Poster #R075

Switching From Prior Long-Term Prophylactic Treatments To Donidalorsen For Hereditary Angioedema: 2-Year Results From OASISplus

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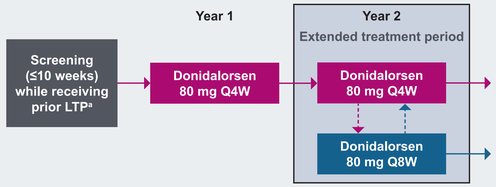
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Introduction

- 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 in patients who continued donidalorsen treatment (open-label extension [OLE] cohort) or in an independent cohort of patients who switched from their prior long-term prophylactic treatment (LTP; lanadelumab, berotralstat, or C1 inhibitor [C1INH]) 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]
- Here, we present interim safety and efficacy results at Year 2 for patients who switched from their prior LTP to donidalorsen 80 mg SC Q4W, or Q8W after 1 year, in the ongoing OASISplus study

Study Design

Figure 1. OASISplus Switch Cohort Design



[a]Prior LTPs included lanadelumab, berotralstat, and C1INH.
C1INH, C1 inhibitor; LTP, long-term prophylactic treatment; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Eligible patients were ≥12 years of age with HAE-C1INH-Type1 or HAE-C1INH-Type2 and on stable doses (≥12 weeks) of lanadelumab, berotralstat, or C1INH
- All patients switched from their prior LTP (lanadelumab, berotralstat, or C1INH) to donidalorsen 80 mg administered SC Q4W, without washout via a predefined algorithm, for the first year of the study
  - Prior lanadelumab: Last dose 14 ± 3 days prior to the first dose of donidalorsen
  - Prior berotralstat or C1INH: Last dose 14 ± 3 days after the first dose of donidalorsen
- After completing Year 1, patients could change dosing frequency to Q8W or back to Q4W
- 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 (on patients' prior LTP) and Year 1 and Year 2 (on donidalorsen)
- Interim 2-year results are reported from a January 2026 data cutoff

Results

Table 1. OASISplus Switch Patient Disposition and Baseline Demographics

	Prior LTP before switching to donidalorsen			
	Lanadelumab (n = 32)	Berotralstat (n = 11)	C1INH (n = 22)	Total (N = 65)
Patients dosed, n (%)	31 (97)	11 (100)	22 (100)	64 (98)
Patients who completed 1 year, n (%)	24 (75)	11 (100)	19 (86)	54 (83)[a]
Patients who completed 2 years, n (%)	22 (69)	11 (100)	18 (82)	51 (78)
Reasons for discontinuation, n (%)				
Voluntary withdrawal	2 (6)	0	2 (9)	4 (6)
Adverse event	1 (3)	0	0	1 (2)
Lack of efficacy	4 (13)	0	1 (5)	5 (8)
Pregnancy	1 (3)	0	0	1 (2)
Loss to follow-up	1 (3)	0	0	1 (2)
Other (not dosed)	1 (3)	0	0	1 (2)
Age, years, mean (SD)	40 (14)	46 (11)	41 (17)	42 (15)
Age category, years, n (%)[b]				
12–17	1 (3)	0	3 (14)	4 (6)
18–39	14 (45)	4 (36)	6 (27)	24 (38)
40–64	15 (48)	7 (64)	12 (55)	34 (53)
≥65	1 (3)	0	1 (5)	2 (3)
Sex, n (%)[b]				
Female	14 (45)	8 (73)	16 (73)	38 (59)
Male	17 (55)	3 (27)	6 (27)	26 (41)
Race, n (%)[b]				
White	26 (84)	11 (100)	20 (91)	57 (89)
Asian	1 (3)	0	0	1 (2)
Black or African American	1 (3)	0	1 (5)	2 (3)
American Indian and/or Alaska Native	0	0	0	0
Multiple	0	0	1 (5)	1 (2)
Other[c]	3 (10)	0	0	3 (5)

[a]One patient in the Switch cohort completed Year 1 and did not consent to enter the extended treatment period through Year 2; they were not counted as a discontinuation.
[b]Percentages were calculated out of the total number of dosed patients.
[c]Patients could select "Other" on the clinical report form and write in an answer.
C1INH, C1 inhibitor; LTP, long-term prophylactic treatment; SD, standard deviation.

- Overall, 64 of 65 (98%) patients received their first dose of donidalorsen and 51 (78%) completed treatment through Year 2
- Thirteen (20%) discontinued the study before the Year 2 analysis: 5 (8%) due to lack of efficacy, 4 (6%) due to voluntary withdrawal, and 1 (2%) each due to adverse events, loss to follow-up, pregnancy, or other (not dosed)
  - Additionally, 1 (2%) patient completed Year 1 but did not consent to continue Year 2 of the study
- A total of 4 patients changed to Q8W dosing during their second year of treatment

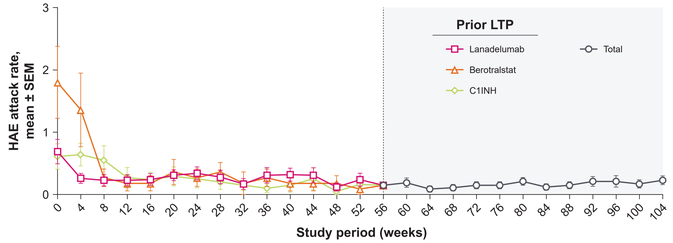
Table 2. Summary of Adverse Events

n (%)	Q4W (n = 64)[a]	Q8W (n = 4)[a]	Total (N = 64)
TEAEs leading to discontinuation	1 (2)	0	1 (2)
Treatment-related TEAEs	28 (44)	2 (50)	29 (45)
Leading to discontinuation	0	0	0
Any serious TEAEs	4 (6)	0	4 (6)
Related to study drug	0	0	0
Deaths	0	0	0
Treatment-related TEAEs in ≥5% of total patients			
Injection-site erythema	9 (14)	0	9 (14)
Injection-site discoloration	5 (8)	0	5 (8)
Injection-site pain	7 (11)	0	7 (11)
Injection-site pruritus	7 (11)	0	7 (11)
Fatigue	5 (8)	0	5 (8)

Patients who changed dosing could be counted under both treatment groups based on what dose they were receiving at the time they reported a TEAE.
[a]Each dose is counted under the dose regimen that patients were assigned to at the onset of the event.
Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

- Overall, most TEAEs (83%) were mild or moderate in severity; 29 (45%) patients reported treatment-related TEAEs, none of which led to treatment discontinuation
- Serious TEAEs were reported in 4 (6%) patients; none were considered study drug related

Figure 2. Mean Monthly HAE Attack Rate Over 2 Years

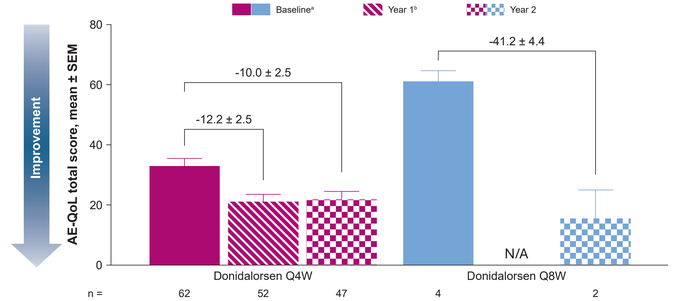


Total, N =	64	64	63	63	61	61	60	60	60	60	59	57	56	55	54	53	53	53	53	53	52	52	52	52	52	52	52
Q4W, n =	64	64	63	63	61	61	60	60	60	60	59	57	56	55	54	53	51	51	51	51	50	50	50	50	49	49	50
Q8W, n =															0	0	2	2	2	2	2	2	2	2	3	3	2

HAE attack rate at each time point is calculated and counted under the dose regimen that the patients were taking at the onset of the event. Patients who changed dosing could be counted under both treatment groups.
During Year 1, all patients received donidalorsen 80 mg Q4W. The flexible dosing period is denoted by a dashed vertical line and gray shading starting at Week 56.
C1INH, C1 inhibitor; HAE, hereditary angioedema; LTP, long-term prophylactic treatment; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- During the 2 years of treatment, patients overall experienced a reduction in HAE attack rate of 71% from baseline on their prior LTP (Q4W, 72%; Q8W, 86%)
  - Patients who changed to Q8W dosing demonstrated an 86% reduction in HAE attack rate compared with their baseline on prior LTPs; changes in the number of patients at the end of Year 2 did not impact efficacy results

Figure 3. AE-QoL Total Scores in the Switch Cohort



[a]Baseline is defined as the last measurement on or prior to Day 1 of OASISplus.
[b]Patients in the Switch cohort could not receive donidalorsen Q8W until entering the flexible dosing period after Year 1.
AE-QoL, Angioedema Quality of Life Questionnaire; N/A, not applicable; 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 on prior LTP

Conclusions

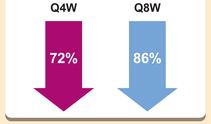
- Donidalorsen treatment demonstrated an acceptable long-term safety profile with no new safety signals
- Patients experienced a 71% reduction overall in HAE attack rates compared with their baseline while on prior LTPs (lanadelumab, berotralstat, or C1INH); 4 patients who changed to Q8W dosing during Year 2 reported an 86% reduction in HAE attack rates compared with baseline on their prior LTP
- Patients maintained a clinically meaningful improvement (≥6 points)[6] in AE-QoL total scores at Year 2, regardless of dosing frequency
- These data support the long-term use of donidalorsen 80 mg Q4W and Q8W in patients who may wish to switch LTPs
  - Q8W dosing is a suitable option for patients with HAE who have achieved controlled disease on a Q4W dosing schedule

Safety

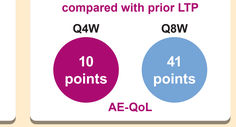
- 78% of patients completed through Year 2
- 83% Mild to moderate TEAEs
- No serious TEAEs related to donidalorsen

Efficacy

Reduction of monthly HAE attack rate vs prior LTP



Clinically significant improvement in quality of life over 2 years of treatment compared with prior LTP



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

REFERENCES

1. Watt M, et al. *Orphanet J Rare Dis*. 2026;21(1):55.
2. Dawnzera (donidalorsen). Full Prescribing Information. Carlsbad, CA: Ionis Pharmaceuticals, Inc.; 2025.
3. Riedl MA, et al. *N Engl J Med*. 2024;391(1):21-31.
4. Lumry WR, et al. *J Asthma Allergy*. 2026;19:592079.
5. Riedl MA, et al. *Allergy*. 2026;81(8):2833-42.
6. Weller K, et al. *Allergy*. 2016;71(8):1203-9.

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