ALPHA-STAR, a Phase 1b/2 Clinical Trial of Single and Multiple Doses of Navenibart (STAR-0215) in Patients with Hereditary Angioedema: Interim Safety and Efficacy Outcomes

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SUMMARY

1 INTERIM RESULTS FROM THE ALPHA-STAR CLINICAL TRIAL INDICATE A FAVORABLE SAFETY PROFILE OF NAVENIBART FOR PATIENTS WITH HAE.

2 SIGNIFICANT CLINICAL BENEFIT OF HAE ATTACK PREVENTION WAS OBSERVED AFTER THE FIRST NAVENIBART DOSE AND SUSTAINED FOR 3-6 MONTHS THEREAFTER.

3 RESULTS SHOW PROOF OF CONCEPT AND SUPPORT PROCEEDING TO PHASE 3 FOR NAVENIBART IN PATIENTS WITH HAE.

OBJECTIVES

- Demonstrate proof-of-concept of navenibart in Hereditary Angioedema (HAE) with interim results from ALPHA-STAR (NCT05695248), an ongoing Phase 1b/2 clinical trial in patients with HAE evaluating the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity after subcutaneous administration of single and multiple doses of navenibart.

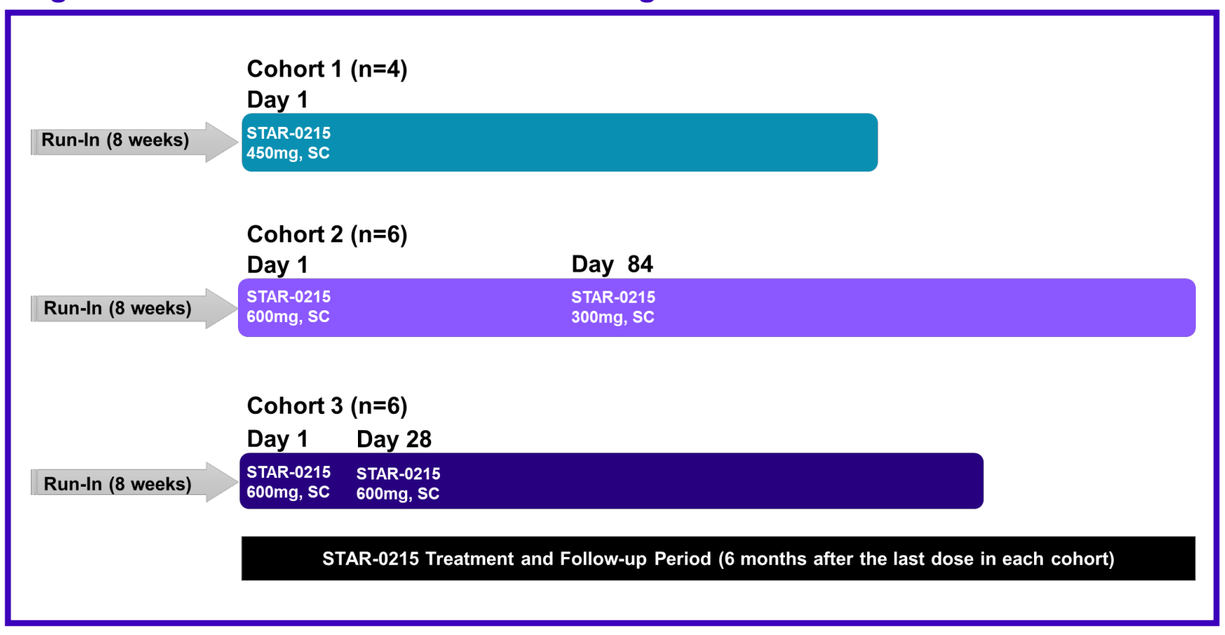
INTRODUCTION

- HAE is a rare, autosomal dominant disease associated with heterogeneous and recurrent clinical manifestations of angioedema with variable severity that can incur substantial morbidity, diminished quality of life, high economic burden, and increased mortality.
- Navenibart is an investigational, long-acting antibody of plasma kallikrein enabled by a YTE-modified Fc domain.

METHODS

- Adults with HAE-C1INH Type 1 and 2, reporting ≥ 2 HAE attacks during the 8-week run-in period, were sequentially assigned to receive navenibart subcutaneously.
- 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)**.
- Results reported here are from data cut-off on 13-Mar-2024.

Figure 1. ALPHA-STAR Clinical Trial Design



RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- At the time of analysis, the initial target enrollment of 16 participants was achieved and each participant was assigned to navenibart treatment (Cohort 1, n=4, Cohort 2, n=6, and Cohort 3, n=6).
- At the cut-off date, ALPHA-STAR participants accrued 6.5 years of exposure to navenibart. Cohort 1 follow-up was complete, while Cohorts 2 and 3 continued to accrue data.
- The mean age of study participants across all three cohorts was 46 years, 56% were female, and 88% had HAE-C1INH Type 1.
- The mean number of HAE attacks in the previous 12 months was 22.

SAFETY

- Most common treatment emergent adverse events (TEAEs), occurring in 2 or more participants who received navenibart, included nasopharyngitis, contusion, and headache (**Table 1**).
- No serious or severe TEAEs and no treatment discontinuations were reported.

CLINICAL EFFICACY

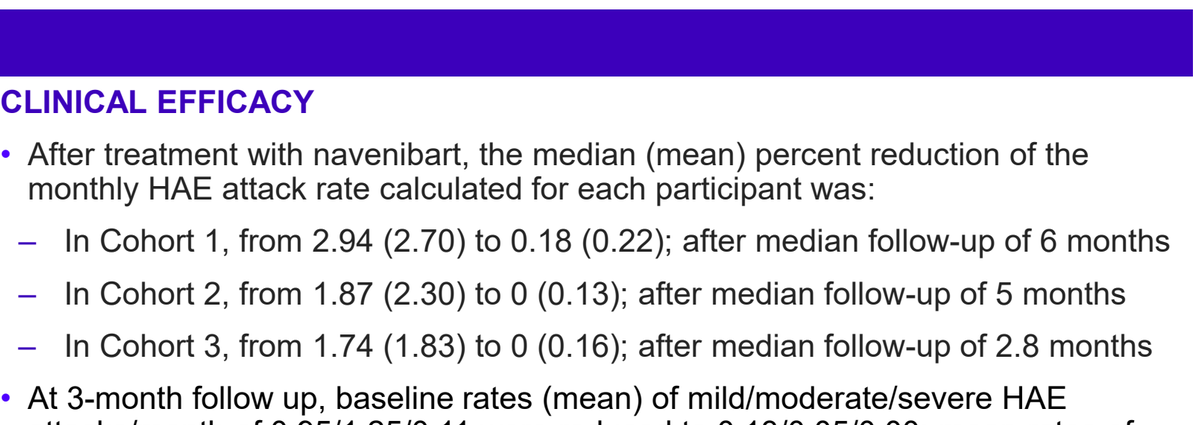
- After treatment with navenibart, the median (mean) percent reduction of the monthly HAE attack rate calculated for each participant was:
  - In Cohort 1, from 2.94 (2.70) to 0.18 (0.22); after median follow-up of 6 months
  - In Cohort 2, from 1.87 (2.30) to 0 (0.13); after median follow-up of 5 months
  - In Cohort 3, from 1.74 (1.83) to 0 (0.16); after median follow-up of 2.8 months
- At 3-month follow up, baseline rates (mean) of mild/moderate/severe HAE attacks/month of 0.95/1.25/0.11 were reduced to 0.13/0.05/0.00; mean rates of HAE attacks/month requiring rescue medication were reduced from 1.86 at baseline to 0.16.
- For the first 3 months (84 days), 50%, 67%, and 50% of participants with available follow-up were HAE attack-free in Cohorts 1-3, respectively (**Figure 3**).
- There were no severe HAE attacks during the treatment phase (**Figure 3**).

Table 1. Cumulative Safety in ALPHA-STAR Participants

	Navenibart 450 mg SC* (N = 4)	Navenibart 600/300 mg SC* (N = 6)	Navenibart 600/600 mg SC* (N = 6)	Navenibart Total (N = 16)
Number of subjects with at least 1 TEAE, n (%)	4 (100)	3 (50)	6 (100)	13 (81)
Subjects with a related TEAE n (%)	0	1 (16.6)	1 (16.6)	2 (12.5)
Subjects with a serious TEAE n (%)	0	0	0	0
Number of TEAEs	20	3	9	22
Number of related TEAEs	0	1[a]	1[b]	2
Number of serious TEAEs	0	0	0	0
Number of TEAEs leading to study discontinuation	0	0	0	0
TEAEs occurring in ≥2 participants (Preferred term)				
Nasopharyngitis n (%)	1 (25)	1 (16.6)	1 (16.6)	3 (18.75)
Contusion n (%)	2 (50)	0	0	2 (12.5)
Headache n (%)	2 (50)	0	0	2 (12.5)

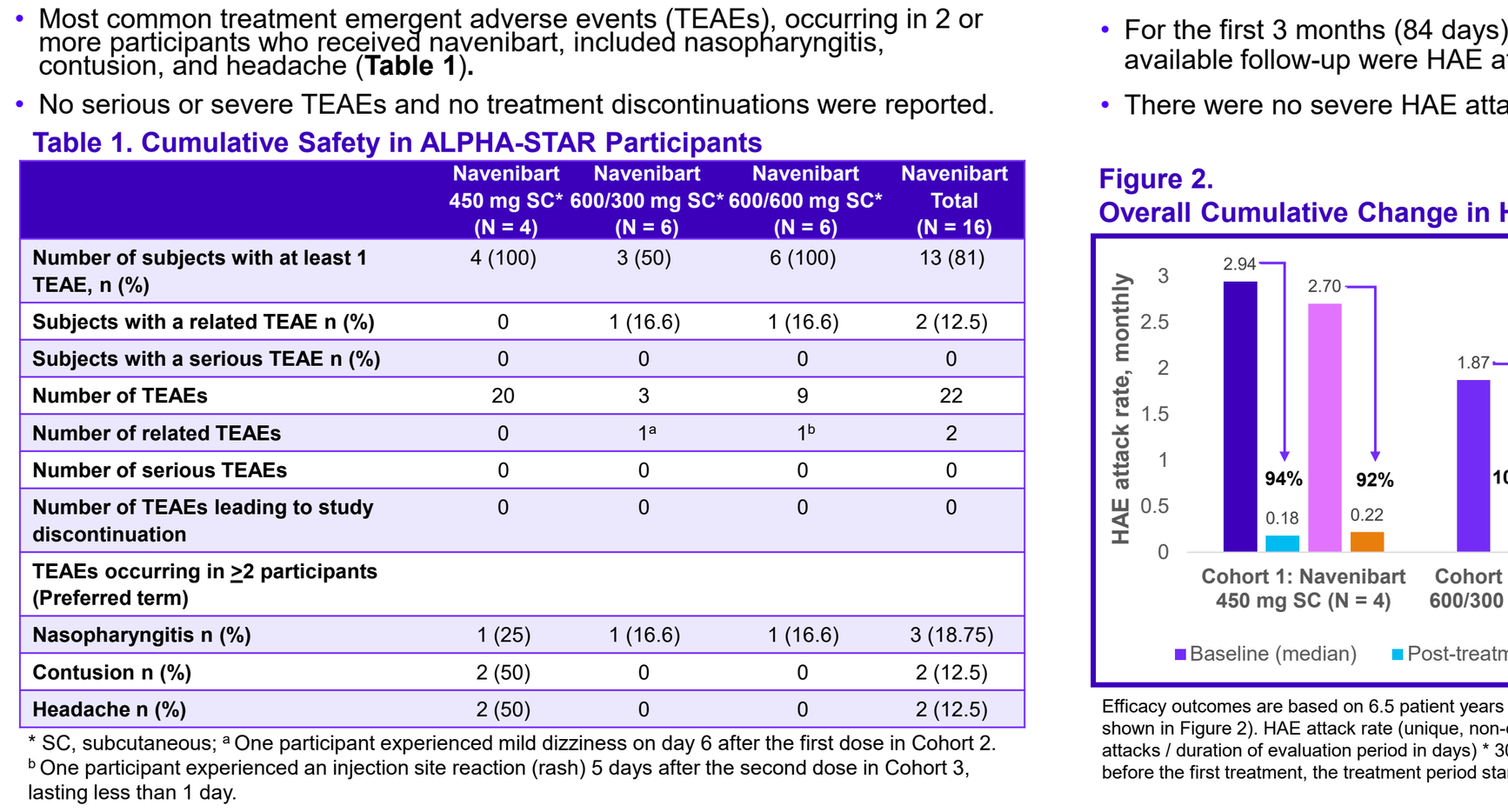
* SC, subcutaneous; [a] One participant experienced mild dizziness on day 6 after the first dose in Cohort 2. [b] One participant experienced an injection site reaction (rash) 5 days after the second dose in Cohort 3, lasting less than 1 day.

Figure 2. Overall Cumulative Change in HAE Attack Rate (Baseline to Post-Treatment)



Efficacy outcomes are based on 6.5 patient years of accumulated follow-up (individual follow-up at the time of data cut-off is shown in Figure 2). HAE attack rate (unique, non-overlapping, investigator-confirmed) was calculated as: (number of HAE attacks / duration of evaluation period in days) * 30.4375; where the run-in period started at the Screening visit until the day before the first treatment, the treatment period started at the first treatment date until the end of study date.

Figure 3. Cumulative HAE Attack Occurrences for Each ALPHA-STAR Participant (Interim Analysis)



Box around each Cohort indicates the 6-month period after the last injection; 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). Vertical lines indicate efficacy analyses at Day 84 (3 months) and Day 168 (6 months). Thickness of vertical bars indicate various duration of discrete HAE attacks. .

CONCLUSIONS

- **This interim analysis provides proof-of-concept of navenibart in HAE.**
- **The results show navenibart has a favorable safety and tolerability profile.**
- **Rapid and durable reductions in HAE attacks were demonstrated for at least 6 months after administration of 1 or 2 doses of navenibart.**
- **These results suggest that navenibart may be administered every 3 months and every 6 months as the first long-acting, long-term preventative treatment for HAE.**
- **Interim results support continued development, including proceeding to a confirmatory Phase 3 trial. The Phase 2 long-term open-label trial ALPHA-SOLAR is ongoing, with initial data expected mid-2025.**

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