Bispecific Antibodies that Bind Aβ Oligomers and Transferrin Receptors Show Enhanced Brain Delivery in Cynomolgus Monkeys

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Disclosures

Dr. Shughrue is an employee of Acumen Pharmaceuticals and is a minor shareholder.

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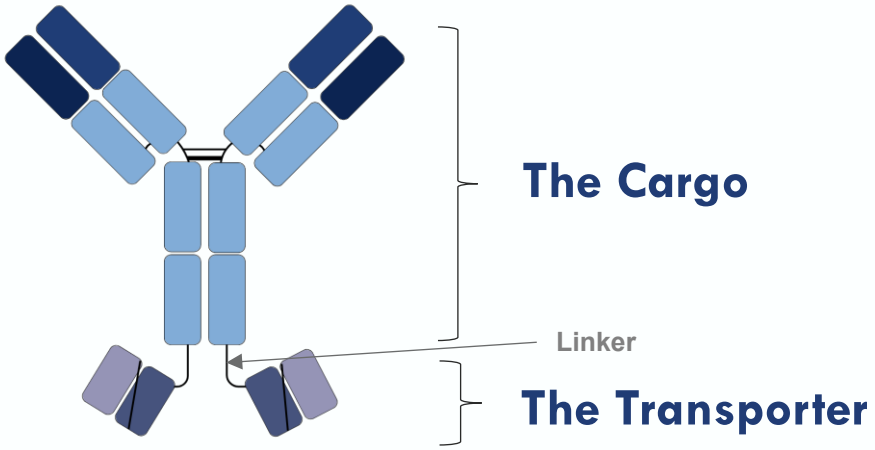
Concept: Building a Bispecific Antibody

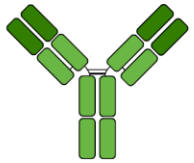
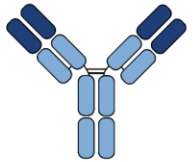
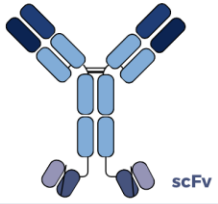
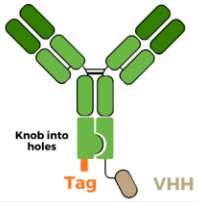
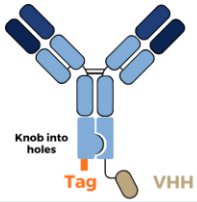
- The Cargo determines the Aβ species (oligomer, monomer, plaque, pyroglutamate) targeted by the bispecific antibody
- Efficacy is dependent on The Cargo

- The Transporter determines the mechanism used to cross the BBB as well as brain PK
- The transporter binding site may have associated safety risks (e.g. TfR and anemia)



- In building two-sided antibodies, careful consideration was given to both sides since they are both essential for success

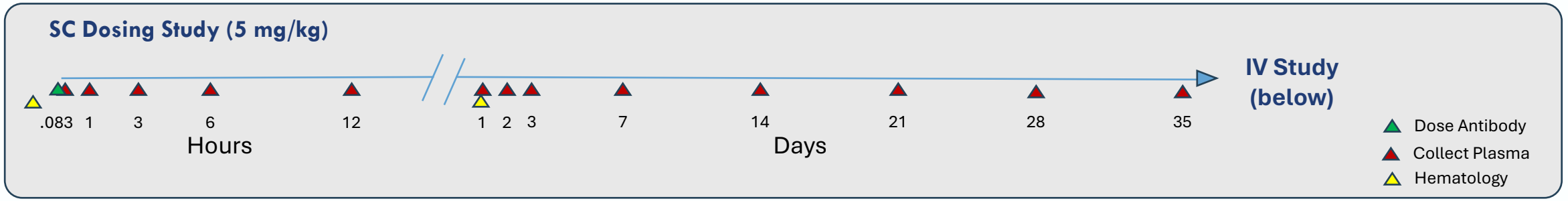
Bispecific Enhanced Brain Delivery™ (EBD™)Antibodies Retain the High Affinity for Transferrin Receptor and Selectivity for Aβ Oligomers

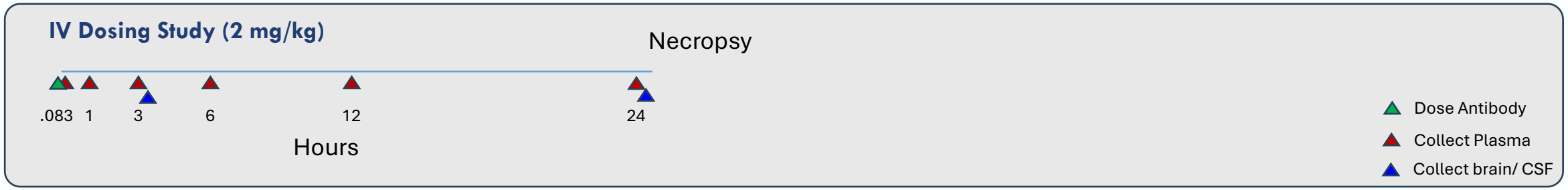
No.	ACU193	ACU234	ACU401	ACU351	ACU451
Candidate Molecules			ACU234*-**scFv** bivalent 	ACU193-**VHH** monovalent 	ACU234*-**VHH** monovalent 
Affinity to human TfR By BLI	N/A	N/A	2.35 nM	13.31 nM	4.98 nM
Affinity to monkey TfR By BLI	N/A	N/A	2.71 nM	18.93 nM	8.68 nM
Oligomer Binding	0.720 nM	0.853 nM*	0.808 nM	0.434 nM	0.389 nM
Monomer Binding	3,921 nM	12,728 nM*	≥ 10,818 nM	2,873 nM	≥ 10,044 nM

*ACU234 data are included from a separate experiment (in which values from ACU193 were similar). All other data are from a single SPR experimental set.

- The bispecific constructs and the monoclonal antibodies ACU193 and ACU234 exhibit similar binding profiles, each showing higher affinity for Aβ oligomers than monomers

Study Design:
Assessment of Bispecific EBD™ Antibodies in Cynomolgus Monkey

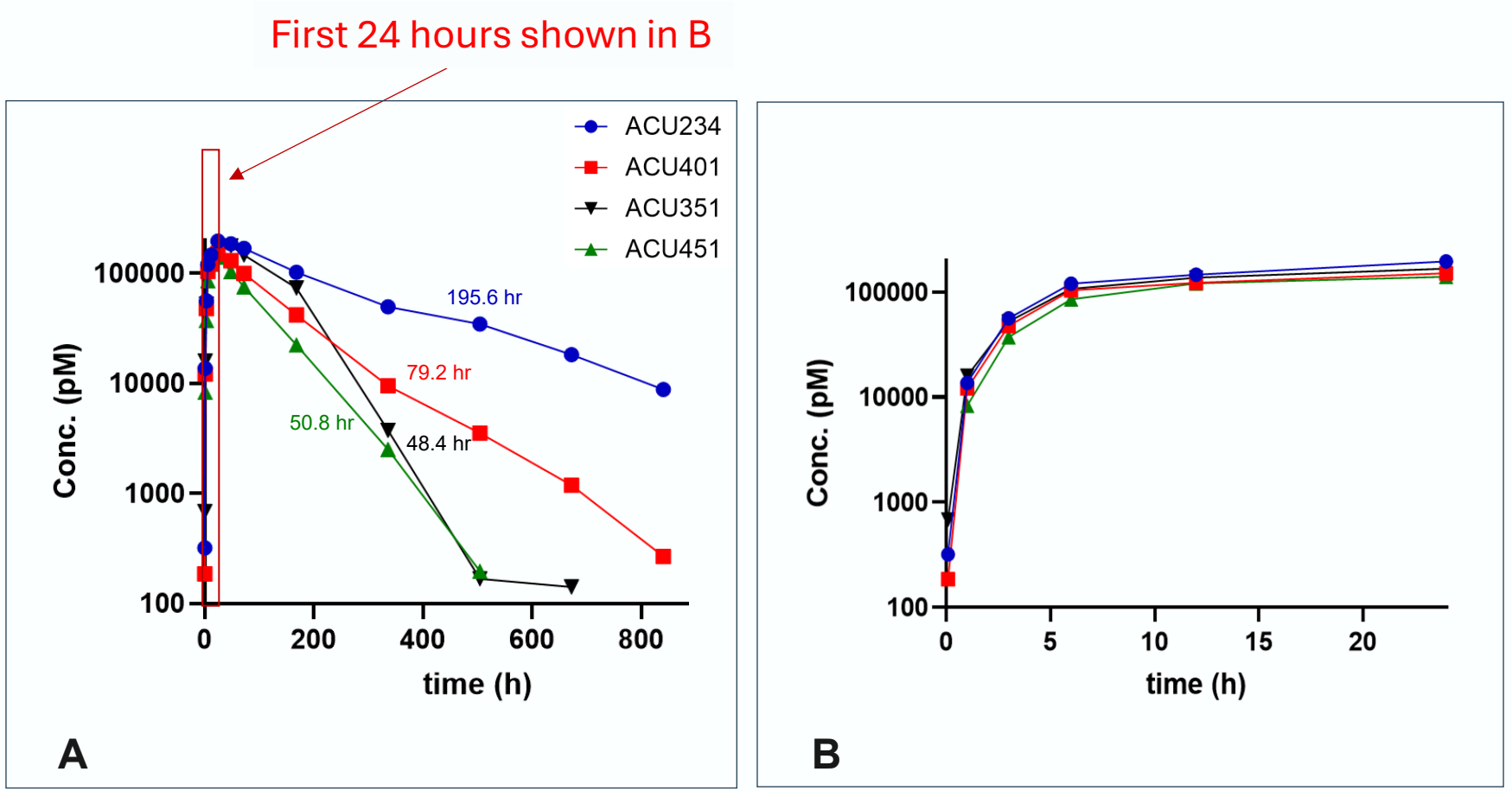




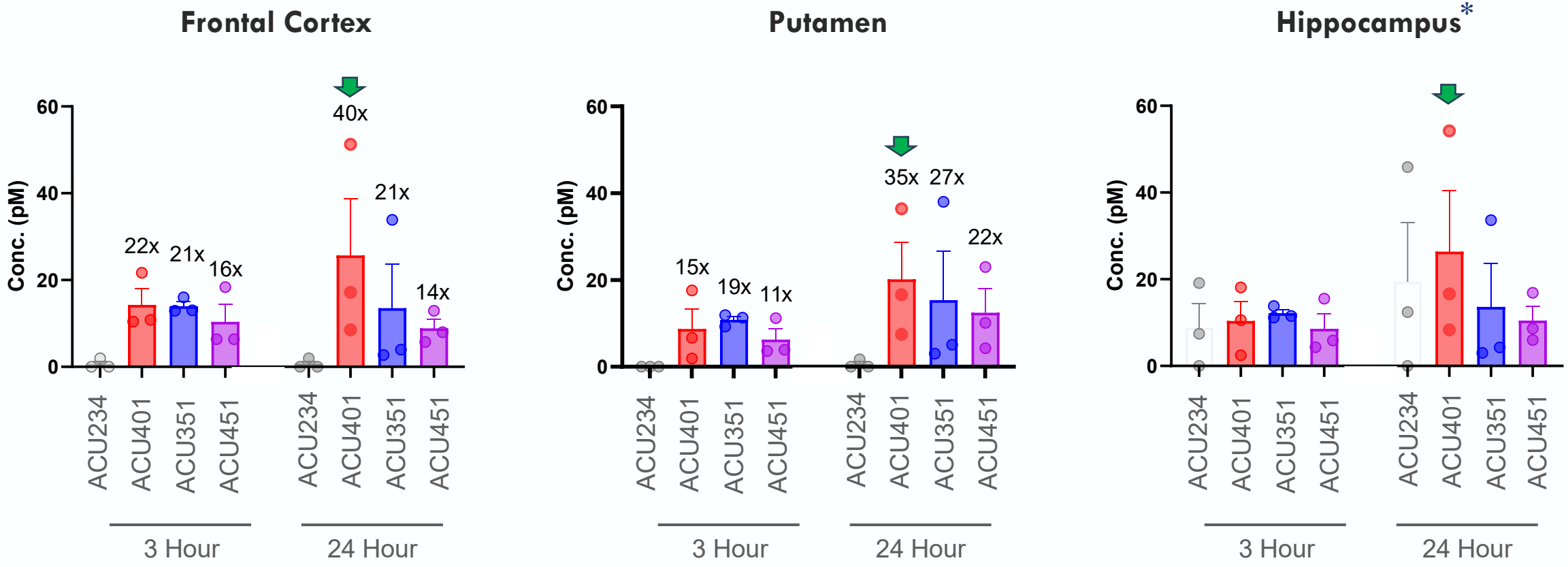
Groups (n=3/ group)

- 3 hours post IV dose:
  - ACU234 mAb
  - ACU401 EBD
  - ACU451 EBD
  - ACU351 EBD
- 24 hours post IV dose:
  - ACU234 mAb
  - ACU401 EBD
  - ACU451 EBD
  - ACU351 EBD

Bispecific Antibodies Exhibit Rapid Plasma Uptake after SC Dosing



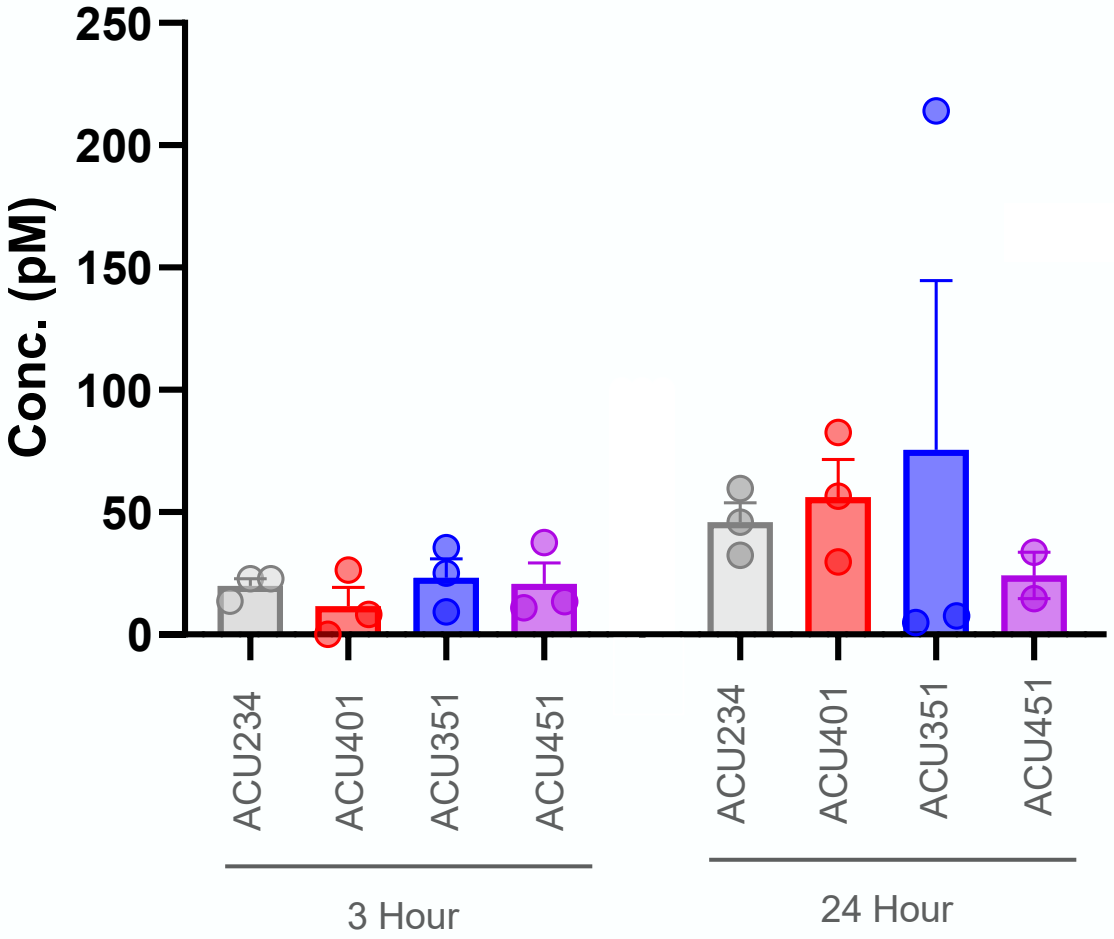
Analysis of Three Brain Regions Showed 22 - 40x Enhancement of Bispecific Antibody Delivery Over Monoclonal Antibody ACU234



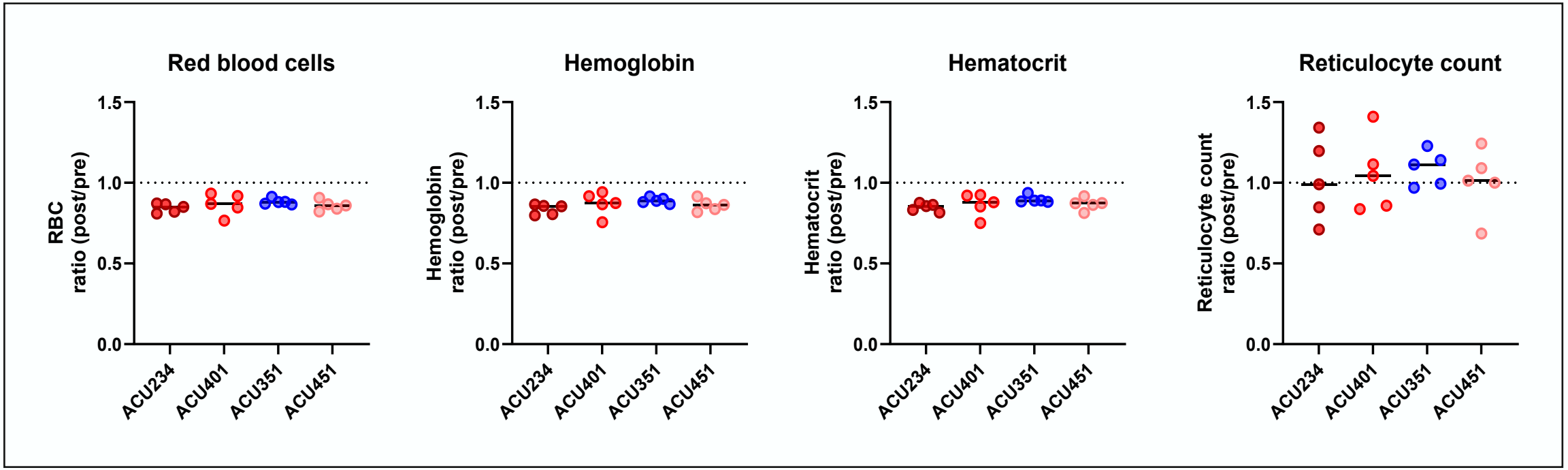
** Currently re-testing hippocampal tissue samples to determine if unexpectedly high levels of ACU234 were caused by contamination or other sampling error.*

- The bispecific antibody ACU401 had the highest brain levels (green arrow) in the three regions evaluated

CSF Concentrations of EBD™ Antibodies Were Comparable to ACU234 after IV Administration in Cynomolgus Monkeys



No Meaningful Changes in Hematology Endpoints Were Observed 24 Hours after SC Dosing of EBD™ Antibodies in Monkeys



Summary

- Bispecific EBD™ constructs of ACU193 or ACU234 with an anti-TfR (scFv or VHH) transporter retain their ability to bind the TfR and to selectively bind Aβ oligomers
- Pharmacokinetic studies demonstrated rapid absorption of all bispecific EBD™ antibodies following SC administration
- Analysis of brain samples 3 or 24 hours after IV administration revealed higher brain levels of all EBD™ antibodies, with ACU401 showing a 40x increase when compared with ACU234
- Interestingly, no differences in CSF concentrations were detected between EBD™ antibodies and ACU234 at the timepoints assessed
- Analysis of a panel of hematological endpoints showed no meaningful changes in any measure assessed 24 hours post-dosing, suggesting a low acute anemia risk for the bispecific EBD™ antibodies evaluated

Thank you!

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