Poster 890

Efficacy and Safety of Donidalorsen in Adolescent Patients With Hereditary Angioedema: A Subanalysis of the Phase 3 OASIS-HAE Study

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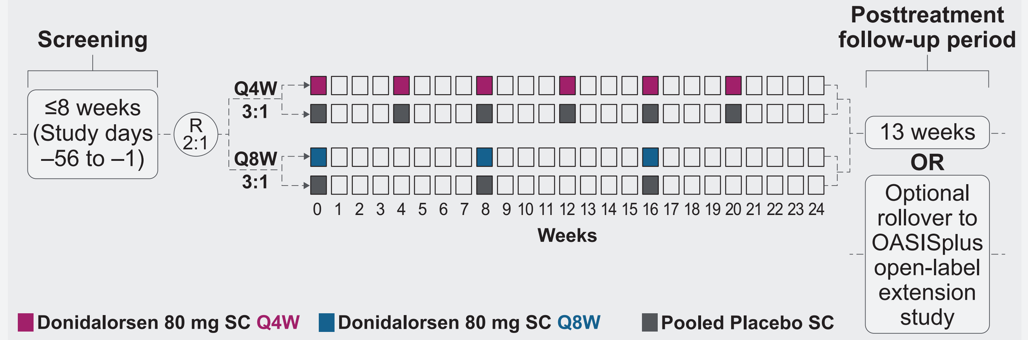
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Background

- Hereditary angioedema (HAE) is a rare disease characterized by frequently severe, potentially life-threatening attacks of tissue swelling[1,2]
- HAE is most often caused by C1 inhibitor (C1INH) deficiency (HAE-C1INH-Type1) or dysfunction (HAE-C1INH-Type2)[3]
- Symptoms usually first present in childhood, and adolescents experiencing HAE attacks report lower quality of life and elevated anxiety compared with healthy controls[4,5]
- Donidalorsen is an investigational RNA-targeted antisense oligonucleotide that specifically reduces prekallikrein production in the liver[6]
- In the phase 3 OASIS-HAE study (NCT05139810), donidalorsen 80 mg subcutaneously (SC) once every 4 weeks (Q4W) or once every 8 weeks (Q8W) significantly reduced HAE attack rate and improved patient-reported quality of life[6]
- Here, we report results for adolescent patients in OASIS-HAE

Study Design

Figure 1. Study Design



Screening
≤8 weeks (Study days −56 to −1)
R 2:1
Q4W 3:1
Q8W 3:1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Weeks
Posttreatment follow-up period
13 weeks
OR
Optional rollover to OASISplus open-label extension study
Donidalorsen 80 mg SC Q4W
Donidalorsen 80 mg SC Q8W
Pooled Placebo SC

Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, randomization; SC, subcutaneously.

- OASIS-HAE was a global, randomized, double-blind, placebo-controlled trial
- Patients were ≥12 years of age with HAE-C1INH-Type1 or HAE-C1INH-Type2
- Patients were randomized to receive donidalorsen 80 mg or placebo SC Q4W or Q8W for 24 weeks
- Endpoints included:
 - Time-normalized HAE attack rate
 - Incidence and severity of treatment-emergent adverse events (TEAEs)
 - Change in Angioedema Quality of Life Questionnaire (AE-QoL) total score (secondary endpoint)
 - Percent of patients with well-controlled disease based on the Angioedema Control Test (AECT; secondary endpoint)
 - Plasma prekallikrein concentrations (exploratory endpoint)

Results

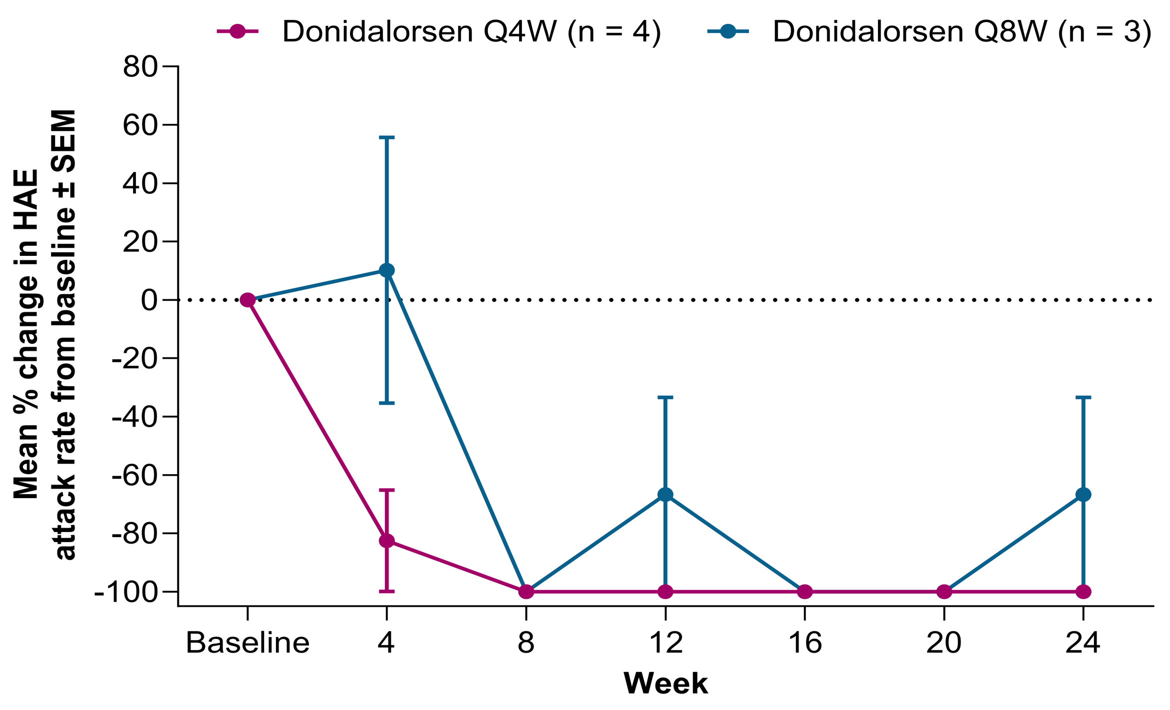
Table 1. Demographics of Adolescent Patients

	Donidalorsen Q4W (n = 4)	Donidalorsen Q8W (n = 3)	Pooled Placebo (n = 0)	Total (N = 7)
Age, years, median (range)	15 (12–17)	15 (12–16)	—	15 (12–17)
Sex, n (%)				
Male	3 (75)	1 (33)	—	4 (57)
Female	1 (25)	2 (67)	—	3 (43)
Race, n (%)				
White	4 (100)	2 (67)	—	6 (86)
American Indian or Alaskan Native	0	1 (33)	—	1 (14)
Region, n (%)				
North America	0	2 (67)	—	2 (29)
Europe	1 (25)	0	—	1 (14)
Middle East	3 (75)	1 (33)	—	4 (57)

Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Seven adolescent patients (12–17 years of age) with HAE enrolled in OASIS-HAE
- No adolescent patients were randomized to placebo (randomization scheme did not stratify by age)

Figure 2. HAE Attack Rate in Adolescents (Weeks 0–24)



Donidalorsen Q4W (n = 4)
Donidalorsen Q8W (n = 3)
Mean % change in HAE attack rate from baseline ± SEM
80
60
40
20
0
-20
-40
-60
-80
-100
Baseline
4
8
12
16
20
24
Week

Baseline was defined as the 56-day run-in period prior to dosing in OASIS-HAE.
HAE, hereditary angioedema; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Compared to baseline, mean HAE attack rates over Weeks 0 to 24 were 97% lower in the Q4W group and 71% lower in the Q8W group
 - Median reductions from baseline in HAE attack rates were −100% in the Q4W group and −87% in the Q8W group

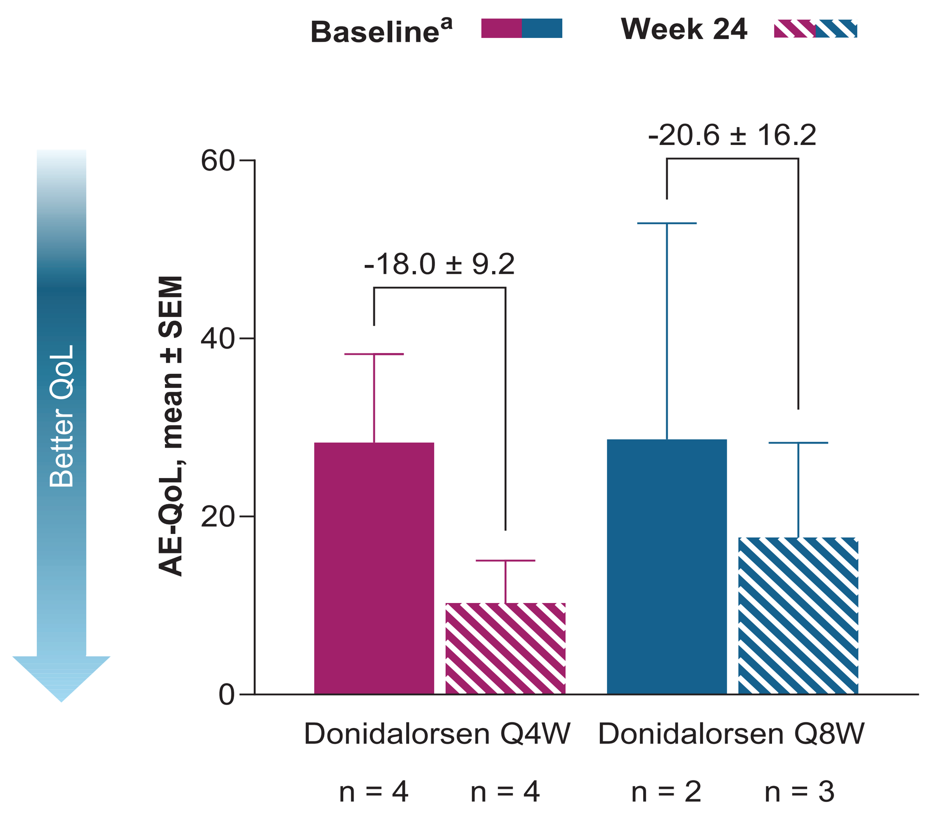
Table 2. Summary of Adverse Events

	Donidalorsen Q4W (n = 4)	Donidalorsen Q8W (n = 3)	Total (N = 7)
Any TEAE,[a] n (%)	2 (50)	1 (33)	3 (43)
Related to study drug[b]	1[c] (25)	0	1[c] (14)
Leading to permanent treatment discontinuation	0	0	0
Any serious TEAE[a], n (%)	0	0	0
Severity of TEAEs[a], n (%)			
Mild	1 (25)	0	1 (14)
Moderate	1 (25)	1 (33)	2 (29)
Severe	0	0	0

[a]A TEAE is defined as any AE starting or getting worse on or after the first dose of the study drug. [b]Related is defined as related, possible, or missing relationship to study drug. [c]The TEAE was an increase in acne judged as possibly related to the study drug.
AE, adverse event; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

- Three adolescent patients had TEAEs, none of which were severe, serious, or led to treatment discontinuation
- The most common TEAE was nasopharyngitis

Figure 3. Patient-Reported Quality of Life (AE-QoL)

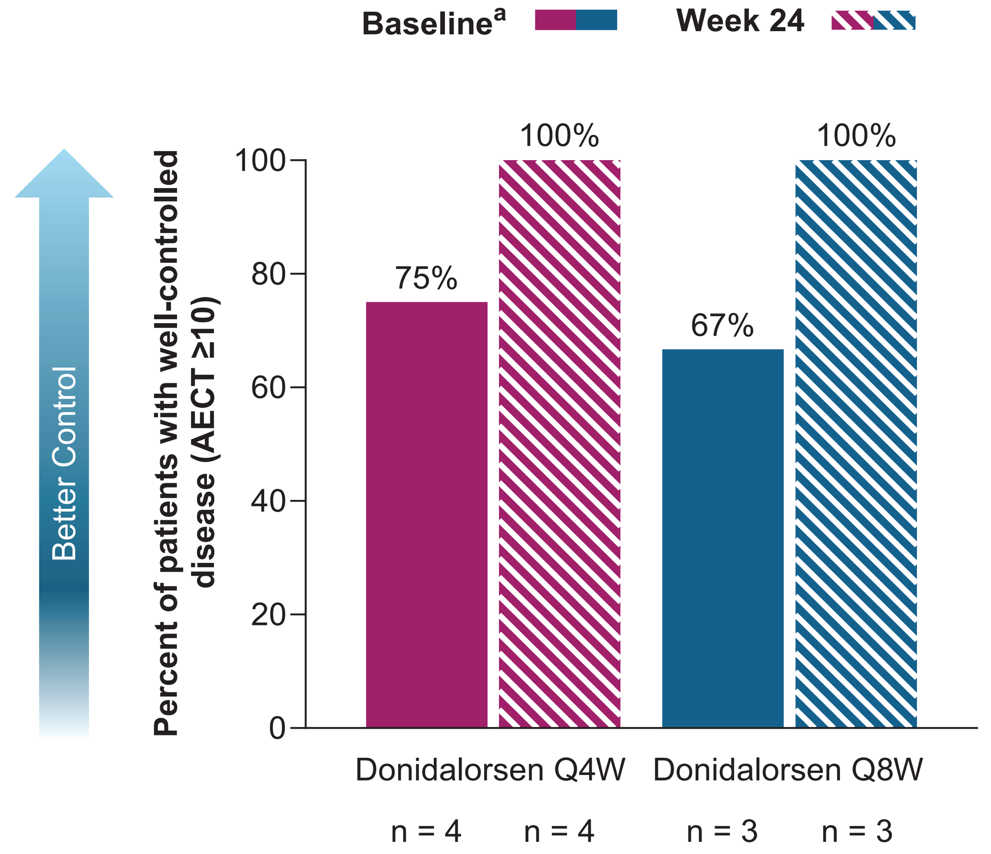


Baseline[a]
Week 24
Better QoL
AE-QoL, mean ± SEM
60
40
20
0
-18.0 ± 9.2
-20.6 ± 16.2
Donidalorsen Q4W
Donidalorsen Q8W
n = 4
n = 4
n = 2
n = 3

The AE-QoL was developed and validated in adult patients.[7]
[a]Defined as available AE-QoL total scores on study day 1.
AE-QoL, Angioedema Quality of Life Questionnaire; Q4W, once every 4 weeks; Q8W, once every 8 weeks; QoL, quality of life; SEM, standard error of the mean.

- Adolescents in both treatment groups reported clinically meaningful improvements in AE-QoL total score (≥6-point reduction)[8] at Week 24

Figure 4. Patients With Well-Controlled Disease (AECT)

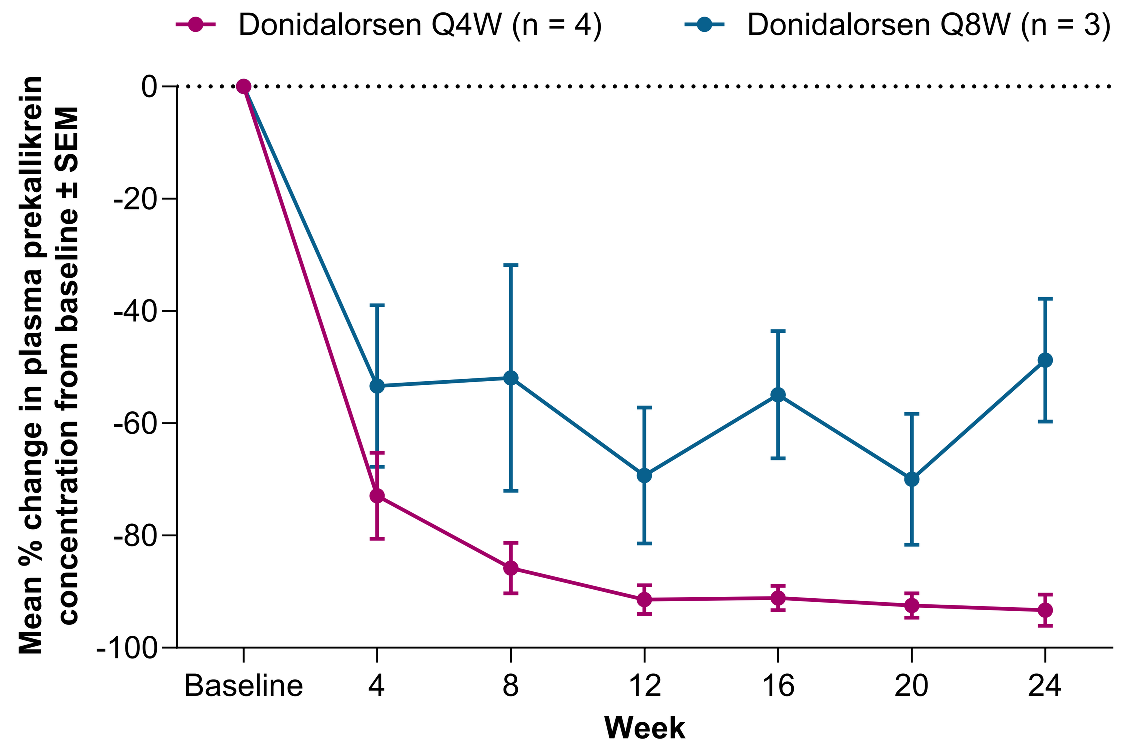


Baseline[a]
Week 24
Better Control
Percent of patients with well-controlled disease (AECT ≥10)
100
80
60
40
20
0
75%
100%
67%
100%
Donidalorsen Q4W
Donidalorsen Q8W
n = 4
n = 4
n = 3
n = 3

The AECT was developed and validated in adult patients.[9]
[a]Defined as AECT scores collected on study day 1.
AECT, Angioedema Control Test; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- By Week 24, all adolescent patients reported well-controlled disease (AECT ≥10)[10] on the AECT

Figure 5. Plasma Prekallikrein Concentrations in Adolescents (Weeks 0–24)



Donidalorsen Q4W (n = 4)
Donidalorsen Q8W (n = 3)
Mean % change in plasma prekallikrein concentration from baseline ± SEM
0
-20
-40
-60
-80
-100
Baseline
4
8
12
16
20
24
Week

Baseline was defined as the average of the pre-dose study day 1 value and the last pre-dose value prior to study day 1. If there was only 1 pre-dose measurement available, it was assigned as baseline.
Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Plasma prekallikrein concentrations decreased from baseline to Week 24 by 93% in the Q4W group and 49% in the Q8W group

Conclusions

HAE Attack Rate

- HAE attack rates in adolescent patients decreased from baseline by 97% in the Q4W group and 71% in the Q8W group over Weeks 0–24
- Improvements in HAE attack rates in adolescent patients were consistent with the overall efficacy results of OASIS-HAE[6]

Safety and Tolerability

- Donidalorsen had an acceptable safety profile in adolescents

Quality of Life and Disease Control

- Adolescent patients reported clinically meaningful improvements in quality of life, and all reported well-controlled disease by Week 24 of treatment

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DISCLOSURES

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