ORIGINAL ARTICLE

Efficacy and Safety of Donidalorsen for Hereditary Angioedema

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ABSTRACT

BACKGROUND

Hereditary angioedema is a rare disorder characterized by episodic, potentially life-threatening swelling caused by kallikrein–kinin dysregulation. Long-term prophylaxis can stabilize this system. Donidalorsen, an antisense oligonucleotide, specifically reduces prekallikrein expression.

METHODS

In this phase 3, double-blind, randomized trial, we assigned patients with hereditary angioedema to receive donidalorsen (80 mg subcutaneously) or placebo once every 4 or 8 weeks. The primary end point was the time-normalized number of investigator-confirmed hereditary angioedema attacks per 4 weeks (attack rate) from week 1 to week 25.

RESULTS

A total of 90 patients received donidalorsen every 4 weeks (45 patients), donidalorsen every 8 weeks (23 patients), or placebo (22 patients). The least-squares mean time-normalized attack rate was 0.44 (95% CI, 0.27 to 0.73) in the 4-week group, 1.02 (95% CI, 0.65 to 1.59) in the 8-week group, and 2.26 (95% CI, 1.66 to 3.09) in the placebo group. The mean attack rate from week 1 to week 25 was 81% lower (95% CI, 65 to 89) in the 4-week group than in the placebo group ($P<0.001$) and 55% lower (95% CI, 22 to 74) in the 8-week group than in the placebo group ($P=0.004$); the median reduction in the attack rate from baseline was 90% in the 4-week group, 83% in the 8-week group, and 16% in the placebo group. The mean attack rate during weeks 5 to 25 was 87% lower (95% CI, 72 to 94) in the 4-week group than in the placebo group ($P<0.001$) and 60% lower (95% CI, 25 to 79) in the 8-week group than in the placebo group. Donidalorsen administered every 4 weeks resulted in an improvement in the least-squares mean total score for the change at week 25 on the Angioedema Quality-of-Life Questionnaire (scores range from 0 to 100, with a score of 100 indicating the worst possible quality of life) that was 18.6 points (95% CI, 9.5 to 27.7) better than that with placebo ($P<0.001$). The most common adverse events were erythema at the injection site, headache, and nasopharyngitis; 98% of adverse events were mild or moderate in severity.

CONCLUSIONS

Donidalorsen treatment reduced the hereditary angioedema attack rate, a finding that supports potential prophylactic use for hereditary angioedema. (Funded by Ionis Pharmaceuticals; OASIS-HAE ClinicalTrials.gov number, NCT05139810.)

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Hereditary angioedema is a chronic rare disease typically caused by pathogenic variants of the complement 1 (C1) inhibitor gene (*SERPING1*) that leads to C1 inhibitor deficiency (type I) or dysfunction (type II).[1] The C1 inhibitor protein is a major regulator of multiple proteases including factor XII. Loss of C1 inhibitor function results in unregulated production of factor XIIa, which leads to uncontrolled activation of plasma prekallikrein into kallikrein. This enzyme can then cleave high-molecular-weight kininogen, which releases bradykinin, a powerful vasodilator.[2] In rare cases, hereditary angioedema may develop in patients with normal C1 inhibitor function because of mutations in other proteins involved in this pathway.[3] Bradykinin-induced vasodilation increases vascular permeability, which causes frequent, unpredictable, painful, and potentially life-threatening episodes of swelling (hereditary angioedema attacks) that can substantially affect the patient's quality of life.[4-6]

Most therapies for hereditary angioedema aim to stabilize the kallikrein–kinin system to prevent bradykinin overproduction, and some aim to reduce bradykinin activity.[7,8] Current management guidelines recommend long-term treatment with prophylactic agents,[7] but the disease burden can persist.[1] Patients may need emergency department visits and hospitalizations to manage breakthrough hereditary angioedema attacks, events that highlight the need for oral on-demand treatment of angioedema attacks (see the article by Riedl et al.,[9] now also published in the *Journal*) and prophylactic treatments with less frequent dosing and better disease control.

Donidalorsen, an investigational antisense oligonucleotide, administered subcutaneously, was designed to selectively bind to prekallikrein messenger RNA (mRNA) and consequently degrade it by means of ribonuclease H1, which results in the reduced production of prekallikrein protein, a key precursor in the kallikrein–kinin cascade.[10,11] Targeted delivery to hepatocytes — the main site of prekallikrein production — is accomplished by means of the conjugation of the antisense oligonucleotide to a triantennary *N*-acetylgalactosamine ($GalNAc_3$) moiety.[10,12] In a phase 2 trial, donidalorsen administered at a dose of 80 mg once every 4 weeks resulted in a significantly lower rate of hereditary angioedema attacks than placebo.[13] Here, we report results from OASIS-HAE (A Study to Evaluate the Safety and Efficacy of Donidalorsen [ISIS 721744 or IONIS-PKK-LRx] in Participants with Hereditary Angioedema), a pivotal phase 3 trial of donidalorsen, administered subcutaneously, at a dose of 80 mg every 4 or 8 weeks in patients with hereditary angioedema.

METHODS

TRIAL DESIGN AND OVERSIGHT

OASIS-HAE was a phase 3, multinational, double-blind, randomized, placebo-controlled trial that was designed to evaluate the efficacy and safety of donidalorsen (80 mg administered subcutaneously) in patients with hereditary angioedema. The protocol and its amendments, available with the full text of this article at NEJM.org, were approved by an independent ethics committee or institutional review board at each participating site. All the patients provided written informed consent. The trial was funded and designed by Ionis Pharmaceuticals; data were collected by investigators and analyzed by an independent organization, Parexel International. The first draft of the manuscript was written by writers employed by Red Nucleus, a medical communications agency whose services were funded by Ionis Pharmaceuticals. The authors critically interpreted the results, prepared the manuscript for submission, decided to submit the manuscript for publication, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The authors agreed to maintain confidentiality of the data during manuscript development.

PATIENTS, RANDOMIZATION, AND TRIAL TREATMENT

Patients 12 years of age or older at the time of screening who had confirmed hereditary angioedema type I or II were eligible for participation in the trial. Patients had to have had at least two investigator-confirmed hereditary angioedema attacks during the run-in period (defined as 56 days to 1 day before randomization) to be eligible for enrollment. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

Patients were screened for up to 56 days and were randomly assigned, in a 2:1 ratio, to either a 4-week dosing interval (the 4-week group) or

an 8-week dosing interval (the 8-week group). Within each dosing-interval group, patients were randomly assigned again, in a 3:1 ratio, to receive donidalorsen at a dose of 80 mg or placebo, administered subcutaneously (data from patients receiving placebo in the 4-week and 8-week groups were pooled for analyses). Trial-site visits occurred at weeks 1 (baseline), 5, 9, 13, 17, 21, and 25 during the treatment period and subsequently at weeks 4, 8, and 13 after the end of the treatment period (Fig. S1 in the Supplementary Appendix).

END POINTS

The primary end point was the time-normalized number of investigator-confirmed hereditary angioedema attacks per 4 weeks (attack rate) from week 1 to week 25. Secondary end points, evaluated from week 5 to week 25, included the time-normalized attack rate during that time period, the incidence of moderate or severe attacks, the clinical response (defined as a ≥50%, ≥70%, or ≥90% reduction in the attack rate from baseline), the number of attacks per 4 weeks that led to the receipt of on-demand therapy, and attack-free status. Additional secondary end points included the change from baseline to week 25 in the total score on the Angioedema Quality-of-Life (AE-QoL) Questionnaire[14] and score on the Angioedema Control Test (AECT; scores range from 0 to 16, with a score of ≥10 indicating well-controlled disease)[15] at week 25. The AE-QoL Questionnaire consists of 17 items and 4 domains (functioning, fatigue/mood, fears/shame, and nutrition). Within each domain, items are scored from 0 to 4, with higher scores indicating attacks that occur more frequently or have a worse effect; raw scores for each domain and the total score are calculated and transformed into a linear scale that ranges from 0 to 100, with a score of 100 indicating the worst possible quality of life. Safety was assessed by means of clinical laboratory findings and the incidence, severity, and relationship to the trial regimen of adverse events. Exploratory end points from week 1 to week 25 included the number of visits to the emergency department, report of improvement ("a little better" or "much better") on the Patient Global Impression of Change (PGI-C) scale, and plasma prekallikrein levels. End points are described in more detail in the Supplementary Appendix.

STATISTICAL ANALYSIS

Statistical power and sample-size estimations were calculated with the use of simulations that were based on a generalized linear model for count data assuming a Poisson distribution. The detectable effect size was an attack rate that was at least 25% lower in the 4-week donidalorsen group than in the placebo group. The primary end point was analyzed with the use of a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model included a categorical fixed effect for trial group, with the time-normalized hereditary angioedema attack rate during the run-in period (the baseline attack rate) and the interaction of trial group with baseline attack rate as covariates and the logarithm time per 4 weeks that each patient was observed from week 1 to week 25 as the offset variable. All statistical tests were conducted with the use of two-sided tests at a 5% type I error rate. Missing data were assumed to be missing at random in this analysis. Further details on statistical models and the handling of missing data for other end points are described in the Supplementary Appendix. To control for multiplicity, a hierarchical testing procedure was applied to a fixed sequence of 24 end points (listed in Table S2). The 95% confidence intervals presented have not been adjusted for multiplicity and should not be used in place of a hypothesis test. The full analysis population that was used for the reporting of primary and secondary efficacy end points was the same as the safety analysis population and included all patients who underwent randomization and received at least one dose of donidalorsen or placebo; this population represents the practically feasible intention-to-treat population as delineated in the International Council for Harmonisation E9 guidelines for Good Clinical Practice.

RESULTS

PATIENTS

Of the 116 patients who were screened, 91 underwent randomization. One patient withdrew before the administration of donidalorsen or placebo began, and 90 patients received at least 1 dose of donidalorsen or placebo; 45 patients received donidalorsen every 4 weeks, 23 received donidalorsen every 8 weeks, and 22 received placebo. The characteristics of the patients at baseline are

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Donidalorsen 4-Wk Group (N=45)	Donidalorsen 8-Wk Group (N=23)	Placebo Group (N=22)
Age — no. (%)			
12–17 yr	4 (9)	3 (13)	0
18–39 yr	19 (42)	12 (52)	15 (68)
40–64 yr	21 (47)	7 (30)	7 (32)
≥65 yr	1 (2)	1 (4)	0
Sex — no. (%)			
Male	17 (38)	11 (48)	14 (64)
Female	28 (62)	12 (52)	8 (36)
Race or ethnic group — no. (%)†			
White	42 (93)	22 (96)	18 (82)
Asian	1 (2)	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Black or African American	1 (2)	0	1 (5)
American Indian or Alaska Native	0	1 (4)	2 (9)
Multiple	0	0	1 (5)
Other	1 (2)	0	0
Body-mass index‡	28±7	27±5	29±9
Hereditary angioedema — no. (%)			
Type I	42 (93)	22 (96)	20 (91)
Type II	3 (7)	1 (4)	2 (9)
Age at onset of hereditary angioedema symptoms — yr	12±10	11±8	13±7
No. of hereditary angioedema attacks in the 12 mo before screening	45.7±43.0	33.3±22.0	29.1±21.1
No. of hereditary angioedema attacks during run-in period§	3.6±2.2	3.2±2.2	2.9±1.7
AE-QoL total score¶	45.6±16.8	47.2±19.0	45.4±17.0

* Plus–minus values are means ±SD.
† Race or ethnic group was reported by the patients at screening.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data from one patient in the placebo group were missing.
§ The hereditary angioedema attack rate during the run-in period was calculated as the number of investigator-confirmed attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28 days.
¶ Scores on the Angioedema Quality of Life (AE-QoL) Questionnaire range from 0 to 100, with a score of 100 indicating the worst possible quality of life.

shown in Table 1, Figure S2, and Table S1. After the dosing period began, 5 patients (1 in each donidalorsen group and 3 in the placebo group) withdrew owing to lack of efficacy, in accordance with a protocol rule that stipulated that if five hereditary angioedema attacks occurred per month for 2 consecutive months after week 5, patients could withdraw. Patients who withdrew owing to lack of efficacy after week 5 were eligible to enroll in the open-label extension (ClinicalTrials.gov number, NCT04307381) in accordance with the investigators' medical judgment (no additional criteria beyond the inclusion criteria were provided to the investigators). In addition, 1 patient (in the placebo group) withdrew because of pregnancy, and another (in the

8-week group) withdrew because of an adverse event. The mean age of the patients was 37 years (range, 12 to 68), and 7 patients were younger than 18 years of age (mean age of patients <18 years, 14 years) (Table 1 and Table S1). A total of 84 of 90 patients (93%) had hereditary angioedema type I, and 6 patients (7%) had hereditary angioedema type II. A total of 47 patients (52%) had a history of laryngeal attacks, and 16 (18%) had received prophylactic therapy for hereditary angioedema previously. Danazol was used concomitantly by 6 patients in this trial: 1 (5%) in the placebo group, 2 (4%) in the 4-week group, and 3 (13%) in the 8-week group.

EFFICACY

Primary End Point

The mean attack rate during the run-in period in the donidalorsen groups was 3.61 in the 4-week group and 3.18 in the 8-week group, as compared with 2.90 in the placebo group (Table 1). The least-squares mean time-normalized attack rate was 0.44 (95% confidence interval [CI], 0.27 to 0.73) in the 4-week group, 1.02 (95% CI, 0.65 to 1.59) in the 8-week group, and 2.26 (95% CI, 1.66 to 3.09) in the placebo group. The mean attack rate from week 1 to week 25 was 81% lower (95% CI, 65 to 89) in the 4-week group than in the placebo group (P<0.001) and 55% lower (95% CI, 22 to 74) in the 8-week group than in the placebo group (P=0.004) (Fig. 1, Table 2, and Fig. S3A). The median reduction from baseline in the attack rate was 90% in the 4-week group, 83% in the 8-week group, and 16% in the placebo group. The change from baseline in the attack rate according to trial visit is shown in Figure S4.

Secondary End Points

In the period from 4 weeks after the first dose (week 5) to week 25, the least-squares mean time-normalized hereditary angioedema attack rate was 0.30 (95% CI, 0.15 to 0.58) in the 4-week group and 2.25 (95% CI, 1.59 to 3.18) in the placebo group, corresponding to an 87% (95% CI, 72 to 94) lower rate with donidalorsen than with placebo (P<0.001) (Table 2 and Fig. S3B). A total of 37 patients (82%) in the 4-week group had a reduction in attacks of 70% or more from baseline (as compared with 4 patients [18%] in the placebo group; P<0.001), and 53% of patients in the 4-week group remained attack-free, as compared with 9% of patients in the placebo group (P=0.003) (Table 2 and Fig. 2). The rate of moderate or severe attacks per 4 weeks was 89% lower (95% CI, 66 to 97) and the use of on-demand therapy was 92% lower (95% CI, 77 to 97) in the 4-week group than in the placebo group (P<0.001 for both comparisons). A clinically meaningful reduction (≥6 points)[16] and a significant improvement of 24.8 points in the least-squares mean AE-QoL total score from baseline to week 25 was observed in the 4-week group (least-squares mean difference from the placebo

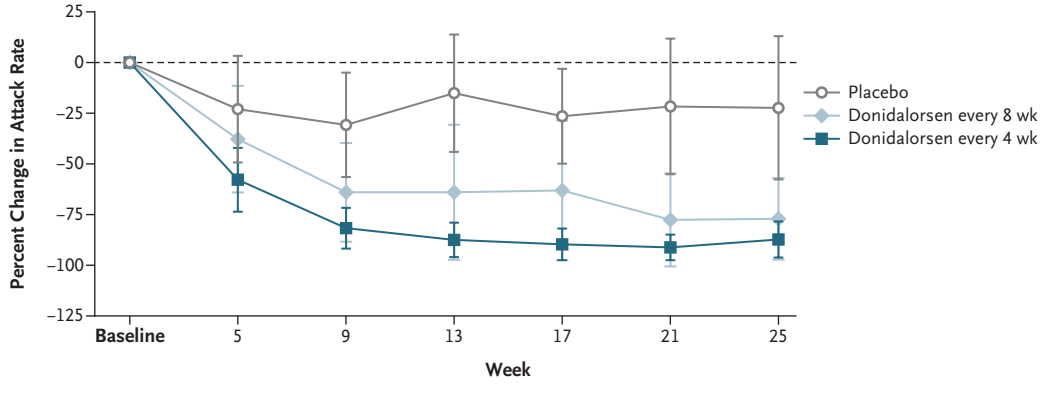

Figure 1. Change in the Rate of Hereditary Angioedema Attacks.

The mean percent change in the number of investigator-confirmed hereditary angioedema attacks per 4 weeks (attack rate) between baseline (week 1) and week 25 among patients receiving 80 mg of donidalorsen (administered subcutaneously) once every 4 weeks, 80 mg of donidalorsen once every 8 weeks, or placebo is shown. I bars indicate 95% confidence intervals.

Table 2. Effect of Treatment on the Rate of Hereditary Angioedema Attacks.*

End Point	Donidalorsen 4-Wk Group (N=45)	Donidalorsen 8-Wk Group (N=23)	Placebo Group (N=22)
No. of hereditary angioedema attacks per 4 wk during run-in period†	3.61±2.24	3.18±2.15	2.90±1.66
Primary end point			
No. of hereditary angioedema attacks per 4 wk, wk 1 to wk 25 — LSM (95% CI)‡	0.44 (0.27 to 0.73)	1.02 (0.65 to 1.59)	2.26 (1.66 to 3.09)
Difference vs. the placebo group — % (95% CI)†	−81 (−89 to −65)	−55 (−74 to −22)	
P value	<0.001	0.004	
Secondary end points			
No. of attacks per 4 wk, wk 5 to wk 25 — LSM (95% CI)‡	0.30 (0.15 to 0.58)	0.90 (0.53 to 1.52)	2.25 (1.59 to 3.18)
Difference vs. the placebo group — % (95% CI)†	−87 (−94 to −72)	−60 (−79 to −25)	
P value	<0.001	0.004	
Clinical response, wk 5 to wk 25			
Reduction in attack rate ≥50% per 4 wk — no. (%)	42 (93)	19 (83)	6 (27)
Odds ratio vs. placebo (95% CI)§	310 (12 to 8280)	15 (3 to 69)	
P value	NR	NR	
Reduction in attack rate ≥70% per 4 wk — no. (%)	37 (82)	15 (65)	4 (18)
Odds ratio vs. placebo (95% CI)§	35 (7 to 165)	9 (2 to 41)	
P value	<0.001	0.004	
Reduction in attack rate ≥90% per 4 wk — no. (%)	28 (62)	11 (48)	2 (9)
Odds ratio vs. placebo (95% CI)§	17 (3 to 86)	9 (2 to 49)	
P value	NR	NR	
Attack-free status, wk 5 to wk 25 — no. (%)	24 (53)	8 (35)	2 (9)
Odds ratio vs. placebo (95% CI)§	12 (2 to 59)	3 (0.5 to 23)	
P value	0.003	NS¶	
No. of moderate or severe attacks, wk 5 to wk 25 — LSM (95% CI)‡	0.12 (0.04 to 0.35)	0.68 (0.37 to 1.23)	1.15 (0.72 to 1.83)
Difference vs. the placebo group — % (95% CI)†	−89 (−97 to −66)	−41 (−72 to 26)	
P value	<0.001	NR	
No. of attacks per 4 wk that led to on-demand therapy, wk 5 to wk 25 — LSM (95% CI)‡	0.15 (0.06 to 0.39)	0.59 (0.31 to 1.15)	1.80 (1.23 to 2.62)
Difference vs. the placebo group — % (95 CI)†	−92 (−97 to −77)	−67 (−85 to −29)	
P value	<0.001	0.004	

* Plus–minus values are means ±SD. CI denotes confidence interval, LSM least squares mean, NR not reported, and NS not significant.
† The percent difference in the mean investigator-confirmed hereditary angioedema attack rate between the donidalorsen groups and the placebo group is calculated as 100% × (mean rate ratio − 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percent change.
‡ The Poisson regression model included treatment groups, baseline rate, and the interaction of trial group with baseline rate as covariates and the logarithm of time as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential overdispersion.
§ The odds ratio, its 95% confidence interval, and P value are calculated on the basis of a logistic regression with baseline rate and the interaction of trial group with baseline rate as a covariate.
¶ The first nonsignificant result in the hierarchical statistical testing procedure and all subsequent end points in the sequence were reported without P values. The 95% confidence intervals have not been adjusted for multiplicity and may not be used to draw inference.

group, 18.6 points; 95% CI, 9.5 to 27.7; P<0.001) (Fig. S5).

Significant reductions in hereditary angioedema attack rates in the 8-week group were also reported from week 5 to week 25. Patients treated with donidalorsen every 8 weeks had a least-squares mean decrease of 0.90 (95% CI, 0.53 to 1.52) in the time-normalized attack rate over the course of weeks 5 to 25, which corresponded to a 60% (95% CI, 25 to 79) lower rate than that in the placebo group (P=0.004). A total of 15 patients (65%) had a reduction in attacks of at least 70% from baseline as compared with 4 (18%) in the placebo group (P=0.004) (Table 2). The difference between the 8-week group and the placebo group in the percentage of patients who remained attack-free was not significant (Table 2). Subsequent end points in the testing sequence were not reported with P values in accordance with the hierarchical testing procedure (Table 2 and Table S2).

On the basis of the AECT scores,[17] 41 patients (91%) in the 4-week group had well-controlled disease (a score of ≥10) at week 25 as compared with 9 patients (41%) in the placebo group (odds ratio, 14.8; 95% CI, 3.9 to 56.1). The least-squares mean AE-QoL total score decreased by 19.9 points from baseline to week 25 in the 8-week group (least-squares mean difference, 13.7; 95% CI, 3.3 to 24.0).

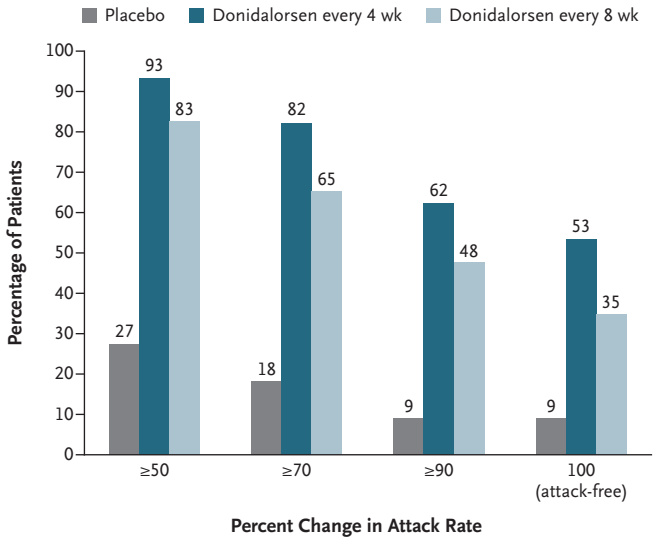

Figure 2. Patients with a Reduction in Hereditary Angioedema Attacks.
Shown are the percentages of patients in each group in whom a reduction in the time-normalized investigator-confirmed hereditary angioedema attack rate was observed from week 5 to week 25.

Exploratory and Other End Points

From week 1 to week 25, patients in the 4-week group had 93% (95% CI, 63 to 99) fewer emergency department visits from any cause than patients in the placebo group (least-squares mean rate, 0.02 vs. 0.26) and 95% (95% CI, 48 to 100) fewer emergency department visits attributable to hereditary angioedema attacks than patients in the placebo group (least-squares mean rate, 0.01 vs. 0.22). Patients in the 8-week group had 92% (95% CI, 33 to 99) fewer emergency department visits from any cause than patients in the placebo group (least-squares mean rate, 0.02 vs. 0.26) and 93% (95% CI, −11 to 100) fewer emergency department visits attributable to hereditary angioedema attacks (least-squares mean rate, 0.01 vs. 0.22). On the basis of PGI-C responses, 39 patients (95%) in the 4-week group and 20 patients (91%) in the 8-week group reported improvements at week 25, as compared with 10 patients (56%) in the placebo group (odds ratio for 4-week group vs. placebo group, 15.6; 95% CI, 2.9 to 85.2; odds ratio for 8-week group vs. placebo group, 8.0; 95% CI, 1.4 to 44.9). A total of 34 patients (83%) in the 4-week group and 17 patients (77%) in the 8-week group reported feeling "much better," as compared with 5 patients (28%) in the placebo group.

Reductions in plasma prekallikrein concentrations (Fig. S6) were consistent with those described in the phase 2 study.[13] The mean circulating prekallikrein concentrations at baseline were 128 μg per milliliter (95% CI, 116 to 141) in the 4-week group, 144 μg per milliliter (95% CI, 119 to 169) in the 8-week group, and 118 μg per milliliter (95% CI, 106 to 129) in the placebo group. By week 5, the mean trough concentration had decreased from baseline by 46% (95% CI, 40 to 53) in the 4-week group and by 52% (95% CI, 42 to 61) in the 8-week group and was essentially unchanged in the placebo group (increase of 2% [95% CI, −7 to 12]). The reduction in trough prekallikrein concentrations from baseline to week 25 was 73% (95% CI, 68 to 78) in the 4-week group and 47% (95% CI, 38 to 56) in the

Table 3. Adverse Events.*

Event	Donidalorsen 4-Wk Group (N=45)	Donidalorsen 8-Wk Group (N=23)	Placebo Group (N=22)
		number (percent)	
Any adverse event	33 (73)	14 (61)	18 (82)
Related to trial regimen†	19 (42)	4 (17)	6 (27)
Leading to discontinuation of trial regimen	0	1 (4)	0
Any serious adverse event	0	0	1 (5)
Related to trial regimen†	0	0	0
Adverse events related to trial regimen in ≥5% of patients†			
Injection-site reactions	9 (20)	1 (4)	0
Headache	3 (7)	0	3 (14)

* Included are adverse events that began or worsened on or after the first dose of donidalorsen or placebo. A full summary of adverse events is provided in Table S3.
† Related events refer to those that were deemed by the investigators to be related or possibly related to donidalorsen or placebo or those for which data regarding the relatedness to the trial regimen were missing.

8-week group. Mean prekallikrein concentration remained essentially unchanged in the placebo group (increase of 2% [95% CI, −5 to 10]).

The least-squares mean rate of laryngeal hereditary angioedema attacks from week 1 to week 25 was 0.01 (95% CI, 0.003 to 0.052) in the 4-week group, 0.01 (95% CI, 0.002 to 0.114) in the 8-week group, and 0.05 (95% CI, 0.020 to 0.142) in the placebo group (the baseline mean rate of laryngeal attacks was 0.11 in the 4-week group, 0.05 in the 8-week group, and 0.26 in the placebo group). Laryngeal hereditary angioedema attacks occurred in two patients (4%) in the 4-week group and in one patient (4%) in the 8-week group, as compared with five patients (23%) in the placebo group.

ADOLESCENT PATIENTS

Seven adolescent patients (mean age, 14 years) were randomly assigned to the donidalorsen groups — four to the 4-week group and three to the 8-week group (Table 1). The mean attack rate decreased by 97% from baseline among the four adolescent patients in the 4-week group and by 71% among the three adolescent patients in the 8-week group, findings that were consistent with those for the adult patients in the donidalorsen groups. The safety profile of donidalorsen was similar in the adolescent and adult patients. No serious adverse events were reported, and all adverse events were considered by the investigators to be unrelated to the trial regimen.

The mean circulating prekallikrein concentrations at baseline among adolescents in the donidalorsen groups were 134 μg per milliliter (95% CI, 92 to 176) in the 4-week group and 132 μg per milliliter (95% CI, 16 to 248) in the 8-week group. By week 5, the mean trough concentrations had decreased from baseline by 73% (95% CI, 49 to 97) in the 4-week group and by 53% (95% CI, −9 to 115) in the 8-week group. Reductions in trough prekallikrein concentrations from baseline to week 25 were 93% (95% CI, 81 to 105) in the 4-week group and 49% (95% CI, 2 to 96) in the 8-week group.

SAFETY

A total of 65 patients (72%) reported adverse events: 33 (73%) in the 4-week group, 14 (61%) in the 8-week group, and 18 (82%) in the placebo group (Table 3 and Table S3). All but 5 of the 281 events (98%) were mild or moderate in severity. Of the five severe events, two events (one each in the 4-week and placebo groups) were headache, one (in the 8-week group) was an increased blood creatine kinase level, one (in the 8-week group) was epicondylitis, and one (in the placebo group) was a limb (thumb) injury that

required surgery and was considered to be a serious adverse event unrelated to the trial (Table S3). The most common events were erythema at the injection site (in 13% of the patients), headache (in 13%), and nasopharyngitis (in 11%) in the 4-week group and nasopharyngitis (in 18%), limb injury (in 18%), and headache (in 18%) in the placebo group. The safety profile of donidalorsen was similar in the 4-week and 8-week groups. All injection-site reactions were mild in severity. Six of 90 patients (7%) — all in the donidalorsen groups and none in the placebo group — reported urinary tract infections. Two patients (9%) in the 8-week group had transient increases in alanine aminotransferase (ALT) levels; one of the two patients had a history of liver disease, and this patient's ALT levels resolved during the trial. The other patient had an increase in ALT level that was reported as possibly related to donidalorsen; however, that patient had been receiving androgen prophylactic treatment for more than 15 years before the trial (this treatment was discontinued on the day of the screening). There were no clinically meaningful changes in creatinine clearance or platelet counts.

DISCUSSION

In the OASIS-HAE phase 3 trial, donidalorsen at a dose of 80 mg administered subcutaneously every 4 or 8 weeks significantly reduced the mean hereditary angioedema attack rate during week 1 to week 25. Donidalorsen administered every 4 weeks resulted in an 81% lower mean hereditary angioedema attack rate than placebo during weeks 1 to 25 and an 87% lower rate during weeks 5 to 25 and reduced the median attack rate from baseline by 90% from week 1 to week 25 and by 100% from week 5 to week 25, findings that add to those observed in the phase 2 randomized trial.[13] By week 25, a reduction from baseline in the hereditary angioedema attack rate was observed in the 8-week group. Donidalorsen at a dose of 80 mg administered every 8 weeks appeared to be less effective over the entire duration of the trial than donidalorsen at the same dose administered every 4 weeks. The longer time necessary for the drug to achieve steady state may explain this finding, because by the end of the trial, the reduction in hereditary angioedema attacks in the 8-week group approached that of the 4-week group. Furthermore, there were fewer adverse events in the 8-week group. This raises the possibility that patients could start receiving donidalorsen every 4 weeks to achieve an initial, rapid clinical response and then switch to every 8 weeks for maintenance, with the option of returning to every 4 weeks if they have an attack. Data from the phase 2, open-label extension in eight patients receiving donidalorsen every 8 weeks showed a reduction in attacks of 83% after 2 years of treatment.[18]

No major safety concerns were identified; adverse events were mild or moderate in severity, and injection-site reactions were reported as the most common donidalorsen-related adverse event. Despite the availability of effective long-term prophylactic medications, there is a need for oral on-demand therapies (see the article by Riedl et al.[9]) and prophylactic therapies with improved efficacy, less frequent dosing, and a reduced treatment burden. Patient-reported outcomes from this trial showed a significant and clinically meaningful improvement in quality of life.[16]

A few aspects of this clinical trial are important to consider. Since donidalorsen targets prekallikrein mRNA in hepatocytes, existing prekallikrein must degrade before the onset of the clinical effect. Prekallikrein is bound to high-molecular-weight kininogen in plasma.[19,20] The estimated plasma half-life of high-molecular-weight kininogen has previously been reported to be 144 hours,[21,22] and thus a new steady-state concentration is reached after approximately 25 to 30 days, which coincides with the second dosing of donidalorsen at study week 5. Indeed, efficacy data captured at week 5 show the mean prekallikrein trough concentrations decreased from baseline by 46% in the 4-week group and by 52% in the 8-week group in this trial, findings that are similar to the donidalorsen phase 2 trial in which a 41% reduction from baseline in total plasma prekallikrein at week 5 correlated with a reduction in attacks with donidalorsen as compared with placebo.[13] Furthermore, although the circulating prekallikrein concentration decreased after donidalorsen treatment, future analyses should correlate clinical responses with reductions in prekallikrein concentrations to determine why some patients have higher numbers of breakthrough attacks. An additional consider-

ation is that the attack rate at baseline was lower in the placebo group than in the donidalorsen groups, which created an imbalance in randomization that may have led to an underestimation of the true treatment effect of donidalorsen. Limitations of the trial also included the small sample size, which reflects the rarity of hereditary angioedema,[8,13,22] and the lack of racial diversity in the participants, which may limit the generalizability of the results. Overall, 94% of eligible patients from the phase 3 OASIS-HAE trial enrolled in the phase 3 open-label extension (OASISplus, NCT05392114).

Donidalorsen at a dose of 80 mg administered subcutaneously every 4 or 8 weeks significantly reduced the hereditary angioedema attack rate and, when administered every 4 weeks, improved patient-reported quality of life. Collectively, the results from the OASIS-HAE trial support the use of donidalorsen as a possible prophylactic treatment for hereditary angioedema.

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APPENDIX

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