Poster #R082

Switching to Donidalorsen for Hereditary Angioedema: 1-Year Results From the Phase 3 OASISplus Study

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Introduction

- Hereditary angioedema (HAE) is a rare disease characterized by frequently severe, unpredictable, and potentially life-threatening attacks of tissue swelling that are potentially life-threatening[1]
- HAE is primarily caused by deficiency or dysfunction of C1 inhibitor (C1INH) activity, leading to dysregulation of the kallikrein-bradykinin cascade[1-3]

Figure 1. Donidalorsen Mechanism of Action

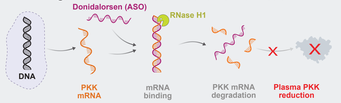
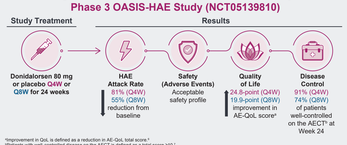


Figure created using BioRender (https://www.biorender.com/).
ASO, antisense oligonucleotide; mRNA, messenger RNA; PKK, prekallikrein; RNase H1, ribonuclease H1.

- 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[4]



*Improvement in QoL is defined as a reduction in AE-QoL total score.†
Well-controlled disease on the AECT is defined as a total score ≥10.[7]
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, improved patient-reported quality of life, and had an acceptable safety and tolerability profile[4]
- Here, we report 1-year interim safety and efficacy of donidalorsen in patients who opted to switch from long-term prophylactic (LTP) medications to donidalorsen in the Switch cohort of the ongoing OASISplus study (NCT05392114)

Study Design

Figure 3. OASISplus Switch cohort

*Patients had the option to switch to Q8W dosing after Year 1.
Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Patients with HAE ≥12 years of age on stable doses (≥12 weeks) of lanadelumab, SC or intravenous C1INH, or berotralstat switched to donidalorsen 80 mg SC Q4W without washout using a predefined algorithm
  - Prior lanadelumab: last dose 14 ± 3 days prior to the first dose of donidalorsen
  - Prior berotralstat/C1INH: last dose 14 ± 3 days after the first dose of donidalorsen
- Endpoints included
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Time-normalized rate of investigator-confirmed HAE attacks per month (HAE attack rate)
  - Angioedema Quality of Life (AE-QoL) at Week 52
  - Well-controlled disease on the Angioedema Control Test (AECT score ≥10)[7] at Week 52
  - Treatment Satisfaction Questionnaire for Medication, version II (TSQM-II) at Week 52
- Data are summarized using descriptive statistics

Results

Table 1. Patient Disposition at 1 Year of Follow-Up

	Prior LTP			
n (%)	Lanadelumab (n = 32)	Berotralstat (n = 11)	C1INH (n = 22)	Total (N = 65)
Patients dosed[a]	31 (96.9)	11 (100.0)	22 (100.0)	64 (98.5)
Completed 1 year	24 (75.0)	11 (100.0)	19 (86.4)	54 (83.1)
Main reasons for discontinuation				
Lack of efficacy	4 (12.5)	0	1 (4.5)	5 (7.7)
Withdrawal by subject	1 (3.1)	0	2 (9.1)	3 (4.6)
Adverse event	1 (3.1)	0	0	1 (1.5)
Lost to follow-up	1 (3.1)	0	0	1 (1.5)
Other	1 (3.1)	0	0	1 (1.5)

[a]Patients with at least 1 dose of the study drug were included in the safety set and the full analysis set.
C1INH, C1 inhibitor; LTP, long-term prophylactic medication.

- Among 65 patients who enrolled, 64 (98.5%) were dosed
- 54 (83.1%) patients completed 1 year of study treatment

Table 2. Baseline Demographics and Characteristics

	Prior LTP			
	Lanadelumab (n = 31)	Berotralstat (n = 11)	C1INH (n = 22)	Total (N = 64)
Age, years, mean (SD)	40.4 (14.2)	45.5 (11.2)	41.3 (16.6)	41.6 (14.5)
Age, years, n (%)				
12–17	1 (3.2)	0	3 (13.6)	4 (6.3)
≥18	30 (96.8)	11 (100.0)	19 (86.4)	60 (93.8)
BMI, kg/m², mean (SD)	30.5 (8.1)	26.6 (5.0)	27.8 (5.2)	28.9 (6.8)
Sex, n (%)				
Male	17 (54.8)	3 (27.3)	6 (27.3)	26 (40.6)
Female	14 (45.2)	8 (72.7)	16 (72.7)	38 (59.4)
Race, n (%)				
White	26 (83.9)	11 (100.0)	20 (90.9)	57 (89.1)
Multiple[a] or other[b]	5 (16.1)	0	2 (9.1)	7 (10.9)
Baseline HAE attack rates				
Mean (SD)	0.69 (1.1)	1.8 (1.9)	0.6 (1.0)	0.9 (1.3)
Median	0	0.9	0.2	0.4
Prior history of LTP, n (%)				
Lanadelumab	—	1 (9.1)	5 (22.7)	37 (57.8)
Berotralstat	5 (16.1)	—	2 (9.1)	18 (28.1)
C1INH	5 (16.1)	0	—	27 (42.2)
Treatment duration of donidalorsen, days				
Mean (SD)	356.1 (88.6)	393.6 (4.5)	366.1 (81.0)	366.0 (78.2)
Median (min, max)	392.0 (28.0, 401.0)	392.0 (390.1, 405.8)	392.9 (99.0, 403.9)	392.0 (28.0, 405.8)

[a]Races represented included American Indian or Alaskan Native, Asian, or Black or African American.
[b]Patients could select "Other" on the clinical report form and write in an answer.
BMI, body mass index; C1INH, C1 inhibitor; HAE, hereditary angioedema; LTP, long-term prophylactic medication; max, maximum; min, minimum; SD, standard deviation.

- Of those who received donidalorsen, the mean age was 42 years, 38 (59.4%) patients were female, and 57 (89.1%) were White
- The median donidalorsen drug exposure was 392 days

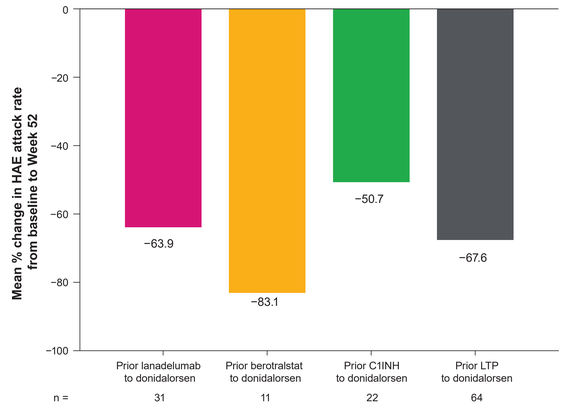
Table 3. Overview of TEAEs

	Prior LTP			
n (%)	Lanadelumab (n = 31)	Berotralstat (n = 11)	C1INH (n = 22)	Total (N = 64)
Any TEAE	26 (83.9)	11 (100.0)	19 (86.4)	56 (87.5)
Related to study drug	12 (38.7)	6 (54.5)	6 (27.3)	24 (37.5)
Leading to discontinuation	1 (3.2)	0	0	1 (1.6)
Any serious TEAE	1 (3.2)	0	0	1 (1.6)
Related to study drug	0	0	0	0
Leading to discontinuation	1 (3.2)	0	0	1 (1.6)
Severity of TEAE				
Mild	4 (12.9)	5 (45.5)	5 (22.7)	14 (21.9)
Moderate	19 (61.3)	5 (45.5)	13 (59.1)	37 (57.8)
Severe	3 (9.7)	1 (9.1)	1 (4.5)	5 (7.8)
Most common TEAEs (>10% of all patients)				
Upper respiratory tract infection	8 (25.8)	2 (18.2)	5 (22.7)	15 (23.4)
Nasopharyngitis	6 (19.4)	3 (27.3)	3 (13.6)	12 (18.8)
Headache	4 (12.9)	3 (27.3)	3 (13.6)	10 (15.6)
Injection-site erythema	4 (12.9)	2 (18.2)	4 (18.2)	10 (15.6)
Fatigue	3 (9.7)	2 (18.2)	2 (9.1)	7 (10.9)
Injection-site pruritus	3 (9.7)	2 (18.2)	2 (9.1)	7 (10.9)

C1INH, C1 inhibitor; LTP, long-term prophylactic medication; TEAE, treatment-emergent adverse event.

- A total of 56 (87.5%) patients reported TEAEs
  - The majority of patients reported TEAEs that were mild and moderate in severity
- One patient who switched from lanadelumab to donidalorsen reported serious TEAEs (acute heart failure exacerbation and kidney lesion) that the study investigator considered unrelated to the study treatment but resulted in drug discontinuation
- The most common TEAE that occurred in 15 (23.4%) patients was upper respiratory tract infection

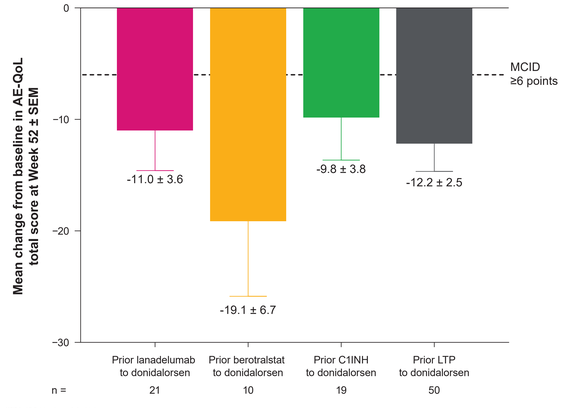
Figure 4. Mean Percent Change in HAE Attack Rate From Baseline to Week 52



C1INH, C1 inhibitor; HAE, hereditary angioedema; LTP, long-term prophylactic medication.

- Overall HAE attack rates decreased by 68% from a mean of 0.85 at baseline (on their prior HAE prophylactic therapy) to 0.28 at Week 52

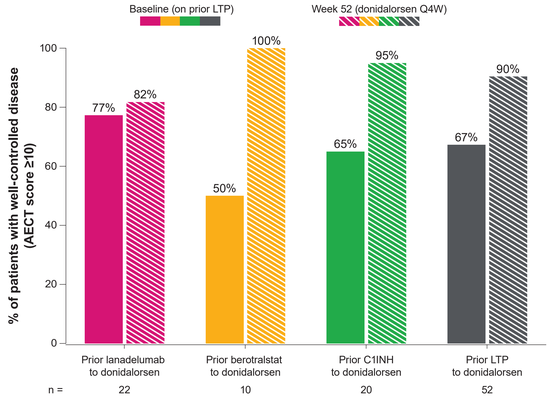
Figure 5. Mean AE-QoL Total Score From Baseline to Week 52



MCID for AE-QoL is a change of ≥6 points.[6]
AE-QoL, Angioedema Quality of Life Questionnaire; C1INH, C1 inhibitor; LTP, long-term prophylactic medication; MCID, minimal clinically important difference; SEM, standard error of the mean.

- Mean AE-QoL total score improved by 12.2 points from baseline at Week 52, which was larger than the ≥6-point threshold for clinically meaningful improvement in quality of life[6]

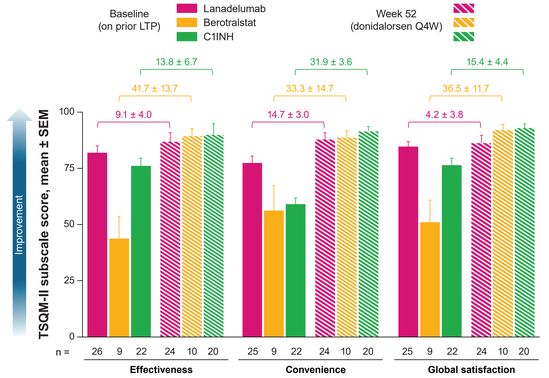
Figure 6. Percentage of Patients With Well-Controlled Disease (AECT Score ≥10) at Baseline and Week 52



AECT, Angioedema Control Test; C1INH, C1 inhibitor; LTP, long-term prophylactic medication; Q4W, once every 4 weeks.

- The percentage of patients reporting well-controlled disease (AECT score ≥10)[7] increased from 67% (baseline) to 90% (Week 52)

Figure 7. Treatment Satisfaction at Baseline on Prior LTP and at Week 52 on Donidalorsen

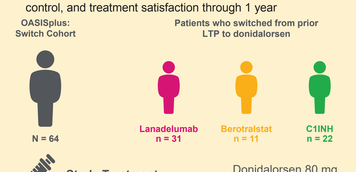


C1INH, C1 inhibitor; LTP, long-term prophylactic medication; Q4W, once every 4 weeks; SEM, standard error of the mean; TSQM-II, Treatment Satisfaction Questionnaire for Medication, version II

- Treatment satisfaction improved across all TSQM-II domains from baseline on prior LTP to Week 52 on donidalorsen
- The side effect domain score was inconclusive due to a low number of side effects reported at Week 52

Conclusions

- Donidalorsen was well tolerated by patients switching from prior LTP medications and resulted in sustained improvements in HAE attack rate, quality of life, disease control, and treatment satisfaction through 1 year



Improvement in QoL is defined as a ≥6-point reduction in AE-QoL total score.
†Well-controlled disease on the AECT is defined as a total score ≥10.[7]
AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; C1INH, C1 inhibitor; HAE, hereditary angioedema; Q4W, once every 4 weeks; QoL, quality of life; TEAE, treatment-emergent adverse event.

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DISCLOSURES

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