# Development of STAR-0215

PKPD Model of STAR-0215, an Engineered IgG1 Monoclonal Antibody Targeting Plasma Kallikrein for the Prevention of HAE

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# Agenda

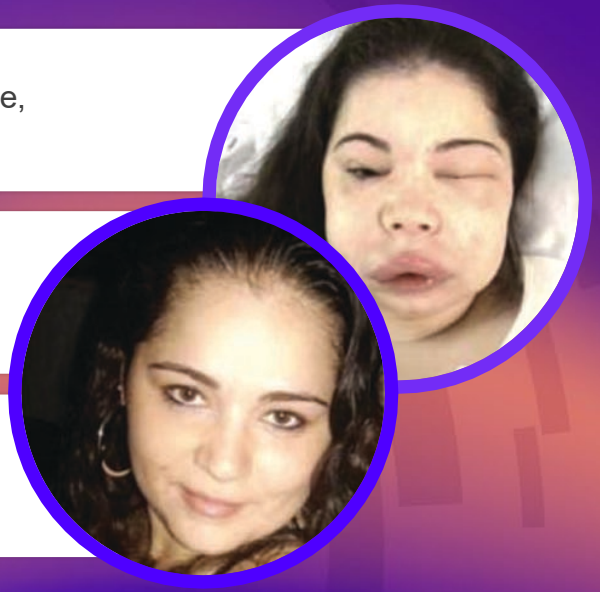
- Hereditary Angioedema (HAE) and the pathogenetic pathway
- Current Therapies
- STAR-0215
- Pharmacokinetic and Pharmacodynamic Modeling and Simulations
- Discussion

# Hereditary Angioedema: A Rare, Disfiguring, and Potentially Life-Threatening Disease

Rare genetic disorder charactered by severe, unpredictable, sometimes **life-threatening** swelling[1]

Affects **<8,000 in the U.S. and <15,000 in the EU,**[2] average age of onset is 11 years old[3]

Standard of care has evolved to both **on-demand** and **preventative treatments**




1. Zuraw BL. N Engl J Med. 2008;359:1027-36.
2. Lumry WR. Front Med. 2018: doi:10.3389/fmed.2018.00022.
3. Bork K, et al. Am J Med. 2006;119:267-274.
4. Images obtained by haeimages.com

# Biologic Mechanism and HAE Disease Pathways

**Hereditary Angioedema (HAE)** is a rare autosomal dominant genetic disease characterized by recurrent, unpredictable, debilitating and potentially life-threatening edema and pain in the skin, abdomen, and airway.

Most HAE cases (Type I and Type II) are caused by mutations in the *SERPING1* gene that lead to a reduction in the amount or function of C1-esterase inhibitor protein encoded by this gene.

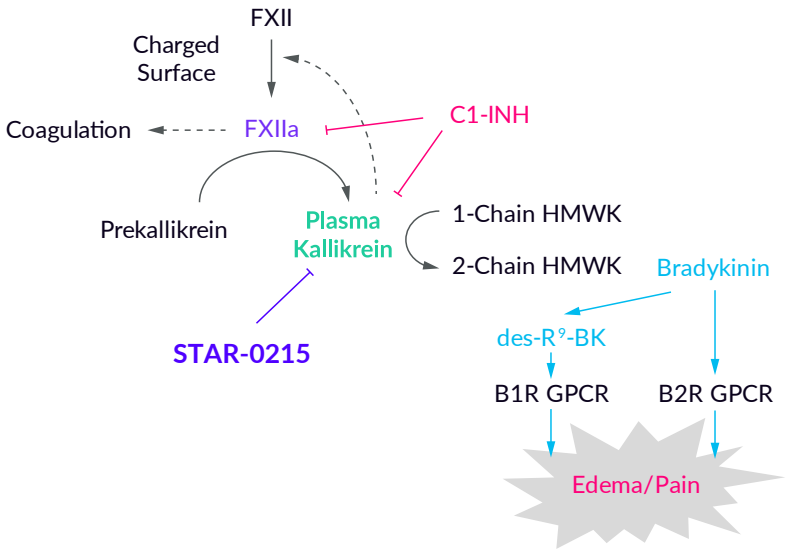



Figure adapted from Kenniston *et al.* 2014

# Approved Preventative HAE Treatments in the U.S.

## Need for Effective Preventative Therapy with Lower Treatment Burden

| Product | Mechanism of Action | Administration | Mean Attack Reduction[1] | % of Attack- Free Patients |
|---|---|---|---|---|
| **CINRYZE** | Plasma derived C1-INH | 2x/week  | 52% | 40% (16 weeks)[2] |
| **HAEGARDA** | Plasma derived C1-INH | 2x/week  | 88% | 18% (12 weeks)[3] |
| **TAKHZYRO** *(lanadelumab)* | Plasma kallikrein inhibitor | 1-2x/month  | 73-87% | 31-44% (26 weeks)[4] |
| **ORLADEYO** *(berotralstat)* | Plasma kallikrein inhibitor | 1x/day  | 30-44% | 2-8% (24 weeks)[5] |

- Plasma kallikrein inhibition is the market leading validated mechanism of action
  - Established PK-PD-efficacy relationship for inhibiting plasma kallikrein and preventing HAE attacks
- Established regulatory and clinical path for HAE
- Opportunity for early clinical PoC with plasma kallikrein inhibition

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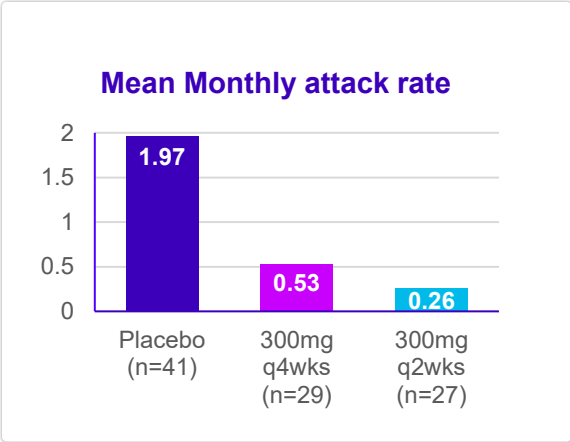
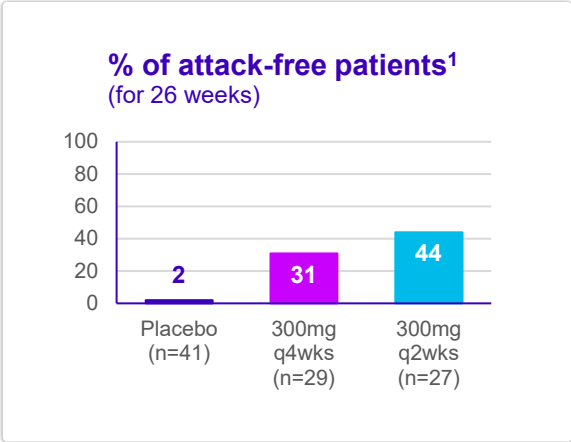
1. Efficacy quoted as reduction in mean attack rate vs placebo; data from respective products' Prescribing Information.
2. CINRYZE Prescribing Information, 2021.
3. HAEGARDA Prescribing Information, 2020.
4. TAKHZYRO Prescribing Information, 2018.
5. Center for Drug Evaluation and Research. NDA/BLA Multidisciplinary Review and Evaluation NDA 214094. Washington DC: CDER (US); 2020.
6. Cortellis, HealthAdvances, EvaluatePharma, and Company research and analysis

# Opportunity to Improve HAE Treatment and Reduce Burden on Patients

**TAKHZYRO® (lanadelumab-flyo)**
is a plasma kallikrein mAb approved for prevention of HAE attacks[1]




**TAKHZYRO is the current global market leader[1]**

**56-69% of patients experienced attacks on TAKHZYRO[2]**

**Published unmet need for improved HAE treatments[3, 4]**

- Despite preventative treatments, patients continue to have attacks and high rates of anxiety and depression

Indicated for dosing every 2 weeks; every 4 weeks may be considered in some patients


1. Takeda FY2021 Q3 Earnings Announcement, February 2022
2. TAKHZYRO Prescribing Information, 2018.
3. Banerji A, et al. Ann Allergy Asthma Immunol. 2020; 124: 600-607. doi: 10.1016/j.anai.2020.02.018.
4. Riedl MA., et al. Ann Allergy Asthma Immunol. 2021; 126: 264-272. doi: 10.1016/j.anai.2020.10.009.

# STAR-0215

## Opportunity for Most Patient-Friendly Preventative Treatment Option

### STAR-0215

- Potential differentiated best-in-class new preventative therapy for HAE
- Monoclonal antibody inhibitor of plasma kallikrein
- Potential for dosing once every 3 months or longer

**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 dosing

**Trusted modality**
To provide patients with improved quality of life

*Astria wholly owns a patent application directed to STAR-0215. If granted, the patent would expire in 2042, excluding any potential patent term extension[1]*

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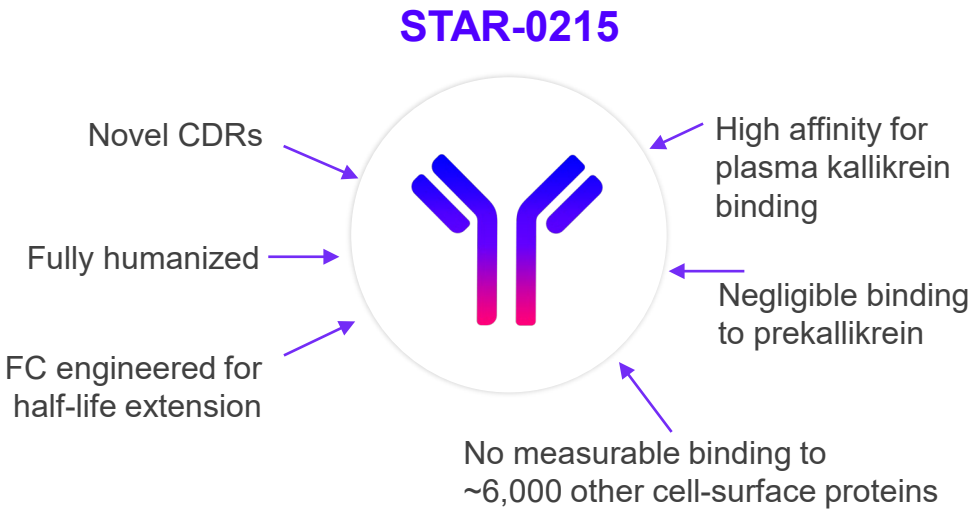
1. This is an international (PCT) patent application that needs to be nationalized and then granted in such nationalized countries, including the US, covered by PCT to have this patent term.

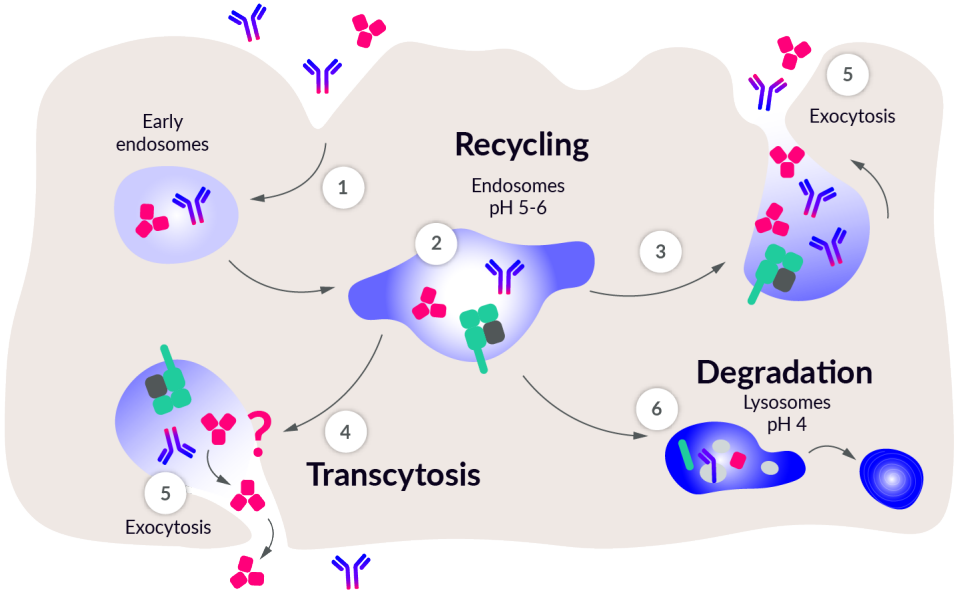
# STAR-0215
# Potential for Best-in-Class Profile in HAE

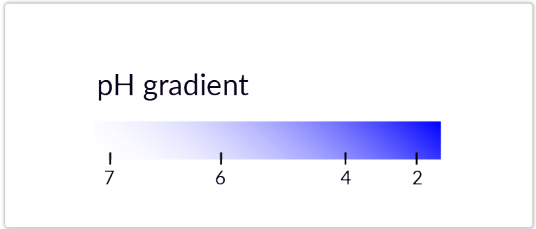



**STAR-0215 Profile:**

- **Route:** SC
- **Frequency:** once every 3 months or longer

# STAR-0215 Leverages the Mechanism of pH-Dependent FcRn Recycling to Extend Circulating Half-Life



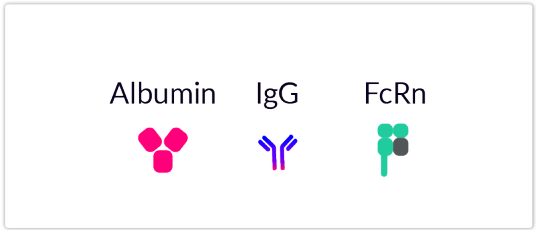
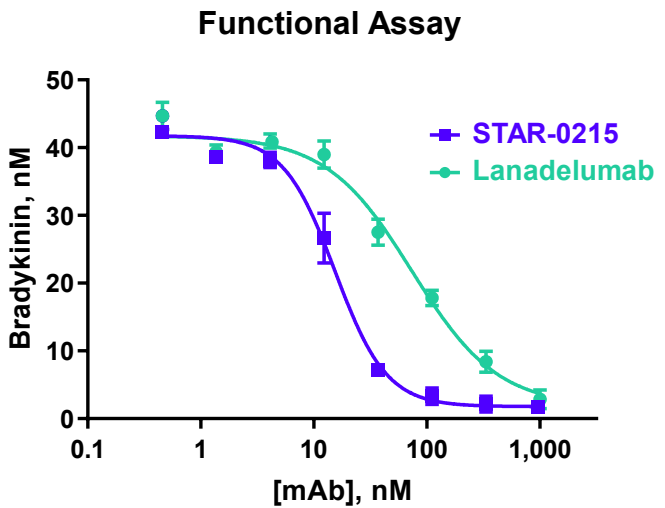




Figure adapted from Vivier *et al.* 2018

# STAR-0215
# Shows High Potency Inhibition of Plasma Kallikrein

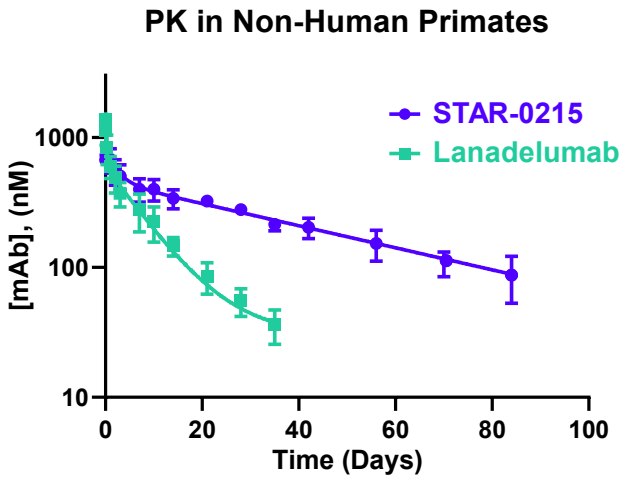
- **STAR-0215** binding affinity for plasma kallikrein is ~10-fold greater than lanadelumab
- **STAR-0215** binds a different site on plasma kallikrein than lanadelumab
- **STAR-0215** is ~10-fold more potent at inhibiting enzymatic activity by 90% than lanadelumab
  - ~90% inhibition of plasma kallikrein is estimated to be required to optimally reduce HAE attack rate and maximize attack free duration




STAR-0215 was more potent than lanadelumab in inhibiting bradykinin production in an *in vitro* assay

IC90 determined by bradykinin ELISA to detect cleavage of high molecular weight kininogen (600 nM) by plasma kallikrein (30 nM)
Plasma kallikrein levels 30-110nM estimated in HAE plasma (Kenniston et al JBC 2014)
Data presented at the 2021 ACAAI Scientific Meeting

# STAR-0215 Has Shown Substantially Prolonged Plasma Half-Life Compared to Lanadelumab in Non-Human Primates



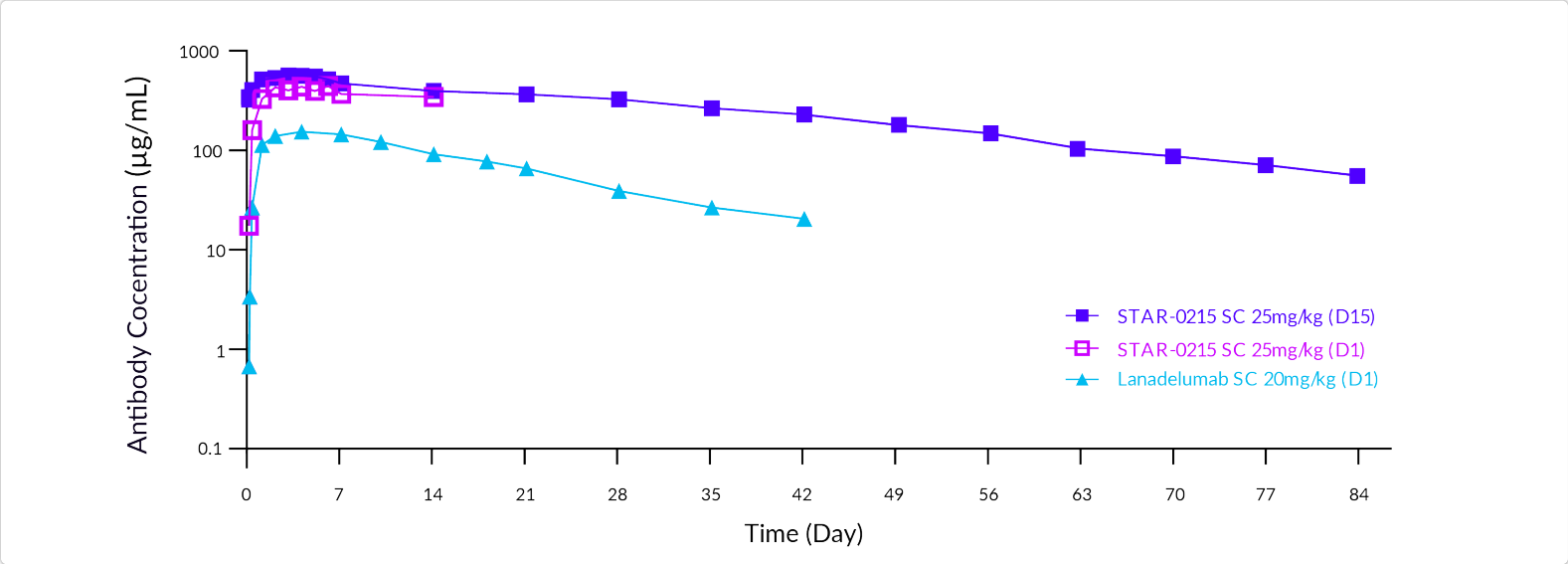

**STAR-0215 engineered with YTE half-life extension technology**

- Enhanced FcRn binding translated to a more than three-fold increase in plasma half-life with STAR-0215 compared to an antibody without YTE modifications
- Half-life of mAbs with similar half-life extension technology
  - Non-human primates: 20 – 40 days
  - Humans: 70 – 120 days

| | Lanadelumab | STAR-0215 |
|---|---|---|
| Mean non-human primate half-life in days (SD) | 10.5 (1.6) | 33.6 (8.3) |

Data from concurrent but independent experiments in cynomolgus monkeys dosed at 5 mg/kg, iv
Lanadelumab data are representative of 3 independent experiments that all showed $t_{1/2}$ ~10 days
Data presented at the 2021 ACAAI Scientific Meeting

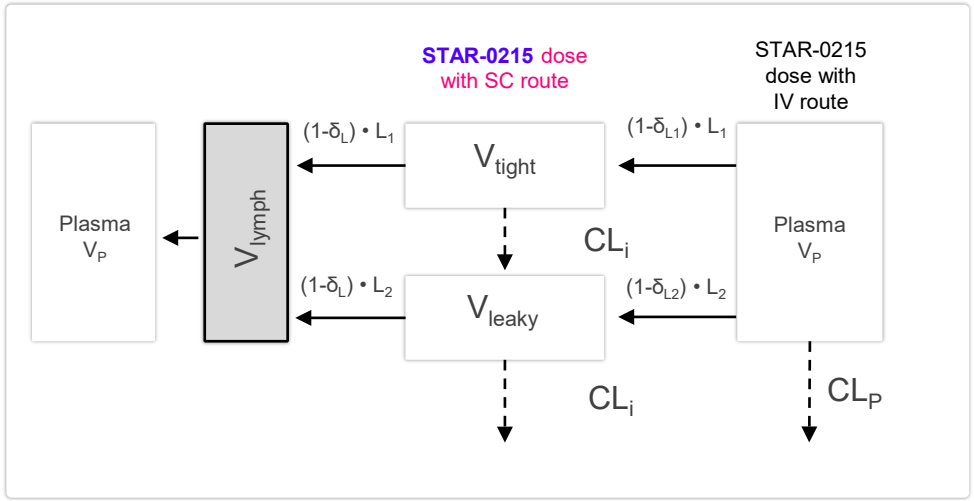
# STAR-0215 Has Shown Substantially Greater SC PK Exposure Compared to Lanadelumab in Non-Human Primates



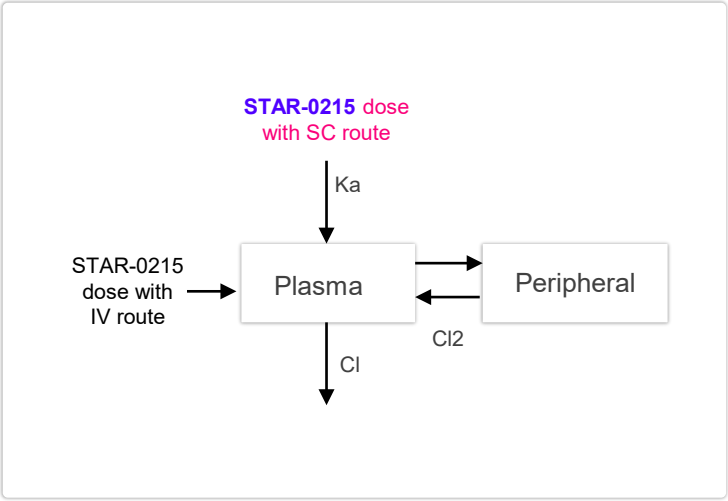

- STAR-0215 SC PK profile is similar to IV, with a prolonged SC half-life of ~30 days in cynomolgus monkeys
- STAR-0215 shows a greater SC PK exposure (~3x) when compared to lanadelumab (dose-normalized)

# Two PK Modeling Approaches Were Assessed to Predict STAR-0215 PK in Humans

## Physiologically-based PK model (PBPK)




## Empirical Model – 2 compartments

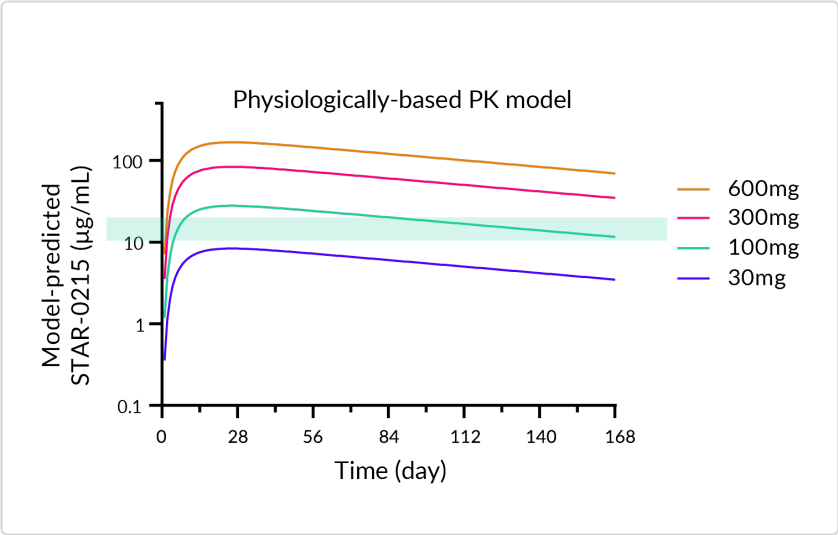


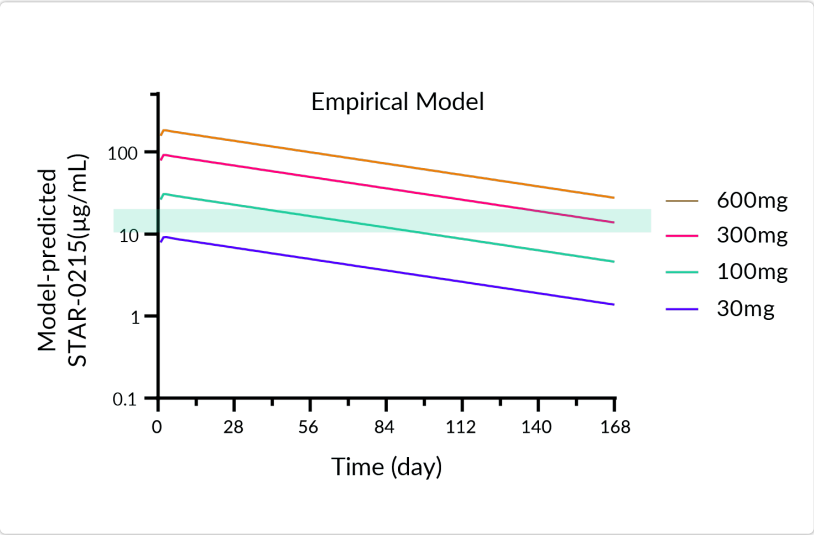

**Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies**



Cao, et al. *J Pharmacokinet Pharmacodyn*. 2013; 40(5). doi: 10.1007/s10928-013-9332-2

# Both PBPK and Empirical Models Suggest Target Concentration of STAR-0215 Can Be Achieved With Once Every 3 Month Dosing Regimen

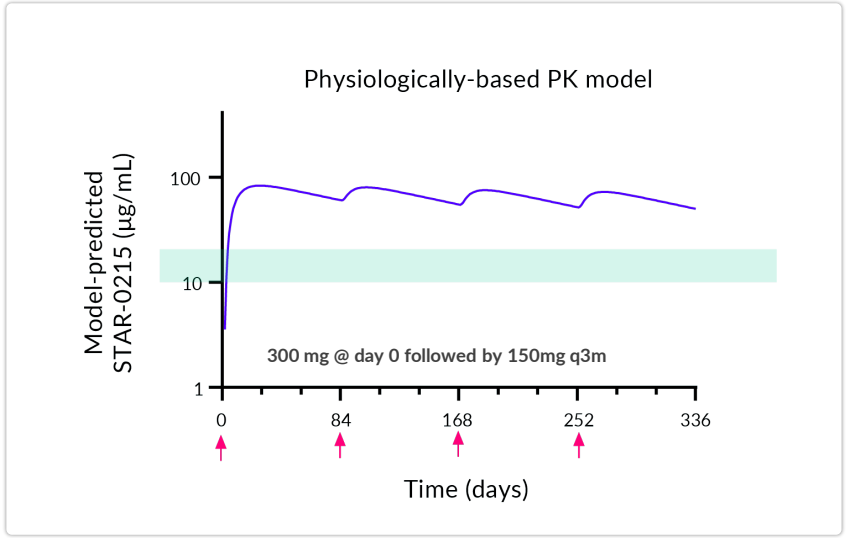


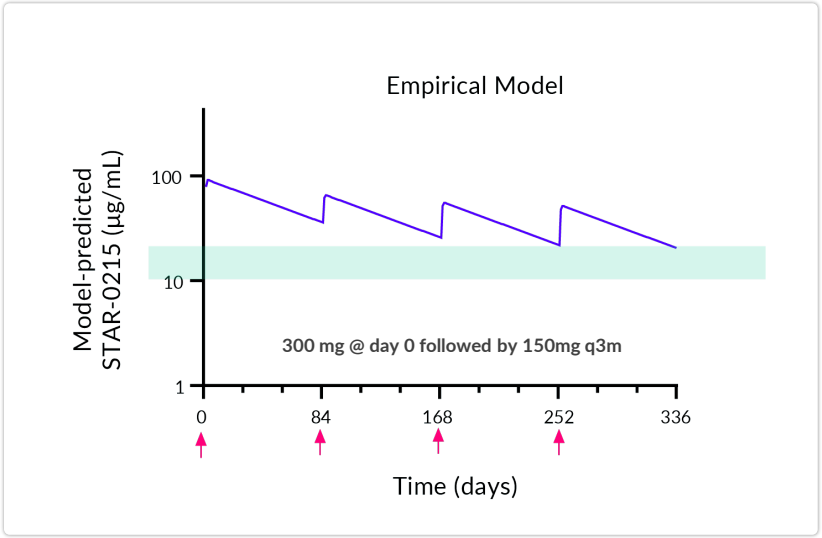




Target concentration (shown in green) expected to be required to completely inhibit plasma kallikrein is defined as the range of plasma kallikrein levels in patients during HAE attacks

# Both PBPK and Empirical Models Suggest the Target Level of STAR-0215 Can Be Achieved/Maintained

## With a Loading Dose of 300mg Followed by the Maintenance Dose of 150mg Every 3 Months




Target concentration (shown in green) expected to be required to completely inhibit plasma kallikrein is defined as the range of plasma kallikrein levels in patients during HAE attacks

# Conclusions

**STAR-0215** is a potent plasma kallikrein inhibitor with a prolonged plasma half-life

PK modeling supports that **STAR-0215** can effectively inhibit plasma kallikrein and prevent HAE attacks with:

- Dosing once every 3 months or longer
- SC dosing volumes that are appropriate for a self-injectable device

# Planned STAR-0215 Phase 1a Trial Design

## Anticipate Initial Proof of Concept Results YE 2022

### DESIGN

- Normal Healthy Volunteers
- Planning for several single ascending dose cohorts
- Randomized, double-blind, placebo-controlled
- Observation period through multiple half-lives

### EXPECTED RESULTS

- Safety and tolerability
- Pharmacokinetics- antibody half-life
- Pharmacodynamics- inhibition of plasma kallikrein

**Goals for Initial Proof of Concept Results:**

- Demonstrate safety and tolerability
- Establish prolonged half-life
- Demonstrate inhibition of plasma kallikrein activity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