Initial Results from a Phase 1a Single Ascending Dose Clinical Trial of STAR-0215, an Investigational Long-Acting Monoclonal Antibody Plasma Kallikrein Inhibitor for Hereditary Angioedema (HAE), in Healthy Adult Subjects Followed for 3 Months

Authors: *William Lumry, Chris Stevens, Jou-Ku Chung, Rafif Dagher, Pradeep Bista, Kristine Bernard, Pamela Gustafson, Michele Gunsior, Andrew Nichols and Christopher Morabito*

BACKGROUND: HAE caused by C1-INH deficiency results in uncontrolled activation of plasma kallikrein that initiates potentially life-threatening HAE attacks. STAR-0215 is an investigational humanized YTE-modified IgG1kappa monoclonal antibody with potent and durable (≥3 month) reduction of plasma kallikrein activity demonstrated in cynomolgus monkeys (Fig. 1). This Phase 1a trial (NCT05477160) in healthy subjects is designed to assess whether a single SC dose of STAR-0215 has the potential for safe and durable suppression of cleaved high molecular weight kininogen (cHMWK). to levels consistent with robust plasma kallikrein inhibition to prevent HAE attacks for ≥3 months in adults living with HAE.

Methods

This is a Phase 1a randomized, blinded, placebo-controlled, single ascending dose trial evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-drug antibody (ADA) formation after subcutaneous (SC) STAR-0215 doses of 100 mg, 300 mg, 600 mg, or placebo in 3 cohorts (3:1 randomization) of healthy adults (18-60 years) subjects in a single study site in the United States. To assess PD, plasma kallikrein activity is measured by change-from-baseline in cleaved high-molecular-weight kininogen (cHMWK) via an ex vivo FXIIa-induced cleavage of plasma HMWK western blot assay and an orthogonal chromogenic reporter-substrate (PFR-pNA) assay.

The duration of the follow-up period is 224 days; this initial report is a Day 84 unblinded interim analysis of safety, PK, PD, and ADA in these three dose cohorts.

Results

SAFETY and TOLERABILITY:
19 subjects received STAR-0215 and 6 received placebo. Related treatment emergent adverse events (TEAEs) were seen in 8 subjects (STAR-0215 n=7; placebo n=1), were mild (Grade 1) in severity, and resolved without intervention (Table 1). The most common TEAEs were injection site reactions (n=6, all STAR-0215), most often erythema. There were no serious adverse events or discontinuations due to an adverse event. No clinically significant changes in laboratory assessments, including activated partial thromboplastin time (aPTT), have been observed.

IMMUNOGENICITY: No treatment-emergent ADAs have been detected.

PHARMACOKINETICS: STAR-0215 demonstrated dose-dependent PK, rapid absorption with an average T_{max} between 6-13 days and an estimated $t_{1/2}$ up to 117 days (Table 2). At Day 84, mean concentrations remained above 80 nM (threshold for potential efficacy) after a single 300 mg SC dose and 3x over 80 nM after 600 mg SC dosing (Fig. 2).

PHARMACODYNAMICS: Suppression of cHMWK to levels consistent with robust plasma kallikrein inhibition was achieved through Day 84 as observed in an ex vivo FXIIa-induced cleavage of plasma HMWK western blot assay and in an orthogonal chromogenic reporter-substrate (PFR-pNA) assay (Fig.3).

Fig. 1: STAR-0215 Overview
Anti-Plasma Kallikrein mAb Engineered for Long Half-Life

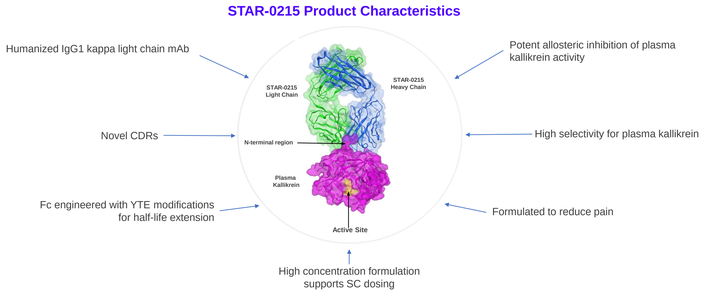
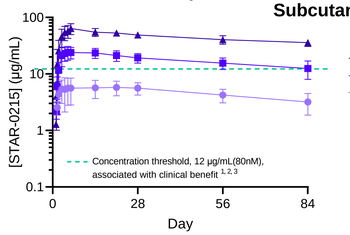


Table 1: Related Treatment-Emergent Adverse Events (TEAEs)

MedDRA System Organ Class Preferred Term	STAR-0215 100 mg (N = 7)	STAR-0215 300 mg (N = 6)	STAR-0215 600 mg (N = 6)	Combined STAR-0215 (N = 19)	Combined Placebo (N = 6)
Number of subjects with at least 1 related TEAE, n (%)	1 (14.3)	2 (33.3)	4 (66.7)	7 (36.8)	1 (16.7)
Number of related TEAEs	1	4	11	16	1
General disorders and administration site conditions, n (%)	0	2 (33.3)	4 (66.7)	6 (31.6)	0
Injection site erythema	0	2 (33.3)	3 (50.0)	5 (26.3)	0
Injection site pruritus	0	1 (16.7)	2 (33.3)	3 (15.8)	0
Injection site swelling	0	0	2 (33.3)	2 (10.5)	0
Injection site inflammation	0	1 (16.7)	0	1 (5.3)	0
Metabolism and nutrition disorders, n (%)	1 (14.3)	0	0	1 (5.3)	0
Abnormal weight gain	1 (14.3)	0	0	1 (5.3)	0
Nervous system disorders, n (%)	0	0	0	0	1 (16.7)
Headache	0	0	0	0	1 (16.7)

Fig. 2 Initial Pharmacokinetic Profile
Results Show Rapid and Sustained STAR-0215 Concentrations After Single Subcutaneous Doses



- Concentrations are proportional to dose
- Long elimination phase consistent with YTE modification
- Estimated half-life is 117 days

**One subject excluded from the analysis due to partial dose administered*

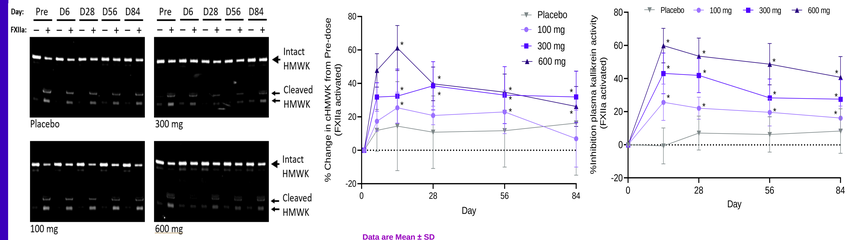
Table 2. Summary of Pharmacokinetic Parameters of STAR-0215

Dose Group		$t_{1/2}$ (day)	T_{max} (day)	C_{max} (µg/mL)	$AUC_{0\text{-}84}$ (day*µg/mL)	C_{last} (µg/mL)
100 mg	**n=6***					
Mean		83	13	6.57	385	2.60
SD		28	11	2.23	118	1.08
300 mg	**n=6**					
Mean		105	8	24.9	1411	12.5
SD		43	4	6.1	301	4.5
600 mg	**n=6**					
Mean		117	6	64.0	3737	35.7
SD		14	3	13.4	576	5.1

**One subject excluded from the analysis due to partial dose administered*

Abbreviations: t1/2, terminal half-life; Tmax, time to reach peak drug concentration; Cmax, peak drug concentration; AUC0-84, area under concentration-time curve from time 0 to 84 days; Clast, drug concentration at the last timepoint.

Fig. 3 Initial Pharmacodynamic Results
STAR-0215 Demonstrates Robust PD Activity Through Day 84 After a Single SC Dose



Data are Mean ± SD
- * = p < 0.05 from pre-dose at indicated doses and timepoints; non-significant (ns) difference at all timepoints for placebo
- Statistical Test: 2-Way ANOVA with Dunnett's test for multiple comparisons

Representative western blot images show STAR-0215 treatment inhibits ex vivo FXIIa-induced cleavage of plasma HMWK after a single subcutaneous dose

Quantification of western blot images shows significant inhibition of cHMWK at all post-dose timepoints for 300 mg and 600 mg cohorts

An orthogonal chromogenic reporter-substrate (PFR-pNA) assay confirms dose-responsive, robust, and long-lasting inhibition of plasma kallikrein activity after single dose of STAR-0215

CONCLUSION:

- STAR-0215 demonstrates robust inhibition of plasma kallikrein for at least 84 days (around 3 months) after a single subcutaneous (SC) dose in healthy subjects (subjects are anticipated to remain in follow-up for 224 days).
- STAR-0215 has rapid absorption with an estimated half-life ($t_{1/2}$) of 117 days and favorable safety profile.
- These results provide early proof of concept for STAR-0215 being a potential long-acting preventative therapy for Hereditary Angioedema (HAE).
- Additional cohorts have been added to the trial to support the potential for once every 6-months administration in people living with HAE.

Presented at the 2023 European Academy of Allergy, Asthma, and Immunology Annual Meeting | Abstract: 000933