopipam significantly improved mean YGTSS-TTS scores (42% improvement from OLE baseline at Month 12; P<0.0001)[6] and was well tolerated, with anxiety (6.6%), insomnia (5.8%), and somnolence (5.8%) being the most common treatment-related adverse reactions

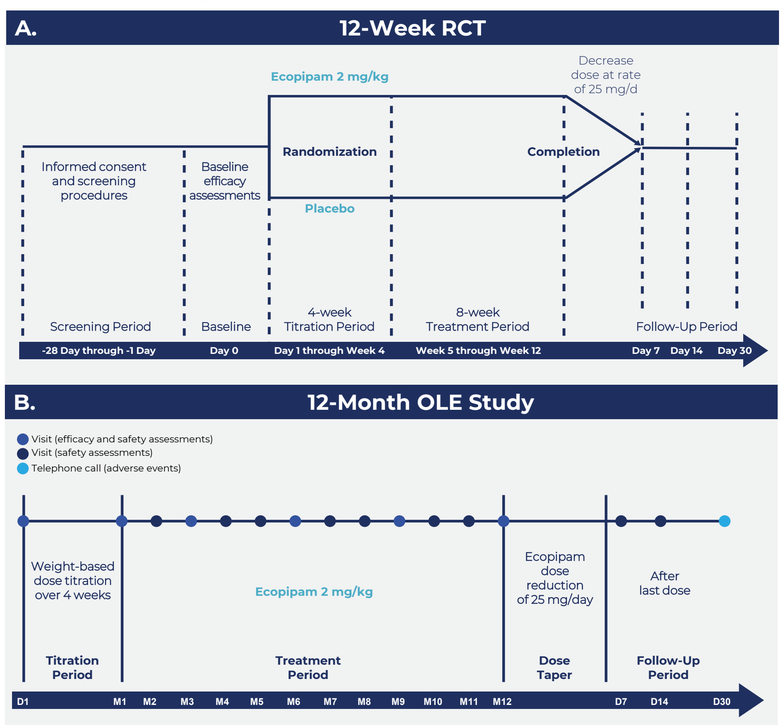
OBJECTIVE

- To determine whether ecopipam is associated with the emergence of clinical features suggestive of metabolic syndrome in pediatric patients with TS

METHODS

- This analysis included participants from a phase 2b RCT[4] and OLE study
  - Patients aged 6 to <18 years with confirmed TS were eligible for the RCT, which included a 4-week titration period and an 8-week treatment period (**Figure 1A**)[4]
  - Any patients aged 6 to ≤18 years who completed the RCT were eligible for the OLE study, which included a 4-week titration period and up to 44 weeks of treatment (**Figure 1B**)

Figure 1. Study Design for the (A) RCT and (B) OLE Study



D = day; M = Month; OLE = open-label extension; RCT = randomized controlled trial.
Figure 1A reproduced from Gilbert DL, et al. Pediatrics. 2023;151(2):e2022059574,[4] via Creative Commons CC-BY-NC-ND license, https://creativecommons.org/licenses/by-nc-nd/4.0.

- Metabolic parameter assessments (mean ± SD) included changes in body mass index (BMI), weight, hemoglobin A1c (HbA1c), total cholesterol and triglyceride levels, and systolic and diastolic blood pressure (BP) measurements
  - z-scores for BMI during OLE were derived from age- and gender-matched data from the Centers for Disease Control and Prevention (CDC)
- Mean changes from RCT baseline to Week 12 or from OLE baseline to Month 12 for metabolic parameters were determined using a mixed model for repeated measures (RCT) or paired t-test (OLE study)

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.** Libowitz MR, et al. *Front Psychiatry*. 2021;12:623681. **5.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574. **6.** Gilbert DL, et al. Presented at the International Congress of Parkinson's Disease and Movement Disorders, August 27–31, 2023, Copenhagen, Denmark.

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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.

RESULTS

Patient Characteristics

- Demographics and baseline characteristics across the RCT and OLE study were comparable (**Table 1**)

Table 1. Demographic and Baseline Characteristics

Parameter	RCT		OLE Study
	Placebo (n=77)	Ecopipam (n=76)	Ecopipam (n=121)
Age, y, mean (SD)	12.6 (2.6)	12.6 (2.8)	12.8 (2.8)
Male, n (%)	53 (68.8)	59 (77.6)	89 (73.6)
Race, n (%)			
White	72 (93.5)	66 (86.8)	110 (90.9)
Black/African American	3 (3.9)	6 (7.9)	7 (5.8)
Asian	2 (2.6)	1 (1.3)	3 (2.5)
Other	0	3 (4.0)	1 (0.8)
Metabolic parameters, mean (SD)			
BMI, kg/m^2	22.2 (6.1)	22.6 (7.2)	22.1 (5.9)
Weight, kg	56.1 (21.5)	58.2 (25.8)	56.7 (21.5)
HbA1c, %	5.3 (0.3)	5.3 (0.4)	5.4 (0.3)
Total cholesterol, mmol/L	4.0 (0.7)	4.0 (0.7)	3.9 (0.7)
Triglycerides, mmol/L	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)
Blood pressure, mmHg			
Systolic	114.5 (11.8)	113.7 (11.5)	112.9 (10.6)
Diastolic	70.4 (11.2)	68.1 (8.6)	69.1 (8.5)

BMI = body mass index; HbA1c = hemoglobin A1c; OLE = open-label extension; RCT = randomized controlled trial.

Metabolic Parameters During RCT

- No significant differences were observed between ecopipam and placebo for mean change from baseline to Week 12 for weight (P=0.97), HbA1c (P=0.11), total cholesterol (P=0.38), triglycerides (P=0.86), systolic BP (P=0.39), and diastolic BP (P=0.28; **Table 2**)

Table 2. Mean Changes in Metabolic Parameters During RCT

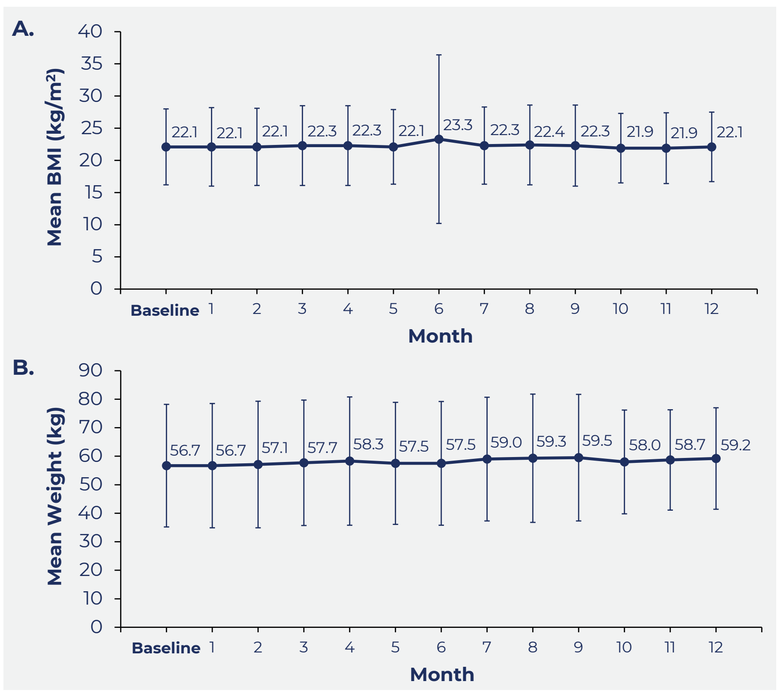
Metabolic Parameter	Mean Change at Week 12 (Ecopipam – Placebo)	*P* Value
Weight, kg	0.07	0.97
HbA1c, %	-0.08	0.11
Total cholesterol, mmol/L	-0.07	0.38
Triglycerides, mmol/L	0.02	0.86
Blood pressure, mmHg		
Systolic	1.5	0.39
Diastolic	1.6	0.28

HbA1c = hemoglobin A1c; RCT = randomized controlled trial.

Metabolic Parameters During OLE Study

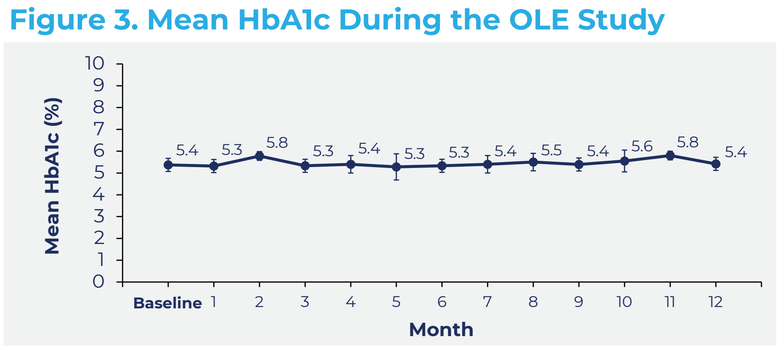
- No adverse effects of ecopipam on metabolic parameters were observed during the 12-month OLE study (**Figures 2-5**)
  - Mean BMI was unchanged from baseline at Month 12 in the OLE (**Figure 2A**)
  - As would be expected in a pediatric population during the 12-month study, there was an increase in mean body weight from OLE baseline to Month 12 of 3.4 kg (P<0.001; **Figure 2B**)
  - The BMI and weight results demonstrated that pediatric patients were maintaining a healthy growth curve
  - HbA1c level was unchanged (**Figure 3**), no marked changes in lipid parameters were observed (**Figure 4**), and mean BP values were unaffected (**Figure 5**)
- No significant changes from baseline at OLE Month 12 were observed for mean (SD) BMI z-scores (0.05 [0.43], P=0.35), HbA1c (0.03% [0.31], P=0.60), total cholesterol (0.2 [0.7] mmol/L, P=0.14), systolic BP (0.3 [11.5] mmHg, P=0.85), and diastolic BP (0.9 [10.0] mmHg, P=0.44)

Figure 2. Mean BMI [A] and Weight [B] During the OLE Study



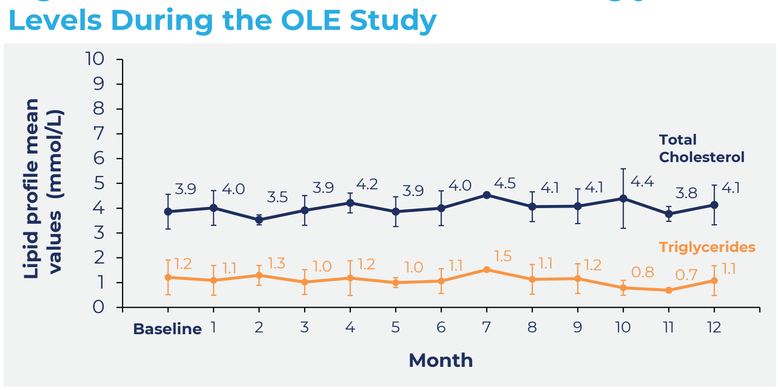
BMI = body mass index; OLE = open-label extension.

Figure 3. Mean HbA1c During the OLE Study



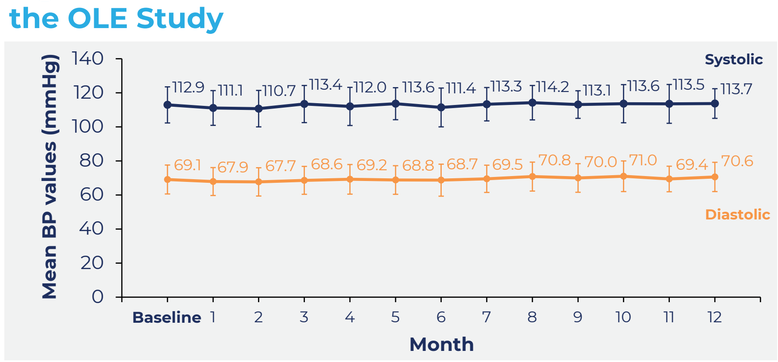
HbA1c = hemoglobin A1c; OLE = open-label extension.

Figure 4. Mean Total Cholesterol and Triglyceride Levels During the OLE Study



OLE = open-label extension.

Figure 5. Mean Blood Pressure Over 12 Months in the OLE Study



BP = blood pressure; OLE = open-label extension.

CONCLUSIONS

- The only US Food and Drug Administration-approved drugs to treat TS are dopamine-2 receptor antagonists and their safety profile includes a risk of weight gain and other adverse metabolic effects[2,3]
- In the current analyses, ecopipam, a first-in-class selective dopamine-1 receptor antagonist under investigation as a treatment for TS, did not adversely affect weight gain or other metabolic parameters associated with an increased risk of metabolic syndrome
  - During the 12-week RCT, no significant differences were observed between ecopipam and placebo in mean changes from baseline in weight, HbA1c, total cholesterol, triglycerides, and systolic and diastolic BP
  - During the 12-month OLE, no significant mean changes from baseline were observed for weight, BMI, BMI z-scores, HbA1c, total cholesterol, triglycerides, and systolic and diastolic BP
- A phase 3 trial of ecopipam for the treatment of TS in patients aged ≥6 years is ongoing (NCT05615220)

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