# Updated Results of a Phase 1a Trial of STAR-0215 for Hereditary Angioedema

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## OBJECTIVE

Confirm the feasibility of Q3M and Q6M (every 3 and 6 months) administration of STAR-0215 with complete follow-up from Phase 1a cohorts.

## 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.
- STAR-0215 is an investigational monoclonal antibody inhibitor of plasma kallikrein with long-lasting activity enabled by a YTE-modified Fc domain.
- Results through final follow-up of the single ascending dose Phase 1a trial (NCT05477160) with follow-up through Day 224 after single doses up to 1200 mg SC aim to demonstrate that STAR-0215 is a long-acting inhibitor of plasma kallikrein that can be effectively administered Q3M and/or Q6M.[1]

## METHODS

Healthy adults (18 to 60 years old) were randomized 3:1 to STAR-0215 or placebo. Subjects received a single dose of STAR-0215 100, 300, 600, or 1200 mg SC or 600 mg intravenous (IV) or placebo. This report is an analysis through day (D) 224 in all cohorts.

**Safety and Tolerability**
- Assessed from adverse events, vital signs, physical examinations, ECG and clinical laboratory results.

**Pharmacokinetic (PK) and Anti-drug antibody (ADA) Assessments**
- Blood samples were collected at regular intervals and serum was analyzed for free STAR-0215 and ADA to STAR-0215 using validated methods.
- Standard two-compartment PK model with adjustments for dose dependency and bioavailability was established and updated with final PK data for simulations of Q3M and Q6M SC dosing and administration profiles.

**Pharmacodynamic (PD) Assessments**
- *Ex vivo* FXIIa-induced plasma kallikrein activity was measured using a reporter-substrate enzymatic assay as well as by changes in %cHWMK levels analyzed by western blot.

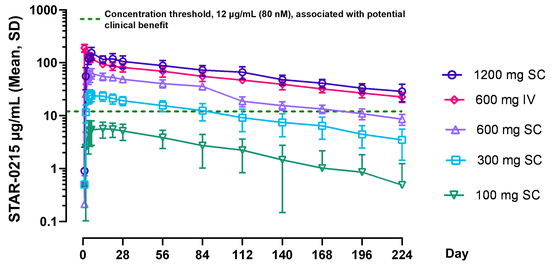
## RESULTS

**Safety and Tolerability**

Total of 41 subjects have participated, 31 participant were administered STAR-0215. Rates of TEAEs were 21/31 (68%) and 6/10 (60%) for subjects that received one dose of STAR-0215 and placebo, respectively.
- No serious or severe adverse events, or discontinuations due to an adverse event.
- All related TEAEs were mild in severity.
- Most common related treatment emergent adverse events occurring in ≥ 2 STAR-0215 subjects include injection site reactions of erythema (22.6%), pruritus (12.9%), swelling (12.9%), and headache (6.5%).

## Figure 1. Single-Dose Pharmacokinetic Profile

- Rapid increases in concentrations after SC and IV administration.
- Mean concentrations remained >12 µg/mL after all single doses (except 100 mg SC) for ≥84 days.




## Table 1. Summary of Pharmacokinetic Parameters of STAR-0215

- Mean half-life ( $t_{1/2}$ ) up to 109 days.
- STAR-0215 concentration associated with anticipated clinical benefit achieved 11 hours after 600 mg SC dose ($t_{12\mu g/mL}$(hours)).

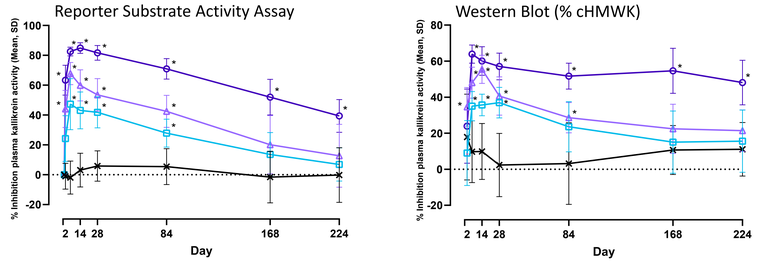
| | STAR-0215 100 mg SC (N = 7) | STAR-0215 300 mg SC (N = 6) | STAR-0215 600 mg SC (N = 6) | STAR-0215 1200 mg SC (N = 6) | STAR-0215 600 mg IV (N = 6) |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL), mean (SD) | 6.4 (2.09) | 24.9 (6.06) | 64.0 (13.36) | 154.2 (40.72) | 203.2 (27.17) |
| $C_{ave}$ (µg/mL), Day 84, mean (SD) | 2.7 (1.70) | 12.5 (4.47) | 35.7 (5.09) | 72.7 (16.18) | 55.5 (11.24) |
| $C_{ave}$ (µg/mL), Day 168, mean (SD) | 1.0 (1.16) | 6.5 (2.87) | 13.4 (2.32) | 41.2 (7.24) | 32.1 (5.09) |
| $T_{max}$ (days), mean (SD) | 13.5 (9.74) | 7.5 (4.27) | 6.3 (3.29) | 4.8 (0.41) | 0.13 (0.10) |
| $t_{12\mu g/mL}$(hours), mean | N/A | 25 | 11 | 7 | <0.1 |
| $t_{1/2}$ (days), mean (SD) | 69 (21.3) | 83 (12.8) | 94 (20.9) | 94 (11.8) | 109 (31.6) |

Abbreviations: $C_{max}$, peak drug concentration; $C_{ave}$, average concentration on specified day; $T_{max}$, time to reach peak drug concentration; $t_{12}$ µg/mL, time to reach concentration threshold; $t_{1/2}$, half-life.

- Treatment-emergent ADAs were observed in 11 subjects from all cohorts combined, all first observed on or after D140. ADAs were determined not to affect the pharmacokinetics or pharmacodynamics of STAR-0215.

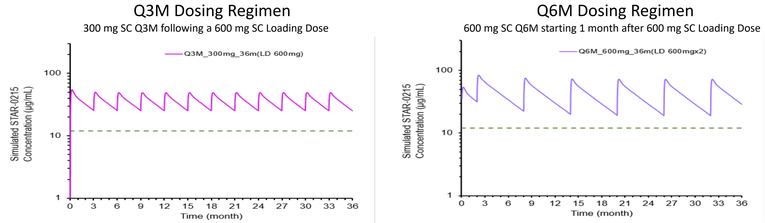
## Figure 2. Pharmacodynamic Activity

- Statistically significant % inhibition of FXIIa-induced plasma kallikrein activity compared to predose was observed using both the reporter substrate enzyme activity assay (left) and western blot assessment of %cHMWK levels (right).
- Percent inhibition of plasma kallikrein consistent with clinical activity was observed for doses ≥ 300 mg.




## Figure 3. Pharmacokinetic Model with Simulations

- STAR-0215 concentrations are sustained above the target threshold (12 µg/mL) when administered, SC, with a loading dose and Q3M or Q6M maintenance dosing.




## CONCLUSIONS

- STAR-0215 was well-tolerated at all doses administered and appears to have a favorable safety profile.
- Rapid, linear, and durable STAR-0215 concentrations were demonstrated after single doses > 100 mg and achieved clinically relevant kallikrein inhibition, consistent with or superior to those achieved by lanadelumab in Phase 1.[2]
- These results support the ongoing Phase 1b/2 ALPHA-STAR trial (NCT05695248) in people with hereditary angioedema.
- Initial results from the ALPHA-STAR trial (expected in Q1 2024) will serve as the proof of concept as a preventative medicine administered as infrequently as Q6M for people with HAE and, if positive, combined with this data, will support Phase 3 dose selection.

**References:** 1. Morabito, C., et al. Initial Results from a Phase 1 Single Ascending Dose Clinical Trial of STAR-0215, an Investigational Long-Acting Monoclonal Antibody Plasma Kallikrein Inhibitor for Hereditary Angioedema (HAE), in Healthy Subjects Followed for at Least 3 Months. Journal of Allergy and Clinical Immunology, 151(2): AB136; 2. Chyung, Y., et al. A Phase 1 Study Investigating DX-2930 in Healthy Subjects. Ann Allergy Asthma Immunol 113(2014):460-466.

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