Final Results from ALPHA-STAR, a Phase 1b/2 Trial of Navenibart in Hereditary Angioedema

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SUMMARY

NAVENIBART, AN INVESTIGATIONAL, LONG-ACTING ANTI–PLASMA KALLIKREIN ANTIBODY, DEMONSTRATED PROOF-OF-CONCEPT AS A INFREQUENTLY DOSED, LONG-TERM PREVENTIVE IN HEREDITARY ANGIOEDEMA (HAE) WITH THE FOLLOWING FINDINGS:

1. **Navenibart was well tolerated with no severe or serious safety concerns in adults with HAE-C1INH.**
2. **Treatment with navenibart produced rapid, robust, and durable reductions in HAE attack rates [overall, ≥86% (mean) or ≥95% (median)] and reduced the need for rescue medication.**
3. **Clinically meaningful improvements in patient-reported quality of life, sustained drug exposure and kallikrein inhibition (PK/PD) support infrequent dosing every 3 or 6 months, now being evaluated in Phase 3 (ALPHA-ORBIT).**

OBJECTIVES

ALPHA-STAR (NCT05695248) was a global (**Figure 1**), dose-ranging, proof-of-concept Phase 1b/2 trial designed to evaluate the safety, tolerability, and clinical activity of subcutaneous navenibart in adults with HAE-C1INH.

Primary Objective:

- Assess the safety and tolerability of single and multiple doses of subcutaneous administration (SC) of navenibart (STAR-0215) in participants with type 1 or type 2 hereditary angioedema (HAE-C1INH)

Secondary Objective:

- Evaluate the clinical activity of SC administration of single and multiple doses of navenibart in participants with HAE-C1INH

Exploratory Objective:

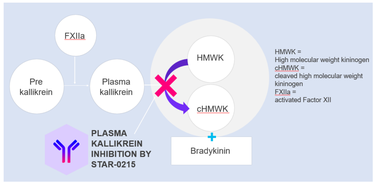
- Assess patient-reported quality of life (QoL) using the angioedema QoL (AE-QoL) questionnaire.

Figure 1. ALPHA-STAR (NCT05695248) global clinical trial sites

INTRODUCTION

- Hereditary angioedema (HAE) is a rare genetic disorder driven by kallikrein overactivation and excessive bradykinin, causing recurrent swelling attacks.
- Navenibart is the first investigational long-acting anti–plasma kallikrein monoclonal antibody with rapid and sustained inhibition of kallikrein activity (**Figure 2**), designed for dosing every 3 or 6 months.
- Presented here are the final results from ALPHA-STAR (NCT05695248), a Phase 1b/2 dose-ranging (**Figure 3**), proof-of-concept trial evaluating the safety and clinical activity of navenibart.

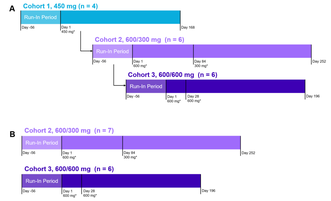
Figure 2. The inhibitory role of navenibart in the pathogenesis of HAE



METHODS

- Participants who had completed required washout from long-term preventive therapies (LTPs), if applicable, entered an 8-week run-in period (baseline) during which they had ≥2 attacks.
- Target enrollment was 16 subjects (A) and expanded to 29 subjects (B) after initial safety review. Participants (n=29) were enrolled into one of three treatment cohorts (**Figure 3**).
- The primary endpoint was safety and tolerability. Secondary endpoints included efficacy.
- HAE attacks were assessed throughout the trial to evaluate the efficacy of navenibart. Assessment of HAE attacks included attack location, severity, timing, and treatment.
- QoL was evaluated using the Angioedema Quality of Life (AE-QoL) questionnaire, a validated, HAE-specific instrument that measures disease impact across four domains: Functioning, Fatigue/Mood, Fear/Shame, and Nutrition.

Figure 3. ALPHA-STAR (NCT05695248) clinical trial design



RESULTS

Table 1. Incidence of Treatment-Emergent Adverse Events

	Cohort 1 450 mg (N = 4)	Cohort 2 600/300 mg (N = 13)	Cohort 3 600/600 mg (N = 12)	Overall Total (N = 29)
Participants with at least 1 Treatment-Emergent Adverse Event (TEAE)	4 (100.0)	9 (69.2)	12 (100.0)	25 (86.2)
Participants with ≥ 1 moderate TEAE	4 (100.0)	2 (15.4)	9 (75.0)	15 (51.7)
TEAEs occurring in ≥2 participants, n (%)				
Headache	2 (50.0)	3 (23.1)	2 (16.7)	7 (24.1)
Nasopharyngitis	1 (25.0)	2 (15.4)	4 (33.3)	7 (24.1)
Urinary tract infection	-	2 (15.4)	1 (8.3)	3 (10.3)
Abdominal discomfort	-	1 (7.7)	1 (8.3)	2 (6.9)
Back pain	-	1 (7.7)	1 (8.3)	2 (6.9)
Contusion	1 (25.0)	-	1 (8.3)	2 (6.9)
Nasal congestion	-	1 (7.7)	1 (8.3)	2 (6.9)
Sinusitis	-	1 (7.7)	1 (8.3)	2 (6.9)
Skin laceration	1 (25.0)	-	1 (8.3)	2 (6.9)
Treatment-related TEAEs (≥ 1 participant, n (%)	-	1 (7.7)	3 (25.0)	4 (13.8)
Injection site erythema	-	-	1 (8.3)	1 (3.4)
Injection site pruritus	-	-	1 (8.3)	1 (3.4)
Injection site rash	-	-	1 (8.3)	1 (3.4)
Injection site swelling	-	-	1 (8.3)	1 (3.4)
Dizziness	-	1 (7.7)	-	1 (3.4)
Serious or Severe TEAE, n (%)	-	-	-	-
TEAE leading to trial discontinuation, n (%)	-	-	-	-
TEAE leading to death, n (%)	-	-	-	-

Table 2. Baseline Characteristics of Trial Participants

	Cohort 1 450 mg (N = 4)	Cohort 2 600/300 mg (N = 13)	Cohort 3 600/600 mg (N = 12)	Overall Total (N = 29)
Age, years Mean (SD)	51.0 (21.2)	43.6 (15.0)	47.9 (17.8)	46.4 (16.6)
Sex, n (%)				
Male	1 (25.0)	6 (46.2)	6 (50.0)	13 (44.8)
Female	3 (75.0)	7 (53.8)	6 (50.0)	16 (55.2)
Race, n (%)				
White	4 (100.0)	9 (69.2)	10 (83.3)	23 (79.3)
Black or African American	-	3 (23.1)	1 (8.3)	4 (13.8)
American Indian or Alaska Native	-	1 (7.7)	-	1 (3.4)
Body mass index, kg/m^2	29.4 (8.4)	28.2 (4.7)	29.2 (5.3)	28.8 (5.3)
HAE type, n (%)				
Type 1	4 (100)	10 (76.9)	11 (91.7)	25 (86.2)
Type 2	-	3 (23.1)	1 (8.3)	4 (13.8)
First attack, Age of onset, year Mean (SD)	10.8 (10.6)	15.2 (8.7)	12.1 (4.3)	13.3 (7.4)
Prior prophylactic HAE treatments, n (%)				
Lanadelumab	1 (25.0)	2 (16.7)	1 (8.3)	4 (14.3)
Berotralstat dihydrochloride	-	3 (25.0)	-	3 (10.7)
C1 esterase inhibitor (IV or SC)	1 (25.0)	4 (33.3)	2 (16.7)	7 (25.0)

Figure 4. Reduction in HAE attack rates following treatment with navenibart in ALPHA-STAR

- **Consistent benefit across doses:** Improvements were observed in all cohorts (450 mg, 600/300 mg, 600/600 mg).
- **Rapid and sustained efficacy:** Mean monthly HAE attack rate (**A**) and moderate/severe attack rate (**B**) declined markedly in the first 3 months after dosing and remained low through 6 months across all cohorts. The reductions from baseline attack rate were sustained through 6 months with a mean and median reduction of 84.0% and 93.4% in cohort 1, 90.2% and 100% in cohort 2, and 91.8% and 100% in cohort 3. Over the full treatment period, the overall mean and median reduction from baseline attack rate were 86.3% and 95.4%.
- **Reduced rescue medication use:** HAE attack rate requiring rescue medication (**C**) dropped substantially after navenibart treatment.
- **High responder rates:**(**D**) Through the full treatment period, almost all (97%) participants had a ≥50% reduction in HAE attacks, and almost half (48%) were attack-free.

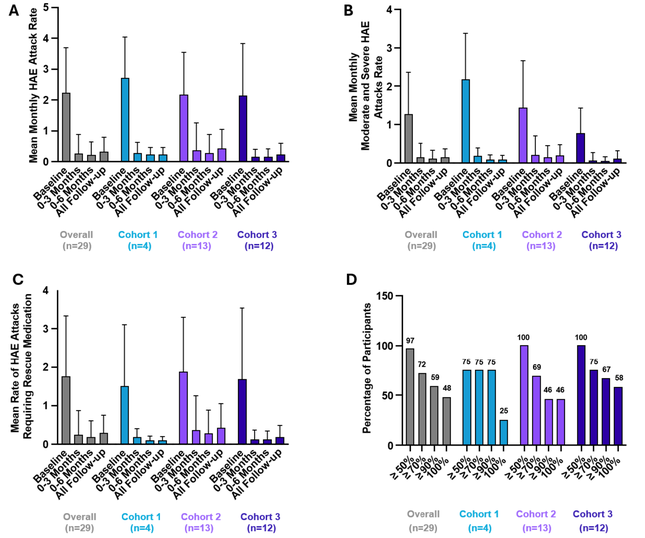
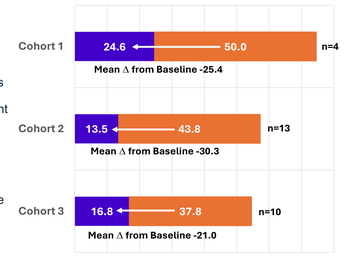


Figure 5. Improvement in AE-QoL after last dose of navenibart in ALPHA-STAR

- **Sustained Improvement In Quality Of Life:** Mean AE-QoL total scores improved from baseline across all cohorts, exceeding the 6-point MCID* threshold for clinical relevance at all time points.
- **Durable Patient Benefit:** Progressive score reductions through 6 months indicate sustained improvement in disease burden and treatment satisfaction with navenibart (Data not shown).



*MCID, minimally clinically important difference

CONCLUSION

- **Navenibart demonstrated rapid, robust and durable efficacy**, with ≥86% (Mean) or ≥95% (Median) overall reduction in HAE attack rate and consistent improvements in moderate/severe attacks and rescue medication use across all dosing cohorts.
- **Clinically meaningful improvements in patient-reported quality of life (AE-QoL) were sustained** through 6 months.
- **Treatment was well-tolerated,** with no severe or serious adverse events reported and very few injection site reactions, all of which were mild and transient.
- Collectively, these data validate infrequent 3- or 6-month dosing in the ongoing Phase 3 ALPHA-ORBIT trial.

Acknowledgement
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References
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