RAPID DOSE-DEPENDENT AMYLOID PLAQUE DEPLETION WITH TRONTINEMAB, A NOVEL BRAINSHUTTLE™ ANTIBODY IN DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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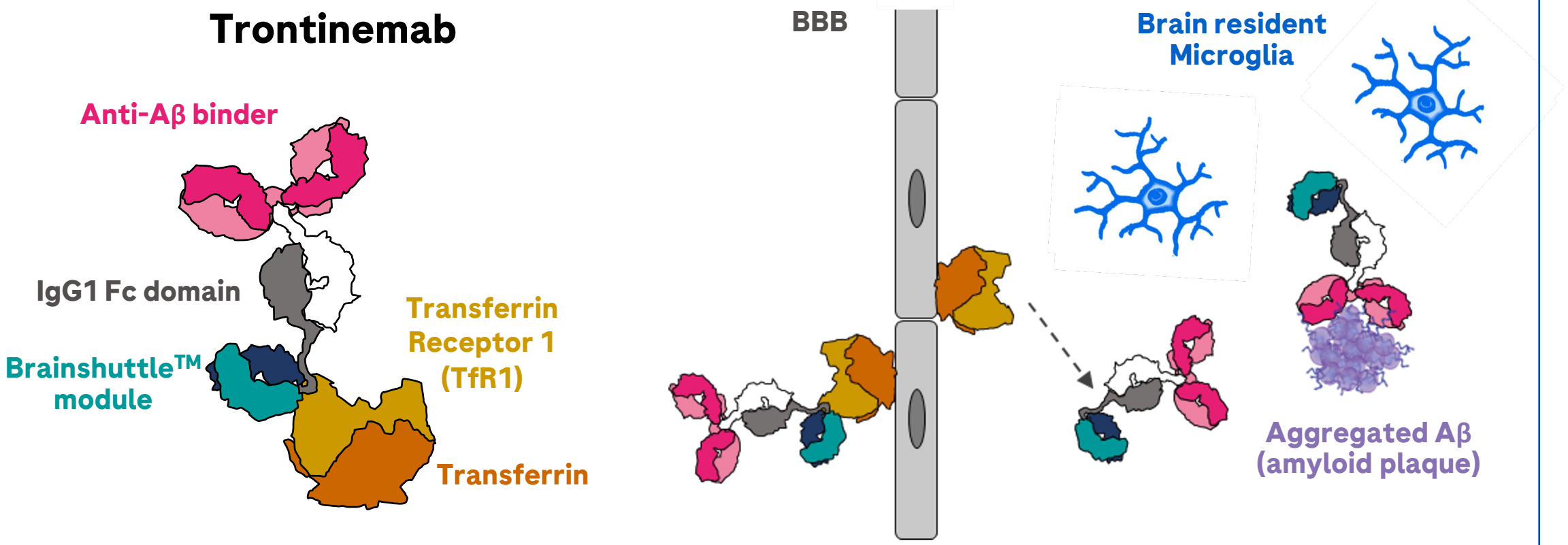
Disclosures

- **Luka Kulic, Fabien Alcaraz, Angeliki Thanasopoulou, Annamarie Vogt, Carsten Hofmann, Maddalena Marchesi, Jakub Wojtowicz, Gregory Klein, Ruth Croney, David Agnew, Denise Sickert, João A. Abrantes, Paul Delmar, and Iris Wiesel** are full-time employees and own stock in 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 significantly increases brain penetration and target engagement

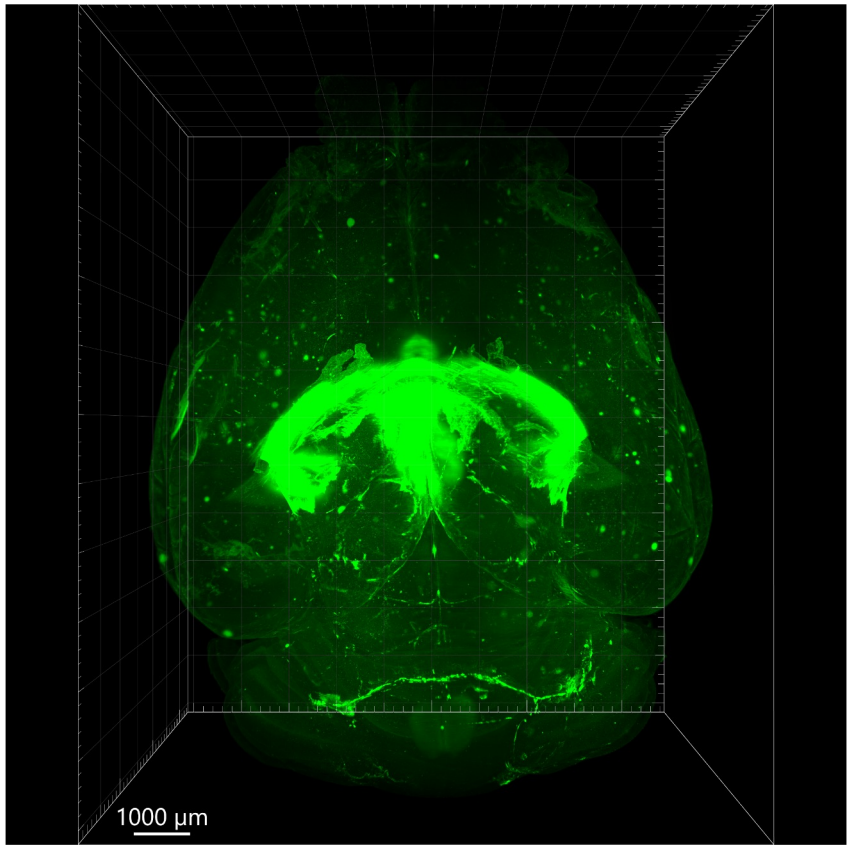


Trontinemab crosses the BBB via TfR1-mediated transcytosis at the capillary level

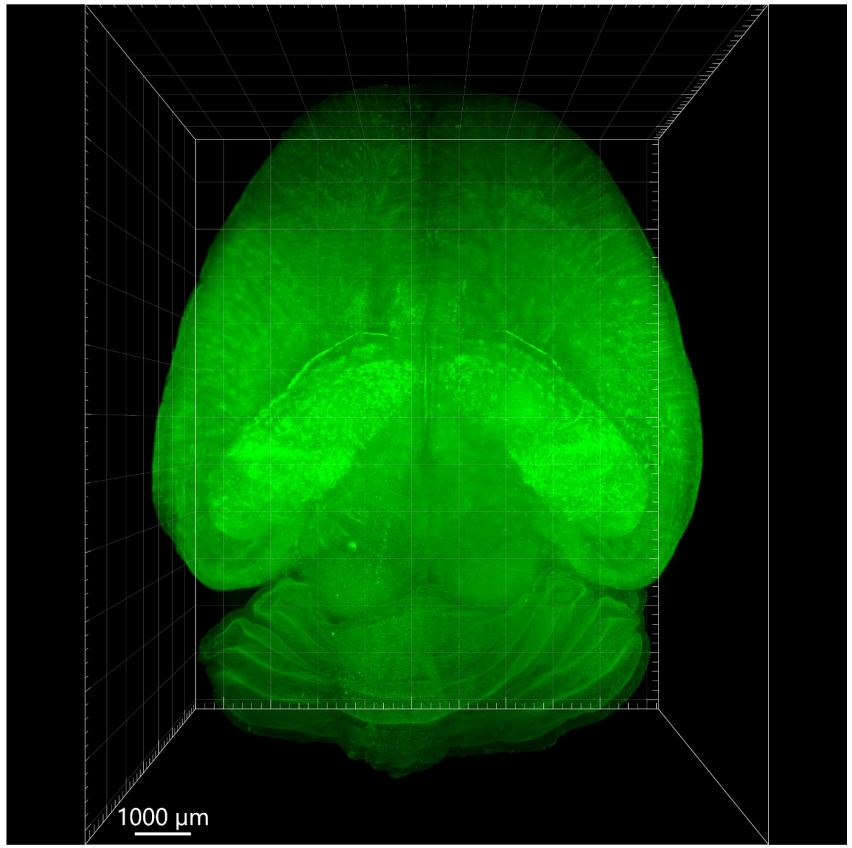
Aβ, amyloid beta; IgG1, immunoglobulin G1; Fc domain, fragment crystallisable domain; BBB, blood brain barrier.

Brainshuttle™ technology enables a higher brain exposure and broader CNS biodistribution of therapeutic antibodies

Standard IgG[1]



Brainshuttle™ IgG[1]



CNS, central nervous system; IV, intravenous. [1] Whole-brain imaging highlights the distribution of classical IgG vs. Brainshuttle™ IgG targeting a neuronal target in mouse brains. Mouse brains were perfused and chemically fixed 5 days after a single IV dose of fluorescently-labelled BrainshuttleTM-IgG (3 mg/kg) or two consecutive IV doses of IgG (2x 6 mg/kg). Images show a 3D volume rendering of the whole brain acquired with a light-sheet microscope.

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

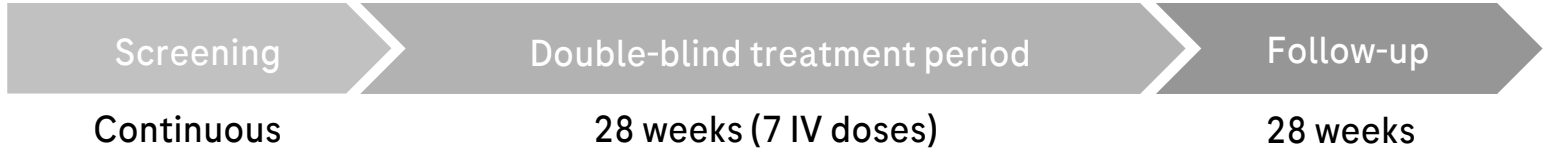
Primary Objective	Endpoints
Safety and Tolerability	Nature, frequency, severity, and timing of AEs, including labs, vital signs, physical and neurological examination, ECG, and brain MRI

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 is a Phase Ib/IIa dose escalation study

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.

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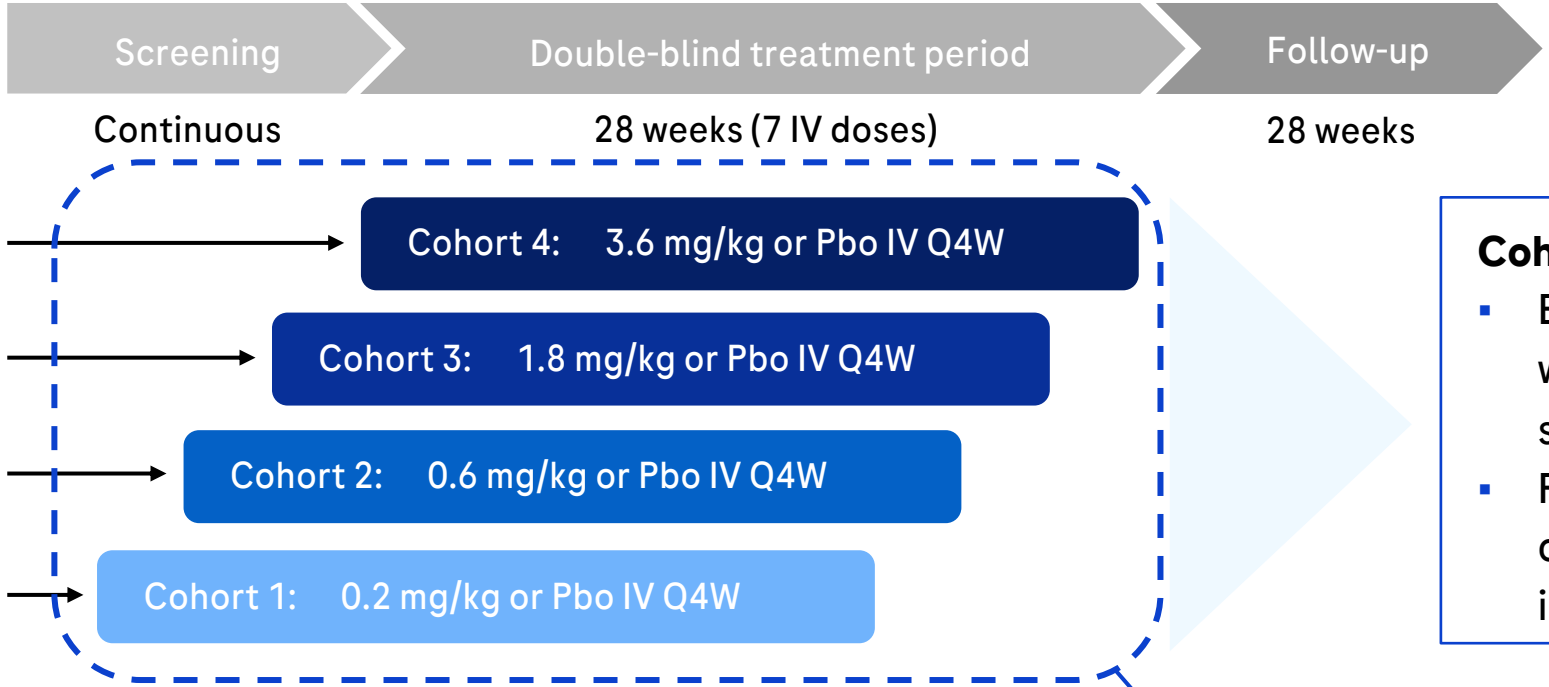

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Amyloid PET	★		★			★	
MRI	★	★	★	★			★
CSF	★				★		

Interim analysis (October 23, 2023): incl. ***Cohort 4 snapshot data at 12 weeks*** *(PK, PD and safety)*

* Day 78 amyloid PET only in cohorts 3 and 4

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

Baseline characteristics are consistent across cohorts

Interim analysis[1] included data from 15 participants in cohort 4 (3.6 mg/kg) at BL[2]

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)	Cohort 4[1] 3.6 mg/kg or Pbo (n = 15)
Age, mean (SD)	70.0 (7.4)	68.6 (9.2)	72.4 (8.0)	**71.9 (5.3)**
Sex, female, n (%)	12 (85.7%)	7 (50.0%)	10 (62.5%)	**9 (60.0%)**
Race, white, n (%)	14 (100%)	14 (100%)	16 (100%)	**14 (93.3%)**
Weight, kg, mean (SD)	60.6 (8.6)	70.0 (12.1)	66.8 (13.1)	**68.6 (13.7)**
CDR-GS, n (%)				
0.5	4 (28.6%)	6 (42.9%)	8 (50.0%)	**7 (50.0%)**
1	6 (42.9%)	8 (57.1%)	7 (43.8%)	**7 (50.0%)**
2	4 (28.6%)	0	1 (6.2%)	**0**
CDR-SB, mean (SD)	5.8 (2.8)	4.8 (1.9)	5.3 (2.9)	**4.8 (1.4)**
MMSE, mean (SD)	20.9 (3.2)	20.4 (4.7)	19.8 (2.8)	**20.7 (2.4)**
***APOE ε4* number of alleles, n (%)**				
0 *ε4*	4 (28.6%)	7 (50.0%)	6 (37.5%)	**5 (33.3%)**
1 *ε4*	7 (50.0%)	6 (42.9%)	8 (50.0%)	**7 (46.7%)**
2 *ε4*	3 (21.4%)	0	2 (12.5%)	**3 (20.0%)**
Missing data	0	1 (7.1%)	0	**0**

SD, standard deviation; APOE, apolipoprotein E. CDR-SB, Clinical Dementia Rating-Sum of Boxes. [1] Snapshot date: 23 October 2023. [2] At snapshot date, BL data from 15 participants (12 on active, 3 on Pbo) and 12-week data (including amyloid PET data) from 10 participants (8 on active, 2 on Pbo) enrolled in cohort 4 were available.

Plasma PK and ADAs

Low incidence of ADAs with no impact on PK in cohort 4 (3.6 mg/kg) up to 12 weeks

PK profile after administration of dose 1 of 3.6 mg/kg was consistent with PK model predictions.

At interim analysis, ADAs (low titer) were detected in one participant in cohort 4 on day 85.

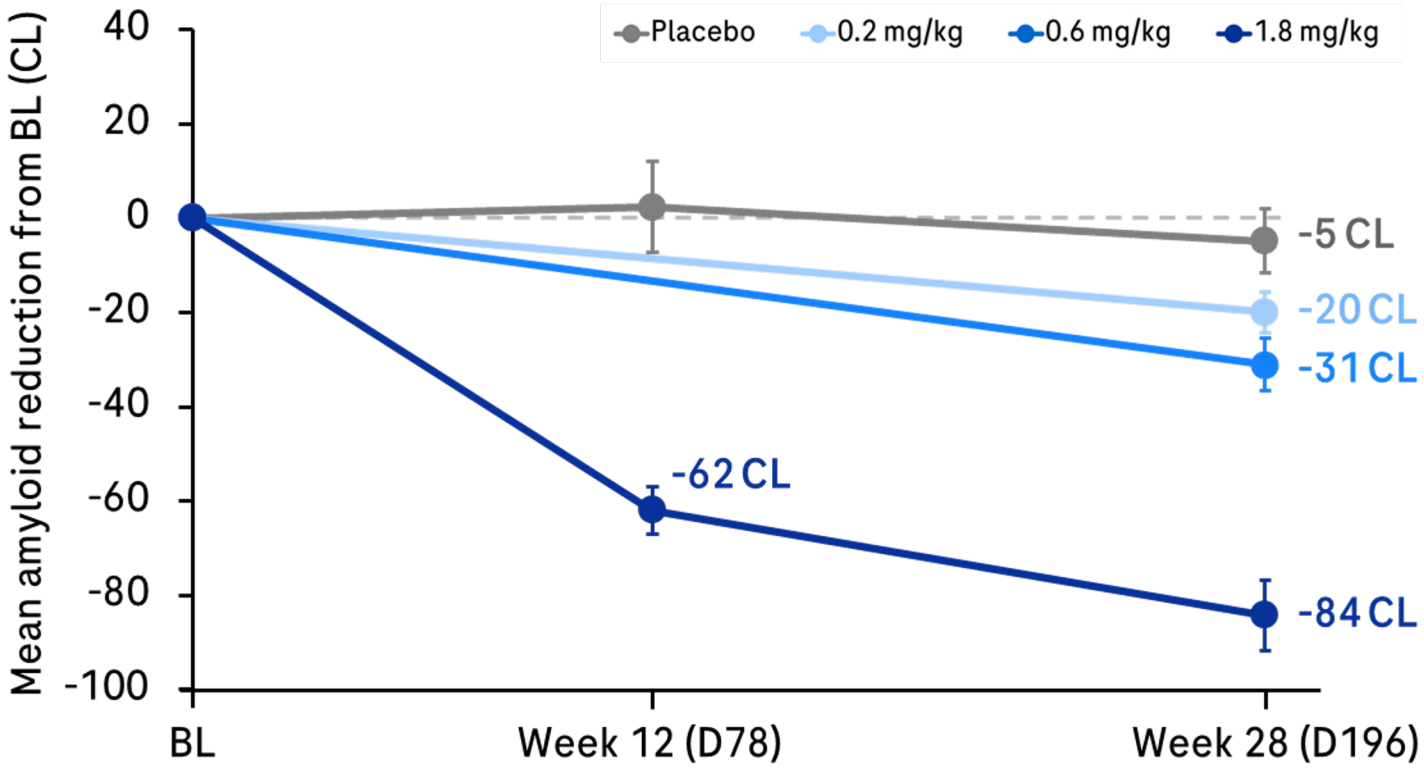
ADAs did not appear to impact PK in ADA positive participant in cohort 4 .

Preliminary cohort 4 results are in line with observed trends from cohorts 1 to 3: overall lower ADA incidence, lower ADA titers and reduced impact of ADAs on PK with increasing dose[1].

Snapshot date: 23 October 2023. ADA, anti-drug antibody. [1] Kulic et al., presented at CTAD 2023, Boston, USA.

Dose-dependent amyloid lowering with trontinemab (cohorts 1 to 3)

Mean amyloid PET change from baseline[1]

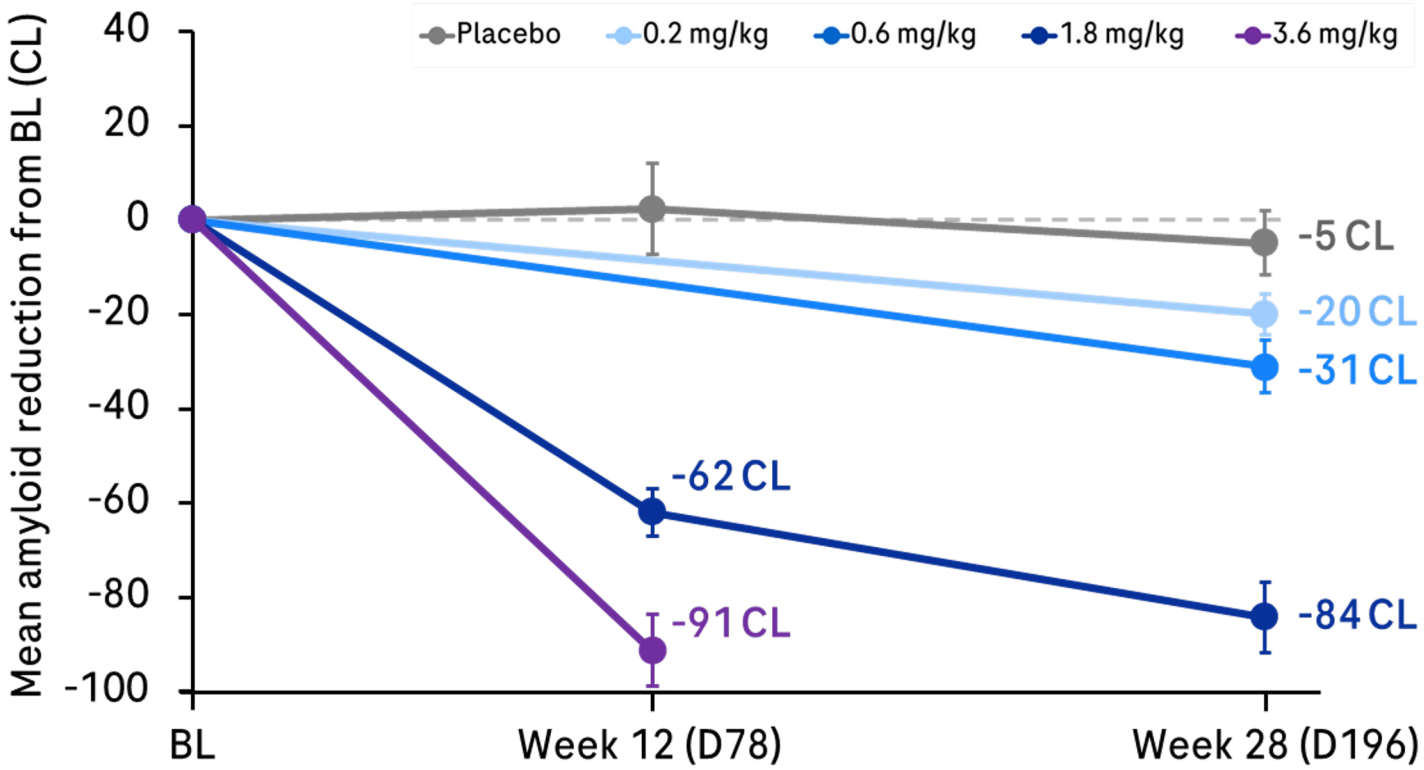


Placebo	n = 12	n = 5	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8

Snapshot date: 23 October 2023. [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).

Further acceleration of amyloid plaque reduction at 3.6 mg/kg

Mean amyloid PET change from baseline[1]



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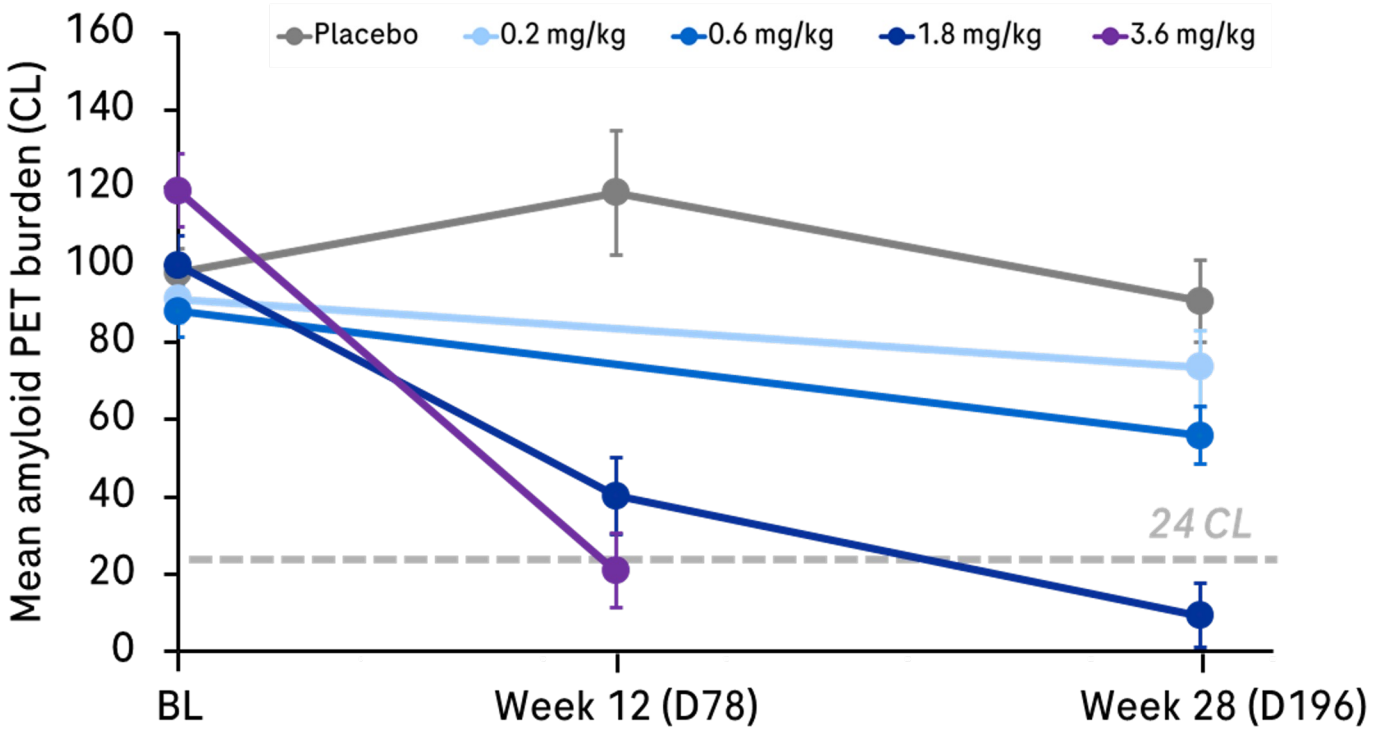
Majority of participants at 3.6 mg/kg amyloid negative at 12 weeks

5 out of 8 participants below the amyloid positivity threshold at interim analysis[1]



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3.6 mg/kg	**n = 12**	**n = 8**	-

Visit	Mean amyloid value in CL at visit (% amyloid negative (<24.1 CL))				
	Pbo	0.2 mg/kg	0.6 mg/kg	1.8 mg/kg	3.6 mg/kg
BL	98 CL (0%)	91 CL (0%)	88 CL (0%)	100 CL (0%)	**119 CL (0%)**
Week 12	119 CL (0%)	-	-	40 CL (36%)	**21 CL (63%) ***
Week 28	91 CL (0%)	74 CL (0%)	56 CL (10%)	9 CL (75%)	-

* 5/8 (63% of participants) <24.1 CL,

4/8 (50%) <11 CL at 3.6 mg/kg after 12 weeks

Snapshot date: 23 October 2023. [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 study discontinuations due to AE

12-week interim analysis

Total number of participants, (%)	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)	Cohort 4 3.6 mg/kg or Pbo (n = 15)
Participants with ≥1 AE	12 (85.7%)	14 (100%)	16 (100%)	**12 (80%)**
Total number of AEs	58	84	113	**52**
Deaths	0	0	0	**0**
Serious AE	1 (7.1%)	1 (7.1%)	0	**2 (13.3%)**
Fall	1 (7.1%)[2]	0	0	**0**
Pulmonary embolism	0	1 (7.1%)[3]	0	**0**
Urinary tract infection	0	0	0	**1 (6.7%)[4]**
Ischemic stroke	0	0	0	**1 (6.7%)[5]**
Serious AE related to blinded study drug	0	0	0	**0**
Study discontinuations due to AE	0	0	2 (12.5%)[6]	**0**

Snapshot date: 23 October 2023.

[1] Blinded safety data by dosing cohorts (data snapshot: 23 October 2023). The study remains ongoing and blinded to individual treatment assignments (randomization active to placebo 4:1). Participants receiving trontinemab and placebo in a respective dose cohort are presented together by dosing cohort to avoid unblinding. Please note the shorter follow-up time in participants in cohort 4 compared to the other cohorts: at snapshot date (23 October 2023), BL data from 15 participants (12 on active, 3 on Pbo) and 12-week data from 10 participants (8 on active, 2 on Pbo) enrolled in cohort 4 were available. [2] Two fall events (Grade 1 and 2) leading to hospitalization in a participant with a preexisting gait imbalance and occasional falls. [3] Grade 2 pulmonary embolism resulting in hospitalization related to recent hallux valgus surgery. [4] Grade 2 UTI leading to hospitalization in a participant with benign prostatic hyperplasia. [5] Grade 3 cerebral ischemia/infarct associated with aphasia leading to hospitalization, in a participant with multiple risk factors (preexisting lacunar infarcts and evidence of significant cerebrovascular disease, untreated hypercholesterolemia, insufficiently controlled hypertension, history of smoking (20 pack-years). [6] Both discontinuations after Grade 2 IRR that was not premedicated (one after first dose, another after second dose of blinded study drug).

Relevant AEs and MRI findings: IRR, anemia and ARIA[1]

Lower IRR incidence with premedication; one mild anemia; no ARIA-E / ARIA-H in cohort 4 to date

12-week interim analysis

Total number of participants with at least one AE , (%)	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)	Cohort 4 3.6 mg/kg or Pbo (n = 15)
Infusion related reaction (IRR)[2]	1 (7.1%)	4 (28.6%)	12 (75.0%)	**7 (46.7%)**
Anemia[3]	2 (14.3%)	0	5 (31.2%)	**1 (6.7%)**

Total number of participants with event [events per participant], (%)	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)	Cohort 4 3.6 mg/kg or Pbo (n = 14)
ARIA-E[4]	0	0	1 [2] (6.7%)	**0**
ARIA-H[5]				
Microhemorrhage	0	0	0	**0**
Leptomeningeal hemosiderosis (LH)	0	0	1 [2] (6.7%)	**0**
ARIA-E with concurrent ARIA-H	0	0	0	**0**
Macrohemorrhage	0	0	0	**0**

Snapshot date: 23 October 2023.
IRR, infusion related reaction; MedDRA, Medical Dictionary for Regulatory Activities. ARIA-E, Amyloid-Related Imaging Abnormalities-Edema. ARIA-H, Amyloid-Related Imaging Abnormalities-Microhemorrhages and Hemosiderin deposition.Radiologic ARIA-E severity according to 5-point grading scale (Bracoud et al., *Alzheimer's & dementia: the journal of the Alzheimer's Association* (2017)..

[1] Blinded safety data by dosing cohorts (data snapshot: 23 October 2023). The study remains ongoing and blinded to individual treatment assignments (randomization active to placebo 4:1). Participants receiving trontinemab and placebo in a respective dose cohort are presented together by dosing cohort to avoid unblinding. Please note the shorter follow-up time in participants in cohort 4 compared to the other cohorts: at snapshot date (23 October 2023), BL data from 15 participants (12 on active, 3 on Pbo) and 12-week data from 10 participants (8 on active, 2 on Pbo) enrolled in cohort 4 were available.

[2] Common IRR symptoms include fever, chills, and headache. In cohorts 1-3, most IRRs occurred after administration of the first study drug dose (without premedication), were mild to moderate in severity and resolved with our without appropriate medication. Subsequently, routine premedication with paracetamol/nonsteroidal anti-inflammatory drugs was implemented in cohorts 3 and 4, which reduced the incidence and symptoms of IRRs. [3] A transient mild anemia was observed in 5 participants in cohort 3 and in one participant in cohort 4. Trends of decreasing mean hemoglobin levels and decreasing red blood cell counts were recorded in all treatments groups (including placebo), suggesting that frequent blood collection likely significantly contributed to the anemia phenotype. [4] One participant in cohort 3 developed two episodes of ARIA-E: first, on routine Day 22 MRI scan, radiographically mild, temporally associated with mildly impaired attention over approximately one week, complete radiographic resolution within 4 weeks; second, on routine on Day 281 MRI, radiographically mild+, asymptomatic, complete radiographic resolution within 8 weeks. [5] One participant in cohort 3 developed 2 asymptomatic ARIA-H findings not concurrent with ARIA-E; one left occipital LH (12 mm) on routine Day 162 MRI, then one right frontal LH (8 mm) on routine Day 281 MRI.

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 and 3.6 mg/kg), compared with standard anti-Aβ monoclonal antibodies.
- Preliminary results at 3.6 mg/kg reveal further acceleration of amyloid plaque reduction and amyloid negativity in a majority of participants already after 12 weeks of treatment.
- Sustained low ARIA incidence (no ARIA-E/ARIA-H at 3.6 mg/kg so far) and overall favourable safety and tolerability profile support further investigation in ongoing Brainshuttle™ AD study.

Acknowledgements

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all the study participants and their families,
the investigators, and site staff
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Brainshuttle™ AD study

Doing now what patients need next