Novel Microsampling Technique for Use in a Clinical Trial of Pediatric Patients with KCNQ2 Developmental and Epileptic Encephalopathy (KCNQ2-DEE)

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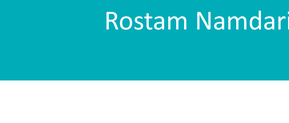
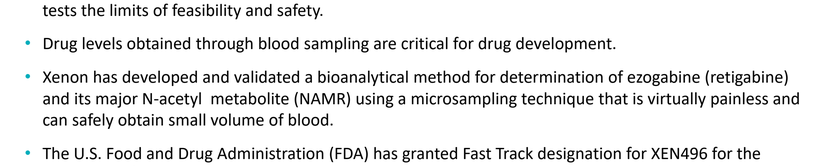
BACKGROUND

- For pediatric subjects, pharmacokinetic (PK) evaluation using standard venous blood sampling techniques tests the limits of feasibility and safety.
- Drug levels obtained through blood sampling are critical for drug development.
- Xenon has developed and validated a bioanalytical method for determination of ezogabine (retigabine) and its major N-acetyl metabolite (NAMR) using a microsampling technique that is virtually painless and can safely obtain small volume of blood.
- The U.S. Food and Drug Administration (FDA) has granted Fast Track designation for XEN496 for the treatment of seizures associated with KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE) and Orphan Drug Designation for the treatment of KCNQ2-DEE.
- Xenon has filed a clinical trial protocol with the FDA and anticipates initiating a Phase 3 clinical trial examining the efficacy of XEN496 in patients with KCNQ2-DEE in 2020.
- To support the planned Phase 3 clinical trial, Xenon completed a PK study testing its proprietary pediatric formulation (XEN496) in 24 healthy adult volunteers. In this poster we present the data from this single-dose PK study to determine whether the levels of ezogabine obtained by a routine venous blood sample are comparable to those by a capillary microsampling technique.

MICROSAMPLING WITH TASSO DEVICE

- The Tasso OnDemand device is a sterile, disposable, integrated capillary blood collection device.
- It includes a lancet assembly and a detachable reservoir for the collection of blood by trained individuals/caregivers at home or in hospital settings.
- The Tasso device is comprised of the collection unit (called Tasso Button) and a collection reservoir that allows collection and storage of the blood up to 300 µL.
- The Tasso device is designed to safely and reliably collect blood in clinical settings without the need of a highly trained phlebotomist while minimizing pain to the patient.





- This technique can also be easily applied to the subject's back.

METHODS

- PK samples obtained by routine venipuncture and Tasso device and were analyzed for ezogabine and NAMR using a validated LC/MS-MS method.

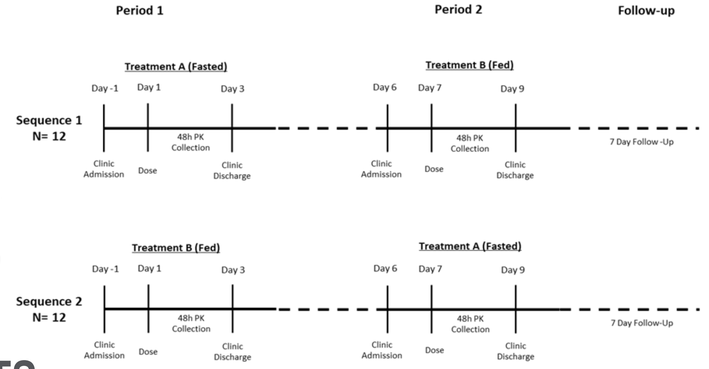


Figure 1: A single-centre, open-label, 2-way crossover study in adult healthy volunteers (n = 24 planned for inclusion in order to obtain ~21 evaluable subjects)

RESULTS

RESULTS - BIOANALYTICAL

- The method for the determination of ezogabine and NAMR in human plasma using HPLC with MS/MS detection met acceptance criteria with respect to specificity, sensitivity, precision, accuracy, matrix effect, linearity, recovery and dilution integrity.
- The lower limit of quantification (LLOQ) was 1 ng/mL and the method cover concentration range of 1.00 ng/mL to 1000.00 ng/mL for both ezogabine and NAMR.
- Carryover was evaluated and was insignificant throughout the validation (≤20.0% of the analyte response of the LLOQ).
- Stability evaluations in matrix and solutions have also met acceptance criteria, demonstrating insignificant degradation over the specified storage durations and conditions.
- Long-term stability in biological matrix i.e., human plasma was confirmed for 126 days at -80°C: accuracy (%Bias): -1.0% for Low Stability QC (quality control) and 2.9% for High Stability QC.
- Longer term stability is ongoing.

RESULTS - PHARMACOKINETICS

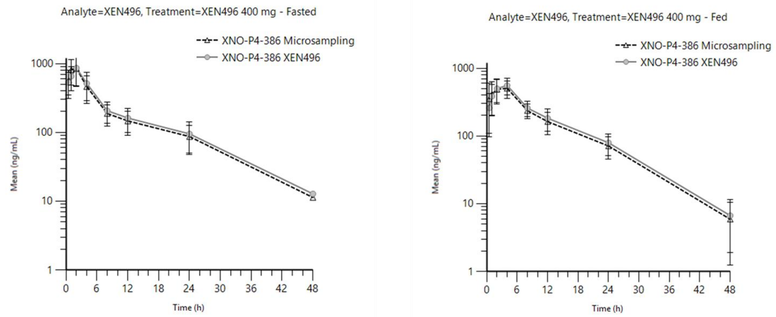


Figure 2: The PK profile of XEN496 (ezogabine) obtained via venipuncture and microsampling

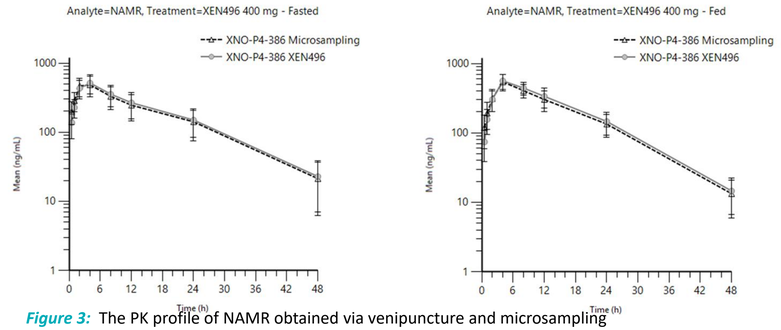


Figure 3: The PK profile of NAMR obtained via venipuncture and microsampling

- As shown in Figure 2, there were no significant differences in XEN496 (ezogabine) concentrations obtained via the two techniques.
- In addition, the PK profiles were virtually superimposed (as shown in Figure 3) for the metabolite i.e., NAMR concentrations further supporting the suitability of the microsampling technique to obtain PK data.
- Furthermore, the concentration agreement between the two techniques was not impacted by status of subject feeding i.e., strong correlation was observed under both fasted and fed states indicating the robustness of the microsampling method.
  - A slope of 0.99 were obtained from linear regression analysis for ezogabine administered under fed and fasted conditions.
  - A slope of 0.92 and 0.93 were obtained from linear regression analysis, respectively, for NAMR under fed and fasted conditions.
- Similar PK profile resulted in comparable PK parameters as shown in Table 1.
- Adult subjects reported no pain during the microsampling procedure.

Treatment	Analyte	PK Parameter (units)	Pearson Correlation	Geometric LSmeans: Method A	Geometric LSmeans: vs Method B	Ratio	90% Confidence Interval: Lower Bound	90% Confidence Interval: Upper Bound
XEN496 400 mg, Fed	XEN496	C_{max} (ng/mL)	0.95	581.85	601.43	0.97	0.93	1.01
		$AUC_{0\text{-}last}$ (h*ng/mL)	0.96	5810.26	6267.65	0.93	0.91	0.94
		$AUC_{0\text{-}t}$ (h*ng/mL)	0.96	5747.77	6199.57	0.93	0.91	0.94
	NAMR	C_{max} (ng/mL)	0.98	544.38	570.85	0.95	0.94	0.97
		$AUC_{0\text{-}last}$ (h*ng/mL)	0.98	8065.72	8601.71	0.94	0.93	0.95
		$AUC_{0\text{-}t}$ (h*ng/mL)	0.98	8095.22	8665.19	0.93	0.92	0.95
XEN496 400 mg, Fasted	XEN496	C_{max} (ng/mL)	0.90	905.12	848.70	1.07	1.00	1.14
		$AUC_{0\text{-}last}$ (h*ng/mL)	0.95	6515.20	6944.22	0.94	0.91	0.96
		$AUC_{0\text{-}t}$ (h*ng/mL)	0.95	6403.46	6828.73	0.94	0.92	0.96
	NAMR	C_{max} (ng/mL)	0.87	488.43	497.40	0.98	0.93	1.04
		$AUC_{0\text{-}last}$ (h*ng/mL)	0.99	7834.06	8259.34	0.95	0.94	0.96
		$AUC_{0\text{-}t}$ (h*ng/mL)	0.99	7465.99	7866.59	0.95	0.94	0.96

Table 1: Bioequivalence analysis for Venous Sampling and Tasso Microsampling

- Comparison of key PK parameters (C_{max} and AUCs) for XEN496 (ezogabine) and NAMR between the 2 sampling methods showed good agreement with ratio and 90% CI within the conventional bioequivalence acceptance range of 0.80 to 1.25.
- In addition, the mean $T_{1/2}$ for each treatment were similar between two the sampling methods.

CONCLUSIONS

- Overall, microsampling could be an accurate alternative to routine blood drawing for determination of drug levels.
- The data from this Phase 1 study indicate that reliable PK data can be obtained via microsampling technique using Tasso device with minimal pain or discomfort to the subjects.
- The use of the capillary microsampling technique in pediatric clinical research could be invaluable to minimize both the discomfort and the volume of blood draws in pediatric subjects.
- In addition, in the context of conducting pediatric clinical trials microsampling technique may facilitate study enrollment since provides flexibility for at home PK sampling, no need for syringe and could be performed by parents/caregivers with minimal training.

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