Development and Clinical Modeling of Kv7 Channel Opener Prodrug for Treatment of Focal Onset Seizures, Status Epilepticus, and Functional Neurological Seizures

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Introduction

- Status Epilepticus (SE) can occur due to an acute event, such as trauma or chemical exposure, or associated with epilepsy, which is a chronic neurological disease characterized by recurrent seizures.
- Current 1st line treatment for SE are benzodiazepines (BZD), which are effective only 66 – 75% of the time.
- Benzodiazepines are contraindicated in functional neurological seizures (FNS).
- Kv7 channel opening has been effective in partial onset seizures with ezogabine (EZG), which is unstable and not soluble in an aqueous vehicle.
- Our goal was to create a stable prodrug of EZG, XYG204, for use as adjunctive injectable therapy with BZD or monotherapy for SE and monotherapy in FNS.

Methods

- From a large prodrug library, identified a water soluble promoiety, that is generally recognized as safe (GRAS).
- For PK Studies, XYG204 was doses IM at 0.5 mL/kg in mouse (45 mg/kg), rat (30 mg/kg), and dog (1 mg/kg) and plasma was analyzed for EZG and XYG204. PK was by linear up/log down noncompartmental methods.
- XYG204 and EZG from XYG204 administration were modeled with 1- or 2- compartmental models. Resulting PK parameters were scaled based on the power model to calculate human XYG204 and EZG exposure following a 300 mg dose.
- MDZ was dosed alone (1.8 mg/kg, IM) or in combination with XYG204 (10 or 30 mg/kg, IM) for evaluation of potential DDI.
- Pentylenetetrazole (PTZ)-induced seizure (96 or 120 mg/kg SC) model in mice dosed XYG204 (75 mg/kg) alone or in combination with MDZ (1.8 mg/kg).
- Maximal electroshock (MES) seizure model (50 mA, corneal stimulation) in rats dosed XYG204 (75 mg/kg, IM). %MPE was calculated as the difference between the measured response and the vehicle response divided by the difference between the maximum (6 sec).

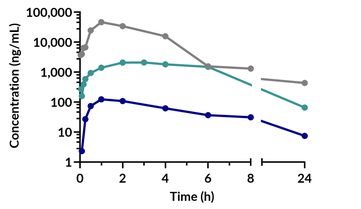
Solubility and Solution Stability

Solubility		
Solvents	EZG (g/L)	XYG204 (g/L)
Water	0.05	>100
0.1 N HCl	16	>100
0.1 N NaCl	0.04	>100

XYG204 and EZG Stability in Solution at Various Conditions				
Compound	Storage	Light	Test Day	% Stability
EZG	RT	Dark	3	65
XYG204	4C	Ambient Light	85	~100
EZG	37C	Obstructed	7	46
XYG204	37C	Obstructed	7	~100

XYG204 has been tested and demonstrated solubility at concentrations > 100 mg/mL in vehicles that are compatible for IM and SC injection. It is stable at refrigerated conditions for ~3 months and body temperature for 7 days. Whereas EZG is unstable.

In vivo Noncompartmental Pharmacokinetics

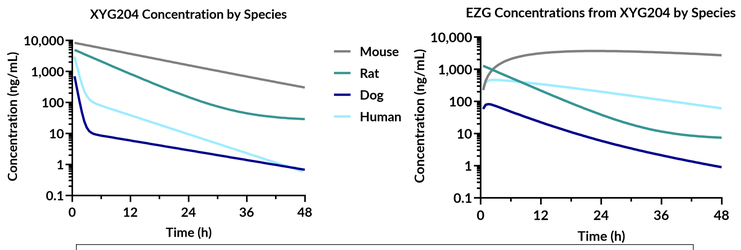


EZG, from XYG204, PK Parameters by Species			
	Mouse	Rat	Dog
XYG204 Dose (mg/kg)	45	30	1
Tmax (h)	1.00	2.67	1.33
Cmax/D (ng/mL/mg/kg)	1030	74.7	125
AUClast/D (h*ng/mL/mg/kg)	3820	600	775

Notes: Values dose normalized based on XYG204 dose

EZG forms quickly from XYG204 with peak exposure occurring 1-3 h post injection. Rat and Dog, tox species for EZG, are similar in normalized exposure

Nonclinical and Human PK Simulations

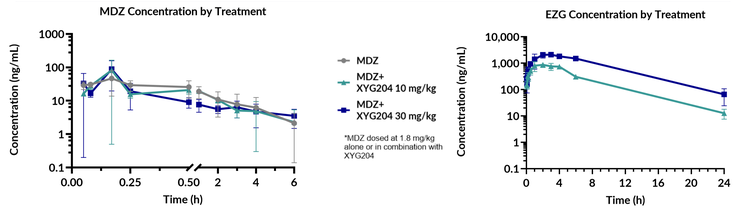


Modeled PK Parameters by Species								
	Mouse		Rat		Dog		Human[a]	
Dose (mg/kg)	45		30		1		300mg	
Analyte	X204	EZG	X204	EZG	X204	EZG	X204	EZG
Tmax (h)	0.050	1.00	0.50	0.50	0.50	1.50	0.50	3.00
Cmax (ng/mL)	8450	3740	4990	1290	704	83.3	3000	472
AUClast (h*ng/mL)	12,700	27,800	34,000	8230	745	796	3800	11,000
T 1/2 (h)	29.7	27.8	41.9	41.5	11.5	10.1	5.89	14.0

Notes: a=Simulated based on nonclinical data

300 mg human dose delivers EZG to 1.57 uM, which is equivalent to the steady state concentration from the efficacious dose of 200 mg TID for focal onset seizures

No Drug-Drug Interaction MDZ

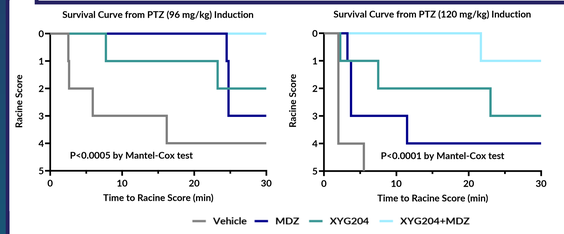


Test Article	Dose Level (mg/kg)	Analyte	Cmax (ng/mL)	Tmax (h)	AUClast (h*ng/mL)	T1/2 (h)
MDZ	1.8	MDZ	50.3	0.109	63.9	1.35
MDZ + XYG204	10	XYG204	3930	0.128	3630	3.79
		EZG	905	1.67	5510	3.58
		MDZ	82.0	0.167	55.6	1.11
	30	XYG204	3800	0.583	12400	4.29
		EZG	2240	2.67	18000	4.02
		MDZ	90.5	0.138	43.3	1.35

Notes: MDZ dosed at 1.8 mg/kg in all scenarios

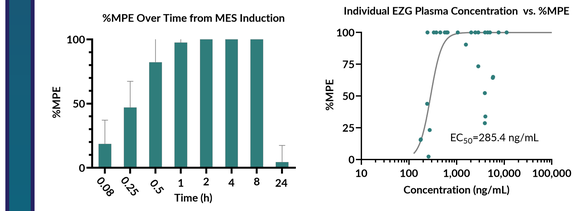
MDZ exposure following a combination dose with XYG204 was similar to MDZ exposure when dosed alone, demonstrating that XYG204 does not interact with MDZ.

In vivo Seizure Protection



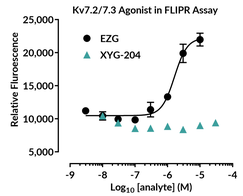
Racine	Behavioral Stage
0	Normal behavior
1	Chewing and facial twitches
2	Head nodding/ shaking
3	Unilateral forelimb clonus without rearing, Straub tail, and extended body postures
4	Bilateral forelimb clonus plus rearing
5	Wild jumping and tonic-colonic activity

MDZ + XYG204 significantly protected against severe chemical seizure



75 mg/kg IM XYG204 reached full protection by 1 h and maintained full protection through 8 h in electroshock assay with minimum effective EZG plasma concentrations of 500 nM and an EC_{50} of 940 nM.

In vitro Kv7.2/7.3 Activity



XYG204's ability to activate Kv7 channels was performed by FluxOR™II Green Potassium Ion Channel assay in transfected HEK293A cells. Run in duplicate.
XYG204 (0.03-30 µM) and EZG (0.01-10 µM). (EC_{50}=1.6 µM)

Conclusions

- Prodrug XYG204 is freely soluble in water and is more soluble in alcohols and aqueous solvents when compared to EZG.
- XYG204 was more stable than EZG under conditions: 4C protected from light, at RT under ambient light, and under acidic conditions at 37C.
- XYG204 delivered EZG to systemic circulation with a rapid onset and sustained exposure over 24 h.
- Allometrically scaled to human, a 300 mg dose is >1 uM at 100 minutes and is sustained for 48 h. The half-life of EZG in humans is simulated at 14 h by the IM route from the Kv7 prodrug compared to 6-8 h by the oral route from the tablet for Potiga®.
- MDZ exposure following combination dose was similar to exposure of MDZ when dosed alone with Cmax ranging from 50.3 – 90.5 ng/mL. EZG from XYG204 remained quantifiable through 24h while MDZ was only detectable through 6h, regardless of being dosed alone or in conjunction with XYG204.
- XYG204 alone or in combination with MDZ, not only reduced seizure severity, but also rescued animal from PTZ-induced seizure death. (data not shown)
- XYG204 (75 mg/kg, IM) had a rapid onset of action to MES with statistically significant effects at 15 minutes. Full protection occurred by 1 h and was maintained through 8 h. Nonlinear regression of EZG concentrations and %MPE data resulted in an EC50 of 285.4 ng/mL, approximately 1 µM.
- XYG203 was inactive while the parent compound, EZG, activated Kv7.2/7.3 channels in a dose-dependent manner.
- These data together support that the Kv7 prodrug of EZG, XYG204, has suitable PK/PD profile for use in SE and since its not a BZD then there is also potential use in FNS.
- As a prodrug of EZG, this prodrug is patent pending and can be developed under the 505(b)(2) regulatory pathway for FOS, SE, and FNS.