# 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): August 7, 2023**

# 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 August 9, 2023, Praxis Precision Medicines, Inc. (the "Company") announced its financial results for the quarter ended June 30, 2023. A copy of the press release is being furnished as Exhibit 99.1 to this Current Report on Form 8-K.

**Item 7.01. Regulation FD Disclosure.**

On August 9, 2023, 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 on Form 8-K.

The information in this Current Report on Form 8-K 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 8.01. Other Events.**

**PRAX-628**

On August 7, 2023, the Company announced the results from an analysis of EEG activity for subjects in the recent Phase 1 study that demonstrated pharmacodynamic activity across all dose levels for study subjects who received PRAX-628 at first administration as compared with subjects who received placebo. In the Phase 1 study, PRAX-628 was administered to 40 healthy participants (PRAX-628 n=30, placebo n=10). Single ascending dose ("SAD") cohorts evaluated PRAX-628 doses ranging from 5 to 45 mg and multiple ascending dose ("MAD") cohorts evaluated PRAX-628 doses of 20 and 30 mg. EEG data were collected over the course of day 1 in the SAD cohort and over three separate days during the course of the 10-day MAD treatment period. qEEG analysis showed a pharmacodynamic effect at all dose levels and was significantly different from placebo at the Tmax timepoint (~2h) for the SAD and all timepoints for the MAD portion.

The Company has begun a Phase 2 study for PRAX-628 in patients with a photo-paroxysmal response to evaluate drug activity and dose finding, and is expected to report topline results in the second half of 2023. Based on these studies and the preclinical results, the Company intends to advance PRAX-628 into a Phase 2 study in focal epilepsy in the first half of 2024.

**Ulixacaltamide**

On August 8, 2023, the Company announced further data from two additional analyses of the Essential1 study for ulixacaltamide.

*Open-Label Extension ("OLE")*

Following completion of the initial 8-week double-blind treatment phase in Essential1, eligible patients had the option to continue their access to ulixacaltamide in an OLE phase. Participants who continued to the OLE phase remained blinded for a six-week lead-in period.

- There was no change to the overall safety results through 14 weeks of treatment.
- 65 patients who completed the double-blinded portion of Essential1 were eligible to participate in the OLE and completed the week 14 assessment. All patients eligible to participate in the OLE phase were enrolled in Essential1 under version 4 of the clinical protocol.

- Patients who were eligible and continued on ulixacaltamide (n= 39) experienced an additional mean improvement in the modified Activities of Daily Living 11 (“mADL11”) of 1.7 points from 3.09 at week 8 (95% CI: 0.98, 5.2) to 4.81 (95% CI: 2.38, 7.23) after 14 weeks of treatment.
- Patients who switched from placebo during the double-blind phase of Essential1 to ulixacaltamide treatment during the OLE 6-week lead-in (n= 26) experienced mean improvement in mADL11 of 3.15 points, from 1.21 at week 8 (95% CI: -1.04, 3.46) to 4.36 (95% CI: 1.68, 7.05).

*Randomized Withdrawal Sub-Study*

Following the announcement of the Essential1 study topline results, the Company amended the open-label protocol to further assess the criteria to be used in the upcoming randomized withdrawal Phase 3 study. In this sub-study, patients were re-randomized in a blinded fashion to either receive placebo or continue to receive ulixacaltamide.

Twenty-one patients who completed assessments at week 14 of the OLE were eligible to participate in the blinded sub-study. Patients were evaluated weekly over a total of six weeks, with 11 patients assigned to ulixacaltamide and 10 to placebo for the initial three-week period, crossing over to either placebo or ulixacaltamide for an additional three-week period. Blinded rescue was triggered for patients on placebo if loss in the mADL11 exceeded two points at any timepoint.

- Patients who switched from ulixacaltamide to placebo experienced an average loss of effect in their mADL11 per week of 47% (mean loss of effect of -1.15 points/week), compared to 6% improvement in global mean change per week (mean improvement of 0.16 points/week) for the periods receiving ulixacaltamide. In addition, 10 patients assigned to placebo met the rescue criteria to restart ulixacaltamide.
- 85% of the patients who received ulixacaltamide (17 of 20) and 52% who received placebo maintained their mADL11 within three points compared to baseline, confirming the definition of patient stability to be used in the Phase 3 program.
- No new safety signals emerged and there was no change to the overall safety results observed in the eight-week double-blind treatment phase.

The results from the sub-study supported a number of proposed design elements for the upcoming Phase 3 randomized withdrawal study, including the responder criteria and feasibility of rescuing patients with ulixacaltamide.

**Forward-Looking Statements**

This Current Report on Form 8-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws, including statements regarding the clinical development of PRAX-628 and ulixacaltamide. The forward-looking statements included in this Current Report on Form 8-K are subject to a number of risks, uncertainties and assumptions, including, without limitation, uncertainties inherent in clinical trials, the expected timing of submission for regulatory approval or review by governmental authorities and other risks as described in the Company's Annual Report on Form 10-K for the year ended December 31, 2022, its Quarterly Reports on Form 10-Q and its other filings with the Securities and Exchange Commission. These statements are based only on facts currently known by the Company and speak only as of the date of this Current Report on Form 8-K. As a result, you are cautioned not to rely on these forward-looking statements and the Company undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future developments or otherwise.

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Press Release, dated August 9, 2023 |
| 99.2 | Praxis Precision Medicines, Inc. August 2023 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: August 9, 2023

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

**Praxis Precision Medicines Provides Corporate Update and Reports Second Quarter 2023 Financial Results**

*On track to initiate Phase 3 studies for ulixacaltamide in Q4 2023 after favorable End-of-Phase 2 meeting with FDA*

*PRAX-628 Phase 1 study showed consistent safety profile and target engagement in measures of qEEG activity at all doses with first administration*

*Praxis will hold an R&D Portfolio Day on October 2*

*Cash of $124.3 million as of June 30, 2023 expected to support runway into Q1 2025*

**BOSTON, August 9, 2023 —** 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 second quarter 2023.

“Our four clinical-stage programs continue to make great progress, and we are excited to be advancing ulixacaltamide into Phase 3,” said Marcio Souza, president and chief executive officer of Praxis. “Our epilepsy portfolio continues to advance, with studies ongoing in each of our three clinical-stage programs that we expect to read out by the end of the year. We are planning to hold an R&D portfolio day on October 2 to elaborate on our science and clinical progress, including more details about the Phase 3 program for ulixacaltamide and additional data from the Essential1 study.”

**Recent Business Highlights and Upcoming Milestones:**

*Cerebrum™ Small Molecule Platform*

- In June 2023, Praxis shared the outcomes of its end-of-phase 2 (EOP2) meeting with the U.S. Food and Drug Administration (FDA) and is planning to initiate two Phase 3 studies as part of the registrational program, using mADL11 as the primary outcome measure. One study will be a parallel control design and the other using a randomized withdrawal design. Both trials will evaluate essential tremor patients at a 60 mg dose of ulixacaltamide for 12 weeks after a short titration period. The EOP2 meeting confirmed other program aspects including safety database, clinical pharmacology and toxicology requirements for registration. Praxis intends to begin enrolling patients in the fourth quarter of 2023, with read outs expected in the second half of 2024.

- In August 2023, Praxis shared the results of two additional analyses of the Essential1 dataset that showed durable effect to 14 weeks and maintenance of the safety profile seen in the Essential1 study.
    - In the open-label extension (OLE) phase, patients who continued on ulixacaltamide experienced an additional mean improvement in mADL11 of 1.7 points from week 8 to after 14 weeks of treatment, while patients who switched from placebo during the Essential1 double blind phase to ulixacaltamide during the 6-week OLE experienced mean improvement in mADL11 of 3.15 points.
    - In a randomized withdrawal sub-study, patients who switched from ulixacaltamide to placebo experienced an average loss of effect in their mADL11 per week of 47% (mean loss of effect of -1.15 points/week), compared to 6% improvement in global mean change per week (mean improvement of 0.16 points/week) for the periods receiving ulixacaltamide.

- In May 2023, Praxis announced initial results from the PRAX-628 Phase 1 safety study, which demonstrated a favorable safety and tolerability profile in healthy volunteers at concentrations more than 15-fold the Maximal Electrical Seizure model (MES $EC_{50}$) and predicted therapeutic range at least 3-fold wider than current market leader based on an MES model. In August 2023, Praxis announced additional data from the Phase 1 study from an analysis of EEG activity that demonstrated pharmacodynamic activity across all dose levels for study subjects who received PRAX-628 at first administration as compared with subjects who received placebo.

- In June 2023, Praxis announced it had initiated a Phase 2 proof of concept study evaluating PRAX-628 in epilepsy patients with a Photo Paroxysmal Response (PPR). The study evaluates the potential effect of PRAX-628 on reducing pre-seizure EEG activity for photo-sensitive patients. The study is expected to read out by year-end 2023 and, upon completion of the PPR study, Praxis plans to initiate a Phase 2 study to evaluate PRAX-628 for the treatment of focal epilepsy in the first half of 2024.

- Praxis expects topline results from the PRAX-562 Phase 2 EMBOLD study for the treatment of pediatric patients with developmental and epileptic encephalopathies (DEEs) in the fourth quarter of 2023. The EMBOLD study is a randomized, double-blind, placebo-controlled Phase 2 clinical trial to evaluate the safety, tolerability, efficacy (motor seizure frequency) and pharmacokinetics of PRAX-562 in pediatric participants aged 2 to 18 years with DEEs, followed by an open-label extension. Approximately 20 participants with SCN2A-DEE or SCN8A-DEE are expected to be enrolled.

*Solidus™ Antisense Oligonucleotide (ASO) Platform*

- Praxis is currently dosing the first dose cohort (Part 1) of the PRAX-222 EMBRAVE study for the treatment of pediatric patients with early-onset SCN2A-DEE in the U.S. Following collection of the safety and efficacy data from Part 1 of the EMBRAVE study, the data will be evaluated and submitted to the FDA to support further dose escalation. Part 1 of the EMBRAVE study is a 21-week open label cohort, in which participants will receive PRAX-222 for up to 13 weeks, designed to determine the safety and tolerability of intrathecal delivery of PRAX-222. Topline results are expected in the second half of 2023.

*Corporate Update*

- In June 2023, Praxis completed an underwritten public offering, which extended Praxis' cash runway into the first quarter of 2025. Praxis sold 64,449,690 shares of common stock at a public offering price of $0.95 per share, including the exercise in full by the underwriters of their option to purchase up to 9,299,690 shares of common stock, and pre-funded warrants to purchase up to an aggregate of 7,050,000 shares of common stock at a public offering price of $0.9499 per share. The net proceeds from the offering were approximately $63.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by Praxis. The proceeds will be used to advance the development of ulixacaltamide into two Phase 3 studies for essential tremor, to continue clinical development of PRAX-562, PRAX-222 and PRAX-628 for various epilepsies, and for working capital and other general corporate purposes.

**Second Quarter 2023 Financial Results:**

As of June 30, 2023, Praxis had $124.3 million in cash and cash equivalents, compared to $100.5 million in cash, cash equivalents and marketable securities as of December 31, 2022. The increase of $23.8 million primarily reflects $63.4 million in net proceeds from Praxis' June 2023 underwritten public offering and $24.1 million in net proceeds from at-the-market offerings of shares of Praxis' common stock, partially offset by cash used in operations of $64.1 million during the six months ended June 30, 2023.

Praxis recognized $0.8 million in collaboration revenue during the three months ended June 30, 2023 related to its Option and License Agreement with UCB.

Research and development expenses were $25.6 million for the three months ended June 30, 2023, compared to $43.6 million for the three months ended June 30, 2022. The decrease in research and development expenses of $18.0 million was primarily attributable to $19.6 million in decreased expenses related to Praxis' Cerebrum™ platform and $4.0 million in decreased personnel-related expenses, partially offset by $5.7 million in increased expenses related to the Solidus™ platform, which includes a $6.9 million one-time milestone related to the initiation of the EMBRAVE study. General and administrative expenses were $10.1 million for the three months ended June 30, 2023, compared to $16.8 million for the three months ended June 30, 2022. The decrease in general and administrative expenses of approximately $6.6 million was primarily due to a decrease in consulting costs, professional fees and personnel-related expenses.

Praxis reported a net loss of $34.3 million for the three months ended June 30, 2023, including one-time milestone expense of $6.9 million related to the PRAX-222 program, and $5.8 million of stock-based compensation expense, compared to $60.2 million for the three months ended June 30, 2022, including $7.6 million of stock-based compensation expense.

As of June 30, 2023, Praxis had 128.5 million shares of common stock outstanding.

**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.

**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 and the development of our product candidates, 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; 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; Praxis' anticipated cash runway; and other risks concerning Praxis' programs and operations as described in its Annual Report on Form 10-K for the year ended December 31, 2022, its Quarterly Reports on Form 10-Q 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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857-702-9452

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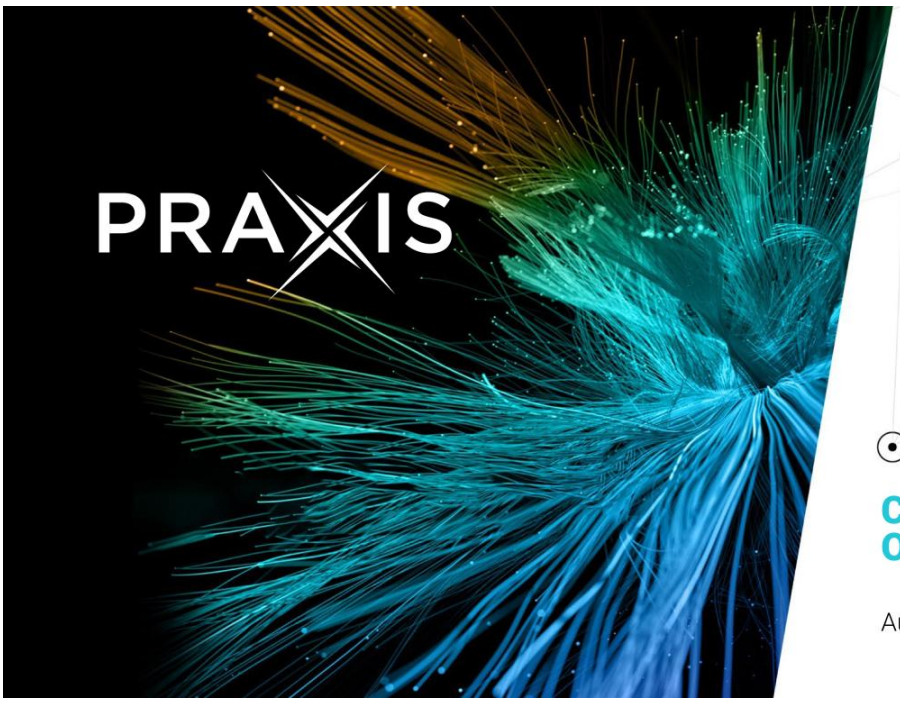
Ian.stone@canalecomm.com
619-849-5388

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

| | June 30, 2023 | December 31, 2022 |
|---|---|---|
| **Assets** | | |
| Cash and cash equivalents | $ 124,300 | $ 61,615 |
| Marketable securities | — | 38,874 |
| Prepaid expenses and other current assets | 5,529 | 10,351 |
| Property and equipment, net | 759 | 971 |
| Operating lease right-of-use assets | 2,494 | 2,901 |
| Other non-current assets | 416 | 416 |
| **Total assets** | $ 133,498 | $ 115,128 |
| **Liabilities and stockholders' equity** | | |
| Accounts payable | $ 8,010 | $ 14,672 |
| Accrued expenses | 13,317 | 15,850 |
| Operating lease liabilities | 3,010 | 3,500 |
| Deferred revenue | 3,536 | 5,000 |
| Common stock | 13 | 5 |
| Additional paid-in capital | 708,023 | 606,918 |
| Accumulated other comprehensive loss | — | (173) |
| Accumulated deficit | (602,411) | (530,644) |
| **Total liabilities and stockholders' equity** | $ 133,498 | $ 115,128 |

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

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | **2023** | **2022** | **2023** | **2022** |
| Collaboration revenue | $ 781 | $ — | $ 1,464 | $ — |
| Operating expenses: | | | | |
| Research and development | 25,614 | 43,620 | 51,118 | 96,272 |
| General and administrative | 10,127 | 16,774 | 23,397 | 32,971 |
| Total operating expenses | 35,741 | 60,394 | 74,515 | 129,243 |
| Loss from operations | (34,960) | (60,394) | (73,051) | (129,243) |
| Other income: | | | | |
| Other income, net | 648 | 200 | 1,284 | 332 |
| Total other income | 648 | 200 | 1,284 | 332 |
| Net loss | $ (34,312) | $ (60,194) | $ (71,767) | $ (128,911) |
| Net loss per share attributable to common stockholders, basic and diluted | $ (0.49) | $ (1.32) | $ (1.17) | $ (2.83) |
| Weighted average common shares outstanding, basic and diluted | 69,740,719 | 45,542,600 | 61,467,774 | 45,499,131 |




# CORPORATE OVERVIEW

August 2023

# 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, our development plans, our preclinical and clinical results and other future conditions. 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) 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 and our collaboration partners' abilities to manufacture our product candidates and scale production, and (viii) our ability to meet any specific milestones set forth herein. 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, 2022, our Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission.

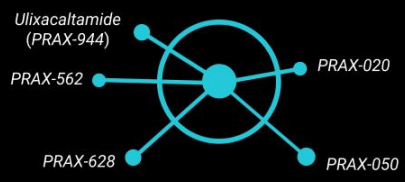
Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have 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.

# Developing Treatments Inspired By The Genetics of Epilepsy

## ENABLED BY TWO PLATFORMS

### CEREBRUM™

*SMALL MOLECULE PLATFORM*

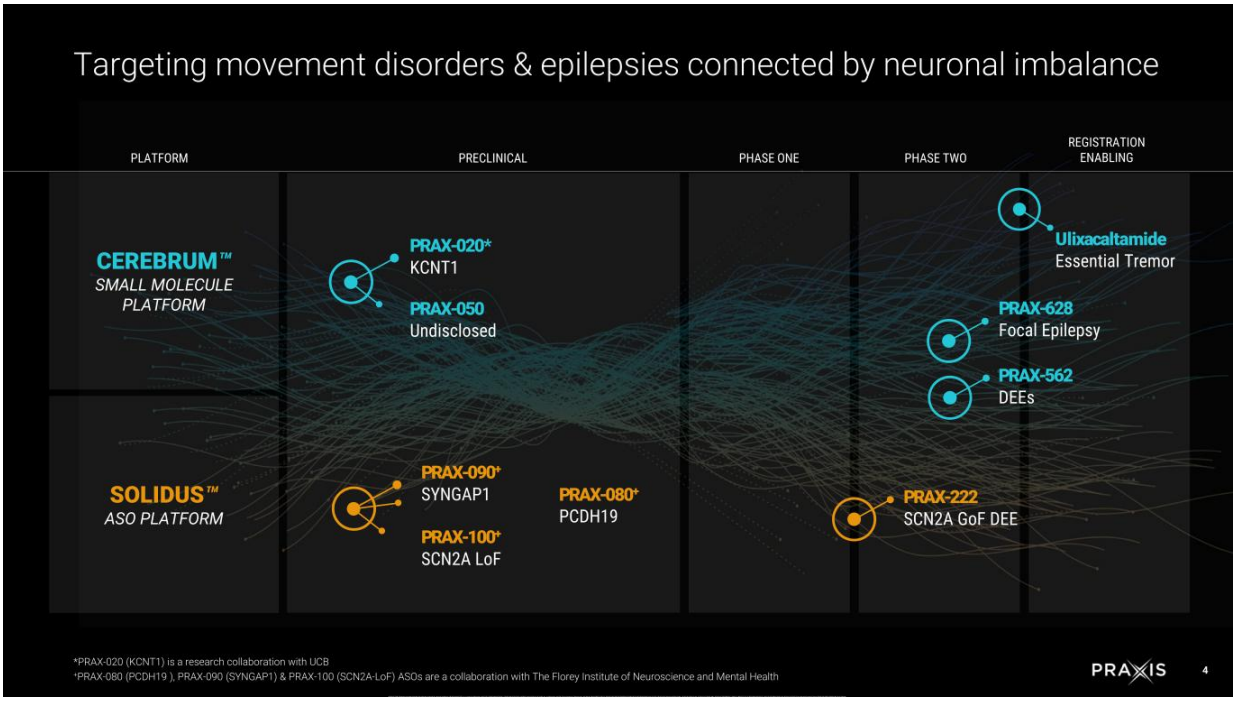



Cerebrum™ utilizes deep understanding of neuronal excitability and neuronal networks and applies a series of computational and experimental tools to develop orally available precision therapies

### SOLIDUS™

*ANTISENSE OLIGONUCLEOTIDE (ASO) PLATFORM*


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


Targeting movement disorders & epilepsies connected by neuronal imbalance
PLATFORM
PRECLINICAL
PHASE ONE
PHASE TWO
REGISTRATION ENABLING
CEREBRUM™
SMALL MOLECULE PLATFORM
PRAX-020*
KCNT1
PRAX-050
Undisclosed
Ulixacaltamide
Essential Tremor
PRAX-628
Focal Epilepsy
PRAX-562
DEEs
SOLIDUS™
ASO PLATFORM
PRAX-090+
SYNGAP1
PRAX-100+
SCN2A LoF
PRAX-080+
PCDH19
PRAX-222
SCN2A GoF DEE
*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
PRAXIS
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# Leveraging genetics to efficiently translate insights into therapies

## GENETICS

Focus on therapeutic targets identified through human genetics

## TRANSLATIONAL TOOLS

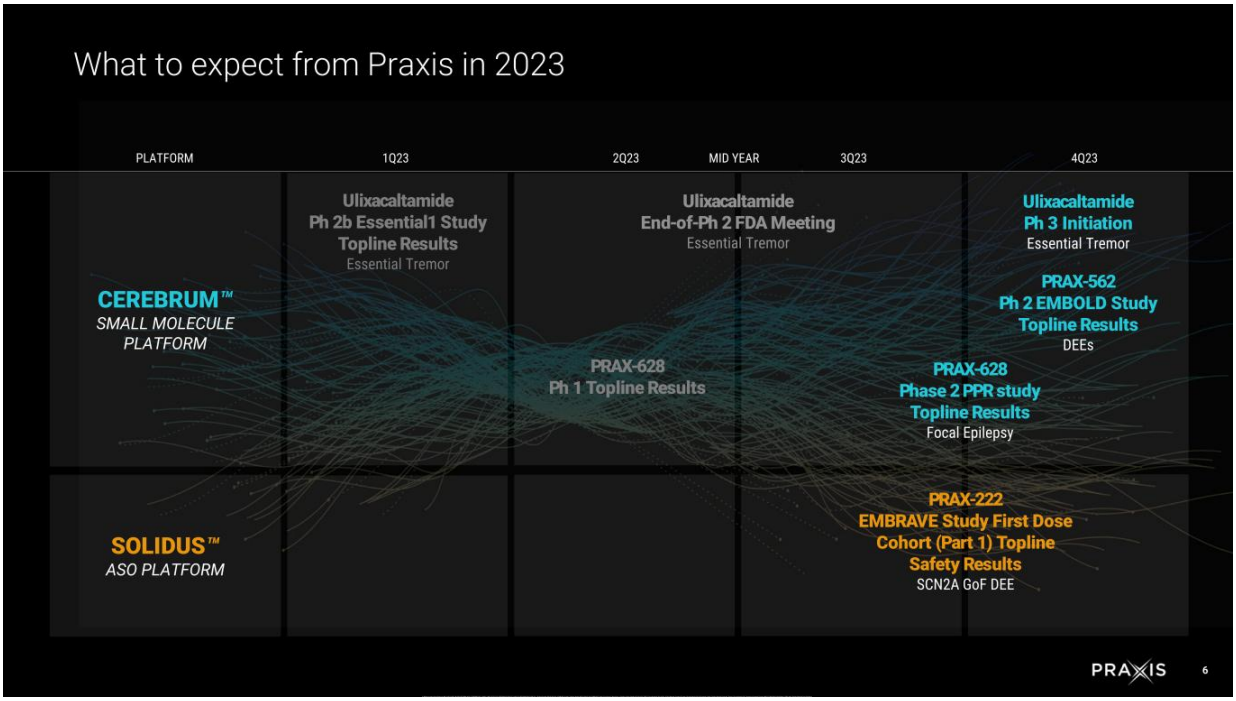
Translational tools validate potential of target and product candidate and can provide early proof of biology

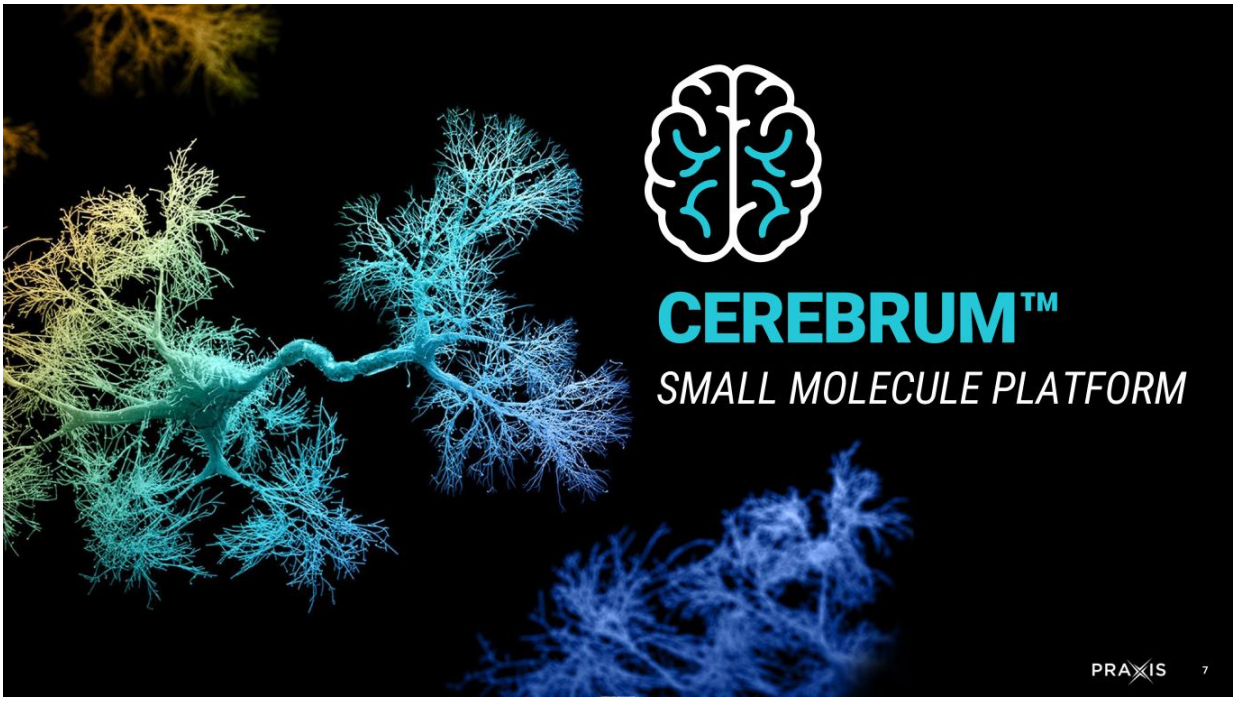
## EFFICIENT & RIGOROUS

Efficient, rigorous clinical development paths to proof-of-concept in humans

## PATIENT-GUIDED

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


What to expect from Praxis in 2023
PLATFORM
1Q23
2Q23
MID YEAR
3Q23
4Q23
Ulixacaltamide
Ph 2b Essential1 Study
Topline Results
Essential Tremor
Ulixacaltamide
End-of-Ph 2 FDA Meeting
Essential Tremor
Ulixacaltamide
Ph 3 Initiation
Essential Tremor
CEREBRUM™
SMALL MOLECULE
PLATFORM
PRAX-562
Ph 2 EMBOLD Study
Topline Results
DEEs
PRAX-628
Ph 1 Topline Results
PRAX-628
Phase 2 PPR study
Topline Results
Focal Epilepsy
PRAX-222
EMBRAVE Study First Dose
Cohort (Part 1) Topline
Safety Results
SCN2A GoF DEE
SOLIDUS™
ASO PLATFORM
PRAXIS
6

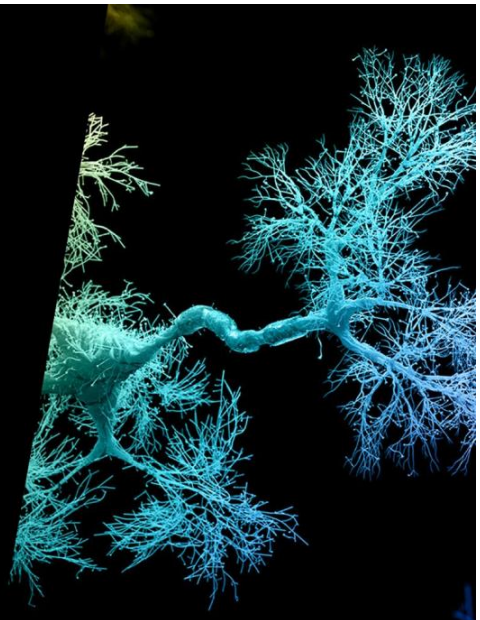

CEREBRUM™
SMALL MOLECULE PLATFORM
PRAXIS
7

# Ulixacaltamide (PRAX-944)

*Essential Tremor*

**KEY UPCOMING MILESTONES**

**Q4 2023**
ET Phase 3 Initiation



# Essential Tremor (ET) is the most common movement disorder…

Up to 7 million people in the United States may have ET[1]

Action tremors significantly disrupt daily living for people with ET

Hallmark feature 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]

SOURCE: 1. GHOSH (2016) (P.231, C.1, PH.1, L.1-2), 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

# …but ET often remains undiagnosed, misdiagnosed, undertreated and untreated

Approximately 1 million people are diagnosed with ET and on treatment, while another 1 million patients are estimated to remain untreated

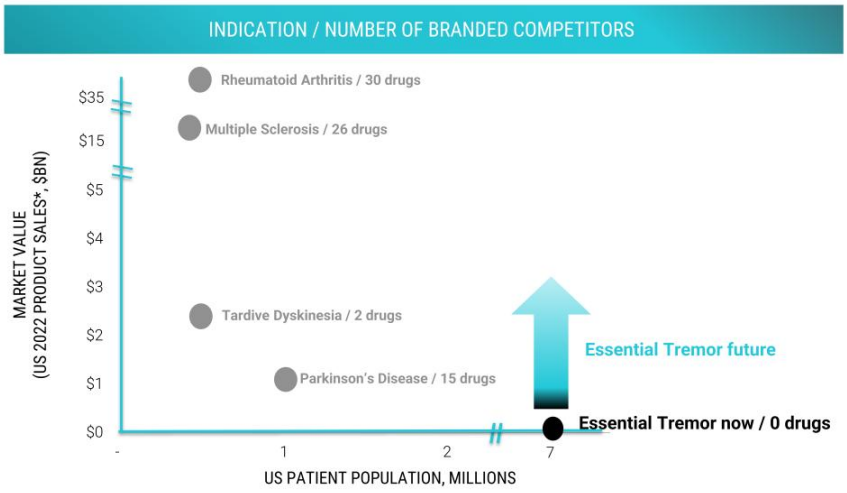

Of patients who seek treatment, ~40% discontinue within 2 years, or 200,000 patients annually

0 medications have been developed specifically for ET & only 1 medication was approved for ET >50 years ago

Many ET patients are frequently misdiagnosed, leading to ET diagnosis about 1.5 years after an initial movement disorder diagnosis

SOURCE: 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

# Essential tremor has a large market potential and limited competition compared with other diseases




Source: Evaluate Pharma US Sales by Product
(#) number of drugs with branded revenue report by company
*US products sales are not indication specific

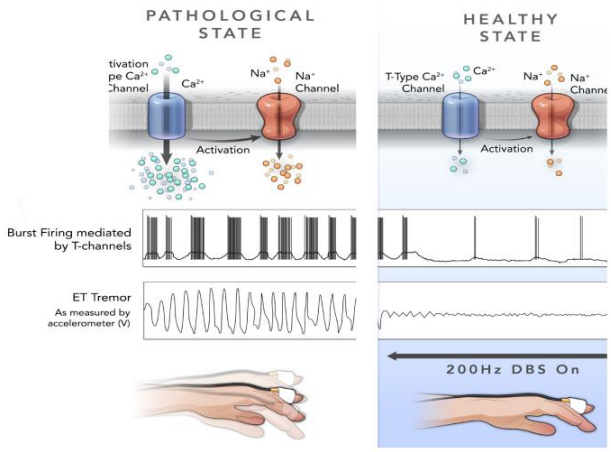
# Active 2023 as ulixacaltamide marches towards Phase 3

**Continue to generate supportive data and de-risk Phase 3 trial design**

| MARCH | JUNE | AUGUST | Q4 |
|---|---|---|---|
| | | | **Initiate Phase 3 studies** |
| **Essential1 Phase 2 Study**<br>• Clinically meaningful effect<br>• Well tolerated safety profile | **EoP2 FDA Meeting**<br>• Confirmed mADL11[1] as primary endpoint<br>• 60 mg as dose for the Phase 3 trials: one parallel design, one randomized withdrawal study | **Essential1 Additional Data**<br>• Patients on ulixacaltamide for 14 weeks see gain in efficacy<br>• Patients switching from ulixacaltamide to placebo lose efficacy | |

[1]mADL11 comprises 11 elements of the TETRAS Activities of Daily Living, excluding social impact, individually scored

# T-type calcium channels are gatekeepers of neuronal firing patterns in the Cerebello-Thalamo-Cortical (CTC) circuit




Mutations in T-type calcium channels (TTCC) are genetically linked to familial ET

TTCC drive burst firing in the CTC circuit

Burst firing in the CTC circuit correlated with tremor in patients with ET

Deep Brain Stimulation reduces burst firing and tremor

Source: Based on Milosevic 2018 figured on actual ET patient intraoperative real-time single-unit recordings of action potentials of individual neurons

# Ulixacaltamide is a differentiated, selective T-type calcium channel blocker in development for movement disorders

**Highly selective for T-type calcium channels**

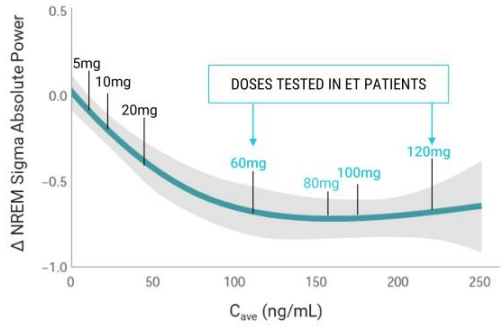
**Highly potent across all three T-type isoforms**

**Potential for effectiveness across range of neuronal activity levels**

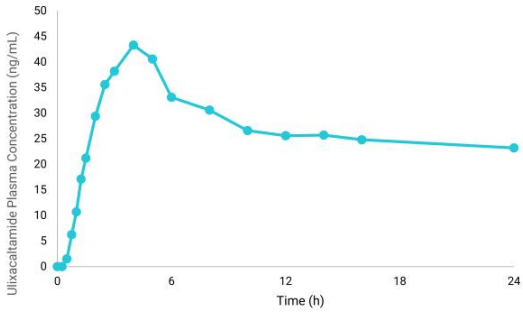
Source: Praxis Data on file, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9310641/

# Ulixacaltamide's wide dosing range and modified release formulation supports late-stage development and registration potential

## PREDICTABLE PK, FLEXIBILITY IN TITRATION & WIDE DOSING RANGE UP TO ~120 MG IN PATIENTS




## SUSTAINED EXPOSURE[1] WITH BLUNTED $C_{MAX}$




Source: Praxis Data on fil. 1. Profile for 20mg dose

# mADL11 as Phase 3 endpoint has been successfully used in the Phase 2 program

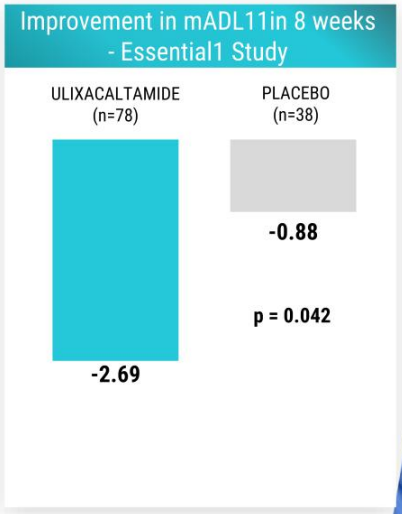
**Modified ADL11 items:**

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task

**Each measure is individually scored from 0-3:**

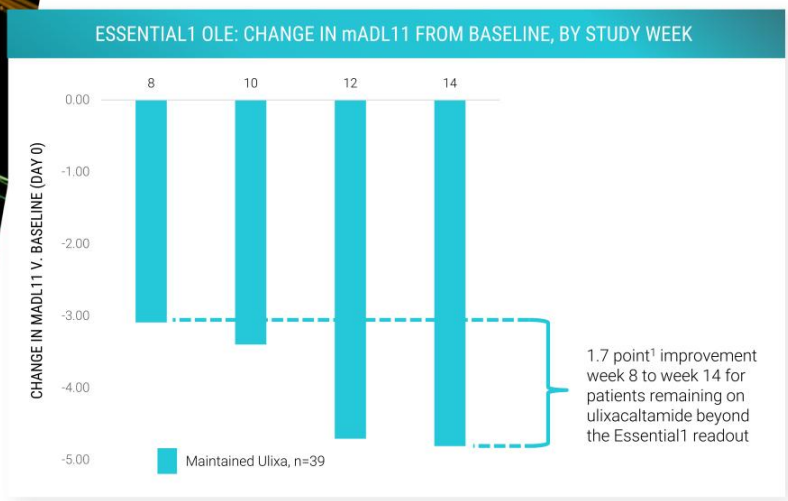
0 = Slightly abnormal. Tremor is present but does not interfere with __.
1 = Mildly abnormal. Spills a little.
2 = Moderately abnormal. Spills a lot or changes strategy to complete task.
3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

**TOTAL SCORE OF UP TO 33**




[1] Results from Essential1 study results. mITT: Modified Intention to Treat population, p values are nominal

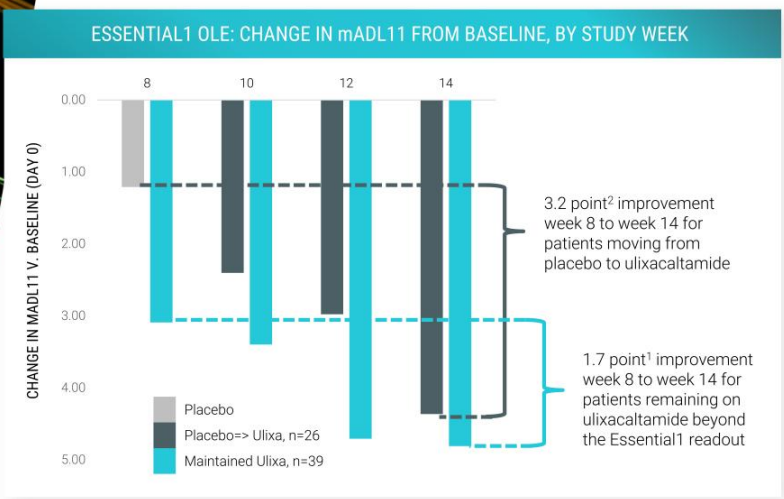
# Ulixacaltamide treated patients continue to benefit after 14 weeks on treatment




- Patients originally on drug continue to show durable effect through 14 weeks

[1]Improvement in the mADL11 of 1.7 points from 3.09 at Week 8 (95% CI: 0.98, 5.2) to 4.81 (95% CI: 2.38, 7.23) after 14 weeks of treatment

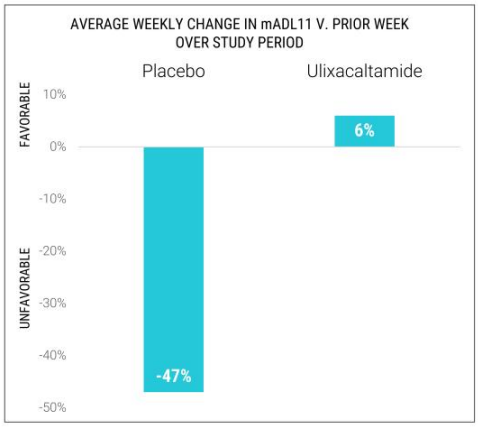
# Transition from placebo to ulixacaltamide supports benefit of treatment




- Patients originally on drug continue to show durable effect through 14 weeks
- Patients originally on placebo experience similar benefit as those seen in the drug arm during the first 8 weeks of Essential1

[1]Improvement in the mADL11 of 1.7 points from 3.09 at Week 8 (95% CI: 0.98, 5.2) to 4.81 (95% CI: 2.38, 7.23) after 14 weeks of treatment
[2]Improvement in mADL11 of 3.2 points, from 1.21 at Week 8 (95% CI: -1.04, 3.46) to 4.36 (95% CI: 1.68, 7.05)

# Randomized withdrawal randomized study supports design of proposed Phase 3




- Patients who switched from ulixacaltamide to placebo experienced an average loss of effect in their mADL11 per week of 47%*
- Patients who remained on ulixacaltamide had an average improvement of 6% per week

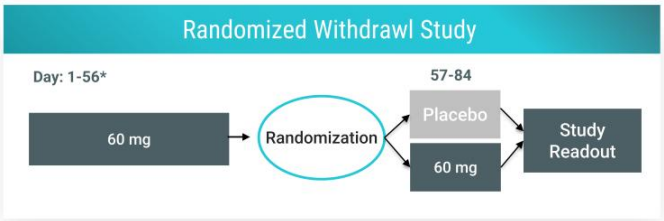
Sub-study design summary: Patients were re-randomized in a blinded-fashion to either receive placebo or continue to receive ulixacaltamide. Twenty-one patients who completed assessments at Week 14 of the OLE were eligible to participate in the blinded sub-study. Patients were evaluated weekly over a total of 6 weeks, with 11 patients assigned to ulixacaltamide and 10 to placebo for the initial 3-week period, crossing over to either placebo or ulixacaltamide for an additional 3-week period. Blinded rescue was triggered for patients on placebo if loss in the mADL11 exceeded 2 points at any timepoint.

*Mean change in effect of the mADL11

PRAXIS

# Phase 3 program comprised of two complementary 12-week studies

**mADL11 as primary endpoint**


- Single dose (60 mg)
- Control for intention tremor, family history and propranolol use by arm
- Agreement on the size of safety database for registration to include 300 subjects for 6 months of exposure and 100 subjects for 12 months of exposure
- Agreement on planned and completed clinical pharmacology and toxicology studies

**On-track for targeted NDA submission in 2025**

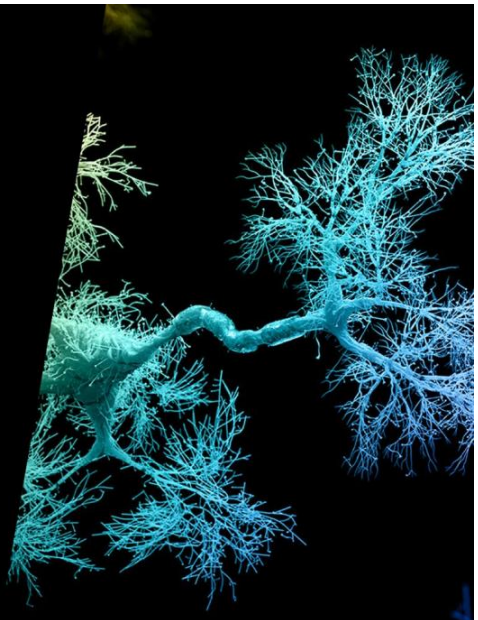
* Includes two-week titration

# PRAX-562

*SCN2A, SCN8A & OTHER DEEs*

**KEY UPCOMING MILESTONES**

**Q4 2023**
Ph 2 EMBOLD Study Topline Results



## Preclinical and emerging clinical data demonstrate PRAX-562 has the potential to be a first- and best- in-class small molecule for DEEs

**PRAX-562**

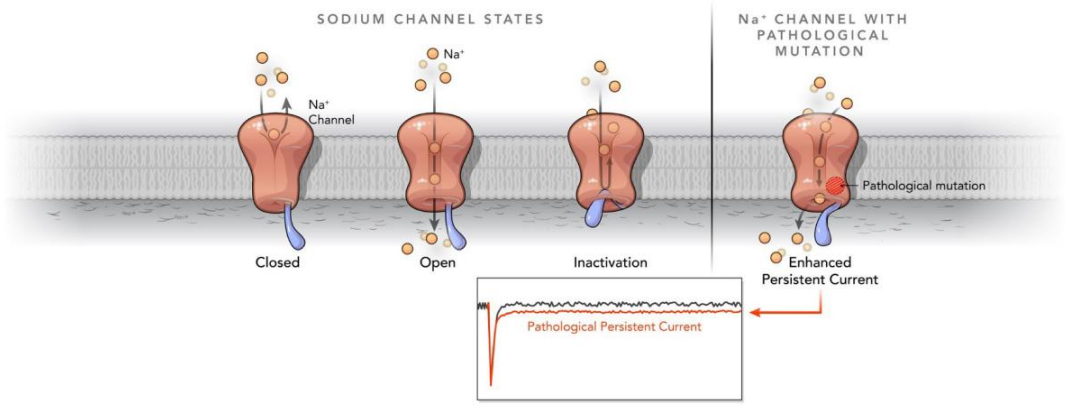
SCN2A, SCN8A
+ OTHER DEEs

FORMULATED FOR
PEDIATRIC USE

SMALL MOLECULE

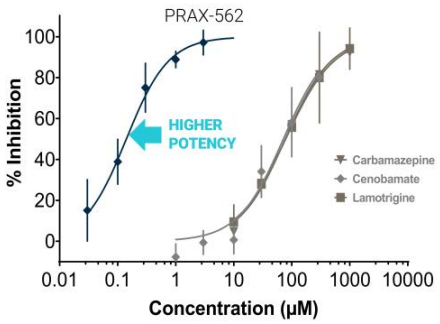
- Superior selectivity for disease-state $Na_V$ channel hyperexcitability
- Unprecedented therapeutic window with potential for superior safety and efficacy
- Convenient auto-titration regimen with stable PK

# Persistent sodium current ($I_{Na}$) is a critical driver of pathological hyperexcitability in CNS disorders



# Broader in vitro panel indicates PRAX-562 has best-in-class preferences

## % INHIBITION OF $hNa_V1.6$ PERSISTENT $I_{Na}$

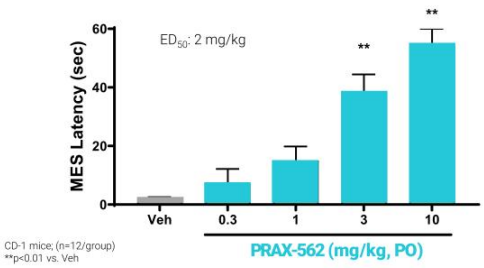



## COMPARISON OF POTENCY AND SELECTIVITY

| | Persistent $I_{Na}$ IC50 (nM) | Ratio of persistent to peak inhibition |
|---|---|---|
| **PRAX-562** | **141** | **60** ← MORE SELECTIVE |
| Carbamazepine | 77,520 | 30 |
| Cenobamate | 73,263 | 23 |
| Lidocaine | 68,230 | 19 |
| Lamotrigine | 78,530 | 16 |
| Lacosamide | 833,100 | n/a* |
| Valproic Acid | <10% @ 1 mM | No inhibition |

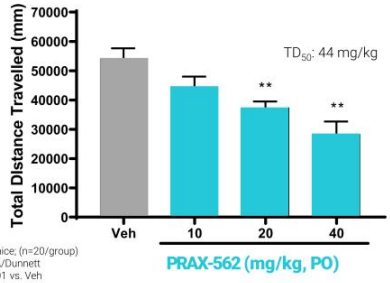
# Our mechanistic hypothesis translates to a wide therapeutic index in vivo for PRAX-562

## MES EFFICACY




CD-1 mice; (n=12/group)
**p<0.01 vs. Veh

## sLMA TOLERABILITY




CD-1 mice; (n=20/group)
ANOVA/Dunnett
**p<0.01 vs. Veh

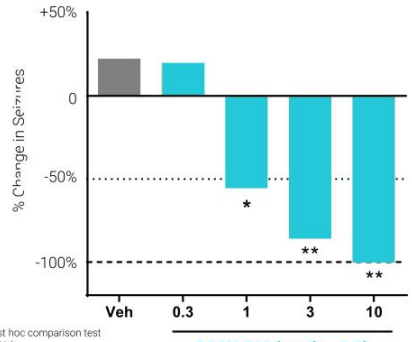
| Molecule | Plasma Therapeutic Index |
|---|---|
| PRAX-562 | 17.2x |

Therapeutic Index (TI) = TC50 / EC50

PRAXIS

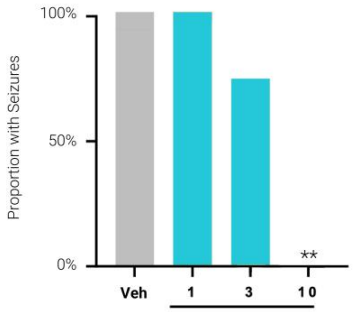
# PRAX-562 completely inhibits seizures in SCN2A and SCN8A GoF mutation mouse models

## IN VIVO POC IN SCN2A SPONTANEOUS SEIZURES[1]




Sidack's post hoc comparison test
*p<0.05 vs. Veh
**p<0.001 vs. Veh

## IN VIVO POC IN SCN8A AUDIOGENIC EVOKED SEIZURES[2]




**Significant protection vs. Veh
$\chi^2_3$ = 16.0, Fisher's p = 0.0002

[1] PRAX-562 inhibition of spontaneous seizures in Q54 GoF mice.
[2] PRAX-562 inhibition of audiogenic seizures in N1768D D/+ mice

# PRAX-562 Phase 1 summary

PRAX-562 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

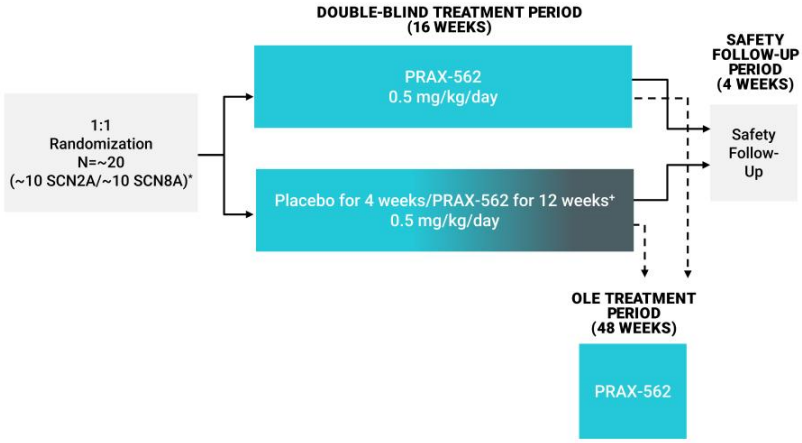
All TEAEs mild to moderate as stand-alone therapy*, with headache & dizziness most common TEAEs

Significant changes observed between placebo and 90 mg of PRAX-562 on qEEG and on ASSR 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 PRAX-562 and oxcarbazepine led to additive sodium blocking effects, including resulting in SAEs

# PRAX-562 Phase 2 EMBOLD study topline data expected 4Q23




**PRIMARY ENDPOINT:**

Incidence and severity of treatment-emergent adverse events (TEAEs)

**KEY SECONDARY:**

Change from baseline in monthly (28 day) motor seizure frequency

* Two distinct cohorts in early-onset SCN2A-DEE and SCN8A-DEE patients

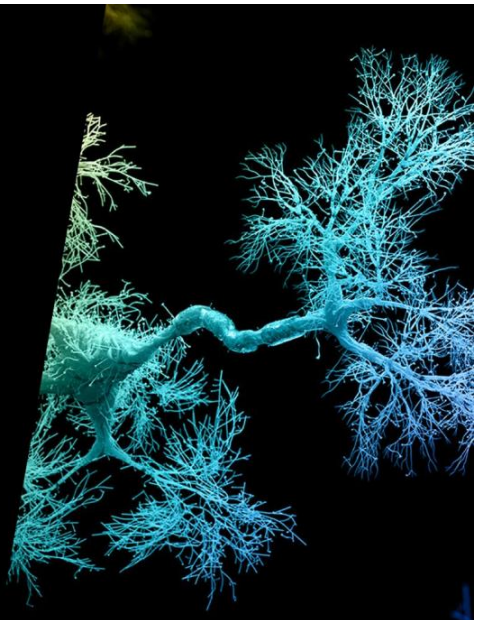
+ Participants receive either 0.5 mg/kg/day PRAX-562 QD for 16 weeks or 0.5 mg/kg/day PRAX-562 QD for 12 weeks & matching placebo QD for 4 weeks. Participants in the PRAX-562/placebo arm will receive placebo for 4 consecutive weeks during the 16-week treatment period, with timing of placebo administration blinded for both participants and investigator. Dose adjustment is permitted to a max of 1.0 mg/kg/day and a min of 0.25 mg/kg/day.

# PRAX-628

*Focal Epilepsy*

**KEY UPCOMING MILESTONES**

**2H 2023**
Topline Results from Phase 2 PPR study



# Focal epilepsy affects ~2 million people in the US alone

Defined as epilepsy that originates in one side or area of the brain and affects one side of the body

Most common type of epilepsy in adults and children - occurs in 60% of epilepsy cases

~ 50% have family history but genetics is not well understood

Most common age of onset is in the first year of life and in the 6th and 7th decade

# Preclinical and Phase 1 data demonstrate potential of PRAX-628 as best-in-class treatment for focal epilepsy

**PRAX-628**

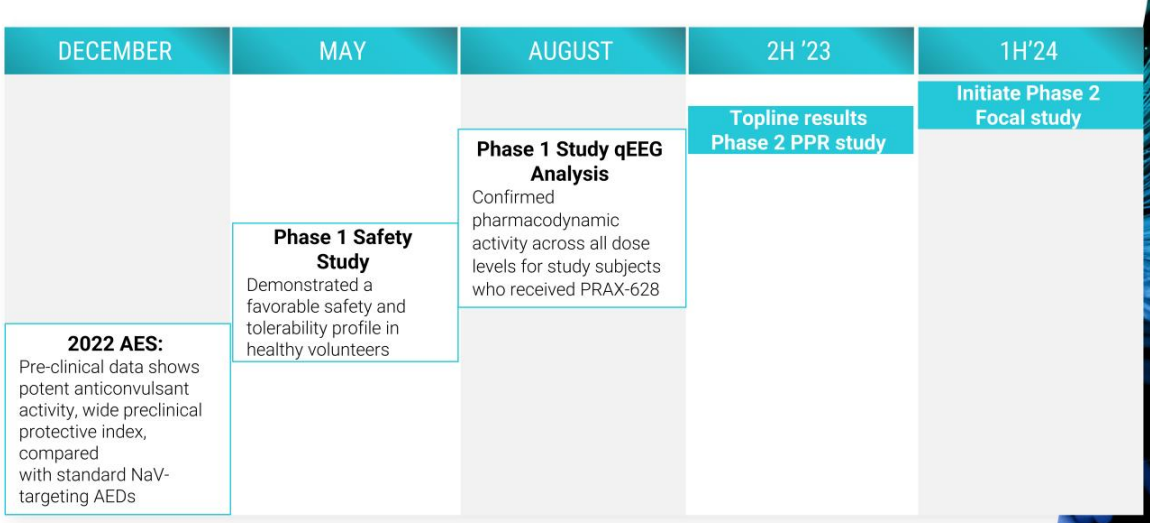
FOCAL EPILEPSY

FUNCTIONALLY SELECTIVE

SMALL MOLECULE

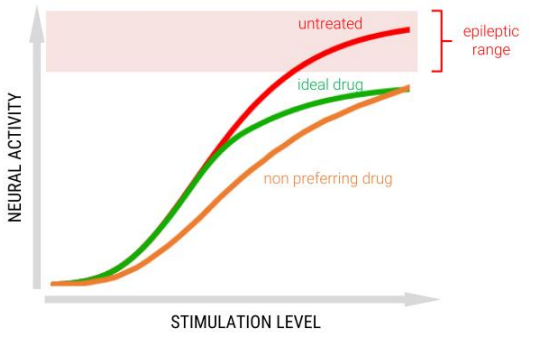
- Superior selectivity for hyperexcitable state of sodium channels in the brain associated with disease
- Unprecedented therapeutic window could translate to superior safety and efficacy
- qEEG analysis confirms CNS activity for doses above 5mg
- Favorable safety and tolerability profile across broad concentration range in healthy volunteers

# PRAX-628: Road to Phase 2 focal epilepsy study



# Restoring physiological neural activity by precisely modulating biophysics

## PREFERENTIAL ACTION AGAINST HYPEREXCITABILITY




## BIOPHYSICAL "LEVERS" TO ACHIEVE PREFERENTIAL ACTION

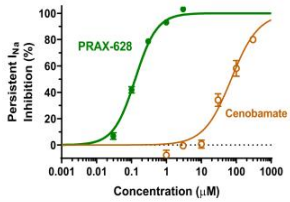
A. Reduce pro-excitatory channel function
   - Inhibit persistent current

B. Dynamic block of channels during high activity
   - Inhibit voltage dependent current
   - Inhibit use dependent current

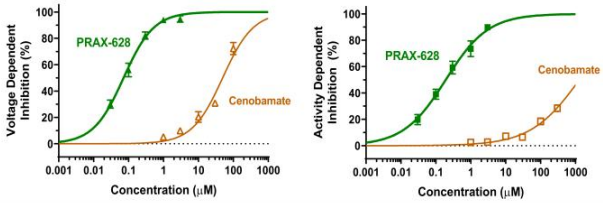
C. Maintain channel availability during low activity
   - Reduce potency against steady state peak current

# PRAX-628 delivers improved potency and separation to tonic (toxic) inhibition

## A. REDUCE PRO-EXCITATORY CHANNEL FUNCTION




## B. DYNAMIC BLOCK OF CHANNELS DURING HIGH ACTIVITY



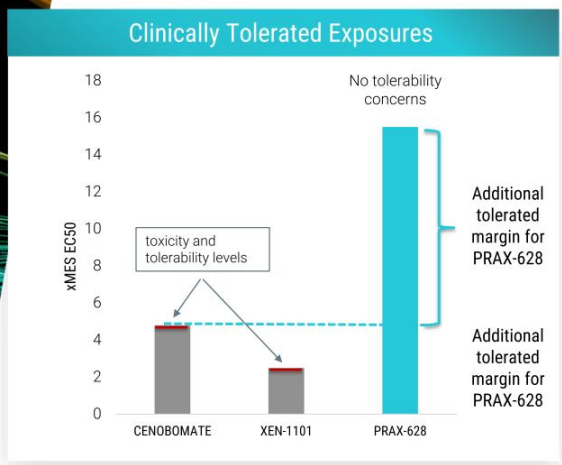

## C. MARGINS BETWEEN DISEASE CURRENT INHIBITION TO TONIC BLOCK OF HEALTY CURRENT

MARGIN TO TONIC BLOCK (TOXIC ACTIVITY)

| | PRAX-628 | CENOBAMATE |
|---|---|---|
| Persistent $I_{Na}$ | 68 | 24 |
| Voltage Dependent | 121 | 35 |
| Activity Dependent | 44 | 1.3 |

Source: Praxis data on file

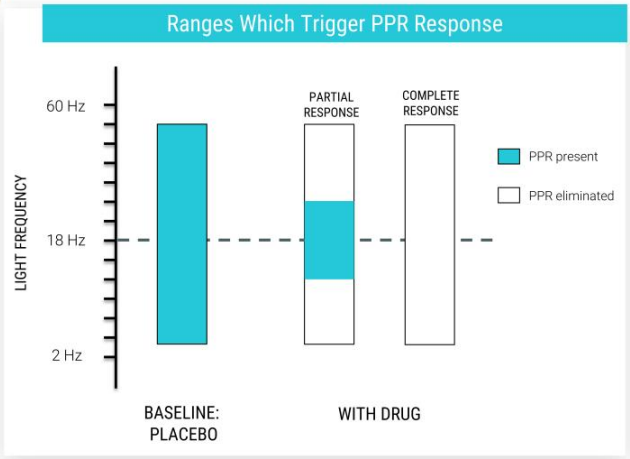
# PRAX-628 has unprecedented margins over best in class ASM's based on MES efficacy and clinical tolerability in humans




| | HUMAN EQUIVALENT OF MOUSE MES $EC_{50}$ NG/ML | MULTIPLE OF MES $EC_{50}$ TOLERATED CLINICALLY |
|---|---|---|
| Cenobamate | 9,600 | 4.8x |
| XEN-1101 | 42 | 2.5x |
| PRAX-628 | 24 | >15.5x* |

Source: Praxis data on file
Cenobamate $C_{max}$: >46,100 ng/mL, 400 mg $C_{max}$ (Vernillet et al 2020)
XEN1101 $C_{max}$: >107 ng/mL (Phase 1 data)
x MES $EC_{50}$ = multiple of predicted human $EC_{50}$ based on the rodent MES model

# Reduction of photosensitivity frequency range relative to baseline or PBO is ASM activity is indicative of AED efficacy




- The PPR Photosensitivity Model has been used to assess many AEDs[1]
- Partial or complete suppression of PPR photosensitivity range by drug versus PBO correlates to drug efficacy in a small sample size (4-6 patients)
- Dosing starting at 15mg

[1] References: First Pub: C.D. Binnie Electroencephalography and clinical neurophysiology A, 1986, 63, 35-41; LEV paper: DGA Kasteleijn-Nolst Trenité Epilepsy Research 25(1996) 225-230; DGA Kasteleijn-Nolst Trenité Neurology 93(6) 2019 e559-e567 cenobamate paper

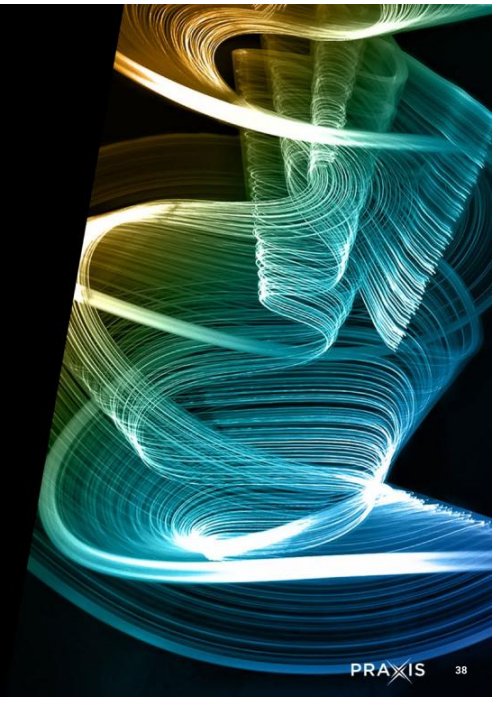

SOLIDUS™
ASO PLATFORM
PRAXIS
37

# PRAX-222

*SCN2A-GoF ASO*

**KEY UPCOMING MILESTONES**

**2H 2023**
EMBRAVE Study First Dose Cohort (Part 1)
Topline Safety Results



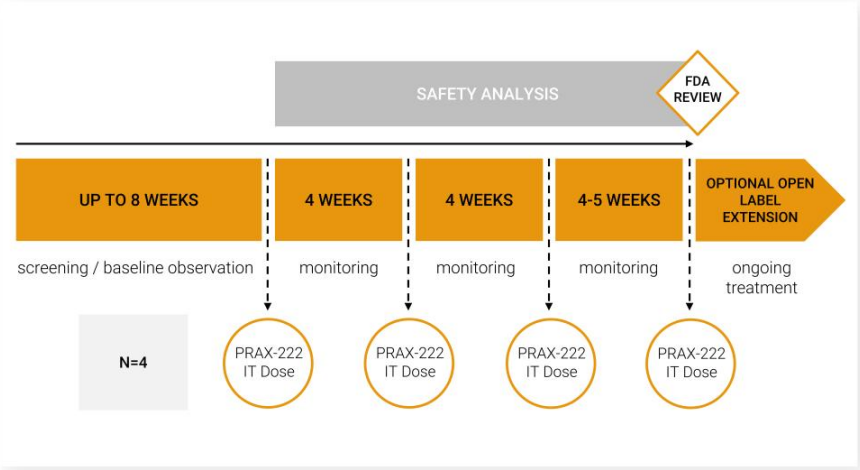
# Preclinical data suggest PRAX-222 has potential to be disease-modifying for early onset SCN2A gain-of-function DEE

**PRAX-222**

INTRATHECALLY-ADMINISTERED ASO for SCN2A GoF DEE

- Dose-dependent reduction in interictal spikes, seizures and increased survival
- Improvement in behavioral and locomotor activity
- Survival benefit extended with repeat dosing

# PRAX-222 EMBRAVE study initial dose cohort (Part 1) results expected 2H23

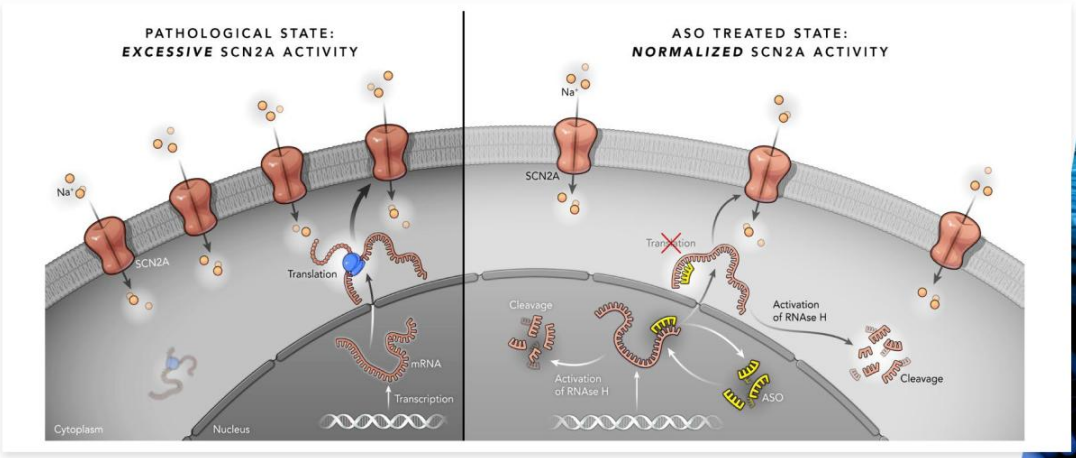



**GOAL:**
Assess preliminary safety of PRAX-222

21-week study

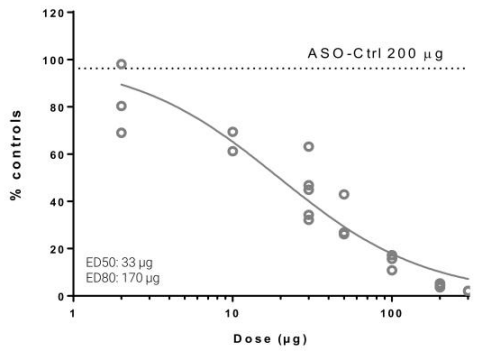
Open label design

# PRAX-222 is an ASO designed to down-regulate SCN2A expression in patients with gain-of-function mutation

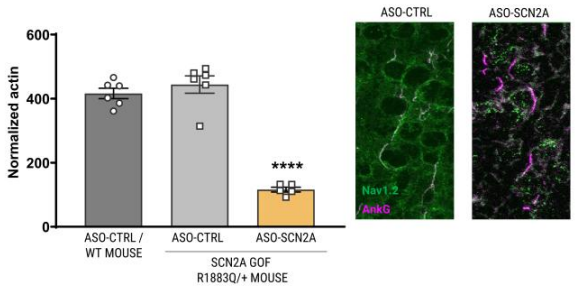


# In vitro, PRAX-222 down-regulates both mRNA and protein

## SCN2A mRNA KNOCKDOWN




## SCN2A PROTEIN KNOCKDOWN

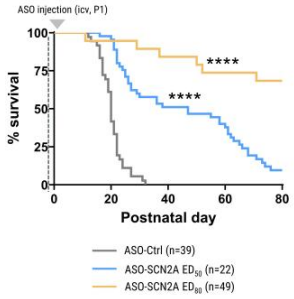



ASOs were administered at P30 and brains were collected 14 days post-ICV for qPCR analysis

# PRAX-222 increases survival in SCN2A GoF mice

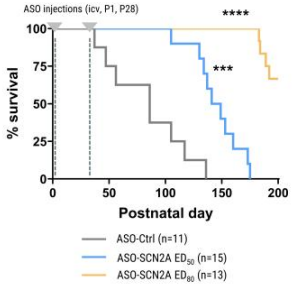
## SCN2A ASO INCREASES SURVIVAL WITH A SINGLE DOSE INJECTION

**SCN2A GOF model**



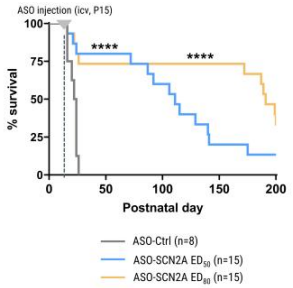

## RE-DOSING SIGNIFICANTLY EXTENDS SURVIVAL

**SCN2A GOF model**




## ADMINISTRATION POST-DISEASE ONSET ALSO EXTENDS SURVIVAL

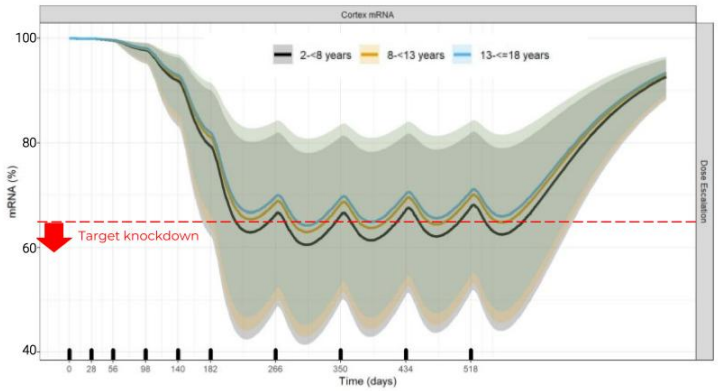
**SCN2A GOF model**




***p<0.001
****p<0.0001
All experiments conducted with SCN2A R1882Q mouse model

PRAXIS

# PRAX-222 PK/PD modeling informs starting dose and proposed escalation based on level of knockdown anticipated to achieve clinical benefit and tolerability




Median and 95% prediction interval illustrated

Simulated mRNA knockdown in human cortex in pediatric patients

Achieves distribution in key areas of brain based on NHP data

Source: Praxis data on file.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