Clinical Outcomes With Navenibart According to Baseline Attack Rate, Body Mass Index, and Age: Results of the ALPHA-STAR Trial

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INTRODUCTION

- Hereditary angioedema (HAE) is a rare, autosomal dominant genetic disorder characterized by kallikrein-kinin system dysregulation, resulting in recurrent swelling attacks and substantial disease burden.[1–3]
- Navenibart is an investigational long-acting monoclonal antibody inhibitor of plasma kallikrein.[4]
- In the Phase 1b/2 ALPHA-STAR trial (NCT05695248), navenibart was well tolerated and reduced HAE attacks (mean reduction of 86.3%) in a trial population of 29 adults with HAE due to C1-esterase inhibitor deficiency (HAE-C1INH).[4]
- The effects of differing patient characteristics on outcomes of long-acting HAE treatments are not well characterized. This *post hoc* analysis of the ALPHA-STAR trial evaluated navenibart clinical outcomes across subgroups defined by baseline attack rate, body mass index (BMI), and age.

METHODS

- ALPHA-STAR was a Phase 1b/2, multicenter, dose-ranging, proof-of-concept, open-label trial that assessed the safety (primary endpoint) and clinical activity of single- and multiple-dose navenibart in adults (≥18 years of age) with HAE-C1INH type 1 or 2.[4]
- Eligible participants were those who experienced at least two HAE attacks during the 8-week trial run-in period.
- Participants were enrolled in three navenibart dose cohorts (single dose of 450 mg on day 1; 600 mg on day 1 followed by 300 mg on day 84; and 600 mg on day 1 and on day 28) and were pooled for the purpose of this *post hoc* analysis.
- *Post hoc* outcomes included the overall change from baseline in monthly HAE attack rate, the rate of attacks treated with on-demand medication, and the rate of moderate or severe attacks. Outcome measures were assessed for 6 months after the last dose.
- *Post hoc* subgroups were defined by:
  - baseline attack rate (low [<2 attacks/month]; medium [2 to <3 attacks/month]; high [≥3 attacks/month])
  - BMI (18.5–24.9, 25–29.9, 30–34.9, 35.0–39.9, and ≥40 kg/m^2)
  - age (<25, 25–44, 45–60, and >60 years)
- Results are summarized descriptively (mean and standard deviation), with nominal changes from baseline and 95% confidence intervals.
- Owing to the small sample size and short-term study design, these data may not fully represent the broader population of patients with HAE.

RESULTS

Table 1. Participant Demographics and Baseline Characteristics (Pooled Data)

	Overall (N=29)
Age, mean (SD), years	46.4 (16.6)
Age subgroup, n (%), years	
<25	5 (17.2)
25–44	7 (24.1)
45–60	9 (31.0)
>60	8 (27.6)
Sex, n (%)	
Male	13 (44.8)
Female	16 (55.2)
Race, n (%)[a]	
White	23 (79.3)
Black or African American	4 (13.8)
American Indian or Alaska Native	1 (3.4)
BMI, mean (SD), kg/m^2	28.8 (5.3)
BMI subgroup, n (%), kg/m^2	
18.5–24.9	6 (20.7)
25.0–29.9	12 (41.4)
30.0–34.9	6 (20.7)
35.0–39.9	5 (17.2)
≥40.0	0 (0.0)
HAE type, n (%)	
Type 1	25 (86.2)
Type 2	4 (13.8)
Age at onset of first HAE symptoms, mean (SD), years	13.3 (7.4)
Number of HAE attacks in past 12 months, mean (SD)	20.4 (20.5)
Attack rate subgroup, n (%)	
Low (<2 attacks/month)	17 (58.6)
Medium (2 to <3 attacks/month)	6 (20.7)
High (≥3 attacks/month)	6 (20.7)

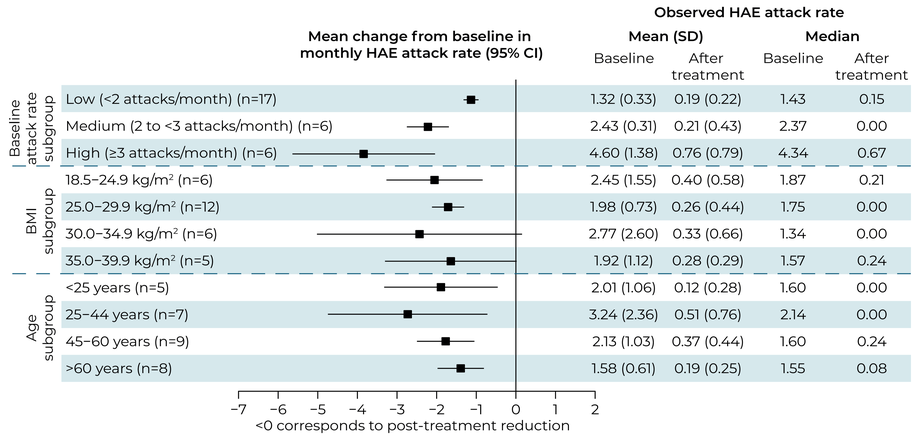
Adapted from Banerji et al. *J Allergy Clin Immunol.* 2026.[4]
BMI, body mass index; HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous; SD, standard deviation.
[a]Race not reported for one participant.

Table 2. Incidence of TEAEs (Pooled Data)

	Overall (N=29)
Participants with ≥1 TEAE, n (%)	25 (86.2)
Participants with ≥1 serious TEAE or death, n	0
Participants who discontinued owing to TEAE, n	0
TEAE present in ≥2 participants, n (%)	
Headache	7 (24.1)
Nasopharyngitis	7 (24.1)
Urinary tract infection	3 (10.3)
Abdominal discomfort	2 (6.9)
Back pain	2 (6.9)
Contusion	2 (6.9)
Nasal congestion	2 (6.9)
Sinusitis	2 (6.9)
Skin laceration	2 (6.9)
TEAE in ≥1 participant, n (%)	4 (13.8)
Injection site erythema[a]	1 (3.4)
Injection site pruritus[a]	1 (3.4)
Injection site rash	1 (3.4)
Injection site swelling	1 (3.4)
Dizziness	1 (3.4)

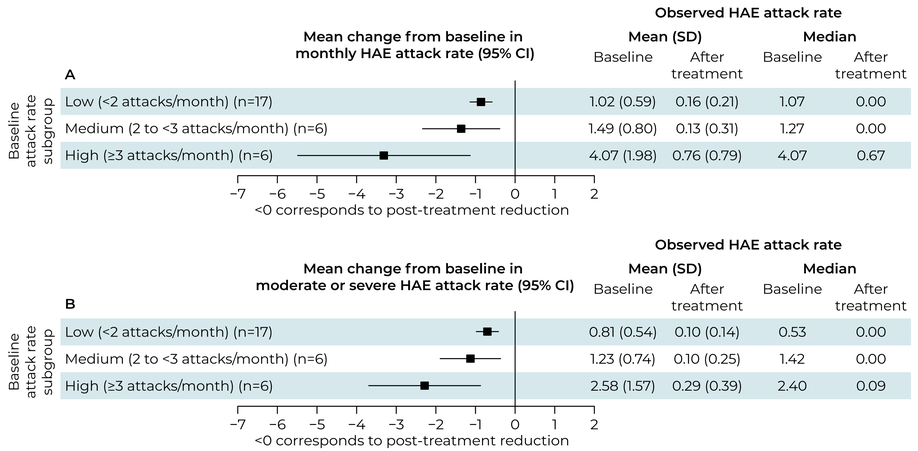
Adapted from Banerji et al. *J Allergy Clin Immunol.* 2026.[4]
TEAE, treatment-emergent adverse event.
[a]One participant experienced two concurrent injection site reactions: mild injection site erythema and mild injection site pruritus.

Figure 1. Mean Change From Baseline in Monthly HAE Attack Rate by Baseline Attack Rate, BMI, and Age Subgroups



HAE attack rate (unique, nonoverlapping, investigator-confirmed) was calculated as: (Number of HAE attacks/Duration of evaluation period in days)×30.4375.
Baseline rates were obtained during the run-in period (screening visit to the day before first treatment); post-treatment rates were obtained during the treatment period (first treatment date to end of trial date).
BMI, body mass index; CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation.

Figure 2. Mean Change From Baseline in Rate of Monthly HAE Attacks Requiring On-Demand ('Rescue') Medication (A) or Rate of Moderate or Severe HAE Attacks (B) by Baseline Attack Rate Subgroup



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Baseline rates were obtained during the run-in period (screening visit to the day before first treatment); post-treatment rates were obtained during the treatment period (first treatment date to end of trial date).
CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation.

Observed Number of Moderate or Severe HAE Attacks by BMI Subgroup

- The number of moderate or severe HAE attacks was lower after treatment vs at baseline for all BMI subgroups.
- Baseline attacks were recorded during the run-in period (screening visit to the day before first treatment), and post-treatment attacks were recorded during the treatment period (first treatment date to end of trial date).

CONCLUSIONS

1. Reductions in HAE attack rate were observed across analyzed subgroups regardless of baseline attack rate, BMI, and age.
2. Reduced rates of attacks requiring on-demand medication and of moderate or severe HAE attacks were observed with treatment in all baseline attack rate subgroups.
   - Reductions in the number of moderate or severe attacks were also observed with treatment across all BMI subgroups.
3. In the overall trial population, navenibart was previously shown to be well tolerated, with no severe or serious treatment-emergent adverse events reported and few injection site reactions.[4]
4. Together with the primary findings from ALPHA-STAR, this analysis supports the ongoing Phase 3 evaluation of navenibart in the ALPHA-ORBIT trial (NCT06842823) as a potential long-acting therapeutic option for the broad HAE population.

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