STAR-0215 Is a Long-Acting Monoclonal Antibody Plasma Kallikrein Inhibitor in Development for 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

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

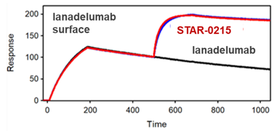
Human Plasma Kallikrein Binding

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

SPR binding at pH 7.4, 37°C

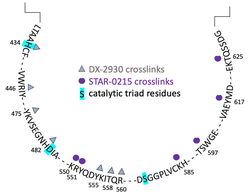
Lanadelumab and STAR-0215 have >1000-fold higher affinity for plasma kallikrein than prekallikrein

STAR-0215 does not compete with lanadelumab for binding to plasma kallikrein



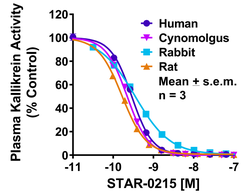
Lanadelumab is an active site binder, suggesting that STAR-0215 does not bind to the active site

STAR-0215 binds a different region of human plasma kallikrein to specifically inhibit enzyme activity



- Each antibody was complexed separately with human plasma kallikrein and crosslinked with DSS
- Shifts in crosslinked peptides by mass spectrometry (XLMS) were compared to non-crosslinked peptides
- Data shows STAR-0215 contacts a different region of the plasma kallikrein protein compared to lanadelumab (DX-2930)

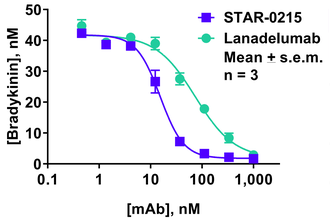
STAR-0215 Potently Inhibits Plasma Kallikrein



	Human	Monkey	Rabbit	Rat
IC_{50} (pM)	290	223	352	167

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

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



	STAR-0215	Lanadelumab
IC_{90} (nM)	30	300

- Bradykinin release from high molecular weight kininogen (600 nM) by plasma kallikrein (30 nM)
- IC_{90} is estimated to be 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 x 10^5	2.29 x 10^{-1}	8.48 x 10^{-7}
STAR-0215	1.84 x 10^5	2.77 x 10^{-2}	1.50 x 10^{-7}

No binding at pH 7.4

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

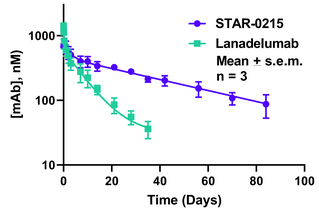
PK Parameters in Cynomolgus Monkeys

	Vss (mL/kg)	Cl (mL/day/kg)	$T_{1/2}$ (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

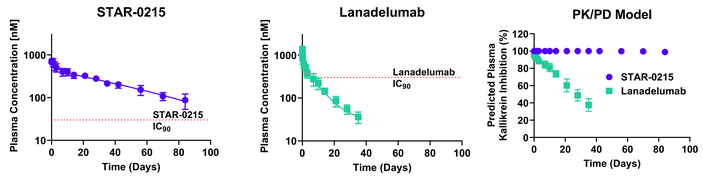
STAR-0215 Has a Prolonged Plasma Half-Life Compared to Lanadelumab in Cynomolgus Monkeys



	STAR-0215	Lanadelumab
Plasma $T_{1/2}$ (days)	33.6 ± 8.3	10.5 ± 1.6

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 in development for the treatment of HAE with potential for dosing once every 3 months or longer

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