Efficacy, Safety, Tolerability and PK of Mazindol Controlled Release (CR) in Adults with ADHD

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Introduction

Mazindol is an indirectly-acting stimulant, originally developed as an antidepressant in 1975, and classified at the time as a 9-hydroxy-controlled substance (a primary metabolite of the antidepressant imipramine). It was withdrawn from markets by 2002 due to commercial reasons unrelated to efficacy or safety. A recent open label study in adults with ADHD suggested the possible re-emergence of mazindol as a "non-CNS stimulant" treatment for ADHD. This is the first controlled study investigating the long-term (≥6 months) safety, efficacy and tolerability of mazindol CR in adult patients with ADHD.

Methods

Objectives

- To evaluate the efficacy of mazindol CR in adults with ADHD
- To characterize the safety and tolerability of mazindol CR

Design

Randomized, double-blind, placebo-controlled, flexible-dose trial of mazindol CR (1-3 mg) or placebo (1-2 mg) in 6 weeks in patients with ADHD (see Figure 1).

Participants

1. Included patients with primary diagnosis of ADHD as established by score of ≥60 on the ADHD-RS-DSM5 at Baseline.

Exclusion Criteria

1. Subjects who scored ≥18 on the Montgomery-Asberg Depression Rating Scale (MADRS).
2. History of head injury, other significant brain injury, cranial surgery, or intracranial hemorrhage.
3. History of substance use disorder (excluding OTC medications).
4. Current/previous DSM-IV-TR axis I or II mental disorder.
5. Taking ADHD medications for >4 weeks prior to screening.
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Assessment Measures (Response to Treatment): Measures were clinician rated and taken at each visit (Table 1).

Primary Outcome: Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-DSM5) total score.

Secondary Outcomes: Responder rates (see Table 2) as measured by the ADHD-RS-DSM5 (minimal response threshold) or CGI (optimal response threshold);

- Safety and tolerability were assessed through adverse event reporting, vital signs, physical examination, laboratory parameters, and assessment of social, home and school functioning.

Results

Results: Efficacy

- ADHD-RS-DSM5 scores: The CI showing mazindol CR over placebo was 21.2% (95% CI: 15.4% to 27.1%). Clinical significance, defined as >20% reduction in ADHD symptoms, was noted for mazindol CR by day 7 (the first post-treatment visit), and with a 50% reduction in ADHD-RS-DSM5 score by day 35 (See Figure 3).

Results: Safety

- CGIs: More subjects were responders on the CGI on mazindol CR compared to placebo from Visits 1 (Day 14) and each subsequent visit.

Conclusion

Mazindol CR has a robust effect on symptoms of ADHD with a placebo-adjusted effect size of 1.09. This effect size is similar to previously reported results using mazindol in non-clinical settings and other studies.

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Pharmacokinetics

- Low levels of the metabolite following mazindol CR administration were equal or to higher than mazindol trough concentrations at steady-state.

Conclusions

- Mazindol CR has a robust effect on symptoms of ADHD with a placebo-adjusted effect size of 1.09. This effect size is similar to previously reported results using mazindol in non-clinical settings and other studies.

- Patients receiving mazindol CR responded quickly with a mean reduction in target scores by Visit 8 (Day 42) were 42.9% on Mazindol CR compared to placebo from Visit 4 (Day 14) and at each subsequent visit.

References

1. Keshwala, D., Villano, I., Messina, A., Valenzano, A., Moscatelli, F., Esposito, T., Monda, V., Esposito, M., Franco and the Worldwide Clinical Trials team for their implementation of the study, and thanks to the investigators for their participation.

Table 1: Description of Responders

Table 2: Summary of the Proportion of Responders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Mazzindol CR vs Placebo</th>
<th>Placebo vs Baseline</th>
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<tbody>
<tr>
<td>ADHD-RS-DSM5 Score</td>
<td>21.2</td>
<td>15.4% to 27.1%</td>
<td>1.09</td>
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