
PRAXIS
DARE FOR MORE®
CORPORATE OVERVIEW
November 2024

Forward-looking statements

This presentation may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to express or implied statements regarding the current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, statements regarding the estimated market for our product candidates, if approved, our development plans, our preclinical and clinical results and other future conditions, including our cash runway, and the safety, efficacy, and regulatory and clinical design or progress, potential regulatory submissions, approvals and timing thereof of any of our product candidates. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and timing of our ongoing clinical trials, (ii) the success and timing of our product development activities and initiating clinical trials, (iii) the success and timing of our collaboration partners' product development activities, (iv) the timing of and our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our collaboration partners' abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) the potential addressable market sizes for product candidates. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

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 filed with the Securities and Exchange Commission ("SEC") and our other filings with the SEC.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

Praxis is positioned to bring more innovation to patients

4

Assets in late stage

>$9B

Commercial opportunity across the portfolio

5

High value clinical readouts within the next eighteen months

2

Discovery platforms to optimize drug development

into

2027

Cash runway

Four pillars guide how we develop medicines

GENETICS

Focus on therapeutic targets identified through human genetics

TRANSLATIONAL TOOLS

Translational tools validate potential of target and product candidate and can provide early proof of biology

EFFICIENT & RIGOROUS

Efficient, rigorous clinical development paths to proof-of-concept in humans applying an agile way of working

PATIENT-GUIDED

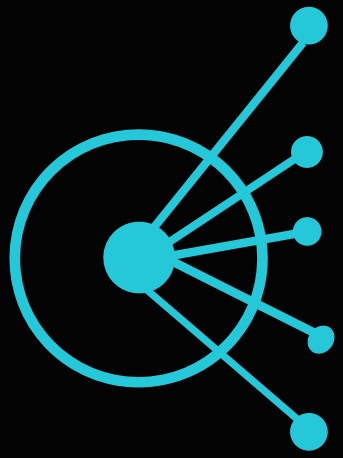
Patient-guided development strategies to deliver on what patients actually need

Two platforms to generate optimized therapies for defined patient populations

CEREBRUM™

SMALL MOLECULE PLATFORM

Cerebrum™ utilizes deep understanding of neuronal excitability and neuronal networks and applies a series of computational and experimental tools to develop orally available precision therapies



Molecule	Indication	Mechanism
ulixacaltamide	Essential Tremor	T-type calcium channel modulator
vormatrigine	Focal Onset Seizures & Generalized Epilepsy	Sodium channel functional state modulator for broad use
relutrigine*	DEE Epilepsies	Sodium channel functional state modulator for pediatric use
PRAX-020^	KCNT1 Epilepsy	KCNT1 specific inhibitor
PRAX-050	Not disclosed	Not disclosed

SOLIDUS™

ANTISENSE OLIGONUCLEOTIDE (ASO) PLATFORM

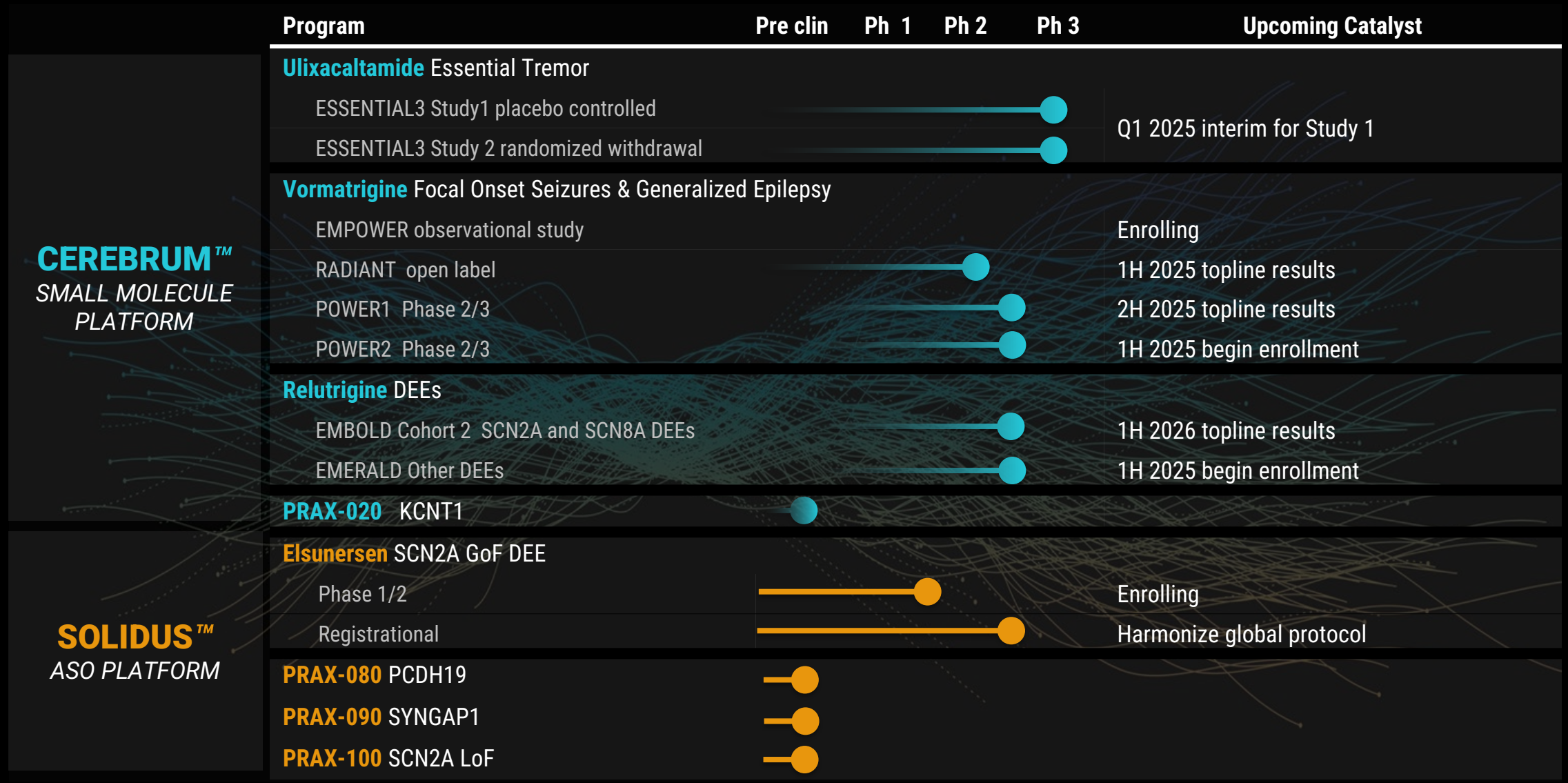
Solidus™ is an efficient, targeted precision medicine discovery and development engine for ASOs anchored on proprietary, computational methodology

Molecule	Indication	Mechanism
elsunersen*	SCN2A GoF	Gapmer ASO
PRAX-080+	PCDH19 Mosaic expression	Gapmer ASO
PRAX-090+	SYNGAP1 LoF	Splice switching ASO
PRAX-100+	SCN2A LoF	Splice switching ASO

^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
* Relutrigine has received ODD and RPD from the FDA, and ODD from the European Medicines Agency for the treatment of SCN2A-DEE and SCN8A-DEE
** Elsunersen has received ODD and RPD from the FDA, and ODD and PRIME designations from the European Medicines Agency (EMA) for the treatment of SCN2A-DEE

PRAXIS

Four clinical stage assets and multitude of early-stage programs



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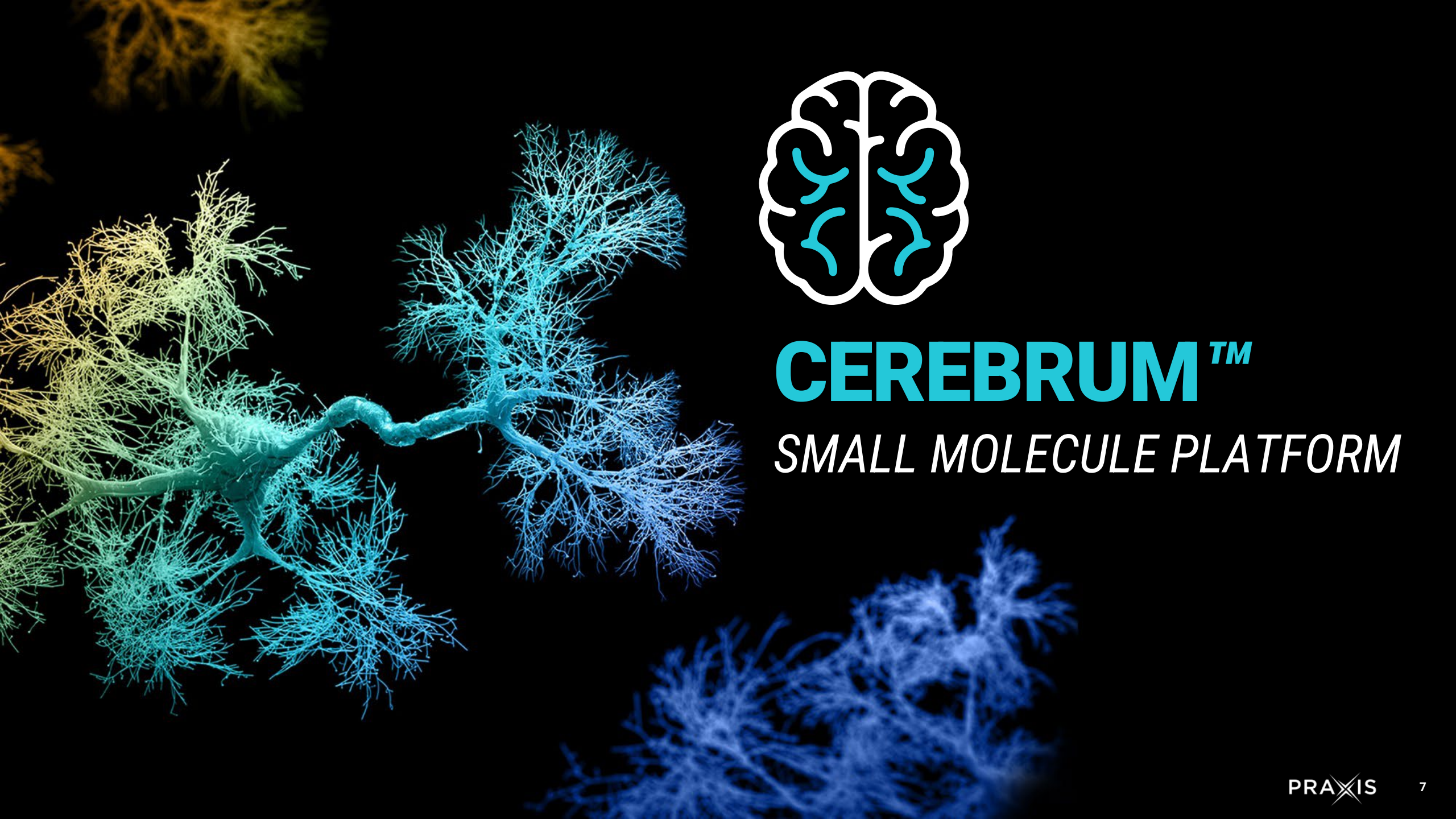
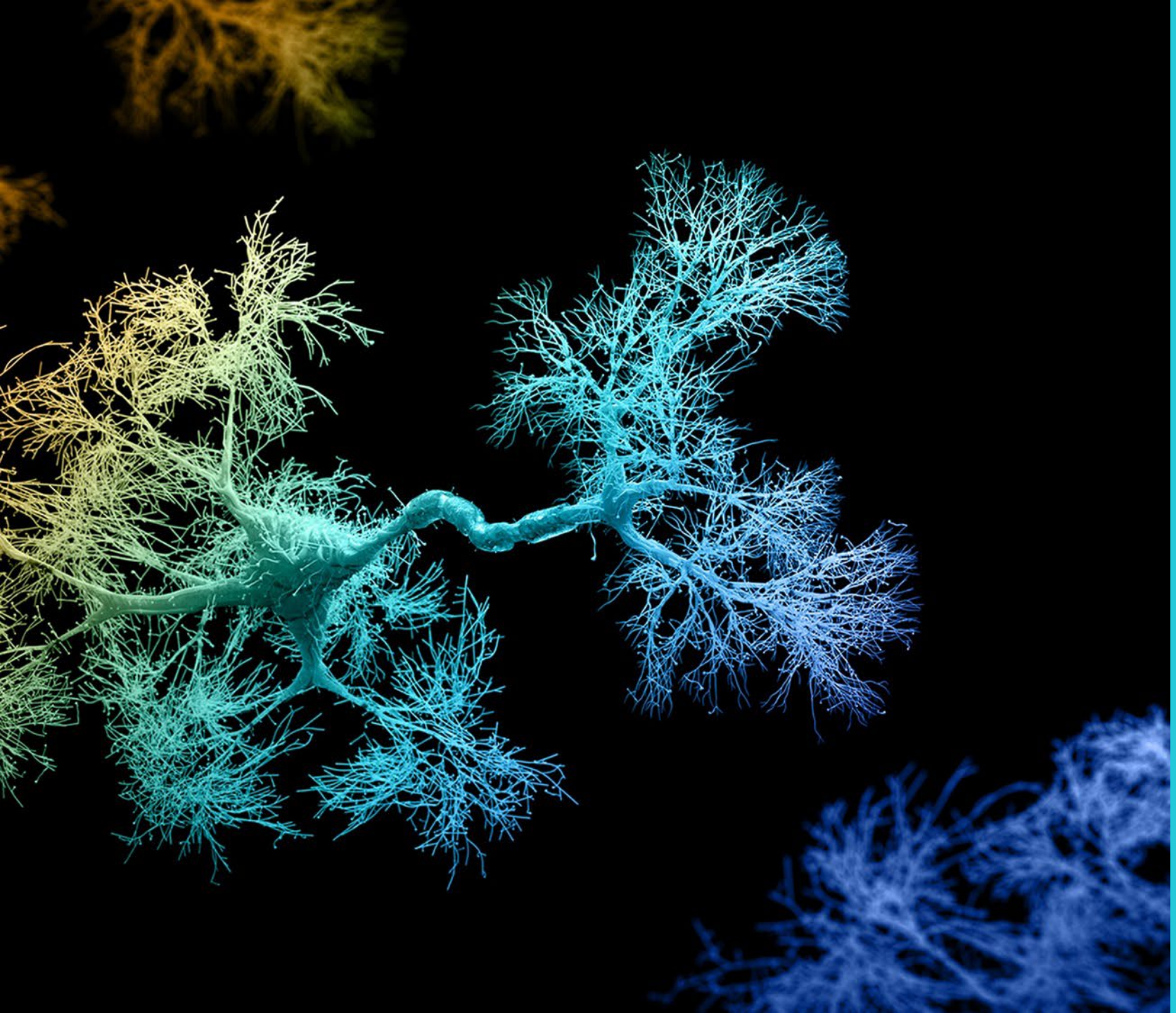


CEREBRUM™

SMALL MOLECULE PLATFORM



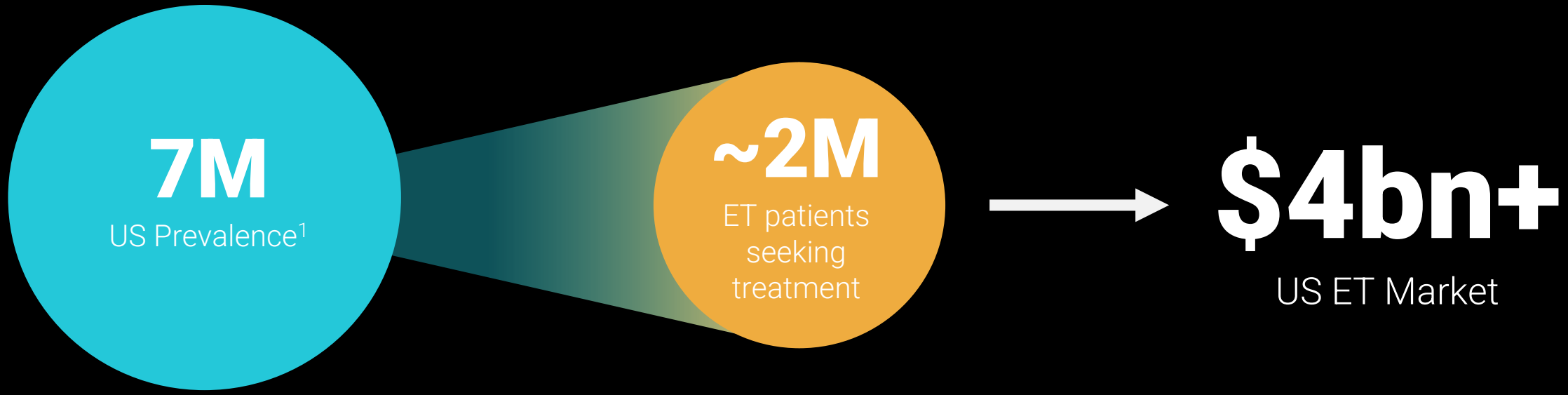
Ulixacaltamide

Milestones

Q1 2025: Study 1 interim analysis

2025: NDA filling

Essential tremor market is significantly underserved and ready for disruption



- Essential Tremor (ET) is the most prevalent movement disorder
- People with ET experience significant disturbance of their daily activities
- Hallmark feature of ET is action tremor that primarily affects the hands[2,3]
- Almost all ET patients suffer from at least one comorbid condition (e.g., depression, anxiety, sleep disorders, cognitive dysfunction)[4]

Vast majority of patients are left without any treatment option

- <30% of patients are eligible to receive propranolol due to other medications/health conditions
- Of those who start propranolol >50% discontinue after only 1 month
- Of those who start propranolol <20% still receive propranolol after 2 years

1. Louis ED, Ottman R. Tremor Other Hyperkinet Mov (N Y). 2014;4:259. 2. Elble RJ. Curr Neurol Neurosci Rep. 2013 Jun;13(6):353. 3. Putzke JD, et al. J Neurol Neurosurg Psychiatry. 2006 Nov;77(11):1235-7. 4. Vetterick, C., Lyons, K.E., Matthews, L.G. et al. The Hidden Burden of Disease and Treatment Experiences of Patients with Essential Tremor: A Retrospective Claims Data Analysis. Adv Ther (2022). https://doi.org/10.1007/s12325-022-02318-8

Modified Activities of Daily Living 11 (mADL11) as Primary Endpoint

11 items from the well-established TETRAS ADL scale

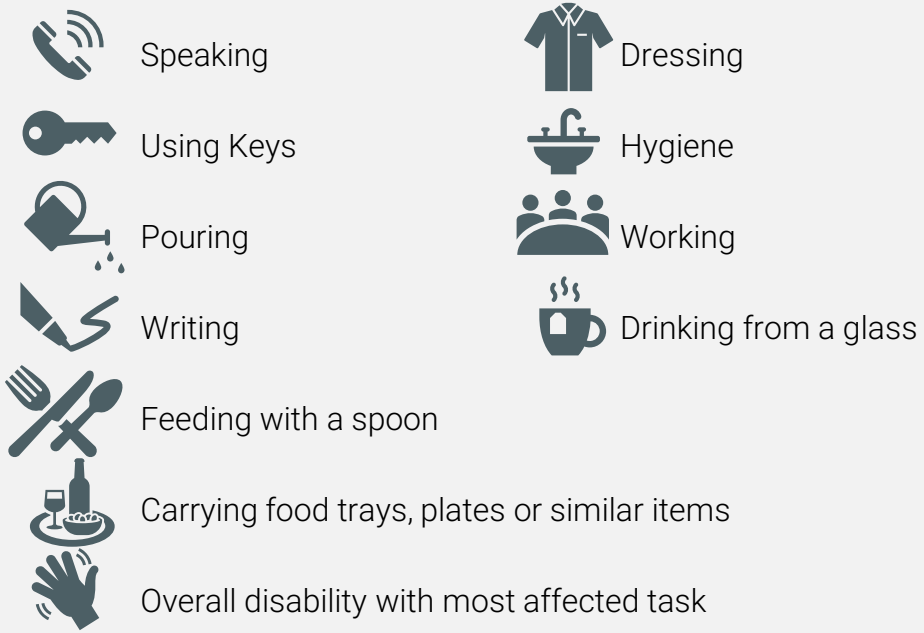
Each item is individually scored, up to a total of 33

0 = Slightly abnormal. Tremor is present but does not interfere with __.

1 = Mildly abnormal. Spills a little.

2 = Moderately abnormal. Spills a lot or changes strategy to complete task.

3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.



Each point reduction provides benefit to a patient's ability to perform regular activities

- Improvement based on regaining function
- ADL assessment performed by a physician
- Aligned with FDA as primary endpoint for Essential3 studies

TETRAS = TRG Essential Tremor Rating Assessment Scale; ADL = Activities of Daily Living

Surveys of >400 ET patients across the US highlight ongoing hidden burden of ET and associated challenges in managing everyday life

ET burden has a profound impact on daily activities

Up to 80% of patients with ET reported needing to adjust how they complete daily tasks due to their symptoms

Top Challenges:

- working / attending social events
- writing
- drinking from a glass

Patients with ET experience high psychosocial burden

Nearly all patients with ET experience a level of psychosocial burden, with many reporting feeling:

- hopeless
- ashamed
- worried
- frustrated
- sad

ET is inadequately managed and undertreated

Up to 77% of patients do not feel their ET symptoms are manageable with current treatments

Up to 50% of patients are not receiving treatment for their ET

Praxis data on file. The Essential Tremor Patient Research was conducted by Fuel Insights (www.fuelinsights.com) from June-July 2024. Two separate surveys were completed online and included 150 US adults living with ET and a further 261 US adults living with ET who were pre-screened, but did not qualify, for the Essential3 study (https://essential3study.com/)

US neurologists emphasize the need for more effective treatments and the importance of patient-physician dialogue in ET

ET burden has a profound impact on daily activities

>90% of neurologists stated their patients' descriptions of their ET symptoms and impact on daily activities influence treatment decisions

Patients with ET experience high psychosocial burden

60% of neurologists reported **mental and emotional challenges** among the top three challenges for their ET patients

ET is inadequately managed and undertreated

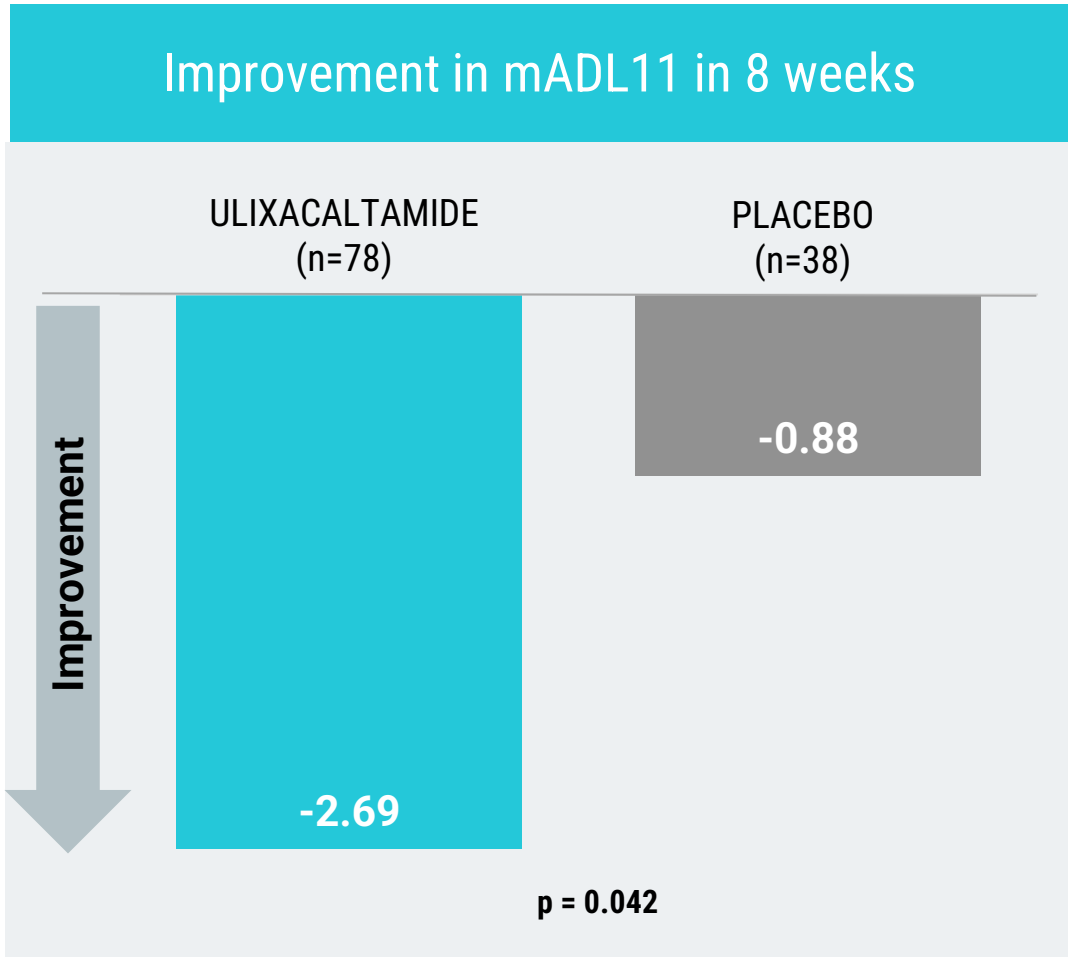
85% of neurologist visits are for patients seeking ET treatment

40% of patients seen by neurologists are not receiving treatment

Nearly 1/2 of neurologists rarely refer ET patients for specialist management

Praxis data on file. The Essential Tremor HCP Research was conducted by Fuel Insights (www.fuelinsights.com) in April 2024. The survey was fielded at the American Academy of Neurology meeting and included 152 neurologists who treat ET in the US, and who were primarily affiliated with academic centers.

Essential1 Phase 2b study set foundation for the Essential3 Phase 3 program



Validated the clinical hypothesis

- Strong efficacy signal with robust endpoint (mADL11)
  - Early clinical benefit in 8-Week Study
  - Long-term, durable benefit
- Well-tolerated with a differentiated safety profile
- Tested Phase 3 design concepts

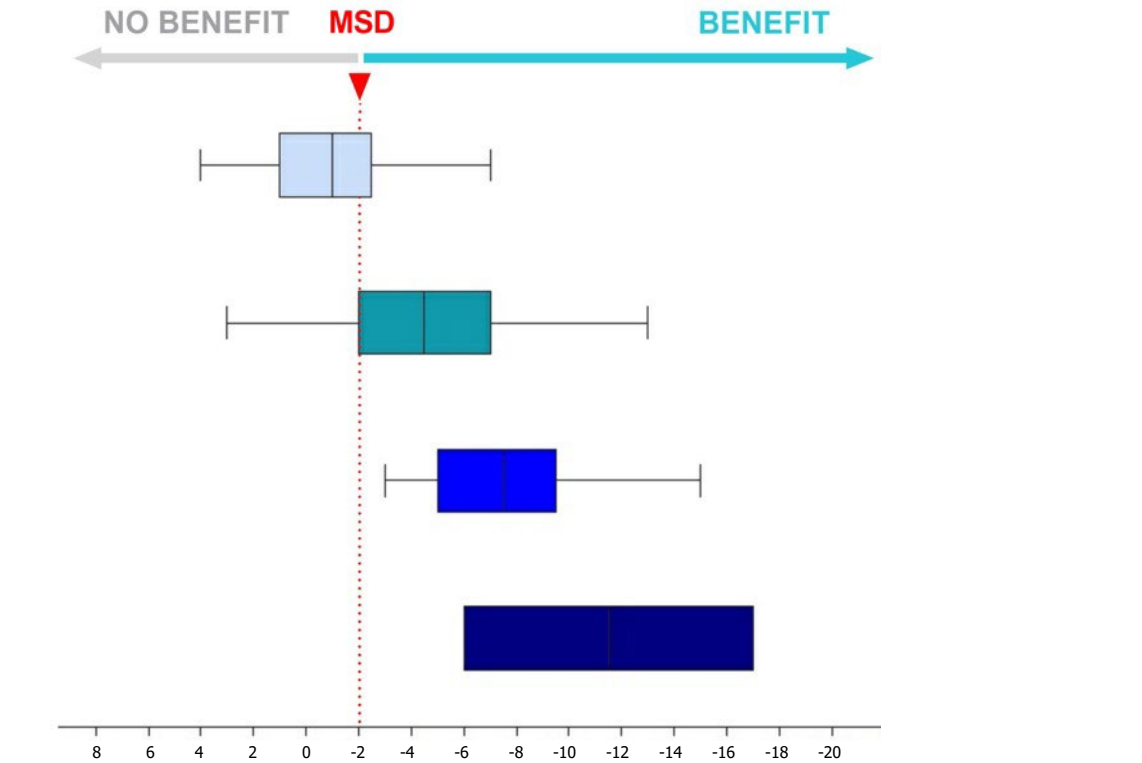
Sets up a clear path to registration

- Alignment with FDA on dose and primary endpoint
- Phase 3 program design structured around patient needs
- Robust recruitment strategy

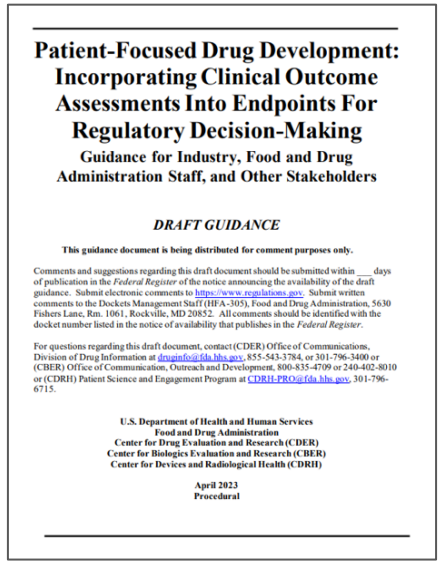
Results from Essential1 study, p value is nominal

Using Essential1 to define clinical meaningfulness in essential tremor

ESSENTIAL1 ANCHOR-BASED ASSESSMENT PGI-C:mADL11



- Patient response on mADL11 endpoint was well-correlated to PGI-C response
- Aligned with recently issued guidance from Clinical Outcomes Assessment for novel endpoints



Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at druginfo@fda.hhs.gov, 855-543-3784, or 301-796-3400 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010 or (CDRH) Patient Science and Engagement Program at CDRH-PRO@fda.hhs.gov, 301-796-6715.

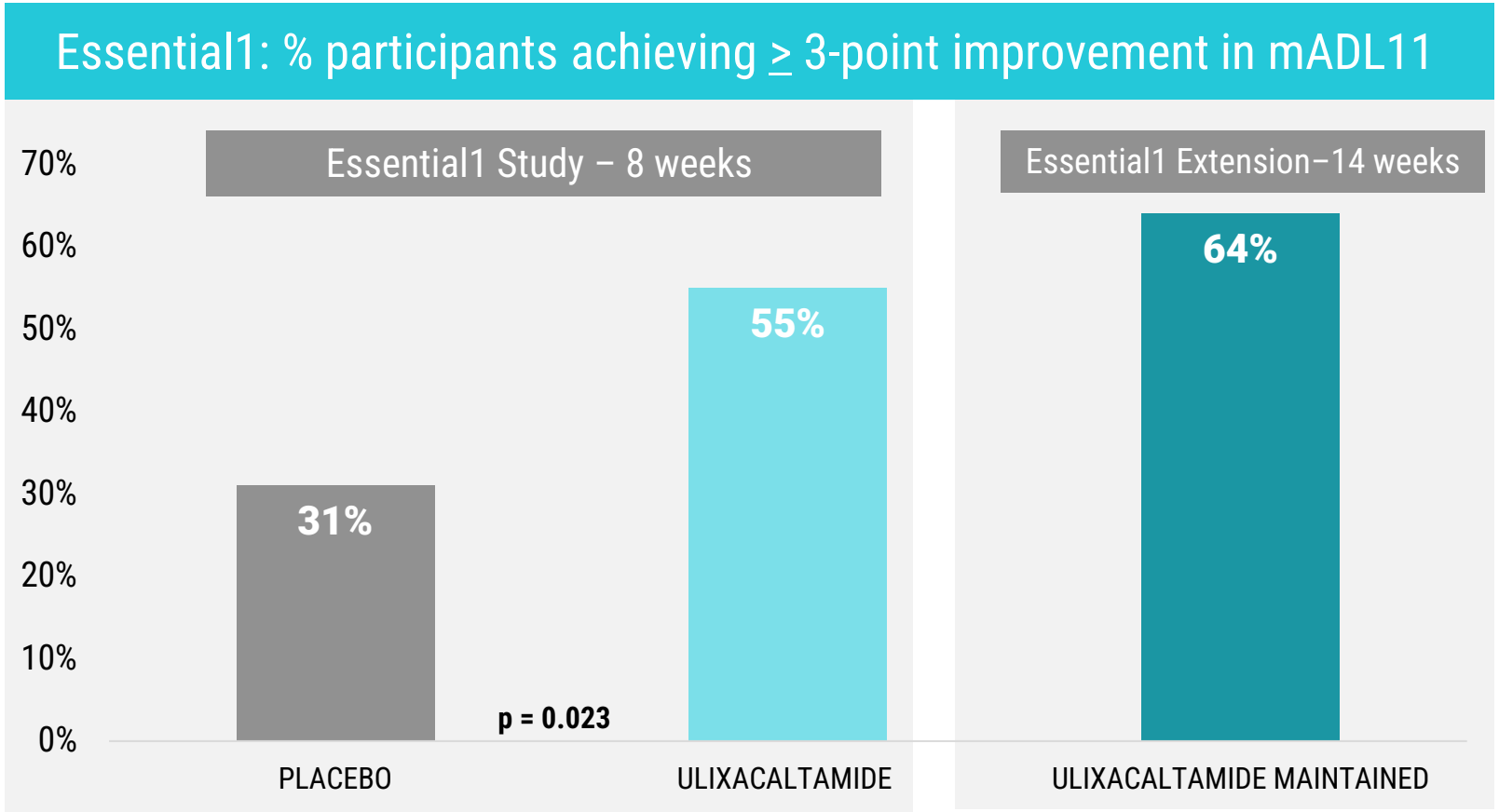
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

April 2023
Procedural

MSD=Meaningful Score Difference, PGI-C = Patient Global Impression of Change

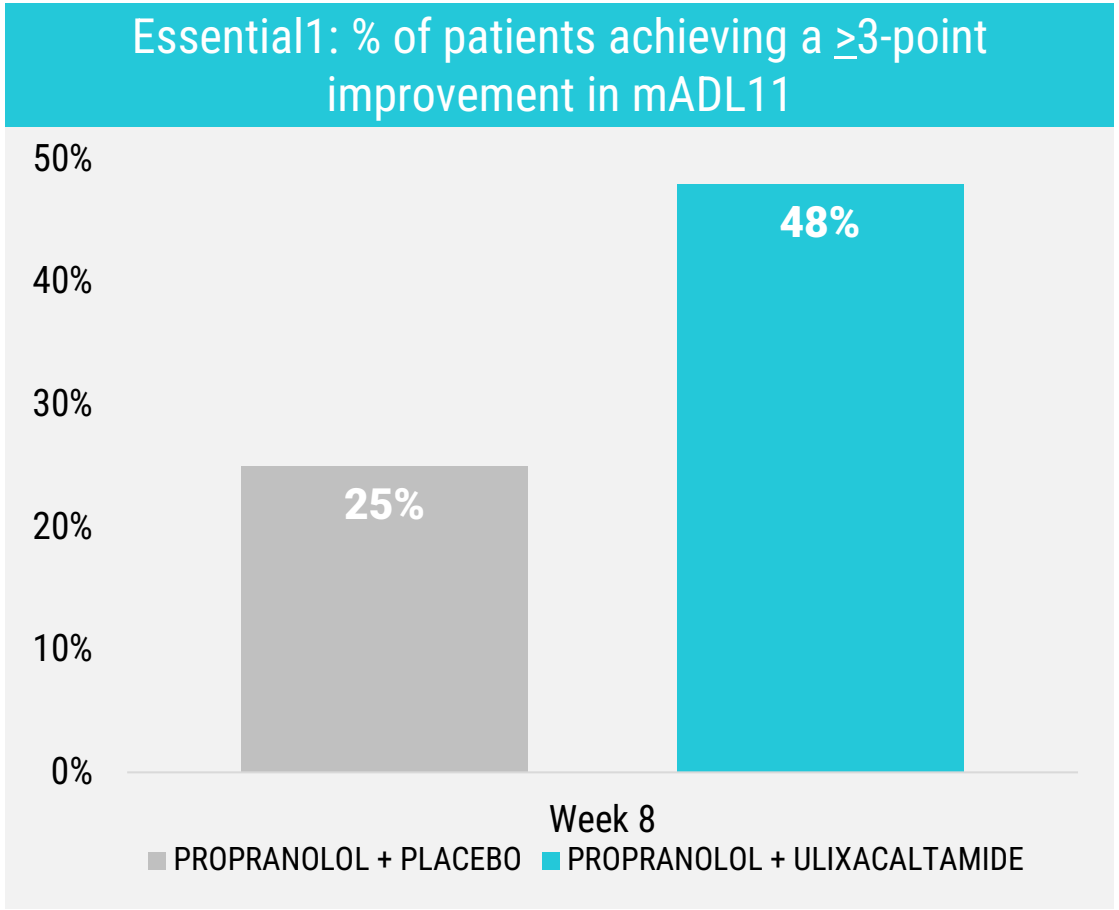
Majority of patients achieved at least a 3-point change in mADL11 at 8 weeks

Durable response in extension study patients who continued through 14 weeks



Results from Essential1 study measuring participants achieving meaningful change at 8 and 14 weeks based on ≥3-point improvement from baseline
https://praxismedicines.com/wp-content/uploads/2023/09/Giroux_MDS2023_E1_MSD_SUBMIT.pdf

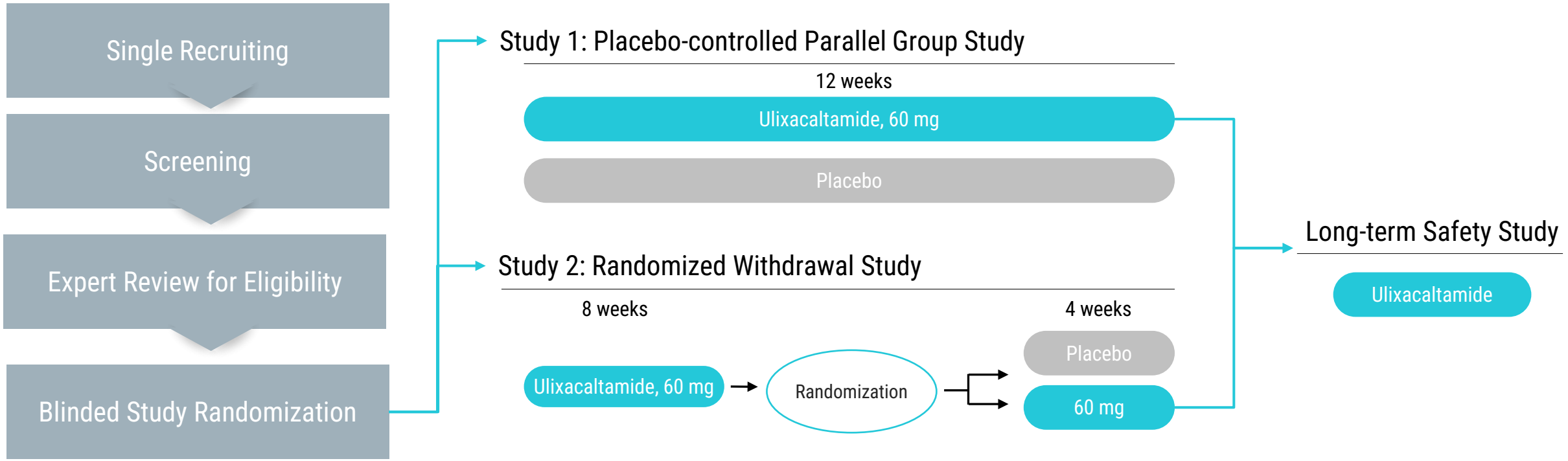
Adding ulixacaltamide benefitted more patients on propranolol



Among patients who could tolerate propranolol, adding ulixacaltamide led to ~2-fold increase in the proportion achieving at least a 3-point improvement in mADL11

Results from Essential1 study showing % of participants on stable propranolol dose achieving meaningful change at 8 weeks based on a meaningful score difference of ≥3 points

Essential3: An innovative Phase 3 program that optimizes all aspects of study conduct



ESSENTIAL 3
AN AT-HOME RESEARCH STUDY

Essential3 Program is well powered

Study	Study 1 – Parallel Design	Study 2 – Randomized Withdrawal
Participants	400	200
Primary endpoint and power	mADL11 Change from Baseline to Week 12 between ulixacaltamide and placebo **90% power to detect difference**	Difference in maintenance of response rate during the 4-week RW period between ulixacaltamide and placebo **90% power to detect difference**
Stratification	Intention tremor status, family history, and propranolol use	
Main Secondary endpoints	○ TETRAS-ADL ○ CGI ○ PGI	

ESSENTIAL 3
AN AT-HOME RESEARCH STUDY

CGI = Clinical Global Impression (Severity); PGI = Patient Global Impression (Severity and Change)

Path to success

De-risked

Trial design based on key learnings from Essential1

Regulatory alignment based on successful End-of-Phase 2 meeting

High Quality and Efficient

Focused execution

Single protocol: Optimized screening, enrollment, analysis

Decentralized study to expand reach and reduce study burden to participants

Interim Analysis

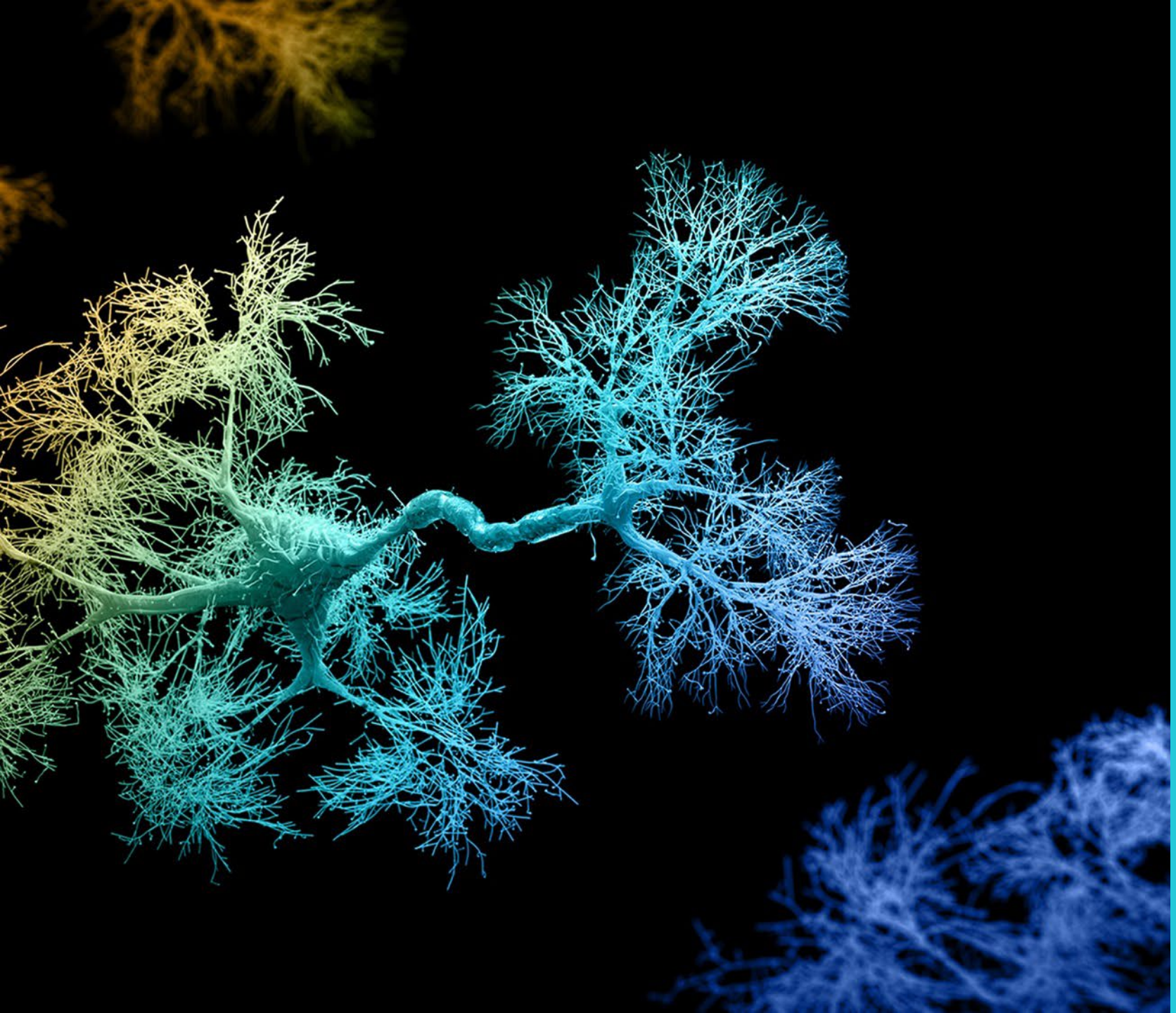
Increases optionality, including potential for sample size re-estimation

Patient-driven Approach

mADL11 as a clinically meaningful primary endpoint

NDA Readiness

Clear path to filing in 2025

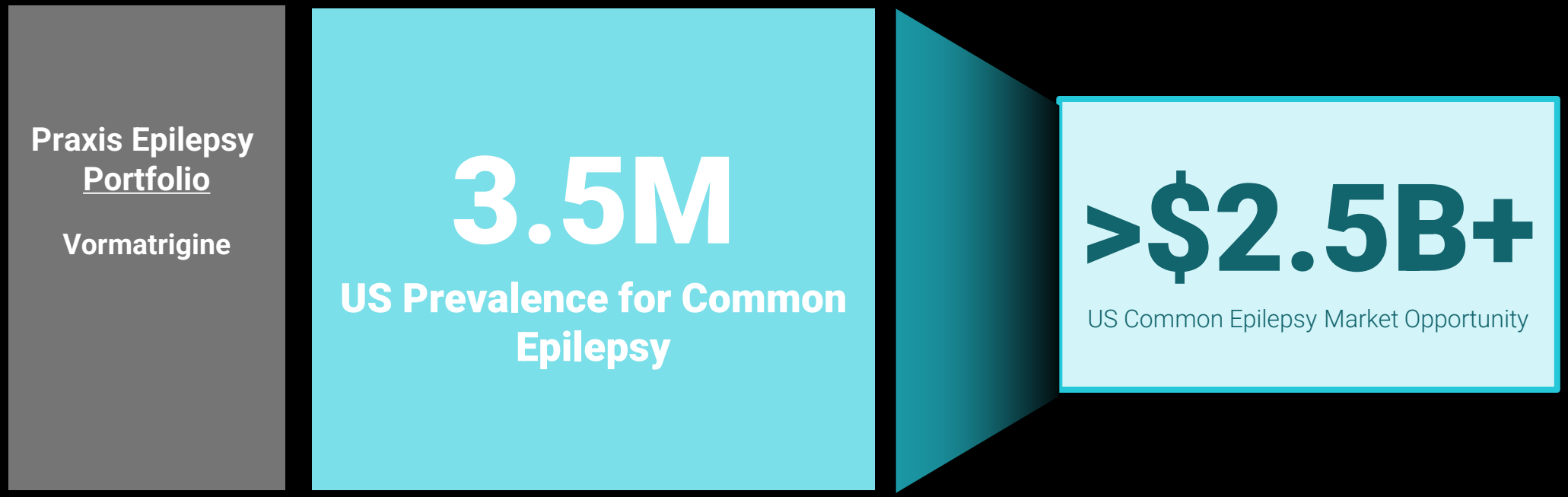


Vormatrigine (PRAX-628)

Milestones

1H 2025: Topline results for RADIANT
1H 2025: Begin enrolling POWER2
2H 2025: Topline results for POWER1

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



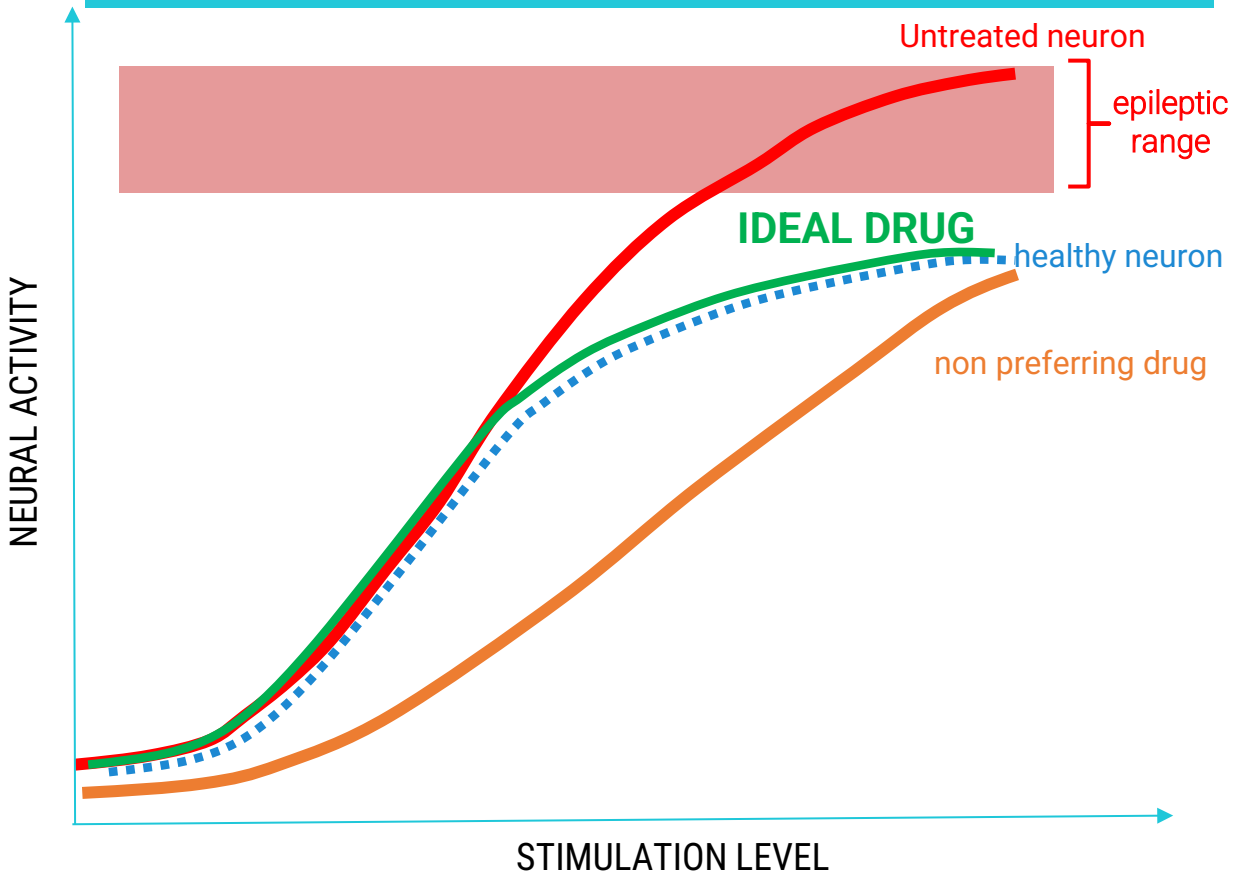
Vormatrigine: Precision medicine therapeutic for focal onset seizures and generalized epilepsy

Differentiated Profile

Next generation, functionally selective small molecule targeting the hyperexcitable states of sodium channels in the brain, with the potential to address limitations of current treatments

- ❑ Ideal safety/tolerability profile
- ❑ Achieves brain penetration
- ❑ Rapidly achieves therapeutic concentrations without titration
- ❑ Favorable half-life and PK profile
- ❑ Optimized efficacy

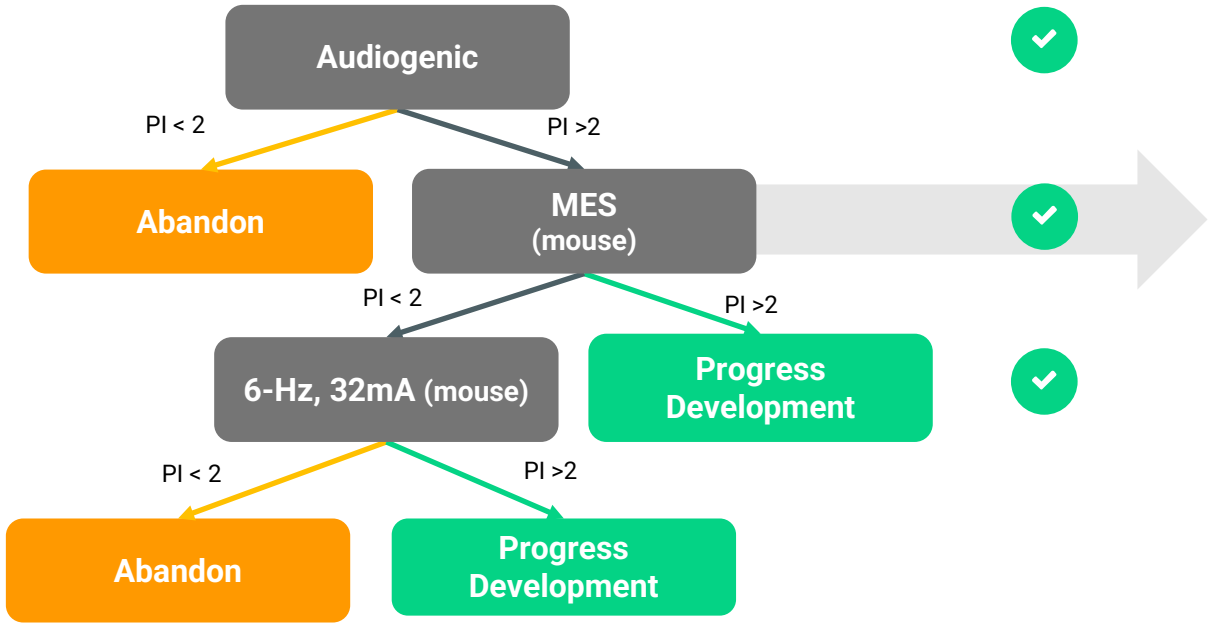
Goal: Preferential action against neuronal hyperexcitability



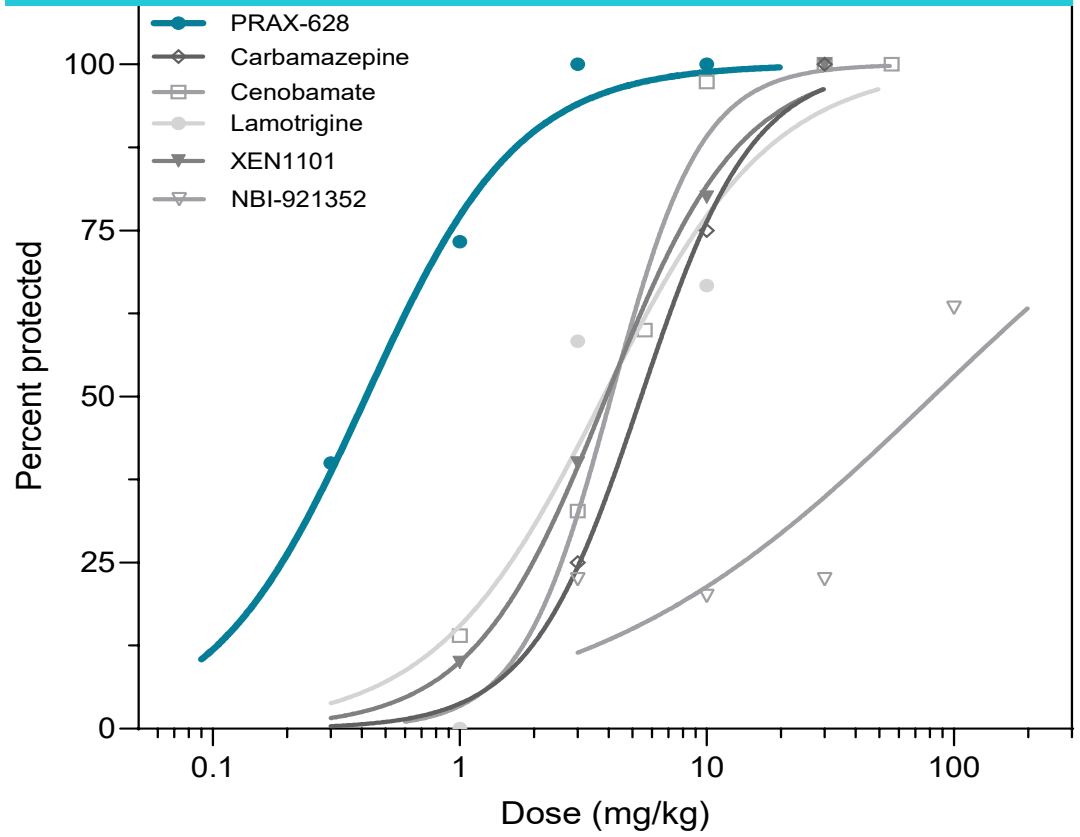
Vormatrigine shows a differentiated pre-clinical profile

Preclinical decision tree optimized for focal seizure drug discovery

Vormatrigine Results



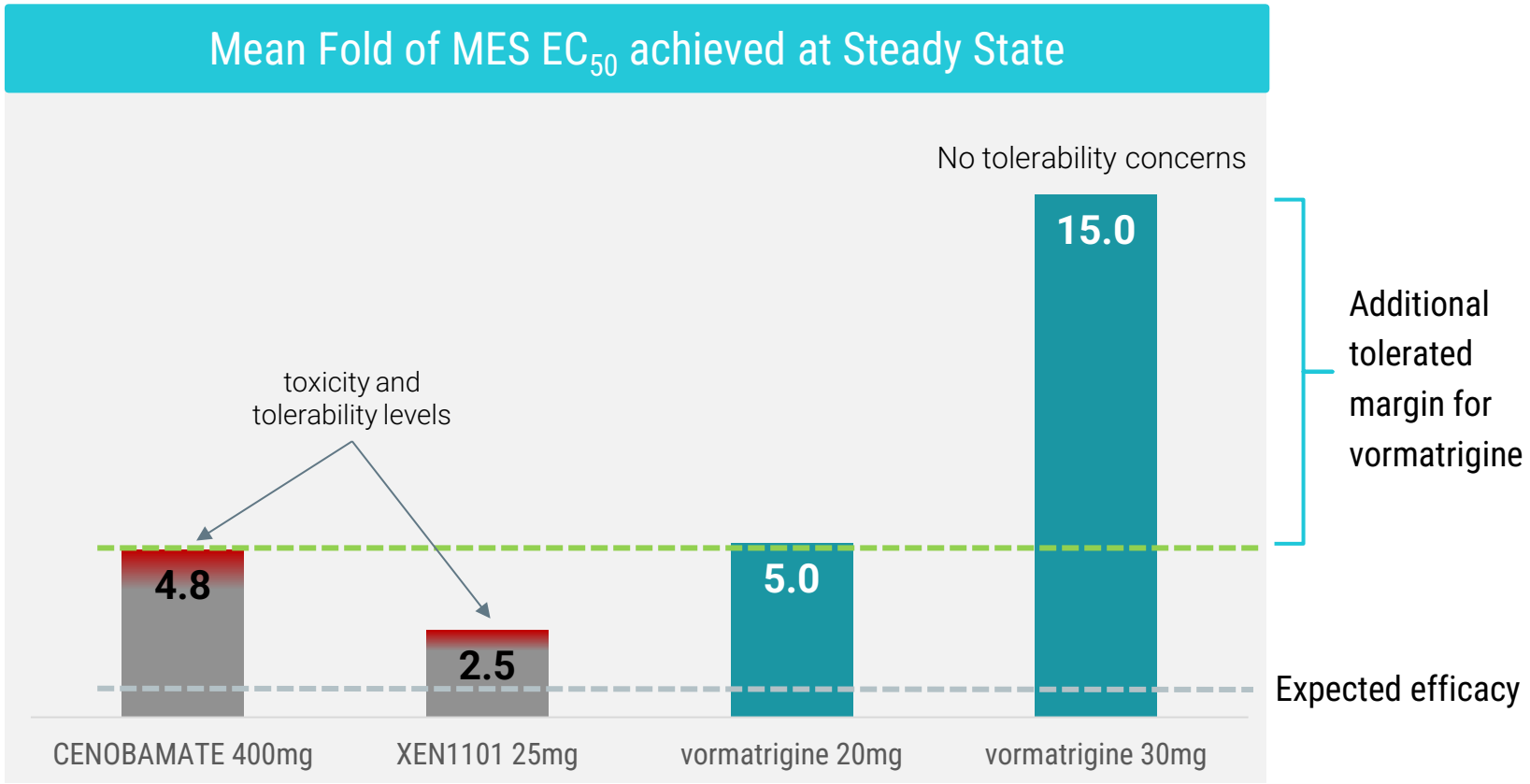
Vormatrigine has differentiated potency in the MES model



Protective index (PI) measured as tolerability / efficacy (TD50 / ED50); MES = maximal electroshock seizure
Praxis data on file; Bialer et al 2024 *Epilepsia*

Ability to significantly exceed therapeutic concentrations while well tolerated

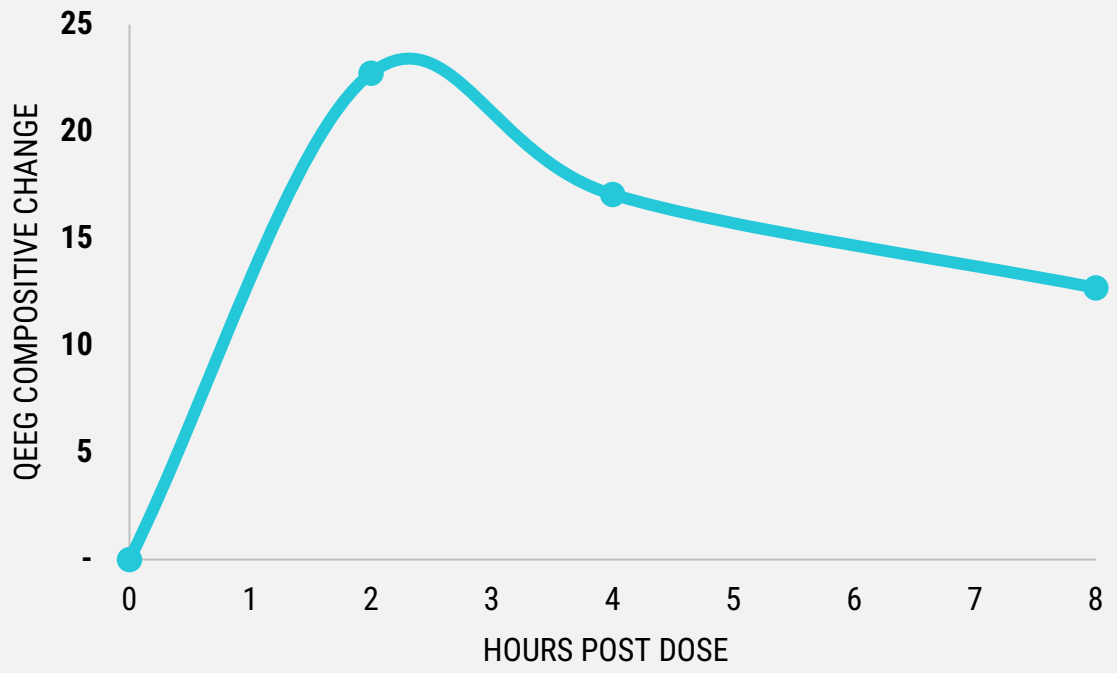
Vormatrigine has unprecedented margins over best-in-class ASMs based on MES efficacy and clinical tolerability in humans



Source: Praxis data on file (Ph1 study), Cenobamate Cmax: >46,100 ng/mL, 400 mg Cmax (Vernillet et al 2020), XEN1101 Cmax: >107 ng/mL (Phase 1 data)
x MES EC50 = multiple of predicted human EC50 based on the rodent MES model; IEC2023_628-SAD-MAD

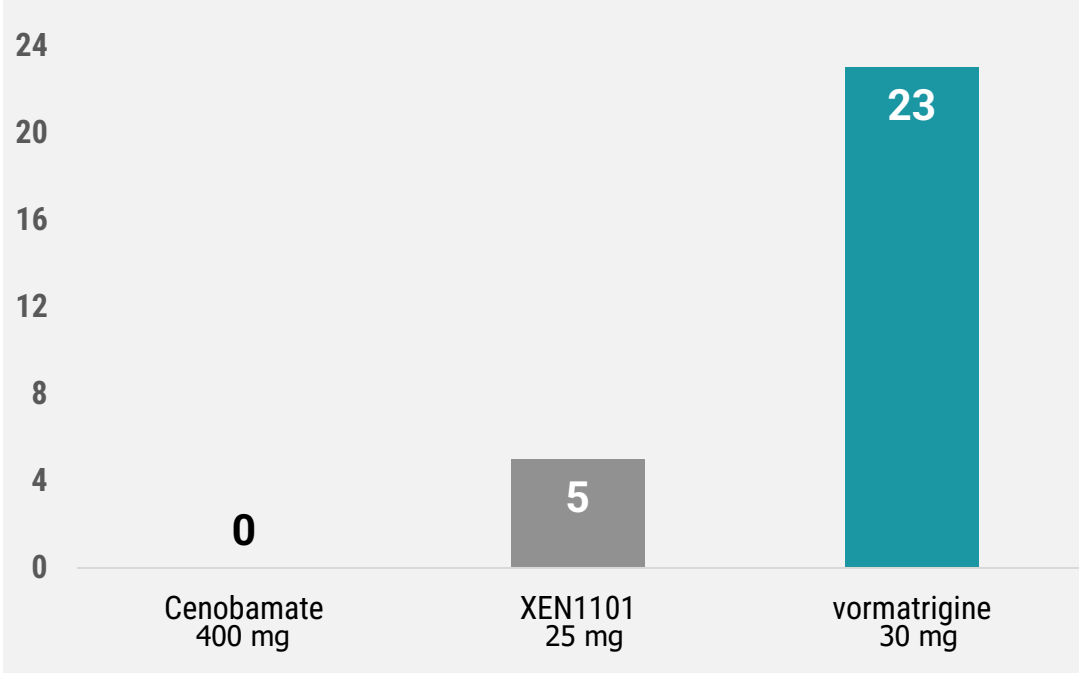
Phase 1 study demonstrated brain activity and rapid achievement of therapeutic concentrations

Vormatrigine composite qEEG change



- Composite endpoint from qEEG showed separation of drug versus placebo in the SAD and MAD cohorts
- Difference between vormatrigine and placebo significant for all doses at first point measured
- Effect consistent with known PK profile

Hours of day 1 drug coverage



- Vormatrigine achieves nearly complete coverage on Day 1

SAD = single ascending dose; MAD = multiple ascending dose

Garimella et al AES 2023; Praxis data on file

The Phase 2 vormatrigine Photo Paroxysmal Response (PPR) study demonstrated proof of concept; de-risks advancing to studies in focal and generalized epilepsy

Study Results

- 100% response in treated patients
- Vormatrigine achieved between 3-13x multiples of MES EC_{50} exposure
- Safety was consistent with prior dose escalation study and AEs were mild

- 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 observation period

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)**

https://investors.praxismedicines.com/static-files/edc15000-7fcb-4d6d-b1de-1819898214a8

Vormatragine presents an ideal precision ASM profile

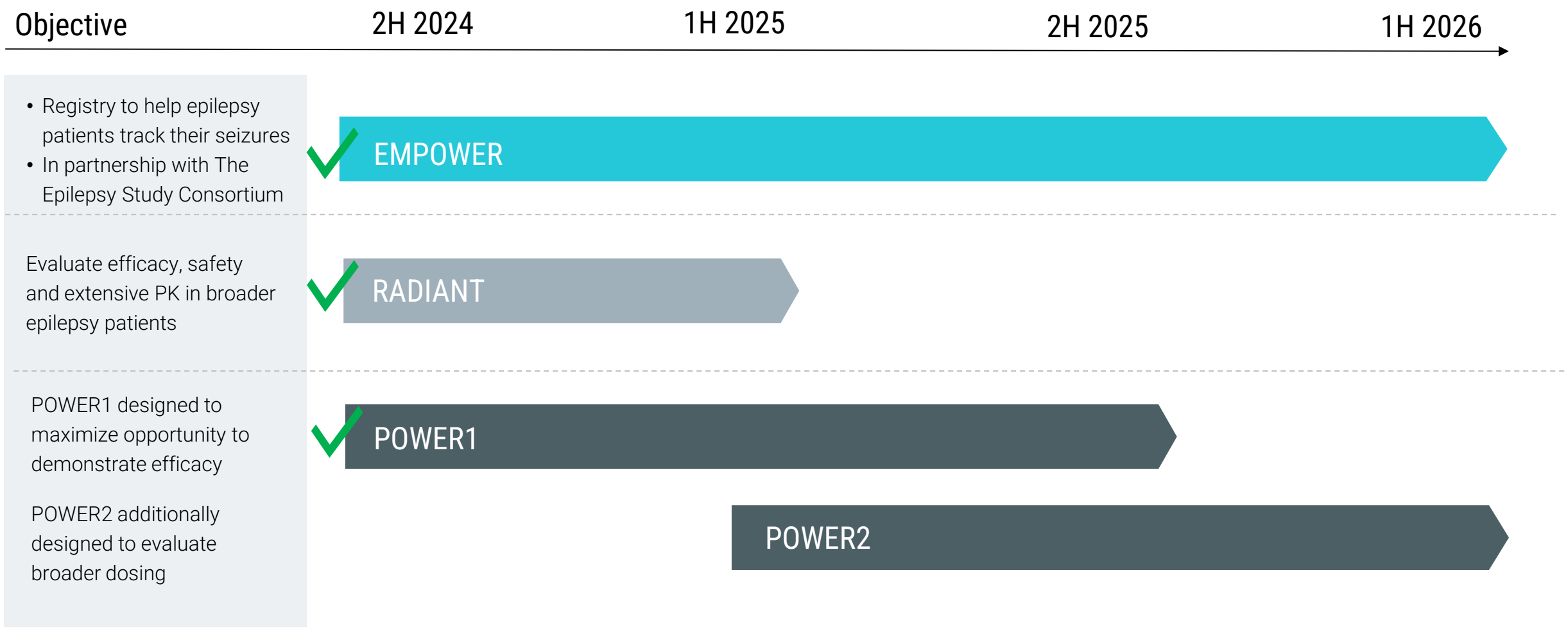
Ideal Treatment

- 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 achieved in epilepsy patients

Three efficacy trials in the ENERGY program

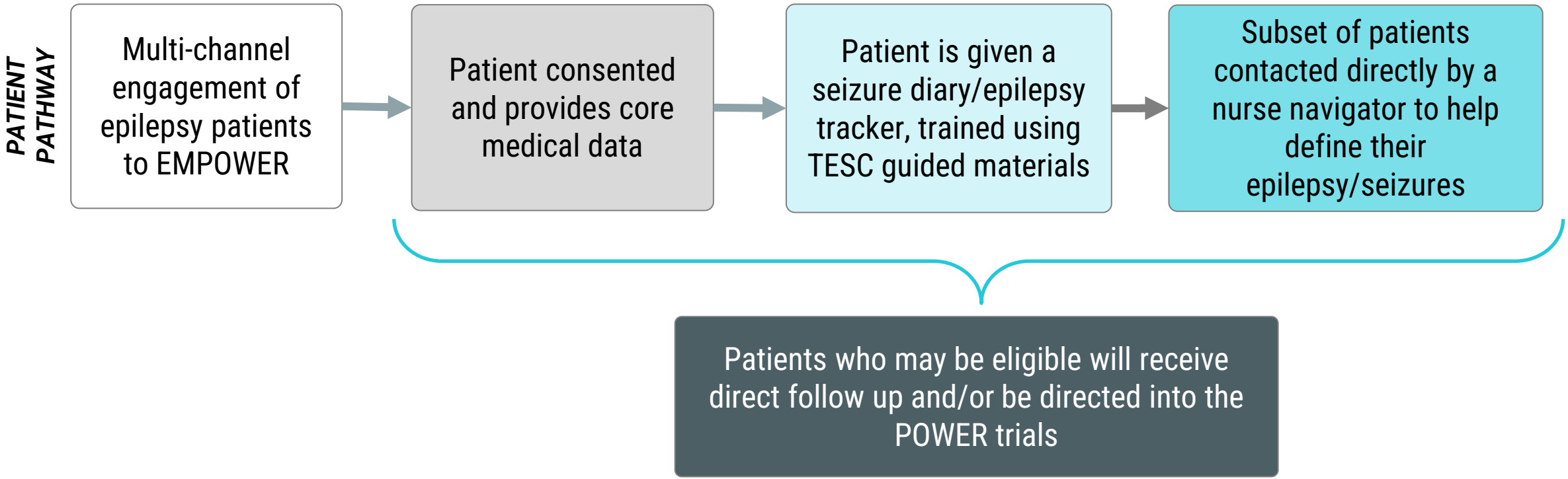
https://praxismedicines.com/wp-content/uploads/2023/12/Kahlig_AES2023_628-In-Vivo_Poster_Final.pdf
https://praxismedicines.com/wp-content/uploads/2023/09/IEC2023_628-SAD-MAD.pdf

Vormatrigine ENERGY program to demonstrate efficacy and bring an improved therapy to focal and generalized epilepsy patients

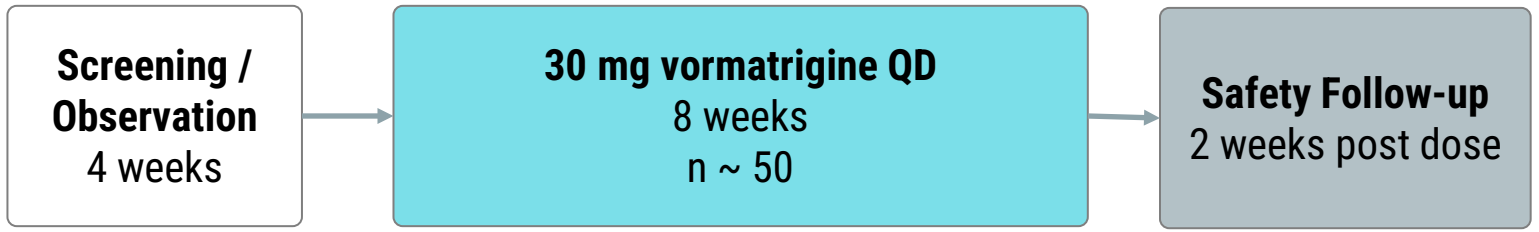


EMPOWER Observational Study to better understand patient journey

In partnership with The Epilepsy Study Consortium (TESC)



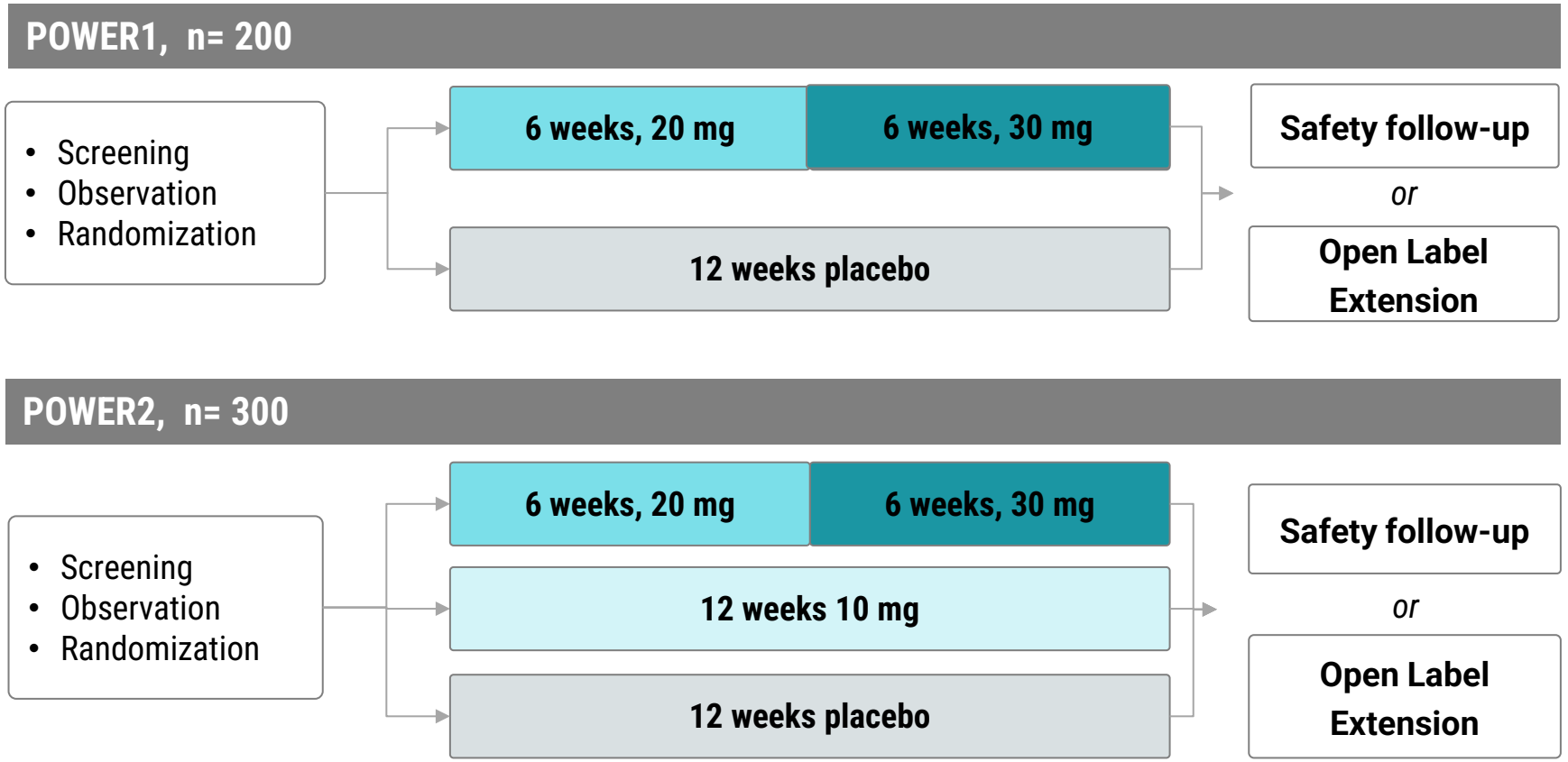
RADIANT Phase 2 open label study to evaluate safety and efficacy in focal onset or generalized epileptic seizures



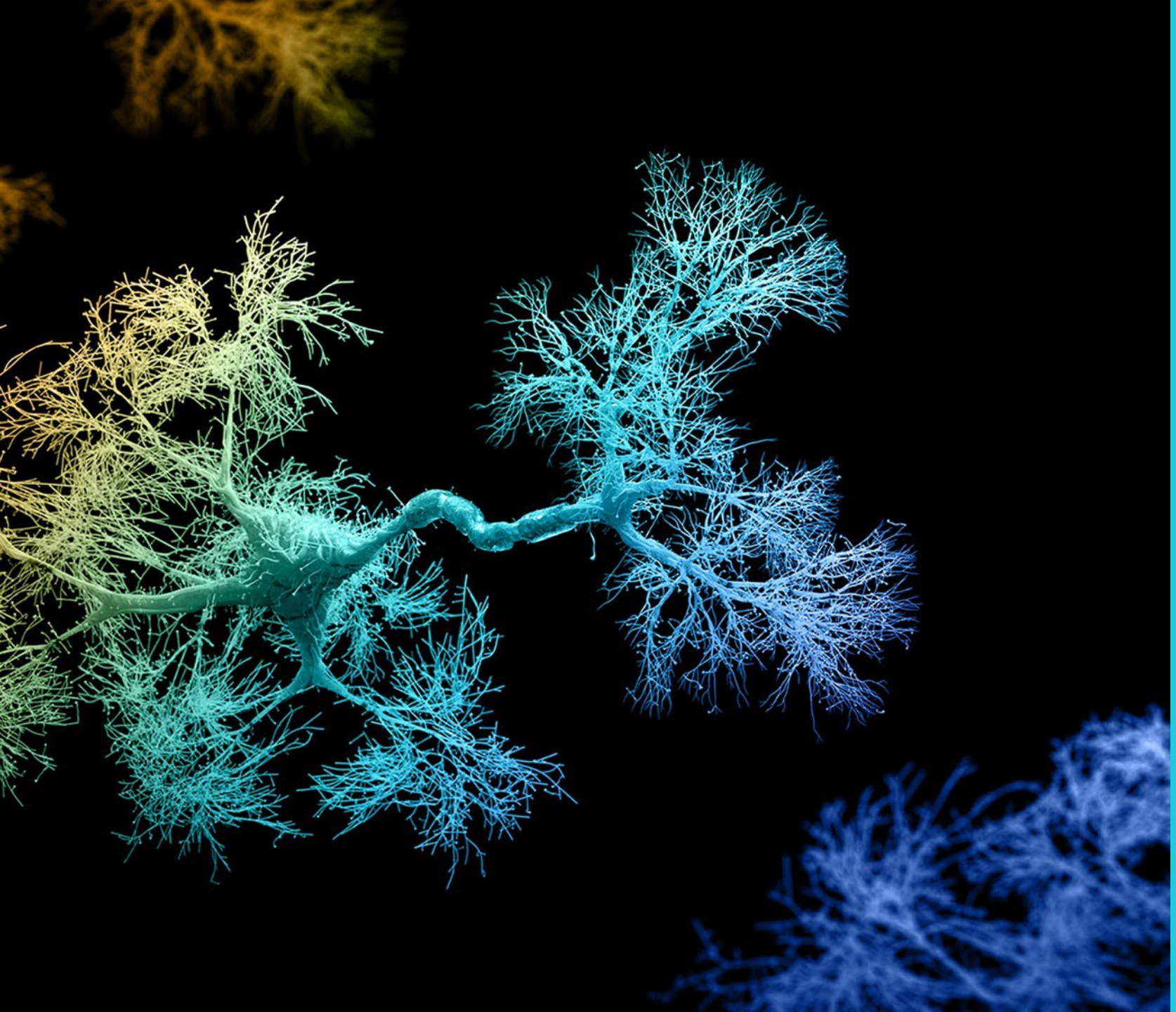
- Measuring seizure frequency, seizure freedom, safety and pharmacokinetics
- Will allow the evaluation of vormatrigine in a broader population, including generalized epilepsy
- Topline results in 1H 2025

QD = Once daily

Proposed study designs for POWER1 and POWER2



- POWER1 initiated in Q4 2024 with topline readout 2H 2025
- POWER2 to initiate in 1H 2025

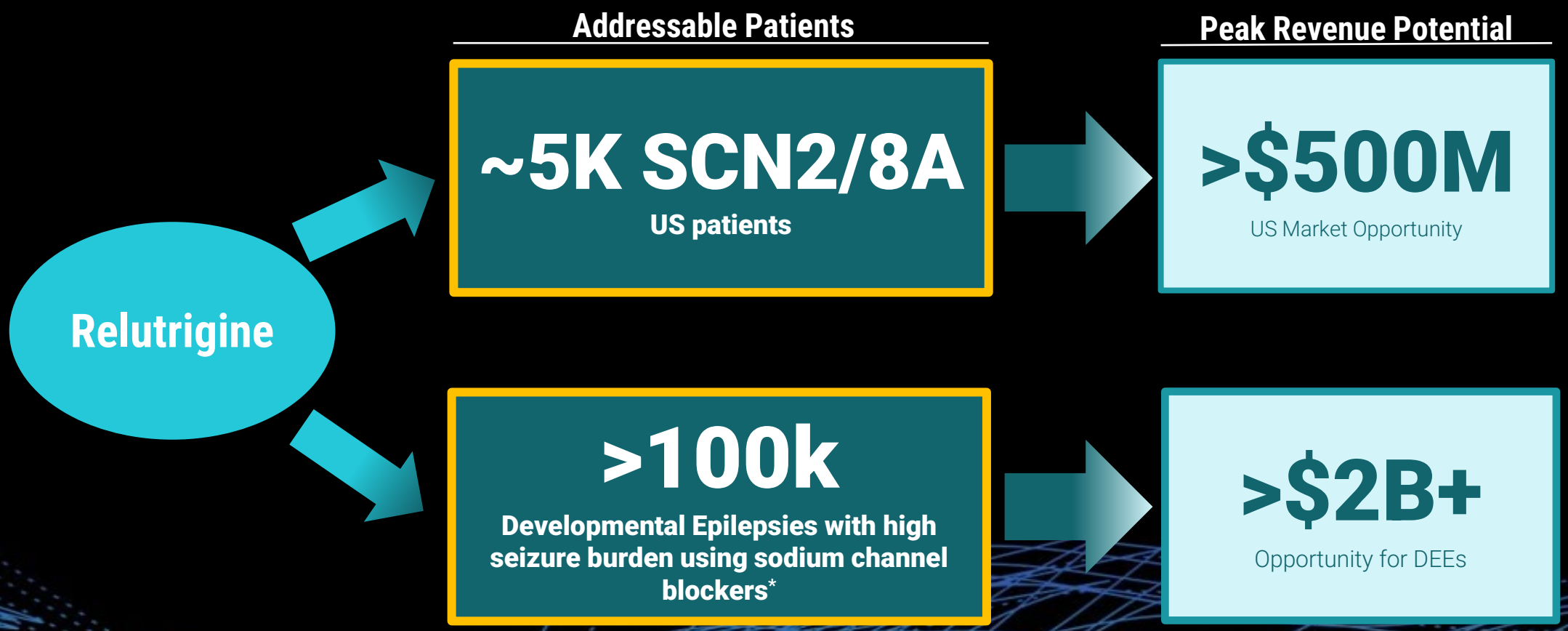


Relutrigine (PRAX-562)

Milestones

2H 2024: EMBOLD Cohort 2 enrolling
1H 2025: Initiate EMERALD study

Relutrigine is poised to disrupt the DEE market



*Poke G, Stanley J, Scheffer IE, Sadleir LG. Epidemiology of Developmental and Epileptic Encephalopathy and of Intellectual Disability and Epilepsy in Children

Preclinical and emerging clinical data demonstrate relutrigine has the potential to be a first- and best-in-class small molecule for DEEs

RELUTRIGINE

SCN2A, SCN8A

FORMULATED FOR PEDIATRIC USE

SMALL MOLECULE

FUNCTIONAL STATE MODULATOR

- Superior selectivity for disease-state Na_V channel hyperexcitability
- Unprecedented therapeutic window with potential for superior safety and efficacy
- Generally well-tolerated with mostly mild to moderate AEs, no drug-related SAEs and no relutrigine dose reduction required
- Demonstrated robust seizure reduction and unprecedented seizure-free status per 28-day period

Relutrigine Phase 1 summary

Relutrigine has been generally well tolerated in over 130 healthy volunteers

No MTD at exposures multiple fold above therapeutic range indicates potential for superior therapeutic index

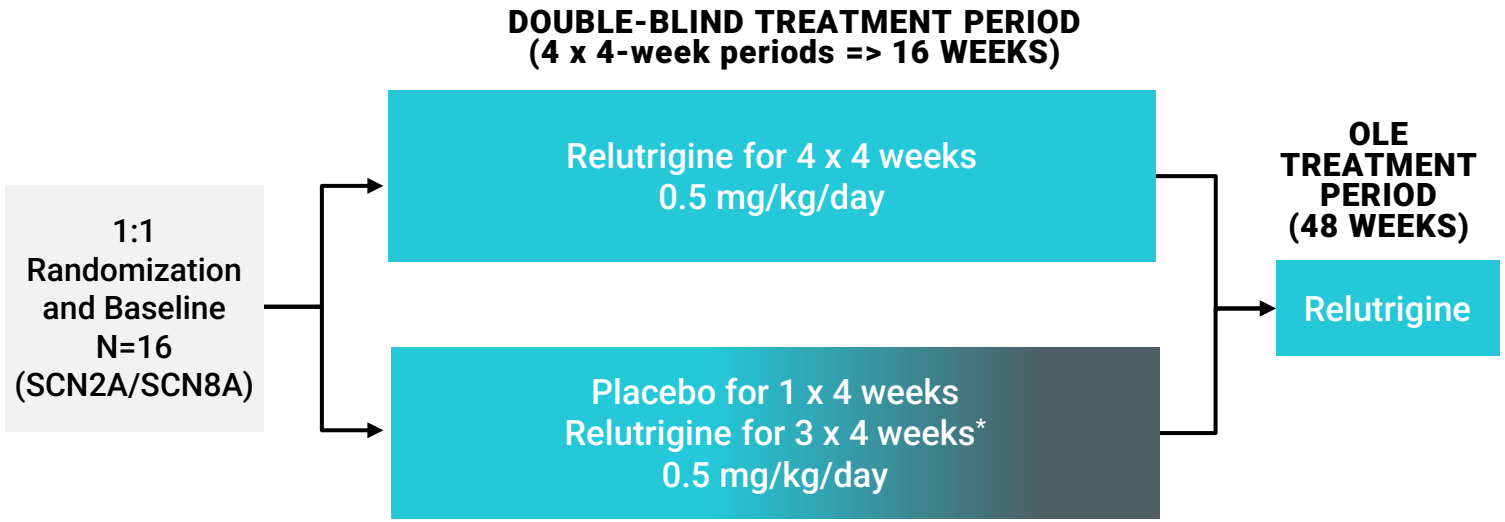
All TEAEs mild to moderate as stand-alone therapy*, with headache & dizziness most common TEAEs

Significant changes observed between placebo and relutrigine on qEEG biomarkers

Source: Praxis data on file; https://investors.praxismedicines.com/news-releases/news-release-details/praxis-precision-medicines-provides-corporate-update-and-5

* Co-administration of supra-therapeutic doses of relutrigine and oxcarbazepine led to additive sodium blocking effects, including resulting in SAEs

Relutrigine Phase 2 EMBOLD study design and endpoints



KEY ENDPOINTS:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Change from baseline in monthly (28-day) motor seizure frequency
- Seizure freedom achieved for a 4-week period
- Clinical and Caregiver Global Impression of Improvement and Severity

EMBOLD

* Participants receive either 0.5 mg/kg/day relutrigine QD for 16 weeks or 0.5 mg/kg/day relutrigine QD for 12 weeks & matching placebo QD for 4 weeks. Participants in the relutrigine/placebo arm will receive placebo for 4 consecutive weeks during the 16-week treatment period, with timing of placebo administration blinded for both participants and investigator. Dose adjustment permitted to a max of 1.0 mg/kg/day and a min of 0.25 mg/kg/day.

Relutrigine demonstrated robust reduction in motor seizures and unprecedented seizure-free status per 28-day period

1,778 Motor Seizures at Baseline (n=15)

46%

placebo-adjusted reduction in motor seizures over double-blind period*

Seizure Freedom Periods Never Seen Before in this Population

5 patients

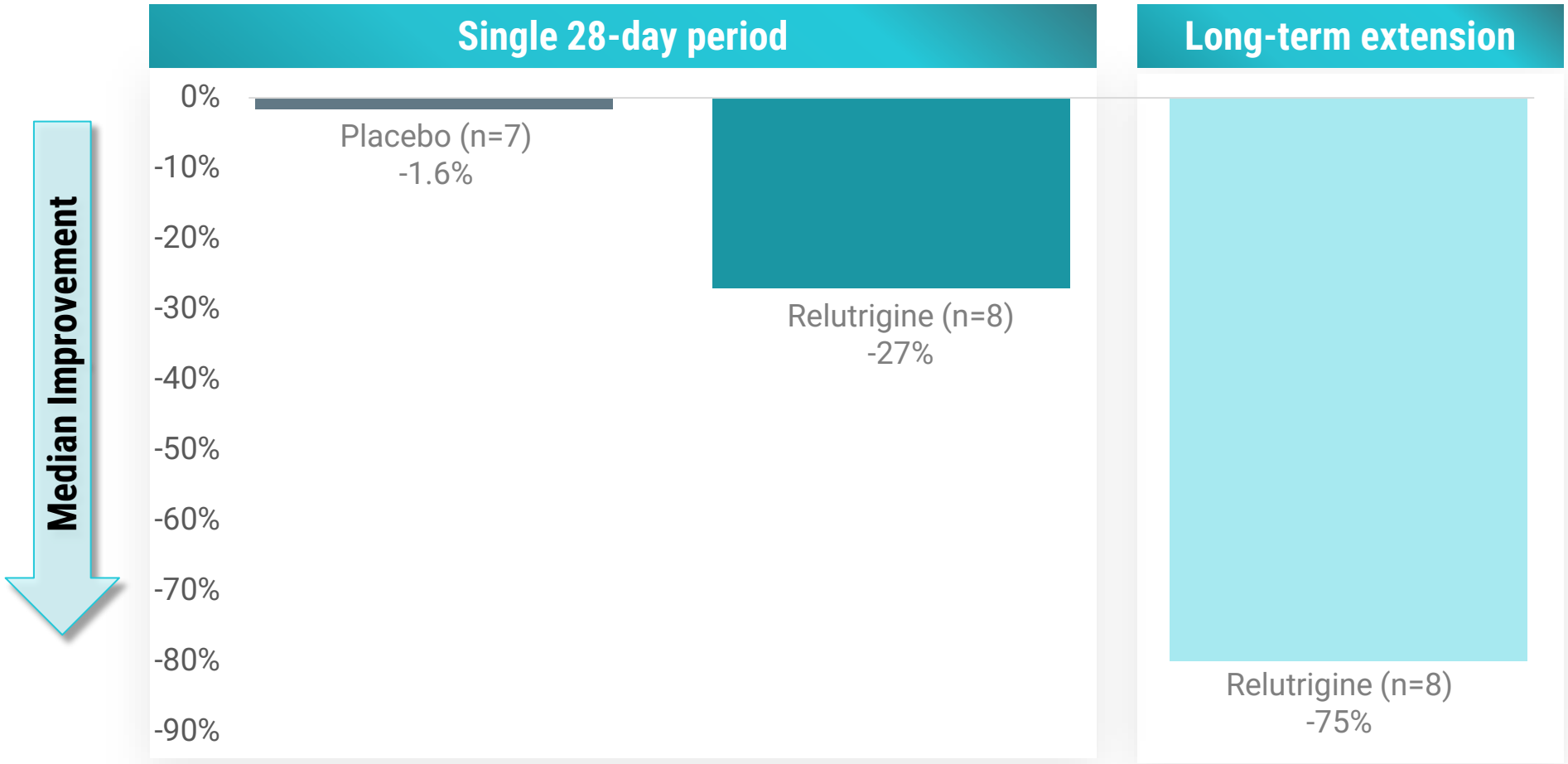
- 33% of patients seizure-free after initiating on relutrigine**
- Longest follow-up >200 days seizure-free

EMBOLD

*Percent reduction derived from log-transformed placebo-adjusted relutrigine effect

**Assessment of motor seizures over the controlled plus open-label periods through August 21, 2024

Relutrigine patients demonstrated significant improvement over the short and long-term in motor seizures



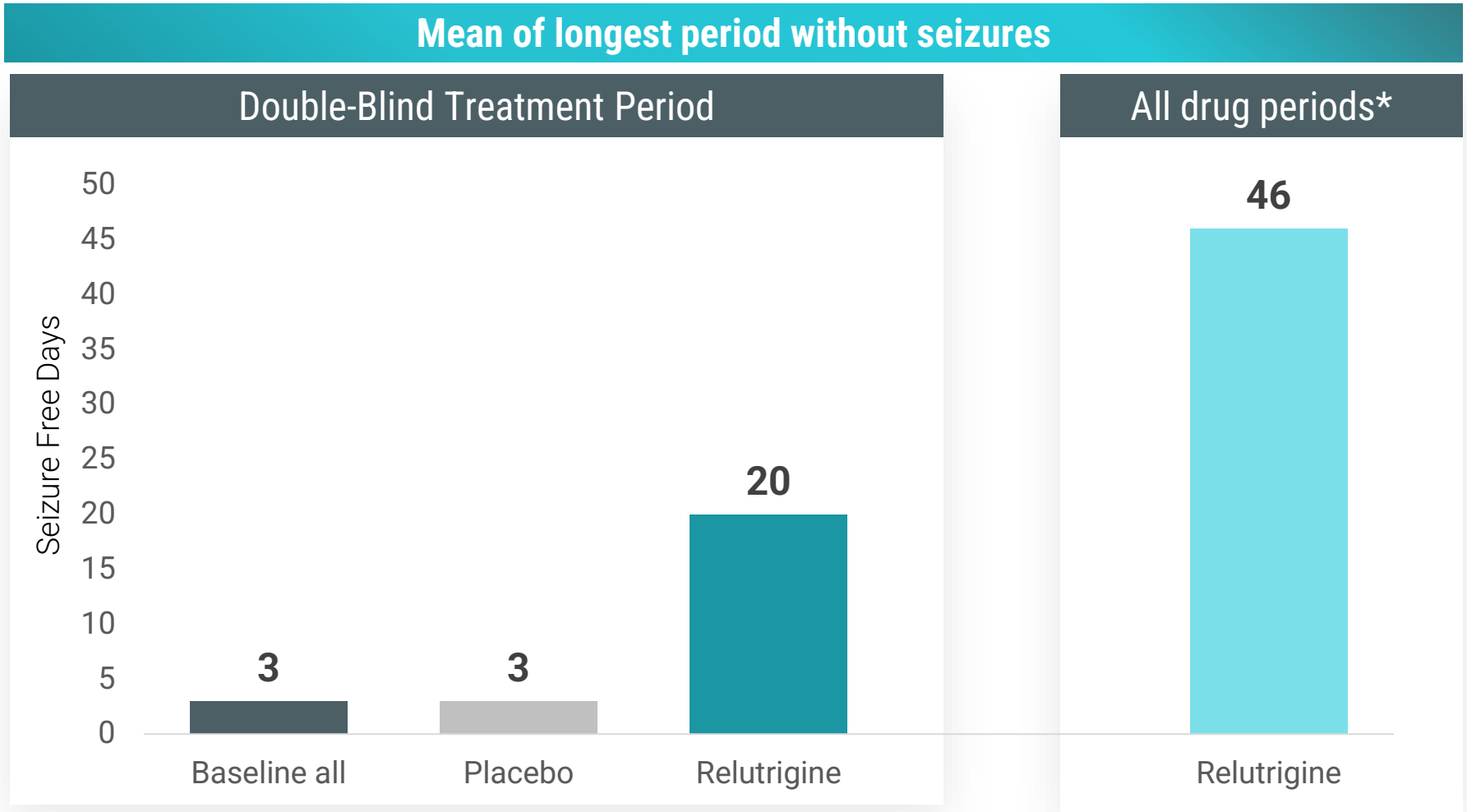
7 patients increased the dose of relutrigine to 1 mg/kg during the double-blind period, 2 additional patients during the long-term extension

Seizure freedom associated with exposures achievable by 1 mg/kg

EMBOLD

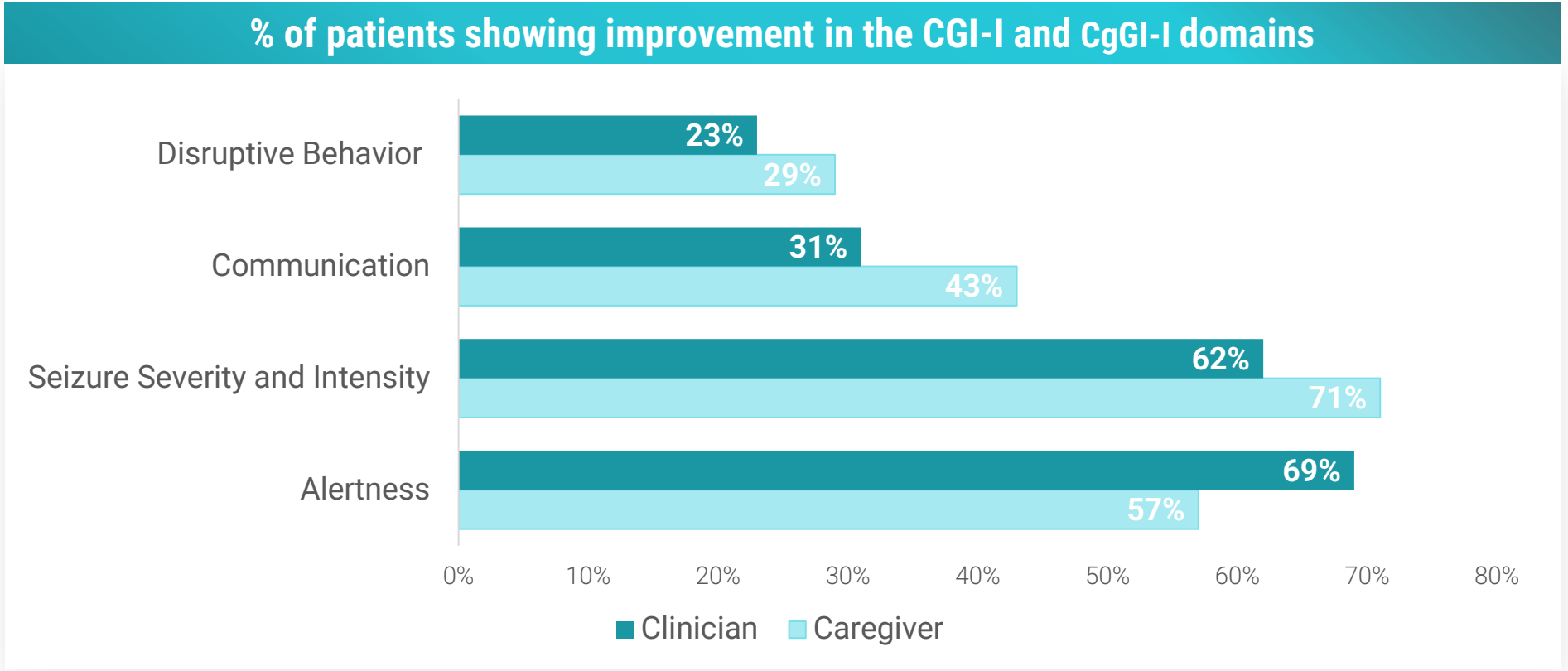
Long-term extension data for 8 patients with data available for at least one 28-day period as of August 21, 2024

Meaningful and consistent impact in days without motor seizures for relutrigine treated patients



* Inclusive of OLE period

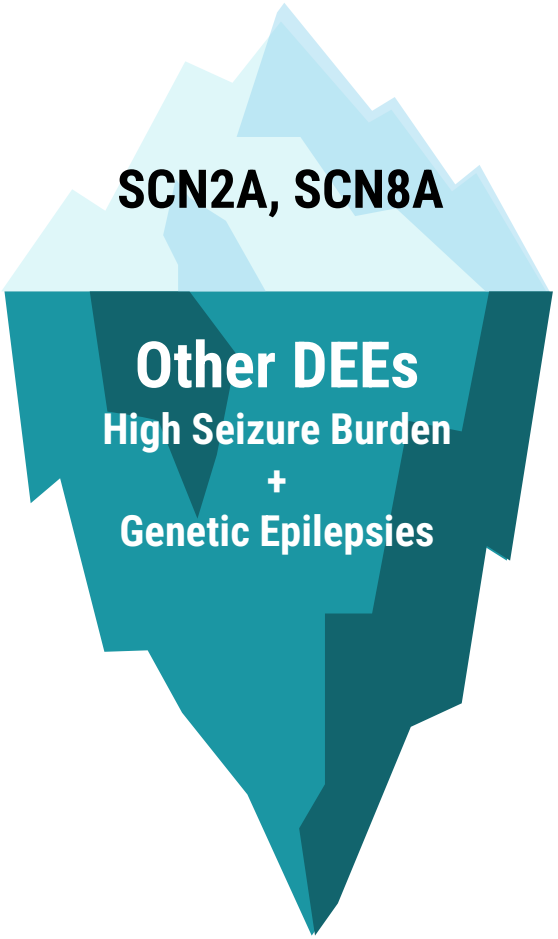
Relutrigine treatment led to disease modifying impact



Meaningful gains in overall well-being of patients, despite severity and historical lack of improvement with available treatments

Clinical Global Impression of Improvement and Caregiver Global Impression of Improvement assessed at Week-16 visit

SCN2A and SCN8A are the tip of the iceberg in addressing the significant unmet needs across the spectrum of other DEEs



EMBOLD

~5,000 patients

>$500m peak revenue

>70%
DEE patients treated with sodium channel blockers*

Low tolerability and inadequate response

>100,000 patients

>$2bn peak revenue market opportunity

*Based on PubMed Search of DEEs that could use SCBs to treat focal seizures when they presented.

Next steps

Initiated EMBOLD cohort 2 registrational trial for SCN2A and 8A, begin enrollment for EMERALD trial in 1H 2025

2H 2024 **1H 2025**

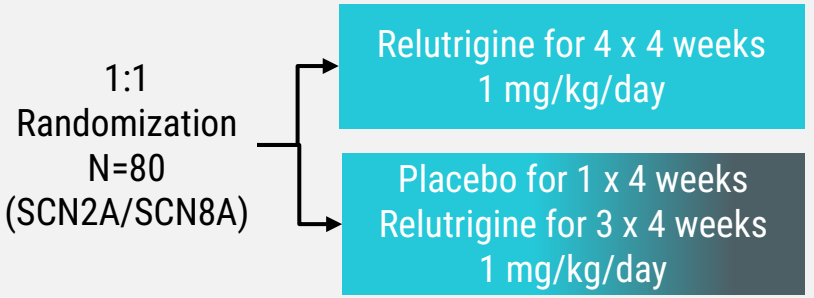
SCN2A /8A

- EMBOLD registrational Cohort 2 initiated
- Leveraging EMBOLD successful study design

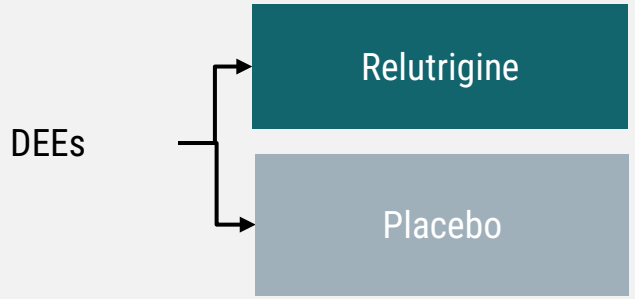
DEES

Regulatory agency input → Initiate EMERALD Trial

Ongoing Study



Preliminary Design



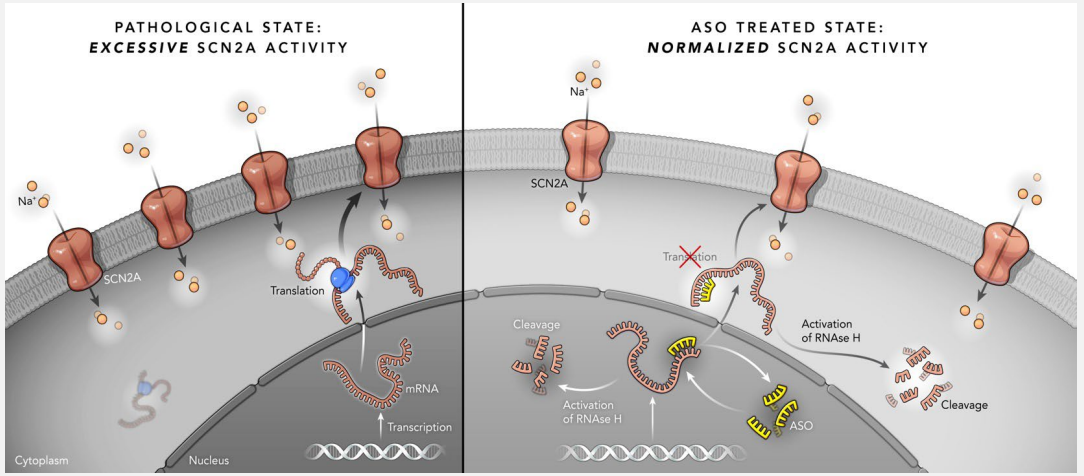
Elsunersen (PRAX-222)

SOLIDUS™ ASO PLATFORM

Elsunersen specifically designed for SCN2A GoF patients

DISEASE OVERVIEW

- Epilepsy and developmental impairment before the age of 16 years occurs in 1 in 340 children
- The majority of these cases result from sporadic de novo genetic variation
- In both de novo and familial forms of epilepsy some 900 genes have been identified
- Many of these genes also represent opportunities for intervention in other neurological disorders
- Patients with SCN2A-DEE have a debilitating and ultimately fatal trajectory
- Affects approximately 1,500 patients in the US



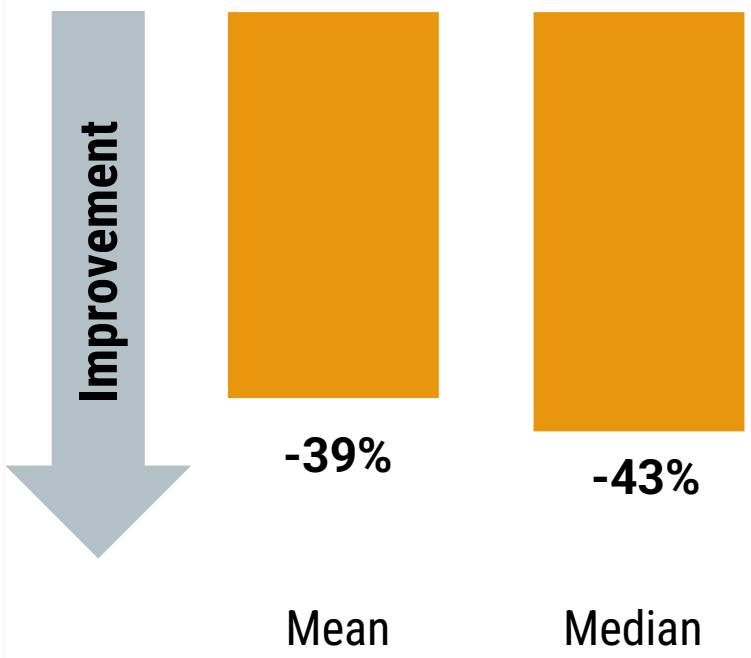
RESEARCH APPROACH

Modifying gene expression to address both gain and loss of function disorders is achieved through various ASO modalities to either silence harmful genes or enhance expression of reduced function or missing genes

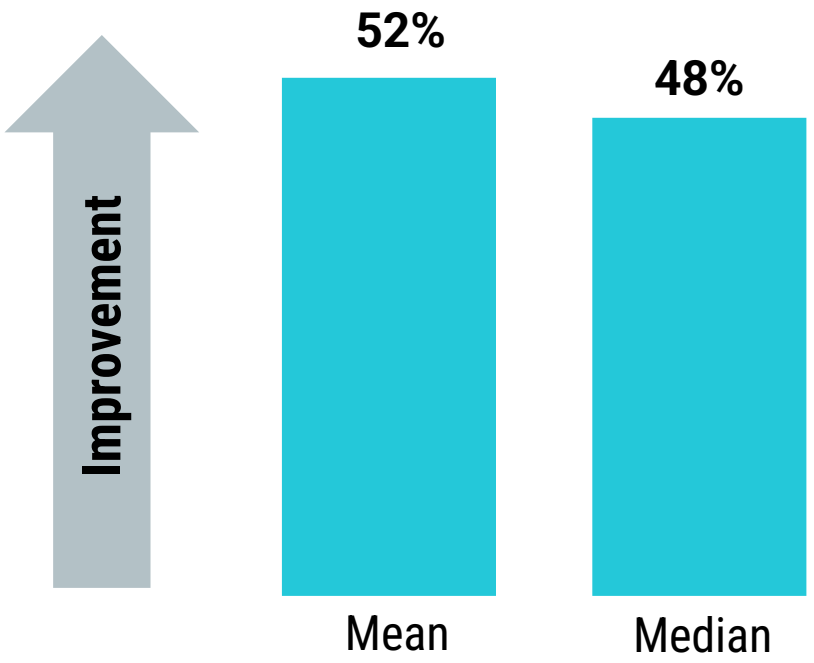
Significant reduction in seizures observed for SCN2A patients

EMBRAVE

Overall % reduction in seizures from 28-day baseline (n=4)



Overall relative % increase in seizure-free days from 28-day baseline (n=4)



- No TEAEs or SAEs considered related to study drug
- All TEAEs recovered/resolved

Data from Part 1 of EMBRAVE Study, https://praxismedicines.com/wp-content/uploads/2023/12/Frizzo_AES2023_EMBRAVE_Poster_Final.pdf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