Design of a Phase 3 Maintenance-of-Effect Trial of Ecopipam in Tourette Syndrome

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*At the time of study design

OBJECTIVE

- To design a confirmatory trial to establish the durability of treatment effect of ecopipam in the treatment of Tourette Syndrome (TS) and to further delineate the safety profile.

BACKGROUND

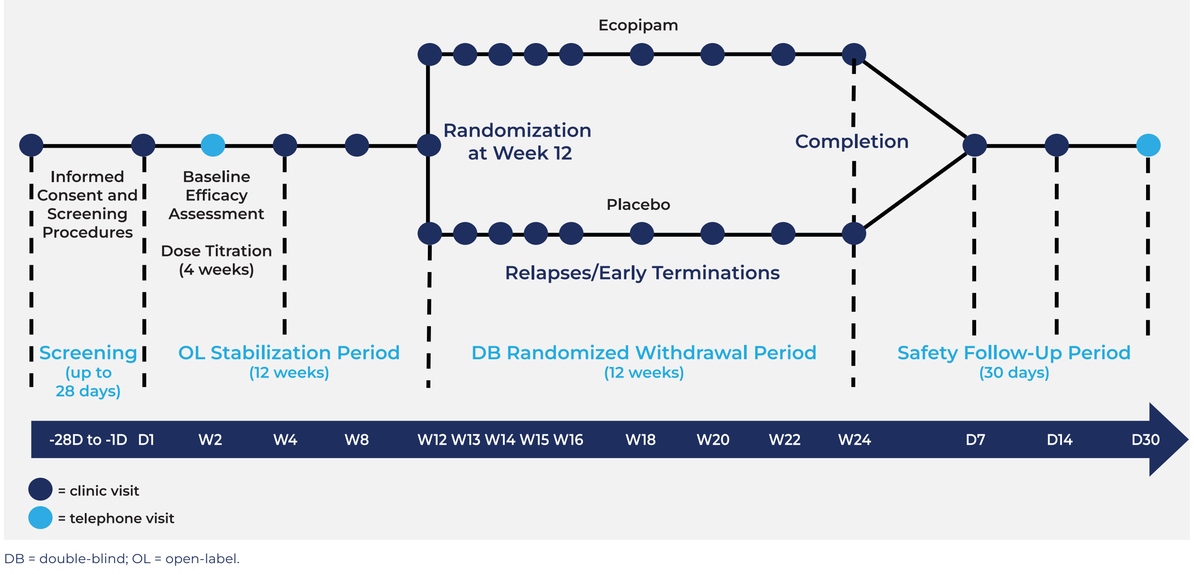
- TS is a rare neurodevelopmental disorder affecting approximately 174,000 children in the United States.[1] TS is associated with both increased morbidity and mortality, including suicide.[2,3] All currently approved therapies for TS in the United States are predominantly dopamine 2 receptor antagonists and associated with a range of adverse events limiting use especially with longer exposure.[4]
- Ecopipam is a first-in-class investigational agent that is being studied as a potential treatment for TS that blocks the actions of the neurotransmitter dopamine at the D1 receptor.[5] The phase 2b randomized, double-blind, parallel-group, placebo-controlled trial of 153 patients aged 6 to <18 years with TS demonstrated that ecopipam at 2 mg/kg/day significantly reduced the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) from baseline at 12 weeks versus placebo (P=0.01).[5] The most commonly reported adverse events with ecopipam were headache, insomnia, fatigue, somnolence, and restlessness, with anxiety reported to a lesser degree, and there was no observable evidence of drug-induced movements, excessive weight gain, or metabolic adverse effects commonly reported with antipsychotic agents.
- The phase 2b (D1AMOND) trial[5] was an adequate and well controlled study that established the treatment effect size of ecopipam as compared to placebo for the treatment of children and adolescents with TS and will serve as one of the registrational trials for marketing approval. However, there were some limitations that influenced the design of the current phase 3 trial. Seventy-six pediatric patients were exposed to ecopipam for a maximum period of 12 weeks. A longer period of observation was desired to establish the durability of treatment effect beyond 12 weeks. In addition, infrequent or later onset adverse events may not have been detected with a study of this size and duration. Finally, adequate data on effect of ecopipam in adults with TS are not currently available. Given that TS is a rare disease, the sponsor sought to explore designs that would provide maximum information. The design of this second registrational phase 3 trial should address these limitations, while maintaining executional feasibility.

METHODS

- After the successful D1AMOND trial,[5] we evaluated 3 different randomized clinical trial designs for the registrational phase 3 trial for ecopipam: a classical randomized, placebo-controlled, parallel group (RCT) study similar to D1AMOND[5]; a randomized, placebo run-in; and a randomized withdrawal (RWD) study. All incorporate a randomized, placebo-controlled component. Design parameters in common were: 85% power and 0.05 alpha; 25% improvement in YGTSS-TTS as a clinically meaningful response[6]; duration of exposure of approximately 24 weeks; and a 1:1 randomization. Criteria for evaluating designs were centered on participant and investigator acceptance, trial objectives (ie, replication of previous study results vs increasing understanding of drug efficacy by demonstrating maintenance of effect), number of patients required, exposure times, and statistical efficiency.
- Subsequently, the RWD design was selected (**Figure 1**). It begins with an open-label, single-arm, active treatment phase (the 12-week stabilization period) to identify clinical responders. Non-responders exit the trial. Responders (YGTSS-TTS reduction ≥25%) are randomized to either continue on active drug or to switch to placebo. After randomization, each patient is followed to determine the time to relapse (ie, the time at which the patient has experienced a prespecified clinically meaningful loss of the benefit observed in the open-label phase). Time to relapse is analyzed with standard methods, including Kaplan-Meier curves and statistical inference using the log-rank test.
- A model of the RWD design was constructed (**Figure 2**) and simulations performed to determine study size and duration over a range of parameters.

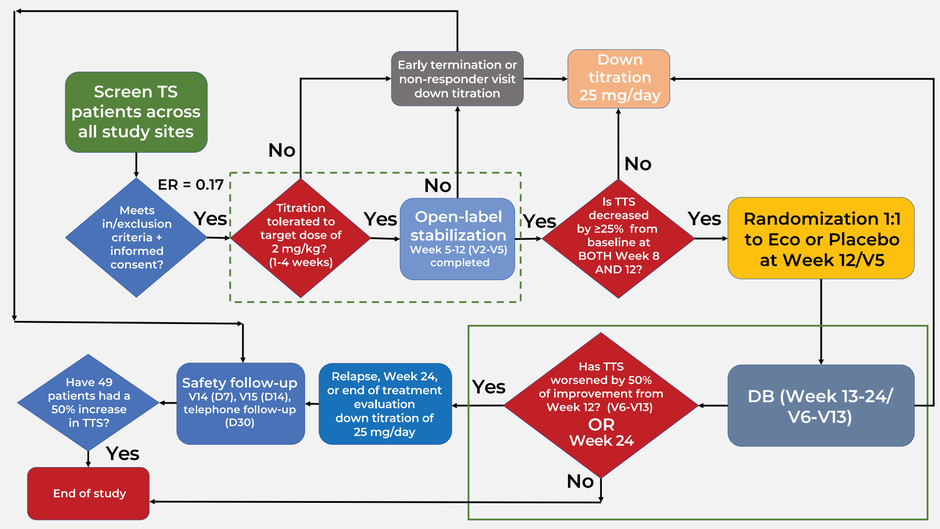
RESULTS

FIGURE 1. RANDOMIZED WITHDRAWAL STUDY DESIGN



DB = double-blind; OL = open-label.

FIGURE 2. RANDOMIZED WITHDRAWAL STUDY PATIENT FLOW CHART



DB = double-blind; Eco = ecopipam; ER = enrollment rate; TS = Tourette Syndrome; TTS = total tic score.

Pre-Specified Study Design Parameters for RWD Trial Simulation:

1. Enrollment rates were estimated at 0.17 patients/site/month (informed by D1AMOND results[5])
2. Approximately 50% of enrolled patients would meet the responder threshold of a 25% improvement at Weeks 8 AND 12 (informed by D1AMOND results[5])
3. A relapse post-randomization was defined as a loss of 50% of the improvement observed during the open-label stabilization period
4. Study duration limited to 24 months
5. For the outcome measure of time to relapse post-randomization, 85% power to detect a difference with 0.05 alpha

- The number of relapses required for power depends, among other factors, on the estimated rates at which patients randomized to placebo and patients randomized to ecopipam relapse. For a 3-month placebo relapse rate of 65% and ecopipam relapse rate of 34%, 49 observed relapses would be required for an 85% power with 0.05 alpha. If the difference between relapse rates is larger, fewer relapses are required for the same power, resulting in shorter or smaller studies (**Figure 3**).

Study duration was assessed across a range of scenarios including:

1. Responder rates
2. Ecopipam relapse rates
3. Placebo relapse rates
4. Dropout rates across the study

- Assuming conservatively a 34% relapse rate of ecopipam and a 65% relapse rate of placebo, with estimations of dropouts (10%), the study requires approximately 217 pediatric patients enrolled in the open-label across 90 sites to achieve a study duration of 23 months. In addition, we anticipate to enroll approximately 40 adult patients, whose data will not be included in the primary efficacy analysis but will be analyzed in a secondary endpoint.
- No prior studies adequately inform the relapse rate for placebo or ecopipam, thus conservative estimates were made in designing the study. To allow for a much greater than expected treatment effect, an interim analysis is planned to occur when 70% (34) of the base case number of relapses have occurred. The "cost" or alpha spend was set at 0.001 for interim analysis. **Table 1** shows, for various population relapse rates, the probability that the study would be terminated early for overwhelming efficacy.

FIGURE 3. SIMULATION RESULTS FOR STUDY DURATION IN MONTHS BY RELAPSE RATES

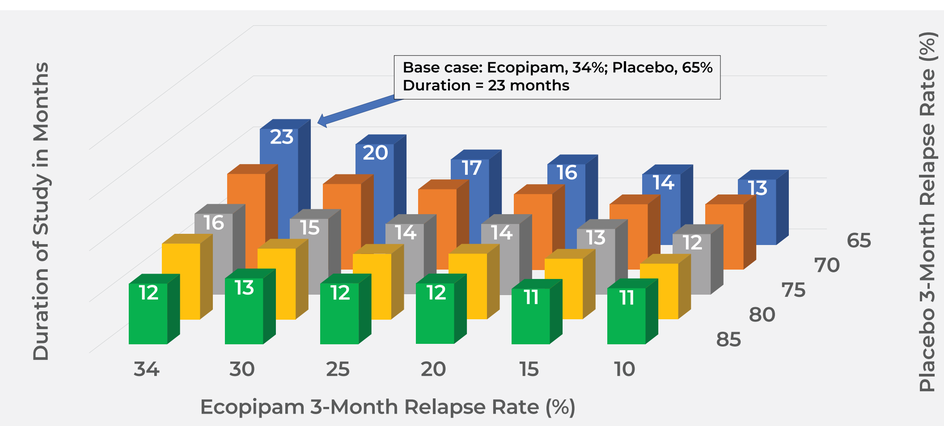


TABLE 1. PROBABILITY OF STOPPING AT IA FOR EFFICACY ACROSS A RANGE OF ECOPIPAM AND PLACEBO 3-MONTH POPULATION RELAPSE RATES

Placebo Relapse Rate	65%	65%	65%	65%	65%	65%	70%	70%	70%	70%	70%
Ecopipam Relapse Rate	34%	30%	25%	20%	15%	10%	30%	25%	20%	15%	10%
Probability of Stopping at IA	22%	33%	50%	68%	82%	93%	44%	60%	75%	87%	94%

IA = interim analysis.

SUMMARY

- We examined 3 potential trial designs and chose an RWD design to better define the maintenance of treatment and risk profile beyond 12 weeks.

The RWD is an example of enriched trial designs, which have several advantages in the context of rare disease:

1. All patients are exposed to the active agent.
2. Those who either had no benefit or experienced a safety or tolerability difficulty exit the trial early and can be treated conventionally.
3. Acceptance of this design is high by both patients and investigators facilitating enrollment and overall trial feasibility. This design is also recognized by regulatory authorities as a valid way to assess efficacy.
4. To allow patients the opportunity to achieve clinical response before randomization, RWD trials are also associated with longer exposures to active drug, thus enhancing the ability to detect less frequent or later-onset adverse events, as well as test the durability of treatment effect.
5. RWD trials can suggest subsets who may be responders over the open-label with support over the randomized withdrawal epochs.

The RWD trial does pose challenges:

1. Inappropriate for indications in which withdrawal poses a risk to patients.
2. Restricted to situations when improvement is expected to be observed after treatment initiation and loss of benefit shortly after withdrawal.
3. Requires a clinically meaningful definition of "responder" for face validity.
4. Requires a precise definition of loss of response for the randomized withdrawal phase.

- For the final design, a clinically meaningful responder criterion for entry into the randomized phase was set as a 25% improvement from baseline observed at Week 8 and confirmed at Week 12. The definition of relapse was defined as a loss of 50% of improvement in the randomized withdrawal phase, initiation of additional medications to treat TS, hospitalization for worsening symptoms of TS, or loss of efficacy as determined by the principal investigator. This definition has face validity and defines a valid endpoint for statistical inference and Kaplan-Meier analysis.

CONCLUSIONS

- The enriched enrollment RWD design meets feasibility requirements, provides up to 24 weeks of safety data, and is powered to determine maintenance of efficacy of ecopipam for TS while reducing placebo exposure for this serious disorder. Results of this effort were used to plan the ongoing phase 3 ecopipam trial, D1AMOND 3 (NCT05615220). Scenario analyses allowed examination of feasibility, including study size, number of sites, and study duration across key parameters. The probability of early study termination was examined for various population relapse rates. Such an approach is especially helpful in RWD trials addressing rare disease. The study design has been accepted by both the US FDA and German Federal Institute for Drugs and Medical Devices (BfArM).

REFERENCES: 1. Bitsko RH, Claussen AH, Lichstein J, et al. Mental Health Surveillance Among Children – United States, 2013 – 2019. *MMWR Suppl*. 2022;71(2):1-48. **2.** Meier SM, Dalsgaard S, Mortensen PB, Leckman JF, Plessen KJ. Mortality risk in a nationwide cohort of individuals with tic disorders and with Tourette syndrome. *Mov Disord*. 2017;32(4):605-609. doi:10.1002/mds.26939 **3.** Virtanen S, Sidorchuk A, Fernandez de la Cruz L, et al. Association of Tourette syndrome and chronic tic disorder with subsequent risk of alcohol- or drug-related disorders, criminal convictions, and death: a population-based family study. *Biol Psychiatry*. 2021;89(4):407-414. doi:10.1016/j.biopsych.2020.09.014 **4.** Pringsheim T, Holler-Managan Y, Okun MS, et al. Comprehensive systematic review summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019;92(19):907-915. **5.** Gilbert DL, Dubow JS, Cunniff TM, et al. Ecopipam for Tourette syndrome: a randomized trial. *Pediatrics*. 2023;151(2):e2022059574. **6.** Jeon S, Walkup JT, Woods DW, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. *Contemp Clin Trials*. 2013;36(2):414-420. doi:10.1016/j.cct.2013.08.012

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DISCLOSURES: TMC and SPW report having equity interest in Emalex Biosciences, Inc., and Paragon Biosciences, LLC (the parent company of Emalex Biosciences, Inc.). DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc. ARM is a former employee of Emalex Biosciences, Inc.

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