Poster #R092

Impact Of Donidalorsen In Patients With Hereditary Angioedema By Baseline Attack Rate From OASISplus

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Background

- Hereditary angioedema (HAE) is a rare disease characterized by recurrent and unpredictable attacks of tissue swelling that are potentially life-threatening[1]
- The most frequent cause of HAE is either deficiency (HAE-C1INH-Type1) or dysfunction (HAE-C1INH-Type2) of C1 inhibitor (C1INH), which leads to kallikrein-bradykinin system dysregulation[1-3]

Figure 1. Donidalorsen Mechanism of Action

Figure created using BioRender (https://www.biorender.com/).
ASO, antisense oligonucleotide; mRNA, messenger RNA; PKK, prekallikrein; RNase H1, ribonuclease H1.

- Donidalorsen is an RNA-targeted antisense oligonucleotide that specifically and reversibly reduces plasma prekallikrein production in the liver[4]
- Donidalorsen is indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients 12 years of age and older[5]

Figure 2. Overview of the OASIS-HAE Study

Phase 3 OASIS-HAE Study (NCT05139810)

[a]Improvement in QoL is defined as a reduction in AE-QoL total score.
[b]Well-controlled on the AECT is defined as a total score ≥10.[3]
AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; Q4W, once every 4 weeks; Q8W, once every 8 weeks; QoL, quality of life.

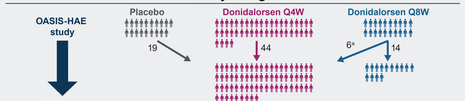
- In the pivotal phase 3 OASIS-HAE study (NCT05139810), donidalorsen administered subcutaneously (SC) once every 4 weeks (Q4W) or 8 weeks (Q8W) significantly reduced HAE attack rate and had an acceptable safety profile[4]
- Here, we report interim safety and efficacy of donidalorsen in patients from OASIS-HAE who subsequently enrolled in the open-label extension (OLE) cohort (NCT05392114) of the ongoing OASISplus study stratified by baseline HAE attack rate

Study Design

- Patients previously treated with donidalorsen or placebo in OASIS-HAE received donidalorsen 80 mg SC according to their original dosing schedule (Q4W or Q8W) over 52 weeks in OASISplus OLE
  - If patients previously on donidalorsen or placebo Q8W in OASIS-HAE were not attack-free for ≥8 weeks (Weeks 16–24 in OASIS-HAE), they received donidalorsen Q4W in OASISplus OLE
- In this post hoc analysis, patients were stratified by baseline attack rate (≤2, >2–5, or >5 attacks/month)

Figure 3. OASISplus OLE Cohort

Study Design



[a]Patients on a Q8W dosing schedule in OASIS-HAE who were not attack-free for ≥8 weeks (Weeks 16–24 in OASIS-HAE) received donidalorsen Q4W in the OLE.
OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Endpoints included:
  - Time-normalized rate of investigator-confirmed HAE attacks per month (HAE attack rate) over Weeks 0–52 and Weeks 4–52
  - HAE attack-free status over Weeks 4–52
  - Incidence of treatment-emergent adverse events (TEAEs)
- Data are summarized using descriptive statistics
- Interim results are reported from a January 2025 data cut

Results

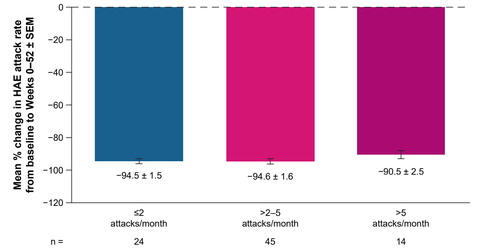
Table 1. Baseline Demographics and Characteristics

n (%)	≤2 attacks/month (n = 24)	>2–5 attacks/month (n = 45)	>5 attacks/month (n = 14)
Age, years, mean (SD)	33.6 (15.5)	37.9 (12.9)	39.9 (12.5)
BMI, kg/m², mean (SD)	27.9 (6.6)	28.1 (6.2)	25.6 (6.7)
Age, years, n (%)			
12–17	5 (20.8)	2 (4.4)	0
≥18	19 (79.2)	43 (95.6)	14 (100)
Sex, n (%)			
Male	14 (58.3)	23 (51.1)	1 (7.1)
Female	10 (41.7)	22 (48.9)	13 (92.9)
Race, n (%)			
White	23 (95.8)	40 (88.9)	13 (92.9)
Multiple[a] or other[b]	1 (4.2)	5 (11.1)	1 (7.1)

[a]Races represented included American Indian or Alaskan Native, Asian, Black or African American.
[b]Patients could select "Other" on the clinical report form and write in an answer.
BMI, body mass index; SD, standard deviation.

- Among 83 patients who were dosed, 75 (90.4%) completed one year of study treatment
- Nine (10.8%) patients terminated the study early and 5 (6.0%) discontinued due to voluntary withdrawal

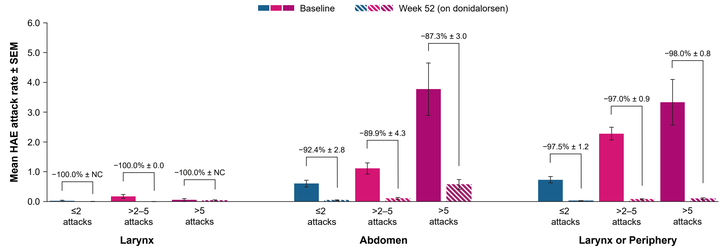
Figure 4. Mean Percent Change From Baseline to Weeks 0–52 in HAE Attack Rate



Baseline was defined as the 56-day run-in period prior to dosing in OASIS-HAE.
HAE, hereditary angioedema; SEM, standard error of the mean.

- Over Weeks 0–52, mean HAE attack rates decreased by 95% (≤2 attacks), 95% (>2–5 attacks), and 90% (>5 attacks) from OASIS-HAE baseline

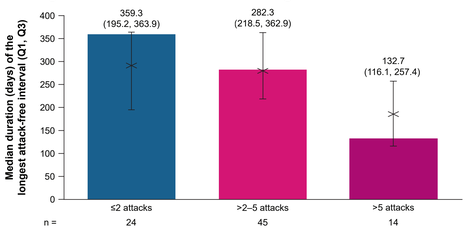
Figure 5. Mean Percent Change From Baseline to Weeks 0–52 in HAE Attack Rate by Anatomical Location



Baseline was defined as the 56-day run-in period prior to dosing in OASIS-HAE. Error bars represent the SEM. Values above the bars indicate mean percent reduction from baseline ± SD.
HAE, hereditary angioedema; NC, not calculated; SD, standard deviation; SEM, standard error of the mean.

- Mean HAE attack rates decreased over Weeks 0–52 regardless of anatomical location; laryngeal attack rates were very low

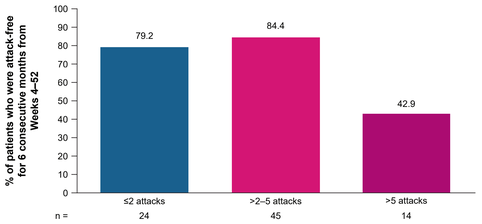
Figure 6. Median Duration of the Longest Attack-Free Interval



Mean duration of the longest attack-free intervals are demarcated by an ×.
Q1, first quartile; Q3, third quartile.

- The median durations of the longest attack-free intervals were 359.3 days (≤2 attacks), 282.3 days (>2–5 attacks), and 132.7 days (>5 attacks)

Figure 7. Percent of Patients Who Were Attack-Free for 6 Consecutive Months From Weeks 4 to 52



- From Weeks 4 through 52, the majority of patients with low (≤2) to moderate (>2–5) attack rates at baseline remained attack-free for 6 consecutive months

Table 2. Summary of Adverse Events

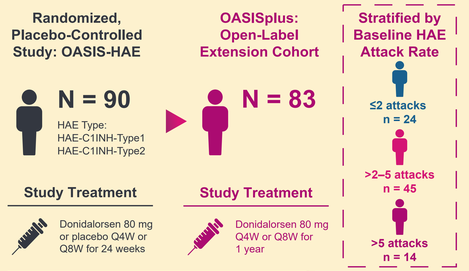
n (%)	≤2 attacks/month (n = 24)	>2–5 attacks/month (n = 45)	>5 attacks/month (n = 14)	Total (n = 83)
Any TEAE	23 (95.8)	40 (88.9)	12 (85.7)	75 (90.4)
Related to study drug[a]	5 (20.8)	12 (26.7)	5 (35.7)	22 (26.5)
Leading to discontinuation	0	2 (4.4)	0	2 (2.4)
Any serious TEAE	2 (8.3)	3 (6.7)	2 (14.3)	7 (8.4)
Related to study drug[a]	0	0	0	0
Severity of TEAE				
Mild	13 (54.2)	16 (35.6)	4 (28.6)	33 (39.8)
Moderate	9 (37.5)	21 (46.7)	6 (42.9)	36 (43.4)
Severe	1 (4.2)	3 (6.7)	2 (14.3)	6 (7.2)
Most common TEAEs (>10% of all patients)				
Influenza	3 (12.5)	9 (20.0)	3 (21.4)	15 (18.1)
Nasopharyngitis	4 (16.7)	10 (22.2)	1 (7.1)	15 (18.1)
Back pain	5 (20.8)	6 (13.3)	1 (7.1)	12 (14.5)
Headache	5 (20.8)	5 (11.1)	1 (7.1)	11 (13.3)
Upper respiratory tract infection	3 (12.5)	4 (8.9)	3 (21.4)	10 (12.0)
COVID-19	3 (12.5)	4 (8.9)	3 (21.4)	10 (12.0)

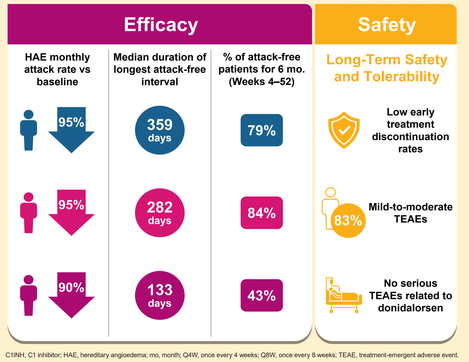
Safety set.
[a]Potentially related is defined as "Related," "Possible," or missing relationship to study drug.
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

- The frequency and severity of TEAEs was similar regardless of baseline HAE attack rate
  - A total of 2 patients (>2–5 attacks) discontinued treatment due to a TEAE
- No serious TEAEs were considered related to treatment
- The most common TEAEs that occurred in 15 (18.1%) patients were influenza and nasopharyngitis

Conclusions

- In this post hoc analysis, donidalorsen improved HAE attack rates by 90%–95% from baseline, including a 100% reduction in all laryngeal attacks, and provided a median longest attack-free period of at least 133 days for all groups, regardless of baseline attack rate
- Donidalorsen had an acceptable safety profile; most TEAEs were mild or moderate in severity





C1INH, C1 inhibitor; HAE, hereditary angioedema; mo, month; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

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