EMBRAVE: A Clinical Trial of PRAX-222, a Novel Antisense Oligonucleotide, in Pediatric Participants with Early Onset *SCN2A* Developmental and Epileptic Encephalopathy

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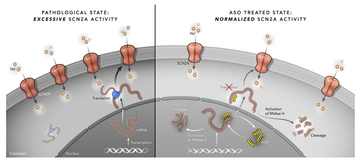
Background

- Early onset *SCN2A* developmental and epileptic encephalopathy (*SCN2A*-DEE) is a rare, severe, and fatal pediatric disorder caused by gain-of-function (GoF) variants in the *SCN2A* gene encoding the voltage-gated sodium channel $Na_V1.2$.
- With no approved therapy specifically for treatment of affected patients, current standard-of-care for seizure treatment includes polypharmacy with antiseizure medications, in addition to medications for other devastating comorbidities.
- In addition to their limited efficacy and significant adverse event profiles, current treatments do not address the profound developmental impairments and outcomes beyond seizure symptomatology in *SCN2A*-DEE, implicating an urgent need for new therapeutic approaches.
- Preclinical evidence suggests selective reduction in *SCN2A* function via human mRNA-targeting antisense oligonucleotides (ASOs) has the potential to achieve more widespread seizure freedom, and potentially improve developmental outcomes following disease onset, by addressing the underlying genetic cause of disease.
- PRAX-222 (elsunursen) is an ASO designed to down-regulate $Na_V1.2$ expression in development for early onset *SCN2A* GoF DEE.

SCN2A disease variations are caused by random nucleotide base changes in the genome resulting in altered protein function. → An ASO is a short, synthetic strand of DNA or RNA designed to bind specifically to a target RNA molecule, typically to alter its function or expression. → Elsunersen is a gapmer ASO with a modified core allowing it to bind to target RNA and induce RNA degradation via RNase H activation. → Preclinical data suggests that elsunersen has the potential to control seizures and to slow disease progression



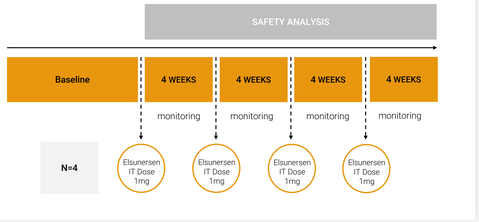
The Rationale For ASO Therapy For SCN2A-DEE

➢ *The EMBRAVE study is a first-in-human clinical trial designed to investigate the safety and efficacy of elsunersen in pediatric participants with early onset SCN2A-DEE.*

Methods

EMBRAVE Study Design

- EMBRAVE (NCT05737784) is a seamless trial designed to explore the safety, tolerability, pharmacokinetics (PK), and efficacy of ascending doses of elsunersen in eligible male and female participants aged 2-18 years, inclusive, with an early onset *SCN2A*-DEE diagnosis.
- The trial was designed to be conducted in 4 parts: the preliminary safety Part 1 (open label, n=4), dose-escalation Part A (double-blind), confirmatory Part B (double-blind), followed by an open-label extension in Part C.
- In Part 1, participants received elsunersen intrathecally at ≥4-week intervals for up to 13 weeks, and the incidence and severity of treatment-emergent adverse events assessed, with preliminary efficacy and safety also assessed after 4 doses.
- Preliminary safety and efficacy findings from Part 1 are presented based on a cutoff date of 4 Nov 2023.



GOAL:

Assess preliminary safety of elsunersen

Figure 1. EMBRAVE Study Design (Part 1).

Elsunersen Demonstrates Unprecedented Clinical Efficacy

- As of cutoff, 4 participants were evaluable through four doses each.
- Participants achieved an 43% median reduction in seizures from baseline on top of best available standard of care.
- Participants had an increased number of days without seizures, achieving a 48% relative median increase in seizure-free days from baseline, with treated participants 1.6x more likely to experience a seizure-free day.

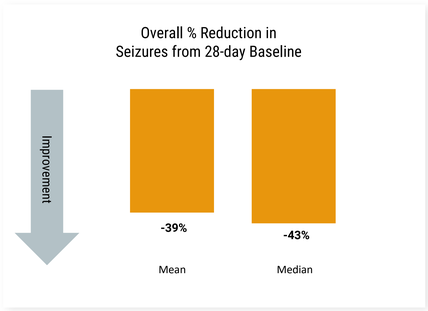


Figure 2. Mean and Median Change from Baseline in Seizure Frequency. Results represent overall percentage reduction from baseline observation through four 28-day periods for 4 participants. November 4, 2023 cutoff.

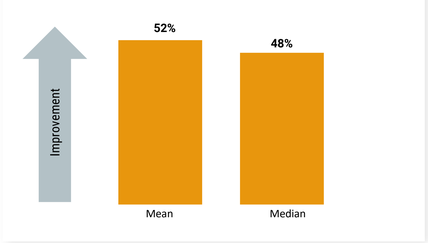


Figure 3. Mean and Median Relative Percentage Change from Baseline in Seizure-free Days. Results represent overall relative percentage increase in proportion of seizure-free days for 4 participants. November 4, 2023 cutoff.

Table 1. Participant Demographics

ID	Age at consent	Gender	Race	Ethnicity
2001	3 years	Female	White	Not Hispanic or Latino
2002	14 years	Male	White	Not Hispanic or Latino
2003	2 years	Female	White	Not Hispanic or Latino
2004	2 years	Female	Other (Hispanic)	Hispanic or Latino

Elsunersen Is Well-tolerated With No Drug-Related AEs

- No TEAEs or SAEs considered related to study drug; all TEAEs recovered/resolved.
- Independent data monitoring committee provided opinion to continue dosing without modifications.

Table 2. Safety Summary

Assessment	Findings
Physical and neurological examinations	No clinically significant findings
Vital sign measurements	No clinically significant changes
Clinical laboratory results	No clinically significant changes in lab results except for 'elevated WBC' reported for 1 participant*
Electrocardiogram (ECG) parameters	No clinically significant changes

*Associated with rhino/enterovirus infection

Number of Participants with any TEAE (n=3)
Non serious TEAE (n=3)
Any serious TEAE (n=2)
Number of Individual TEAEs (n=10)
Non serious TEAE (n=5)
Any serious TEAE (n=5)*
TEAEs/SAEs considered related to study drug (n=0)

*Infection, common in this patient population

*See also **Poster #3.459** for **first-in-patient** findings in a preterm infant with **refractory status epilepticus** demonstrating elsunersen **tolerability** and **temporal** association with **seizure reduction** following 7 doses*

Conclusions

- **Elsunersen has the potential to be the first disease-modifying treatment for early onset *SCN2A* GoF DEE.**
- **The EMBRAVE trial is intended to identify and confirm a safe and efficacious elsunersen dose for seizure control, with preliminary results from Part 1 demonstrating tolerability and unprecedented efficacy in early onset *SCN2A*-DEE.**
- **Cohort extension planned for 1H2024; Praxis seeking regulatory advice on advancing development.**

EMBRAVE

SCAN ME

ELSUNERSEN

INTRATHECALLY-ADMINISTERED ASO for *SCN2A* GoF DEE

- Significant and sustained seizure reduction at 1mg dose levels
- Unexpected benefits across all treated participants
- Well-tolerated with no drug-related AEs

In November 2023, elsunersen received PRIME Designation from EMA for treatment of SCN2A GoF Developmental Epilepsies

Received Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation from FDA, and ODD from EMA for the treatment of SCN2A-DEE

References

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Acknowledgments We thank the participants and their families, the EMBRAVE Study Team, as well as our collaborators for their contributions to this work.

Funding All studies were funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews in accordance with Good Publication Practice (GPP3).

Disclosures All authors are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

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Presented at:
2023 AES Annual Meeting
December 1-5
Orlando, FL

2023 PAME Conference
November 30
Orlando, FL