Long-term Safety and Efficacy of Navenibart in Participants with Hereditary Angioedema (HAE): Initial Combined Results from ALPHA-STAR and ALPHA-SOLAR

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OBJECTIVE

- To evaluate the long-term safety and effectiveness of navenibart as prophylaxis in patients with hereditary angioedema (HAE).

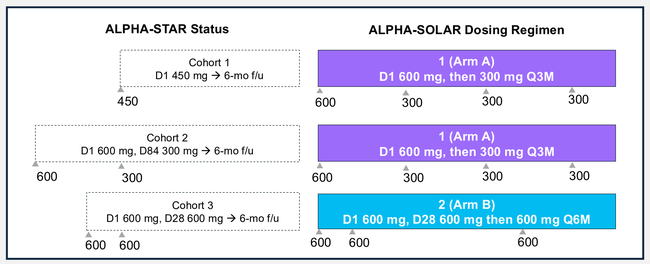
INTRODUCTION

- HAE is a rare, autosomal dominant disease associated with dysregulation of the kallikrein-kinin system.
- Navenibart is a novel investigational therapeutic monoclonal antibody inhibitor of plasma kallikrein with extended half-life.
- Here, we report the initial results from ALPHA-SOLAR, a Phase 2 long-term open-label trial (NCT06007677), combined with ALPHA-STAR, a Phase 1b/2 trial (NCT05695248), with navenibart in participants with HAE.

METHODS

- ALPHA-SOLAR is a long-term open-label extension trial for participants who completed the ALPHA-STAR Phase 1b/2 trial (**Figure 1**).
- Participants entering ALPHA-SOLAR were assigned to one of two Arms:
  - Arm A (Cohort 1 and Cohort 2 of ALPHA-STAR): 600 mg and then 300 mg navenibart every 3 months.
  - Arm B (Cohort 3 of ALPHA-STAR): 600 mg and then 600 mg navenibart on Day 28 followed by 600 mg navenibart every 6 months.
- The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs).
- Secondary endpoints included efficacy assessments, including attack frequency, severity, and use of rescue medication.
- This initial analysis was performed once participants had achieved approximately 12-18 months of follow-up since the start of ALPHA-STAR and 6-12 months since the start of ALPHA-SOLAR. Participation may continue for up to 4 years.

Figure 1. ALPHA-SOLAR Clinical Trial Design



SUMMARY

1. **WITH >17 MONTHS (MEAN) FOLLOW-UP, NAVENIBART WAS WELL TOLERATED AND THE SAFETY PROFILE WAS FAVORABLE.**
2. **IN ALPHA-SOLAR, NAVENIBART SHOWED AN OVERALL MONTHLY REDUCTION OF 92% IN MEAN HAE ATTACK RATES AFTER A MEAN FOLLOW-UP OF 10.1 MONTHS.**
3. **A SIMILAR REDUCTION IN RATES OF MODERATE AND SEVERE HAE ATTACKS AND ATTACKS REQUIRING RESCUE MEDICATION WERE OBSERVED (95% AND 92%, RESPECTIVELY).**
4. **NAVENIBART CONTINUES TO DEMONSTRATE FAVORABLE SAFETY AND ROBUST EFFICACY FOR HAE. Q3M AND Q6M REGIMENS ARE BEING EVALUATED IN AN ONGOING PIVOTAL PHASE 3 TRIAL, ALPHA-ORBIT (NCT06842823).**

ACKNOWLEDGMENT: Authors acknowledge Jan Markind, PharmD, for medical writing and data visualization.

Presented at 2025 US HAEA National Summit • July 10 to 13th, 2025 • Baltimore, MD

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- All 16 participants in the initial cohort completed ALPHA-STAR and enrolled in ALPHA-SOLAR.
- The overall mean (SD) age was 46 (20) years, and 9 (56%) were female (**Table 1**).
- The mean (median) duration of follow-up is 17.4 (17.1) months across ALPHA-STAR and ALPHA-SOLAR, and 10.1 (9.1) months on ALPHA-SOLAR alone.

Table 1. ALPHA-STAR and ALPHA-SOLAR Baseline Demographics and Disease Characteristics

	Arm A (600/300 Q3M) (n=10)	Arm B (600/600/600 Q6M) (n=6)	Total (n=16)
Age (Years), Mean (SD)	44 (17)	49 (24)	46 (20)
Sex, n (%)			
Female	7 (70)	2 (33)	9 (56)
Race, n (%)			
White	9 (90)	5 (83)	14 (88)
Black or African-American	2 (20)	1 (17)	3 (19)
Multiracial	2 (20)	-	2 (13)
American Indian or Alaska-native	1 (10)	-	1 (6)
HAE-C1INH type, n (%)			
Type 1	9 (90)	5 (83)	14 (88)
Type 2	1 (10)	1 (17)	2 (13)
Age at the onset of first HAE symptoms (years), Mean (SD)	13 (9)	12 (6)	13 (8)
Baseline (run-in) monthly attack rate, Mean (SD)	2.5 (1.4)	1.8 (0.6)	2.2 (1.2)

Abbreviations: n, total number of participants; Q3M, every 3 months; Q6M, every 6 months; SD, standard deviation.

SAFETY

- Navenibart was well tolerated in ALPHA-STAR and ALPHA-SOLAR, with a combined mean (median) follow-up of 17.4 (17.1) months (**Table 2**).
- No treatment-related serious adverse events or discontinuations were reported.
- The most common treatment-emergent adverse events related to navenibart were injection site reactions, occurring in 3 participants.
- No navenibart-related, clinically significant changes in safety labs (including aPTT), vital signs, or ECGs were reported.
- No safety signals for navenibart have been observed across ALPHA-STAR and ALPHA-SOLAR.

Table 2. Safety in Combined ALPHA-STAR and ALPHA-SOLAR

	Arm A (600/300 Q3M) (n=10)	Arm B (600/600/600 Q6M) (n=6)	Total* (n=16)
Participants with at least 1 Treatment-Emergent Adverse Event (TEAE)	10	6	16
TEAEs occurring in ≥2 participants			
Nasopharyngitis	3	2	5
Sinusitis	2	1	3
Urinary tract infection	2	1	3
Skin Laceration	2	1	3
Nasal congestion	1	1	2
Headache	2	-	2
Participants with ≥1 related TEAE	1	3	4
Injection site reaction[1]	-	1	1
Injection site erythema[2]	-	1	1
Injection site pruritus[2]	-	1	1
Injection site rash[3]	-	1	1
Dizziness[4]	1	-	1

1. One participant experienced 2 injection site reactions starting 0-1 day after the first and second doses in STAR-0215-202 Arm B (tenderness and pruritus lasting <1 day; erythema and pruritus lasting 5 days).
2. One participant experienced 2 injection site reactions: injection site erythema and injection site pruritus occurring 1 day after the second dose in STAR-0215-201 Cohort 3 and lasting <1 day.
3. One participant experienced injection site rash occurring 5 days after the second dose in STAR-0215-201 Cohort 3 and lasting < 1 day.
4. One participant experienced mild dizziness occurring 6 days after the first dose in STAR-0215-201 Cohort 2 and lasting < 1 day.

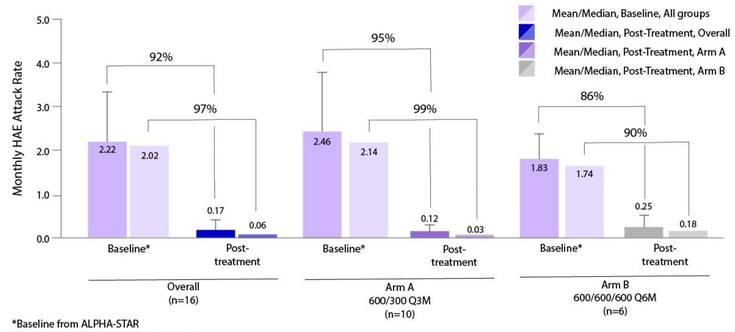
*Mean (Median) follow-up: 17.4 (17.1) months

Abbreviations: n, number of participants; Q3M, every 3 months; Q6M, every 6 months; SD, standard deviations.

EFFICACY

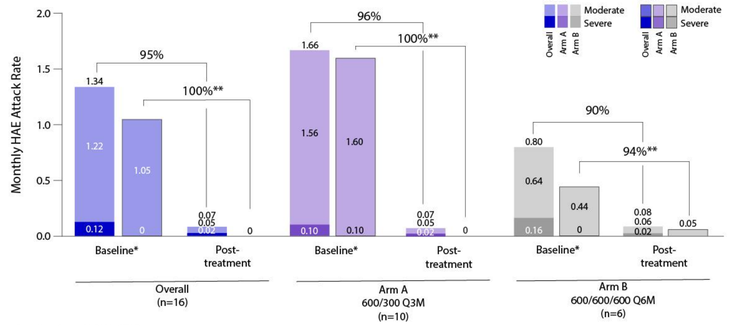
- In ALPHA-SOLAR, monthly HAE attack rate decreased after treatment and remained low throughout a mean (median) follow-up of 10.1 (9.1) months (**Figure 2**).
- Overall, there was a 92% (97%) reduction in mean (median) rate of time-normalized monthly HAE attacks, from 2.22 (2.02) at baseline (from ALPHA-STAR) to 0.17 (0.06) during the ALPHA-SOLAR treatment period.
- The reduction from baseline in Arm A / Arm B was 95% (99%) / 86% (90%) mean (median).
- Moderate-severe attacks (**Figure 3**) and attacks requiring rescue medication (**Figure 4**) were markedly reduced in alignment with overall attack rate reduction. Findings were consistent across treatment groups.
  - There was a 95% (100%) reduction in mean (median) rate of time-normalized monthly moderate-severe attack rate, from 1.34 (1.2) at baseline (from ALPHA-STAR) to 0.07 (0.0) during the ALPHA-SOLAR treatment period.
  - Overall proportion of moderate-severe attacks compared to mild attacks was lower post-treatment.
  - There was a 92% (98%) reduction in mean (median) monthly rate of attacks requiring on-demand treatment (rescue medication), from baseline of 1.74 (1.55) (ALPHA-STAR) to 0.14 (0.03) during the ALPHA-SOLAR treatment period.

Figure 2. Changes in Mean and Median Monthly Time-Normalized HAE Attack Rates in ALPHA-SOLAR.



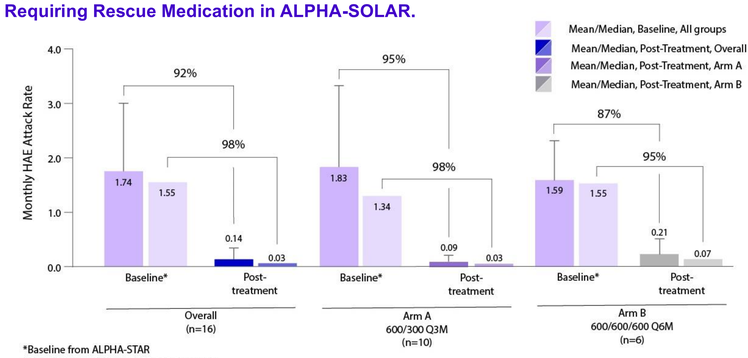
*Baseline from ALPHA-STAR
Mean (median) follow-up 10.1 (9.1) months

Figure 3. Changes in Mean and Median Moderate or Severe Monthly Time-Normalized HAE Attack Rates in ALPHA-SOLAR.



*Baseline from ALPHA-STAR
**Percent differences for median values of moderate and severe attacks combined
Mean (median) follow-up 10.1 (9.1) months

Figure 4. Changes in Mean and Median Monthly Time-Normalized Rates of HAE Attacks Requiring Rescue Medication in ALPHA-SOLAR.



*Baseline from ALPHA-STAR
Mean (median) follow-up 10.1 (9.1) months

CONCLUSIONS

- These initial results demonstrate navenibart's favorable safety profile and robust, durable efficacy for the treatment of HAE attacks and potential as a long-acting first choice prophylaxis in HAE.
- The ongoing phase 3 global pivotal trial, ALPHA-ORBIT (NCT06842823), is investigating the efficacy and safety of navenibart when administered Q3M and Q6M to adults and adolescents with HAE.