CNS Assets Presentation

May 2025

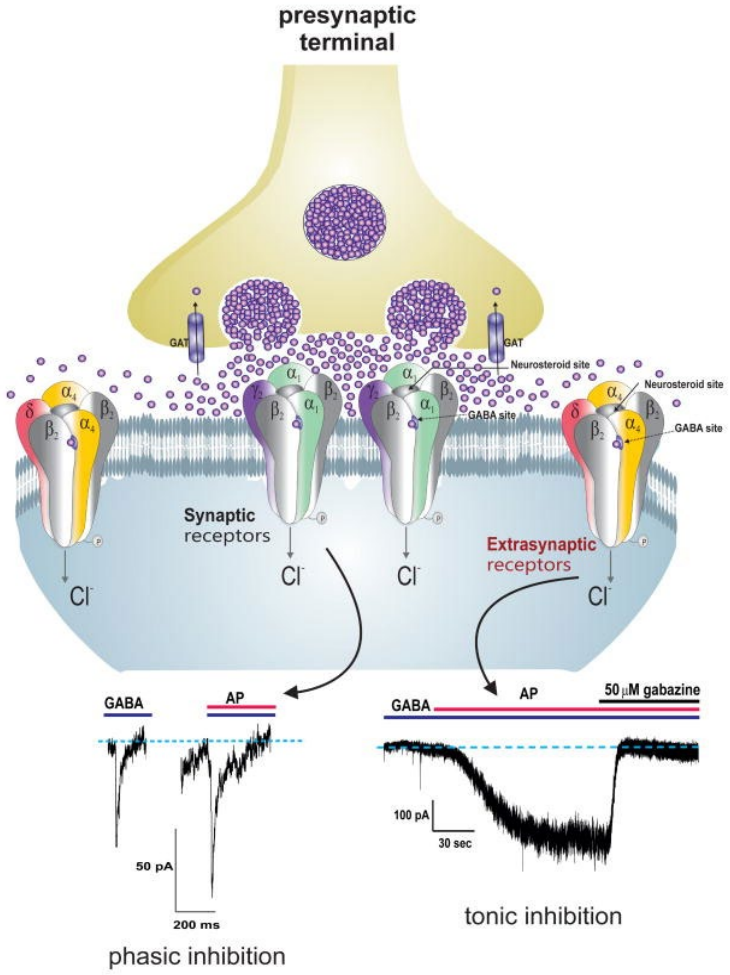
LIPOCINE®
ENHANCING HEALTH

LPCN 2101

Endogenous Neuroactive Steroid
for Epilepsy

LPCN 2101: Positive Allosteric Modulator (PAM) of the $GABA_A$ receptor

Lipocine Endogenous Neuroactive Steroid Epilepsy Targets



Women With Epilepsy (WWE)

Focal Onset Seizure (FOS)

Acute Repetitive Seizure (ARS)

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Reddy and Estes, Trends Pharmacol Sci 2016

Anti-Seizures Activities of NAS and AEDs in Preclinical Models

Neurosteroid	Tonic currents		Seizure protection
	$E_{1\,\mu M}$ (pA)[a]	$EF_{(2\text{-fold GABA})}$ (nM)[b]	ED_{50} (mg kg^{-1})[c]
Brexanolone (AP)	100.6	80	4.2 (2.7-5.8)
Ganaxolone	64.0	290	1.5 (1.3-1.7)
Pregnanolone	44.4	780	7.7 (6.6-8.8)
Isopregnanolone	15.3	> 10 000	> 100
Allotetrahydrodeoxycorticosterone (THDOC)	66.6	410	5.0 (2.6-7.4)
Alfaxolone	40.9	990	8.8 (6.1-11.4)
ORG-20599	86.4	120	18.6 (16.6-20.6)
Androstanediol	33.2	1710	44.0 (30.2-58.8)

[a] $E_{1\,\mu M}$ values represent the mean normalized tonic current responses of drug at 1 μM concentration co-applied with 1 μM GABA. GABA 1 μM tonic current: 0.66 ± 0.22 pA/pF, 19.6 pA.

[b] EF values represent the effective functional concentration of drug (nM) required to double or triple the 1 μM GABA response.

[c] ED_{50} values represent the dose (mg kg^{-1}) that protected 50% of animals in the 6 Hz seizure stimulation test. 95% confidence intervals are listed in parenthesis, according to a normal distribution. Data adapted with permission from Carver and Reddy (Ref. 29).

Reddy DS Journal of Neuroendocrinology. 2021;00:e13028
https://doi.org/10.1111/jne.13028

	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)
Ezogabine	29.51	>50	33	>50	12.1
XEN1101	6.1 (2.2)	3.9	9.86	2.59	3.7
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

Epilepsy Foundation Pipeline Conference 2018

- **Neuroactive steroids (NAS) activities in protection of mice in most of the tonic and/or clonic and generalized seizures induced by PTZ, Pilocarpine, Kainic Acid, Picrotoxin, Bicuculline, Metrazol and NMDA**

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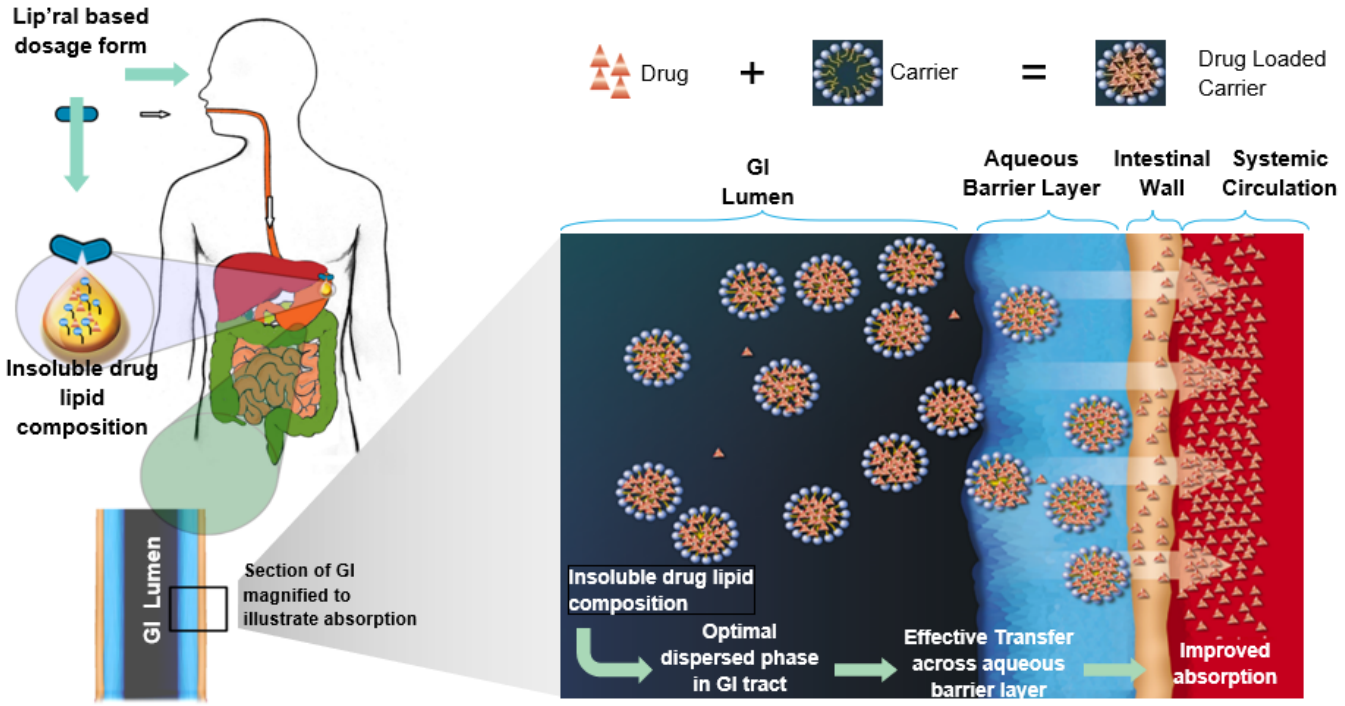
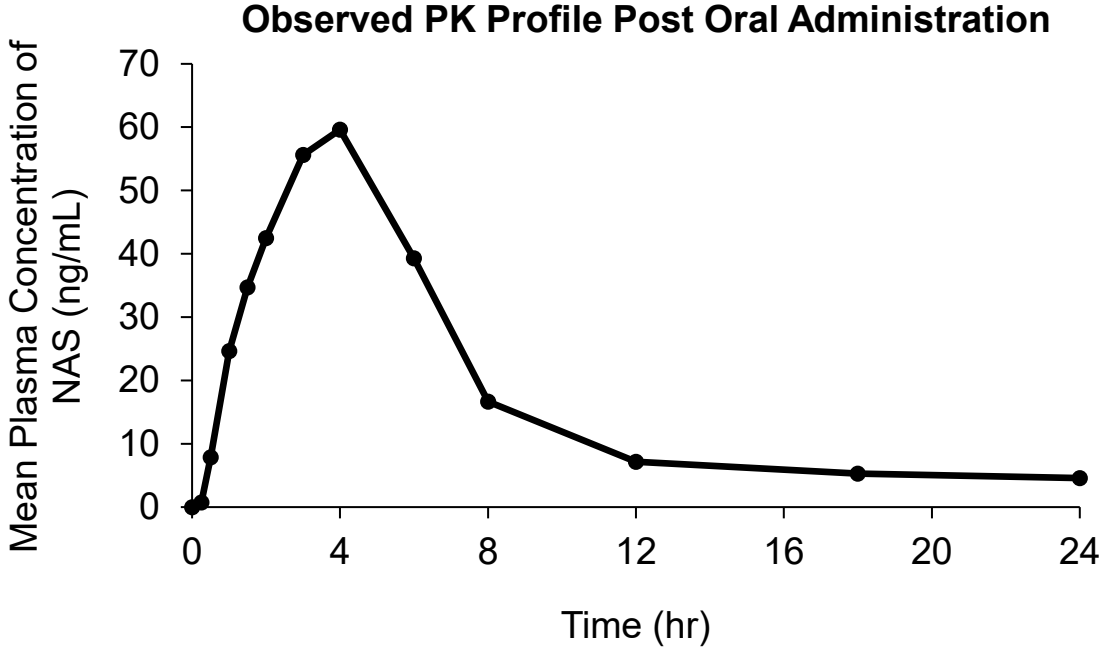
Validated Proprietary Lip'ral Technology Platform

Oral Enablement of Neuroactive Steroid (NAS)

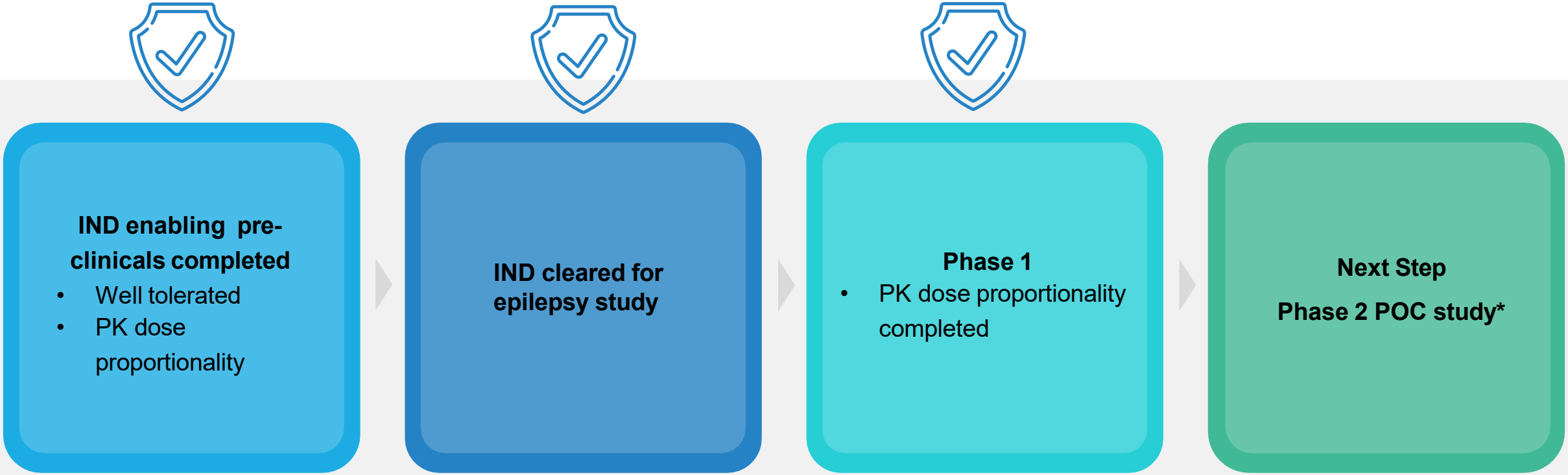


Achieved Relevant Systemic Levels in Phase 1 Study



Study in post-menopausal women (n=12) with Lip'ral based oral dosage form

LPCN 2101 Development Status



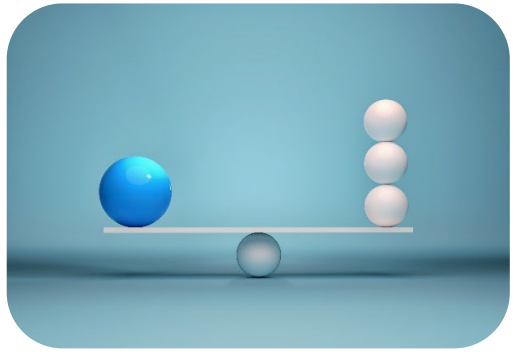
*Photosensitive epilepsy for NAS and dose evaluation under consideration

Woman with Epilepsy (WWE)

Women with Epilepsy (WWE) of Childbearing Age

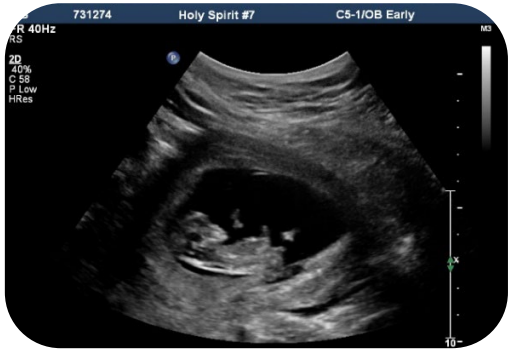
900,000 of childbearing age women suffer from active epilepsy in US

Treatment Challenges for WWE



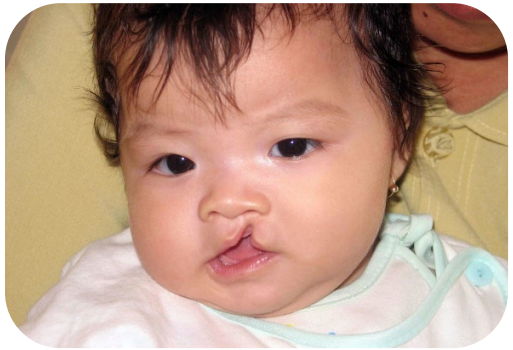
Seizure Control

- Drug-drug interaction



Pre-Pregnancy

- Planned pregnancy
  - AED selection
- Unplanned pregnancy
  - Contraception failure



Pregnancy

- Fetal/neonatal toxicity
- Adherence to AEDs
- Lowest effective dose, monotherapy AED preferred

Comorbidities

- Anxiety
- Depression

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AED = Antiepileptic Drug

S.Bangar et al. Functional Neurology 2016; 31(3): 127-134
Reimers et al. Seizure. 2015 May;28:66-70.

Women with Epilepsy (WWE) of Childbearing Age - Opportunity

Prevalence

~ 900,000 of women of childbearing (CB) suffer from active epilepsy in US[1,2]

~ 80% of WWE reported at least one unintended pregnancy[3]

Depression is the most frequent psychiatric comorbidity in epilepsy[4]

Standard of Care Limitations

No drug approved specifically for WWE

Most approved ASMs have fetal toxicity risk

~ One third of adult patients are non-responsive[5]

Limited options to address mood disorder comorbidities

Drug-drug interaction risk

Unmet Need

Seizure control with low/no teratogenic risk

Address special considerations for WWE

Novel MOA

Address associated mood disorders

1. https://www statista.com/statistics/241488/population-of-the-us-by-sex-and-age/
2. https://www cdc.gov/mmwr/volumes/66/wr/mm6631a1.htm
3. Herzog et al. Neurology. 2017 Feb 21;88(8):728-733
4. Kanner AD, Epilepsy Curr. 2006 Sep; 6(5): 141–146
5. https://www epilepsy.com/treatment/medicines/drug-resistant-epilepsy

ASM = Antiseizure Medication

LPCN 2101

Novel Potential Alternative for WWE

Product Attributes

Positive Allosteric Modulator (PAM) of the $GABA_A$ receptor

Oral dosage form comprising a neuroactive steroid

Product Candidate Differentiation

Novel MOA specifically addressing WWE unmet needs

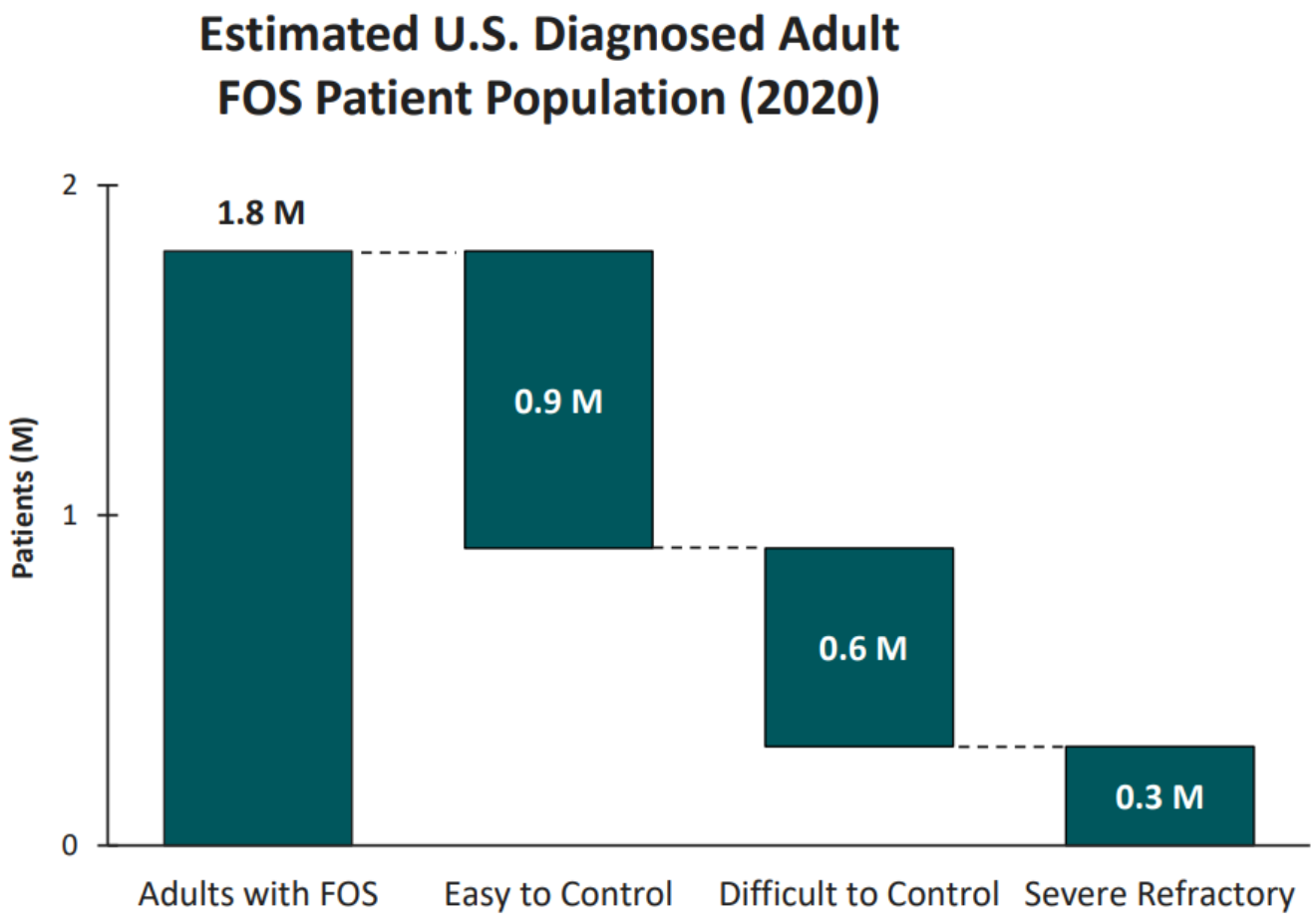
Active molecule is endogenous to women

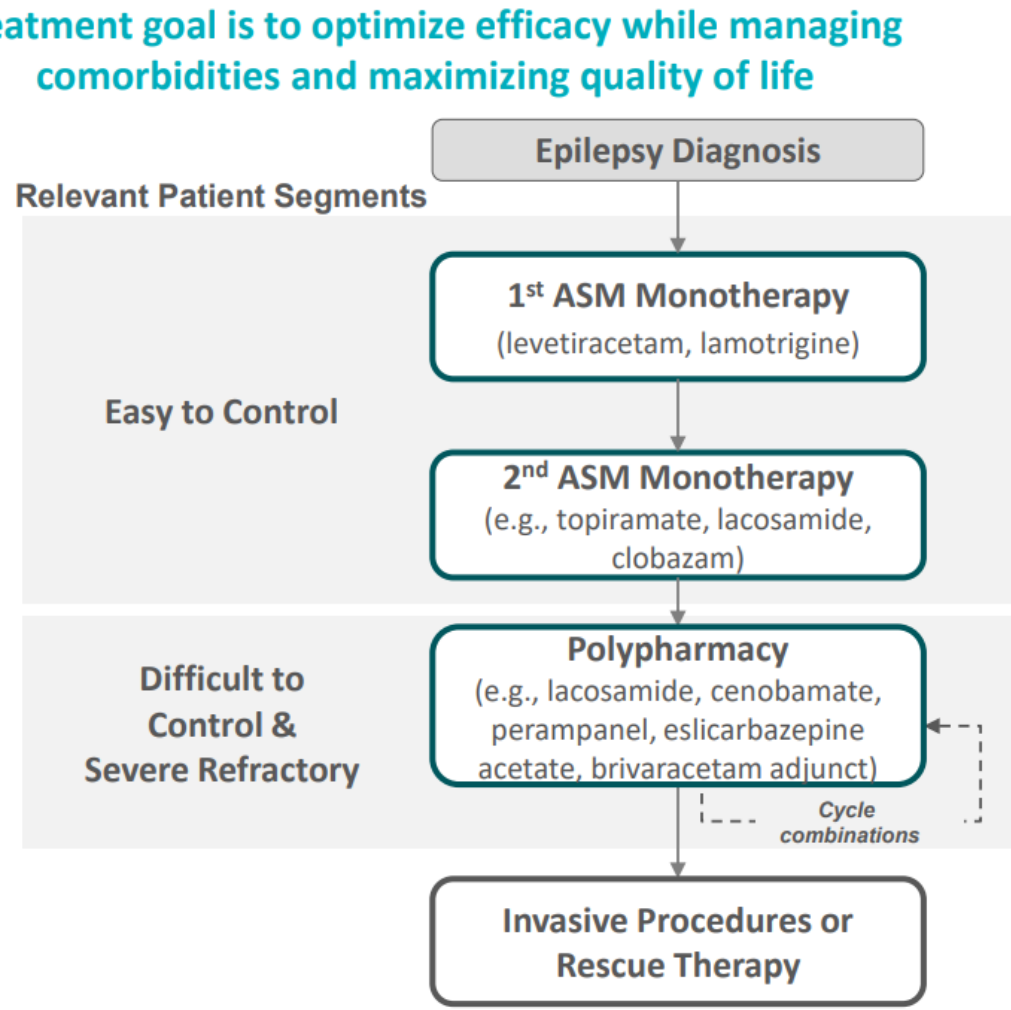
Potential to address psychiatric comorbidities (depression, anxiety, sleep disorders)

No significant drug-drug interactions are expected

Focal Onset Seizure (FOS)

Adult Focal Onset Seizure Landscape

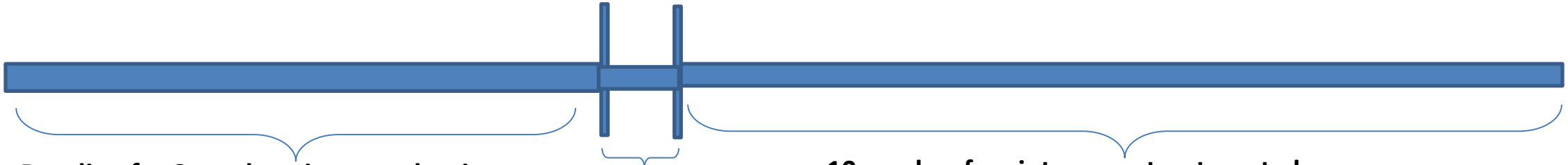




Source: Xenon sponsored market research

Typical POC & Pivotal Trial Design

Multicenter, double blind, randomized placebo-controlled adjunct therapy design for focal onset seizures



Baseline for 8 weeks seizure evaluation
- Average of ≥ 4 seizures in 28 days

Two weeks dose – ramp

10 weeks of maintenance treatment phase
- seizure frequency: Median and % CBL as primary endpoint
- Responder rate (≥ 50%) as secondary endpoint

- Follow up period for about 2 weeks
- Typically, about 100 subjects per arm
- At least two clinical trials to show the statistical significance for the difference between active and placebo arm

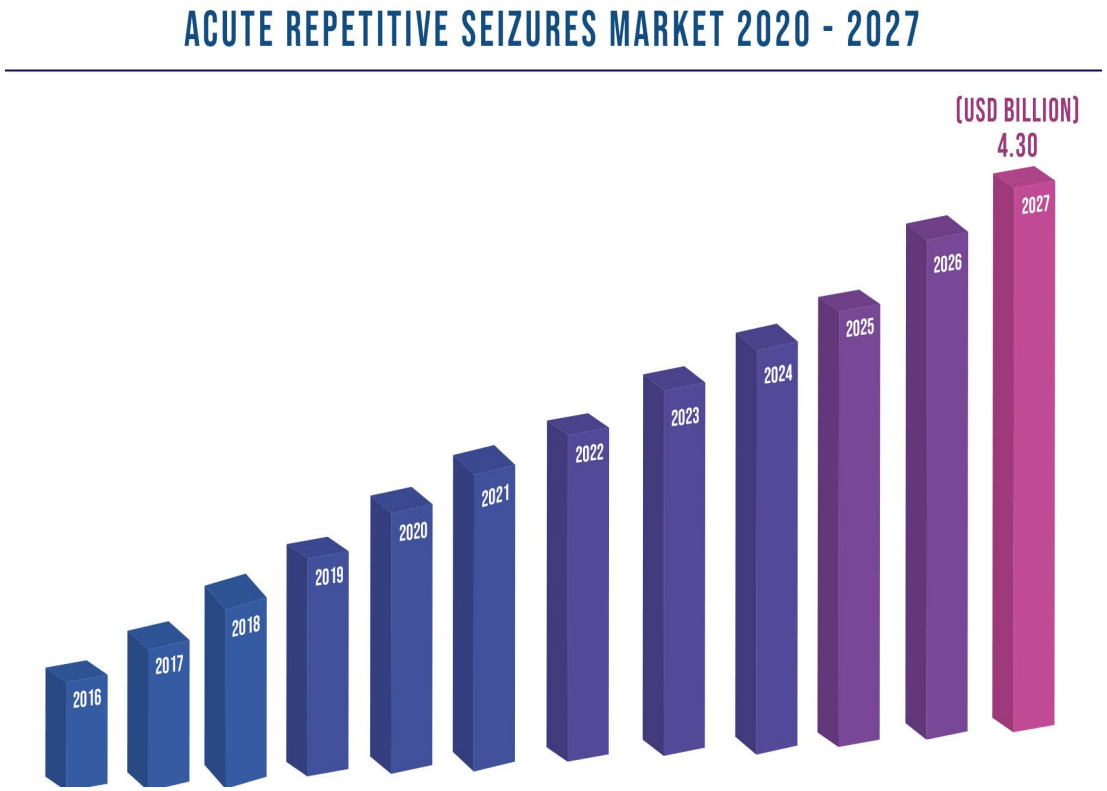
Acute Repetitive Seizure (ARS)

Potential for Orphan Drug Designation

ACUTE REPETITIVE SEIZURE (ARS) PREVALENCE AND MARKET POTENTIAL

MARKET SIZE TO SURPASS AROUND US$ 4.3 BN BY 2027

- Many names: **Cluster seizures**, serial seizures, crescendo seizures, seizure flurries, recurrent seizures, or cyclical seizures
- More than 2-3 seizures in 24 hours, or in some studies in 6-8 hours
- Associated with an evolution into status epilepticus
- More than **150,000 people in the U.S**. with uncontrolled epilepsy also experience seizure clusters



https://www.globenewswire.com/en/news-release/2020/12/14/2144602/0/en/Acute-Repetitive-Seizures-Market-Size-to-Surpass-Around-US-4-3-Bn-by-2027.html

Press Release: UCB Announces availability of NAYZILAM® (midazolam) Nasal Spray CIV, the first and only nasal rescue treatment for seizure clusters in the U.S. | UCB (ucb-usa.com) Zack M, R Kobau. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy. CDC MMWR. 2017. 66:821-825.
Kwan P, M Brodie. Early Identification of Refractory Epilepsy. NEJM. 2005. 342:314-319.
Chen B, Choi H, Hirsch L, et al. Prevalence and risk factors of seizure clusters in adult patients with epilepsy. Epilepsy Res. 2017;133:98-102.

https://www.epilepsyfoundationmn.org/2020/01/14/acute-repetitive-seizures-ars-or-cluster-seizures/

CANDIDATE ATTRIBUTES FOR ARS INDICATION

Fast onset: Tmax: ≤ 90 min*

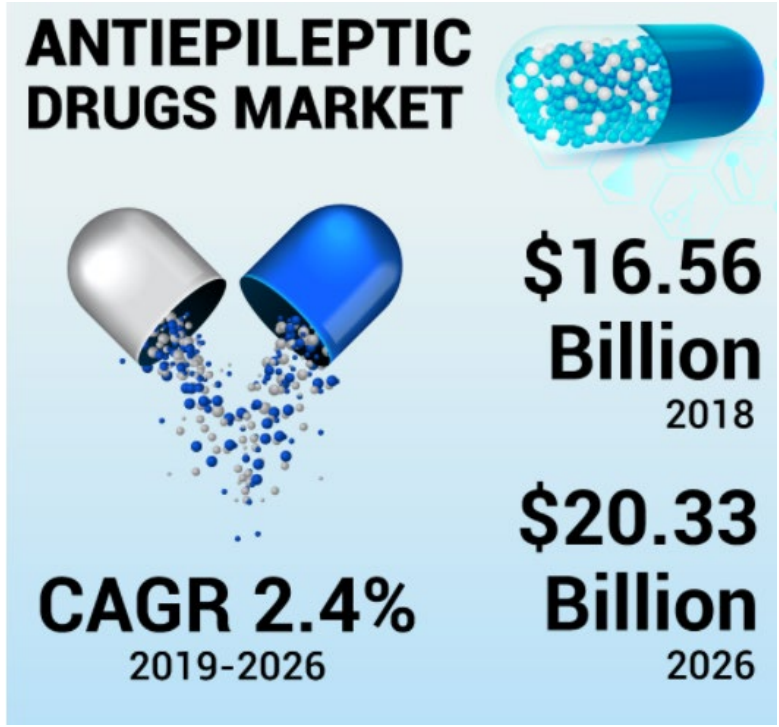
Endogenous NAS

Bioavailable through oral administration*

Easy to administer

Portability

*Based on Lipocine Phase 1 studies results



ANTI-EPILEPTIC DRUG (AED) MARKET POTENTIAL

HTTPS://WWW.FORTUNEBUSINESSINSIGHTS.COM/INDUSTRY-REPORTS/SEGMENTATION/ANTIEPILEPTIC-DRUG-MARKET-101189

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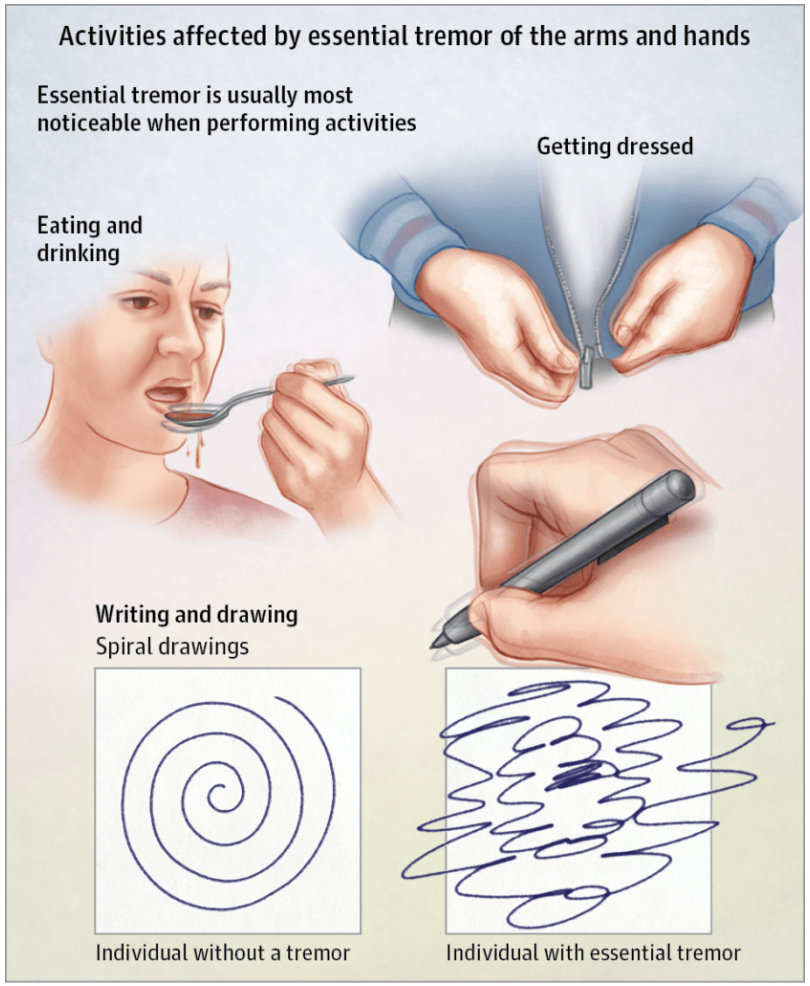
LPCN 2203

Oral NAS for Essential Tremor

Essential Tremor (ET)

No new drug approved in 50+ years



- Tremor highly disabling and stigmatizing
- Stress can aggravate tremor in social setting
- Major impact on activities of daily living leading to unemployment, anxiety and depression[1]
  - Most common impacts on activities of daily living are pouring liquids and writing/typing (100%) and grooming/hygiene, drinking, dressing, eating, and reading (80-85%)
  - 90% of participants indicated the emotional impact of ET
  - 75% reported tremor-related worry or anxiety
- Majority of patients require caregiving[1]

Picture:: https://birminghamhandandplasticsurgery.com/essential-tremors-birmingham-hand-surgery/
1. Gerbasi et al. Patient experiences in essential tremor: Mapping functional impacts to existing measures using qualitative research. MDS 2023.

ET Patient Journey and Commonly used medications

- First line treatment of propranolol frequently started at PCP
- 2nd and 3rd line treatments (e.g., primidone, benzodiazepine, gabapentin, topiramate) at general neurologist and movement disorder clinics
- Patient survey indicates on-going management by PCP (26%), general neurologist (23%), movement disorder specialist (19%)

ESSENTIAL TREMOR: COMMONLY USED MEDICATIONS

DRUG	PROPRANOLOL	PRIMIDONE	GABAPENTIN	ALPRAZOLAM	TOPIRAMATE	NIMODIPINE	ZONIZAMIDE
Brand	Inderal ®	Mysoline ®	Neurontin ®	Xanax ®	Topamax ®	Nimotop ®	Zonegran
Use in ET I	1st line	1st line	2nd line	2nd line	2nd line	3rd line	3rd line
Class	beta-blocker	anti-convulsant	AED	anti-anxiety	AED	vasodilator	AED
MoA	beta blocker	barbiturate	GABA analog	benzodiazepine	complex	L-type Ca2+ chan.	CA inhibitor
daily dosing / frequency	80-160 mg BID	50-250 mg every bedtime	100-300 mg TID	up to 3mg TID	150-300 mg BID	120 mg QID	
Evidence-level	Level A; FDA approved	Level A	Level B	Level B	Level B	Level C	Insuff. Evidence
Response rate	~40-60%	~30-50%	30%	75%	30-40%	50%	50%
Tremor Reduction	50%	50-70%	30-40%	50%	20-37%	50%	25%
dropout rate	20-35%	20-30%	10%	<10%	30%	unknown	unknown
Side Effects	44.90% AE dizziness, fatigue	72% AE flu like symptoms significant sedation	"Generally well tolerated" sedation, dizziness, ataxia, weight gain in 30-40% pts	sedation, cognitive impairment,	concentration difficulties,somnelence, fatigue	hypotension, edema, headaches in 10-20% pts	trouble concentrating, body aches, flu symptoms, sore mouth; back pain
Alcohol DDI	Moderate	Major	can increase side effects	increased effects of EtOH	moderate, can increase side effects	moderate additive effect	can increase side effects
Number of major DDI	68	232	7	138	360	53	361

Essential Tremor Management – Opportunity

Daytime efficacy and improved tolerability remains an unmet need

Prevalence

- ~7 million patients in US[1]
- Estimated that only ~40% of patients are diagnosed
- Propranolol is the first line therapy
- 65% in need of 2nd line treatment
- ~44% of diagnosed patients treated with propranolol or primidone[2]

Standard of Care Limitations

Unfavorable benefit to risk profile[3]

- Most of patients are intolerant or have an inadequate response to first line propranolol or primidone
- 33% experienced no benefit from propranolol and 35% discontinued due to side effects
- 17% reported no benefit from primidone and 23% discontinued due to side effects

Unmet Need

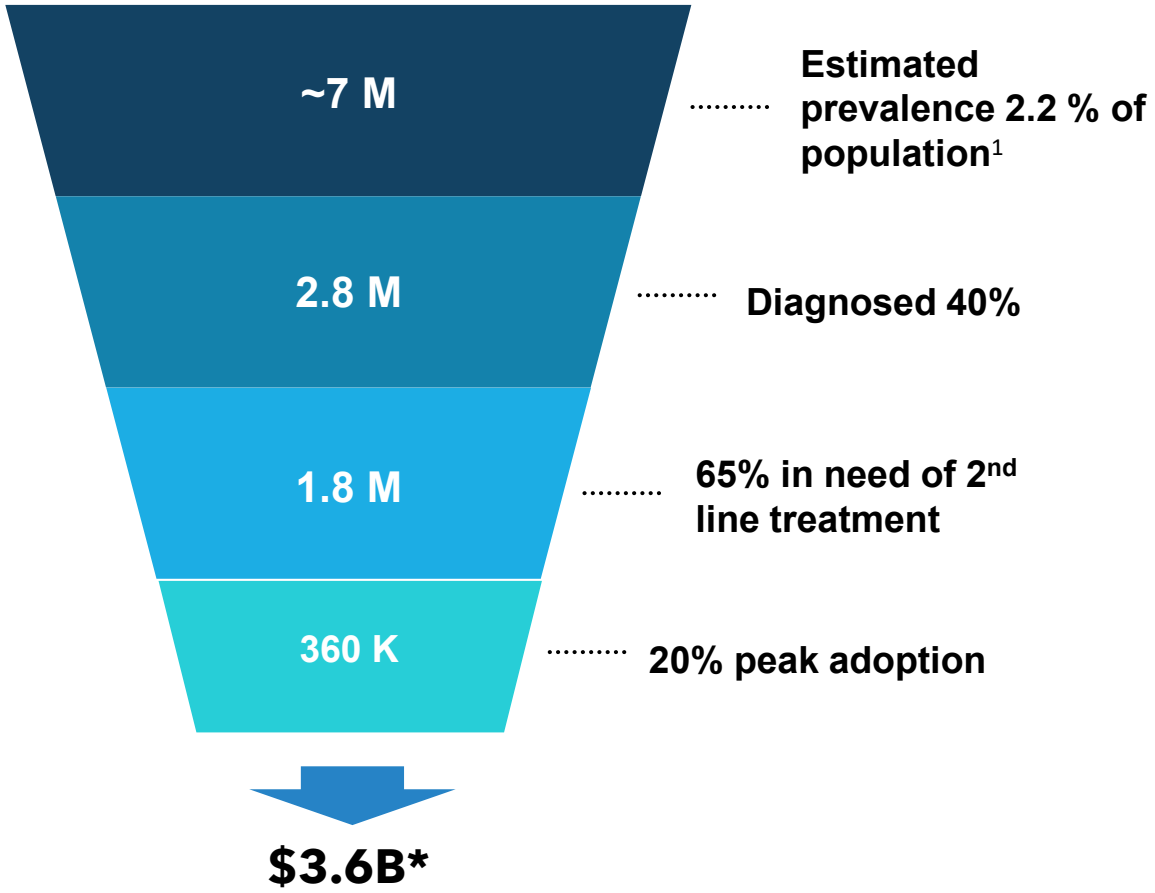
Superior benefit to risk profile

- Improve efficacy
- Fewer side effects
  - somnolence
  - dizziness
- Address anxiety/depression comorbidity
- Disease-modifying effects

1. Louis ED, Ottman R. Tremor Other Hyperkinet Mov (N Y). 2014;4:259
2. Vetterick et al. Adv Ther. 2022; 39(12): 5546–5567
3. Clinical Parkinsonism & Related Disorders 5 (2021) 100101

Market Potential and Competitive Development Landscape

$3B+ blockbuster opportunity as 2nd line with 20% peak adoption



Products in Development*

SAGE-324: Adverse events - somnolence 68%, dizziness 38%, balance disorder 15%, diplopia 12%, dysarthria 12%, and gait disturbance 12%

38% discontinuation due to at least 1 AE

PRAX-944: Dizziness 14%, constipation 10%, headache 9%, fatigue 9%, anxiety 7%, feel abnormal 7%, paraesthesia 7%

JZP-385: Adverse events included dizziness (21% vs 6% in placebo), somnolence 2%

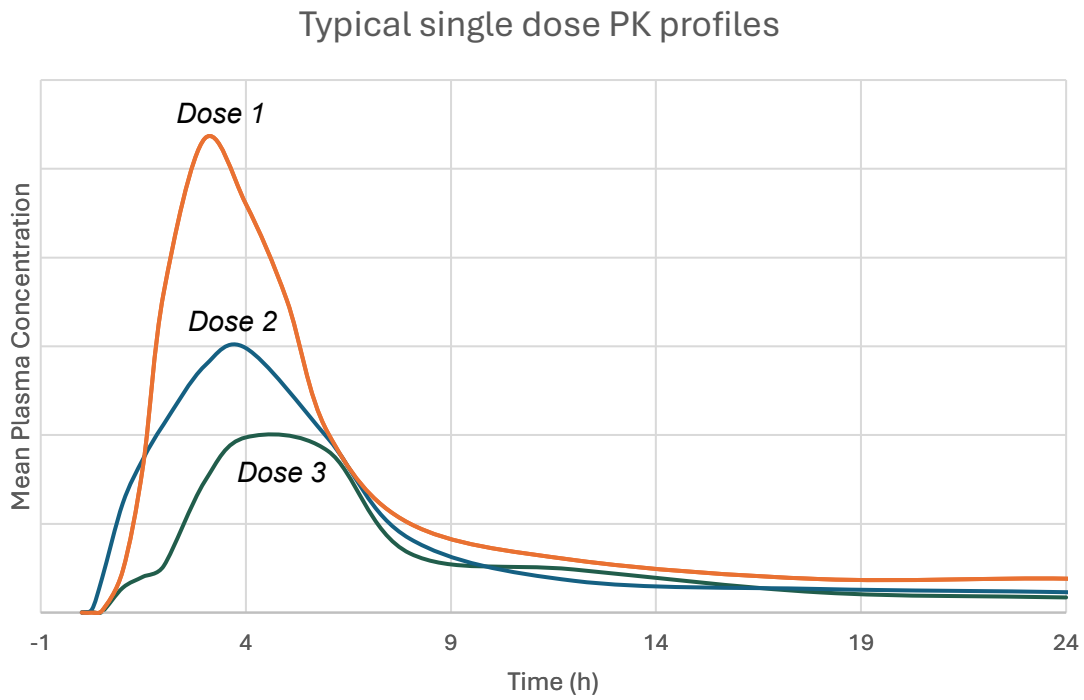
17% vs 4% discontinuation due to at least 1 AE

1. Louis ED, Ottman R. Tremor Other Hyperkinet Mov (N Y). 2014;4:259
*indicative pricing ~ $10K/patient/year

https://www.sagerx.com/
https://www.jazzpharma.com/
https://praxismedicines.com/
*Phase 2 data reported in public domains

LPCN 2203: Oral GABA Positive Allosteric Modulator

Achieved relevant target levels with good tolerability in Phase 1 studies



LPCN 2203 TEAEs

Clinical Study Experience, N=28, 304 doses:

- LOC 0%
- Somnolence, sedation 0%
- Dizziness, presyncope, vertigo 0%

LPCN Product Target Differentiation

Novel MOA

Favorable benefit to risk profile

Daytime efficacy

Endogenous NAS

Potential to address anxiety and depression comorbidities

Appendix

LPCN 2101 Additional Potential Indications

Other Convulsion Disorders

- Status epilepticus (SE)
- Catamenial epilepsy
- Generalized onset seizures
- Absence seizures
- Lennox-Gastaut Syndrome
- Dravet Syndrome

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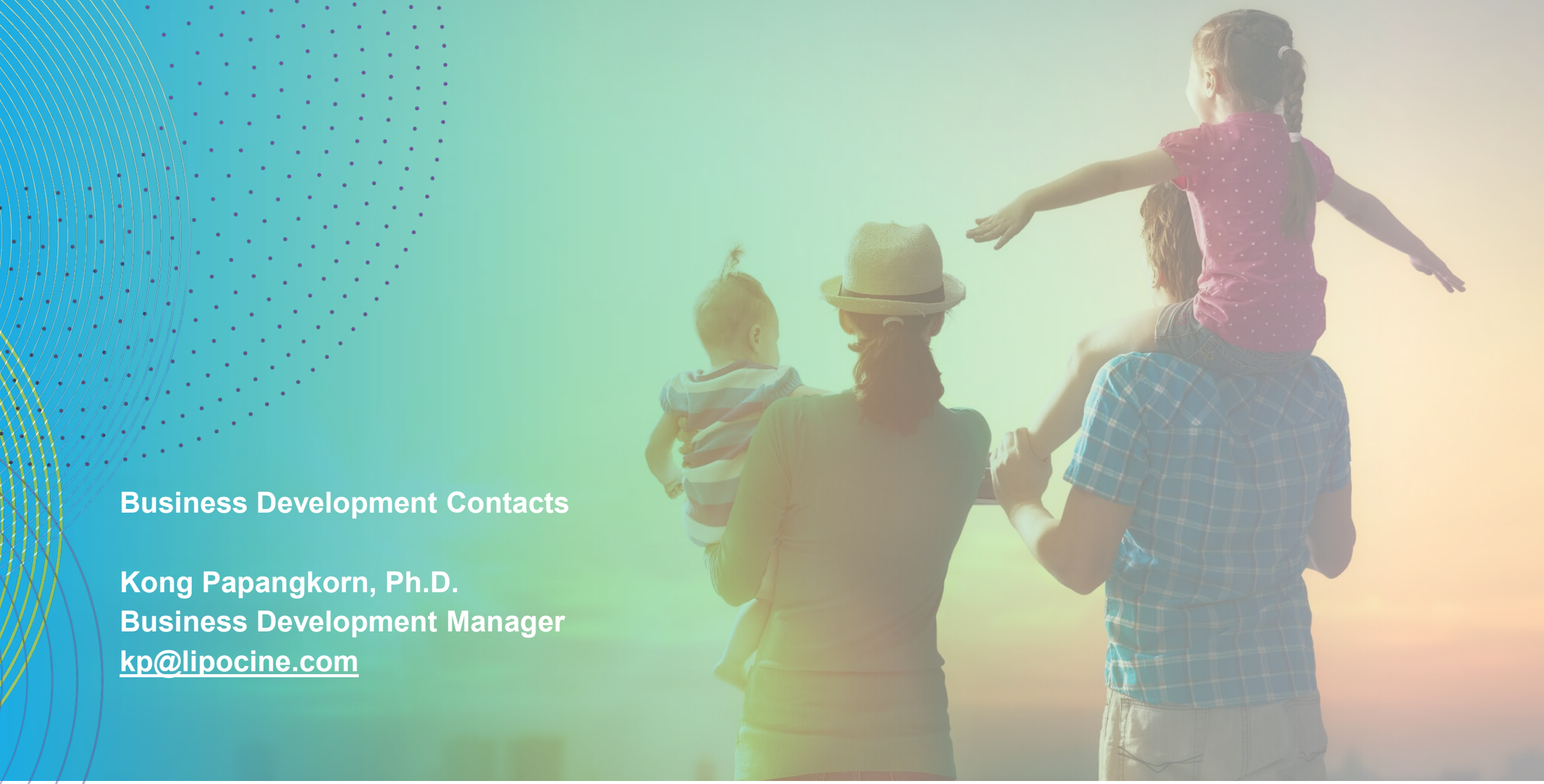
Mechanism of Action of AEDs Related to $GABA_A$ receptor Support LPCN 2101 MOA

TABLE 1. *Main mechanisms of actions of old- and new-generation AEDs*

	Blockade of voltage-dependent sodium channels	Increase in brain or synaptic GABA levels	Selective potentiation of $GABA_A$-mediated responses	Direct facilitation of chloride ion influx	Blockade of calcium channels	Other actions
First-generation AEDs						
Benzodiazepines	–	–	++	–	–	–
Carbamazepine	++	?	–	–	+ (L-type)	+
Ethosuximide	–	–	–	–	++ (T-type)	–
Phenobarbital	–	+	+	++	?	+
Phenytoin	++	–	–	–	?	+
Valproic acid	?	+	?	–	+ (T-type)	++
Second-generation AEDs						
Felbamate	++	+	+	–	+ (L-type)	+
Gabapentin	?	?	–	–	++ (N-, P/Q-type)	?
Lamotrigine	++	+	–	–	++ (N-, P/Q-, R-, T-type)	+
Levetiracetam	–	?	+	–	+ (N-type)	++
Oxcarbazepine	++	?	–	–	+ (N- and P-type)	+
Pregabalin	–	–	–	–	++ (N-, P/Q-type)	–
Tiagabine	–	++	–	–	–	–
Topiramate	++	+	+	–	+ (L-type)	+
Vigabatrin	–	++	–	–	–	–
Zonisamide	++	?	–	–	++ (N-,P-,T-type)	+

++, Primary action; +, secondary action; -, no action described; ?, controversial evidence; GABA, γ-aminobutyric acid. Modified from Perucca (8).



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