Clinical Study Summary: Study B4Z-MC-LYAU

A Double-Blind Crossover Study of Tomoxetine Hydrochloride and Methylphenidate Effects on Neural Activity in Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 16 February 2007

**Brief Summary of Results**

This was a 16-week (approximately), double-blind, crossover comparison of tomoxetine and methylphenidate in children aged at least 6 years and <13 years with Attention-Deficit/Hyperactivity Disorder (ADHD) who had not been on treatment for at least 3 weeks prior to starting the study. The primary objective of Study B4Z-MC-LYAU (LYAU) was to test the hypothesis that regional neuronal activation of prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxetine in children with ADHD was greater than baseline neural activity.

Due to a malfunction of the functional Magnetic Resonance Imaging (fMRI) equipment at the investigative site during data recording, an analysis of the efficacy of tomoxetine on regional neuronal activation of prefrontal cortical and subcortical areas is unavailable. The following summary provides the available data from this trial.

<table>
<thead>
<tr>
<th><strong>Title of Study:</strong></th>
<th>A Double-Blind Crossover Study of Tomoxetine Hydrochloride and Methylphenidate Effects on Neural Activity in Attention-Deficit/Hyperactivity Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigators:</strong></td>
<td>This single-center study included 3 principal investigators.</td>
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<tr>
<td><strong>Study Center:</strong></td>
<td>This study was conducted at 1 study center in 1 region.</td>
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<tr>
<td><strong>Length of Study:</strong></td>
<td>1 year 7 months</td>
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<tr>
<td>First patient enrolled (assigned to therapy):</td>
<td>16 February 2002</td>
</tr>
<tr>
<td>Last patient completed:</td>
<td>20 September 2003</td>
</tr>
<tr>
<td><strong>Phase of Development:</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Objectives:</strong></td>
<td>The primary objective of Study LYAU was to test the hypothesis that regional neuronal activation of prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxetine (maximum total daily dose 1.8 mg/kg/day given as a twice-daily [BID] dose, not to exceed 120-mg dose regardless of weight) in children with ADHD was greater than baseline neural activity. Extent of activation was measured during 3 cognitive tasks (probes of attention, working memory, and inhibitory</td>
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control) which were performed while undergoing blood oxygenation level dependent (BOLD), fMRI before treatment (baseline scan) in comparison with posttreatment with tomoxtine.

The secondary objectives of the study were as follows:

- To test the hypothesis that the percentage of increase in activity during specific cognitive performance tasks in prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxtine in children with ADHD was greater than baseline (unmedicated condition). The 3 cognitive tasks are probes of attention, working memory, and inhibitory control performed while undergoing BOLD fMRI.

- To test the hypothesis that the extent of neuronal activation and percentage of increase in activation in prefrontal cortical and subcortical areas following approximately 6 weeks of treatment with tomoxtine were different from those following 6 weeks of treatment with methylphenidate (Ritalin®) (maximum total daily dose 1.5 mg/kg given as a 3 times daily [TID] dose). The extent (volume of activation) and percentage increase in activity of frontal and subcortical structures were measured during 3 cognitive tasks: probes of attention, working memory, and inhibitory control performed while undergoing BOLD fMRI before treatment (baseline scan) in comparison with posttreatment with tomoxtine and methylphenidate.

- To test the hypothesis that changes in percentage of neural activation (and/or decreased activation volume) of dorso lateral prefrontal cortex (DLPFC) were correlated with changes in working memory and inhibitory control task performance.

- To test the hypothesis that changes in percentage of neural activation (and/or decreased activation volume) of DLPFC were correlated with changes in clinical measures of ADHD symptomatology including the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S), and others.

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The investigator requested an addendum to the protocol to gather baseline data in healthy controls. The addition of control subjects without ADHD enabled determinations as to whether there were any practice effects associated with multiple administrations of the cognitive battery. In addition, it was possible to test the hypothesis that ADHD children exhibited more diffuse activation and less striatal activation during task performance compared to normal children.

Other objectives that were tested by the inclusion of normal controls included:

- To test the hypothesis that unmedicated ADHD children exhibited more diffuse task-related activation when compared with normal children.

- To test the hypothesis that task-related activation in medicated ADHD children approximated task-related activation when compared to normal children.

- To test the hypothesis that task-related activation in medicated ADHD children did not vary significantly when the tasks were repeated 5 to 6 weeks apart.

**Study Design:** This study was a 16-week (approximately), double-blind, crossover comparison of tomoxtine and methylphenidate in children aged at least 6 years and <13 years with ADHD who had not been on treatment for at least 3 weeks prior to starting the study. Study Period I was the screening, medication washout, and assessment phase. Study Period II consisted of the double-blind, acute treatment period. Study Period III was the study drug washout period, where patients crossed over, leading into Study Period IV, a second double-blind, acute treatment period. Study Period V was the discontinuation of study drug phase [See Figure 1].
For the study addendum, there was a maximum of 4 visits completed by at least half the children: Visit 1 (Screening), Visit 2 (Practice Session in Mock Scanner), Visit 3 (Scanning Procedure and tests) and Visit 4 (Scanning Procedure and tests). Visits 1 and 2 procedures could be performed on the same day if time allowed. One-half of the sample was asked to repeat the scan session about 5 to 6 weeks after the first scan in order to assess for practice effects. Control children and parents were screened using the same structured interview [Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, (KSADS)] completed by the ADHD children and parents. Control children completed the same task training as ADHD children. They also underwent a scan session identical to the scan session used with the ADHD sample. The ADHDRS assessment and CGI-ADHD-S were performed at Visit 1 only.

Number of Patients:
Planned Completers: 16
Randomized: 8 tomoxetine then methylphenidate, 8 methylphenidate then tomoxetine
Completed: 5 tomoxetine then methylphenidate, 6 methylphenidate then tomoxetine

Main Criteria for Inclusion: Subjects must be right-handed and meet the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for ADHD as assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Behavioral) at Visit 1 and by investigator assessment using DSM-IV criteria. In addition, all subjects must have scored at least 1.0 standard deviation above norms for age and sex on either subscale or the combined scale for his or her diagnostic subtype of the ADHDRS-IV-Parent:Inv at Visit 1.
Inclusion criteria for the study addendum required subjects to be right-handed, at least 6 years of age, but <13 years of age, who had not yet reached Tanner Stage II, and who were generally healthy without a history of neurological illness, seizures, or head trauma.

Test Product, Dose, and Mode of Administration: Tomoxetine: Administered as divided (BID) dose beginning at .5 mg/kg/day and with a maximum dose of 1.8 mg/kg/day, supplied in 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules. Placebo: Placebo capsules, given once-daily (QD; noontime).
Note: patients randomized to tomoxetine received 2 doses of tomoxetine and 1 dose of placebo per day.

Comparator Dose and Mode of Administration: Methylphenidate: 0.45 to 1.8 mg/kg/day TID; Methylphenidate capsules, 5 mg and 10 mg.

Duration of Treatment: 12 weeks of active treatment (approximately 16 weeks of study participation).

Variables:
Efficacy: fMRI, ADHDRS-IV-Parent:Inv, CGI-ADHD-S, Task Performance
Safety: AEs, laboratory analytes, vital signs, ECGs
Note: Subjects in the study addendum were not treated with tomoxetine or methylphenidate; therefore, data from this group is not included in this summary.
Evaluation Methods:
Primary Efficacy: A whole-brain, 2-way (Treatment X Order), within-subject, repeated-measures analysis of variance (ANOVA) for each task activation map using an *a priori* threshold of p=.002 was used to identify those regions whose activation was associated with a tomoxetine and methylphenidate treatment. Alternatively, regions of interest (ROI) analysis utilized a mean baseline activation map as a mask to define activated ROIs for each subject. The resultant activation mask was applied to each treatment condition yielding mean percent and extent of activation for each condition within the ROI.

Secondary Efficacy: Changes in secondary efficacy measures were summarized by sequence group and treatment period. The sum and difference of the scores for each period for each subject was computed. The test for carryover effect was performed by comparing the sum score values between the 2 sequence groups using the Wilcoxon rank sum test. The test for treatment effect (assuming no carryover effect) was performed using the difference score values between the 2 sequence groups using the Wilcoxon rank sum test. If a statistically significant carryover effect was found (p<.10) for a variable, then a treatment comparison was performed using the Wilcoxon rank sum test only on data from the first crossover period. Treatment group comparisons were performed only on subjects who did not discontinue prior to entering the second treatment period.

Safety: For treatment-emergent computations (AEs and abnormal, high, or low laboratory values), Visits 1 and 2 were used as baseline. Categorical safety parameters were analyzed by first placing subjects into 1 of 4 classifications based on their response in each treatment period (subjects experiencing no incidence in either Period I or II [0,0], no incidence in Period I and incidence in Period II [0,1], incidence in Period I and no incidence in Period II [1,0], and incidence in both Periods I and II [1,1]). The frequency of subjects in each classification was then obtained for each sequence group. Carryover effect was determined by combining the [0,1] and [1,0] classifications within each sequence group and performing a chi-square test on the resulting 2 by 3 contingency table. Treatment effect was assessed by comparing the [1,0] and [0,1] categories for each sequence group using a chi-square test on the 2 by 2 contingency table. Changes in vital signs and laboratory data were analyzed similar to the secondary efficacy measures.
Study Design

<table>
<thead>
<tr>
<th>I</th>
<th>II Double-Blind, Dose-Titration Acute Treatment Phase</th>
<th>III Study Drug Washout</th>
<th>IV Double-Blind, Dose-Titration Acute Treatment Phase</th>
<th>V Discontinuation from Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening, Medication Washout, Assessment Phase</td>
<td>Visits 2-6: 5-10 Days (7 Days suggested)</td>
<td>Visits 9-13: 5-10 Days (7 Days suggested)</td>
<td>Visits 10-20 Days (14 Days suggested)</td>
<td>Visits 13-14: 5-18 Days (10 Days suggested)</td>
</tr>
<tr>
<td>10-20 Days (14 Days suggested)</td>
<td>Visits 6-7: 5-18 Days (10 Days suggested)</td>
<td>Visits 14: 5-18 Days (10 Days suggested)</td>
<td>Visits 15: 1-7 Days (3 Days suggested)</td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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Tomoxetine

Methylphenidate

Note: Visits 2, 7, and 14 will have an fMRI administered.

Figure 1. Illustration of study design for Study B4Z-MC-LYAU.

Patient Disposition

A total of 16 patients were randomized in this trial, 8 patients who were initially randomized to tomoxetine and then crossed over to methylphenidate, and 8 patients initially randomized to methylphenidate who crossed over to tomoxetine. Thirteen patients completed Study Period II, and 11 patients completed the entire study.

Primary Efficacy Measures

Due to a malfunction of the fMRI equipment at the investigative site during data recording, an analysis of the efficacy of tomoxetine on regional neuronal activation of prefrontal cortical and subcortical areas is unavailable.

Secondary Efficacy Measures

Both methylphenidate and tomoxetine were associated with symptomatic improvement on the ADHDRS-IV-Parent:Inv total and subscales and the CGI-ADHD-S score compared with study baseline. For the ADHDRS-IV-Parent:Inv rating scale score, a responder to either tomoxetine or methylphenidate was considered to be a patient who achieved at the end of the treatment period for the relevant drug a $\geq 25\%$ decrease from baseline.
Safety

Adverse Events

There were no deaths or serious adverse events (SAEs) in this study. During Study Period II, 10 patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were decreased appetite, headache, initial insomnia, and irritability. Three patients reported at least 1 TEAE during Study Period IV. The most common TEAEs were decreased appetite and irritability. In the entire study, 2 patients discontinued due to AEs. There were no statistically significant differences between treatment groups for TEAEs and discontinuations due to AEs.

Vital Signs

There were no statistically significant differences in vital signs or ECG measurements (including QT intervals) between treatment groups.