Donidalorsen for the Treatment of Hereditary Angioedema: Results From a Phase 3, Randomised, Placebo-Controlled Trial

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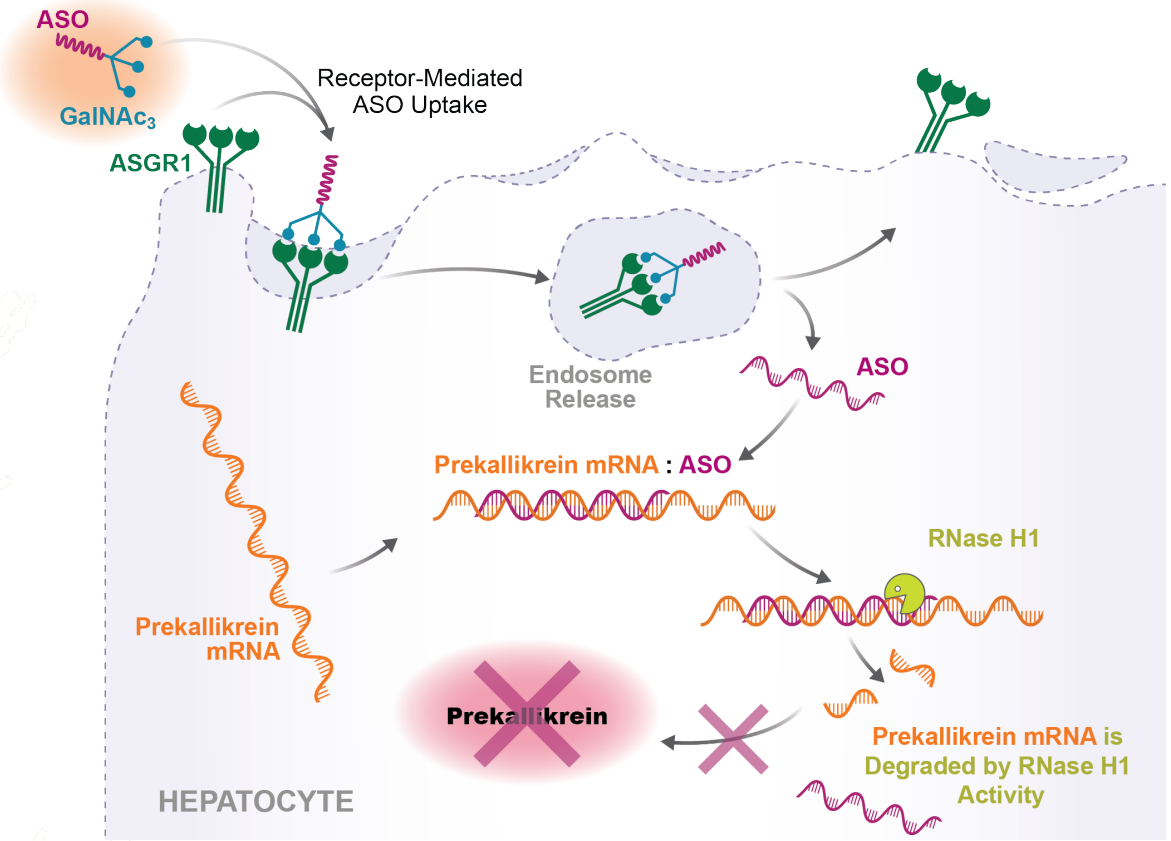
Disclosures

- Donidalorsen is an investigational drug in late-stage development
- **Danny M. Cohn** has received speaker fees, research funding, and/or consultancy fees from Astria Therapeutics, BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharming, Pharvaris, and Shire/Takeda

Donidalorsen: A Potential Prophylactic Treatment for HAE

- Hereditary angioedema (HAE) is a rare chronic disease with frequently severe, potentially life-threatening tissue swelling[1-4]
- Patients emphasise treatment goals of improved disease control and overall well-being[5,6]
- Long-term prophylaxis aims to achieve these goals by stabilising the kallikrein-kinin system[7]
- Donidalorsen is designed to specifically degrade prekallikrein mRNA in hepatocytes[1,8]
- In a phase 2 study, donidalorsen 80 mg administered subcutaneously (SC) once every 4 weeks (Q4W) significantly reduced the monthly rate of HAE attacks vs. placebo over 16 weeks[9]

Donidalorsen in the Liver



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

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. Cicardi M, et al. *Allergy*. 2014;69(5):602-16. 5. Caballero T, et al. *J Investig Allergol Clin Immunol*. 2023;33:238-49. 6. Maurer M, et al. *J Allergy Clin Immunol*. 2021;148:1526-32. 7. Mendivil J, et al. *Allergy Asthma Clin Immunol*. 2023;19:48. 8. Crooke ST, et al. *Nucleic Acid Ther*. 2019;29:16-32. 9. Fijen LM, et al. *N Engl J Med*. 2022;386(11):1026-33.

Donidalorsen OASIS-HAE Phase 3 Study (NCT05139810)

DESIGN

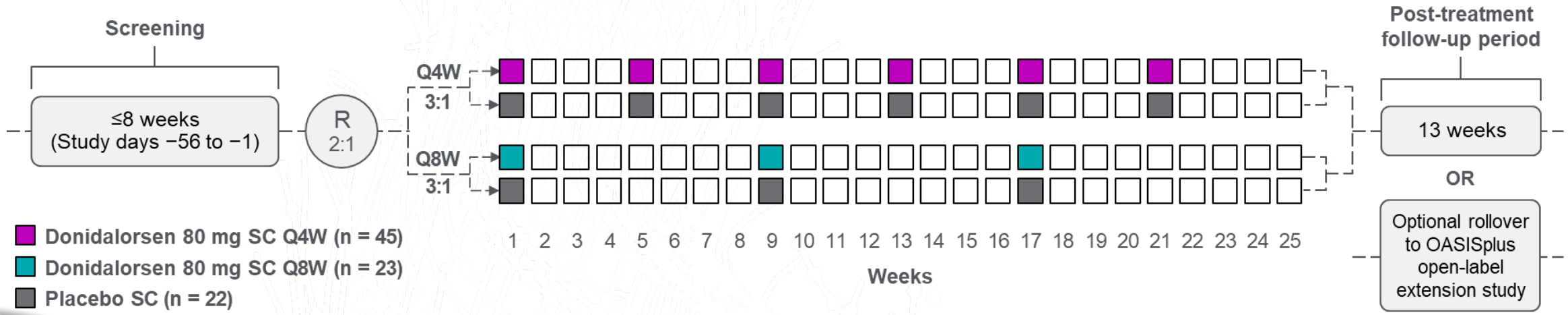
- Global, randomised, double-blind, placebo-controlled trial of patients aged ≥12 years with HAE-C1INH-Type1 or HAE-C1INH-Type2
- Donidalorsen 80 mg SC Q4W or once every 8 weeks (Q8W)

PRIMARY OBJECTIVE

- To evaluate the efficacy of donidalorsen in patients with HAE

PRIMARY ENDPOINT

- Time-normalised HAE attack rate over Weeks 1 to 25



C1INH, complement protein 1 inhibitor; R, randomisation.

Secondary and Other Endpoints

KEY SECONDARY ENDPOINT

- Time-normalised HAE attack rate over Weeks 5 to 25

OTHER SECONDARY ENDPOINTS[a]

- HAE attacks requiring acute therapy
- Moderate to severe HAE attacks
- Percentage of attack-free patients
- Clinical response (≥70% reduction from baseline in HAE attack rate) from Week 5 to Week 25
- Mean change from baseline in Angioedema Quality-of-Life (AE-QoL) questionnaire total score at Week 25
- Percentage of patients who were well controlled on the Angioedema Control Test (AECT; score ≥10 points)[1] at Week 25

EXPLORATORY ENDPOINTS[a]

- Plasma prekallikrein concentration and ER visits

SAFETY ENDPOINTS

- Incidence, severity, and dose relationship of adverse events

[a]The subset of trial endpoints included in this presentation are listed.
ER, emergency room.
1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4.

Patient Disposition

- 91 patients were randomised; 90 were dosed
- 83 of 91 (91%) randomised patients completed the study treatment
- 94% of eligible patients in OASIS-HAE enrolled in the long-term open-label extension OASISplus study (NCT05392114)[a]

Patient disposition	Donidalorsen Q4W	Donidalorsen Q8W	Placebo
Patients randomised	46	23	22
Full analysis set (dosed), n (%)	**45 (97.8)**	**23 (100)**	**22 (100)**
Early termination, n (%)	2 (4.3)	2 (8.7)	4 (18.2)
Lack of efficacy[b]	1 (2.2)	1 (4.3)	3 (13.6)
Voluntary withdrawal	1 (2.2)[c]	0	0
Adverse event	0	1 (4.3)[d]	0
Pregnancy	0	0	1 (4.5)
Completed treatment, n (%)	44 (95.7)	21 (91.3)	18 (81.8)

[a]Patients were eligible for enrolment in the OASISplus open-label extension study if they completed the OASIS-HAE study or were allowed to exit the OASIS-HAE study per protocol with an acceptable safety and tolerability profile.
[b]Early terminators with at least 5 HAE attacks/month for 2 consecutive months after Week 5 were enrolled directly into the open-label extension OASISplus study per protocol (safety valve).
[c]One patient in the donidalorsen Q4W group voluntarily withdrew after randomisation but before receiving study drug.
[d]One patient in the donidalorsen Q8W group discontinued based on investigator recommendation due to patient noncompliance and a treatment-emergent adverse event (TEAE). The TEAE was an elevation of alanine aminotransferase (ALT) >3 times the upper limit of normal that did not meet the stopping rule per protocol.

Patient Demographics and Disease Characteristics

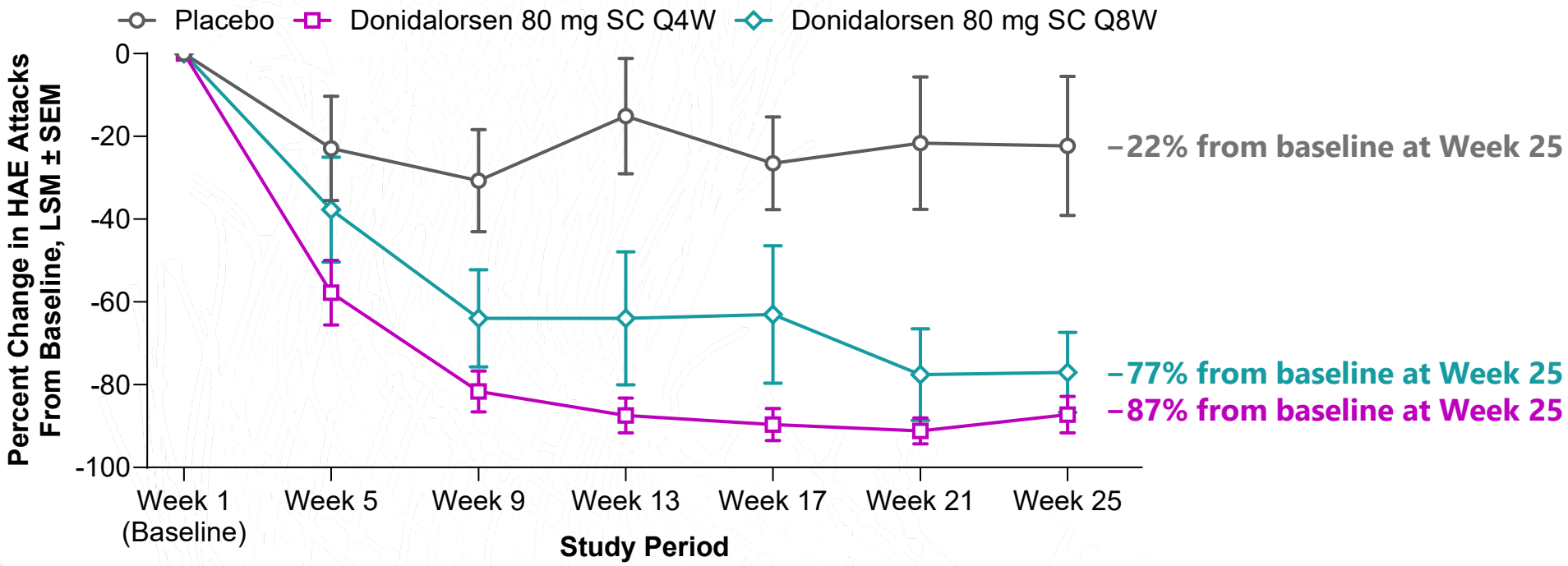
	Donidalorsen Q4W n = 45	Donidalorsen Q8W n = 23	Placebo n = 22
Age, years, n (%)			
12–17	4 (8.9)	3 (13.0)	0
≥18	41 (91.1)	20 (87.0)	22 (100)
Sex, n (%)			
Male	17 (37.8)	11 (47.8)	14 (63.6)
Female	28 (62.2)	12 (52.2)	8 (36.4)
Race, n (%)			
White	42 (93.3)	22 (95.7)	18 (81.8)
Multiple or other	3 (6.7)	1 (4.3)	4 (18.2)
HAE, n (%)			
HAE-C1INH-Type1	42 (93.3)	22 (95.7)	20 (90.9)
HAE-C1INH-Type2	3 (6.7)	1 (4.3)	2 (9.1)
Number of HAE attacks in last 12 months,[a] mean ± SD	**45.7 ± 43.04**	**33.3 ± 21.95**	**29.1 ± 21.13**
Number of HAE attacks during run-in period,[b] mean ± SD	**3.61 ± 2.24**	**3.18 ± 2.15**	**2.90 ± 1.66**

- Donidalorsen treatment groups had higher burden of disease relative to placebo

[a]The number of HAE attacks in the last 12 months refers to the time before screening visit. [b]The run-in period HAE attack rate for each patient was calculated as the number of investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28 days.

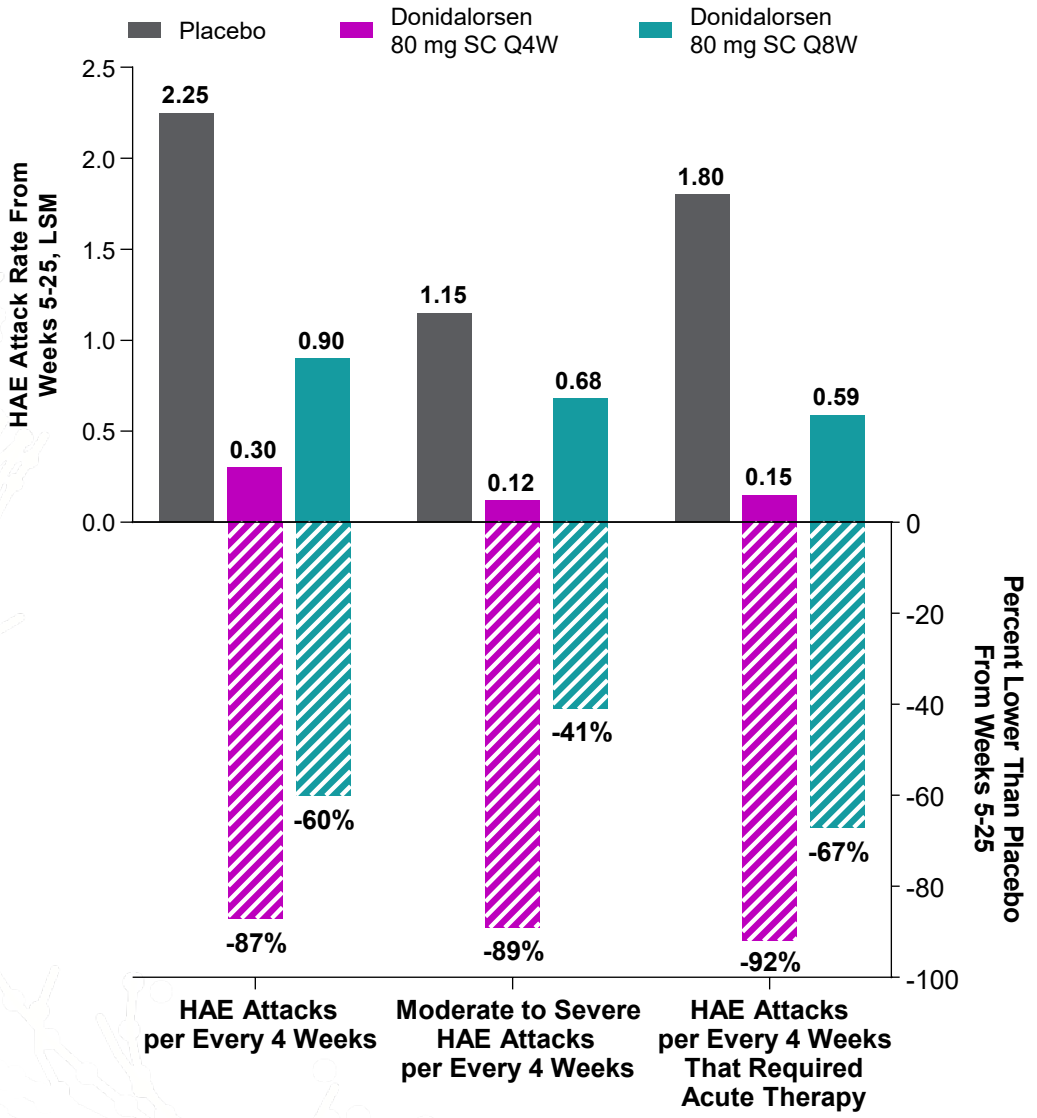
Primary Endpoint: HAE Attack Rate Over Weeks 1 to 25

- The least squares mean (LSM) difference HAE attack rate over Weeks 1 to 25 was 81% lower in the donidalorsen Q4W group than in the placebo group (P <0.001)
  - Q8W, 55% LSM difference vs. placebo (P = 0.004)
- Q8W dosing had a similar effect to Q4W dosing by Week 25



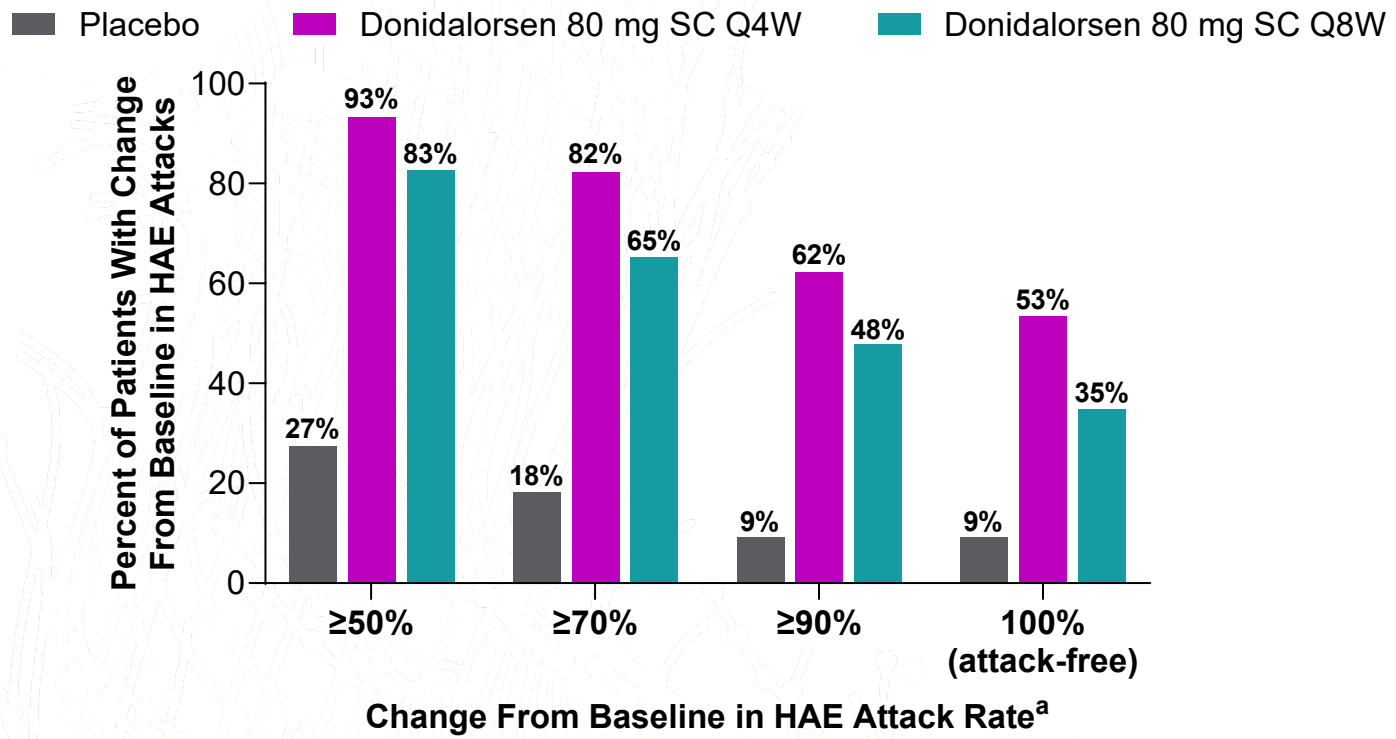
Secondary Endpoints: HAE Attack Rates Over Weeks 5 to 25

- Donidalorsen decreased HAE attack rates vs. placebo from Weeks 5 to 25
  - Q4W by 87% (**key secondary endpoint**; *P* <0.001)
  - Q8W by 60% (*P* = 0.004)
  - Rate of moderate to severe HAE attacks (Q4W, *P* <0.001)
  - Rate of HAE attacks requiring acute therapy (Q4W, *P* <0.001; Q8W, *P* = 0.004)



Secondary Endpoint: Clinical Response Over Weeks 5 to 25

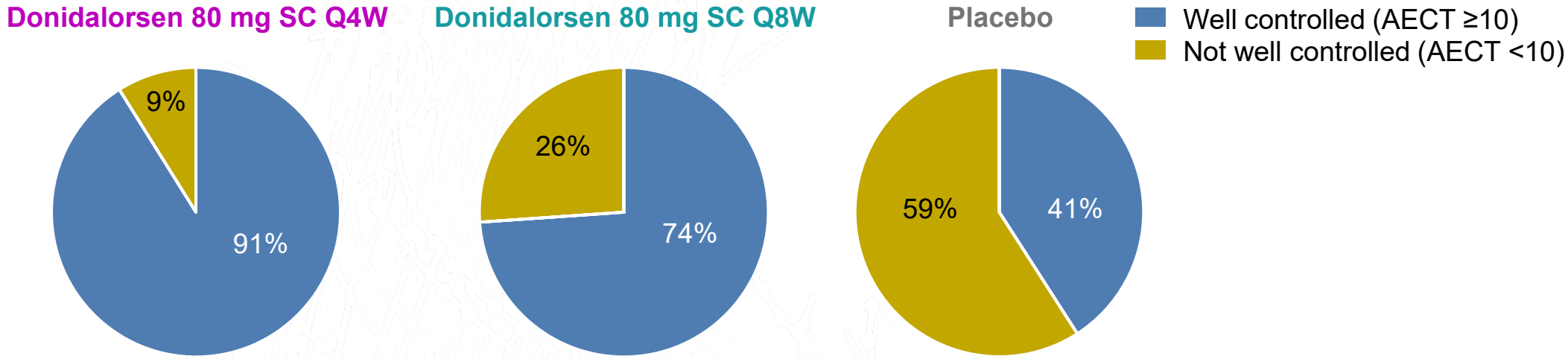
- In both donidalorsen groups, a higher percentage of patients had a ≥70% reduction from baseline in HAE attack rate vs. placebo (Q4W, *P* <0.001; Q8W, *P* = 0.004)



[a]Percentage of patients who achieved a threshold change from baseline in time-normalised investigator-confirmed HAE attack rate over Weeks 5 to 25.

Secondary Endpoints: Quality of Life (AE-QoL) and Disease Control (AECT) at Week 25

- Donidalorsen improved LSM[a] AE-QoL total score from baseline to Week 25[2]
  - Q4W by 25 points vs. placebo by 6 points (*P* <0.001)
  - Q8W by 20 points (*P* = 0.010)[b]
- Most patients in the donidalorsen groups were well controlled[c] on the AECT[1] at Week 25[d]



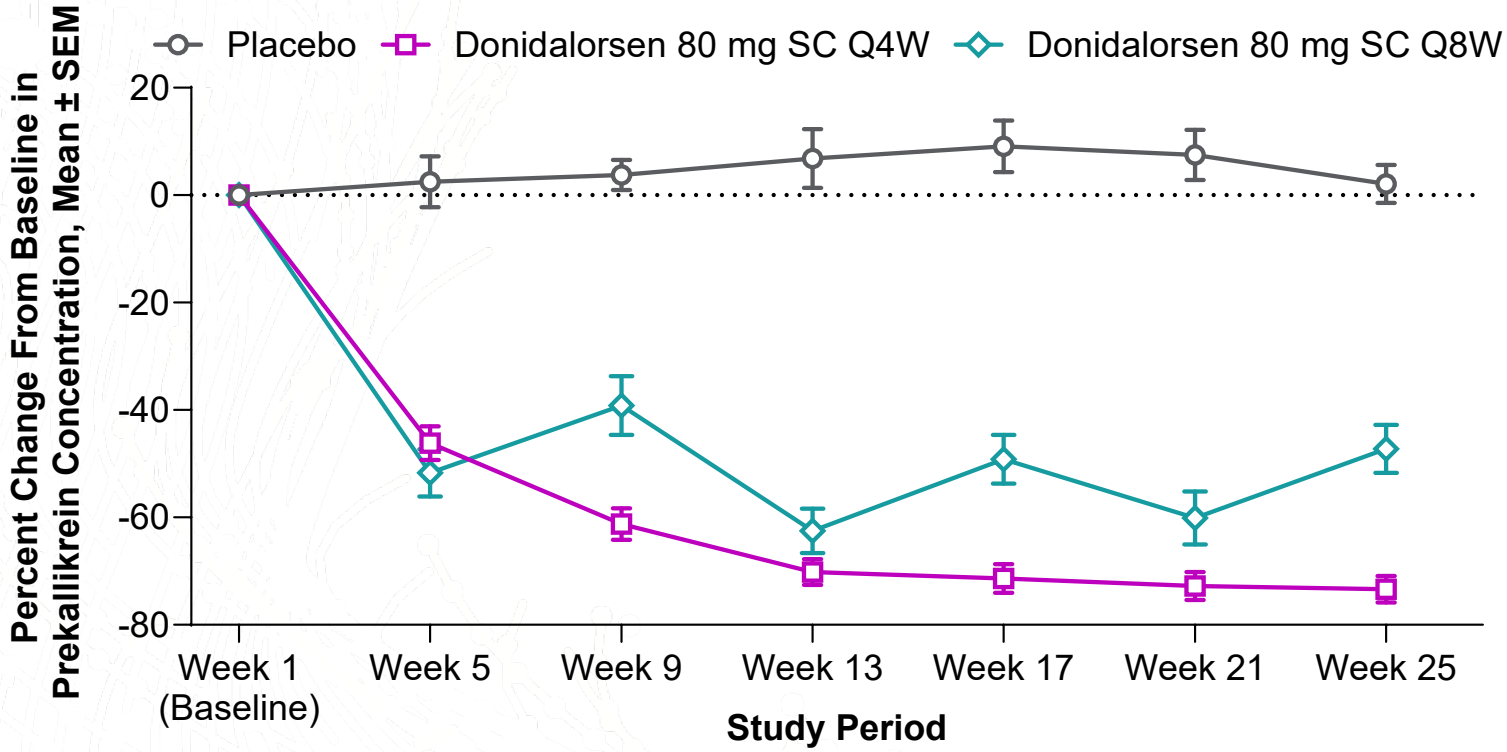
[a]LSMs are based on a mixed model for repeated measures. [b]Nominal *P*-value. [c]Well controlled is defined as an AECT score ≥10.[1] [d]Based on Last Observation Carried Forward (LOCF) imputation. An improvement of 6 points or more in the AE-QoL total score is considered clinically meaningful.[2]

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):1203-1209.

Exploratory Endpoints: Reduction in ER Visits & Plasma Prekallikrein

- Donidalorsen treatment was associated with a 92% to 95% lower incidence of all-cause and HAE attack–specific ER visits over Weeks 1 to 25 vs. placebo

- Donidalorsen reduced mean prekallikrein concentration from baseline to Week 25
  - Q4W by 73%
  - Q8W by 47%



Summary of Adverse Events

	Donidalorsen Q4W n = 45	Donidalorsen Q8W n = 23	Placebo n = 22
Any TEAE,[a] n (%)	33 (73.3)	14 (60.9)	18 (81.8)
Related to study drug[b]	19 (42.2)	4 (17.4)	6 (27.3)
Leading to study drug discontinuation	0	1 (4.3)	0
Any serious TEAE, n (%)	0	0	1 (4.5)
Related to study drug	0	0	0
TEAEs related to study drug (≥5% of patients),[b] n (%)			
Injection-site reactions	9 (20.0)	1 (4.3)	0
Headache	3 (6.7)	0	3 (13.6)

- Injection-site reactions were the most common donidalorsen-related TEAEs
- One patient in the donidalorsen Q8W group discontinued based on investigator recommendation due to patient noncompliance and a TEAE[c]

[a]A TEAE is defined as any adverse event 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 the study drug (donidalorsen or placebo).
[c]TEAE was an elevation of alanine aminotransferase (ALT) >3 times the upper limit of normal that did not meet the stopping rule per protocol.

Conclusions

- Donidalorsen Q4W demonstrated efficacy on all HAE attack primary and secondary endpoints
- Donidalorsen Q8W significantly reduced HAE attack rate
- Donidalorsen improved quality of life and achievement of disease control
- Donidalorsen had an acceptable safety and tolerability profile

Acknowledgements

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ORIGINAL ARTICLE

Efficacy and Safety of Donidalorsen for Hereditary Angioedema

Marc A. Riedl, M.D., Raffi Tachdjian, M.D., M.P.H., William R. Lumry, M.D., Timothy Craig, D.O., Gül Karakaya, M.D., Asli Gelincik, M.D., Marcin Stobiecki, M.D., Ph.D., Joshua S. Jacobs, M.D., Nihal M. Gokmen, M.D., Avner Reshef, M.D., Mark M. Gompels, M.D., Michael E. Manning, M.D., Laura Bordone, Ph.D., Kenneth B. Newman, M.D., Sabrina Treadwell, Ph.D., Sophie Wang, M.S., Aaron Yarlas, Ph.D., and Danny M. Cohn, M.D., Ph.D., for the OASIS-HAE Team*

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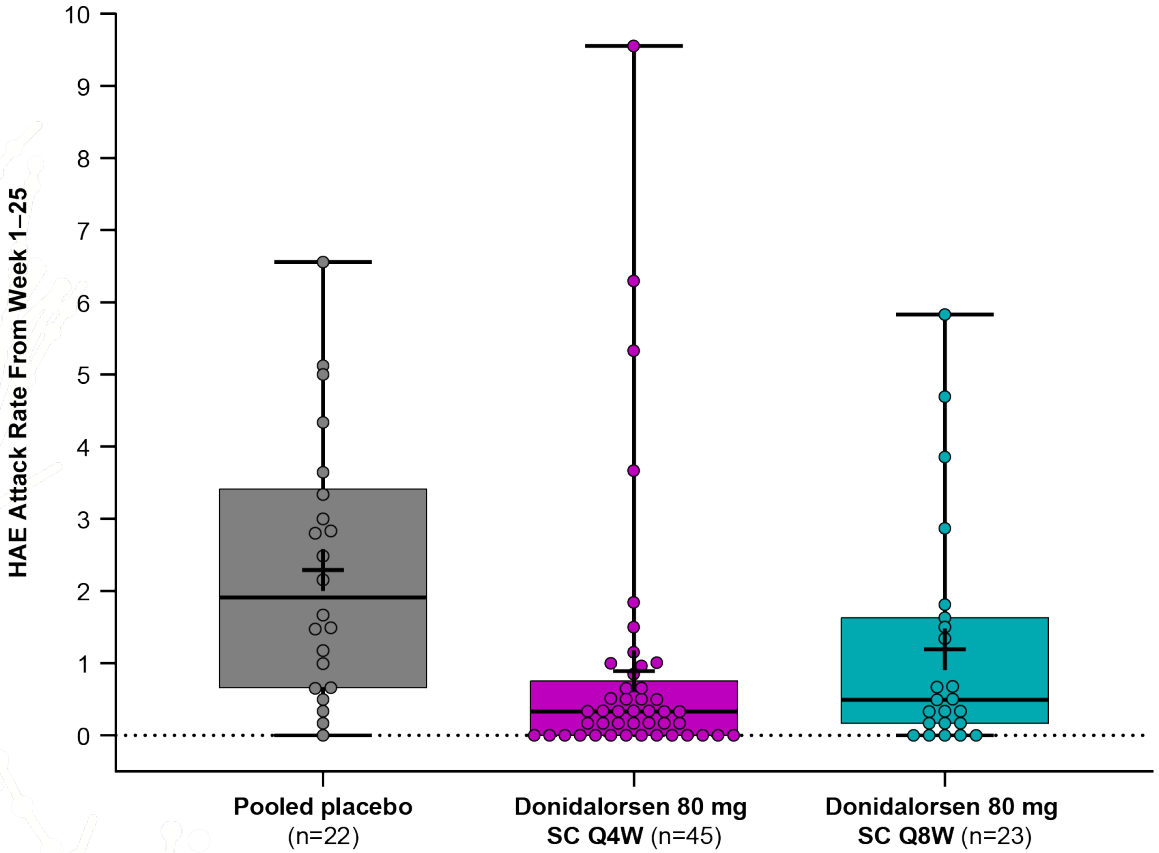
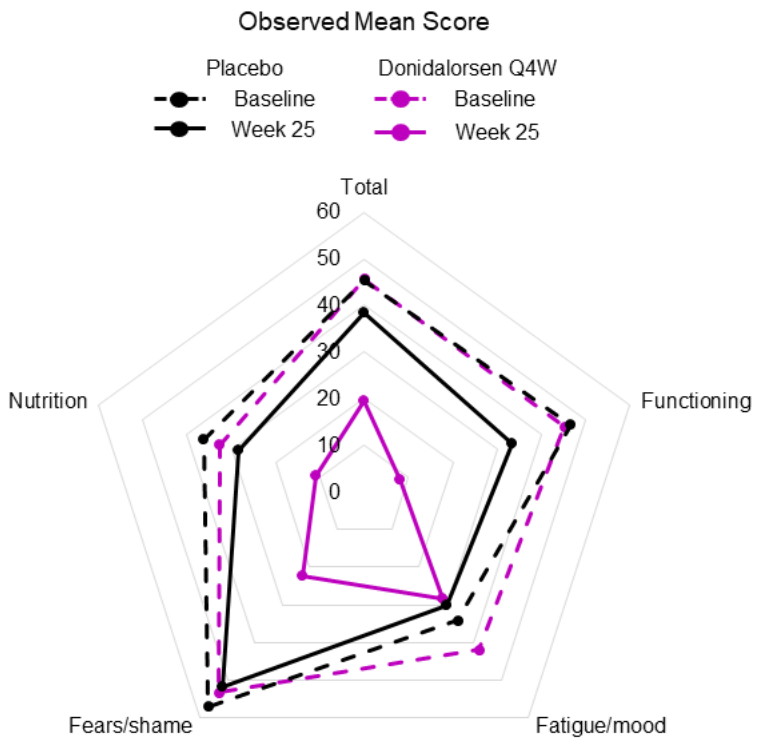
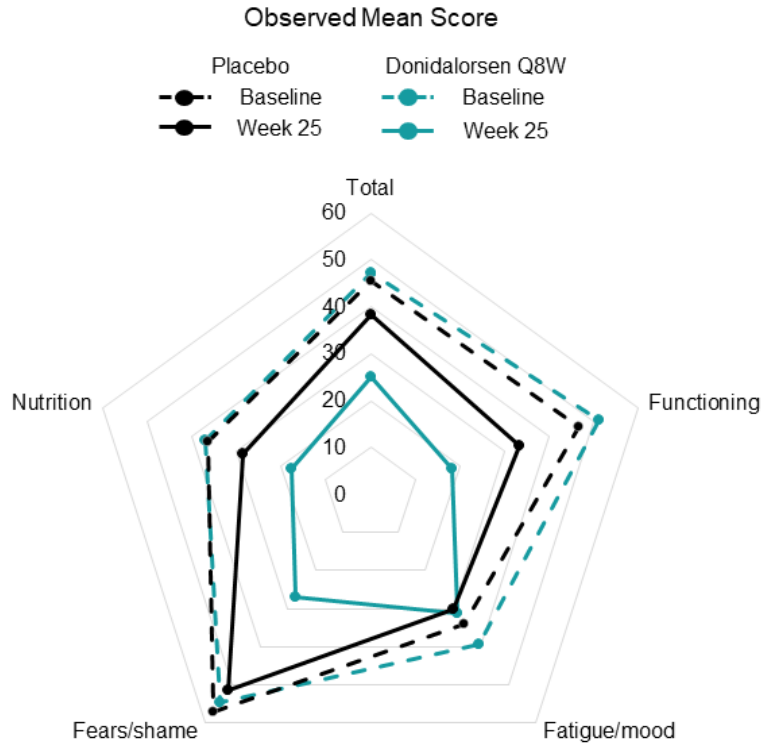
Primary (Q4W and Q8W) Endpoint (Median HAE Attack Rate)

- Donidalorsen Q4W treatment led to a median 90% reduction from baseline in HAE attack rate over Weeks 1 to 25
- Patients treated with donidalorsen Q8W had a median 83% reduction in HAE attack rate
- LSM HAE attack rate
  - Placebo 2.26 (95% CI, 1.66 to 3.09)
  - Q4W 0.44 (95% CI, 0.27 to 0.73; *P* <0.001 vs. placebo)
  - Q8W 1.02 (95% CI, 0.65 to 1.59; *P* = 0.004 vs. placebo)



Secondary Endpoints: Quality of Life (AE-QoL)





The figure shows observed mean AE-QoL domain and total scores.
Quality of life was assessed by means of the validated, angioedema-specific and patient-reported Angioedema Quality of Life Questionnaire in patients who received placebo and donidalorsen every 4 or 8 weeks. The questionnaire consists of 17 items and four domains (functioning, fatigue and mood, fears and shame, and nutrition). Within each domain, five questions are scored 1–5, with higher scores indicating a more adverse effect. Raw scores for each domain and the total score are calculated and transformed into a linear 0–100 scale, with a score of 100 indicating the worst possible impairment of life. An improvement of 6 points or more in the AE-QoL total score is considered clinically meaningful.[1]

1. Weller K et al. *Allergy*. 2016;71(8):1203–9.