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2734 17 Avenue SW,
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+15878858911
editorial-office@sciformat.ca

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ANTISENSE OLIGONUCLEOTIDE THERAPY FOR DRAVET SYNDROME: A CRITICAL REVIEW OF THE EVIDENCE FOR DISEASE MODIFICATION WITH ZOREVUNERSEN

Oliwia Żmuda (Corresponding Author, Email: o.zmuda.21@gmail.com)

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0005-0415-786X

Anna Halot

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0004-7349-4651

Patrycja Walo

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0008-1515-0331

Natalia Skórka

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0008-7336-9569

Magdalena Tatara

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0007-3283-6389

Karolina Skórka

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0003-1523-925X

Klaudia Wydra

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0004-9085-8920

Jakub Jakubiec

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0009-7201-6056

Michał Szubartowski

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0005-5322-319X

Adam Szymczyk

Medical University of Lublin, Lublin, Poland

ORCID ID: 0009-0006-0244-9452

ABSTRACT

Dravet syndrome is a severe developmental and epileptic encephalopathy caused primarily by SCN1A haploinsufficiency, and no approved disease-modifying therapy addresses its underlying channelopathy. Zorevunersen, an intrathecal splice-modulating antisense oligonucleotide, is designed to increase NaV1.1 expression. This critical narrative review appraises the available human evidence for disease modification using explicit operational criteria and a documented, provenance-based search. The peer-reviewed evidence base centers on two open-label phases 1–2a studies (MONARCH and ADMIRAL; n=81) and their open-label extensions (SWALLOWTAIL and LONGWING; n=75; data cut May 30, 2025). In descriptive analyses, median convulsive-seizure reductions ranged from –58.8% to –90.9% across one-month intervals through Month 20 in the 70-mg subgroup, and at Month 36 both clinicians and caregivers rated 94.7% of patients with available assessments as at least minimally improved; least-squares mean Vineland-3 raw-score changes were 7.56 (expressive) and 6.06 (receptive). Dose-group comparisons were post hoc; confidence intervals were not adjusted for multiplicity, and late extension outcomes were based on available data without a concurrent control. We conclude that current human evidence supports a hypothesis of disease modification but does not establish it, and we delineate what the randomized, sham-controlled EMPEROR trial can and cannot confirm, with implications for patients, clinicians, and the communication of preliminary results.

KEYWORDS

Dravet Syndrome, SCN1A, Antisense Oligonucleotide, Zorevunersen, Disease Modification

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1. Introduction

Dravet syndrome is one of the most severe developmental and epileptic encephalopathies of childhood. It typically presents in the first year of life with prolonged febrile seizures and evolves into a lifelong disorder characterized by multiple seizure types, developmental slowing, cognitive and behavioral impairment, motor dysfunction, and an elevated risk of sudden unexpected death in epilepsy (SUDEP) [5,33]. Population-based estimates place the incidence of Dravet syndrome at approximately 1 in 15,700 births in the United States, with SCN1A-associated Dravet syndrome accounting for roughly 1 in 20,900 births [34]. Mortality is elevated across the lifespan, and SUDEP is a principal contributor, with the risk exceeding that of the general epilepsy population [7,27]. Most cases are caused by pathogenic variants in one copy of the SCN1A gene, which encodes the $\alpha 1$ subunit of the voltage-gated sodium channel NaV1.1 [5,33]. In the predominant loss-of-function form of Dravet syndrome, reduced functional NaV1.1 results in haploinsufficiency [33]. The channel is highly expressed in GABAergic inhibitory interneurons, and reduced NaV1.1 current impairs inhibitory network function, producing cortical hyperexcitability and seizures [35,18,3]. The clinical consequences extend well beyond seizures: severe communication delays can persist independently of seizure burden, and neurodevelopmental trajectories show marked slowing relative to typically developing peers [19,24]. Genotype scope matters for therapy development: therapies that augment expression of the wild-type allele presuppose a loss-of-function or haploinsufficiency mechanism, and gain-of-function SCN1A variants which may behave differently are excluded from zorevunersen eligibility in the phase 3 program [2,31].

The burden of Dravet syndrome on patients, families, and health systems is considerable [23]. Patients commonly require multiple antiseizure medications (ASMs); in the phase 1–2a program evaluated here, more than 80% of participants were taking three or more ASMs at baseline [15]. The approved ASM portfolio for Dravet syndrome stiripentol, cannabidiol, and fenfluramine has demonstrated seizure-frequency reductions in randomized, placebo-controlled trials [4,9,14]. Despite polypharmacy, seizures remain in refractory in many patients, and no approved ASM has established disease modification of the developmental trajectory [33,23]. Caregivers consistently rank non-seizure outcomes of communication, behavior, and daily living skills among

the most important treatment targets [32,13]. This mismatch between seizure-focused therapy and family priorities is a central clinical rationale for disease-modifying approaches in Dravet syndrome [8].

Zorevunersen (formerly STK-001) is an investigational antisense oligonucleotide (ASO) administered by intrathecal injection. It is designed to increase NaV1.1 expression from the unaffected allele by preventing the inclusion of a non-productive "poison exon" in SCN1A pre-mRNA, thereby increasing productive transcript and protein output [16,2]. This mechanism Targeted Augmentation of Nuclear Gene Output (TANGO) was selected because most Dravet-associated SCN1A variants cause loss of function, making upregulation of the wild-type allele a mechanistically coherent strategy for haploinsufficiency-associated disease [12,33]. In a mouse model of Dravet syndrome, the same approach increased Scn1a expression and reduced seizures and SUDEP incidence, providing the preclinical rationale for clinical development [12].

In March 2026, results of the phase 1–2a studies MONARCH and ADMIRAL and interim results of the open-label extensions SWALLOWTAIL and LONGWING were published in the New England Journal of Medicine [15], and the program is now being evaluated in EMPEROR, a randomized, sham-controlled phase 3 trial (NCT06872125) [31]. Sponsor communications framed the publication as the first data to demonstrate the potential for disease modification in Dravet syndrome [21]. This framing is consequential. "Disease modification" is a claim with regulatory, therapeutic, and communicative weight: it implies that treatment alters the underlying disease process rather than suppressing symptoms, and it shapes expectations of patients, families, payers, and regulators [8].

This review therefore asks a deliberately narrow question: to what extent does the available human evidence support zorevunersen as a disease-modifying therapy rather than an antiseizure therapy with additional exploratory functional signals, when judged against explicit efficacy, developmental, durability, safety, and risk-of-bias criteria? In answering it, the review applies an explicit evidence-provenance framework, an operational definition of disease modification, and a critical appraisal of the primary publication. It also situates the question within the broader technology-and-society debate: how novel RNA-based precision therapies are evaluated, how preliminary clinical signals are communicated, and what standards should govern claims made to families and the public.

2. Methods

2.1 Review approach

We conducted a critical narrative review with a documented search and a source-provenance framework, using the Scale for the Assessment of Narrative Review Articles (SANRA) as an internal quality checklist [1]. SANRA evaluates six attributes: an explanation of why the review was undertaken, a statement of the question or objectives, a description of the literature search, referencing standards, scientific reasoning in the discussion, and appropriate presentation of data. SANRA was applied during drafting. The approach was chosen because the research question concerns the interpretation of a single clinical program within a broader literature, rather than the aggregation of multiple controlled trials; a systematic review or meta-analysis was not intended, and no such process is claimed.

2.2 Search strategy

We searched PubMed/MEDLINE, ClinicalTrials.gov, the ISRCTN registry, the EU Clinical Trials Register, and open-access institutional repositories (including the University of Glasgow eprints), supplemented by hand-searching of reference lists. Search strings combined the following concepts: "zorevunersen OR STK-001"; "SCN1A AND (antisense oligonucleotide OR ASO OR splice-switching OR poison exon)"; "Dravet syndrome AND (disease modification OR disease-modifying OR antisense OR gene therapy OR ETX101)"; "nusinersen AND cerebrospinal fluid"; "tofersen OR Qalsody AND SOD1"; "Dravet syndrome AND (natural history OR BUTTERFLY OR ENVISION)". Embase and Cochrane Library were not accessible during preparation; this limitation is stated transparently rather than concealed. Bibliographic, registry, regulatory, conference, and sponsor records cited in the manuscript were rechecked on August 23, 2026.

2.3 Evidence provenance and source hierarchy

Clinical evidence sources were classified as peer-reviewed (PR), registry (REG), conference abstract or presentation (ABS), sponsor-reported (SP), or regulatory (REGULATORY). Multiple reports of the same dataset of journal articles, conference materials, and press releases were treated as reports of one clinical program rather than independent confirmations. Sponsor communications were used for operational facts, framing, and clearly labeled post-publication updates, but not as independent confirmation of clinical efficacy. The primary peer-reviewed source is Laux et al. [15], checked against the peer-reviewed full text. Press releases and conference materials superseded by the primary publication were not treated as independent confirmations. For each outcome domain, we recorded study identifiers, dose group, analysis set and denominator, timepoint, result with uncertainty, analytic method, and provenance; where a denominator was not published, it was recorded as unavailable rather than estimated.

2.4 Operational criteria for disease modification

Because no accepted disease-modification definition exists for Dravet syndrome, we used five operational criteria, adapted from the disease-modification concept literature and from the registered endpoints of the EMPEROR trial [8,31]:

1. **Efficacy beyond seizure control:** improvement in a developmental or functional domain (e.g., Vineland-3 subdomains, global impression measures) that is not explained solely by seizure reduction;
2. **Durability against natural history:** maintenance or continued gain with uniform maintenance dosing, benchmarked against prospective natural-history data;
3. **Mechanistic coherence and target engagement:** human evidence of target engagement consistent with NaV1.1 upregulation;
4. **Acceptable long-term safety:** a safety profile consistent with chronic intrathecal administration;
5. **Level of evidence:** confirmation in a randomized, controlled setting, or the absence of plausible confounding sufficient to preclude earlier confirmation.

A therapy is judged to meet the disease-modification standard for the purposes of this review only if criteria 1–4 are supported by evidence and criterion 5 is satisfied, or the evidence cannot otherwise be adjudicated.

2.5 Assessment structure

For each outcome domain (seizures; global impression; adaptive behavior; safety), we report the published result with its sample, timepoint, denominator when available, analytic method, and provenance, and we assess it against the operational criteria and known sources of bias, including open-label design, missing data, post hoc subgroup emphasis, and uncorrected multiplicity.

3. Results

3.1 The clinical program and participant flow

MONARCH (United States) and ADMIRAL (United Kingdom) were open-label, multicenter, phase 1–2a studies enrolling children and adolescents aged 2 to <18 years with Dravet syndrome. Eligibility required an established diagnosis confirmed by an external expert consortium, a pathogenic, likely pathogenic, or uncertain-significance SCN1A variant, at least four convulsive seizures during an initial 28-day observation period despite prior use of at least two ASMs and at least one concomitant ASM [15]. MONARCH included single ascending doses of 10–70 mg and multiple ascending doses of 20–45 mg (Days 1, 29, and 57); ADMIRAL included multiple ascending-dose cohorts of 30, 45, and 70 mg (Days 1, 57, and 85), with six patients in the 70-mg cohort receiving only two doses (Days 1 and 57). The primary objectives were safety, plasma pharmacokinetics (PK), and cerebrospinal fluid (CSF) exposure; clinical efficacy endpoints were secondary or exploratory [15].

Eighty-one patients received at least one dose (MONARCH 62; ADMIRAL 19), and 80 completed phase 1–2a studies (MONARCH 61; ADMIRAL 19). Of these completers, 58 of 61 (95.1%) from MONARCH and 17 of 19 (89.5%) from ADMIRAL rolled over to the open-label extension studies SWALLOWTAIL and LONGWING, in which three initial doses were administered (Day 1, Month 4, Month 8) followed by 45 mg every 4 months. As of the May 30, 2025, data cut, all extension patients received 45 mg, and 58 of 75 (45 of 59 in SWALLOWTAIL; 13 of 16 in LONGWING) remained enrolled. For the overall OLE Vineland-3

analysis, 74 patients contributed OLE-baseline data; the MMRM analyses used available data without imputation. Global-impression proportions were reported among participants with available assessments. Because follow-up duration varied and some participants discontinued, late OLE estimates should not be interpreted as if all baseline participants had reached Month 36 [15].

Pharmacokinetic data document systemic and CSF exposure but do not constitute direct pharmacodynamic evidence of NaV1.1 target engagement in humans. In the phase 1–2a studies, plasma zorevunersen concentrations generally increased proportionally with dose, and zorevunersen was detected in CSF up to 6 months after the last dose in all cohorts; in the multiple-dose cohorts, CSF concentrations increased 3 months after the last dose, suggesting accumulation in CSF. In the extensions, no apparent plasma accumulation was observed across dose levels with every-4-months dosing, whereas mean trough CSF concentrations generally increased with successive dosing over the first year before approaching steady state [15]. These findings show sustained CSF exposure compatible with central nervous system delivery, while the relationship between exposure, NaV1.1 upregulation, and clinical outcomes remains unquantified in humans.

3.2 Seizure outcomes

Seizure data were analyzed descriptively: no formal sample-size calculation or hypothesis testing was performed, and confidence intervals (CIs) were not adjusted for multiplicity; the publication states that CIs "should not be used to infer treatment effects" [15]. The baseline median convulsive-seizure frequency in the 77 clinically evaluable patients was 17.0 (range 4.0–2335.4) per 28 days [15].

In phase 1–2a studies, median reductions from baseline at 3 and 6 months after the last dose were 42.81% and 57.30% after a single 70-mg dose, and 84.80% and 73.61% after two or three 70-mg doses. In the extensions, median reductions from phase 1–2a baseline ranged from 6.94% to 77.38% across one-month intervals through Month 36 in patients initially treated with doses below 70 mg, and from 58.82% to 90.91% across one-month intervals through Month 20 in patients who received one or more 70-mg doses. The phase 1–2a primary seizure analysis excluded intervals following ASM modification; sensitivity analyses including all data were consistent, and no exclusions for ASM modification were made in the extensions [15].

Three features constrain the interpretation of these findings. First, the widely cited range 58.82%–90.91% is a range of interval medians in a selected dose subgroup, not a pooled program-wide effect estimate; participant availability varied across later intervals. Second, the publication states explicitly that comparisons between dose groups were post hoc and that the study design did not support formal statistical comparisons among dose groups. Third, CIs reported for these medians were unadjusted for multiplicity and carry no confirmatory inferential weight [15]. On the operational criteria applied here, the seizure data support an antiseizure signal of uncertain magnitude and durability, and they cannot by themselves support a disease-modification claim.

3.3 Overall clinical status and quality of life (CGI-C and CaGI-C)

Clinicians and caregivers rated overall change on the Clinical Global Impression of Change (CGI-C) and Caregiver Global Impression of Change (CaGI-C), seven-point scales ranging from "very much improved" to "very much worse." At 6 months after the last phase 1–2a dose, clinicians and caregivers rated 84.2% and 94.8%, respectively, of patients who had received one or more 70-mg doses as at least minimally improved. At Month 36 of the extensions, both clinicians and caregivers rated 94.7% of participants with available assessments as at least minimally improved relative to OLE baseline. Quality-of-life measures (EQ-5D-Y/EQ-VAS) were consistent with these signals [15].

These proportions warrant four cautionary notes. First, they come from unblinded assessments in an open-label program and are susceptible to caregiver and clinician's expectation bias; the authors acknowledge this susceptibility for Vineland-3 and quality-of-life measures. Second, denominators for these proportions are not stated in the article text, and the values are reporting proportions rather than controlled effect estimates with uncertainty. Third, the emphasized 70-mg subgroup comparisons are post hoc per publication. Fourth, the Month-36 value (94.7% for both raters) must not be conflated with the 6-month post-dose 70-mg values (84.2% clinician; 94.8% caregiver); the two figures describe different timepoints and analytic groups [15].

3.4 Adaptive behavior (Vineland-3)

Adaptive behavior was an exploratory outcome measured with the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) [20] in ADMIRAL, and the extensions. Analyses used mixed-effects models for repeated measures (MMRM) adjusting baseline prognostic covariates; missing data were not imputed. Three subdomains with substantial floor effects (Written, Domestic, Community) were excluded from primary modeling; at OLE baseline, 26 of 71 (36.6%), 49 of 71 (69.0%), and 48 of 71 (67.6%) of patients scored at or below floor in these subdomains, respectively [15].

In the ADMIRAL cohort (n=17–18 at screening), least-squares (LS) mean changes from ADMIRAL baseline were 3.29 (expressive communication) and 5.21 (receptive communication) at Month 9, and 6.55 and 10.00 by Month 17 of LONGWING. In the overall OLE analysis (n=74 at OLE baseline), LS mean changes from OLE baseline at Month 36 were 7.56 (expressive) and 6.06 (receptive). Reported CIs were not adjusted for multiplicity [15]. Two interpretative safeguards apply. First, raw-score changes are not age-normalized developmental gains; they cannot be read as restoration to typical function, particularly given the floor effects documented in several subdomains. Second, no validated Dravet-specific minimal clinically important difference has been established. A qualitative study found that improvements of 1–3 raw-score points across subdomains were considered meaningful by at least half of caregivers, with clinical-expert feedback broadly aligned; these findings provide an interpretative anchor rather than a validated psychometric threshold [6]. The study included sponsor employees and sponsor-contracted contributors, so it should not be treated as independent validation of a threshold [6]. Under the operational criteria, the Vineland-3 data constitute exploratory developmental signals that are material to a disease-modification hypothesis, but their causal attribution is limited by the open-label design and the absence of a comparator. A subsequent sponsor-reported four-year OLE update described continued seizure reductions and improvements in cognition and behavior at annual follow-up through Year 4 [36]. Because detailed peer-reviewed estimates for that later data cut were not available at the review cutoff, these observations are treated as supportive sponsor-reported follow-up rather than independent confirmation of efficacy.

3.5 Safety

Safety data in the publication are among the most complete elements of the program. In phase 1–2a studies, 78 of 81 patients (96.3%) reported at least one treatment-emergent adverse event (TEAE); in the extensions, 75 of 75 (100%). The most common TEAE was post-lumbar-puncture syndrome (24.7% of phase 1–2a patients) and CSF protein increase (45.3% of extension patients). Treatment-related TEAEs occurred in 24 of 81 (29.6%) phase 1–2a patients and 40 of 75 (53.3%) extension patients; treatment-related CSF protein increase accounted for much of this difference (13.6% and 44.0%, respectively) [15].

Serious TEAEs were reported in 18 phase 1–2a patients (22.2%) and 22 extension patients (29.3%); only one, in phase 1–2a, was considered treatment-related. That patient, in the ADMIRAL 70-mg multiple-dose cohort, experienced procedural vomiting and reduced fluid intake with hospitalization after the second dose and, approximately two months after a third dose, developed cortical visual impairment, an eye movement disorder, and neurological decompensation that persisted at study end; these events were considered treatment-related in the absence of an alternative explanation and were not associated with CSF protein elevation. No TEAEs of hydrocephalus or increased intracranial pressure were reported; one patient had CSF pleocytosis (white blood cell count 11/ μ L). One extension patient discontinued study drug because of an adverse event. Three deaths were reported: two from SUDEP (one each in MONARCH and SWALLOWTAIL) and one from malnutrition (SWALLOWTAIL), described by the authors as consistent with the underlying disease. CSF protein elevations are reported as a class effect of intrathecal ASOs and are the subject of ongoing surveillance; the monitoring plan comprises scheduled neurological examinations and CSF laboratory testing throughout continued dosing [15].

The published safety findings were considered sufficient to support continued clinical development [15]. However, the treatment-related serious neurological event, frequent CSF protein elevations, and limited follow-up beyond 36 months preclude a complete assessment of long-term safety and therefore of criterion 4. A subsequent sponsor-reported four-year update stated that elevated CSF protein laboratory values had occurred in approximately 94% of patients, with 59% classified as treatment-emergent adverse events; no serious or severe clinical manifestations associated with the CSF protein elevations and no hydrocephalus were reported [36]. These later sponsor-reported figures should not be conflated with the 45.3% CSF-protein-increase TEAE frequency in the peer-reviewed extension dataset [15], and they reinforce the need for continued long-term surveillance.

3.6 Comparator context: approved ASMs, natural history, and other ASO programs

Approved Dravet therapies include stiripentol, cannabidiol, and fenfluramine, each supported by randomized, placebo-controlled evidence for seizure reduction [4,9,14]. These agents have established antiseizure efficacy, but none has established a disease-modifying effect on the developmental trajectory [23,33]. The zorevunersen publication also uses the BUTTERFLY natural-history study as an external benchmark; the cross-study comparison available at the time was based on conference-level natural-history reporting [15,26]. A subsequently peer-reviewed 24-month BUTTERFLY analysis reported no significant modeled change in convulsive-seizure frequency through Month 24 (+10.61%; 95% CI, -32.97 to 54.19; $p=0.63$; $n=23$) under standard care [25]. Cross-study comparisons with zorevunersen remain hypothesis-generating, not confirmatory [15]. Prospective natural-history studies, including BUTTERFLY and ENVISION-derived analyses, have documented pronounced developmental slowing and widening gaps from neurotypical trajectories [19,24,25], providing context against which developmental claims can be judged.

Two other intrathecal ASOs frame the regulatory context. Nusinersen, a splice-switching ASO, established the paradigm of intrathecal ASO therapy in spinal muscular atrophy, with a randomized, sham-controlled demonstration of clinical benefit [11]. Tofersen, an RNase-H gapmer that reduces SOD1 protein, illustrates the cautionary case: its randomized trial did not show a statistically significant effect on its primary clinical endpoint, but a biomarker effect (plasma neurofilament light chain) supported accelerated approval, contingent on verification of clinical benefit [17,30]. Neither precedent transfer automatically to SCN1A-related disease modification: spinal muscular atrophy and SOD1-ALS differ in mechanism, trajectory, and outcomes. The comparison is informative only as an illustration of evidentiary standards for novel ASOs.

3.7 Regulatory status and the EMPEROR trial

Zorevunersen holds US orphan-drug, rare-pediatric-disease, and breakthrough-therapy designations for Dravet syndrome with a confirmed mutation not associated with gain-of-function, and orphan designation in the European Union; a Stoke–Biogen collaboration governs development and commercialization [21]. The registrations of MONARCH (NCT04442295), ADMIRAL (ISRCTN99651026), SWALLOWTAIL (NCT04740476), and LONGWING (ISRCTN12811235) are public [15].

EMPEROR (NCT06872125) is an ongoing, randomized, sham-controlled phase 3 trial in children aged 2 to <18 years with SCN1A mutations not associated with gain-of-function, with a planned blinded 52-week treatment period after an 8-week baseline. Participants are randomized 1:1 to intrathecal zorevunersen or sham. The official title describes the study as double-blind, whereas the structured ClinicalTrials.gov design field lists quadruple masking (participant, care provider, investigator, outcomes assessor) [31]. The primary endpoint is the percentage change from baseline in major-motor-seizure frequency at Week 28. Key secondary endpoints address durability of effect and adaptive and global measures, including Vineland-3 subdomains (expressive communication, receptive communication, interpersonal relationships, coping skills, personal skills) and the CGI-C and CaGI-C; additional endpoints include the Bayley Scales of Infant and Toddler Development (BSID-IV) [31]. Sponsor communications reported completion on June 30, 2026, of enrollment of 162 patients in the United States, United Kingdom, and Japan, the planned primary-analysis population for the U.S. NDA; an additional European cohort was enrolling, and a phase 3 readout was anticipated in the third quarter of 2027 [22].

Precision is necessary when stating what the EMPEROR can establish. A favorable Week-28 seizure endpoint would confirm antiseizure efficacy in a controlled setting; developmental and global outcomes could strengthen a disease-modification interpretation but are not the registered primary efficacy requirement. Neither a seizure-endpoint success nor breakthrough-therapy designation predicts whether regulators will accept developmental outcomes as the basis for a disease-modification label claim. The review therefore treats EMPEROR as necessary but not sufficient for adjudicating disease modification [31].

3.8 The broader genetic-therapy landscape in Dravet syndrome

Zorevunersen is not the only mechanism-directed approach in development. ETX101, an AAV9-based gene-regulatory therapy designed to increase endogenous SCN1A transcription selectively in GABAergic interneurons, has progressed from preclinical development [28] into the POLARIS clinical program, which includes ENDEAVOR, EXPEDITION, and WAYFINDER [10]. Sponsor-reported interim data have suggested seizure reductions and exploratory developmental signals in small cohorts; the clinical results cited here are sponsor-reported and are not treated as peer-reviewed confirmation [10]. The existence of parallel mechanism-directed programs underscores that the evidentiary standard proposed here applies across the field, not only to one sponsor's asset: for emerging genetic therapies, the distinction between antiseizure effect, developmental signal, and demonstrated disease modification must be maintained in scientific communication and regulatory decision-making.

3.9 Evidence summary

Table 1 condenses the key human evidence assessed in this review, with the sample, timepoint, result, and principal limitation for each domain. The table is intended to serve as an at-a-glance reference that prevents the conflation of timepoints, and analysis sets discussed in the text. Taken together, the rows illustrate a consistent pattern: the strongest signals cluster in uncontrolled, descriptive analyses of the 70-mg subgroup, while controlled and long-term confirmatory data remain outstanding.

Table 1. Summary of key peer-reviewed human evidence for zorevunersen in Dravet syndrome [15] (data cut May 30, 2025)

Domain	Analysis set and timepoint	Result	Principal limitation
Convulsive seizures (phase 1–2a)	70 mg ×1, 3/6 months after last dose	Median change –42.81% / –57.30%	Descriptive; unadjusted CIs; post-ASM-change intervals excluded
Convulsive seizures (phase 1–2a)	70 mg ×2–3, 3/6 months after last dose	Median change –84.80% / –73.61%	Descriptive; unadjusted CIs
Convulsive seizures (OLE)	<70 mg initial dose, through Month 36	Median change range –6.94% to –77.38% across 1-month intervals	Range of interval medians; participant numbers vary by interval
Convulsive seizures (OLE)	70 mg ×1–3 initial doses, through Month 20	Median change range –58.82% to –90.91% across 1-month intervals	Post hoc subgroup emphasis; participant numbers vary by interval
CGI-C / CaGI-C	70-mg subgroup, 6 months after last dose	84.2% (clinicians) and 94.8% (caregivers) at least minimally improved	Unblinded; denominator not stated
CGI-C / CaGI-C	OLE Month 36 (participants with assessments)	94.7% (both raters) at least minimally improved vs OLE baseline	Available-assessment proportion; unblinded
Vineland-3 expressive communication	OLE baseline → Month 36 (n=74 at baseline)	LS mean change 7.56 (raw score)	Exploratory; MMRM, no imputation; no validated DS-specific threshold
Vineland-3 receptive communication	OLE baseline → Month 36 (n=74 at baseline)	LS mean change 6.06 (raw score)	Exploratory; floor effects in 3 subdomains excluded
Safety	Phase 1–2a (n=81); OLE (n=75)	PLPS 24.7%; CSF protein increases 45.3% (OLE); 3 deaths; 1 treatment-related serious event	Long-term CSF protein signal of uncertain clinical significance

4. Discussion

4.1 What the human evidence supports

On the operational criteria used here, the available human evidence drawn almost entirely from one open-label program reported in a single peer-reviewed publication supports four conclusions. First, the mechanism is coherent: upregulation of the wild-type SCN1A allele by poison-exon exclusion is a biologically rational strategy for a haploinsufficiency disorder, with supportive preclinical data [12,16]. Second, the published safety findings support continued clinical development, although long-term safety remains incompletely characterized [15]. Third, the program shows descriptive signals of seizure reduction, largest in patients initially treated with 70 mg, across multiple one-month intervals in the extensions [15]. Fourth, exploratory adaptive-behavior and global-impression signals were reported through Month 36 among participants with available follow-up [15]. These observations are clinically relevant but remain limited by the design and analysis of constraints described above. Later sponsor-reported follow-up extends the duration of observation but does not change the evidentiary level because those later results remain uncontrolled and were not peer-reviewed at the review cutoff [36].

4.2 What the evidence does not support

The evidence does not support a claim of established disease modification, for structural rather than incidental reasons. The studies are open-label and uncontrolled; global-impression and adaptive-behavior instruments are susceptible to expectation bias; seizure analyses are descriptive with multiplicity-unadjusted CIs; Vineland analyses are exploratory, unblinded, and use available-data MMRM without imputation; the dose-group emphasis that generates the most favorable seizure numbers is post hoc; no validated Dravet-specific clinically important difference has been established for Vineland-3; and the natural-history comparison is cross-study and partly supported by conference-level evidence [6,15,26]. Nor does the evidence address patients with gain-of-function SCN1A variants, who were excluded from the phase 3 program [31]. Design does not merely accompany these findings it determines their evidentiary ceiling. A seizure signal of uncertain magnitude, a functional signal of uncertain attribution, and a subgroup emphasis of post hoc origin cannot, in combination, cross the threshold set by the operational criteria in Section 2.4.

4.3 The 70-mg subgroup and the language of claims

The most visible numbers in public discussion of this program seizure reductions of 58.8%–90.9% and caregiver improvement of 94.8% come from the 70-mg subgroup and specific timepoints [15]. Their use outside the full analytic context illustrates a wider problem at the intersection of technology and society: qualified preliminary findings can become more categorical as they move into public communication. Sponsor communications themselves use the qualified formulation "potential for disease modification" [21]; retaining that qualification is important because the underlying human evidence remains open-label, exploratory or descriptive, and partly post hoc. This review therefore argues for a shared evidentiary vocabulary in which "a hypothesis of disease modification is supported" is distinguished from "disease modification has been demonstrated," and in which headline numbers are accompanied by their timepoint, subgroup, denominator when available, and analysis class. Such discipline is consistent with, rather than a criticism of, the cautions in the primary publication.

4.4 Implications for patients, families, and clinicians

For families, the distinction has immediate practical meaning. Early-phase data can generate understandable expectations about developmental benefits, but the available evidence does not establish long-term disease modification. Discussions during clinical counseling and informed consent should therefore distinguish, in plain language, between the possibility of developmental benefit and the observed open-label antiseizure signal. Until controlled results are available, clinicians should describe zorevunersen as investigational, with an open-label antiseizure signal and exploratory functional signals whose disease-modifying effects await controlled confirmation [15,31]. For payers and health-technology assessments, reimbursement decisions should mirror evidence of quality: access decisions can follow controlled efficacy and safety evidence, while claims of developmental benefit should track the strength of supporting data. For regulators, the program illustrates the value and limits of expedited pathways: regulatory designations can facilitate development and interaction but do not convert open-label signals into established outcomes [21].

The publication itself notes that real-world implementation of zorevunersen, if licensed, would raise practical considerations: sedation for intrathecal injections in children, interdisciplinary care across neurology and developmental services, and ongoing monitoring of CSF parameters and neurological status [15]. Each of these carries resource implications for families and health systems, and each interacts with the evidentiary questions discussed here: a therapy requiring repeated lumbar punctures in children must justify that burden with benefits that are robust and, ultimately, controlled. Uncertainty about the clinical significance of CSF protein increases a laboratory signal shared with other intrathecal ASOs further underscores the need for structured long-term follow-up before the benefit-risk balance can be considered fully characterized.

4.5 What EMPEROR can and cannot establish

EMPEROR can establish controlled antiseizure efficacy at Week 28; it can measure durability within the blinded period; and it can provide randomized comparisons on global and adaptive measures. Three limits, however, are structural. First, a single randomized trial in a heterogeneous syndrome, with caregiver-reported adaptive endpoints, cannot by itself separate a developmental disease-modifying effect from an indirect seizure-mediated improvement; the registered design, while strong, does not include a prospective natural-history benchmark within the same analysis. Second, Week-28 seizure endpoints and Week-52 adaptive endpoints leave open questions of durability beyond the blinded period, to be answered by extension data and

post-approval studies. Third, regulatory acceptance of developmental outcomes as a disease-modification basis is an open question that no single trial resolves. Post-publication correspondence has also highlighted treatment timing as an unresolved mechanistic question: because the early-phase program enrolled patients 2 to 18 years of age, the current evidence does not establish whether intervention earlier in neurodevelopment changes the attainable developmental benefit [37]. The review's conclusion is therefore conditional: EMPEROR is necessary, but not sufficient, to establish disease modification [31].

4.6 Regulatory pathways and evidentiary standards

The regulatory context illustrates both the promise and the uncertainty surrounding this program. Under the US accelerated approval framework, approval may rest on a surrogate endpoint reasonably likely to predict clinical benefit, subject to post-approval confirmatory obligations [29]; tofersen's accelerated approval on the basis of plasma neurofilament light chain reduction, despite a non-significant primary clinical endpoint, is the most direct precedent in the intrathecal ASO class [17,30]. For zorevunersen, breakthrough designation can expedite regulatory interaction, whereas orphan and rare-pediatric-disease designations have distinct incentive frameworks; none of these designations establishes efficacy or predicts which endpoint seizure frequency, durability, or developmental measures will anchor a submission [21]. The central regulatory question is whether developmental outcomes can be measured with instruments, benchmarks, and analysis methods that support a disease-modification label claim; the exploratory status and psychometric limitations of the current Vineland-3 analyses (floor effects, no validated Dravet-specific clinically important difference, caregiver-reported, unblinded) suggest that this standard will be demanding. Prudent regulatory and payer planning should therefore allow for the possibility that the evidence ultimately supports an antiseizure indication with developmental outcomes reported, but not labeled, as disease-modifying.

4.7 Broader implications for RNA-based precision medicine

The zorevunersen case generalizes across the emerging RNA-therapy and genetic-therapy landscape, including concurrent gene-regulatory programs in Dravet syndrome. Four lessons deserve emphasis. First, mechanistic plausibility should not be conflated with demonstrated clinical benefits. Second, communication is part of the evidence system: when preliminary results are described without their design and analysis limitations, patients and the credibility of the field bear the consequences. Third, the evidentiary standard for disease modification should be made explicit before interpreting confirmatory results, so that future trials, including EMPEROR, can be judged against a transparent framework [31]. Fourth, natural-history benchmarks deserve the same methodological discipline as interventional endpoints: prospective cohorts such as BUTTERFLY and ENVISION-derived analyses should be specified in advance when used as external comparators for developmental claims [19,24,25]. None of this diminishes the scientific achievement represented by the program; it defines what the achievement currently demonstrates.

4.8 Limitations of this review

This review has several limitations. It is a narrative review: the search was primarily conducted in freely accessible sources; Embase and Cochrane were not available, and screening was performed by a single reviewer without duplicate independent screening. The evidence base itself is narrow in one open-label program which limits the generalizability of any assessment. Denominators for several reported proportions are not stated in the primary article of text, constraining interpretation. The EMPEROR record is internally inconsistent in terminology: its official title describes a double-blind study, whereas the structured ClinicalTrials.gov masking field lists quadruple masking; we report both rather than adjudicating the discrepancy [31]. The review could not verify supplementary figures at the level of individual-patient data. Bibliographic details and claim-to-source mappings were rechecked against available publisher, registry, regulatory, conference, or sponsor records before finalization, but this does not substitute for independent duplicate review. Post-publication sponsor updates provide longer follow-up but lack the peer-reviewed analytic detail of the primary report; they were therefore treated as supplementary, not confirmatory, evidence. These limitations are disclosed rather than hidden, consistent with the review's own evidentiary standards.

Two further limitations concern the review's own positioning. First, it is written for a journal spanning technology and society, and it deliberately engages with the communication of clinical evidence sponsor press releases and conference materials alongside peer-reviewed sources; such material is inherently more vulnerable to framing effects than journal articles, and the provenance classification in Methods 2.3 makes this exposure explicit rather than eliminating it. Second, because individual-patient data are not available, no

estimate reported here was re-derived: descriptive statistics are reproduced as published, with their reported timepoints and analysis sets, and ambiguities in denominators are left explicit rather than silently resolved. Finally, some implications discussed in section 4.4 rest on resource and burden considerations (repeated intrathecal administration, caregiver demands, health-system capacity) that are argued qualitatively rather than quantified; this is appropriate for a critical appraisal whose aim is evidentiary discipline rather than health-technology assessment.

5. Conclusions

Zorevunersen is a biologically rational, technically innovative investigational candidate for disease modification in SCN1A-related Dravet syndrome. The peer-reviewed human evidence, however, is currently limited to an open-label program whose most prominent seizure results are descriptive and partly post hoc, while developmental results remain exploratory and based on available follow-up [15]. On the operational criteria used in this review, the available evidence supports a hypothesis of disease modification but does not establish it. Controlled confirmation requires the randomized, sham-controlled EMPEROR trial, interpreted with endpoints and benchmarks capable of adjudicating developmental outcomes, not seizures alone; longer-term developmental and safety questions may require extension or post-approval evidence [31]. Until then, the scientifically and ethically defensible description is that zorevunersen is an investigational therapy with an open-label antiseizure signal and exploratory functional signals and a plausible, unproven candidate for modifying the course of Dravet syndrome. For researchers, clinicians, regulators, and communicators alike, the case illustrates a central evidentiary discipline of modern precision medicine: separating what a technology promises from what it has been shown to do. Future work should prioritize controlled, adequately powered developmental endpoints, prospectively specified natural-history benchmarks where appropriate, and communication standards that track the strength of evidence at each stage of a program.

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