
PRAXIS
DARE FOR MORE™
PRAX-628
March 26, 2024

Forward-looking statements

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For further information regarding the risks, uncertainties and other factors that may cause differences between our expectations and actual results, you should review the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2023 and other filings with the Securities and Exchange Commission.

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Today's Agenda

MARCIO SOUZA

- **PRAX-628 – Poised to revolutionize the epilepsy treatment paradigm**

STEVE PETROU, Ph.D.

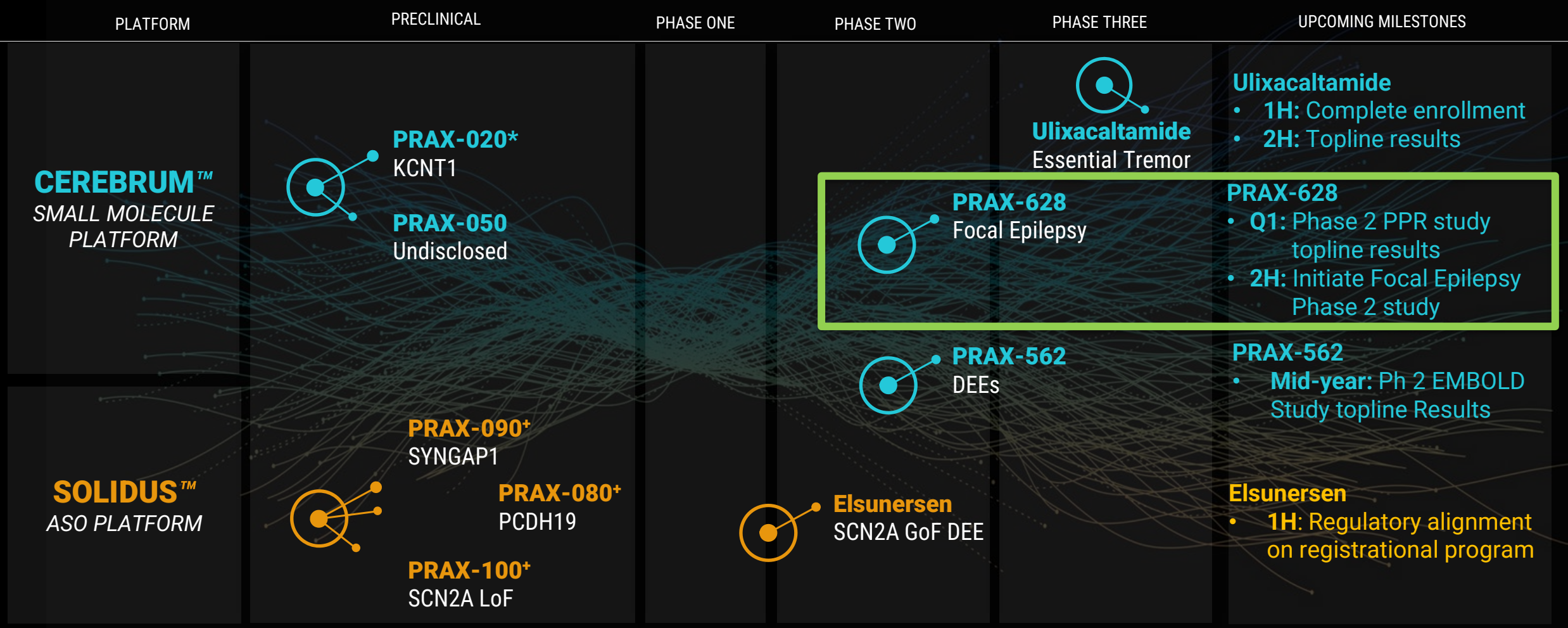
- **Photoparoxysmal response in photosensitive epilepsy – Study topline results**

DANIEL FRIEDMAN, M.D., MSc.

- **Perspectives from Clinical Practice**

Q&A SESSION

Four clinical stage assets and multitude of early-stage programs



*PRAX-020 (KCNT1) is a research collaboration with UCB

+PRAX-080 (PCDH19), PRAX-090 (SYNGAP1) & PRAX-100 (SCN2A-LoF) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health

The Praxis epilepsy portfolio targets significant unmet need in both the common and rare epilepsy markets

Praxis Epilepsy Portfolio

PRAX-628

PRAX-020[2]
PRAX-080[3]
PRAX-090[3]
PRAX-100[3]
PRAX-222
PRAX-562

3.5M

US Prevalence for Common Epilepsy

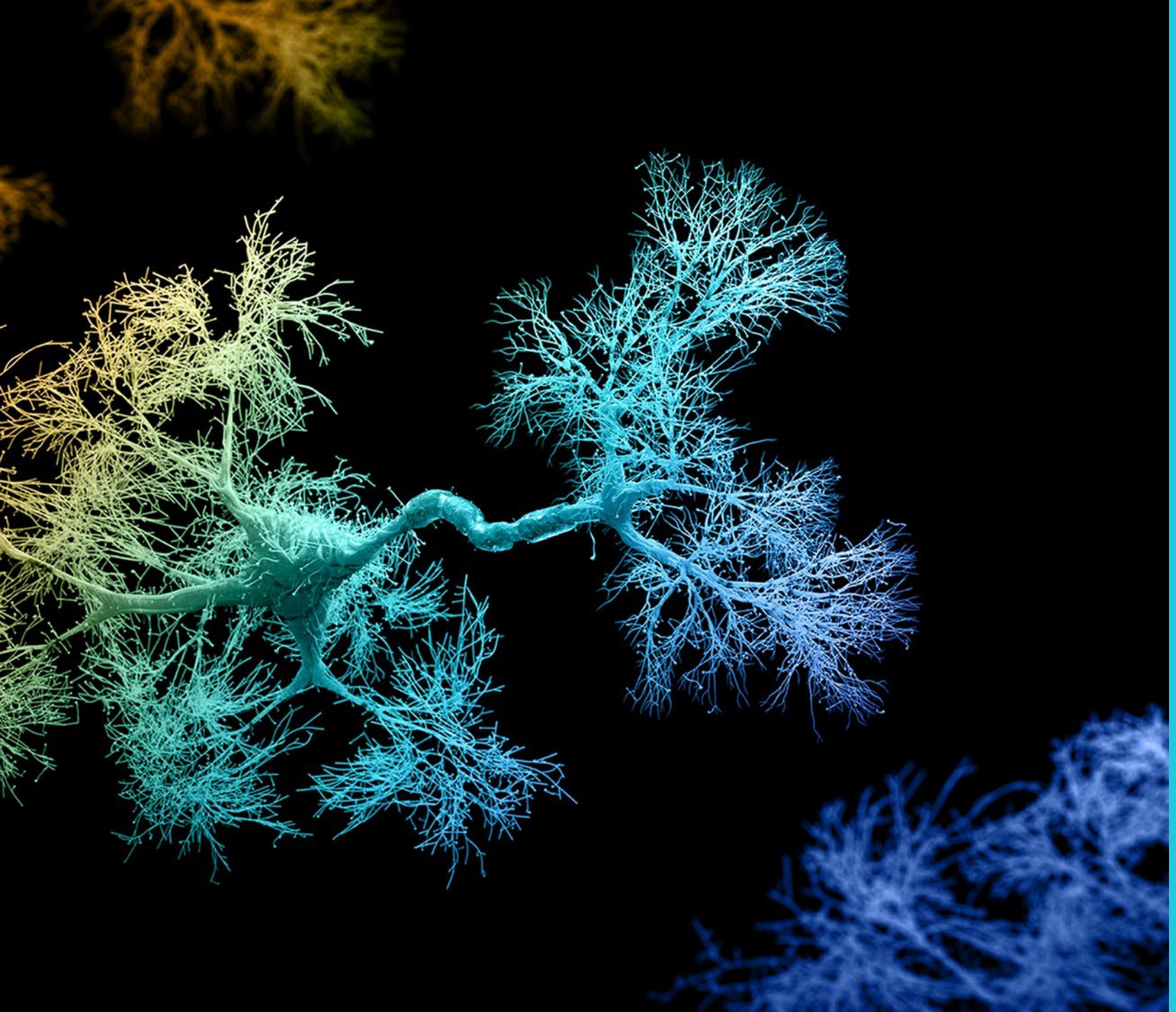
14K+

US Prevalence for Rare Epilepsies covered by Praxis' Portfolio[1]

>$3B+

US Common and Developmental Epilepsy Market Opportunity

[1] SCN2A Gof, SCN2A LoF, SYNGAP1, PCDH19, SCN8A, KCNT1 developmental epilepsies
[2] PRAX-020 (KCNT1) is a research collaboration with UCB
[3] PRAX-080 (PCDH19), PRAX-090 (SYNGAP1) & PRAX-100 (SCN2A-LoF) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health



PRAX-628

PRAX-628 has presented an ideal precision ASM profile

Ideal Treatment

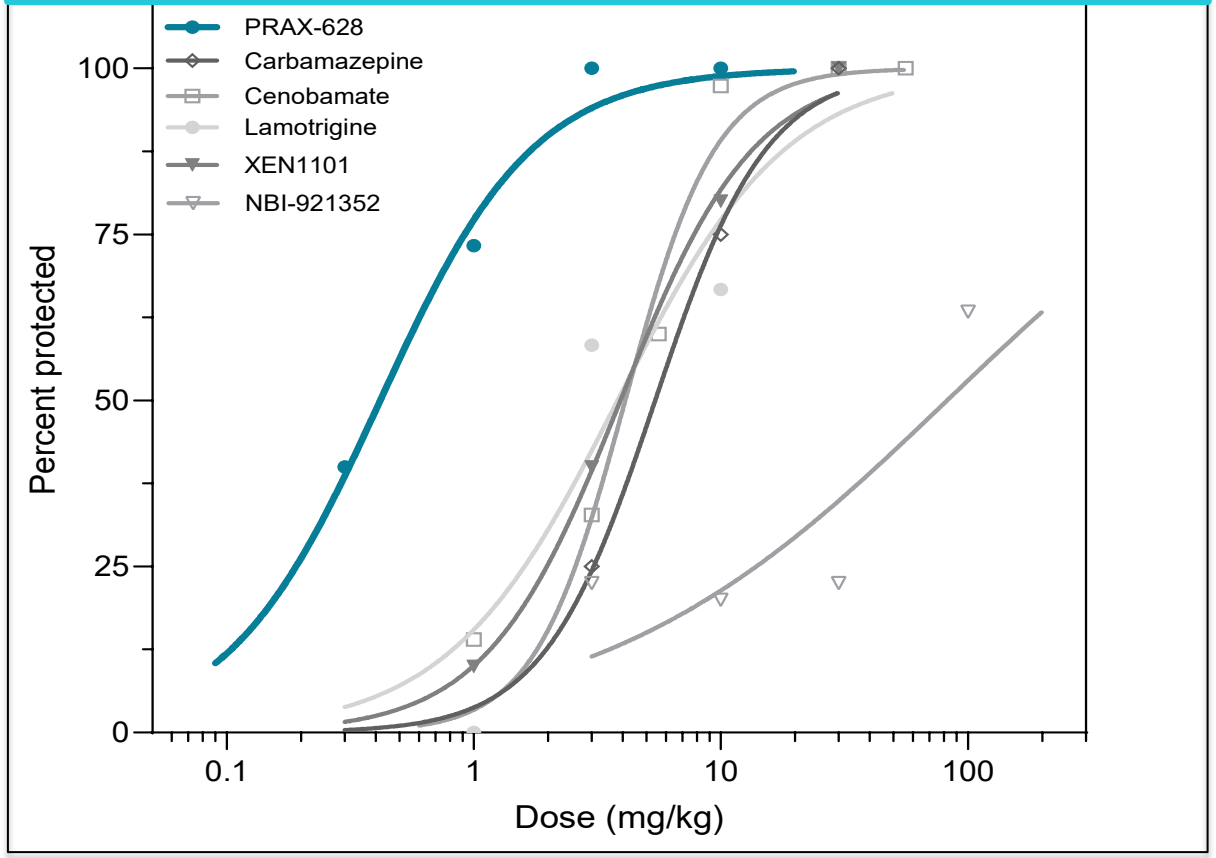
- Significantly more potent than competitive molecules in highly translatable pre-clinical models
- Rapidly achieves therapeutic concentrations after once-daily dose
- Ability to significantly exceed therapeutic concentrations while well tolerated
- Proof of concept in epilepsy patients achieved

Poised to revolutionize the epilepsy treatment paradigm

Significantly more potent than competitive molecules in highly translatable pre-clinical models

Ideal Treatment

PRAX-628 has differentiated potency in the MES model



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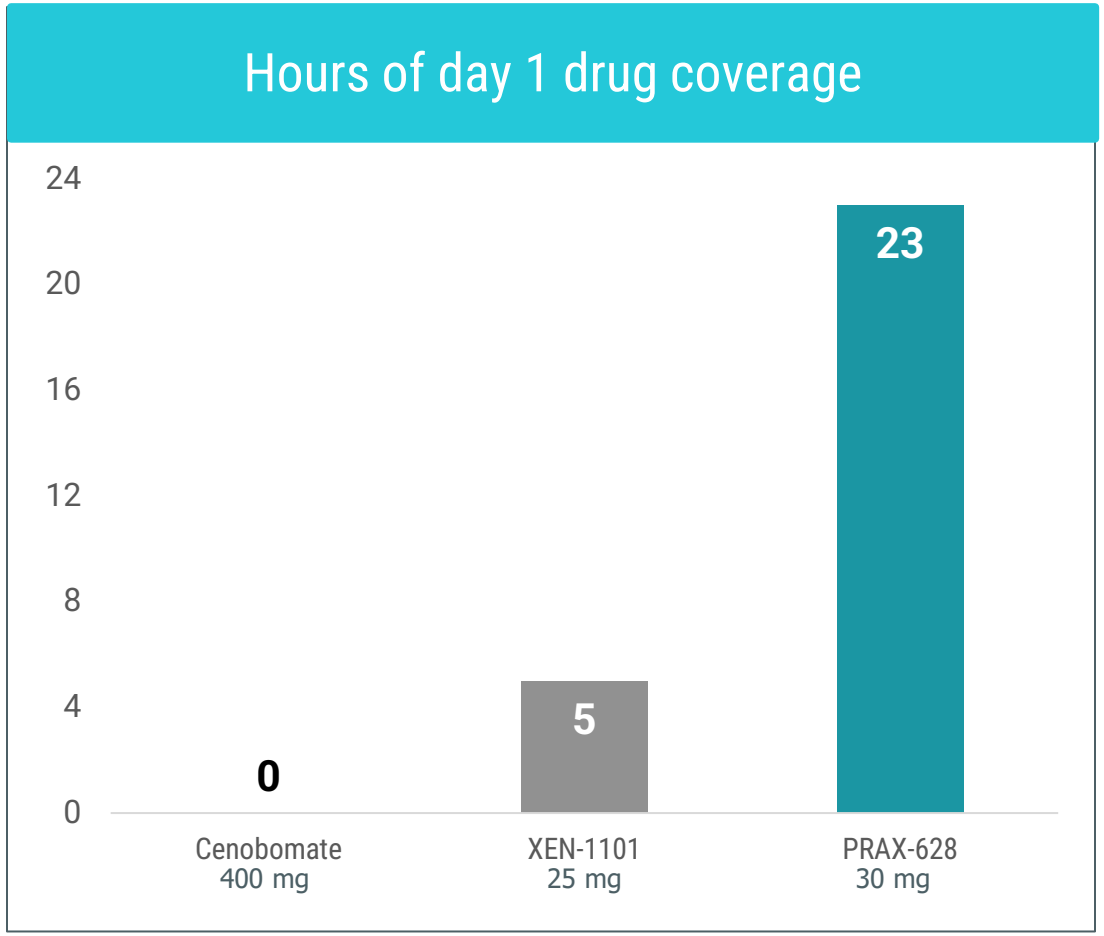
Rapidly achieves therapeutic concentrations after once-daily dose

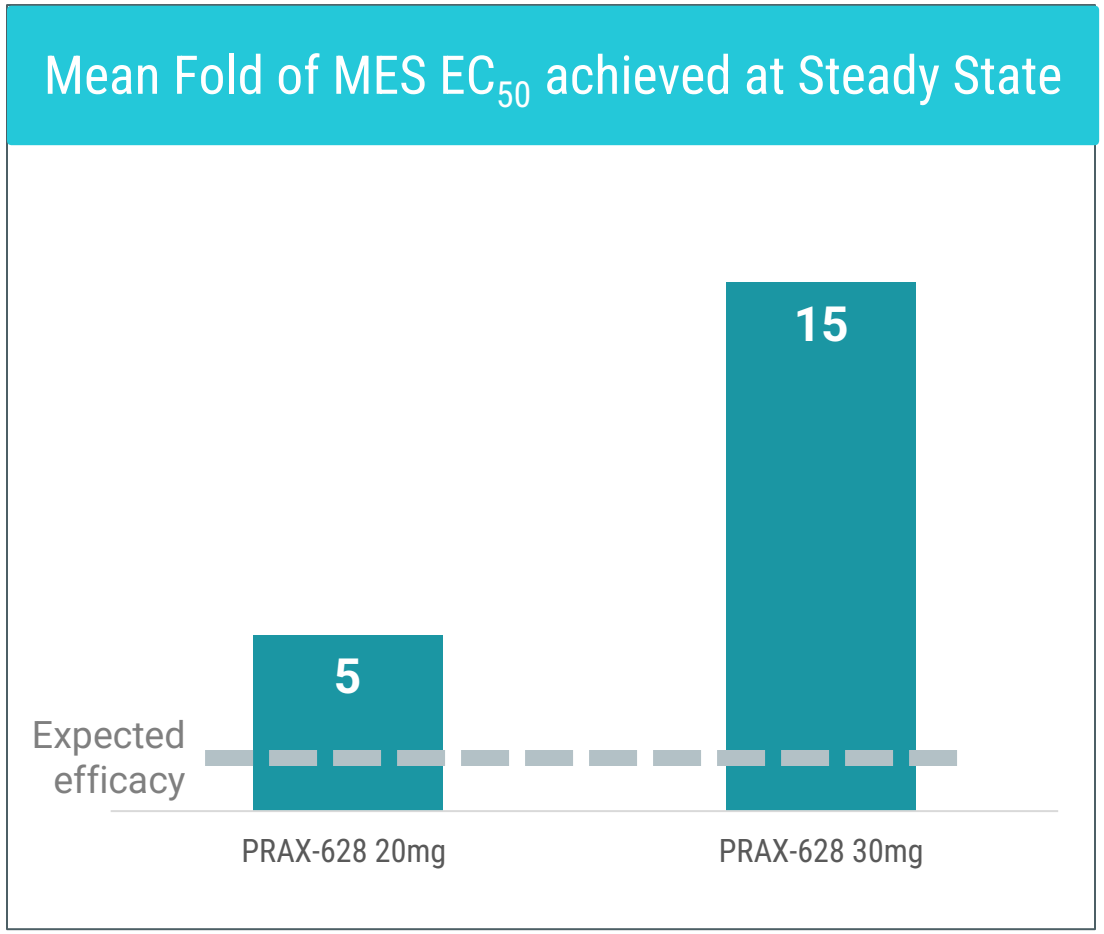
Ideal Treatment



Praxis data on file

Ability to significantly exceed therapeutic concentrations while well tolerated

Ideal Treatment



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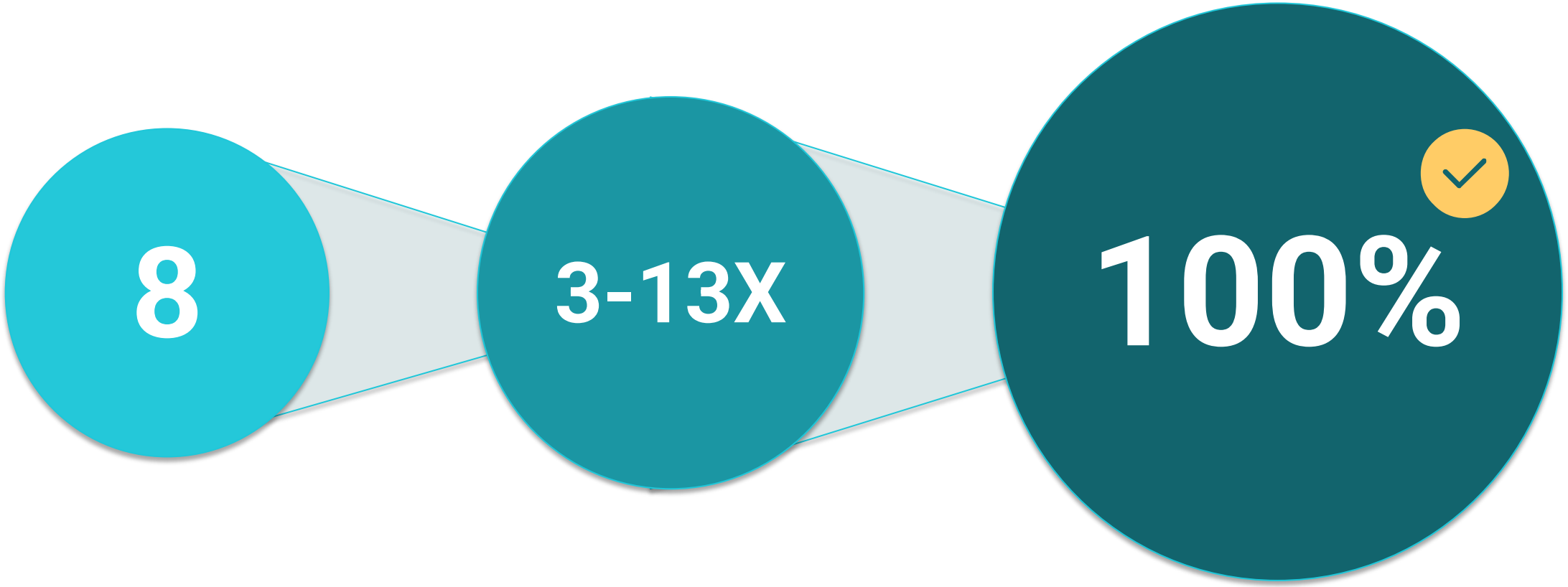
Proof of concept in epilepsy patients achieved in PPR study

Ideal Treatment



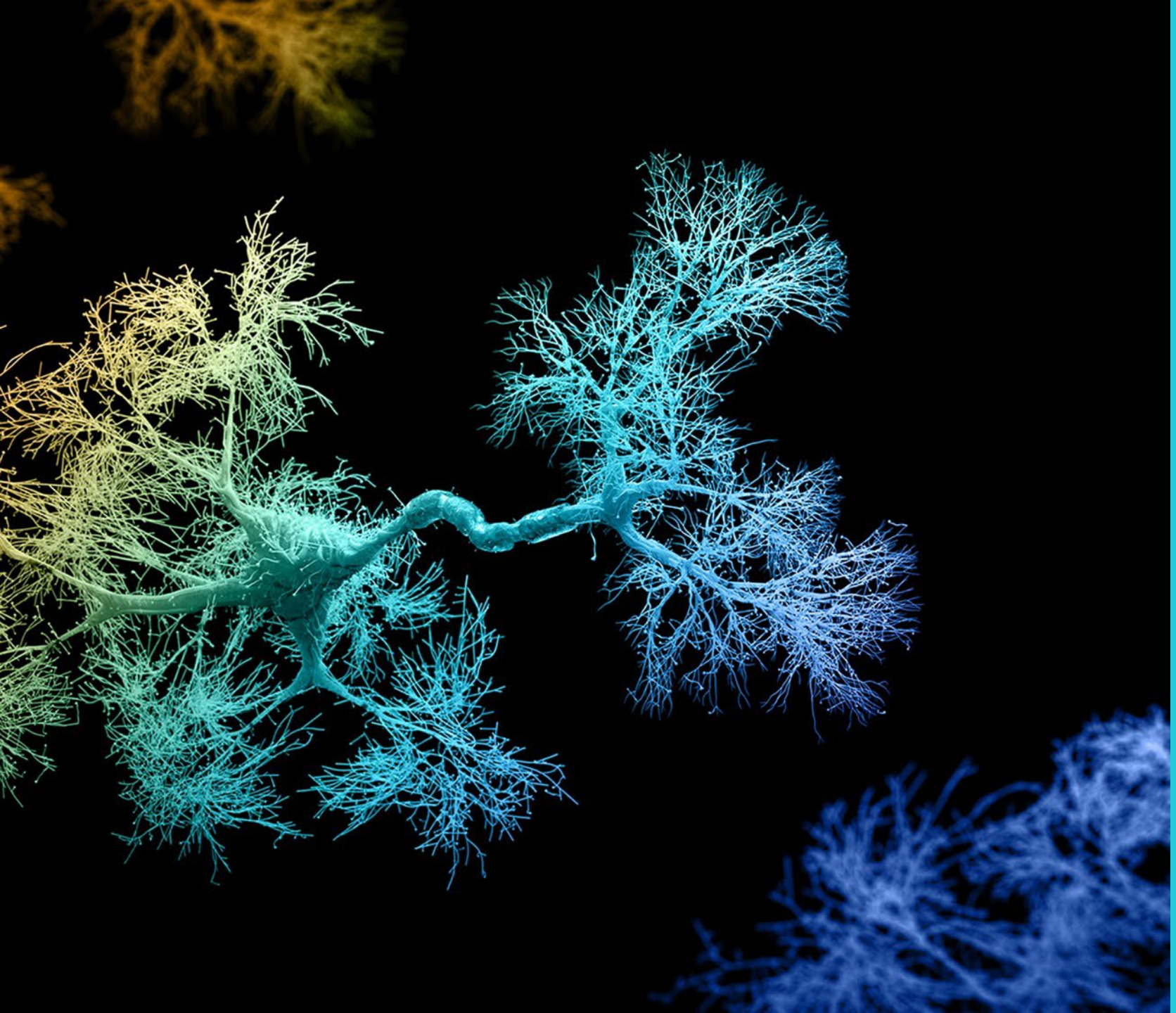
Evaluable patients

Multiples of MES EC_{50} Exposure

Response rate

Praxis data on file

PRAX-628 is poised to revolutionize the epilepsy treatment paradigm

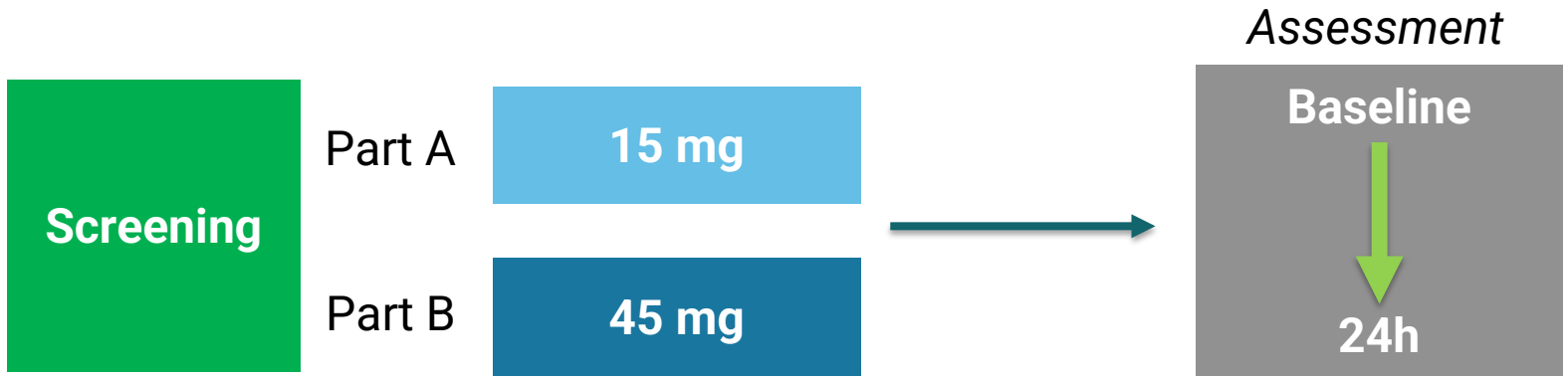


PRAX-628

Photoparoxysmal response in photosensitive epilepsy topline results

PRAX-628 PPR study

De-risks further development in epilepsy



- Patients must demonstrate PPR response during screening and baseline to be evaluable
- Response Assessment
  - **Partial:** Reduction, other than to zero, in the number of generalized PPR events at any assessment period vs baseline
  - **Complete:** Reduction to zero in the number of generalized PPR events at any assessment period vs baseline
- Safety monitored and PK samples collected during entire observation period

Intermittent Photic Stimulation (IPS) to elicit Photo Paroxysmal Response (PPR)

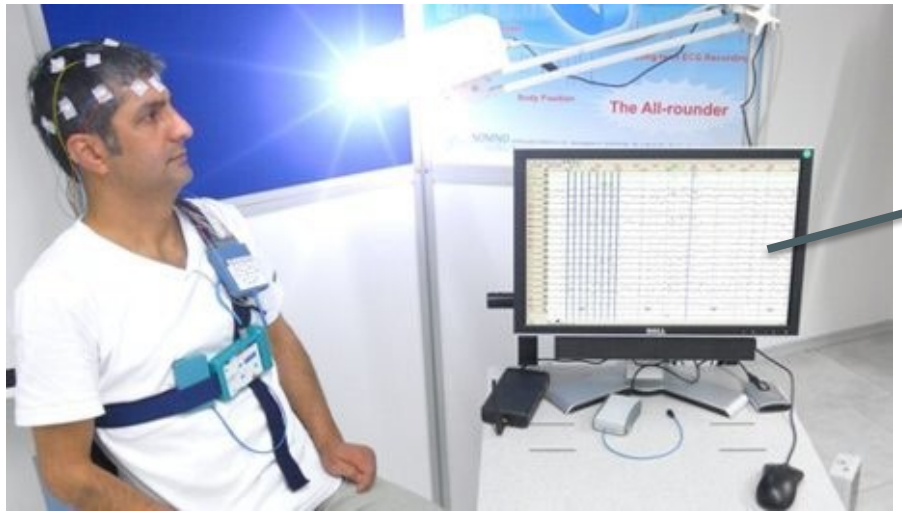
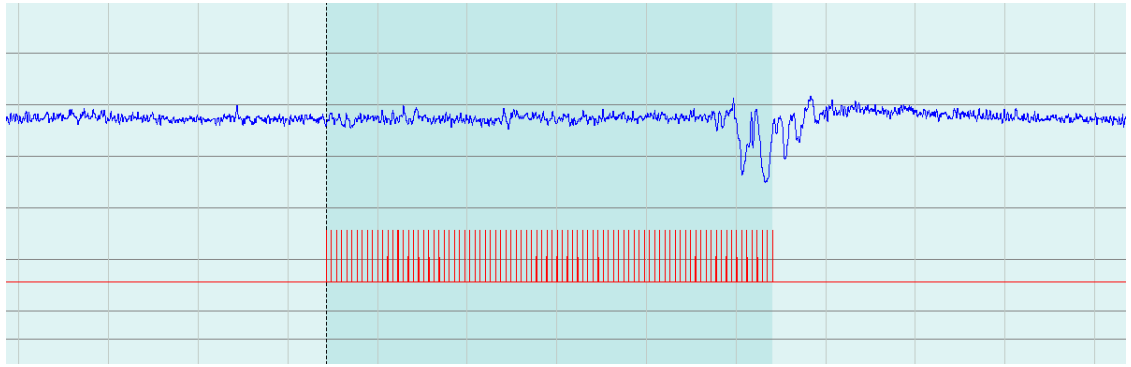


Image Source: Pricillia, I. L. & Azhari, A. (2022). Electroencephalogram Detection for Insomnia Patients: A Preliminary Study. Biosaintifika: Journal of Biology & Biology Education, 14 (2), 191-199

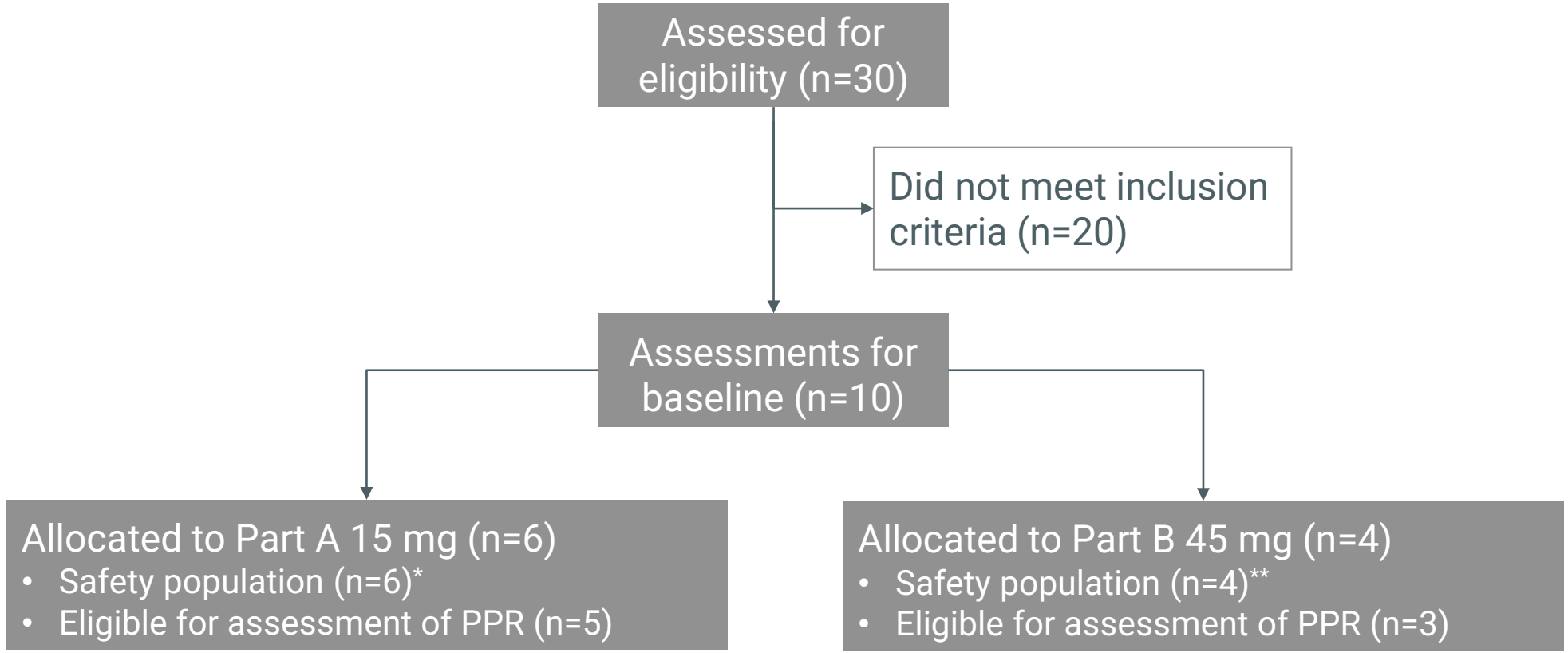
Example of PPR response



EEG signal

IPS trigger

Study disposition



* 1 participant did not meet the criteria for presence of PPR response at baseline

** Due to sponsor decision on eligibility, 1 participant was withdrawn after placebo day, prior to PRAX-628 exposure

Study demographics – evaluable patients per treatment group

		Placebo N=7*	15 mg N=5	45 mg N=3
Age (Years)	Mean (min, max)	32 (18, 61)	37.4 (20, 61)	34 (19, 61)
Sex	M, F	2,5	1,4	1,2
Weight (Kg)	Mean	74.7	74.6	81.7
BMI (Kg/m^2)	Mean (SD)	24.5 (4.5)	25.0 (5.5)	27.4 (6.4)
Concomitant medication (N)	Brivaracetam Lamotrigine Valproic Acid	1 1 1	1 1 1	0 1 0
Duration of epilepsy diagnosis (Years)	Mean (min, max)	19 (1,47)	23 (5,47)	18 (1,47)

* Represents unique patients

Safety population – All AEs were mild in severity

	Placebo N=7*	PRAX-628 15 mg N=6	PRAX-628 45 mg N=3
Patients with any AEs	6 (86%)	6 (100%)	3 (100%)
Patients with severe AEs	0	0	0
Patients with TEAEs	6 (86%)	6 (100%)	3 (100%)
Serious AEs	0	0	0
AEs by Preferred Term (Patients with AE)**	17 (6)	14 (6)	10 (3)
Fatigue	7 (5)	3 (3)	2 (2)
Headache	4 (2)	0	1
Somnolence	1	0	2 (2)
Feeling of relaxation	1	1	0
Nausea	1	0	1
Dizziness	1	0	1
End-of-study follow up***			
Sleep paralysis	0	3 (1)	0

* Patients receiving any placebo treatment (3 patients received placebo in both Parts A & B for a total of 7 unique patients)

** AEs occurring only once in one patient not included

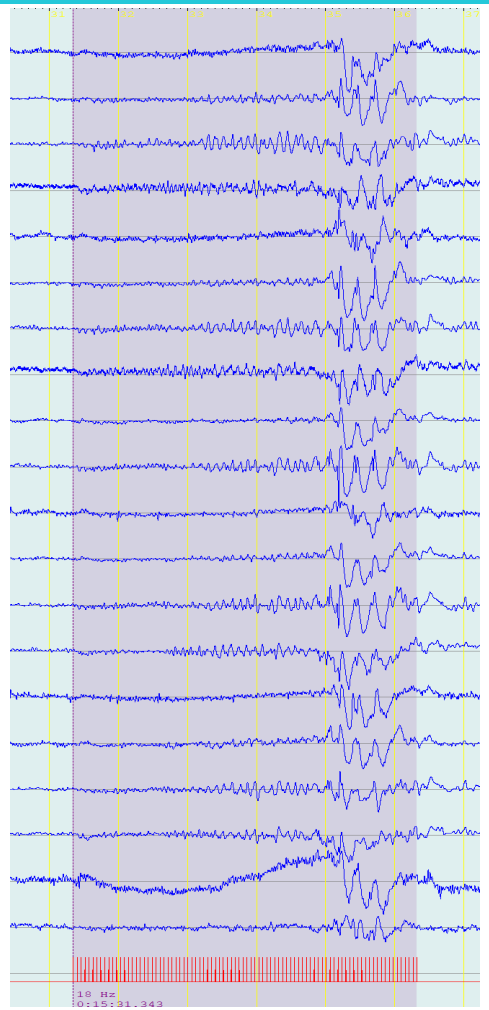
*** Occurred post-treatment during safety follow-up period (Day 4 through end of study)

100% of evaluable patients responded to PRAX-628

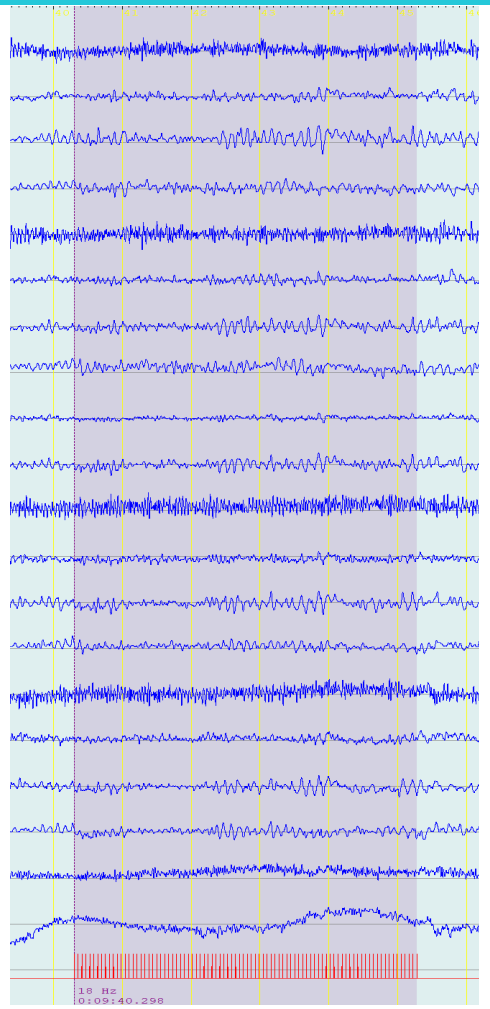
Dose	Categorical Response	Response Rate
15 mg	None	0% (0/5)
	Partial	20% (1/5)
	Complete	80% (4/5)
45 mg	None	0% (0/3)
	Complete	100% (3/3)
	Evaluable Response	**100% (8/8)**

Example: PRAX-628 eliminating PPR response

Pre PRAX-628



Post PRAX-628



Therapeutic gaps in focal epilepsy

Daniel Friedman, MD, MSc

3-26-2024

Why should we (still) care about focal epilepsy?

- Focal epilepsy accounts for the vast majority of epilepsy types world-wide
- 53-88% of adults with epilepsy have focal onset seizures: 1.6 – 2.6 million adults in US
- 42-60% of children with epilepsy have focal onset seizures: 196 – 282 thousand children in US
- Incidence of focal epilepsy increases with age
- About 1/3rd are not fully controlled with currently available therapy (up to 800k patients in US)
- 10-40% of patients reported side effects from medications spontaneously, and 60-95% in structured interviews

Behr et al, Revue neurologique. 2016 Jan 1;172(1):27-36.
Perucca et al, Lancet Neurol 2012;11:792-802
https://www.cdc.gov/epilepsy/data/index.html

Navigating the current treatment landscape for focal epilepsy

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Despite the high number of marketed ASMs, more choices are needed

Phenobarbital	Leviteracetam
Phenytoin	Zonisamide
Carbamazepine	Pregabalin
Valproate	Lacosamide
Gabapentin	Clobazam
Felbamate	Ezogabine/Retigabine
Lamotrigine	Eslicarbazepine
Vigabatrin	Perampanel
Topiramate	Brivaracetam
Oxcarbazepine	Cenobamate

28 yr old woman with depression and new onset focal epilepsy

Phenobarbital
Phenytoin
Carbamazepine
Valproate
Gabapentin
Felbamate
Lamotrigine
Vigabatrin
Topiramate
Oxcarbazepine
Leviteracetam
Zonisamide
Pregabalin
Lacosamide
Clobazam
Ezogabine/Retigabine
Eslicarbazepine
Perampanel
Brivaracetam
Cenobamate

28 yr old woman with depression and new onset focal epilepsy

Who is on oral contraceptives and is concerned about weight gain

Phenobarbital
Phenytoin
Carbamazepine
Valproate
Gabapentin
Felbamate
Lamotrigine
Vigabatrin
Topiramate
Oxcarbazepine
Leviteracetam
Zonisamide
Pregabalin
Lacosamide
Clobazam
Ezogabine/Retigabine
Eslicarbazepine
Perampanel
Brivaracetam

28 yr old woman with depression and new onset focal epilepsy

Who is on oral contraceptives and is concerned about weight gain

Who wants to have children in the near future

Phenobarbital
Phenytoin
Carbamazepine
Valproate
Gabapentin
Felbamate
Lamotrigine
Vigabatrin
Topiramate
Oxcarbazepine
Leviteracetam
Zonisamide
Pregabalin
Lacosamide
Clobazam
Ezogabine/Retigabine
Eslicarbazepine
Perampanel
Brivaracetam

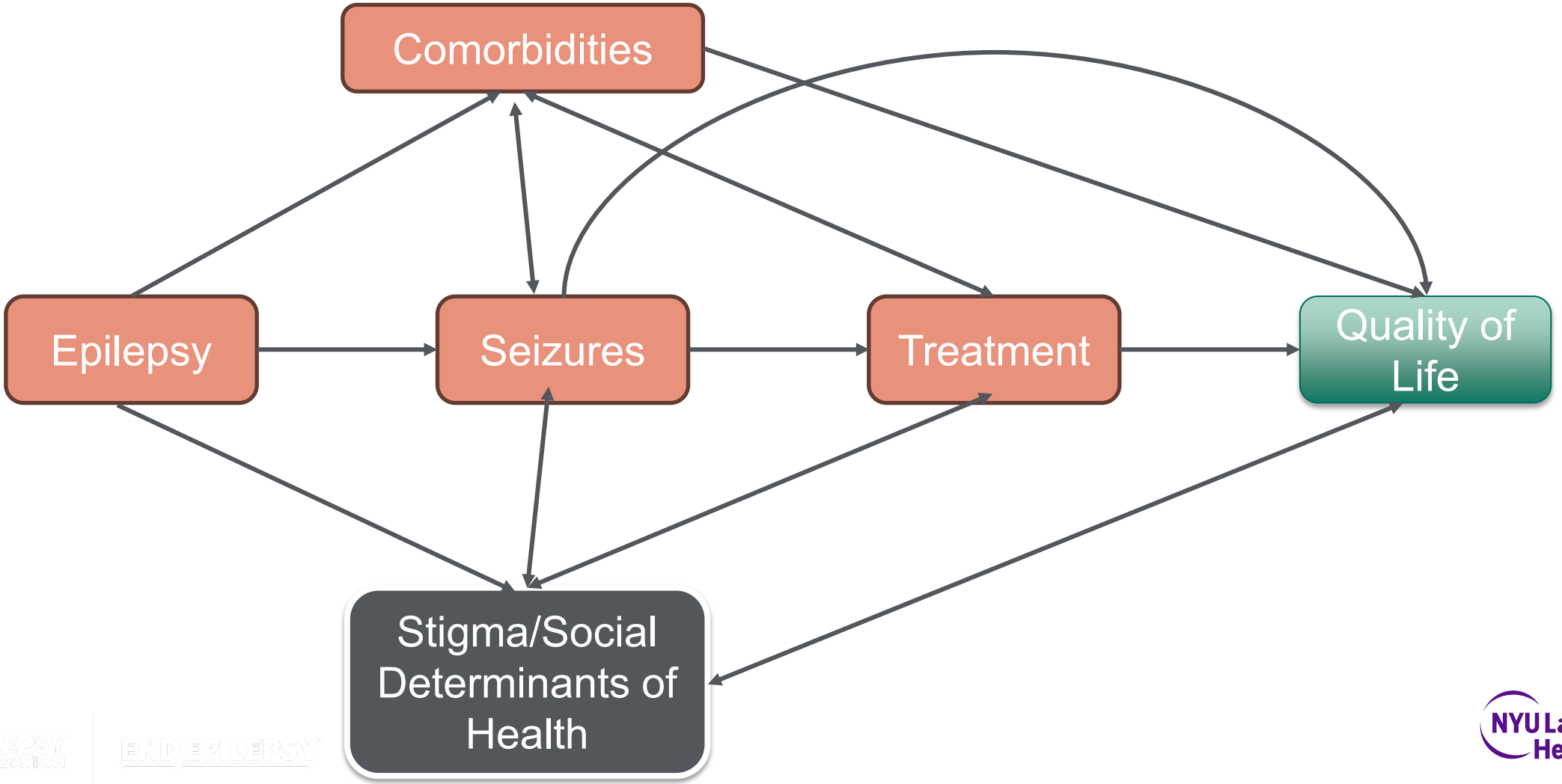
28 yr old woman with depression and new onset focal epilepsy

Who is on oral contraceptives and is concerned about weight gain

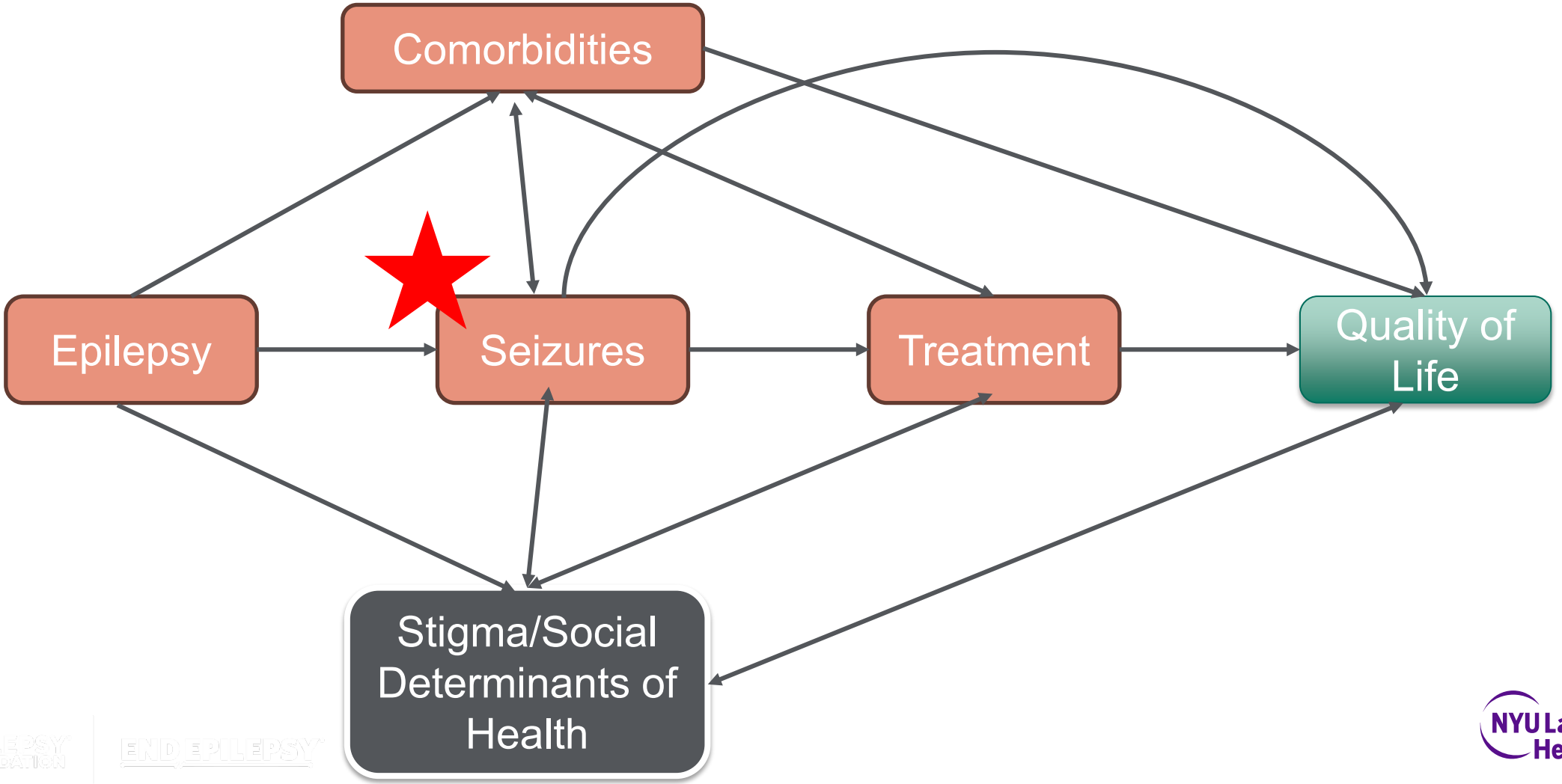
Who wants to have children in the near future

Who is having frequent tonic-clonic seizures

Epilepsy Outcomes: Opportunities for improvement

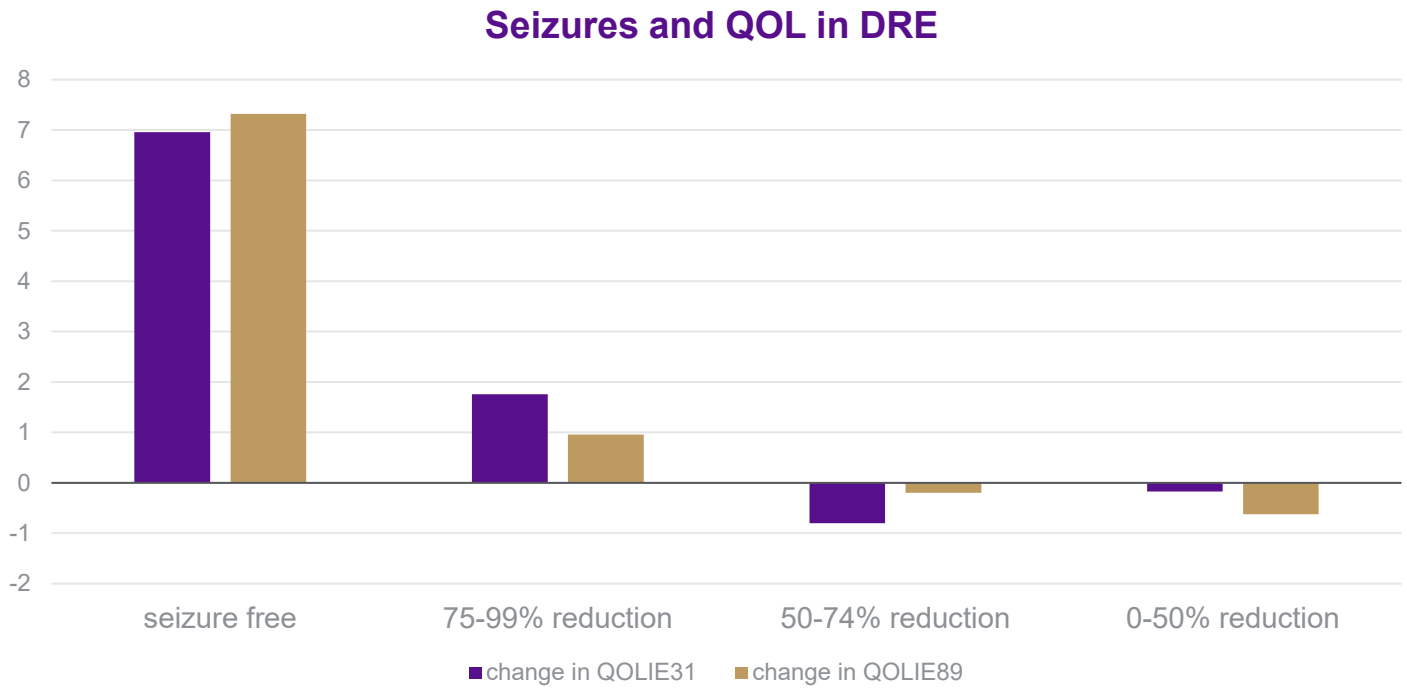


Epilepsy Outcomes: Opportunities for improvement



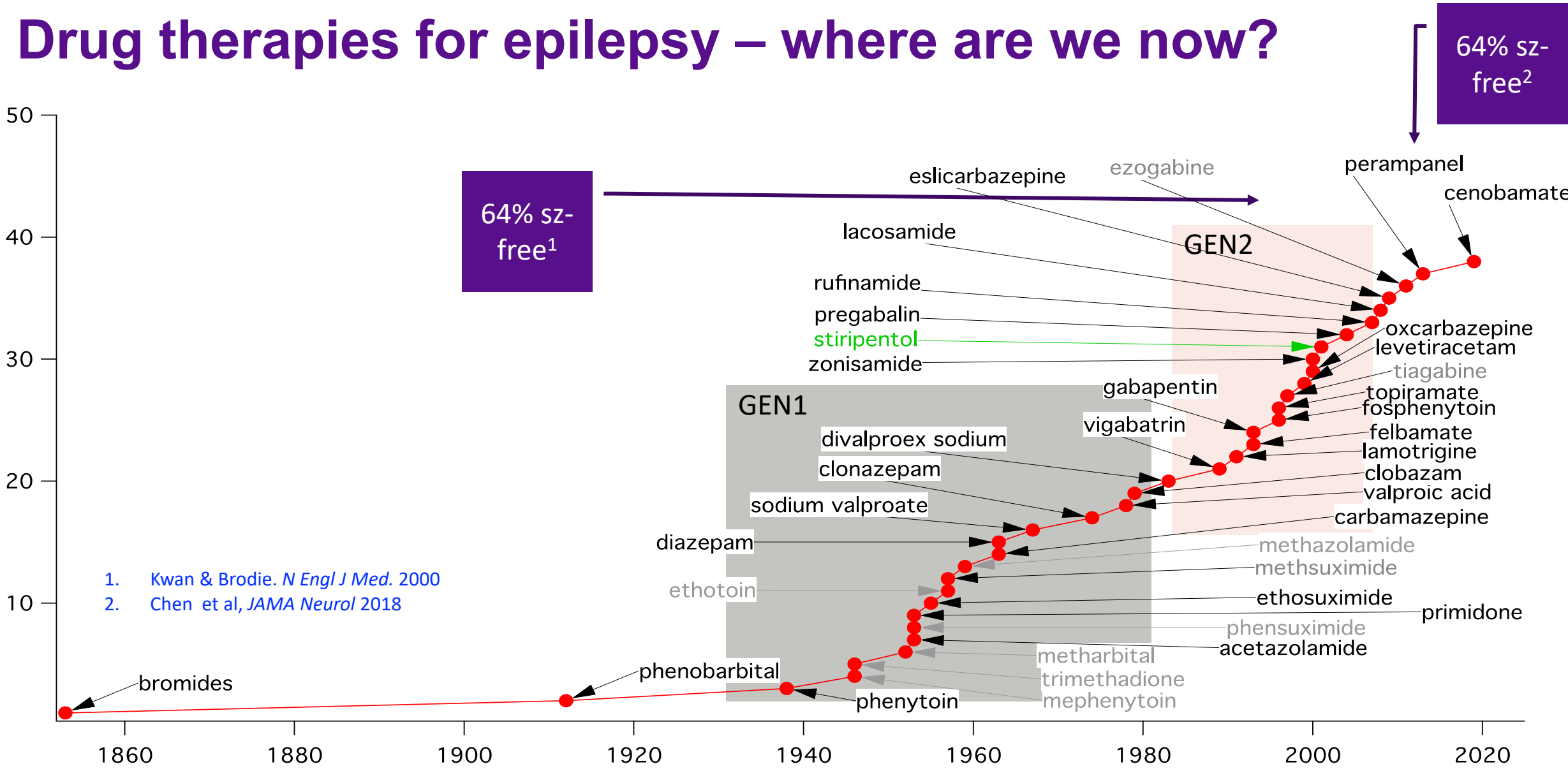
Efficacy

Seizure freedom is perhaps the largest single driver of QOL in patients with DRE focal epilepsy



From Birbeck et al, Epilepsia 2002

Drug therapies for epilepsy – where are we now?



1. Kwan & Brodie. *N Engl J Med.* 2000
2. Chen et al, *JAMA Neurol* 2018

Adapted from Loscher & Schmidt Epilepsia 2011

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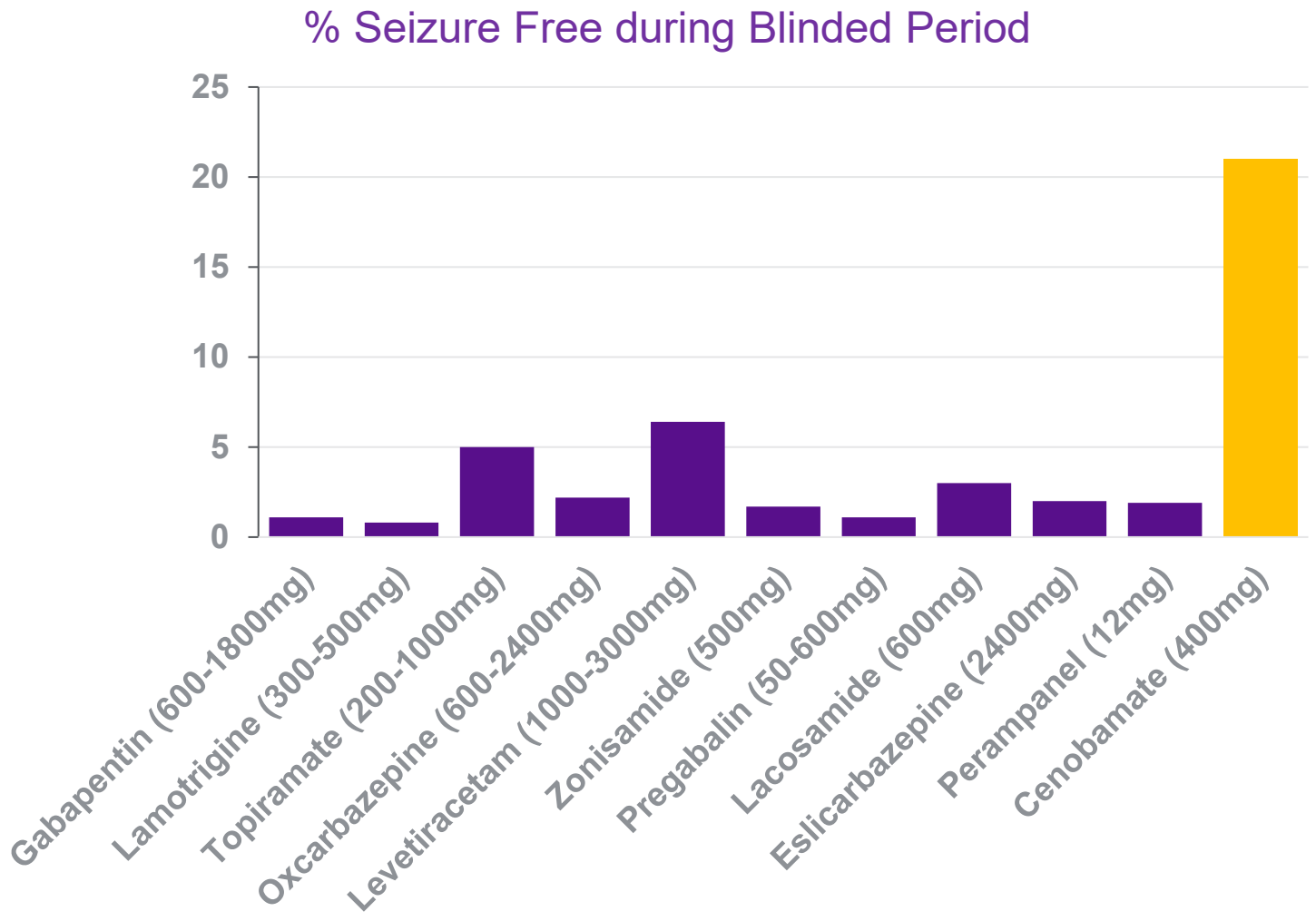
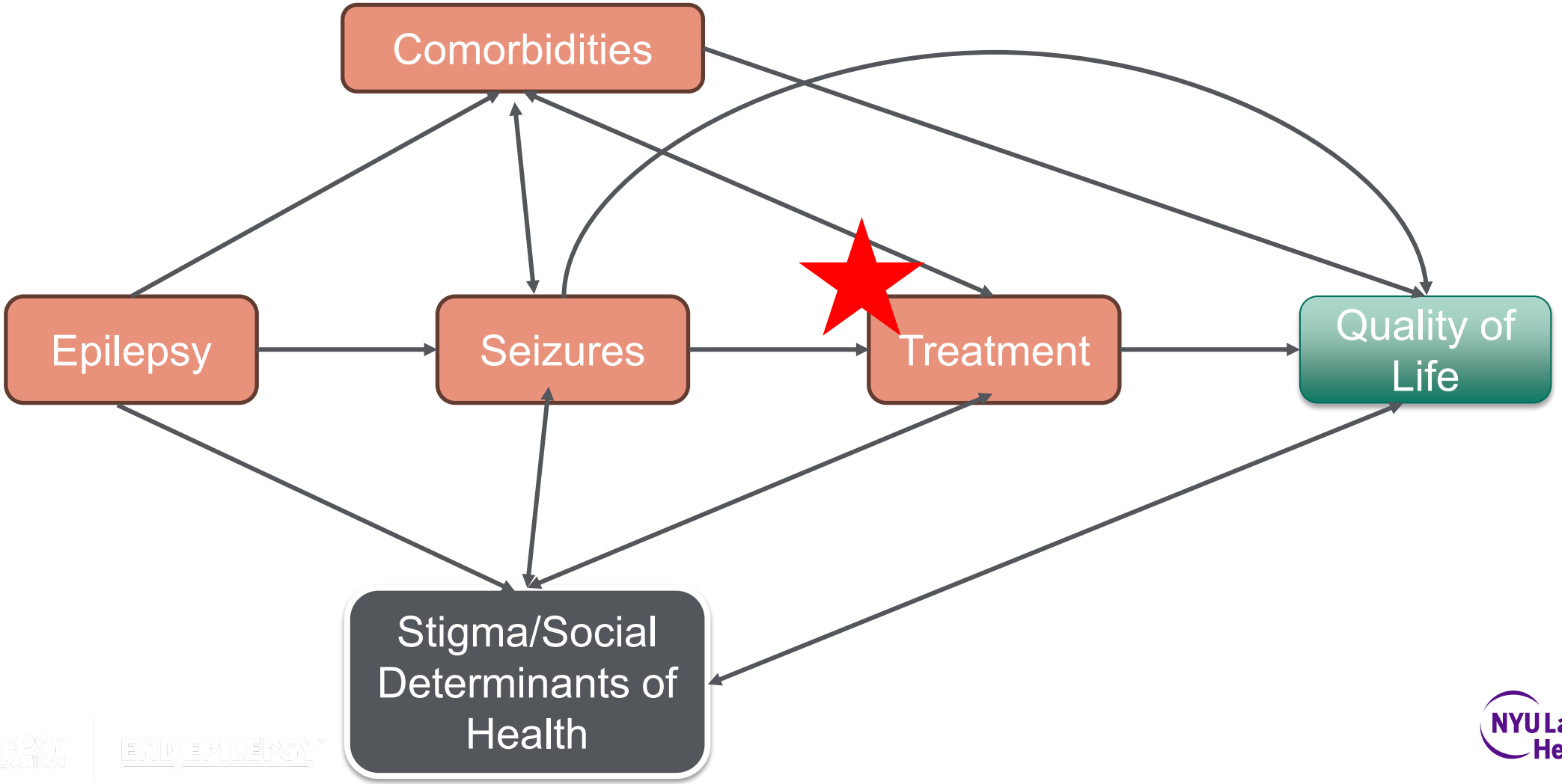
Seizure-freedom in focal seizure add-on trials



Epilepsy Outcomes: Opportunities for improvement



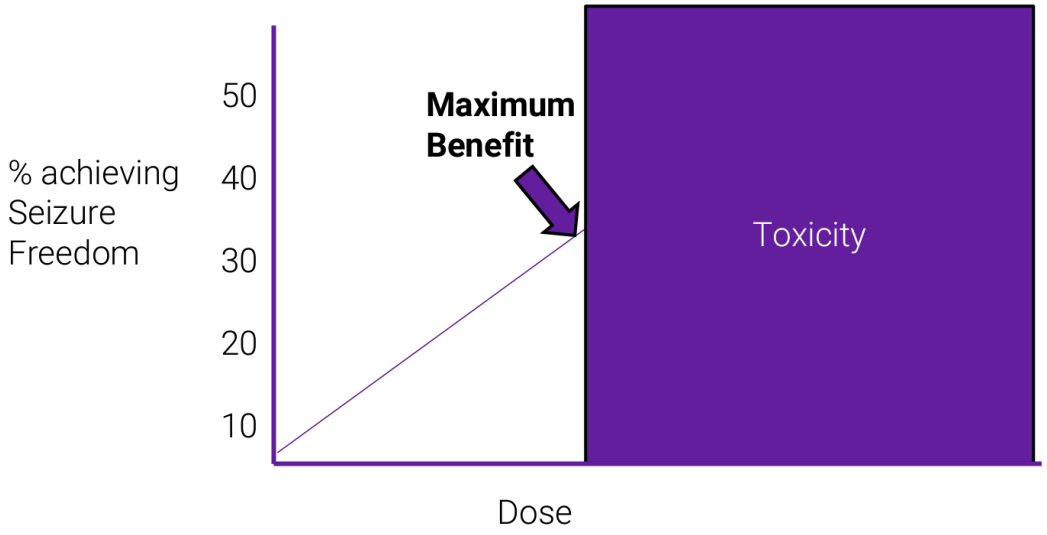
Tolerability

- Medication side effects are significant burden for people with epilepsy
- Adverse events are a large contributor to negative QOL
- Multiple types of intolerability:

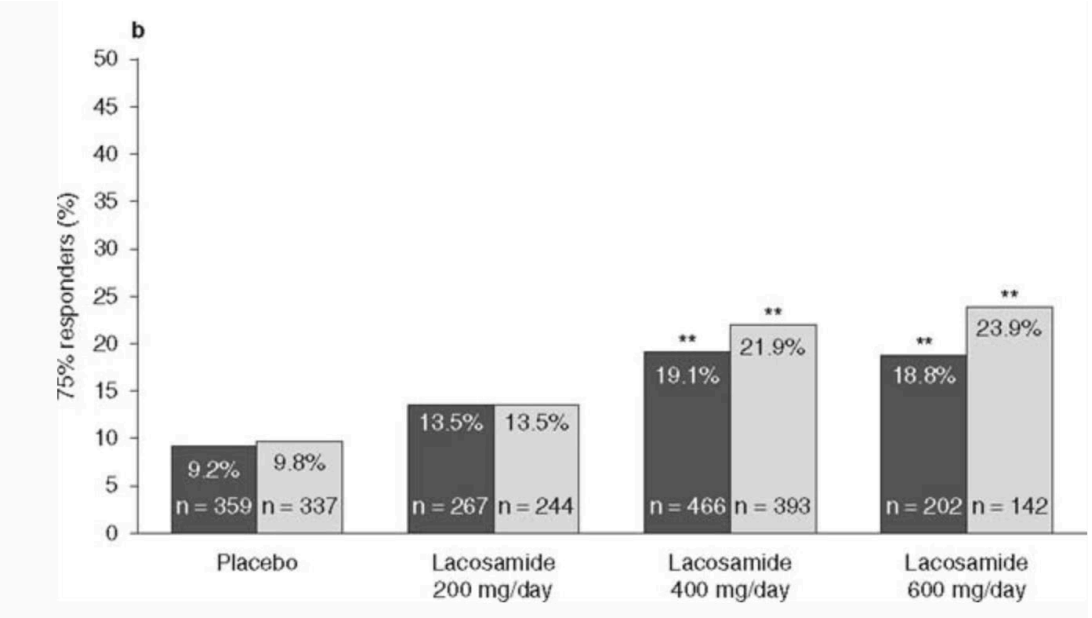
Type	Examples
Acute, *predictable*	Fatigue, vertigo, ataxia, CNS depression, cognitive changes, diplopia, tremor, mood changes
Acute, unpredictable, rare	Rash, immunological reactions, liver toxicity, bone marrow toxicity, aseptic meningitis
Chronic, related to cumulative exposure, common, predictable	Bone density loss, weight changes, neuropathy, visual field changes, gingival hyperplasia, connective tissue disorder
Pharmacodynamic and kinetic drug interactions, predictable	Added CNS toxicity, decreased OCP effectiveness, hepatotoxicity

Perucca & Gilliam *Lancet Neurol*. 2012;11(9):792-802.

Impact of Tolerability on Efficacy



- Do some drugs lack sufficient efficacy due to narrow therapeutic ranges?



Chung et al. *CNS Drugs*. 2010;24(12):1041-1054.

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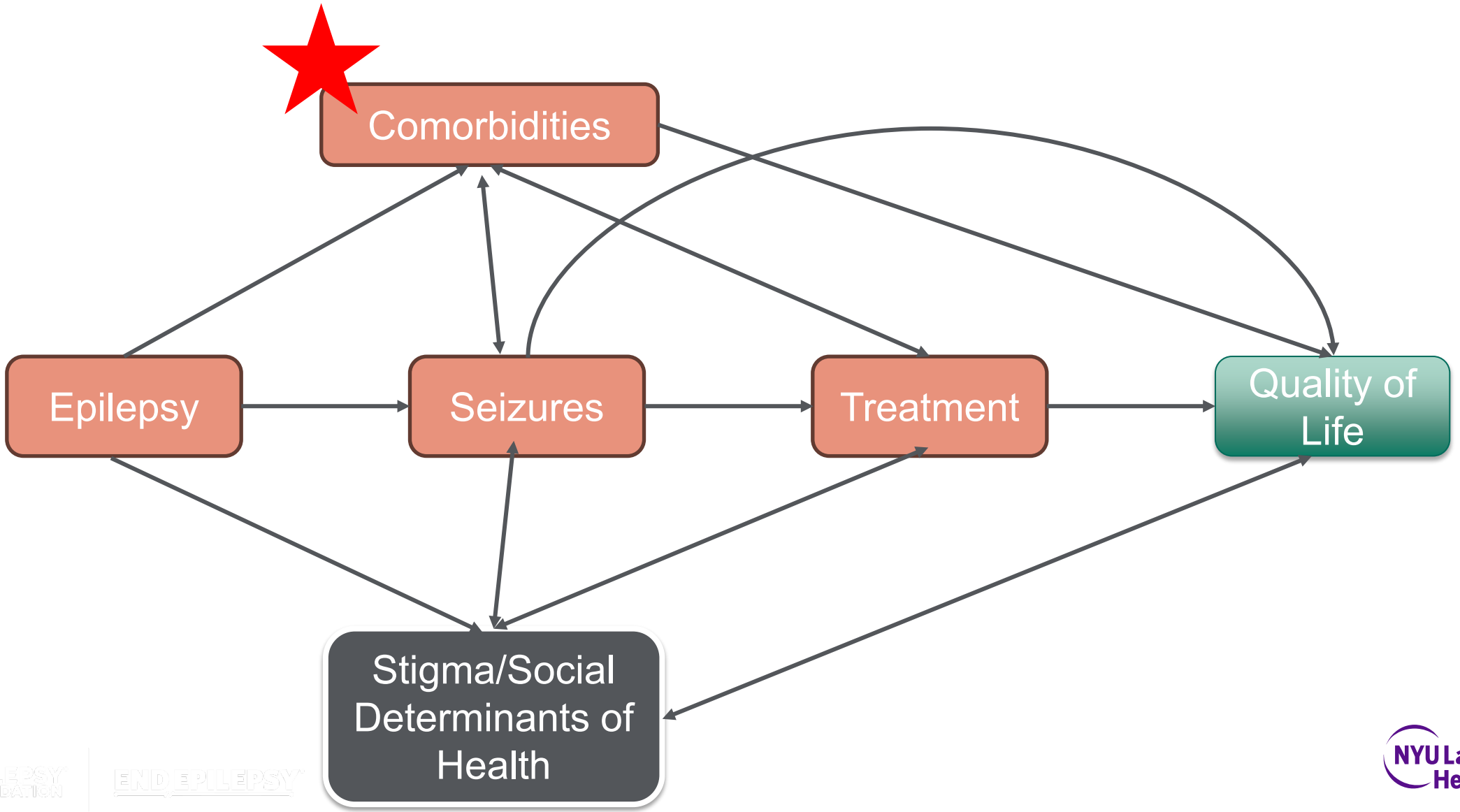
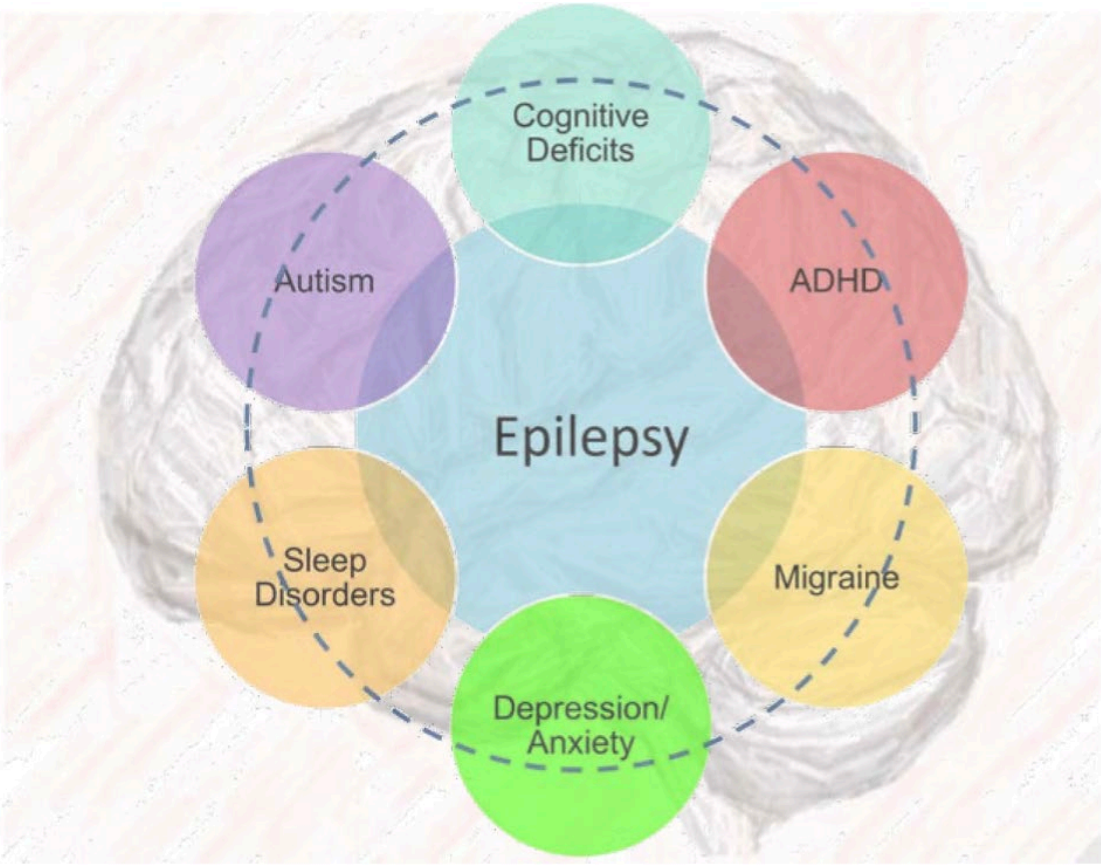
Epilepsy Outcomes: Opportunities for improvement

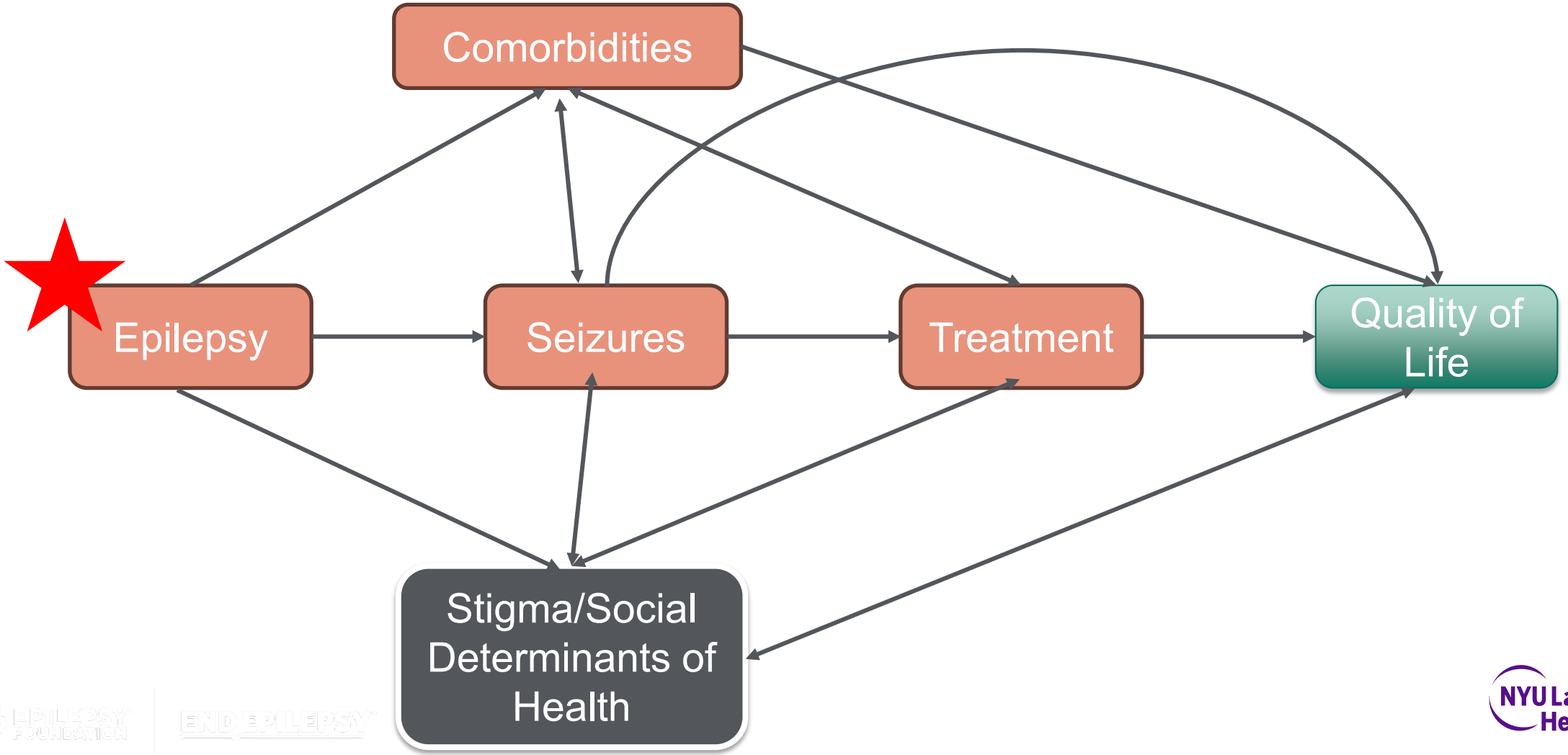


Comorbidities

- Depression, anxiety, memory disturbance are focal epilepsy comorbidities
- More common among drug-resistant patients
- Causes include:
  - Seizures
  - Medication effects
  - *Underlying biological abnormalities leading to epilepsy*



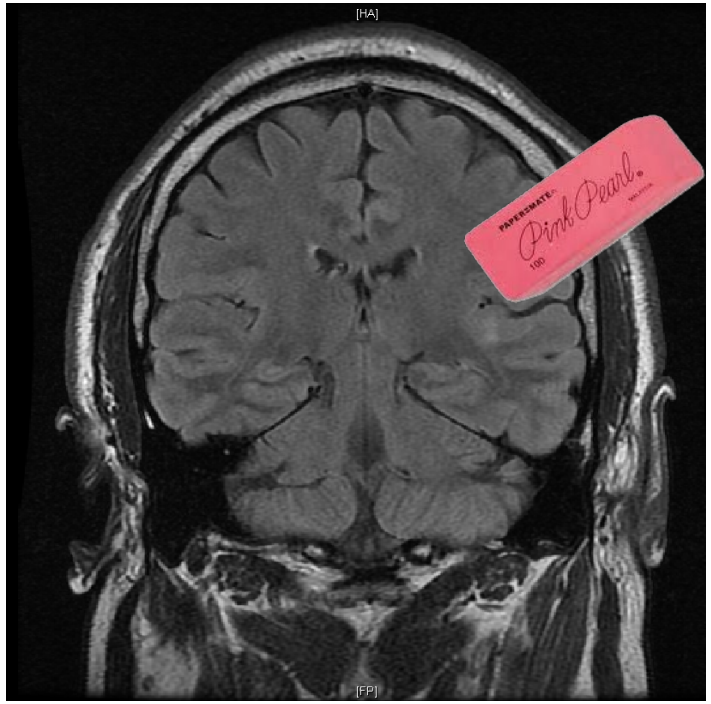
Epilepsy Outcomes: Opportunities for improvement



Disease modification

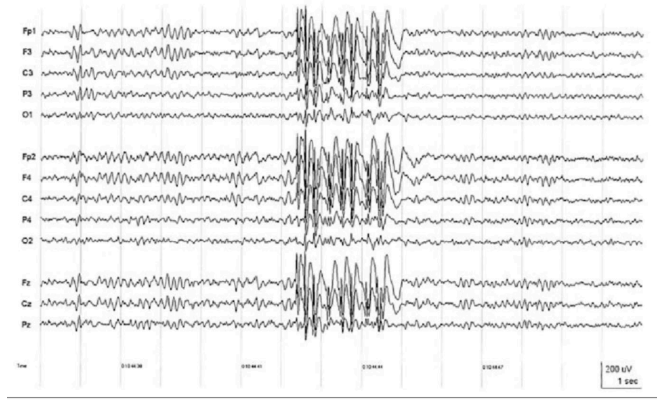
No treatments yet:

- Alter the underlying mechanism leading to increased seizure susceptibility
- Prevent epilepsy after a high risk injury
- Turn drug-resistant epilepsy into drug-sensitive epilepsy



Other gaps..

- Treatments for generalized or unknown epilepsy
- Teratogenicity



MONEAD

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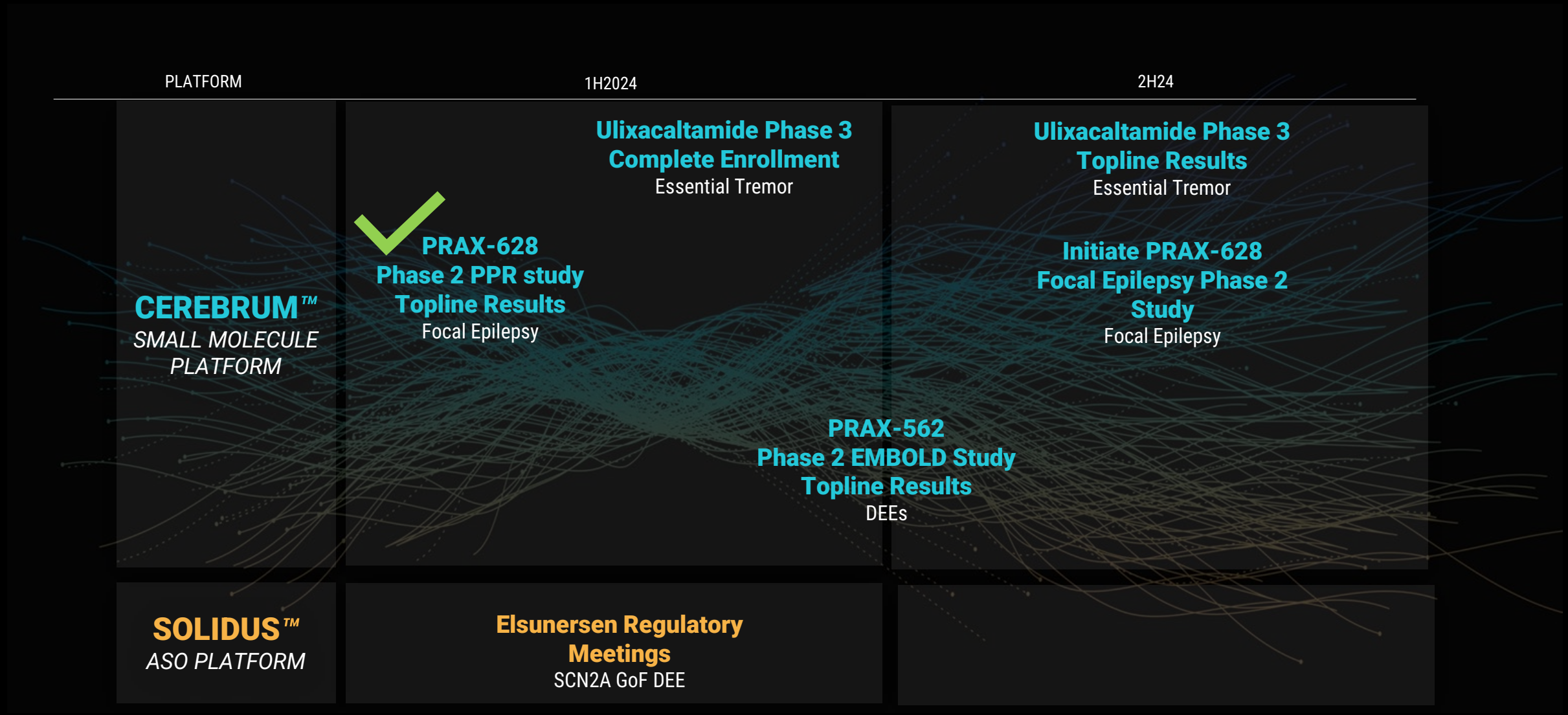
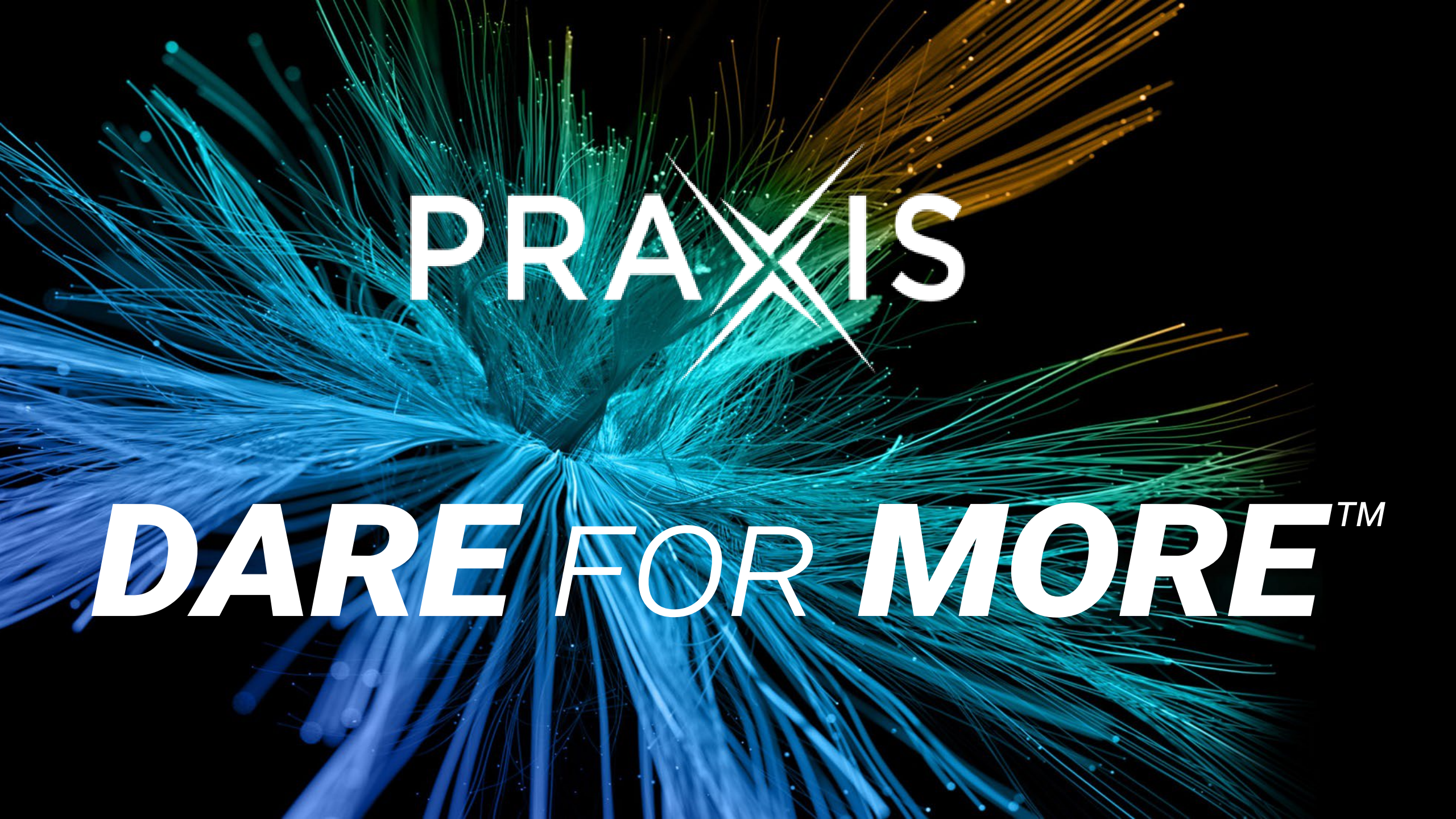
Conclusions

Despite 18+ marketed ASMs for focal and generalized seizures, options fall short for many patients
-Lack of efficacy
-Intolerable side effects
-Limited choices for women who may become pregnant
-Burden of daily medication taking

Shortcomings of available ASMs present opportunities for the differentiation of new therapies

What to expect from Praxis during 2024

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