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Donidalorsen For Hereditary Angioedema: Results From The OASISplus Open-Label Extension Study

Raffi Tachdjian[1], Marc A. Riedl[2], Laura Bordone[3], Kenneth B. Newman[3], Sabrina Treadwell[3], Tao Lin[3], Aaron Yarlas[3], Danny M. Cohn[4]

[1]Division of Allergy, Immunology, and Rheumatology, University of California Los Angeles, Los Angeles, CA, USA; [2]Division of Allergy and Immunology, University of California San Diego School of Medicine, La Jolla, CA, USA; [3]Ionis, Carlsbad, CA, USA; [4]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

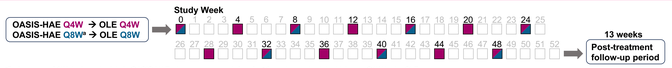
INTRODUCTION

- Hereditary angioedema (HAE) is a rare, chronic disease characterized by frequently severe and potentially fatal attacks of tissue swelling[1-3]
- HAE is most frequently caused by either deficiency (HAE-C1INH-Type1) or dysfunction (HAE-C1INH-Type2) of C1 inhibitor (C1-INH), which leads to kallikrein-kinin system dysregulation[1-3]
- Donidalorsen is an investigational RNA-targeted antisense oligonucleotide that specifically reduces plasma prekallikrein production in the liver[4]
- In the phase 3 OASIS-HAE study (NCT05139810), donidalorsen 80 mg administered subcutaneously (SC) once every 4 weeks (Q4W) or every 8 weeks (Q8W) significantly reduced the monthly rate of HAE attacks vs placebo and improved patient-reported quality of life over 24 weeks[4]
- Here, we report interim results of patients from OASIS-HAE who subsequently enrolled in the ongoing OASISplus open-label extension (OLE) study (NCT05392114)

METHODS

- Patients previously on placebo or donidalorsen in the phase 3 OASIS-HAE study (NCT05139810) received donidalorsen 80 mg SC per their original dosing schedule (Q4W or Q8W) over 52 weeks
  - If patients who received donidalorsen or placebo Q8W in OASIS-HAE were not attack-free for ≥8 weeks, they received donidalorsen Q4W in the OLE
- Primary endpoint: Incidence of treatment-emergent adverse events (TEAEs)
- Other endpoints:
  - Time-normalized rate of investigator-confirmed HAE attacks per month (HAE attack rate) over Weeks 0–52 in OASISplus
  - Angioedema Quality of Life (AE-QoL) questionnaire total score[5]
  - Well-controlled disease (Angioedema Control Test [AECT] total score ≥10)[6] at Week 24 in OASISplus
  - HAE-QoL total score (scored 25–125, with higher scores indicating greater QoL) at Week 24 in OASISplus
    - The HAE-QoL questionnaire evaluates disease-specific quality of life[7]
    - HAE-QoL was not evaluated as an endpoint in the parent OASIS-HAE study; therefore, only index placebo patients had a baseline assessment in the OLE prior to initiating donidalorsen
- Interim results are reported from a February 2024 data cut

Figure 1. Study Design



[a]Patients on a Q8W dosing schedule in OASIS-HAE who were not attack-free for ≥8 weeks received donidalorsen Q4W in the OLE.
OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

RESULTS

Table 1. Patient Demographics and Disposition

	Donidalorsen 80 mg Q4W (n = 69)	Donidalorsen 80 mg Q8W (n = 14)	Total (N = 83)
Age, years, mean (SD)	38 (14)	30 (9)	37 (14)
Age, years, n (%)			
12–17	5 (7.2)	2 (14.3)	7 (8.4)
≥18	64 (92.8)	12 (85.7)	76 (91.6)
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)	76 (91.6)
Multiple/other[a]	7 (10.1)	0	7 (8.4)
Study treatment exposure, days, mean (SD)	227.2 (80.3)	232.4 (92.3)	228.1 (81.9)
Patients enrolled, n	69	14	83
Patients dosed, n (%)	69 (100)	14 (100)	83 (100)
Patients who completed one year of study treatment, n (%)	5 (7.2)	2 (14.3)	7 (8.4)
Patients who terminated study treatment early, n (%)	2 (2.9)	0	2 (2.4)
Withdrawal by subject	2 (2.9)	0	2 (2.4)
COVID-19–related impact	0	0	0

[a]Includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, multiple races, or "other."
COVID-19; coronavirus disease 2019; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation.

- Of 20 patients from OASIS-HAE who originally received donidalorsen Q8W, 6 adjusted to donidalorsen Q4W in OASISplus OLE, and 14 continued with donidalorsen Q8W
- All patients who received donidalorsen Q4W or placebo in OASIS-HAE received donidalorsen Q4W in the OLE
- As of February 2024, the OLE included 83 patients
  - Two (2%) terminated the study early, 81 (98%) were ongoing, and 7 (8.4%) completed 1 year of treatment
- Mean donidalorsen exposure was 228 days

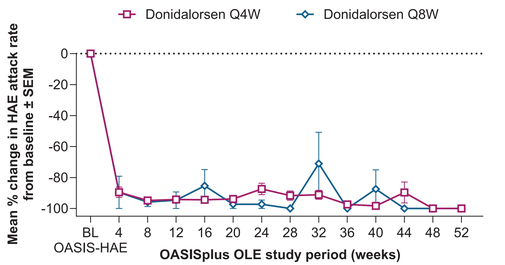
Table 2. Incidence and Severity of TEAEs

	Donidalorsen 80 mg Q4W (n = 69)	Donidalorsen 80 mg Q8W (n = 14)	Total (N = 83)
Any TEAE	56 (81.2)	10 (71.4)	66 (79.5)
Related to study drug	16 (23.2)	2 (14.3)	18 (21.7)
Leading to discontinuation	0	0	0
Severity of TEAEs			
Mild	28 (40.6)	5 (35.7)	33 (39.8)
Moderate	26 (37.7)	4 (28.6)	30 (36.1)
Severe	2 (2.9)	1 (7.1)	3 (3.6)
Any serious TEAE	4 (5.8)	0	4 (4.8)
Related to study drug	0	0	0
Leading to discontinuation	0	0	0
TEAEs in ≥5% of all patients			
Influenza	12 (17.4)	2 (14.3)	14 (16.9)
Nasopharyngitis	9 (13.0)	4 (28.6)	13 (15.7)
Upper respiratory tract infection	9 (13.0)	0	9 (10.8)
Headache	8 (11.6)	1 (7.1)	9 (10.8)
Back pain	7 (10.1)	2 (14.3)	9 (10.8)
COVID-19	7 (10.1)	1 (7.1)	8 (9.6)
Injection site discoloration	4 (5.8)	1 (7.1)	5 (6.0)
Oropharyngeal pain	4 (5.8)	1 (7.1)	5 (6.0)
Nausea	3 (4.3)	2 (14.3)	5 (6.0)

Data are presented as n (%).
COVID-19; coronavirus disease 2019; Q4W, every 4 weeks; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

- Sixty-six of 83 patients (80%) reported TEAEs
  - 95% (63/66) reported events that were at most mild or moderate in severity
  - 73% (48/66) reported TEAEs that were unrelated to the study drug
- No TEAEs led to treatment discontinuation
- The most common treatment-related TEAEs were injection-site reactions (injection-site erythema, discoloration, pain, and pruritus)

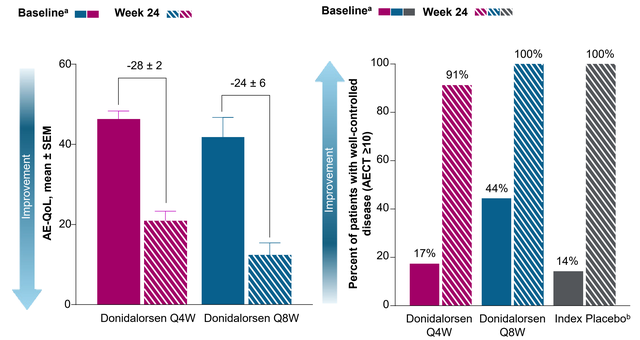
Figure 2. HAE Attack Rates by Study Visit



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

- As of the data cutoff, both dosing groups experienced improvements in mean HAE attack rate from baseline in OASIS-HAE to the data cutoff in the OLE (Q4W, 93%; Q8W, 92%)

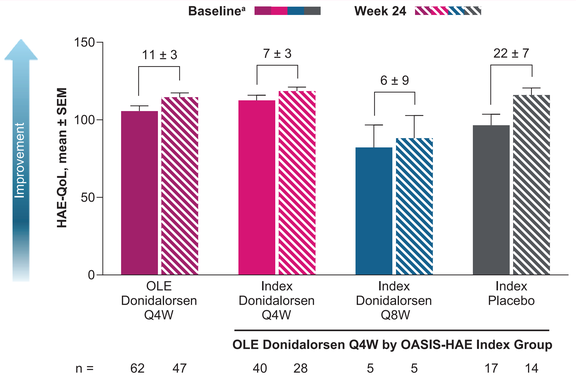
Figure 3. Patient-reported Quality of Life (AE-QoL) and Disease Control (AECT) at OASIS-HAE Baseline and Week 24 in OASISplus



[a]Week 0 in the OASIS-HAE study. [b]Index placebo is a subgroup of patients in the OASISplus donidalorsen Q4W group (ie, these patients received placebo in OASIS-HAE and initiated donidalorsen Q4W in OASISplus).
AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- In both dosing groups, patients reported clinically meaningful improvements from OASIS-HAE baseline in AE-QoL total score (reduction of ≥6 points)[8] at Week 24
  - Patients in the index placebo group also experienced clinically significant improvements from baseline in AE-QoL total score at Week 24 after initiating donidalorsen treatment (Q4W, 24 points)
- By Week 24, ≥90% of patients reported well-controlled disease based on AECT scores
  - All 14 patients previously on placebo in OASIS-HAE (index placebo group) reported well-controlled disease on the AECT

Figure 4. Patient-reported HAE-Specific Quality of Life: HAE-QoL at Baseline and Week 24 in OASISplus



[a]Week 0 in the OASISplus study.
HAE, hereditary angioedema; HAE-QoL, HAE Quality of Life Questionnaire; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Among index placebo patients, HAE-QoL total scores improved by 22 points from OASISplus baseline

CONCLUSIONS

- In this cohort of patients from the phase 3 OASIS-HAE study who continued in the open-label extension OASISplus study:

Safety and Tolerability

- Donidalorsen Q4W and Q8W had an acceptable safety profile as of the data cutoff, consistent with the primary results of OASIS-HAE[4]

Efficacy

- Improvements in HAE attack rate in the OASIS-HAE study were sustained in the OLE

Quality of Life and Disease Control

- Patients, especially those who previously received placebo in the OASIS-HAE study, reported clinically meaningful improvements in quality of life, and ≥90% had well-controlled disease at Week 24 of treatment

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DISCLOSURES

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REFERENCES

1. Riedl MA, et al. *J Allergy Clin Immunol Pract.* 2023;11(8):2450-2456.e6.
2. Raasch J, et al. *World Allergy Organ J.* 2023;16(6):100792.
3. Sinnathamby ES, et al. *Adv Ther.* 2023;40(3):814-827.
4. Riedl MA, et al. *N Engl J Med.* 2024;391(1):21-31.
5. Weller K, et al. *Allergy.* 2012;67(10):1289-98.
6. Weller K, et al. *J Allergy Clin Immunol Pract.* 2020;8(6):2050-2057.e4.
7. Prior N, et al. *Health Qual Life Outcomes.* 2012;10:82.
8. Weller K, et al. *Allergy.* 2016;71(8):1203-9.