PRAXIS

CORPORATE OVERVIEW

December 2020

Forward-looking statements

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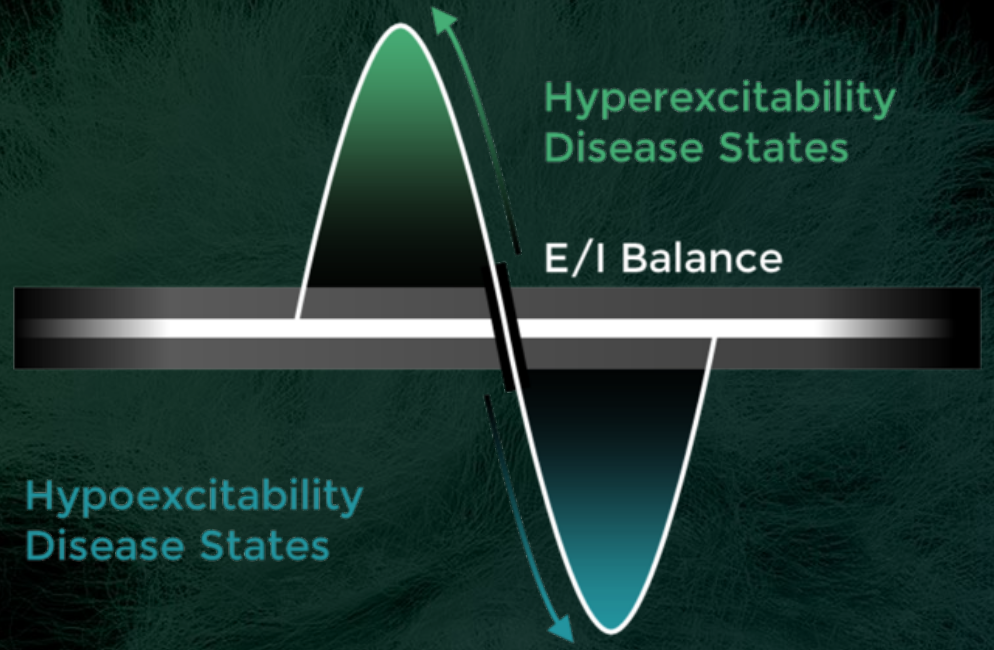
A CLINICAL STAGE CNS COMPANY LEVERAGING BREAKTHROUGHS IN GENETICS

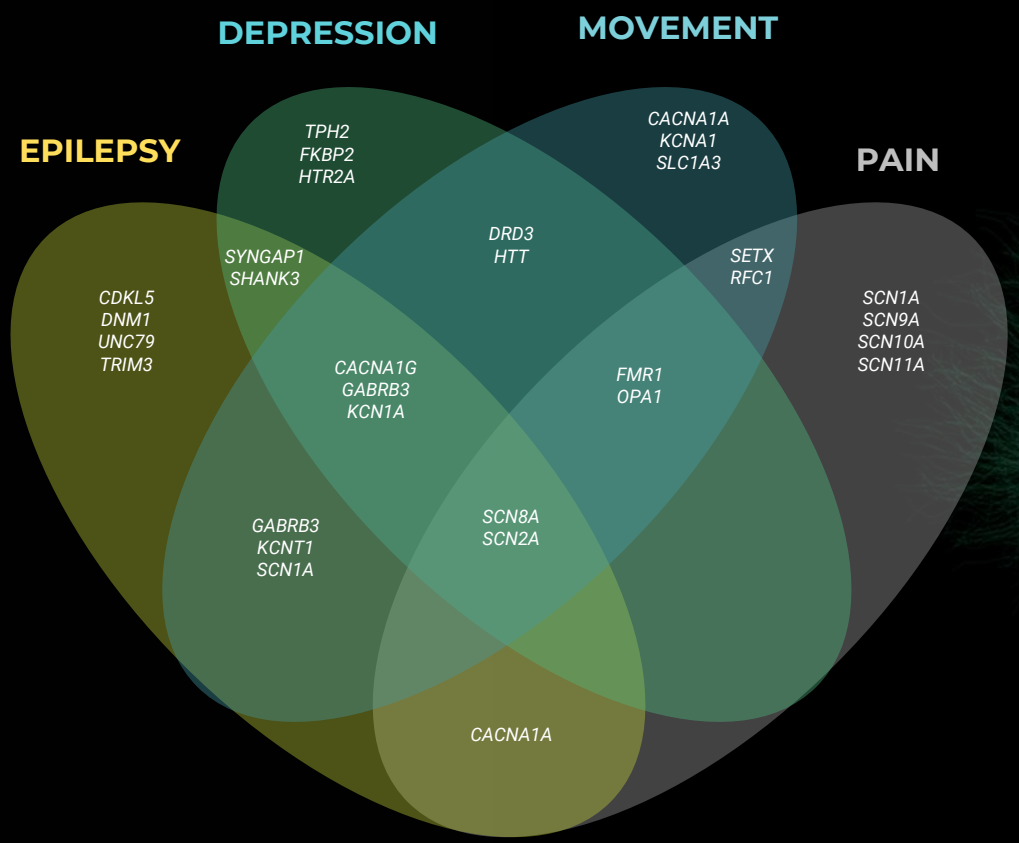
AIMING TO POSITIVELY IMPACT THE LIVES OF PATIENTS WITH COMMON & RARE CONDITIONS

Targeting Diseases Connected By Neuronal Imbalance



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

Targets Elucidated By Genetics



- Targets inspired by recent breakthroughs in genetics in severe pediatric epilepsies
- Large scale genome sequencing efforts (Epi25k, ILAE) have illuminated brain circuits that are commonly dysregulated in diseases ranging from epilepsy, to mood disorders, pain syndromes, and movement disorders
- Targets identified in genetic epilepsy studies are well positioned to impact neural circuits in broader CNS conditions

Leveraging genetics to efficiently translate insights into therapies

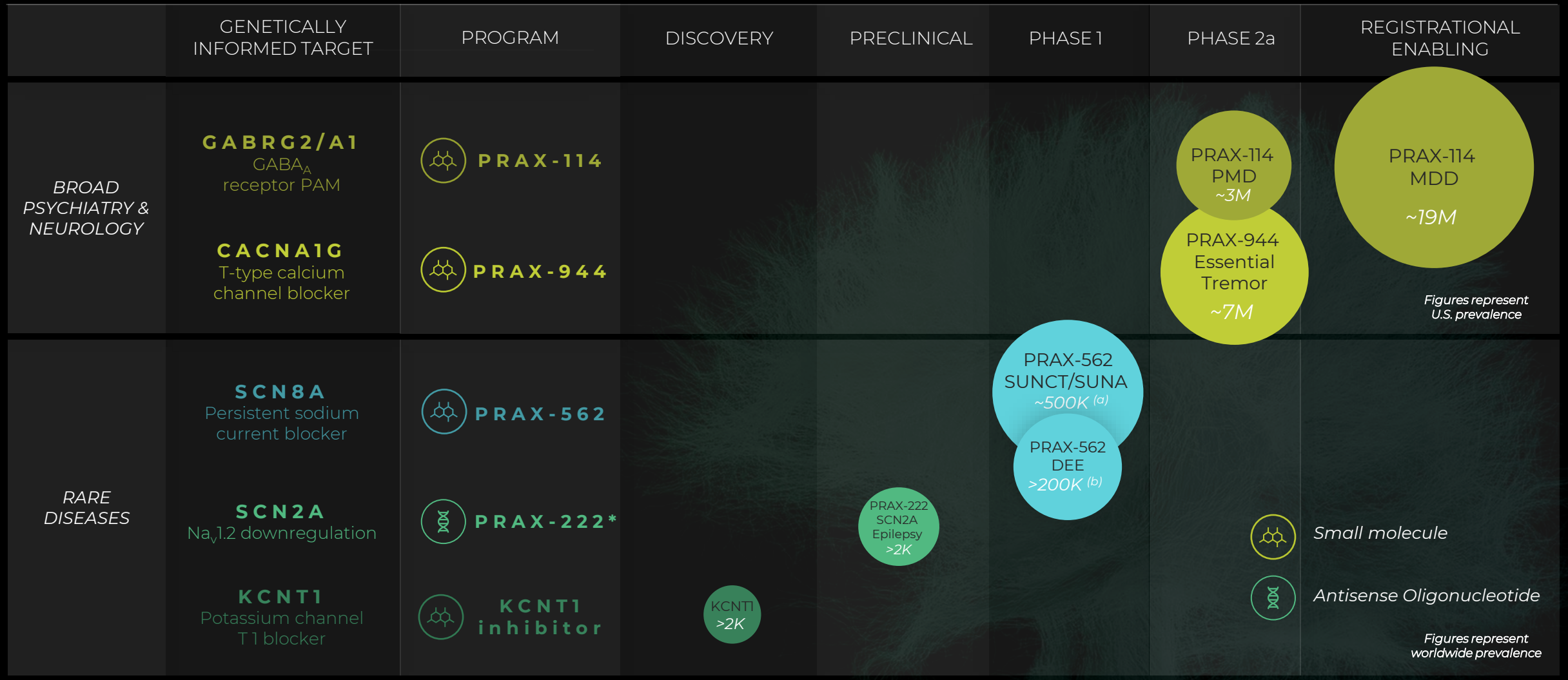
01 **Targets identified through genetics**

02 **Translational tools to inform development**

03 **Efficient, rigorous clinical development paths to PoC**

04 **Patient-centric development strategies**

Broad portfolio of highly differentiated programs across multiple CNS disorders



(a) Modeled based on estimated prevalence of 6.6 per 100k Willams et. al. 2008
(b) Estimated prevalence of all DEE worldwide
*PRAX-222 is a collaboration with Ionis Pharmaceuticals, and RogCon Inc. Ionis is eligible to receive double-digit royalties on net product sales worldwide.

Substantial potential for value creation across the portfolio

BROAD PSYCHIATRY & NEUROLOGY

RARE DISEASES

PRAX-114
Depression

$GABA_A$ receptor PAM

Phase 2/3 for Major Depressive Disorder
Phase 2a for Peri-menopause Depression

H1 2022
TOPLINE

PRAX-944
Movement Disorders

T-type calcium channel blocker

Phase 2a for Essential Tremor

H1 2021
TOPLINE

PRAX-562
Rare Diseases

Selective persistent sodium current blocker

Adult Cephalgia and Severe Pediatric Epilepsies

2021 Ph2
INITIATION

Preclinical
Genetically Defined Epilepsies

Two differentiated preclinical candidates

PRAX-222 for SCN2A Epilepsy and Inhibitor for KCNT1 Epilepsies

2H 2021
FIRST IND

Indication Expansion

Multiple indication expansion opportunities across the portfolio

MULTIPLE POTENTIAL VALUE-CREATING MILESTONES
EXPECTED WITHIN THE NEXT 18 MONTHS

PRAX-114

GABRG2

$GABA_A$ Receptor

PH2

Depression

Expected H1-2022

Ph2/3 MDD Topline

PRAXIS

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

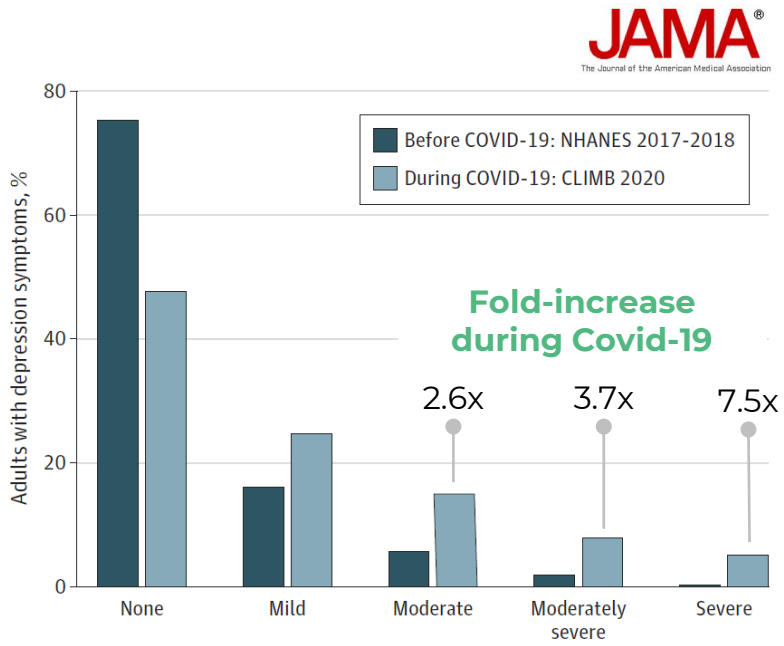
~19 million Americans and an estimated
300 million people worldwide affected by MDD

- **Slow onset** of action for existing treatment options
- **Low response rate**
- **Limiting safety profile** can lead to discontinuation of treatment

Source: Rush et al 2006, Masand et al 2003, Kupfer et 2005, DSM-5 2013, ExpressScripts MDD Report 2020

Prevalence of depression has increased during the COVID-19 pandemic in the US and globally

Depression symptoms have increased in the US by more than 3-fold overall during the COVID-19 pandemic

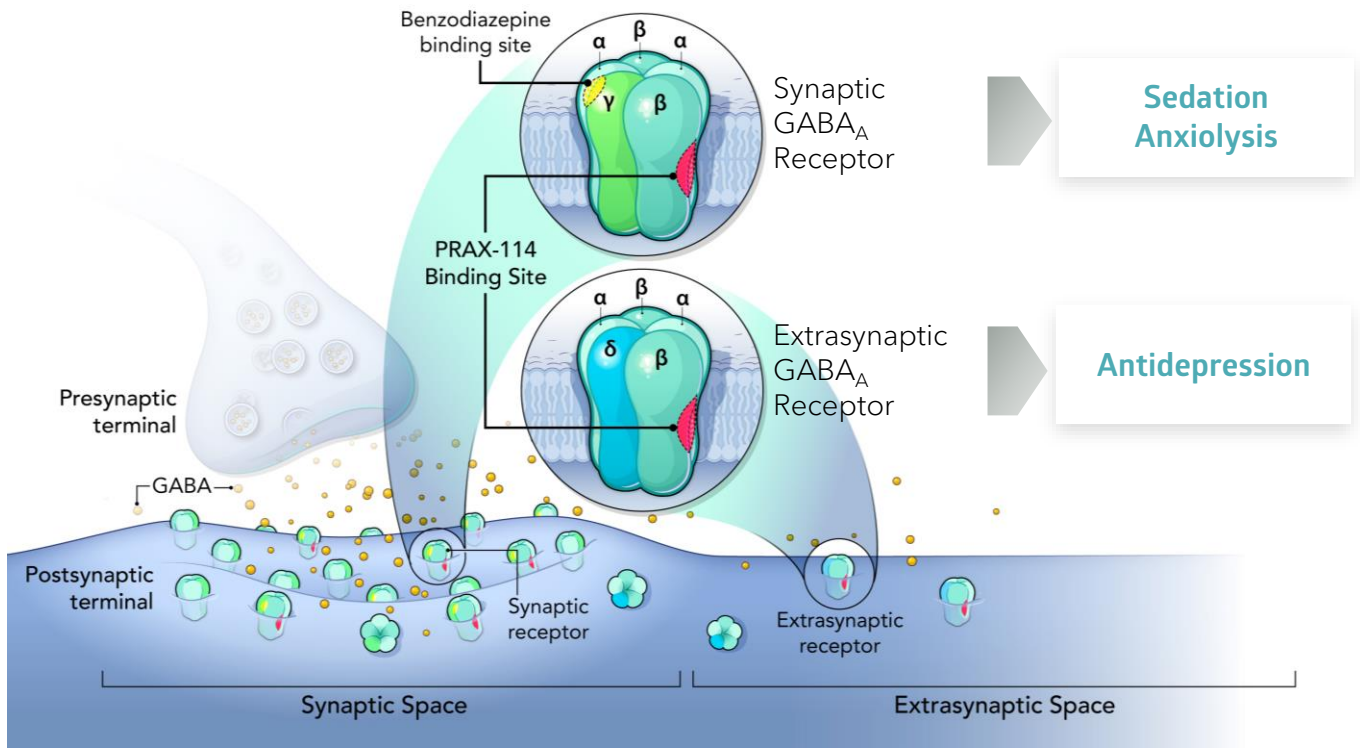


1441 respondents during COVID-19 pandemic (March 31, 2020 to April 13, 2020)
5065 respondents before pandemic (2017-2018)

- **27.8%** of participants reported depressive symptoms during COVID-19
- **Moderate to Severe** depression showed the greatest fold increase during COVID-19
- Other psychiatric symptoms that have increased during COVID-19 are anxiety, stress, and PTSD

Source: Ettman et al JAMA 2020, Newby et al Plos ONE 2020

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

		Potentiation		Fold Potentiation
	Dosing	$\alpha_4\beta_3\delta$ %*	$\alpha_1\beta_2\gamma_2$ %	$\alpha_4\beta_3\delta$/ $\alpha_1\beta_2\gamma_2$
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

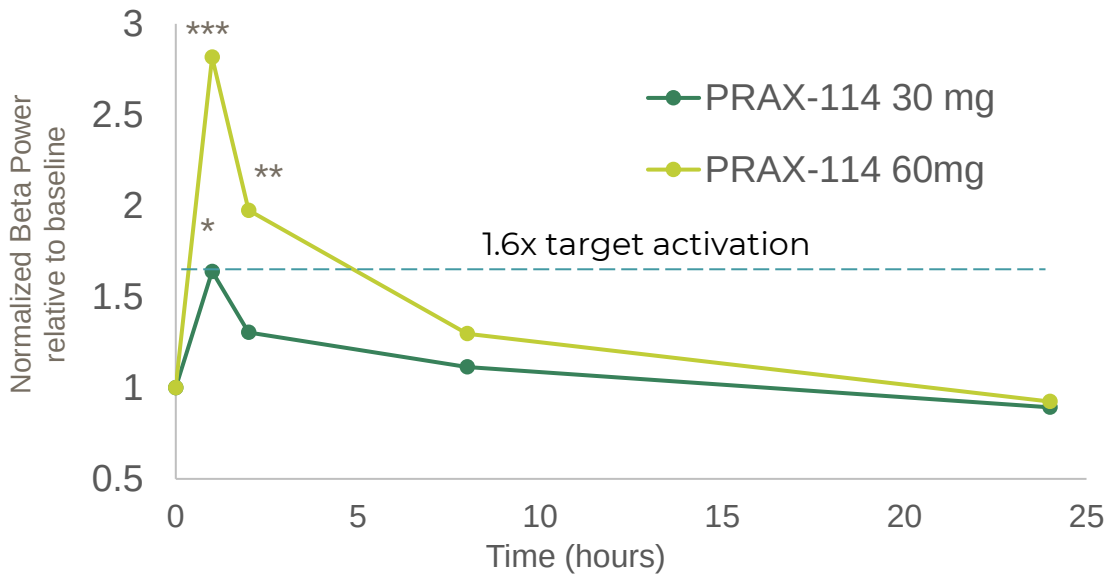
$\alpha_4\beta_3\delta$: extrasynaptic $GABA_A$ receptor **$\alpha1\beta_2\gamma_2$:** synaptic $GABA_A$ receptor

* Equivalent of full activation by GABA

Source: PRAXIS data

Extrasynaptic $GABA_A$ preference allows PRAX-114 the potential to achieve high-levels of GABAergic activation with improved tolerability

PRAX-114 (30mg and 60mg) shows robust qEEG signal and target activation



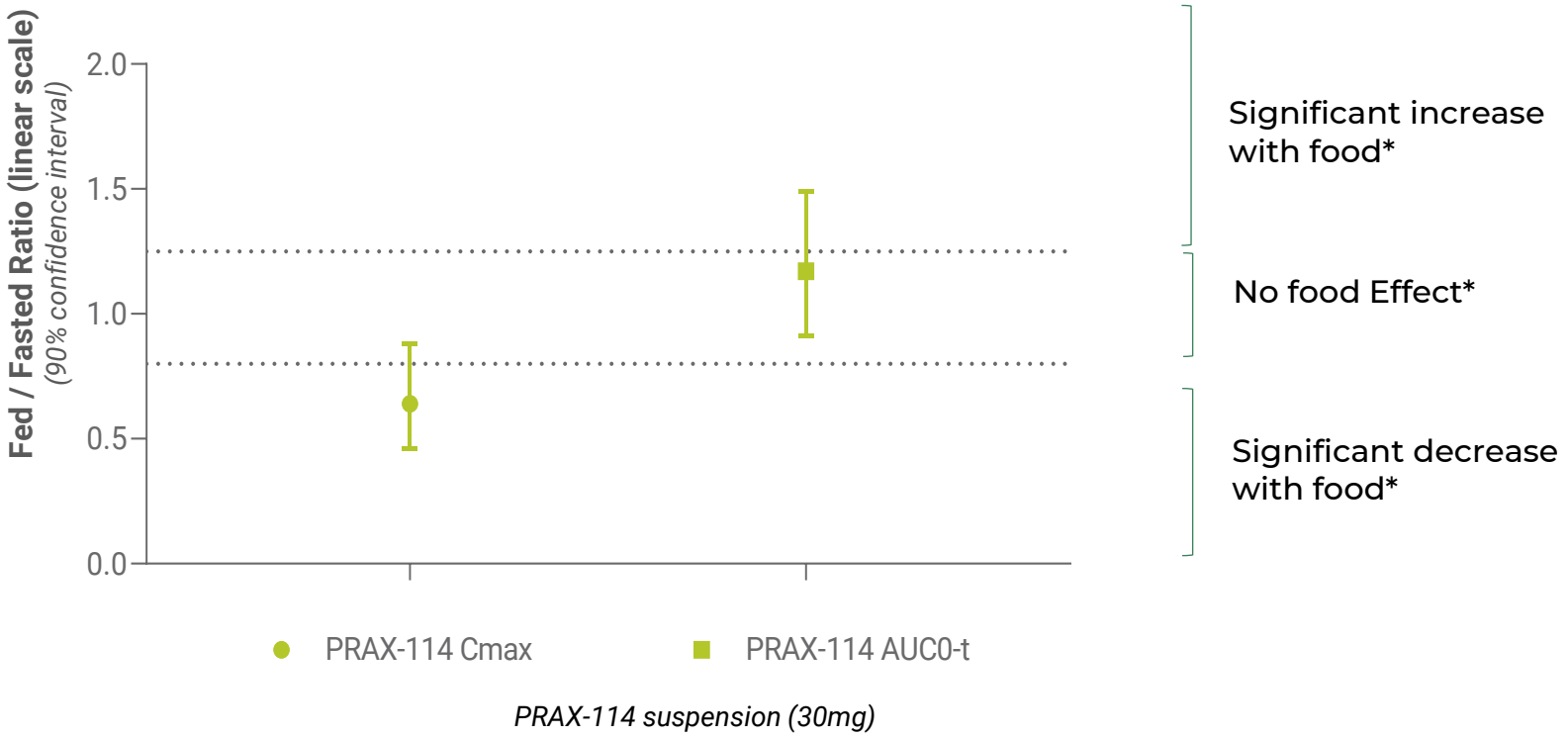
- N= 7-9 human subjects per dose, PRAX-114 only *p* compared to placebo control, *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

- **No MTD identified** up to 80mg
- **Tolerability profile** maintained throughout dose escalation
- **Dose-dependent rates of somnolence further supports target engagement**
  - Resolved in 1 to 3 hours post-dosing, consistent with peak concentrations

Source: Praxis Data CSR as of Sept. 27, 2019

PRAX-114 can be dosed at bedtime without food

Effect of High-Fat Meal on Pharmacokinetics



PRAX-114 suspension (30mg)

*Definition of food effect from FDA guidance - Assessing the Effects of Food on Drugs in INDs and NDAs

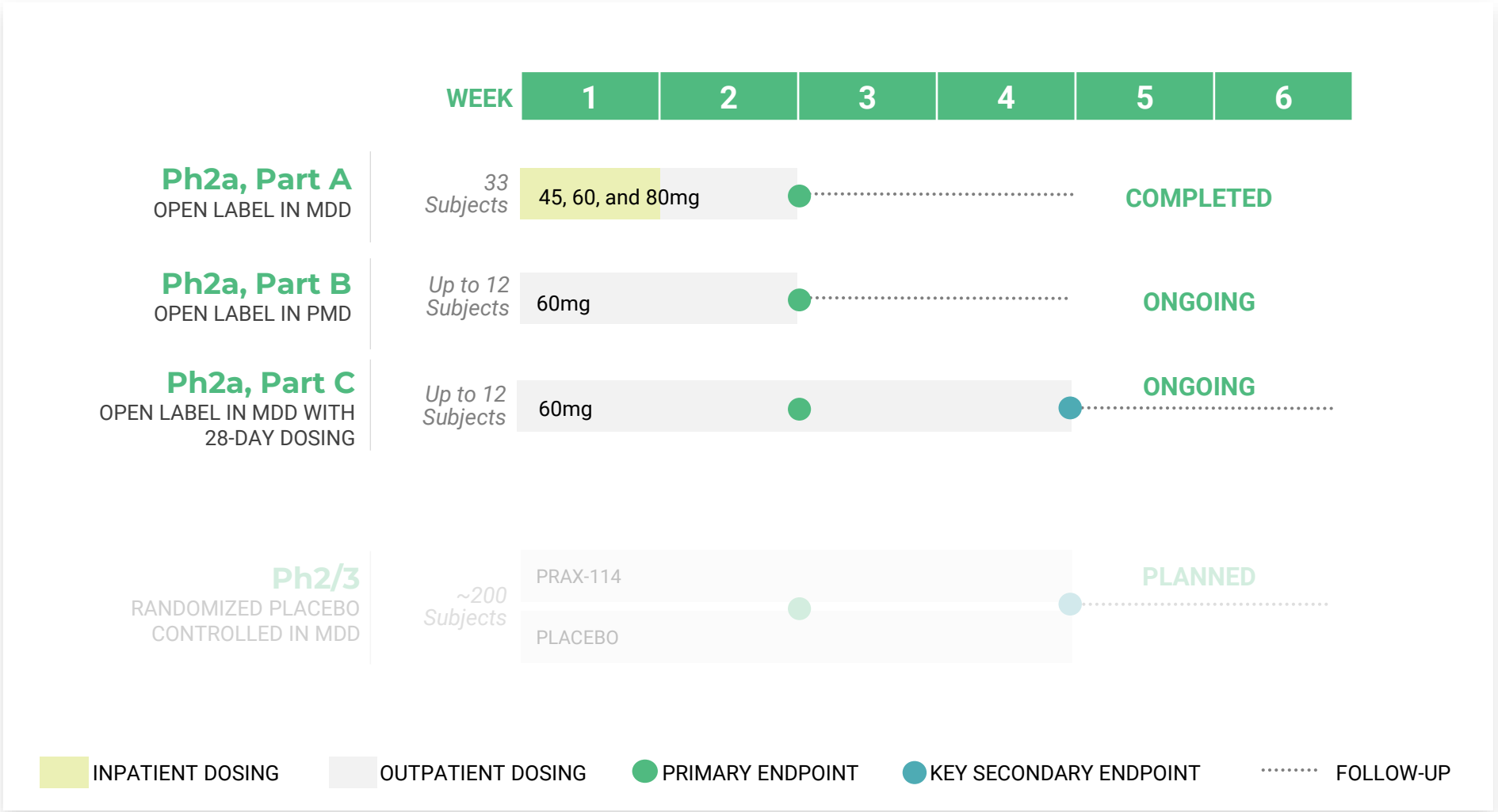
Source: Praxis Data CSR as of Sept. 27, 2019

PRAX-114 Phase 2a clinical development overview informing registrational studies

PHASE 2a

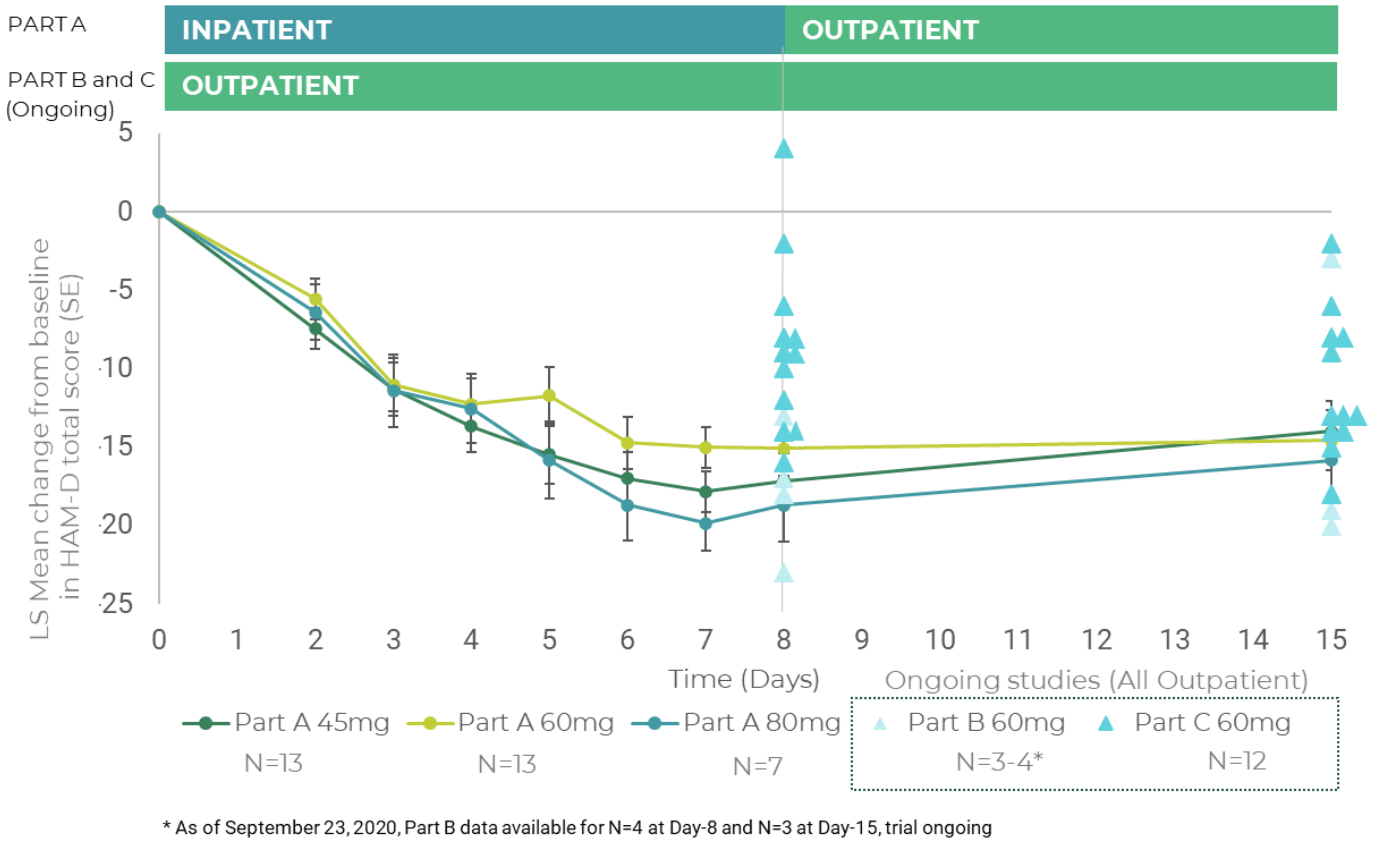
OBJECTIVE

To evaluate the change in the HAM-D score from baseline at Day 15 to demonstrate the rapid effect of PRAX-114 and **inform Phase 2/3 development plan**



PRAX-114: rapid and marked improvement in depression scores

Phase 2a open label trial in moderate to severe MDD



* As of September 23, 2020, Part B data available for N=4 at Day-8 and N=3 at Day-15, trial ongoing

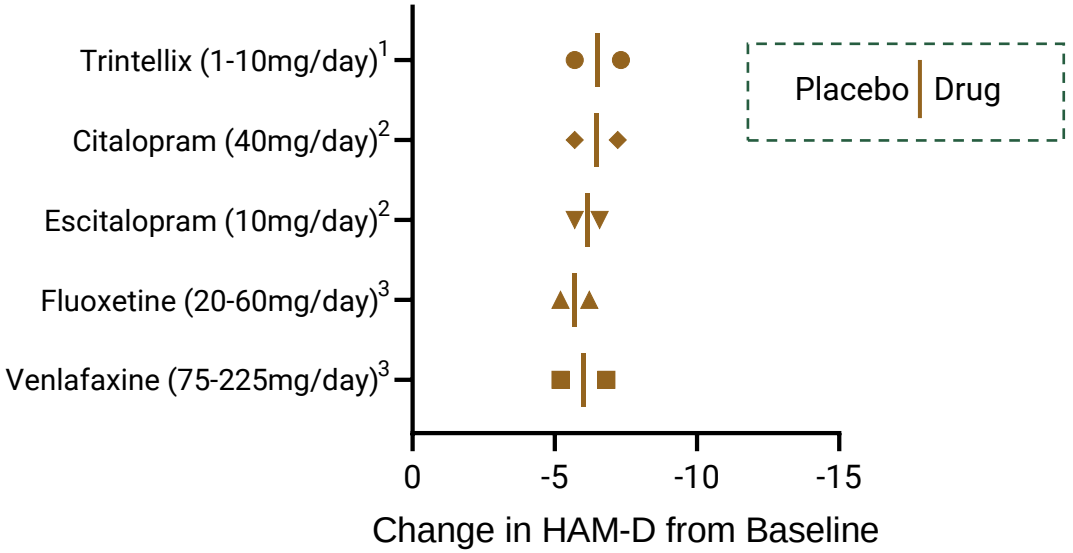
Rapid and marked improvement in depression scores in a difficult-to-treat population

- Moderate to severe MDD patients (mean baseline HAM-D = 25)
  - **>70% were unresponsive to an antidepressant** during the current depressive episode
- **> 60% of patients were responders or in remission** at two weeks
- **All Parts demonstrate a well tolerated profile throughout treatment schedule**

Source: Praxis Data as of September 23, 2020

Slow onset of action and limited response relative to placebo is substantial unmet need in MDD

Mean HAM-D change from baselines at 2-weeks



- Antidepressants shown account for ~40% of TRx in US

Source: (1) Trintellix Study 305 FDA SBA 2011, (2) Burke et al 2002, (3) Nemeroff et al 2007, IQVIA Report 2018

PRAX-114 Phase 2a clinical development overview informing registrational studies

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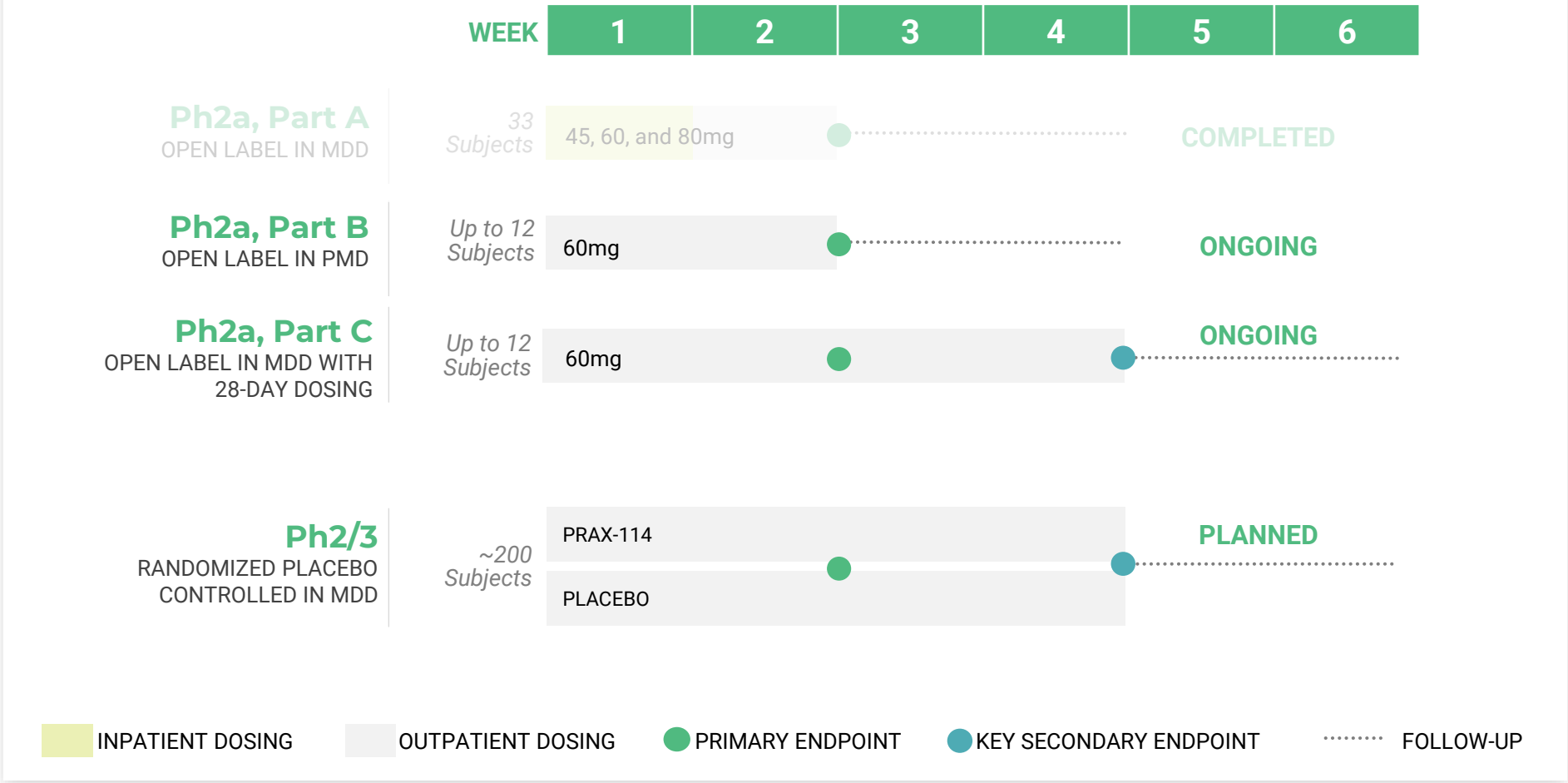


PRAX-944

CACNA1G

T-Type calcium channel

PH2

Essential Tremor

Expected H1-2021

Ph2a Essential Tremor Topline

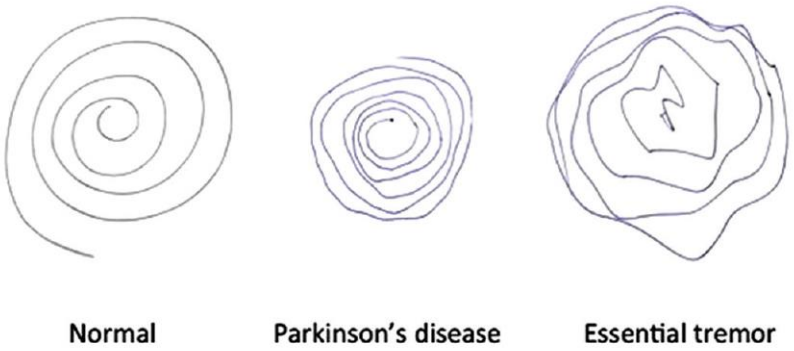
PRAXIS

PRAX-944 is a selective T-type calcium channel inhibitor for the treatment of Essential Tremor

ET is the most common movement disorder

Characterized by involuntary progressive tremor especially in the hands

Tremor markedly impairs activities of daily living (ADL), including eating, dressing, and speaking



Normal | Parkinson's disease | Essential tremor

Up to 7 million patients in the U.S.

1-2% of the world population lives with essential tremor

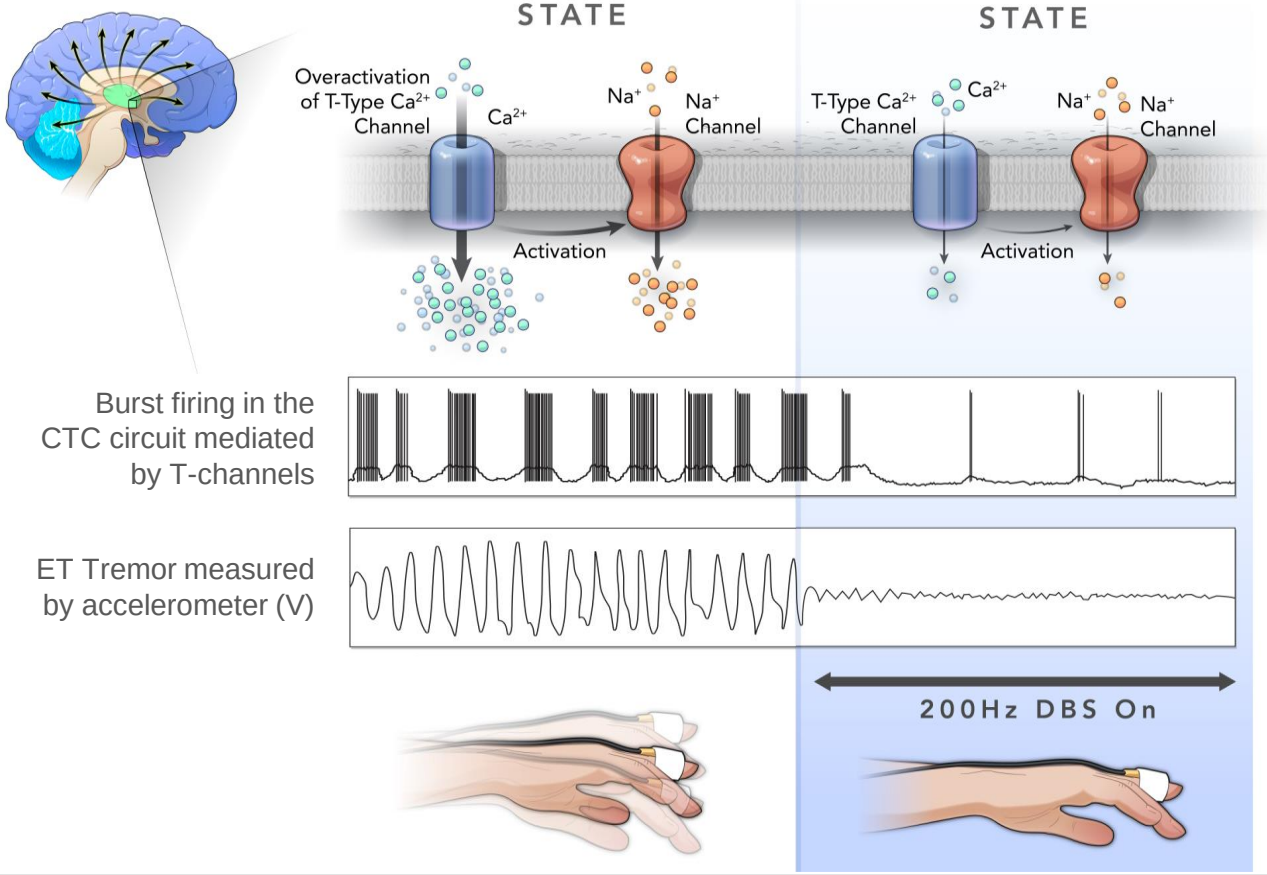
80% estimated discontinuation rate for available therapies due to limited efficacy and poor tolerability

Last option is invasive brain surgery

Source: Louis 2014; Diaz & Louis 2010; Praxis ET Claims Analysis; Uptodate.com; Annals of Indian Academy of Neurology

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

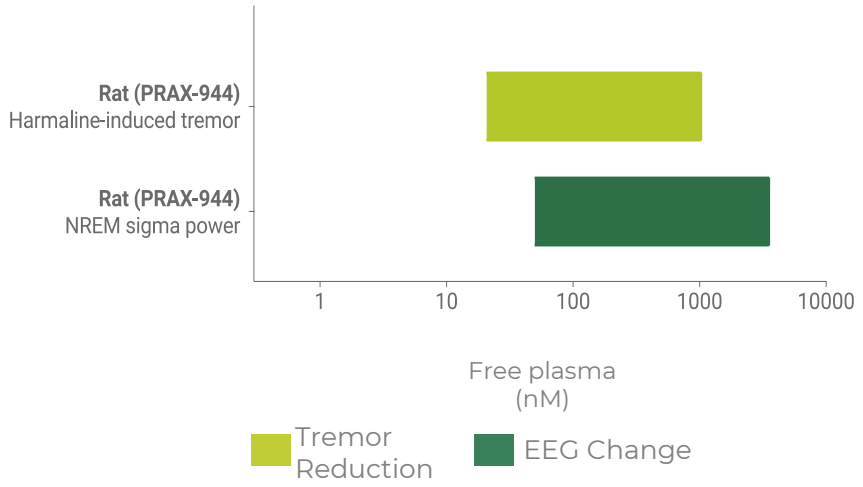
Abnormal neuron burst firing in the CTC circuit correlated with tremor activity in ET patients

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

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

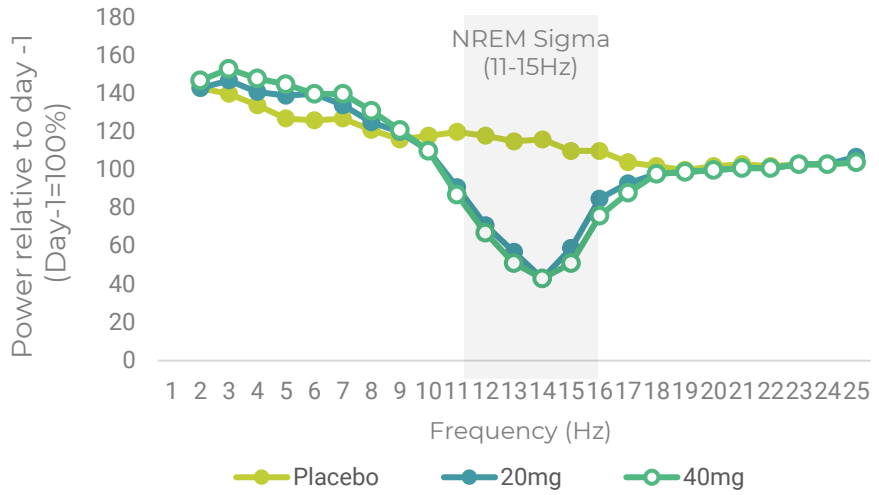
Brain T-type calcium channel blockade evidenced by EEG biomarker change in healthy volunteers, guiding clinical development

Strong Preclinical Correlation Between EEG Change and Tremor Reduction



- Decrease in NREM sigma power indicating thalamocortical T-type calcium channel blockade
- Preclinically, harmaline tremor reduction is associated with doses that reduce NREM sigma activity

Robust Pharmacodynamic EEG Effects in Humans

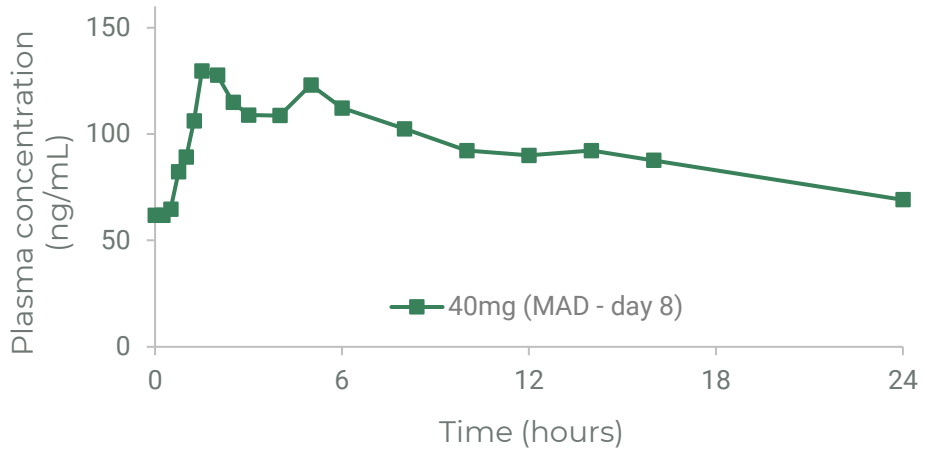


- Clinically, PRAX-944 demonstrated robust reduction in NREM sigma at 20mg and 40mg
- Based on the preclinical data and human EEG biomarker data, 20mg and 40mg are expected to reduce tremor in patients

Source: Praxis Data

PRAX-944 is a T-type calcium channel inhibitor designed to enable once daily dosing and a well-tolerated safety profile

Phase 1 MAD trial on MR formulation



Sustained exposure with blunted Cmax ideal for ET where tolerability is key for success

On-going titration trial in healthy volunteers

Well tolerated with no MTD identified up to 120 mg per day with titration in HV with no SAEs and no severe AEs

AEs observed across both Phase 1 trials were mild-moderate and transient

Source: Represents preliminary analysis of safety data as of Sep 1st, 2020

Keys to successful development in Essential Tremor for ongoing Phase 2a proof-of-concept trial

Phase 2a open label trial of adult ET patients (up to n=12 per cohort)

TAILORED FORMULATION FOR IDEAL PK

- Cohort A - daily morning dosing of PRAX-944 at 20mg during Week 1 followed by 40mg during Week 2
- Cohort B - daily morning dosing of PRAX-944 up to 120mg

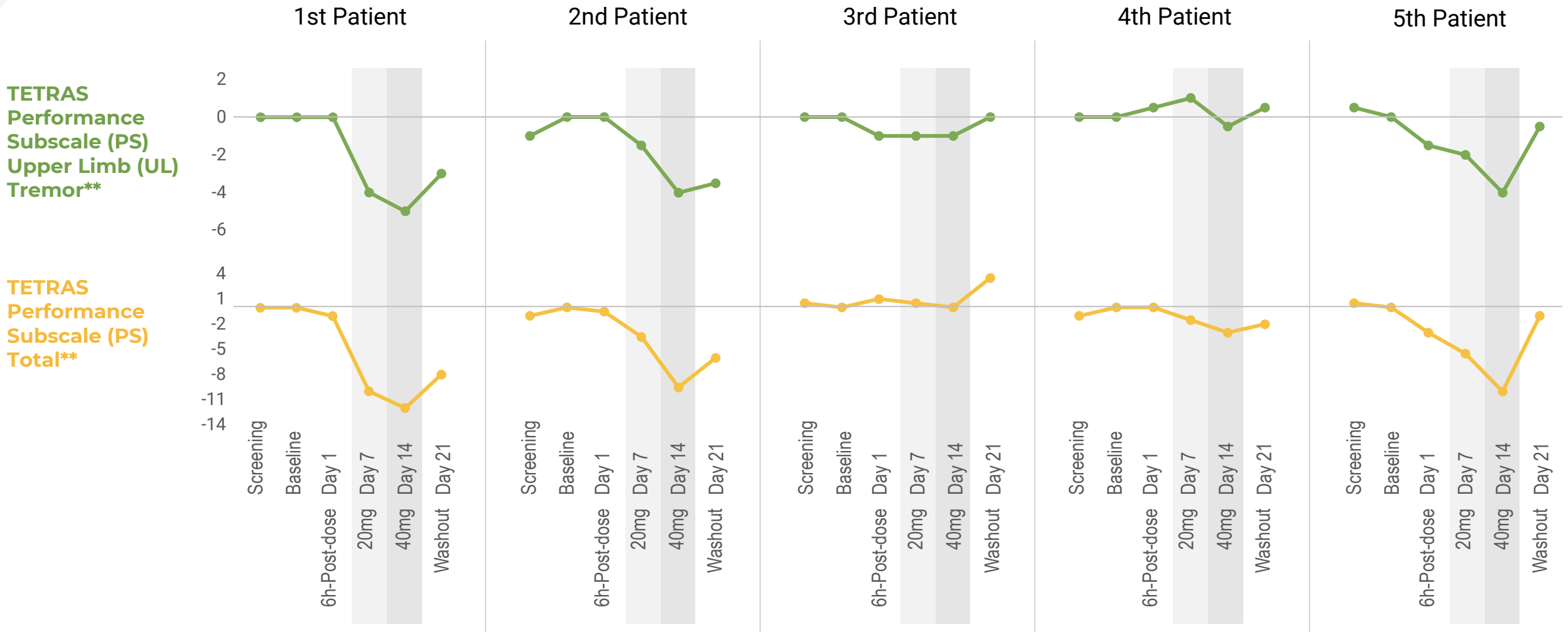
RIGOROUS PATIENT SELECTION

- Patients with clear and measurable dynamic range for detecting a treatment response
  - ET consistent with Movement Disorders Society Criteria: ET of at least 3 years
  - Combined bilateral score of ≥10 on the TETRAS UL items as confirmed by site and central video review

OPTIMIZED TRIAL DESIGN & EXECUTION

- Measuring changes in tremor with different, complementary approaches
  - 1°: efficacy on upper limb tremor (main driver of disability) at Day 7 and 14 vs. baseline
  - 2°: TETRAS performance scale (both site and central video rating) and accelerometry
- Established rigorous procedures for training and for blinded scoring of efficacy
  - Centralized video assessment with randomization of videos and masking

Preliminary site data from on-going ET OL trial (N=5)



**All values displayed are score reduction from baseline

Source: Praxis Data as of September 23, 2020; Complete Kinesia ONE data on the five participants pending

EARLY STAGE PIPELINE

PRAX-562 – Na_v Channels
PRAX-222 – SCN2A
KCNT1 Program – KCNT1

PRAXIS

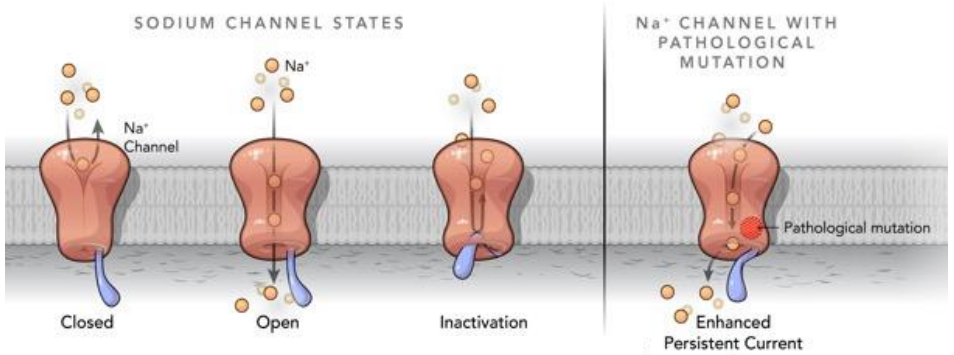
Block of persistent sodium current can reduce neuronal hyperexcitability and impact multiple disease states

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

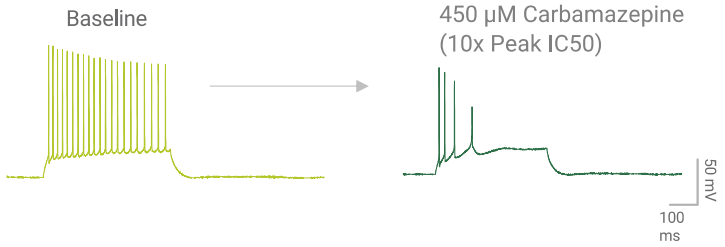
- All standard NaV blockers target peak sodium current
- Standard sodium channel blockers are an important class of medicines in neurology and psychiatry, broadly used in epilepsy, pain, migraine, and bipolar disorder
- In general efficacy is limited by side effects

Depakote divalproex sodium
Tegretol-XR carbamazepine extended-release tablets
Lidoderm LIDOCAINE PATCH 5%
Oxtellar XR (oxcarbazepine) extended-release tablets 600 mg 300 mg 150 mg
Dilantin (extended phenytoin sodium capsules, USP)
EXPAREL (bupivacaine liposome injectable suspension)
Lamictal

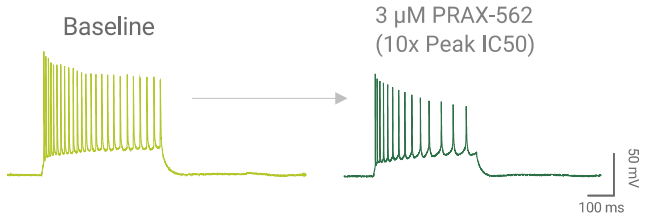
Modulation of persistent sodium current reduces hyperexcitability without disrupting AP



Carbamazepine Representative AP Traces



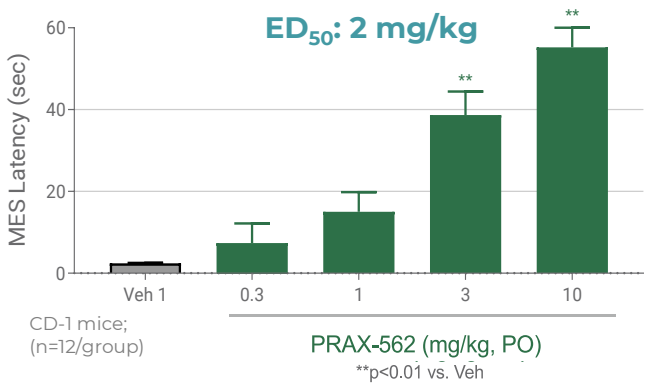
PRAX-562 Representative AP Traces

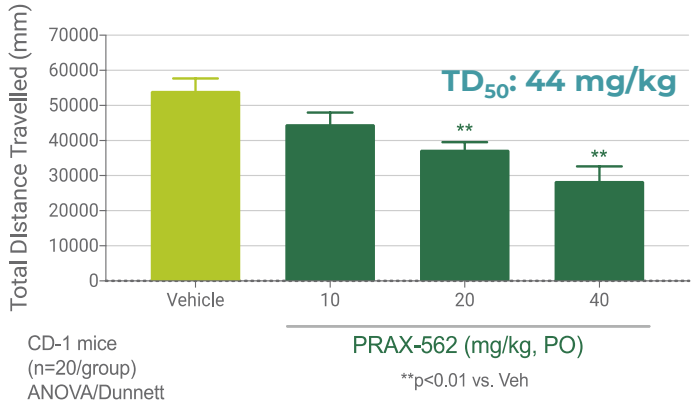


Source: Schachter et al. antiseizure drugs UptoDate 2020, Praxis data

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

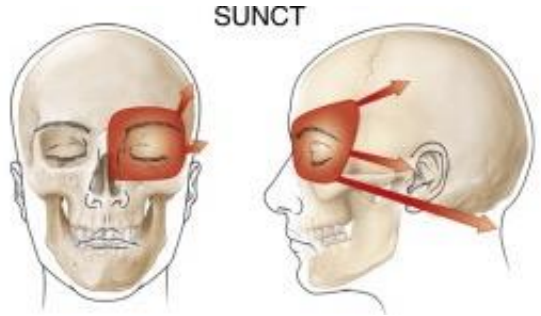
Molecule	Brain Therapeutic Index
PRAX-562	**16.4x**
Carbamazepine	5.9x
Lamotrigine	4.6x

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

PRAX-562 has broad potential in rare CNS conditions

SUNCT is a devastating, high frequency headache without an FDA approved drug



ESTIMATED PREVALENCE IN U.S. OF **~10k (6.6/100k)**

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

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 DEE 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

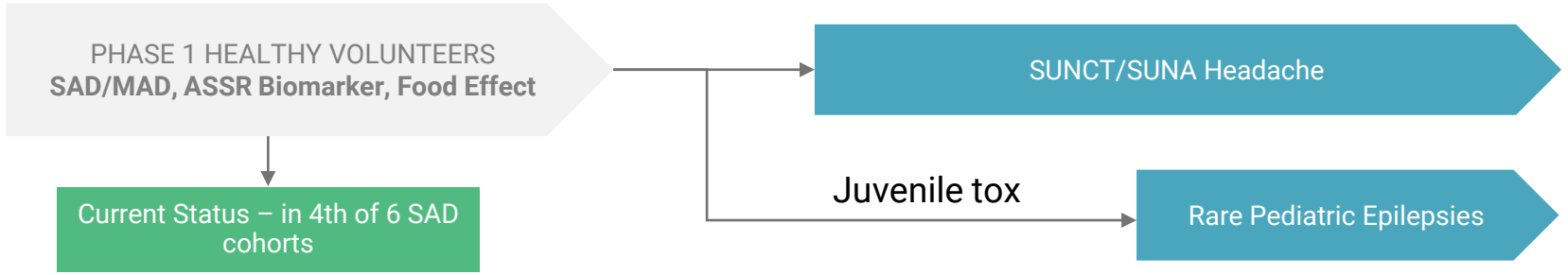
Source: Williams et al 2006, Eltze et al. 2013 ; Howell et al 2018

PRAX-562 development strategy in SUNCT/SUNA and pediatric epilepsies

OBJECTIVE

Identify PoC and safety in SUNCT/SUNA headaches, and expand to rare pediatric epilepsies

Clinical Strategy



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

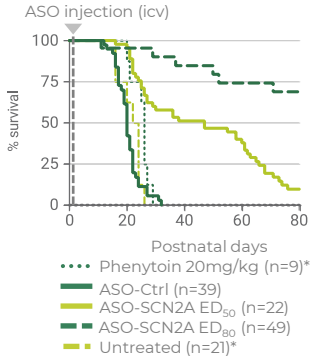
Study Design	▪ Randomized, double blind
Patient Population	▪ ♀ or ♂ 18-55 years of age ▪ Healthy Volunteers
Study Objectives	▪ 1°: Safety and tolerability of single and multiple ascending doses of PRAX-562 in healthy volunteers ▪ 2°: Pharmacokinetics of single and multiple ascending doses of PRAX-562 in healthy volunteers ▪ Exploratory: EEG Auditory Steady-state Response (ASSR)

Preclinical pipeline addressing genetically defined rare epilepsies with precision medicine approach

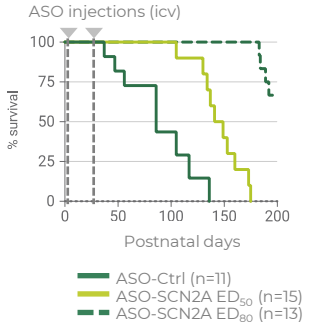
PRAX-222: SCN2A GoF Epilepsy

- 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

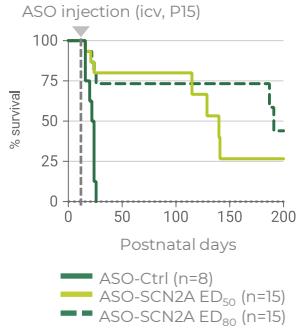
Increased Survival with Single ASO Dose at P1



Redosing Significantly Extends Survival



Administration Post-Disease Onset Also Extends Survival

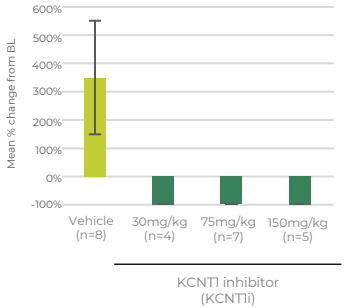


IND filing anticipated in 2021

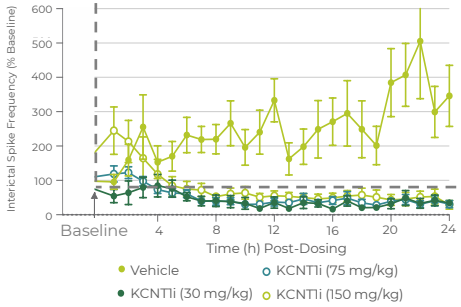
KCNT1 Inhibitor: KCNT1 GoF Epilepsy

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

*KCNT1 Inhibitor Eliminated Seizure***



KCNT1 Inhibitor Decreased Interictal Spike Frequency



Development candidate (DC) nomination anticipated in 2021

Source: Praxis Data

*Data separate from experiment **All mice with zero seizure at baseline were excluded from the analysis; If all mice were included, the values would be 273%, -80%, -87%, -83% for vehicle, 30mg/kg, 75mg/kg and 150mg/kg group

Substantial potential for value creation across the portfolio

BROAD PSYCHIATRY & NEUROLOGY

RARE DISEASES

PRAX-114
Depression

$GABA_A$ receptor PAM

Phase 2/3 for Major Depressive Disorder
Phase 2a for Peri-menopause Depression

H1 2022
TOPLINE

PRAX-944
Movement Disorders

T-type calcium channel blocker

Phase 2a for Essential Tremor

H1 2021
TOPLINE

PRAX-562
Rare Diseases

Selective persistent sodium current blocker

Adult Cephalgia and Severe Pediatric Epilepsies

2021 Ph2
INITIATION

Preclinical
Genetically Defined Epilepsies

Two differentiated preclinical candidates

PRAX-222 for SCN2A Epilepsy and Inhibitor for KCNT1 Epilepsies

2H 2021
FIRST IND

Indication Expansion

Multiple indication expansion opportunities across the portfolio

MULTIPLE POTENTIAL VALUE-CREATING MILESTONES
EXPECTED WITHIN THE NEXT 18 MONTHS