Navenibart Delays Time to First Attack in Hereditary Angioedema: Results from ALPHA-STAR

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SUMMARY

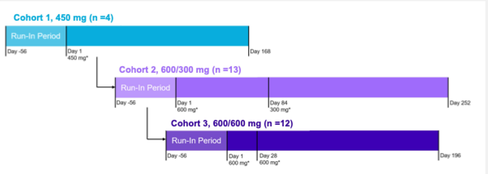
NAVENIBART, AN INVESTIGATIONAL, LONG-ACTING ANTI–PLASMA KALLIKREIN ANTIBODY, DEMONSTRATED PROOF-OF-CONCEPT AS A INFREQUENTLY DOSED, LONG-TERM PREVENTIVE IN HEREDITARY ANGIOEDEMA (HAE) WITH THE FOLLOWING FINDINGS:

1. **Navenibart was well tolerated with no severe or serious safety events in adults with HAE-C1INH.**
2. **Treatment with navenibart produced rapid, robust, and durable reductions in HAE attack rates [mean: ≥86% or median ≥95%]**
3. **Navenibart delayed time to first attack after the first and last dose in adults with HAE-C1INH.**
4. **Favorable safety and early efficacy findings support infrequent dosing every 3 or 6 months, now being evaluated in Phase 3 (ALPHA-ORBIT**

INTRODUCTION

- Hereditary angioedema (HAE) is a rare genetic disorder driven by plasma 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, designed for dosing 2 or 4 times per year.
- Presented here are the final results from ALPHA-STAR (NCT05695248), a Phase 1b/2 dose-ranging (**Figure 1**), proof-of-concept trial evaluating the safety and clinical activity of navenibart.

Figure 1. ALPHA-STAR (NCT05695248) clinical trial design



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.
- Twenty-nine participants (n=29) were enrolled into one of three treatment cohorts (Figure 1).
- Participants were followed for 6 months after their final dose of navenibart
- HAE attacks were assessed throughout the trial to evaluate the efficacy of navenibart. Assessment of HAE attacks included attack location, severity, timing, and treatment.

Table 1. Baseline Characteristics of Trial Participants

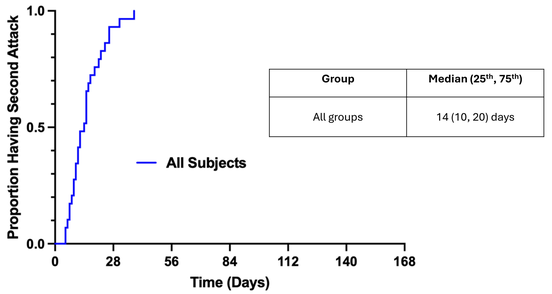
	Overall Total (N = 29)
Age, years, Mean (SD)	46.4 (16.6)
Sex, n (%), Female	16 (55.2)
Race, n (%)	
White	23 (79.3)
Black or African American	4 (13.8)
American Indian or Alaska Native	1 (3.4)
Body mass index, kg/m^2	28.8 (5.3)
HAE type, n (%)	
Type 1	25 (86.2)
Type 2	4 (13.8)
First attack, Age of onset, year Mean (SD)	13.3 (7.4)
Prior prophylactic HAE treatments, n (%)	
Lanadelumab	4 (14.3)
Berotralstat dihydrochloride	3 (10.7)
C1 esterase inhibitor (IV or SC)	7 (25.0)

RESULTS

Table 2. Incidence of Treatment-Emergent Adverse Events (TEAE)

	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 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 occurring in ≥ 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 (%)	-	-	-	-

Figure 2. Interval between 1st and 2nd attack during run in period



Group	Median (25th, 75th)
All groups	14 (10, 20) days

Figure 2. Kaplan-Meier plot of time from first to second attack during the 8-week run-in period. The median (25th , 75th percentiles) was 14 (10, 20) days.

Acknowledgement
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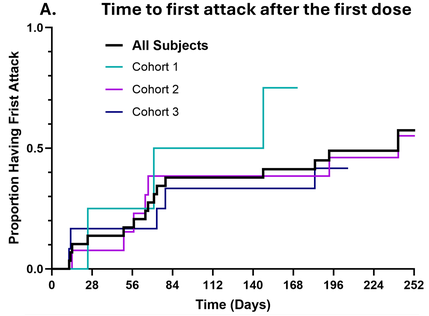
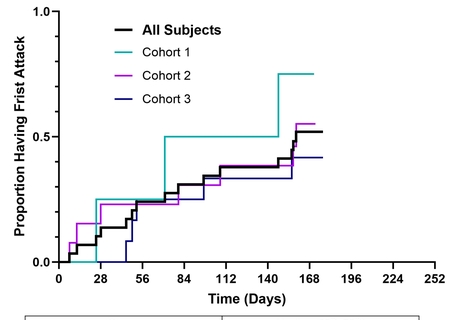
Figure 3. Navenibart delays time to first attack after the first and last dose

A. Time to first attack after the first dose



Group	Median (25th, 75th)
Overall	241 (67, NE) days
Cohort 1	109 (48, NE) days
Cohort 2	241 (65, NE) days
Cohort 3	Not estimable >50% of patients had no attacks during observation

B. Time to first attack after the last dose



Group	Median (25th, 75th)
Overall	159 (71, NE) days
Cohort 1	109 (48, NE) days
Cohort 2	159 (80, NE) days
Cohort 3	Not estimable >50% of patients had no attacks during observation

Figures 3A & 3B. Kaplan–Meier plots of time to first HAE attack following the first dose of navenibart (Fig. 3A) and the last dose of navenibart (Fig. 3B). All cohorts showed delayed time to first attack following treatment initiation and after the final dose.

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

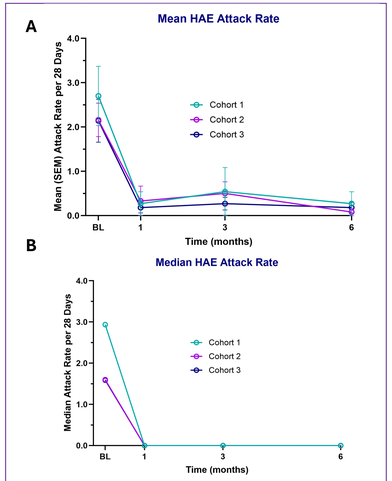


Figure 4. Reduction in HAE attack rates following treatment with navenibart. (A) Mean and (B) median monthly HAE attack rates from baseline, Month 1, 3 and 6 for Cohorts 1–3. All dose cohorts demonstrated rapid reductions in attack frequency by Month 1, with sustained low attack rates through Month 6. Overall mean (SD) monthly attack rate of 2.23 (1.46) at baseline was reduced to 0.31 (0.48) after treatment.

CONCLUSION

- **Rapid and durable efficacy:** Navenibart demonstrated rapid reductions in HAE attack rates across all dose cohorts, with mean and median reductions of ≥86% from baseline and sustained low attack rates throughout the treatment period.
- **Delayed time to first attack:** Kaplan–Meier analyses showed that a high proportion of participants remained attack-free following the first and last dose of navenibart, with low HAE attack rates maintained over the treatment period.
- **Favorable safety and tolerability:** Treatment was generally well tolerated, with no severe or serious treatment-emergent adverse events; injection-site reactions were the most common events and were mild and transient.
- Collectively, these data support infrequent 3- or 6-month dosing in the ongoing Phase 3 ALPHA-ORBIT trial.

References
Lumry WR. Am J Manag Care. Sinnathamby ES et al. Adv Ther. 2023; Busse P et al. J Allergy Clin Immunol Pract. 2022

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