INTRODUCTION

NBI-921352 (also known as XEN901) is a potent and highly selective Na,v,1.6 inhibitor intended for the treatment of SCN9A developmental and episodic encephalopathy (SCN9A-DEE) and other forms of epilepsy.

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.

Phenytoin, a strong inducer of CYP3A4 and a moderate inducer of CYP1A2 and CYP2C9, is a commonly administered antiepileptic medication and is recognized as a reference P450 inducer by the U.S. Food and Drug Administration.

The objective of this study was to evaluate the effect of phenytoin on the pharmacokinetics 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.

The key inclusion criteria included:

- 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/m²

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).

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

The geometric mean ratio (GMR) for NBI-921352 Cmax was 92.8% (81.8%, 105.2%) and AUC0-τ was 96.0% (92.5%, 101.7%), indicating that phenytoin administration did not affect total systemic exposure of NBI-921352 (Figure 3).

The geometric mean ratio (GMR) for NBI-921352 Cmax with phenytoin compared to its administration alone was 121.5%, however, the GMR for NBI-921352 AUC0-τ and AUC0-τ was 96.0% and 92.5%, indicating that phenytoin administration did not affect total systemic exposure of NBI-921352 (Figure 3).

Median T1/2 of NBI-921352 was unchanged with or without phenytoin, and mean T1/2 of NBI-921352 alone was comparable to NBI-921352 with phenytoin (Figure 3).

SAFETY

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, asthma, 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 ECG findings.

CONCLUSIONS

In this 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 or other strong inducers of CYP3A4 and moderate inducers of CYP2C9.

REFERENCES


2. Neurocrine Biosciences, Inc., San Diego, CA, USA.