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 Potently Binds Plasma Kallikrein Active Site Over a Novel Region

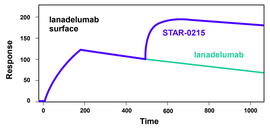
Human Plasma Kallikrein Binding

	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, 37ºC

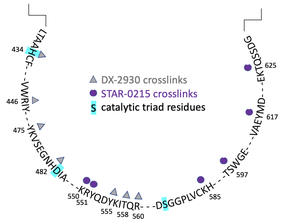
Lanadelumab and STAR-0215 have >1000-fold higher affinity for plasma kallikrein than prekallikrein

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



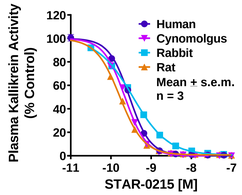
Lanadelumab and STAR-0215 both bind to different parts of the active site to inhibit plasma kallikrein function.

STAR-0215 binds a different region of human plasma kallikrein to 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 show STAR-0215 contacts a different region of the plasma kallikrein protein compared to lanadelumab (DX-2930)

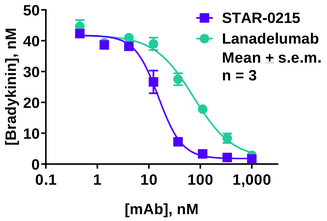
STAR-0215 Potently Inhibits Plasma Kallikrein



	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

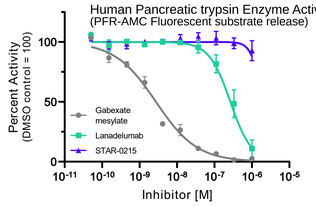
STAR-0215 Inhibits Bradykinin Production in a Physiologically Relevant Assay



	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

STAR-0215 Has Superior Off-Target Profile Against Enzymes Closely Related to Plasma Kallikrein

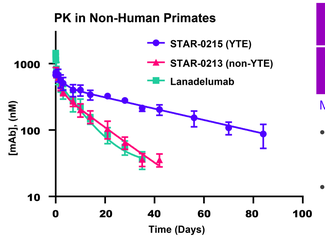


IC_{50} [M]	Trypsin	Hepsin	Thrombin
Gabexate mesylate (positive control)	2.23 x 10^{-9}	5.10 x 10^{-8}	8.37 x 10^{-7}
Lanadelumab	3.09 x 10^{-7}	1.51 x 10^{-6}	1.71 x 10^{-6}
STAR-0215	n.d.	n.d.	n.d.

n.d., IC_{50} value could not be determined (>10^{-6} M)

- STAR-0215 was also fully inactive against 16 additional proteases including other Kallikreins, Granzyme B, Cathepsin G, and complement and coagulation pathway proteases

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

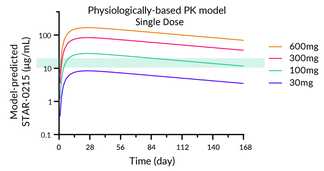


	STAR-0215 (Fc YTE)	Lanadelumab	STAR-0213 (non-YTE)
Plasma $T_{1/2}$ (days)	33.6 ± 8.3	10.5 ± 1.6	10.9 ± 0.4

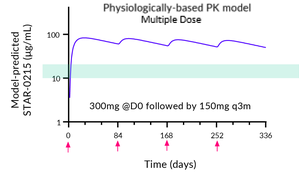
Mean ± SD

- STAR-0215 (Fc YTE modification) has increased pH-dependent hFcRn binding compared to unmodified parent mAb, STAR-0213 (without YTE modification)
- Increased pH-dependent FcRn binding translates into slower clearance and extended half-life in cynomolgus monkeys

Physiologically-Based PK Model Supports a Dosing Frequency of Every 3 Months or Longer



Model suggests the minimum target concentration of STAR-0215 required for long-term inhibition of plasma kallikrein can be achieved with a single dose above 30mg



Model suggests target level of STAR-0215 can be achieved with a loading dose of 300mg followed by a 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

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. A Phase 1a trial of STAR-0215 is expected to initiate this year.

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