

# 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 at Least 3 Months

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**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. 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 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 adult (18-60 years) subjects. 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. 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. 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.

**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.

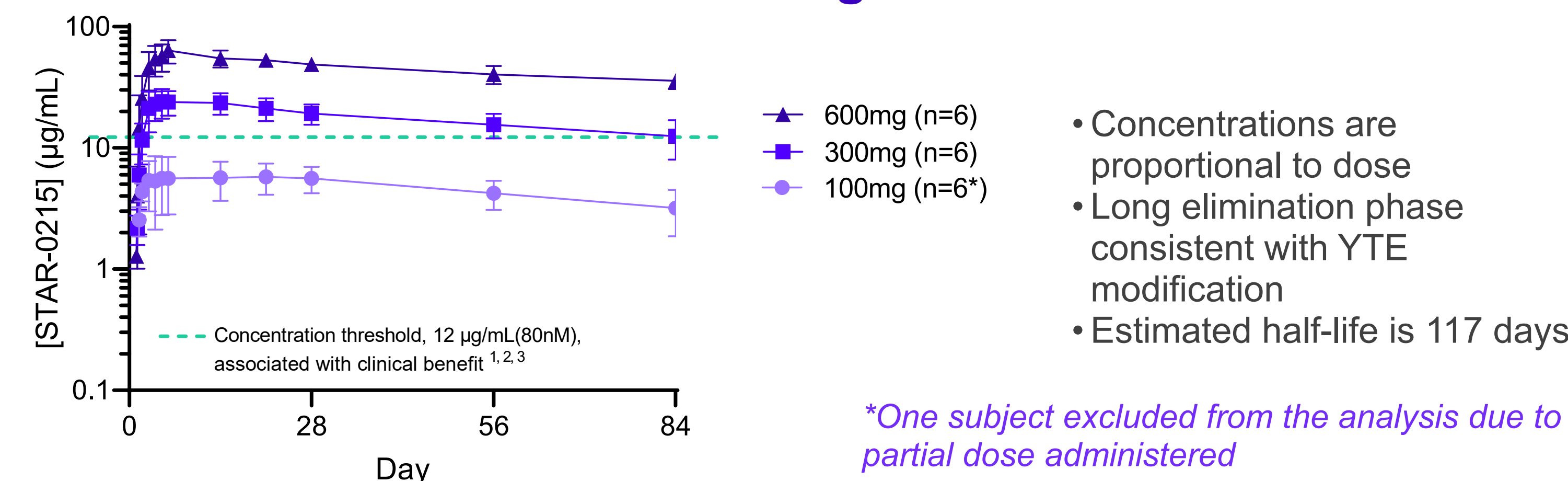
## Subject Demographics

	STAR-0215 100 mg (N = 7)	STAR-0215 300 mg (N = 6)	STAR-0215 600 mg (N = 6)	Combined Placebo (N = 6)	Overall (N = 25)
<b>Sex, n (%)</b>					
Female	2 (28.6)	3 (50.0)	3 (50.0)	3 (50.0)	11 (44.0)
Male	5 (71.4)	3 (50.0)	3 (50.0)	3 (50.0)	14 (56.0)
<b>Race, n (%)</b>					
Black or African American	1 (14.3)	4 (66.7)	6 (100.0)	6 (100.0)	17 (68.0)
White	6 (85.7)	2 (33.3)	0	0	8 (32.0)
<b>Ethnicity, n (%)</b>					
Not Hispanic or Latino	7 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	25 (100.0)
<b>Age (years)</b>					
Mean (SD)	41.1 (11.80)	39.3 (7.42)	33.8 (10.19)	38.2 (11.75)	38.2 (10.21)
Min, Max	26, 58	29, 48	18, 50	24, 56	18, 58
<b>Weight (kg)</b>					
Mean (SD)	94.66 (10.645)	88.13 (15.698)	80.57 (11.415)	78.30 (14.269)	85.78 (13.942)
Min, Max	83.8, 113.8	73.4, 112.6	66.2, 95.6	54.4, 93.2	54.4, 113.8
<b>Height (cm)</b>					
Mean (SD)	174.07 (6.445)	177.67 (11.178)	174.17 (7.216)	170.23 (8.519)	174.04 (8.325)
Min, Max	166.0, 182.0	166.5, 192.0	165.5, 183.5	159.5, 179.6	159.5, 192.0
<b>Body mass index (kg/m<sup>2</sup>)</b>					
Mean (SD)	31.1 (2.85)	28.0 (4.52)	26.7 (4.76)	26.8 (4.83)	28.3 (4.41)
Min, Max	28, 34	22, 35	21, 35	21, 33	21, 35

## 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)

## Results Show Rapid and Sustained STAR-0215 Concentrations After Single Subcutaneous Doses



1. Kaufman 1991 June 15. Blood 77(12): 2660-2667  
2. Wang et al. Clin Transl Sci. 2020 Nov, 13(6): 1208-1216. doi: 10.1111/cts. 12806 Epub 2020 May 26.  
3. Ecallantide EMA Assessment Report. 2011 June 23. EMA/CHMP/476818/2011

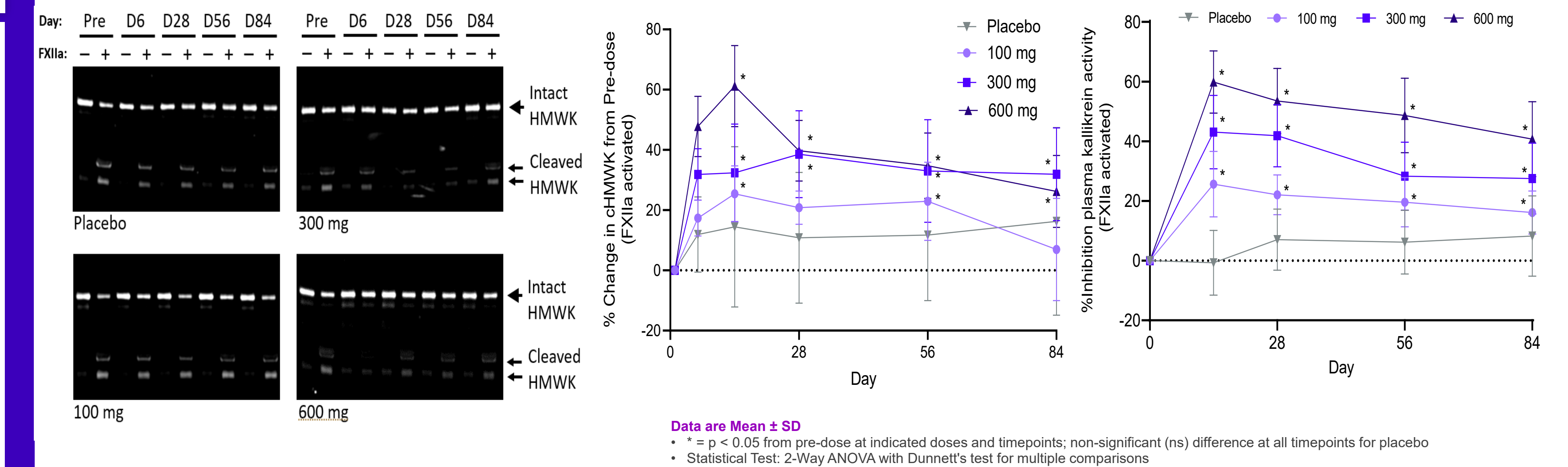
## Summary of Pharmacokinetic Parameters of STAR-0215

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

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

Abbreviations:  $t_{1/2}$ , terminal half-life;  $T_{max}$ , time to reach peak drug concentration;  $C_{max}$ , peak drug concentration;  $AUC_{0-84}$ , area under concentration-time curve from time 0 to 84 days;  $C_{last}$ , drug concentration at the last timepoint.

## STAR-0215 Demonstrates Robust PD Activity Through Day 84 After a Single SC Dose



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:** With rapid absorption and an estimated  $t_{1/2}$  of 117 days, STAR-0215 has a favorable safety profile and demonstrates robust inhibition of plasma kallikrein for at least 84 days (approximately 3 months) after a single SC dose in healthy subjects. These results demonstrate early proof of concept for STAR-0215 as a potential long-acting preventative therapy for HAE. Additional cohorts have been added to this trial to assess the potential for once every 6-months administration. Continued investigations in adults living with HAE are warranted.