



# STAR-0215 Is a Long-Acting Monoclonal Antibody Plasma Kallikrein Inhibitor for the Potential Treatment of HAE

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**Background:** Plasma kallikrein is a validated target for prevention of HAE attacks. High potency and long duration of action are key drivers of prophylactic efficacy of plasma kallikrein inhibitors. We sought to generate a monoclonal antibody (mAb) plasma kallikrein inhibitor with high potency and potential for long duration of action.

## The Discovery and Design of STAR-0215

**GOAL: Best-in-class plasma kallikrein inhibitor offering the most patient friendly prophylactic treatment for the prevention of HAE attacks**

- High affinity and selectivity for plasma kallikrein versus prekallikrein
- Reduced immunogenicity and CMC liabilities
- Extended plasma half-life

Note: STAR-0215 was previously known as QLS-215



## STAR-0215 Binds Plasma Kallikrein More Potently and in a Different Manner than Lanadelumab

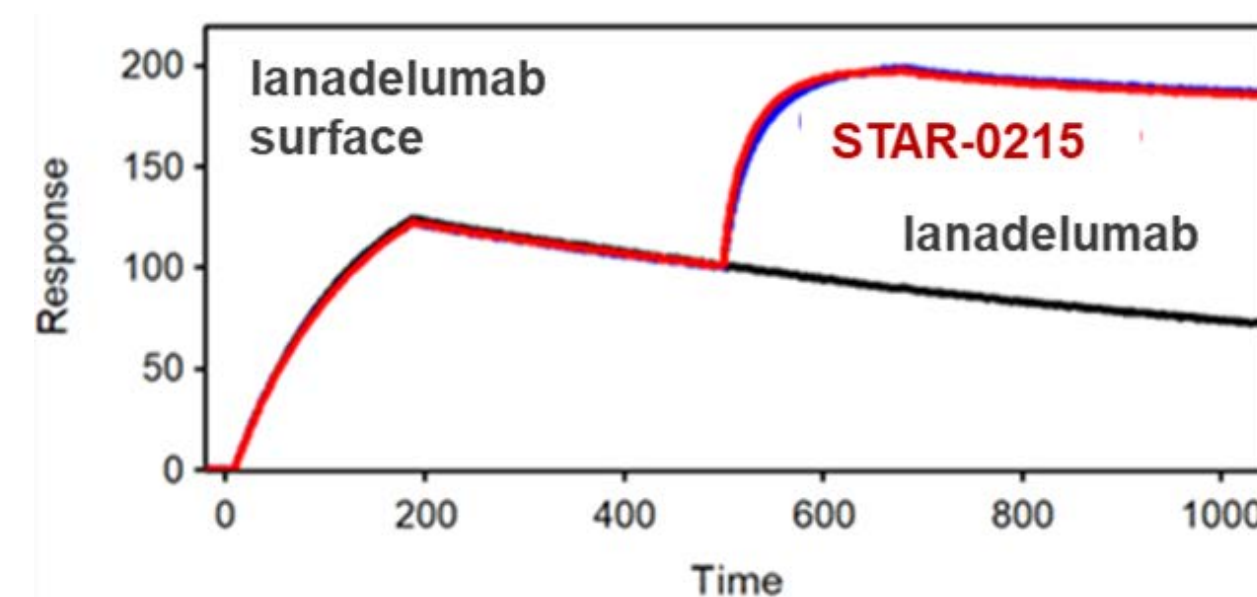
STAR-0215 Potently and Selectively Binds Human Plasma Kallikrein

	$K_a$ (1/Ms)	$K_d$ (1/s)	$K_D$ (nM)
STAR-0215	$6.8 \times 10^4$	$7.3 \times 10^{-5}$	1.1
Lanadelumab	$3.1 \times 10^4$	$5.6 \times 10^{-4}$	18

SPR binding at pH 7.4, 37°C

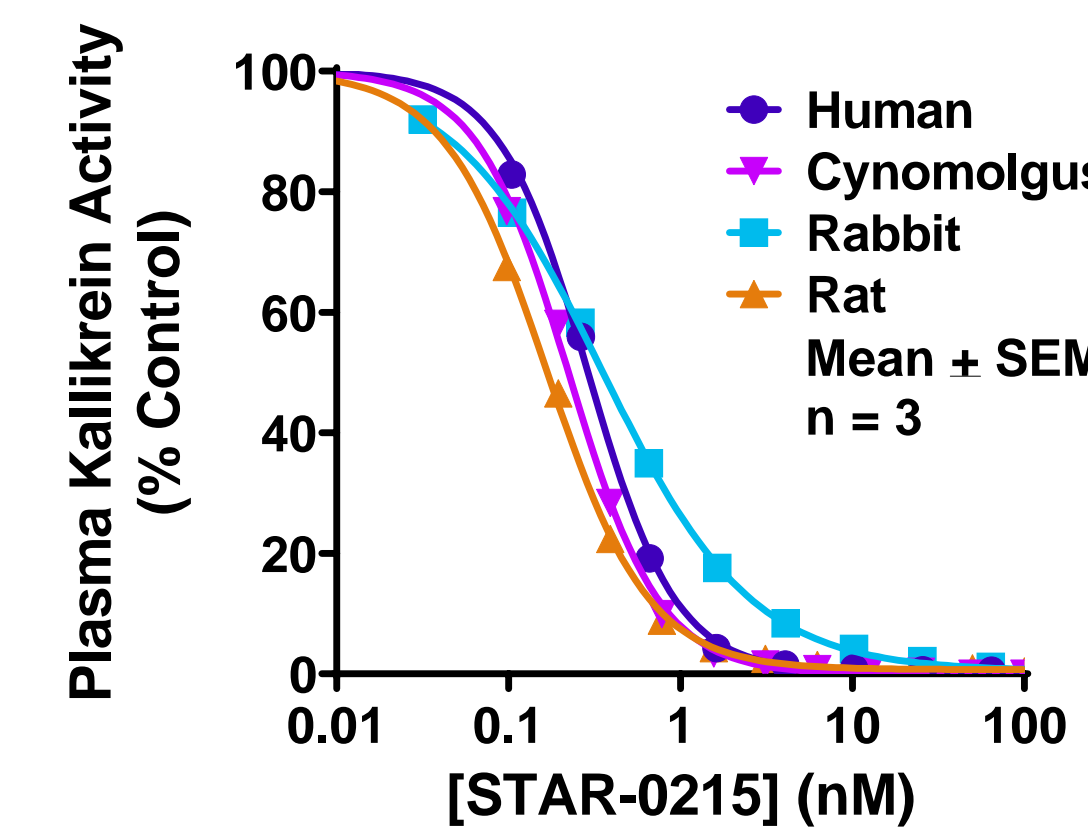
Lanadelumab and STAR-0215 have >1000-fold higher affinity for plasma kallikrein than prekallikrein

STAR-0215 Does Not Compete With Lanadelumab



Lanadelumab is an active site binder, suggesting that STAR-0215 does not bind to the active site

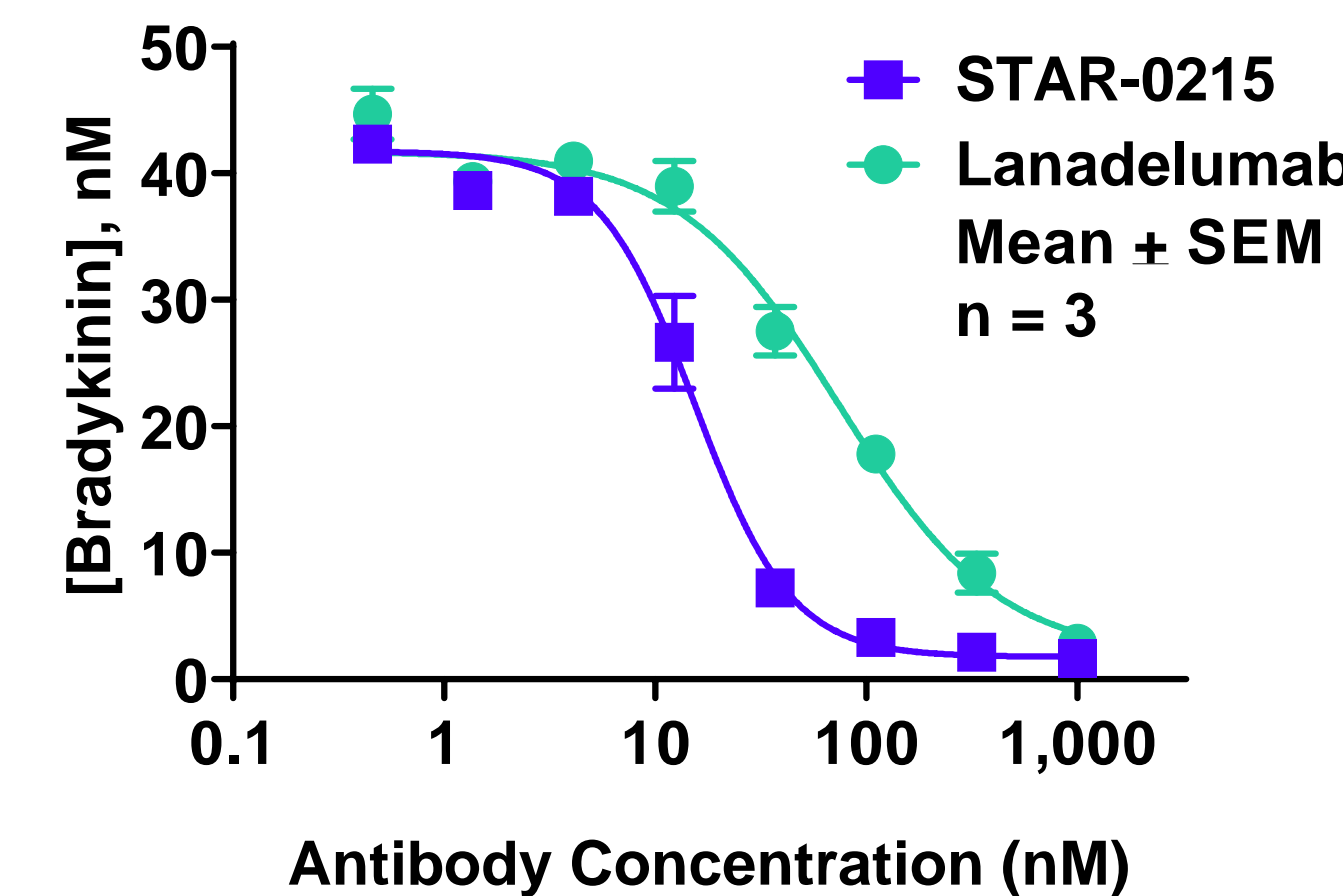
## STAR-0215 Potently Inhibits Plasma Kallikrein



	Human	Monkey	Rabbit	Rat
IC <sub>50</sub> (pM)	290	223	352	167

- Plasma kallikrein activity measured using the fluorogenic reporter substrate, Pro-Phe-Arg-AMC (PFR-AMC) at 37°C
- Plasma kallikrein: 1 nM
- PFR-AMC: 10 μM

## STAR-0215 Is More Potent than Lanadelumab in Inhibiting Bradykinin Production In a Physiologically Relevant Assay



	STAR-0215	Lanadelumab
IC <sub>90</sub> (nM)	30	300

- Bradykinin release from high molecular weight kininogen (600 nM) by plasma kallikrein (30 nM)
- IC<sub>90</sub> is estimated to be the required level for prevention of HAE attacks
- Lanadelumab potency consistent with plasma levels required for clinical efficacy

## Half-Life Extension by Fc YTE Modification

hFcRn Binding at pH 6.0

	$K_a$ (1/Ms)	$K_d$ (1/s)	$K_D$ (M)
STAR-0213	$2.70 \times 10^5$	$2.29 \times 10^{-1}$	$8.48 \times 10^{-7}$
STAR-0215	$1.84 \times 10^5$	$2.77 \times 10^{-2}$	$1.50 \times 10^{-7}$

No binding at pH 7.4

STAR-0215 (Fc YTE modification) has increased pH-dependent hFcRn binding due to a reduced off rate compared to parent mAb, STAR-0213

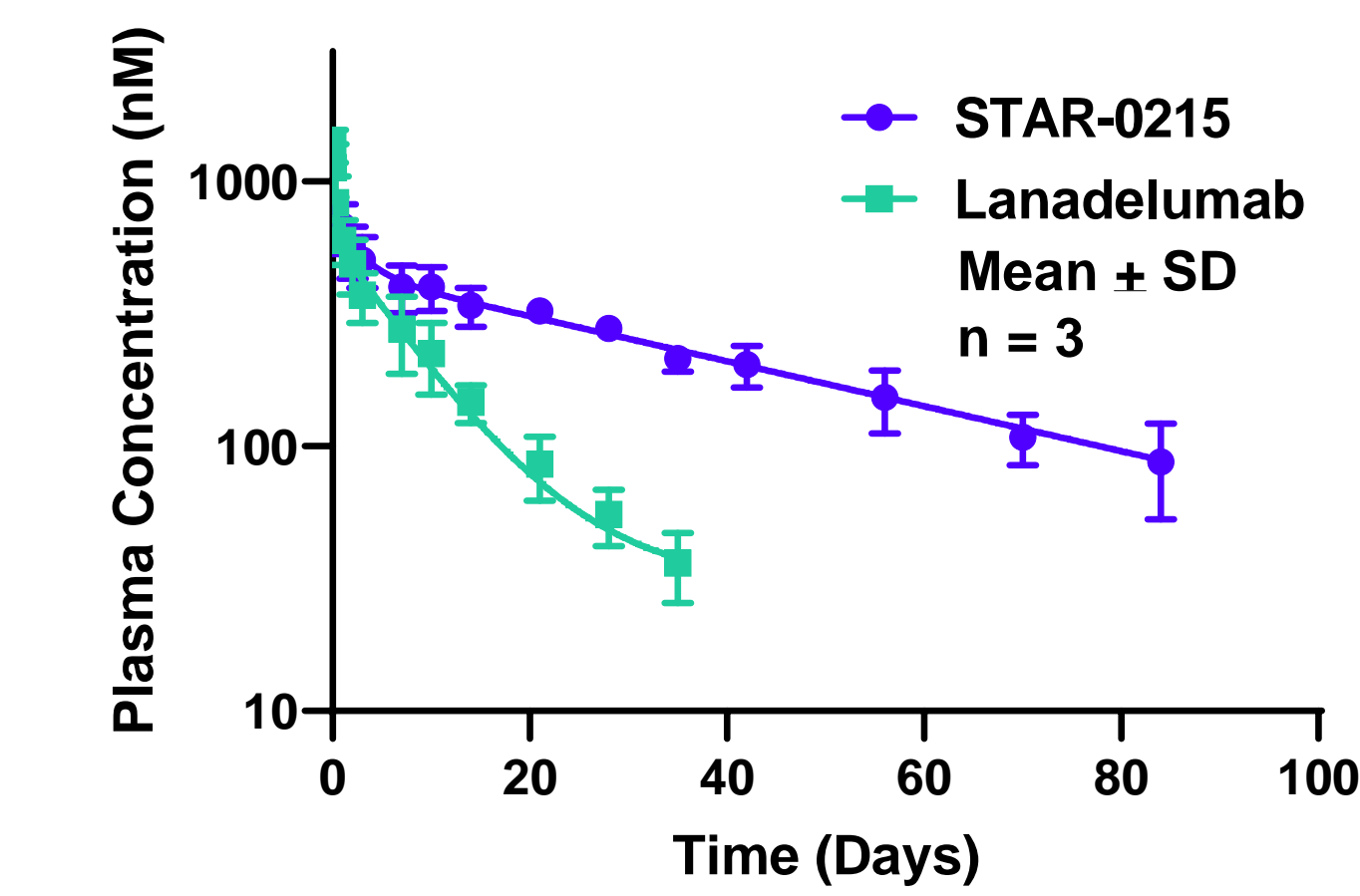
PK Parameters in Cynomolgus Monkeys

	V <sub>ss</sub> (mL/kg)	Cl (mL/day/kg)	T <sub>1/2</sub> (days)
STAR-0213	72	4.85	10.9
STAR-0215	67	1.44	33.6

Dose: 5 mg/kg, iv

The increased pH-dependent FcRn binding translates into slower clearance and extended half-life in cynomolgus monkeys

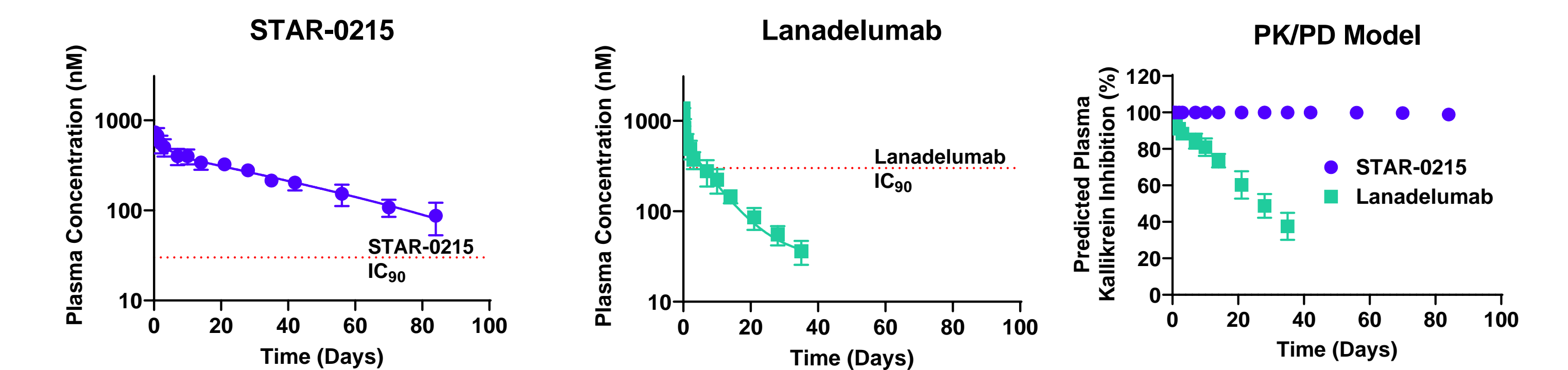
## STAR-0215 Has a Prolonged Plasma Half-Life Compared to Lanadelumab in Cynomolgus Monkeys



	STAR-0215	Lanadelumab
Plasma T <sub>1/2</sub> (days)	33.6 ± 8.3	10.5 ± 1.6

Dose: 5 mg/kg, iv  
Mean ± SD

## The Human *in vitro* Potency and Cynomolgus Pharmacokinetic Data Predict a Substantially Longer Duration of Action for STAR-0215 than Lanadelumab



Model based on plasma concentrations from cynomolgus monkey pharmacokinetic studies and human plasma kallikrein inhibition determined in *in vitro* functional assay

**Conclusion:** STAR-0215 is a novel, potent and long-acting monoclonal antibody plasma kallikrein inhibitor with potential for the treatment of HAE with a dosing frequency of 3 months or longer