# EMBOLD: A Clinical Trial of PRAX-562 in Subjects with Developmental and Epileptic Encephalopathies Followed by an Open-Label Extension

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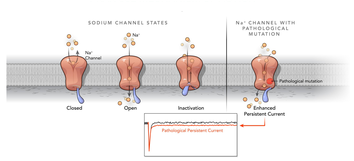
## Background

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood, characterized by severe, frequent seizures and increased mortality, as well as developmental delay, intellectual disability, and other comorbidities.
- Gain-of-function pathogenic variants in voltage-gated sodium channel ($Na_v$) genes can increase $Na_v$ activity leading to the neuronal hyperexcitability observed in severe DEEs.
- PRAX-562 is a next-generation antiseizure molecule targeting the disease state in multiple DEEs, tailored for pediatric needs, with demonstrated superior selectivity for disease-state $Na_v$ hyperexcitability.
- PRAX-562 has been generally well tolerated in over 130 healthy volunteers.
- This profile suggests a wide therapeutic window and potential for superior safety and efficacy over standard-of-care.

➢ The EMBOLD study is a Phase 2 randomized clinical trial designed to explore the safety, tolerability, efficacy, and pharmacokinetics (PK) of PRAX-562 in pediatric participants with seizures associated with early onset *SCN2A*-DEE and *SCN8A*-DEE.

PRAX-562 MECHANISM OF ACTION





**PRAX-562 received Orphan Drug Designation for severe pediatric epilepsy indications from FDA and EMA and Rare Pediatric Disease designation from FDA**

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

## Participant Eligibility

*Table 1. EMBOLD Study Eligibility*

| KEY INCLUSION CRITERIA |
|---|
| Documented rare missense variant in *SCN2A* with seizure onset in first 3 months of life; or diagnosis of *SCN8A*-DEE supported by clinical and genetic findings |
| Male or female aged 2-18 years inclusive; weight at least 10 kg |
| At least 8 countable motor seizures* both in the 4 weeks immediately prior to Screening AND during the 28-day Baseline Observation Period |
| On stable doses of ASMs for at least 1 month prior to Screening; no more than one sodium channel blocker at trial entry; all antiseizure therapies kept stable throughout trial |
| **KEY EXCLUSION CRTIERIA** |
| Significant ongoing disease, disorder, lab abnormalities, alcohol or drug abuse or dependence, environmental factor, or ongoing/history of any psychiatric, medical, or surgical condition that may interfere with drug metabolism or trial outcomes |
| Any clinically significant or known pathogenic or likely 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 |
| Any other/additional etiology for epilepsy |
| Documented, functionally characterized loss-of-function missense variant or a presumed LoF variant |
| 2 or more episodes of convulsive *status epilepticus* requiring hospitalization and intubation in the 6 months prior to Screening |

*Countable motor seizures defined as generalized tonic-clonic seizures, tonic seizures (bilateral), atonic seizures (with fall or risk of fall), clonic seizures (bilateral), focal motor seizures (aware, impaired or unknown awareness), and focal to bilateral tonic-clonic seizures. Myoclonic seizures, absence seizures, atonic seizures (without fall or risk of fall), focal non-motor seizures, or epileptic spasms will not be considered as countable motor seizures for this clinical trial.

## Safety and Efficacy Assessments

*Table 2. EMBOLD Safety and Efficacy Assessments (Part A)*

| Trial Period | Screening | | Double-Blind Treatment | | | | | | | | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Day/Week** | **Days -42 to -29** | **Days -28 to -1 (BL)** | **Day 1** | **Week 2** | **Week 4** | **Week 6** | **Week 8** | **Week 10** | **Week 12** | **Week 16/EOT** | **Week 20/EOS** |
| **Visit** | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 |
| **SAFETY ASSESSMENTS** | | | | | | | | | | | |
| Physical examination | X | | X | | X | | X | | X | X | |
| Clinical laboratory evaluations | X | | X | X | X | X | X | X | X | X | |
| ASM levels sampling | X | | X | X | X | X | X | X | X | X | |
| Vital signs | X | | X | | X | | X | | X | X | |
| 12-lead ECG | <- | - | - | - | - | X | - | - | - | - | -> |
| C-SSRS (Baseline/Screening) | X | | | | | | | | | | |
| C-SSRS (Since Last Visit) | | | X | | X | | X | | X | X | |
| AE monitoring | <- | - | - | - | - | X | - | - | - | - | -> |
| Concomitant Meds/procedures | <- | - | - | - | - | X | - | - | - | - | -> |
| **EFFICACY ASSESSMENTS** | | | | | | | | | | | |
| Seizure diary | <- | - | - | - | - | X | - | - | - | - | -> |
| Nelli | <- | - | - | - | - | X | - | - | - | - | -> |
| CGI-S and CgGI-S | | | X | | | | | | | X | |
| CGI-I and CgGI-I | | | | | X | | X | | X | X | |

*Table 3. EMBOLD Safety and Efficacy Assessments (Part B)*

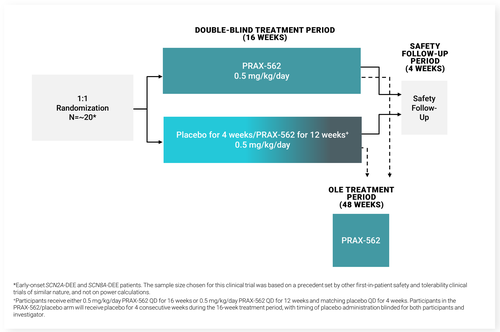
| Trial Period | Open-Label Treatment | | | | | | Safety Follow-up |
|---|---|---|---|---|---|---|---|
| **Visit Day/Month** | **Day 1** | **Week 4** | **Week 16** | **Week 32** | **Week 48/EOT** | **Unscheduled Visit** | **Week 52/EOS** |
| **Visit** | V1 | V2 | V3 | V4 | V5 | | V6 |
| **SAFETY ASSESSMENTS** | | | | | | | |
| Physical examination | X | | X | X | X | | |
| Clinical laboratory evaluations | X | X | X | X | X | X | |
| ASM levels sampling | X | X | X | X | X | X | |
| Vital signs | X | | X | X | X | | |
| 12-lead ECG | X | | X | X | X | | |
| C-SSRS (Since Last Visit) | X | | X | X | X | | |
| AE monitoring | <- | - | - | X | - | - | -> |
| Concomitant Meds/procedures | <- | - | - | X | - | - | -> |
| **EFFICACY ASSESSMENTS** | | | | | | | |
| Seizure diary | X | X | X | X | X | | |
| CGI-S and CgGI-S | X | | | | X | | |
| CGI-I and CgGI-I | X | | | | X | | |

AE=adverse event; ASM=antiseizure medication; BL=baseline; CgGI-I=Caregiver Global Impression-Improvement; CgGI-S=Caregiver Global Impression-Severity; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment (including early termination); V=visit.

## Methods

*EMBOLD Study Design*

- EMBOLD (NCT05818553) is a multicenter, double-blind, placebo-controlled, randomized study, followed by open-label extension (OLE), which will enroll ≈20 eligible male and female participants aged 2-18 years, inclusive, with a diagnosis of early onset *SCN2A*-DEE or *SCN8A*-DEE.
- Participants will be randomized (1:1) to receive 0.5 mg/kg/day PRAX-562 QD for 16 weeks, or 0.5 mg/kg/day PRAX-562 QD for 12 weeks and matching placebo QD for 4 weeks, administered orally or via gastrostomy/jejunostomy tube (G/J-tube).
- Dose adjustment is permitted to a maximum of 1.0 mg/kg/day and a minimum of 0.25 mg/kg/day.
- Part A (randomized, double-blind) will consist of the following periods: Screening, Double-Blind Treatment, and Safety Follow-up.
- Part B (OLE) will consist of the following periods: OLE Treatment and Safety Follow-up.
- Participants will have the option to be enrolled to undergo the study assessments in a hybrid fashion (with in-clinic and at-home visits) or with at-home visits only.




**PRIMARY ENDPOINT:**

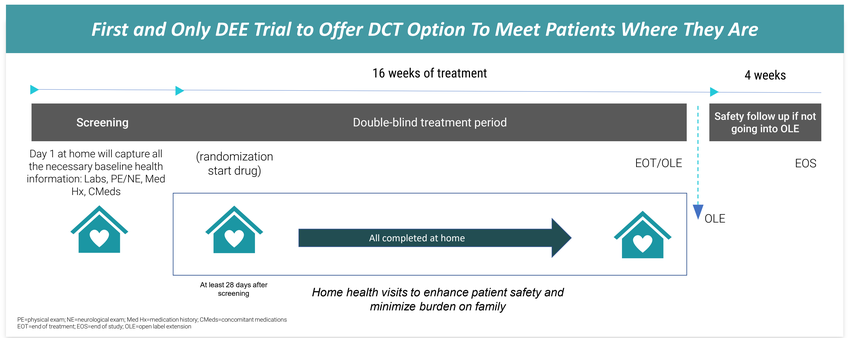
Incidence and severity of treatment-emergent adverse events (TEAEs)

**KEY SECONDARY:**

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

***Figure 1. EMBOLD Study Design.*** Secondary endpoints will include plasma concentrations of PRAX-562, while further exploratory endpoints will examine the effect of PRAX-562 on additional efficacy and safety outcomes beyond those captured in primary and key secondary endpoints.

## EMBOLD Decentralized Clinical Trial Design: Patient-Centric, Clinical Rigor




- ❖ User-friendly electronic seizure diaries
- ❖ Streamlined at-home nurse services for collection of labs
- ❖ State-of-the-art seizure detection and measurement at home
- ❖ Reduced in-clinic visits to minimize travel burden for patients and caregivers

- ❖ Open-label extension to continue benefiting from treatment

- ❖ Designed with families' needs in mind
- ❖ Balancing scientific rigor and safety
- ❖ Increased inclusion for potential patients normally excluded
- ❖ Families also have the option of a hybrid model with some visits at home and some in the clinic if they choose

***Figure 2. EMBOLD Study (Part A) – DCT At Home.*** Families can participate in the EMBOLD trial from their homes, with the clinic coming to them. The DCT nature of the trial allows all study related procedures to be done at home, with doctors and nurse visits ensuring the trial is conducted in a manner more convenient for families.

## Conclusions

- **PRAX-562 has the potential to be a first- and best-in-class treatment for DEEs.**
- **Expanding on preliminary findings, the EMBOLD trial will provide important findings regarding the safety, tolerability, efficacy and PK of PRAX-562 in pediatric patients with *SCN2A*-DEE and *SCN8A*-DEE.**
- **PRAX-562 Phase 2 EMBOLD study topline data is expected 1H2024.**

EMBOLD

SCAN ME

## References

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