



Long-Term, Sustained, Robust Hereditary Angioedema Attack Suppression with Navenibart Administered Every 3 and 6 Months: ALPHA-SOLAR Interim Results

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OBJECTIVE

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

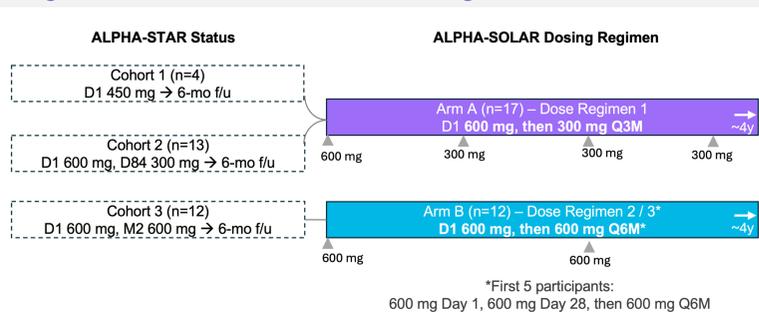
INTRODUCTION

- HAE is a rare, autosomal dominant disease associated with dysregulation of the kallikrein-kinin system, resulting in recurrent swelling attacks.
- Navenibart is the first investigational long-acting anti-plasma kallikrein monoclonal antibody with rapid and sustained inhibition of plasma kallikrein activity, designed for dosing 2 or 4 times per year.
- Here, we report the interim results from treatment with navenibart in participants with HAE from ALPHA-SOLAR, a Phase 2 long-term open-label trial (NCT06007677).

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 every 6 months (the first 5 participants in Arm B received 600 mg, then 600 mg 28 days later and then 600 mg every 6 months)
- The primary endpoint was treatment-emergent adverse events (TEAEs).
- Secondary endpoints included efficacy assessments, including attack frequency, severity, and use of on-demand medication.
- This interim analysis was conducted when the first participant enrolled had completed 2 years of treatment.

Figure 1. ALPHA-SOLAR Clinical Trial Design



SUMMARY

- IN ALPHA-SOLAR, NAVENIBART SHOWED AN OVERALL REDUCTION OF 91% IN MEAN HAE ATTACK RATES AFTER A MEAN FOLLOW-UP OF 12.5 MONTHS.
- A REDUCTION IN RATES OF MODERATE AND SEVERE HAE ATTACKS AND ATTACKS TREATED WITH ON-DEMAND MEDICATION WERE OBSERVED.
- NAVENIBART CONTINUES TO DEMONSTRATE FAVORABLE SAFETY AND ROBUST EFFICACY FOR PEOPLE WITH HAE. Q3M AND Q6M REGIMENS ARE BEING EVALUATED IN AN ONGOING PIVOTAL PHASE 3 TRIAL, ALPHA-ORBIT (NCT06842823).

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RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- All 29 participants who completed ALPHA-STAR enrolled in ALPHA-SOLAR.
- The mean (SD) age was 46 (16.6) years, and 16 (55.2%) of 29 participants were female (**Table 1**).
- The mean (median) duration of follow-up is 12.5 (12.3) months in ALPHA-SOLAR, with a maximum of 24 months at this interim analysis.

Table 1. Baseline Demographics and Disease Characteristics

	Arm A (600/300 Q3M) (n=17)	Arm B (600 Q6M) (n=12)	Total (n=29)
Age (Years), Mean (SD)	45 (16.2)	48 (17.8)	46 (16.6)
Sex, n (%)			
Female	10 (58.8)	6 (50.0)	16 (55.2)
Race, n (%)			
White	13 (76.5)	10 (83.3)	23 (79.3)
Black or African-American	3 (17.6)	1 (8.3)	4 (13.8)
Multiracial	2 (11.8)	-	2 (6.9)
American Indian or Alaska-native	1 (5.9)	-	1 (3.4)
HAE-C1INH type, n (%)			
Type 1	14 (82.4)	11 (91.7)	25 (89.7)
Weight (kg), mean (SD)	79.8 (20.1)	82.63 (22.2)	81.9 (20.7)
Number of attacks in the prior 12 months, Mean (SD)	25.6 (23.3)	13.1 (13.3)	20.4 (20.5)
Baseline (run-in) time-normalized monthly HAE attack rate, Mean (SD)	2.3 (1.3)	2.1 (1.7)	2.2 (1.5)
Duration of follow-up, mean (SD)*	13.3 (5.9)	11.9 (2.9)	12.7 (4.9)

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

SAFETY

- Navenibart was well-tolerated on ALPHA-SOLAR, with a mean follow-up of 12.5 months (**Table 2**).
- One serious adverse event (invasive ductal breast carcinoma) led to discontinuation.
- No treatment-related serious adverse events or discontinuations occurred due to related TEAE.
- The most common treatment-emergent adverse events related to navenibart were injection site reactions.
- No navenibart-related, clinically significant changes in safety labs (including aPTT), vital signs, or ECGs were reported.
- No safety signals for navenibart were observed.

Table 2. ALPHA-SOLAR Treatment-Emergent Adverse Events (TEAEs)

	Arm A (600/300 Q3M) (n=17)	Arm B (600 Q6M) (n=12)	Total* (n=29)
Participants with ≥1 TEAE, n (%)	12 (70.6)	8 (66.7)	20 (69.0)
TEAEs occurring in ≥2 participants, n (%)			
Nasopharyngitis	2 (11.8)	1 (8.3)	3 (10.0)
Urinary tract infection	2 (11.8)	1 (8.3)	3 (10.0)
Headache	3 (17.6)	-	3 (10.0)
Injection site reaction**	1 (5.9)	2 (16.7)	3 (10.0)
Myalgia	2 (11.8)	1 (8.3)	3 (10.0)
Skin laceration	1 (5.9)	2 (16.7)	3 (10.0)
Nasal congestion	1 (5.9)	1 (8.3)	2 (6.9)
Arthralgia	1 (5.9)	1 (8.3)	2 (6.9)
Participants with ≥1 related TEAE	2 (11.8)	3 (2.5)	5 (17.0)
Injection site reaction	1 (5.9)	2 (16.7)	3 (10.0)
Myalgia	-	1 (8.3)	1 (3.4)
Dizziness	1 (5.9)	-	1 (3.4)
Participants with ≥1 serious TEAE	1 (5.9)	-	1 (3.4)
Invasive ductal breast carcinoma	1 (5.9)	-	1 (3.4)
Participants with TEAE leading to navenibart discontinuation	1 (5.9)	-	1 (3.4)
Participants with TEAE leading to death	-	-	-

**most commonly redness / erythema occurring in 3 (10%) participants

EFFICACY

- In ALPHA-SOLAR, time-normalized monthly HAE attack rates decreased from baseline and remained low in both treatment Arms and overall while on treatment (overall mean / median duration of follow up: 12.5 / 12.3 months) (**Figure 2**).
- Overall, mean monthly HAE attack rate decreased from 2.23 at baseline (from ALPHA-STAR) to 0.16 during ALPHA-SOLAR treatment (90.9% reduction). Median monthly HAE attack rate decreased from 1.60 to 0.07 (96.9% reduction).
- By arm, mean reduction from baseline was 91.6% in Arm A and 89.9% in Arm B. Median reduction from baseline was 96.9% in Arm A and 96.6% in Arm B.

Figure 2. Mean and median HAE attack rate in ALPHA-SOLAR

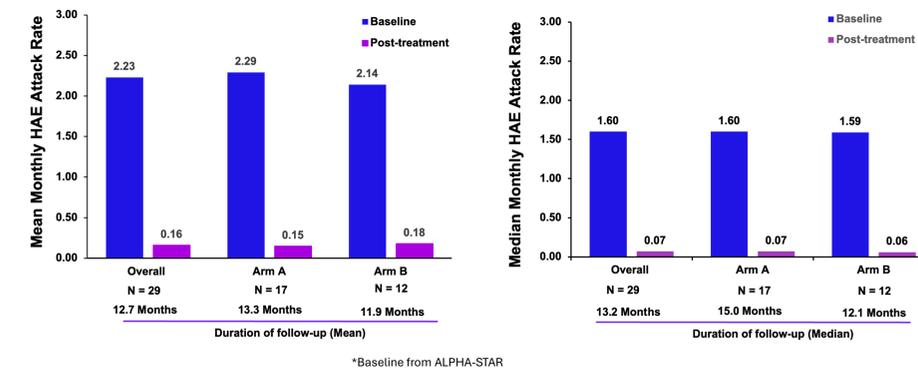


Figure 3. Mean and median moderate or severe HAE attack rates in ALPHA-SOLAR

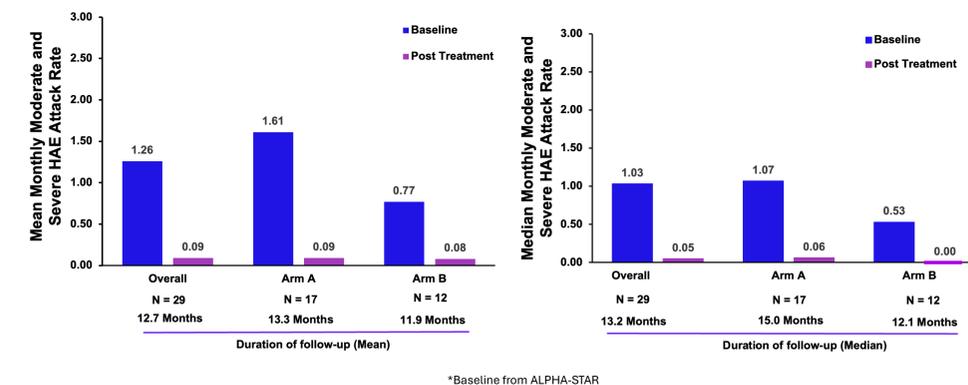
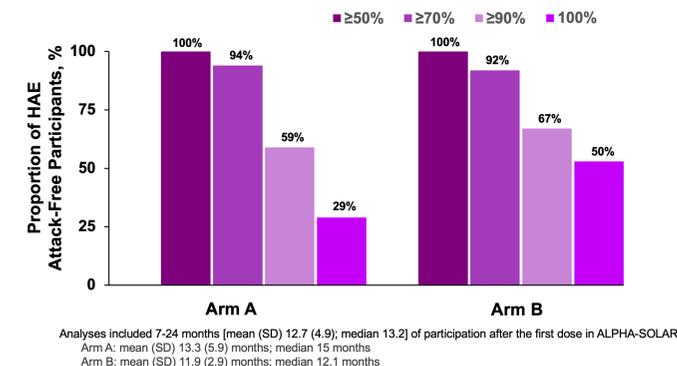


Figure 4. Proportion of participants with attack rate reductions of ≥50%, ≥70%, ≥90%, ≥100% following treatment with navenibart in ALPHA-SOLAR



Analyses included 7-24 months [mean (SD) 12.7 (4.9); median 13.2] of participation after the first dose in ALPHA-SOLAR
Arm A: mean (SD) 13.3 (5.9) months; median 15 months
Arm B: mean (SD) 11.9 (2.9) months; median 12.1 months

Proportion of participants achieving thresholds of attack rate reduction (≥50%, ≥70%, ≥90%, 100%) are shown by Arm (Figure 4).

- In Arm A, all participants achieved ≥50% attack rate reduction, 94% achieved ≥70% attack rate reduction, 59% achieved ≥90% attack rate reduction, and 29% were attack-free.
- In Arm B, all participants achieved ≥50% attack rate reduction, 92% achieved ≥70% attack rate reduction, 67% achieved ≥90% attack rate reduction, and 50% were attack-free.

CONCLUSIONS

- Navenibart demonstrated favorable long-term safety and durable efficacy with a mean follow up of 12.5 months.
- The ongoing phase 3 global pivotal trial, ALPHA-ORBIT (NCT06842823), is investigating the efficacy and safety of navenibart when administered Q3M or Q6M to adults and adolescents with HAE.