Cardiovascular Safety Results of INP104 (POD-DHE) from the STOP 301 Phase 3 Study

Karen Craig, PhD1; John Hoekman, PhD1; Maria Jeleva, PhD1; Jasna Hocevar-Trnka, MD1; Sheena Aurora, MD1; Stephen Shrewsbury, MB ChB1

Introduction

- Dihydroergotamine (DHE) has long been used and recommended for the treatment of migraine due to its high response rate and sustained efficacy.
- However, despite over 70 years of clinical experience, DHE product labels warn of potential cardiovascular (CV) and peripheral ischemic events.
- INP104 is a novel, investigational drug-device combination product that targets delivery of DHE mesylate to the upper nasal cavity using a gas-propelled Precision Olfactory Delivery (POD®) device, version 1.
- A Phase 1 study (STOP 101) found INP104 to be well tolerated and readily absorbed, showing ~1/10 the CV disease events or presented with significant risk factors for cardiovascular (CV) or peripheral ischemic events.

Study Design

- This was a pivotal Phase 3, interventional, open-label, single-group assignment study, assessing the safety, tolerability, exploratory efficacy, and patient acceptability of INP104 over long-term use.
- The study comprised a 4-week screening period, a 24-week treatment period for all patients, a 2-week post-treatment follow-up period for all patients.
- Although the primary focus of this study was on nasal safety (integrity and function), CV effects (treatment-emergent adverse events [TEAEs], concomitant medication use, vital signs, and ECGs) were regularly collected and reviewed against preexisting conditions, concomitant medication use, and INP104 exposure.

Study Patients and Treatment

- Patients were adult (18–65 years) males and females with a documented diagnosis of frequent migraine, defined as experiencing a minimum of 2 migraine attacks, with or without aura, each month not related to INP104, but not with INP104, and no electrocardiogram (ECG) changes were observed.
- Phase 1 data showed significant blood pressure increases with IV DHE mesylate, but not with INP104, and no electrocardiogram (ECG) changes were observed.
- STOP 301 was a pivotal Phase 3 safety study on the use of INP104 for the acute treatment of migraine over 24 and 52 weeks.

Methods

- To report the cardiovascular results of INP104 from the STOP 301 study.

Objective

- No patient experienced a cardiac-related TEAE over 24 weeks.
- Over 24 weeks, 5 patients (1.4%) experienced vascular TEAEs (Table 1).
- 4 patients (1.1%) experienced (mild) hypertension – 2 patients (Patients 2 and 3) had ongoing hypertension at the start of the study for which they were receiving treatment.
- Worsening hypertension for Patient 2 was assessed as related to INP104; however, the event resolved with additional treatment after 116 days.
- 1 patient (0.3%) experienced a hematoma that was not related to INP104, but was sustained during a motorcycle accident.
- Overall, minimal mean changes from baseline were observed for systolic and diastolic blood pressure and for median heart rate, aggregate PR interval, QRS duration, QT interval, QT corrected with Fridericia’s formula (QTcF), and RR interval over 24 weeks (Table 2 and 3).
- No patient had an overall interpretation of an abnormal clinically significant ECG or experienced a TEAE associated with an abnormal ECG.

Concomitant Medication Use

- INP104 overuse and use with triptans (contraindicated) did not lead to concerning TEAEs.

Adverse Events

- No serious AEs were considered related to INP104 use.

Results

- Cardiac TEAEs:
  - No patient experienced a cardiac-related TEAE over 24 weeks.
- Vascular TEAEs:
  - Over 24 weeks, 5 patients (1.4%) experienced vascular TEAEs (Table 1).
  - 4 patients (1.1%) experienced (mild) hypertension – 2 patients (Patients 2 and 3) had ongoing hypertension at the start of the study for which they were receiving treatment.
  - Worsening hypertension for Patient 2 was assessed as related to INP104; however, the event resolved with additional treatment after 116 days.
  - 1 patient (0.3%) experienced a hematoma that was not related to INP104, but was sustained during a motorcycle accident.
- Blood Pressure and ECG:
  - Overall, minimal mean changes from baseline were observed for systolic and diastolic blood pressure and for median heart rate, aggregate PR interval, QRS duration, QT interval, QT corrected with Fridericia’s formula (QTcF), and RR interval over 24 weeks (Table 2 and 3).
  - No patient had an overall interpretation of an abnormal clinically significant ECG or experienced a TEAE associated with an abnormal ECG.

Concomitant Medication Use

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Table 2 and 3

Continued Next Page
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### Table 1. Vascular TEAEs Overview (24-Week FSS, N=354)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration (Days)</th>
<th>INP104 Doses at TEAE Start</th>
<th>Related to INP104</th>
<th>Relevant Medical History</th>
<th>Relevant Prior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ongoing 10</td>
<td>10</td>
<td>No</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>17</td>
<td>Yes</td>
<td>Hypertension</td>
<td>Hydrochlorothiazide/irbesartan</td>
</tr>
<tr>
<td>3</td>
<td>Ongoing 6</td>
<td>6</td>
<td>No</td>
<td>Obesity, Hypertension</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>4</td>
<td>Ongoing 22</td>
<td>22</td>
<td>No</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Ongoing 11</td>
<td>11</td>
<td>No</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*The TEAE was ongoing as of last contact with patient.

** Verbatim term was worsening hypertension.

FSS = full safety set; TEAE = treatment-emergent adverse event.

### Table 2. Mean Systolic and Diastolic Blood Pressure (24-Week FSS, N=354)

<table>
<thead>
<tr>
<th>Week</th>
<th>Systolic BP (mmHg, Mean ± SD)</th>
<th>Diastolic BP (mmHg, Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline*</td>
<td>118.1 ± 12.44</td>
<td>77.3 ± 9.67</td>
</tr>
<tr>
<td>4</td>
<td>117.6 ± 12.38</td>
<td>77.1 ± 8.99</td>
</tr>
<tr>
<td>8</td>
<td>117.9 ± 13.34</td>
<td>77.0 ± 9.38</td>
</tr>
<tr>
<td>12</td>
<td>116.9 ± 12.67</td>
<td>76.1 ± 9.25</td>
</tr>
<tr>
<td>16</td>
<td>118.2 ± 12.88</td>
<td>77.5 ± 9.17</td>
</tr>
<tr>
<td>20</td>
<td>117.4 ± 12.35</td>
<td>76.9 ± 8.69</td>
</tr>
<tr>
<td>24</td>
<td>117.0 ± 12.55</td>
<td>76.7 ± 8.96</td>
</tr>
<tr>
<td>26 (Follow-up)</td>
<td>116.8 ± 12.51</td>
<td>77.0 ± 8.72</td>
</tr>
</tbody>
</table>

*Baseline is defined as the last non-missing observation prior to the date of patient’s enrollment into the study on Day 0.

**Post-baseline only includes data from patients who started the first INP on/before the visit evaluated.

BP = blood pressure; FSS = full safety set; SD = standard deviation.

### Table 3. Mean ECG Parameters (24-Week FSS, N=354)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (Mean ± SD)</th>
<th>Week 24 (Mean ± SD)</th>
<th>End of Period (24-wk Trt, Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Heart Rate (beats/min)</td>
<td>69.7 ± 11.27</td>
<td>69.4 ± 10.61</td>
<td>69.5 ± 10.54</td>
</tr>
<tr>
<td>PR Interval, Aggregate (msec)</td>
<td>154.9 ± 20.89</td>
<td>153.2 ± 21.80</td>
<td>153.1 ± 21.19</td>
</tr>
<tr>
<td>QR Duration, Aggregate (msec)</td>
<td>88.6 ± 9.88</td>
<td>88.3 ± 10.76</td>
<td>88.8 ± 10.13</td>
</tr>
<tr>
<td>QT Interval, Aggregate (msec)</td>
<td>391.6 ± 28.08</td>
<td>392.1 ± 27.19</td>
<td>390.6 ± 27.12</td>
</tr>
<tr>
<td>QTcF Interval, Aggregate (msec)</td>
<td>410.9 ± 18.84</td>
<td>410.6 ± 19.58</td>
<td>409.6 ± 19.11</td>
</tr>
<tr>
<td>RR Interval, Aggregate (msec)</td>
<td>878.58 ± 144.11</td>
<td>877.90 ± 127.76</td>
<td>877.53 ± 129.98</td>
</tr>
</tbody>
</table>

References


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