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

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SUMMARY

1 STAR-0215 WAS WELL-TOLERATED AT ALL DOSES ADMINISTERED AND APPEARS TO HAVE A FAVORABLE SAFETY PROFILE

2 RAPID, LINEAR, AND DURABLE STAR-0215 CONCENTRATIONS WERE DEMONSTRATED AFTER SINGLE DOSES

3 ADMINISTERED DOSES >100 MG ACHIEVED CLINICALLY RELEVANT KALLIKREIN INHIBITION

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

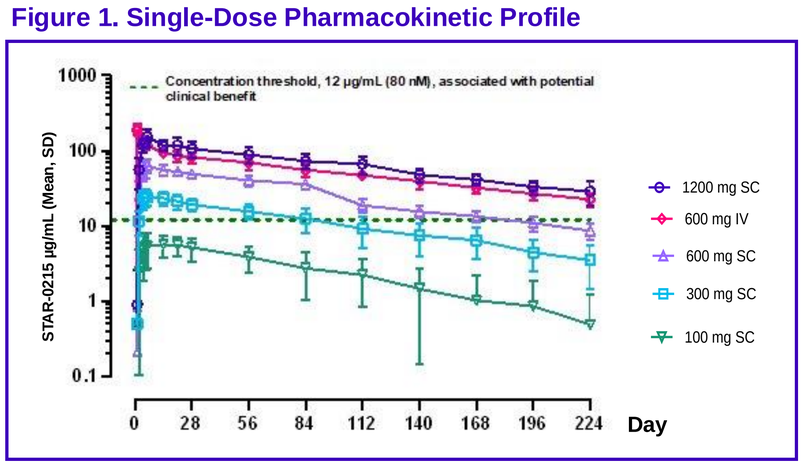
Total of 41 subjects have participated, 31 participant were administered STAR-0215. Rates of TEAEs were 21/31 (68%) and 6/10 (60%) for subjects that received one dose of STAR-0215 and placebo, respectively.

- 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%).

PK ASSESSMENTS

- 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.

Figure 1. Single-Dose Pharmacokinetic Profile



- 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)).

Table 1. Summary of Pharmacokinetic Parameters of STAR-0215

	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: Cmax, peak drug concentration; Cave, average concentration on specified day; Tmax, time to reach peak drug concentration; t12 µg/mL, time to reach concentration threshold; t1/2, half-life.

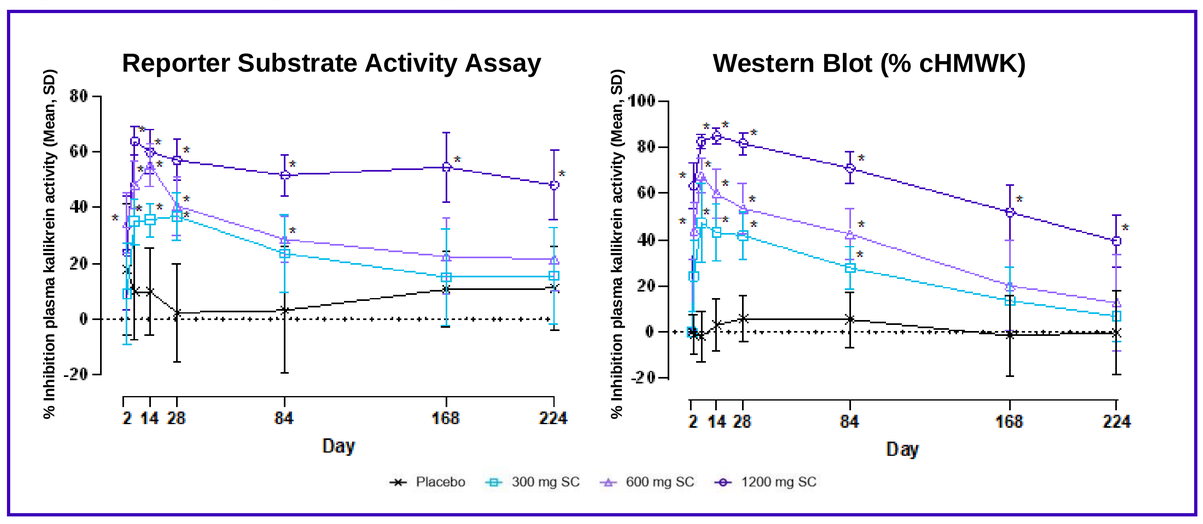
ADA ASSESSMENTS (IMMUNOGENICITY)

- 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.

PD ASSESSMENTS

- 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.

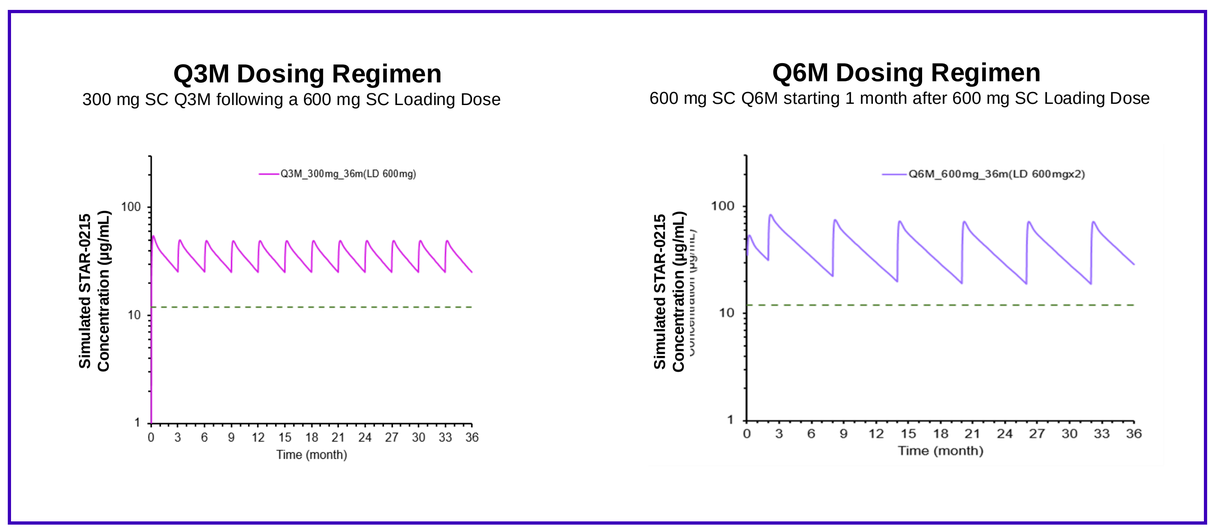
Figure 2. Pharmacodynamic Activity



PHARMACOKINETIC MODELING

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

Figure 3. Pharmacokinetic Model with Simulations



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 and achieved clinically relevant kallikrein inhibition at dose levels > 100 mg, 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 (to be presented at EADV conference in Amsterdam, September 25-28, 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.**

ACKNOWLEDGMENTS: Authors acknowledge Larisa Miller for medical writing and design of the poster.

REFERENCES: 1. Morabito, C. et al. *Journal of Allergy and Clinical Immunology, 2023.* 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.*

Presented at Bradykinin Symposium • September 5-6, 2024 • Berlin, Germany

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