Poster #R074

Donidalorsen For Long-Term Management Of Hereditary Angioedema: 2-Year Results From The OASISplus Open-Label Extension Cohort

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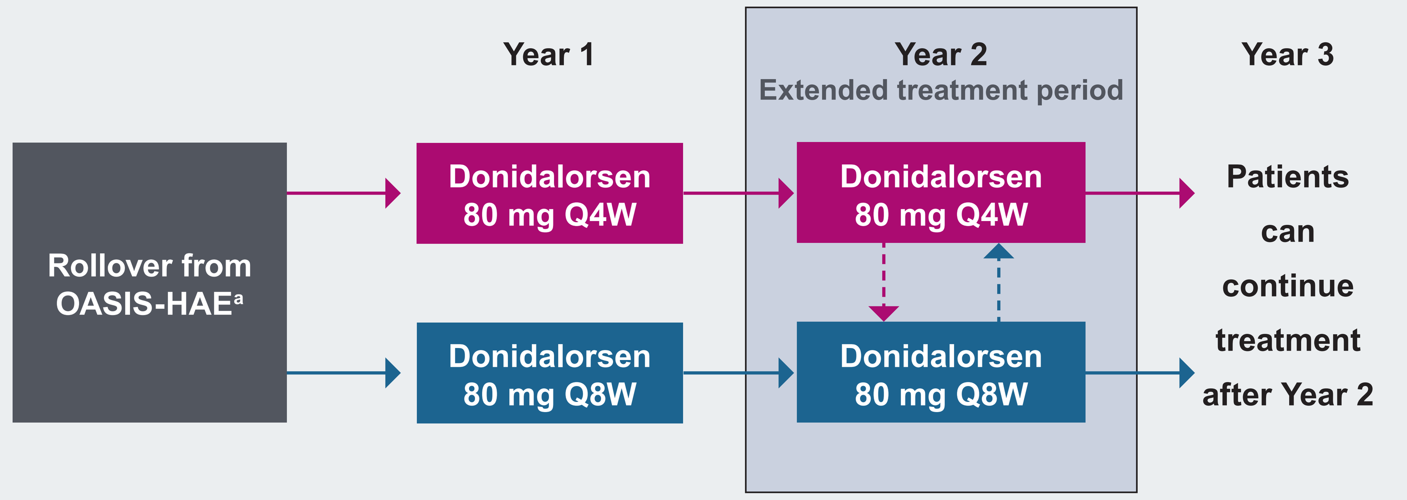
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Introduction

- Hereditary angioedema (HAE) is a rare disease characterized by painful and potentially life-threatening attacks of tissue swelling[1]
- Donidalorsen is a prekallikrein messenger RNA–targeted antisense oligonucleotide approved for prophylaxis to prevent HAE attacks in adults and adolescents[2]
- In the pivotal phase 3 OASIS-HAE study (NCT05139810), donidalorsen administered subcutaneously (SC) once every 4 weeks (Q4W) and once every 8 weeks (Q8W) demonstrated acceptable safety, reductions in HAE attack rate, and improvements in quality of life and disease control for 24 weeks[3]
- Following OASIS-HAE, the phase 3 OASISplus study (NCT05392114) is assessing the long-term safety and efficacy of donidalorsen 80 mg SC Q4W or Q8W among patients who continued treatment (open-label extension [OLE] cohort) or in an independent cohort of patients who switched from their prior long-term prophylaxis to donidalorsen Q4W
  - At Year 1, patients in both the OLE and Switch cohorts maintained reductions in HAE attack rate and improvements in quality of life with no safety signals[4,5]
  - After completing the first year, patients entered an extended treatment period where they could change between Q4W and Q8W dosing
- Here, we present 2-year safety and efficacy results from the OASISplus OLE cohort of patients who received donidalorsen 80 mg SC Q4W or Q8W

Study Design

Figure 1. Study Design for the OASISplus OLE Cohort



[a]Patients who were not attack-free for ≥8 weeks (Weeks 16–24 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.
HAE, hereditary angioedema; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Eligible patients were ≥12 years of age with HAE-C1 inhibitor (C1INH)-Type1 or HAE-C1INH-Type2 and completed 24 weeks of the OASIS-HAE study or had ≥5 HAE attacks per month, in which case they could enter the OLE study early and receive donidalorsen Q4W
  - Through Year 1, patients received donidalorsen Q4W if they had received donidalorsen or placebo Q4W in OASIS-HAE; patients received donidalorsen Q8W if they had received donidalorsen or placebo Q8W in OASIS-HAE, unless they experienced an HAE attack within the last 8 weeks of OASIS-HAE (Weeks 16–24), in which case they were assigned to donidalorsen Q4W in OASISplus
  - After completing 1 year of treatment, patients could change dosage to donidalorsen Q4W or Q8W and were allowed to revert back to their prior dosage after changing
- The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs)
- Additional endpoints included the following:
  - The time-normalized rate of investigator-confirmed HAE attacks per month for 2 years
  - Angioedema Quality of Life Questionnaire (AE-QoL) total score at baseline (in OASIS-HAE) and Year 1 and Year 2 (in OASISplus)
- Interim 2-year results are reported from a January 2026 data cutoff

Results

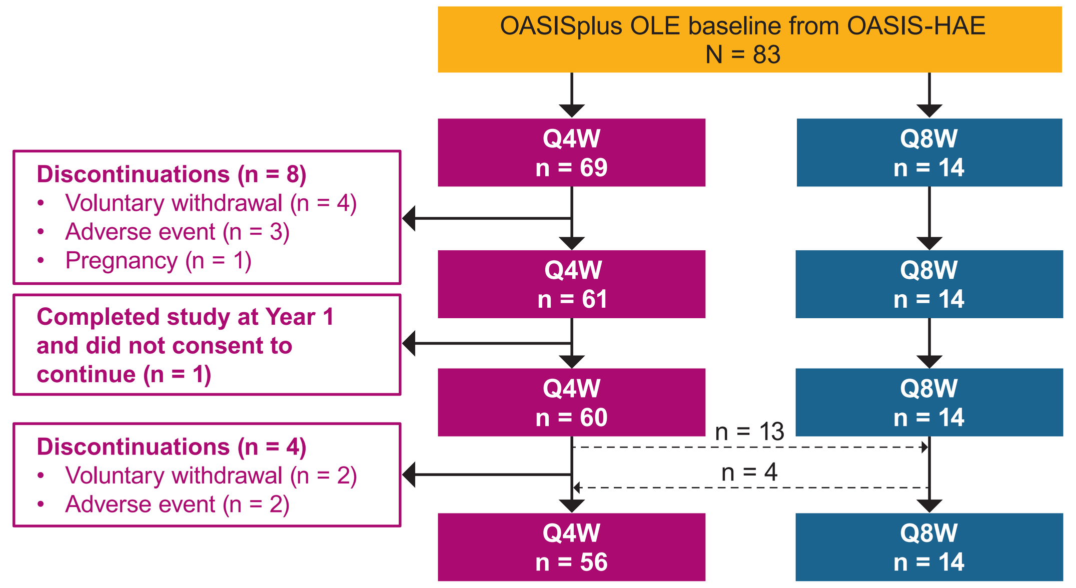
Table 1. OASISplus OLE Cohort Patient Disposition and Baseline Demographics

	Q4W (n = 69)	Q8W (n = 14)	Total (N = 83)
Patients who completed 2 years, n (%)	56 (81)	14 (100)	70 (84)
Reasons for discontinuation, n (%)			
Voluntary withdrawal	6 (9)	0	6 (7)
Adverse event	5 (7)	0	5 (6)
Lack of efficacy	0	0	0
Pregnancy	1 (1)	0	1 (1)
Age, years, mean ± SD	38 (14)	30 (9)	37 (14)
Age category, years, n (%)			
12–17	5 (7)	2 (14)	7 (8)
18–39	32 (46)	10 (71)	42 (51)
40–64	31 (45)	2 (14)	33 (40)
≥65	1 (1)	0	1 (1)
Sex, n (%)			
Female	40 (58)	5 (36)	45 (54)
Male	29 (42)	9 (64)	38 (46)
Race, n (%)			
White	62 (90)	14 (100)	76 (92)
American Indian and/or Alaska Native	3 (4)	0	3 (4)
Asian	1 (1)	0	1 (1)
Black or African American	1 (1)	0	1 (1)
Multiple	1 (1)	0	1 (1)
Other[a]	1 (1)	0	1 (1)

[a]Patients could select "Other" on the clinical report form and write in an answer.
OLE, open-label extension; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation.

- A total of 83 (Q4W, 69; Q8W, 14) patients completed OASIS-HAE and enrolled in the OASISplus OLE cohort
- Twelve (14%) patients discontinued during the 2-year study: 6 (7%) due to voluntary withdrawal, 5 (6%) due to an adverse event, and 1 (1%) due to pregnancy
  - Additionally, 1 (2%) patient completed Year 1 but did not consent to continue the extended treatment period with flexible dosing (Year 2) of the study and was not counted as a discontinuation

Figure 2. Flow of Patients in the OASISplus OLE Cohort



Disposition shown here is based on the patient's index treatment group and does not account for changing between Q4W and Q8W groups.
HAE, hereditary angioedema; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- After Year 1, 13 (19%) patients changed from Q4W to Q8W dosing, resulting in a total of 27 patients in the Q8W group at Year 2
  - Four patients changed from Q8W to Q4W dosing, resulting in a total of 73 patients in the Q4W group
  - One patient who changed to Q8W dosing reverted back to Q4W dosing

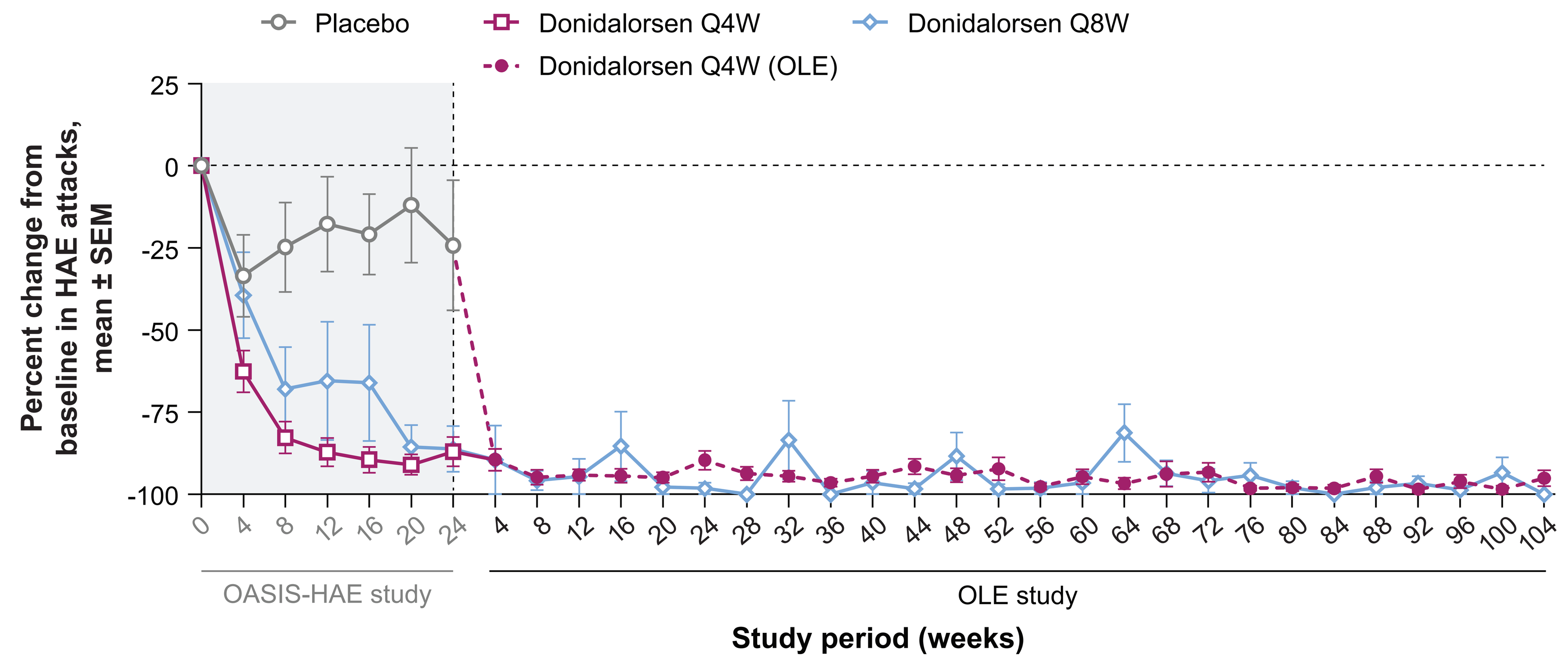
Table 2. Summary of Adverse Events Categorized by Dose at the Time of the Event in the OASISplus OLE Cohort

n (%)	Q4W (n = 73)[a]	Q8W (n = 27)[a]	Total (N = 83)
TEAEs leading to discontinuation	5 (7)	0	5 (6)
Treatment-related TEAEs	28 (38)	4 (15)	30 (36)
Leading to discontinuation	4 (5)	0	4 (5)
Any serious TEAEs	9 (12)	0	9 (11)
Related to study drug	0	0	0
Deaths	1 (1)	0	1 (1)[b]
Related to study drug	0	0	0
Treatment-related TEAEs in ≥5% of total patients			
Injection-site erythema	6 (8)	0	6 (7)
ALT increased	4 (5)	1 (4)	5 (6)
Injection-site discoloration	5 (7)	1 (4)	5 (6)
Injection-site pain	4 (5)	0	4 (5)
Injection-site pruritus	4 (5)	0	4 (5)

Patients who changed dosing could be counted under both treatment groups (donidalorsen 80 mg Q4W and Q8W).
[a]Each event is counted under the dose regimen that patients were receiving at the time of the event.
[b]Suicide deemed by study investigator as not treatment related.
ALT, alanine aminotransferase; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

- Most (83%) TEAEs were mild or moderate in severity, and 30 (36%) patients reported treatment-related TEAEs
  - One death (suicide) occurred during the study and was deemed by the investigator as not treatment related
- Serious TEAEs were reported in 9 (11%) patients; none were considered study drug related

Figure 3. Percent Change From Baseline (in OASIS-HAE) in Monthly HAE Attack Rate in the OLE Cohort

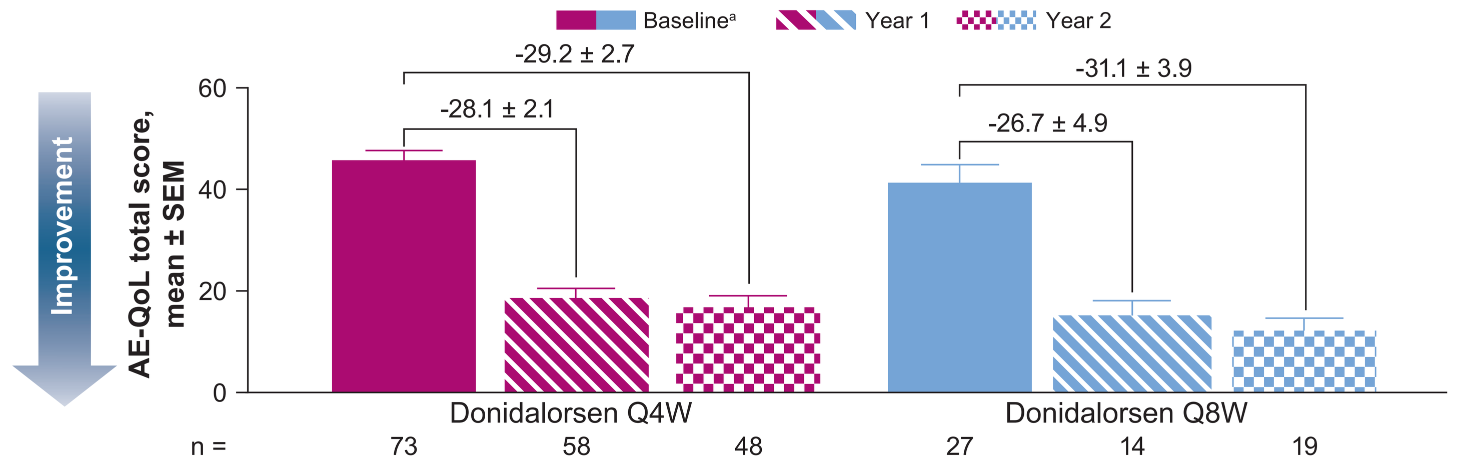


Placebo, n = 19 19 19 19 18 17 16
Doni 80 mg Q4W, n = 44 44 44 44 44 43 43 69 69 68 68 68 68 68 68 66 65 62 61 61 61 55 54 53 53 53 56 55 55 53 51 50 50
Doni 80 mg Q8W, n = 20 20 20 20 20 20 19 14 14 14 14 14 14 14 14 14 14 14 14 14 14 19 20 21 21 21 18 19 18 19 20 20 20

HAE attack rate at each time point is calculated and counted under the dosing regimen that the patients were on at the onset of the event. Patients who changed dosing regimen could be counted under both treatment groups.
The OASIS-HAE study is indicated by gray shading.
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.

- Patients who entered OASISplus maintained a 95% reduction overall from baseline in HAE attack rates throughout the 2-year OLE in both dosing groups (Q4W, 95%; Q8W, 93%)

Figure 4. AE-QoL Total Scores in the OLE Cohort

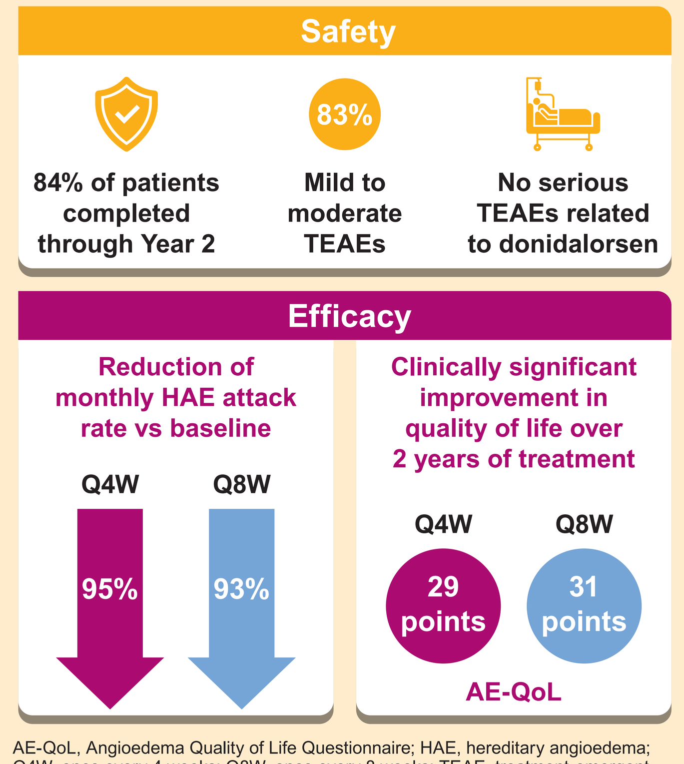


[a]Week 0 in the OASIS-HAE study.
AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Overall, patients reported clinically meaningful improvements (≥6 points)[6] in mean AE-QoL total score at Year 1 and Year 2 compared with their baseline in OASIS-HAE
  - Similar improvements from baseline in AE-QoL total scores were observed in patients from both the Q4W and Q8W dosing groups by Year 2 (Q4W, 29.2; Q8W, 31.1)

Conclusions

- Donidalorsen treatment demonstrated an acceptable long-term safety profile with no new safety signals for 2 years
  - Patients experienced a 95% reduction overall in HAE attack rates compared with their baseline in OASIS-HAE; a total of 13 patients changed to Q8W dosing
  - The reduction in HAE attack rates was sustained during 2 years of donidalorsen treatment regardless of dosing frequency
- Patients maintained a clinically meaningful improvement (≥6 points)[6] in AE-QoL total scores from their baseline in OASIS-HAE through Year 2 of OASISplus, regardless of dosing frequency
- These data support the long-term use of donidalorsen 80 mg Q4W and Q8W in patients with HAE and demonstrate the feasibility of transitioning to Q8W dosing in some patients



AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

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