Characterization of BHV-7000: A Novel Kv7.2/7.3 Activator for the Treatment of Seizures

Kelly Picchione, PhD; Lynn Resnick, PhD; Michael Bozik, MD; Steven Dworetzky, PhD

Biohaven Pharmaceuticals, Inc.

Dr. Picchione has received personal compensation for serving as an employee of Biohaven Pharmaceuticals, Inc.; has stock in Biohaven Pharmaceuticals, Inc.; and has received intellectual property interests from a discovery or technology relating to health care.

Kv7.2/7.3 as a Target for Epilepsy

Key regulator of excitatory/inhibitory balance

- Voltage-gated potassium channels
- Broadly expressed in the CNS
- Molecular substrate of the M-Current
- Pharmacological validation

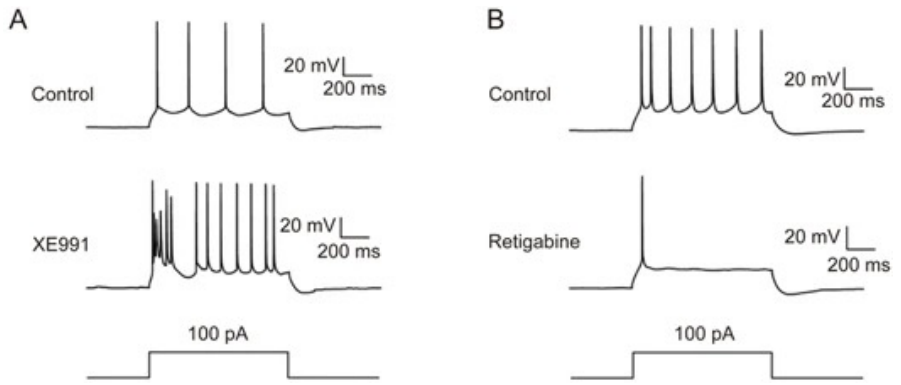
Genetics

- Strong association between mutations in the Kv7 genes (KCNQ2) and (KCNQ3) and epilepsy

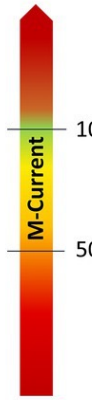
Clinical validation

- First-in-class Kv7 activator Ezogabine

Pharmacological Modulation of Kv7 Alters the Intrinsic Excitability of Neurons



Link between Kv7 Current and Clinical Phenotype



Mutation	Disorder	Clinical Phenotype
Gain of Function	KCNQ2-E	Developmental delay Infantile or childhood onset seizures Startle-like myoclonus
Loss of Function	KCNQ2-B	Neonatal seizures
Dominant Negative Loss of Function	KCNQ2-E	Developmental delay Neonatal seizures

1. https://doi.org/10.1038/aps.2017.72.
2. https://doi.org/10.3389/fphys.2020.570588.

Strategy - Best-in-Class Kv7.2/7.3 Activator

Ezogabine

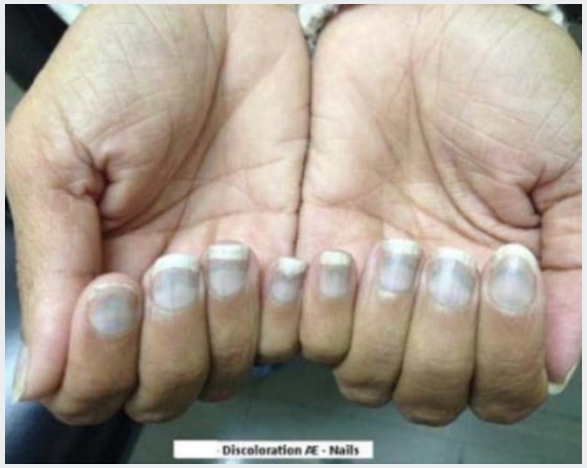
- Approved for adjunctive treatment of partial-onset seizures in 2011
  - TID dose schedule and dose titration
  - FDA issued boxed warning in 2016
- Withdrawn from the market in 2017
  - Poor market uptake

Address High Unmet Need

- Adult focal onset
  - Many patients are treatment refractory and experience burdensome side effects
- KCNQ2-DEE
  - Target therapy

Best-in-Class

- Address chemical instability
- Improve potency, selectivity, and tolerability
- QD dosing with no dose titration required

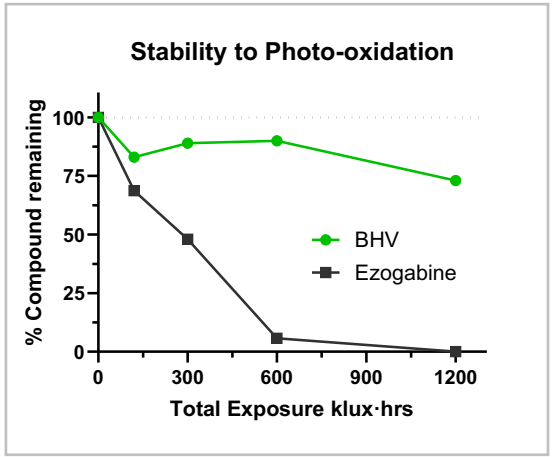


FDA Drug Safety Communication

FDA approves label changes for anti-seizure drug Potiga (ezogabine) describing risk of retinal abnormalities, potential vision loss and skin discoloration.

Program Strategy

- Key points of **differentiation** along the testing cascade
- Development of a **best-in-class** Kv7 Activator

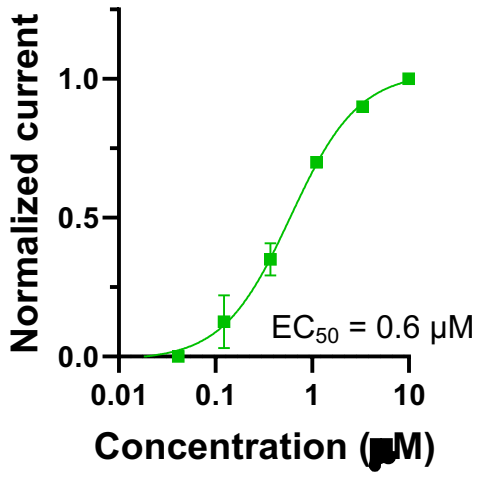
Medicinal chemistry approach	Screening and Tier I ADME	*In vivo*	IND enabling
Novel Scaffold	Functional primary screen	Rodent PK	Photoreactive potential
	Solubility and stability	Anti-seizure activity and tolerability	Genotoxicity
	CYPs, binding MDCK, viability		Second species PK
	Plasma stability		CYP induction, TDI, phenotyping
	Off-target screening (GABA)		Metabolite ID
			Non-GLP tox studies

= Key areas of differentiation to discover and develop best-in-class Kv7 activator

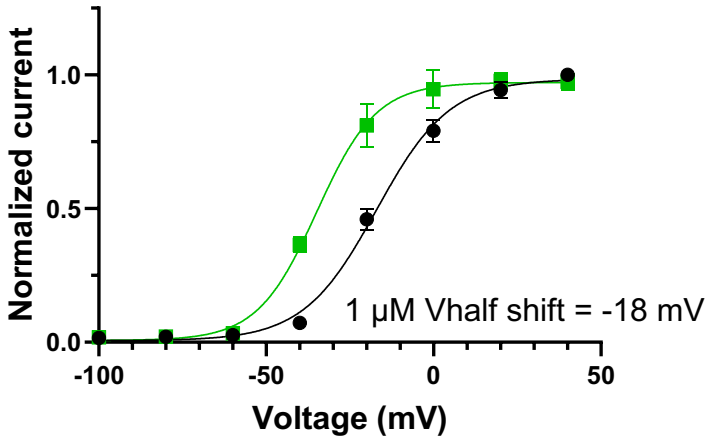
Functional Screening

- Internal screening campaign discovered and characterized BHV-7000
- Activation parameters of Kv7.2/7.3 that promote an increase in open probability

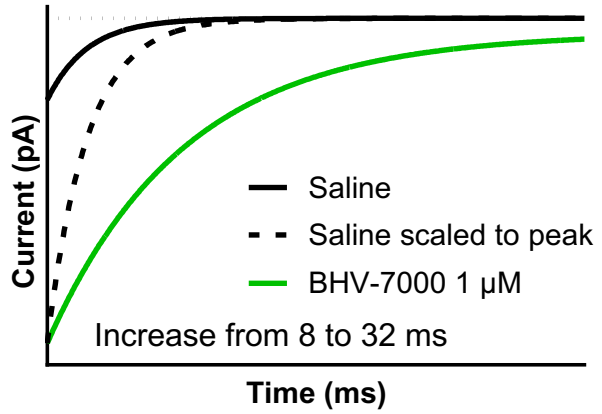
Increase in Current



Shift in Voltage Dependence



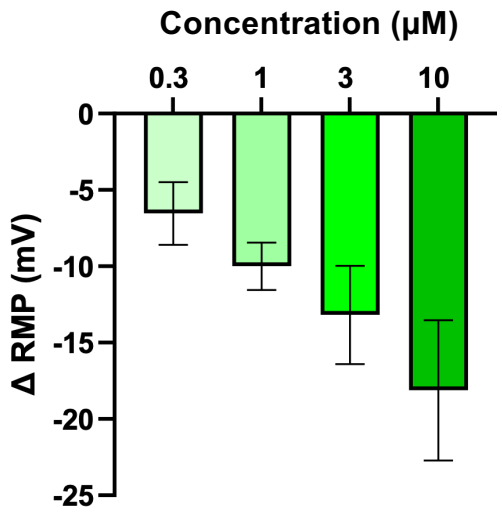
Prolonged Deactivation Kinetics



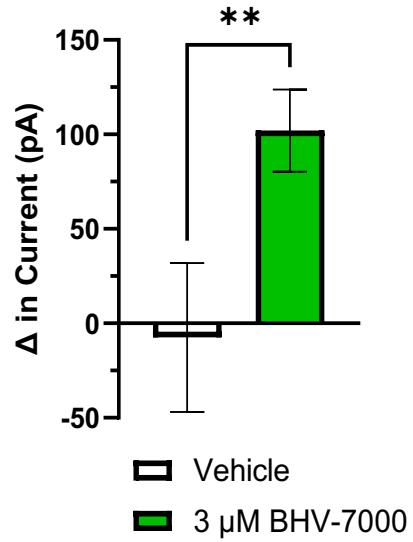
In vitro Characterization

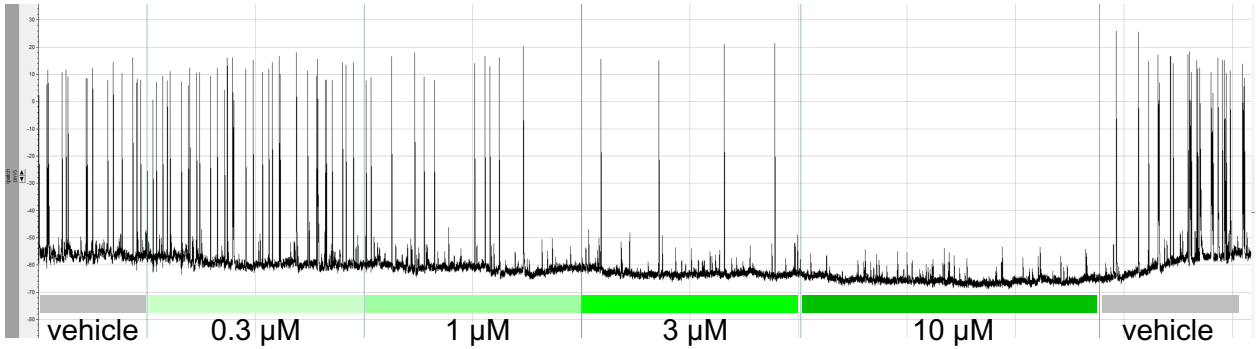
- BHV-7000 modulates cortical neuron excitability
  - Hyperpolarizes the resting membrane potential
  - Increases threshold for action potentials
  - Reduces spontaneous activity

Resting Membrane Potential



AP Threshold





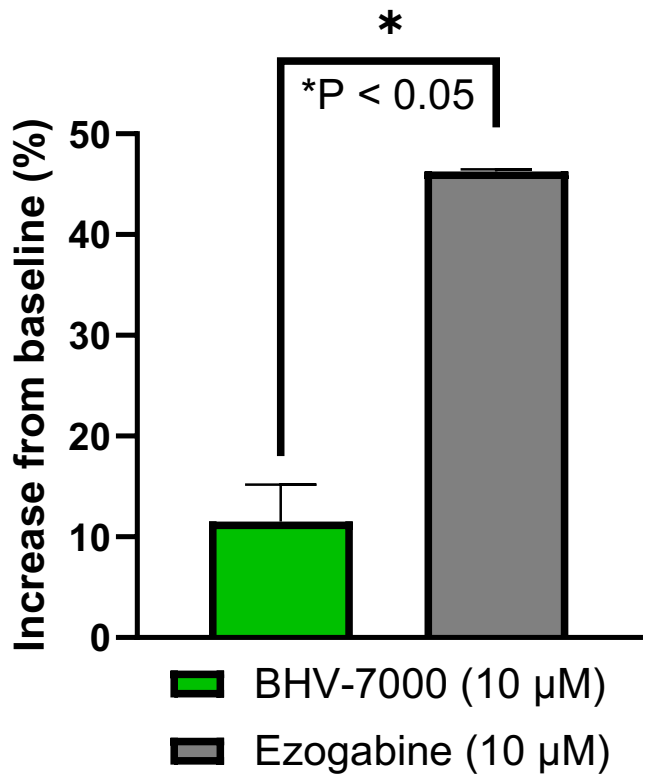
No Significant Off-target Activity

Tested against:

- Binding panel of 55 targets
- Cardiac ion channel screen
- Functional $GABA_AR$ (α1β3γ2) assay

Site and Average inhibition	BZD [^{3}H]flunitrazepam	Cl- channel [^{35}S]TBPS	GABA [^{3}H]GABA
BHV-7000	1	8	-15
Ezogabine	-9	39	-12

$GABA_AR$ Positive Allosteric Modulation

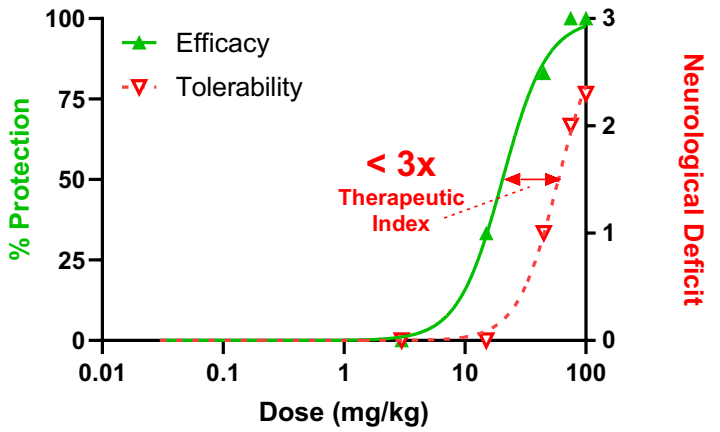


In vivo Efficacy

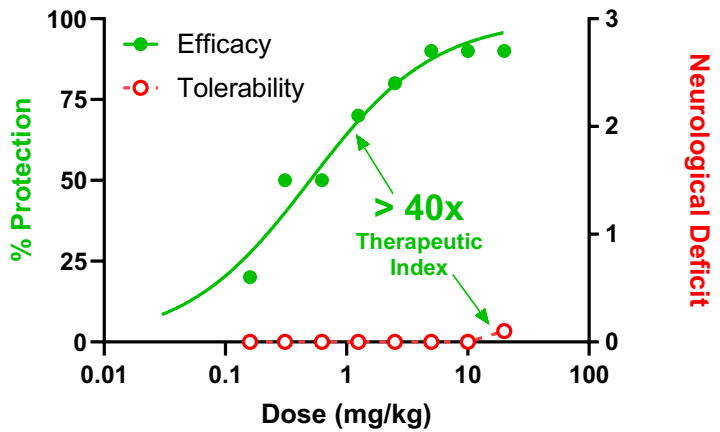
- Efficacious in the rat maximal electroshock model
  - Low brain exposures required for efficacy
  - Well-tolerated as measured by neurological score
  - No impact in rotarod (motor function)

	Ezogabine	BHV-7000
ED50 (mg/kg)	20	0.5
TD50 (mg/kg)	59	>20
Therapeutic Index	~3x	>40x

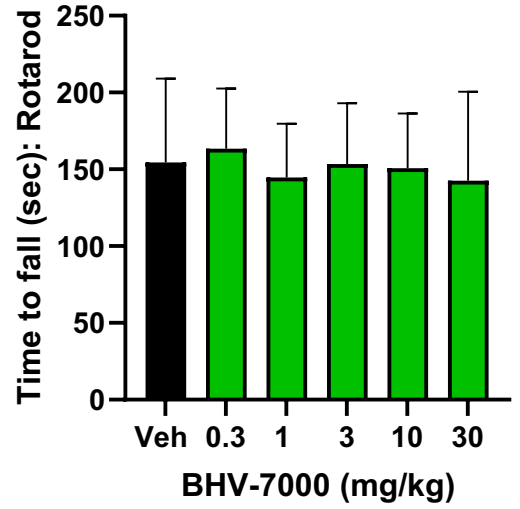
Ezogabine



BHV-7000



Rotarod



Summary

- BHV-7000 is a potent, selective activator of Kv7 potassium channels, a clinically validated target to regulate the hyperexcitable state in epilepsy
- Well-tolerated in Phase 1 SAD/MAD study without dose-limiting CNS adverse effects typically associated with other anti-seizure medications
- Phase 1 EEG biomarker study confirmed evidence of target engagement in the CNS
- Currently in clinical development for focal and generalized epilepsy as well as neuropsychiatric disorders

BHV-7000 posters at AAN:

- P8.007: Phase 1 SAD/MAD Study
- P8.011: Phase 1 EEG Study

Acknowledgements

- Work supported in part by a NIH Blueprint grant 1U44NS093160-01A1
- NIH staff and consultants
- Knopp Biosciences
  - David Mareska
- Biohaven Pharmaceuticals
  - Michael Bozik
  - Steven Dworetzky
  - Andrew Inglis
  - Lynn Resnick

Thank you!