Potential Drug-Drug Interactions Between NBI-921352/XEN901 (a Novel $Na_v1.6$-Selective Sodium Channel Blocker) and a Strong Inducer of CYP3A4 (Phenytoin) in Healthy Volunteers

Rostam Namdari,[1] Gregory N. Beatch,[1] Jay A. Cadieux,[1] Gordon Loewen,[2] Ernesto Aycardi[1]

[1]Xenon Pharmaceuticals Inc., Burnaby, BC, CAN; [2]Neurocrine Biosciences, Inc., San Diego, CA, USA

INTRODUCTION

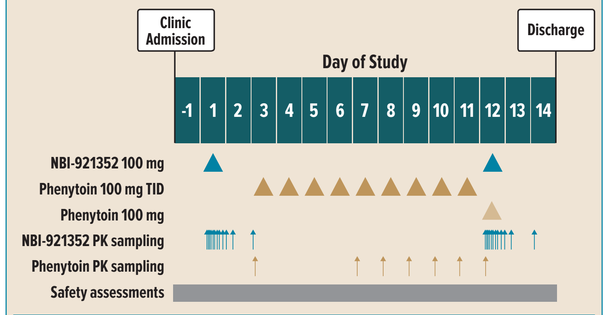
- NBI-921352 (also known as XEN901) is a potent and highly selective $Na_v1.6$ inhibitor intended for the treatment of SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) and other forms of epilepsy[1]
- In early clinical development, NBI-921352 will be used as adjunctive therapy with other antiepileptic medications, many of which are potent cytochrome P450 (CYP) inducers[2]
- Phenytoin, a strong inducer of CYP3A4 and a moderate inducer of CYP1A2 and CYP2C19, is a commonly administered antiseizure medication and is recognized as a reference P450 inducer by the US Food and Drug Administration[2,3]
- The objective of this study was to evaluate the effect of phenytoin on the pharmacokinetics (PK) of NBI-921352

METHODS

STUDY DESIGN

- In this single-center, open-label, randomized study, 18 healthy adult subjects received a single oral dose of NBI-921352 (100 mg) after an overnight fast on Day 1 and Day 12 (**Figure 1**)
- On Days 3 to 11, phenytoin (100 mg) was administered three times per day (TID); on Day 12, a single morning dose of phenytoin 100 mg was administered one hour before the NBI-921352 dose

Figure 1. Study Design



PK, pharmacokinetics; TID, three times per day.

SUBJECTS

- Key inclusion criteria
  - Healthy non-Asian, non-Black men and women, aged 18-55 years (Asian and Black individuals were excluded due to potential risk of serious dermatologic reactions and/or hypersensitivity to phenytoin)
  - Body mass index of 18.5 to 30.0 kg/m^2
- Key exclusion criteria
  - Electrocardiogram (ECG): 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, phenytoin, 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 the following timepoints for determination of NBI-921352 and phenytoin plasma concentrations using validated liquid chromatography-tandem mass spectrometry methods:
  - NBI-921352: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post dose on Days 1 and 12
  - Phenytoin: trough levels prior to the morning dose on Day 3 and Days 7 to 12
- PK parameters 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 elimination half-life ($T_{1/2}$)
- Safety evaluations included adverse event (AE) monitoring, laboratory tests, vital signs, ECGs, physical examinations, Columbia Suicide Severity Rating Scale (C-SSRS) and neurological function tests

RESULTS

- Of the 17 evaluable subjects, 14 (82.4%) were male and 17 (100.0%) were White; mean age was 41.6 years (**Table 1**)

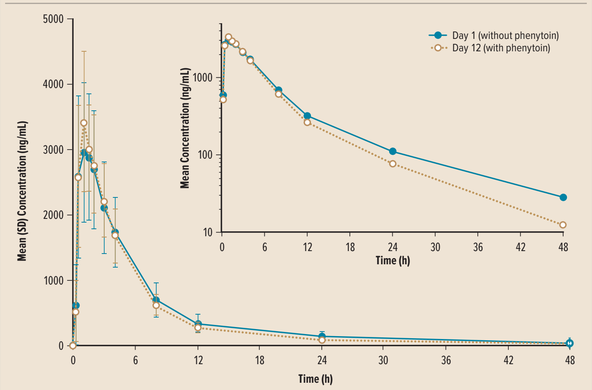
Table 1. Baseline Characteristics

	All Subjects (N=17[a])
Age, mean (SD), years	41.6 (8.8)
Male, n (%)	14 (82.4)
White, n (%)	17 (100.0)
BMI, mean (SD), kg/m^2	25.3 (2.9)

[a]One subject was withdrawn from the study on Day 1 for PK reasons (subject vomited ~1 hour after NBI-921352 dosing).
BMI, body mass index; SD, standard deviation.

- Mean plasma concentration-time profiles for NBI-921352 were similar with or without phenytoin (**Figure 2**)

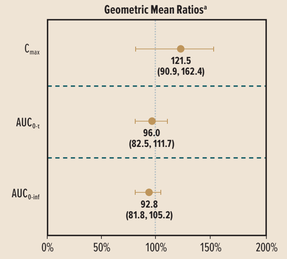
Figure 2. Plasma NBI-921352 Concentrations With or Without Phenytoin



- The geometric mean ratio (GMR) for NBI-921352 C_{max} with phenytoin compared to its administration alone was 121.5%; however, the GMR for NBI-921352 AUC_{0-t} and AUC_{0-inf} were 96.0% and 92.8%, indicating that phenytoin administration did not affect total systemic exposure of NBI-921352 (**Figure 3**)
- Median T_{max} of NBI-921352 was unchanged with or without phenytoin, and mean $T_{1/2}$ of NBI-921352 alone was comparable to NBI-921352 with phenytoin (**Figure 3**)

Figure 3. PK Parameters and Geometric Mean Ratios for NBI-921352 With or Without Phenytoin

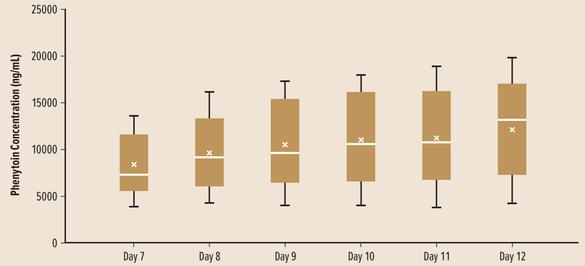
Parameter, Mean (SD)	Day 1 (without phenytoin) (n=17)	Day 12 (with phenytoin) (n=17)
C_{max}, ng/mL	3297.2 (1152.9)	3720.1 (1102.7)
AUC_{0-t}, ng•h/mL	19139.1 (5004.2)	17850.4 (3169.9)
AUC_{0-inf}, ng•h/mL	19815.8 (4787.0)	18046.0 (3057.5)
T_{max}, h[b]	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)
$T_{1/2}$, h	10.3 (6.9)	7.8 (2.8)



[a]Geometric Mean Ratios are shown with 90% CIs for NBI-921352 administered with vs without phenytoin.
[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; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration.

- Phenytoin trough levels reached apparent steady state by Day 10 (**Figure 4**)

Figure 4. Trough Plasma Phenytoin Concentrations



The box plots represent the median (solid line), mean (cross), interquartile range, and data spread (whiskers). One outlier (22592.6 ng/mL) on Day 11 was excluded.

SAFETY

- 15 (83%) subjects reported AEs, the most common of which were dizziness (8 [44.4%]), headache (11 [61.1%]), and nausea (7 [38.9%]); the majority of AEs were mild
- No deaths, serious AEs, or discontinuations due to AEs occurred during the study; 1 subject had a clinically significant increase in pulse rate and AEs of headache, asthenia, and vomiting ~1 hour after NBI-921352 dosing on Day 1
- There were no clinically significant changes in clinical laboratory values, ECGs, physical or neurological examinations, or C-SSRS findings

CONCLUSIONS

- In this study in healthy adults, no change was observed in the total systemic exposure of NBI-921352 after 10 days of administration of phenytoin, indicating no meaningful drug-drug interaction between NBI-921352 and phenytoin
- No apparent impact on safety was observed when NBI-921352 was co-administered with phenytoin
- These results indicate that no dose adjustment will be required if NBI-921352 is co-administered with phenytoin or other strong inducers of CYP3A4 and/or moderate inducers of CYP1A2 and CYP219

REFERENCES

1. Bialer M, Johannessen SI, Koepp MJ, et al. *Epilepsia.* 2018;59(10):1811-1841.
2. Johannessen SI, Landmark CJ. *Curr Neuropharmacol.* 2010;8(3):254-267.
3. FDA Drug Development and Drug Interactions. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3.

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

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