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XEN1101, a Novel Modulator of Kv7.2/3 for the Treatment of Epilepsy

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This presentation and the accompanying oral commentary contain forward-looking statements that involve risks, uncertainties and assumptions. If the risks or uncertainties ever materialize or the assumptions prove incorrect, our results may differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact could be deemed forward-looking, including, but not limited to, statements regarding our ability to achieve milestones in both our proprietary and partnered development programs, the anticipated timing of IND submissions with regulatory agencies, the initiation of future clinical trials, the timing of and results from our and our collaborators' ongoing clinical trials and pre-clinical development activities, the plans of our collaboration partners and their interactions with regulatory agencies, the potential efficacy, future development plans and commercial potential of our and our collaborators' product candidates and the progress and potential of ongoing development programs.

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XEN1101: Improved 2nd Generation $K_V7.2$ Opener

- Human genetic validation of KCNQ2 target
  - *De novo* dominant negative missense mutations cause EIEE7
- Good pharmacological validation as ezogabine was approved in 2011 for treatment resistant epilepsy
- Potential for best-in-class $K_V7.2$ opener
  - XEN1101 has improved pharmacokinetics, selectivity and pharmacology over ezogabine
    - Removed from the market in mid-2017 for commercial reasons
- Clear clinical and regulatory pathway
- FIH study initiated October 2017
- Anticipate early PD readout via TMS study currently underway as part of Phase 1 trial

XEN1101: Improved 2nd Generation $K_V7.2$ Opener

- No potential to form colored dimers
- ~20-fold more potent for $K_V7.2/7.3$ heterotetramers over ezogabine
- ~2-3-fold more selective over $K_V7.4$ and $K_V7.5$
- No activity on $K_V7.1$, hERG, GABA
- Greater potency than ezogabine and other AEDs in multiple animal models
- Higher therapeutic index based on rat rotarod and mouse TD_{50} compared to ezogabine
- Improved PK predicts once daily dosing in humans leading to reduced frequency of C_{max} related CNS AEs

XEN1101: Potent Efficacy in Animal Models

- More potent than ezogabine and other AEDs in animal models

	Mice IP MES ED_{50} (mg/kg)	Mice IP Metrazol ED_{50} (mg/kg)	Mice IP Picrotoxin ED_{50} (mg/kg)	Mice IP Bicuculline ED_{50} (mg/kg)	Mice IP 6 Hz, 32 mA ED_{50} (mg/kg)	Mice IP 6 Hz, 44 mA ED_{50} (mg/kg)
Ezogabine	29.51	>50	33	>50	12.1	20.25
XEN1101	6.1 (2.2)	3.9	9.86	2.59	3.7	5.0
Carbamazepine	**7.81**	> 50	> 18.2	> 50	**75% @ 40 mg/kg**	
Gabapentin	**78.1**	47.5	> 500	> 500	**No activity**	
Lamotrigine	**7.47**	> 40	> 40	> 40	**50% @ 20 mg/kg**	
Levetiracetam	**> 500**	> 500	> 500	4.7	**19.4**	
Topiramate	**33**	> 800	> 500	> 500	**> 300**	

Electrically induced seizures: MES and 6 Hz
$GABA_A$ antagonists: Bicuculline and Picrotoxin
Chemical convulsant: Metrazol

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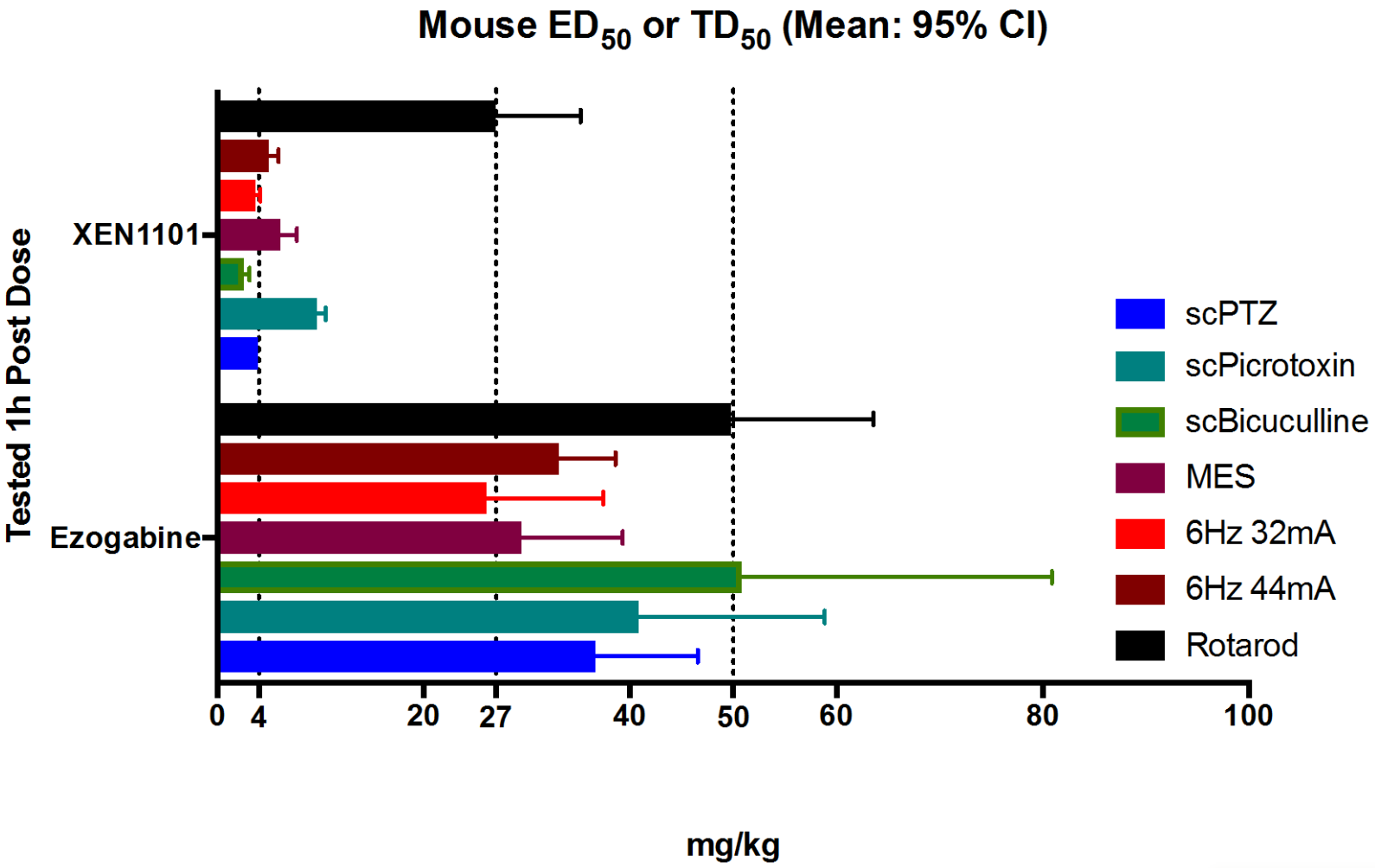
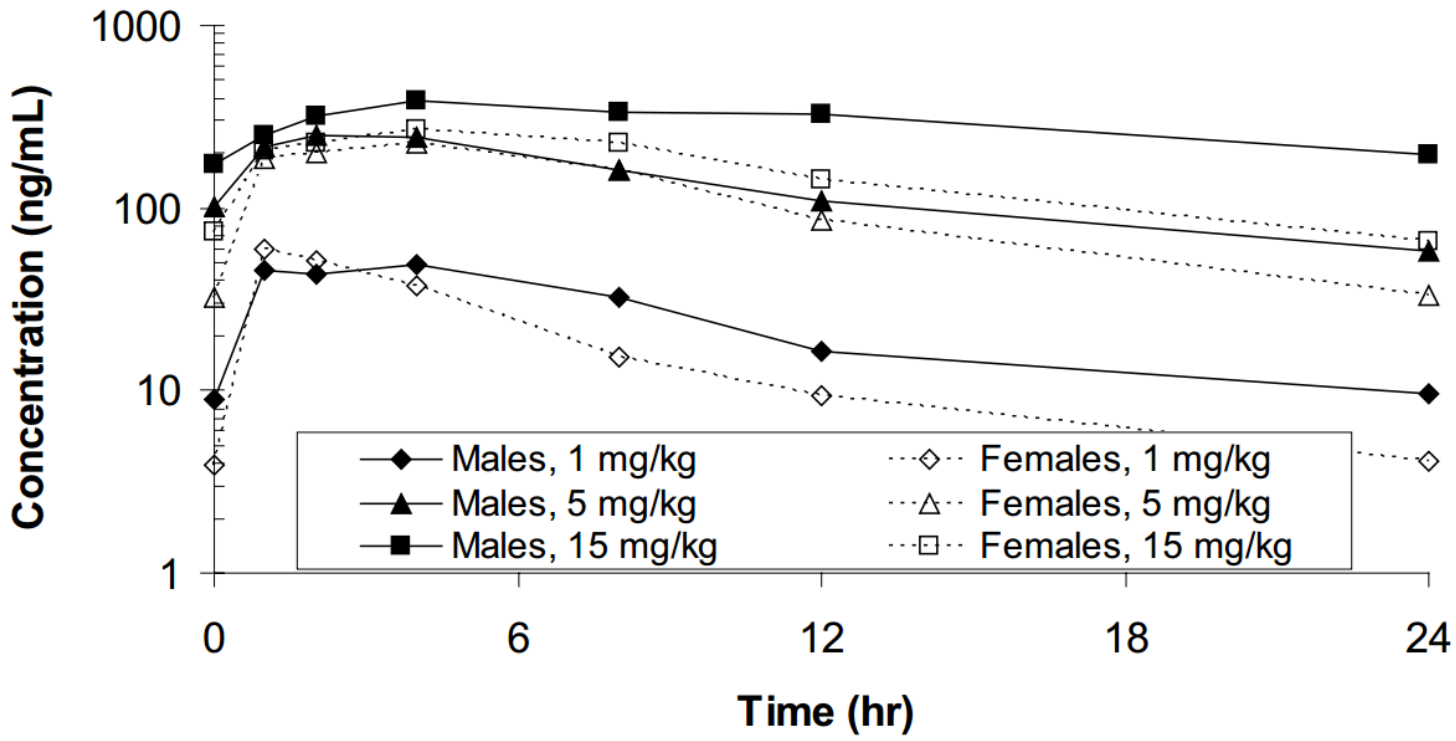
XEN1101 Improved Therapeutic Index Versus Ezogabine



PK in NHP Predicts Once Daily Dosing in Humans



- Mean plasma concentrations in NHP after repeat oral dosing
- Low peak to trough ratio
- Supports QD dosing

XEN1101 Development Overview

- Phase 1: Adaptive integrated design underway, readout expected mid 2018
- SAD/MAD study with pilot TMS (transcranial magnetic stimulation)
- TMS cross-over study
  - Dosing following selection of dose from SAD/MAD/pilot TMS
- Chronic GLP toxicology studies in rat and NHP in progress
- Phase 2 to follow ezogabine precedent in refractory focal seizures
- Exploring treating early onset epileptic encephalopathies including KCNQ2-encephalopathy (EIEE7)

XEN1101 Summary

- Best/only-in-class $K_V7.2/3$ modulator
- Highly genetically and clinically validated mechanism
- Highly efficacious in a broad range of epilepsy animal models
- Excellent oral PK in animal models predicts once daily dosing
- Expect lower C_{max} related CNS AEs compared to ezogabine
- No potential for pigmentation as seen with ezogabine
- Human PK, safety and PD studies ongoing
- Phase 2 planned to initiate H2:2018 in focal adult-onset seizures
- Parallel evaluation of precision medicine strategy to treat KCNQ2-encephalopathy

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