PRAXIS

PRAX-562-221 SYNOPSIS REVIEW

26-July-2022

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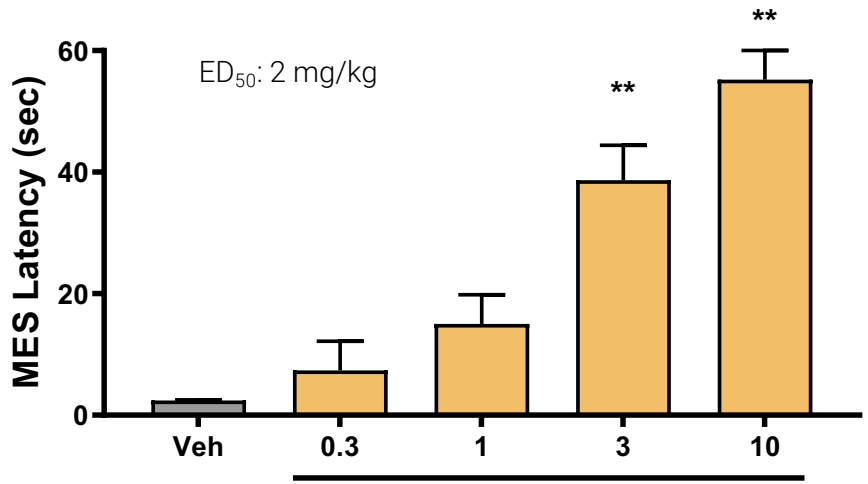
Imperatives which Guide our Epilepsy Portfolio Build

Focus directly on underlying genetic defects in rare epilepsy	Focus on implicated genes in common diseases	Focus on nodes of pathophysiological convergence informed by genetics
PRAX-222* *ASO*	**PRAX-944** *SMALL MOLECULE*	**PRAX-562** *SMALL MOLECULE*
PRAX-020 *SMALL MOLECULE*		**PRAX-628** *SMALL MOLECULE*
PRAX-080* *ASO*		
PRAX-090* *ASO*		
PRAX-100* *ASO*		
PRAX-030 *SMALL MOLECULE*		

*PRAX-222 in collaboration with Ionis Pharmaceuticals and RogCon, Inc. PCDH19 (PRAX-080), SYNGAP1(PRAX-090), SCN2A-LOF (PRAX-100) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health.

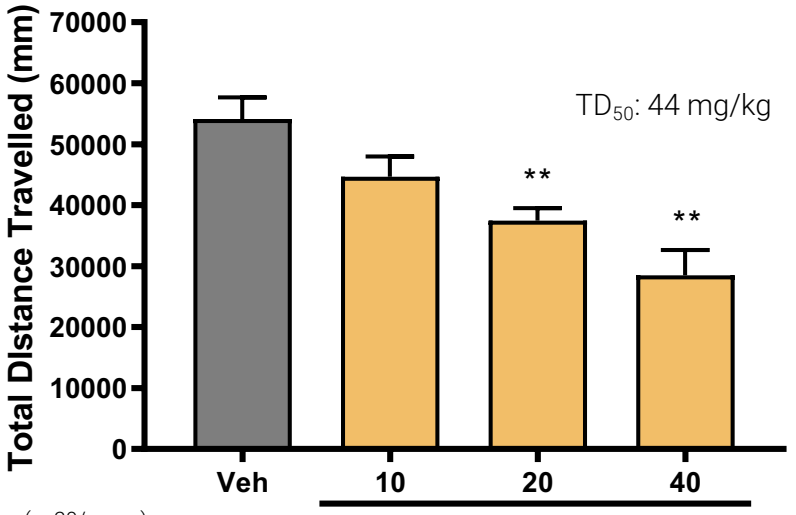
PRAX-562 Preclinical Data

MES EFFICACY



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

sLMA TOLERABILITY



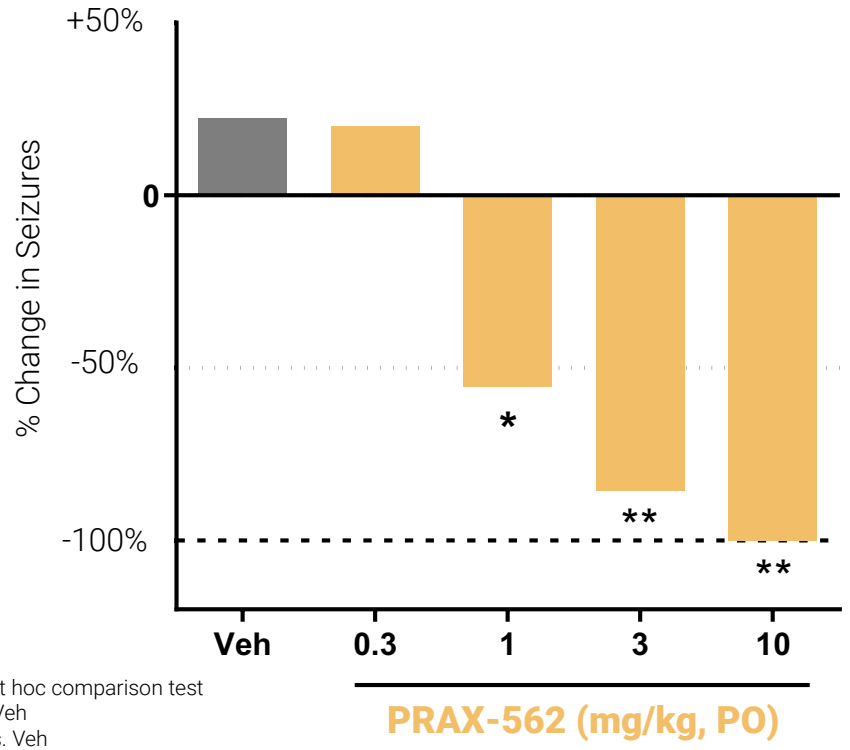
CD-1 mice; (n=20/group)
ANOVA/Dunnett
**p<0.01 vs. Veh

Therapeutic Index = TC_{50} / EC_{50}
MES, maximal electroshock
sLMA, spontaneous locomotor activity

Kahlig KM et al. Epilepsia. 2022;00:1–12.

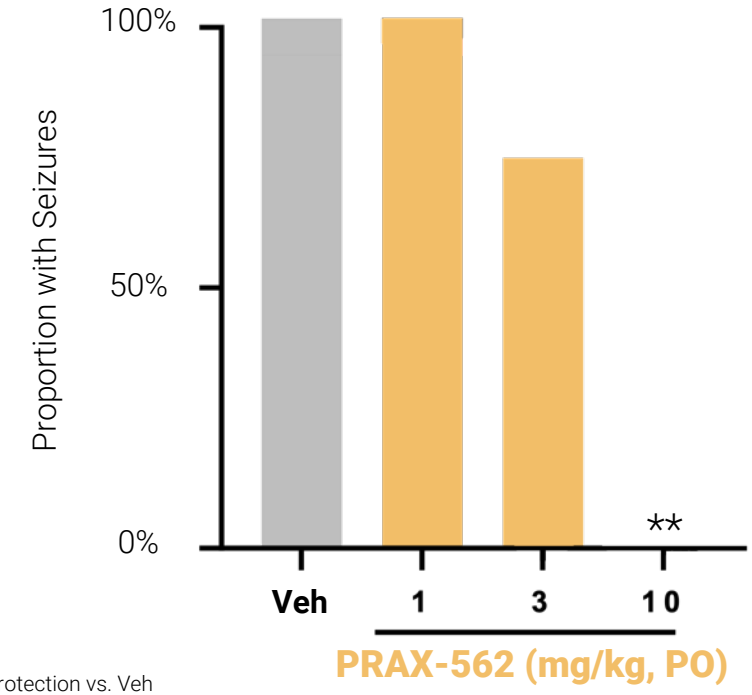
PRAX-562 Preclinical Data

IN VIVO POC IN SCN2A SPONTAEOUS 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
χ^2_2 = 16.0, Fisher's p = 0.0002

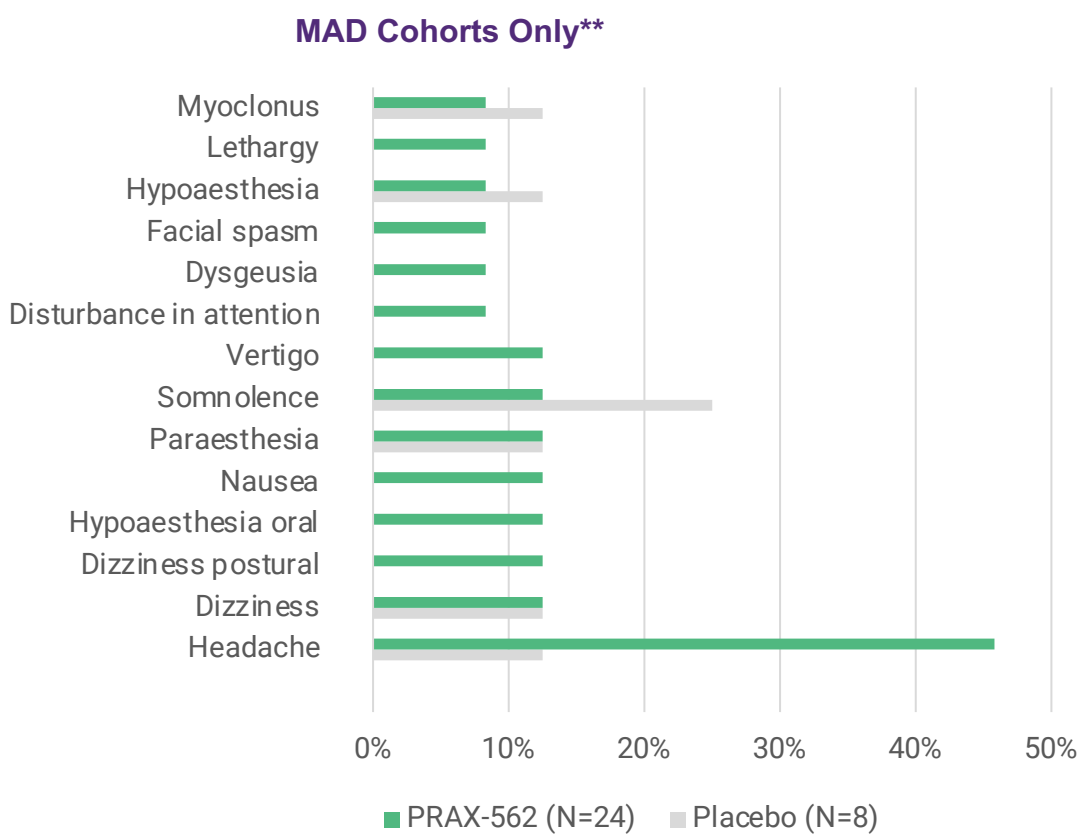
[1] PRAX-562 inhibition of spontaneous seizures in Q54 GoF mice.
[2] PRAX-562 inhibition of audiogenic seizures in N1768D D/+ mice

PRAX-562 Emerging Clinical Data

- Superior selectivity for disease-state NaV channel hyperexcitability
- Therapeutic window with potential for superior safety and efficacy
- Convenient auto-titration regimen with stable PK

PRAX-562 Well Tolerated in Phase 1 Study in Healthy Adults

Percentage of treatment emergent adverse events (TEAEs) reported in ≥5% of PRAX-562 participants*



- All TEAEs mild to moderate in severity
- No drug-related SAEs or severe AEs
- No significant aberrations in clinical safety labs, ECGs, or assessments of suicide

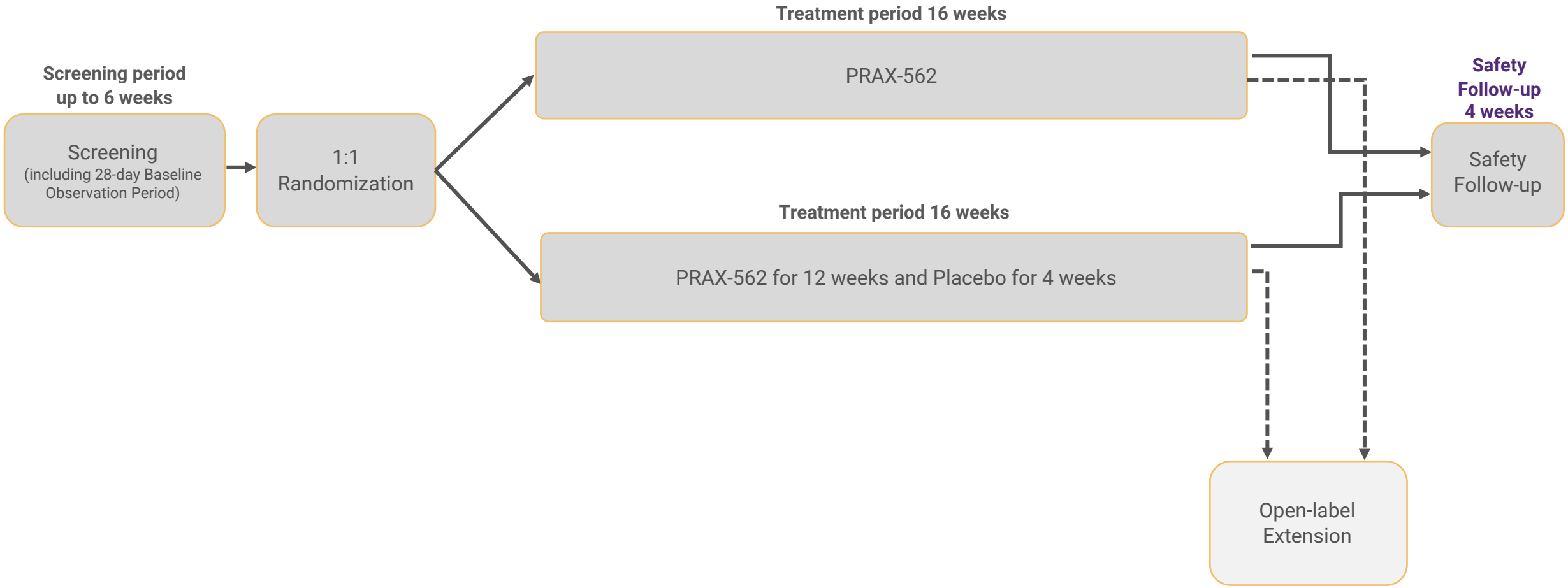
*TEAEs related to blood sample collection excluded
**112 participants were administered PRAX-562 across the SAD, MAD, and food effect cohorts in PRAX-562-101.

MAD, multiple ascending dose; SAD, single ascending dose

PRAX-562-221

- Proposed Phase 2 Double Blind, Randomized Clinical trial to Explore the Safety, Tolerability, Efficacy, and Pharmacokinetics of PRAX-562 in Pediatric Participants with Developmental and Epileptic Encephalopathies followed by Open Label Extension

Study Schema - Parts A and B



Key Inclusion Criteria

~10 from each cohort (SCN2A, SCN8A)

1. Has a documented variant in SCN2A or SCN8A (Has a documented de novo (not observed in either parent) missense variant in SCN2A with onset of seizures occurring in the first three months of life or has a documented de novo (not observed in either parent) missense variant in SCN8A with onset of seizures occurring in the first six months of life.
2. Age ≥2 and ≤18 years at Screening
3. Has a seizure frequency as follows:

   - At least 8 countable motor seizures in the 4 weeks immediately prior to Screening

   AND

   - At least 8 countable motor seizures during the 28-day Baseline Observation Period

Key Exclusion Criteria

- Has any clinically significant or known pathogenic genetic variant other than in SCN2A and SCN8A, or a genetic variant that may explain or contribute to the participant's epilepsy and/or developmental disorder.
- Has a known documented loss-of-function variant based on genetic testing and/or clinical evidence that prior exposure to a sodium channel blocker medication worsened seizures.
- Has received any other experimental or investigational drug, device, or other therapy within 30 days or 5 half-lives (whichever is longer) prior to Screening.

Study Design

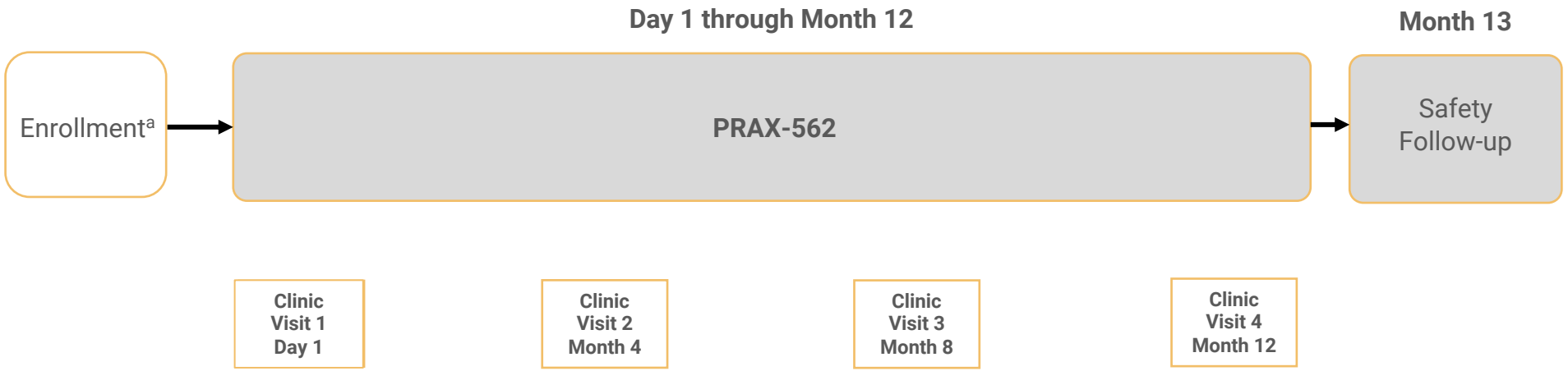
- 2-week Screening period
- 4-week Baseline observation period
- E-diary and seizure watch (wearable device) given at start of baseline observation period (after meeting eligibility criteria)
- Baseline labs and EEG
- 1:1 randomization of each cohort to 16-week treatment period vs 12-week treatment period with 4 consecutive weeks of placebo

Key Study Assessments or Activities

- E-diary
- Seizure watch
- In person visit every 4 weeks during part A of the study
- EKG every in person visit
- Labs every 2 weeks (weeks 2, 6, 10 can be performed at home or in clinic)
- EEG at baseline and around week 12
- CGI-I caregiver and clinician

CGI-I, Clinical Global Impression-Improvement

Study Schema for OLE (Part B)



[a] Enrollment (Day 1) is the end of treatment (EOT) visit of the preceding trial; participants who enter the OLE will have uninterrupted treatment.

Summary of OLE Study Visits (Part B)

OLE Visit every 4 months

- Review labs
- CGI-I, CgGI-I
- Seizure diary for 1 week before the visit

4-week safety follow-up phone call

- Assessments

- Treatment satisfaction questionnaire

CGI-I, Clinical Global Impression-Improvement; CgGI-I Caregiver Global Impression-Improvement

Questions?