Clinical Updates from the Elsunersen Emergency Use Program: A Novel ASO for Treatment of 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 pediatric disorder caused by gain-of-function (GoF) variants in the *SCN2A* gene encoding the voltage-gated sodium channel $Na_v1.2$.
- Patients are at high risk of premature death and present with frequent epileptic seizures, typically beginning within days of birth, and often difficult to control with standard-of-care anti-seizure medications.
- Preclinical evidence suggests selective reduction in *SCN2A* function via human mRNA-targeting antisense oligonucleotides (ASOs) may alter the disease course in patients, with the potential to achieve more widespread seizure freedom, and potentially improve developmental outcomes following disease onset.
- Elsunersen (PRAX-222) is an intrathecally administered ASO in development for early onset GoF SCN2A-DEE, designed to down-regulate $Na_v1.2$ expression, with emerging clinical data highlighting its potential to be disease modifying.

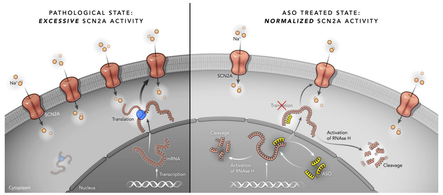
➢ *Here, we provide clinical updates from 4 patients currently receiving elsunersen under an Emergency Use Program.*

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

Elsunersen EAP Summary To Date

- **Robust Therapeutic Impact.** Demonstrates durable seizure reduction, resolution of status epilepticus, and notable quality-of-life improvements across emergency use cases.
- **Strong Safety and Tolerability.** No severe or serious drug-related adverse events; dosing and intrathecal administration consistently well tolerated even after multiple administrations.
- **Promising Potential for Long-Term Benefits.** Early data suggest sustained seizure control and possible neurodevelopmental stabilization with ongoing follow up poised to strengthen these findings.
- **Global Trial Expansion.** First arm initiated in Brazil, with U.S. and European expansion planned for 2025.
- **Pioneering Disease-Modifying Therapy.** Represents a paradigm shift in SCN2A-DEE treatment, offering hope to patients and their families.

Elsunersen First-In-Patient Emergency Use Case: Germany

- Elsunersen has been administered in Germany since March 2023 for treatment of a preterm infant (29+4 weeks gestation) diagnosed prenatally with a pathogenic *SCN2A* variant.
- The patient was in constant, life-threatening *status epilepticus* (SE), with only partial effect of high-dose sodium channel blockers (SCBs).
- Elsunersen treatment commenced at age 6 weeks, with 18 doses administered to date (118.5 mg total).
- Early dosing led to SE cessation and revealed a temporal association with seizure reduction.
- Seizure frequency remains stable with ongoing dosing; maintained after tapering phenytoin at age 14 months, with no worsening of neurodevelopment at age 18 months.

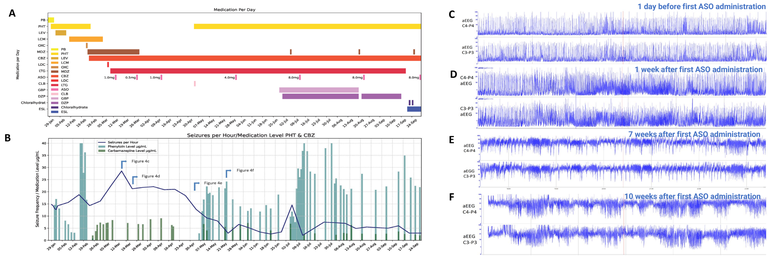


Figure 1. Patient clinical course following introduction of elsunersen treatment regimen and effects on seizures. **A)** Clinical course including high-dose SCBs and introduction of elsunersen dosing regimen. Associated reduction in seizure frequency is shown (*bottom*). **B)** A total of seven elsunersen (intrathecal) doses were administered between 13-Mar-2023 and 29-Sep-2023 (30.5 mg total), with a further 11 doses (8 mg) administered to date (*data not shown*). **C-F)** Corresponding aEEG traces. **C)** Week 7 (1 day before first ASO administration) showing peak seizure frequency (*status epilepticus*). Modulation/reduction of seizure activity (often in close timely relationship to SCB administration) 1, 7 and 10 weeks after first administration of elsunersen (**D-F**, respectively).
NB: seizure exacerbation between July 2nd and 9th was due to urosepsis and concomitant decrease of SCB plasma levels.

Table 1. Elsunersen first-in-patient clinical experience summary of findings

First-in-Patient Summary
• Temporal association of elsunersen intrathecal administration with seizure reduction including cessation of *status epilepticus* in combination with sodium channel blockers
• Seizure reduction was observed as early as 8 days after first administration and further declined after a cumulative dose of 2.5 mg over 5 weeks
• Well-tolerated with no drug-related severe or serious adverse events after a 118.5 mg total cumulative dose of elsunersen across 18 doses
• Hammersmith score <10 at 8 months chronological age resembling severe disability; no further worsening through 18 months of age

Elsunersen Emergency Use Case: Australia

- An 8-year-old patient with GoF *SCN2A*-DEE has been receiving elsunersen in Australia since December 2023, following a history of refractory seizures, global cerebral atrophy, global developmental delay, frequent oculogyric movement, and severe dystonia while awake.
- To date, 13 doses have been administered (38 mg total).
- Since starting elsunersen, ethosuximide has been successfully weaned, with no increase in seizures.
- Significantly fewer clinical and electrographic seizures were noted, with several notable quality-of-life improvements communicated by caregivers and medical personnel.
- No reported drug-related severe or serious AEs following ongoing dosing.

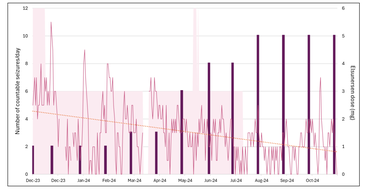


Figure 2. Patient clinical course following elsunersen treatment regimen. Reduction in seizure frequency following the 13 doses from December 2023 to present. Purple bars denote dose administration; red line denotes countable motor seizures per day; light pink shading denotes non-countable seizures (facial twitching), full height denoting seizures present day and night, half height present at night only, and no height denoting absent seizures. Gap denotes missing data.

Caregiver Global Impression of Severity

	Extremely severe	Very severe	Quite severe	Moderately severe	Somewhat severe	A little severe	Not at all severe	Not applicable
Overall		●				●		
Epilepsy		●	●			●		
Development	●			●				
Behaviour				●			●	
Movement disorder*	●	●	●					
Gastrointestinal							●	●
Sleep		●		●		●		

*i.e. dystonia, chorea, etc

● baseline ● after dose 2 ● after dose 11

Caregiver Global Impression of Change (Ratings relative to baseline)

	Very much improved	Much improved	Slightly improved	No change	Slightly worse	Much worse	Very much worse	Not applicable
Overall		●						
Epilepsy		●						
Development			●	●				
Behaviour		●	●					
Movement disorder*			●					
Gastrointestinal		●						●
Sleep	●		●					

*i.e. dystonia, chorea, etc

● after dose 2 ● after dose 11

Figure 3. Caregiver Global Impression of Severity (top) and Change (bottom) scale measures at baseline (severity only), after dose 2 (both scales) and after dose 11 (both scales) of elsunersen. Findings demonstrate caregiver-perceived improvements in, and reduced severity of, overall disease and individual clinical features. Changes were identified early, and greater reduction in severity was reported at the later timepoint.

Elsunersen Emergency Use Cases: United States

- Two *SCN2A*-DEE patients from the completed EMBRAVE study were granted emergency access to continue receiving elsunersen in US.
- Both patients have received seven 1-mg doses since April and March 2024, respectively.
- Both had previously demonstrated marked median reduction in seizures from baseline on top of best available standard of care during EMBRAVE Part 1, as well as an increased number of days without seizures.
- Seizure frequency remains stable with ongoing dosing.
- One patient has been able to discontinue oxygen therapy, while the other is weaning from ketogenic diet.
- Both procedure and dosing continue to be well-tolerated.

References

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