



Oppenheimer

Rare & Orphan Disease Summit

May 2021

Forward-looking statements

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For further information regarding the risks, uncertainties and other factors that may cause differences between Praxis’ expectations and actual results, you should review the “Risk Factors” section of our Annual Report on Form 10-K filed for the period ended December 31, 2020 and subsequent 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 Praxis believes 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.

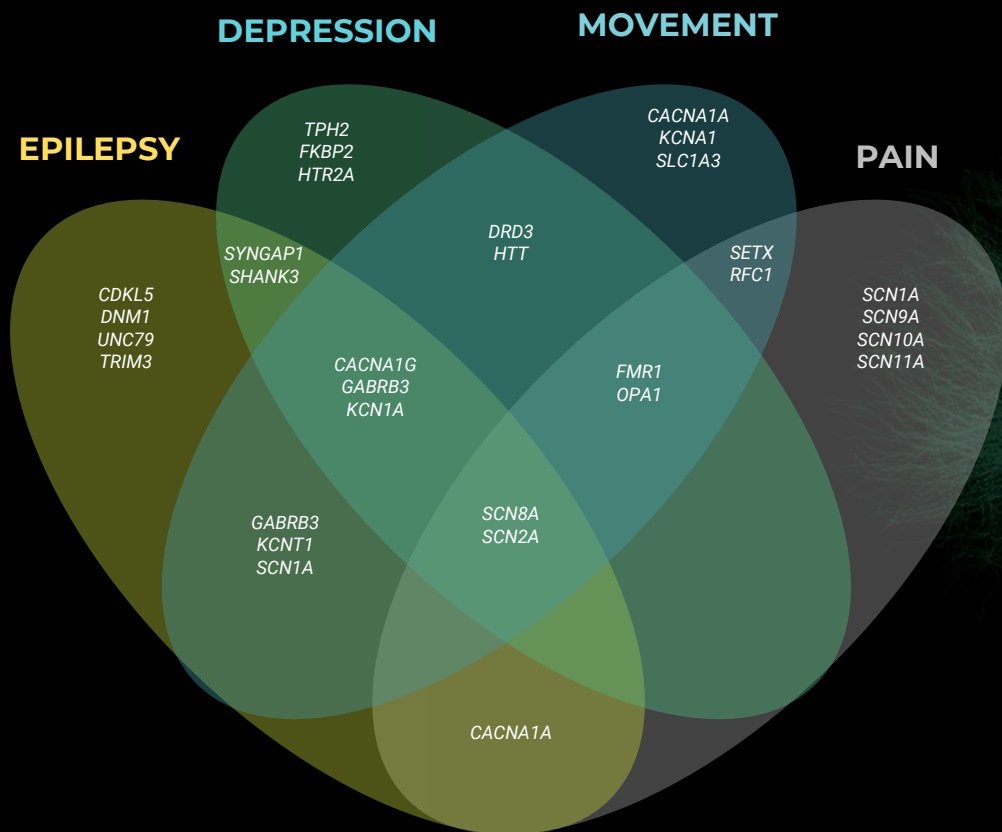
A PATIENT-GUIDED CNS COMPANY

DEVELOPING NEW CLASSES OF TREATMENTS

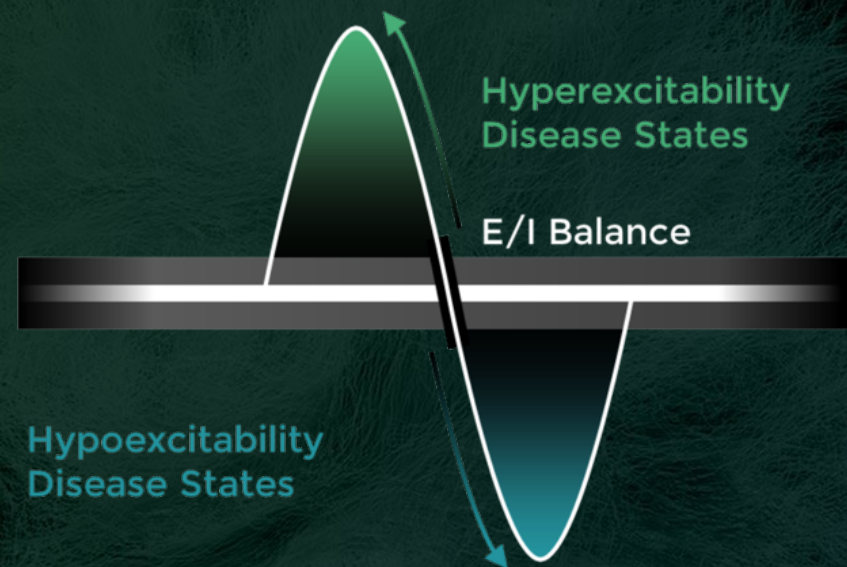
INSPIRED BY HUMAN GENETICS

The biology of epilepsy offers insights into brain function for CNS disorders

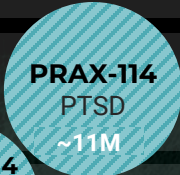

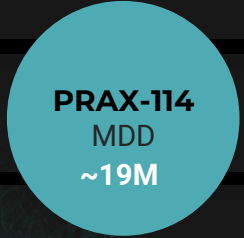
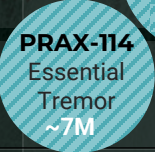

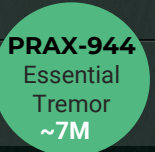







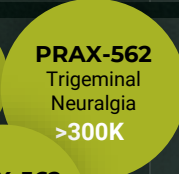



Targets Elucidated By Genetics



Targeting Common & Rare Diseases Connected By Neuronal Imbalance



Broad portfolio of highly differentiated programs across multiple CNS disorders

| FOCUS AREA | MECHANISM OF ACTION | PROGRAM | DISCOVERY | PRECLINICAL | PHASE 1 | PHASE 2 | REGISTRATIONAL ENABLING |
|--------------------|------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PSYCHIATRY | GABA_A receptor PAM <small>GABRG2/A1</small> | PRAX-114 <i>Small molecule</i> | | | |   |  |
| MOVEMENT DISORDERS | GABA_A receptor PAM <small>GABRG2/A1</small> | PRAX-114 <i>Small molecule</i> | | | |  | |
| | T-type calcium channel blocker <small>CACNA1G</small> | PRAX-944 <i>Small molecule</i> | | | |   | |
| RARE DISEASES | Persistent sodium current blocker <small>SCN8A</small> | PRAX-562 <i>Small molecule</i> | | | |  | <div>   Figures represent est. U.S. prevalence </div> <div>    Figures represent est. worldwide prevalence </div> |
| | Potassium channel T1 blocker <small>KCNT1</small> | KCNT1 INHIBITOR <i>Small molecule</i> |  | | |  | |
| | Nav1.2 downregulation <small>SCN2A</small> | PRAX-222* <i>Antisense Oligonucleotide</i> | |  | |  | |
| | Nav1.2 upregulation <small>SCN2A</small> | SCN2A-LOF** <i>Antisense Oligonucleotide</i> |  | | | | |
| | | | | | | | |

* PRAX-222 is a collaboration with Ionis Pharmaceuticals, and RogCon Inc; Ionis is eligible to receive double-digit royalties on net product sales worldwide.

** SCN2A-LOF is a collaboration with The Florey Institute; collaboration includes 2 additional ASOs with undisclosed targets

Prevalence based on internal estimates

PRAX-114 Phase 2 trials for ET and PTSD and PRAX-944 Phase 2 trial for PD have not initiated

Leveraging genetics to efficiently translate insights into therapies

- 01 **Targets identified through genetics**
- 02 **Translational tools to inform development**
- 03 **Efficient, rigorous clinical development paths to PoC**
- 04 **Patient-guided development strategies**



Substantial potential for value creation across the portfolio

MULTIPLE POTENTIAL VALUE-CREATING MILESTONES EXPECTED WITHIN THE NEXT 12+ MONTHS

| MID 2021 | 2H 2021 | 1H 2022 | 2H 2022 |
|-------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------|
| PRAX-114 Initiate Phase 2 Adjunctive MDD Trial | PRAX-114 Phase 2a PMD Topline | PRAX-114 Phase 2/3 Monotherapy MDD Aria Study Topline | PRAX-114 Phase 2 PTSD Topline |
| PRAX-944 Phase 2a ET Topline | PRAX-944 Initiate Phase 2 Randomized Controlled ET Trial | PRAX-114 Phase 2 Adjunctive MDD Topline | PRAX-114 Phase 2 ET Topline |
| PRAX-562 Phase 1 Safety, Tolerability & PK | PRAX-114 Initiate Phase 2 PTSD Trial | PRAX-944 Initiate Phase 2 PD Trial | PRAX-944 Phase 2 Randomized Controlled ET Topline |
| | PRAX-114 Initiate Phase 2 ET Trial | PRAX-562 Initiate Phase 2 DEE Trial | |
| | PRAX-562 Initiate Phase 2 Adult Cephalgia Trial | PRAX-222 Initiate Phase 1/2 SCN2A-DEE Trial | |
| | PRAX-222 Complete IND-enabling Toxicology Studies for PRAX-222 | | |
| | KCNT1 INHIBITOR Nominate Development Candidate for KCNT1 | | |

PRAX-114

GABA_A Receptor PAM

*PSYCHIATRY &
MOVEMENT DISORDERS*

Depression
Post-traumatic Stress Disorder
Essential Tremor

UPCOMING MILESTONES

MID 2021

Initiate Ph 2 Adjunctive MDD Trial

2H 2021

Ph 2a PMD Topline

2H 2021

Initiate Ph 2 PTSD Trial

2H 2021

Initiate Ph 2 ET Trial

1H 2022

Ph 2/3 Monotherapy MDD Aria Study Topline

1H 2022

Ph 2 Adjunctive MDD Topline

2H 2022

Ph 2 PTSD Topline

2H 2022

Ph 2 ET Topline

Major depressive disorder is a growing and debilitating disorder with substantial unmet need despite numerous treatment options

~19 million Americans and an estimated 300 million people worldwide affected by MDD

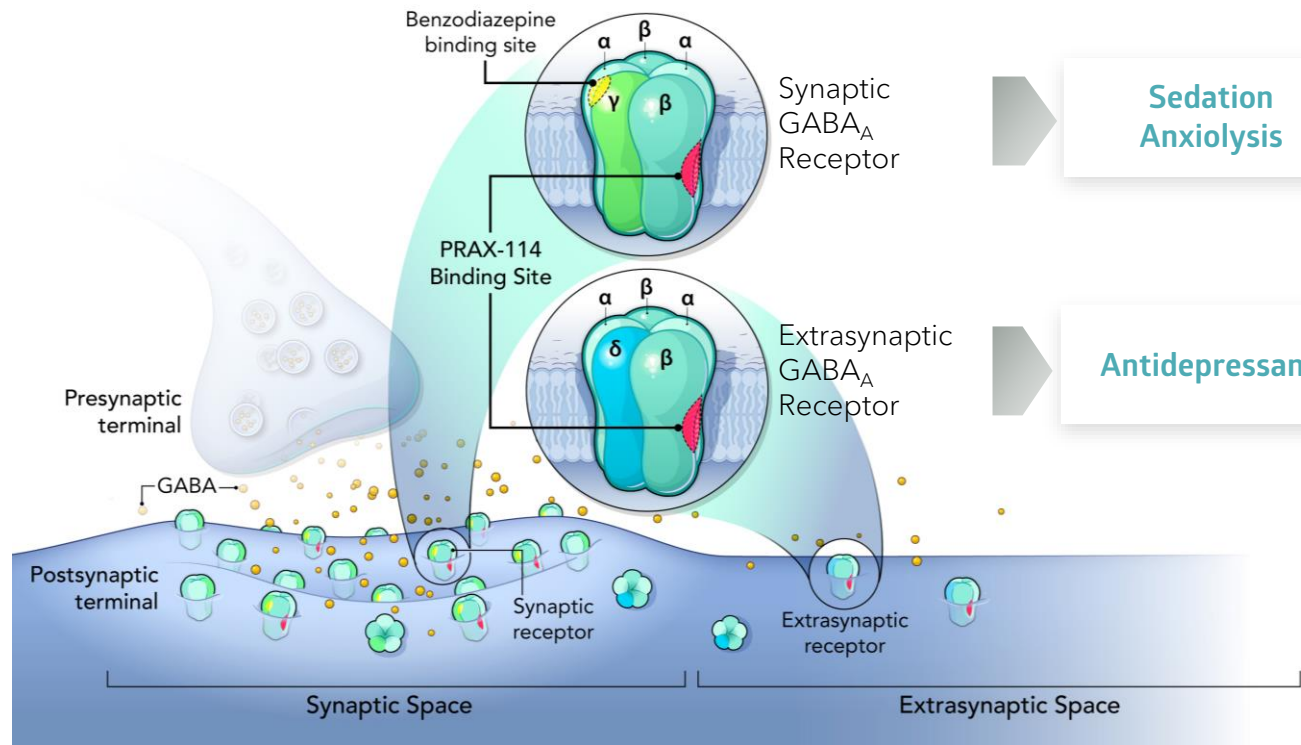


Slow onset of action for existing treatment options

Low response rate

Limiting safety profile can lead to discontinuation of treatment

Preference for extrasynaptic GABA_A receptors has the potential of marked antidepressant effect with an improved tolerability profile



GABA: Gamma-aminobutyric acid; GABA_A PAMs: GABA_A receptor positive allosteric modulators

PRAX-114 shows 10.5-Fold greater potentiation of extrasynaptic than synaptic GABA_A receptors

| Dosing | | Potentiation | | Fold Potentiation |
|-----------------|-------------|------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------|
| | | α ₄ β ₃ δ %* | α ₁ β ₂ γ ₂ % | α ₄ β ₃ δ/ α ₁ β ₂ γ ₂ |
| PRAX-114 | Oral | 300% | 29% | 10.5 |
| Zuranolone | Oral | 300% | 117% | 2.6 |
| Ganaxolone | IV, Oral | 300% | 794% | 0.4 |
| Zulresso | IV | 300% | 306% | 1.0 |

α₄β₃δ: extrasynaptic GABA_A receptor α₁β₂γ₂: synaptic GABA_A receptor

* Equivalent of full activation by GABA

Source: PRAXIS data

PRAX-114 phase 2a: rapid and marked improvement in depression scores

Phase 2a MDD combined* HAM-D monotherapy & adjunctive results

| Visit | HAM-D <i>Monotherapy</i> | HAM-D <i>Adjunctive</i> |
|-----------------|-----------------------------|----------------------------|
| | Mean (SD) N=11 | Mean (SD) N=35 |
| Day 1 (BL) | 25.2 (1.94) | 24.7 (2.94) |
| Day 8 (CFB) | -17.5 (4.95) | -13.5 (7.99) |
| Day 15 (CFB) | -16.4 (5.75) | -12.7 (6.88) |

Phase 2a MDD combined* HAM-A anxiety and HAM-D insomnia item results

| Visit | HAM-A <i>Anxiety Rating Scale</i> | HAM-D <i>Insomnia Item Total (max score of 6)</i> |
|-----------------|------------------------------------------|----------------------------------------------------------|
| | Mean (SD) N=46 | Mean (SD) N=46 |
| Day 1 (BL) | 22.0 (4.08) | 4.1 (1.4) |
| Day 8 (CFB) | -12.0 (7.53) | -2.8 (1.9) |
| Day 15 (CFB) | -11.1 (6.66) | -3.1 (1.67) |

PRAX-944

T-Type calcium channel
inhibitor

MOVEMENT DISORDERS

**Essential Tremor
Parkinson's Disease**

UPCOMING MILESTONES

Mid 2021

Ph2a ET Topline

2H 2021

Initiate Ph2 Randomized Controlled ET
Trial

1H 2022

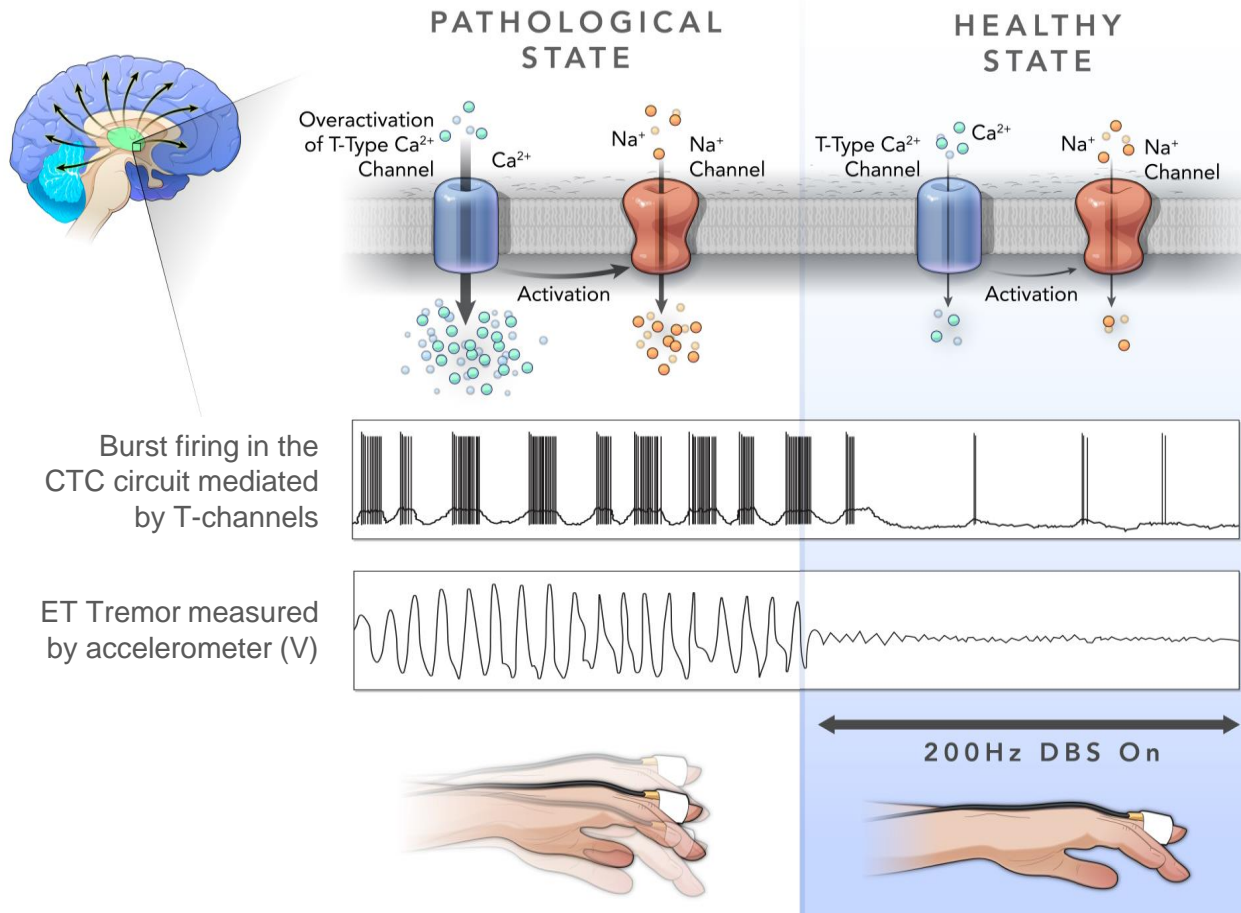
Initiate Ph2 PD Trial

2H 2022

Ph2 Randomized Controlled ET Topline

Large body of clinical, preclinical and human genetic evidence supporting key role of T-type calcium channels in ET

T-Type calcium channels are gatekeepers of neuronal firing patterns



T-type calcium channels drive burst firing in the cerebello-thalamo-cortical (CTC) circuit

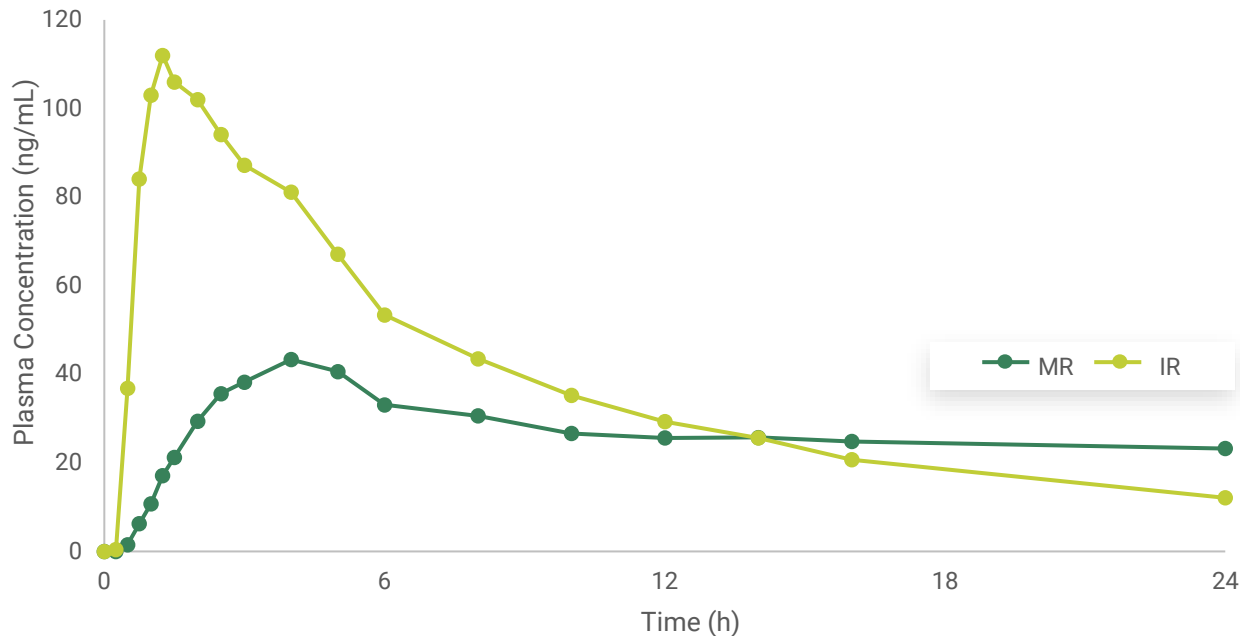
Mutations in T-type calcium channels are genetically linked to early onset familial ET

Abnormal neuron burst firing in the CTC circuit correlated with tremor activity in ET patients

Deep Brain Stimulation (DBS) leads to near complete silencing of bursting firing and significant tremor reduction

PRAX-944 is designed to enable once daily dosing and a well-tolerated safety profile

Sustained exposure with blunted MR C_{max} allows for potential of sustained efficacy and improved tolerability



Mean PRAX-944 Concentration-Time Profiles after single 20 mg Modified Release (MR) and Immediate release (IR) oral doses

MR formulation is well-tolerated

Titration and fit for purpose formulation are key to tolerability profile

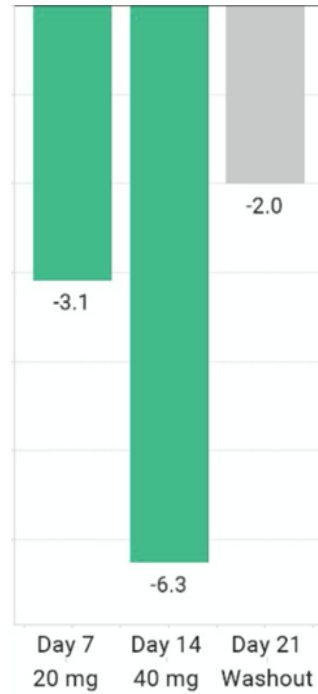
No MTD identified up to 120 mg per day

Majority of AEs have been mild, transient and resolved without intervention

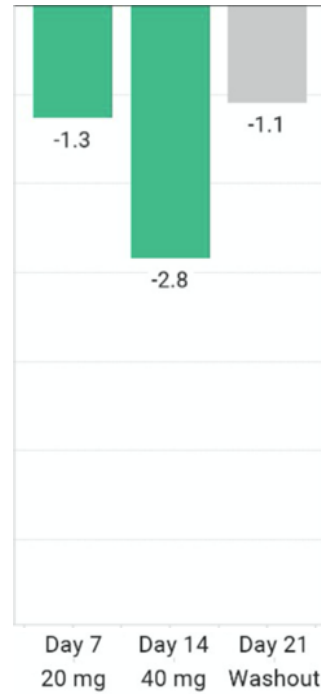
PRAX-944 phase 2a ET Part A data shows dose dependent reduction in tremor amplitude

Change from baseline in TETRAS score (N=6)

PERFORMANCE SCALE (PS)



UPPER LIMB (UL)



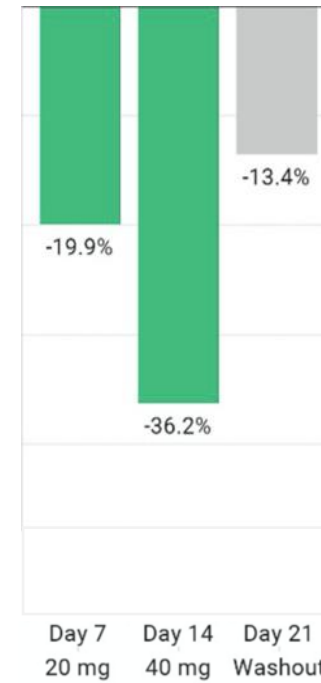
ON TREATMENT



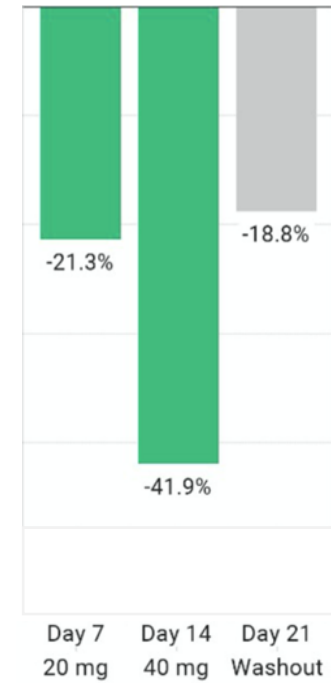
WASHOUT

Percent change in tremor amplitude (N=6)

PERFORMANCE SCALE (PS)



UPPER LIMB (UL)



ON TREATMENT

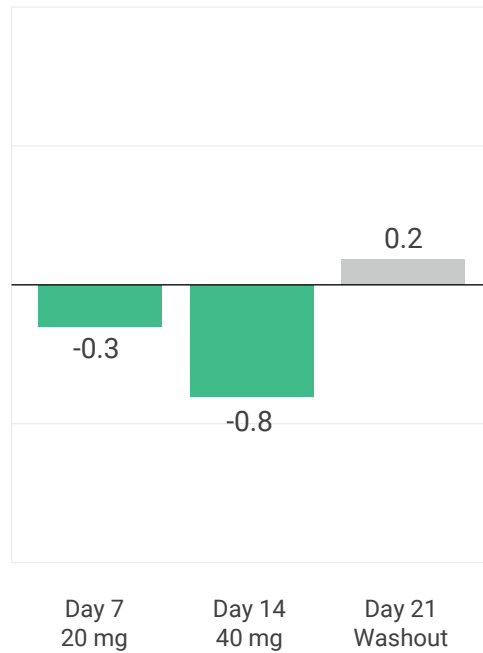


WASHOUT

PRAX-944 phase 2a ET Part A Archimedes spiral data indicates functional improvement

Change from baseline in TETRAS score
(N=6)

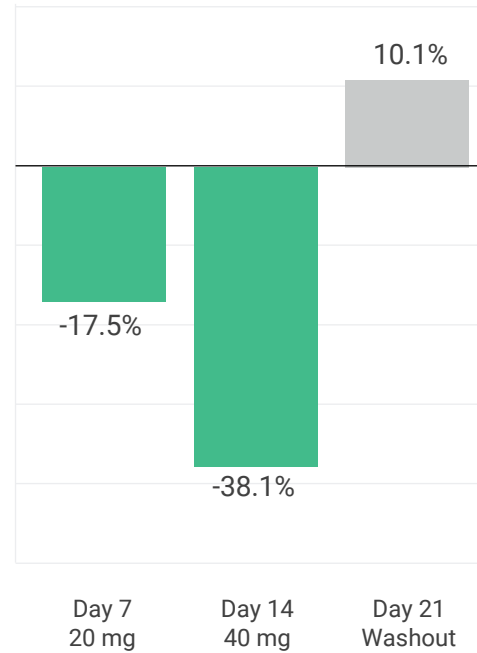
TETRAS ARCH. SPIRALS (AS)
Site Rating



ON TREATMENT WASHOUT

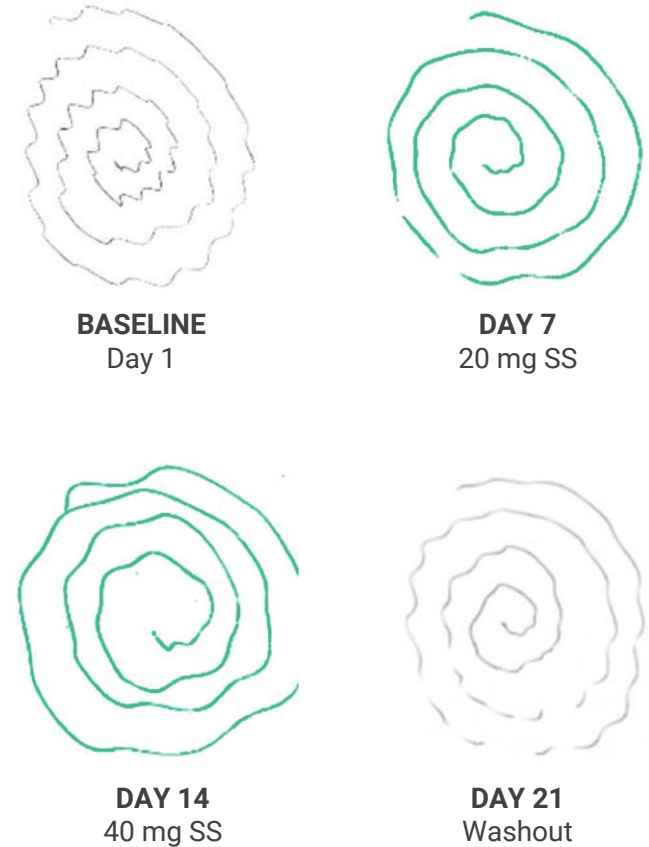
Percent change in tremor amplitude
(N=6)

TETRAS ARCH. SPIRALS (AS)
Site Rating



ON TREATMENT WASHOUT

PRAX-944 Archimedes spiral*



PRAX-562

Persistent Sodium Channel
Blocker

RARE DISEASES

Adult Cephalgias
Pediatric Epilepsies (DEEs)

UPCOMING MILESTONES

Mid 2021

Ph 1 Safety, Tolerability & PK

2H 2021

Initiate Ph 2 Adult Cephalgia Trial

1H 2022

Initiate Ph 2 DEE Trial

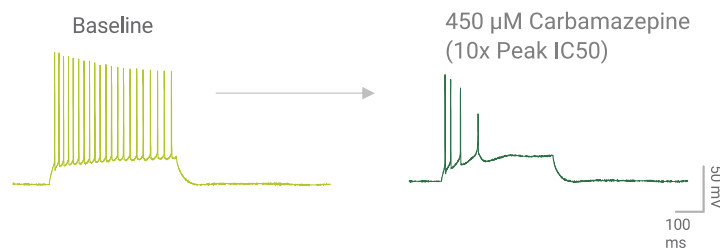
Block of persistent sodium current can reduce neuronal hyperexcitability and impact multiple disease states

Standard sodium channel blockers target peak sodium current and disrupt AP, leading to side effects

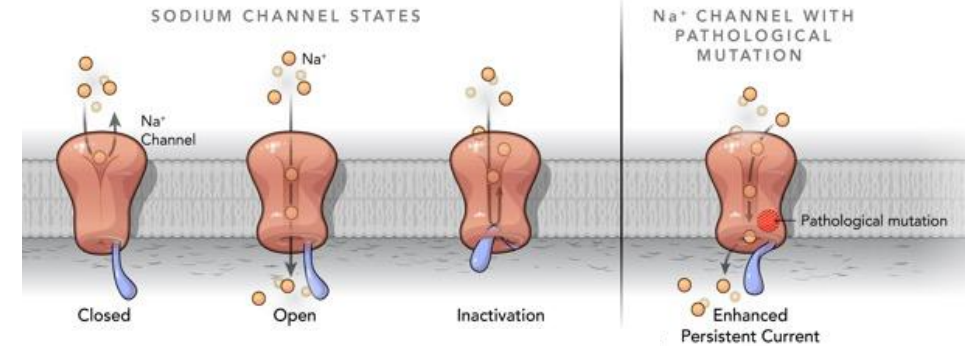
- Standard sodium channel blockers are an important class of medicines in neurology and psychiatry, broadly used in epilepsy, pain, migraine, and bipolar disorder
- All standard NaV blockers target peak sodium current
- In general, efficacy is limited by side effects



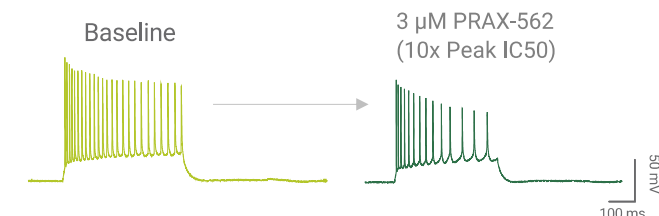
Carbamazepine Representative AP Traces



Modulation of persistent sodium current reduces hyperexcitability without disrupting AP

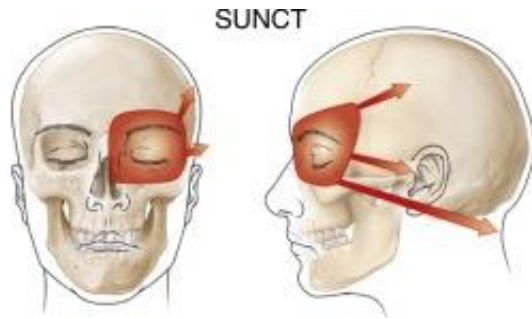


PRAX-562 Representative AP Traces



PRAX-562 has broad potential in rare CNS conditions

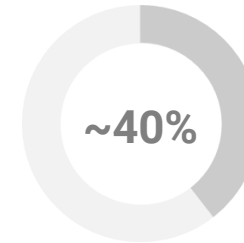
SUNCT, SUNA & TN are devastating headache disorders with limited treatment options



SUNCT and SUNA Cephalgias are devastating primary headaches highly responsive to IV sodium channel blockers

Trigeminal Neuralgia is characterized by intense, stabbing, electric-shock pain typically in the lower face and jaw, usually on one side of the face

DEE is a group of monogenic disorders with severe seizure, developmental delay & high mortality rate



Caused by a single gene mutation

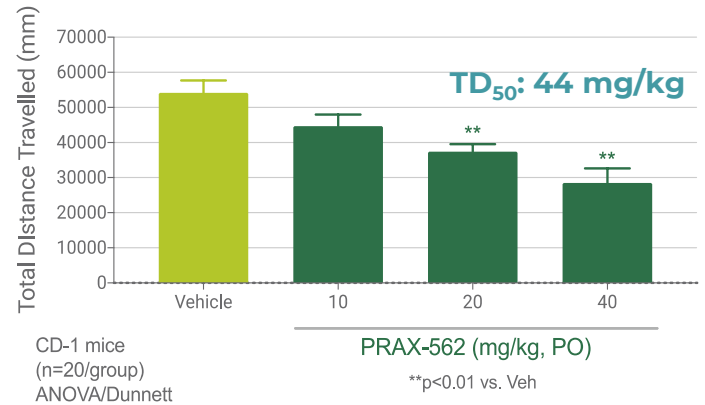
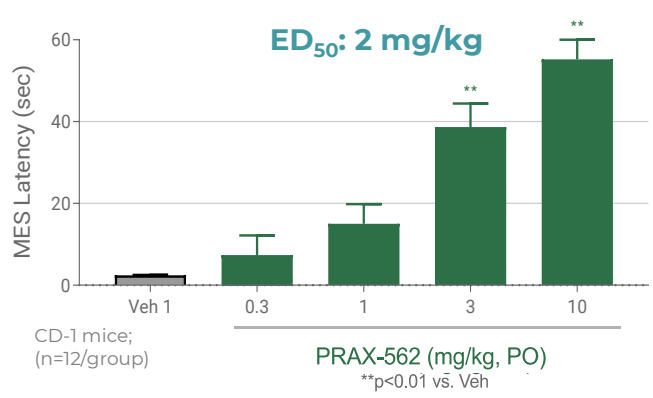
200k+
CHILDREN WITH
DEEs WORLDWIDE

A pathologic feature of many DEEs is the dysregulated neuronal activity leading to hyperexcitability and seizure

This phenomenon is observed in pediatric epilepsies with an identified genetic cause, such as SCN8A, SCN2A and others

PRAX-562 mediated persistent current block protects mice from seizure with a wide therapeutic window *in-vivo*

PRAX-562 shows robust anti-seizure activity without impairment of locomotor activity



PRAX-562 showed significantly improved TI as compared to currently prescribed sodium channel blockers

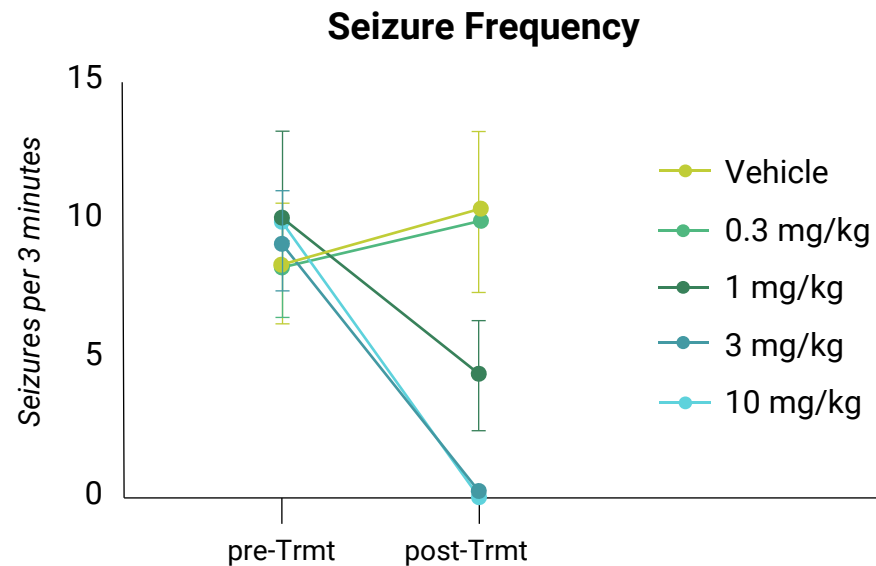
| Molecule | Brain Therapeutic Index |
|---------------|-------------------------|
| PRAX-562 | 16.4x |
| Carbamazepine | 5.9x |
| Lamotrigine | 4.6x |

Therapeutic Index (TI) = TC_{50} / EC_{50}

PRAX-562 had an increased ratio between drug levels that demonstrated preclinical anti-seizure activity versus those that caused toxicity

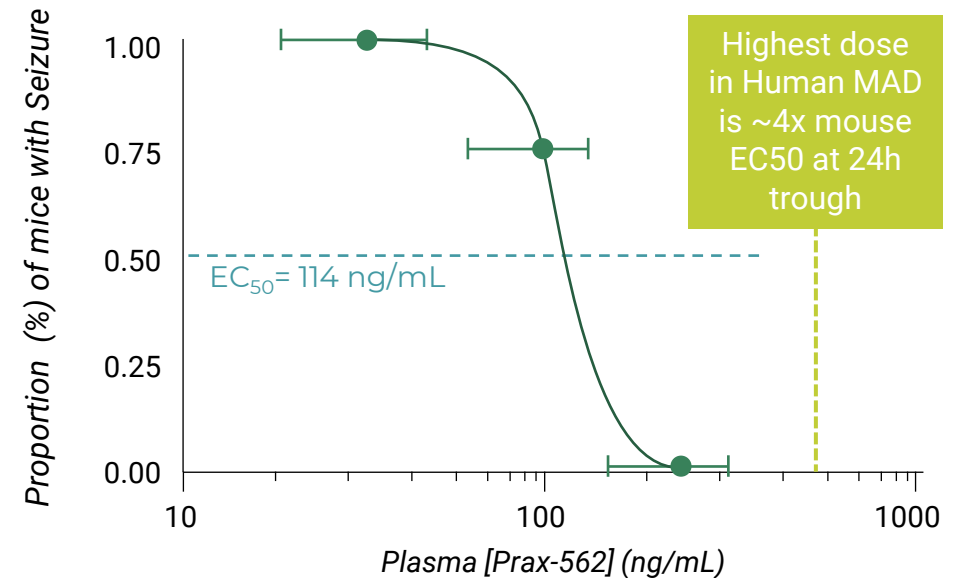
Treatment with PRAX-562 has shown significant reduction of seizures in genetic pediatric epilepsy animal models

PRAX-562 elicited dose-dependent prevention of seizures in SCN2A* mouse model



Baseline seizure frequency was measured for 30 minutes prior to treatment (Pre) and then again 30 minutes after treatment (Post). Symbols represent mean \pm SEM, n=6-10 per symbol.

PRAX-562 elicited dose-dependent prevention of seizures in SCN8A* mouse model



PRAX-562 inhibition of audiogenic seizures in D/+ mice

PRAX-562 development strategy in headache and pediatric epilepsies

OBJECTIVE

Identify PoC and safety in SUNCT/SUNA & Trigeminal Neuralgia headaches while continuing efforts to expand to rare pediatric epilepsies

Clinical Strategy

PHASE 1 HEALTHY VOLUNTEERS
SAD/MAD, ASSR Biomarker, Food Effect

SUNCT/SUNA & Trigeminal Neuralgia Headache

Juvenile tox

Rare Pediatric Epilepsy

Current Status – higher doses to be explored in MAD cohort

HEALTHY VOLUNTEER PHASE 1 SAD/MAD, ASSR, AND FOOD EFFECT

Study Design

- Randomized, placebo controlled

Patient Population

- ♀ or ♂ 18-55 years of age
- Healthy Volunteers

Study Objectives

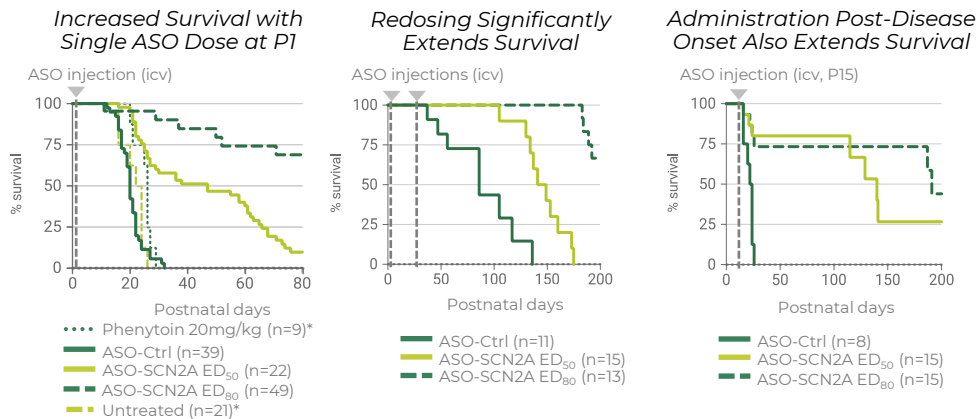
- 1°: Safety and tolerability of single and multiple ascending doses of PRAX-562 in healthy volunteers
- 2°: Pharmacokinetics of single and multiple ascending doses of PRAX-562 in healthy volunteers
- Exploratory: EEG Auditory Steady-State Response (ASSR)

Preclinical pipeline addressing genetically defined rare epilepsies with precision medicine approach

PRAX-222: SCN2A GoF Epilepsy



- Severe early onset epilepsy estimated to affect thousands of patients worldwide
- Antisense oligonucleotide (ASO) to down-regulate SCN2A expression
- Three-way collaboration with Ionis and RogCon

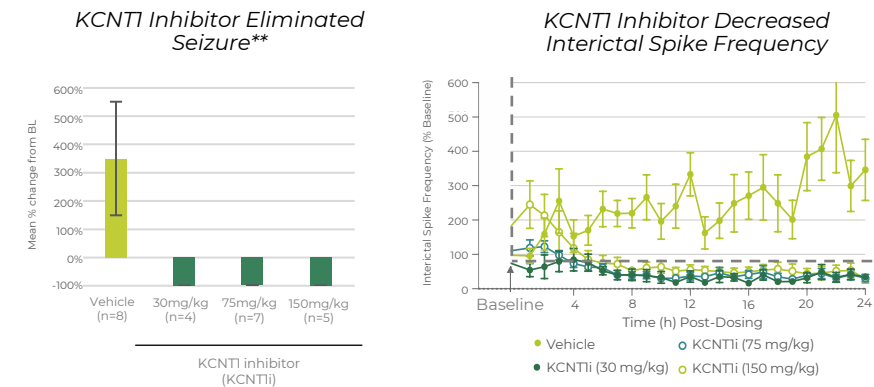


IND filing anticipated in early 2022

KCNT1 Inhibitor: KCNT1 GoF Epilepsy



- Severe early onset epilepsy estimated to affect thousands of patients worldwide
- Lead small molecule inhibitor demonstrated disease modifying potential



Development candidate (DC) nomination anticipated in 2021

Substantial potential for value creation across the portfolio

MULTIPLE POTENTIAL VALUE-CREATING MILESTONES EXPECTED WITHIN THE NEXT 12+ MONTHS

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| | PRAX-222 Complete IND-enabling Toxicology Studies for PRAX-222 | | |
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