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Impact Of Donidalorsen On Patient-Reported Outcomes: Results From The Phase 3 OASIS-HAE Study

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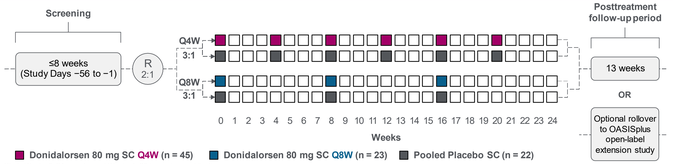
INTRODUCTION

- Hereditary angioedema (HAE) is a rare, debilitating disease characterized by recurrent, unpredictable, and potentially life-threatening attacks of tissue swelling[1,2]
- HAE has substantial negative impacts on patients' quality of life (QoL), including increased anxiety/depression and disruptions to work, education, and other normal activities of daily living[3-5]
- Donidalorsen is an investigational RNA-targeted antisense oligonucleotide that specifically reduces plasma prekallikrein production in the liver
- In the OASIS-HAE phase 3 clinical trial (NCT05139810), donidalorsen significantly reduced HAE attack rate and improved QoL and disease control in patients with HAE, with an acceptable safety and tolerability profile[7]
- Here, we report further analysis of donidalorsen's impact on patient-reported outcomes (PROs), including measures of individual QoL domains, disease control, and work/school impairment from OASIS-HAE

METHODS

- OASIS-HAE was a phase 3, multicenter, double-blind, placebo-controlled, randomized clinical trial
- Eligible patients were ≥12 years of age with HAE-C1INH-Type1 or HAE-C1INH-Type2
- Patients received 80 mg donidalorsen or placebo subcutaneously once every 4 weeks (Q4W) or once every 8 weeks (Q8W) over 24 weeks. Patients receiving placebo Q4W or Q8W were pooled for analyses

Figure 1. Study Design



Study Weeks 0–24 were termed Weeks 1–25 in previous publications.
Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, randomization; SC, subcutaneously.

- PRO endpoints assessed at baseline (Week 0) and Week 24 included:
  - Angioedema Quality of Life Questionnaire (AE-QoL)
    - Four domains: functioning, fatigue/mood, fears/shame, and nutrition
    - Scores range from 0 to 100; higher scores indicate worse QoL
    - The minimum clinically important difference (MCID) is a reduction of 6 points in total score[8]
  - Angioedema Control Test (AECT)
    - Scores range from 0 to 16; higher scores indicate better disease control
    - Scores ≥10 indicate well-controlled disease; scores <10 indicate poorly controlled disease[9]
    - The MCID is an increase of ≥3 points[10]
  - Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)
    - Four domains: absenteeism, presenteeism, overall work/school impairment, and activity impairment
    - Scores are expressed as percentage impairment due to HAE; higher values indicate greater impairment
- All analyses reported here are exploratory or post hoc, and corresponding *P*-values are nominal

RESULTS

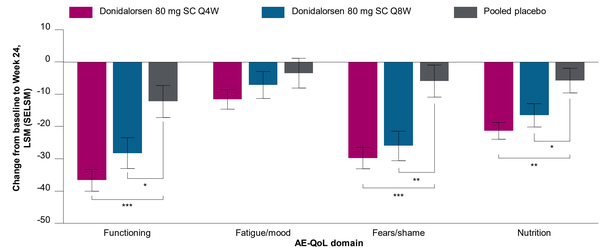
Table 1. Patient Disposition and Demographics

	Donidalorsen Q4W	Donidalorsen Q8W	Pooled Placebo
Patients randomized, n	46	23	22
Patients dosed, n (%)	45 (98)	23 (100)	22 (100)
Completed treatment, n (%)	44 (96)	21 (91)	18 (82)
Age, years, n (%)			
12–17	4 (9)	3 (13)	0
≥18	41 (91)	20 (87)	22 (100)
Sex, n (%)			
Male	17 (38)	11 (48)	14 (64)
Female	28 (62)	12 (52)	8 (36)
Race, n (%)			
White	42 (93)	22 (96)	18 (82)
Multiple or other[a]	3 (7)	1 (4)	4 (18)

The denominator for age, sex, and race percentages is the number of dosed patients.
[a]Races represented in other included American Indian or Alaskan Native, Asian, and Black or African American.
Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Ninety-one patients were randomized and 90 were dosed
- In total, 83 patients (91%) completed the study treatment

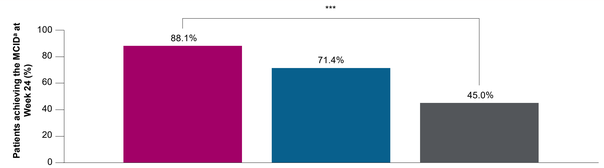
Figure 2. Change From Baseline to Week 24 in AE-QoL Domain Scores



*P <0.05; **P <0.01; ***P <0.001 based on a mixed effects model with repeated measures with fixed effects of treatment, time, treatment-by-time interaction, baseline, and treatment-by-baseline interaction.
AE-QoL, Angioedema Quality of Life Questionnaire; LSM, least squares mean; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously; SELSM, standard error of the least squares mean.

- Patients receiving donidalorsen Q4W or Q8W reported statistically significant improvements in QoL, relative to pooled placebo, in terms of functioning, fears/shame, and nutrition

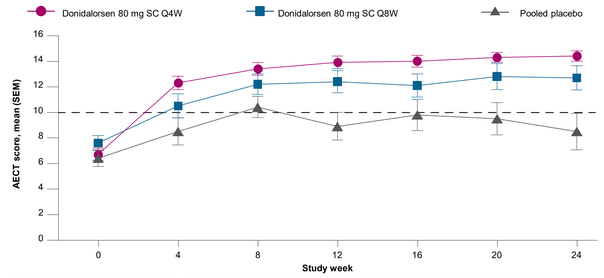
Figure 3. Percentage of Patients Achieving the MCID in AE-QoL Total Score at Week 24



[a]The MCID on the AE-QoL is defined as a 6-point reduction.[8]
***P <0.001 based on a logistic regression with baseline and treatment-by-baseline interaction as covariates.
AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimum clinically important difference; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Relative to pooled placebo, a significantly larger proportion of the donidalorsen Q4W group achieved the MCID in AE-QoL total score from baseline to Week 24

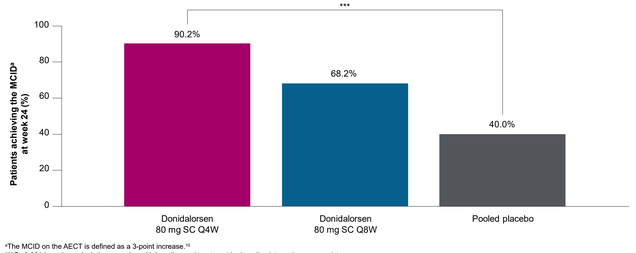
Figure 4. AECT Total Score by Study Visit



Observed means are presented here; continuous AECT scores were modeled only at baseline and Week 24. The dashed line represents the value at which patients' disease is considered well-controlled (AECT ≥10).[9]
AECT, Angioedema Control Test; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously; SEM, standard error of the mean.

- Donidalorsen produced larger least squares mean (LSM) improvements in AECT total scores vs pooled placebo from baseline to Week 24
- LSM changes from baseline to Week 24 exceeded the 3-point MCID for both donidalorsen groups but not the pooled placebo group (Q4W: 7.2 points, *P* <0.001; Q8W: 5.2 points, *P* = 0.003; pooled placebo: 1.2 points)

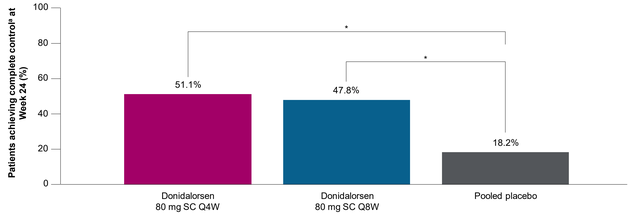
Figure 5. Percentage of Patients Achieving the MCID on the AECT at Week 24



[a]The MCID on the AECT is defined as a 3-point increase.[10]
***P <0.001 based on a logistic regression with baseline and treatment-by-baseline interaction as covariates.
AECT, Angioedema Control Test; MCID, minimum clinically important difference; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Most patients in both donidalorsen groups reached the MCID in AECT total score at Week 24

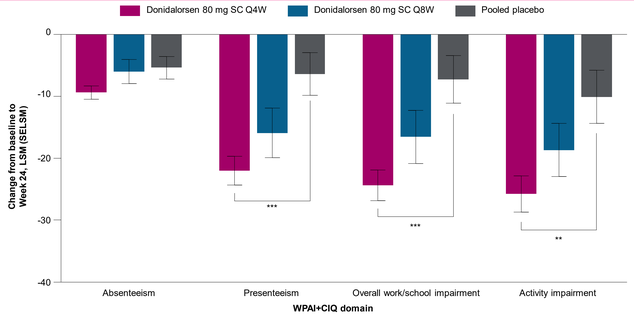
Figure 6. Percentage of Patients Reporting Complete Control on the AECT at Week 24



[a]Complete control is defined as a perfect AECT score of 16.
*P <0.05 based on a logistic regression model with the treatment as a factor
AECT, Angioedema Control Test; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Approximately half of patients in each donidalorsen group reported complete disease control (AECT = 16) at Week 24

Figure 7. Change From Baseline to Week 24 in WPAI+CIQ Domain Scores



**P <0.01; ***P <0.001 based on a mixed effects model with repeated measures with fixed effects of treatment, time, treatment-by-time interaction, baseline value, and treatment-by-baseline interaction.
LSM, least squares mean; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously; SELSM, standard error of the least squares mean; WPAI+CIQ, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

- Donidalorsen Q4W led to significantly greater improvements in three of four WPAI+CIQ domains vs pooled placebo: presenteeism, overall work/school impairment, and activity impairment

CONCLUSIONS

- In the 24-week OASIS-HAE study, donidalorsen led to improvements vs placebo in PROs

Quality of Life

- Donidalorsen Q4W or Q8W significantly improved patient-reported QoL vs pooled placebo across three of four AE-QoL domains
- A significantly larger proportion of donidalorsen Q4W patients reported clinically meaningful improvements in QoL vs pooled placebo patients

Disease Control

- Patients in the donidalorsen groups reported significantly larger, clinically meaningful improvements in disease control based on AECT total scores compared with patients in the pooled placebo group
- A significantly larger percentage of donidalorsen Q4W patients achieved the MCID on the AECT compared with pooled placebo patients, and greater proportions of both donidalorsen groups achieved complete disease control vs the pooled placebo group

Work/School Impairment

- Donidalorsen Q4W reduced impairment of work and school activity compared with pooled placebo

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DISCLOSURES

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