

Development of XEN496, a Pediatric Immediate-Release Formulation of the Potassium Channel Opener Ezogabine

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BACKGROUND

XEN496: A pediatric formulation of ezogabine suitable for weight-based dosing

XEN496 is a pediatric formulation of ezogabine (retigabine), a neuronal KCNQ (Kv7) potassium channel modulator under development by Xenon Pharmaceuticals as a precision medicine treatment for KCNQ2-related neonatal developmental and epileptic encephalopathy (KCNQ2-DEE).

Ezogabine was previously marketed by GlaxoSmithKline as a coated immediate-release (IR) tablet formulation (Potiga®/Trobalt™) for adjunctive treatment of focal seizures in patients aged 18 years and older, but it was withdrawn from the global market in July 2017 for commercial reasons.

While the tablet formulation was used off-label (Table 1) in the KCNQ2-DEE pediatric population, a pediatric formulation was not marketed. Moreover, ezogabine has never been studied in a formal clinical trial in this population.

In view of our clinical development plans for ezogabine in KCNQ2-DEE, we developed a pediatric-friendly formulation (XEN496) to allow for flexible weight-based dosing without requiring extemporaneous compounding.



Case Study of 11 KCNQ2-DEE Patients Millichap 2016 ¹	Medical Record Review/Parent Interviews Olson 2017 (8 Families) ²
Ezogabine associated with improvements in seizures and/or development in:	Interviews/medical record review of KCNQ2-DEE patients prescribed ezogabine:
<ul style="list-style-type: none"> 3 of the 4 infants treated before 6 month old were seizure free or occasional seizures <1/week 2 of the 7 treated later No serious adverse effects 	<ul style="list-style-type: none"> Sustained improvement in seizure frequency in 5 of the 6 children with at least weekly seizures Improvements in development or cognition in all 8 children Urinary retention/hesitation in 3 patients, but overall well tolerated

Table 1 ¹ Millichap et al. *Neurol. Genet.* Oct 2016, 2:1-5.; ² Olson et al. 2017 AES Annual Meeting, Abstract 3.176

METHODS

- A modified quality-by-design approach was implemented in the formulation development of this Biopharmaceutical Classification System Class 2 (low water solubility, high permeability) drug. In addition, a risk-based matrix was developed to guide the advancement of different prototypes.
- Excipient compatibility for ezogabine was established through an accelerated-condition (40°C, 75% relative humidity) stability study of mixtures of ezogabine and excipients. Lead blends within the compatibility space were then designed and their *in vitro* dissolution profiles determined.
- Blends with the most promising dissolution profiles were dry granulated through roller compaction and re-tested for dissolution prior to stability assessment.
- The impact of drug loading on dissolution performance was also assessed, along with the potential for non-specific binding of formulated ezogabine to common plastics such as those employed in feeding bottles and nasogastric feeding tubes.
- The candidate formulation was then advanced to rat pharmacokinetic (PK) studies in order to confirm its biopharmaceutical performance *in vivo* and placed on long-term stability studies.

RESULTS

Blend #	Composition (% w/w)						% Increase in TRS*
	API	MCC	Starch 1500	PVP	HPMC	BHT	
1	5	45	44.99	--	5	0.01	0.38
2	5	45	44.99	5	--	0.01	0.50
3	5	42.5	42.49	--	10	0.01	0.27
4	5	37.5	37.49	--	20	0.01	< 0.05
5	5	--	89.99	--	5	0.01	0.17
6	5	89.99	--	--	5	0.01	0.33
7	5	--	89.99	5	--	0.01	0.17
8	5	17.5	72.49	--	5	0.01	0.34

Table 2: Chemical Stability Evaluation of Ungranulated Prototype Formulations

The microcrystalline cellulose (MCC)/starch system, combined with the use of HPMC as binder, was most compatible with ezogabine

* Percentage increase in Total Related Substances (TRS) (i.e., degradants) by HPLC/UV after 4 weeks of open storage at 40°C/75% relative humidity; PVP = poly(vinylpyrrolidone) (binder); HPMC = (hydroxypropyl) methylcellulose (binder); BHT = butylated hydroxytoluene (preservative)

Superior release of ezogabine was found with adding a super-disintegrant at an optimal drug load of 20%

Blend #	Composition (% w/w)						% Released at T = 30/60 minutes*
	API	BHT	HPMC	Starch 1500	MCC	Other Excipients	
1	5	0.01	5	44.99	45	--	64.1 / 70.2
2	5	0.01	20	37.49	37.5	--	85.8 / 89.4
3	5	0.01	5	42.49	42.5	Croscarmellose sodium (5%)	89.7 / 93.1
4	20	0.01	5	19.99	45	Polyplasdone® XL (10%)	96.9 / 100.5
5	5	0.01	5	24.99	25	Lactose (40%)	70.4 / 74.7
6	5	0.01	5	59.99	30	--	63.9 / 69.4
7	6.98	0.01	6.98	79.05	--	Croscarmellose sodium (6.98%)	80.6 / 84.2
8	10	0.01	5	29.99	45	Polyplasdone® XL (10%)	80.3 / 82.1
9	10	0.01	5	29.99	45	Polyplasdone® Ultra (10%)	84.3 / 90.4
10	10	0.01	5	42.49	45	--	80.5 / 81.6
11	20	0.01	5	37.49	37.5	--	88.3 / 91.9
12	10	0.01	5	19.99	40	Lactose (20%) + CCNa (5%)	85.9 / 86.3

Table 3: Dissolution Testing of Ungranulated Prototype Formulations

* pH 1 (0.1 N HCl), 37 °C, n = 6

- Incorporation of Polyplasdone® XL (crospovidone, USP/NF) as a super-disintegrant led to significant improvements in the dissolution profile (Blend 4 vs. Blend 1).
- Superior results were obtained using a 20% w/w API loading (Blend 4 vs. Blend 8).
- Blend 4 was progressed into dry granulation/roller compaction to afford XEN496.
- Following granulation, the dissolution profiles of ezogabine (neat API) and of XEN496 were determined in USP pH 1.2 buffer at 37 °C. XEN496's dissolution profile is consistent with an immediate-release drug product.

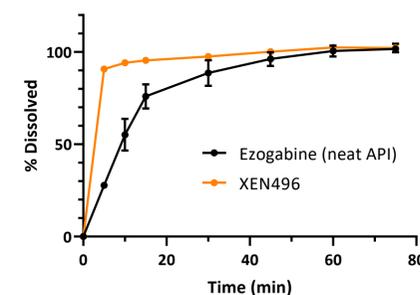


Figure 1: Dissolution Profile of XEN496

XEN496 rapidly and efficiently releases ezogabine

XEN496 is compatible with pediatric dosing, including common feeding devices

	Diameter (µm)	Material	Recovery (%)
XEN496 d ₁₀	13.4 ± 0.4	Glass	100.0
XEN496 d ₅₀	41.6 ± 1.6	Polyether sulfone	96.9
XEN496 d ₉₀	153 ± 31	Polyphenyl sulfone	96.7
Typical baby bottle nipple aperture	> 500	Polypropylene	96.5
Size 4 Fr pediatric NG tube	1330		

- The particle size distribution of XEN496 was determined by laser light scattering. XEN496 is expected to be compatible with baby bottle nipples and pediatric naso-gastric (NG) feeding tubes.

- Spike-recovery experiments with XEN496 showed only negligible non-specific binding of ezogabine to materials commonly-employed in baby bottles and NG tubes.

XEN496 was comparable to compounded Potiga® tablets in rats

- XEN496 was compared to crushed Potiga® tablets (mimic of compounding/previous pediatric clinical practice) in a rat cross-over PK study.
- N = 6, male Sprague-Dawley rats, dose level 10 mg/kg
- Test articles suspended (1 mg/mL) in 0.02% w/v aq. CMC (viscosity-matched to infant formula) and dosed by oral gavage.

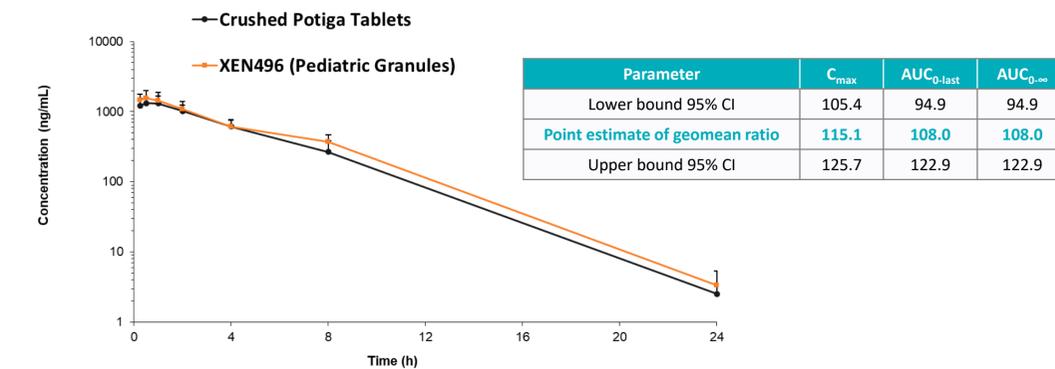


Figure 2: Plasma Concentrations of Ezogabine after PO Dosing of XEN496 (Pediatric Granules) and Crushed Potiga® (Powdered Ezogabine Tablets) in Rats

CONCLUSIONS

- XEN496, a pediatric formulation of ezogabine (granules suitable for dispersal in breast milk, infant formula or soft foods, packaged in single-use sachets or sprinkle capsules of varying fill weights) was developed and progressed into clinical development.
- This formulation was studied in a Phase I study in adult healthy volunteers (see Poster #246).
- The bulk formulation is chemically stable for at least one year (ICH ambient conditions), with total related substances (TRS) remaining < 0.2%.
- XEN496 has promising *in vitro* and *in vivo* properties consistent with marketed pediatric drug products.



Figure 3: XEN496 & XEN496 Sprinkle Capsules