Mechanistic Modeling and Simulations Predict Long-Term HAE Attack Prevention with STAR-0215 |

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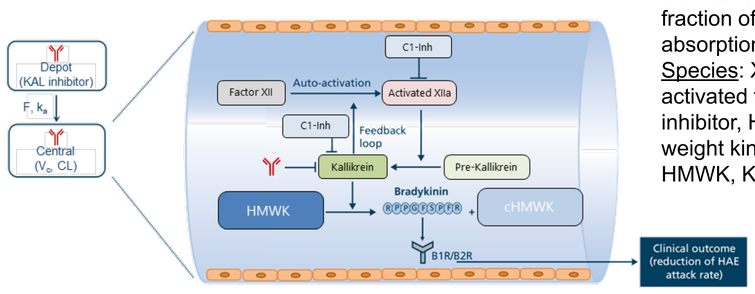
Introduction
Inhibition of plasma kallikrein is a validated mechanism for prevention of hereditary angioedema (HAE) attacks. Clinically, STAR-0215 demonstrated a long circulating half-life (estimated up to 117 days) and prolonged plasma kallikrein inhibition (through at least 84 days). Simulations of different dose regimens were performed using a mechanistic quantitative systems pharmacology (QSP) model to explore the potential for the reduction of HAE attacks.

Objective
Evaluate the potential for long-acting HAE attack suppression by STAR-0215 with administration every three months (84 days) or every six months (168 days).

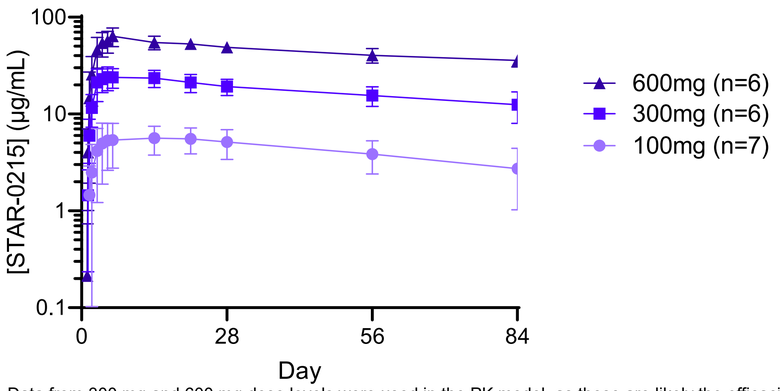
Methods
A simplified QSP model was established based on published reaction parameters for the plasma kallikrein-kininogen pathway in the vascular space and adjacent to the endothelial surface. The human pharmacokinetic (PK) parameters of STAR-0215 were derived from healthy adult subject results in the Phase 1a trial. The virtual cohorts were established using human PK parameters and their variabilities identified from healthy subjects who received STAR-0215. The average baseline attack frequency of virtual HAE cohorts was approximately 3 attacks per month (28 days).

Method Figure 1 – Simplified QSP Model Diagram



PK parameters: V_c = volume of distribution, CL = clearance, F = fraction of dose absorbed, k_a = absorption rate constant
Species: XII = factor XII, XIIa = activated factor XII, C1-Inh = C1-inhibitor, HMWK = high molecular weight kininogen, cHMWK = cleaved HMWK, KAL = plasma kallikrein

Method Figure 2 – STAR-0215 PK in Healthy Adult Human Subjects in a Phase 1a Trial



Data from 300 mg and 600 mg dose levels were used in the PK model, as those are likely the efficacious dose range
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Non-Compartmental PK Parameters of STAR-0215 From a Phase 1a Trial in Healthy Human Subjects

Dose Group	$t_{1/2}$ (Days)	T_{max} (Days)	C_{max} (µg/mL)	AUC_{0-84} (day*µg/mL)	C_{last} (µg/mL)
100 mg (n=7)					
Mean	65	13	6.4	354	3.0
SD	25	10	2.1	136	1.3
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

AUC_{0-84} = area under the concentration versus time curve from the start of administration to 84 days post-dose; C_{last} = last measurable concentration; C_{max} = maximum drug concentration; SD = standard deviation; t½ = terminal half-life; T_{max} = time to maximum drug concentration.
Note: Treatment was a single subcutaneous dose of STAR-0215 administered on Day 1 as follows: 100 mg, 300 mg, 600 mg, or placebo.
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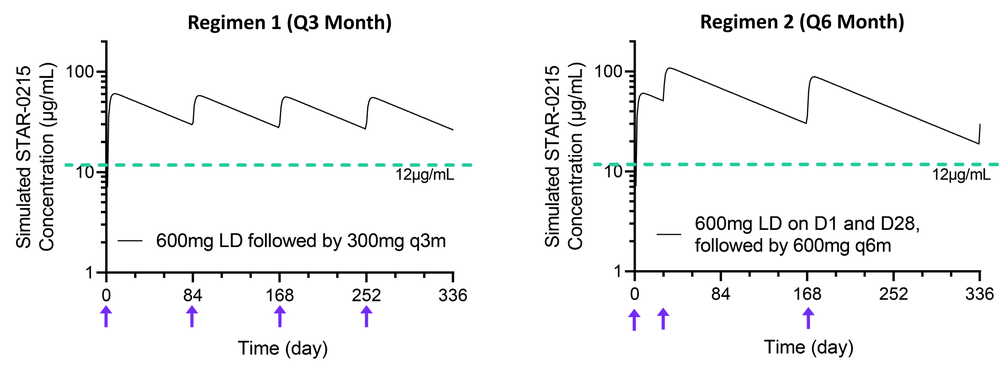
Dose Regimens Simulated

Regimen 1 (Q3 Month)- 600 mg SC loading dose followed by 300 mg SC maintenance doses every 3 months

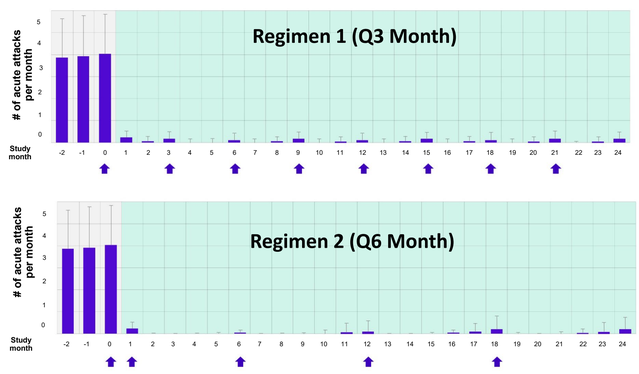
Regimen 2 (Q6 Month)- 600 mg SC loading doses on days 1 and 28, followed by 600 mg SC maintenance dose every 6 months

Results – Pharmacometric Model Shows STAR-0215 Could Sustain Exposure Above Target Threshold with Both Q3 and Q6 Month Regimens



Concentration threshold, 12ug/mL (80nM), associated with clinical benefit [1, 2, 3]
1. Kaufman 1991 June 15, Blood 77(12):2660-2667
2. Wang el al. Clin Transl Sci. 2020 Nov, 13(6):1208-1216
3. Ecallantide EMA Assessment Report 2011 June 23. EMA/CHMP/476618/2011

Results - QSP Model Predicts STAR-0215 May Produce Robust and Long-Lasting HAE Attack Suppression



- A population simulation using virtual patients (n=500 per cohort)
- Model estimated a ≥90% reduction in monthly HAE attack rate starting at the 1st month of treatment, for both Q3 and Q6 month dose regimens
- Model estimated 75% and 86% of treated HAE patients to be attack-free during the first 6 months of treatment for the Q3 and Q6 month regimens, respectively.

Results
QSP model showed that effective HAE attack prevention could be achieved with the following dosing regimens:
- A 600mg SC loading dose, followed by 300mg SC maintenance dose every 3 months
- 600mg SC loading doses on Days 1 and 28, followed by SC maintenance dose of 600mg every 6 months

Both pharmacometric and QSP models showed subcutaneously administered STAR-0215 could potentially sustain required PK threshold and provide prolonged duration (up to 6 months) of robust HAE attack suppression

Conclusions
STAR-0215 is a novel, potent and selective long-acting monoclonal antibody plasma kallikrein inhibitor for the potential treatment of HAE. Results from both pharmacometrics and QSP models support STAR-0215 administration once every 3 or 6 months for long-acting robust suppression of HAE attacks.

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