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

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Disclosures

KK Tomczak is a clinical trial site investigator for Emalex Biosciences, Inc.; has received travel support from Emalex Biosciences, Inc.; and has received consulting fees from Frazier Life Sciences, Gerson Lehrman Group, Guidepoint Global, Health Advances, and Jazz Pharmaceuticals.

SD Atkinson, DJB Kim, MM Miller, PM Rice, GB Karkanias, and FE Munschauer are employees of and have personal equity interest in Emalex Biosciences, Inc.

SP Wanaski and TM Cunniff are employees of Paragon Biosciences, LLC, which has controlling equity interest in Emalex Biosciences, Inc., and have personal equity interest in Emalex Biosciences, Inc.

DL Gilbert is a clinical trial site investigator for Emalex Biosciences, Inc., Neurocrine Biosciences, PTC Therapeutics, and Quince Therapeutics. He has received consulting fees from Acadia Pharmaceuticals, Emalex Biosciences, Inc., Health Advances, and Vima Therapeutics; travel support from Emalex Biosciences, Inc.; compensation for producing educational content for MEDLIVE and PTC Therapeutics; and book royalties from Elsevier and Wolters Kluwer.

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Introduction

- TS treatment options include behavioral therapy and pharmacotherapy (ie, α-2 adrenergic agonists, D2R modulators [antipsychotics])[1]
  - Current pharmacotherapy is limited by potential adverse effects, including:
    - Fatigue, hypotension (α-2 adrenergic agonists)[2]
    - Weight gain, drug-induced movement disorders (D2R modulators)[1]
  - Discontinuation rates are high[3,4]
- Ecopipam is a first-in-class selective D1R antagonist in development for TS[5,6]
- In children and adolescents, ecopipam improved YGTSS-TTS
  - Phase 2b RCT showed a mean improvement of 30% at Week 12 (P=0.01 vs placebo)[6]
  - OLE study showed a mean improvement of 40.3% at Month 12 (P<0.0001 vs baseline)[5]
- Most common AEs in phase 2b RCT (ecopipam vs placebo)[6]
  - Headache (15.8% vs 9.1%), insomnia (13.1% vs 2.6%), fatigue (7.9% vs 0%), somnolence (7.9% vs 2.6%), anxiety (5.3% vs 0%), nausea (5.3% vs 1.3%), and restlessness (5.3% vs 0%)

AE = adverse event; D1R = dopamine D1 receptor; D2R = dopamine D2 receptor; OLE = open-label extension; RCT = randomized controlled trial; TS = Tourette syndrome; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

1. Pringsheim T, et al. *Neurology*. 2019;92(19):896-906. **2.** Cothros N, et al. *Tremor Other Hyperkinet Mov (N Y)*. 2019;9. **3.** Tomczak K, et al. *Neurology*. 2025;104(7 suppl 1):P11-6.001. **4.** Wolicki SB, et al. *Psychiatry Res*. 2020;293:113400. **5.** Gilbert DL, et al. *Mov Disord Clin Pract*. 2025;12(8):1157-1166. **6.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574.

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Objective

- To evaluate the durability of efficacy and the safety/tolerability of ecopipam through 24 weeks of treatment in children, adolescents, and adults with TS

TS = Tourette syndrome.

Key Inclusion/Exclusion Criteria

Inclusion

- Age ≥6 years with weight ≥18 kg
- TS diagnosis by DSM-5-TR criteria (motor + phonic tics ≥1 year) with impairment
- YGTSS-TTS ≥20 at both screening and baseline visits
- Trial of non-pharmacologic therapy (European sites only)

Exclusion

- Unstable medical or CNS illness, including a significant risk of suicidal behavior
- ≥25% change in YGTSS-TTS between screening and baseline visits
- Receiving other medications or new psychological treatment for tics for 14 days prior to baseline
- Taking medications that strongly inhibit UGT, CYP2D6 (eg, valproate, duloxetine, fluoxetine), or VMAT-2, or taking tricyclics or MAO inhibitors
- Not considered suitable candidate per investigator

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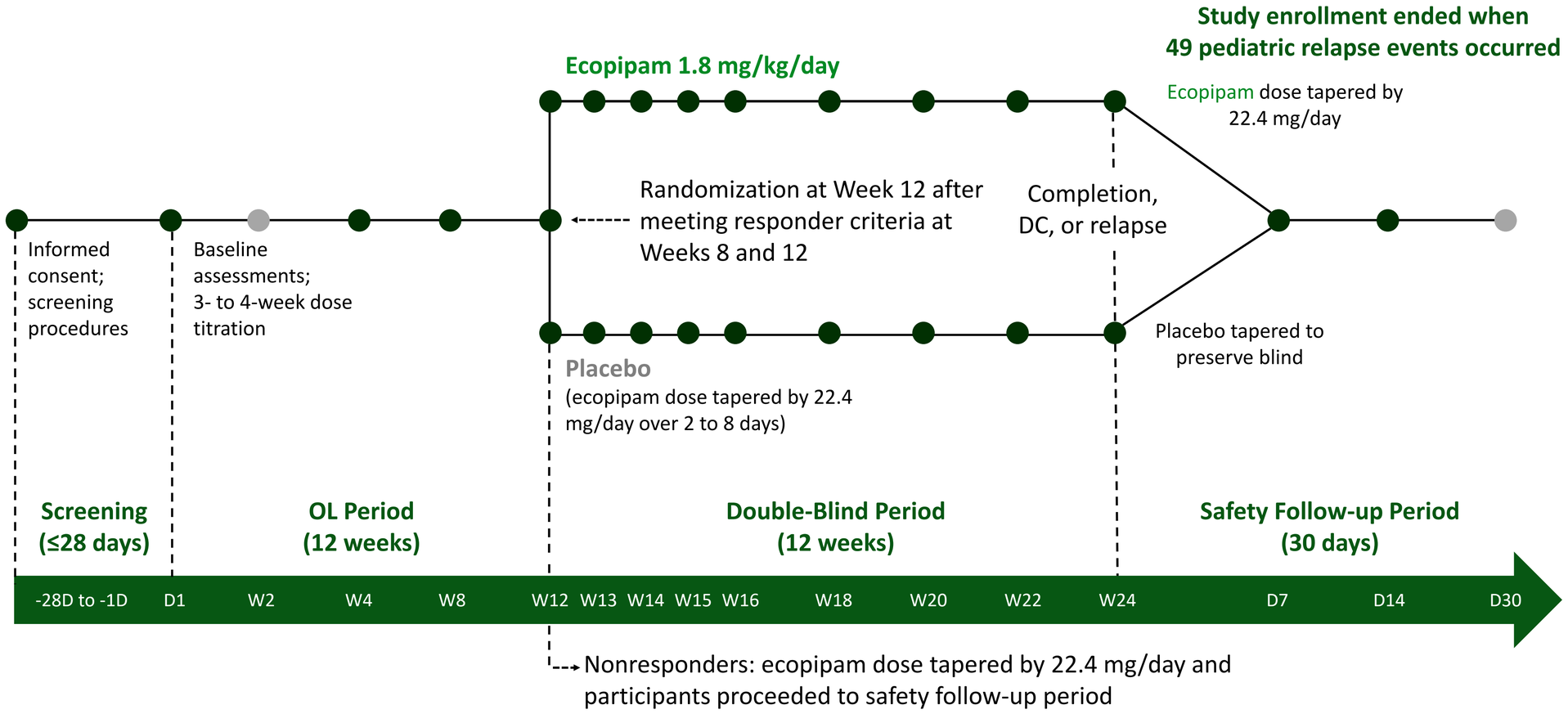
CNS = central nervous system; CYP2D6 = cytochrome P450 2D6; DSM-5-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision; MAO = monoamine oxidase; TS = Tourette syndrome; UGT = uridine 5'-diphospho-glucuronosyltransferase; VMAT-2 = vesicular monoamine transporter 2; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

Study Design

Phase 3, double-blind, placebo-controlled, randomized withdrawal trial



Gray dot indicates phone visit. Responder if ≥25% improvement from baseline in YGTSS-TTS at Weeks 8 and 12. Relapse defined as ≥50% loss of improvement in YGTSS-TTS observed from baseline to Week 12, initiation of additional treatment for Tourette syndrome symptoms, or hospitalization related to worsening symptoms.

D = day; DC = discontinuation; OL = open-label; W = week; YGTSS-TTS, Yale Global Tic Severity Scale Total Tic Score.

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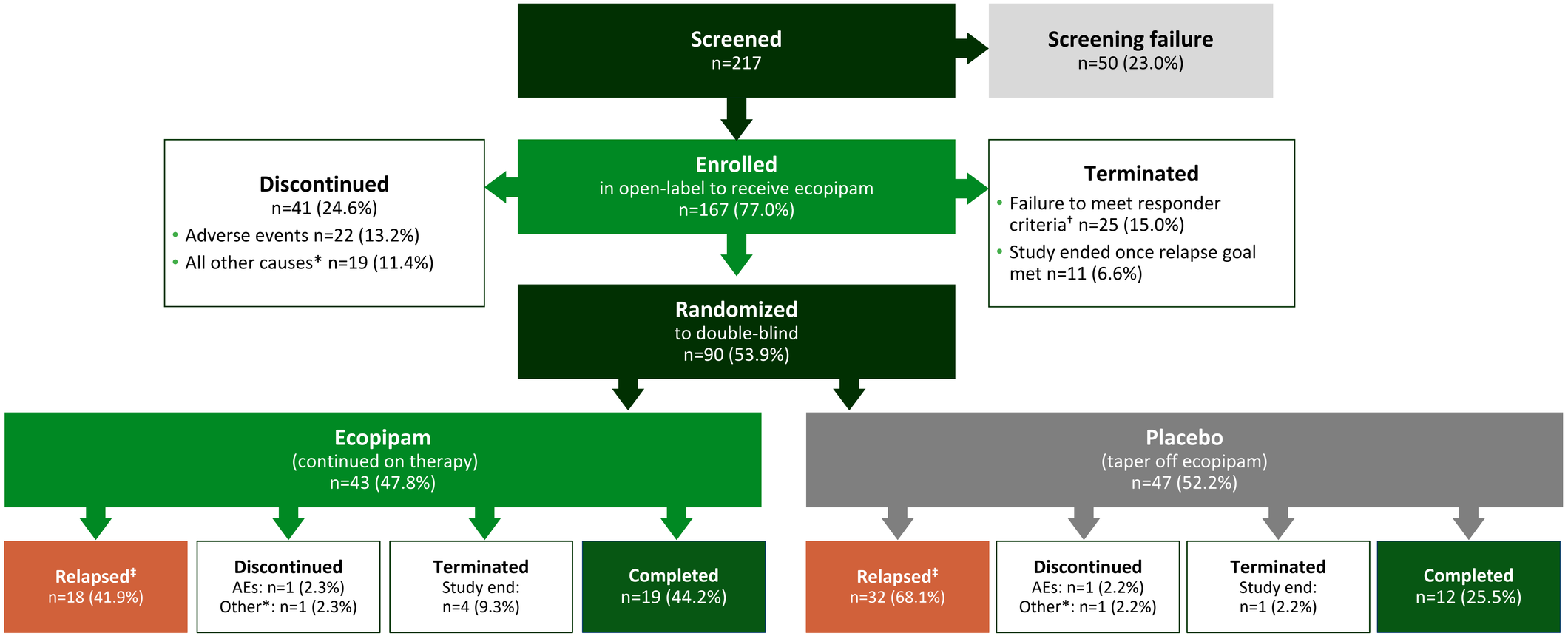
Participant Disposition (Pediatric)



*Included withdrawal of consent, lack of efficacy, or lost to follow-up. †≥25% improvement from baseline in YGTSS-TTS at Weeks 8 and 12. ‡≥50% loss of improvement in YGTSS-TTS previously observed from baseline to Week 12, initiation of additional medications for Tourette syndrome symptoms, or hospitalization related to worsening symptoms.

AE = adverse event; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

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Demographics and Baseline Characteristics

Parameter	Open-label period (12 weeks)	Double-blind period (12 weeks)	
	Ecopipam (n=216)	Ecopipam (n=51)	Placebo (n=53)
Age, y			
Mean (SD)	16.3 (8.8)	14.3 (5.5)	14.0 (5.8)
Range	6-58	6-36	6-41
Age group, n (%)			
Children (6-11 y)	56 (25.9)	15 (29.4)	16 (30.2)
Adolescents (12-17 y)	111 (51.4)	28 (54.9)	31 (58.5)
Adults (≥18 y)	49 (22.7)	8 (15.7)	6 (11.3)
Sex, n (%)			
Male	146 (67.6)	37 (72.5)	35 (66.0)
Female	70 (32.4)	14 (27.5)	18 (34.0)
Race, n (%)			
White	196 (90.7)	46 (90.2)	50 (94.3)
Black	7 (3.2)	1 (2.0)	2 (3.8)
Asian	3 (1.4)	0	1 (1.9)
Other*	10 (4.6)	4 (7.8)	0
Psychiatric comorbidities, n (%)†			
ADHD	88 (40.7)	24 (47.1)	20 (37.7)
OCD	44 (20.4)	13 (25.5)	8 (15.1)
Anxiety	40 (18.5)	11 (21.6)	10 (18.9)
Depression	17 (7.9)	3 (5.9)	2 (3.8)

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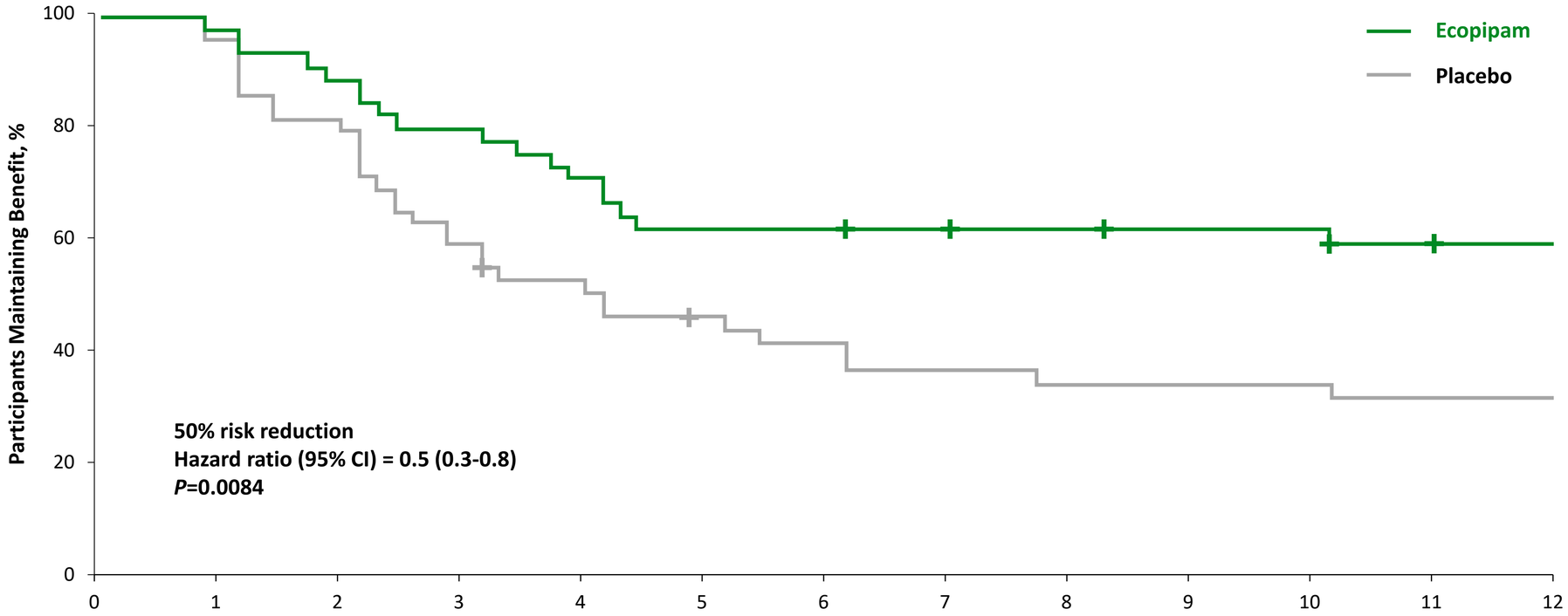
*Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or multiple.
†Based on past medical history collected at screening.

ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder.

Primary Endpoint: Time to Relapse* (Pediatric)



Participants at risk, n													
Ecopipam	43	42	38	34	30	26	26	24	24	23	23	19	19
Placebo	47	45	37	27	21	18	16	14	13	13	13	12	12

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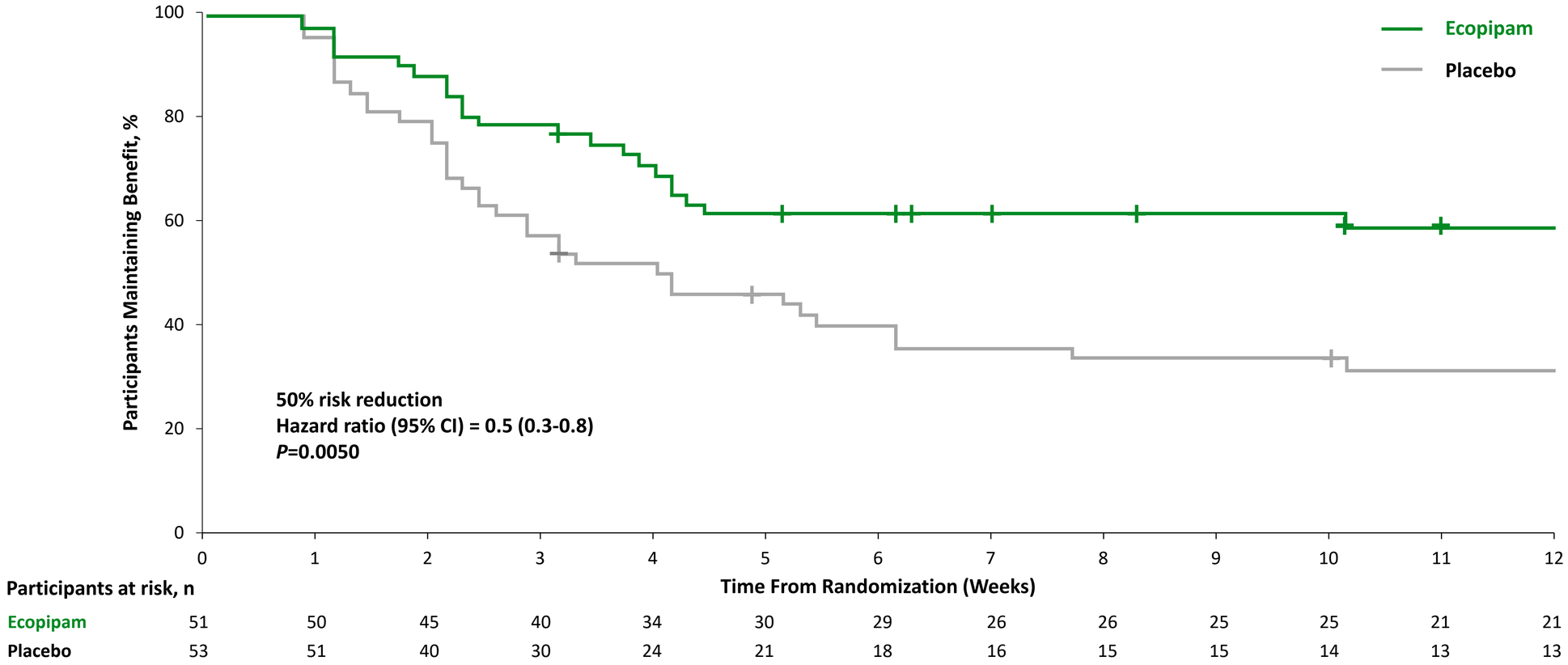
*From randomization (Week 12) in participants aged 6 to ≤17 years. Plus (+) sign indicates censored data. Relapse defined as ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score observed from baseline to Week 12, initiation of additional treatment for Tourette syndrome symptoms, or hospitalization related to worsening symptoms.

Secondary Endpoint: Time to Relapse* (Pediatric and Adult)



Participants at risk, n													
Ecopipam	51	50	45	40	34	30	29	26	26	25	25	21	21
Placebo	53	51	40	30	24	21	18	16	15	15	14	13	13

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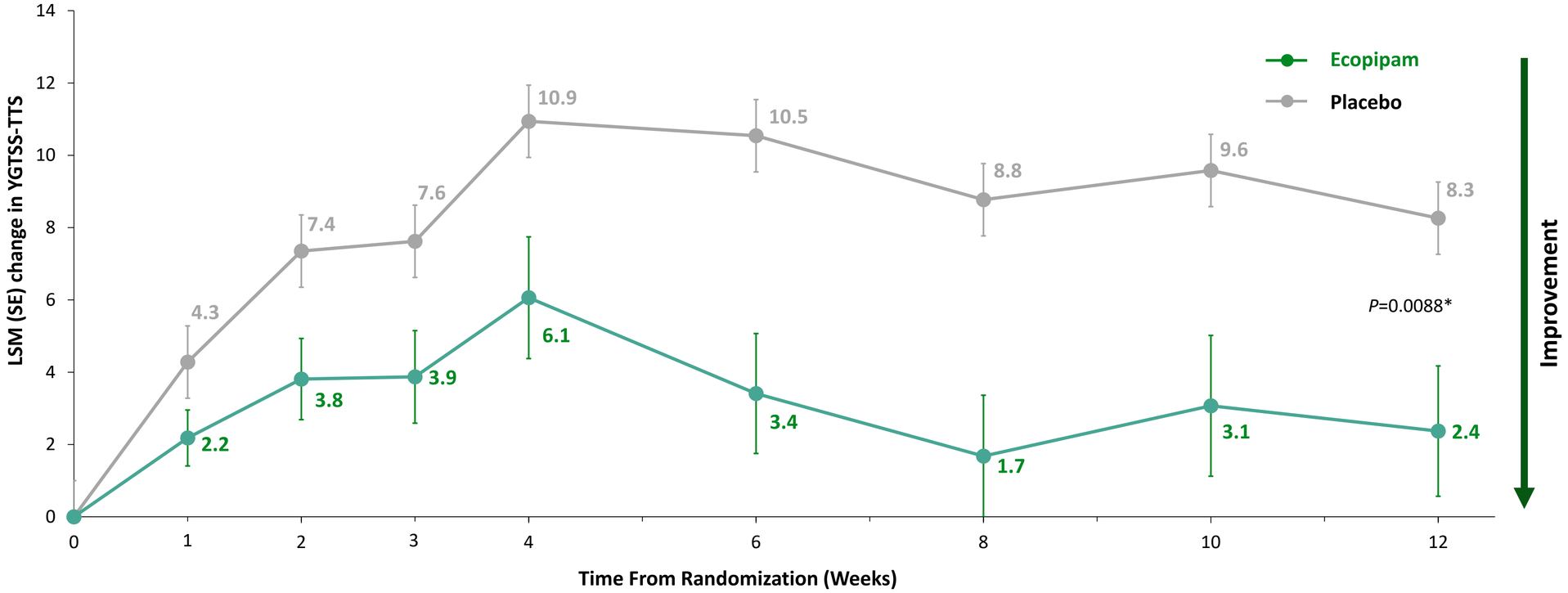
*From randomization (Week 12) in pediatric and adult participants. Plus (+) sign indicates censored data. Relapse defined as ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score observed from baseline to Week 12, initiation of additional treatment for Tourette syndrome symptoms, or hospitalization related to worsening symptoms.

Exploratory Endpoint: Change From Randomization in YGTSS-TTS (Pediatric and Adult)



Participants evaluated, n

Ecopipam	51	44	39	36	34	23	21	20	21
Placebo	53	46	39	31	24	19	15	14	13

*Ecopipam versus placebo. Due to competing risk related to participant loss, data are based on a mixed model for repeated measures ANCOVA 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. YGTSS-TTS score range of 0 (“none”) to 50 (“severe”).

ANCOVA = analysis of covariance; LSM = least-squares mean; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

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AE Summary (Pediatric and Adult)

Participants with an AE, n (%)	Open-label period (12 weeks)	Double-blind period (12 weeks)		All periods (24 weeks)
	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)
Serious AE	1 (0.5)*	1 (2.0)†	2 (3.8)‡	2 (0.9)
Treatment discontinuation due to AE§	34 (15.7)	0	1 (1.9)	34 (15.7)
Most frequent 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)

*Acute kidney injury, blood creatine phosphokinase increased, and obsessive-compulsive disorder (all considered possibly or probably related to treatment). †Type 1 diabetes mellitus. ‡Suicidal ideation (considered possibly related to treatment) and Tourette syndrome in 1 participant each. §Included tic (3.2% of ecopipam-treated participants), anxiety (2.8%), somnolence (2.8%), depressed mood (1.4%), depression (1.4%), insomnia (1.4%), and suicidal ideation (1.4%). ¶≥5.0% of ecopipam-treated participants.

AE = adverse event.

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AESI* Summary (Pediatric and Adult)

Participants with an AESI, n (%)	Open-label period (12 weeks)	Double-blind period (12 weeks)		All periods (24 weeks)
	Ecopipam (n=216)	Ecopipam (n=51)	Placebo (n=53)	Ecopipam (n=216)
Any AESI	84 (38.9)	7 (13.7)	6 (11.3)	89 (41.2)
Select AESIs				
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)
Drug-induced movement related	0†	0	0	0†

*Prespecified. †Tremor and dystonia reported in 1 participant each during open-label period and determined to be unrelated to ecopipam by a masked clinical adjudication committee.

AESI = adverse event of special interest.

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Conclusions

- Statistically significant response was seen in both the pediatric (primary endpoint) and overall (secondary endpoint) populations with ecopipam
  - Demonstrates a 50% reduced risk of relapse versus placebo during the 12-week withdrawal period
  - Supports maintenance and durability of treatment effect
- Ecopipam observations
  - Most common AEs were somnolence, anxiety, headache, insomnia, tic, and fatigue
  - No drug-induced movement-related AEs attributed to ecopipam
  - No ecopipam-related clinically relevant adverse metabolic effects or weight gain

AE = adverse event.