Pharmacokinetics, Food Effect, and Relative Bioavailability of Two Formulations of NBI-921352/XEN901 (Novel $Na_V1.6$-Selective Sodium Channel Blocker) in Healthy Adults: Pediatric Granules and Adult Tablets

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BACKGROUND

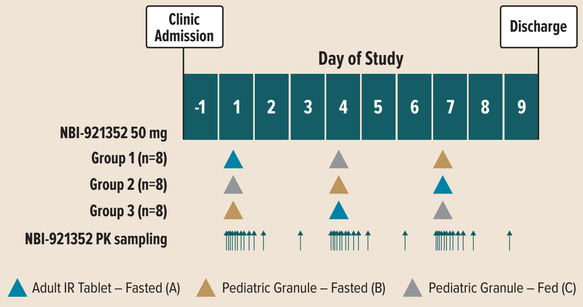
- NBI-921352 (also known as XEN901) is a potent and highly selective $Na_V1.6$ inhibitor intended for the treatment of SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) and other forms of epilepsy[1]
- A pediatric-appropriate (granule) formulation of NBI-921352, which can be mixed with soft 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

Figure 1. Study Design



IR, immediate-release; PK, pharmacokinetics.

SUBJECTS

- Key inclusion criteria
  - Healthy men and women, aged 18-55 years
  - Body mass index of 18.5 to 30.0 kg/m^2
- Key exclusion criteria
  - PR interval <110 msec, QRS interval >120 msec, and Fridericia-corrected QT interval >440 msec
  - Use of any prescription or over-the-counter medication within 30 days or 5 half-lives that was judged likely to interfere with the study (except hormonal contraception)
  - 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 (C_{max}), area under the curve from time 0 to the last measurable concentration (AUC_{0-t}), area under the curve from time zero to infinity (AUC_{0-inf}), time to maximum plasma concentration (T_{max}), and terminal elimination half-life ($T_{1/2}$)

RESULTS

- Of the 24 evaluable subjects, 16 (66.7%) were male and 15 (62.5%) were white; mean age was 37.0 years (**Table 1**)

Table 1. Baseline Characteristics

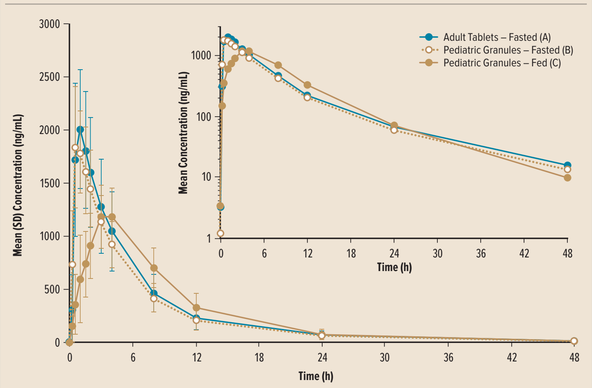
	All Subjects (N=24)
Age, mean (SD), years	37.0 (10.3)
Male, n (%)	16 (66.7)
Race, n (%)	
White	15 (62.5)
Black	5 (20.8)
Other	4 (16.7)
BMI, mean (SD), kg/m^2	25.4 (2.7)

BMI, body mass index; SD, standard deviation.

BIOEQUIVALENCE 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 T_{max} 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 (Fed)

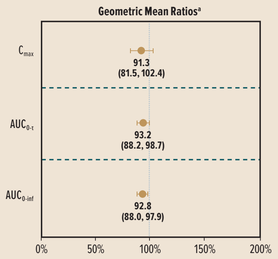


IR, immediate-release; SD, standard deviation.

- Geometric mean ratio (GMR) and 90% confidence intervals (CI) for the C_{max}, AUC_{0-t}, and AUC_{0-inf} of the pediatric granule formulation compared with adult IR tablets in the fasted state were within the bioequivalence (BE) range of 80-125% (**Figure 3**)
- Following absorption, NBI-921352 plasma concentrations declined in a mono-exponential manner with a $T_{1/2}$ of 8.5 hours for both formulations (**Figure 3**)

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

Parameter, Mean (SD)	Pediatric Granule Fasted (N=24)	Adult IR Tablet Fasted (N=24)
C_{max}, ng/mL	2022.8 (430.8)	2239.3 (539.7)
AUC_{0-t}, ng•h/mL	11094.1 (2568.5)	12109.0 (3554.6)
AUC_{0-inf}, ng•h/mL	11303.7 (2643.4)	12381.5 (3683.9)
T_{max}, h[b]	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)
$T_{1/2}$, h	8.5 (2.5)	8.5 (3.8)



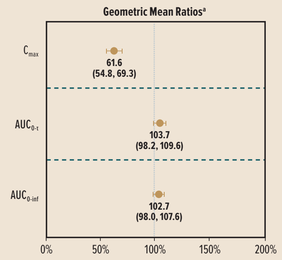
[a]Geometric Mean Ratios are shown with 90% CIs for the pediatric vs adult formulation of NBI-921352 administered in the fasted state.
[b]Median (min, max) is shown for T_{max}.
AUC_{0-inf}, area under the curve from time 0 to infinity; AUC_{0-t}, area under the curve from time 0 to the last measurable concentration; C_{max}, maximum plasma concentration; CI, confidence interval; IR, immediate-release; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration.

FOOD EFFECTS ON THE PEDIATRIC FORMULATION

- The median T_{max} was delayed ~2 hours and C_{max} 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 C_{max} was 61.6% in the fed state versus fasted state; however, the GMRs and associated 90% CI for AUC_{0-t} and AUC_{0-inf} were within the BE range, indicating there was no significant food effect on the total systemic exposure of NBI-921352 (**Figure 4**)
- $T_{1/2}$ for the pediatric granule was 6.5 hours in the fed state and 8.5 hours in the fasted state (**Figure 4**)

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

Parameter, Mean (SD)	Pediatric Granule Fed (N=24)	Pediatric Granule Fasted (N=24)
C_{max}, ng/mL	1246.7 (298.3)	2022.8 (430.8)
AUC_{0-t}, ng•h/mL	11666.9 (3433.6)	11094.1 (2568.5)
AUC_{0-inf}, ng•h/mL	11769.8 (3546.2)	11303.7 (2643.4)
T_{max}, h[b]	3.0 (1.0, 4.0)	1.0 (0.5, 2.0)
$T_{1/2}$, h	6.5 (1.0)	8.5 (2.5)



[a]Geometric Mean Ratios are shown with 90% CIs for the pediatric formulation of NBI-921352 administered in the fed vs fasted state.
[b]Median (min, max) is shown for T_{max}.
AUC_{0-inf}, area under the curve from time 0 to infinity; AUC_{0-t}, area under the curve from time 0 to the last measurable concentration; C_{max}, maximum plasma concentration; CI, confidence interval; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration.

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 fed state (with a high-fat meal) delayed the rate, but not the extent, of absorption when compared to the fasted state
- The favorable PK of the pediatric formulation (e.g., IR characteristics, BE to adult IR tablet; no significant food effect on total systemic exposure) make this formulation suitable for further clinical development of NBI-921352 in pediatric patients with SCN8A-DEE

REFERENCES

1. Bialer M, Johannessen SI, Koepp MJ, et al. *Epilepsia*. 2018;59(10):1811-1841.

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Please email medinfo@neurocrine.com if you have any questions on this presentation.

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