ORIGINAL ARTICLE

Zorevunersen in Children and Adolescents with Dravet Syndrome

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ABSTRACT

BACKGROUND

Dravet syndrome is a severe developmental and epileptic encephalopathy caused primarily by *SCN1A* haploinsufficiency. Risks of sudden unexpected death in epilepsy and cognitive deficits are higher among patients with this syndrome than in the general population with epilepsy. The effects of zorevunersen, an antisense oligonucleotide designed to up-regulate $Na_v1.1$ sodium channels, in patients with Dravet syndrome are not known.

METHODS

We enrolled patients 2 to 18 years of age with Dravet syndrome who were receiving standard antiseizure medications in two phase 1–2a, open-label, multicenter studies (MONARCH and ADMIRAL). Patients were included in either a single-ascending-dose cohort, in which zorevunersen (10 to 70 mg) was administered on day 1 only, or a multiple-ascending-dose cohort, in which zorevunersen (20 to 70 mg) was administered two or three times in a 3-month period. Patients eligible for rollover to the two open-label extension studies (SWALLOWTAIL and LONGWING) continued to receive zorevunersen (≤45 mg) every 4 months. The safety and pharmacokinetics of zorevunersen were assessed in the primary analysis; clinical effects were also evaluated.

RESULTS

A total of 81 patients were enrolled in the phase 1–2a studies. As of May 30, 2025, a total of 75 patients had entered the extension studies. Most adverse events were mild or moderate. The most common adverse event was post–lumbar puncture syndrome (in 25% of patients) in the phase 1–2a studies and was an elevated protein level in cerebrospinal fluid (in 45%) in the extension studies. One patient had suspected unexpected serious adverse reactions, 1 had an adverse event that led to study withdrawal, 2 died from sudden unexpected death in epilepsy, and 1 died from malnutrition. Patients who received 70 mg of zorevunersen (one, two, or three doses) in the phase 1–2a studies, followed by up to 45 mg in the extension studies, had a median change from baseline in convulsive-seizure frequency ranging from −58.82% to −90.91% across 1-month intervals during the first 20 months of the extension studies. The data supported improvements in overall clinical status, quality of life, and adaptive behavior with continued treatment for up to 36 months in the extension studies.

CONCLUSIONS

The safety profile and initial clinical improvement support the continued development of zorevunersen as a potential disease-modifying treatment for Dravet syndrome. (Supported by Stoke Therapeutics; MONARCH and SWALLOWTAIL ClinicalTrials.gov numbers, NCT04442295 and NCT04740476, respectively; ADMIRAL and LONGWING ISRCTN Registry numbers, ISRCTN99651026 and ISRCTN12811235, respectively.)

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Dravet syndrome is a severe developmental and epileptic encephalopathy caused primarily by variants in one copy of the voltage-gated sodium channel type 1 alpha subunit gene (*SCN1A*), which result in *SCN1A* haploinsufficiency and reduced expression of $Na_V1.1$ sodium channels.[1,2] These channels are highly expressed in inhibitory interneurons associated with γ-aminobutyric acid (GABA) and in some excitatory interneurons associated with glutamate in the brain.[3,4] Reductions in $Na_V1.1$ disrupt the excitatory–inhibitory balance, leading to general hyperexcitability and seizures.[3,5]

The clinical phenotype of Dravet syndrome includes a spectrum of symptoms that emerge early and evolve.[6] Most patients have cognitive deficits, communication and behavioral impairments, motor dysfunction, growth delays, and autistic traits.[7-13] Difficulties with feeding, poor appetite, and weight loss are also common.[8,14] These impairments reduce quality of life for patients and caregivers.[15] In addition, the risk of sudden unexpected death in epilepsy is higher among patients with Dravet syndrome than in the general population of patients with epilepsy.[16,17]

Current standard care for Dravet syndrome includes the use of antiseizure medications, dietary therapy, neuromodulation, or a combination of these approaches, with the goal of seizure control.[18] However, these treatments do not lead to seizure control in most patients, and their effect on nonseizure symptoms is minimal.[9,19] Moreover, reductions in seizure frequency may not necessarily correspond to improvements in nonseizure outcomes, which are a major concern of caregivers.[8,19] Disease-modifying therapies that directly target the underlying channelopathy to address both seizure and nonseizure symptoms are needed.[11,15,20]

Zorevunersen (formerly STK-001), an antisense oligonucleotide, was designed to target the channelopathy that underlies Dravet syndrome. In eukaryotes, precursor messenger RNA (mRNA) matures into mRNA through splicing, the process by which introns are removed and exons are joined together.[21,22] Nonproductive (poison) exons contain a premature termination codon, which, if included in mRNA, results in its degradation.[21,22] Zorevunersen binds to precursor mRNA of *SCN1A* to prevent the inclusion of nonproductive exons, thereby increasing productive mRNA synthesis and $Na_V1.1$ protein expression.[21,23] Restoring $Na_V1.1$ to physiologic levels in the brain could improve overall function, including cognition and behavior, in patients with Dravet syndrome. Here, we present results from the phase 1–2a MONARCH and ADMIRAL studies, which investigated the effects of zorevunersen in patients with Dravet syndrome, including safety, pharmacokinetics, and effects on seizure frequency, overall clinical status, quality of life, and adaptive behavior. We also present interim results (data cutoff, May 30, 2025) from the ongoing SWALLOWTAIL and LONGWING open-label extension studies.

METHODS

STUDY DESIGN

The MONARCH and ADMIRAL studies were open-label, multicenter studies that were conducted in the United States and the United Kingdom, respectively, to facilitate broader recruitment of and access to patients with Dravet syndrome. Patients were followed for at least 6 months after they received the last dose of zorevunersen. Those who completed the MONARCH or ADMIRAL study and met enrollment criteria were eligible for rollover to the SWALLOWTAIL or LONGWING open-label extension study (conducted in the United States and the United Kingdom, respectively), in which treatment with zorevunersen was continued. The timeline is shown in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The MONARCH study included single-ascending-dose cohorts, in which patients received the assigned dose of zorevunersen (10, 20, 30, 45, or 70 mg) on day 1 only, and multiple-ascending-dose cohorts, in which patients received the assigned dose of zorevunersen (20, 30, or 45 mg) on days 1, 29, and 57, for evaluation of the dose level and interval of dose administration. Details regarding sentinel dose administration are provided in the Supplementary Appendix. The ADMIRAL study had multiple-ascending-dose cohorts in which patients received the assigned dose of zorevunersen (30, 45, or 70 mg) on days 1, 57, and 85. For evaluation of a reduced dose schedule at the highest dose level, a subgroup of patients in the 70-mg multiple-ascending-dose cohort of the ADMIRAL study received only two doses of zorevunersen, on days 1 and 57.

In the extension studies, patients receive three initial doses, which are administered on day 1, at

month 4 (week 16), and at month 8 (week 32). Those who complete all three initial doses receive additional doses every 4 months (16 weeks) until study discontinuation. All the patients who were enrolled in the extension studies at the data cutoff were receiving continued doses of 45 mg of zorevunersen. Details regarding the intrathecal administration of zorevunersen, the history of doses administered, and end-of-study ands follow-up visits are provided in the Supplementary Appendix.

STUDY OVERSIGHT

For each study, the review board or ethics committee at each participating institution approved the study protocol (available at NEJM.org). The studies were conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. All the patients or their legal representatives provided written informed consent.

The sponsor (Stoke Therapeutics) provided the study drug, developed the study protocols, and participated in data collection. All the authors contributed to the collection, analysis, and interpretation of the data and vouch for the accuracy and completeness of the data and for the fidelity of the studies to the protocols. The sponsor paid for medical-writing support and made the decision to submit the manuscript for publication in agreement with all the authors, who reviewed and approved the submitted version. Confidentiality agreements between the authors and the sponsor were signed.

PATIENTS

The MONARCH and ADMIRAL studies had similar eligibility criteria, although the MONARCH study enrolled patients 2 to 18 years of age and the ADMIRAL study enrolled patients 2 to younger than 18 years of age. Patients were eligible for inclusion in the studies if they had an established diagnosis of Dravet syndrome, which had been confirmed by an external consortium with expertise in the condition, together with a pathogenic variant, likely pathogenic variant, or variant of uncertain significance in *SCN1A*. Eligible patients also had four or more convulsive seizures during the 28-day observation period despite concomitant use of at least one antiseizure medication and previous use of at least two such medications.

Patients who had completed the MONARCH or ADMIRAL study within the previous 4 weeks (or were approved by the sponsor) with an acceptable safety profile on the basis of investigator judgment were eligible for rollover to the SWALLOWTAIL or LONGWING study. Details regarding the inclusion and exclusion criteria are provided in the study protocols.

END POINTS

In the MONARCH–ADMIRAL studies, the primary end points were the safety profile, measures of pharmacokinetics in plasma, and measures of exposure in cerebrospinal fluid (CSF) with a single dose and with multiple doses of zorevunersen. In the SWALLOWTAIL–LONGWING studies, the primary end point was the safety profile with multiple doses of zorevunersen.

Across all the studies, common secondary end points were the change from baseline in the frequency of convulsive seizures, calculated in 1-month (28-day) intervals; the change from baseline in overall clinical status, as measured with the Clinical and Caregiver Global Impression of Change assessments; and the change from baseline in patient quality of life, as measured with the European Quality of Life Visual Analogue Scale (EQ-VAS) component of the European Quality of Life 5-Dimension Youth (EQ-5D-Y) instrument. The Clinical and Caregiver Global Impression of Change assessments are based on a Likert scale with scores ranging from 1 (very much improved) to 7 (very much worse).[24] The EQ-VAS is based on a vertical scale with scores ranging from 0 (the worst imaginable health) to 100 (the best imaginable health).[25] Secondary end points specific to the SWALLOWTAIL–LONGWING studies were measures of pharmacokinetics in plasma and measures of exposure in CSF with multiple doses of zorevunersen.

Exploratory end points included additional measures of seizure frequency and the change from baseline in adaptive behavior, as measured with the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), in the ADMIRAL study and the SWALLOWTAIL–LONGWING studies. Vineland-3 raw scores range from 0 to 116, with higher scores indicating better adaptive behavior and with the upper limit varying according to subdomain.[26] Caregivers have been reported to consider increases of 1 to 3 raw-score points as meaningful improvements.[27] Details regarding the

Vineland-3 domains and subdomains are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

No formal sample-size calculation or hypothesis testing was performed for the MONARCH–ADMIRAL studies, given that they were primarily dose-finding studies. For the primary end points, the analysis populations are described in the Supplementary Appendix. Data are reported for adverse events that were first identified or that worsened in intensity after the administration of the first dose of the study drug.

Seizure frequency was analyzed in 1-month (28-day) intervals. The baseline frequency was calculated from seizure data for the month (28

Table 1. Characteristics of the Patients in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies at Baseline.*

Characteristic	MONARCH–ADMIRAL (N=81)	SWALLOWTAIL–LONGWING (N=75)
Age at screening — yr		
Mean	9.9±5.1	10.4±5.0
Median (range)	10.0 (2–18)	11.0 (2–19)
Age group — no. (%)		
2–12 yr	46 (57)	42 (56)
≥13 yr	35 (43)	33 (44)
Sex — no. (%)		
Male	41 (51)	38 (51)
Female	40 (49)	37 (49)
Race — no. (%)†		
Asian	5 (6)	5 (7)
Black	5 (6)	5 (7)
White	71 (88)	66 (88)
Prefer not to answer	4 (5)	3 (4)
Ethnic group — no. (%)†		
Hispanic or Latino	10 (12)	10 (13)
Not Hispanic or Latino	70 (86)	64 (85)
Prefer not to answer	1 (1)	1 (1)
SCN1A variant type — no. (%)		
Missense	37 (46)	32 (43)
Nonsense	44 (54)	43 (57)
Antiseizure medications used concomitantly at baseline — no. (%)‡		
≥3	66 (81)	NA
≥4	41 (51)	NA
Concomitant use of fenfluramine at baseline — no. (%)	40 (49)	40 (53)
Median no. of convulsive seizures in 28-day observation period (range)§	17.0 (4.0–2335.4)	NA

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NA denotes not applicable.
† Race and ethnic group were reported by the caregiver. Multiple selections for race could be entered.
‡ The most common antiseizure medications used at baseline in the MONARCH–ADMIRAL studies were clobazam (70%), fenfluramine (49%), cannabidiol (44%), and valproate compounds (44%).
§ Data are shown for the 77 patients (58 in MONARCH; 19 in ADMIRAL) who met the criteria for clinical evaluation in accordance with the statistical analysis plan.

days) before the first dose of zorevunersen was administered in the MONARCH–ADMIRAL studies. In the main analysis, 1-month intervals in which seizure data were available for less than 50% of the days were excluded; in the MONARCH–ADMIRAL studies only, all 1-month intervals that occurred after modification of antiseizure medication were excluded. Sensitivity analyses of the frequency of convulsive seizures included all collected seizure data, with no exclusion for modification of antiseizure medication. All the analyses of seizure frequency are descriptive; medians and 95% confidence intervals are reported. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer treatment effects.

For analyses of overall clinical status, quality of life, and adaptive behavior, mixed models for repeated measures (MMRMs) were used to estimate outcome trajectories over time. This approach enhances interpretability, maintains consistency across time points, and adjusts for potential confounding factors that are inherent in longitudinal data analyses. Details regarding the MMRMs are provided in the statistical analysis plans, available with the protocols. Missing data were not imputed; in MMRMs, data are assumed to be missing at random, and all available data are included. All the statistical analyses were performed with the use of SAS software, version 9.4, and JMP Pro software, version 18.2 or higher (SAS Institute).

RESULTS

STUDY POPULATION

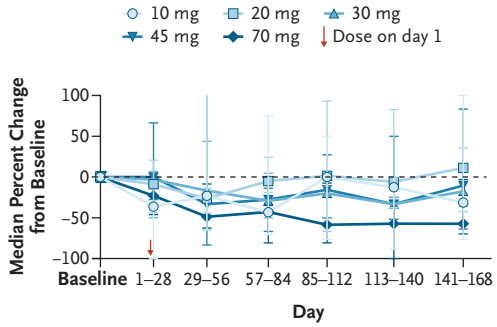
The MONARCH study was conducted from June 29, 2020, to November 16, 2023; the ADMIRAL study was conducted from July 29, 2021, to November 7, 2023. Of the patients who were receiving background therapy with standard antiseizure medications, 81 received at least one dose of zorevunersen (62 in MONARCH; 19 in ADMIRAL) (Figs. S2 and S3), and 80 completed the study (61 in MONARCH; 19 in ADMIRAL). The reduced dose schedule was evaluated in 6 patients in the 70-mg dose cohort of the ADMIRAL study. The SWALLOWTAIL study began on January 20, 2021; the LONGWING study began on May 9, 2022. As of May 30, 2025, a total of 58 of the 61 patients (95%) who had completed the MONARCH study

Table 2. Summary of Adverse Events in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.*

Event	MONARCH–ADMIRAL (N=81)	SWALLOWTAIL–LONGWING (N=75)
	number of patients (percent)	
Any adverse event	78 (96)	75 (100)
Treatment-related adverse event	24 (30)	40 (53)
Adverse event related to CSF collection or study-drug administration	43 (53)	45 (60)
Grade ≥3 adverse event		
Any	13 (16)	12 (16)
Related to treatment	1 (1)	0
Serious adverse event		
Any	18 (22)	22 (29)
Related to treatment	1 (1)	0
Potential dose-limiting toxic effect†	1 (1)	0
Adverse event that led to treatment discontinuation	0	1 (1)
Adverse event that led to study withdrawal	0	1 (1)
Adverse event that led to death†	1 (1)	2 (3)

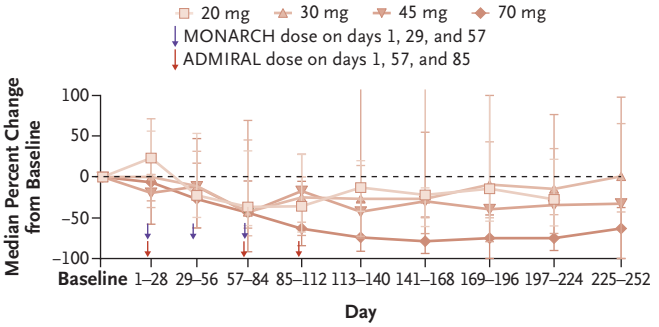
* Shown are adverse events that were first identified or that worsened in intensity after the administration of the first dose of the study drug. Treatment-related adverse events were considered by the investigator to be related to treatment. CSF denotes cerebrospinal fluid.
† No adverse events that led to death occurred in the patient who had a potential dose-limiting toxic effect.

A Change in Seizure Frequency in MONARCH Single-Ascending-Dose Cohorts According to Zorevunersen Dose



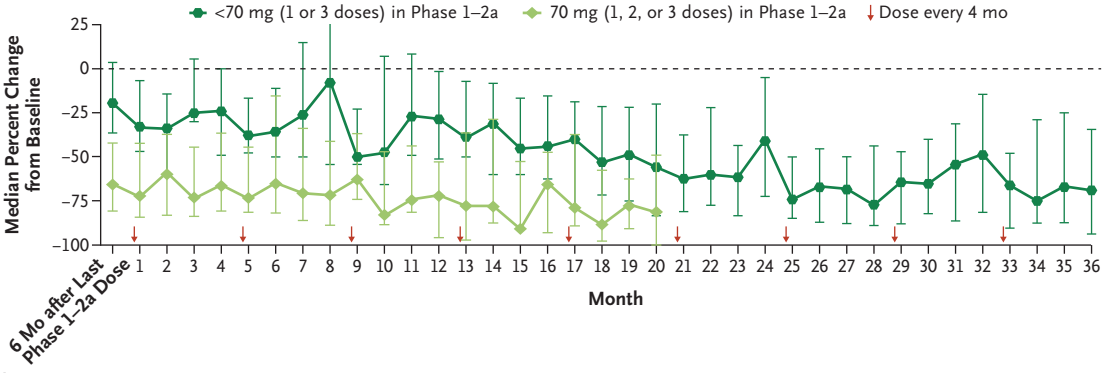
No. of Patients						
10 mg	4	4	4	3	3	3
20 mg	4	4	4	4	4	4
30 mg	5	5	5	4	3	3
45 mg	5	5	5	5	5	5
70 mg	8	8	8	8	8	7

B Change in Seizure Frequency in MONARCH–ADMIRAL Multiple-Ascending-Dose Cohorts According to Zorevunersen Dose



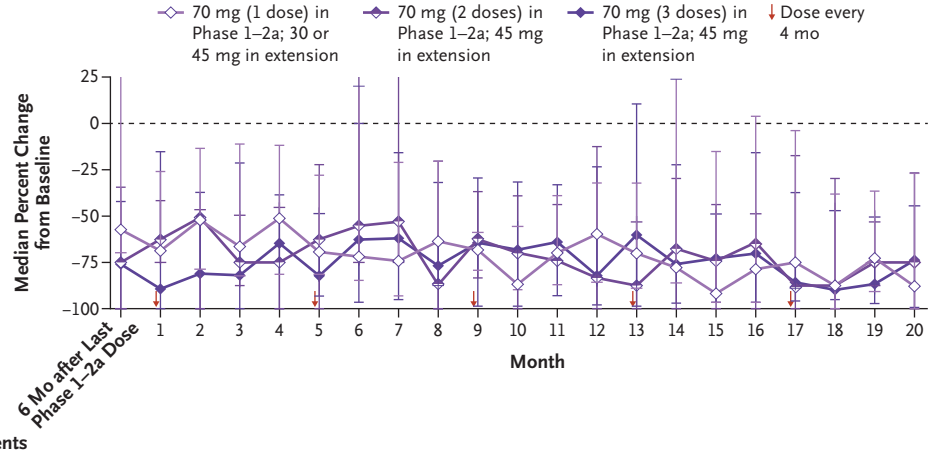
No. of Patients									
20 mg	6	6	6	6	6	4	4	4	
30 mg	18	17	17	17	16	15	14	14	3
45 mg	16	16	15	14	13	13	12	12	3
70 mg	11	11	10	10	10	10	9	9	9

C Change in Seizure Frequency among Patients in SWALLOWTAIL–LONGWING According to Zorevunersen Dose Received in Phase 1–2a Study



No. of Patients																																					
<70 mg (1 or 3 doses)	52	53	53	53	53	52	52	52	46	46	47	47	45	45	45	41	38	41	41	40	38	39	39	39	36	36	36	36	32	30	30	30	25	20	19	19	16
70 mg (1, 2, or 3 doses)	16	17	17	17	17	17	17	17	17	17	17	17	16	17	17	17	15	16	16	16	16																

D Change in Seizure Frequency among Patients in SWALLOWTAIL–LONGWING Who Received 70 mg of Zorevunersen in Phase 1–2a Study, According to Number of Doses Received



No. of Patients																					
70 mg (1 dose)	7	8	8	8	8	8	8	8	8	8	8	8	7	8	8	8	6	7	7	7	7
70 mg (2 doses)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
70 mg (3 doses)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

Figure 1 (facing page). Change in the Frequency of Convulsive Seizures in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the median percent change from baseline in the frequency of convulsive seizures through at least 6 months after the last dose of zorevunersen in the single-ascending-dose cohorts of the MONARCH study and in the multiple-ascending-dose cohorts of the MONARCH–ADMIRAL studies, respectively. In the MONARCH multiple-ascending-dose cohorts, zorevunersen (20, 30, or 45 mg) was administered on days 1, 29, and 57. In the ADMIRAL multiple-ascending-dose cohorts, zorevunersen (30, 45, or 70 mg) was administered on days 1, 57, and 85 or on days 1 and 57 with the reduced schedule. Panel C shows the median percent change from baseline (of the phase 1–2a studies) in the frequency of convulsive seizures among patients in the SWALLOWTAIL–LONGWING studies who had received zorevunersen at a dose level of less than 70 mg (one or three doses) in the phase 1–2a studies and those who had received zorevunersen at a dose level of 70 mg (one, two, or three doses) in the phase 1–2a studies. Panel D shows the median percent change from baseline in the frequency of convulsive seizures among patients in the SWALLOWTAIL–LONGWING studies who had received 70 mg of zorevunersen in the phase 1–2a studies, according to the number of doses received in the phase 1–2a studies. At 6 months after the last dose was administered in the phase 1–2a studies, data are shown only for patients who were enrolled in the extension studies. No exclusions were made for modification to antiseizure medications in the extension studies. Convulsive seizures included the following types: hemiclonic, focal with motor signs, focal-to-bilateral tonic–clonic, generalized tonic–clonic, tonic, tonic–atonic (drop attacks), and clonic. Seizure frequencies were calculated in 1-month (28-day) intervals. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

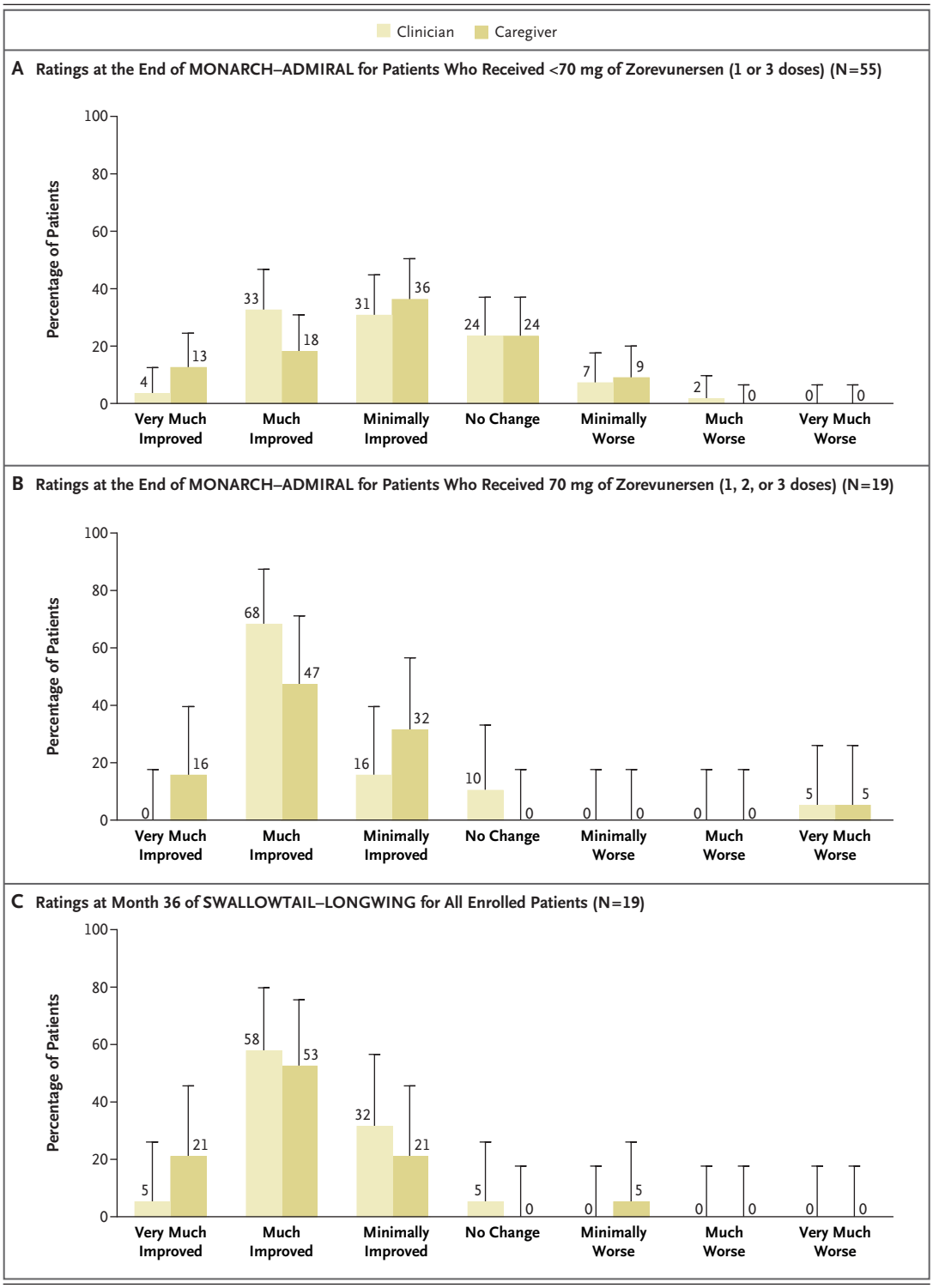
had entered the SWALLOWTAIL study, and 17 of the 19 patients (89%) who had completed the ADMIRAL study had entered either the LONGWING study or the SWALLOWTAIL study (Figs. S4 and S5). Of these 75 patients, 45 of the 59 (76%) in the SWALLOWTAIL study and 13 of the 16 (81%) in the LONGWING study remained enrolled at the data cutoff.

Characteristics of the patients at baseline in the MONARCH–ADMIRAL studies were similar to those in the SWALLOWTAIL–LONGWING studies (Table 1). The mean (±SD) age at baseline was 9.9±5.1 years in the MONARCH–ADMIRAL studies and was 10.4±5.0 years in the SWALLOWTAIL–LONGWING studies. In the MONARCH–ADMIRAL studies, 81% of the patients were taking three or more antiseizure medications at baseline; the most common were clobazam (70%), fenfluramine (49%), cannabidiol (44%), and valproate compounds (44%). The study populations were representative of the patient populations in the respective study regions in terms of the expected sex distribution and prevalence of Dravet syndrome (Table S2).

SAFETY

A total of 78 of the 81 patients (96%) in the MONARCH–ADMIRAL studies and 75 of the 75 patients (100%) in the SWALLOWTAIL–LONGWING studies had at least one adverse event (Table 2). Most adverse events were mild or moderate in severity. The most common adverse event in the MONARCH–ADMIRAL studies was post–lumbar puncture syndrome (in 25%), whereas the most common adverse event in the SWALLOWTAIL–LONGWING studies was an elevated CSF protein level (in 45%) (Tables S3 and S4). Serious adverse events were reported in 18 patients (22%) in the MONARCH–ADMIRAL studies and in 22 patients (29%) in the SWALLOWTAIL–LONGWING studies; serious adverse events were considered by the investigator to be related to treatment in 1 patient. Across both the phase 1–2a studies and the extension studies, the most common serious adverse events were seizure (in 5% in both MONARCH–ADMIRAL and SWALLOWTAIL–LONGWING) and status epilepticus (in 1% and 5%, respectively) (Tables S5 and S6).

Treatment-related adverse events were reported in 24 patients (30%) in the MONARCH–ADMIRAL studies and in 40 patients (53%) in the SWALLOWTAIL–LONGWING studies. Treatment-related adverse events were mild or moderate in severity, except for those occurring in 1 patient in the 70-mg dose cohort of the ADMIRAL study, who had suspected unexpected serious adverse reactions. Approximately 1 day after receiving the second dose of zorevunersen, this patient had vomiting after lumbar puncture and reduced fluid intake that led to hospitalization and that resolved after approximately 1 week. No elevations in the CSF protein level were observed. Approximately 2 months after receiving a third dose of zorevunersen, this patient had cortical visual impairment, eye movement disorder, and



neurologic decompensation. These events were present at the end of the study and, in the absence of an alternative explanation, are considered to be related to treatment. Across both the phase 1–2a studies and the extension studies, the most common treatment-related adverse event was an elevated CSF protein level (14% in MONARCH–ADMIRAL; 44% in SWALLOWTAIL–

Figure 2 (facing page). Change in Overall Clinical Status in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the change from baseline in overall clinical status, as measured with the Clinical and Caregiver Global Impression of Change assessments, at the end of the MONARCH–ADMIRAL studies (6 months after the last dose of zorevunersen) among patients who received zorevunersen at a dose level of less than 70 mg (one or three doses) and those who received zorevunersen at a dose level of 70 mg (one, two, or three doses), respectively. Panel C shows the change from baseline (of the extension studies) in overall clinical status at month 36 of the SWALLOWTAIL–LONGWING studies among all enrolled patients. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. Comparison of dose cohorts was performed in a post hoc analysis.

LONGWING) (Tables S7 through S10). No patients had adverse events of hydrocephalus or increased intracranial pressure; 1 patient had an adverse event of CSF pleocytosis, with a CSF white-cell count of 11 per microliter. Adverse events that were related to CSF collection or study-drug administration are described in Tables S11 and S12.

One patient (in SWALLOWTAIL) had an adverse event that led to discontinuation of treatment and withdrawal from the study. Two patients (1 in MONARCH and 1 in SWALLOWTAIL) died from sudden unexpected death in epilepsy as a result of their underlying disease, and 1 patient (in SWALLOWTAIL) died from malnutrition. Details are provided in the Supplementary Appendix.

PHARMACOKINETICS AND EXPOSURE

In the MONARCH–ADMIRAL studies, zorevunersen levels in plasma generally increased proportionally with the dose level (Fig. S6). Zorevunersen was detected in CSF up to 6 months after the administration of the last dose across all dose cohorts. In the multiple-ascending-dose cohorts, zorevunersen levels in CSF were higher 3 months after the last dose than they had been 1 month after the first or second dose, a finding that suggests that zorevunersen accumulation in CSF occurs when the drug is administered monthly or every 2 months (Fig. S7).

In the SWALLOWTAIL–LONGWING studies, with zorevunersen administered every 4 months, no apparent evidence of zorevunersen accumulation in plasma was observed across all dose levels. Mean trough CSF concentrations generally increased with each dose administered during the first year before reaching close to steady-state levels. Additional pharmacokinetics data are provided in Table S13.

SEIZURE FREQUENCY

Seizure data were available for most patients at all time points (Table S1). At baseline, the median number of convulsive seizures per 1-month interval was 17.0 (range, 4.0 to 2335.4) among 77 patients in the phase 1–2a studies and ranged from 8.3 to 64.0 across dose cohorts (Table 1 and Table S14). The median change from baseline in the frequency of convulsive seizures over 1-month intervals across dose cohorts in the MONARCH–ADMIRAL studies is shown in Figures 1A and 1B. The median change in the frequency of convulsive seizures at 3 months and 6 months after the last dose was −42.81% and −57.30%, respectively, among patients who received a single dose of 70 mg of zorevunersen and was −84.80% and −73.61%, respectively, among patients who received two or three doses of 70 mg of zorevunersen (Figs. S8 and S9). The percentage of patients who had a reduction in the frequency of convulsive seizures of at least 50%, at least 75%, and 100% (Table S15), the median change from baseline in the number of convulsive seizure–free days (Table S16), and the median change from baseline in the total seizure frequency (Table S17) were assessed at 3 months and 6 months after the last dose of zorevunersen. Results of the sensitivity analyses were similar to those of the main analysis.

The median change from baseline (of the phase 1–2a studies) in the frequency of convulsive seizures over time among patients in the SWALLOWTAIL–LONGWING studies is shown in Figures 1C and 1D. Among patients who received zorevunersen at a dose level of less than 70 mg (one or three doses) in the phase 1–2a studies, the median change from baseline in the frequency of convulsive seizures ranged from −6.94% to −77.38% across 1-month intervals through month 36 of the extension studies. Among patients who received zorevunersen at a dose level of 70 mg (one, two, or three doses) in the

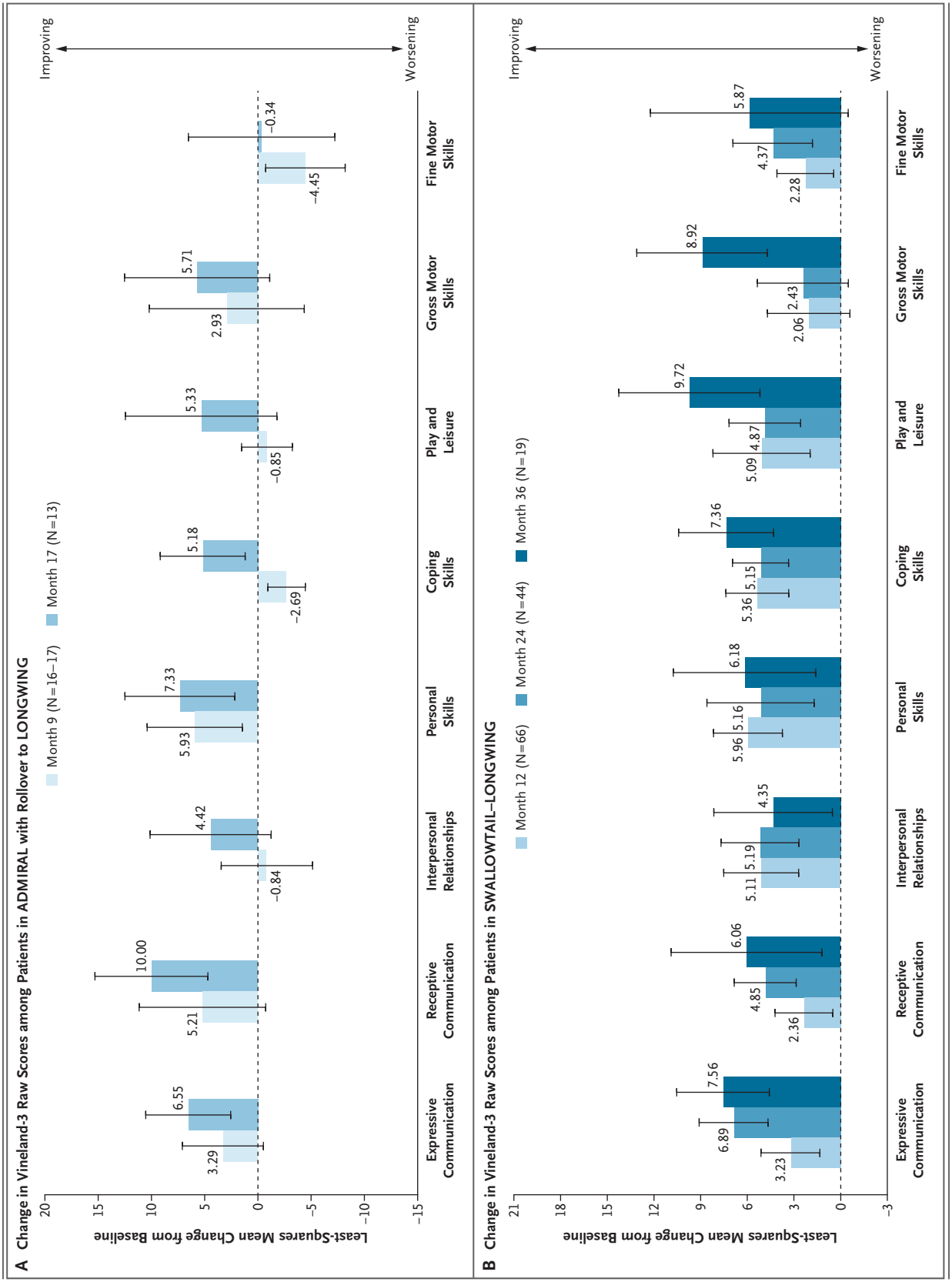


Figure 3 (facing page). Change in Adaptive Behavior in the ADMIRAL Study with Rollover to the LONGWING Study and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the change from baseline in adaptive behavior, as measured with the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), among patients in all dose cohorts of the ADMIRAL study with rollover to the LONGWING study and among patients in the SWALLOWTAIL–LONGWING studies, respectively. Vineland-3 raw scores range from 0 to 116, with higher scores indicating better adaptive behavior and with the upper limit varying according to subdomain. The least-squares mean change from baseline in Vineland-3 raw scores was estimated over time with adjustment for baseline prognostic covariates. Mixed models for repeated measures were used to analyze data from the ADMIRAL study (17 or 18 total patients, depending on the subdomain, at baseline) and through week 96 of the LONGWING study (which corresponds to week 132 after baseline of the ADMIRAL study), as well as to analyze available data from the extension studies (74 total patients at baseline of the extension studies). The analyses focused on seven subdomains without minimum age criteria and one subdomain with a minimum age criterion of 2 years. With regard to the remaining three subdomains (Written, Domestic, and Community), baseline scores were at or below the age-equivalent lower limit in 9 of 17 patients (53%), 15 of 17 patients (88%), and 13 of 17 patients (76%), respectively, in the ADMIRAL study and in 26 of 71 patients (37%), 49 of 71 patients (69%), and 48 of 71 patients (68%), respectively, in the extension studies. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

phase 1–2a studies, the median change from baseline in the frequency of convulsive seizures ranged from −58.82% to −90.91% across 1-month intervals through month 20 of the extension studies. Although the study design did not support formal statistical comparisons between dose cohorts, the median reductions in seizure frequency were largest among patients who received multiple doses of 70 mg of zorevunersen in the phase 1–2a studies, a finding consistent with a dose–effect relationship.

OVERALL CLINICAL STATUS AND QUALITY OF LIFE

At the end of the MONARCH–ADMIRAL studies, clinicians provided a rating of minimally improved, much improved, or very much improved from baseline for 84% of the patients who received 70 mg of zorevunersen (one, two, or three doses), and caregivers provided the same rating for 95% of those patients (Fig. 2). At month 36 of the SWALLOWTAIL–LONGWING studies, clinicians and caregivers both provided a rating of minimally improved, much improved, or very much improved from baseline (of the extension studies) for 95% of all enrolled patients.

Exploratory cross-study comparisons that were adjusted for baseline prognostic covariates suggested that improvements in overall clinical status among patients with Dravet syndrome who were treated with zorevunersen (Figs. S10 and S11) appeared to differ from the minimal change detected in a study of the typical disease course (Fig. S12). Data on quality of life were also consistent with improved outcomes (Figs. S13 and S14).

ADAPTIVE BEHAVIOR

The change from baseline in adaptive behavior, as measured with Vineland-3 subdomains, among patients in the ADMIRAL study with rollover to the LONGWING study and among patients in the extension studies is shown in Figures 3A and 3B, respectively. Patients in the ADMIRAL study with rollover to the LONGWING study had improvements in the Expressive Communication and Receptive Communication subdomains, with a least-squares mean change from baseline in the Vineland-3 raw score of 3.29 points and 5.21 points, respectively, at the end of the ADMIRAL study (month 9) and of 6.55 points and 10.00 points, respectively, at month 17 of the LONGWING study. Among patients in the extension studies, the least-squares mean change from baseline (of the extension studies) in the Vineland-3 raw score for the Expressive Communication and Receptive Communication subdomains was 7.56 points and 6.06 points, respectively, at month 36.

Exploratory cross-study comparisons that were adjusted for baseline prognostic covariates suggested that changes in adaptive behavior among patients with Dravet syndrome who were treated with zorevunersen appeared to differ from the minimal change detected in a study of the typical disease course (Fig. S15).[28] Real-life effects on activities of daily living were recorded for a patient in the ADMIRAL study with rollover to the LONGWING study, showing clinical improvements. Video 1 shows this patient performing

Videos showing the patient before and after treatment are available at NEJM.org

activities of daily living before and after treatment with zorevunersen.

DISCUSSION

The results reported here support the continued development of zorevunersen as a potential disease-modifying treatment for Dravet syndrome. Most treatment-related adverse events were mild or moderate, with the most common across both the MONARCH–ADMIRAL studies and the SWALLOWTAIL–LONGWING studies being elevated CSF protein levels as observed on routine laboratory screening. Similar elevations in the CSF protein level have been reported with other intrathecal antisense oligonucleotides that have been approved by the Food and Drug Administration.[29-31] Elevations in the CSF protein level have been reported with repeated doses of nusinersen; the CSF protein level may be a therapeutic marker.[32] No patients had adverse events of hydrocephalus or increased intracranial pressure. One patient had CSF pleocytosis. Ongoing safety monitoring includes neurologic examinations and CSF laboratory testing.

Zorevunersen treatment appeared to be associated with improvements in seizure outcomes in patients with Dravet syndrome whose disease was refractory to standard treatment with antiseizure medications. Although the study design did not support formal statistical comparisons between dose cohorts, the median reductions in seizure frequency were largest among patients who received multiple doses of 70 mg of zorevunersen in the phase 1–2a studies, a finding consistent with a dose–effect relationship. Continued treatment in the extension studies appeared to be associated with stabilized reductions in the frequency of convulsive seizures through 36 months. The data support differences in the risk of seizure from that observed in a study of the typical disease course,[28] in which patients with Dravet syndrome who were receiving the best available standard treatment on average showed no improvement in the frequency of convulsive seizures through 24 months.

Treatment with zorevunersen appeared to be associated with improvements in overall clinical status, quality of life, and adaptive behavior, outcomes that would be consistent with the mechanism of zorevunersen of up-regulating *SCN1A* in the context of the most common underlying cause of Dravet syndrome. No approved therapies target the underlying cause of Dravet syndrome, and caregivers have indicated that alleviation of nonseizure symptoms is important for new treatments.[33] Continuing improvements were noted across Vineland-3 subdomains. These included Expressive Communication and Receptive Communication, which caregivers have viewed as some of the most important disease aspects to address with treatment.[27,33] The changes in adaptive behavior and overall clinical status among patients with Dravet syndrome who were treated with zorevunersen appeared to be different from those observed in the study of the typical disease course and warrant further evaluation as part of ongoing clinical development.

The demographic characteristics of the patients in the MONARCH–ADMIRAL studies and in the SWALLOWTAIL–LONGWING studies reflected the expected sex distribution and prevalence of Dravet syndrome in the respective study regions (Table S2). Study limitations include the open-label design, the lack of placebo or sham control, the small sample sizes, the lack of formal power calculations, uncorrected multiple comparisons, and variability in baseline measures (e.g., seizure frequency across dose cohorts), all of which prevent us from drawing conclusions about efficacy. Moreover, the measures of adaptive behavior and quality of life that were used in the studies may be susceptible to caregiver bias with the open-label design. The MONARCH–ADMIRAL studies and the SWALLOWTAIL–LONGWING studies were primarily safety and dose-finding studies, and information on clinical outcomes requires further evaluation in a controlled and adequately powered study. Another limitation is generalizability; restricting eligibility to patients with a minimum number of convulsive seizures may limit applicability to those with fewer seizures. Real-world implementation of zorevunersen treatment may involve considerations such as sedation for intrathecal injections, interdisciplinary care needs, and ongoing monitoring to optimize patient outcomes.

Overall, these data support the potential for disease modification with zorevunersen. Further

assessment in a phase 3, randomized, controlled trial is under way (ClinicalTrials.gov number, NCT06872125). These data also support the selection of initial and continued doses of 70 mg and 45 mg of zorevunersen, respectively, in the ongoing phase 3 trial.

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