LATEST INTERIM RESULTS FROM THE BRAINSHUTTLE™ AD STUDY, A PHASE IB/IIA STUDY OF TRONTINEMAB IN PEOPLE WITH ALZHEIMER'S DISEASE

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Disclosures

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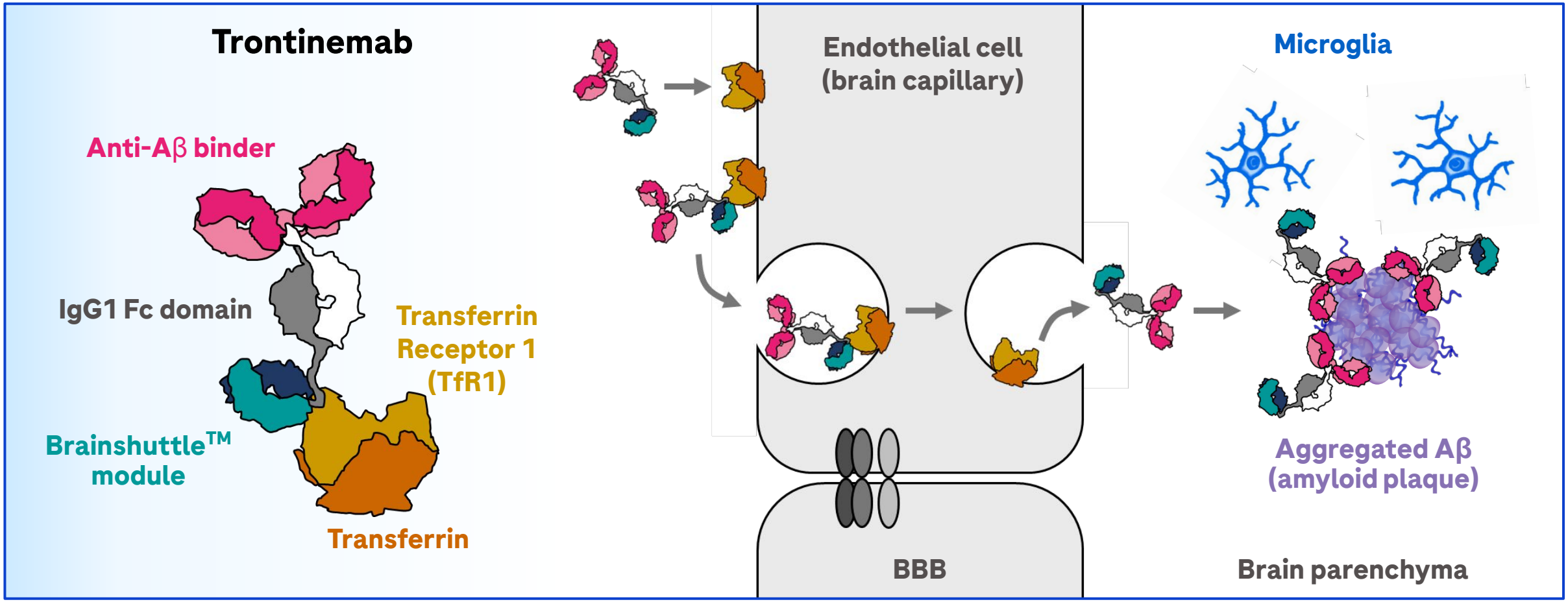
- **Silke Ahlers** is an external business partner of F. Hoffmann-La Roche Ltd.

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™ AD study design

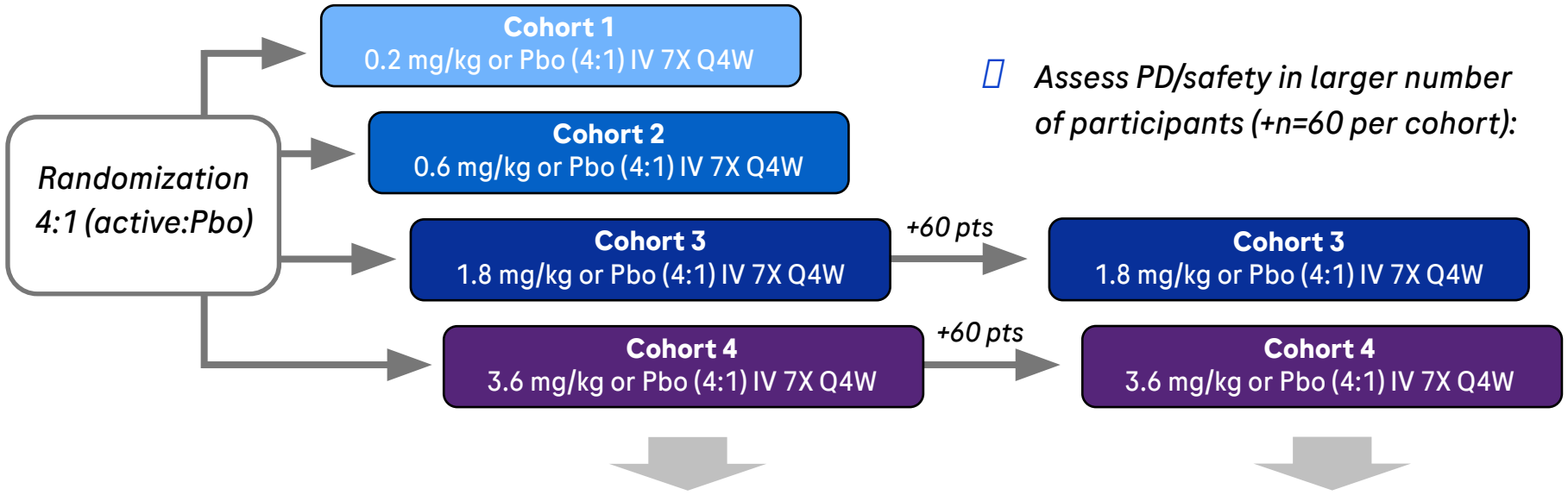
Phase Ib/IIa study assessing the safety, tolerability, PK and PD of trontinemab in participants with AD

- **Study Population:** MCI due to AD or mild-to-moderate AD[1]; amyloid PET: >50 CL; MMSE: 18–28; CDR-GS: 0.5-2

Dose Escalation (Part 1): n=60

Dose Expansion (Part 2): n=120

PK/PD (Part 3): n=30



- *Assess PD/safety in larger number of participants (+n=60 per cohort):*

- *Assess the PK/PD effect of different dosing regimens*
- *Open label*

Open Label Extension (Part 4): offered to all study participants enrolled in Part 1, 2 and 3

PK, pharmacokinetics; PD, pharmacodynamics; AD, Alzheimer's disease; MCI, Mild cognitive impairment; PET, Positron Emission Tomography; MMSE, Mini Mental State Examination; CDR-GS, Clinical Dementia Rating-Global Score; Pbo, Placebo. Q4W, every four weeks. [1] Consistent with the National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al, *Alzheimer's Dement* (2011); McKhann et al., *Alzheimer's Dement* (2011)).

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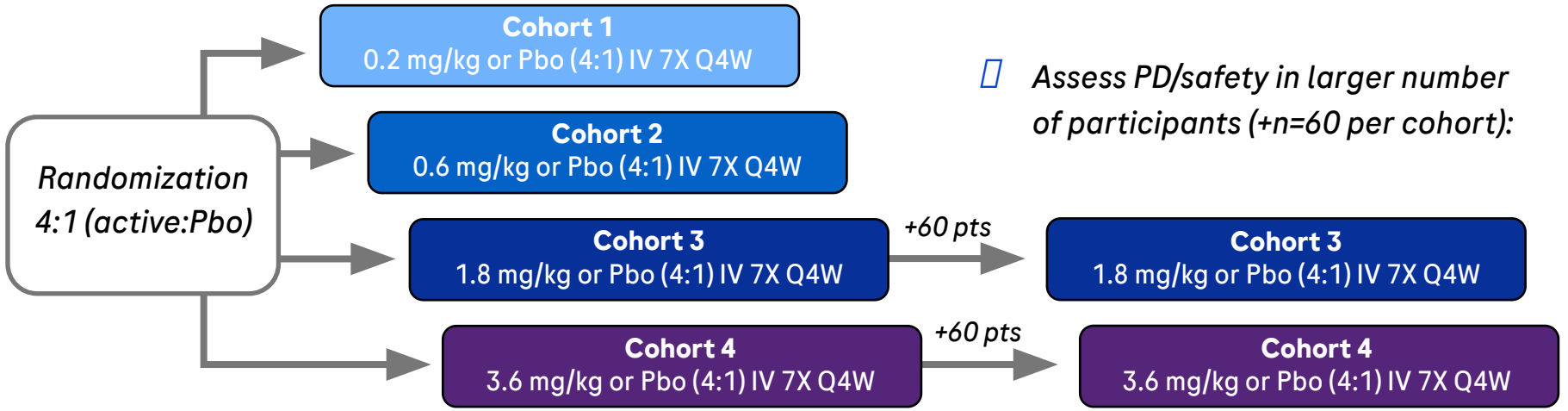

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- *Open label*

Interim analysis (September 2, 2024):

- ***Complete Part 1 data*** *(Safety + PD)*
- ***Interim data of ongoing Part 2*** *(Safety)*

Open Label Extension (Part 4): offered to all study participants enrolled in Part

PK, pharmacokinetics; PD, pharmacodynamics; AD, Alzheimer's disease; MCI, Mild cognitive impairment; PET, Positron Emission Tomography; MMSE, Mini Mental State Examination; CDR-GS, Clinical Dementia Rating-Global Score; Pbo, Placebo. Q4W, every four weeks. [1] Consistent with the National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al, *Alzheimer's Dement* (2011); McKhann et al., *Alzheimer's Dement* (2011)).

Baseline characteristics at interim analysis[1]

Analysis included 160 participants enrolled in Part 1 and Part 2 of the Brainshuttle™ AD study

	Completed[1]				*Not yet completed (interim data)*[1]	
	PART 1 (n=60)				**PART 2 (n=100)**	
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 3.6 mg/kg or Pbo (n = 16)**	**Cohort 3 1.8 mg/kg or Pbo (n = 60)**	**Cohort 4 3.6 mg/kg or Pbo (n = 40)**
Age, mean (SD)	69.7 (7.3)	68.5 (9.1)	72.2 (7.9)	71.7 (5.2)	71.2 (6.8)	72.5 (7.3)
Sex, female, n (%)	12 (85.7%)	7 (50.0%)	10 (62.5%)	9 (56.2%)	40 (66.7%)	27 (67.5%)
Race, white, n (%)	14 (100%)	14 (100%)	16 (100%)	16 (100%)	53 (88.3%)	33 (82.5%)
Weight, kg, mean (SD)	60.6 (8.4)	70.1 (12.1)	66.8 (13.0)	69.5 (13.8)	67.2 (14.9)	70.0 (17.0)
CDR-GS, n (%)						
0.5	4 (28.6%)	6 (42.9%)	8 (50.0%)	9 (56.2%)	41 (68.3%)	20 (50.0%)
1	6 (42.9%)	8 (57.1%)	7 (43.8%)	7 (43.8%)	17 (28.3%)	17 (42.5%)
2	4 (28.6%)	0	1 (6.2%)	0	2 (3.3%)	1 (2.5%)
Missing data	0	0	0	0	0	2 (5.0%)
CDR-SB, mean (SD)	5.8 (2.8)	4.8 (1.9)	5.3 (2.9)	4.6 (1.6)	4.0 (2.0)	4.3 (2.0)
MMSE, mean (SD)	20.9 (3.2)	20.4 (4.7)	19.8 (2.8)	21.0 (2.6)	23.1 (3.7)	23.5 (3.1)
***APOE ε4* number of alleles, n (%)**						
0 *ε4*	4 (28.6%)	7 (50.0%)	6 (37.5%)	5 (31.2%)	25 (41.7%)	12 (30.0%)
1 *ε4*	7 (50.0%)	6 (42.9%)	8 (50.0%)	8 (50.0%)	27 (45.0%)	22 (55.0%)
2 *ε4*	3 (21.4%)	0	2 (12.5%)	3 (18.8%)	6 (10.0%)	5 (12.5%)
Missing data	0	1 (7.1%)	0	0	2 (3.3%)	1 (2.5%)

Snapshot date: 2 September 2024. SD, standard deviation; APOE, apolipoprotein E. [1] Please note the shorter mean follow-up time in participants enrolled in ongoing Part 2 compared to participants enrolled in completed Part 1: at snapshot date (2 September 2024), participants in cohort 3 Part 2 had received a mean (SD) number of 5.4 (1.6) doses, whereas participants in cohort 4 Part 2 had received a mean number of 2.9 (1.6) doses.

Blinded safety profile[1]

Number of participants with safety events or study discontinuations due to AE

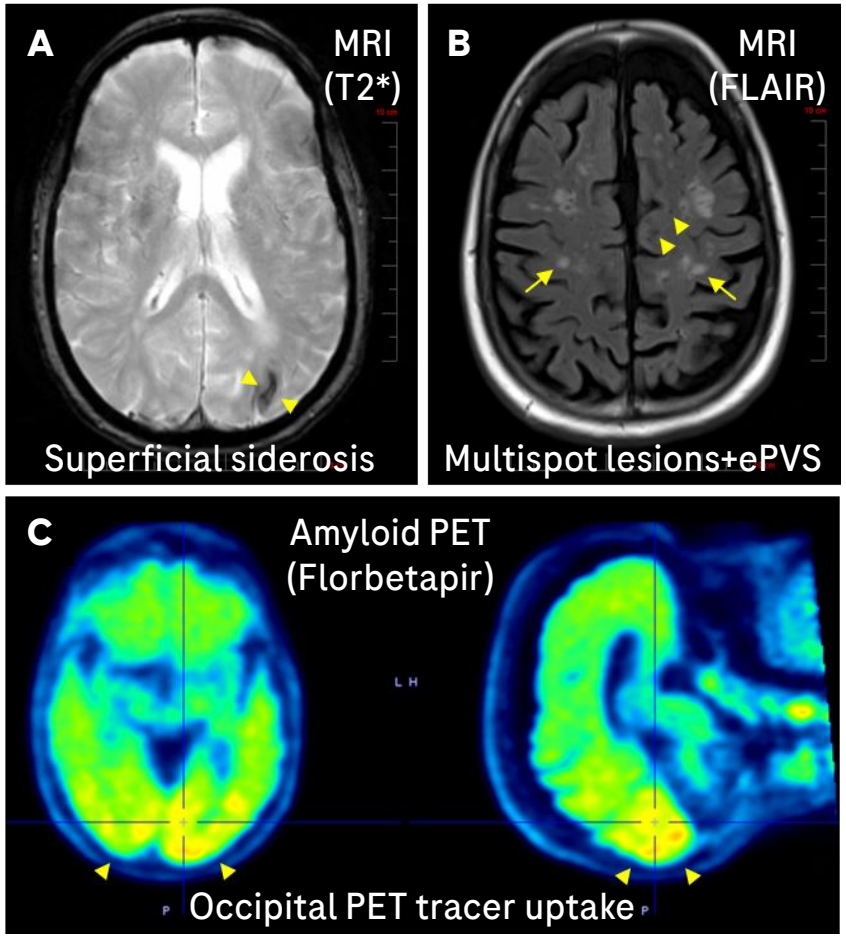
	Completed[1]				*Not yet completed (interim data)*[1]	
	PART 1 (n=60)				**PART 2 (n=100)**	
Total number of participants (%)	**Cohort 1 0.2 mg/kg or Pbo (n = 14)**	**Cohort 2 0.6 mg/kg or Pbo (n = 14)**	**Cohort 3 1.8 mg/kg or Pbo (n = 16)**	**Cohort 4 3.6 mg/kg or Pbo (n = 16)**	**Cohort 3 1.8 mg/kg or Pbo (n = 60)**	**Cohort 4 3.6 mg/kg or Pbo (n = 40)**
Participants with ≥1 AE	12 (85.7%)	13 (92.9%)	15 (93.8%)	15 (93.8%)	52 (86.7%)	25 (62.5%)
Total number of AEs	33	61	90	100	192	68
Deaths	0	0	0	0	1 (1.7%)[7]	0
Serious AE	1 (7.1%)	1 (7.1%)	0	2 (12.5%)	2 (3.3%)[7,8]	0
Fall	1 (7.1%)[2]	0	0	0	0	0
Pulmonary embolism	0	1 (7.1%)[3]	0	0	0	0
Urinary tract infection	0	0	0	1 (6.3%)[4]	0	0
Ischemic stroke	0	0	0	1 (6.3%)[5]	0	0
IRR	0	0	0	0	1 (1.7%)[8]	0
Cerebral macrohemorrhage	0	0	0	0	1 (1.7%)[7]	0
Serious AE related to blinded study drug	0	0	0	0	2 (3.3%)[7,8]	0
Participants withdrawn from study due to AE	0	0	2 (12.5%)[6]	0	0	0

AE, adverse event; IRR, infusion related reaction. [1] Blinded safety data by dosing cohorts (data snapshot: 2 September 2024). The study remains ongoing and blinded to individual treatment assignments (randomization active to placebo 4:1 in both Part 1 and 2). Participants receiving trontinemab and placebo in a respective dose cohort are presented together by dosing cohort to avoid unblinding. Please note the shorter mean follow-up time in participants enrolled in ongoing Part 2 compared to participants enrolled in completed Part 1: at snapshot date, participants in cohort 3 Part 2 had received a mean (SD) number of 5.4 (1.6) doses, whereas participants in cohort 4 Part 2 had received a mean number of 2.9 (1.6) doses. [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 cerebrovascular risk factors. [6] Both discontinuations after Grade 2 IRR that was not premedicated (one after first dose, another after second dose of blinded study drug). [7] On study day 44, a 78-year-old female participant on 1.8 mg/kg trontinemab was admitted to the emergency room with acute stroke-like neurological signs/symptoms including a right sided fixed gaze and left sided weakness. CT scan upon admission revealed a life-threatening right frontal lobe cerebral macrohemorrhage of 60x40x55mm with some blood in the subarachnoid space and leaking into the ventricle, mass effect with midline shift and brain herniation. The diagnosis of an amyloid-related lobar hemorrhage was made, a surgical intervention was not indicated. Wish of relatives to proceed with comfort care measures. Participant passed away two days later. [8] Grade 1 IRR (increase in temperature) following late infusion on a Friday afternoon. Participant was referred to an external hospital to monitor temperature as a precautionary measure.

Case of intracerebral macrohemorrhage in Part 2 of the study

Key risk factor: probable cerebral amyloid angiopathy (CAA) with superficial siderosis at screening

- On study day 44, a 78-year-old woman in cohort 3 Part 2 experienced a right frontal lobar macrohemorrhage and passed away:
  - **Screening MRI: large occipital area of superficial siderosis (A), consistent with diagnosis of probable CAA[1].**
  - Superficial siderosis in people with CAA is considered a key MRI prognostic risk factor for future macrohemorrhages[2].
  - Additional imaging findings (B, C) + participant's genetic predisposition (APOE ε2/ε3 genotype) may have contributed to increased CAA risk[3-5].
- In-depth evaluation of the case led to **protocol amendment and exclusion of participants with superficial siderosis** from the study.
  - Measures in line with recently published appropriate use recommendations for approved anti-Aβ therapies[6].



CAA, cerebral amyloid angiopathy; MRI, Magnetic Resonance Imaging; SS, superficial siderosis; ePVS, enlarged perivascular spaces; FLAIR, Fluid attenuated inversion recovery; SAE. Serious adverse event. A: ~3.5 cm left occipital superficial siderosis lesion (arrowheads). B: "Multispot" pattern subcortical white matter lesions (arrows) and ePVS in centrum semiovale bilaterally (arrrowheads). C: pronounced occipital amyloid PET tracer uptake (arrowheads). [1] Charidimou et al., *Lancet Neurology* (2022): The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. [2] Charidimou et al., *Neurology* (2019): Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy - a meta-analysis. [3] Johnson et al., *Ann Neurol* (2007): Imaging of amyloid burden and distribution in cerebral amyloid angiopathy . [4] Greenberg et al., *Neurology* (1998): Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. [5] Biffi et al., *Ann Neurology* (2010): Variants at APOE Influence Risk of Deep and Lobar Intracerebral Hemorrhage. [6] Cummings et al., *J Prev Alzheimers Dis* (2023): Lecanemab: Appropriate Use Recommendations.

Reduced incidence of IRR and limited, mostly mild anemia in Part 2 so far

Successful mitigation of IRR by implementation of premedication in cohort 4 (Part 1) and in Part 2. Lower incidence of anemia in Part 2 may be explained by lower blood volume drawn in Part 2 vs. Part 1.

	Completed[1]				*Not yet completed (interim data)*[1]	
	PART 1 (n=60)				**PART 2 (n=100)**	
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 = 16)**	**Cohort 3 1.8 mg/kg or Pbo (n = 60)**	**Cohort 4 3.6 mg/kg or Pbo (n = 40)**
Infusion related reaction (IRR)[2]	1 (7.1%)	4 (28.6%)	12 (75.0%)	7 (43.8%)	23 (38.3%)	13 (32.5%)
Anemia[3]	1 (7.1%)	0	5 (31.2%)	3 (18.8%)	8 (13.3%)	0

IRR, infusion related reaction; ARIA-H, Amyloid-Related Imaging Abnormalities-Microhemorrhages and Hemosiderin deposition. Radiologic ARIA-E severity according to 5-point grading scale (Bracoud et al., *Alzheimers Dementia* (2017)).

[1] Blinded safety data by dosing cohorts (data snapshot: 2 September 2024). The study remains ongoing and blinded to individual treatment assignments (randomization active to placebo 4:1 in both Part 1 and 2). Participants receiving trontinemab and placebo in a respective dose cohort are presented together by dosing cohort to avoid unblinding. Please note the shorter mean follow-up time in participants enrolled in ongoing Part 2 compared to participants enrolled in completed Part 1: at snapshot date, participants in cohort 3 Part 2 had received a mean (SD) number of 5.4 (1.6) doses, whereas participants in cohort 4 Part 2 had received a mean number of 2.9 (1.6) doses.

[2] In cohorts 1-3 (Part 1), most IRR occurred after administration of the first study drug dose (without premedication), were mild to moderate in severity and resolved with or without appropriate medication. Subsequently, routine premedication was implemented, which reduced the incidence and symptoms of IRR in cohort 4 Part 1 and in Part 2.

[3] A transient, mostly mild anemia was observed in 5 participants in cohort 3 Part 1 and in 3 participants in cohort 4 Part 1. In Part 2, the observed lower anemia incidences might be associated with less frequent blood collection implemented in Part 2.

Latest interim results support low ARIA incidence with trontinemab

3 ARIA-E cases occurred in Part 1 and Part 2 as of snapshot date on September 2nd, 2024

	Completed[1]				*Not yet completed (interim data)*[1]	
	PART 1 (n=60)				**PART 2 (n=95)**	
Total number of participants with event (%)	**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 = 16)**	**Cohort 3 1.8 mg/kg or Pbo (n = 60)**	**Cohort 4 3.6 mg/kg or Pbo (n = 35)**
ARIA-E[2]	0	0	1 (6.3%)	0	2 (3.3%)	0
ARIA-H	0	0	1 (6.3%)	0	4 (6.7%)	2 (5.7%)
Microhemorrhage	0	0	0	0	2 (3.3%)	2 (5.7%)
Superficial siderosis	0	0	1 (6.3%)	0	2 (3.3%)	0
Concurrent ARIA-E + ARIA-H	0	0	0	0	0	0

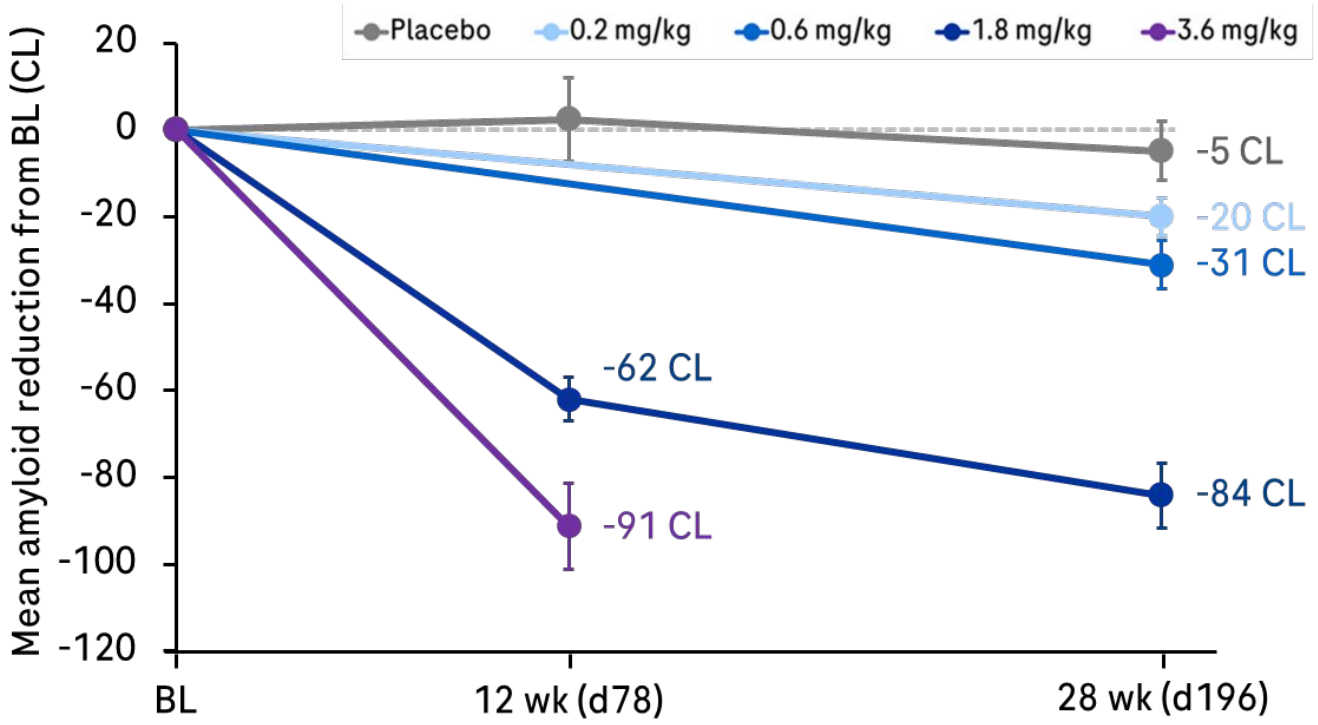
ARIA-E, Amyloid-Related Imaging Abnormalities-Edema/Effusion. ARIA-H, Amyloid-Related Imaging Abnormalities-Microhemorrhages and Hemosiderin deposition. Radiologic ARIA-E severity according to 5-point grading scale (Bracoud et al., *Alzheimers Dementia* (2017)).

[1] Blinded safety data by dosing cohorts (data snapshot: 2 September 2024). The study remains ongoing and blinded to individual treatment assignments (randomization active to placebo 4:1 in both Part 1 and 2). Participants receiving trontinemab and placebo in a respective dose cohort are presented together by dosing cohort to avoid unblinding. Please note the shorter mean follow-up time in participants enrolled in ongoing Part 2 compared to participants enrolled in completed Part 1: at snapshot date, participants in cohort 3 Part 2 had received a mean (SD) number of 5.4 (1.6) doses, whereas participants in cohort 4 Part 2 had received a mean number of 2.9 (1.6) doses.

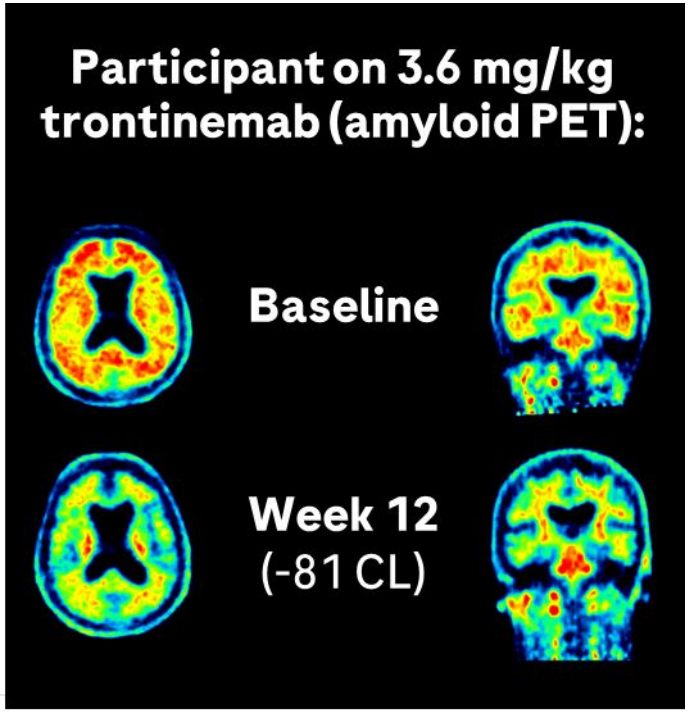
[2] One participant in cohort 3 Part 1 developed two episodes of ARIA-E: first, on routine Day 22 MRI scan, radiographically mild, temporally associated with mildly impaired attention over approximately one week, complete radiographic resolution within 4 weeks; second, on routine on Day 281 MRI, radiographically mild+, asymptomatic, complete radiographic resolution within 8 weeks. In cohort 3 Part 2, one participant developed a mild+ asymptomatic ARIA-E on routine Day 22 MRI, another participant developed a mild ARIA-E on routine Day 78 MRI. Both ARIA-E events in Part 2 resolved within 4 weeks.

Amyloid PET in Part 1 (Snapshot date: 23 October 2023)

Rapid and robust amyloid plaque depletion: -91 CL at 3.6 mg/kg after 12 weeks of treatment[1]



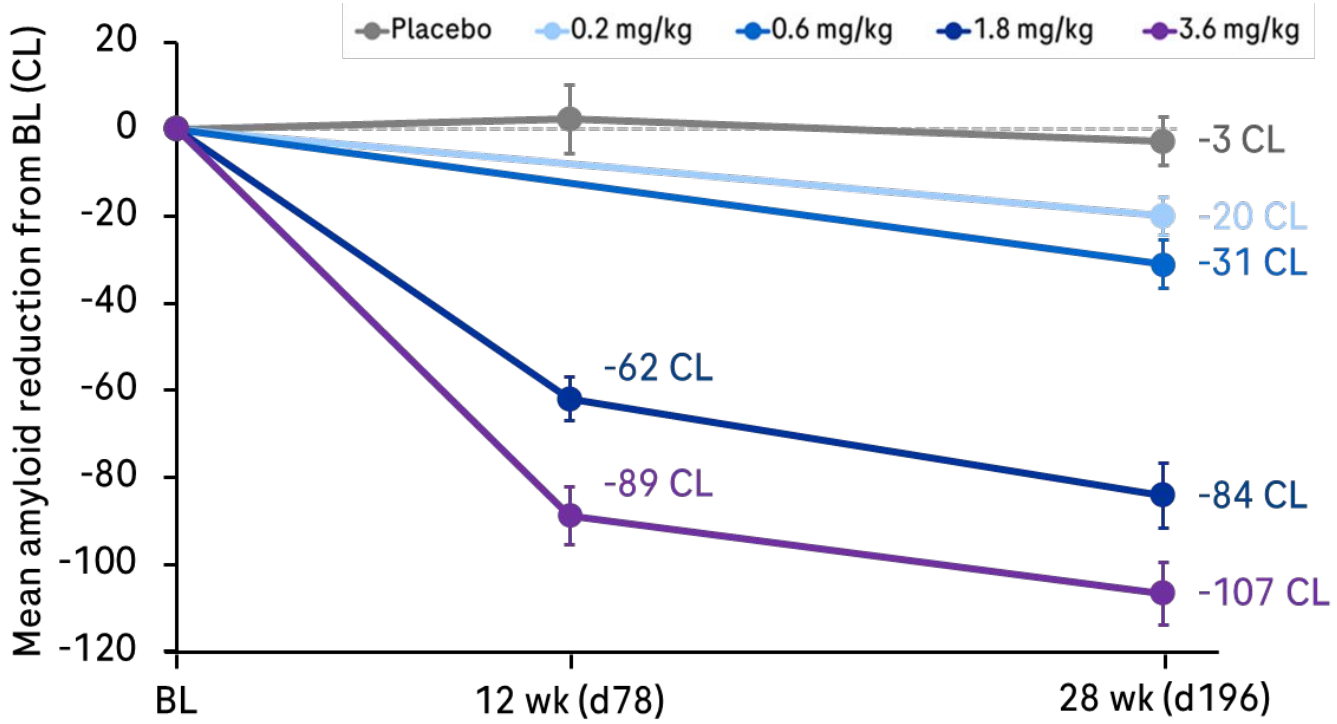
Placebo	n = 12	n = 5	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8
3.6 mg/kg	n = 12	n = 8	-



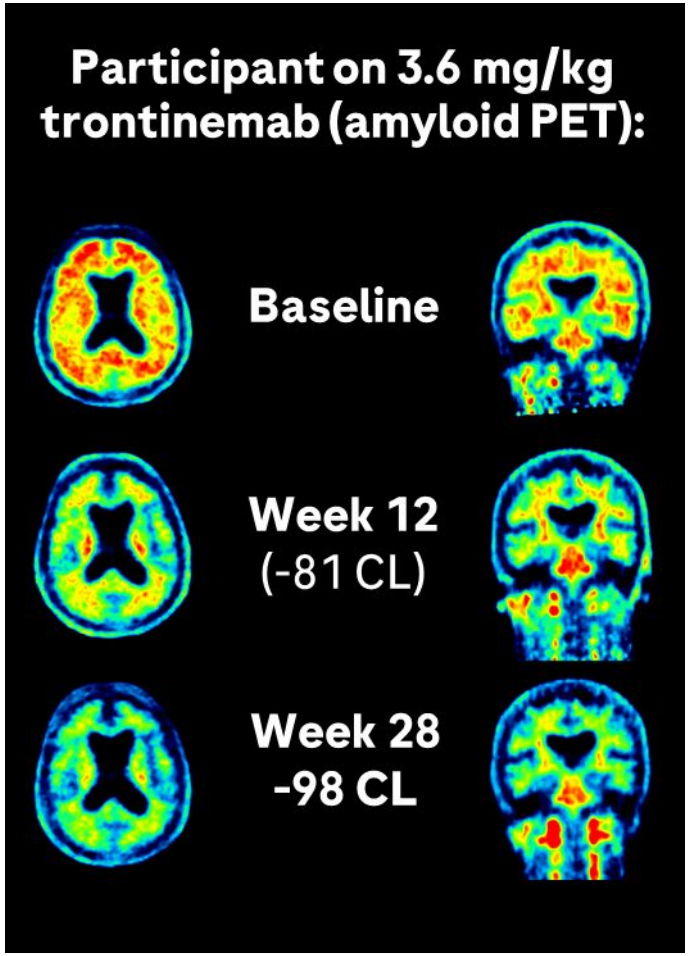
Snapshot date: 2 September 2024. [1] Mean values ±SE (standard errors) of available PET results at the different visit time points are plotted. CL, Centiloid units. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with Centiloid).

Amyloid PET in Part 1 (Snapshot date: 2 September 2024)

Rapid and robust amyloid plaque depletion: -107 CL at 3.6 mg/kg after 28 weeks of treatment[1]



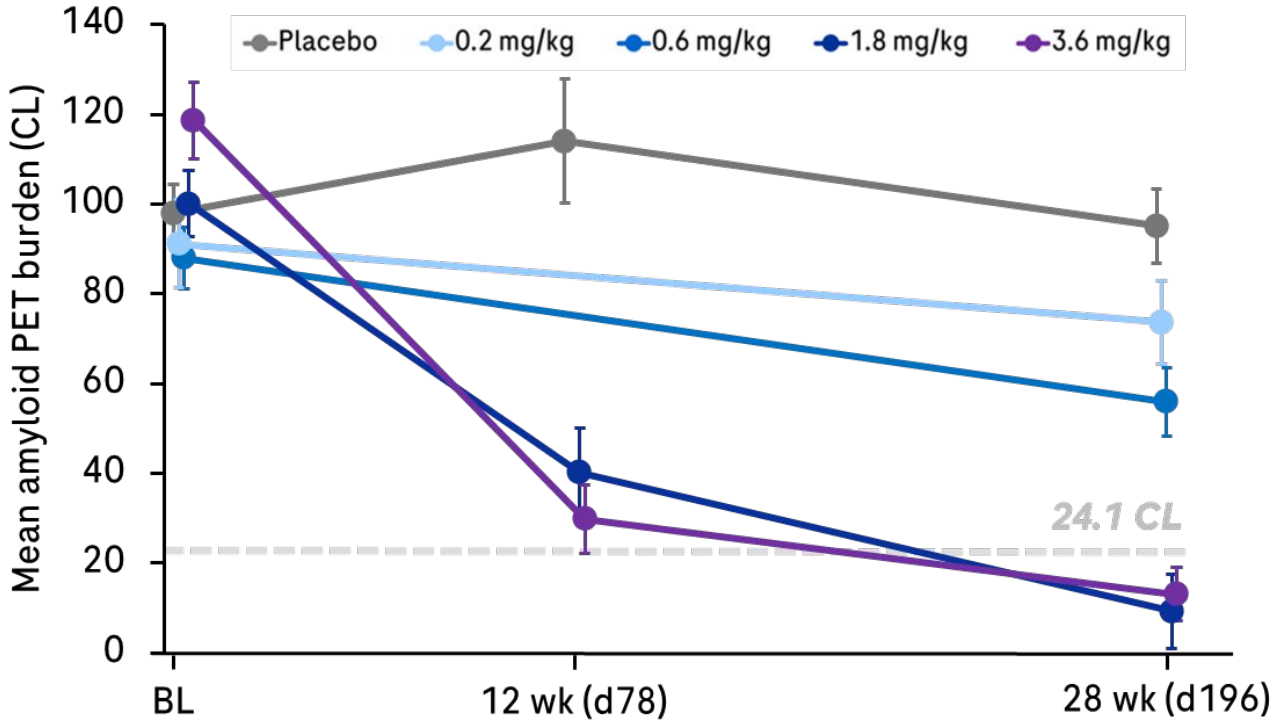
Placebo	n = 12	n = 6	n = 12
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8
3.6 mg/kg	n = 13	n = 13	n = 12



Snapshot date: 2 September 2024. [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).

Amyloid PET in Part 1 (Snapshot date: 2 September 2024)

Most participants on 3.6 mg/kg are amyloid negative at 28 weeks[1]



Placebo	n = 12	n = 6	n = 12
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
3.6 mg/kg	n = 13	n = 13	n = 12

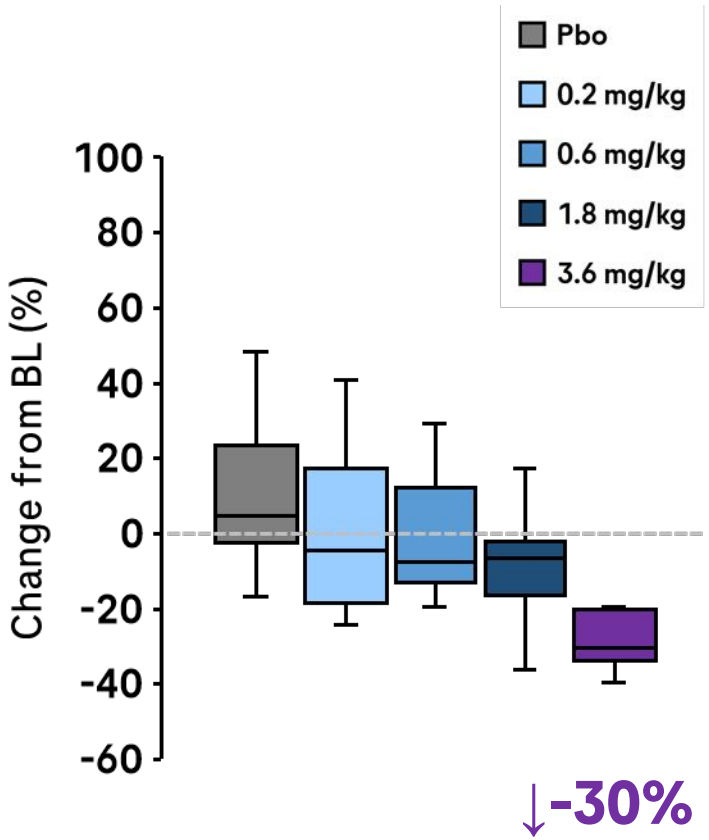
Visit	Mean amyloid value in CL at visit (% amyloid negative (<24.1 CL))				
	Pbo	0.2 mg/kg	0.6 mg/kg	1.8 mg/kg	3.6 mg/kg
BL	98 CL (0%)	91 CL (0%)	88 CL (0%)	100 CL (0%)	119 CL (0%)
Week 12	114 CL (0%)	-	-	40 CL (36%)	30 CL (46%)
Week 28	91 CL (0%)	74 CL (0%)	56 CL (10%)	9 CL (75%)	13 CL (67%)

Snapshot date: 2 September 2024. [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).

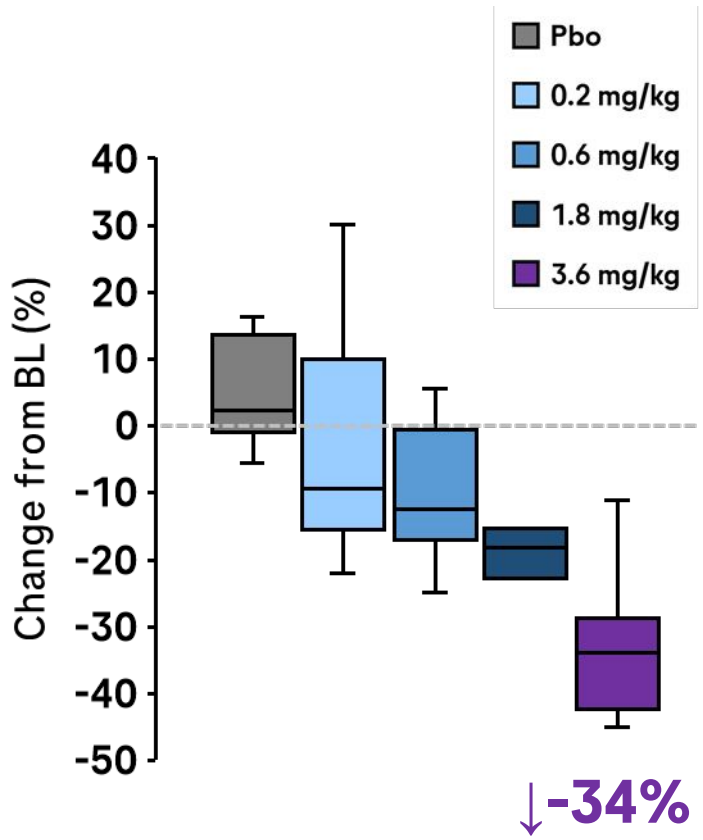
Preliminary fluid biomarker results (Part 1)

Dose-dependent, large magnitude effects of trontinemab on key downstream biomarkers in CSF

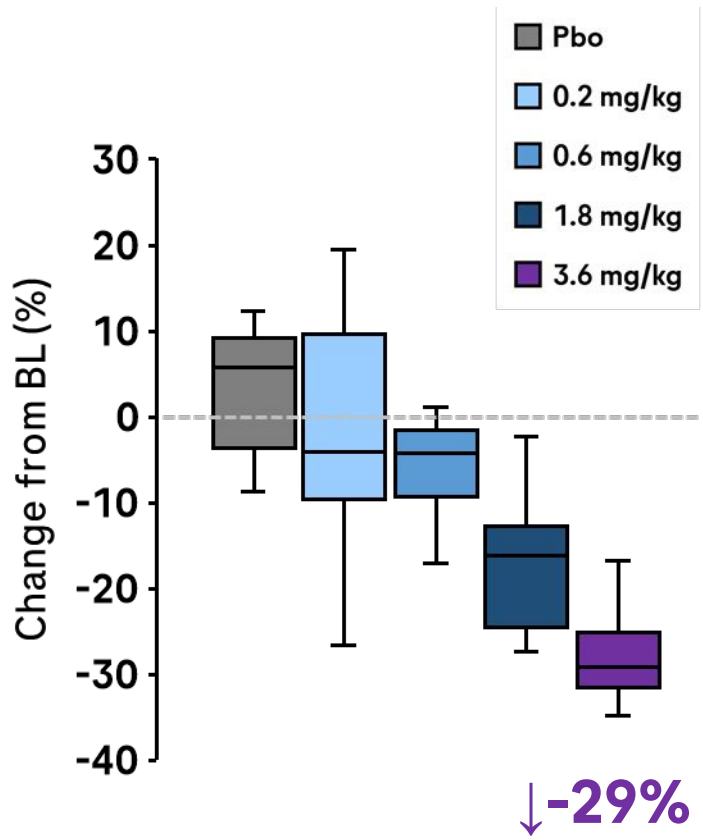
CSF total tau (week 25)



CSF ptau181 (week 25)



CSF Neurogranin (week 25)



Snapshot date: 2 September, 2024. CSF, cerebrospinal fluid. CSF samples were collected on study day 172 or study day 176 and were measured by the Roche NeuroToolKit (NTK), a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Sample size for CSF total tau: n=9 (Pbo), n=10 (0.2 mg/kg), n=8 (0.6 mg/kg), n=6 (1.8 mg/kg), n=9 (3.6 mg/kg); CSF Neurogranin: n=9 (Pbo), n=10 (0.2 mg/kg), n=8 (0.6 mg/kg), n=6 (1.8 mg/kg), n=10 (3.6 mg/kg); CSF ptau181 n=9 (Pbo), n=10 (0.2 mg/kg), n=8 (0.6 mg/kg), n=5 (1.8 mg/kg), n=10 (3.6 mg/kg). Outliers not plotted.

Summary

- Trontinemab has an overall favourable safety profile with very limited ARIA-E observed.
  - Lobar macrohemorrhage in a participant with significant risk factors and probable CAA led to a protocol amendment and exclusion of participants with superficial siderosis from the study.
- Results from the completed Part 1 of the Brainshuttle™ AD study demonstrated rapid and robust amyloid plaque depletion at 1.8 mg/kg and 3.6 mg/kg after 12 to 28 weeks of treatment.
- Preliminary Part 1 data suggest that rapid amyloid removal is accompanied by large magnitude changes in relevant downstream biomarkers including total tau, ptau181 and Neurogranin in CSF.
- Latest Brainshuttle™ AD study interim results in n=160 randomized participants support the continued expansion of the trontinemab program.

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