Design of a Phase 1b/2 Proof-of-Concept Trial of STAR-0215 as a Long-Acting Preventative Therapy in Patients with Hereditary Angioedema (HAE) Types I or II

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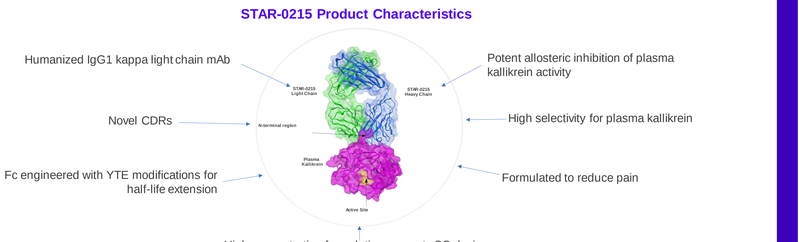
BACKGROUND

HAE is a rare, disfiguring, and potentially life-threatening disease that occurs in 1 in 10,000 to 1 in 50,000 people. HAE is characterized by severe, unpredictable, sometimes life-threatening swelling attacks of various parts of the body. The majority of HAE cases are caused by C1-INH deficiencies, resulting in uncontrolled activation of plasma kallikrein. Available HAE treatments require frequent dosing for patients, significantly impacting quality of life. There is an unmet need for preventative therapy with lower treatment burden. STAR-0215 is an investigational YTE-modified humanized IgG1 kappa monoclonal antibody with potent and durable (≥3 month) reduction of plasma kallikrein activity demonstrated in cynomolgus monkeys (Fig. 1).

Fig. 1. STAR-0215 Overview

Anti-Plasma Kallikrein mAb Engineered for Long Half-Life

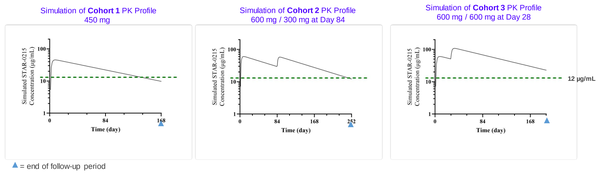


CDR, complementarity-determining regions; IgG1, immunoglobulin G subclass 1; mAb, monoclonal antibody; SC, subcutaneous; YTE, triple mutation (M257Y/S254T/T256E)

Fig. 2. Dose Selection Rationale

Dose regimens selected based on potential to provide long-term benefit (HAE attack prevention)

Model and Simulations of ALPHA-STAR Dose Regimens:



Targeting STAR-0215 concentrations above 12 µg/mL is expected to confer HAE attack prevention[1-3] (green dashed line)

1. Compartmental PK model built from available Phase 1a healthy subject data. 2. Kaufman 1991 June 15. Blood 77(12): 2660-2667. 3. Wang et al. Clin Transl Sci. 2020 Nov; 13(6): 1208-1216. doi:10.1111/cts. 12808. Epub 2020 May 26. 4. Icatibant EMA Assessment Report. 2011 June 23. EMA/CHMP/674618/2011.
HAE, hereditary angioedema; PK, pharmacokinetic.

Fig. 3. Population Characteristics

Key Inclusion/Exclusion Criteria

Inclusion Criteria

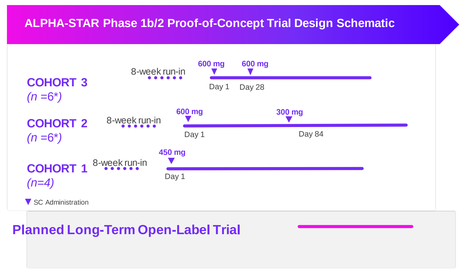
- **+18 years** old or older
- Documented **diagnosis of HAE due to C1 -Inhibitor deficiency** or dysfunction
- Must have **2 or more HAE attacks in the 8-week run-in period** to qualify for STAR-0215 administration

Exclusion Criteria

- **Any concomitant diagnosis** of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE type 3), idiopathic angioedema, or angioedema associated with urticaria.
- **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, within 7 days
- Any **exposure to androgens** within 7 days prior to screening.

HAE, hereditary angioedema.

Fig. 4. Trial Design and Overview



Includes details of the planned amendment. Cohorts planned to be opened sequentially.
*Up to 6 additional subjects may be added to Cohorts 2 and/or 3; additional cohorts may be added. For more detailed information, visit www.clinicaltrials.gov; NCT05695248
PD, pharmacodynamics; PK, pharmacokinetics; QOL, quality of life.

- Three dose-ranging cohorts to inform pivotal trial design
- For each cohort, **efficacy will be assessed at 3 months and 6 months** after the last STAR-0215 dose administered
- **Initial proof-of-concept results**
- Assessing safety and tolerability, PK, PD, attack rate, and QOL in these 3 cohorts
- Goal: significant reduction in attacks following STAR-0215 treatment

Statistical Considerations

Primary Outcome Measure:

Safety:

Number of Participants Experiencing Treatment-Emergent Adverse Events

Secondary Outcome Measures:

Efficacy:

Change From Baseline in Monthly HAE Attack Rate
Severity of HAE Attacks Experienced By Participants
Duration of HAE Attacks
Number of Participants Experiencing HAE Attacks Requiring On-Demand Therapy
Time to First HAE Attack After First And Last Dosing

Open-Label Trial:

Endpoints are objective and change-from-baseline HAE attacks will inform efficacy
HAE attacks are confirmed by investigators

Sample size:

Up to 28 participants*

Planned amendment will increase sample size to maximum 28 participants. For more detailed information, visit www.clinicaltrials.gov; NCT05695248.
ADA, anti-drug antibodies; HAE, hereditary angioedema; PD, pharmacodynamic; PK, pharmacokinetic

Partnering with the HAE Community

Pre-Trial

Established Relationships with Advocacy Leaders

- Incorporated feedback into protocol design available solutions for trial experience
- Engaged global advocacy leaders to advise on trial sites

Engaged Patients

Conducted patient interviews to understand unmet needs, most meaningful endpoints; input on design

Review ICFs and recruitment materials to ensure simplicity, clarity

Collaborate with trial sites to mitigate potential patient challenges

During Trial

Advocacy group has mechanisms for trial awareness

- Inclusion in newsletters, "clinical trials" pages on website
- Proactive regional outreach by some groups to patients

HAE, hereditary angioedema; ICF, Informed Consent Forms.

Operational Considerations

Approximately 25 sites in US, Canada, UK, and EU

- Initiated in US and Canada; UK and EU site initiations are in process

Expect initial proof-of-concept results in mid-2024

- Results will inform plans for the Phase 3 trial, if favorable

Long-Term Open Label trial planned to open in time for the first completers of ALPHA-STAR to opt-in

See www.astrazs.com/for-patients/alpha-star-trial for up-to-date map information. For more detailed information, visit www.clinicaltrials.gov; NCT05695248

CONCLUSION:

- STAR-0215 is a **potential long-term preventative treatment** for HAE-C1INH (Type 1 or 2), administered SC every 3 or 6 months
- Phase 1a healthy volunteer results show potential best-in-class pharmacokinetic profile and durable plasma-kallikrein inhibition for at least 3 months after single doses
- ALPHA-STAR is a proof-of-concept trial of STAR-0215 in adults living with HAE
  - Proof-of-concept will be defined by ability to achieve durable clinical benefits safely when administered every 3 or 6 months
- Trial has been initiated and enrollment is ongoing, **initial results are expected in mid-2024**

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