# 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): February 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 February 7, 2023, Praxis Precision Medicines, Inc. (the "Company") announced its financial results for the quarter and full year ended December 31, 2022. 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 February 7, 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 9.01. Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Press Release, dated February 7, 2023 |
| 99.2 | Praxis Precision Medicines, Inc. February 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: February 7, 2023

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

**Praxis Precision Medicines Provides Corporate Update and Reports Fourth Quarter and Full Year 2022 Financial Results**

*Ulixacaltamide (PRAX-944) Phase 2b Essential1 study topline results for essential tremor expected in 1Q23; Praxis to enter quiet period following market close on Thursday, February 9*

*Topline results expected for each of three clinical-stage epilepsy programs in 2023 – PRAX-222 first-in-patient EMBRAVE Study safety data mid-2023, PRAX-628 first-in-human Phase 1 data mid-2023, PRAX-562 Phase 2 EMBOLD Study results in 2H23*

*Cash and investments of $100.5 million as of December 31, 2022 supports runway into 1Q24*

**BOSTON, February 7, 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 fourth quarter and full year 2022.

"This year is set up to be transformative for Praxis and for the patients that we serve, with topline results for the ulixacaltamide Essential1 study imminent and data expected from each of our four clinical-stage programs in 2023," said Marcio Souza, president and chief executive officer of Praxis. "Based on our understanding of epilepsy genetics and unique capabilities to translate these insights into therapies for patients suffering from a broad range of CNS disorders, we have built two proprietary platforms, Cerebrum™ for small molecules and Solidus™ for antisense oligonucleotides, that we expect will drive continuous innovation and value creation this year and beyond."

**Recent Business Highlights and Upcoming Milestones:**

*Cerebrum™ Small Molecule Platform*

- Praxis expects topline results from the ongoing ulixacaltamide (PRAX-944) Essential1 study for the treatment of moderate to severe essential tremor (ET) in the first quarter of 2023. Essential1 is a randomized, double-blind, placebo-controlled, dose-range-finding Phase 2b trial evaluating the efficacy, safety and tolerability of once-daily daytime treatment of 60 or 100 mg of ulixacaltamide compared to placebo after 56 days. The primary endpoint is change from baseline to day 56 in the modified Activities of Daily Living (mADL[1]) score. Following topline results, Praxis intends to request an end-of-Phase 2 meeting with the FDA and initiate its ulixacaltamide Phase 3 development program for the treatment of ET in mid-2023.

- The Company is also conducting a randomized, double-blind, placebo-controlled Phase 2 trial to evaluate the efficacy, safety and tolerability of once-daily treatment of up to 100 mg of ulixacaltamide as a non-dopaminergic treatment for the motor symptoms of Parkinson's disease. The primary endpoint for the study is change from baseline in the International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS), Part III (motor examination) score in the OFF state. Topline results are expected in the fourth quarter of 2023.

- In November 2022, Praxis announced plans to initiate the PRAX-562 Phase 2 EMBOLD study for the treatment of pediatric patients with developmental and epileptic encephalopathies (DEEs), following FDA authorization to proceed with the study as Praxis proposed, up to the planned maximum dose of 1.0 mg/kg/day. 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 (PK) of PRAX-562 in pediatric participants aged 2 to 18 years with DEEs, followed by an open-label extension. Approximately 20 participants will be enrolled initially in

[1]mADL is a composite sum of items 1 to 11 of the TETRAS-ADL subscale and items 6 (bilateral) and 7 of the TETRAS-PS; mADL score is calculated as the sum of all 13 items (item 6 of TETRAS-PS x2) and ranges from 0 to 42

two distinct cohorts (n≈10 for SCN2A-DEE and n≈10 for SCN8A-DEE). Topline results for both cohorts are expected in the second half of 2023.

- The Company is conducting a Phase 1 healthy volunteer study of PRAX-628 to evaluate the tolerability, PK, pharmacodynamics and food effect of PRAX-628 across single and multiple ascending dose cohorts. Topline results from the Phase 1 study are expected in mid-2023, with plans to initiate a Phase 2 study in focal epilepsy in the fourth quarter of 2023.

- In December 2022, Praxis announced that it entered into a strategic collaboration, based upon its PRAX-020 program, with UCB for the discovery of small molecule therapeutics as potential treatments for KCNT1 epilepsies. Under the terms of the collaboration, UCB retains an exclusive option to in-license global development and commercialization rights to any resulting KCNT1 small molecule development candidate. Praxis received an upfront payment from UCB, and if the option is exercised by UCB, would be eligible to receive an option fee and future success-based development and commercialization milestone payments, for a total of up to approximately $100 million, in addition to tiered royalties on net sales of any resulting products from the collaboration.

- In December 2022, Praxis presented the following posters at the American Epilepsy Society (AES) 2022 Annual Meeting:
  - PRAX-562 is a Well-tolerated, Novel Persistent Sodium Channel Blocker with Broad Anticonvulsant Activity in Multiple DEE Mouse Models (Abstract Number: 1.281)
  - A Phase 1 Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Food Effect of PRAX-562 in Healthy Volunteers (Abstract Number: 2.24)
  - A Phase 1 Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of PRAX-562 in Healthy Volunteers (Abstract Number: 2.478)
  - Disease Impact and Burden in Patients with SCN2A-Related Developmental and Epileptic Encephalopathy (Abstract Number: 2.092)
  - A Novel Approach to Assess the Impact of Disease in Patients with SCN8A-Related Developmental and Epileptic Encephalopathy (Abstract Number: 2.096)
  - PRAX-628: A Novel Sodium Channel Blocker with Greater Potency and Activity Dependence Compared to Standard of Care (Abstract Number: 3.311)
  - PRAX-628 is a Novel, Well-tolerated, Activity Dependent Sodium Channel Blocker with Potent Anticonvulsant Activity (Abstract Number: 3.28)

*Solidus™ Antisense Oligonucleotide (ASO) Platform*

- Praxis is conducting 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 the initial cohort of patients in 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 from Part 1 of the PRAX-222 EMBRAVE study are expected in mid-2023.

- The Company remains on track to nominate a development candidate for its most advanced preclinical ASO program, PRAX-080 for the treatment of PCDH19, in the second half of 2023.

**Fourth Quarter and Full Year 2022 Financial Results:**

As of December 31, 2022, Praxis had $100.5 million in cash, cash equivalents and marketable securities, compared to $275.9 million in cash, cash equivalents and marketable securities as of December 31, 2021. This decrease of $175.4 million primarily reflects cash used in operations of $185.0 million during the year ended December 31, 2022, partially offset by $9.6 million in net proceeds from at-the-market offerings of shares of the Company's common stock. The Company’s cash, cash equivalents and marketable securities as of December 31, 2022 are expected to fund operations into the first quarter of 2024.

Research and development expenses were $28.3 million for the fourth quarter of 2022, compared to $43.5 million for the fourth quarter of 2021. Research and development expenses were $155.0 million for the year ended December 31, 2022, compared to $120.3 million for the year ended December 31, 2021. The increase in research and development expenses for full year 2022 of $34.7 million was primarily attributable to $29.9 million in increased expenses related to the Company's Cerebrum™ and Solidus™ platforms.

General and administrative expenses were $13.1 million for the fourth quarter of 2022, compared to $15.1 million for the fourth quarter of 2021. General and administrative expenses were $59.9 million for the year ended December 31, 2022, compared to $47.1 million for the year ended December 31, 2021. The increase in general and administrative expenses for full year 2022 of $12.8 million was primarily attributable to an increase of $11.8 million in personnel-related expenses due to changes in headcount, including an increase of $5.3 million in stock-based compensation expense.

Praxis reported a net loss of $41.2 million for the fourth quarter of 2022, including $6.4 million of stock-based compensation expense, compared to $58.6 million for the fourth quarter of 2021, including $6.1 million of stock-based compensation expense. Praxis reported a net loss of $214.0 million for the year ended December 31, 2022, including $28.6 million of stock-based compensation expense, compared to a net loss of $167.1 million for the year ended December 31, 2021, including $22.7 million of stock-based compensation expense.

As of December 31, 2022, Praxis had 49.4 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 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 expectations, plans and timing for our clinical data, the anticipated timing of our clinical trials and regulatory interactions, the development of our product candidates, including the design of our clinical trials and the treatment potential of our product candidates, and the sufficiency of our cash, cash equivalents and marketable securities, 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 submissions for regulatory approval or review by governmental authorities; regulatory approvals to conduct trials; Praxis' ability to continue as a going concern; 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 to be filed 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.

**Investor Contact**
Alex Kane
Praxis Precision Medicines
investors@praxismedicines.com
617-300-8481

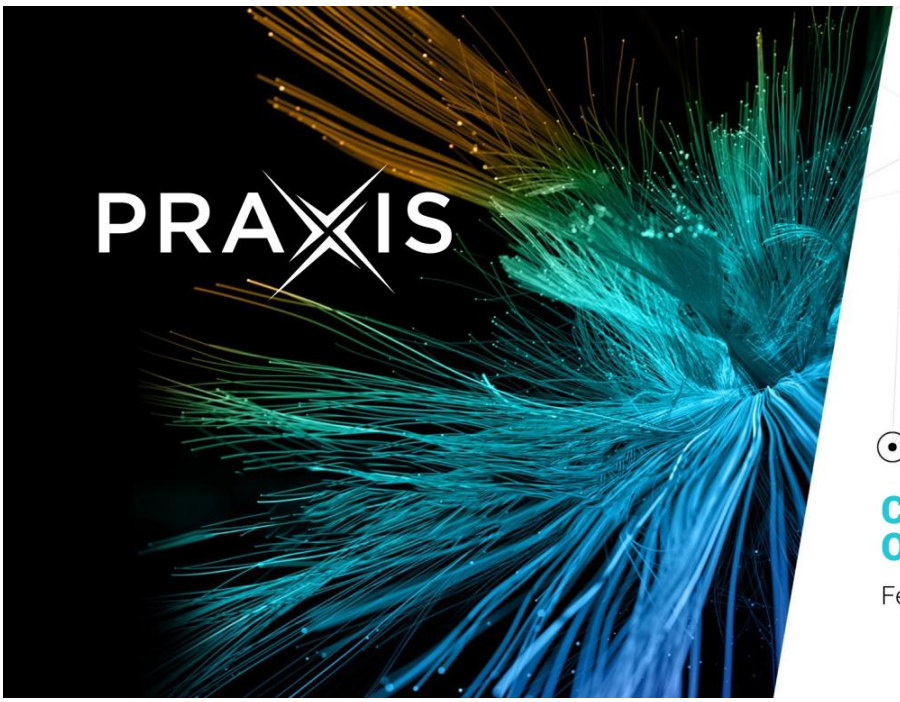
**Media Contact**
Ian Stone
Canale Communications
Ian.stone@canalecomm.com
619-849-5388

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

| | December 31, | |
|---|---|---|
| | **2022** | **2021** |
| **Assets** | | |
| Cash and cash equivalents | $ 61,615 | $ 138,704 |
| Marketable securities | 38,874 | 137,207 |
| Prepaid expenses and other current assets | 10,351 | 11,498 |
| Property and equipment, net | 971 | 1,213 |
| Operating lease right-of-use assets | 2,901 | 3,653 |
| Other non-current assets | 416 | 472 |
| **Total assets** | $ 115,128 | $ 292,747 |
| **Liabilities and stockholders' equity** | | |
| Accounts payable | $ 14,672 | $ 10,780 |
| Accrued expenses | 15,850 | 26,844 |
| Operating lease liabilities | 3,500 | 4,311 |
| Deferred revenue | 5,000 | — |
| Common stock | 5 | 5 |
| Additional paid-in capital | 606,918 | 567,598 |
| Accumulated other comprehensive loss | (173) | (176) |
| Accumulated deficit | (530,644) | (316,615) |
| **Total liabilities and stockholders' equity** | $ 115,128 | $ 292,747 |

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

| | Three Months Ended December 31, | | Year Ended December 31, | |
|---|---|---|---|---|
| | 2022 | 2021 | 2022 | 2021 |
| Operating expenses: | | | | |
| Research and development | $ 28,329 | $ 43,511 | $ 155,040 | $ 120,257 |
| General and administrative | 13,124 | 15,146 | 59,946 | 47,075 |
| Total operating expenses | 41,453 | 58,657 | 214,986 | 167,332 |
| Loss from operations | (41,453) | (58,657) | (214,986) | (167,332) |
| Other income: | | | | |
| Other income, net | 280 | 70 | 957 | 271 |
| Total other income | 280 | 70 | 957 | 271 |
| Loss before benefit from income taxes | (41,173) | (58,587) | (214,029) | (167,061) |
| Benefit from income taxes | — | 5 | — | — |
| Net loss | $ (41,173) | $ (58,582) | $ (214,029) | $ (167,061) |
| Net loss per share attributable to common stockholders, basic and diluted | $ (0.87) | $ (1.30) | $ (4.64) | $ (3.94) |
| Weighted average common shares outstanding, basic and diluted | 47,594,823 | 44,964,580 | 46,096,737 | 42,454,055 |




# CORPORATE OVERVIEW

February 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 to be filed 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™

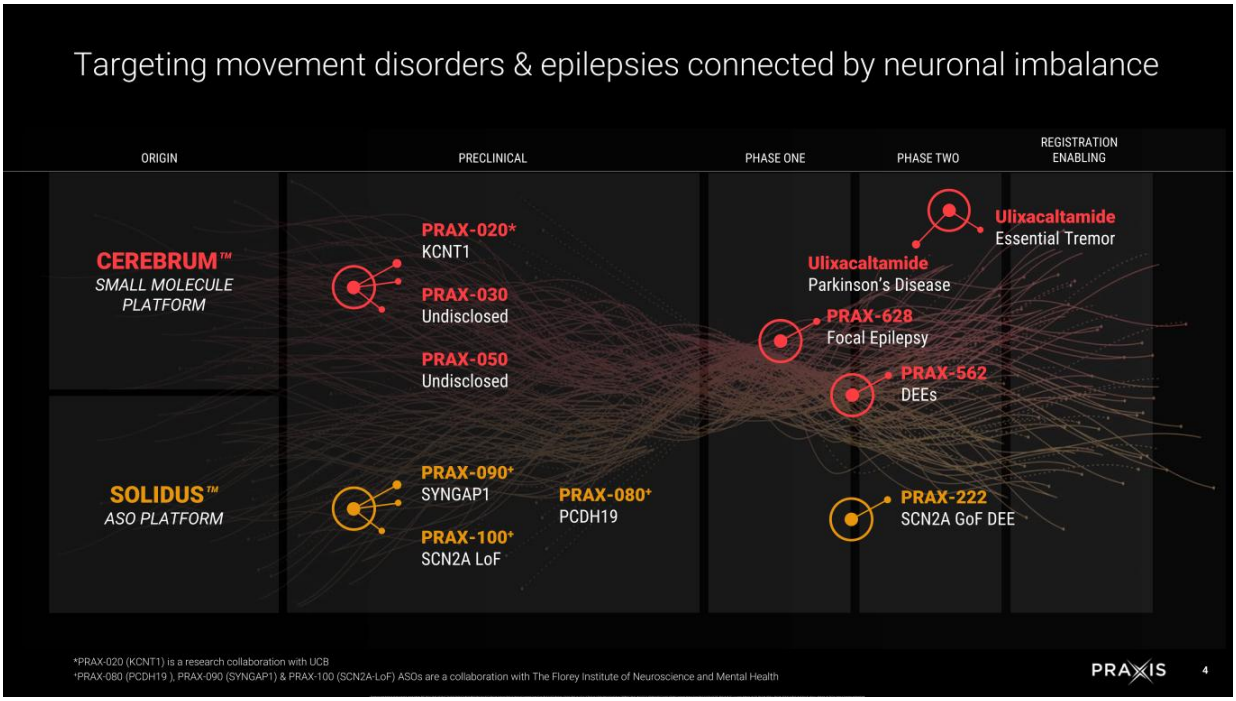
*SMALL MOLECULE PLATFORM*


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
ORIGIN
PRECLINICAL
PHASE ONE
PHASE TWO
REGISTRATION ENABLING
CEREBRUM™
SMALL MOLECULE PLATFORM
SOLIDUS™
ASO PLATFORM
PRAX-020*
KCNT1
PRAX-030
Undisclosed
PRAX-050
Undisclosed
PRAX-090+
SYNGAP1
PRAX-100+
SCN2A LoF
PRAX-080+
PCDH19
Ulixacaltamide
Essential Tremor
Ulixacaltamide
Parkinson's Disease
PRAX-628
Focal Epilepsy
PRAX-562
DEEs
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
4

## 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

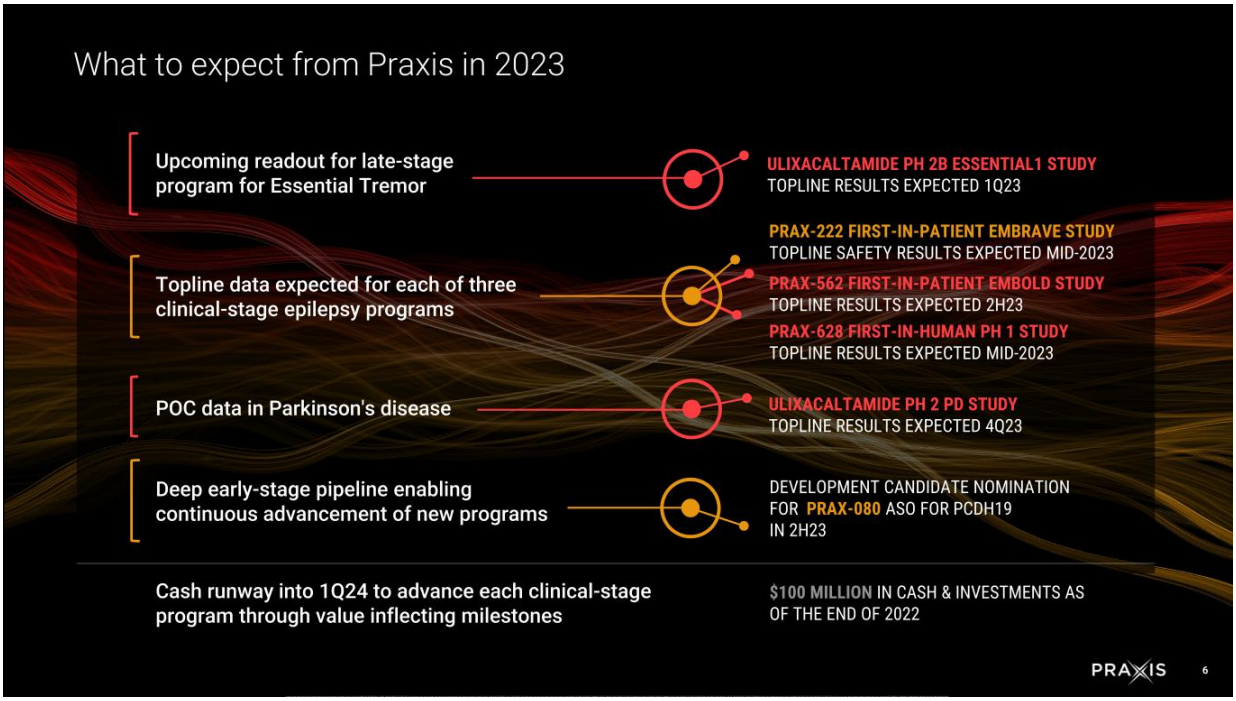
### EFFICIENT & RIGOROUS

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

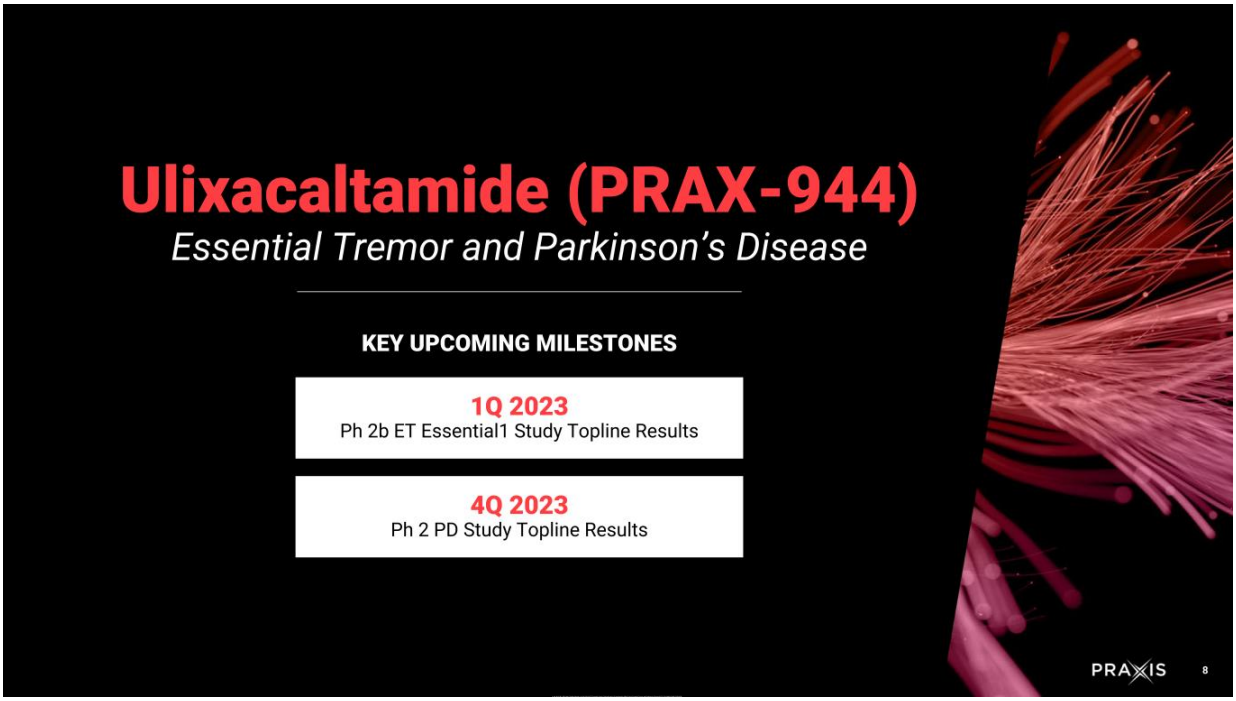
### PATIENT-GUIDED

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

# What to expect from Praxis in 2023




CEREBRUM™
SMALL MOLECULE PLATFORM
PRAXIS
7


Ulixacaltamide (PRAX-944)
Essential Tremor and Parkinson's Disease
KEY UPCOMING MILESTONES
1Q 2023
Ph 2b ET Essential1 Study Topline Results
4Q 2023
Ph 2 PD Study Topline Results
PRAXIS
8

# 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

PRAXIS

Ulixacaltamide is a differentiated, selective T-type calcium channel blocker in development for ET and Parkinson's disease

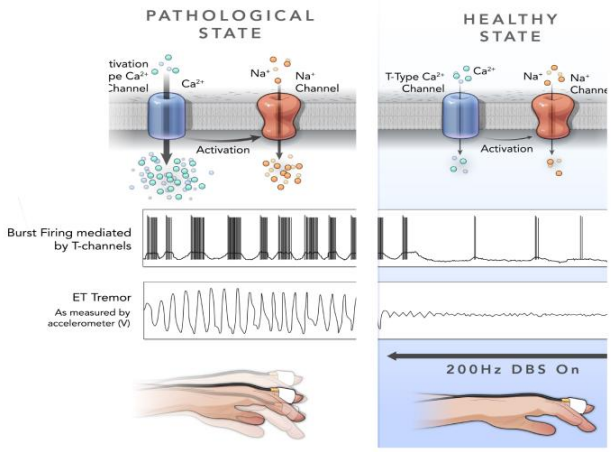
**Highly selective for T-type calcium channels**

**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/

# 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

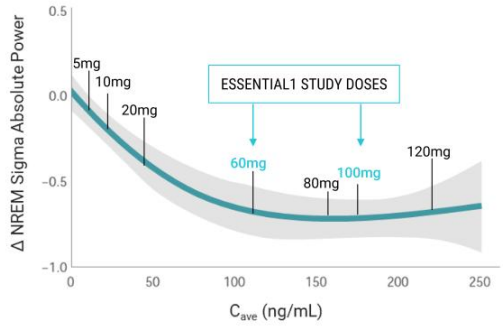
Burst firing in the CTC circuit correlated with tremor in patients with ET and PD

Deep Brain Stimulation reduces burst firing and tremor

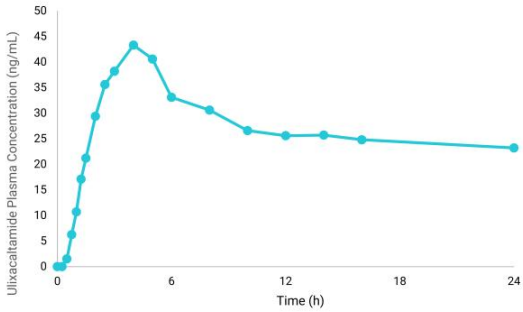
Source: Based on Milosevic 2018 figured on actual ET patient intraoperative real-time single-unit recordings of action potentials of individual neurons

# Ulixacaltamide's wide dosing range and modified release formulation may support tolerability & efficacy profile

## PREDICTABLE PK, WIDE DOSING RANGE UP TO ~100 mg & FLEXIBILITY IN TITRATION

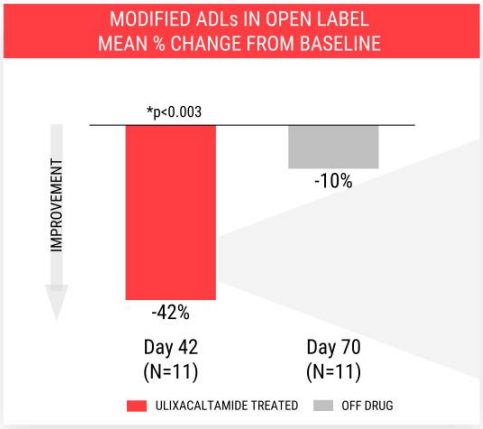


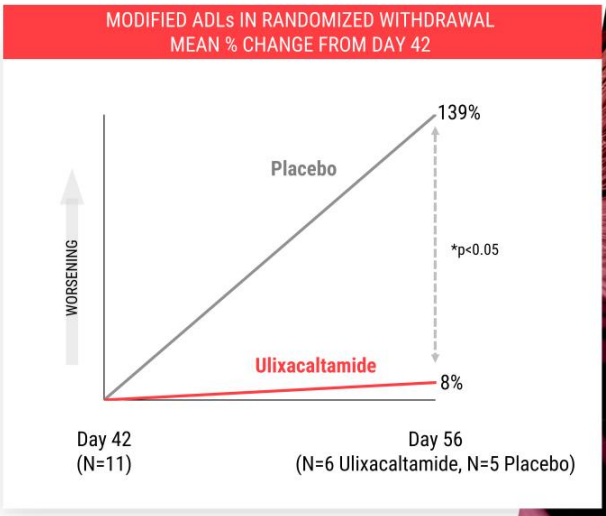

## SUSTAINED EXPOSURE WITH BLUNTED $C_{MAX}$




Source: Praxis Data on file

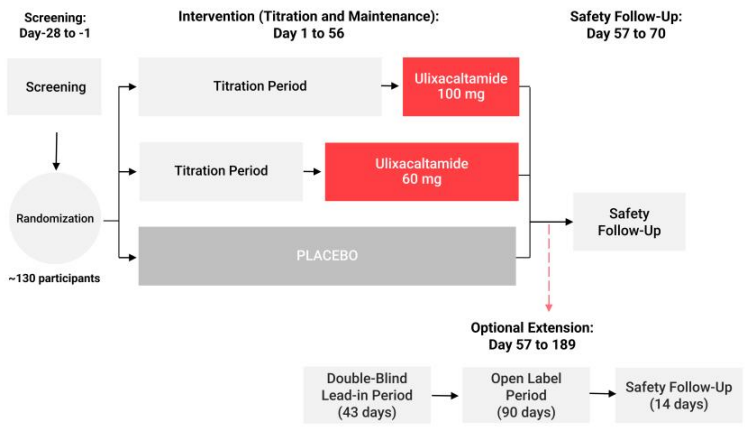
# Marked functional benefit observed in ulixacaltamide patients in Ph 2a study




*Nominal p-value based on ANCOVA
Source: Praxis Data on file from Part B of Phase 2a study

# Ulixacaltamide Phase 2b Essential1 study topline results expected 1Q23




**PRIMARY ENDPOINT:**

Change from baseline to Day 56 in the Modified ADL*, functionally relevant & FDA-suggested endpoint

**STUDY POWERING:**

33 evaluable participants per regimen provides 80% power to detect 0.6 effect size between pooled ulixacaltamide and placebo groups, or placebo adjusted difference of 3.6 pts in mADL at Day 56 (SD=6)

*Composite sum of items 1 to 11 of TETRAS-ADL subscale and items 6 (bilateral) and 7 of TETRAS-PS; modified ADL score is calculated as the sum of all 13 items and ranges from 0 to 42
clinicaltrials.gov/ct2/show/NCT05021991

# Modified ADLs: A modified measure of TETRAS activities of daily living (ADLs) that is functionally relevant and FDA recommended

**TETRAS ADL measures observed:**

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
12. Social Impact

**Each measure is individually scored from 0-4:**

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

**TOTAL SCORE OF UP TO 48**

**Modified ADL measures observed:**

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
12. Handwriting
13. Spirals (x2)
14. ~~Social impact~~

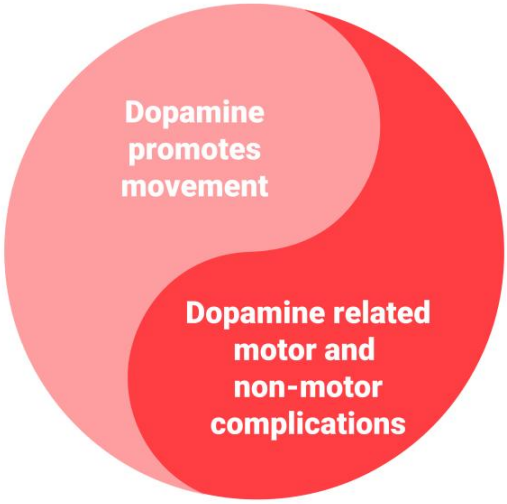
**Each measure is individually scored from 0-3:**

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.

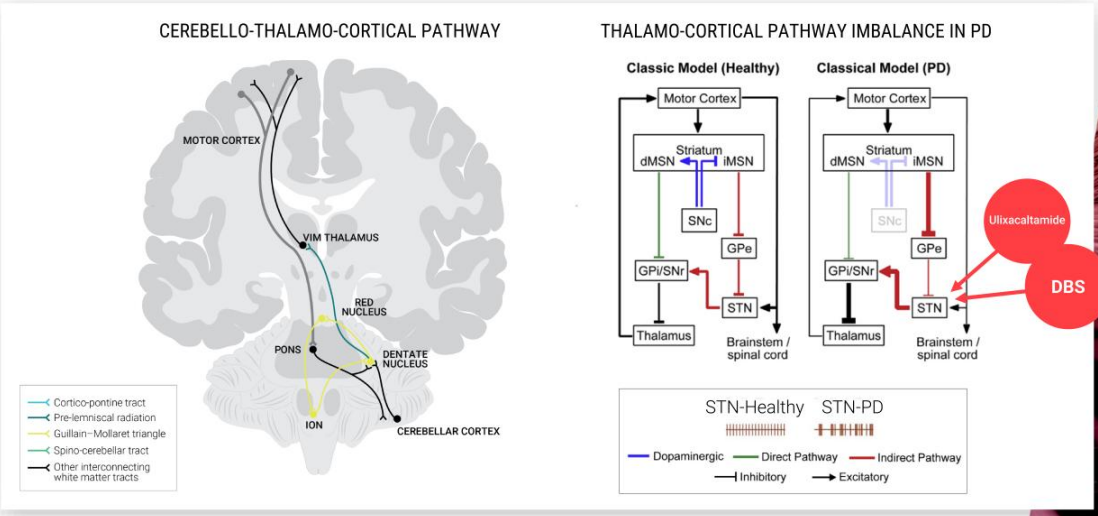
**TOTAL SCORE OF UP TO 42**

PRAXIS

Ulixacaltamide has potential to be a non-dopaminergic therapy for motor function for people with Parkinson's disease



# T-type calcium channels modulate the motor circuit in Parkinson's disease and overlap with target for Deep Brain Stimulation

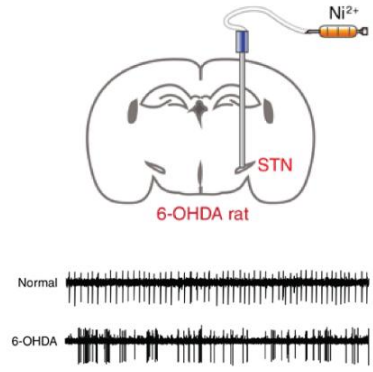



Mcgregor mm, nelson ab. Neuron. 2019. Doi:10.1016/j.Neuron.2019.03.004
Tai c-h et al. J clin invest. 2011. Doi:10.1172/jci46482

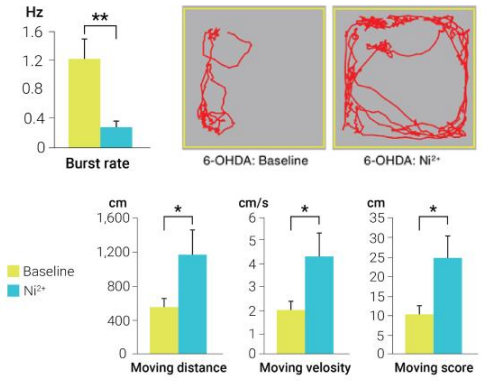
PRAXIS

# Blocking T-type calcium channels with $Ni^{2+}$ improves motor function in burst firing model of movement deficit in Parkinson's disease

## BURST FIRING IN STN OF 6-OHDA PARKINSON'S MODEL

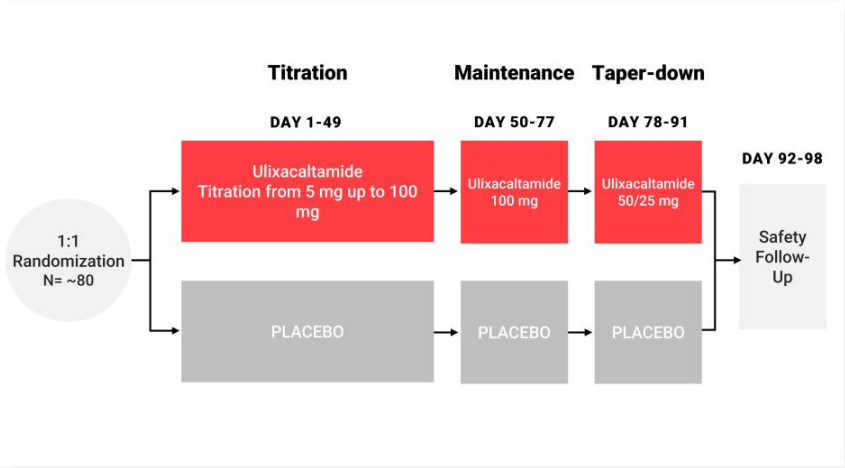



## BLOCK OF BURST FIRING IMPROVES MOVEMENT IN 6-OHDA PARKINSON'S MODEL




Pan et al (2016) j clin invest doi: 10.1172/jci88170

# Ulixacaltamide Phase 2 Parkinson's disease study topline data expected 4Q23




**PRIMARY ENDPOINT:**

Change from baseline to Day 77 in the International Parkinson and Movement Disorder Society (MDS) Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination) score in the OFF state


PRAX-562
SCN2A, SCN8A & OTHER DEEs
KEY UPCOMING MILESTONES
2H 2023
Ph 2 EMBOLD Study Topline Results
PRAXIS
21

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

**PRAX-562**

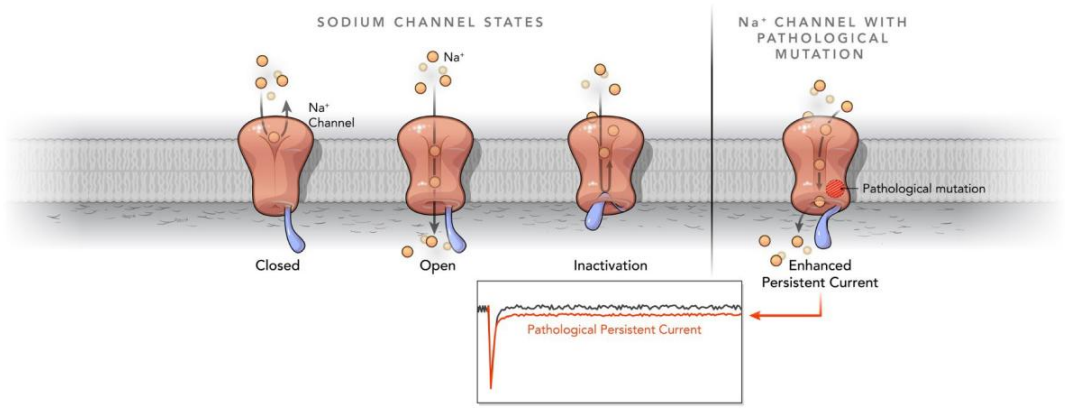
SCN2A, SCN8A
+ OTHER DEEs

PAN-$NA_V$ BLOCKER

SMALL MOLECULE

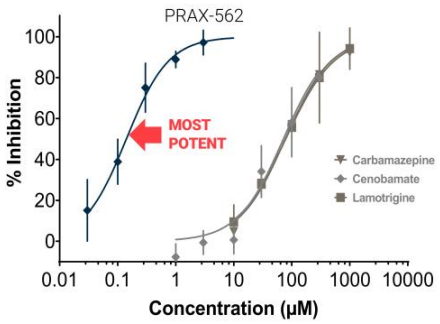
- Superior selectivity for disease-state $Na_V$ channel hyperexcitability
- Unprecedented therapeutic window with potential for superior safety and efficacy
- Convenient auto-titration regimen with stable PK

# 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 $I_{Na}$

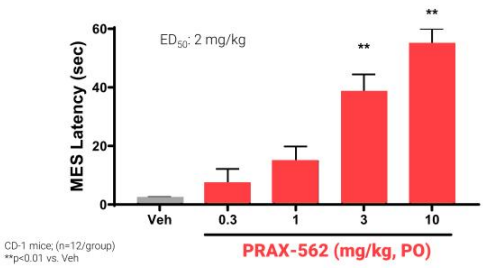



## COMPARISON OF POTENCY AND SELECTIVITY

| | Persistent $I_{Na}$ IC50 (nM) | Ratio of persistent to peak inhibition | |
|---|---|---|---|
| **PRAX-562** | **141** | **60** | ← MOST SELECTIVE |
| Carbamazepine | 77,520 | 30 | |
| Cenobamate | 73,263 | 23 | |
| Lidocaine | 68,230 | 19 | |
| Lamotrigine | 78,530 | 16 | |
| Vixotrigene (BIIB074) | 3,676 | 14 | |
| Lacosamide | 833,100 | n/a* | |
| Valproic Acid | <10% @ 1 mM | No inhibition | |

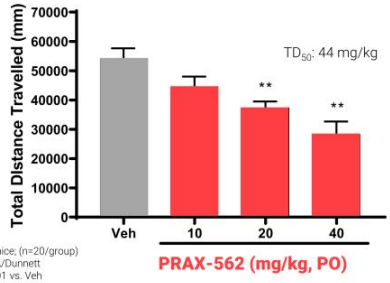
# Our mechanistic hypothesis translates to a wide therapeutic index in vivo for PRAX-562

## 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

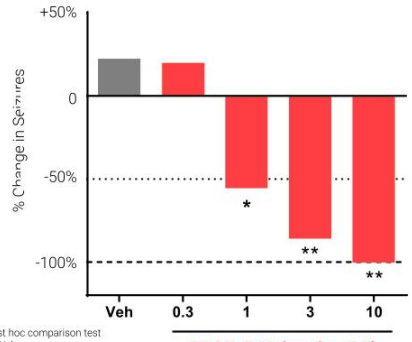
| Molecule | Plasma Therapeutic Index |
|---|---|
| PRAX-562 | 17.2x |

Therapeutic Index (TI) = TC50 / EC50

PRAXIS

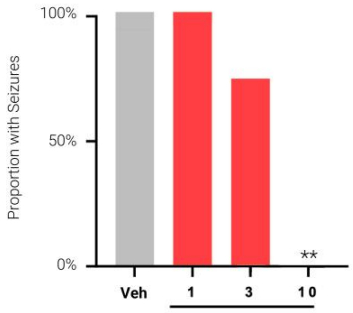
# PRAX-562 completely inhibits seizures in SCN2A and SCN8A GoF mutation mouse models

## 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

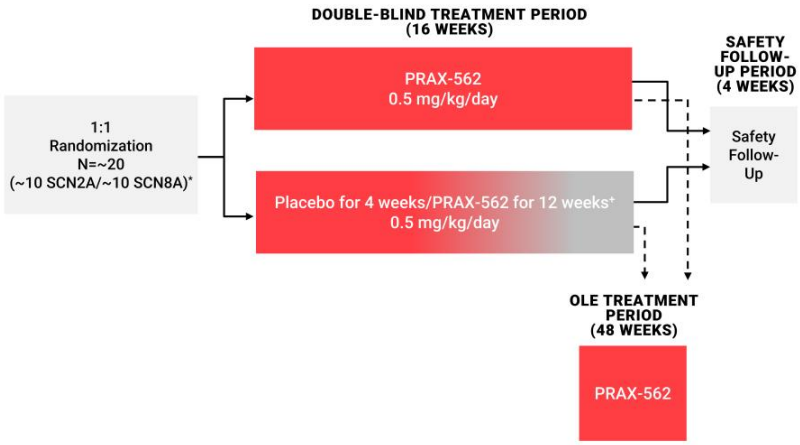
No MTD at exposures multiple fold above therapeutic range indicates potential for superior therapeutic index

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 2H23




**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**

**Mid-2023**
Ph 1 Topline Results

**4Q 2023**
Initiate Focal Epilepsy Study

# Preclinical data demonstrates PRAX-628 may be a best-in-class $Na_V$ blocker for focal epilepsy

**PRAX-628**

FOCAL EPILEPSY

PAN-$NA_V$ ACTIVITY DEPENDENT BLOCKER

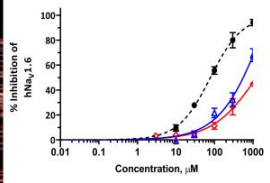
SMALL MOLECULE

- Superior selectivity for disease-state $Na_V$ channel hyperexcitability
- Unprecedented therapeutic window translating to superior safety and efficacy
- PK differentiated for broad epilepsy population

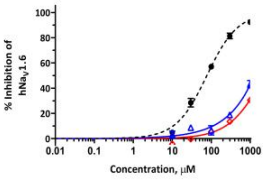
# Our internal discovery effort focused on developing a $Na_V$ blocker with high disease-state dependence and wide therapeutic index

## LOW DISEASE-STATE DEPENDENCE THIN THERAPEUTIC INDEX

LAMOTRIGINE



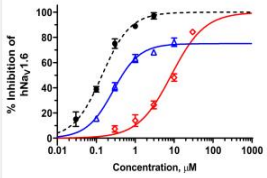

CARBAMAZEPINE



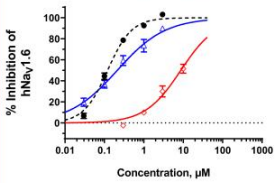

"$Na_V$ Fingerprint"
Persistent $I_{NaL}$ Inhibition
Peak $I_{NaL}$ UDV-10Hz (Disease-State Dependence) Inhibition
Peak $I_{NaL}$ Tonic Block Inhibition

## HIGH DISEASE-STATE DEPENDENCE WIDE THERAPEUTIC INDEX

PRAX-562

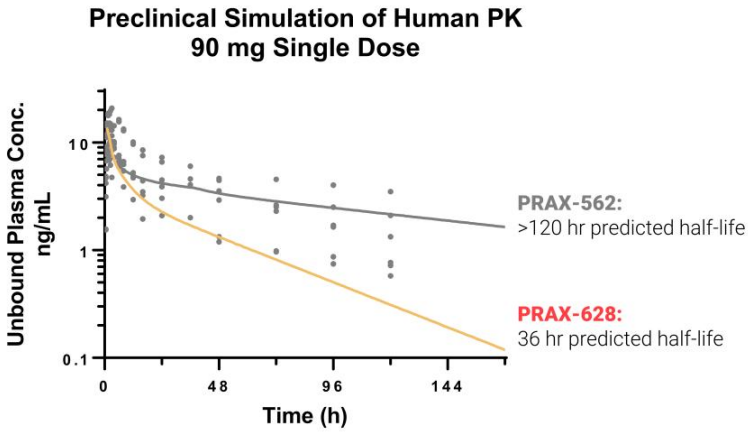



**PRAX-628**




Source: Praxis data on file

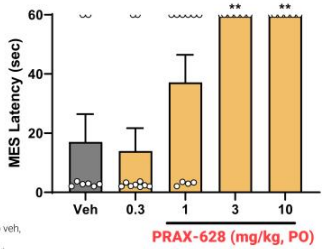
# PRAX-628 has unique pharmacological properties that enable acute dosing in a broader patient population




Modeling 90mg, single dose of PRAX-628 or PRAX-562. Preclinical simulation recapitulates PRAX-562 clinical data.

# PRAX-628 protects mice from seizures with a wide therapeutic window

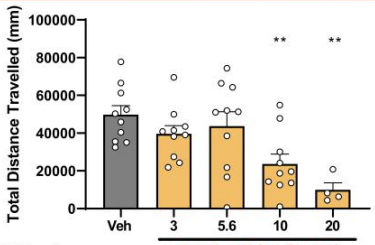
## MES EFFICACY




CD-1 mice; (n=8/group veh, n=10 PRAX)
ANOVA/Dunnett (PRAX)
**p<0.01 vs. Veh

$ED_{50}$: 0.67 mg/kg

## sLMA TOLERABILITY




CD-1 mice; (n=10/group)
ANOVA/Dunnett
**p<0.01 vs. Veh

$TD_{50}$: 10.3 mg/kg

| Molecule | Plasma Therapeutic Index |
|---|---|
| PRAX-628 | 16.7x |

Therapeutic Index (TI) = TC50 / EC50

# 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


SOLIDUS™
ASO PLATFORM
PRAXIS
35


PRAX-222
SCN2A-GoF ASO
KEY UPCOMING MILESTONES
Mid-2023
EMBRAVE Study First Dose Cohort (Part 1)
Topline Results
PRAXIS
36

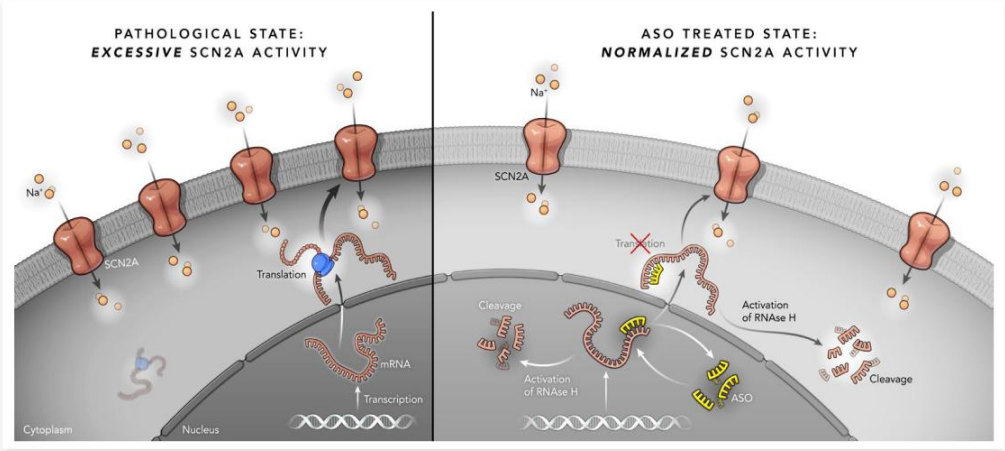
## Preclinical data suggest PRAX-222 has potential to be disease-modifying for early onset SCN2A gain-of-function DEE

**PRAX-222**

INTRATHECALLY-ADMINISTERED ASO for SCN2A GoF DEE

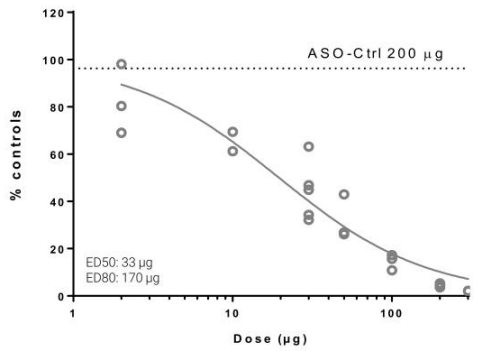
- Dose-dependent reduction in interictal spikes, seizures and increased survival
- Improvement in behavioral and locomotor activity
- Survival benefit extended with repeat dosing

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

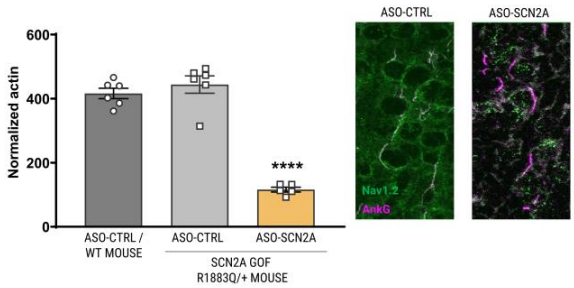


# In vitro, PRAX-222 down-regulates both mRNA and protein

## SCN2A mRNA KNOCKDOWN




## SCN2A PROTEIN KNOCKDOWN

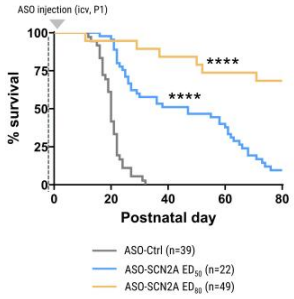



ASOs were administered at P30 and brains were collected 14 days post-ICV for qPCR analysis

# PRAX-222 increases survival in SCN2A GoF mice

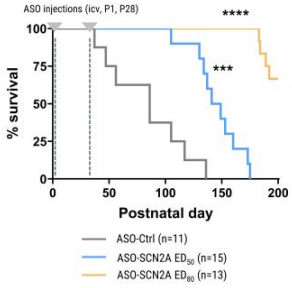
## SCN2A ASO INCREASES SURVIVAL WITH A SINGLE DOSE INJECTION

**SCN2A GOF model**



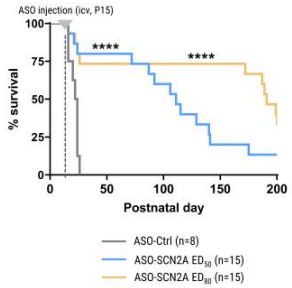

## RE-DOSING SIGNIFICANTLY EXTENDS SURVIVAL

**SCN2A GOF model**




## ADMINISTRATION POST-DISEASE ONSET ALSO EXTENDS SURVIVAL

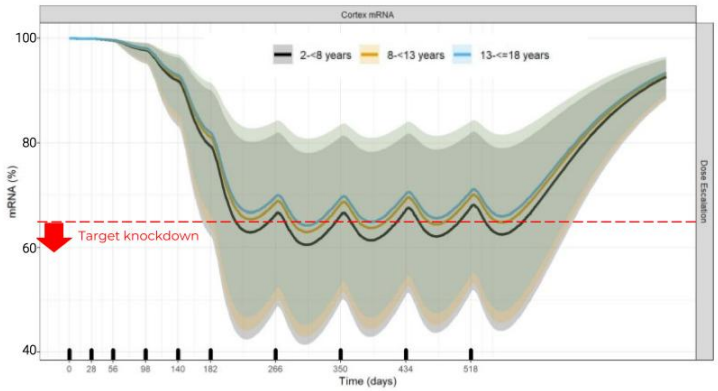
**SCN2A GOF model**




***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



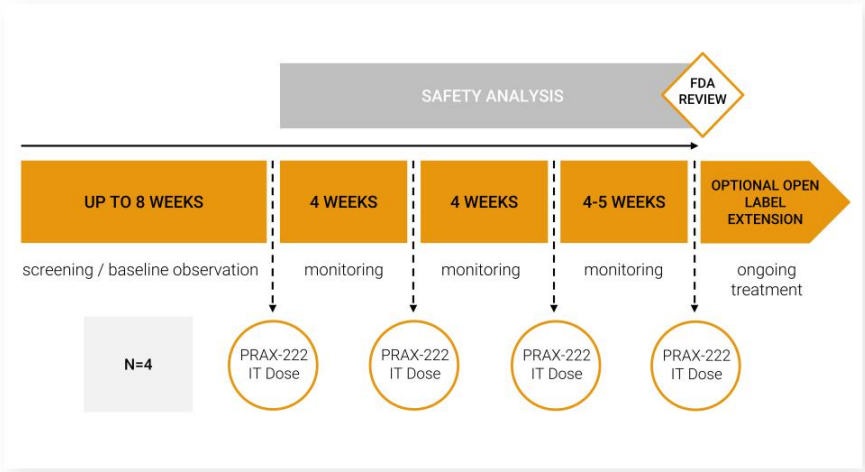

Median and 95% prediction interval illustrated

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.

# PRAX-222 EMBRAVE study initial dose cohort (Part 1)




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

21-week study

Open label design


PRAXIS
DARE FOR MORE™