Navenibart (STAR-0215) Induces Rapid Improvements of Quality of Life in HAE Patients in the ALPHA-STAR Trial

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OBJECTIVES AND INTRODUCTION

- An interim analysis was conducted to assess the effectiveness of navenibart in the ALPHA-STAR (NCT05695248), an ongoing Phase 1b/2 clinical trial in patients with HAE that evaluates single and multiple-doses of navenibart with six months follow-up after the last dose.
- HAE is a rare, autosomal dominant disease associated with heterogeneous, recurrent, and unpredictable clinical manifestations of angioedema with variable severity.
- HAE attacks can incur substantial morbidity, diminished quality of life, high economic burden, and increased mortality.
- Navenibart (STAR-0215) is an investigational monoclonal antibody inhibitor of plasma kallikrein with long-lasting activity enabled by a YTE-modified Fc domain. Recently demonstrated proof-of-concept in the ALPHA-STAR clinical trial highlights a favorable safety profile and >90% reduction of HAE attacks, maintained for 3-6 months after the navenibart administration.[1]

SUMMARY

Navenibart had a rapid impact on normalizing the lives of patients with HAE during the first 28 days by:

1. **Reducing HAE attack rate by 93-94%**
2. **Improving quality of life (results show clinically significant improvements in AE-QoL)**
3. **Demonstrating a favorable safety profile**

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REFERENCES: **1.** Maurer et al. (2024), 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, EADV 2024, Amsterdam.

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METHODS

- Adults with HAE-C1INH-Types 1 and 2 were recruited into 3 dose cohorts, all subcutaneously:
  - Cohort 1: 450 mg (day 1);
  - Cohort 2: 600 mg (day 1), 300 mg (day 84);
  - Cohort 3: 600 mg (day 1 and day 28).
- Pharmacokinetic (PK) assessments: plasma concentrations of navenibart were measured by a validated immunoassay.
- Pharmacodynamic (PD) assessments: plasma kallikrein activity was measured by changes in cleaved high molecular weight kininogen (cHWMK) levels analyzed by western blot.
- Quality of life was assessed at baseline and monthly thereafter using the Angioedema Quality of Life (AE-QoL) questionnaire, that has a minimal clinically important difference (MCID) of –6 points in Total AE-QoL score.

RESULTS

- This analysis of data accrued during the first 28 days of the treatment period includes 4 participants who received 450 mg SC and 12 participants who received 600 mg SC (6 in Cohort 2 and 6 in Cohort 3) on day 1.
- Data from 16 participants who received the navenibart treatment (Cohort 1, n=4, Cohort 2, n=6, and Cohort 3, n=6) were analyzed.
- The baseline characteristics of enrolled participants as of the data cut-off (March 13, 2024) are presented in **Table 1**.

Demographic	Navenibart 450 mg SC (N = 4)	Navenibart 600/300 mg SC (N = 6)	Navenibart 600/600 mg SC (N = 6)	Navenibart All Cohorts (N = 16)
Age, years; mean (SD)	51.0 (21.2)	38.5 (15.4)	48.8 (23.5)	45.5 (19.6)
Sex, Female; %	75.0	66.7	33.3	56.3
Race, white, %	100.0	83.3	83.3	87.5
BMI, kg/m; mean (SD)	29.4 (8.4)	30.0 (1.6)	31.5 (6.0)	30.4 (5.3)
HAE-C1INH, Type 1, %	100.0	83.3	83.3	87.5
Age at onset of the first HAE symptoms, years; mean (SD	10.8 (10.6)	14.0 (8.3)	12.2 (5.8)	12.5 (7.7)
Number of HAE attacks in the previous 12 months; mean (SD)	18.3 (23.3)	34.0 (29.2)	11.2 (8.7)	21.5 (22.9)

SAFETY

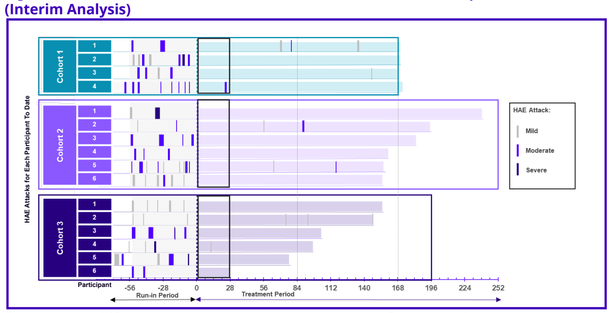
- The most common treatment-emergent adverse events (TEAEs), occurring during the first 28 days in 2 or more participants who received navenibart, were contusions, none of which were considered related to the treatment.
- There were no reports of serious or severe TEAEs and no treatment discontinuations.

CLINICAL EFFECTIVENESS, PHARMACOKINETICS, PHARMACODYNAMICS AND QUALITY OF LIFE

REDUCTION IN HAE ATTACKS

- At the cut-off date, ALPHA-STAR participants accrued 6.5 years of exposure to navenibart.
- In the first month post navenibart administration, HAE attacks were reduced from baseline by 93% in Cohort 1 and 94% in Cohorts 2/3 (Boxes in **Figure 1**).

Figure 1. HAE Attack Occurrence in Individual ALPHA-STAR Participants (Interim Analysis)



The duration of the HAE attack correlates with the thickness of each vertical bar. Shaded bars indicate the duration of follow-up at the time of the data cut-off. Vertical lines indicate efficacy analyses at Day 84 (3 months) and Day 168 (6 months). Boxes indicate the first 28 days of follow-up for each dosing cohort.

RAPID INHIBITION OF PLASMA KALLIKREIN

- Navenibart plasma concentrations increased rapidly after administration of 450 mg and 600 mg SC (**Figure 2**).
- Within 7 days, maximal changes in %cHMWK were achieved.
- Plasma concentrations and kallikrein inhibition were sustained for the duration of follow up (after 28 days).
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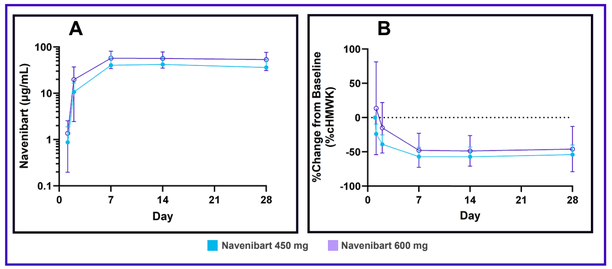
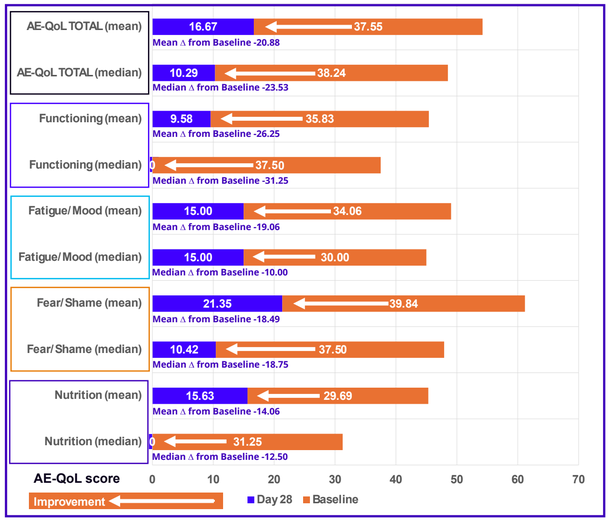
Figure 2. (A) Pharmacokinetics and (B) Pharmacodynamics of Navenibart in ALPHA-STAR (First 28 Days)



IMPROVEMENTS IN AE-QOL

- Navenibart treatment resulted in clinically meaningful improvements in total AE-QoL scores (MCID=-6 points) for 80% of participants over the first 28 days in the ALPHA-STAR clinical trial.
- Clinically meaningful improvements in the first 28 days, in total AE-QoL scores and across all AE-QoL domains, were demonstrated (**Figure 3**).

Figure 3. Improvement in AE-QoL in the First Month after Navenibart in ALPHA-STAR (Interim Analysis; n=15)



CONCLUSIONS

- Rapid inhibition of plasma kallikrein was associated with reductions in HAE attacks and with a favorable safety profile during the first 28 days of the navenibart treatment.
- ALPHA-STAR participants experienced rapid improvements in quality of life across all 4 domains of AE-QoL.
- Clinical benefits were associated with a rapid rise in navenibart concentrations and a corresponding decline in kallikrein activity.
- The registrational Phase 3 clinical trial is planned to commence in Q1 2025 and is aiming to provide further clinical evidence of the normalization of the lives of patients with HAE.