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

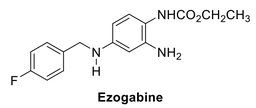
Jay A. Cadieux; Matthew D. Tandy; Rostam Namdari; Ernesto Aycardi

Xenon Pharmaceuticals Inc., 3650 Gilmore Way, Burnaby, BC, Canada

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

- 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(Potiga®/Trobalt™) for adjunctive treatment of focal seizures in patients aged 18 years and older, but it was withdrawn from the global market in July 2017 for commercial reasons.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 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 development plans for ezogabine in KCNQ2-DEE, we undertook the development of 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: • 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	Interviews/medical record review of KCNQ2-DEE patients prescribed ezogabine: • 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

[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 1: 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 2: 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.

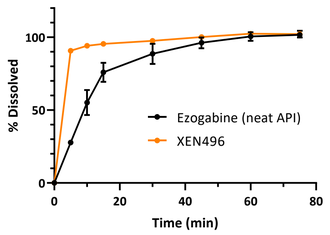


Figure 1: Dissolution Profile of XEN496

XEN496 rapidly and efficiently releases ezogabine

XEN496 is compatible with pediatric dosing, including common feeding devices

	Diameter (µm)
XEN496 d_{10}	13.4 ± 0.4
XEN496 d_{50}	41.6 ± 1.6
XEN496 d_{90}	153 ± 31
Typical baby bottle nipple aperture	> 500
Size 4 Fr pediatric NG tube	1330

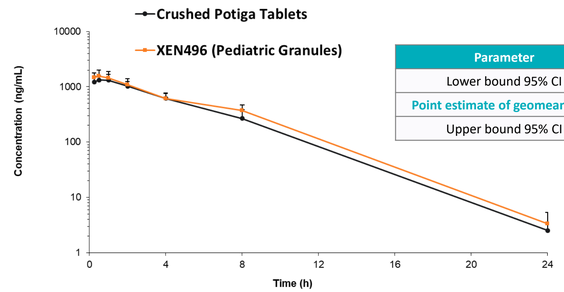
- The particle size distribution of XEN496 was determined by laser light scattering. XEN496 is expected to be compatible with baby bottle nipples and pediatric naso-gastric (NG) feeding tubes.

Material	Recovery (%)
Glass	100.0
Polyether sulfone	96.9
Polyphenyl sulfone	96.7
Polypropylene	96.5

- 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.



Parameter	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0\text{-}\infty}$
Lower bound 95% CI	105.4	94.9	94.9
Point estimate of geomean ratio	115.1	108.0	108.0
Upper bound 95% CI	125.7	122.9	122.9

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 is presently the focus of a PK study in adult healthy volunteers.
- Results from the human PK study will inform the need for potential dose adjustments in an planned pivotal study of XEN496 in KCNQ2-DEE.
- XEN496 has promising *in vitro* and *in vivo* properties consistent with marketed pediatric drug products.


Figure 3: XEN496 & XEN496 Sprinkle Capsules

XENON