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CLINICAL TRIAL REPORT

Donidalorsen for Long-Term Prophylaxis of Hereditary Angioedema Attacks: Results from the OASISplus Open-Label Extension Cohort at Year 1

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Background: Donidalorsen, a prekallikrein-directed antisense oligonucleotide indicated for prophylaxis of hereditary angioedema (HAE) attacks in patients aged ≥12 years, demonstrated efficacy and acceptable safety in the phase 3, placebo-controlled OASIS-HAE trial (NCT05139810). Here, we report 1-year results from the corresponding open-label extension (OLE) cohort of the OASISplus study (NCT05392114).

Methods: OASISplus included patients who rolled over from OASIS-HAE. Patients who received donidalorsen 80 mg or placebo subcutaneously every 4 weeks (Q4W) in OASIS-HAE received donidalorsen Q4W in OASISplus. Patients who received donidalorsen 80 mg or placebo every 8 weeks (Q8W) in OASIS-HAE received donidalorsen Q8W or Q4W, if not attack-free in the final 8 weeks of OASIS-HAE. The primary endpoint was safety (ie, incidence of treatment-emergent adverse events [TEAEs]). Secondary endpoints included the monthly rate of HAE attacks and Angioedema Quality of Life (AE-QoL).

Results: The OLE cohort included 83 patients (Q4W, n=69 [83%]; Q8W, n=14 [17%]). Of these, 75 (90.4%) completed Year 1, and 6 patients receiving donidalorsen Q8W in OASIS-HAE switched to the Q4W dosing group in the OLE. Median donidalorsen exposure was 392.3 days. From Weeks 0 to 52, reductions in mean HAE attack rate from OASIS-HAE baseline were 94% (Q4W) and 95% (Q8W), and patients reported clinically meaningful improvements in mean AE-QoL total score at Week 52 (Q4W, 28.1 points; Q8W, 26.7 points). Twenty-two (27%) patients reported treatment-related TEAEs; none were serious, and injection-site reactions were the most frequently reported.

Conclusion: Donidalorsen demonstrated sustained reductions in HAE attack rate, improvements in QoL, and an acceptable safety profile after 1 year of treatment.

Keywords: disease control, donidalorsen, hereditary angioedema, open-label, phase 3

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Introduction

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent, potentially life-threatening episodes of angioedema (HAE attacks), resulting from dysregulation of the kallikrein-kinin system.[1–4] HAE is caused by pathological mutations in the *SERPING1* gene, encoding for C1 inhibitor (C1INH).[1] C1INH deficiency or dysfunction causes dysregulation of the plasma kallikrein-kinin pathway with consequent downstream overproduction of bradykinin, a potent vasodilator that increases vascular permeability, leading to tissue edema.[1]

Patients with HAE often suffer from disfiguring swelling attacks, severe abdominal pains, fatigue, and impaired ability to function in daily life, all of which negatively impact their quality of life (QoL) and mental health.[5] Some patients experience impaired performance or reduced attendance at work or school.[6] Moreover, patients often experience increased rates of anxiety and depression due to fear of painful, unpredictable, and potentially fatal HAE attacks (eg, oropharyngeal attacks) which further contribute to reduced QoL.[6,7] Long-term prophylactic treatments (LTPs) aim to prevent HAE attacks and reduce the burden of disease and its complications, and prior clinical trials and real-world studies reported LTP use improved QoL and productivity in patients with HAE.[8–11] Current LTPs include replacement therapies, like plasma-derived intravenous (IV) or subcutaneous (SC) C1INH concentrates, and targeted therapies, like inhibitors of activated factor XII (FXIIa), plasma kallikrein, and plasma prekallikrein, each with widely varying dosing schedules.[1] For example, plasma-derived C1INH concentrate is administered SC twice per week;[12] FXIIa inhibitor garadacimab is injected once a month;[13] plasma kallikrein inhibitor berotralstat is taken orally once daily;[14] and plasma kallikrein inhibitor lanadelumab is administered SC every 2 weeks (or up to every 4 weeks).[15] While modern LTPs have reduced treatment burden and improved QoL among patients with HAE, patients may still experience breakthrough attacks, undesirable side effects, or treatment burden related to the route of administration of their current LTP (ie, oral, SC, or IV) or dosing frequency, pointing to an ongoing unmet need for additional treatment options.[16,17]

Donidalorsen is a triantennary *N*-acetylgalactosamine (GalNAc)-conjugated antisense oligonucleotide (ASO) therapy designed to specifically and reversibly reduce plasma prekallikrein messenger RNA and induce its degradation in the liver, leading to reductions in plasma prekallikrein and ultimately to reduced bradykinin concentration.[18] Donidalorsen was approved in the United States in 2025 for prophylaxis to prevent HAE attacks in adult and pediatric patients 12 years of age and older, therefore offering an alternative LTP therapy for patients who wish to begin LTP treatments for their HAE or may not be satisfied with their current LTP therapy.[19] The safety and efficacy of donidalorsen vs placebo were assessed in 90 patients over the 24-week, pivotal, phase 3, double-blind, randomized OASIS-HAE study (NCT05139810).[20] Donidalorsen 80 mg administered SC every 4 weeks (Q4W) or every 8 weeks (Q8W) significantly reduced mean monthly HAE attack rates from Weeks 0 to 24 by 81% or 55%, respectively, as compared with placebo, and improved QoL and indices of disease control at Week 24. Donidalorsen had an acceptable safety and tolerability profile, with only one discontinuation due to treatment-emergent adverse events (TEAEs), and the majority of TEAEs were mild or moderate in severity.

The majority of patients enrolled in OASIS-HAE (83/90, 92.2%) rolled over into the open-label extension (OLE) cohort of the ongoing OASISplus study (NCT05392114), which is designed to evaluate the long-term safety and efficacy of donidalorsen treatment. Here, we report results from a prespecified interim analysis at 1 year in the OLE study.

Materials and Methods

Trial Design and Participants

OASISplus is an ongoing multicenter, phase 3 study composed of 2 cohorts: a de novo cohort of patients who switched from prior LTPs to donidalorsen 80 mg Q4W (Switch cohort), and an OLE cohort of patients who rolled over from the OASIS-HAE study.[16] Enrollment criteria in OASIS-HAE are published.[20] Briefly, patients with HAE-C1INH-Type1 or HAE-C1INH-Type2 were enrolled in OASIS-HAE if they experienced two or more HAE attacks during the ≤56-day screening period. Patients were eligible to enroll in the OLE if they successfully completed the OASIS-HAE study or if they had five or more attacks/month for two consecutive months after Week 4 of OASIS-HAE, in which case they could rollover early into the OLE and receive donidalorsen Q4W (ie, early rollover; Supplemental Figure 1).

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Protocols were reviewed and approved by an independent ethics committee and institutional review board in each country and research site.

Study Treatment

In the OLE cohort of the OASISplus study, patients received donidalorsen 80 mg (0.8 mL of a 100-mg/mL solution per vial or per autoinjector) based on the dosing schedule they were assigned to in OASIS-HAE (Q4W or Q8W; Supplemental Figure 1). Patients who received donidalorsen 80 mg or placebo Q4W in OASIS-HAE received donidalorsen 80 mg Q4W in OASISplus. Patients who received donidalorsen 80 mg or placebo Q8W in OASIS-HAE received donidalorsen 80 mg Q8W in OASISplus, unless they were not attack-free during the last 8 weeks (Weeks 16–24) in OASIS-HAE, in which case they received donidalorsen Q4W in OASISplus. Patients who rolled over into the OLE cohort early received donidalorsen 80 mg Q4W in the OLE. This prespecified analysis of the ongoing OASISplus study reports results for patients who completed the OLE through Week 52 (including 28 additional days of follow-up, defined as the on-treatment period) as of a January 27, 2025 data cut.

Endpoint Measures

The primary endpoint was the incidence of TEAEs, as defined by the Medical Dictionary for Regulatory Activities System Organ Class, and TEAE severity. Safety was assessed via clinical laboratory parameters and adverse event (AE) incidence, severity, and relationship to treatment. AEs were defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of donidalorsen, regardless of whether it was considered related to the treatment. Treatment-relatedness and AE severity were determined by the investigator. The severity of TEAEs was defined based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[21] Additional information regarding AE classification is provided in the Supplemental Methods.

Efficacy endpoints were based on HAE attack rates and patient-reported outcomes. HAE attack rates were confirmed by the investigator and severity was assessed using the following criteria: mild, transient or mild discomfort; moderate, mild-to-moderate limitation in activity and the patient needed some assistance; severe, marked limitation in activity and the patient required assistance. Rates of HAE attacks were time-normalized per every 4-week period (28 days), also termed monthly. Secondary efficacy endpoints included HAE attack rates from Weeks 0 to 52 and Weeks 4 to 52, number of moderate or severe HAE attacks compared with the OASIS-HAE run-in period (baseline), number of HAE attacks requiring on-demand therapy compared with OASIS-HAE baseline, mean percentage of total days patients were attack-free from Weeks 4 to 52, and QoL, as measured by the Angioedema Quality of Life (AE-QoL) questionnaire at Week 52. AE-QoL is a validated, 17-item, disease-specific, self-administered questionnaire with four domains calculated using a scale of 0 to 100, with lower scores indicating better QoL, and a minimal clinically important difference of ≥6 points.[22] The AE-QoL total scores at OASIS-HAE baseline and OASISplus OLE Week 52 were captured.

Exploratory endpoints included disease control measured by the Angioedema Control Test (AECT) at OASIS-HAE baseline and OLE Week 52, and HAE-specific health-related QoL measured by the Hereditary Angioedema Quality of Life (HAE-QoL) questionnaire and treatment satisfaction assessed by the Treatment Satisfaction Questionnaire for Medication version 2 (TSQM-II) compared with OASISplus OLE baseline (first assessment of these outcomes was at baseline in OASISplus). The AECT is a 4-week recall, patient-reported questionnaire consisting of four questions related to the frequency and severity of angioedema, with scores ranging from 0 to 16. Scores of 10 or higher indicate well-controlled disease.[23] The HAE-QoL is a 25-item questionnaire with seven dimensions available in 18 languages with good reliability and validity; total scores range from 25 to 135, with higher scores indicating better QoL,[24] and the TSQM-II is an 11-item questionnaire with four domains.[25] Each domain of the TSQM-II yields a scaled score ranging from 0 to 100, with higher scores indicating greater satisfaction.[25]

Statistical Analysis

No formal sample size calculations were performed, and results were summarized with descriptive statistics including observed mean, median, patient numbers, and percentages. The sample size for the OLE cohort was dictated by the number of patients enrolled in the OASIS-HAE study and their eligibility for the study. There were no stratification factors. Patient disposition, demographics, baseline characteristics, and data for all safety and efficacy endpoints were summarized using descriptive statistics. All endpoints were analyzed using data from the safety and full analysis sets, both defined as all patients who received at least one dose of donidalorsen.

Results

Patients

Of 90 patients who enrolled in OASIS-HAE, 83 (92%) rolled over into the OASISplus OLE. Of these, 69 (83%) received donidalorsen Q4W and 14 (17%) received donidalorsen Q8W (Table 1). In the donidalorsen Q4W arm, 44 patients were originally assigned to Q4W dosing in the OASIS-HAE study, six patients changed from donidalorsen Q8W in OASIS-HAE to Q4W dosing in OASISplus, and 19 patients from the OASIS-HAE placebo group were assigned to receive donidalorsen Q4W (Figure 1).

As of the data cutoff date (January 27, 2025), 75 patients (90%) completed Week 52 in the OLE study. Eight patients (10%) discontinued treatment early due to voluntary withdrawal (n = 4), AEs (n = 3), or pregnancy (n = 1; Supplemental Table 1). Among enrolled patients, 38 of 83 (46%) were male, and 76 of 83 (92%) were White, with a mean (standard

Table 1 Patient Demographics and Baseline Clinical Characteristics

	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Age, years, mean (SD)	38 (14)	30 (9)	37 (14)
Age category, years, n (%)			
12–17	5 (7.2)	2 (14.3)	7 (8.4)
18–39	32 (46.4)	10 (71.4)	42 (50.6)
40–64	31 (44.9)	2 (14.3)	33 (39.8)
≥65	1 (1.4)	0	1 (1.2)
Sex, n (%)			
Male	29 (42.0)	9 (64.3)	38 (45.8)
Female	40 (58.0)	5 (35.7)	45 (54.2)
Race, n (%)			
White	62 (89.9)	14 (100.0)	76 (91.6)
American Indian/Alaska Native	3 (4.3)	0	3 (3.6)
Black or African American	1 (1.4)	0	1 (1.2)
Asian	1 (1.4)	0	1 (1.2)
Multiple	1 (1.4)	0	1 (1.2)
Other	1 (1.4)	0	1 (1.2)
BMI, kg/m^2, mean (SD)	27.8 (6.6)	26.9 (5.4)	27.6 (6.4)
Baseline HAE attack rates			
Mean (SD)	3.5 (2.1)	2.9 (2.1)	3.4 (2.1)
Median (min, max)	3.0 (0.5, 10.0)	2.3 (0.7, 8.4)	3.0 (0.5, 10.0)
Treatment duration, days			
Mean (SD)	377.1 (55.0)	394.4 (5.3)	380.0 (50.5)
Median (min, max)	392.3 (55.9, 412.0)	392.5 (390.0, 411.0)	392.3 (55.9, 412.0)

Notes: HAE attacks are defined as the number of time-normalized attacks occurring every 4 weeks.
Abbreviations: BMI, body mass index; HAE, hereditary angioedema; max, maximum; min, minimum; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SD, standard deviation.

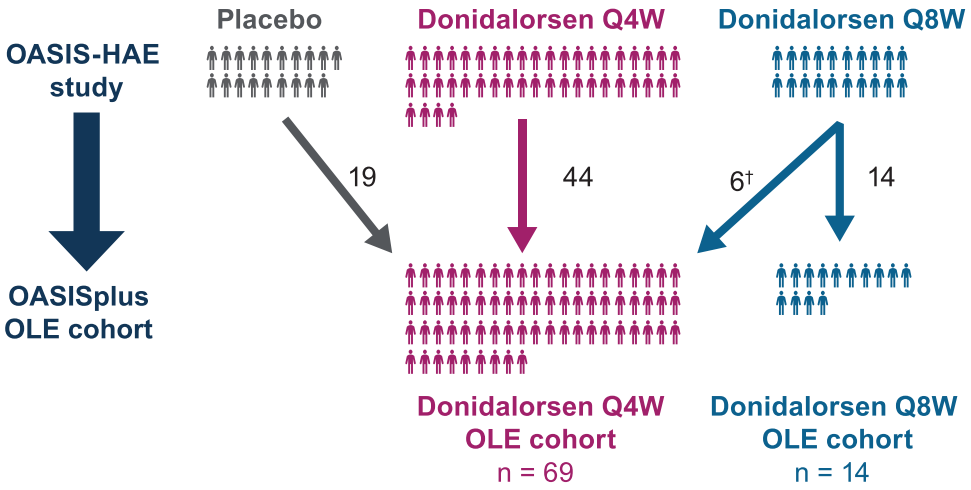
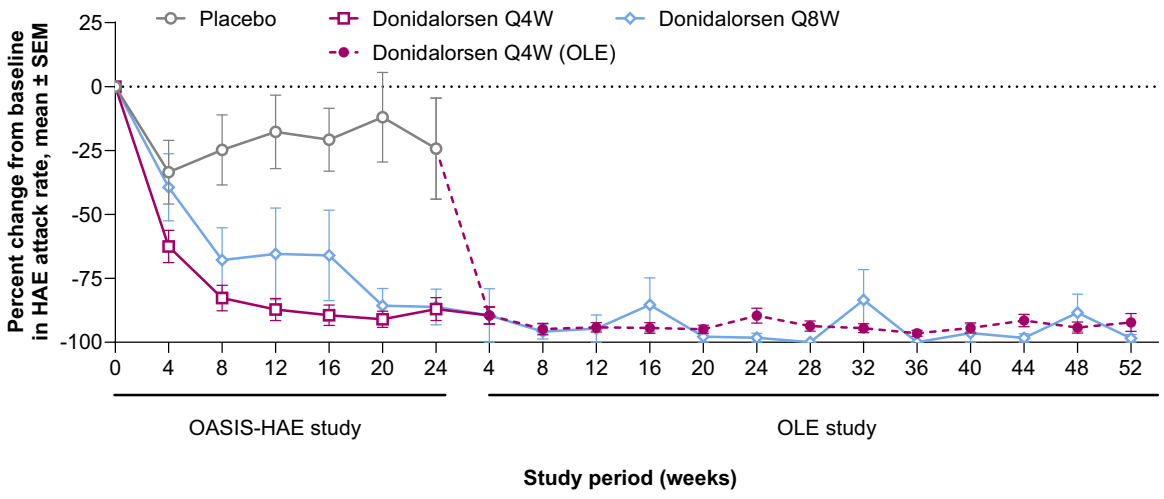


Figure 1 Flow of patients from OASIS-HAE to the OASISplus OLE. †Patients who were not attack-free for ≥8 weeks (Weeks 16–24 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.
Abbreviations: OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneous.

deviation [SD]) age of 37 (14) years. The study population included seven adolescents aged 12 to 17 years (Table 1). The overall median (minimum, maximum) donidalorsen exposure was 392.3 (55.9, 412.0) days.

Efficacy

Mean HAE attack rates were lower at each measured time point in the OASISplus OLE compared with baseline attack rates in the OASIS-HAE study (Figure 2). Overall, patients indexed to any treatment arm in OASIS-HAE experienced a mean reduction of 94% (median, 98%) from baseline in HAE attack rates during Weeks 0 to 52 in the OASISplus OLE. Reductions in HAE attack rate with donidalorsen treatment were observed regardless of the treatment received during OASIS-HAE (baseline to Weeks 48 to 52: donidalorsen Q4W, 90%; donidalorsen Q8W, 96%; placebo, 99%). The mean reduction in HAE attack rate over the 52-week OLE was 94% (median, 98%) in the Q4W group (including patients who



Placebo, n =	19	19	19	19	18	17	16														
Doni 80 mg Q4W, n =	44	44	44	44	44	43	43	69	69	68	68	68	68	68	68	66	65	62	61	61
Doni 80 mg Q8W, n =	20	20	20	20	20	20	19	14	14	14	14	14	14	14	14	14	14	14	14	14

Figure 2 HAE attack rate at baseline through Week 52 of the OASISplus OLE.
Abbreviations: Doni, donidalorsen; HAE, hereditary angioedema; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

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moved from Q8W dosing in OASIS-HAE to Q4W in the OLE) and 95% (median, 96%) in the donidalorsen Q8W group. This corresponded to a reduction in mean (SD) time-normalized monthly HAE attack rate from 3.5 (2.13) and 2.9 (2.06) at baseline to 0.3 (0.45) and 0.1 (0.10) over Weeks 0 to 52 in the Q4W and Q8W dosing groups, respectively.

Similar results were observed from Weeks 4 to 52. During this period, there was a 94% reduction from OASIS-HAE baseline in the Q4W group (median, 100%) and a 95% reduction in the Q8W group (median, 96%). The mean (SD) time-normalized HAE attack rate was 3.5 (2.13) in the Q4W group at baseline, which decreased to 0.2 (0.45) over Weeks 4 to 52, with similar improvements in the Q8W group (baseline, 2.9 [2.06]; Weeks 4–52, 0.1 [0.11]; Figure 3). Overall, patients who received donidalorsen experienced a 94% reduction in moderate or severe HAE attacks over Weeks 4 to 52 compared with baseline (Q4W, 94%; Q8W, 91%). This corresponded to a reduction in mean (SD) monthly HAE attack rates from 2.3 (2.01) overall (Q4W, 2.4 [2.02]; Q8W, 1.5 [1.86]) at baseline to 0.2 (0.36) overall (Q4W, 0.2 [0.39]; Q8W, 0.1 [0.10]) over Weeks 4 to 52 of the OLE. Compared with the OASIS-HAE baseline, patients experienced a 94% lower rate of monthly HAE attacks requiring on-demand therapy overall over Weeks 4 to 52 of the OLE treatment period (Q4W, 93%; Q8W, 97%), corresponding to a mean (SD) decrease from 2.5 (2.18) overall (Q4W, 2.6 [2.19]; Q8W, 2.5 [2.19]) at baseline to 0.2 (0.41) over the same period (Q4W, 0.2 [0.45]; Q8W, 0.1 [0.10]). The majority of patients in both treatment groups experienced a clinical response of ≥50% (Q4W, 99%; Q8W, 100%), ≥70% (Q4W, 97%; Q8W, 100%), or ≥90% (Q4W, 78%; Q8W, 79%) reduction from baseline in HAE attack rates during Weeks 4 to 52. A total of 48% (Q4W) and 29% (Q8W) were attack-free during the same period (Supplemental Figure 2); patients had a median (minimum, maximum) longest attack-free duration of 282.3 (28.0, 379.1) days overall (Q4W, 282.3 [28.0, 379.1] days; Q8W, 289.0 [129.6, 370.8] days).

Safety

Overall, 75 of 83 (90%) patients experienced ≥1 TEAE (mild, 33 [40%]; moderate, 36 [43%]; severe, 6 [7%]; Table 2). The incidence and severity of TEAEs were similar regardless of the patients' index treatment in OASIS-HAE, including those who had received placebo before initiating donidalorsen in the OLE (Supplemental Table 2).[20] Seven (8%) patients, all of whom received donidalorsen Q4W, reported serious AEs; none were considered drug related. These serious AEs included miscarriage (experienced by the patient's partner), persistent epistaxis, brain meningioma and pulmonary edema, hallux valgus, unresolved heart valve disease, mastoiditis and chronic suppurative otitis media, and one uterine fibroid growth. One patient in the Q4W group died by suicide, considered unrelated to treatment. Two patients, both on

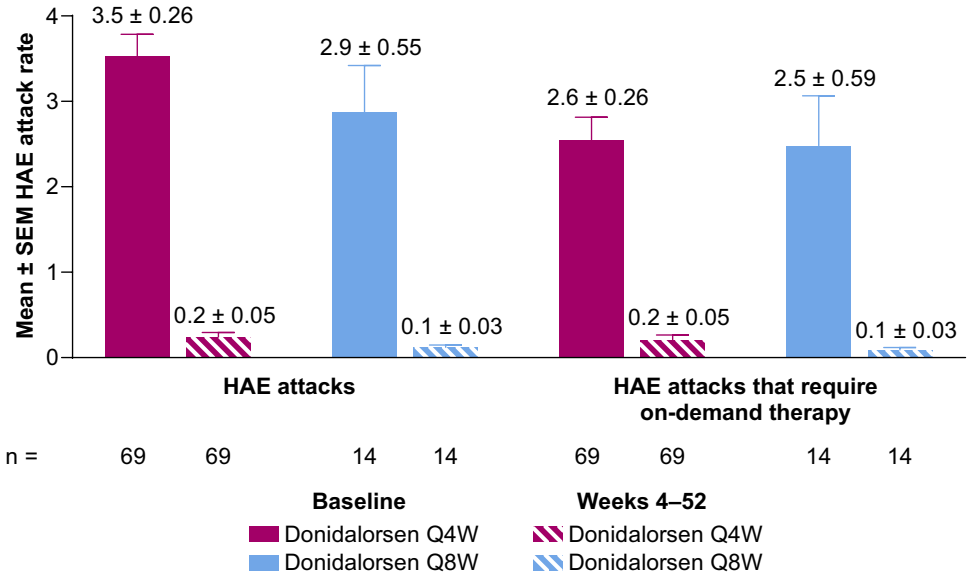

Figure 3 Mean HAE attack rate secondary endpoint measures (Weeks 4–52). HAE attacks are defined as the number of time-normalized attacks occurring every 4 weeks.
Abbreviations: HAE, hereditary angioedema; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

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Table 2 Summary of Adverse Events

n (%)	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Any TEAE	64 (92.8)	11 (78.6)	75 (90.4)
Related to study drug[a]	19 (27.5)	3 (21.4)	22 (26.5)
Leading to discontinuation	3 (4.3)	0	3 (3.6)
Any serious TEAE	7 (10.1)	0	7 (8.4)
Related to study drug[a]	0	0	0
Severity of TEAE			
Mild	28 (40.6)	5 (35.7)	33 (39.8)
Moderate	31 (44.9)	5 (35.7)	36 (43.4)
Severe	5 (7.2)	1 (7.1)	6 (7.2)
Most common TEAEs (>5% of all patients)			
Influenza	13 (18.8)	2 (14.3)	15 (18.1)
Nasopharyngitis	11 (15.9)	4 (28.6)	15 (18.1)
Back pain	9 (13.0)	3 (21.4)	12 (14.5)
Headache	10 (14.5)	1 (7.1)	11 (13.3)
Upper respiratory tract infection	10 (14.5)	0	10 (12.0)
COVID-19	9 (13.0)	1 (7.1)	10 (12.0)
ALT increased	5 (7.2)	2 (14.3)	7 (8.4)
Nausea	4 (5.8)	2 (14.3)	6 (7.2)
Diarrhea	5 (7.2)	1 (7.1)	6 (7.2)
Dyspepsia	5 (7.2)	0	5 (6.0)
Oropharyngeal pain	4 (5.8)	1 (7.1)	5 (6.0)
GGT increased	4 (5.8)	1 (7.1)	5 (6.0)
Upper abdominal pain	4 (5.8)	1 (7.1)	5 (6.0)
Injection-site discoloration	4 (5.8)	1 (7.1)	5 (6.0)
Injection-site erythema	5 (7.2)	0	5 (6.0)
Urinary tract infection	4 (5.8)	1 (7.1)	5 (6.0)

Notes: [a]Potentially related is defined as "related," "possible," or missing relationship to study drug.
Abbreviations: ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; GGT, gamma-glutamyl transferase; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

the Q4W dosing regimen, discontinued the study treatment due to treatment-related TEAEs: one experienced chest tightness, dyspnea, and back pain, and the other had a 30-day persistence of alanine aminotransferase levels at >5 times the upper limit of normal (ULN) with normal blood bilirubin concentration that resolved after treatment discontinuation. Two additional patients (one each in the Q4W and Q8W groups) had transient increases in alanine aminotransferase levels at >3 × ULN, with normal blood bilirubin concentrations, that resolved before the data cut; both patients remained on treatment.

Twenty-two (27%) patients experienced TEAEs that were considered drug related, all of which were mild or moderate in severity (Table 2). The most frequently reported TEAEs (≥10% of all patients) were influenza (18%), nasopharyngitis (18%), back pain (14%), headache (13%), COVID-19 (12%), and upper respiratory tract infection (12%; Table 2). Injection-site reactions were the most common treatment-related TEAEs; these included discoloration (6%), erythema (5%), bruising (4%), and pain (5%; Supplemental Table 3). There were no major bleeding events or treatment-related trends in activated partial thromboplastin time observed during the treatment period. No patients had a nadir platelet count below 100 x 10^9/L.

QoL, Disease Control, and Treatment Satisfaction

Compared with OASIS-HAE baseline, by Week 52, the mean improvement in AE-QoL total score in both treatment groups surpassed the clinically meaningful threshold (minimal clinically important difference ≥6 points; Figure 4 and

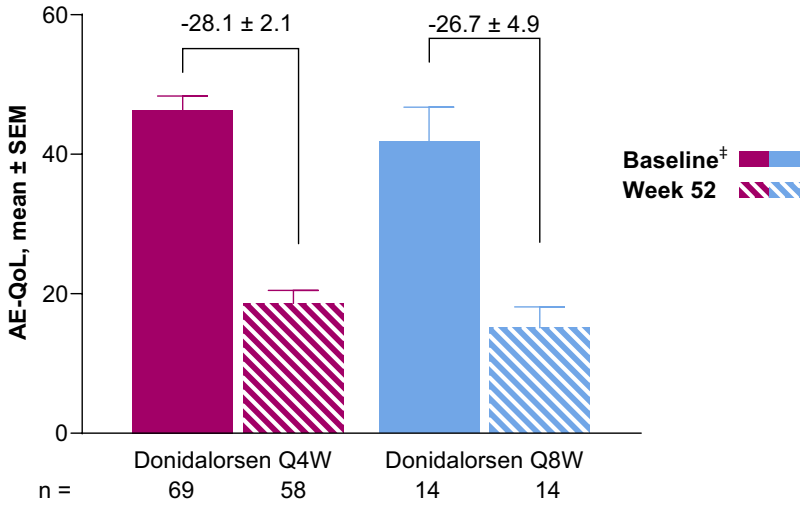

Figure 4 AE-QoL total scores† at OASIS-HAE baseline and Week 52 of the OASISplus OLE. †Mean ± SEM reductions in AE-QoL total score from baseline to Week 52 of OASISplus are presented above the bars. A minimal clinically important difference is ≥6 points.[22] ‡Week 0 in the OASIS-HAE study.
Abbreviations: AE-QoL, Angioedema Quality of Life; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

Supplemental Table 4 for total and domain scores).[22] The mean (SD) reduction from baseline in AE-QoL total score at Week 52 was 27.8 (16.1) points overall, 28.1 (15.7) points in the Q4W group, and 26.7 (18.2) points in the Q8W group. Furthermore, 68 of 70 (97%) patients with an AECT evaluation at both OASIS-HAE baseline and OASISplus Week 52 reported well-controlled disease (AECT score ≥10)[23] at Week 52; the results were similar in each treatment group (Q4W, 55 of 57 [96%]; Q8W, 13 of 13 [100%]; Supplemental Table 4).

Compared with scores at OASISplus Week 0, at Week 52, the mean (SD) HAE-QoL total scores increased from 108.0 (25.3) at baseline to 120.5 (15.4) overall, out of a maximum score of 135 points. For each treatment group, scores increased from 105.7 (26.0) at baseline to 120.2 (15.7) at Week 52 in the Q4W group, and from 120.9 (16.3) at baseline to 121.6 (14.6) at Week 52 in the Q8W group. For the TSQM-II assessment, the mean (SD) domain scores were high across all treatment groups at Week 52: effectiveness domain scores were 92.8 (13.5) overall, 92.7 (14.5) in the Q4W group, and 93.5 (8.1) in the Q8W group; convenience domain scores 89.8 (11.8) overall, 90.0 (11.0) in the Q4W group, and 88.9 (15.1) in the Q8W group; and global satisfaction domain scores were 91.3 (11.6) overall, 91.4 (11.7) in the Q4W group, and 91.1 (11.5) in the Q8W group (Supplemental Figure 3). The side effects domain is not reported as only five patients reported the presence of side effects at Week 52.

Discussion

In the OLE cohort of the ongoing OASISplus study, continued treatment with donidalorsen over 1 year of follow-up led to sustained reductions in the frequency of HAE attacks with no safety signals, consistent with results observed over 24 weeks of treatment in the parent OASIS-HAE phase 3 trial. In the OASISplus OLE cohort, patients in both dosing groups experienced a ≥94% reduction in HAE attack rate from baseline, and patients reported clinically meaningful improvement in QoL based on mean AE-QoL total score and favorable HAE-specific health-related QoL on the HAE-QoL questionnaire.[22] Moreover, 97% of patients in the study reported well-controlled disease based on the AECT at Week 52, and the majority of patients in both dosing groups were satisfied with their treatment as assessed by the TSQM-II. Of note, no safety signals were identified in the OLE cohort during the treatment period, with a median donidalorsen exposure of 392 days. The types of TEAEs were consistent with previous studies; no serious TEAEs were related to the study drug, and most events were mild to moderate in severity.[19,20,26–28]

The primary goal of HAE LTP therapy is to achieve total control of the disease and normalize patients' lives.[5] In this study, patients in the Q4W and Q8W dosing groups, including those in the placebo group in the OASIS-HAE trial who switched to donidalorsen in the OLE, experienced >90% reductions in the mean rate of moderate or severe attacks and

attacks requiring on-demand therapy. Among all patients, the median longest attack-free duration was 282 days, and even patients receiving donidalorsen with the less frequent Q8W dosing regimen experienced a substantial median longest attack-free duration of 289 days, although the Q8W group included only those who were not experiencing breakthrough attacks in the last 8 weeks of OASIS-HAE. Nonetheless, these results suggest that patients who respond well to treatment continue to do so in the long term, which supports the potential that patients who respond well to Q4W dosing may be successfully managed by transitioning to the less frequent Q8W dosing regimen.

These results from the OASISplus OLE cohort further corroborate the efficacy of donidalorsen observed during the phase 2 randomized controlled study (NCT04030598) and its corresponding OLE (NCT04307381) with follow-up through 4 years of treatment.[26–28] In the parent phase 2 trial, the mean HAE attack rate in the donidalorsen group was 90% lower than the mean HAE attack rate in the placebo group over 16 weeks,[28] which was maintained up to 4 years in the phase 2 OLE to a 97% (Q4W) reduction from baseline.[27] A subgroup of patients who initiated Q8W dosing in the phase 2 OLE also maintained a mean 83% reduction in HAE attack rate from baseline at Year 4.[27] While not explored in the trials to date, long-term data from the phase 2 and 3 studies and their OLEs suggest that initiating treatment with Q4W dosing and switching to Q8W dosing after HAE attacks are well controlled could be considered a viable long-term treatment option for some patients. Together, long-term follow-up data collected in the phase 2 OLE and through 1 year of treatment in the OASISplus OLE highlight the efficacy of the Q4W and Q8W dosing regimens of donidalorsen,[19] which provides clinicians and patients the flexibility to switch to a reduced dosing regimen for patients whose HAE is well controlled on Q4W dosing.

The safety profile of donidalorsen at 1 year in the OASISplus OLE is also consistent with the phase 2 and parent phase 3 OASIS-HAE studies.[20] Across all studies, rates of treatment discontinuations were low, and most TEAEs were mild to moderate in severity.[20,26,28] Out of all long-term safety data collected to date, the most common treatment-related events from donidalorsen treatment are mild to moderate injection-site reactions,[26,27] including injection-site discoloration, erythema, and pain as reported in this study. While not included in the present analysis of the OASISplus OLE as it was after the first year, one patient experienced a serious type 1 hypersensitivity reaction characterized by rash, dyspnea, perioral swelling, and chest pain after receiving the 29th dose of donidalorsen Q4W (being on this regimen for approximately 2.5 years). The patient fully recovered on the same day after receiving epinephrine and diphenhydramine, and donidalorsen was permanently discontinued. Overall, the results collected across phase 2 and phase 3 studies to date support an acceptable long-term safety and tolerability profile for donidalorsen.

Beyond the objective efficacy and safety assessments, patients in the OLE cohort completed several self-reported assessments of QoL, treatment satisfaction, and perceived disease control while on treatment with donidalorsen. Patients broadly reported clinically meaningful improvements in both QoL assessed by AE-QoL, and disease control assessed by the AECT. The mean (SD) improvement in AE-QoL total score was 27.8 (16.1) overall, far exceeding the minimum clinically meaningful threshold of 6 points.[22] Substantial improvements for all patients were also evident for each AE-QoL domain, as patients overall reported a mean improvement of at least 11 points for each. These data are in agreement with long-term AE-QoL assessments from the phase 2 OLE, where patients also reported clinically significant improvements of at least 21 points in both the Q4W and Q8W dosing groups after 3 years of donidalorsen treatment.[27] Similarly, in the OASISplus OLE study described here, the majority (96% in the Q4W group and all patients in the Q8W group) reported well-controlled disease on the AECT assessment at 1 year. At this same time point, patients were also highly satisfied with their treatment, as both groups scored donidalorsen favorably (≥91 out of 100 points) on the TSQM-II assessment. Together, these data further support the substantial impact of donidalorsen treatment on patients in managing their overall disease burden and improving QoL.

These results from the OLE cohort provide evidence for the safety and efficacy of long-term treatment with donidalorsen among patients who rolled over from OASIS-HAE, and the potential for switching from a prior LTP to donidalorsen is under investigation in the Switch cohort of the OASISplus study.[16] This de novo cohort of patients switched from stable doses of lanadelumab, berotralstat, or C1INH concentrates to donidalorsen 80 mg Q4W. Interim results through Week 16 after switching suggested that donidalorsen had an acceptable safety profile and reduced monthly HAE attack rates.[16] Results at 1 year of follow-up will elucidate the long-term safety and efficacy of donidalorsen after switching.

This study has some limitations. Similar to most HAE studies, the majority of patients in the OLE cohort were White; therefore, assessment of safety and efficacy data of donidalorsen in other races and ethnicities is limited. As few patients received Q8W dosing in the OASISplus OLE, additional long-term follow-up and real-world studies of donidalorsen at this dosing regimen may provide further insight on the efficacy and safety of Q8W dosing. Furthermore, OLE studies have a risk of selection bias, as patients with favorable safety and efficacy tend to continue in the trial, although the majority (92.2%) of patients enrolled in OASIS-HAE continued on into the OLE, and among all patients who entered the OLE, a high percentage (90.4%) have completed Year 1. Finally, the lack of a placebo group comparator, intrinsic to open-label study designs, prevents inferential statistics and may limit interpretation of the results.

Conclusions

Overall, the 1-year results from the OASISplus OLE study support the long-term safety of donidalorsen, consistent with previous results up to 4 years of long-term treatment.[27] This analysis suggests that both patients who continued donidalorsen from OASIS-HAE and those who transitioned from placebo in the OASISplus OLE cohort experienced sustained reductions in HAE attack rates and improvements in their QoL and disease control with 52 weeks of treatment. Donidalorsen was recently approved in the United States in 2025 for the prophylaxis of HAE attacks in adults and pediatric patients 12 years of age and older, and these long-term results from the OASISplus OLE cohort add to the evidence supporting the efficacy and safety of donidalorsen for the long-term management of HAE, which will be further elucidated as real-world evidence emerges.

Abbreviations

HAE, hereditary angioedema; C1INH, C1 inhibitor; QoL, quality of life; LTP, long-term prophylactic treatment; SC, subcutaneous; GalNAc, triantennary *N*-acetylgalactosamine; ASO, antisense oligonucleotide; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event; OLE, open-label extension; AE-QoL, Angioedema Quality of Life; AECT, Angioedema Control Test; HAE-QoL, Hereditary Angioedema Quality of Life; TSQM-II, Treatment Satisfaction Questionnaire for Medication version 2; SD, standard deviation.

Data Sharing Statement

Data requests from qualified researchers to the corresponding author (Danny M. Cohn) will be considered once all three of the following criteria are met: (1) 12 months from marketing approval of the study drug in both the United States and European Union; (2) 18 months from the conclusion of the study; and (3) 6 months from publication of this article. For additional information, visit https://vivli.org/ourmember/ionis/.

Ethics Approval and Consent to Participate

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Protocols were reviewed and approved by an independent ethics committee and institutional review board in each country. All participants provided written informed consent prior to entering the study.

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