Abstract No. #4840; Program #P10.001

Relative Bioavailability, Pharmacokinetic and Food Effect Assessment of Two Immediate-Release Formulations of the $Na_V1.6$-Selective Sodium Channel Blocker NBI-921352/XEN901: Pediatric Granules and Adult Tablets

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Disclosures

- Drs. Namdari, Beatch, Cadieux and Aycardi are employed by Xenon Pharmaceuticals, Inc. They receive salaries and may hold stock or stock options in Xenon Pharmaceuticals.
- Dr. Loewen is employed by Neurocrine Biosciences, Inc. He receives a salary and may hold stock or stock options in Neurocrine Biosciences.
- Neurocrine Biosciences, Inc. has an exclusive license to NBI-921352/XEN901 and other pre-clinical selective $Na_V1.6$ inhibitors and dual $Na_V1.2/1.6$ inhibitors.
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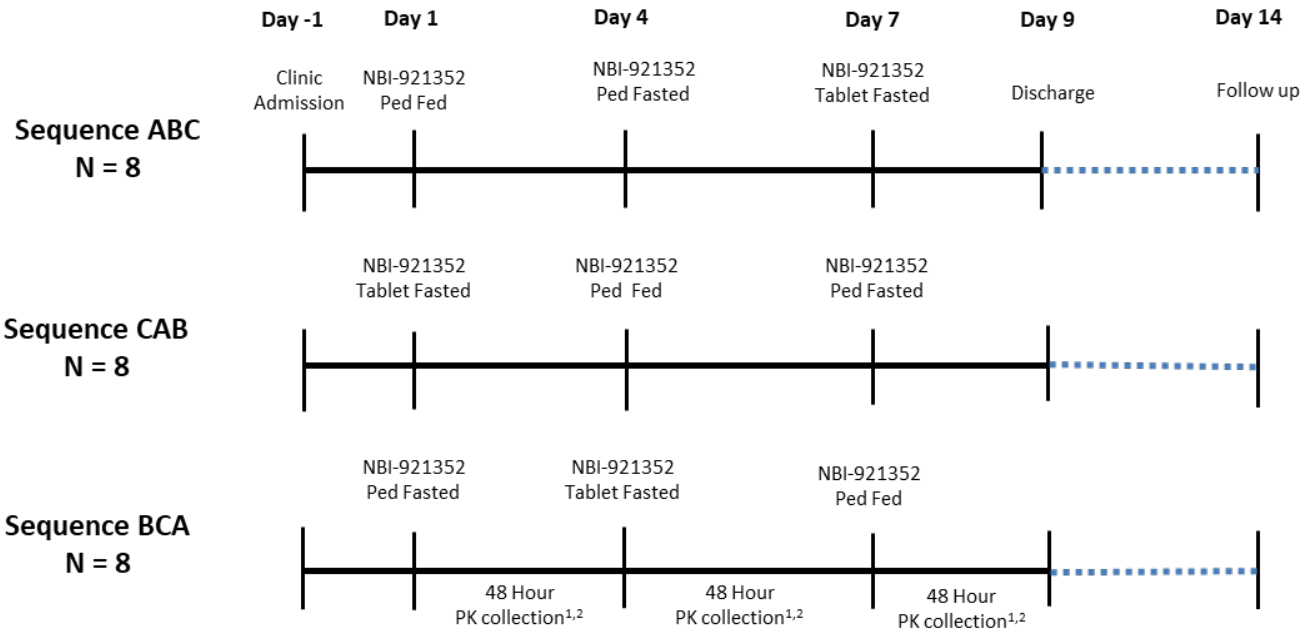
Introduction

- NBI-921352/XEN901 is a potent and highly selective $Na_V1.6$ inhibitor being developed for the treatment of adult focal seizures and as a precision medicine for SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) caused by gain-of-function mutation of $Na_V1.6$.
- We have developed a pediatric-friendly formulation of NBI-921352 which is intended to be mixed with milk, formula or soft foods prior to dosing.
- A granule dosage form was selected to facilitate dosing on a mg per kg body weight basis over a wide pediatric age and weight range.
- A Phase 1 pharmacokinetic (PK) study was performed to assess the PK of NBI-921352 pediatric formulation (granules), the impact of food (high-fat meal) on this formulation, and its relative bioavailability to an immediate-release (IR) tablet formulation previously studied in adult patients in order to support a Phase 2 study in pediatric patients with SCN8A-DEE.

Methods

- This was a single center, open-label, randomized study in which 24 subjects received NBI-921352 adult IR tablet or pediatric formulation in a fasted or fed state (high-fat meal) in a 3-period, 3-sequence crossover design (please see the next slide for details)
- A 50 mg dose was used in this adult PK study based on the PK and safety data available from an earlier Phase 1 study
- Serial PK samples were obtained pre-dose and at specific timepoints through 48 h post-dose
- Plasma concentrations of NBI-921352 were determined using validated liquid chromatography with tandem mass spectrometry method

Study Design



A: Pediatric (Ped) Formulation – Fed
B: Pediatric (Ped) Formulation – Fasted
C: Adult IR Tablet

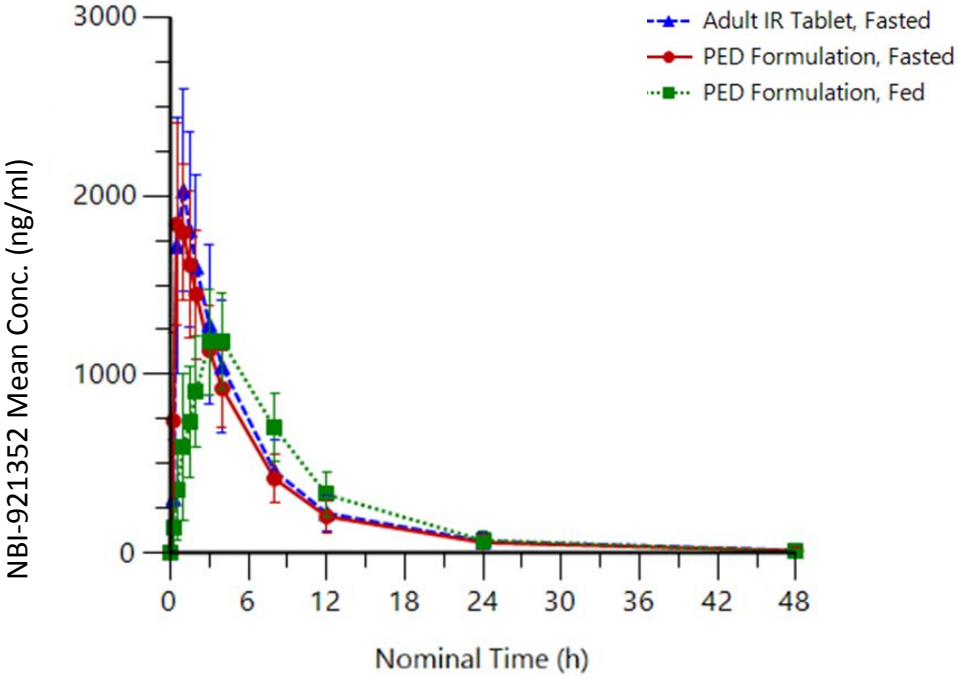
[1]NBI-921352 Pediatric (Ped) Formulation PK samples

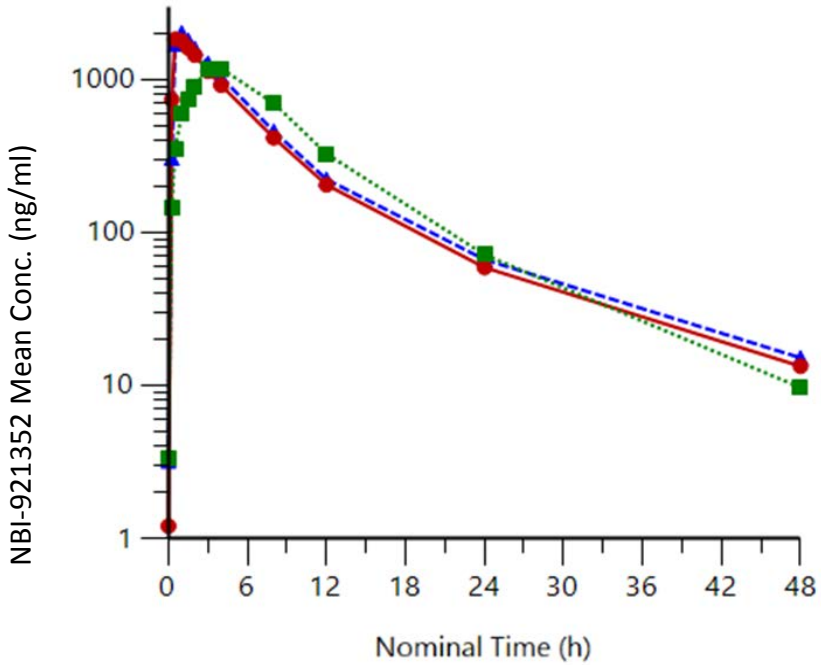
[2]NBI-921352 Tablet Formulation PK samples

Demographics

Gender, n (%)	N=24
Male	16 (66.7)
Female	8 (33.3)
Age at informed consent (years)	
Mean	37.0
SD	10.3
Range	20-54
Race, n (%)	
Caucasian	15 (62.5)
Black	5 (20.8)
Asian	2 (8.3)
Other	2 (8.3)
Ethnicity	
Not Hispanic or Latino	23 (95.8)
Hispanic or Latino	1 (4.2)
BMI (kg/m^2)	
Mean	25.4
SD	2.7

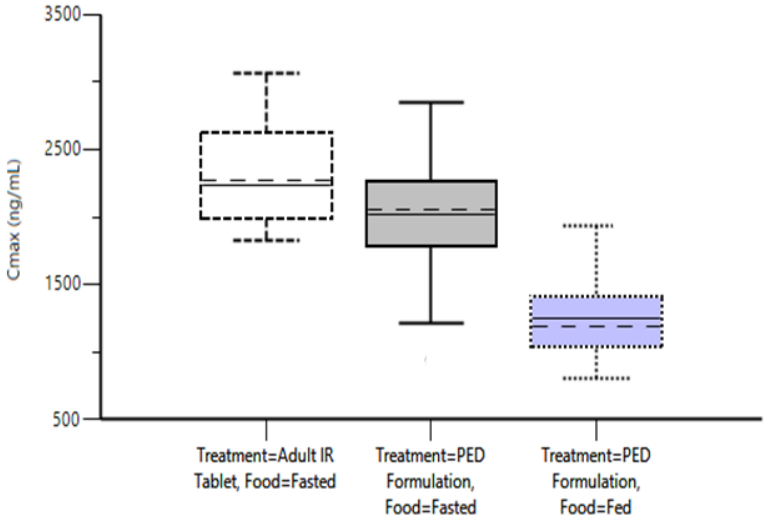
Results: PK Profiles

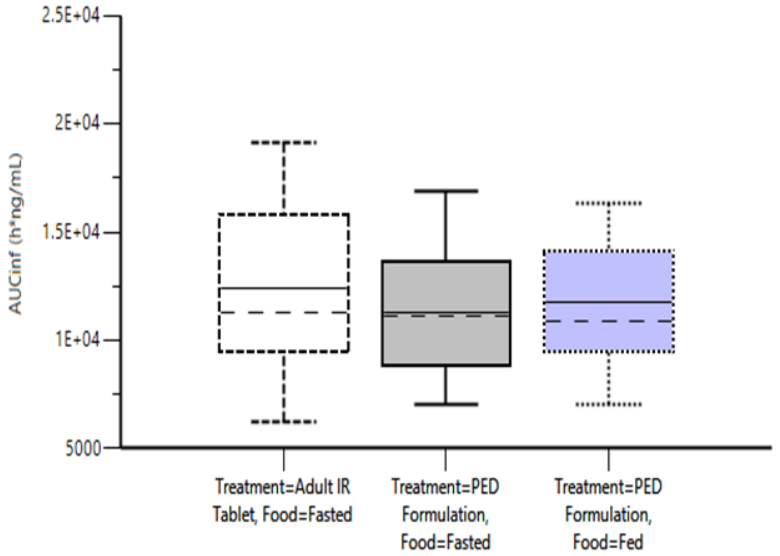




Data represents mean ± SD

Results: Summary of C_{max} and AUC_{inf} of NBI-921352





The box plots represent the mean (solid line), median (dashed line), inter-quartile range, and 90% confidence interval of the mean

Results: Bioequivalence Analysis

Bioequivalence Analysis of NBI-921352 PK Parameters Following Administration of Pediatric Formulation and Adult Tablet Formulation under Fasting Conditions

Parameter	Geometric least-square mean data (N=24)		
	Ratio (%)	Lower limit	Upper limit
C_{max}	91.33	81.48	102.38
AUC_{0-t}	93.21	88.02	98.70
AUC_{0-inf}	92.84	88.03	97.92

Adult IR tablets served as the reference formulation and pediatric granules as the test formulation

Results: Formulation Comparison

- Following administration of a single 50 mg dose of NBI-921352 as an adult tablet or pediatric formulation, NBI-921352 was rapidly absorbed under fasting conditions with the median time to peak plasma concentration (T_{max}) of ~ 1 h
- Following the absorption phase, NBI-921352 plasma concentration declined in a mono-exponential manner with a terminal elimination half-life ($t_{1/2}$) of 8.5 h for both formulations
- NBI-921352 peak plasma concentration (C_{max}), area under the curve from time 0 to the last sampling time point and to infinity (AUC_{0-t}, and AUC_{0-inf}, respectively) were comparable between formulations
  - The Geometric Mean Ratio (GMR) and its 90% confidence interval (CI) were within the bioequivalence (BE) range of 80-125%
  - The intra-subject CV% ranged between 11 to 23%

Results: Bioequivalence Analysis

Bioequivalence Analysis of NBI-921352 PK Parameters Following Administration of Pediatric Formulation under Fasting and Fed Conditions

Parameter	Geometric least-square mean data (N=24)		
	Ratio (%)	Lower limit	Upper limit
C_{max}	61.63	54.84	69.26
AUC_{0-t}	103.74	98.23	109.57
AUC_{0-inf}	102.67	97.98	107.58

The fasted state served as the reference condition and the fed state as the test condition

Results: Food Effect on Pediatric Formulation

- Following administration of a single dose (50 mg) of the pediatric formulation of NBI-921352, the T_{max} was delayed by 2 h and the C_{max} decreased by ~38% under the fed state (high fat meal) compared to the fasted state
  - The GMR for C_{max} and its 90% CI were not contained within the BE limit of 80-125%
  - The intra-subject CV% for C_{max} was 24%
- NBI-921352 total systemic exposure, as indicated by the AUC_{0-t} and AUC_{0-inf}, was comparable between the fasted and the fed state
  - The GMR with its 90% CI was within the BE limit
  - The intra-subject CV%s were 11% and 9% under the fasted and the fed state, respectively
- The $t_{1/2}$ was 8 h and 6 h under fasted and fed states, respectively

Conclusions

- The PK data obtained in this study indicate that a single 50 mg dose of NBI-921352 pediatric formulation is bioequivalent to the IR adult tablet formulation (1 x 50 mg) under fasted conditions
- Administration of a single 50 mg dose of NBI-921352 pediatric formulation under fed state (with a high-fat meal) delayed the rate, but not the extent of NBI-921352 absorption, compared to that of the fasted state
- The favorable PK of the pediatric formulation i.e., IR characteristics, no significant food effect on its total systemic exposure and BE to the adult formulation along with its ease of preparation, make this formulation suitable for further clinical development of NBI-921352 in pediatric patients with SCN8A-DEE