THE ANTI-AMYLOID BETA BRAINSHUTTLE™ ANTIBODY TRONTINEMAB RAPIDLY REDUCES AMYLOID PLAQUES IN PARTICIPANTS WITH ALZHEIMER'S DISEASE

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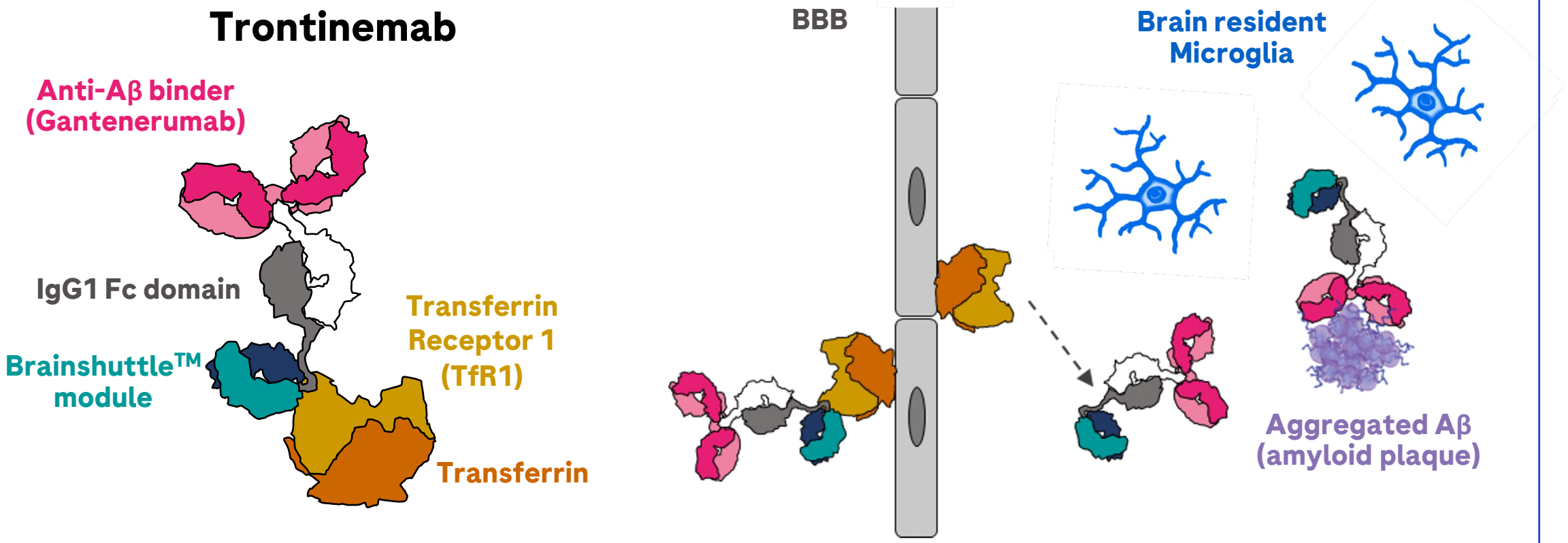
Disclosures

- **Luka Kulic, Fabien Alcaraz, Annamarie Vogt, and Carsten Hofmann, Maddalena Marchesi, Jakub Wojtowicz, Gregory Klein, Ruth Croney, David Agnew, Denise Sickert, Niels Janssen, João A. Abrantes, Paul Delmar, and Iris Wiesel** are full-time employees and own stock in F. Hoffmann-La Roche Ltd.
- **Philip Barrington** is an external business partner of F. Hoffmann-La Roche Ltd.
- **Silke Ahlers** is an external business partner of F. Hoffmann-La Roche Ltd.
- **Hanno Svoboda** is a full-time employee of Roche Diagnostics GmbH and owns stocks in F. Hoffmann-La Roche Ltd.

Trontinemab - a novel Brainshuttle™ antibody targeting Aβ

Active transport across the BBB may enable superior brain penetration and target engagement



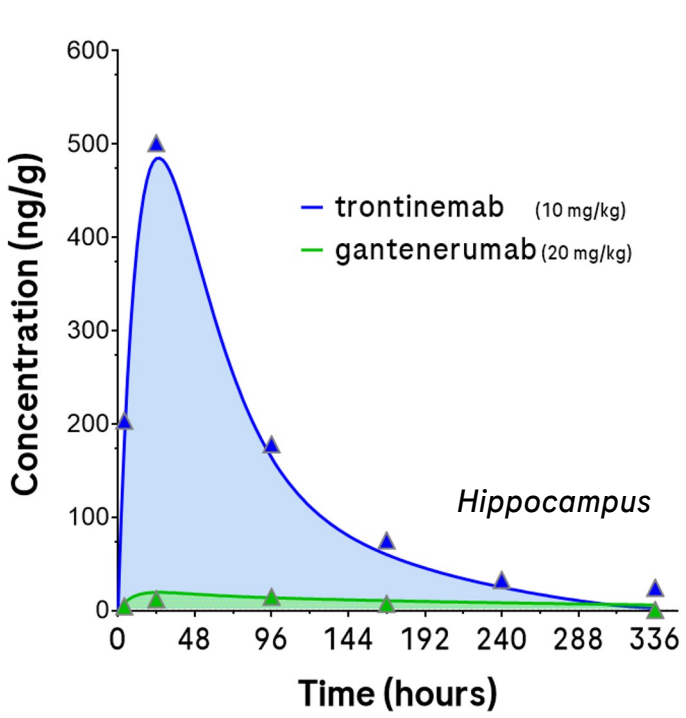
Trontinemab crosses the BBB via TfR1-mediated transcytosis at the capillary level

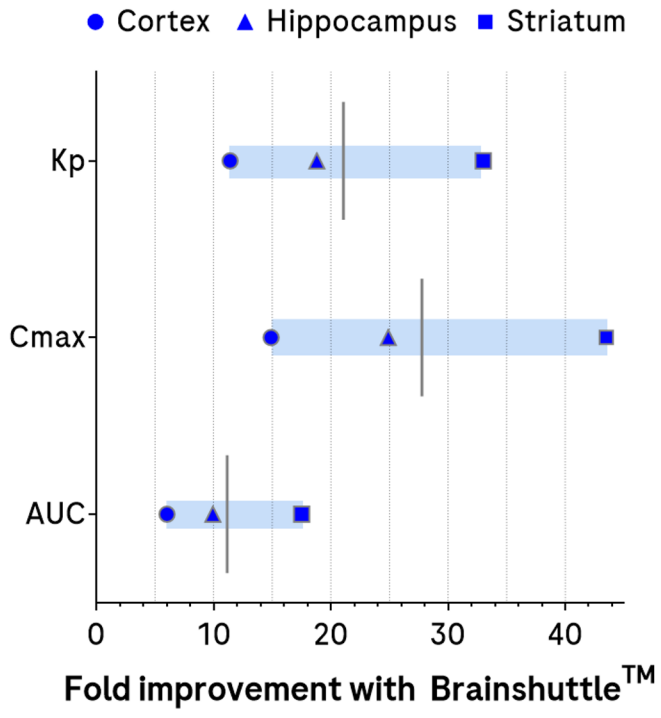
Aβ, amyloid beta; IgG1, immunoglobulin G1; Fc domain, fragment crystallisable domain; BBB, blood brain barrier.

Substantially higher CNS exposure due to shuttling

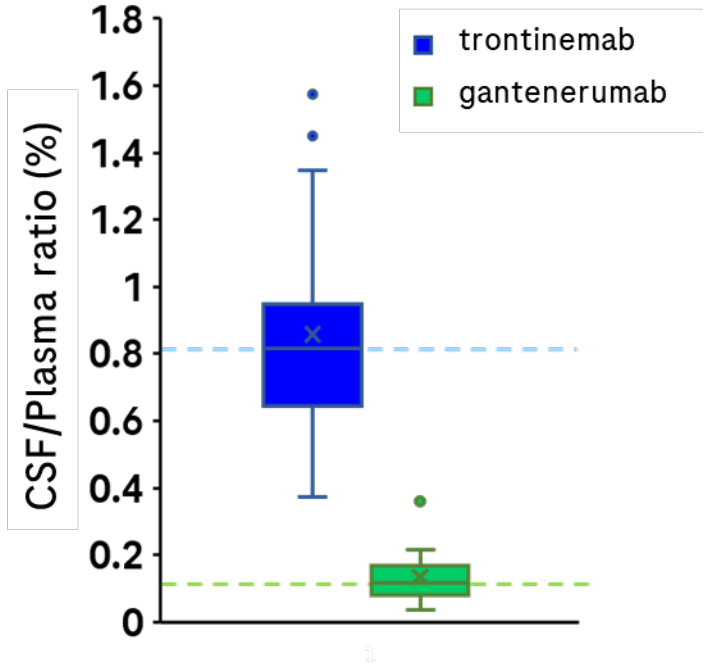
Evidence from nonhuman primates and the First-in-Human study of trontinemab

6-17-fold higher brain exposure (AUC) in nonhuman primates (trontinemab compared with gantenerumab)[1,2]





8-fold increase in CSF/plasma ratio in healthy volunteers[1,3]



CNS, central nervous system; AUC, area under the curve at steady state; Cmax, maximum observed concentration; CSF, cerebrospinal fluid; IV, intravenous; Kp, partition coefficient. Vertical lines (middle graph) represent mean parameters across all three brain regions. [1] Kulic L, et al. Presented at AD/PD 2021, virtual conference. [2] Single IV dose study in Cynomolgus monkey: administration of 10 mg/kg trontinemab vs. 20 mg/kg gantenerumab IV. [3] Single ascending dose (SAD) study in healthy volunteers (NCT04023994): trontinemab results were compared with historical data from a previous gantenerumab SAD study (BN18726).

Brainshuttle™ AD is a Phase Ib/IIa study assessing the safety, tolerability, PK and PD of trontinemab in participants with AD

Study Population

MCI due to AD or mild-to-moderate AD (NIA-AA criteria)

- 50 to 85 years of age
- MMSE score 18–28
- CDR-GS score = 0.5, 1, or 2
- Amyloid pathology confirmed by amyloid PET[1]

MRI exclusion criteria:

- >2 lacunar infarcts
- Territorial infarct >1 cm^3
- Significant white matter lesions (Fazekas score 3)
- >5 combined microhemorrhages and leptomeningeal hemosiderosis or >3 leptomeningeal hemosiderosis
- ARIA-E

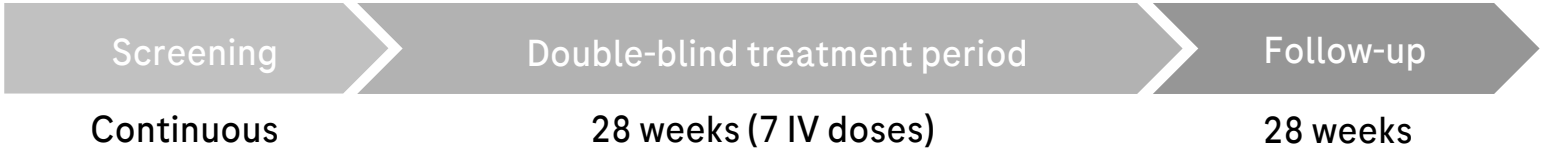
Primary Objective	Endpoints
Safety and Tolerability	Nature, frequency, severity, and timing of AEs, including labs, vital signs, physical and neurological examination, ECG, and brain MRI

Secondary Objectives	Endpoints
Pharmacodynamics	Change from BL in amyloid plaque burden on amyloid PET
Pharmacokinetics	Concentration of trontinemab in plasma and CSF
Immunogenicity	Incidence and titer of anti-drug antibodies (ADAs)

PK, pharmacokinetics; PD, pharmacodynamics; AE, adverse event; ECG, electrocardiogram; MRI, Magnetic Resonance Imaging; BL, baseline; NIA-AA, The National Institute on Aging and the Alzheimer's Association; MMSE, Mini Mental State Examination; CDR-GS, Clinical Dementia Rating-Global Score; PET, Positron Emission Tomography; ARIA-E, Amyloid-Related Imaging Abnormalities-Edema/Effusion. [1] Amyloid PET cut-off: >50 Centiloid (CL) units.

Brainshuttle™ AD study design

Staggered, parallel-group, adaptive study design with 4 initial sequential cohorts



Dose escalation:

- ≥10 study participants randomized 4:1 (active: Pbo) within each cohort

- Cohort 4: 3.6 mg/kg or Pbo IV Q4W
- Cohort 3: 1.8 mg/kg or Pbo IV Q4W
- Cohort 2: 0.6 mg/kg or Pbo IV Q4W
- Cohort 1: 0.2 mg/kg or Pbo IV Q4W

Cohort Expansion:

- Expansion of cohorts with optimal safety/PD profile
- Robust assessment of safety, PK, PD and immunogenicity

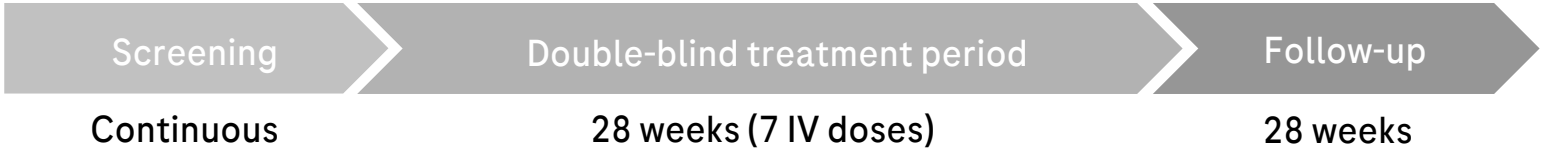
Days	Screening/BL	22	**78 ***	162	172/176	**196**	281
Amyloid PET	★		★			★	
MRI	★	★	★	★			★
CSF	★				★		

* Day 78 amyloid PET only in cohorts 3 and 4

Pbo, placebo; IV, intravenous; Q4W, every four weeks.

Brainshuttle™ AD study design

Staggered, parallel-group, adaptive study design with 4 initial sequential cohorts



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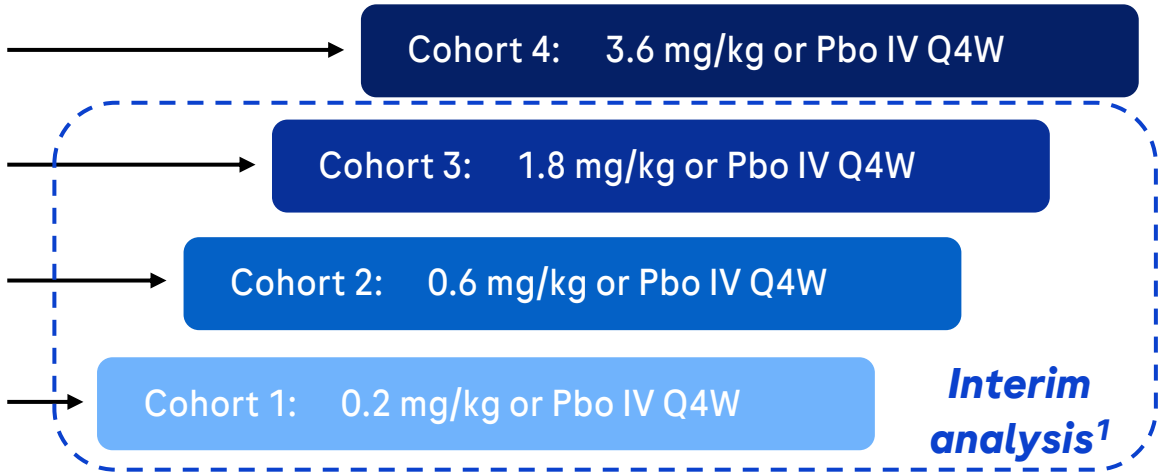

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Amyloid PET	★		★			★	
MRI	★	★	★	★			★
CSF	★				★		

* Day 78 amyloid PET only in cohorts 3 and 4

[1] Cut-off date: 30 June 2023. Pbo, placebo; IV, intravenous; Q4W, every four weeks.

Baseline characteristics at interim analysis

Analysis included 44 participants enrolled in dose escalation cohorts 1 to 3

Baseline demographic and disease characteristics	Cohort 1 0.2 mg/kg or Pbo (n = 14)	Cohort 2 0.6 mg/kg or Pbo (n = 14)	Cohort 3 1.8 mg/kg or Pbo (n = 16)	All Participants (n = 44)
Age, mean (SD)	70.0 (7.4)	68.6 (9.2)	72.4 (8.0)	70.4 (8.2)
Sex, female, n (%)	12 (85.7%)	7 (50%)	10 (62.5%)	29 (65.9%)
Race, white, n (%)	14 (100%)	14 (100%)	16 (100%)	44 (100%)
Weight, kg, mean (SD)	60.6 (8.6)	70.0 (12.1)	66.8 (13.1)	65.8 (11.9)
CDR-GS, n (%) 0.5 1 2	 4 (28.6%) 6 (42.9%) 4 (28.6%)	 6 (42.9%) 8 (57.1%) 0	 8 (50.0%) 7 (43.8%) 1 (6.3%)	 18 (40.9%) 21 (47.7%) 5 (11.4%)
CDR-SB, mean (SD)	5.8 (2.8)	4.8 (1.9)	5.3 (2.9)	5.3 (2.6)
MMSE, mean (SD)	20.9 (3.2)	20.4 (4.7)	19.8 (2.8)	20.3 (3.6)
***APOE ε4* carrier status, n (%)** Carrier Non-carrier Missing data	 10 (71.4%) 4 (28.6%) 0	 6 (42.9%) 7 (50.0%) 1 (7.1%)	 10 (62.5%) 6 (37.5%) 0	 26 (59.1%) 17(38.6%) 1 (2.3%)

SD, standard deviation; APOE, apolipoprotein E.

Plasma PK and ADAs

Impact of ADAs on exposure was dose-dependent and less pronounced at higher dose

PK after 1st dose was in line with PK results from previous SAD study in healthy volunteers.

ADAs developed in a majority of participants 2-3 months after start of the treatment.

The effect of ADAs on median exposure (AUC) after administration of dose 7 was dose-dependent:

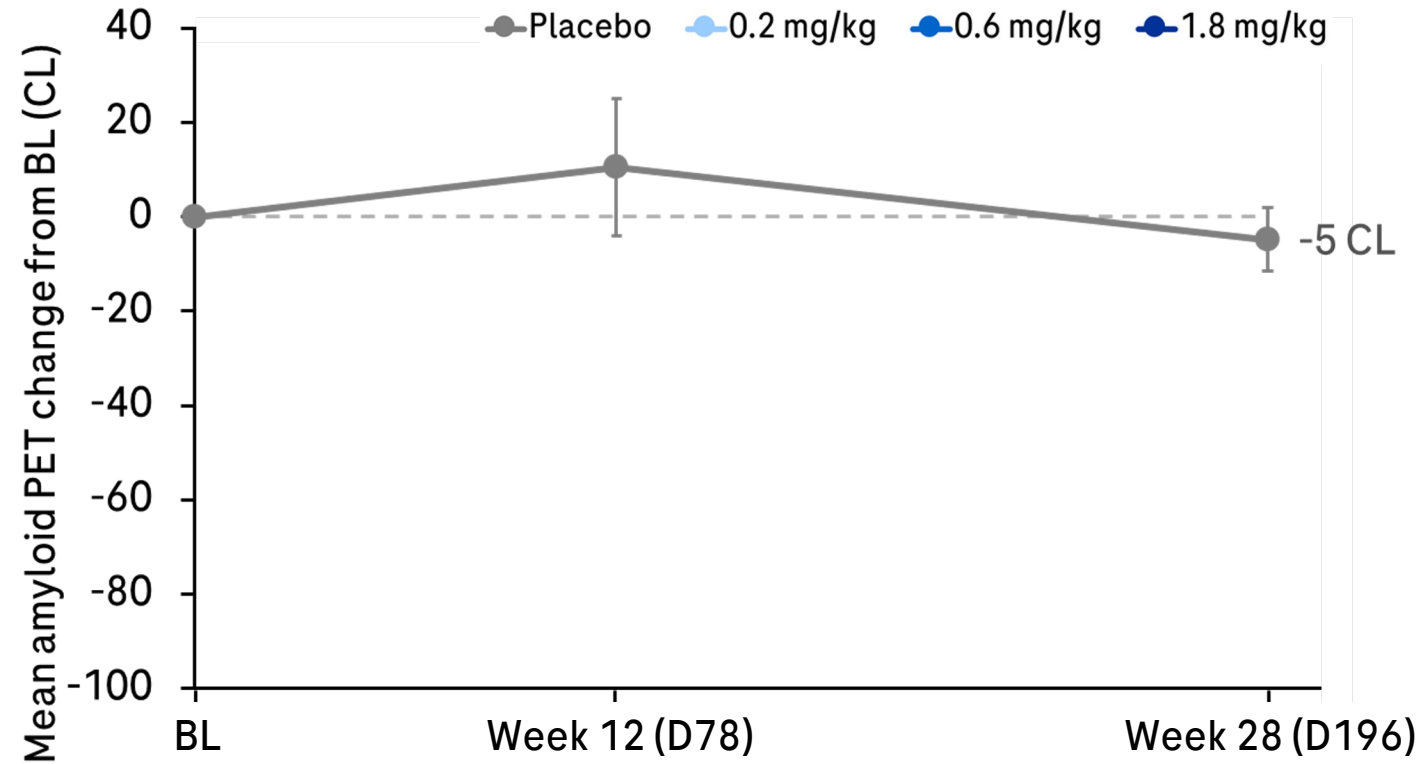
- ~70% and ~60% AUC reduction in cohort 1 (0.2 mg/kg) and 2 (0.6 mg/kg), respectively
- only moderately (~25%) lower AUC due to ADAs in cohort 3 (1.8 mg/kg)

An overall lower ADA incidence and lower ADA titers were observed at higher dose (1.8 mg/kg).

ADA, anti-drug antibody. AUC, area under the curve.

Dose-dependent amyloid plaque lowering with trontinemab

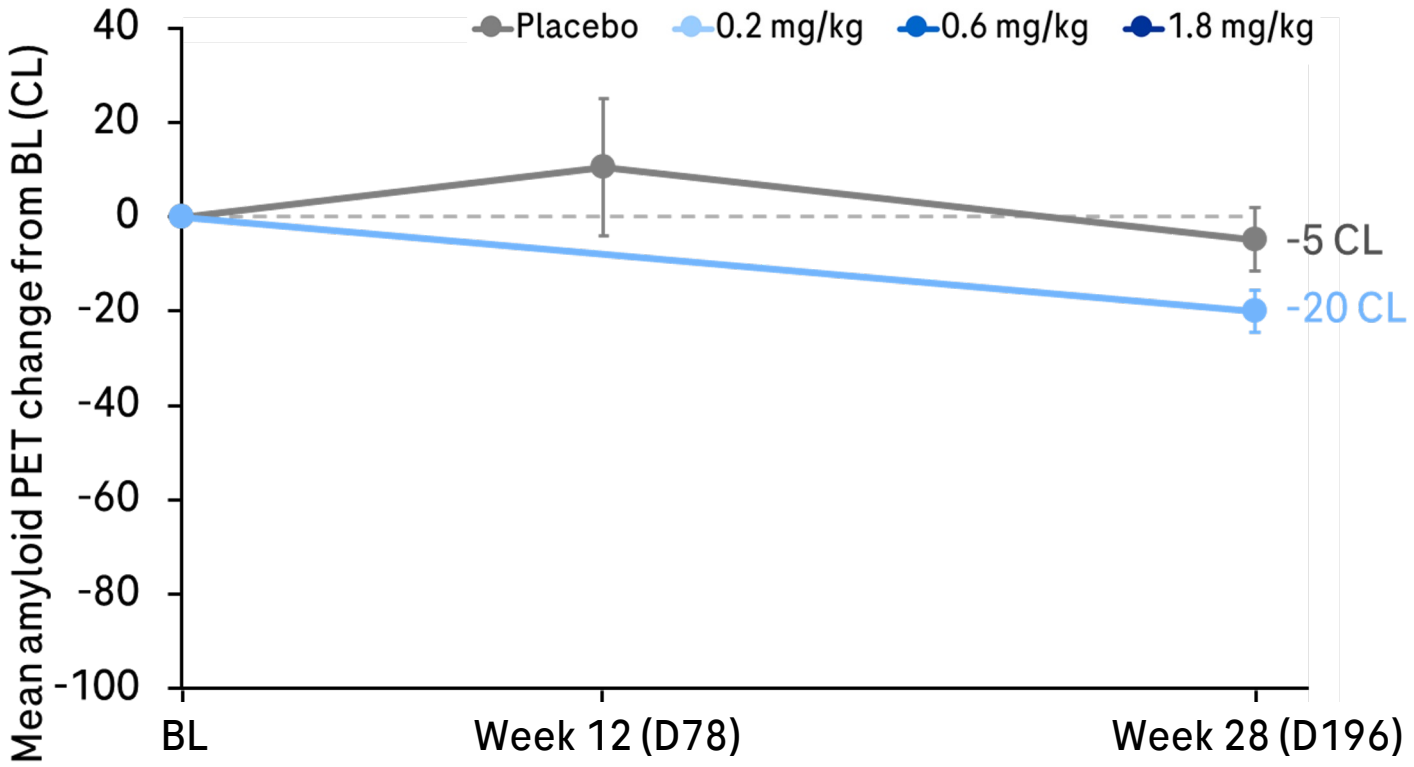
Mean amyloid PET change from baseline[1]



[1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with centiloid).

Dose-dependent amyloid plaque lowering with trontinemab

Mean amyloid PET change from baseline[1]



Placebo	n = 9	n = 3	n = 9
0.2 mg/kg	n = 11	-	n = 10

[1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with centiloid).

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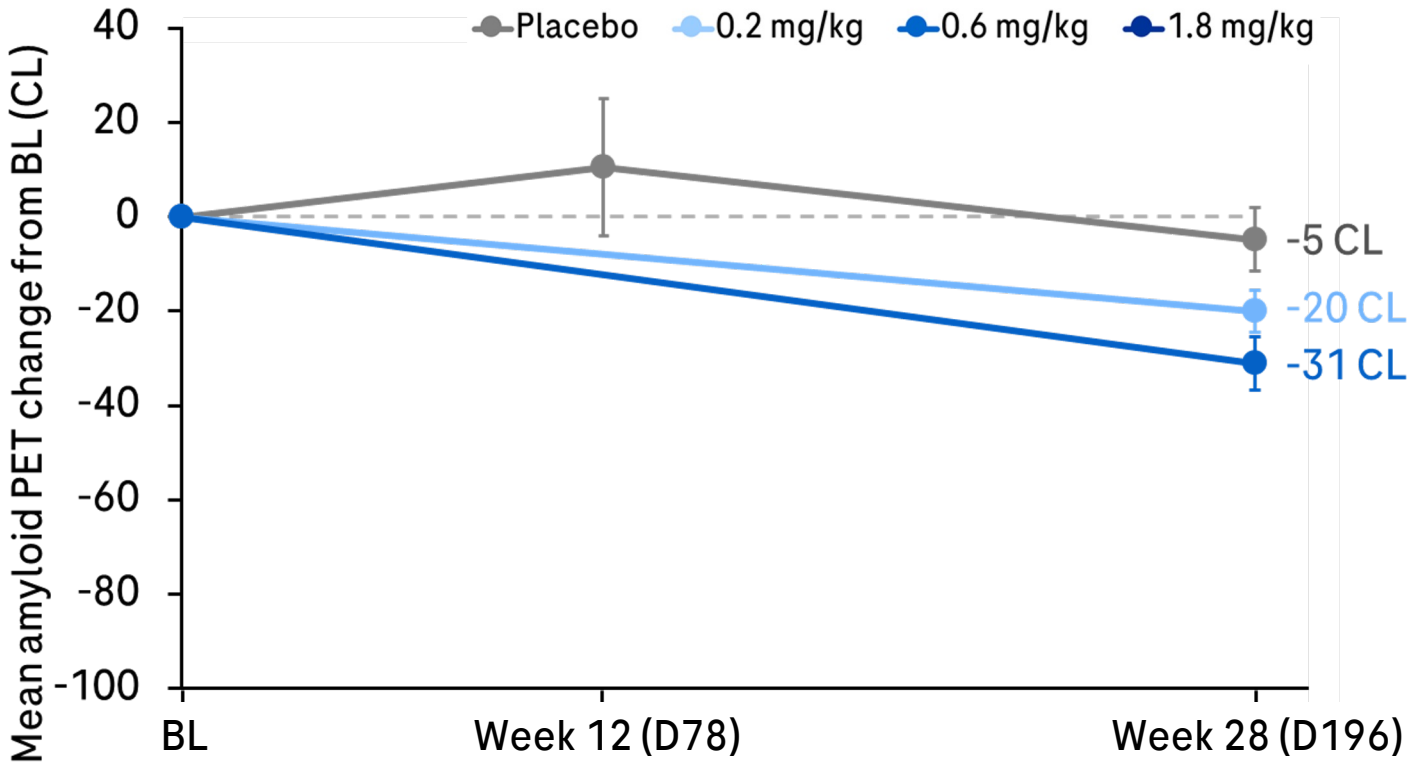
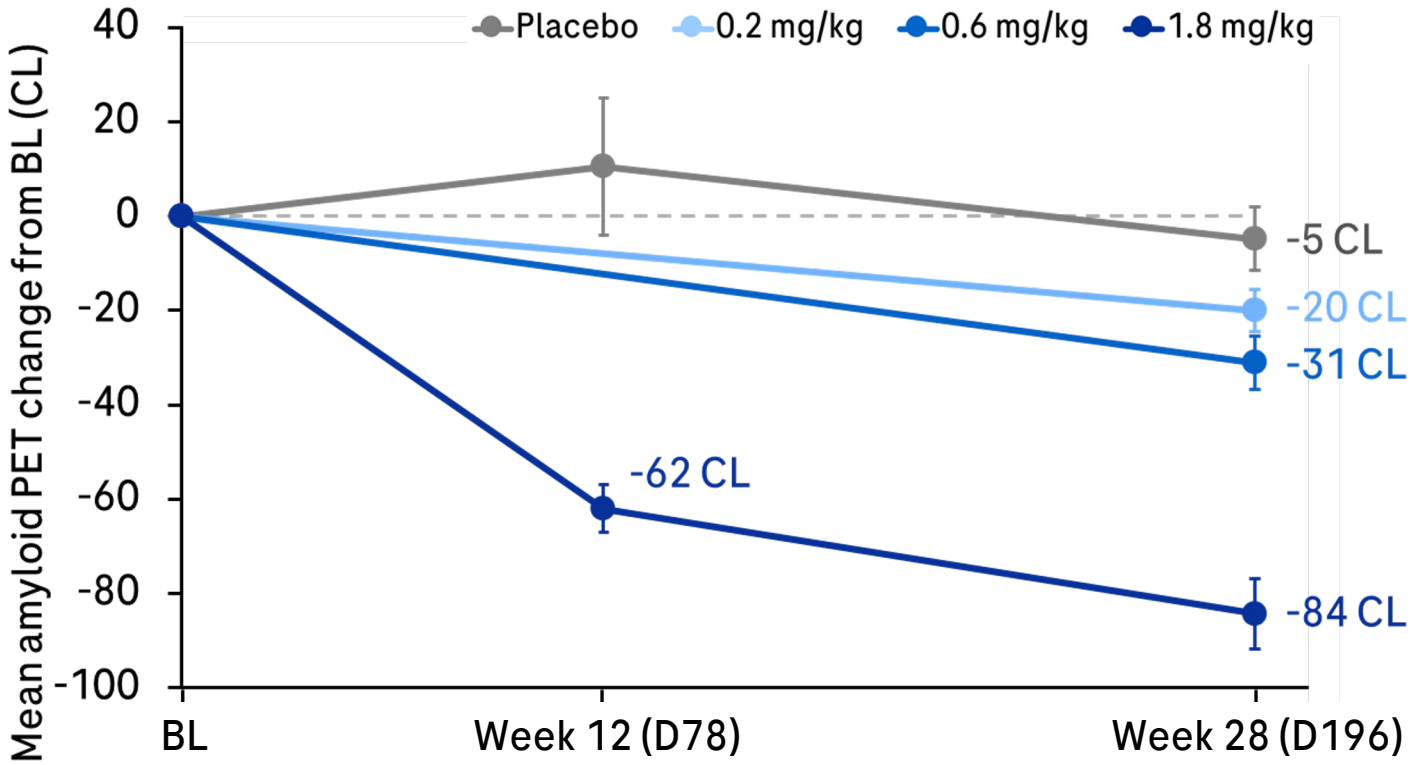


Placebo	n = 9	n = 3	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10

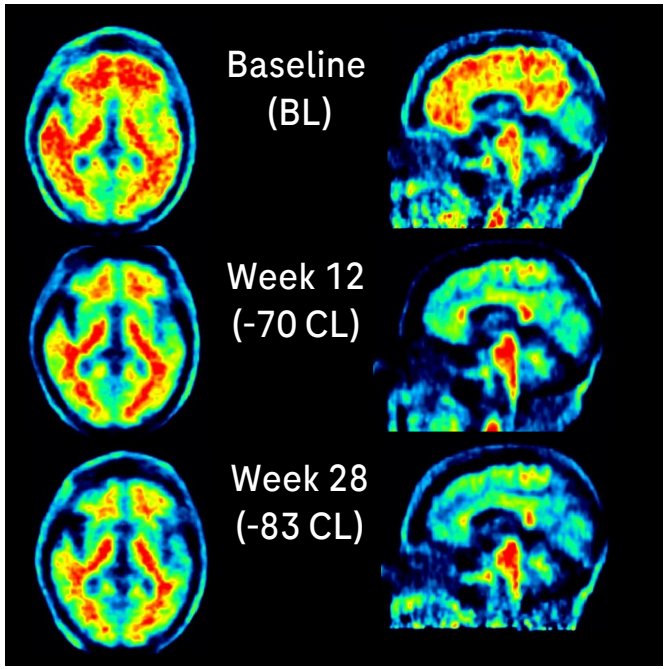
[1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with centiloid).

Dose-dependent amyloid plaque lowering with trontinemab

Mean amyloid PET change from baseline[1]



Placebo	n = 9	n = 3	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8

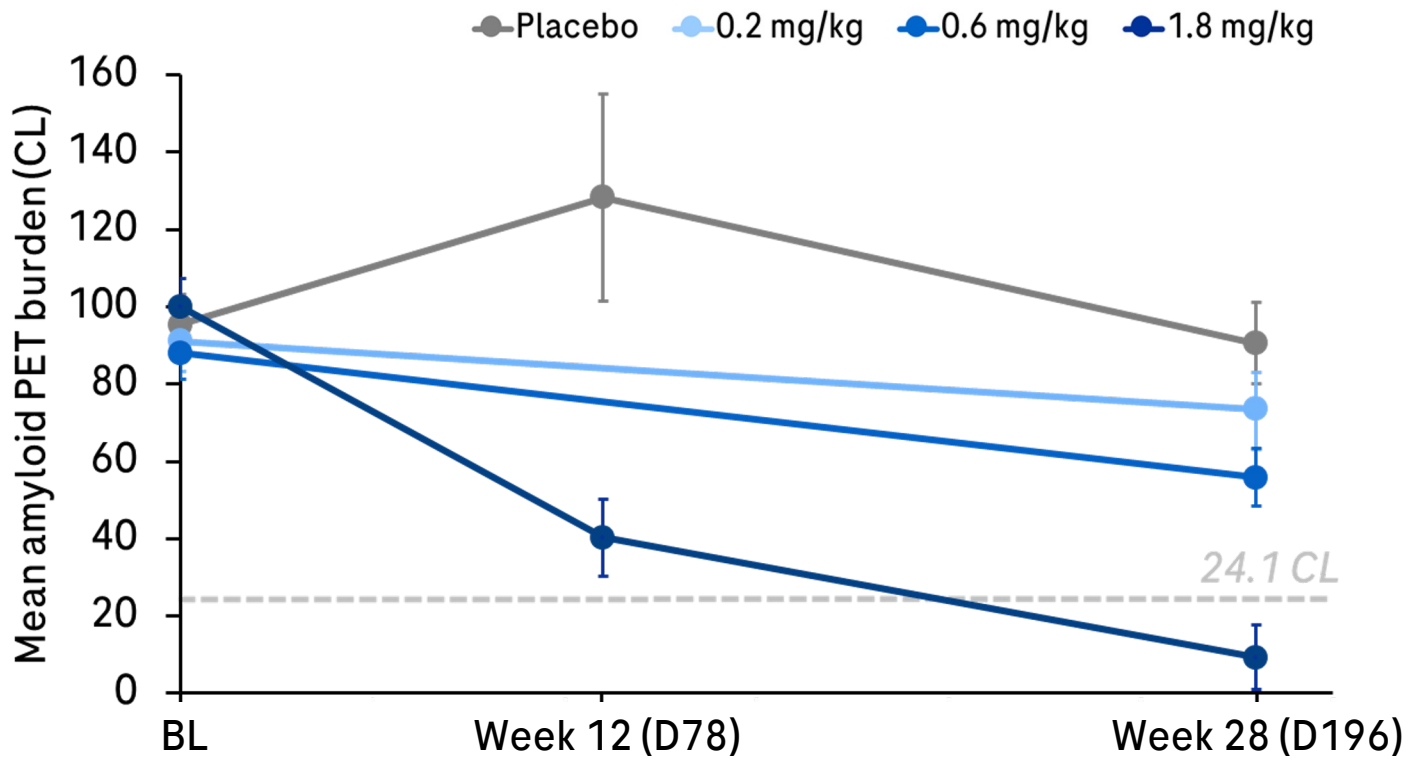


Longitudinal amyloid PET images in a participant who was treated with 1.8 mg/kg trontinemab

[1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with centiloid).

Rapid amyloid depletion at 1.8 mg/kg

4/11 (36% of participants) below the amyloid positivity threshold at week 12, 6/8 (75%) at week 28[1]



Placebo	n = 9	n = 3	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8

Visit	Mean amyloid value in CL at visit (% amyloid negative (<24.1 CL))			
	Placebo	0.2 mg/kg	0.6 mg/kg	1.8 mg/kg
BL	95 (0)	91 (0)	88 (0)	**100 (0)**
Week 12 (D78)	128 (0)	-	-	**40 (36)**
Week 28 (D196)	91 (0)	74 (0)	56 (10)	**9 (75) ***

* 6/8 (75% of participants) <24.1 CL, 5/8 (63%) <11 CL at 1.8 mg/kg after 28 weeks

[1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with centiloid).

Blinded safety profile[1]

Number of participants with safety events or early discontinuations

Participants, n (%)	Cohort 1 0.2 mg/kg or Pbo (n = 14)	Cohort 2 0.6 mg/kg or Pbo (n = 14)	Cohort 3 1.8 mg/kg or Pbo (n = 16)	Total (n = 44)
Participants with ≥1 AE	12 (85.7%)	14 (100%)	16 (100%)	42 (95.5%)
Deaths	0	0	0	0
Serious AE Fall Pulmonary embolism	1 (7.1%) 1 (7.1%)[2] 0	1 (7.1%) 0 1 (7.1%)[3]	0 0 0	2 (4.5%) 1 (2.3%) 1 (2.3%)
Serious AE deemed related to study drug	0	0	0	0
Early discontinuation from study AEs Withdrawal by participant Physician decision	0 0 0	0 2 (14.3) 0	2 (12.5%)[4] 3 (18.8%)[5] 1 (6.2%)	2 (4.5%) 5 (11.4%) 1 (2.3%)

[1] Blinded safety data by dosing cohorts (cut-off date: 30 June 2023). Please note that the ongoing Ph Ib/IIa study remains blinded to individual treatment assignments. Participants receiving trontinemab and Pbo in a respective dose cohort are presented together by dosing cohort to avoid unblinding at the individual level. [2] Deemed not related to study drug by the investigator (two fall events in one participant). [3] One Grade 2 pulmonary embolism deemed related to recent hallux valgus surgery and considered not related to the study treatment by the investigator. [4] One discontinuation occurred after Grade 2 infusion related reaction (IRR) following administration of the first dose of the study drug (without premedication), another discontinuation occurred after Grade 2 IRR following administration of the second dose of study of the study drug (again without implementation of premedication). [5] Three discontinuations occurred for personal or administrative reasons (caregiver unavailability).

IRRs and a transient mild anemia were more common AEs in cohort 3

Most IRRs occurred without premedication (after dose 1) and were mild or moderate in severity
Frequent blood draw contributed to a mild decrease in hematological parameters in all groups

Common treatment-emergent AEs of all causality (MedDRA Preferred Term)[1]	Cohort 1 0.2 mg/kg or Pbo (n = 14)	Cohort 2 0.6 mg/kg or Pbo (n = 14)	Cohort 3 1.8 mg/kg or Pbo (n = 16)	All Participants (n = 44)
Infusion related reaction (IRR)[2]	**1 (7.1%)**	**4 (28.6%)**	**12 (75.0%)**	**17 (38.6%)**
COVID-19	0	7 (50.0%)	4 (25.0%)	11 (25.0%)
Headache	3 (21.4%)	4 (28.6%)	1 (6.2%)	8 (18.2%)
Fall	5 (35.7%)	1 (7.1%)	1 (6.2%)	7 (15.9%)
Back pain	1 (7.1%)	2 (14.3%)	2 (12.5%)	5 (11.4%)
Anemia[3]	**1 (7.1%)**	**0**	**3 (18.8%)**	**4 (9.1%)**
Arthralgia	3 (21.4%)	0	1 (6.2%)	4 (9.1%)
C-reactive protein (CRP) increased[2]	**0**	**0**	**3 (18.8%)**	**3 (6.8%)**
Dizziness	0	1 (7.1%)	2 (12.5%)	3 (6.8%)
⋮				
Iron deficiency anemia[3]	**0**	**0**	**2 (12.5%)**	**2 (4.5%)**

IRR, infusion related reaction; MedDRA, Medical Dictionary for Regulatory Activities. [1] Blinded safety data by dosing cohorts (cut-off date: 30 June 2023). Please note that the ongoing Ph Ib/IIa study remains blinded to individual treatment assignments. Participants receiving trontinemab and Pbo in a respective dose cohort are presented together by dosing cohort to avoid unblinding at the individual level. [2] IRR incidence increased with increasing dose of the study drug (trontinemab or Pbo). Most IRRs occurred after administration of the first dose of the study drug (without premedication), were mild to moderate in severity and resolved with our without appropriate medication. Premedication (e.g., with paracetamol) appears to effectively mitigate the incidence and symptoms of IRRs. IRRs were associated with increases in acute phase proteins (e.g., CRP) in some participants. [3] A transient mild anemia was observed in 5 participants in cohort 3 (1.8 mg/kg). Trends of decreasing mean hemoglobin levels and decreasing red blood cell counts were recorded in all treatments groups (including Pbo), suggesting that frequent blood collection likely contributed to the anemia phenotype.

Low incidence of ARIA despite robust amyloid lowering at 1.8 mg/kg

One ARIA-E and one ARIA-H case occurred in cohort 3 (at 1.8 mg/kg trontinemab or Pbo)[1]

Total number of participants [events per participant], (%)[2]	Cohort 1 0.2 mg/kg or Pbo (n = 14)	Cohort 2 0.6 mg/kg or Pbo (n = 13)	Cohort 3 1.8 mg/kg or Pbo (n = 15)	All Participants (n = 42)
ARIA-E	0	0	1 [1] (6.7%)	1 (2.4%)
ARIA-H				
Microhemorrhage	0	0	0	0
Leptomeningeal hemosiderosis (LH)	0	0	1 [2] (6.7%)	1 [2] (2.4%)
Concurrent ARIA-E and ARIA-H	0	0	0	0
Macrohemorrhage	0	0	0	0

One participant in cohort 3 developed a radiographically mild symptomatic ARIA-E:

- detected on routine Day 22 MRI scan[3]; complete resolution on control MRI 4 weeks later
- temporally associated with mildly altered consciousness (transiently impaired attention)

Another participant in cohort 3 developed 2 asymptomatic ARIA-H events (LH)[4].

ARIA-H, Amyloid-Related Imaging Abnormalities-Microhemorrhages and Hemosiderin deposition [1] Blinded safety data by dosing cohorts (cut-off date: 30 June 2023). Please note that the ongoing Ph Ib/IIa study remains blinded to individual treatment assignments. Participants receiving trontinemab and Pbo in a respective dose cohort are presented together by dosing cohort to avoid unblinding at the individual level. [2] Only participants with at least one post-baseline MRI are counted. [3] Detected in left temporal lobe. [4] Left occipital LH (12 mm) on routine Day 162 MRI; right frontal LH (8 mm) on routine Day 281 MRI (Safety Follow-Up). ARIA-H was not associated with concurrent ARIA-E.

Summary

Trontinemab is a novel Brainshuttle™ Aβ antibody that crosses the blood brain barrier via active TfR1 mediated transcytosis at the capillary level.

In people with AD, trontinemab demonstrated rapid and robust amyloid plaque reduction at relatively low doses (1.8 mg/kg Q4W), compared with standard Aβ monoclonal antibodies.

Interim PD and safety data (including a low ARIA incidence) support further investigation of trontinemab in the ongoing Ph Ib/IIa Brainshuttle™ AD study.

Preliminary results provide pharmacodynamic proof-of-concept for Brainshuttle™ platform approach.

Acknowledgements

We thank
all the study participants and their families,
the investigators, and site staff
for their time and commitment to the
Brainshuttle™ AD study

Doing now what patients need next