

# Potential Drug-Drug Interactions Between NBI-921352/XEN901 (a Novel Na<sub>v</sub>1.6-Selective Sodium Channel Blocker) and a Strong Inducer of CYP3A4 (Phenytoin) in Healthy Volunteers

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## INTRODUCTION

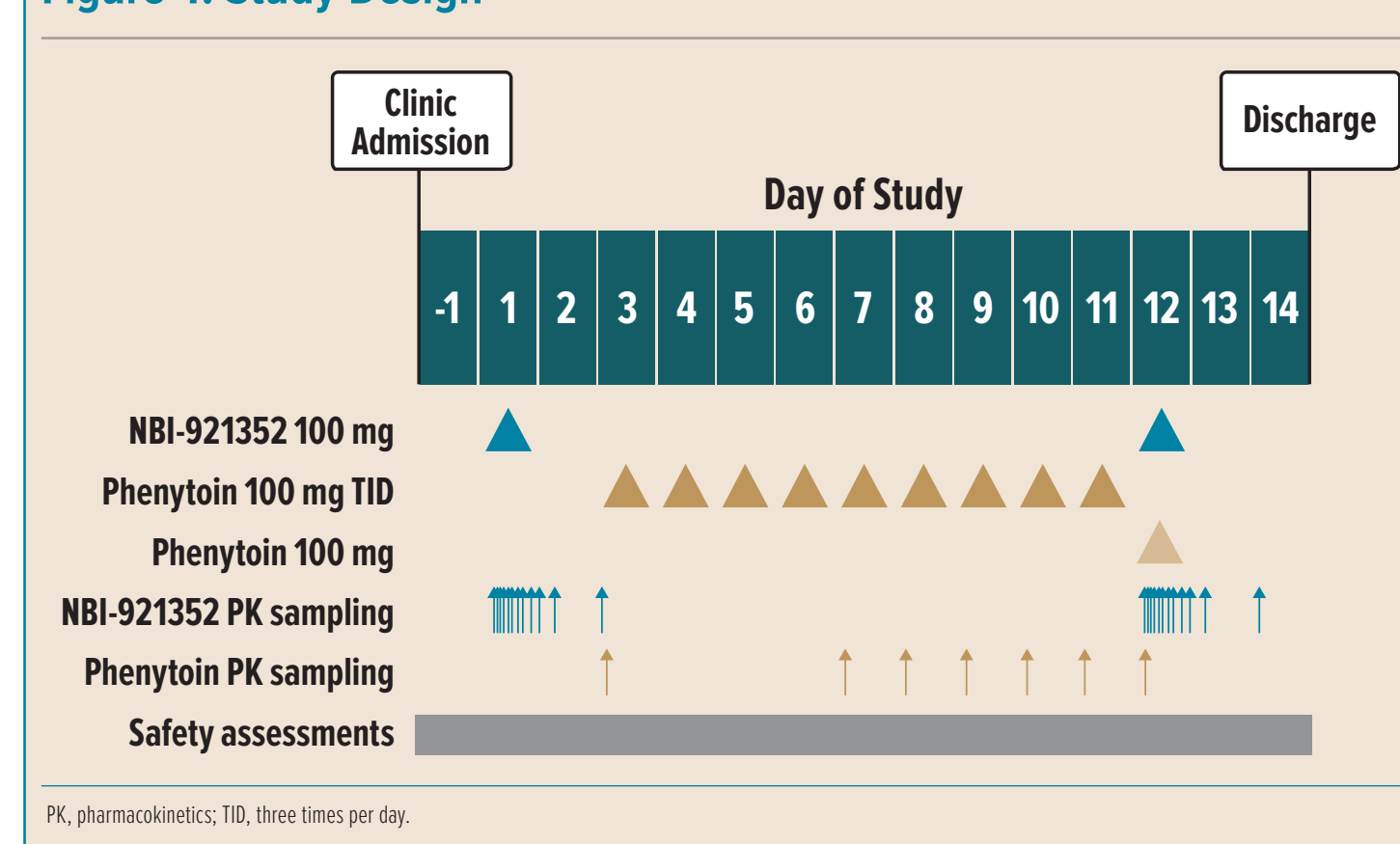
- NBI-921352 (also known as XEN901) is a potent and highly selective Na<sub>v</sub>1.6 inhibitor intended for the treatment of SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) and other forms of epilepsy<sup>1</sup>
- In early clinical development, NBI-921352 will be used as adjunctive therapy with other antiepileptic medications, many of which are potent cytochrome P450 (CYP) inducers<sup>2</sup>
- 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<sup>2,3</sup>
- 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



## 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<sup>2</sup>

### 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<sub>max</sub>), area under the curve from time 0 to the last measurable concentration (AUC<sub>0-t</sub>), area under the curve from time zero to infinity (AUC<sub>0-inf</sub>), time to maximum plasma concentration (T<sub>max</sub>), and elimination half-life (T<sub>1/2</sub>)
- 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)

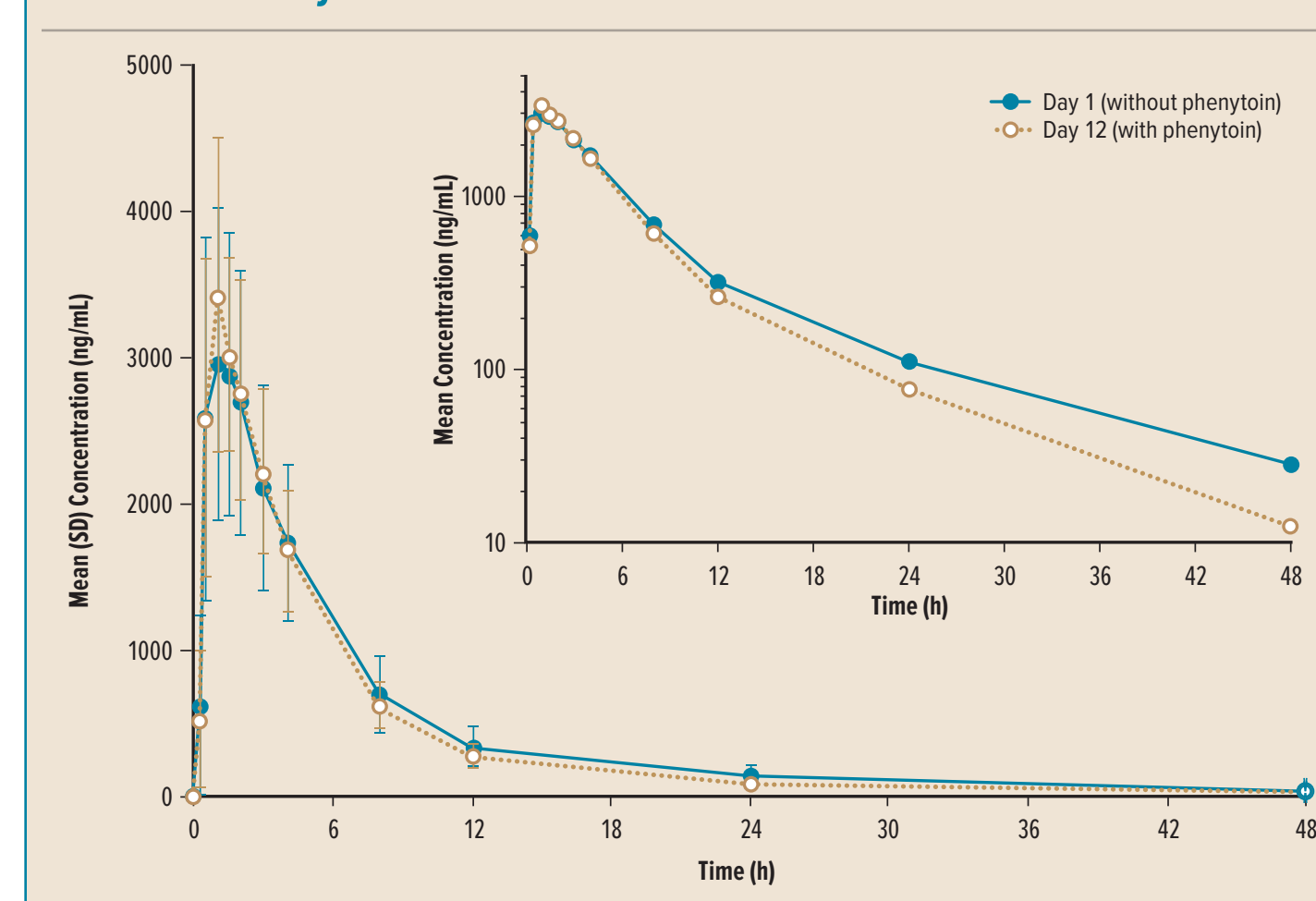
Table 1. Baseline Characteristics

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

<sup>a</sup>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.

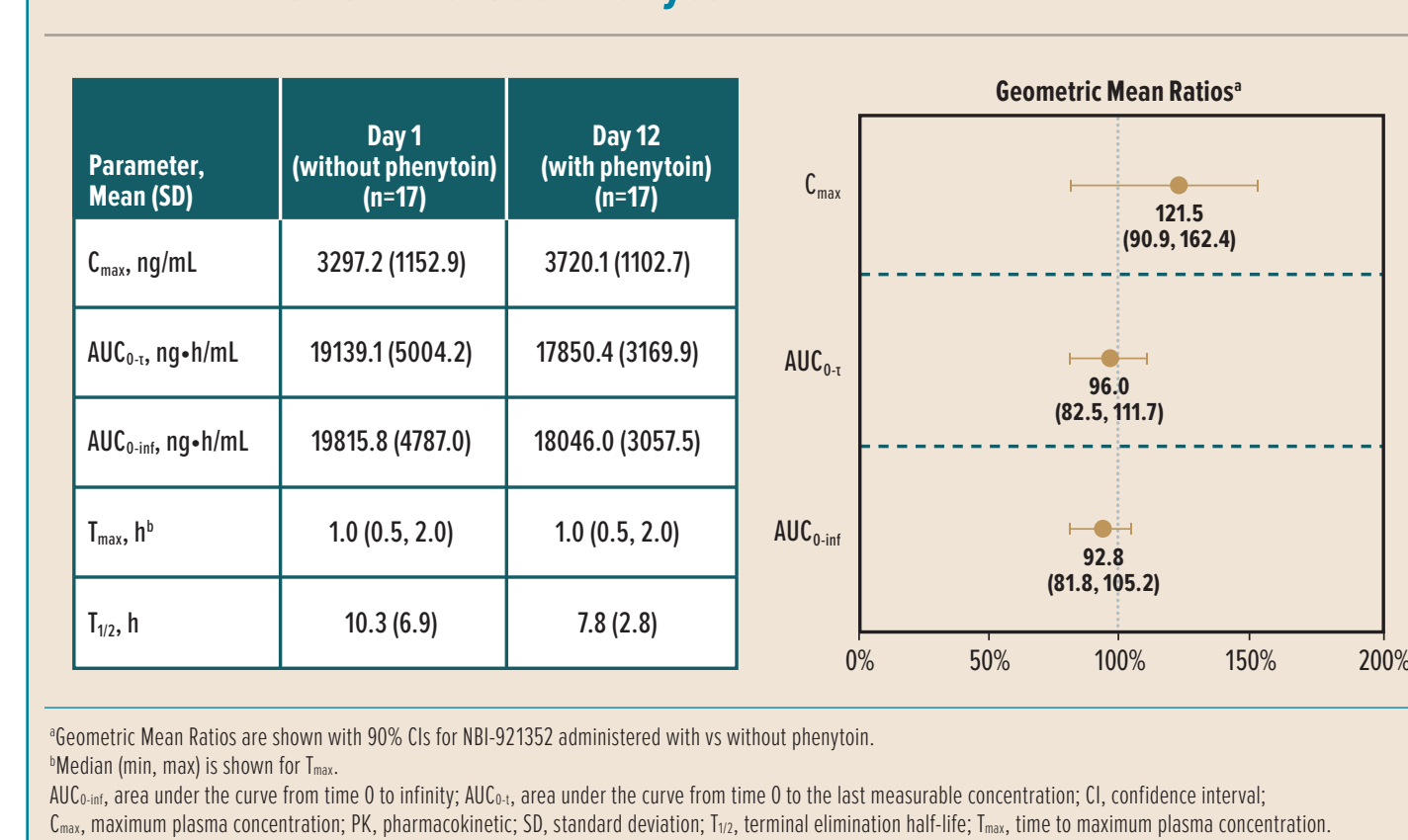
- Mean plasma concentration-time profiles for NBI-921352 were similar with or without phenytoin (Figure 2)

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



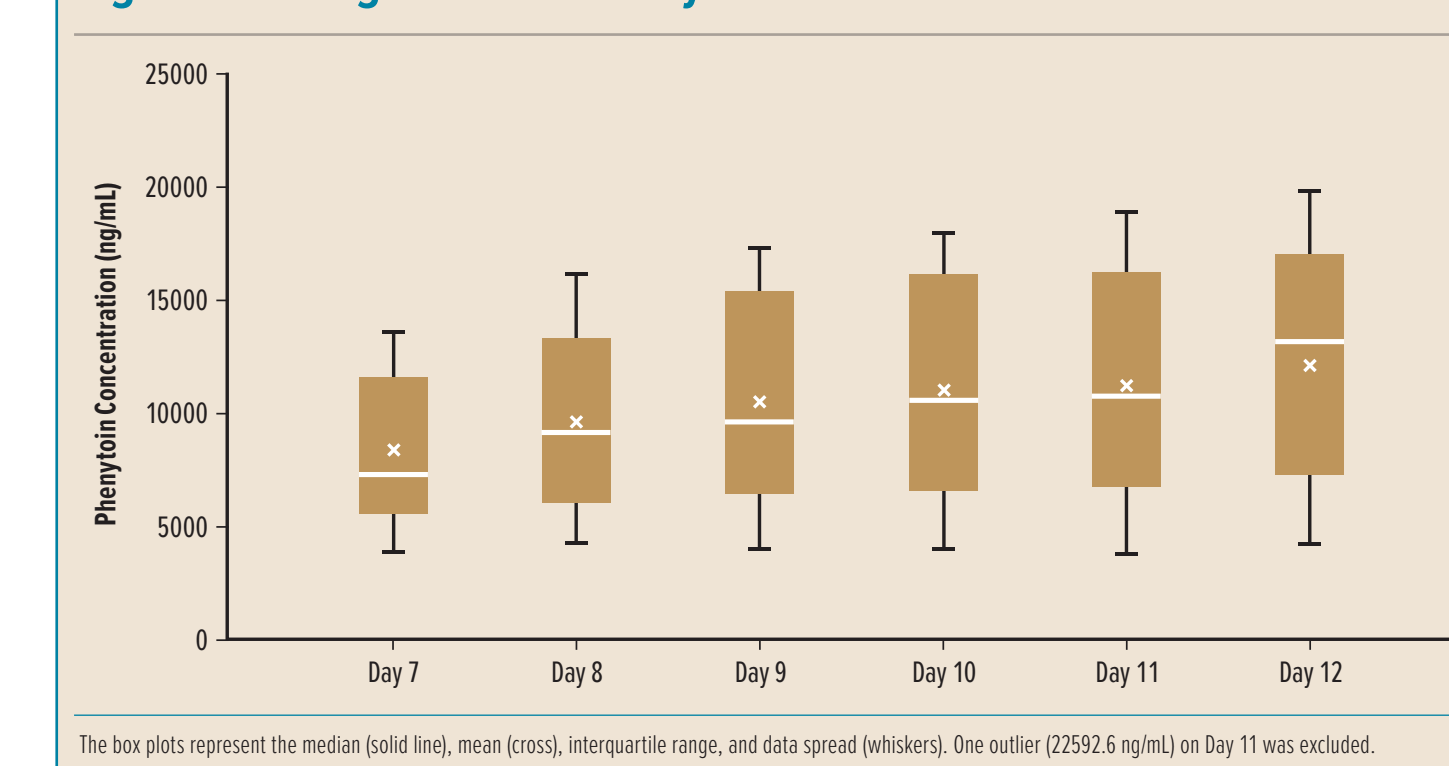
- The geometric mean ratio (GMR) for NBI-921352 C<sub>max</sub> with phenytoin compared to its administration alone was 121.5%; however, the GMR for NBI-921352 AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> were 96.0% and 92.8%, indicating that phenytoin administration did not affect total systemic exposure of NBI-921352 (Figure 3)
- Median T<sub>max</sub> of NBI-921352 was unchanged with or without phenytoin, and mean T<sub>1/2</sub> 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



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

Figure 4. Trough Plasma Phenytoin Concentrations



## 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

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