The PK data from this study indicate that the pediatric granule formulation of NBI-921352/XEN901 (Novel Na,1.6-Selective Sodium Channel Blocker) in Healthy Adults: Pediatric Granules and Adult Tablets

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BACKGROUND

- NBI-921352 (also known as XEN901) is a potent and highly selective Na,1.6 inhibitor intended for the treatment of SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) and other forms of epilepsy.
- A pediatric appropriate (granule) formulation of NBI-921352, which can be mixed with soft foods or liquid prior to dosing, was developed to enable a study in SCN8A-DEE patients.
- The current study was conducted to assess the pharmacokinetics (PK) of the NBI-921352 pediatric granule formulation and its relative bioavailability compared to an adult immediate-release (IR) tablet formulation, as well as the impact of a high-fat meal on the pediatric formulation.

METHODS

STUDY DESIGN

- In this single-center, open-label, crossover study, 24 healthy adults were randomized into 3 groups (n=8 each) to receive 3 NBI-921352 treatments, separated by at least 72 hours between treatments (Figure 1):
  - Treatment A: Adult IR tablet (50 mg) after an overnight fast
  - Treatment B: Pediatric granules (50 mg) in oral suspension after an overnight fast
  - Treatment C: Pediatric granules (50 mg) in oral suspension 30 minutes after a high-fat, high-calorie meal

KEY EXCLUSION CRITERIA

- Known or suspected intolerance or hypersensitivity to NBI-921352 or any closely related compound
- History of seizures, allergic reaction, or significant disease that could affect clinical assessments or laboratory evaluations

ANALYSES

- Blood samples were obtained at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post-dose on Days 1, 4, and 7 for determination of plasma NBI-921352 concentrations using validated liquid chromatography-tandem mass spectrometry methods.
- PK parameters assessed included maximum concentration (Cmax), area under the curve from time 0 to the last measurable concentration (AUC0-τ), area under the curve from time 0 to infinity (AUC0-inf), time to maximum plasma concentration (Tmax), and terminal elimination half-life (T1/2).

RESULTS

- Of the 24 evaluable subjects, 16 (66.7%) were male and 14 (58.3%) were white; mean age was 37.0 years (Table 1).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>All Subjects (N=24)</th>
<th>Age, mean (SD), years</th>
<th>37.0 (10.3)</th>
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</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>18 (66.7)</td>
<td></td>
<td></td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (66.7)</td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>5 (20.8)</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>3 (12.5)</td>
<td></td>
<td></td>
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<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>25.4 (8.7)</td>
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</tbody>
</table>

Table 1. Baseline Characteristics

BIODEQUILIBRIUM OF PEDIATRIC VERSUS ADULT FORMULATIONS

- Following single-dose administration in the fasted state, mean plasma concentration-time profiles were similar for the pediatric granule and adult IR tablet formulations; both formulations were rapidly absorbed with a median Tmax of 1.0 hour (Figure 2 and Figure 3).

Figure 2. Plasma NBI-921352 Concentrations for the Pediatric Granule Formulation (Fed and Fasted) and Adult IR Tablet Formulation (Fasted)

Figure 3. PK Parameters and Geometric Mean Ratios of the Pediatric Granule Versus Adult IR Tablet Formulation of NBI-921352

FOOD EFFECTS ON THE PEDIATRIC FORMULATION

- The median Tmax was delayed 2.0 hours and Cmax was decreased by 38% for the pediatric granules in the fed state versus fasted state, indicating that a high-fat meal delayed the rate of NBI-921352 absorption (Figure 2 and Figure 4).
- The GMR for the NBI-921352 Cmax was 61.6% in the fed state versus fasted state; however, the GMRs and associated 90% CI [AUC0-τ, AUC0-inf] were within the BE range, indicating there was no significant food effect on the total systemic exposure of NBI-921352 (Figure 4).
- T1/2 for the pediatric granules was 6.5 hours in the fed state and 8.5 hours in the fasted state (Figure 4).

CONCLUSIONS

- The PK data from this study indicate that the pediatric granule formulation of NBI-921352 was bioequivalent to the IR adult tablet after single-dose administration in the fasted state.
- Administration of the pediatric granule formulation of NBI-921352 in the fasted state (both a high-fat meal delayed the rate, but not the extent, of absorption compared to the fasted state).
- The favorable PK of the pediatric formulation (e.g., IR characteristics, BE to adult IR tablet; Figure 4) make this formulation suitable for further clinical development of NBI-921352 in pediatric patients with SCN8A-DEE.

REFERENCES

2. Geometric mean ratio (GMR) and 90% confidence intervals (CI) for the Cmax and AUC0-τ for the pediatric formulation compared with adult IR tablets in the fasted state.

Figure 4. PK Parameters and Geometric Mean Ratios of the Pediatric Granule Formulation (Fed and Fasted) and Adult IR Tablet Formulation (Fasted)

Figure 4. PK Parameters and Geometric Mean Ratios of the Pediatric Granule Versus Adult IR Tablet Formulation of NBI-921352 Administered in Fed Versus Fasted State

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