Signal Detection in Schizophrenia Clinical Trials: Contribution of Responders vs. Partial/Non-Responders

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ABSTRACT

INTRODUCTION: Placebo response has increased over several decades, contributing to decreased drug-placebo difference in randomized, placebo-controlled trials in patients with psychiatric illness. The magnitude of placebo (or drug) response and its impact on symptom severity, functioning and quality of life outcomes remain poorly understood. The objective of this post-hoc analysis was to compare lurasidone ("drug") response and placebo response, and to assess contribution to signal detection by responders vs. partial responders (or non-responders) in placebo-controlled, clinical trials in schizophrenia.

METHODS: Patients were randomized to receive fixed doses of lurasidone 18.5 mg/d to 148 mg/d (N=1015) or placebo (N=491) at 200 study sites in 5 US-based and multiregional schizophrenia clinical trials. Primary and key secondary study endpoints were change from baseline to week 6 on PANSS and Clinical Global Impression of Severity (CGI-S), respectively. Symptom improvement was assessed by mean change in PANSS total score at week 6 study endpoint. Response was defined as CGI-S ≤ 3 at week 6 for responders (i.e., no response) or ≤ 3 for partial responders. Partial response (or non-response) was defined as CGI-S > 3 at week 6 for responders. Symptom improvement was assessed by mean change in PANSS scores from baseline to week 6 study endpoint.

RESULTS: In pooled analysis of 5 short-term schizophrenia trials responders to placebo showed similar magnitude of symptom improvement (mean week 6 change in PANSS total score = -17.4 ± 11.8) compared to lurasidone responders (mean change = -14.1 ± 10.3 for lurasidone 37 mg/d; -11.4 for lurasidone 74 mg/d; -10.3 for lurasidone 111 mg/d; and -13.4 for lurasidone 148 mg/d, N=335, 335, 329, and 334 for lurasidone 37 mg/d, 74 mg/d, 111 mg/d, and 148 mg/d, respectively). For patients who did not meet the CGI-S response criterion (CGI-S > 3 at week 6), responders improvement (in PANSS total score from baseline to week 6 endpoint in each lurasidone dose group: 5.2 for lurasidone 37 mg/d, -1.0 for lurasidone 74 mg/d, -6.3 for lurasidone 111 mg/d, -8.1 for lurasidone 148 mg/d, N=415, 415, 413, and 413 for lurasidone 37 mg/d, 74 mg/d, 111 mg/d, and 148 mg/d, respectively).

CONCLUSION: The post-hoc analysis from 5 placebo-controlled studies in patients with schizophrenia showed the magnitude of symptom improvement (as assessed by mean change in PANSS score) was comparable for patients classified as lurasidone and placebo responders. In contrast, significantly greater improvement was observed at study endpoint for lurasidone compared to placebo among patients classified as responders vs. partial responders (or non-responders). These findings suggest that signal detection is more likely to be robust among patients with schizophrenia who did not fully respond to either active drug or placebo treatment.

OBJECTIVES

The objectives of this post-hoc analysis was to compare lurasidone ("drug") response and placebo response, using five double-blind, placebo-controlled, randomized clinical trials that demonstrated efficacy of lurasidone in patients with schizophrenia. The current analysis explored the contribution to signal detection by responders vs. partial responders (or non-responders) in placebo-controlled, clinical trials in schizophrenia, in addition to examining the hypothesis link between placebo response and drug response based on the 200 pooled investigator sites from these 5 multinational, randomized trials.

METHODS

• The analysis population included patients who were randomized to receive fixed doses of lurasidone 18.5 mg/d to 148 mg/d (N=1015) or placebo (N=491) at 200 study sites in 5 US-based and multiregional acute schizophrenia trials.
• Response was defined as having a score ≤ 3 on the Clinical Global Impression of Severity (CGI-S) at week 6 for responders. Partial response (or no response) was defined as having a score > 3 on CGI-S at week 6 for responders. Symptom improvement was assessed by mean change in PANSS total score at week 6 study endpoint.
• ANCOVA model for mediation analysis was applied to examine the drug-placebo difference in symptom improvement and treatment outcomes among the responders and partial responders (or non-responders).

RESULTS

Table 1: Change from Baseline to Week 6 (LOCF) in PANSS Score

<table>
<thead>
<tr>
<th>Studies</th>
<th>Lurasidone 37 mg/d</th>
<th>Lurasidone 74 mg/d</th>
<th>Lurasidone 111 mg/d</th>
<th>Lurasidone 148 mg/d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-Responder</td>
<td>-14.0</td>
<td>-13.0</td>
<td>-10.3</td>
<td>-11.4</td>
<td>-6.2</td>
</tr>
<tr>
<td>CGI-Partial/Non-Responder</td>
<td>-14.1</td>
<td>-10.3</td>
<td>-8.1</td>
<td>-9.9</td>
<td>-5.5</td>
</tr>
</tbody>
</table>

DISCUSSION

• This post-hoc analysis based on 5 placebo-controlled studies in patients with schizophrenia showed the magnitude of symptom improvement (as assessed by mean change in PANSS score) was comparable for patients classified as lurasidone and placebo responders.
• In contrast, significantly greater improvement was observed at study endpoint for lurasidone compared to placebo among patients classified as responders vs. partial responders (or non-responders).
• These findings suggest that signal detection is more likely to be robust among patients with schizophrenia who did not fully respond to either active drug or placebo treatment.

REFERENCES


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