

# Additional Benefit of Switching to Donidalorsen for Patients with Hereditary Angioedema Having Breakthrough Attacks: Findings from the OASISplus Study

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## BACKGROUND

- Hereditary angioedema (HAE) is a rare, genetic form of angioedema, characterized by attacks of cutaneous and submucosal swelling<sup>1</sup>
- Patients with HAE may experience breakthrough attacks of severe swelling despite long-term prophylactic (LTP) treatment<sup>2</sup>
- Breakthrough attacks can significantly impact multiple dimensions of quality of life (QoL), including physical and emotional well-being<sup>2,3</sup>
- Donidalorsen, an FDA-approved prekallikrein-directed antisense oligonucleotide, provides an effective HAE treatment with a 68% reduction in HAE attacks over 1 year after switching<sup>4</sup>
- The relative impact of baseline attack rates on treatment benefits has not been documented

## OBJECTIVE

- To explore the relationship between baseline investigator-confirmed HAE attack rate and subjective disease control and QoL in patients who switched to donidalorsen

## METHODS

### Data Source

- Post hoc analyses of data from a 52-week, open-label extension study of patients who switched from a prior LTP therapy (lanadelumab, C1-INH, or berotralstat) to donidalorsen (OASISplus, NCT05392114, N=72)

### Measures

- Objective disease control: Time-normalized, investigator-confirmed HAE 28-day attack rate
  - Assessed using number of HAE attacks normalized to 28 days
  - Baseline HAE attack rate was used to define subgroups as "low" (a rate of less than 1 breakthrough attack / month during the screening period) and "high" (1 or more breakthrough attacks per month during the screening period)
- Subjective disease control: Angioedema Control Test (AECT) total score
  - 4-item measure of angioedema symptom frequency/severity in the past 4 weeks<sup>5</sup>
  - Total score ranges from 0-16; higher scores indicate greater disease control
  - Administered at Baseline (Week 0) and at Week 52
- QoL: Hereditary Angioedema Quality of Life Questionnaire (HAE-QoL) total score
  - 25-item, disease-specific measure of health-related QoL over a 6-month period<sup>6,7</sup>
  - Total scores range from 25-135 with higher scores indicating better health-related QoL
  - Administered at Baseline (Week 0) and at Week 52
- QoL: Angioedema Quality of Life Questionnaire (AE-QoL) total and domain scores
  - 17-item, symptom-specific measure of the global impact of HAE on functioning and well-being over a 4-week period<sup>8</sup>
  - Total and domain scores (functioning, fatigue/mood, fears/shame, nutrition) range from 0-100; lower scores indicate better QoL
  - Administered at Baseline (Week 0) and at Week 52

## STATISTICAL ANALYSIS

- Independent samples *t*-tests evaluated statistically significant differences in mean change in AECT, HAE-QoL, and AE-QoL scores from Baseline to Week 52 across baseline HAE attack rate subgroups ( $\alpha = 0.05$ )
- Cohen's *d* effect sizes for standardized mean differences were calculated to estimate the magnitude of the effects between subgroups
  - Cohen's *d* effect size interpretation: small = 0.20, medium = 0.50, large = 0.80

## RESULTS

**Table 1. Magnitude of Mean Change in AECT, HAE-QoL Total, and AE-QoL Total and Domain Scores at Week 52 by Baseline Attack Rate Subgroups**

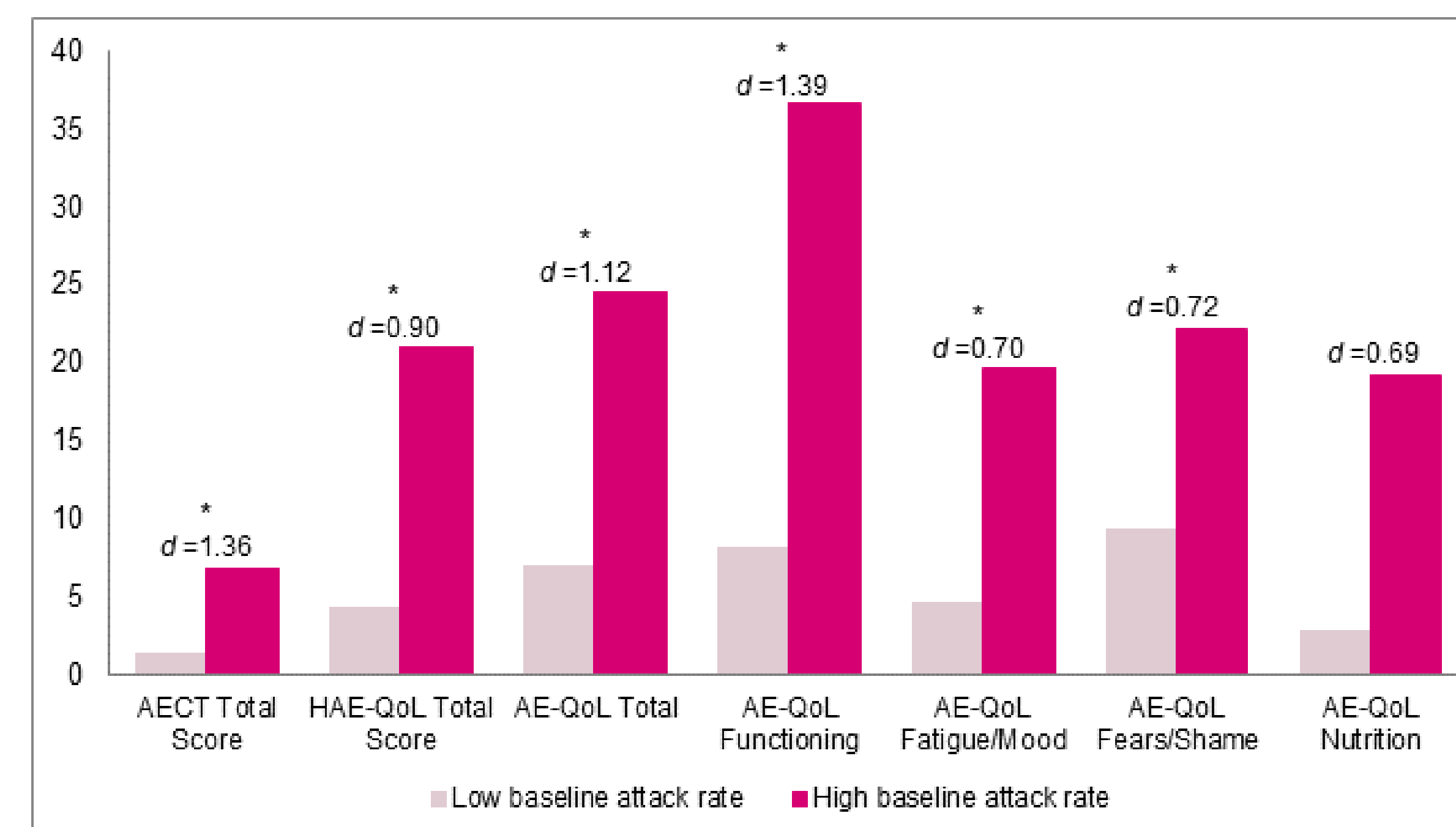
	Baseline HAE Attack Rate Subgroups						<i>p</i> -value <sup>a</sup>
	Low (< 1 attack)			High (≥ 1 attack)			
	n	Mean	SD	n	Mean	SD	
<b>AECT Total Score</b>	38	1.3	3.5	14	6.8	5.2	<b>&lt;0.001</b>
<b>HAE-QoL Total Score</b>	35	4.4	15.5	15	21.0	24.2	<b>0.024</b>
<b>AE-QoL Score</b>							
<b>Total</b>	35	-6.9	12.8	15	-24.5	21.2	<b>0.008</b>
<b>Functioning</b>	35	-8.2	19.3	15	-36.7	23.1	<b>&lt;0.001</b>
<b>Fatigue/Mood</b>	35	-4.6	19.5	15	-19.7	25.7	<b>0.027</b>
<b>Fears/Shame</b>	35	-9.3	16.3	15	-22.2	21.3	<b>0.024</b>
<b>Nutrition</b>	35	-2.9	19.2	15	-19.2	32.3	0.085

Abbreviations: AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; ES, effect size; HAE, hereditary angioedema; HAE-QoL, Hereditary Angioedema Quality of Life Questionnaire; SD, standard deviation.

<sup>a</sup> Based on independent samples *t*-test.

Note(s): Bolded values indicate significance at  $p < 0.05$ . HAE attack rate subgroups are defined as: Low baseline attack rate (< 1 attack), and High baseline attack rate (≥ 1 attack).

**Figure 1. Greater Improvement in Subjective Disease Control and QoL for those with Higher Baseline HAE Attack Rate, Larger Effect Sizes (*d*) = Stronger Effects**



Abbreviations: AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; *d*, Cohen's *d* effect size; HAE, hereditary angioedema; HAE-QoL, Hereditary Angioedema Quality of Life Questionnaire. Note(s): \* indicates significant difference in mean change at  $p < 0.05$ ; HAE attack rate subgroups are defined as: Low baseline attack rate (< 1 attack), and High baseline attack rate (≥ 1 attack); absolute values for mean change and Cohen's *d* effect sizes shown.

Switching to donidalorsen from prior LTP treatment resulted in improvements in AECT, HAE-QoL, and AE-QoL regardless of baseline attack rate

Patients with high baseline HAE attack rates had significantly greater mean improvements in AECT (high: 6.8 vs. low: 1.3;  $d = 1.36$ ), HAE-QoL (low: 4.4 vs. high: 21.0;  $d = 0.90$ ), and AE-QoL (high: -6.9 vs. low: -24.5;  $d = 1.12$ ), total scores, compared to the low baseline HAE attack rate subgroup (all  $p < 0.05$ )

Significant differences were observed in mean change for all AE-QoL domain scores across baseline attack rate subgroups ( $d$  range: 0.70 to 1.39; all  $p < 0.05$ ), except for the AE-QoL Nutrition domain, though the effect size was medium ( $d = 0.69$ )

## LIMITATIONS

- Results may be subject to selection bias, as patients' decisions to switch therapies could be associated with underlying clinical factors or patient preferences
- This study did not control for other factors that may have influenced the relationship between attack rate and subjective disease control or QoL

## CONCLUSIONS

- Patients with HAE on LTP treatment who switched to donidalorsen experienced improvements in subjective disease control and QoL regardless of the baseline HAE attack rate
- Patients with a high rate of baseline breakthrough attacks reported significantly greater improvements in subjective disease control and QoL, compared to those with a low baseline breakthrough attack rate
- Patients with relatively low disease activity, less than 1 HAE attack per month, showed notable improvement in subjective disease control and QoL after switching to donidalorsen
- These findings underscore the need to optimize therapy for patients who may appear well-controlled on LTP treatment, as even residual attacks may impact patients' perceptions of disease control and QoL

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## DISCLOSURES

Marc Riedl has received consultancy fees from Astria, Biocryst, Biomarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, Kalvista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda; and received research support from Astria, Biocryst, Biomarin, CSL Behring, Intellia, Ionis, Kalvista, Pharvaris, Takeda; and provided speaker presentations for Biocryst, CSL Behring, Grifols, Pharming, Takeda.

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