Modeling and Simulation Predicts Robust HAE Attack Suppression with Every 3 Month Dosing of STAR-0215

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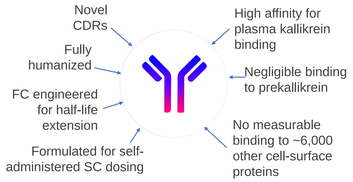
BACKGROUND: Inhibition of plasma kallikrein is a validated mechanism for prevention of hereditary angioedema (HAE) attacks. STAR-0215 is an investigational, long-acting monoclonal antibody inhibitor of plasma kallikrein. We sought to generate a mechanistic quantitative systems pharmacology (QSP) model to explore the potential for reduction of HAE attacks with different dosing regimens of STAR-0215.

OBJECTIVE: Evaluate the potential for long-acting HAE attack suppression by STAR-0215 dosed every three months

STAR-0215 – Potential for Best-in-Class Profile in HAE

Preclinical Profile of STAR-0215



Encouraging preclinical results
Demonstrated high potency for plasma kallikrein and long plasma half-life

Differentiated profile
Potential benefits include long duration without breakthrough attacks and infrequent SC dosing - once every 3 months or longer

Trusted modality
To provide patients with improved quality of life

Astria wholly owns an international patent application directed to STAR-0215. If nationalized in the U.S. and granted, the patent would expire in 2042, excluding any potential patent term extension[1]

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 pharmacokinetic (PK) parameters of STAR-0215 were derived from cynomolgus monkey PK studies and scaled to estimate human PK parameters.

Variability in PK parameters was simulated using a standard deviation of 50% and a Poisson distribution was applied to randomly determine the timing of trigger events with an average attack frequency of 3 per month.

VIRTUAL HAE PATIENT COHORT

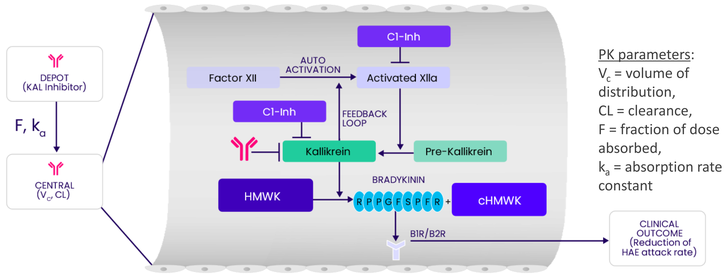
Variability in acute attack triggers

- Acute attack events was sampled based on an input of an average attack frequency from a patient population (e.g., 3 time/mo), and a Poisson distribution was applied to randomly determine the timing of trigger event
- Attack was triggered by an increase in FXII auto-activation. A normal distribution was assumed for the increase of auto-activation, and it was sampled so that bradykinin levels during attacks were in line with literature range. The duration of increased auto-activation was set to be 12 hours based on duration of attack development
- Attack event occurred if bradykinin level was above threshold level (20 pM)

Variability in PK

- A S.D. at 50% of calibrated value for each parameter was assumed for the PK samplings
- In HAE cohorts (n=100), a C1-Inhibitor at 30% of the Healthy control levels was assumed

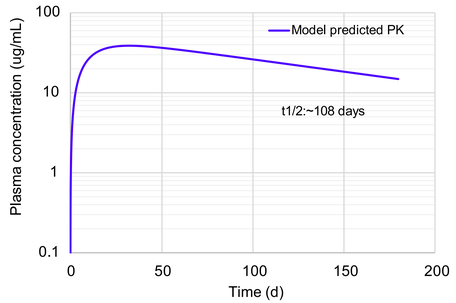
Method Figure 1 – Simplified Model Diagram



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, Kallikrein = plasma kallikrein

Method Figure 2 – Model Predicted PK

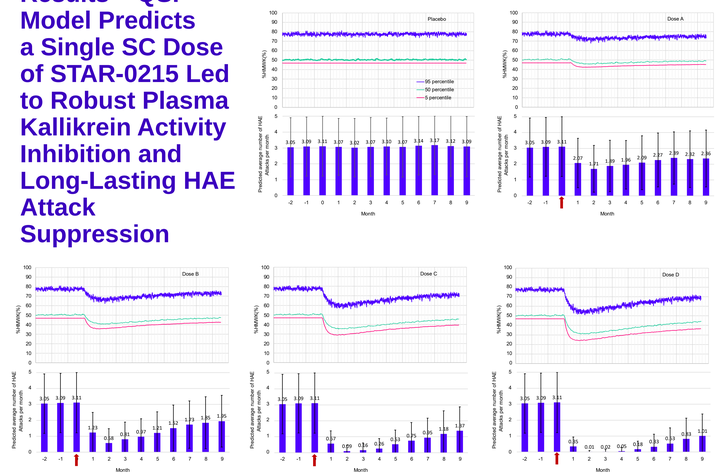


Parameter	Unit	Value
V_F	L	4.13
CL_F	L/h	0.00122
ka	1/h	0.00348

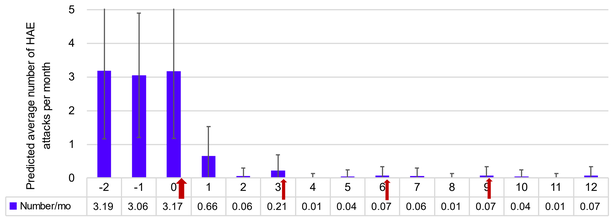
Results

A long circulating half-life of STAR-0215 in humans (~108 days) was predicted from empirically obtained PK parameters in cynomolgus monkeys. The QSP model predicted the inhibition of plasma kallikrein activity and the long-term robust HAE attack suppression following a single subcutaneous administration of STAR-0215 at a wide dose range. The QSP model simulations also showed subcutaneously administered STAR-0215 could provide a potential prolonged HAE attack suppression with a once every 3 months dose regimen.

Results – QSP Model Predicts a Single SC Dose of STAR-0215 Led to Robust Plasma Kallikrein Activity Inhibition and Long-Lasting HAE Attack Suppression



Results – Long-Term HAE attack suppression can be achieved with a Q3 month regimen



	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
Number/mo	3.19	3.06	3.17	0.66	0.06	0.21	0.01	0.04	0.07	0.06	0.01	0.07	0.04	0.01	0.07

SUMMARY: STAR-0215 is an investigational, novel, potent and selective long-acting monoclonal antibody plasma kallikrein inhibitor for the potential treatment of HAE. Results from the QSP model support STAR-0215 dosing once every 3 months or longer, including the potential for a loading dose and maintenance dose, for robust suppression of HAE attacks.

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