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An Anchor-Based Method to Establish Clinically Meaningful Changes in YGTSS-TTS Using Data From the Phase 2b and Safety Extension Studies of Ecopipam, a Selective D1 Receptor Antagonist, in Tourette Syndrome

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BACKGROUND

- The Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) and Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) are used to determine treatment response in clinical trials of patients with Tourette syndrome (TS), each with distinct advantages[1-3]
- The US Food and Drug Administration encourages sponsors to assess the clinical meaningfulness of trial outcomes and propose appropriate thresholds for clinically meaningful within-patient change[4]
- Previous work demonstrated that a ≥25% YGTSS-TTS improvement corresponds with a positive response (ie, "much improved" or "very much improved") on the Clinical Global Impression–Improvement scale in patients receiving behavioral therapy for TS[5]
- No known studies published to date have used the CGI-TS-S to establish a threshold for clinically meaningful improvement in YGTSS-TTS in children and adolescents with TS
- The selective dopamine 1 receptor antagonist ecopipam significantly improved YGTSS-TTS scores from baseline to Week 12 in a phase 2b trial of patients aged ≥6 to <18 years with TS (30% mean percentage change) and through Month 12 in the open-label extension (OLE; 42% mean percentage change at Month 12)[2,6]

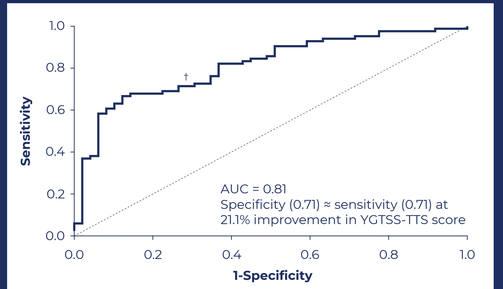
OBJECTIVE

- To determine the percentage improvement in YGTSS-TTS indicative of clinically meaningful improvement using the CGI-TS-S as an anchor

METHODS

- Post hoc receiver operating characteristic (ROC) analyses, with CGI-TS-S as the anchor measure, were performed using data from the phase 2b, randomized, double-blind, placebo-controlled trial (RCT) of ecopipam in patients aged ≥6 to <18 years with confirmed TS[2] or its OLE[6]
  - In the RCT, patients were randomly assigned to receive ecopipam 2 mg/kg/d or placebo for 12 weeks (4-week weight-based titration phase and 8-week treatment phase), followed by dose tapering by 25 mg/d until off study drug
  - In the OLE, patients who completed the RCT received ecopipam 2 mg/kg/d for 12 months (4-week weight-based titration phase and 11-month treatment phase)
  - YGTSS-TTS and CGI-TS-S were assessed at baseline and Weeks 4, 6, 8, and 12 of the RCT and at baseline and Months 1, 3, 6, 9, and 12 of the OLE

Figure 1. ROC Curve for YGTSS-TTS Versus CGI-TS-S*



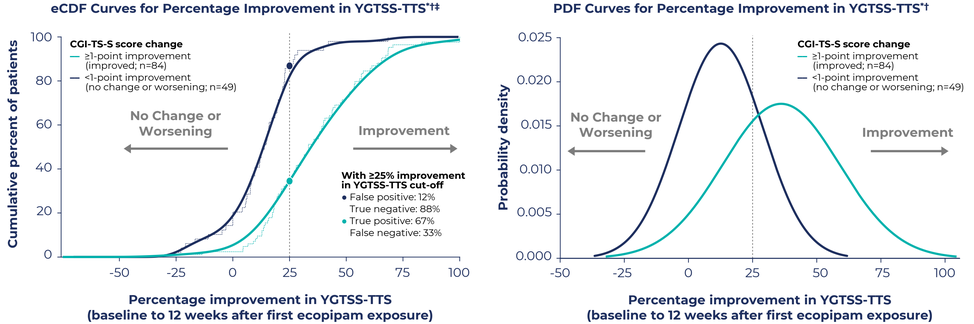
*One data point per patient using the value closest to 12 weeks after first exposure to ecopipam (≥4 weeks after baseline). †Specificity = sensitivity.
AUC = area under the curve; CGI-TS-S = Clinical Global Impression of Tourette Syndrome Severity; ROC = receiver operating characteristic; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

Table 1. ROC Analysis Results

	Cut-Off Method	
ROC Parameter	Specificity ≈ Sensitivity	Youden's J
YGTSS-TTS improvement cut-off	21.1%	25.0%
True positive rate (sensitivity)	0.71	0.67
True negative rate (specificity)	0.71	0.88
False positive rate (1–specificity)	0.29	0.12
False negative rate (1–sensitivity)	0.29	0.33
Positive predictive value	0.81	0.90
Negative predictive value	0.59	0.61
Accuracy	0.71	0.74

One data point per patient using the value closest to 12 weeks after first exposure to ecopipam (≥4 weeks after baseline).
AUC = area under the curve; ROC = receiver operating characteristic; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

Figure 2. Patients With Improvement on the CGI-TS-S Tend to Show Greater Percentage Improvement in YGTSS-TTS



*One data point per patient using the value closest to 12 weeks after first exposure to ecopipam (≥4 weeks after baseline). Dashed vertical line represents Youden's J cut-off value for percentage improvement in YGTSS-TTS that discriminated between patients with and without improved CGI-TS-S scores. ROC analysis to determine cut-off value used unsmoothed data. †Solid curves show smoothed data. ‡Dashed curves show unsmoothed data.
eCDF = empirical cumulative distribution function; CGI-TS-S = Clinical Global Impression of Tourette Syndrome Severity; PDF = probability density function; ROC = receiver operating characteristic; YGTSS-TTS = Yale Global Tic Severity Scale Total Tic Score.

CONCLUSIONS

- This analysis used 2 approaches to identify an appropriate threshold for clinically meaningful within-patient improvement in YGTSS-TTS
  - The specificity ≈ sensitivity cut-off for percentage improvement in YGTSS-TTS score that discriminated between patients with improvement versus those with no change or worsening on the CGI-TS-S was 21.1%, whereas the Youden's J cut-off was 25.0%
- These findings are consistent with previous behavioral therapy work[5] and support a ≥25% improvement in YGTSS-TTS as an appropriate minimum threshold to define clinically meaningful improvement in children and adolescents with TS
- This is the first known analysis to establish this threshold using the CGI-TS-S as an anchor in a pediatric population receiving pharmacotherapy for TS
- The 30% and 42% mean improvement in YGTSS-TTS during the ecopipam RCT[2] and OLE,[6] respectively, exceed both previously published[5] and herein defined thresholds for clinically meaningful improvement

DISCLOSURES

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

METHODS (Cont.)

- ROC analysis determined optimal cut-offs for percentage improvement in YGTSS-TTS score that distinguished patients with ≥1-point improvement on the CGI-TS-S from those with no change or worsening at 12 weeks (or value closest to 12 weeks) after first exposure to ecopipam
  - Smoothed empirical cumulative distribution function (eCDF) and probability density function (PDF) curves were created to visualize the separation of these patient subsets
- Spearman's correlation coefficient was calculated between percentage improvement in YGTSS-TTS and CGI-TS-S score at Week 12 (or closest value)

RESULTS

- A total of 133 patients were included in the analyses; 84 patients (63.2%) had improvement in CGI-TS-S score and 49 (36.8%) had no change or worsening
- According to the ROC analysis, a 21.1% improvement in YGTSS-TTS distinguished patients with versus without improvement in CGI-TS-S (AUC, 0.81; sensitivity ≈ specificity, 0.71); using Youden's J, the cut-off was 25.0% improvement in YGTSS-TTS (**Figure 1; Table 1**)
- Overall, ≥25% improvement in YGTSS-TTS was seen in 67% of patients with improved CGI-TS-S scores and 12% of patients with no change or worsening
- There was a significant correlation between YGTSS-TTS improvement and post-treatment CGI-TS-S score (r=−0.65; P<0.001)
- Consistent with the correlation finding, patients with improvement on the CGI-TS-S tended to show greater percentage improvement in YGTSS-TTS than those with no change or worsening (**Figure 2**)

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