Clinical Updates from the Elsunersen Emergency Use Program: A Novel ASO for Treatment of Early Onset *SCN2A* Developmental and Epileptic Encephalopathy

Matias Wagner[1], Ingo Borggraefe[1], James Wheless[2], Christopher Troedson[3], Katherine Howell[4], William Burns[5], Silvana Frizzo[6], Robert Horton[6], Henry Jacotin[6], Dharit Patel[6], William Motel[6], Brian Spar[6], Steven Petrou[6], Marcio Souza[6]

[1]Ludwig Maximilians University Hospital, Munich, Germany; [2]Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA; [3]The Children's Hospital at Westmead, Sydney, Australia; [4]Department of Neurology, Royal Children's Hospital, Melbourne, Australia; [5]Nationwide Childrens, Columbus Ohio; [6]Praxis Precision Medicines, Boston, MA, USA

Background

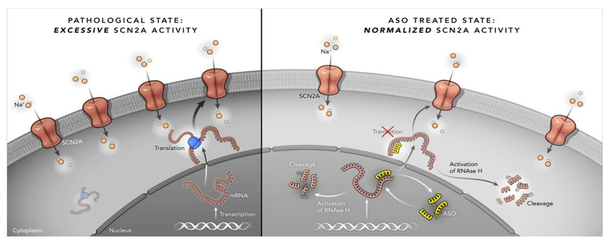
- Early onset *SCN2A* developmental and epileptic encephalopathy (*SCN2A*-DEE) is a rare, severe pediatric disorder caused by gain-of-function (GoF) variants in the *SCN2A* gene encoding the voltage-gated sodium channel $Na_V1.2$.
- Patients are at high risk of premature death and present with frequent 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 is an intrathecally administered ASO in development for early onset *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 5 patients currently receiving elsunersen under the global 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 Early Onset SCN2A GoF DEE

Elsunersen Emergency Use Cases: United States

- A 4-month old *SCN2A*-DEE patient has received 3 1-mg doses since May 2025 after being granted emergency use access to elsunersen at 8 weeks of age.
  - >90% seizure reduction observed since ASO initiation, with both procedure and dosing well-tolerated.
- Two *SCN2A*-DEE patients from the completed EMBRAVE study were granted emergency access to continue receiving elsunersen in US at ages 2 and 3 years, respectively.
  - Both patient have received 16 and 14 1-mg doses since March 2024 and April 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.

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 26 doses administered to date (182.5 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 through age 2 years.
- Two years after ASO commencement, the treatment strategy was adjusted to include adjunctive precision sodium channel modulation via an emergency use provision for relutrigine (0.5 mg/kg daily dose), with the objective of stabilizing excitability and enhancing clinical outcomes.
- As early as three weeks after relutrigine commencement, parents and nursing staff reported moderate-to-significant improvement including fewer, less severe seizures, with no new safety findings.
- As of the most recent evaluation, seizure frequency has decreased to as low as 2 seizures per hour (*see also poster* **P504**), with just one seizure observed during a 2-hour EEG, enabling meaningful parent–child interaction for the first time.
- Continued improvement in clinical status has permitted a previously unattainable reduction in background medications including carbamazepine dosage.

Elsunersen Emergency Use Case: Australia

- A 9-year-old patient with early onset *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, 21 doses have been administered (77 mg total).
- Significantly fewer clinical and electrographic seizures were noted over the course of the first year of treatment.
- Caregiver and medical personnel have reported notable improvements in a number of domains, with benefit for quality-of-life.
- Seizure burden is currently stable, and there have been no dose- or treatment-limiting AEs.

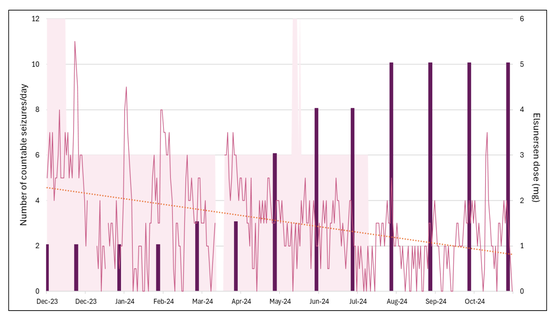


Figure 2. Patient clinical course in the first year following elsunersen treatment regimen. Reduction in seizure frequency following elsunersen commencement. A total of 13 doses were administered between December 2023 and November 2024 (age at first dose, 8 years), with a further 8 doses administered to date (*data not shown*). 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.

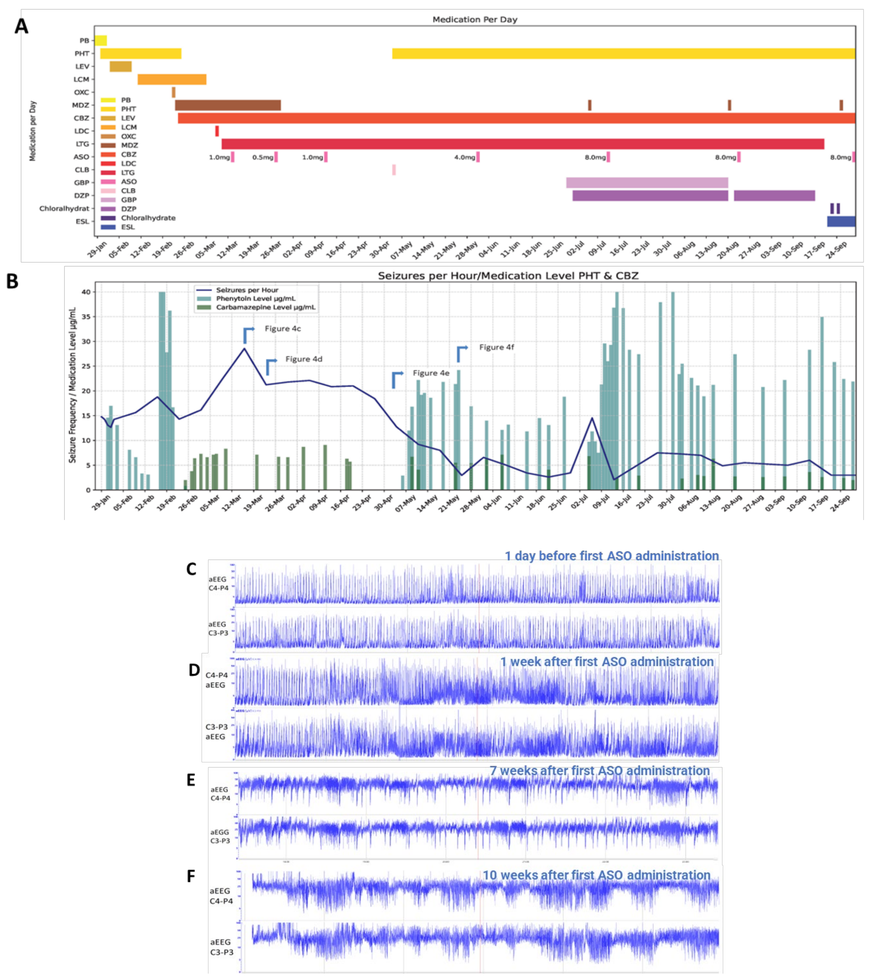


Figure 1. Patient clinical course following introduction of elsunersen treatment regimen and effects on seizures in the first year. **A)** Clinical course including high-dose SCBs and introduction of elsunersen dosing regimen. Associated reduction in seizure frequency is shown (*bottom*). **B)** A total of seven elsunersen (intrathecal) doses were administered between 13-Mar-2023 and 29-Sep-2023 (30.5 mg total), with a further 19 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 (**B**) 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
• Well-tolerated with no drug-related severe or serious adverse events after a 182.5 mg total cumulative dose of elsunersen across 26 doses
• Hammersmith score <10 at 8 months chronological age resembling severe disability; no further worsening through 2 years of age
• Early clinical experience with elsunersen and relutrigine highlights the potential for complementary precision sodium channel modulation for early onset SCN2A DEE (see also **P504**).

Elsunersen EAP Summary To Date

- **Robust Therapeutic Impact.** Elsunersen demonstrates durable seizure reduction, resolution of *status epilepticus*, and meaningful quality-of-life improvements across emergency use cases.
- **Strong Safety and Tolerability.** 80 doses across global EAP. No severe or serious drug-related adverse events; intrathecal dosing consistently well tolerated even with repeated 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.** EMBRAVE Part A ongoing, and global expansion underway via the EMBRAVE3 registrational study.
- **Pioneering Disease-Modifying Therapy.** Elsunersen represents a paradigm shift in early onset *SCN2A*-DEE treatment, offering hope to patients and their families. Its potential may be further enhanced by precision sodium channel modulation to address residual network hyperexcitability.

References

1. Sanders et al. 2018 *Trends Neurosci*
2. Howell et al. 2015 *Neurology*
3. Howell et al. 2018 *Epilepsia*
4. Ware et al. 2019 *Epilepsia Open*
5. Wolff et al. 2017 *Brain*
6. Wolff et al. 2019 *Epilepsia*
7. Scheffer et al. 2017 *Epilepsia*
8. Zeng et al. 2022 *Front Mol Neurosci*
9. Frizzo et al 2024 EEC Meeting
10. Wagner et al 2025 *Nat Med*

Funding Elsunersen and relutrigine made available under an emergency use provision from Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews and George Fahmy in accordance with Good Publication Practice (GPP3).

Disclosures SF, RH, DP, HJ, WM, BS, SP and MS are current or former employees/consultants of Praxis Precision Medicines and may be Praxis shareholders.

@PraxisMedicines
Praxismedicines.com
Praxis Precision Medicines
clinicaltrials@praxismedicines.com

Presented at:
International Epilepsy Congress
30 Aug - 3 Sept 2025
Lisbon, Portugal