A Novel Antisense Oligonucleotide for the Treatment of Early Onset *SCN2A* Developmental and Epileptic Encephalopathy: A First-in-Patient Report in a Preterm Infant with Refractory Status Epilepticus

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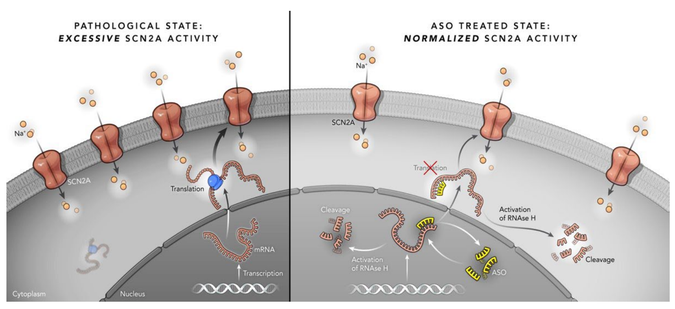
Background

- Early onset *SCN2A* developmental and epileptic encephalopathy (*SCN2A*-DEE) is a rare, severe pediatric disorder caused by gain-of-function (GoF) mutations in the *SCN2A* gene encoding the voltage-gated sodium channel $Na_V1.2$.[1-3]
- High risk of premature death and high burden of epileptic seizures, typically beginning within days of birth and difficult to control with anti-seizure medications (ASMs).[1,4-8]
- Comorbidities include profound global developmental impairment as well as movement disorders, gastrointestinal symptoms, severe irritability, variable sleep problems and frequent hospitalization.[1,9]
- Drug development efforts for early onset *SCN2A*-DEE have been scarce.
- Preclinical findings suggest that gapmer antisense oligonucleotides (ASOs) that down regulate *SCN2A* expression may have potential to alter the disease course in patients.[10]



➢ *Here, we describe the first clinical experience of intrathecally administered elsunersen (PRAX-222), a novel gapmer ASO, in an infant with early onset SCN2A-DEE and refractory status epilepticus (SE).*

Variant Characterization and GoF Confirmation

- Voltage clamp experiments confirmed structural modeling predictions that the p.Ala1329Asp variant interferes with binding of the inactivation motif that would lead to GoF via impaired inactivation and increased persistent current.
- Dynamic action potential clamp (DAPC) experiments, performed to assess the impact of the variant on intrinsic neuronal excitability, showed a large increase in action potential firing across the entire input range and significantly reduced rheobase compared to WT.

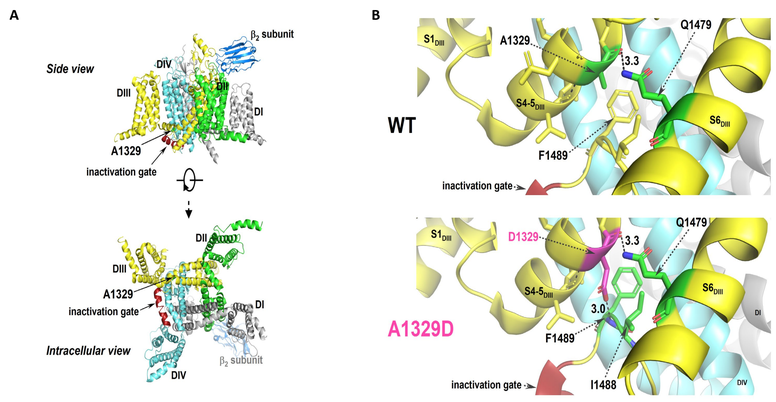


Figure 2. Location of the A1329D Nav1.2 channel mutation. A) Side and intracellular views of the 3D structure of $Na_V1.2$ highlighting the A1329 residue (red stick) in the intracellular linker between transmembrane segments S4 and S5 in domain III (S4-5_{DIII}). Note the color-coded four domains (DI–DIV), the inactivation gate (firebrick red), and the β_2 subunit (blue). **B)** Zoomed-in views of S4-5_{DIII} region, before and after *in silico* mutagenesis (*top*, WT; *bottom*, A1329D). The D1329-F1489 interaction is likely to affect the binding of the IFM inactivation motif to its receptor pocket, resulting in delayed inactivation and persistent current.

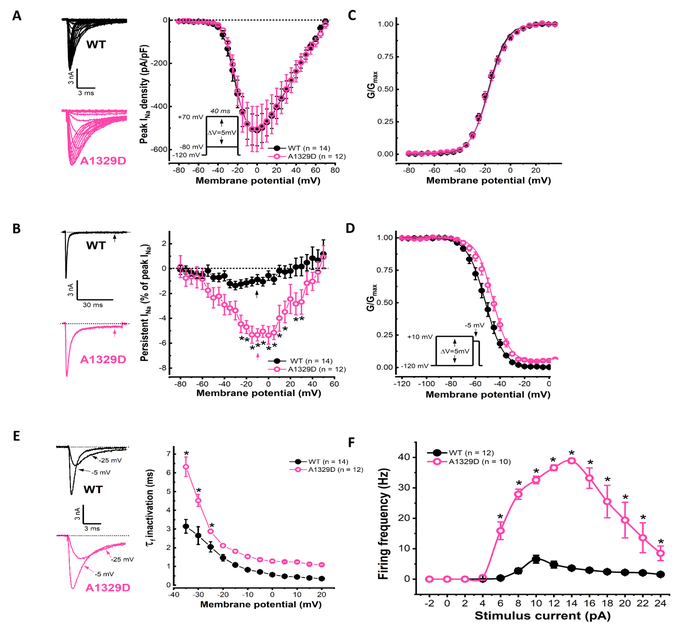


Figure 3. Biophysical characteristics of the A1329D variant and its impact on neuronal excitability relative to WT. A) Sodium current (I_{Na}) density-voltage relationships (*inset* voltage protocol). *Left*: Representative I_{Na} traces. **B)** Persistent inward I_{Na}-voltage relationships. *Left*: representative I_{Na} traces elicited by -10 mV depolarizations. **C** and **D)** Voltage dependence of activation and inactivation, respectively. **E)** Dependence of the time course of I_{Na} inactivation on the membrane potential. Left: Representative WT and A1329D I_{Na} traces elicited by −25 and −5 mV voltages. **F)** Input-output relationships for WT and A1329D variant. Data presented as mean ± SEM; *P<0.05 vs. WT.

Methods

Patient Case Presentation and Eligibility for *SCN2A* ASO (Elsunersen)

- A preterm infant (29+4 weeks gestation; birthweight 1400g) was diagnosed prenatally (exome sequencing) with the pathogenic *SCN2A* variant c.3986C>A p.Ala1329Asp (p.A1329D).
- Infant presented with *status epilepticus* (SE, **Fig. 1**) and a history of intrauterine seizures and arthrogryposis.
- Anti-seizure treatment with phenobarbital did not reveal any improvement. High-dose treatment with sodium channel blockers (SCB) including phenytoin revealed significant seizure reduction (**Fig. 1B**); however, seizure reduction was not sustainable even with potentially toxic levels (>40µg/ml, **Fig. 4B**) of phenytoin.
- Eligibility for elsunersen treatment was evaluated using *in silico* protein structural modeling and *in vitro* electrophysiology studies[9-12] to ascertain *SCN2A* GoF status and inform dosing strategies.
- Ongoing safety assessments included ECG, vitals, blood exam, clinical exam, CSF monitoring, cranial ultrasound and MRI.
- Written informed consent of both parents was obtained prior to ASO administration.

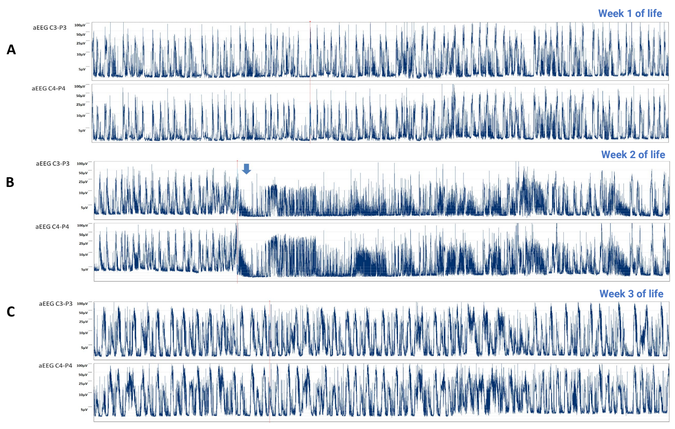


Figure 1. Patient clinical course in the first 3 weeks of life. A) Representative aEEG trace (all aEEG traces shown on this poster comprise 6h of recording) showing a typical sawtooth pattern resembling EEG-status in week 1 of life. **B)** Seizure reduction after several loading doses of phenytoin (arrow) in week 3 of life. **C)** Seizure reduction was not sustainable as status pattern reoccurred even with phenytoin levels >40µg/ml. Seizures were subclinical or motor seizures.

First-in-Patient Results Demonstrate Elsunersen Safety and Temporal Association with Seizure Reduction

- Following confirmation of GoF status, treatment with elsunersen initiated when patient was 1 month and 2 weeks old, with 15 doses administered to date (**Fig. 4**).
- Elsunersen treatment (intrathecal dosing) in combination with best standard-of-care ASMs (mainly SCBs) was well-tolerated with no drug-related severe or serious adverse events following a 94.5 mg cumulative dose across 15 doses.
- Eight days after first administration, SE was interrupted intermittently and ultimately ceased following continued dosing
- A >50% reduction in seizure frequency was observed during follow-up, with seizure symptoms being markedly attenuated.
- Longer term follow up from age 9 to 18 months demonstrated stable seizure frequency at ≤5 seizures/hour, maintained after tapering phenytoin at age 14 months.
- Despite some neurodevelopmental progress (i.e. patient switched from nasogastric tube to bottle feeding), neurodevelopment was severely affected at 8 months chronological age; with no further worsening through 18 months of age.

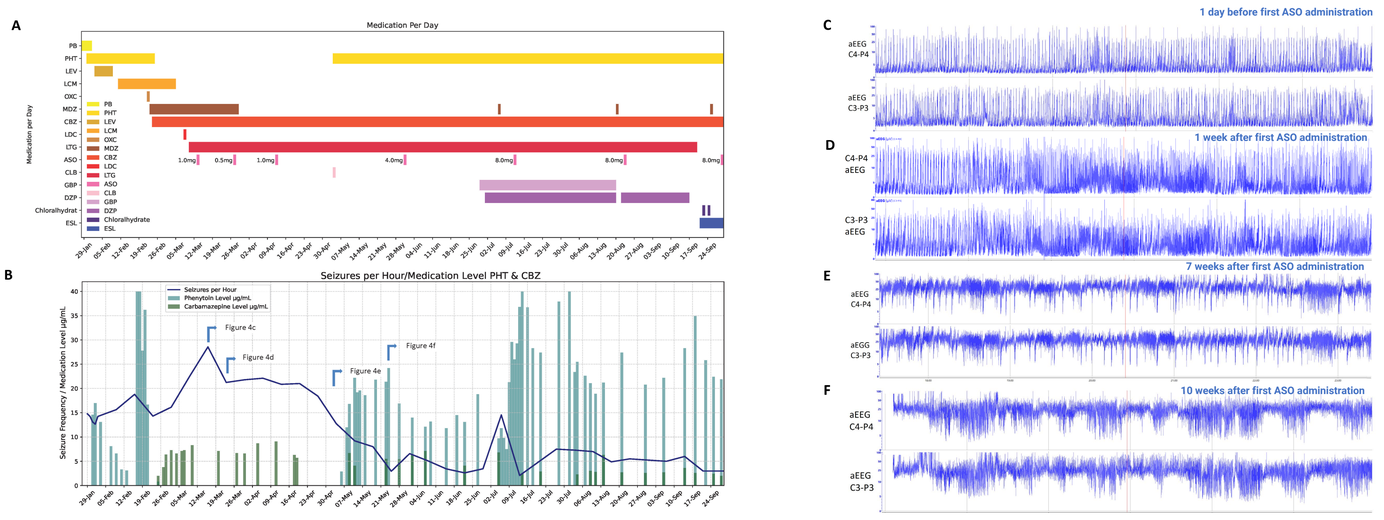


Figure 4. Patient clinical course following introduction of elsunersen treatment regimen and effects on seizures. **A)** Clinical course including high-dose SCBs and introduction of elsunersen dosing regimen. Associated reduction in seizure frequency is shown (*bottom*). **B)** A total of seven elsunersen (intrathecal) doses were administered between 13-Mar-2023 and 29-Sep-2023 (30.5 mg total), with a further 8 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 early 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 94.5 mg total cumulative dose of elsunersen across 15 doses
• Hammersmith score <10 at 8 months chronological age resembling severe disability; no further worsening through 18 months of age

Conclusions

- First-in-patient findings highlight the potential for elsunersen to be the first disease-modifying treatment for early onset GoF SCN2A-DEE.
- Early clinical experience in combination with SCBs indicates safety and a temporal association with seizure reduction, including cessation of previous refractory SE.
- We hypothesize that severe neurodevelopmental outcome in this case is related to disease severity and an extrapolated seizure load of about 60 seizures in 8 months.
- Ongoing follow up will determine long-term effects of repeated administration of elsunersen on seizure frequency and intensity, and associated comorbidities.
- Elsunersen is currently being evaluated in the EMBRAVE study (NCT05737784) with promising findings from the first four patients in the U.S. demonstrating no adverse events and unprecedented efficacy in early onset *SCN2A*-DEE.

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