Poster #286

Study Design and Rationale of the ASCEND Study in Patients With Dravet Syndrome

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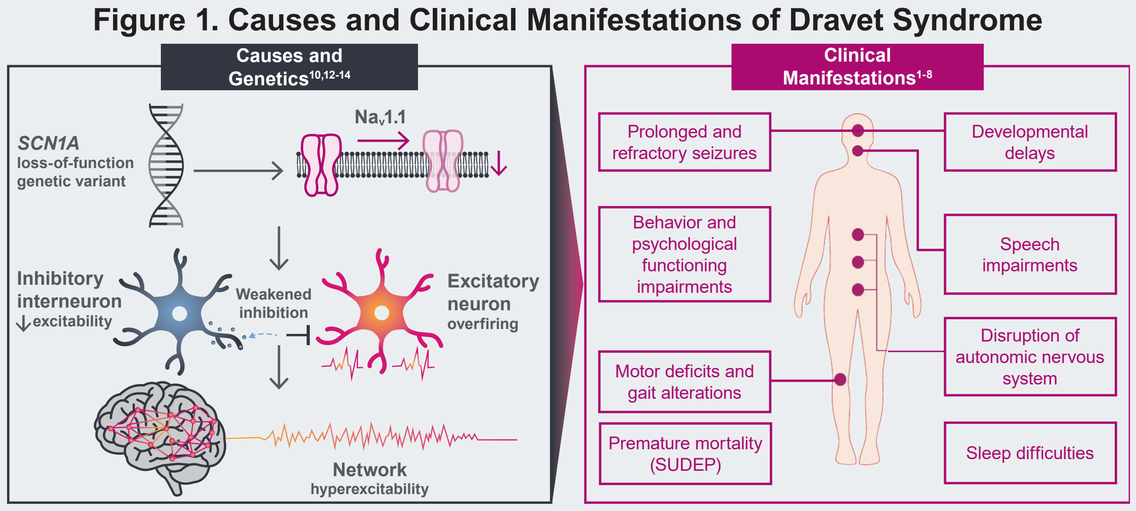
Conclusions

- The novel chemistry of ION337 is designed to enhance antisense oligonucleotide performance, potentially enabling sustained voltage-gated sodium channel α-subunit type 1 ($Na_V1.1$) restoration with infrequent dosing and without the need for a loading dose
- The ASCEND study will evaluate the safety and tolerability of ION337, as well as its pharmacokinetics, pharmacodynamics, and effects on seizure frequency in patients with Dravet syndrome (DS)
- Additional exploratory endpoints will assess the impact of ION337 on broader DS comorbidities to inform future development
- Study enrollment is ongoing in 2026

Introduction

- DS is a rare and severe developmental epileptic encephalopathy (**Figure 1**)[1,2]
  - Seizures in individuals with DS typically begin within the first year of life[1,3]
  - Although seizures may lessen in severity and frequency with age,[3,4] they remain highly refractory to treatment into adolescence and adulthood in most affected individuals, with a risk of premature death (including Sudden Unexpected Death in Epilepsy [SUDEP], status epilepticus, and seizure-related accidents)[1,3]
  - Almost all individuals with DS also develop cognitive, motor, and behavioral impairments, which can significantly impact daily functioning and quality of life[1,5-8]
- More than 85% of individuals with DS harbor genetic variants of the sodium voltage-gated channel alpha subunit 1 gene (*SCN1A*), most of which are loss-of-function (LoF) variants[6,9-11]
  - *SCN1A* encodes $Na_V1.1$, a critical ion channel that is highly expressed in the brain and required for the regulation of the excitability of inhibitory neurons[12]
  - LoF variants in one copy of the *SCN1A* gene result in haploinsufficiency with inadequate levels of $Na_V1.1$ function[10,13]
    - In murine models, $Na_V1.1$ deletion or haploinsufficiency decreases the excitability of inhibitory interneurons, leading to overexcitation of excitatory neurons and widespread neurologic symptoms consistent with DS[12,14]

Figure 1. Causes and Clinical Manifestations of Dravet Syndrome



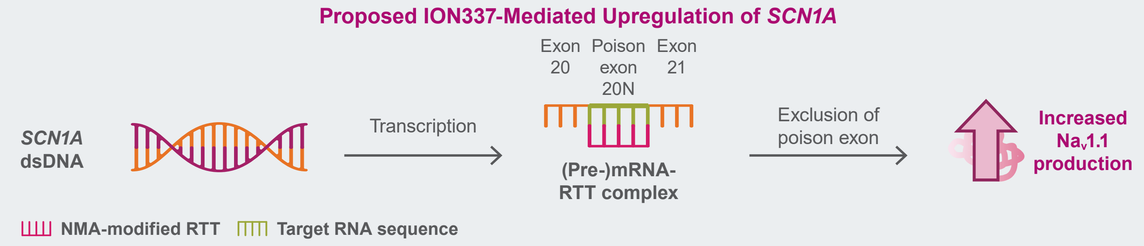
$Na_V1.1$, voltage-gated sodium channel α-subunit type 1; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene; SUDEP, Sudden Unexpected Death in Epilepsy.

- While current antiseizure medications (ASMs) may reduce seizures, they do not address the underlying *SCN1A*-related pathobiology and have limited impact on the broader developmental and behavioral burden of DS[1,15]
- Genetic and mechanism-targeted therapies are in development, yet a significant unmet need remains for a safe treatment that addresses the root cause of the disease and provides sustained seizure control along with improvements in cognition and quality of life while requiring infrequent dosing[1,15]

ION337

- ION337 is a novel splice-switching antisense oligonucleotide that incorporates next-generation chemical modifications including[16]
  - NMA (2'-O-[2-(methylamino)-2-oxoethyl]) modifications of the ribose sugar leading to 3- to 4-fold greater potency compared with MOE (2′-O-methoxyethyl)[16,17]
  - An MsPA (mesyl phosphoramidate) linkage enabling a long duration of action (**Figure 2**)[18]
- ION337 is designed to durably and robustly increase *SCN1A* mRNA levels and consequently $Na_V1.1$ protein expression (**Figure 2**)[17,19]

Figure 2. Mechanism of ION337 for the Treatment of Dravet Syndrome



dsDNA, double-stranded DNA; mRNA, messenger RNA; $Na_V1.1$, voltage-gated sodium channel α-subunit type 1; NMA, 2'-O-(2-[methylamino]-2-oxoethyl); RTT, RNA-targeted therapy; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene.

- ION337 binds the poison exon 20N in *SCN1A* pre-mRNA and promotes its exclusion during splicing. This reduces nonsense-mediated decay and increases production of full-length *SCN1A* mRNA[17]
  - ION337 resulted in specific, potent, and durable upregulation of productively spliced *SCN1A* transcripts *in vivo*, supporting a mechanistically targeted approach to restoring $Na_V1.1$ function[17]

Objective

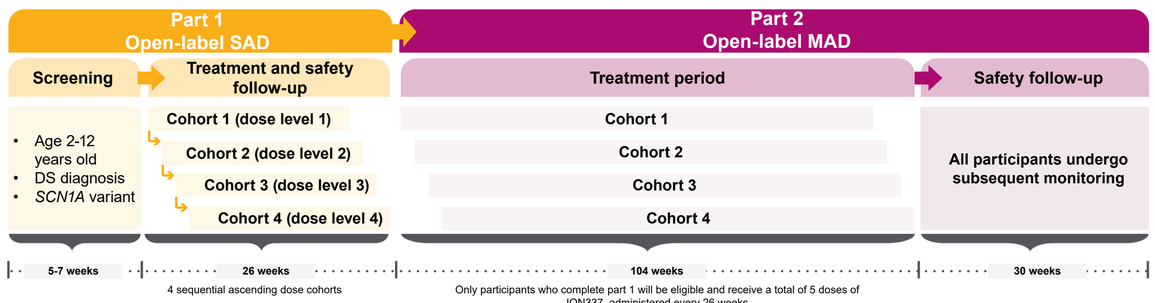
- Here we describe the design and rationale for ASCEND (NCT07531745), a first-in-patient study evaluating ION337 as a potential disease-modifying therapy for individuals with DS[20]

Methods

Study Design

- ASCEND is a phase 1–2 open-label, single ascending dose (SAD) and multiple ascending dose (MAD) study in children living with DS with pathogenic or likely pathogenic *SCN1A* variants
- The primary objective of the study is to evaluate ION337 safety and tolerability; secondary objectives focus on ION337 clinical pharmacology and antiseizure activity
- The study consists of 2 parts (**Figure 3**)
  - Part 1 (SAD): screening period (5–7 weeks) and treatment and follow-up period (26 weeks)
  - Part 2 (MAD): treatment period (104 weeks) with dosing every 26 weeks and safety follow-up period (30 weeks)

Figure 3. ASCEND Study Design Overview



The study design figure reflects the conceptual sequence of progression between cohorts rather than the precise timing at which these events occur. The orange arrows represent the review of safety and pharmacokinetics data by an independent DSMB to gate entry into the subsequent cohort.
DS, Dravet syndrome; DSMB, data and safety monitoring board; MAD, multiple ascending dose; SAD, single ascending dose; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene.

Participants

- Key eligibility criteria include being 2 to 12 years of age, with a formal diagnosis of DS and a confirmed pathogenic or likely pathogenic *SCN1A* variant (**Table 1**)

Table 1. Key Inclusion and Exclusion Criteria

Key inclusion criteria	• ≥2 to ≤12 years of age at the time of informed consent • At least 1 parent or caregiver ≥18 years of age who is willing and able to provide informed consent (signed and dated) and attend all scheduled study visits • Documented diagnosis of DS according to the ILAE criteria and as agreed by the ESCI • Confirmed pathogenic or likely pathogenic *SCN1A* variant • Currently receiving ≥1 concomitant ASM at a stable dose/regimen for ≥4 weeks prior to informed consent • All other interventions for epilepsy (including ketogenic diet or VNS), as well as any other concomitant medications including medications for behavioral management, sleep, and supplements or nutritional support, have been stable for ≥4 weeks prior to informed consent; VNS implantation must have occurred ≥6 months prior to informed consent • Experiences the required number of MMS during the screening period
Key exclusion criteria	• Known brain or spinal disease that would interfere with the LP procedure or CSF circulation, or presence of other factors that would affect the safety of the LP procedure • Pathogenic or likely pathogenic variant in another gene that causes epilepsy • Prior treatment with or current enrollment in an interventional clinical trial for a gene therapy or for another ASO for the treatment of DS • Prior treatment with or current enrollment in an interventional clinical trial of any other investigational drug, biological agent, or device within 30 days prior to screening, or 5 half-lives of investigational agent, whichever is longer • Current treatment with an ASM acting primarily as a sodium channel blocker, as maintenance treatment • Prior brain surgeries including corpus callosotomy, implantation of device for deep brain stimulation, or any other palliative brain surgery intended to reduce seizure burden

ASM, antiseizure medication; ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; DS, Dravet syndrome; ESCI, Epilepsy Study Consortium, Inc.; ILAE, International League Against Epilepsy; LP, lumbar puncture; MMS, major motor seizures; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene; VNS, vagus nerve stimulator.

Treatment

- In part 1 (SAD), 32 participants will be assigned to 1 of 4 sequential ascending dose cohorts, each receiving a single intrathecal bolus injection of ION337 on day 1
- During part 2 (MAD), each participant in all cohorts will receive a total of 5 doses of ION337, administered every 26 weeks

Endpoints

- The primary endpoint is safety and tolerability of ION337; secondary endpoints include pharmacokinetics and percent change from baseline in 28-day normalized major motor seizure (MMS) frequency (**Table 2**)

Table 2. Primary and Secondary Endpoints of ASCEND

Primary endpoints (by study part)	• Incidence of TEAEs and SAEs • Clinically significant changes from baseline in safety laboratory values, vital signs, and ECGs • Physical/neurological exam measures • C-SSRS
Secondary endpoints	• Predose ION337 trough concentration in CSF and plasma for all doses in part 1/SAD and part 2/MAD • Postdose C_{max}, AUC, and $t_{½}$ λ_z from plasma in part 1/SAD • Postdose C_{max}, AUC, and $t_{½}$ λ_z from plasma in part 2/MAD – first dose only • Percent change from baseline in 28-day normalized MMS frequency in part 1/SAD and part 2/MAD

AUC, area under the curve; C_{max}, maximum concentration; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; MAD, multiple ascending dose; MMS, major motor seizure; SAD, single ascending dose; SAE, serious adverse event; $t_{½}$ λ_z, elimination half-life; TEAE, treatment-emergent adverse event.

- Key exploratory endpoints include seizure freedom and MMS response rate over the treatment periods
- Other exploratory endpoints include meaningful patient- and caregiver-relevant outcomes, including functional and neurodevelopmental measures

Acknowledgments

We thank the Dravet Syndrome Foundation and members of the Dravet syndrome community for their support in guiding in the design of this trial. We also sincerely thank the study participants and their families, as well as the investigators, study coordinators, site staff, and principal investigators at participating study centers for their contributions to this study. The ASCEND study is funded by Ionis Pharmaceuticals, Inc. Medical writing and editorial assistance were provided by Elisabetta Lauretti, PhD, of Red Nucleus, and funded by Ionis Pharmaceuticals, Inc.

Disclosures

TSk, SK, VM, AY, and **CC** are employees and stockholders of Ionis. **DD** has received research support from The Epilepsy Study Consortium. **KK** has received research funds from Longboard/Lundbeck, Stoke, and UCB; has received consulting funds from Encoded Therapeutics, Stoke, The Epilepsy Study Consortium, and UCB and is part of a data and safety monitoring board for Harmony. **EM** has been a site PI for the study and has a service contract with Ionis. **SO** has nothing to disclose. **TSa** received grant funding from Ionis.

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