Effect of Ecopipam, a Selective Dopamine-1 Receptor Antagonist, on Tic Characteristics as Assessed by the YGTSS: Results From the Phase 2b Randomized, Double-Blind, Placebo-Controlled Clinical Trial in Tourette Syndrome

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INTRODUCTION

- Ecopipam is a first-in-class D_1 receptor antagonist in development for Tourette syndrome (TS)[1]
- In a phase IIb, randomized, double-blind, placebo-controlled trial, ecopipam (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)[1]
  - No weight gain or drug-induced movement disorders were identified, and headache (9.2%), fatigue (6.6%), somnolence (6.6%), insomnia (5.3%), and restlessness (5.3%) were the most common treatment-related adverse events reported
- Whether features of tics are more or less responsive to treatment is unknown

OBJECTIVE

- To compare effects of ecopipam treatment in patients aged 6 to <18 years with TS on individual motor and phonic tic dimensions that comprise the YGTSS-TTS: number, frequency, intensity, complexity, interference
  - Alternate analyses may help us better understand how patients benefit from treatment

METHODS

- The phase 2b, randomized, double-blind, placebo-controlled D1AMOND trial included patients aged 6 to <18 years with confirmed TS and YGTSS-TTS ≥20 at screening[1]
- Patients were randomly assigned (1:1) to ecopipam (n=76) or placebo (n=77) for a 4-week titration period, an 8-week treatment period, and a taper/follow-up period (**Figure 1**)[1]
- This post-hoc analysis examined YGTSS-TTS characteristics (**Figure 2**) at baseline and Weeks 4, 6, 8, and 12, utilizing a mixed model for repeated measures analysis with an unstructured covariance matrix unless otherwise indicated
  - Data were analyzed for all randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline YGTSS assessment

Figure 1. Study Design

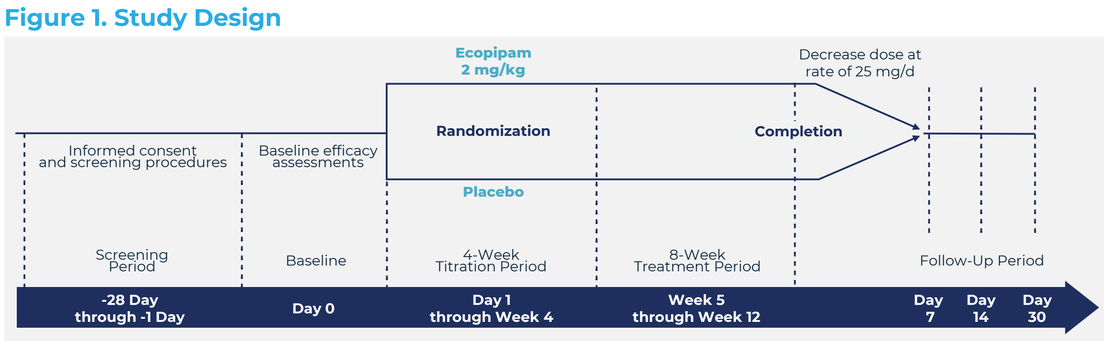

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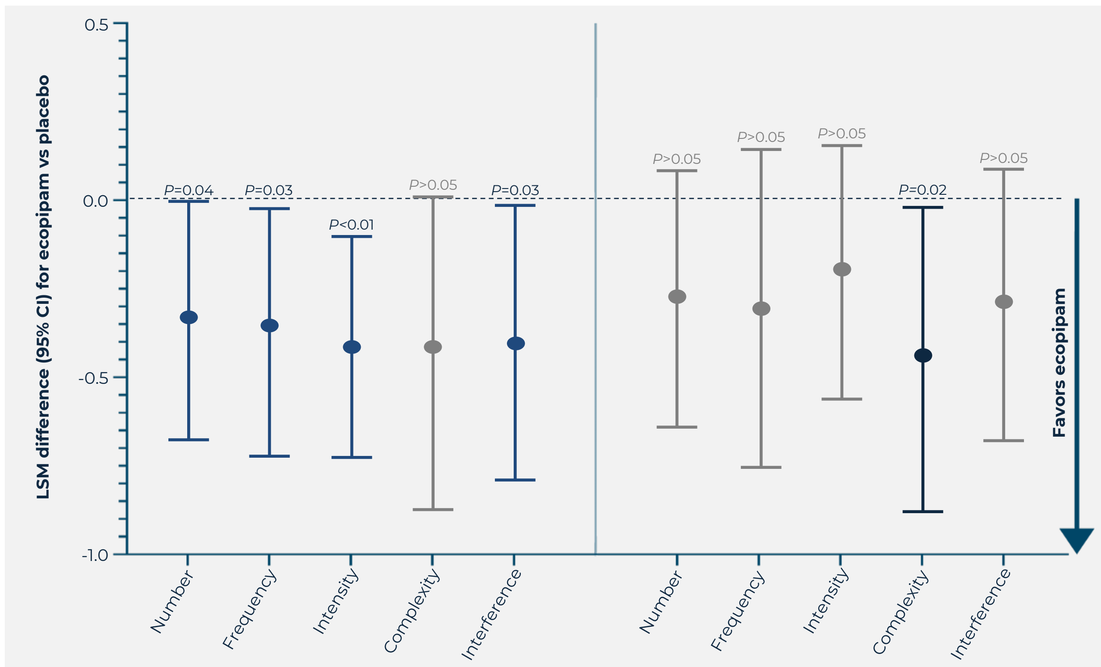
Figure 2. Tic Dimension Score Categories

Figure created from Leckman JF, et al. *J Am Acad Child Adolesc Psychiatry*. 1989;28(4):566-573.[2]

RESULTS

- For motor tic scale, the greatest difference was observed in the dimension of intensity (ecopipam minus placebo least-square means [LSM] difference, -0.48; *P*<0.01) (**Figure 3**)
  - A significant difference favoring ecopipam versus placebo was also observed for motor tic dimensions of number, frequency, and interference (LSM difference vs placebo ranged from -0.34 to -0.43; all *P*<0.05), but not complexity (-0.43)
  - For YGTSS phonic tic dimensions, only complexity was significant with ecopipam (LSM difference vs placebo, -0.48; *P*=0.02)

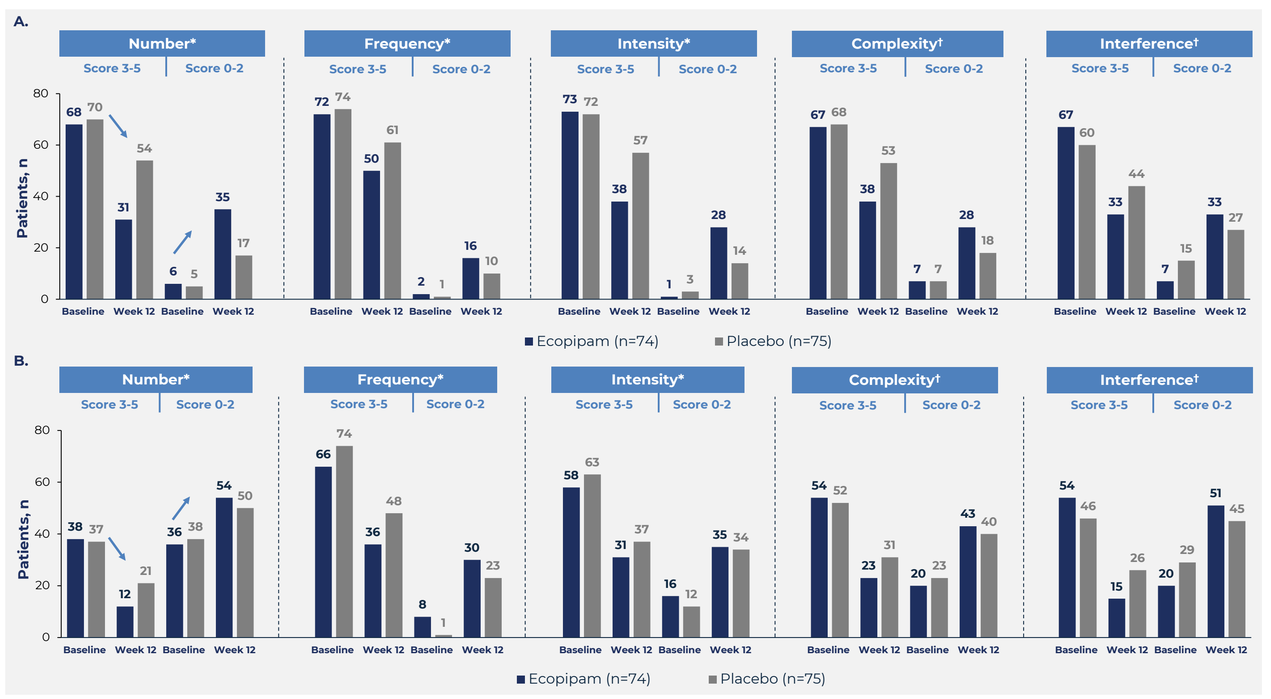
Figure 3. Change in YGTSS Tic Dimension Scores (Baseline to Week 12)



Dark blue coloring indicates significant difference favoring ecopipam (LSM difference, ecopipam – placebo).
LSM = least-squares mean; YGTSS = Yale Global Tic Severity Scale.

- The shift in the number of patients by motor tic scale dimension score at baseline and Week 12 are shown in **Figure 4A**; for phonic tic scale dimensions, **Figure 4B**
- Analysis of the percentage of participants going from bad (score 3-5) to good (score 0-2) at Week 12, by tic dimension, also shows improvements with ecopipam compared with placebo (**Figure 5**)

Figure 4. Number of Patients by Motor Tic (A) and Phonic Tic (B) Dimension Score at Baseline and Week 12



*Ranges were as follows: number (0 "none" to 5 "multiple discrete tics plus several [>2] orchestrated patterns of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics"); frequency (0 "none" to 5 "always"); and intensity (0 "absent" to 5 "severe"). Lower score indicated less "severe".
†Range for complexity and interference was 0 "none" to 5 "severe". Lower score indicated less "severe".

Figure 5. Percentage of Participants Going From Bad (Score 3-5) to Good (Score 0-2), by Tic Dimension (Week 12)

Type	Dimension	Ecopipam	Placebo	Difference*	*P* value†
Motor	Number	-54%	-23%	-32%	0.04
Phonic	Interference	-72%	-43%	-29%	>0.05
Motor	Intensity	-48%	-21%	-27%	<0.01
Phonic	Number	-68%	-43%	-25%	>0.05
Motor	Interference	-51%	-27%	-24%	0.03
Motor	Complexity	-43%	-22%	-21%	>0.05
Phonic	Complexity	-57%	-40%	-17%	0.02
Motor	Frequency	-31%	-18%	-13%	0.03
Phonic	Frequency	-45%	-35%	-10%	>0.05
Phonic	Intensity	-47%	-41%	-5%	>0.05

*Ecopipam minus placebo.
†Data were analyzed using a mixed model for repeated measures with multiple imputation for intercurrent events.

CONCLUSIONS

- Whether features of motor and phonic tics in TS are more or less responsive to treatment is unclear
- Ecopipam treatment for 12 weeks significantly improved motor tic characteristics in 4 of the 5 dimensions versus placebo
- Significant differences favoring ecopipam versus placebo for phonic tic characteristics were limited to the complexity dimension
- These data have increased our understanding of the effects of ecopipam on TS tic characteristics, and additional data are anticipated
  - A phase 3 trial (NCT05615220) is ongoing

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REFERENCES

1. Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574. **2.** Leckman JF, et al. *J Am Acad Child Adolesc Psychiatry*. 1989;28(4):566-573.

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DISCLOSURES

DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc., and PTC Therapeutics. GBK, SDA, and FEM are employees of Emalex Biosciences, Inc. SPW and TMC are employees of Paragon Biosciences, LLC, a company that founded Emalex Biosciences, Inc.