Long-Term Safety of Donidalorsen for the Treatment of Hereditary Angioedema

Results From the Phase 3 Open-Label Extension OASISplus 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, La Jolla, CA, USA; [3]Ionis Pharmaceuticals, Carlsbad, CA, USA; [4]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

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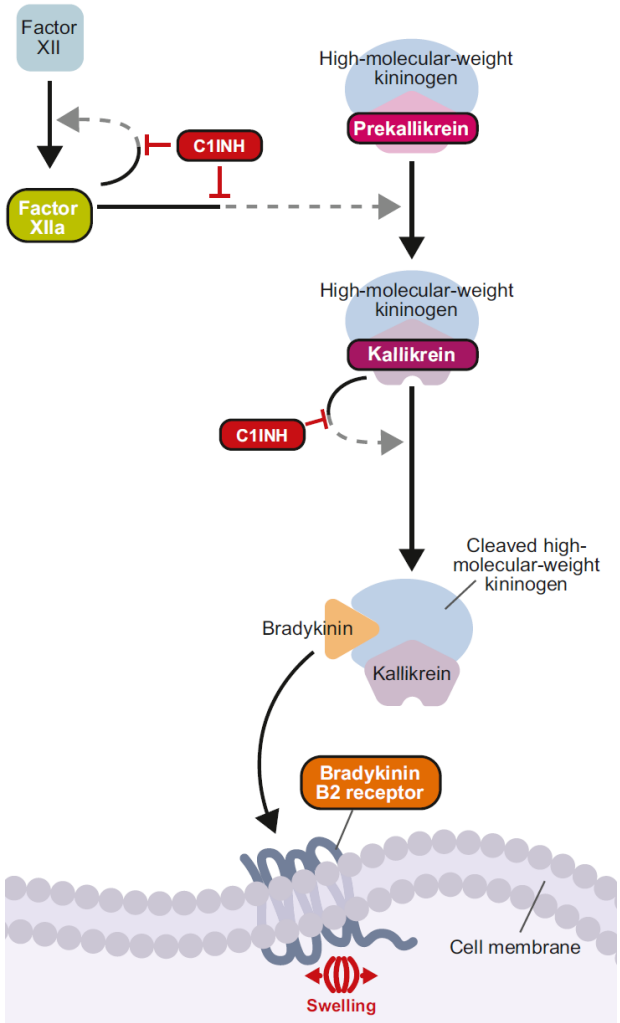
Disclosures

- Donidalorsen is an investigational drug in late-stage development
- **Raffi Tachdjian** has received grants or research support from Astria Therapeutics, BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharvaris, and Takeda; is a speaker for BioCryst, CSL Behring, Pharming, AstraZeneca, Sanofi-Regeneron Pharmaceuticals, GSK, and Takeda; and has served as a consultant for BioCryst, CSL Behring, KalVista Pharmaceuticals, Pharming, and Takeda

Hereditary Angioedema (HAE)

- A rare chronic disease characterised by frequent, severe, and potentially life-threatening tissue swelling[1-3]
- Usually caused by pathogenic variants of *SERPING1* and consequent kallikrein-kinin system dysregulation[1,2]
- Long-term prophylaxis aims to stabilise the kallikrein-kinin system and improve disease control and overall well-being[4–6]
- Substantial disease burden persists, and many patients switch medications due to frequent breakthrough HAE attacks, highlighting the need for new treatments[6]



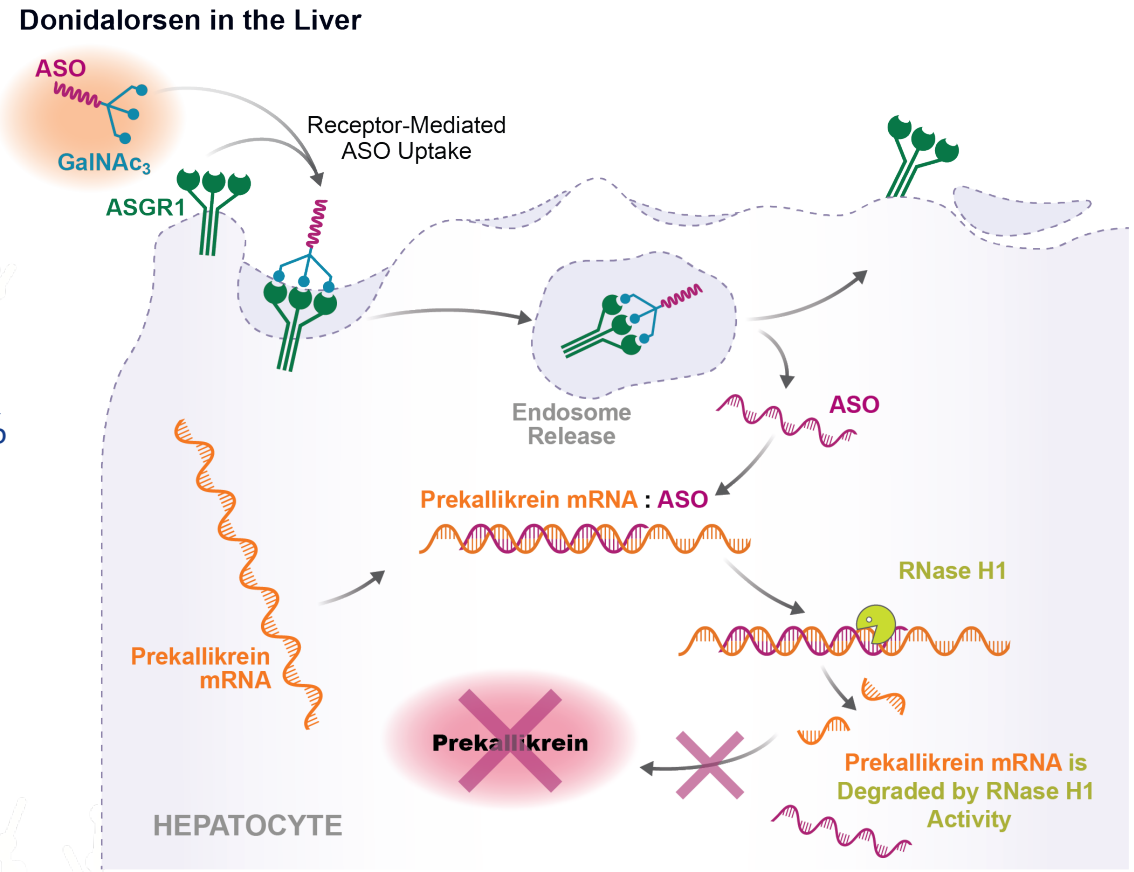
C1, complement protein 1; C1INH, C1 inhibitor.

1. Riedl MA, et al. *J Allergy Clin Immunol Pract*. 2024;12:911-8. 2. Raasch J, et al. *World Allergy Organ J*. 2023;16:100792. 3. Sinnathamby ES, et al. *Adv Ther*. 2023;40:814-27. 4. Caballero T, et al. *J Investig Allergol Clin Immunol*. 2023;33:238-49. 5. Maurer M, et al. *J Allergy Clin Immunol*. 2021;148:1526-32. 6. Mendivil J, et al. *Allergy Asthma Clin Immunol*. 2023;19:48.

Based on Riedl MA, et al. *J Allergy Clin Immunol Pract*. 2024;12:911-8.

Donidalorsen: A Potential Prophylactic Treatment for HAE

- Donidalorsen is a triantennary N-acetylgalactosamine ($GalNAc_3$)-conjugated antisense oligonucleotide designed to specifically degrade prekallikrein messenger RNA in hepatocytes[1,2]
- In the phase 3 OASIS-HAE study,[3] donidalorsen 80 mg subcutaneously (SC) every 4 weeks (Q4W) or every 8 weeks (Q8W)
  - Demonstrated least squares mean HAE attack rates 81% lower (Q4W) and 55% lower (Q8W) vs placebo over Weeks 1 to 25
  - Improved quality of life (QoL) and disease control
  - Had an acceptable safety and tolerability profile
- The ongoing OASISplus study (NCT05392114) includes an **open-label extension (OLE) cohort** from OASIS-HAE and a separate switch cohort from prior long-term prophylaxis



Adapted from Crooke ST, et al. *Nucleic Acid Therapeutics*, 2019;29:16–32. ASGR1, asialoglycoprotein protein receptor 1; ASO, antisense oligonucleotide; $GalNAc_3$, triantennary N-acetylgalactosamine; mRNA, messenger RNA.

1. Crooke ST, et al. *Nucleic Acid Thera*. 2019;29:16-32. 2. Riedl MA, et al. *J Allergy Clin Immunol Pract*. 2024;12:911-8. 3.Riedl MA, et al. *NEJM*. 2024. doi:10.1056/NEJMoa2402478.

Study Design and Primary Endpoint: OASISplus Phase 3 Trial[a] (OLE Cohort)

DESIGN

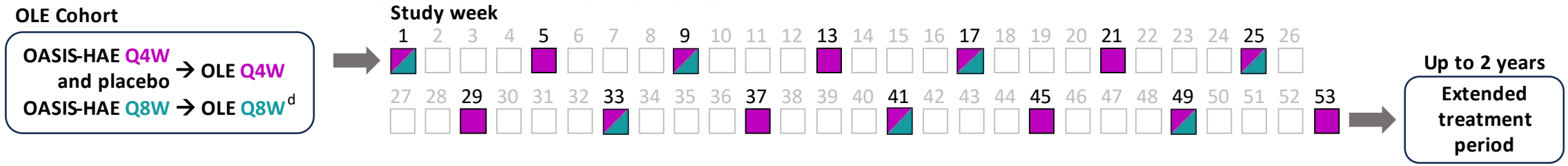
- OLE trial in patients aged ≥12 years with HAE-C1INH-Type1 or HAE-C1INH-Type2[b]
- Donidalorsen 80 mg SC Q4W or Q8W

PRIMARY OBJECTIVE

- To evaluate the safety of long-term dosing with donidalorsen in patients with HAE

PRIMARY ENDPOINT

- Incidence and severity of treatment-emergent adverse events (TEAEs)[c]



[a]NCT05392114. [b]HAE-C1INH-Type1 = C1-INH deficiency; HAE-C1INH-Type2 = C1-INH dysfunction. [c]Data shown are from an interim data cut from February 28, 2024. [d]Patients who were not attack free for ≥8 weeks (Weeks 17–25 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.

OASISplus Phase 3 Trial OLE Cohort: Additional Objectives and Endpoints

SECONDARY OBJECTIVES

- To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the QoL of patients with HAE

SECONDARY ENDPOINTS

- Time-normalised number of HAE attacks per month (Weeks 1–53)
- Angioedema quality of life (AE-QoL) questionnaire total score over 53 weeks[a]

EXPLORATORY OBJECTIVE

- To further characterise the effects of donidalorsen on self-reported disease control

EXPLORATORY ENDPOINTS

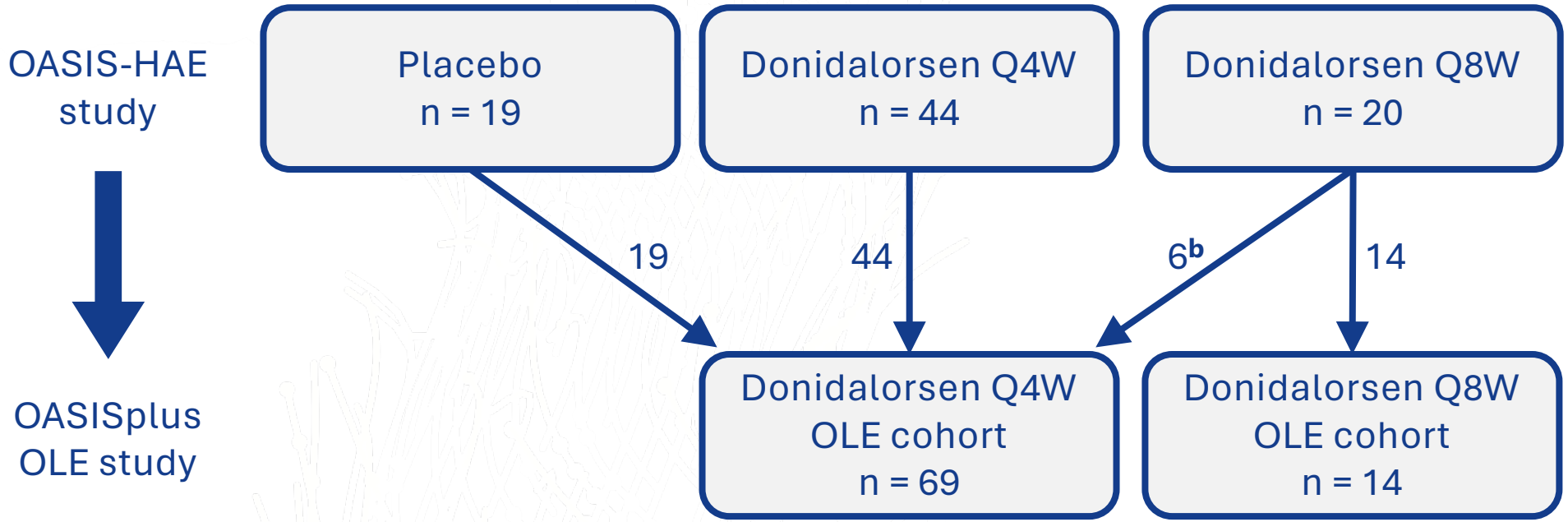
- Percentage of patients with well controlled disease[1] over 53 weeks assessed by the Angioedema Control Test (AECT)[a,b]

[a]Interim data shown for patients who completed through Week 25 due to the limited number of patients who have completed later timepoints in the ongoing study.
[b]Defined as an AECT score ≥10.[2]

1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4. 2. Weller K, et al. *Allergy*. 2020;75(5):1165–77.

Flow of Patients From OASIS-HAE to OASISplus OLE

- In total, 94% of eligible[a] patients in the OASIS-HAE trial rolled over into the OLE study



[a]83 of 88 eligible patients rolled over into the OLE study [b]Patients who were not attack free for ≥8 weeks (Weeks 17–25 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.

Patient Disposition

- Of those patients that rolled over into the OASISplus OLE, 98% remained in the study as of February 28, 2024

	Donidalorsen Q4W	Donidalorsen Q8W	Total
Patients dosed, n	69	14	83
Completed 1 year of follow-up, n (%)	5 (7)	2 (14)	7 (8)
Patients still in the study, n (%)	67 (97)	14 (100)	81 (98)
Early termination, n (%)			
Voluntary withdrawal	1 (1)	0	1 (1)
Family planning	1 (1)	0	1 (1)

[a]83 of 88 eligible patients rolled over into the OLE study.

Patient Demographics

	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Age, years, mean (standard deviation)	38 (14)	30 (9)	37 (14)
Age group, n (%)			
12–17 years old	5 (7)	2 (14)	7 (8)
≥18 years old	64 (93)	12 (86)	76 (92)
Sex, n (%)			
Male	29 (42)	9 (64)	38 (46)
Female	40 (58)	5 (36)	45 (54)
Race, n (%)			
White	62 (90)	14 (100)	76 (92)
Multiple or other[a]	7 (10)	0	7 (8)

[a]Includes Asian, Black or African American, and "other."

Primary Endpoint: Incidence and Severity of TEAEs

	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Any TEAE,[a] n (%)	56 (81)	10 (71)	66 (80)
Related to study drug	16 (23)	2 (14)	18 (22)
Leading to discontinuation	0	0	0
Any serious TEAE, n (%)	4 (6)	0	4 (5)
Related to study drug	0	0	0
Severity of TEAEs related to study drug, n (%)			
Mild	14 (20)	2 (14)	16 (19)
Moderate	2 (3)	0	2 (2)
Severe	0	0	0

- No patients discontinued due to TEAEs
- No serious TEAEs related to the study drug
- Most TEAEs were mild or moderate in severity

[a]TEAE is defined as any adverse event starting or worsening on or after the first dose of donidalorsen in the OLE.

Primary Endpoint: Most Common TEAEs

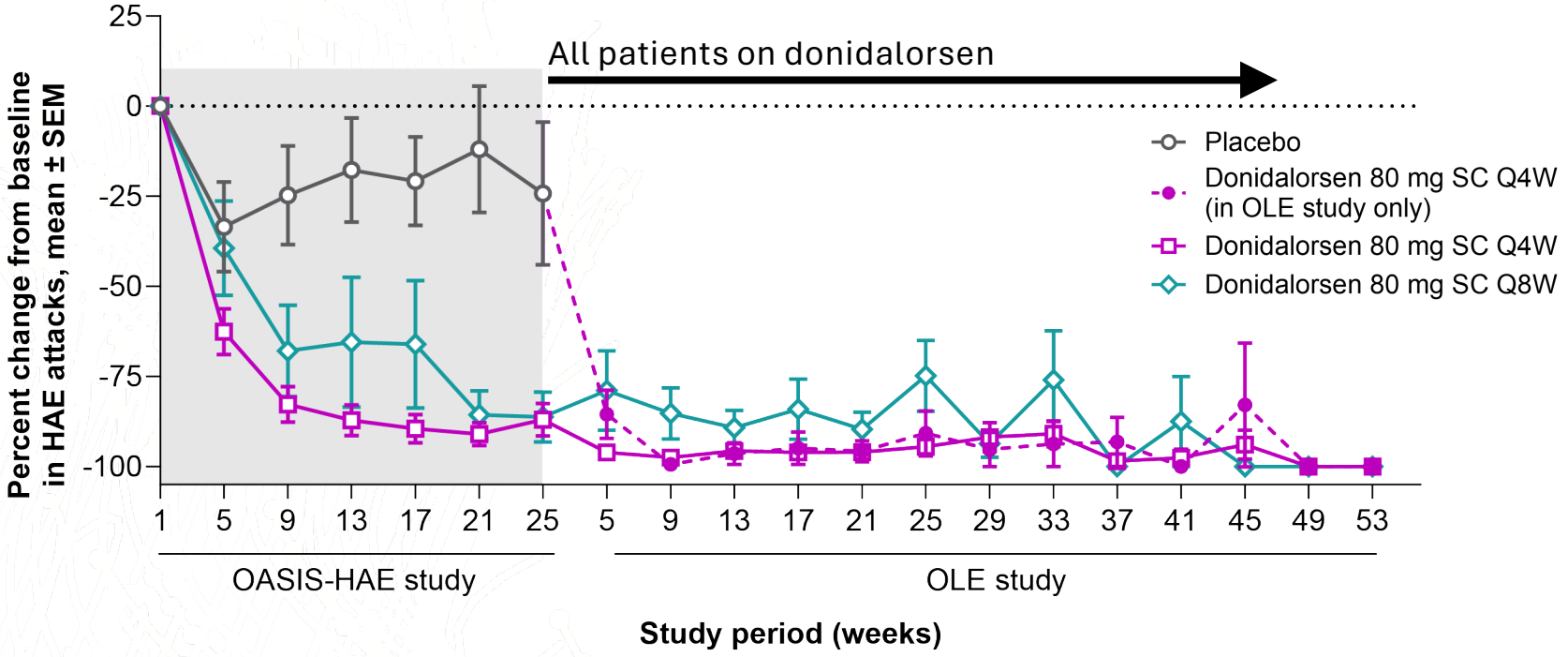
	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Most common TEAEs[a] (≥5% of all patients), n (%)			
Influenza	12 (17)	2 (14)	14 (17)
Nasopharyngitis	9 (13)	4 (29)	13 (16)
Upper respiratory tract infection	9 (13)	0	9 (11)
Back pain	7 (10)	2 (14)	9 (11)
Headache	8 (12)	1 (7)	9 (11)
Coronavirus disease 2019	7 (10)	1 (7)	8 (10)
Nausea	3 (4)	2 (14)	5 (6)
Injection-site discoloration	4 (6)	1 (7)	5 (6)
Oropharyngeal pain	4 (6)	1 (7)	5 (6)

- Overall, no safety concerns were identified from the OLE safety data

[a]TEAE is defined as any adverse event starting or worsening on or after the first dose of donidalorsen in the OLE.

Secondary Endpoint: Time-Normalised Number of HAE Attacks per Month (Weeks 1–53)

- Both Q4W and Q8W groups had a 92-93% reduction in HAE attacks compared with OASIS-HAE baseline



Placebo, n =	19	19	19	19	18	17	16	19	19	19	19	16	15	13	10	6	5	5	4	2
Donidalorsen 80 mg Q4W, n =	44	44	44	44	44	43	43	44	44	43	43	36	30	26	24	18	11	8	4	3
Donidalorsen 80 mg Q8W, n =	20	20	20	20	20	20	19	20	20	20	20	16	14	13	12	8	4	3	2	2

SEM, standard error of the mean.
The "n"s represent the numbers of patients indexed in the OASIS-HAE study. All placebo patient rolled into the donidalorsen Q4W dosing schedule for the OLE study.

Patient-Reported Outcomes at Week 25 of OLE

Donidalorsen Q4W	Donidalorsen Q8W
28-point mean improvement in AE-QoL score[a]	24-point mean improvement in AE-QoL score[a]
42/46[b] (91%) patients reported well controlled disease[1] based on AECT	9/9[b] (100%) patients reported well controlled disease[1] based on AECT

[a]Change from baseline in the phase 3 OASIS-HAE study. An improvement of 6 points or more is considered clinically meaningful for AE-QoL.[2]
[b]Reported at the time of data cut and defined as an AECT score ≥10.[3]

1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4. 2. Weller K, et al. *Allergy*. 2016;71(8):1203-9. 3. Weller K, et al. *Allergy*. 2020;75(5):1165–77.

Conclusions

HAE Attack Rate

- Donidalorsen Q4W led to a 93% reduction from baseline in monthly HAE attack rate

Safety and Tolerability

- Donidalorsen had an acceptable safety and tolerability profile
  - No patients discontinued due to TEAEs
  - There were no serious TEAEs related to the study drug
  - Most TEAEs were mild or moderate in severity

QoL and Disease Control

- Patients reported a ≥24-point improvement in mean AE-QoL scores[a]
- More than 90% of patients reported well controlled disease[b]

[a]An improvement of 6 points or more is considered clinically meaningful for AE-QoL.[1] [b]Defined as an AECT score ≥10.[2]

1. Weller K, et al. *Allergy*. 2016;71(8):1203-9. 2. Weller K, et al. *Allergy*. 2020;75(5):1165–77.

Acknowledgments

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