New Kv7 Channel Opener Chemistry for the Treatment of Seizures

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Rationale

K_v7 ("M-type," KCNQ) K^+ currents, play dominant roles in controlling neuronal excitability. They act as a "brake" against hyperexcitable states in the central and peripheral nervous systems. Ezogabine (EZG), the first Kv7 channel opener, demonstrated clinical effectiveness in Focal Onset Seizures. Preclinical studies suggest that Kv7 openers my be useful in treating other diseases characterized by neuronal hyperexcitability, such as migraine, depression, anxiety, mania, and addiction.

Objective

Develop novel Kv7 chemistry for the treatment of disorders associated with neuronal excitability.

Methods

- Screening conducted in rubidium (Rb(+)) efflux assay using PC-12 cells expressing Kv7.2.
- Secondary Kv7.2/7.3 in vitro testing was conducted in whole cell (CHO-K1) patch clamp assay for binding activity and ½ Vmax shift assessment.
  - Currents were evoked from the testing potential of -120mV to 30mV in 10 mV increments.
- For PK studies; CD-1 mice and SD rats were dosed orally with XYG-A and XYG-B at 10 mg/kg and 8 mg/kg, respectively.
  - XYG-A and XYG-B concentrations were determined by LC-MS/MS by a qualified method.
  - PK parameters in mice and rats were determined using linear up/log down NCA methods. Simulated human values were modeled using a 2-compartmental model and multispecies allometric scaling.
- Anti-seizure efficacy after oral dosing was tested in mice (n=4) and rats (n=6) via MES 0.5 h post-dose.
- PK parameters were allometrically scaled and a 5 mg single dose in humans was simulated with and without a maintenance dose.

Chemical Design and Activity

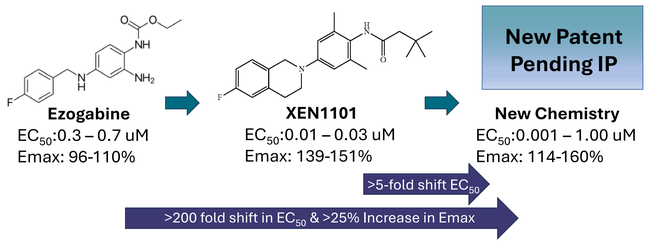
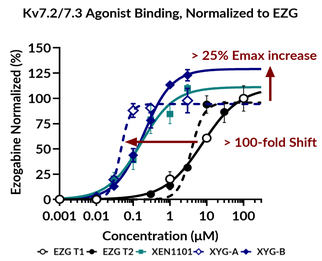


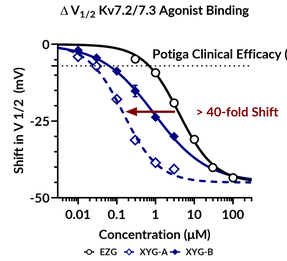
Figure 1. Rational New Chemistry and Kv7.2 Activity. The efflux (F: in the presence of compound in depolarization buffer) and compound concentration relationship was plotted to calculate an EC_{50} value - concentration for 50% of maximal Rb efflux.

In vitro Kv7.2/7.3 Activity



Compound	EC_{50} (μM)
EZG	4-5.6
XEN1101	0.161
XYG-A	0.050
XYG-B	0.173

Figure 2. Kv7.2/7.3 Dose Response Compared to EZG and XEN1101. Lead molecules were >20-fold more potent than EZG and > 33% more potent than XEN1101.



Compound	EC_{50} (μM)
EZG	4.23
XYG-A	0.113
XYG-B	0.249

Figure 3. ½Max V Shift. Lead molecules exhibited a shift in concentration required for a >7 mV threshold shift in activation, which is the in vitro correlate for EZG clinical efficacy.

In Vivo Efficacy – Rodent MES Seizure Model

Maximal Electroshock Seizure (MES)

Seizure is induced with corneal electrode stimulation at 150 mA (rat) and 50 mA (mice) for a duration of 0.2 sec. Protection is achieved when there is no hind limb extension for 6 seconds.

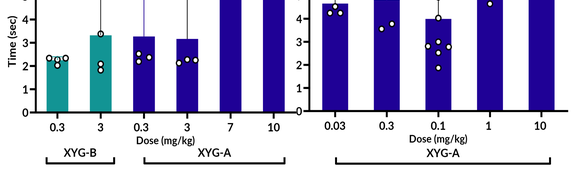


Figure 4. Efficacy in MES Seizure Model. In mouse, 7 mg/kg 30 delivered full protection from MES and at 0.3 mg/kg 25% were protected 30 min post-dose. In rat, 0.1 mg/kg protected 3/4 animals from MES with 0.03 mg/kg demonstrating statistically significant prolongation over vehicle.

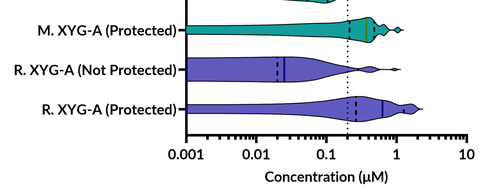


Figure 5a. Mouse (M) and Rat (R) Plasma Concentrations for MES Seizure Protection. Dotted line=25% quartile threshold conc. for protection.

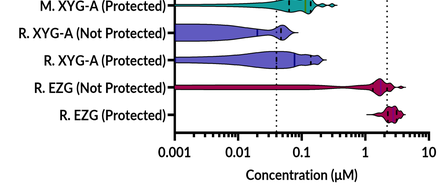


Figure 5b. Mouse (M) and Rat (R) Brain Concentrations for MES Seizure Protection. Dotted line=25% quartile threshold conc. for protection. Mean levels in protected mice were 115 nM with a minimum of 30 nM required for protection in mice and rats.

Simulated Human Pharmacokinetics

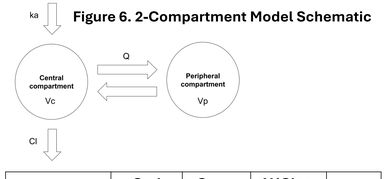


Figure 6. 2-Compartment Model Schematic

Species	Oral Dose	Cmax (nM)	AUClast (h*nM)	T ½ (h)
Mouse	10 mg/kg	282	509	4.5
Rat	3 mg/kg	484	1580	8.3
Human (60 kg)	5 mg	350	6280	31.2

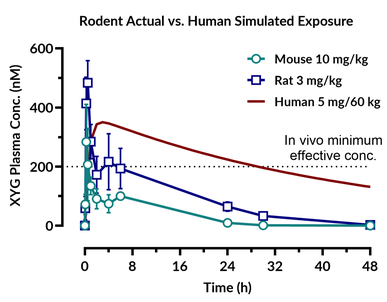
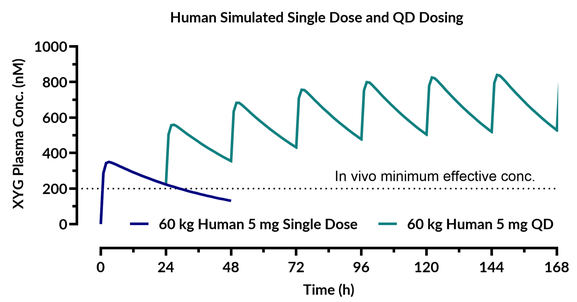


Figure 6a & 6b. Actual Rodent and Simulated Human XYG-A Concentrations in Plasma Over Time.



Conclusions

- Lead molecules exhibited a 200+-fold shift in Kv7.2 EC_{50} with a >25% increase in Emax over EZG and >5-fold more potent than XEN1101.
- In vivo PO efficacy in rodent MES is >10-fold over XEN1101 (ED50 > 4 mg/kg) and BHV7000 (full protection at 3 mg/kg).
- 100-fold less XYG-A brain conc. required for protection compared to EZG conc. in rats.
- It is anticipated that the lead molecule, based on an in vivo minimum effective brain concentration of >20 nM for MES in mice and rats, a half maximal voltage shift of ~7 mV at < 50 nM, and a brain:plasma ratio of >0.7 in rodents, may be effective at a plasma conc. of 30 nM, as a threshold conc., for clinical seizure protection in humans.

Key Takeaways

Rank order of Kv7.2/7.3 by EC_{50}
XYG-A [50 nM] < XEN1101 [161 nM] < BHV7000 [440 nM][a]

Rank order of ½ Max V Shift at 1 uM
EZG [-9 mV] < BHV7000 [-16 mV][a] < XYG-A [-39 mV]

Rank order of Rodent ED_{50}
XYG-A [<0.3 mg/kg] < BHV7000 [0.5 mg/kg] < XEN1101 [~4 mg/kg][b]

BHV7000 in Phase 3 for Focal Onset Seizures at 50 mg and 75 mg; Generalized Seizures at 75 mg [c]
XEN1101 in Phase 3 for Focal Onset Seizures at 15 mg and 25 mg; Generalized Seizures 25 mg [d]

XYG-A Steady State Modeling suggests 5 mg in a 60 kg human as a possible maximum dose.

References

a=AESNET 2019
b=Biohaven Oct 2022 Investor Presentation
c=Biohaven Jan 2024 42nd Annual JP Morgan Presentation; NCT06309966 (RISE3), NCT06132893 (RISE2), NCT06435159 (SHINE)
d=XENON Website November 2024; NCT05716100 (X-TOLE3), NCT05667142 (X-ACKT)