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

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RESULTS

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

Blends with the most promising dissolution profiles were dry granulated through roller compaction (HMP and MCC-based matrix was developed to guide the advancement of different formulations) for adjunctive treatment of focal seizures in patients aged 18 years and older, but it was withdrawn from the global market in July 2017 for commercial reasons.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 extreme compounding.

Case Study of 11 KCNQ2-DEE Patients

Medical Record Review/Parent Interviews

• Interviewed/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/impaired voiding (in 5 patients, but overall well tolerated)


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.

Exipient compatibility for ezogabine was established through an accelerated stability study (product stability studies). The particle size distribution of XEN496 was consistent with marketed pediatric drug products.

Improvements in development or cognition in all 8 children with at least weekly seizures were observed. Ezogabine associated with improvements in seizures and/or development in: 3 of the 4 infants treated before 6 months old were seizure free or occasional seizures (<1/week) at T = 30/60 minutes

Percentage increase in Total Related Symptoms (TRS) (i.e., degradation) by F1/F2/UV after 6 weeks of cold storage at 25°C & 5% relative humidity (RH) and 68°C & 75% RH (pH 7.0). The results are expressed as 100/(1 - observed/truth) * 100.

Y = 42.49 + 0.01X

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.

Conclusions

XEN496 is comparable to compounded Potiga® tablets in rats

• XEN496 was compared to crushed Potiga® tablets (m/s of compounding/prescription pediatric clinical practice) in a rat cross-over PK study.
• N = 6, 2 male/4 female rats, dose level 50 mg/kg
• Test article suspended (1 mg/mL) in 0.02% w/v CMC (acidity-matched to infant formula) and dosed by oral gavage.

• Incorporation of Polyplasdone® XL (crospovidone, USP/NF) as a super disintegrant was significant. Incorporation of Polyplasdone® XL (crospovidone, USP/NF) and PVP-10K was determined by UPLC at pH 2 and 7.2 buffer at 37°C. XEN496’s dissolution profile is consistent with an immediate-release drug product.

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.

XEN496 is compatible with pediatric dosing, including common feeding devices

• The particle size distribution of XEN496 was determined by laser light scattering. XEN496 in crushed form is expected to disintegrate in commonly-employed baby bottles and NG tubes.

• Table recovery experiments with XEN496 showed only negligible non-specific binding of ezogabine to plastic material (crushed Potiga® tablets).

• XEN496 was comparable in PK to crushed Potiga® tablets and commensurate with marketed pediatric drug products.

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 coformulated 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 extreme compounding.