# *Self-Reported Treatment Preferences of Patients Switching From Prior Prophylactic Therapies to Donidalorsen for the Treatment of Hereditary Angioedema*

Results From the OASISplus Study

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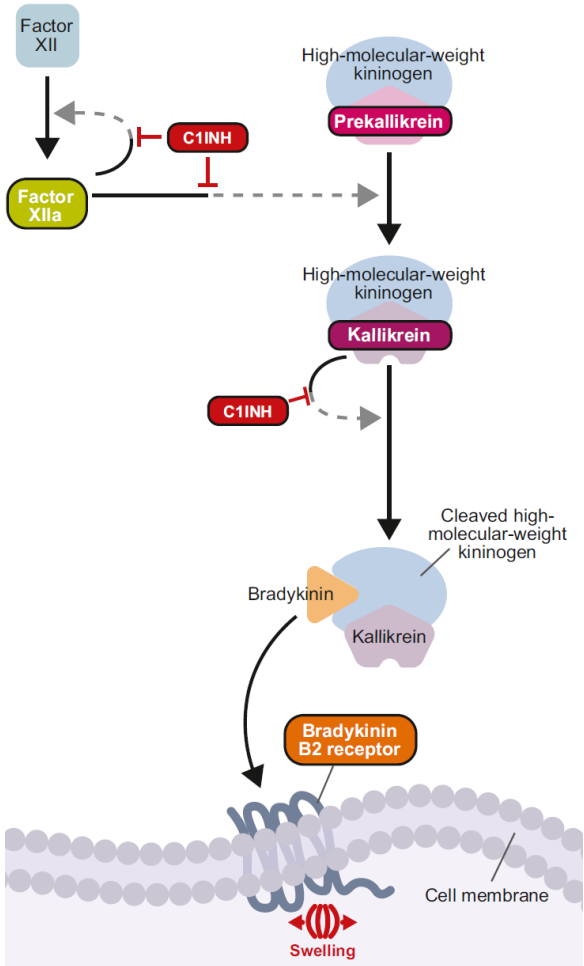
# Disclosures

- Donidalorsen is an investigational drug in late-stage development
- **Marc A. Riedl** has received research grants from BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista Pharmaceuticals, and Pharvaris; consulted for BioCryst, BioMarin Pharmaceutical, CSL Behring, Cycle Pharma, Fresenius-Kabi, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pfizer, Pharming, Pharvaris, Regeneron Pharmaceuticals, REGENXBIO, Shire/Takeda, and Spark Therapeutics; and provided speaker presentations for CSL Behring, Grifols, Pharming, and Shire

# Hereditary Angioedema (HAE)

- A rare chronic disease characterised by frequent, severe, and potentially life-threatening tissue swelling[1–3]
- Usually caused by pathogenic variants of *SERPING1* and consequent kallikrein-kinin system dysregulation[1,2]
- Long-term prophylaxis aims to stabilise the kallikrein-kinin system and improve disease control and overall well-being[4–6]
- Substantial disease burden persists, and patients switch products due to breakthrough HAE attacks, highlighting the need for new treatments[6]



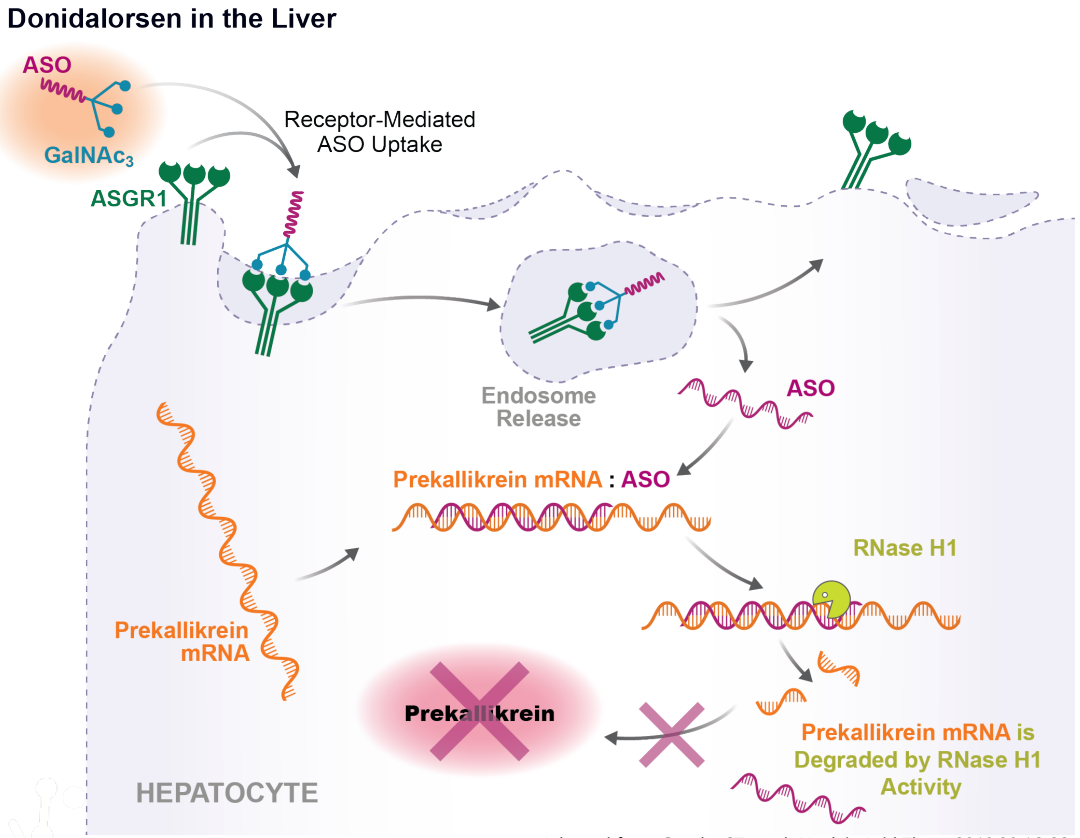

C1, complement protein 1; C1-INH, C1 inhibitor.

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. Caballero T, et al. *J Investig Allergol Clin Immunol.* 2023;33:238-49. 5. Maurer M, et al. *J Allergy Clin Immunol.* 2021;148:1526-32. 6. Mendivil J, et al. *Allergy Asthma Clin Immunol.* 2023;19:48.

Based on Riedl MA, et al. *J Allergy Clin Immunol Pract.* 2024;12:911-18.

# Donidalorsen: A Potential Prophylactic Treatment for HAE

- Donidalorsen is a triantennary N-acetylgalactosamine ($GalNAc_3$)–conjugated antisense oligonucleotide designed to specifically degrade prekallikrein mRNA in hepatocytes[1,2]
- In the phase 3 OASIS-HAE study,[3] donidalorsen 80 mg subcutaneously (SC) every 4 weeks (Q4W) or every 8 weeks (Q8W)
  - Demonstrated least squares mean HAE attack rates 81% lower (Q4W) and 55% lower (Q8W) vs placebo over Weeks 1 to 25
  - Improved quality of life (QoL) and disease control
  - Had an acceptable safety and tolerability profile
- The ongoing OASISplus study (NCT05392114) includes an open-label extension (OLE) cohort from OASIS-HAE and a **switch cohort** from prior long-term prophylaxis




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

1. Crooke ST, et al. *Nucleic Acid Ther.* 2019;29:16-32. 2. Riedl MA, et al. *J Allergy Clin Immunol Pract.* 2024;12:911-18. 3. 3.Riedl MA, et al. *NEJM.* 2024. doi:10.1056/NEJMoa2402478.

# Study Design and Primary Endpoint: OASISplus Phase 3 Trial[a] (Switch Cohort)

## DESIGN

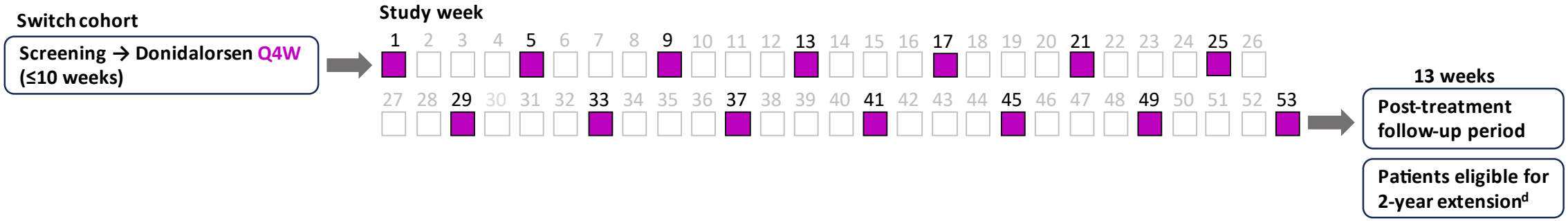
- Patients aged ≥12 years with HAE-C1INH-Type1 or HAE-C1INH-Type2[b] on a stable dose of prophylactic treatment (lanadelumab, C1-INH, or berotralstat) for ≥12 weeks prior to the screening period
- Donidalorsen 80 mg SC Q4W

## PRIMARY OBJECTIVE

- To evaluate the safety of long-term dosing with donidalorsen in patients with HAE

## PRIMARY ENDPOINT

- Incidence and severity of treatment-emergent adverse events (TEAEs)[c]




[a]NCT05392114. [b]HAE-C1INH-Type1 = C1-INH deficiency; HAE-C1INH-Type2 = C1-INH dysfunction. [c]Data shown are from an interim data cut from February 28, 2024. [d]Patients could change to Q8W dosing after Year 1.

# OASISplus Phase 3 Trial: Additional Objectives and Endpoints

## SECONDARY OBJECTIVES

- To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the QoL of patients with HAE

## SECONDARY ENDPOINTS

- Time-normalised number of HAE attacks per month (Weeks 1–53)[a]
- Angioedema quality of life (AE-QoL) questionnaire total score at Week 53[a]

## EXPLORATORY OBJECTIVE

- To further characterise the effects of donidalorsen on patient-reported outcomes

## EXPLORATORY ENDPOINTS

- Percentage of patients with well controlled disease[1] over 53 weeks by the Angioedema Control Test (AECT) Treatment preference at Week 17[a,b]

[a]Interim data shown for patients who completed through Week 17 due to the limited number of patients who have completed later timepoints in the ongoing study. [b]Defined as an AECT score ≥10.[2]

1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4. 2. Weller K, et al. *Allergy*. 2020;75(5):1165–77.

# Patient Demographics

| | Patients switching to donidalorsen 80 mg Q4W from: | | | |
|---|---|---|---|---|
| | Lanadelumab (n = 31) | Berotralstat (n = 11) | C1-INH (n = 22) | Total (N = 64) |
| **Age, years, mean (standard deviation [SD])** | 40 (14) | 46 (11) | 41 (17) | 42 (15) |
| **Age group, n (%)** | | | | |
| 12–17 years old | 1 (3) | 0 | 3 (14) | 4 (6) |
| ≥18 years old | 30 (97) | 11 (100) | 19 (86) | 60 (94) |
| **Sex, n (%)** | | | | |
| Male | 17 (55) | 3 (27) | 6 (27) | 26 (41) |
| Female | 14 (45) | 8 (73) | 16 (73) | 38 (59) |
| **Race,[a] n (%)** | | | | |
| White | 26 (84) | 11 (100) | 20 (91) | 57 (89) |
| Multiple or other[b] | 5 (16) | 0 | 2 (9) | 7 (11) |

[a]Race was self-reported by patients during screening. [b]Includes Asian, Black or African American, and "other."

# Patient Disposition

- In total, 88% of patients[a] remained in the study as of February 28, 2024
- Mean exposure to donidalorsen was 263 days

| | Lanadelumab | Berotralstat | C1-INH | Total |
|---|---|---|---|---|
| **Patients enrolled, n** | 32 | 11 | 22 | 65 |
| **Patients dosed, n** | 31 | 11 | 22 | 64 |
| **Completed Week 17 of treatment, n (%)** | 28 (88) | 10 (91) | 20 (91) | 58 (89) |
| **Early termination, n (%)** | | | | |
| Lack of efficacy | 3 (9) | 0 | 1 (5) | 4 (6) |
| Serious adverse event | 1 (3) | 0 | 0 | 1 (2) |
| Lost to follow-up | 1 (3) | 0 | 0 | 1 (2) |
| Voluntary withdrawal | 0 | 0 | 1 (5) | 1 (2) |
| Other (not dosed) | 1 (3) | 0 | 0 | 1 (2) |

[a]56 of 64 dosed patients remained on study as of February 28, 2024.

# Primary Endpoint: Incidence and Severity of TEAEs

| | Donidalorsen Q4W (N = 64) |
|---|---|
| **Any TEAE,[a] n (%)** | 50 (78) |
| Related to study drug | 21 (33) |
| Leading to discontinuation | 1 (2) |
| **Any serious TEAE, n (%)** | 1 (2) |
| Related to study drug | 0 |
| **Severity of TEAEs related to study drug, n (%)** | |
| Mild | 15 (23) |
| Moderate | 5 (8) |
| Severe | 1[b] (2) |

- One TEAE that was not related to study drug led to discontinuation
- No serious TEAEs related to the study drug
- Most TEAEs were mild or moderate in severity

[a]TEAE is defined as any adverse event starting or worsening on or after the first dose of donidalorsen. [b]Headache was assessed as possibly related and nonserious, and there was no action taken with the study drug.

# Primary Endpoint: Most Common TEAEs

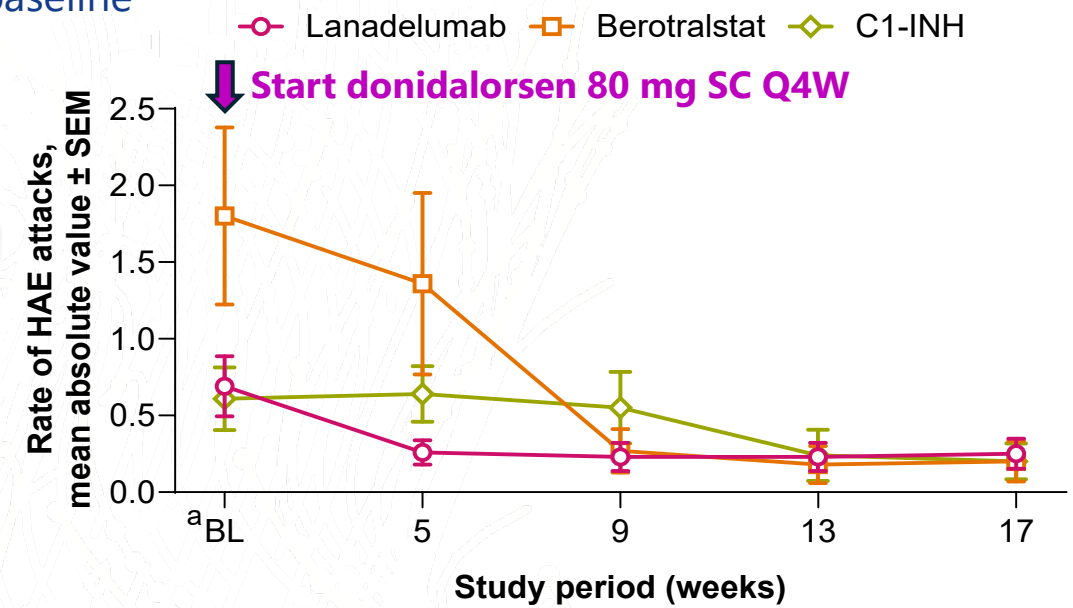
| | Donidalorsen Q4W (N = 64) |
|---|---|
| **Most common TEAEs[a] (≥5% of all patients), n (%)** | |
| Upper respiratory tract infection | 14 (22) |
| Nasopharyngitis | 12 (19) |
| Injection-site erythema | 9 (14) |
| Injection-site pruritus | 7 (11) |
| Headache | 7 (11) |
| Fatigue | 6 (9) |
| Sinusitis | 5 (8) |
| Urinary tract infection | 5 (8) |
| Injection-site pain | 4 (6) |
| Nausea | 4 (6) |
| Vomiting | 4 (6) |
| Muscle strain | 4 (6) |
| Cough | 4 (6) |
| Hepatic enzyme increased[b] | 4 (6) |

- Overall, no safety concerns related to donidalorsen treatment were identified in the Switch study.

[a]TEAE is defined as any adverse event starting or worsening on or after the first dose of donidalorsen. [b]TEAEs of hepatic enzyme increased were mild or moderate in severity, and no action was taken with the study drug. Those of moderate severity were associated with AST levels >3x ULN and considered unrelated to study drug.

# Time-Normalised Number of HAE Attacks per Month (Weeks 1–17)

- Patients with HAE who switched from prior long-term prophylactics (LTPs) to donidalorsen Q4W had a mean 62% reduction in attack rate from baseline




[a]Baseline attack rate during the screening period for the Switch study.
SEM, standard error of the mean.

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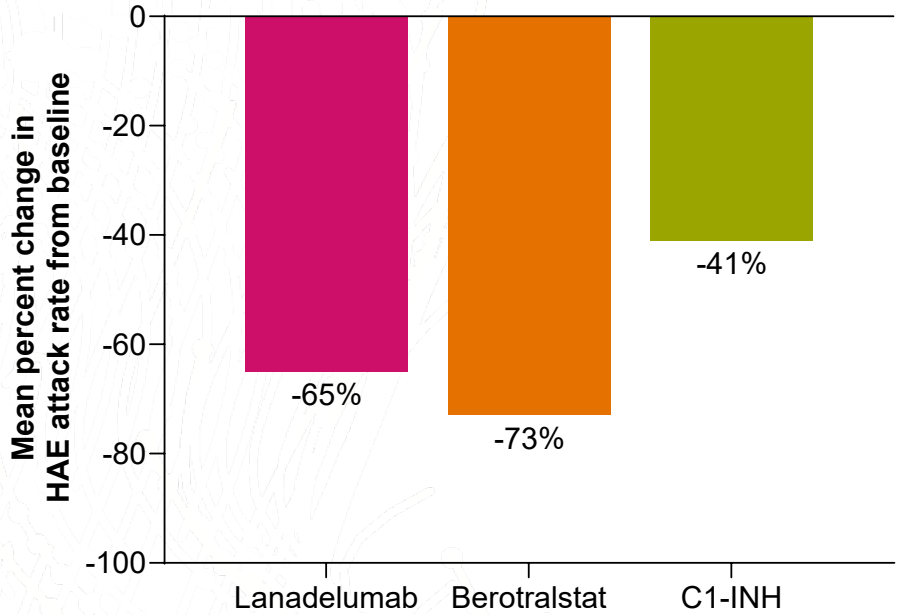
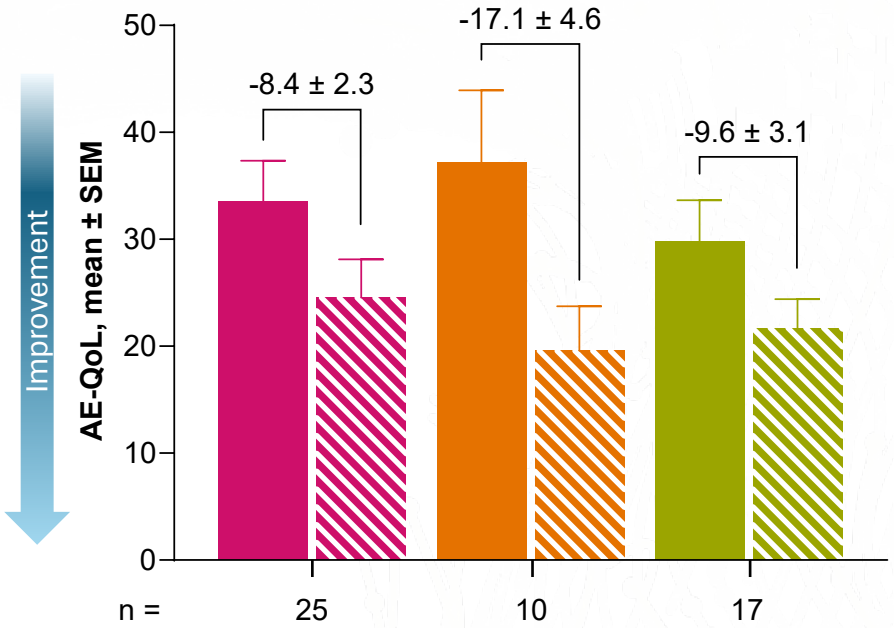
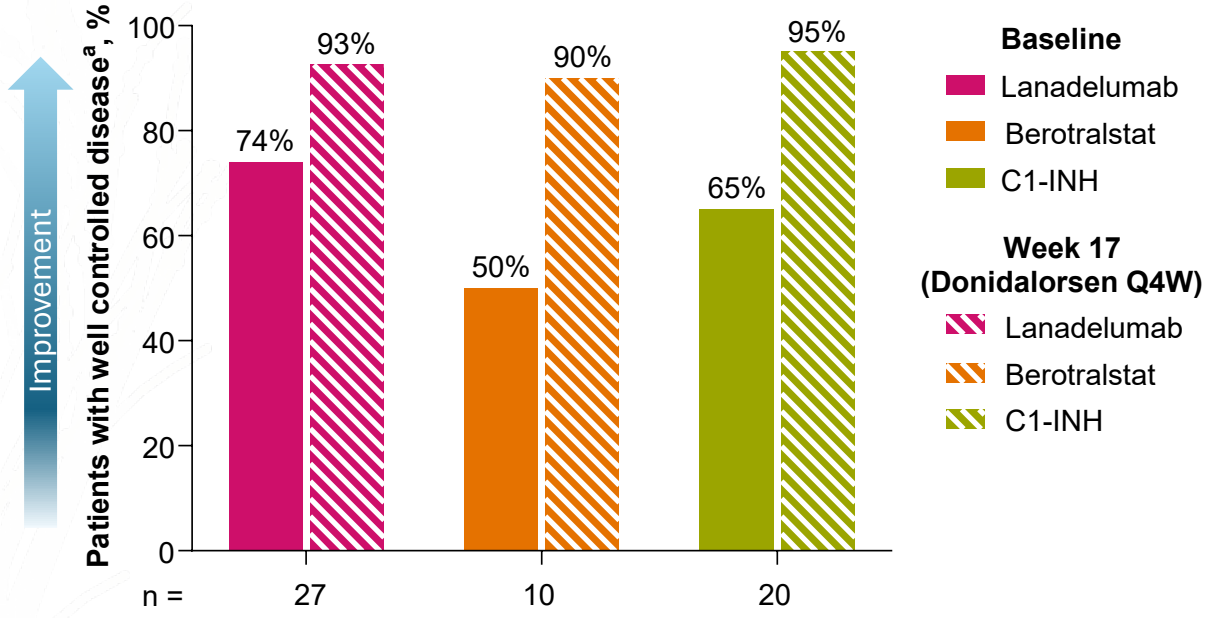



| | Lanadelumab | Berotralstat | C1-INH |
|---|---|---|---|
| n = | 31 | 11 | 22 |
| Baseline, mean ± SD = | 0.69 ± 1.09 | 1.80 ± 1.92 | 0.61 ± 0.96 |
| Donidalorsen Q4W (Week 17), mean ± SD = | 0.24 ± 0.33 | 0.48 ± 0.53 | 0.36 ± 0.69 |

Baseline HAE attack rate during the screening period for the Switch study.

# Patient-Reported Outcomes at Baseline and Week 17: AE-QoL and AECT Scores

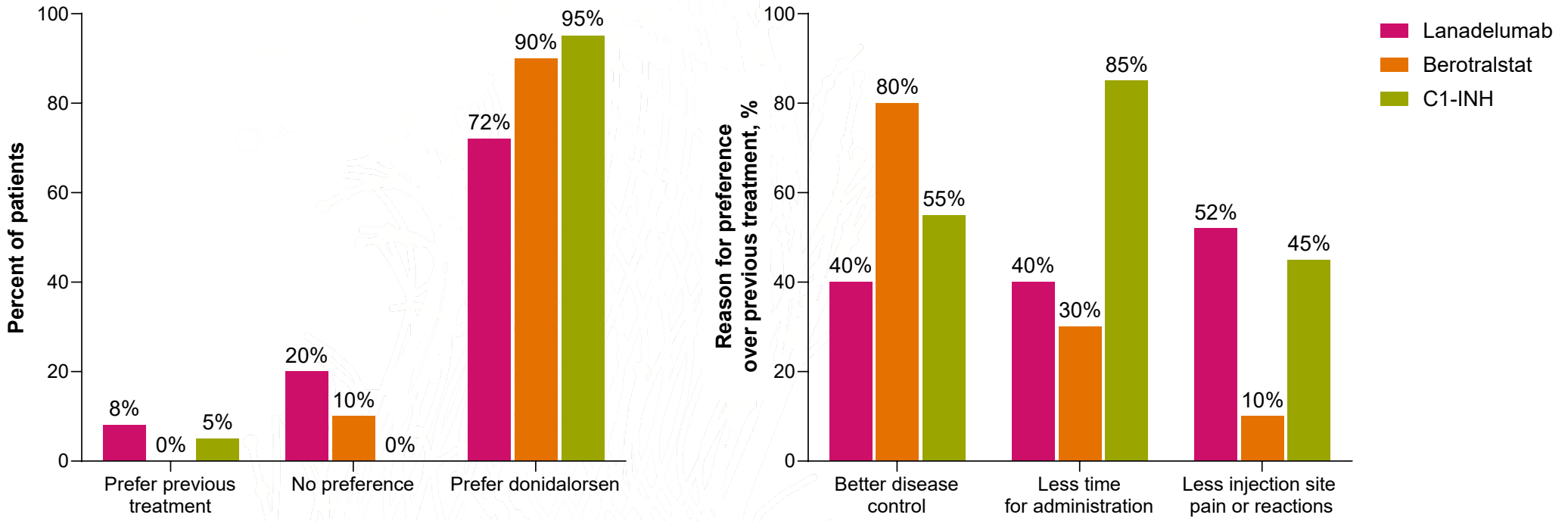



- Regardless of previous treatment, patients reported ≥8-point improvements in AE-QoL scores
- By Week 17, ≥90% of patients reported well controlled[a] disease based on AECT scores

[a]Based on the AECT and defined as an AECT score ≥10.

# Patient-Reported Outcomes at Week 17: Treatment Preference




- Most patients preferred treatment with donidalorsen, regardless of their previous treatment

# Conclusions

**Efficacy**

- By Week 17, patients with HAE who switched from prior LTPs to donidalorsen Q4W had a mean 62% reduction in attack rate from baseline

**Safety and Tolerability**

- Donidalorsen had an acceptable safety and tolerability profile
  - One TEAE that was not related to study drug led to discontinuation
  - There were no serious TEAEs related to the study drug
  - Most TEAEs were mild or moderate in severity

**Patient-Reported Outcomes and Preference**

- Self-reported QoL and disease control improved after switching to donidalorsen
- The vast majority of patients preferred donidalorsen to their previous treatment

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