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Assessment of Potential Pharmacokinetic and Pharmacodynamic Interactions between NBI-921352/XEN901, a Novel $Na_V1.6$-Selective Sodium Channel Blocker, and Phenytoin (a Non-selective Na_V Blocker) in Adult Healthy Subjects

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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.
- All trademarks are the property of their respective owners.

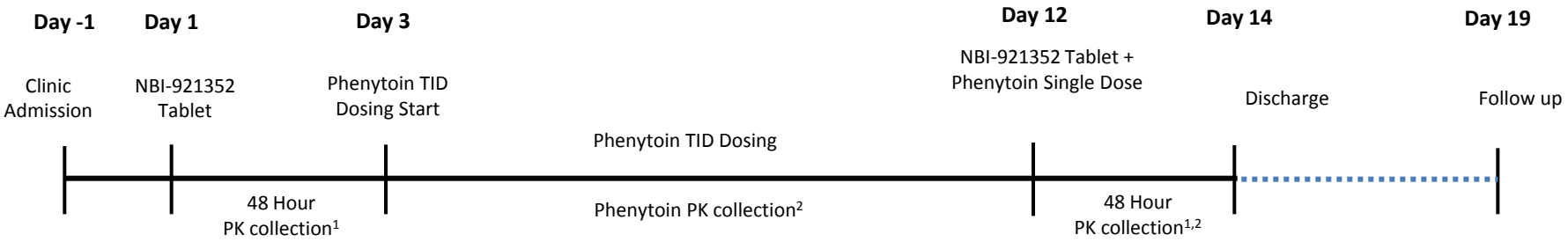
Introuduction

- 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) which is caused by gain-of-function mutations of $Na_V1.6$.
- In early clinical development, it is anticipated that NBI-921352 will be studied as adjunctive therapy with other antiseizure medications (ASMs) many of which are potent CYP inducers eg, carbamazepine and phenytoin.
- Phenytoin is a more potent CYP inducer than carbamazepine and is recommended for clinical drug-drug interaction studies by the Food and Drug Administration. In addition, CYP reaction phenotyping data suggest that CYP3A4 contributes to the majority of XEN901 metabolism.
- The objective of this study was to evaluate the impact of phenytoin a strong inducer of CYP3A4 and a moderate inducer of CYP1A2 & CYP2C19 on the pharmacokinetics (PK) of NBI-921352, and potential pharmacodynamic (PD) interactions between NBI-921352 and phenytoin.

Methods

- This was a single-center, open-label, randomized study where 18 healthy adult subjects (non-Asian and non-black) received a single 100 mg (2 x 50 mg immediate release (IR) tablet) oral dose of NBI-921352 on Days 1 and 12 after an overnight fast
- Phenytoin (ie, Dilantin® capsule, 100 mg) was administered TID on Day 3 after initiating NBI-921352 dosing on Day 1 and was continued through Day 12, on which only the morning dose was administered one hour prior to NBI-921352 dosing
- Serial PK samples were obtained at specific timepoints (see the next slide for details)
- Safety evaluations included adverse event (AE) monitoring, laboratory tests, vital signs, electrocardiograms (ECG), physical examinations, Columbia Suicide Severity Rating Scale (C-SSRS) and neurological function tests
- NBI-921352 and phenytoin plasma concentrations were determined using validated liquid chromatography with tandem mass spectrometry method

Study Design



[1] NBI-921352 PK Samples: pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post dose

[2]Phenytoin PK Samples: trough levels (i.e., prior to the morning dose) on Day 3 and Days 7 to Day 12

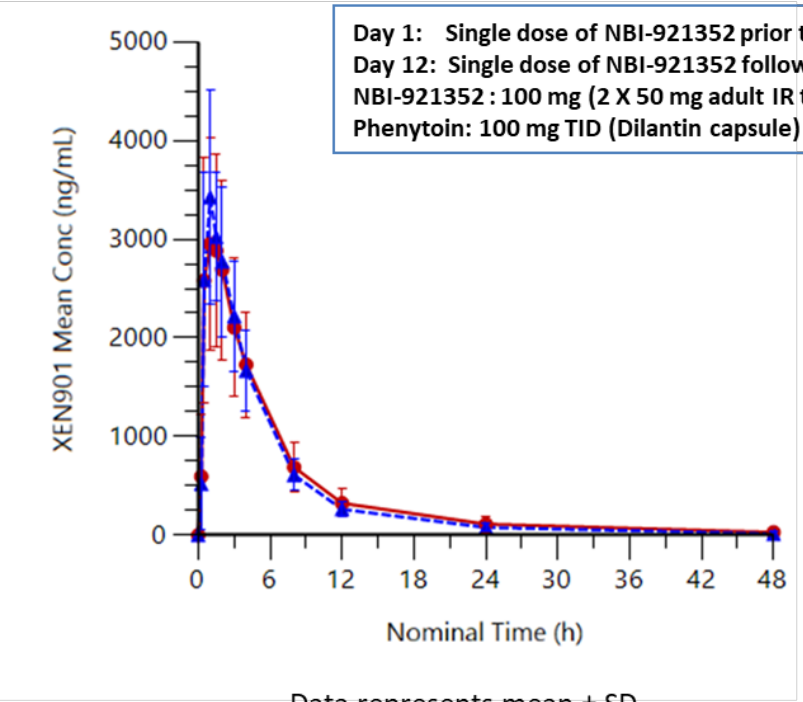
Demographics

Gender, n (%)	N=17
Male	14 (82.4)
Female	3 (17.6)
Age at informed consent (years)	
Mean	41.6
SD	8.8
Range	25-55
Race, n (%)	
Caucasian	17 (100)
Ethnicity	
Not Hispanic or Latino	17 (100)
BMI (kg/m^2)	
Mean	25.3
SD	2.9

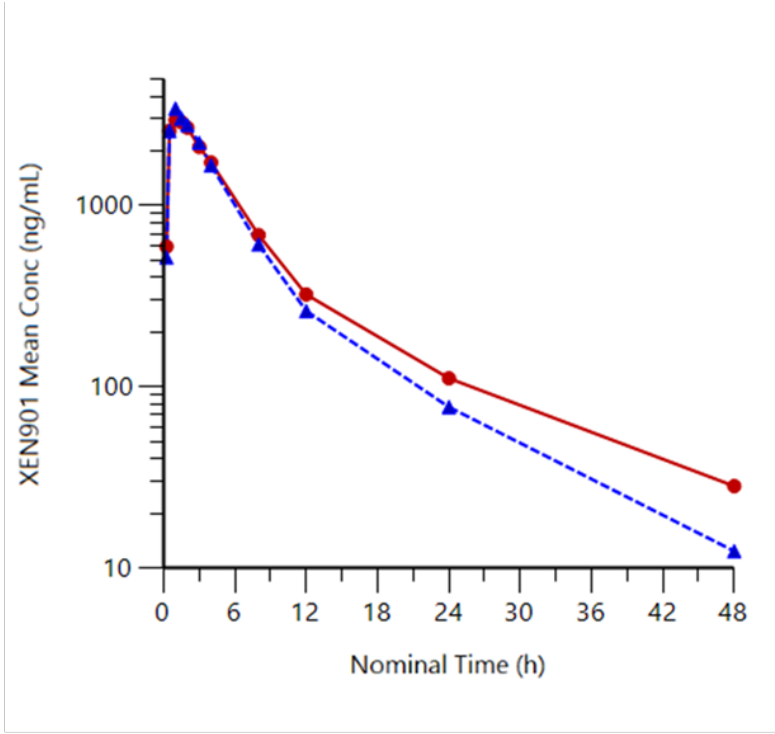
Note: One subject received NBI-921352/XEN901 on Day 1 only and was withdrawn from the study for PK reasons by the Sponsor due to vomiting shortly after dosing

Results: PK Profile in the Presence and Absence of Phenytoin

Day 1: Single dose of NBI-921352 prior to phenytoin (started Day 3)
Day 12: Single dose of NBI-921352 following 10 days of phenytoin
NBI-921352 : 100 mg (2 X 50 mg adult IR tablet)
Phenytoin: 100 mg TID (Dilantin capsule)

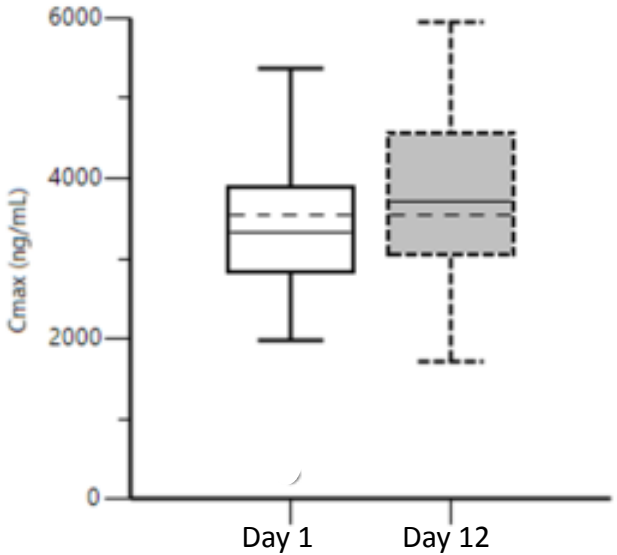


Data represents mean ± SD

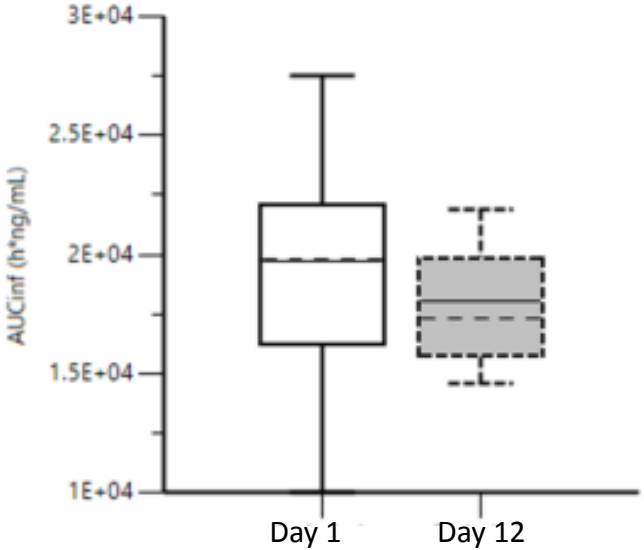


Results: C_{max} and AUC_{inf}

C_{max}



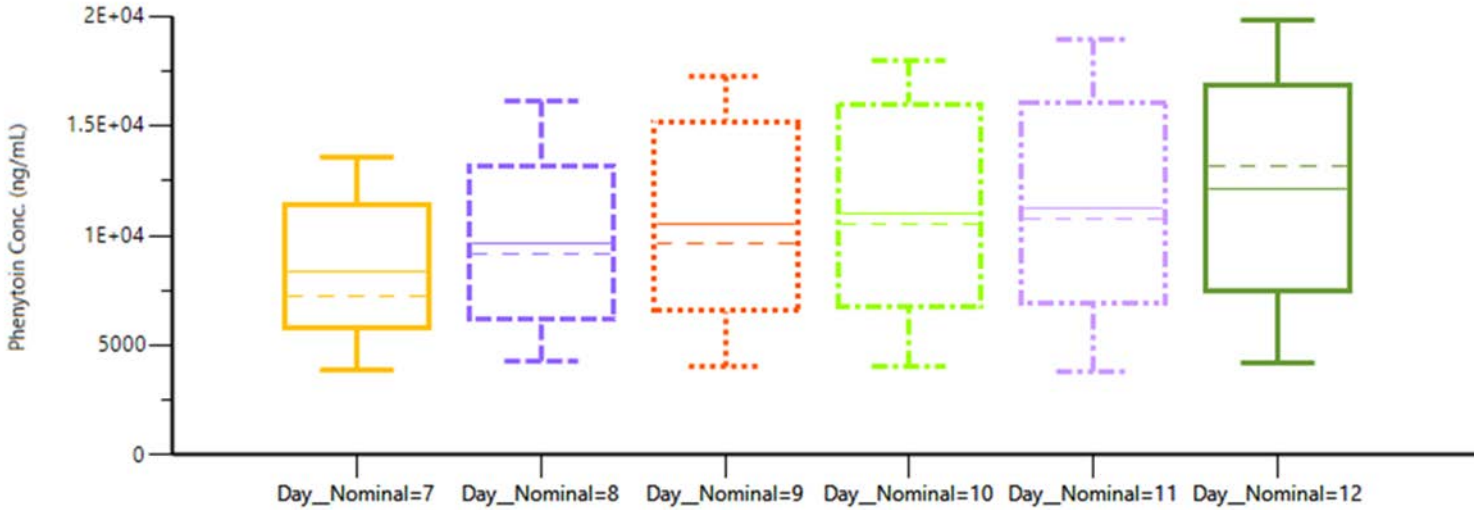
AUC_{inf}



The box plots represent the mean (solid line), median (dashed line), inter-quartile range, and 90% confidence interval of the mean (N=17)

Results: Phenytoin Trough Levels

Phenytoin Trough Plasma Concentration



Results: Pharmacokinetics

- Following single-dose administration of NBI-921352 (100 mg), either in combination with phenytoin (100 mg TID for 10 days) or alone, NBI-921352 time to peak plasma concentrations (T_{max}) did not change, the median T_{max} was ~1 h
- NBI-921352 peak plasma concentration (C_{max}) increased by ~22%
  - The geometric mean ratio (GMR) was within the bioequivalence (BE) range of 80-125% but its upper 90% confidence interval (CI) was higher when co-administered with phenytoin
  - The intra-subject CV% for C_{max} was 53%
- NBI-921352 area under the curve from time 0 to the last sampling time point (AUC_{0-t}) and to infinity (AUC_{0-inf}), were comparable between treatments
  - The GMR and its 90% CI were within the BE limit, the intra-subject CV% was 22%-26%
- The terminal elimination half-life was comparable following administration of NBI-921352 alone or with phenytoin (10 h and 8 h, respectively)
- Phenytoin trough levels reached apparent steady state by Day 10

Results: Safety

- No deaths or serious AEs occurred in the study, and no subject was withdrawn by the Investigator for safety reasons due to a treatment-emergent adverse event (TEAE); the majority of AEs were mild
  - The most common TEAEs were dizziness, headache and nausea
  - Aside from a clinically-significant increase in pulse rate recorded in one subject who experienced headache, asthenia and vomiting ~1 h following administration of NBI-921352 alone on Day 1, there were no notable changes from baseline on vital signs measures during the study
  - Clinical laboratory values were generally within the reference range and there were no subjects with clinically significant ECG, physical examination, neurological examination or C-SSRS findings
- Overall, the safety data indicate that NBI-921352 was safe and generally well tolerated at individual plasma C_{max} up to ~6000 ng/mL, when co-administered with Phenytoin (trough levels up to ~20000 ng/mL)

Conclusions

- Following oral administration of phenytoin (clinical index strong inducer of CYP3A4 and moderate inducer of CYP1A2 and CYP2C19) at its recommended clinical dose (i.e., 100 mg TID) for 10 days in healthy adult subjects, no significant changes were observed in the PK of NBI-921352, indicating no meaningful PK interactions between NBI-921352 and phenytoin
- In addition, based on the safety data obtained in this study, no PD interactions were noted between NBI-921352 and phenytoin
- These data support, from a PK perspective, dose adjustment is not required when NBI-921352 is co-administered with phenytoin or other strong inducers of CYP3A4 and/or moderate inducers of CYP1A2 and CYP2C19