Support for STAR-0215 Administered Every Three- or Six-Months for Hereditary Angioedema: Phase 1a Results

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BACKGROUND:

- Hereditary angioedema (HAE) is a rare autosomal dominant disorder associated with uncontrolled activation of plasma kallikrein that can cause painful and potentially life-threatening swelling in the face, limbs, abdomen, and airway.
- Guidelines recommend long-term preventative therapies for patients living with HAE[1], current treatment options are burdensome and/or partially effective.
- STAR-0215 is an investigational monoclonal antibody inhibitor of plasma kallikrein with long-lasting activity enabled by a YTE-modified Fc domain.
- Initial results of the single ascending dose Phase 1a trial (NCT05477160) with 3-month follow-up after single doses up to 600 mg SC support the potential of STAR-0215 as a long-acting inhibitor of plasma kallikrein administered once Q3M and Q6M (every 3 and 6 months).[2]
- The objective of this update is to confirm the feasibility of Q3M and Q6M dosing of STAR-0215 with complete follow-up from initial Phase 1a cohorts and initial data from two single dose cohorts.

METHODS:

- Healthy adult (18-60-year-old) subjects were randomized 3:1 to STAR-0215 or placebo.
- Subjects received a single dose of STAR-0215 100, 300, 600, or 1200 mg subcutaneous (SC) or 600 mg intravenous (IV) or matched placebo (0.9% NaCl solution).
- This report is a day (D) 224 final analysis in the 100, 300, and 600 mg SC cohorts, and an interim analysis for the ongoing 1200 mg SC and 600 mg IV cohorts (D112 and D84 respectively); data cut-off June 26, 2023, with additional PD data from the 1200 mg SC cohort.

Safety and Tolerability

- Assessed from adverse events, vital signs, physical examinations, 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 for simulations of Q3M and Q6M SC dose and administration profiles.

Pharmacodynamic (PD) Assessments

- *Ex vivo* FXIIa induced plasma kallikrein activity was measured using a reporter-substrate assay as well as by changes of cleaved high-molecular-weight kininogen (cHMWK) assessed by western blot.

RESULTS:

Table 1. Subject Demographics

- Total of 41 subjects have participated: 31 have received one dose of STAR-0215 and 10 have received one dose of matched placebo (placebo group data are pooled).

	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)	Combined Placebo (N=10)	Overall (N=41)
Age, mean, (SD), years	41.1 (11.80)	39.3 (7.42)	33.8 (10.19)	40.2 (8.80)	37.8 (16.17)	39.4 (10.18)	38.8 (10.56)
Female, n (%)	2 (28.6%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	5 (50.0%)	19 (46.3%)
African American, n (%)	1 (14.3%)	4 (66.7%)	6 (100.0%)	2 (33.3%)	1 (16.7%)	7 (70.0%)	21 (51.2%)
White, n (%)	6 (85.7%)	2 (33.3%)	0	3 (50.0%)	5 (83.3%)	1 (10.0%)	17 (41.5%)

Table 2. Overall Summary of Treatment-Emergent Adverse Events

- No serious adverse events, severe adverse events, or discontinuations due to an adverse event.
- Most common related treatment emergent adverse events occurring in >2 STAR-0215 subjects include injection site reactions of erythema (22.6%), pruritus (12.9%), and swelling (12.9%).[#]

	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)	Combined STAR-0215 (N = 31)	Combined Placebo (N = 10)
Any TEAE, n (%)	5 (71.4)	3 (50.0)	6 (100.0)	4 (66.7)	3 (50.0)	21 (67.7)	5 (50.0)
Related TEAE, n (%)	1 (14.3)	2 (33.3)	4 (66.7)	3 (50.0)	0	10 (32.3)	1 (10.0)
General Disorders and Administrative Site, N (%)							
Injection site erythema	0	2 (33.3)	3 (50.0)	2 (33.3)	0	7 (22.6)	0
Injection site pruritus	0	1 (16.7)	2 (33.3)	1 (16.7)	0	4 (12.9)	0
Injection site swelling	0	0	2 (33.3)	2 (33.3)	0	4 (12.9)	0

TEAE = Treatment emergent adverse event.
[#]One subject in combined STAR-0215 group (in 1200 mg SC cohort) experienced injection site pain.

PHARMACOKINETICS:

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

Figure 1. Single Dose Pharmacokinetic Profiles

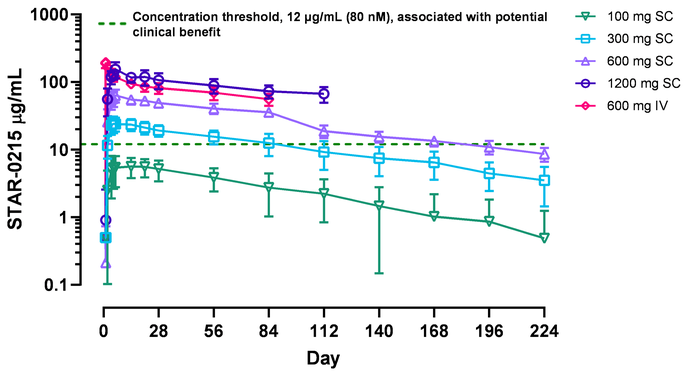


Table 3. Summary of Pharmacokinetic Parameters of STAR-0215

- Estimated half-life up to 127 days
- Dose-related increases in C_{max} and AUC
- STAR-0215 concentration > 12 µg/mL achieved ~11 hours after 600 mg SC dose
- Treatment-emergent ADAs were observed in 6 subjects from completed cohorts, all occurring after D 84. Assessment of ADA impact on PK/PD is ongoing.

	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} Day 84, mean (SD)	2.7 (1.70)	12.5 (4.47)	35.7 (5.09)	72.7 (16.18)	55.5 (11.24)
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
$AUC_{0\text{-}84\ day}$ (h*µg/mL), mean (SD)	9253 (2828.8)	34680 (7545.6)	90300 (13961.0)	194400 (42268.0)	159800 (25865.0)
CL/F (mL/h), mean (SD)	5.4 (1.99)	4.8 (1.87)	3.7 (0.67)	n/a	n/a
$t_{1/2}$ (days), mean (SD)	69 (21.3)	83 (12.8)	94 (20.9)	127 (36.7)	109 (35.8)

Abbreviations: C_{max}, peak drug concentration; C_{ave}, average concentration on day 84; T_{max}, time to reach peak drug concentration; t 12 µg/mL, time to reach concentration threshold; $AUC_{0\text{-}84\ day}$, area under concentration-time curve from time 0 to 84 days; CL/F, clearance, $t_{1/2}$, half-life.

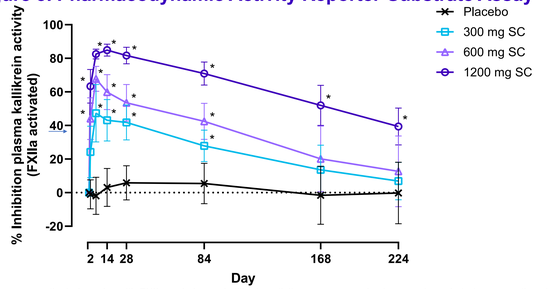
References:

1. Maurer M., et al. The International WAO/EAACI Guideline for the Management of Hereditary Angioedema - The 2021 revision and update. World Allergy Organ J. 2022 Apr 7;15(3):100627.
2. 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.
3. Chyung, Y., et al. A Phase 1 Study Investigating DX-2930 in Healthy Subjects. Ann Allergy Asthma Immunol 113(2014):460-466.

PHARMACODYNAMICS:

- Statistically significant inhibition of *ex vivo* FXIIa-activated plasma kallikrein activity was observed through D 84 after single doses of 300 mg and 600 mg, and through D 224 after a single dose of 1200 mg SC.

Figure 3. Pharmacodynamic Activity Reporter-Substrate Assay

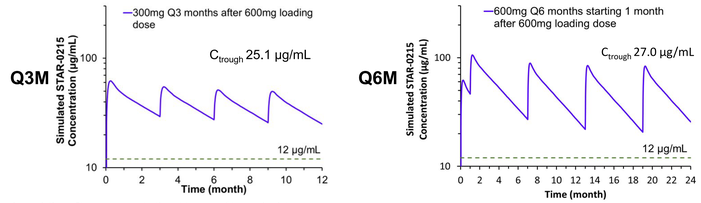


Note: Plasma samples were activated *ex vivo* with FXIIa and plasma kallikrein activity was measured using reporter substrate enzymatic activity assay. Percent inhibition was determined relative to predose timepoints. Data points represent mean (SD). Asterisk (*) = p < 0.005.
In Phase 1, lanadelumab (DX-2930) demonstrated peak %inhibition of plasma kallikrein of <40% at 3 mg/kg SC (single dose).[3]

- Data from the western blot assay assessing inhibition of cHMWK is consistent with the reporter assay for the 300 and 600 mg cohorts through day 224 and the 1200 mg cohort through day 84. Data are pending for the 1200 mg cohort through day 224.

Figure 4. PK Model with Simulations

Concentrations are sustained above the target threshold (12 µg/mL) when administered SC Q3M and Q6M chronically (mean values).



Abbreviations: Ctrough, concentration at the end of the dosing interval.

CONCLUSIONS:

These results confirm the approach to continue to study the potential to administer STAR-0215 Q3M and Q6M.

Safety:

- STAR-0215 was well-tolerated and had a favorable safety profile, with low risk for injection site pain.

PK:

- Concentrations after single doses reached therapeutic threshold quickly (approximately ≤1 day), implying potential for rapid-onset clinical benefit in preventing HAE attacks and were sustained above threshold for ≥ 3 months at doses >100 mg SC.
- PK model simulations inclusive of a loading dose demonstrated sustained levels above the therapeutic threshold with STAR-0215 SC Q3M and Q6M.

PD:

- Plasma kallikrein inhibition effects were rapid, sustained, and consistent with or superior to those achieved by lanadelumab in Phase 1.

Initial proof-of-concept results from the ongoing Phase 1b/2 ALPHA-STAR trial (NCT05695248) are expected in mid-2024. Combined, the results from ALPHA-STAR, if positive, and these Phase 1a results will support Phase 3 dose selection.