UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 6, 2024

PRAXIS PRECISION MEDICINES, INC.
(Exact name of registrant as specified in its charter)

Delaware	001-39620	47-5195942
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

Praxis Precision Medicines, Inc.
99 High Street, 30th Floor
Boston, Massachusetts 02110
(Address of principal executive offices, including zip code)

(617) 300-8460
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**PRAX**	**The Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02. Results of Operations and Financial Condition.

On November 6, 2024, Praxis Precision Medicines, Inc. (the "Company") announced its financial results for the quarter ended September 30, 2024. A copy of the press release containing these announcements is furnished as Exhibit 99.1 to this Current Report on Form 8-K (the "Current Report").

Item 7.01. Regulation FD Disclosure.

On November 6, 2024, the Company updated its corporate presentation for use in meetings with investors, analysts and others. The presentation is available in the "Investors + Media" portion of the Company's website at investors.praxismedicines.com and a copy is furnished as Exhibit 99.2 to this Current Report.

The information in this Current Report under Items 2.02 and 7.01, including Exhibit 99.1 and Exhibit 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated November 6, 2024
99.2	Praxis Precision Medicines, Inc. November 2024 Corporate Presentation
104	Cover Page Interactive Data File (embedded within the inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRAXIS PRECISION MEDICINES, INC.

Date: November 6, 2024

By: /s/ Marcio Souza
Marcio Souza
Chief Executive Officer

Praxis Precision Medicines Provides Corporate Update and Reports Third Quarter 2024 Financial Results

Interim analysis for Study 1 of Essential3 Phase 3 program for ulixacaltamide in essential tremor (ET) confirmed for Q1 2025; NDA filing anticipated in 2025

Registrational Cohort 2 of EMBOLD study recruiting following unprecedented seizure freedom seen in positive topline EMBOLD results for Cohort 1 in SCN2A and SCN8A developmental and epileptic encephalopathies (DEEs)

Vormatrigine (PRAX-628) on track for topline from POWER1 study in focal epilepsy and RADIANT study in focal and generalized epilepsy in 2025

Maintains runway into 2027

BOSTON, November 6, 2024 — Praxis Precision Medicines, Inc. (NASDAQ: PRAX), a clinical-stage biopharmaceutical company translating genetic insights into the development of therapies for central nervous system (CNS) disorders characterized by neuronal excitation-inhibition imbalance, today provided a corporate update and reported financial results for the third quarter 2024.

"This quarter we made substantial strides in advancing our pipeline, notably progressing a third molecule with blockbuster potential, relutrigine, into late-stage development, while for ulixacaltamide we have finalized the operational plan to complete the interim analysis for Essential3 Study 1 in mid-Q1 2025. The positive topline results we shared this quarter from EMBOLD cohort 1 underscore relutrigine's promise as a first- and best-in-class therapy for DEEs, demonstrating unmatched seizure-freedom and reduction in SCN2A and 8A patients, along with disease-modifying effects. As a result, we have rapidly advanced the SCN2A/8A program to registrational stage and are expanding our studies to cover a broader range of DEEs" said Marcio Souza, president and chief executive officer of Praxis.

Mr. Souza continued, "Our ENERGY program for vormatrigine (PRAX-628) is moving forward with strong interest, driven by insights from the ongoing observational EMPOWER study, and we are on track with our RADIANT and POWER1 trials. Additionally, we are actively exploring lifecycle expansion opportunities in Parkinson's Disease and pain. With strong financial and clinical positioning, we are set to build on this momentum, advancing all four clinical programs towards registrational readiness in 2025."

Recent Highlights and Anticipated Milestones:

Cerebrum™ Small Molecule Platform

- **Ulixacaltamide for Essential Tremor (ET):** Results of the planned interim analysis for Essential 3 Study 1 are expected Q1 2025.
  - Timing of topline read-out for Study 1 and Study 2 in the Phase 3 Essential3 program will be updated upon review of the interim analysis.
  - In anticipation of positive outcomes with ulixacaltamide in ET, Praxis expects to re-initiate the Parkinson's disease program in 2025.
  - Highlighting the unmet need in ET, Praxis recently shared two surveys at the Movement Disorder Specialist Conference, with neurologist respondents sharing that 85% of their visits with ET patients are about finding treatment, while a survey of 400 ET patients show up to 80% adjust their daily activities due to their disease.
- **Vormatrigine (PRAX-628) for Focal Onset Seizures and Generalized Epilepsy:** Praxis continues to execute on its broad-ranging ENERGY program in focal onset seizures (FOS) and generalized epilepsy
  - The EMPOWER observational study, in partnership with the Epilepsy Study Consortium, aiming to better characterize seizure burden, started enrolling patients in the third quarter of 2024 and has already enrolled over 1,000 patients. Praxis expects the findings in EMPOWER to positively impact the ability to enroll patients in the ENERGY studies.

- RADIANT is a Phase 2 pharmacokinetics, safety and efficacy open-label study in patients with FOS or generalized epilepsy; topline results are anticipated in the first half of 2025.
- POWER1 and POWER2 are 12-week Phase 2/3 studies in patients with FOS aiming to show efficacy of PRAX-628. POWER1 has recently been initiated, with topline results anticipated in the second half of 2025.
- Given that vormatrigine is a potent Nav 1.7 and 1.8 inhibitor, Praxis is currently evaluating the potential for expansion into pain indications.

- **Relutrigine (PRAX-562) for DEEs:** In the third quarter, Praxis announced positive topline results for the Phase 2 EMBOLD cohort 1 study (N=15)
  - Highlights from the topline results included:
    - 46% placebo-adjusted reduction in monthly motor seizure from baseline over a 16-week period.
    - For patients continuing onto the ongoing open label extension (OLE), n=9, saw a 75% reduction in motor seizures from baseline.
    - Over 30% of patients (n=5) achieved seizure freedom status while on relutrigine.
    - Meaningful gains observed in alertness, communication and seizure severity suggest relutrigine has a disease modifying effect.
    - Relutrigine was generally well-tolerated with no drug-related serious adverse events or dose reductions required.
  - Based on the positive results of cohort 1, Praxis initiated a second cohort of the EMBOLD study to be sufficient for registration, aiming to enroll 80 patients, with topline results in the first half of 2026.
  - Sodium channel blockers are used broadly by DEE patients. Praxis has decided to initiate a registrational study (EMERALD) in all DEEs, which is planned to initiate in the first half of 2025 after alignment with regulators.
  - Relutrigine has received Orphan Drug Designation (ODD) and Rare Pediatric Designation (RPD) from the FDA, and ODD from the European Medicines Agency (EMA) for the treatment of SCN2A-DEE and SCN8A-DEE.

Solidus™ Antisense Oligonucleotide (ASO) Platform

- **Elsunersen (PRAX-222) for early-seizure-onset SCN2A Developmental Epilepsies:** Elsunersen has previously received ODD and RPD from the FDA, and ODD and PRIME designations from the EMA for the treatment of SCN2A-DEE
  - In Q3, Praxis dosed the first patient in Brazil as part of a continuation of Part A of the EMBRAVE study.
  - Praxis is continuing to harmonize the registrational study protocol, with plans to expand in the U.S. and Europe.

Third Quarter 2024 Financial Results:

As of September 30, 2024, Praxis had $411.2 million in cash, cash equivalents and marketable securities, compared to $81.3 million in cash and cash equivalents as of December 31, 2023. The increase of $329.9 million is primarily due to net proceeds from Praxis' January 2024 and April 2024 follow-on public offerings and net proceeds from at-the-market sales of common stock, offset by cash used in operating activities.

Praxis recognized $0.3 million in collaboration revenue during the three months ended September 30, 2024, compared to $0.5 million during the three months ended September 30, 2023. The decrease of $0.2 million is associated with a decrease in the revenue recorded under the UCB Collaboration Agreement due to timing of work performed.

Research and development expenses were $41.9 million for the three months ended September 30, 2024, compared to $17.3 million for the three months ended September 30, 2023. The increase in research and development expenses of $24.6 million was primarily attributable to a $21.6 million increase in expense related to Praxis' Cerebrum™ platform, a $4.0 million increase in personnel-related costs and a $0.4 million increase in indirect expenses, partially offset by a $1.5 million decrease in expense related to Praxis' Solidus™ platform. General and administrative expenses were $15.3 million for the three months ended September 30, 2024, compared to $8.7 million for the three months ended September 30, 2023. The increase in general and administrative expenses of approximately $6.6 million was primarily

due to a $4.6 million increase in personnel-related costs, a $1.4 million increase in professional expenses and a $0.5 million increase in other expenses.

Praxis reported a net loss of $51.9 million for the three months ended September 30, 2024, including $12.4 million of stock-based compensation expense, compared to $24.6 million for the three months ended September 30, 2023, including $5.8 million of stock-based compensation.

As of September 30, 2024, Praxis had 17.8 million shares of common stock outstanding.

Conference Call

Praxis Precision Medicines will host a conference call and webcast today at 8:00 a.m. ET to review the third quarter 2024 financial results and recent business highlights. Individuals may register for the conference call by clicking the registration link. Once registered, participants will receive dial-in details and a unique PIN which will allow them to access the call. An audio webcast will be accessible through the Events & Presentation page under the Investor Relations section of the Company's website. Following the live webcast, an archived replay will also be available.

About Ulixacaltamide

Ulixacaltamide is a differentiated and highly selective small molecule inhibitor of T-type calcium channels designed to block abnormal neuronal burst firing in the Cerebello-Thalamo-Cortical (CTC) circuit correlated with tremor activity. Ulixacaltamide, the most advanced program within Praxis' Cerebrum™ small molecule platform, is currently in late-stage development for the treatment of essential tremor, www.praxisessentialtremor.com.

About Vormatrigine (PRAX-628)

Vormatrigine is a next-generation, functionally selective small molecule targeting the hyperexcitable state of sodium-channels in the brain that is currently being developed as a once daily, oral treatment for adult focal onset seizures and generalized epilepsy. Preclinical data demonstrates vormatrigine is differentiated from standard of care, with the potential to be best-in-class for focal epilepsy. In vitro, vormatrigine has demonstrated superior selectivity for disease-state Na_V channel hyperexcitability. In vivo studies of vormatrigine have demonstrated unprecedented potency in the maximal electroshock seizure (MES) model, a highly predictive translational model for efficacy in focal epilepsy. Data from the PRAX-628-101 study demonstrated that vormatrigine can be safely dosed in healthy subjects to greater than 15 times the predicted human equivalent of the rodent MES EC50.

About Relutrigine (PRAX-562)

Relutrigine is a first-in-class small molecule in development for the treatment of developmental and epileptic encephalopathy (DEE) as a preferential inhibitor of persistent sodium current, shown to be a key driver of seizure symptoms in early onset SCN2A-DEE and SCN8A-DEE. Relutrigine's mechanism of sodium channel blocking is consistent with superior selectivity for disease state sodium channel (NaV) channel hyperexcitability. In vivo studies of relutrigine have demonstrated dose-dependent inhibition of seizures up to complete control of seizure activity in SCN2A, SCN8A and other DEE mouse models. Relutrigine has been generally well-tolerated in three Phase 1 studies and has demonstrated biomarker changes indicative of NaV channel blocking effects. 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. To learn more about the EMBOLD study, please visit https://www.emboldstudy.com.

About Elsunersen (PRAX-222)

Elsunersen is an antisense oligonucleotide (ASO) designed to selectively decrease SCN2A gene expression, directly targeting the underlying cause of early-seizure-onset SCN2A-DEE to treat seizures and other symptoms in patients with gain-of-function SCN2A mutations. In vitro studies of elsunersen have demonstrated reduction in both SCN2A gene expression and protein levels. In vivo, elsunersen has demonstrated significant, dose-dependent reduction in seizures, improvement in behavioral and locomotor activity and increased survival in SCN2A mouse models, with potential to be the first disease-modifying treatment for SCN2A-DEE. Elsunersen has received ODD and RPD from the FDA, and ODD and PRIME designations from the European Medicines Agency for the treatment of SCN2A-DEE. The Elsunersen program is

ongoing under a collaboration with Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), and RogCon, Inc. To learn more about the EMBRAVE study, please visit https://www.embravestudy.com/.

About Praxis

Praxis Precision Medicines is a clinical-stage biopharmaceutical company translating insights from genetic epilepsies into the development of therapies for CNS disorders characterized by neuronal excitation-inhibition imbalance. Praxis is applying genetic insights to the discovery and development of therapies for rare and more prevalent neurological disorders through our proprietary small molecule platform, Cerebrum™, and antisense oligonucleotide (ASO) platform, Solidus™, using our understanding of shared biological targets and circuits in the brain. Praxis has established a diversified, multimodal CNS portfolio including multiple programs across movement disorders and epilepsy, with four clinical-stage product candidates. For more information, please visit www.praxismedicines.com and follow us on Facebook, LinkedIn and Twitter/X.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 and other federal securities laws, including express or implied statements regarding Praxis' future expectations, plans and prospects, including, without limitation, statements regarding the anticipated timing of our clinical trials, the development of our product candidates and plans to initiate new clinical programs, the anticipated timing of regulatory submissions and interactions and our projected cash runway, as well as other statements containing the words "anticipate," "believe," "continue," "could," "endeavor," "estimate," "expect," "anticipate," "intend," "may," "might," "plan," "potential," "predict," "project," "seek," "should," "target," "will" or "would" and similar expressions that constitute forward-looking statements under the Private Securities Litigation Reform Act of 1995.

The express or implied forward-looking statements included in this press release are only predictions and are subject to a number of risks, uncertainties and assumptions, including, without limitation: uncertainties inherent in clinical trials; preliminary analyses from ongoing studies differing materially from final data from preclinical studies and completed clinical trials; the expected timing of clinical trials, data readouts and the results thereof, and submissions for regulatory approval or review by governmental authorities; regulatory approvals to conduct trials; and other risks concerning Praxis' programs and operations as described in its Annual Report on Form 10-K for the year ended December 31, 2023 and other filings made with the Securities and Exchange Commission. Although Praxis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on information and factors currently known by Praxis. As a result, you are cautioned not to rely on these forward-looking statements. Any forward-looking statement made in this press release speaks only as of the date on which it is made. Praxis undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future developments or otherwise.

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PRAXIS PRECISION MEDICINES, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(Amounts in thousands)
(Unaudited)

	September 30, 2024	December 31, 2023
Assets		
Cash and cash equivalents	$ 168,645	$ 81,300
Marketable securities	242,528	—
Prepaid expenses and other current assets	3,016	3,580
Property and equipment, net	277	588
Operating lease right-of-use assets	1,374	2,064
Other non-current assets	416	416
Total assets	$ 416,256	$ 87,948
Liabilities and stockholders' equity		
Accounts payable	$ 15,010	$ 5,815
Accrued expenses	15,457	7,416
Operating lease liabilities	1,660	2,495
Deferred revenue	1,463	2,553
Common stock	14	13
Additional paid-in capital	1,159,382	723,577
Accumulated other comprehensive gain	1,331	—
Accumulated deficit	(778,061)	(653,921)
Total liabilities and stockholders' equity	$ 416,256	$ 87,948

PRAXIS PRECISION MEDICINES, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(Amounts in thousands, except share and per share amounts)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Collaboration revenue	$ 302	$ 468	$ 1,090	$ 1,932
Operating expenses:				
Research and development	41,881	17,260	96,125	68,378
General and administrative	15,256	8,724	41,174	32,121
Total operating expenses	57,137	25,984	137,299	100,499
Loss from operations	(56,835)	(25,516)	(136,209)	(98,567)
Other income:				
Other income, net	4,925	884	12,069	2,168
Total other income	4,925	884	12,069	2,168
Net loss	$ (51,910)	$ (24,632)	$ (124,140)	$ (96,399)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.75)	$ (2.72)	$ (7.21)	$ (16.73)
Weighted average common shares outstanding, basic and diluted	18,884,562	9,039,427	17,210,604	5,763,121

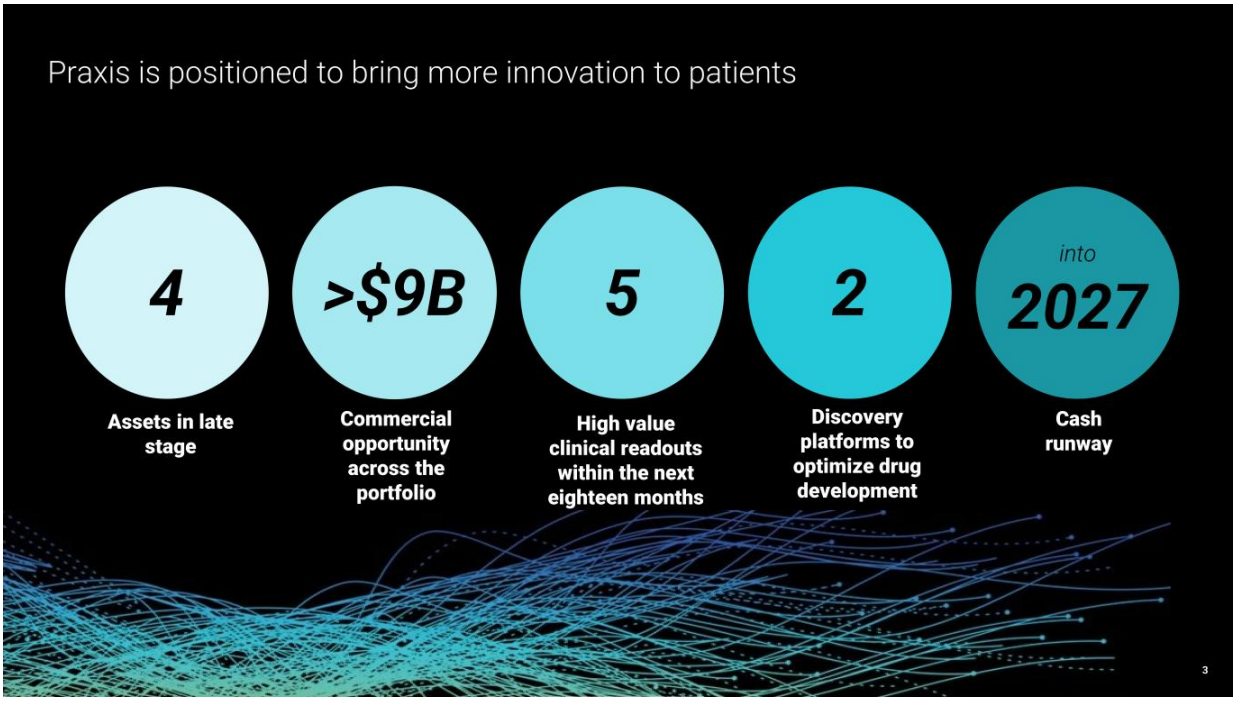

PRAXIS
DARE FOR MORE®
CORPORATE OVERVIEW
November 2024

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
3

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™

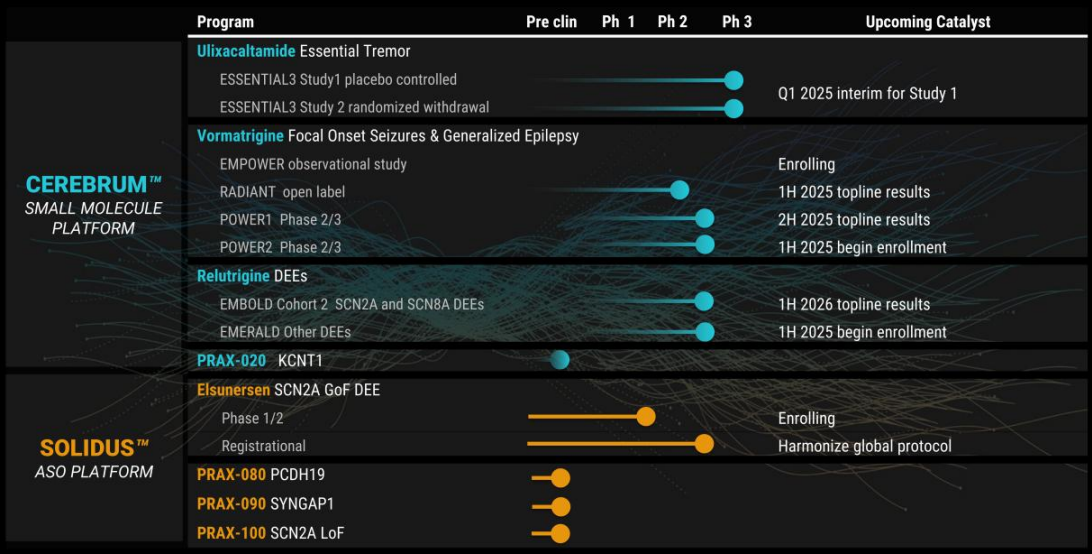
ANTISENSE OLIGONUCLEOTIDE (ASO) PLATFORM

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

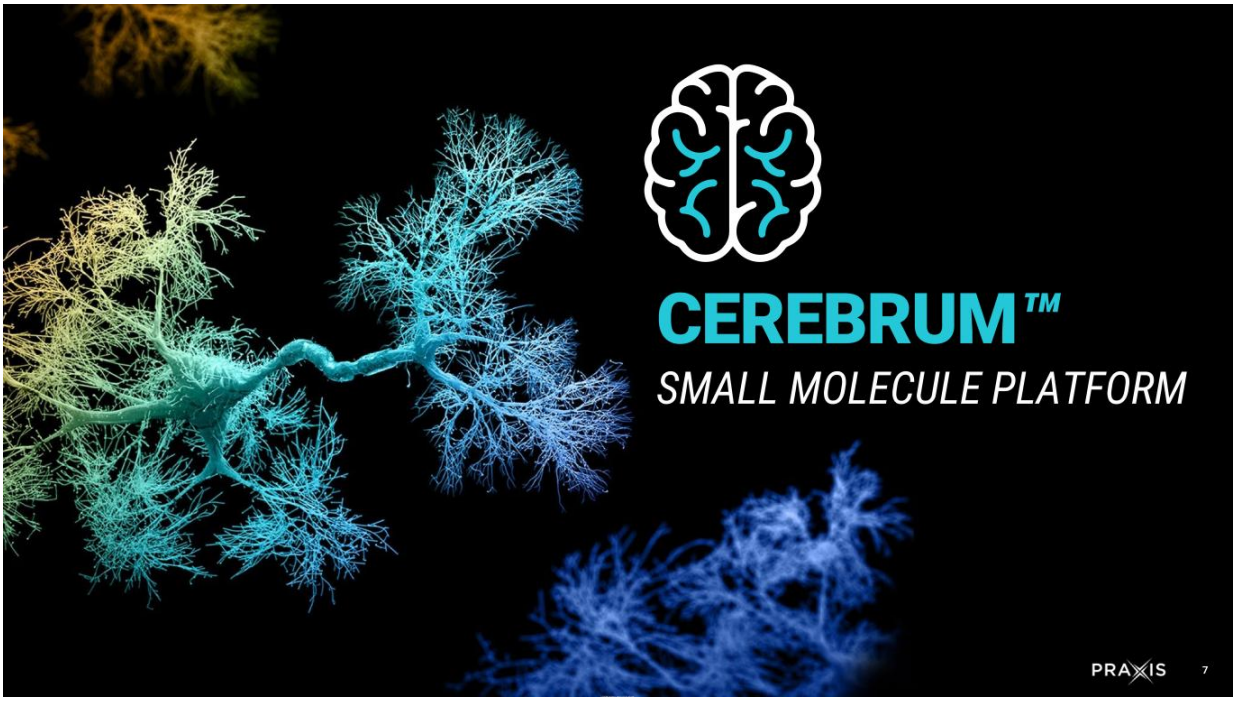
^PRAX-020 (KCNT1) is a research collaboration with UCB
+PRAX-080 (PCDH19), PRAX-090 (SYNGAP1) & PRAX-100 (SCN2A-LoF) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health
* Relutrigine has received ODD and RPD from the FDA, and ODD from the European Medicines Agency for 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

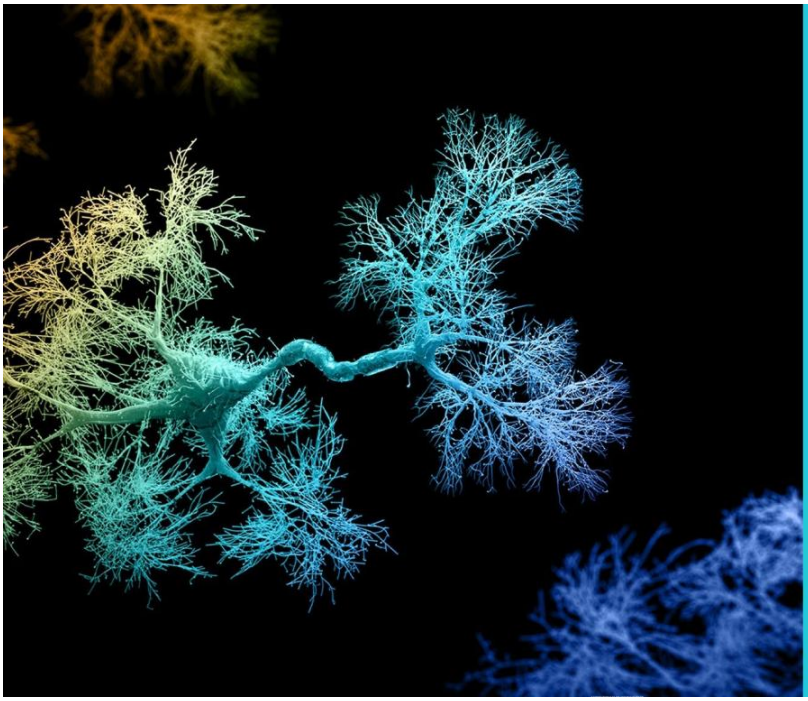
Four clinical stage assets and multitude of early-stage programs



*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


CEREBRUM™
SMALL MOLECULE PLATFORM
PRAXIS
7



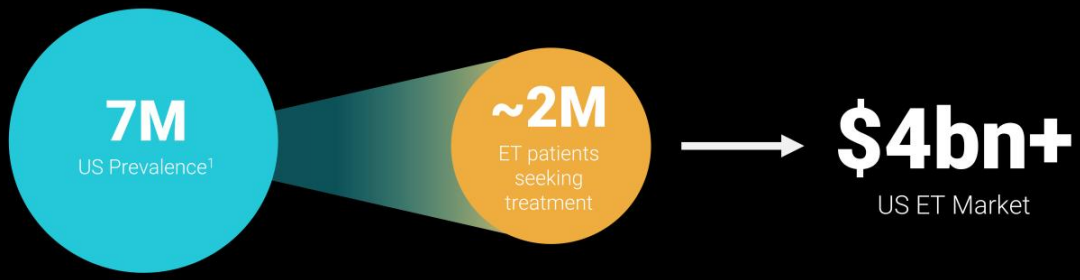
Ulixacaltamide

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

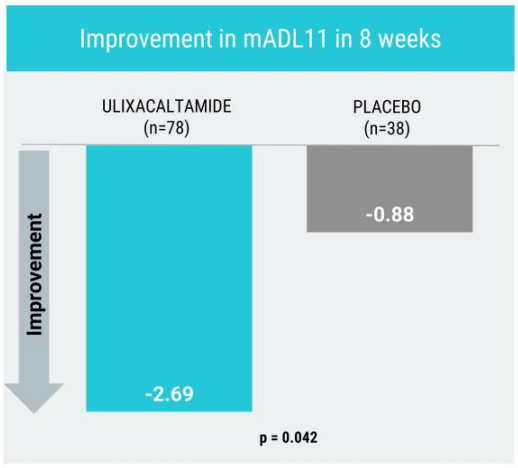
85% of neurologist visits are for patients seeking ET treatment

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

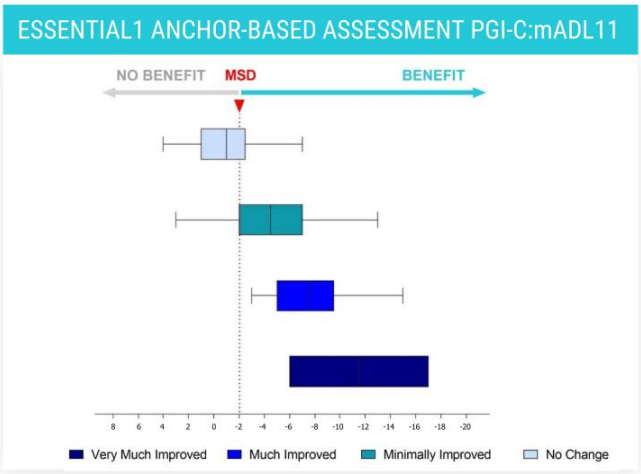
- Strong efficacy signal with robust endpoint (mADL11)
  - Early clinical benefit in 8-Week Study
  - Long-term, durable benefit
- Well-tolerated with a differentiated safety profile
- Tested Phase 3 design concepts

Sets up a clear path to registration

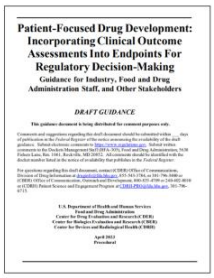
- Alignment with FDA on dose and primary endpoint
- Phase 3 program design structured around patient needs
- Robust recruitment strategy

Results from Essential1 study, p value is nominal

Using Essential1 to define clinical meaningfulness in essential tremor



- 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.

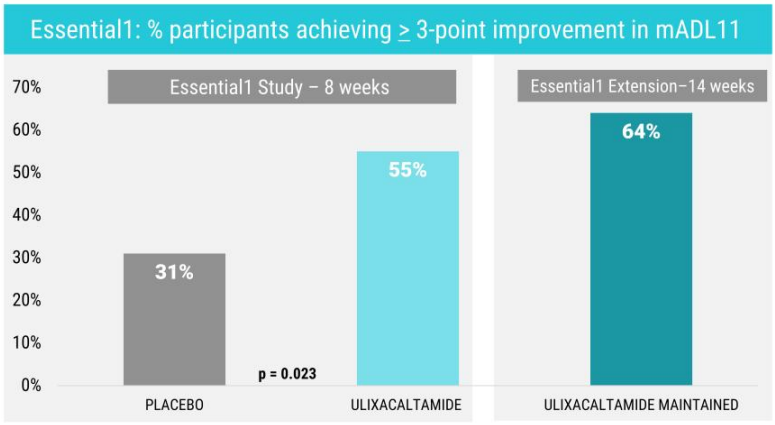
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

April 2022
Procedural

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

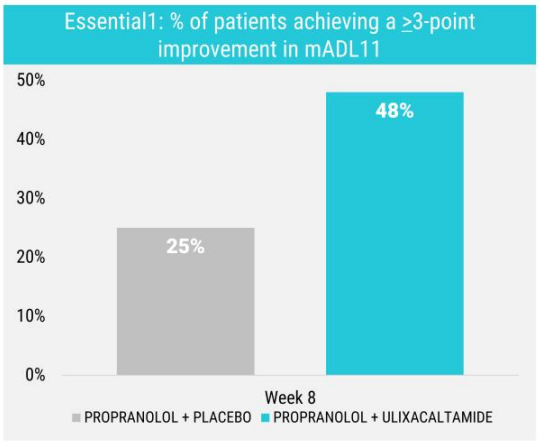
Majority of patients achieved at least a 3-point change in mADL11 at 8 weeks

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

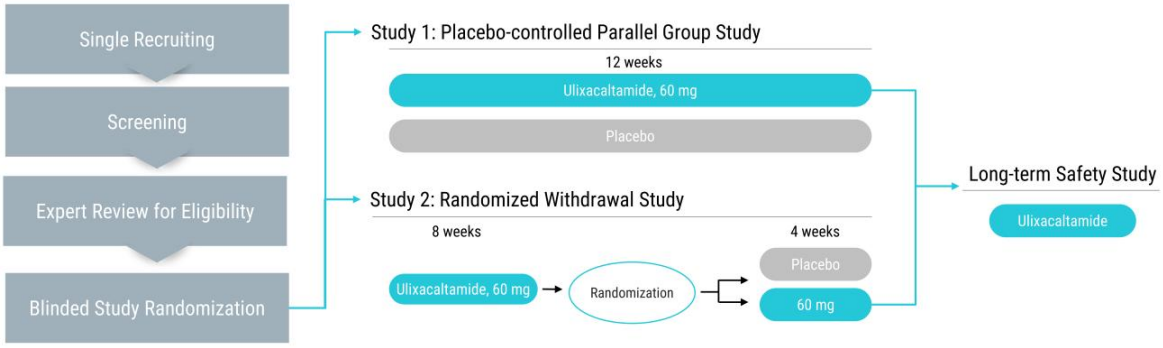
Adding ulixacaltamide benefitted more patients on propranolol



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



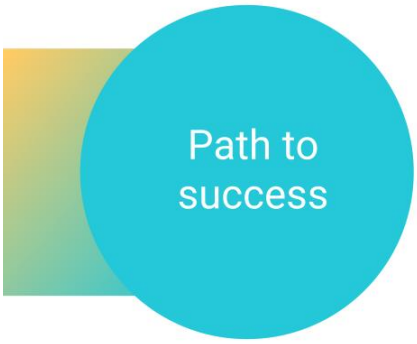
ESSENTIAL 3
AN AT-HOME RESEARCH STUDY

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)



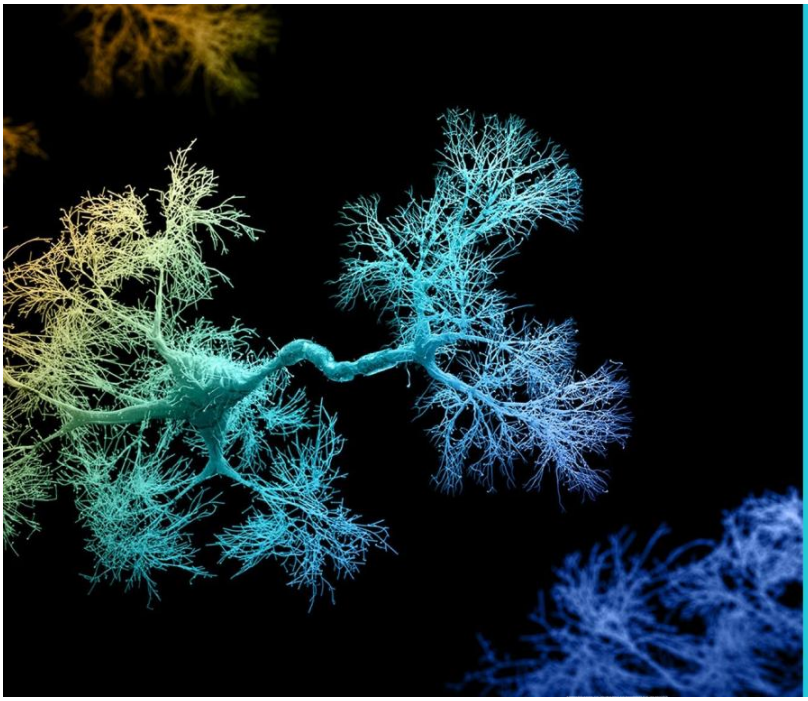
De-risked
Trial design based on key learnings from Essential1
Regulatory alignment based on successful End-of-Phase 2 meeting

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

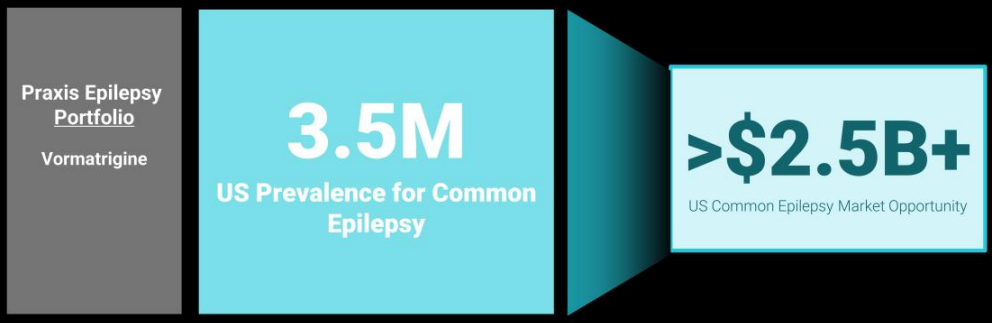


Vormatrigine (PRAX-628)

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



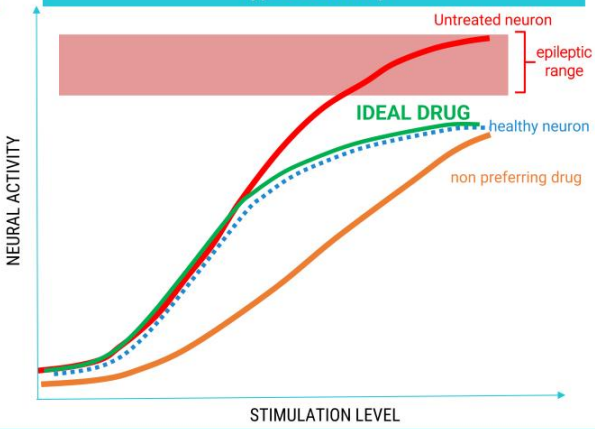
Vormatrigine: Precision medicine therapeutic for focal onset seizures and generalized epilepsy

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

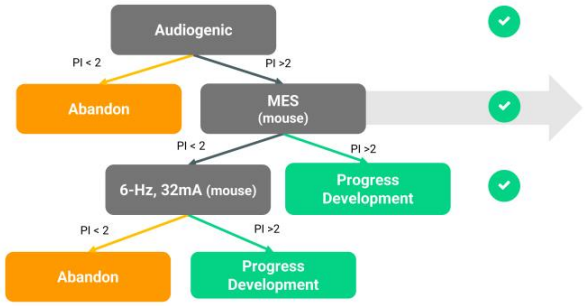
- ❑ Ideal safety/tolerability profile
- ❑ Achieves brain penetration
- ❑ Rapidly achieves therapeutic concentrations without titration
- ❑ Favorable half-life and PK profile
- ❑ Optimized efficacy

Goal: Preferential action against neuronal hyperexcitability



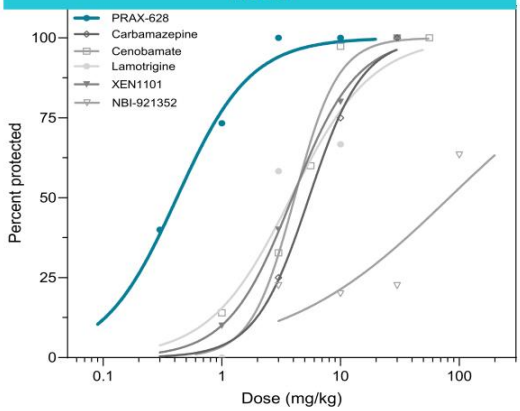
Vormatrigine shows a differentiated pre-clinical profile

Preclinical decision tree optimized for focal seizure drug discovery



Vormatrigine Results

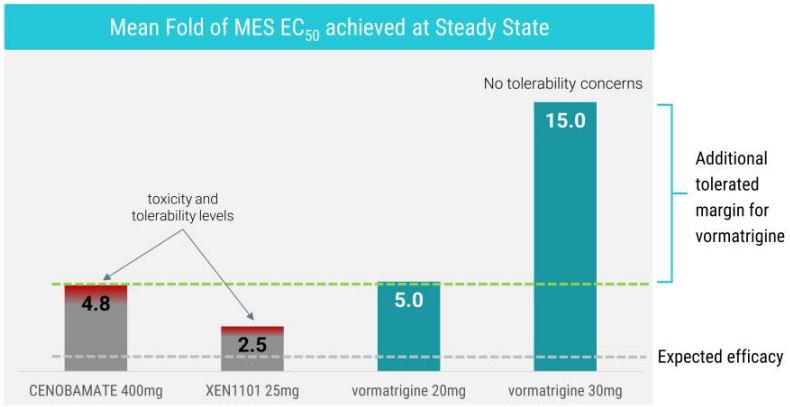
Vormatrigine has differentiated potency in the MES model



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

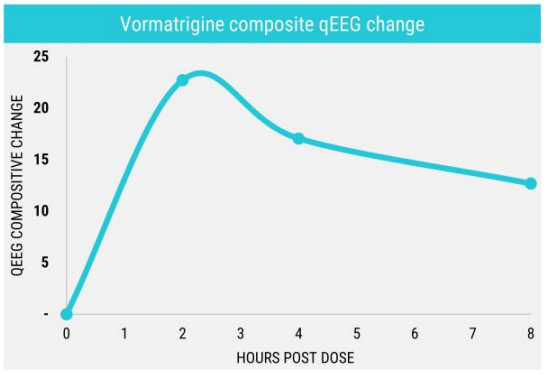
Ability to significantly exceed therapeutic concentrations while well tolerated

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

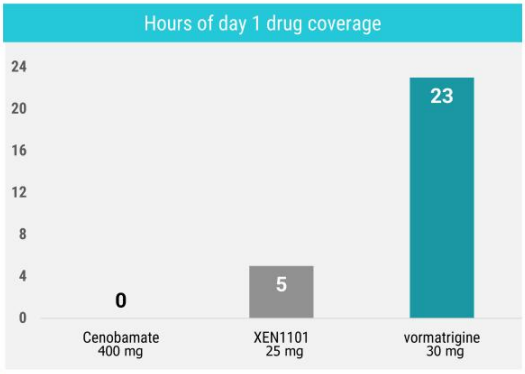


Source: Praxis data on file (Ph1 study), Cenobamate Cmax: >46,100 ng/mL, 400 mg Cmax (Vernillet et al 2020), XEN1101 Cmax: >107 ng/mL (Phase 1 data)
x MES EC50 = multiple of predicted human EC50 based on the rodent MES model; IEC2023_628:SAD-MAD

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



- 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



- 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)

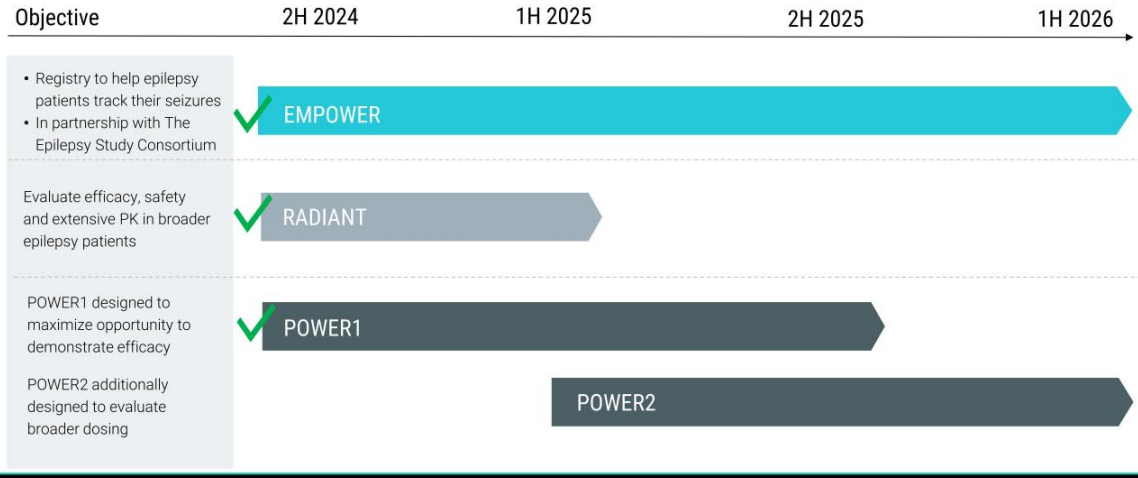
Vormatragine presents an ideal precision ASM profile

- 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

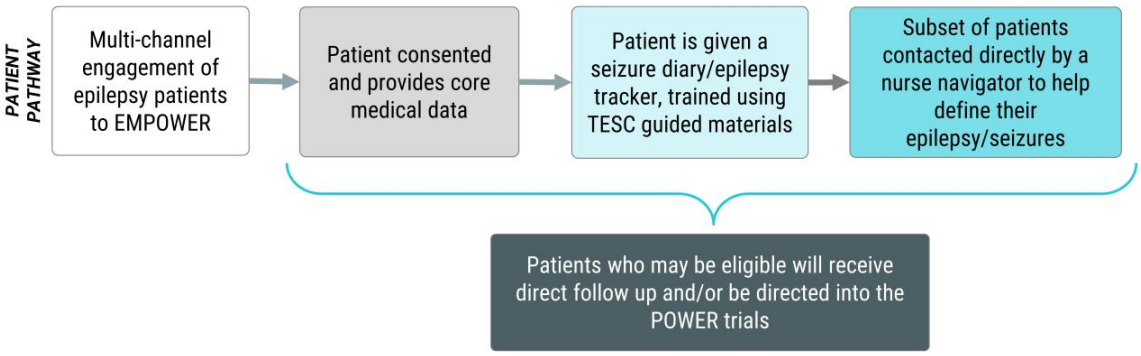
Vormatrigine ENERGY program to demonstrate efficacy and bring an improved therapy to focal and generalized epilepsy patients



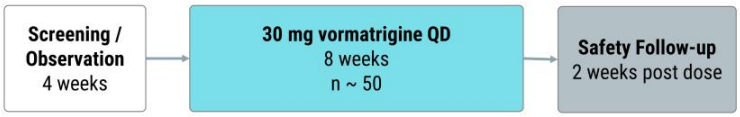
empower

EMPOWER Observational Study to better understand patient journey

In partnership with The Epilepsy Study Consortium (TESC)



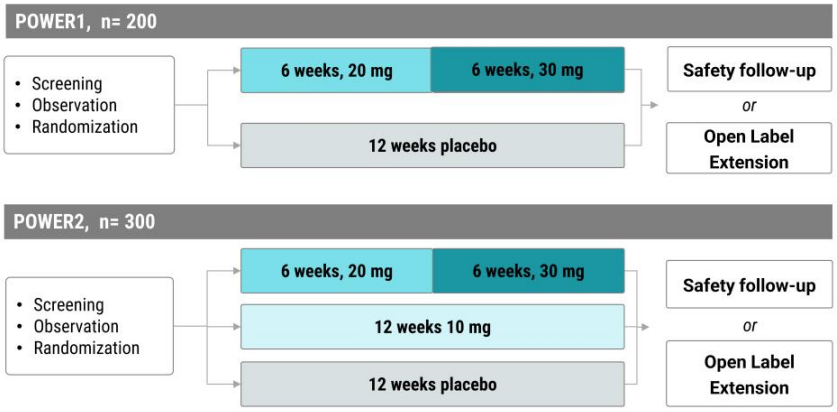
RADIANT Phase 2 open label study to evaluate safety and efficacy in focal onset or generalized epileptic seizures



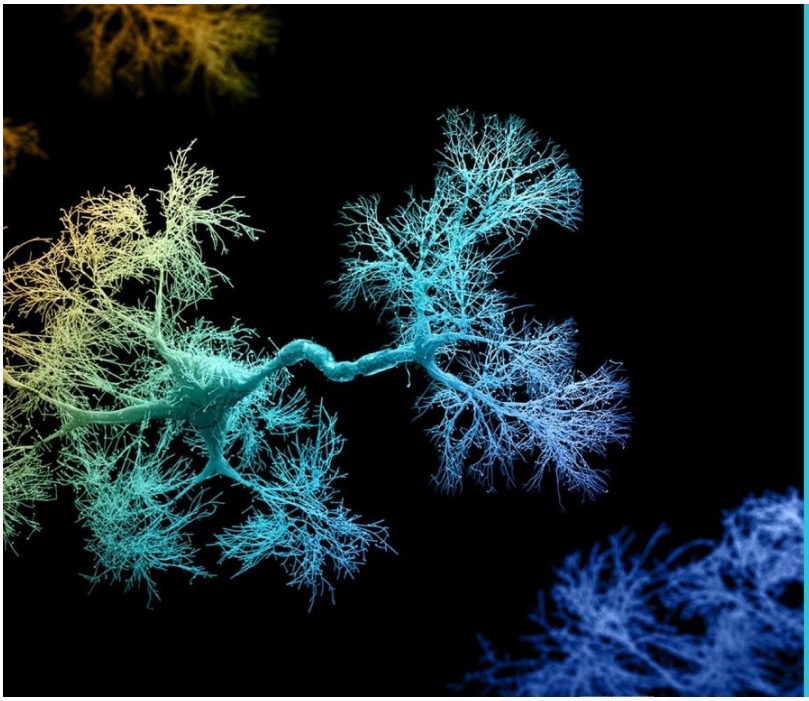
- Measuring seizure frequency, seizure freedom, safety and pharmacokinetics
- Will allow the evaluation of vormatrigine in a broader population, including generalized epilepsy
- Topline results in 1H 2025

QD = Once daily

Proposed study designs for POWER1 and POWER2



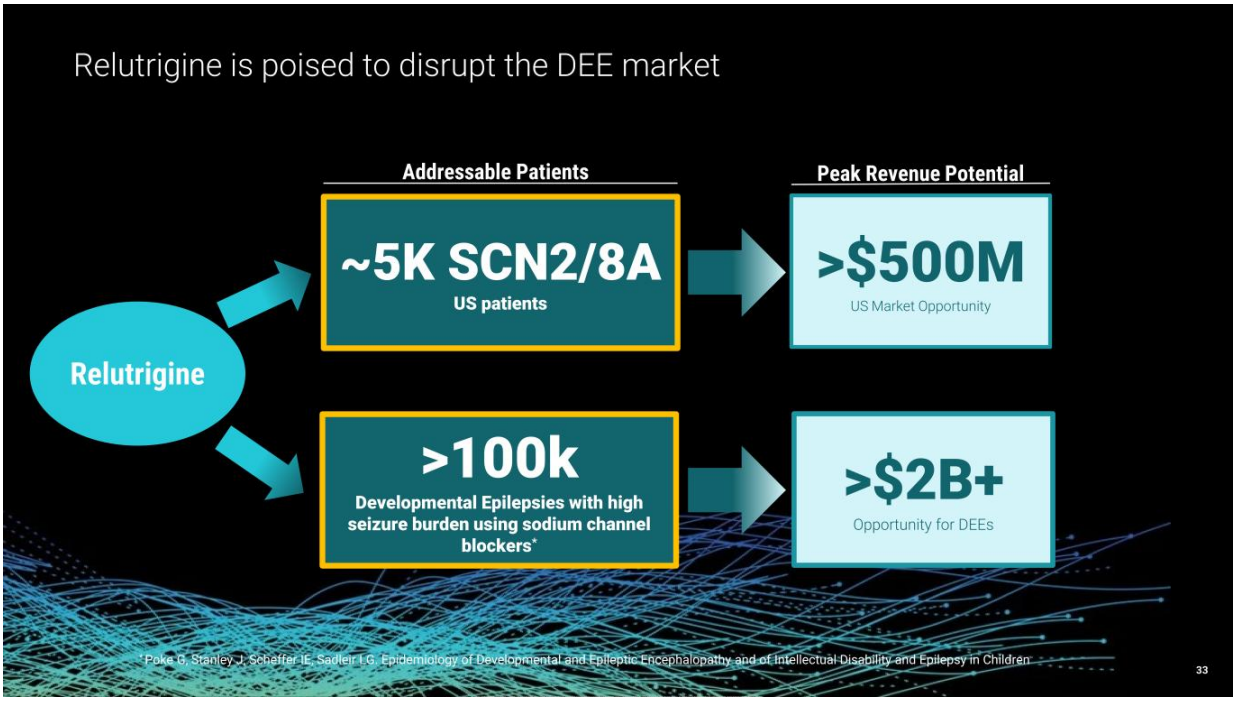
- POWER1 initiated in Q4 2024 with topline readout 2H 2025
- POWER2 to initiate in 1H 2025



Relutrigine (PRAX-562)

Milestones

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


Relutrigine is poised to disrupt the DEE market
Addressable Patients
Peak Revenue Potential
Relutrigine
~5K SCN2/8A
US patients
>$500M
US Market Opportunity
>100k
Developmental Epilepsies with high seizure burden using sodium channel blockers*
>$2B+
Opportunity for DEEs
*Poke G, Stanley J, Scheffer IE, Sadleir LG. Epidemiology of Developmental and Epileptic Encephalopathy and of Intellectual Disability and Epilepsy in Children.
33

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

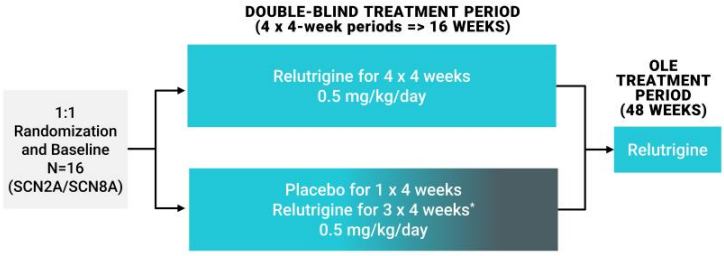
All TEAEs mild to moderate as stand-alone therapy*, with headache & dizziness most common TEAEs

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

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



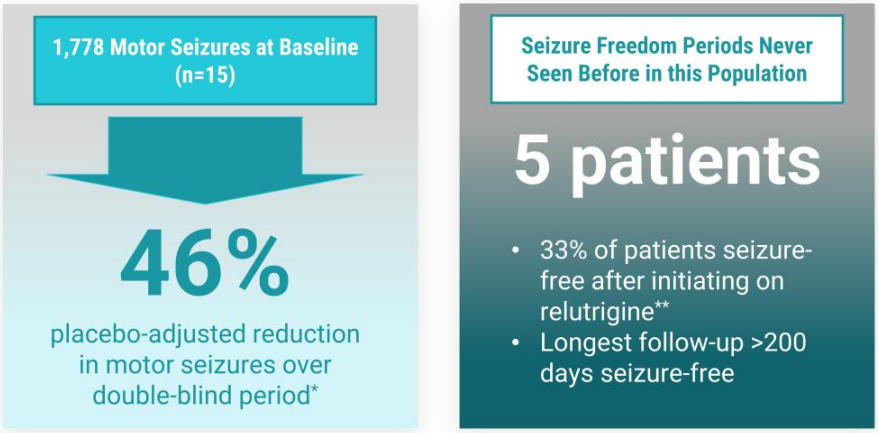
KEY ENDPOINTS:

- 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.

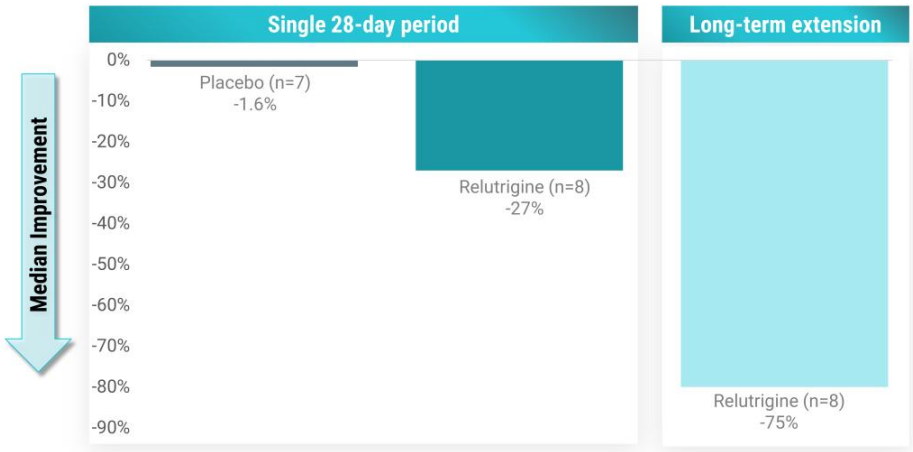
Relutrigine demonstrated robust reduction in motor seizures and unprecedented seizure-free status per 28-day period



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



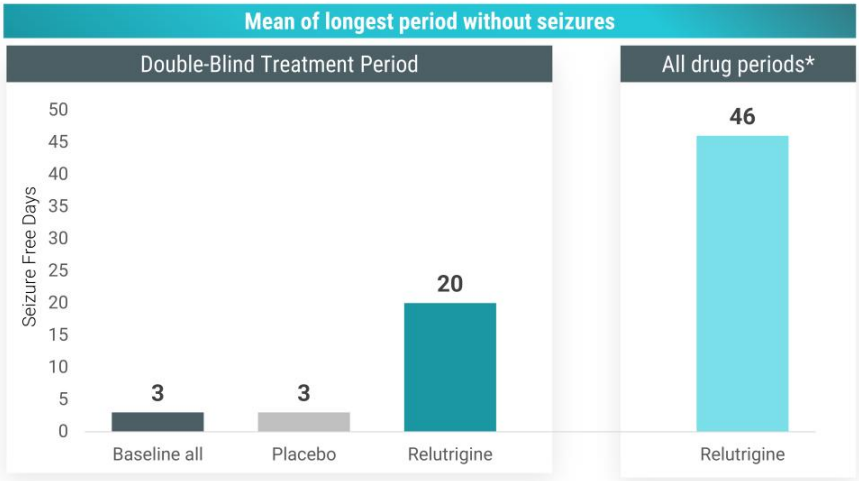
7 patients increased the dose of relutrigine to 1 mg/kg during the double-blind period, 2 additional patients during the long-term extension

Seizure freedom associated with exposures achievable by 1 mg/kg

EMBOLD

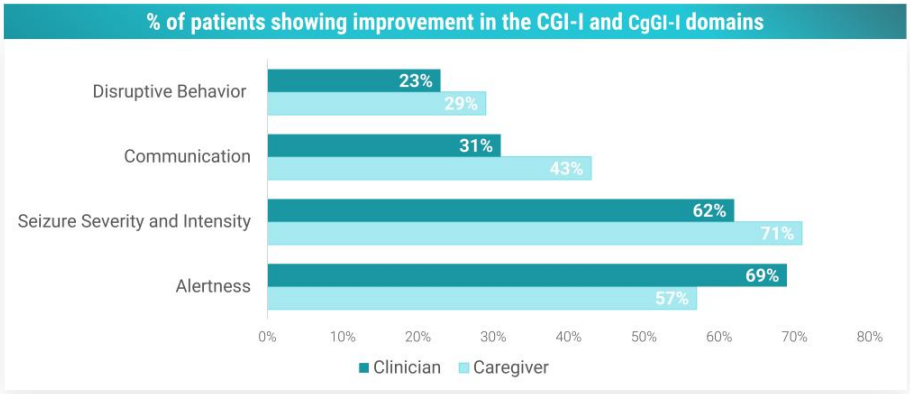
Long-term extension data for 8 patients with data available for at least one 28-day period as of August 21, 2024

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



* Inclusive of OLE period

Relutrigine treatment led to disease modifying impact

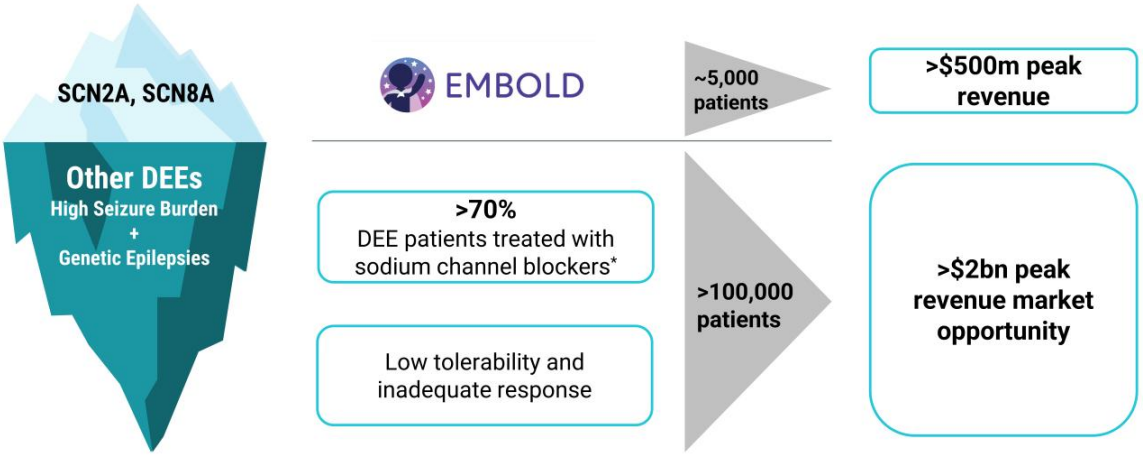


Meaningful gains in overall well-being of patients, despite severity and historical lack of improvement with available treatments

EMBOLD

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

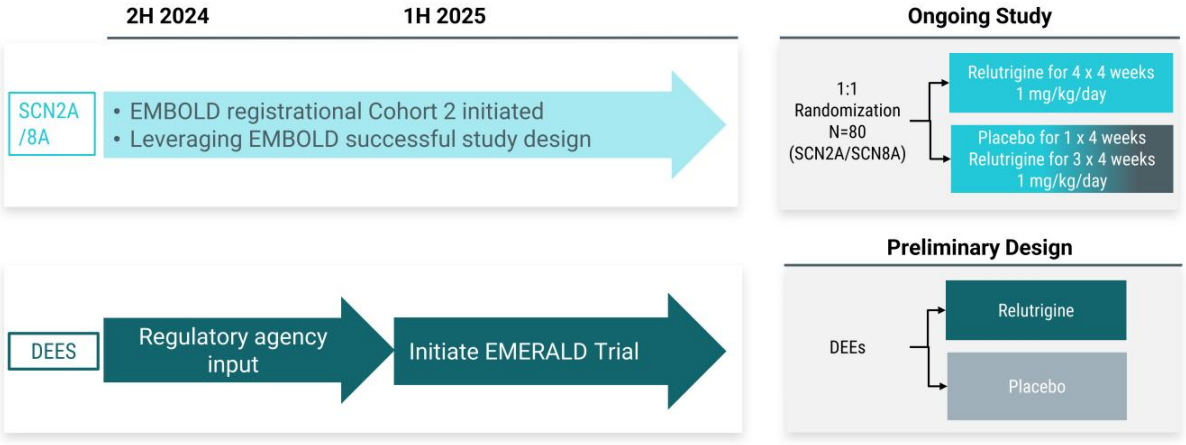
SCN2A and SCN8A are the tip of the iceberg in addressing the significant unmet needs across the spectrum of other DEEs



*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

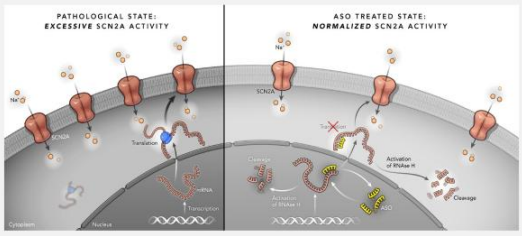



Elsunersen (PRAX-222)
SOLIDUS™ ASO PLATFORM
PRAXIS
43

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

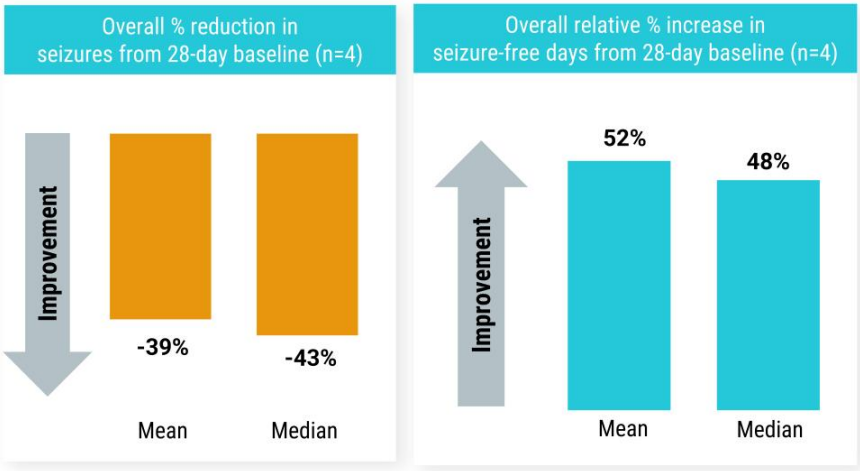


RESEARCH APPROACH

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



- 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


PRAXIS
DARE FOR MORE®