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Pharmacokinetic and Food Effect Assessment of XEN496 (Pediatric Formulation of Ezogabine) in Healthy Adults and Relative Bioavailability Assessment with Potiga® (Adult Formulation of Ezogabine)

Jay A. Cadieux, Rostam Namdari, Gregory N. Beatch, Ernesto Aycardi

Xenon Pharmaceuticals Inc.

Disclosures

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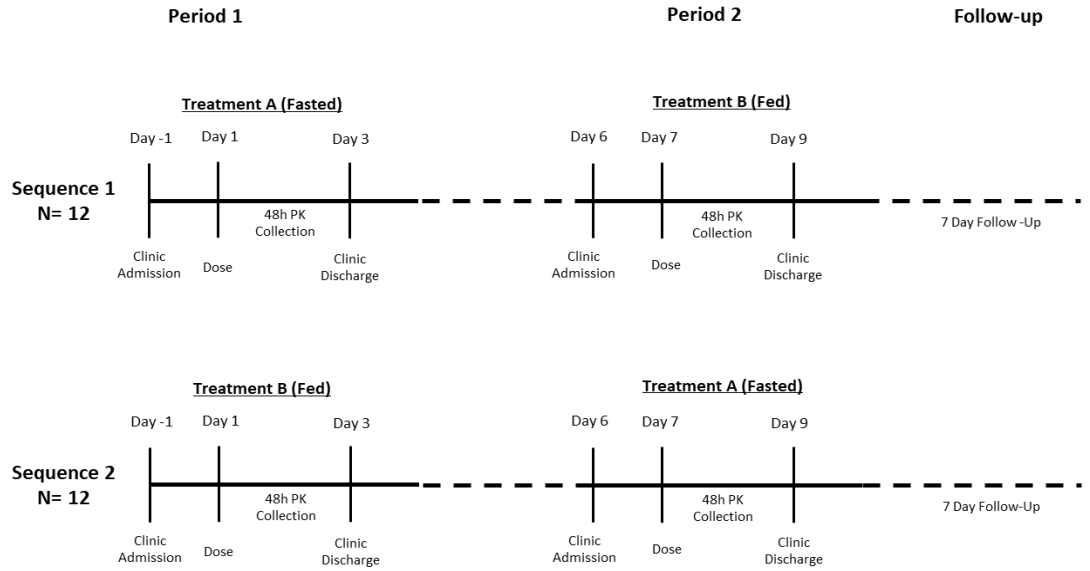
Introduction

- We are developing XEN496, a pediatric immediate-release formulation[1] of the $K_V7.2/K_V7.3$ potassium channel activator ezogabine (retigabine), for the treatment of KCNQ2-related developmental and epileptic encephalopathy (KCNQ2-DEE) caused by a genetic loss of Kv7.2/Kv7.3 activity.
- Ezogabine, as the immediate-release tablet formulation Potiga® (Trobalt™, GlaxoSmithKline), was previously approved by the U.S. FDA for the treatment of adult focal onset seizures.
- Potiga was withdrawn from the global market in July 2017 for commercial reasons.
- Ezogabine has shown promising benefits as a precision medicine in KCNQ2-DEE patients.[2]
- We have been granted orphan drug designation from the FDA as a treatment for KCNQ2-DEE and have received FDA feedback supportive of studying XEN496 in infants and children.
- A Phase 1 pharmacokinetic (PK) study was performed in order to:
  - guide the dosing regimen for an upcoming pediatric efficacy trial of XEN496 in KCNQ2-DEE in which XEN496 will be dosed with food; and
  - to conduct a retrospective PK and safety assessment to bridge between XEN496 and Potiga.

[1] Cadieux *et al.* Poster No. 2.265, 73rd Annual Meeting of the American Epilepsy Society, December 2019, Baltimore, MD, USA.
[2] Millichap *et al.*, *Neurol. Genet.* 2016, 2:1-5.

Methods

- This was a single-centre, open-label, 2-way crossover study in adult healthy volunteers (n=24 planned for inclusion in order to obtain ~21 evaluable subjects)



- PK samples were analyzed for XEN496 (ezogabine) and for ezogabine's major *N*-acetyl metabolite (NAMR) using a validated LC/MS-MS method

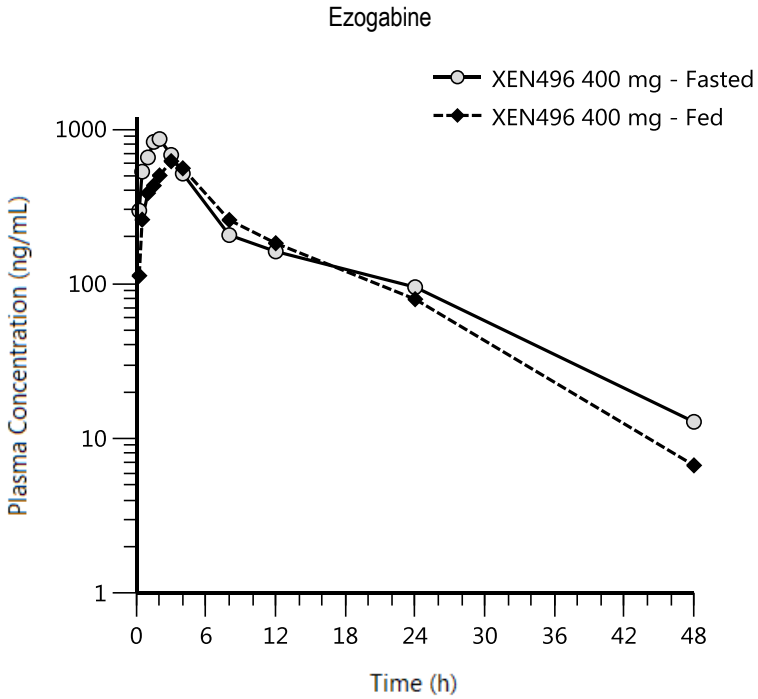
Results: Safety

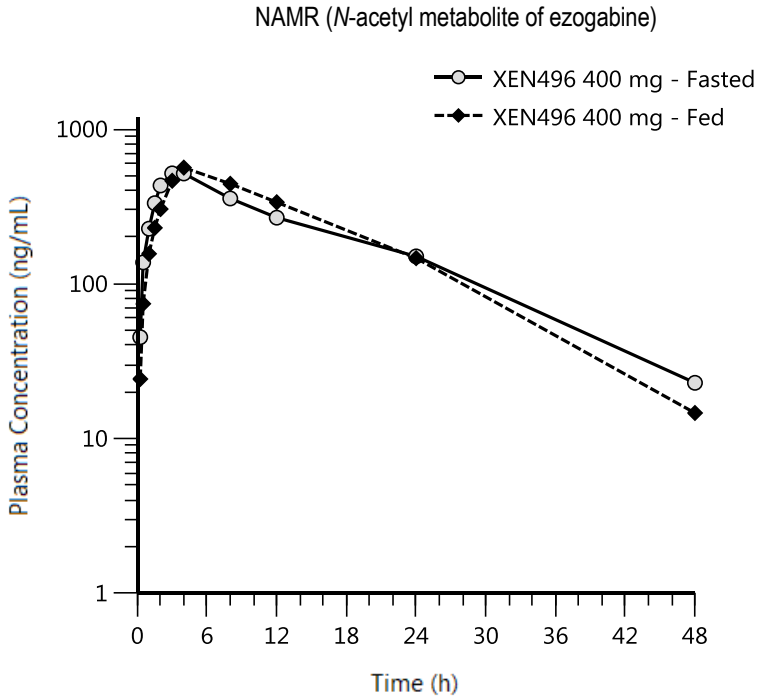
- XEN496 was generally safe and well-tolerated in this study
- Safety assessments included incidence of AEs, vital signs, electrocardiograms (ECGs), physical and ophthalmic examination findings, laboratory abnormality assessments, the American Urological Association Symptom Index (AUA-SI) and the Columbia-Suicide Severity Rating (C-SSRS) questionnaire
- There were no unexpected AEs. No deaths or SAEs occurred in the study. No subject was withdrawn by the Investigator for safety reasons due to a TEAE
- The most common TEAEs were dizziness [12 subjects (52%) fasted and 6 subjects (27%) fed], oral hypoesthesia [6 subjects (26%) fasted and 3 subjects (14%) fed] and fatigue [5 subjects (22%) fasted and 7 subjects (32%) fed]
- The majority (87%) of TEAEs were considered mild. Two subjects (8%) experienced TEAEs that were considered severe in intensity:
  - 1 subject experienced syncope (following a blood draw) about 1 h after receiving XEN496 (fasted)
  - 1 subject experienced depressed mood 3 days after receiving XEN496 (fasted)
  - Both TEAEs were considered possibly related to drug administration

Results: Safety (cont'd)

- Mean clinical laboratory, vital signs, and ECG values were generally within the reference range and there were no clinically significant findings.
- There were no subjects with clinically significant neurological examination findings.
- No QT prolongation or urinary retention were observed.
- Three subjects (13%) presented clinically significant physical examination findings during the study, which were associated with TEAEs of mild to severe intensity: erythema (mild and unrelated), upper limb fracture (mild and unrelated) and depressed mood (severe and possibly related).
- One subject (8%) had a positive answer on the C-SSRS questionnaire, which was associated with a severe TEAE of depressed mood.
- Three subjects withdrew consent or were withdrawn from the study prior to dosing Period 2 (for reasons other than safety or tolerability); these subjects were excluded from the PK analysis

Results: PK – Food Effect





Results: PK – Food Effect (cont'd)

Analyte	PK Parameter	Geometric least-squares means		Ratio (Fed/Fasted) (%)	90% Confidence Limits (%)	
		XEN496 400 mg, Fed (N=21)	XEN496 400 mg, Fasted (N=21)		Lower	Upper
XEN496	C_{max}	642	887	72.39	63.88	82.04
	AUC_{0-t}	6300	6906	91.22	84.43	98.55
	AUC_{0-inf}	6254	7040	88.84	82.40	95.77
NAMR	C_{max}	569	509	111.85	101.77	122.92
	AUC_{0-t}	8695	7900	110.07	104.63	115.79
	AUC_{0-inf}	8632	8044	107.32	102.24	112.64

- For XEN496, the fed and fasted states were equivalent (i.e., 90% CIs were within the reference range of 80-125%) for AUC and close to equivalent for C_{max}
- For NAMR, the fed and fasted states were equivalent for both AUC and C_{max}

Results: PK – Food Effect (cont'd)

- XEN496 exhibited pharmacokinetics and biopharmaceutical performance consistent with those of a typical immediate-release dosage form
- When compared to administration in the fasted state, administration of XEN496 under fed (high-fat meal) conditions:
  - slightly reduced and delayed ezogabine's peak plasma concentration
  - did not affect the extent of ezogabine's systemic exposure
- Although food slightly delayed the time to reach NAMR (ezogabine metabolite) peak plasma concentration, total systemic exposure was not affected
- Overall, variability in C_{max} and AUC was low, irrespective of fed/fasted status

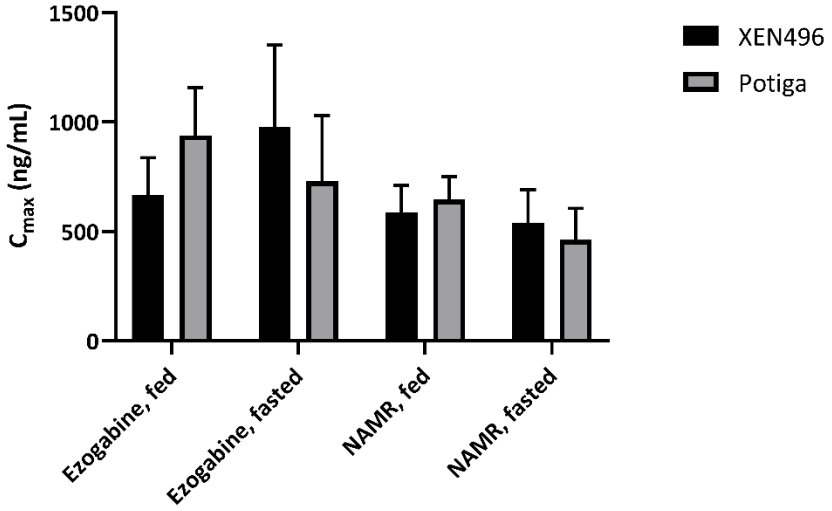
XEN496 Sprinkle Capsules

XEN496 Bulk Formulation

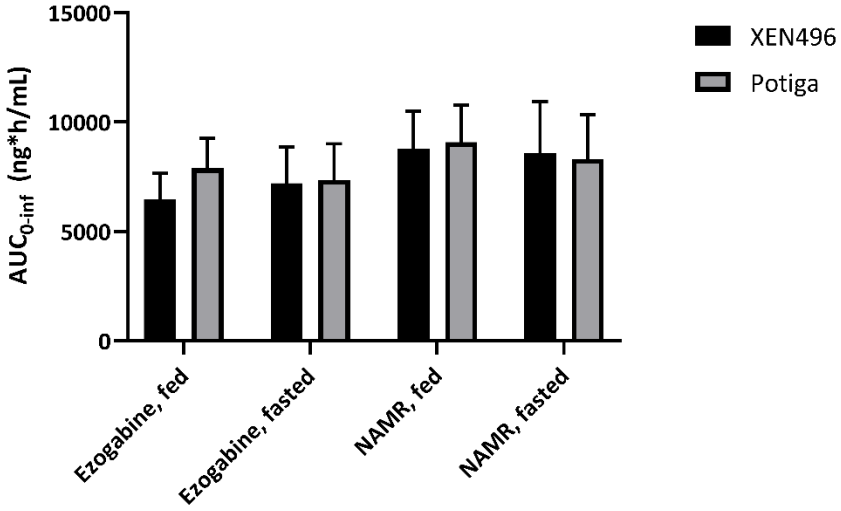
Results: PK – XEN496 Comparison with Potiga

- Due to the withdrawal of Potiga from the worldwide market in 2017, we were unable to perform a head-to-head PK comparison of XEN496 and Potiga; however, we were able to carry out a comparison with historical Potiga data.[1]

Peak Concentrations Following a Single 400 mg Oral Dose



Exposures Following a Single 400 mg Oral Dose



[1] FDA Review of NDA 022345, Study VRX-RET-E22-104

Results: PK – XEN496 Comparison with Potiga (cont'd)

- In general, XEN496 exhibited comparable pharmacokinetics to Potiga

Parameter	Ratio of Geometric Means – XEN496 to Potiga	
	Fed	Fasted
C_{max}	0.70	1.32
$AUC_{0\text{-}inf}$	0.82	1.02

- From a PK perspective, no dose adjustments arising from differences in formulation are anticipated for the upcoming efficacy study in KCNQ2-DEE

Conclusions

- In this Phase 1 PK and safety study in healthy adult volunteers, XEN496 was generally safe and well-tolerated.
- Overall, XEN496's safety profile was comparable to that of Potiga.
- XEN496 performed as expected for an immediate-release pediatric dosage form.
- Administration of a single 400 mg dose of XEN496 in the fed state slightly reduced and delayed ezogabine's peak plasma concentration, but did not affect its extent of systemic exposure, compared to the fasted state.
- Although food slightly delayed the time to reach NAMR (ezogabine metabolite) peak plasma concentration, total systemic exposure of NAMR was not affected.
- The biopharmaceutical performance of XEN496 was comparable to that of Potiga, suggesting that no formulation-related dose adjustments are indicated for future clinical studies.