# Results from the ALPHA-STAR Trial, a Phase 1b/2 Single and Multiple Dose Study to Assess the Safety, Tolerability, Clinical Activity, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Navenibart (STAR-0215) in Participants with Hereditary Angioedema (HAE)

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## OBJECTIVE

- To evaluate safety, tolerability, clinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of navenibart (STAR-0215) in adult participants with hereditary angioedema (HAE).

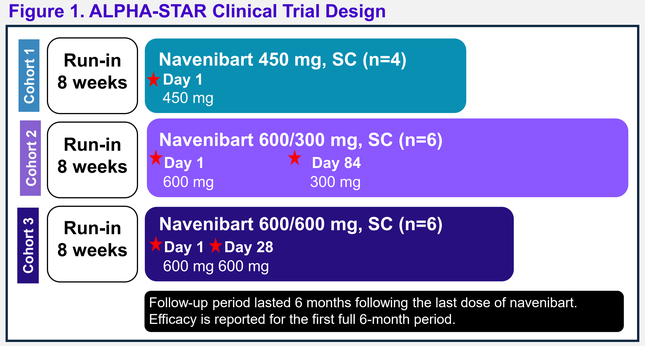
## INTRODUCTION

- HAE is a rare, autosomal dominant disease associated with dysregulation of the kallikrein-kinin system.
- Navenibart is a novel investigational extended half-life monoclonal antibody inhibitor of plasma kallikrein.
- Here we present results from the target enrollment group (n=16) in the ALPHA-STAR (NCT05695248) clinical trial of navenibart (STAR-0215) subcutaneously (SC) administered in adult participants with hereditary angioedema (HAE).

## METHODS

- In this multi-center, dose-ranging proof of concept phase 1b/2 trial, patients with HAE-C1INH Type 1 or 2 were recruited from 14 sites in the USA, Canada, UK, Bulgaria, and Czechia. The target enrollment group was from 9 sites in the USA and Canada.
- Participants were recruited into 3 dose cohorts, Cohort 1: 450 mg (day 1); Cohort 2: 600 mg (day 1), 300 mg (day 84); Cohort 3: 600 mg (day 1), 600 mg (day 28); all cohorts were followed for 6 months after the last dose (**Figure 1**).
- Assessments included safety, tolerability, and change from baseline in time-normalized (monthly) HAE attack rates. Efficacy is reported for the first full 6-month period.
- PK, PD, and immunogenicity (anti-drug antibody levels, ADA) were assessed using validated methods.

### Figure 1. ALPHA-STAR Clinical Trial Design




## SUMMARY

**1** IN THIS PROOF-OF-CONCEPT CLINICAL TRIAL, NAVENIBART SHOWED 91-95% REDUCTION IN MEAN MONTHLY ATTACK RATE COMPARED TO RUN-IN BASELINE AND A MEDIAN REDUCTION OF 94-100% DURING THE FIRST 6 MONTHS AFTER NAVENIBART ADMINISTRATION.

**2** NAVENIBART WAS WELL TOLERATED; THERE WERE NO SEVERE OR SERIOUS TEAES AND NO TREATMENT DISCONTINUATIONS THROUGHOUT THE FOLLOW-UP PERIOD.

**3** RAPID AND SUSTAINED PLASMA CONCENTRATIONS OF NAVENIBART WERE ASSOCIATED WITH SUSTAINED DECREASES IN PLASMA KALLIKREIN ACTIVITY.


**ACKNOWLEDGMENTS:** Authors acknowledge Kusumam Joseph, PhD, for medical writing and data visualization



Presented at European Academy of Allergy and Clinical Immunology
June 13-June 16, 2025 • Glasgow, UK


## RESULTS

### DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- The mean (SD) age was 46 (20) years, and 9 (56%) of 16 participants were female (**Table 1**).

### Table 1. Baseline Demographics and Disease Characteristics

| | Navenibart 450 mg (N = 4) | Navenibart 600/300 mg (N = 6) | Navenibart 600/600 mg (N = 6) | Navenibart Total (N = 16) |
|---|---|---|---|---|
| Age (Years), Mean (SD) | 51 (21) | 39 (15) | 49 (24) | 46 (20) |
| Sex, n (%) | | | | |
| Female | 3 (75) | 4 (67) | 2 (33) | 9 (56) |
| Race, n (%) | | | | |
| White | 4 (100) | 5 (83) | 5 (83) | 14 (88) |
| Black or African-American | - | 2 (33) | 1 (17) | 3 (19) |
| Multiracial | - | 2 (33) | - | 2 (13) |
| American Indian or Alaska-native | - | 1 (17) | - | 1 (6) |
| HAE-C1INH type, n (%) | | | | |
| Type 1 | 4 (100) | 5 (83) | 5 (83) | 14 (88) |
| Type 2 | - | 1 (17) | 1 (17) | 2 (13) |
| Age at the onset of first HAE symptoms (Years), Mean (SD) | 11 (11) | 14 (8) | 12 (6) | 13 (8) |
| Baseline (run-in) monthly attack rate, Mean (SD) | 2.7 (1.3) | 2.3 (1.5) | 1.8 (0.6) | 2.2 (1.2) |

### SAFETY

- Fifteen of 16 participants (94%) had ≥1 treatment-emergent adverse event (TEAE) (**Table 2**).
  - All TEAEs were mild to moderate in severity.
  - No serious TEAEs or deaths were reported.
  - Most TEAEs were assessed as not related to navenibart by the investigator.
- No participants discontinued from the trial because of a TEAE.
- No navenibart-related, clinically significant changes in safety labs (including aPTT), vital signs, or ECGs were reported.

### Table 2. Cumulative safety in ALPHA-STAR participants

| | Navenibart 450 mg (N = 4) | Navenibart 600/300 mg (N = 6) | Navenibart 600/600 mg (N = 6) | Navenibart Total (N = 16) |
|---|---|---|---|---|
| At least 1 TEAE, n (%) | 4 (100) | 5 (83) | 6 (100) | 15 (94) |
| TEAEs occurring in ≥2 participants | | | | |
| Nasopharyngitis | 1 (25) | 1 (17) | 2 (33) | 4 (25) |
| Sinusitis | - | 1 (17) | 1 (17) | 2 (13) |
| Headache | 2 (50) | - | - | 2 (13) |
| Participants with ≥1 navenibart-related TEAE[1], n (%) | - | - | 2 (33) | 3 (19) |
| Injection site erythema | - | - | 1 (17) | 1 (6) |
| Injection site pruritus | - | - | 1 (17) | 1 (6) |
| Injection site rash | - | - | 1 (17) | 1 (6) |
| Dizziness | - | 1 (17) | - | 1 (6) |
| Serious TEAE, n (%) | - | - | - | - |
| TEAE leading to trial discontinuation, n (%) | - | - | - | - |
| TEAE leading to death, n (%) | - | - | - | - |

TEAE = treatment-emergent adverse event. [1]If a participant experienced >1 event in a given category, that participant is counted only once in that category. One participant experienced mild dizziness occurring 6 days after the first dose in Cohort 2 and lasting <1 day. One participant experienced 2 injection sit reactions: injection site erythema and injection site pruritus occurring 1 day after the second dose in Cohort 3 and lasting <1 day. One participant experienced injection site rash occurring 5 days after the second dose in Cohort 3 that lasted <1 day. Safety follow-up occurred through 6 months after the last dose administered.

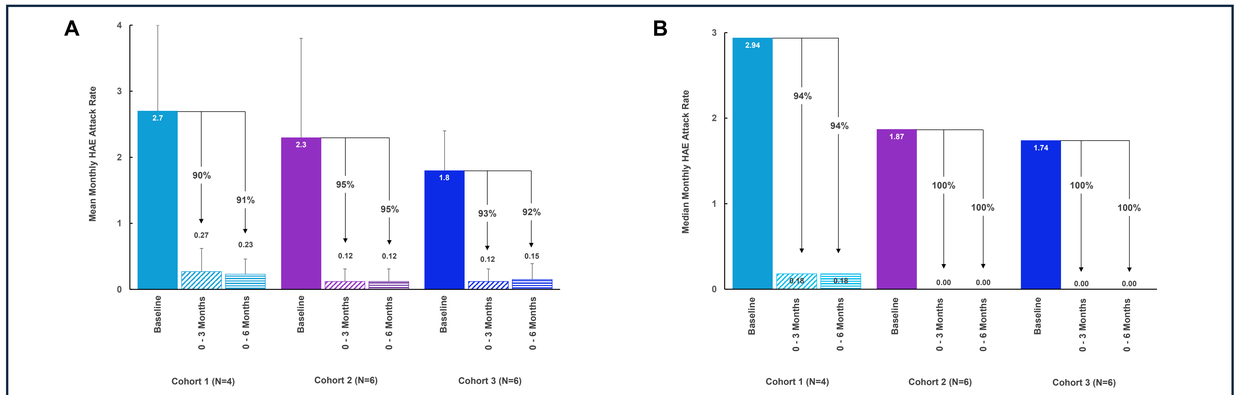
### PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY

- Navenibart achieved maximum concentration ($C_{max}$) at 7-10 days after the first dose with slow elimination; navenibart concentrations were measurable throughout the 6-month follow-up in all cohorts.
- Navenibart inhibited plasma kallikrein activity, measured by changes in %cHMWK assessed by western blot assay, by ≥50% within 7 to 14 days, and this was sustained through the follow-up period.
- Five of 16 participants (31.3%) were positive for treatment-emergent ADA; ADA titers were low, and there was no apparent impact of ADAs on PK or PD.

### REDUCTION IN HAE ATTACKS

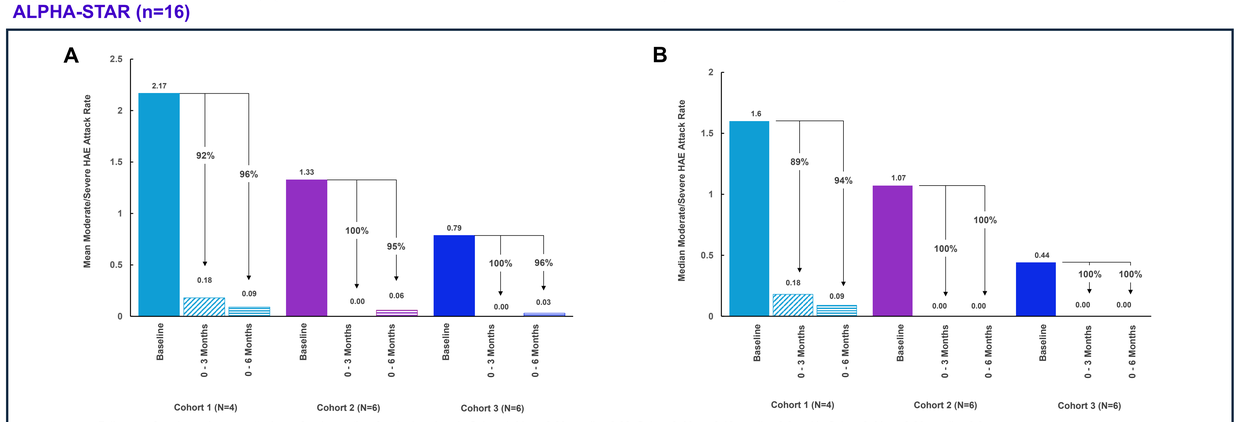
- After 6 months of treatment with navenibart, time-normalized mean / median monthly HAE attack rate was reduced by 91-95% (mean, **Figure 2A**) / 94-100% (median, **Figure 2B**).
- Treatment with navenibart reduced HAE attacks requiring rescue medication by 88-94%.
- After 6 months of treatment with navenibart, time-normalized mean / median monthly moderate / severe HAE attack rate was reduced by 95-96% (mean, **Figure 3A**) / 94-100% (median, **Figure 3B**).

### Figure 2. Mean (A) / Median (B) Time-Normalized Monthly HAE Attacks during the Run-in and Treatment Periods in ALPHA-STAR (n=16)




Follow-up of monthly attack rate for six months after the last dose in Cohort 1: Mean 0.23, median 0.18; Cohort 2: Mean 0.53, median 0.18 and in Cohort 3: Mean 0.32, median 0.0.

### Figure 3. Mean (A) / Median (B) Moderate / Severe Time-Normalized Monthly HAE Attacks during the Run-in and Treatment Periods in ALPHA-STAR (n=16)




Follow-up of moderate / severe attack rate for six months after the last dose in Cohort 1: Mean 0.09, median 0.09; Cohort 2: Mean 0.18, median 0.0 and in Cohort 3: Mean 0.08, median 0.0.

## CONCLUSIONS

- Navenibart was well tolerated after both 1 and 2 doses and reduced attack frequency and severity for at least 6 months.
- This proof-of-concept trial demonstrates that navenibart has the potential to become an effective and safe preventative treatment for HAE, with administration every 3 or 6 months, and is supportive of the ongoing phase 3 global pivotal trial, ALPHA-ORBIT (NCT06842823).