Rationale and Design of the ALPHA-SOLAR Clinical Trial of Navenibart (STAR-0215) for the Treatment of Hereditary Angioedema (HAE)

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OBJECTIVES

- The goal of the ALPHA-SOLAR clinical trial is to enable the collection of information about long-term safety and efficacy of navenibart (STAR-0215) in participants with HAE.

SUMMARY

1. ALPHA-SOLAR long-term open-label trial evaluates the long-term safety and efficacy of navenibart
2. Initial results of the ALPHA-STAR trial demonstrated a favorable safety and tolerability profile of navenibart
3. ALPHA-STAR and ALPHA-SOLAR support the potential of navenibart to provide disease control and normalize the lives of patients with HAE

ALPHA-SOLAR ENDPOINTS

Primary endpoint
- To assess long-term safety and tolerability of STAR-0215 in participants with Type 1 or Type 2 HAE

Secondary endpoints:
- To assess the long-term clinical efficacy of STAR-0215 in participants with Type 1 or Type 2 HAE
- Pharmacokinetics
- Pharmacodynamics
- Immunogenicity

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REFERENCES: 1. Lumry, W. et al. *Journal of Allergy and Clinical Immunology,* 2024;153(2).

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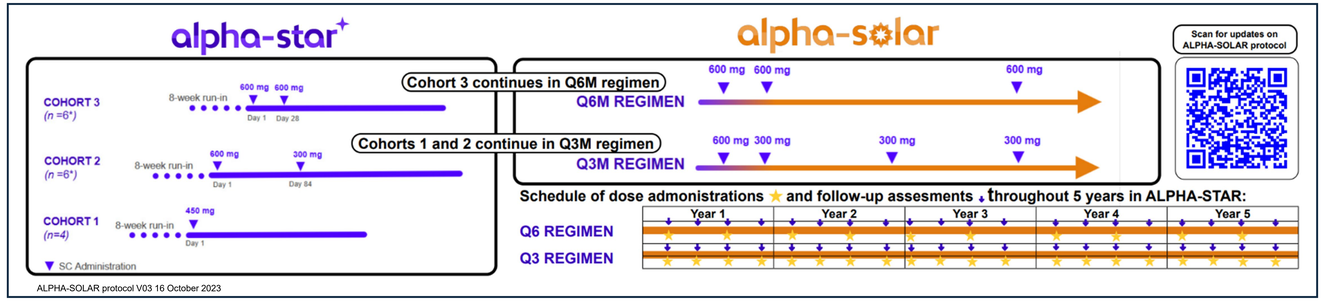
INTRODUCTION

- Hereditary angioedema (HAE), a rare genetic disorder, causes episodic attacks of localized swelling which can be disabling and potentially fatal.
- In patients with HAE due to C1-inhibitor deficiency or dysfunction, normal regulation of plasma kallikrein activity is lacking leading to increases in plasma kallikrein activity and release of bradykinin resulting in angioedema attacks.
- Navenibart is an investigational monoclonal antibody inhibitor of plasma kallikrein with long-lasting activity enabled by a YTE-modified Fc domain.
- Results from the single ascending dose Phase 1a trial (NCT05477160) demonstrated that navenibart was well tolerated at all doses administered and achieved clinically relevant kallikrein inhibition after single doses > 100 mg.[1]
- These results support the ongoing Phase 1b/2 ALPHA-STAR trial (NCT05695248); initial results demonstrate a rapid reduction in monthly attack rates (90-96%) after 3 and 6 months of follow up, coupled with a favorable safety profile.
- There were no reports of injection site pain with administration of navenibart in HAE patients in ALPHA-STAR.
- Here, we describe the design of the ongoing Phase 2 extension study (NCT06007677) that is investigating the long-term safety of navenibart in patients with HAE.

METHODS

- ALPHA-SOLAR is an open-label, phase 2 clinical trial (NCT06007677) open to participants in the ongoing Phase 1b/2 ALPHA-STAR trial (adults, HAE type 1 or 2) who meet eligibility requirements.
- This trial will enroll up to 56 participants globally. Enrolled participants will receive a subcutaneous (SC) loading dose (600 mg) and either 300 mg SC every 3 months (Q3M) or 600 mg SC every 6 months (Q6M) of navenibart. ALPHA-SOLAR participants who continue from ALPHA-STAR cohorts 1 and 2 will receive a SC loading dose and Q3M; participants from ALPHA-STAR cohort 3 will receive a SC loading dose and Q6M. The assessments occur every 3 and 6 months. The trial is expected to continue for 5 years (**Figure 1**).

Figure 1. ALPHA-STAR and ALPHA-SOLAR clinical trial design



KEY INCLUSION CRITERIA

- Open to participants from (NCT05695248) who have met one of the following conditions:
  - Completed ALPHA-STAR (follow up through 6 months after their last dose);
  - Eligible for ALPHA-STAR and entered the Run-In period but did not qualify for the Treatment Period because they did not meet the criterion for the minimum number of HAE attacks;
  - Eligible for ALPHA-STAR and entered the Run-In period but did not complete it for reasons other than not meeting the criterion for the minimum number of HAE attacks (eligibility requires consultation with the Medical Monitor); or
  - Discontinued ALPHA-STAR (for reasons other than safety) after having completed at least 84 days of trial follow-up since their last dose of navenibart (eligibility requires consultation with the Medical Monitor).

KEY EXCLUSION CRITERIA

- Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-esterase inhibitor protein (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
- Any exposure to angiotensin-converting enzyme inhibitors or any estrogen-containing medications with systemic absorption (such as hormonal contraceptives or hormone replacement therapy) within 28 days prior to Screening.
- Any exposure to androgens (for example, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 7 days prior to Screening.
- Use of therapies prescribed for the prevention of HAE attacks prior to Screening: lanadelumab within 90 days; berotralstat within 21 days; all other prophylactic therapies, discuss with the Medical Monitor.

Note: Other inclusion and exclusion criteria may apply.

CONCLUSIONS

- **The goal of the ALPHA-SOLAR long-term open-label trial is to evaluate the long-term safety and efficacy of navenibart as a potential long-acting preventative therapy for HAE. Initial results from the ongoing ALPHA-STAR trial demonstrate a favorable safety and tolerability profile, clinically relevant prevention of HAE attacks, and potential for Q3M and Q6M administration. These results support the potential of navenibart to provide disease control and normalize the lives of HAE patients, which is the overarching goal of HAE management. The ALPHA-SOLAR clinical trial will provide additional data of navenibart in patients with HAE.**