Preclinical In Vitro and In Vivo Comparison of the Kv7 Activator XEN1101 with Ezogabine


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CONCLUSIONS

- XEN1101 is a differentiated Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders.
- Ezogabine (trade names Potiga® and Trobalt™) was previously approved by the U.S. FDA for the treatment of adult focal onset seizures; however, it was withdrawn from the global market in July 2017 for commercial reasons, and no Kv7 activating drugs are currently available for the treatment of epilepsy.
- XEN1101 and ezogabine overlap in their mechanism of action; therefore, an assessment was conducted to compare their preclinical in vitro and in vivo profiles.

METHODS

- In vitro, Human Embryonic Kidney cells stably expressing Kv7.2/7.3 channels were used to examine the potency of XEN1101 and ezogabine in a K+ flux assay and whole-cell patch clamp electrophysiology.
- Electrophysiological recordings were made on a Sophion Qube-384 planar patch-clamp system. Standard intra- and extracellular solutions were used and the voltage protocol shown below was used to assess the effect of compound on the biophysics of the channel. Tail current measurements were made at the 0 mV test pulse after the conditioning prepulses.

RESULTS

- XEN1101 and ezogabine both demonstrated a concentration-dependent increase in Gmax that was maximal at ~2-fold increase in the conductance magnitude.

Efficacy of XEN1101 and Ezogabine in the Mouse AC-MES Assay

- In line with the in vitro data, XEN1101 requires ~15-fold less plasma and ~8-fold less brain exposure than ezogabine for half-maximal activity in an AC-MES mouse model. Data is binned by plasma and brain concentrations.

CONCLUSIONS

- Preclinical in vitro and in vivo comparison of XEN1101 with ezogabine demonstrates that XEN1101 has a similar mechanism of action to ezogabine but potentially offers substantial improvements:
  - More potent modulation of K\textsubscript{v}7.2/7.3;
  - Slows deactivation of K\textsubscript{v}7.2/7.3 channels to a greater degree, enhancing its ability to reduce hyper excitability;
  - More potent anti-seizure activity in preclinical models;
  - No pigmentated dimers and no predicted discoloration liability.
- XEN1101 is a novel chemical entity that has a strong rationale as a potential anti-seizure medication providing a mechanism of action that is not currently available for the treatment of epilepsy.
- A Phase 2b clinical trial is underway to evaluate the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in approximately 300 adult patients with focal epilepsy.

Ezogabine Phenazinium-Type Dimer

- Ezogabine can form a number of dimeric species, including highly-coloured phenazinium-type dimers, which have been implicated in the pigmentary abnormalities observed with long-term ezogabine exposure.
- Ezogabine has a secondary aniline function, which is key to forming phenazinium-type dimers.
- XEN1101 instead has a tertiary aniline at the corresponding position and this key structural difference prevents XEN1101 forming analogous dimers.

Normalized G\textsubscript{max} Curves for Kv7.2/7.3 Channels in Presence of XEN1101 or Ezogabine

- XEN1101 speeds the kinetics of K\textsubscript{v}7.2/7.3 channel activation to a similar degree as ezogabine.
- Deactivation of K\textsubscript{v}7.2/7.3 channels is slowed ~2-fold more by XEN1101 than ezogabine, enhancing its ability to reduce hyper excitability.

Discoloration by Ezogabine Due to Dimer Formation

- Ezogabine can form a number of dimeric species, including highly-coloured phenazinium-type dimers, which have been implicated in the pigmentary abnormalities observed with long-term ezogabine exposure.