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Design and Characterization of KRSA-028, A Novel Bispecific Antibody Targeting Amyloid Beta and Transferrin Receptor With Selective Effector Function Modulation

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KEY TAKEAWAYS

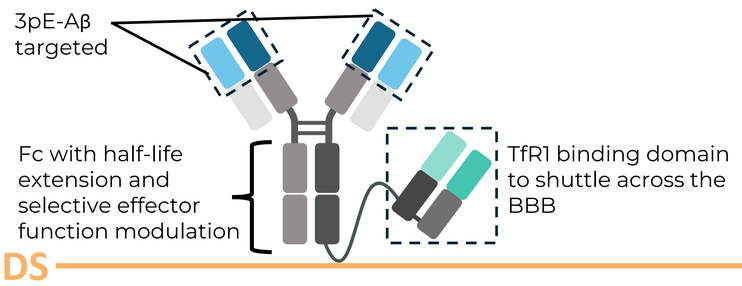
- KRSA-028 is a novel bispecific antibody with potent binding and phagocytosis of pyroglutamate modified amyloid beta (3pE-Aβ), and TfR1-mediated transport across the blood brain barrier (BBB)
- KRSA-028 was designed with half-life extension and selective effector function modulation, with reduced complement-dependent cytotoxicity (CDC) and antibody-dependent cytotoxicity (ADCC), avoiding acute reticulocyte depletion
- Preclinically, KRSA-028 demonstrated robust serum and brain exposure, supporting clinical development for the treatment of Alzheimer's disease

BACKGROUND

- There are currently two monoclonal antibodies (mAbs) targeting amyloid beta (Aβ), lecanemab and donanemab, approved for the treatment of Alzheimer's disease.[1,2]
- These first-generation therapies have limited brain exposure and the risk of amyloid-related imaging abnormalities (ARIA).[3]
- Efforts are underway to improve the brain exposure and safety profile of mAb therapies by including transferrin receptor 1 (TfR1) targeted shuttling domains to promote transcytosis across the BBB.[4]
  - One such antibody, trontinemab, is in phase 3 clinical trials.[5]
  - However, this approach may be limited by fast systemic clearance and off-target adverse events associate with antibody effector function.[4,6]
- KRSA-028 was engineered as a TfR1-shuttled antibody with an Fc domain with selective effector function.
  - The Fc domain was designed to improve pharmacokinetics, preserve Aβ plaque clearing phagocytic activity, and improve safety and tolerability by avoiding antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

KRSA-028 Structure

An investigational bispecific mAb with a modified IgG backbone that targets N-terminal pyroglutamate-modified amyloid beta (3pE-Aβ) and has a TfR1-binding domain to facilitate transcytosis across the BBB.



METHODS

Internally-Generated Control mAbs

As a negative control for TfR1 binding, an anti-3pE-Aβ IgG was produced based on the published sequence of the investigational product **remternetug**.

As a positive control for TfR1 binding, a bispecific anti-Aβ/anti-TfR1 mAb was produced based on the sequence of the investigational product **trontinemab**.

As a control for effector function, an effector function null bispecific anti-3pE-Aβ/anti-TfR1 mAb was produced based on the sequence of the investigational product **ABBV-1758**.

Henceforth, these control mABs are referred to as remternetug, trontinemab, and ABBV-1758, respectively.

- All data are presented as mean ± SEM unless otherwise noted.

- **Antibody-Dependent Cellular Cytotoxicity (ADCC)** potential was tested using human natural killer cells as the effectors and HEK293-TfR1 as the target cells.
- **Antibody-Dependent Cellular Phagocytosis (ADCP)** of pHrodo Red-labeled 3pE-Aβ(3-42) fibrils were tested with interferon-gamma (IFNγ)-stimulated phagocytic Fcγ-receptor-expressing and TfR1-expressing U937 cells.

- **Naïve male cynomolgus monkeys** (non-human primates, or NHPs) were given a single, equimolar intravenous (IV) dose of drug.
- Concentration of drug was quantified in capillary-depleted brain lysates at each timepoint.
- PK parameters were estimated using noncompartmental analysis.

Doses for Complete Blood Count and PK (n=3/group, IV, single-dose)	
KRSA-028	19.9 mg/kg
Trontinemab	20 mg/kg
Remternetug	14.9 mg/kg*

*Equimolar to 20 mg/kg KRSA-028.

Doses for Brain Biodistribution (n=3/group, IV, single-dose)	
KRSA-028	9.9 mg/kg
Trontinemab	10 mg/kg
Remternetug	19.9 mg/kg

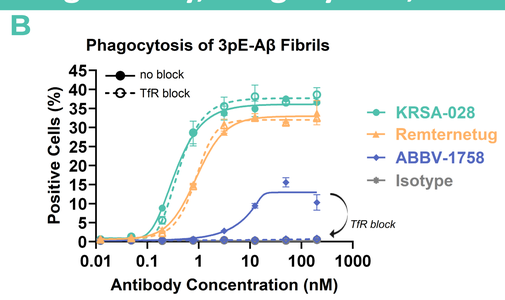
RESULTS

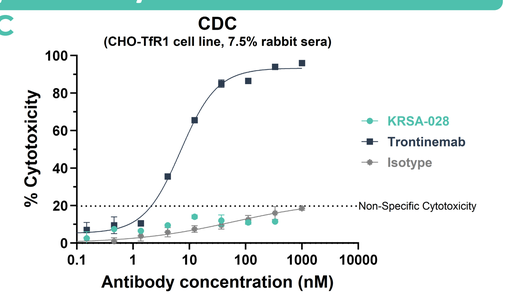
KRSA-028 Binding Affinity, Phagocytosis, and Cytotoxicity

A

Aβ Peptides	KRSA-028 K_D (nM)	Remternetug K_D (nM)
Aβ1-40	N/D	N/D
Aβ3-16	796	N/D
3pE-Aβ (3-16)	16.3	323
3pE-Aβ (3-42)	6.00	55.9

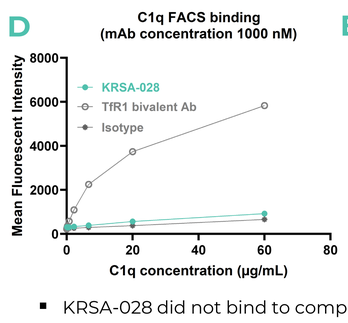
Aβ, amyloid beta; K_D, binding affinity; N/D, not determined.

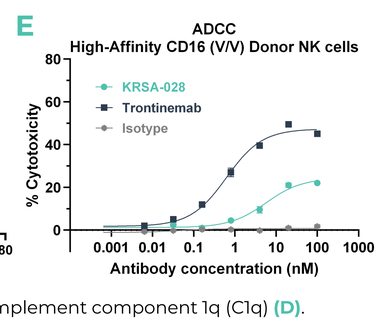


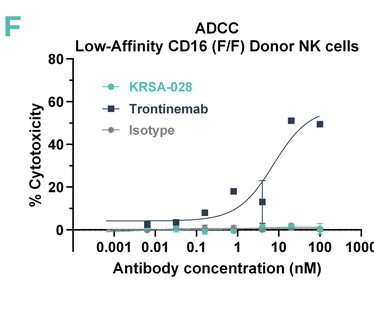


KRSA-028 binds with higher affinity to the 3pE-Aβ form of Aβ compared to remternetug **(A)**.

- KRSA-028 binds with similar affinity to both human and NHP TfR1 compared with trontinemab:
  - KRSA-028 binds to human TfR1 with K_D=139 nM and cynomolgus monkey TfR1 with K_D = 85.1 nM.
  - Trontinemab binds to human TfR1 with K_D = 111 nM and cynomolgus monkey TfR1 with K_D = 71.9 nM.
- KRSA-028 induced robust, concentration-dependent antibody-mediated uptake of 3pE-Aβ by U937 cells *in vitro* via Fc-dependent phagocytic mechanisms, and maintained effector function even when its TfR1-binding domain was blocked **(B)**.
- KRSA-028 did not elicit detectable complement-dependent cytotoxicity (CDC) **(C)**.

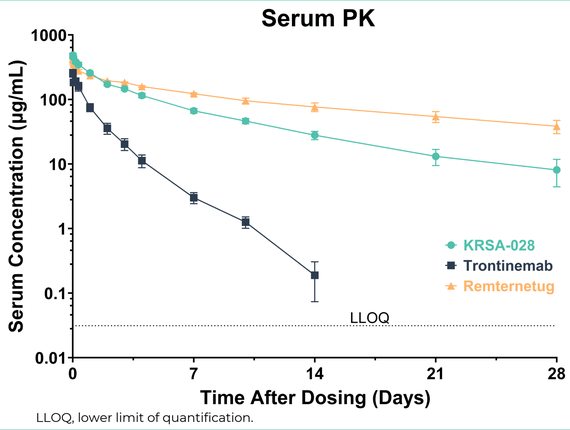






- KRSA-028 did not bind to complement component 1q (C1q) **(D)**.
- KRSA-028 had low antibody-dependent cytotoxicity (ADCC).
  - KRSA-028 had reduced cytotoxic activity with a high-affinity CD16 (V/V) donor (EC_{50} = 5.66), approximately 9-fold lower potency than that of trontinemab (EC_{50} = 0.62) **(E)**, and complete attenuation of detectable ADCC with a low-affinity CD16 (F/F) donor **(F)**.

KRSA-028 Pharmacokinetics



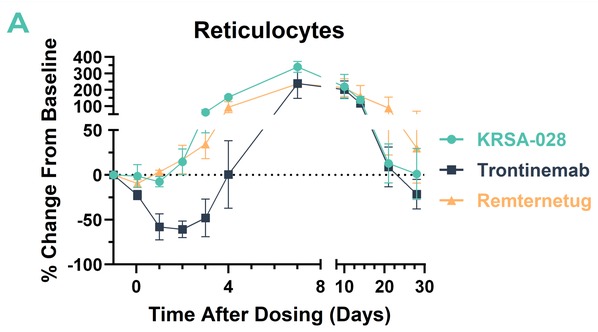
LLOQ, lower limit of quantification.

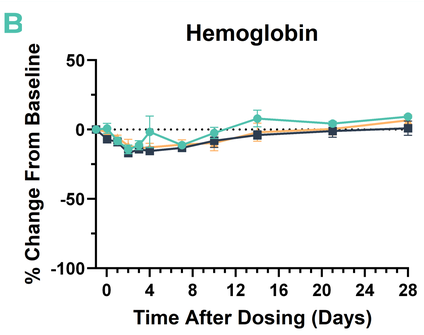
PK Parameter	Geometric Mean (%CV)[a] KRSA-028 (n=3)	Trontinemab (n=3)	Remternetug (n=3)
AUC_∞ (day*µg/mL)	1710 (21)	254 (28)	3460 (25)
C_{max} (µg/mL)	483 (13)	261 (8.2)	419 (13)
$t_{½}$ (day)	7.7 (4.2, 11)	1.5 (1.2, 2.1)	15.1 (10, 16)
CL (mL/day)	39.3 (12)	277 (21)	14.5 (34)

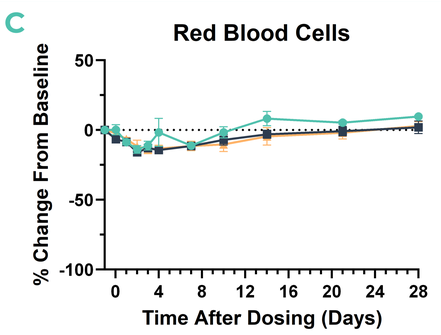
AUC, area under the curve; CL, systemic clearance; CV, coefficient of variance; $t_{1/2}$, terminal elimination half-life.
[a] Half life is reported as median(range).

- KRSA-28 had 7 times the systemic exposure (AUC_∞) of trontinemab.
- Systemic clearance (CL) of KRSA-028 was 7-fold slower relative to trontinemab.
- The impact on KRSA-028 clearance resulted in a 5-fold longer terminal elimination half-life relative to trontinemab.

KRSA-028 Hematologic Parameters

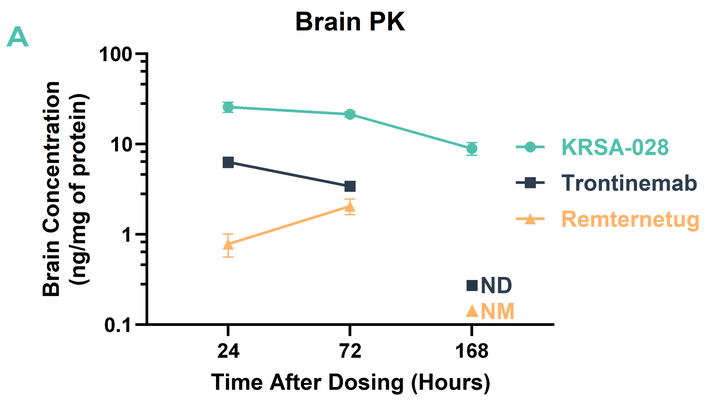




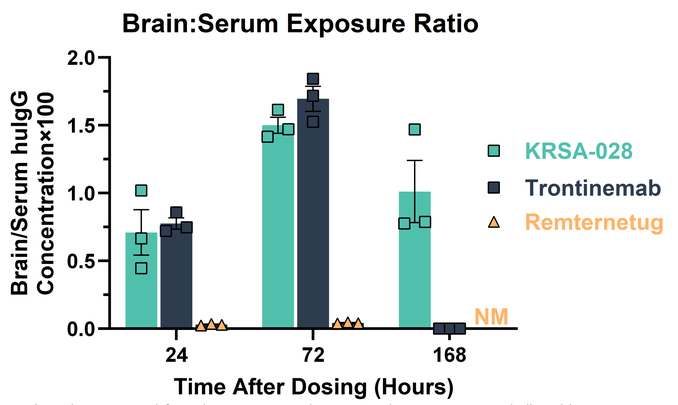


- There was no detectable acute loss of reticulocytes following single dose of KRSA-028 and remternetug, while a decrease was observed 24h to 3 days following a dose of trontinemab **(A)**.
- Changes in hemoglobin and red blood cells were similar across the 3 groups **(B,C)**.

KRSA-028 Brain Biodistribution



Brain regions averaged: frontal cortex, temporal cortex, caudate, putamen, cerebellum, hippocampus.
ND, not detected; NM, not measured.



Brain regions averaged: frontal cortex, temporal cortex, caudate, putamen, cerebellum, hippocampus.
NM, not measured.

- KRSA-028 had high and sustained brain exposure **(A)**, with mean (SD) $AUC_{0\text{-}168}$ = 2589 (219.5) 6.5-fold greater than trontinemab (397.1 [38.7]) and 37-fold greater than remternetug (69.85 [16.1]).
- Trontinemab was not detectable at 168 hours, and remternetug concentration was not measured (NM) at 168 hours **(A, B)**.
- The % brain (ng/mL of tissue) to serum (ng/mL) ratio was similar for KRSA-028 and trontinemab **(B)**.

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Disclosures

BL, MC, KJK, KP, AAM, BHK, GNF, JO and **MM** are employees of Paragon Laboratories. **JV** is an employee of Paragon Therapeutics. **MR, JS** and **AS** are employees of Korsana Biosciences and hold financial interests in Korsana Biosciences. **BL, KJK, EC, JV, BHK, GNF, JO,** and **MM** hold an equity interest in Korsana Biosciences. **EC** and **RS** are former employees of Paragon Therapeutics..

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