
Tourette syndrome.

Study duration was assessed across a range of scenarios including:

Pre-Specified Study Design Parameters for RWD Trial Simulation:

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

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

Pre-Specified Study Design Parameters for RWD Trial Simulation:

1. Enrollment rates were estimated at 0.17 patient/month/site.

2. Approximately 50% of enrolled patients would meet the responder threshold of a 25% improvement at Weeks 8 and 12.

3. A relapse post-randomization was defined as a loss of 50% of the improvement observed during the open-label stabilizing drug phase.

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 rate at which patients randomized to placebo and patients randomized to ecopipam relapse. For a 3-month placebo relapse rate of 65% and an 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 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.

The most commonly reported adverse events with ecopipam were headache, insomnia, fatigue, somnolence, and restless leg, with anxiety reported to a lesser degree, and there was no observable evidence of drug-induced weight gain, or metabolic adverse effects commonly reported with antipsychotics.

The phase 2b (DIAMOND) trial 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 registration 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, the design of the phase 2b trial assumed that TS is a rare disease, the sponsor sought to explore designs that would provide maximum information. This design was not logistically feasible.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo Relapse Rate</th>
<th>65%</th>
<th>65%</th>
<th>65%</th>
<th>65%</th>
<th>75%</th>
<th>75%</th>
<th>75%</th>
<th>75%</th>
<th>75%</th>
<th>100%</th>
<th>100%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Relapse Rate</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Probability of Stopping at IA</td>
<td>32%</td>
<td>35%</td>
<td>25%</td>
<td>20%</td>
<td>15%</td>
<td>10%</td>
<td>30%</td>
<td>20%</td>
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<td>15%</td>
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</tbody>
</table>

CONCLUSIONS

1. The enriched enrichment RWD design meets feasibility requirements, provides 24 weeks of data safety, and is powered to determine maintenance of efficacy of ecopipam for TS while reducing placebo exposure for the overwhelming majority of patients. These data were used to plan the ongoing phase 3 ecopipam trial (DIAMOND3, NCT06153290). 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).

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 740,000 children in the United States; it is associated with both increased morbidity and mortality, including suicide.1 All currently approved therapies for TS in the United States are predominantly dopamine receptor antagonists and associated with a range of adverse events limiting use especially with longer exposure.2 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.3 The phase 2b, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in 150 patients aged 5-18 yrs with TS demonstrated that ecopipam at 2 high/daily significantly reduced the global CTRATS Severity Score from baseline to 12 weeks versus placebo (P<0.01).4 The most commonly reported adverse events with ecopipam were headache, insomnia, fatigue, somnolence, and restless leg, with anxiety reported to a lesser degree, and there was no observable evidence of drug-induced weight gain, or metabolic adverse effects commonly reported with antipsychotics.

After the successful DIAMOND trials5 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 DIAMOND; 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 (a clinically meaningful response); duration of exposure of participants not current; and a 2-month placebo run-in. 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 then enter into a withdrawal phase when they are randomized to placebo and patients randomized to ecopipam relapse. A relapse post-randomization was defined as a loss of 50% of the improvement observed during the open-label stabilizing drug phase.

The RWD trial design poses three key 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 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 at 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, based on additional medications to treat the primary condition and tolerability and safety data (Figure 3).

The only randomized withdrawal trial in Tourette syndrome.

Table 1 shows, for various population relapse rates, the probability that the study would be terminated early for overwhelming efficacy.

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 final RWD trial design was approved by the RESCUE-EU Steering Committee for the ongoing phase 3 ecopipam trial called D1AMOND3 (NCT06153290). 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).

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