Development and Clinical Modeling of Kv7 Channel Opener Prodrug for Treatment of Neuropathic Pain

Christopher Crean, Sarah Thrasher, and Polina Danshina

Xyzagen Inc.

PSTR069.21/C160

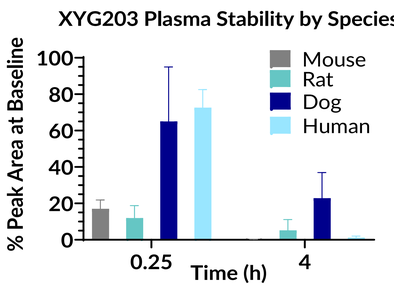
Introduction

- Neuropathic pain still remains an unmet medical need.
- There are no FDA-approved treatments for central neuropathic pain (available therapies are not sufficient nor FDA approved).
- Kv7 channels are widely expressed in peripheral and central neuronal cells, and directly opening these channels can produce an inhibitory effect on action potential propagation .
- Ezogabine (EZG), approved for partial onset seizure and flupirtine (both Kv7 openers), has demonstrated clinical success and were approved in management of chronic pain in Europe.
- The large peak to trough swing, short half-life, and TID administration limited EZG's potential clinical use due to tolerability AEs.
- Xyzagen has developed XYG203, a novel prodrug of ezogabine, for this unmet medical need.

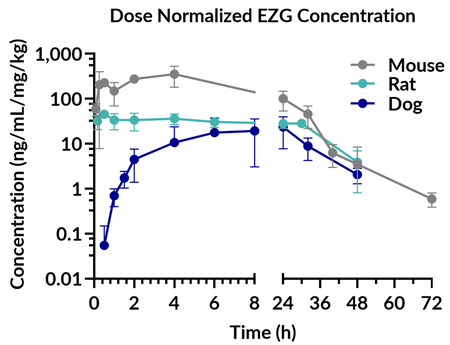
Methods

- XYG203 and EZG concentrations were determined by LC-MS/MS by a qualified method.
- In vitro Plasma stability in plasma at 1000 ng/mL was assessed at 37°C. XYG203 degradation and increase of EZG concentrations measured at 0.25 and 4 h.
- Determination of EZG prodrug ability to activate Kv7 channels was performed by FluxOR™II Green Potassium Ion Channel assay in transfected HEK293A cells.
- For PK studies; CD-1 mice, SD rats and beagle dogs were dosed orally with XYG203 at 45 mg/kg; 60 mg/kg and 75 mg, respectively. (N=3/time point)
- PK parameters in mice, rats and dogs were determined using linear up/log down NCA methods. Simulated human values were modeled under first order kinetics using a 2- compartmental model and multispecies allometric scaling.
- The pain efficacy after PO dosing was tested in two pain models: chronic constriction injury (CCI) and cisplatin-induced peripheral neuropathy (CIPN) rat models via pinprick 1 h post PO dose or via Von Frey Hair testing up to 2 days post PO dose. Doses 1-40 mg/kg (CCI) and 10-30 mg/kg (CIPN) were evaluated.
- PK parameters were allometrically scaled and a 200 mg single dose in humans was simulated with and without a 30 mg maintenance dose.

In Vitro/In Vivo Stability, Concentration-time Data and Nonclinical Pharmacokinetics



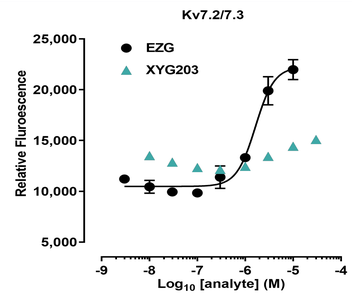
XYG203 converts to EZG faster in mouse and rat plasma than dog and human



EZG from XYG203 PK Parameters by Species			
	Mouse	Rat	Dog
Dose (mg/kg)	45	60	7.5
Tmax (h)	4.00	1.00	24.0
Cmax/D (ng/mL/ mg/kg)	533	70.8	51.6
AUClast/D (h*ng/mL/ mg/kg)	8730	1670	902
Half life (h)	9.40	18.9	7.22
Notes: Values dose normalized based on EZG molar equivalence			

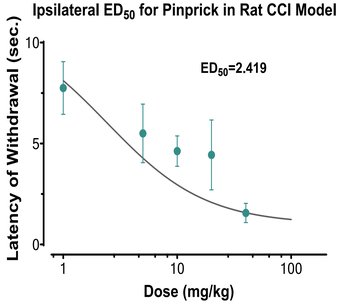
EZG half-life (MRT) from XYG203 is substantially longer than EZG administered by itself and exposure is prolonged through 24-36 h, minimizing peak to trough swing.

In Vitro Kv7.2/3 Opening

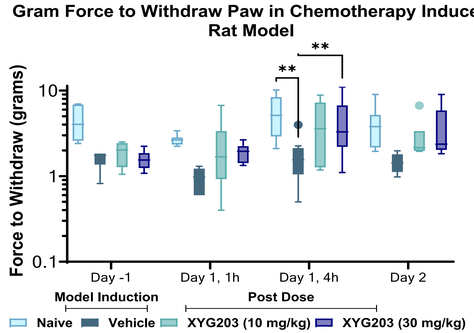


XYG203 is inactive on channel opening

In Vivo Pain Efficacy (CCI Model and CIPN Model)

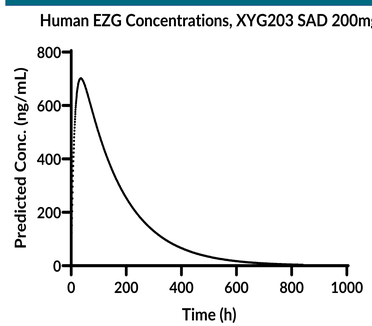


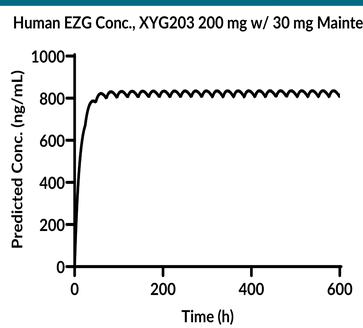
Dose proportional response to pinprick test in CCI model following PO administration of XYG203. SD male rats with CCI (n=8/group) were administered XYG203 at 1, 5, 10, 20, or 40 mg/kg, by PO. Animals were tested for pinprick 1 h post dose and latency of paw withdrawal for ipsilateral paw (sec.) was plotted (Mean ± SD) by dose.



Significant response to Von Frey Test in CIPN Model following PO administration of XYG203. CIPN-induced SD male rats (n=6/group) were administered PO dose of XYG203 at 10 or 30 mg/kg. Rats underwent Von Frey Hair testing at 1, 4, and 26 h post dose, and the maximum gram force needed to withdraw hind paw was recorded with an ultimate maximum of 11 g.

Human PK Simulation of XYG203; with or without Loading Dose





EZG from XYG203 Predicted PK Parameters in Human		
	200 mg	200 mg w/ 30 mg Maintenance
Tmax (h)	35	35
Cmax (ng/mL)	702	835
Cthrough (ng/mL)	NA	809
AUCinf (h*ng/mL)	132,000	NA
Half life (h)	103	NA
Notes: 2-compartment model w/ 1st order absorption Simulation based on mouse, rat, and dog data		

Results

- XYG203 was inactive while the parent compound, EZG, activated Kv7.2/7.3 channels.
- In plasma, XYG203 converted to EZG completely within 1 h (mouse and rat) and 4 h (human).
- Human exposure simulation predicts a 5 x increase in half life for humans (103 h for XYG203 versus 6-8 h for EZG). Loading dose 200 mg with small QD. maintenance doses (30mg) delivers targeted exposure that may improve tolerability due to low swing.

Conclusions

- Kv7 channel opener ezogabine was conjugated to a GRAS promoiety that allows for enhanced and sustained absorption into systemic circulation through the entire GI tract after oral administration.
- XYG203 is effective in a rodent models of neuropathic pain and addresses the ezogabine downsides in PK and tolerability.
- XYG203 is patent pending and can be developed under the 505(b)(2) regulatory pathway.