Axelopan Phase 2b Study Demonstrates a Sustained Increase in Bowel Movement Frequency in Patients Regardless of Duration of Opioid-Induced Constipation

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Introduction

Opioid analgesics such as morphine continue to play a critical role in chronic and non-cancer pain control. Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction.1

Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.2

Axelopan (formerly TD-1211) is an investigational, peripherally selective, multivalent mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.3

Safety and efficacy results, including the primary and key secondary endpoints, from a 5-week, Phase 2b study in chronic non-cancer pain OIC patients have been previously reported.4 Since OIC is not prone to tolerance and patients can experience OIC for the duration of opioid therapy, patients were divided into short and long duration of OIC groups (<5 and ≥5 years) to explore if OIC duration impacts axelopan treatment response.

Methods

A 5-week, double-blind, randomized, multi-center, placebo-controlled, parallel-group study was conducted in chronic non-cancer pain patients with OIC, defined as ≥5 spontaneous bowel movements (SBMs) over a 2-week baseline period and at least one additional symptom of constipation in at least 25% of the bowel movements. For the first 4 days of dosing, patients randomized to axelopan received 1 mg daily and on Day 5, remained at 5 mg or were dose escalated to 10 mg or 15 mg daily for the remainder of the treatment period. Patients randomized to placebo received placebo for all 5 weeks. At least 14 days prior to Day 1, patients were on a stable chronic opioid regimen, with a total daily dose of ≤30 mg morphine equivalent units (MEU).

Patients were required to stop laxatives and bowel regimens, except protocol permitted rescue laxative use, throughout the study. Electronic diaries collected bowel frequency, timing, and symptoms of bowel movements; use of laxatives and opioids; daily pain scores; and satisfaction with quality of life metrics. Primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment. Key secondary endpoint was the change from baseline in weekly average spontaneous bowel movements (SBMs) over the same period.

Week 1 was excluded from the primary analysis in order to confirm the durability of response and predictability of longer term efficacy studies. Patients were divided into short and long duration of OIC groups (<5 and ≥5 years) and evaluated on the study’s primary and key secondary endpoints.

Results

Patient baseline demographics

As summarized in the Table, baseline characteristics were similar for all treatment groups in the overall population as well as the short and long duration of OIC groups. Subjects were on a representative spectrum of opioids. Daily opioid doses ranged from 30-1740 oral MEU. Back pain was the most commonly reported reason for chronic opioid use. Mean and range of OIC duration in the study were 6.0 years and 0.2-39.3 years, respectively.

Table 1: Patient Baseline Demographics by Duration of OIC

<table>
<thead>
<tr>
<th>Duration of OIC</th>
<th>Mean Age (SD)</th>
<th>Gender</th>
<th>Mean SBM (SD)</th>
<th>Mean CSM (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 Years</td>
<td>54.9 (18.1)</td>
<td>Female: 60%</td>
<td>12.6 (6.1)</td>
<td>5.8 (2.4)</td>
</tr>
<tr>
<td>≥5 Years</td>
<td>54.9 (18.1)</td>
<td>Female: 55%</td>
<td>12.6 (6.1)</td>
<td>5.8 (2.4)</td>
</tr>
</tbody>
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Efficacy Endpoints by Duration of OIC Group

The baseline frequency of CSBMs and SBMs was similar for short and long duration of OIC groups (Figs 1-2).

During weeks 2-5, all doses of axelopan resulted in higher average CSBMs and SBMs per week compared to placebo for the overall population & both OIC duration groups (Figs 1-2). For the ≥5 year OIC duration group, there was a dose-response relationship in average CSBMs and SBM frequency during weeks 2-5 and similarly in the overall population for SBM frequency (Figs 1-2, Table 2).

Axelopan Conclusions

10mg and 15mg demonstrated a clinically meaningful, sustained response in CSBM and SBM frequency over the 5-week treatment period in patients irrespective of their duration of OIC. Generally well-tolerated with no treatment-related SAEs. Majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

References