Roche Neurology Update

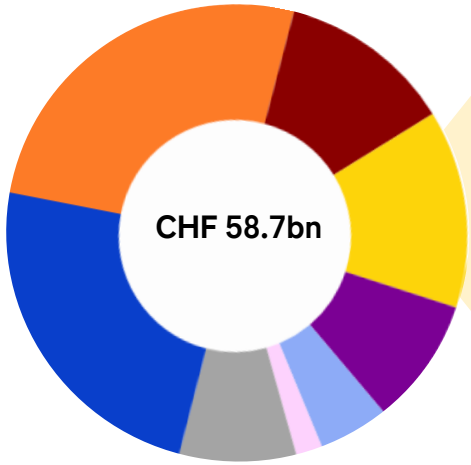
Virtual IR Event

March 11th 2024

Roche is #1 in Neurology

Neurology portfolio accounting already for 1/5 of Pharma sales

FY 2023 sales (YoY CER growth)



CHF 8.4bn +16%

- Diagnostics
- Oncology solid tumors
- Hematology
- Other pharma
- Neurology
- Immunology
- Ophthalmology
- Infectious diseases

OCREVUS® ocrelizumab

Ocrevus:
6.4 CHF bn
+13%

- Market leader in US/EU5 with 24% global patient share
- Further growth expected with SC approval in US / EU (expected 2024)
- HD Ocrevus (Ph3 data expected 2025)

Evrysdi risdiplam

Evrysdi:
1.4 CHF bn
+39%

- Global SMA market leader in patient share achieved in 2024
- Proven efficacy sustained for 4+ years with >15,000 pts treated to date
- The only non-invasive SMA therapy with at-home dosing
- High patient satisfaction (90% of pts remain on therapy in first 12 months)

ENSPRYNG™ satralizumab-mwge subcutaneous injection | 120 mg/mL

Enspryng:
0.3 CHF bn
+49%

- Strong growth in NMOSD with >4,000 pts treated
- High treatment satisfaction with Q4W SC administration in clinic or at home by patients or caregivers
- Development program in gMG, MOG-AD, AIE on-going

MS=multiple sclerosis; SC=subcutaneous; HD=high dose; SMA=spinal muscular atrophy; NMOSD=neuromyelitis optica spectrum disorders; Q4W=every 4 weeks; MOG-AD=myelin oligodendrocyte glycoprotein antibody-associated disease; AIE=autoimmune encephalitis; gMG=generalised myasthenia gravis

Late-stage pipeline updates scheduled for 2024/25

Upcoming IR events: "Diagnostics Day" on May 22nd and "ASCO Oncology Update" (date tbc)

Pharmaceuticals

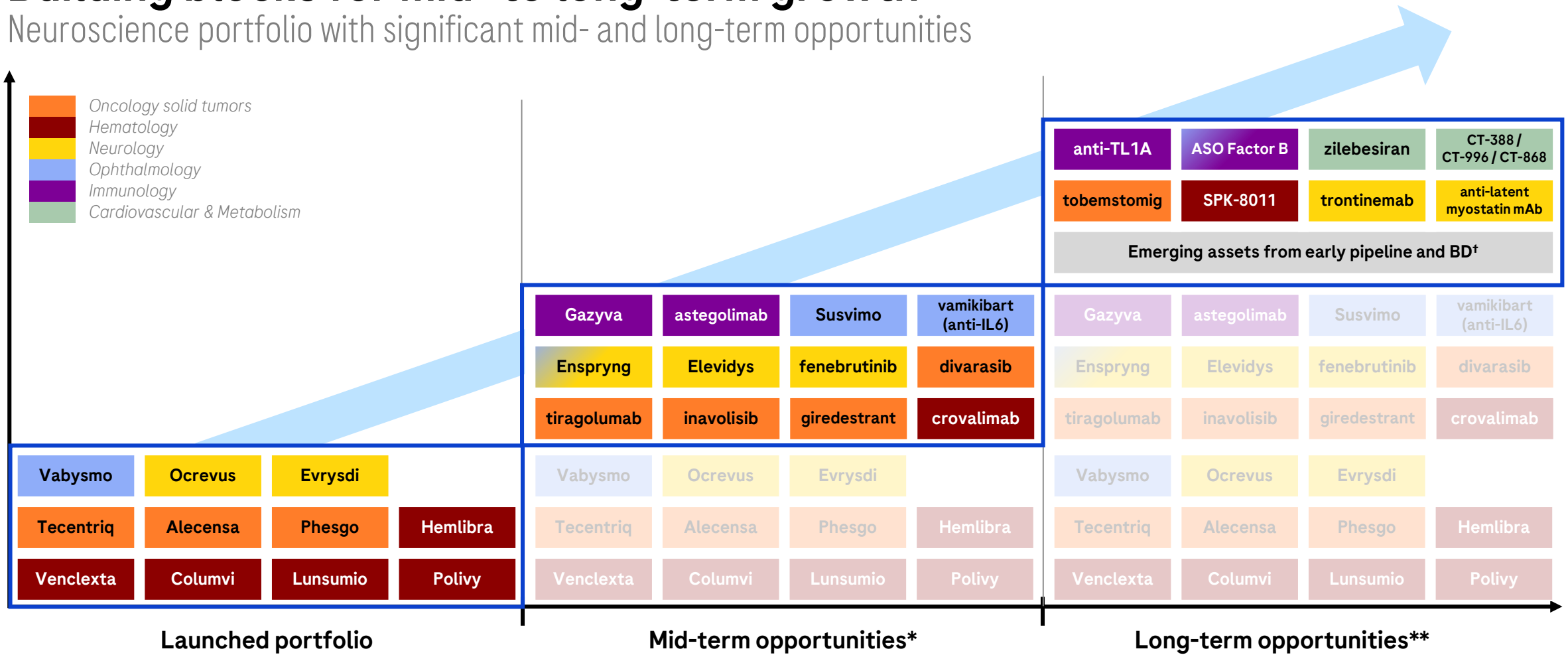
	NME	Indication	Newsflow	Timing
Oncology / Hematology	**tiragolumab**	NSCLC	Final Ph III data	H2 2024
	inavolisib	BC	US/EU filing	2024
	divarasib	NSCLC	Ph I/II readout	2024/25
	giredestrant	BC	Ph III readout	2025
Neurology	**Elevidys**	DMD	Ph III readout	2024/25
	prasinezumab	PD	Ph IIb readout	2024
	Evrysdi + GYM329	SMA	Ph II readout	2024
	trontinemab	AD	Ph I/II readout	2024
	fenebrutinib	MS	Ph III readout	2025
Immunology	**Gazyva**	LN	Ph III readout	2024
	anti-TL1A	IBD	Ph III initiation	2024
	astegolimab	COPD	Ph III readout	2025
Ophthalmology	**vamikibart (anti-IL6)**	DME/UME	Ph II/III readout	2024/25
	ASO factor B	GA	Ph II readout	2024
Cardiovascular & Metabolism	**zilebesiran**	HT	Ph II readout	2024
	CT-388/868/996 (GLP-1/GIP)	Obesity	Ph I/II readout	2024

Diagnostics

	Product	Description	Launch
Core Lab	**i601 mass spec**	Total solution for clinical mass spectrometry and first reagent ipack	2024
	cobas pro serology solution	Roche blood safety solution for the US donor screening market	2024
	cobas c703 & ISE neo	High-throughput clinical chemistry and ISE testing on cobas pro	2024
	Elecsys Amyloid Plasma Panel	Rule-out blood-based test for amyloid pathology detection in AD	2025
Molecular Lab	**cobas 6800/8800 v2.0**	Upgrade with increased testing flexibility, throughput and automation	2024
	cobas Respiratory flex	Novel TAGS® multiplex technology for respiratory testing on cobas x800	2024
	Next generation sequencing	Nanopore sequencer with unique sequencing by expansion technology	2025+
Diabetes Care	**Accu-Chek SmartGuide**	Roche's first generation continuous glucose monitoring solution	2024
Point of Care	**cobas Liat Resp. panel**	Detection & differentiation of four most prevalent respiratory targets	2024

Building blocks for mid- to long-term growth

Neuroscience portfolio with significant mid- and long-term opportunities



*mid-term defined as filing 2024-2026, **long-term defined as filing after 2026, BD=business development; †including GSM=Gamma-secretase modulator (GSM)

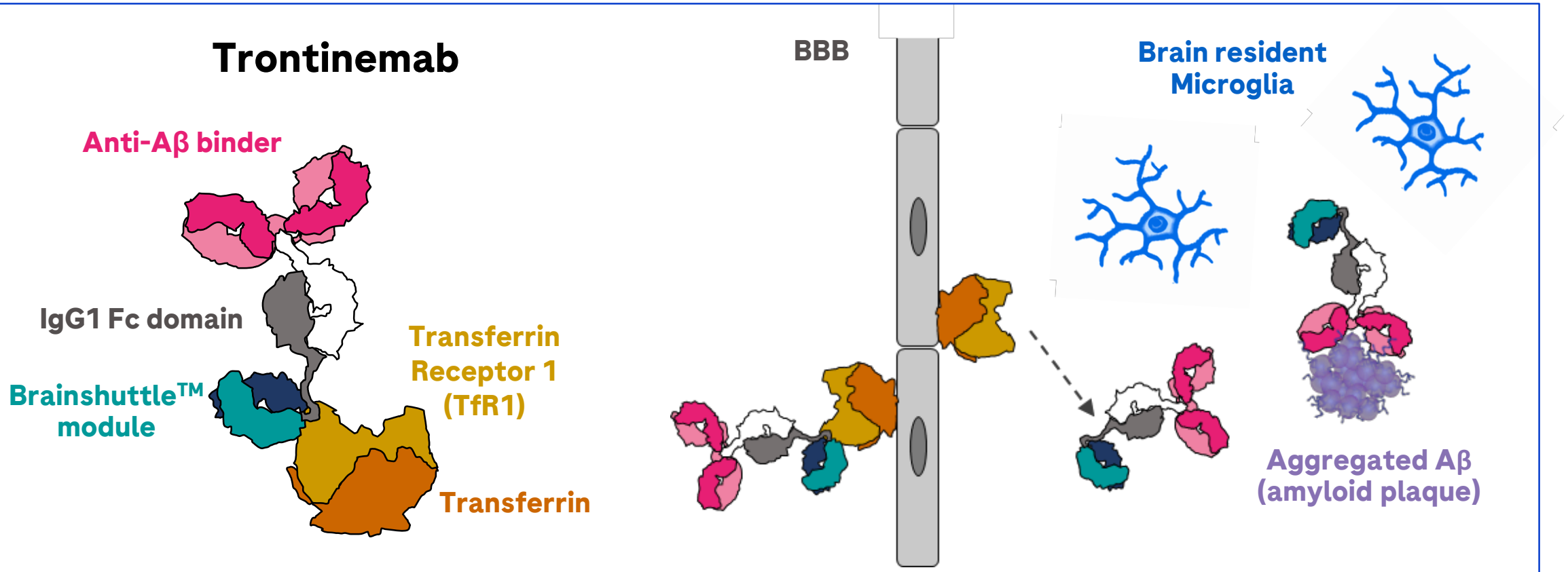
RAPID DOSE-DEPENDENT AMYLOID PLAQUE DEPLETION WITH TRONTINEMAB, A NOVEL BRAINSHUTTLE™ ANTIBODY IN DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Luka Kulic[1], Fabien Alcaraz[1], Angeliki Thanasopoulou[1], Annamarie Vogt[1], Carsten Hofmann[2], Maddalena Marchesi[3], Jakub Wojtowicz[3], Gregory Klein[1], Ruth Croney[4], David Agnew[4], Denise Sickert[2], João A. Abrantes[2], Silke Ahlers[5], Paul Delmar[6], Hanno Svoboda[1,7], Iris Wiesel[1]

9 March 2024 | AD/PD™ 2024

Trontinemab - a novel Brainshuttle™ antibody targeting Aβ

Active transport across the BBB significantly increases brain penetration and target engagement

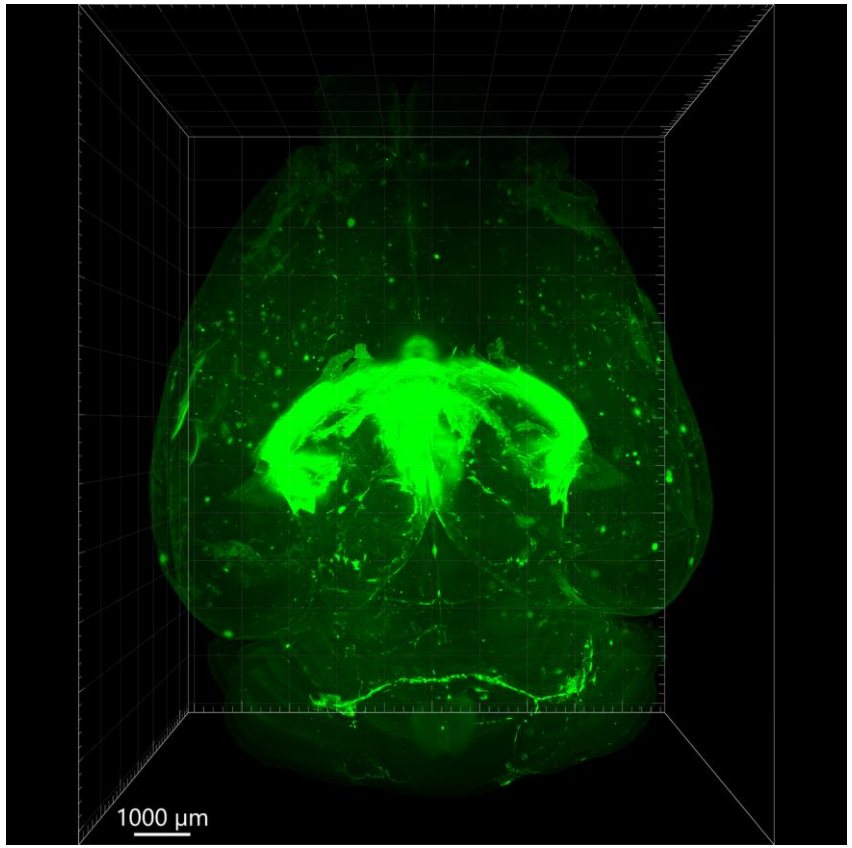


Trontinemab crosses the BBB via TfR1-mediated transcytosis at the capillary level

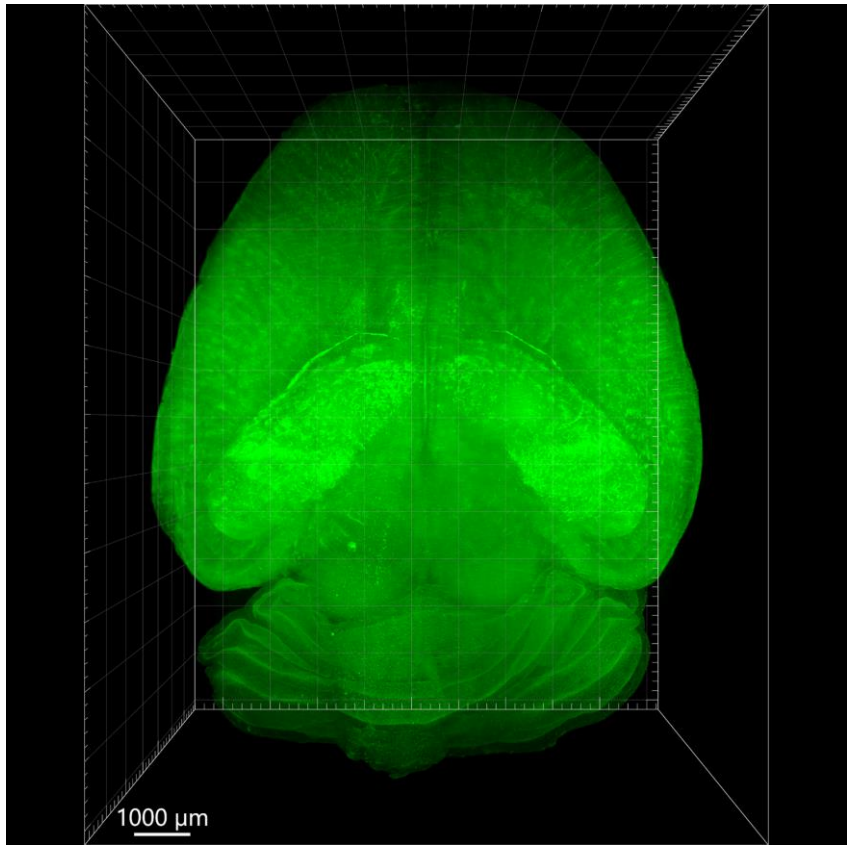
Aβ, amyloid beta; IgG1, immunoglobulin G1; Fc domain, fragment crystallisable domain; BBB, blood brain barrier.

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

Standard IgG[1]



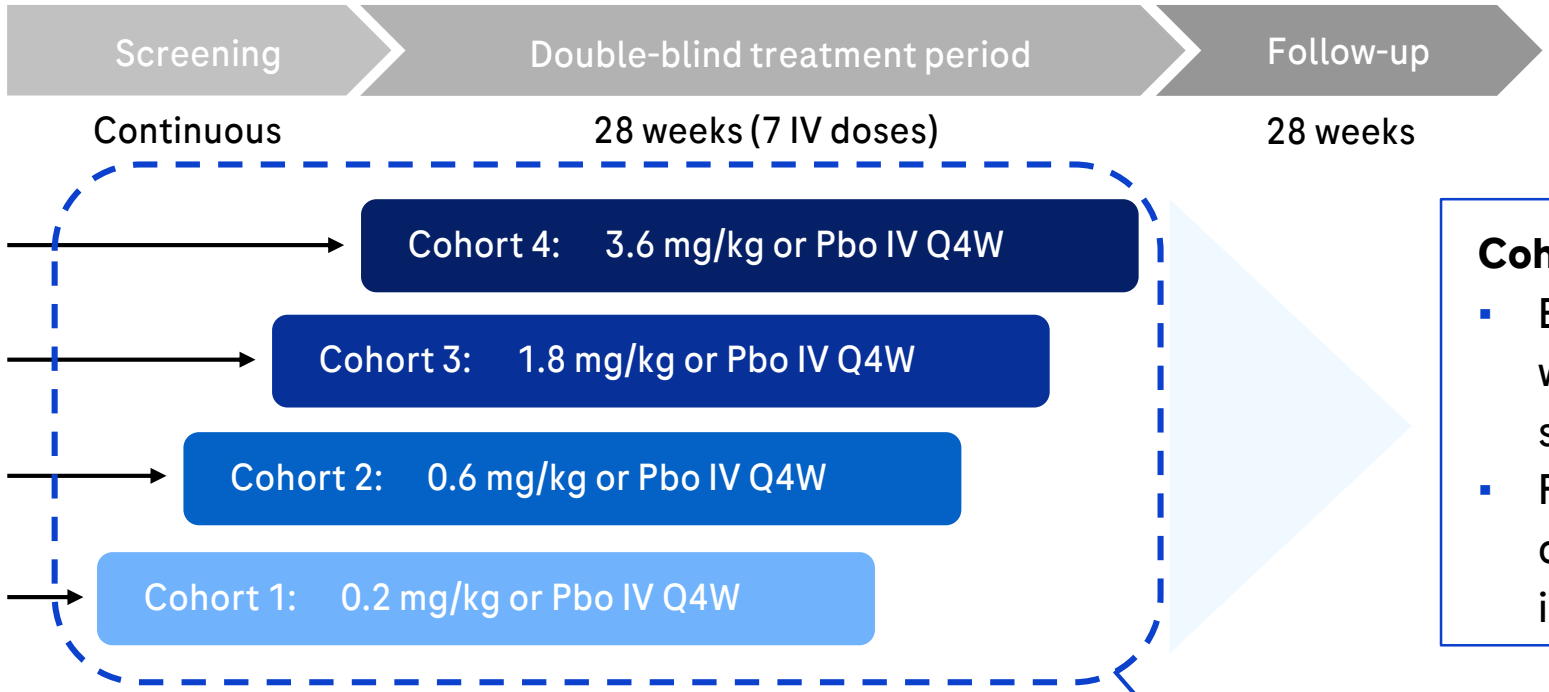
Brainshuttle™ IgG[1]



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 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 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	★				★		

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

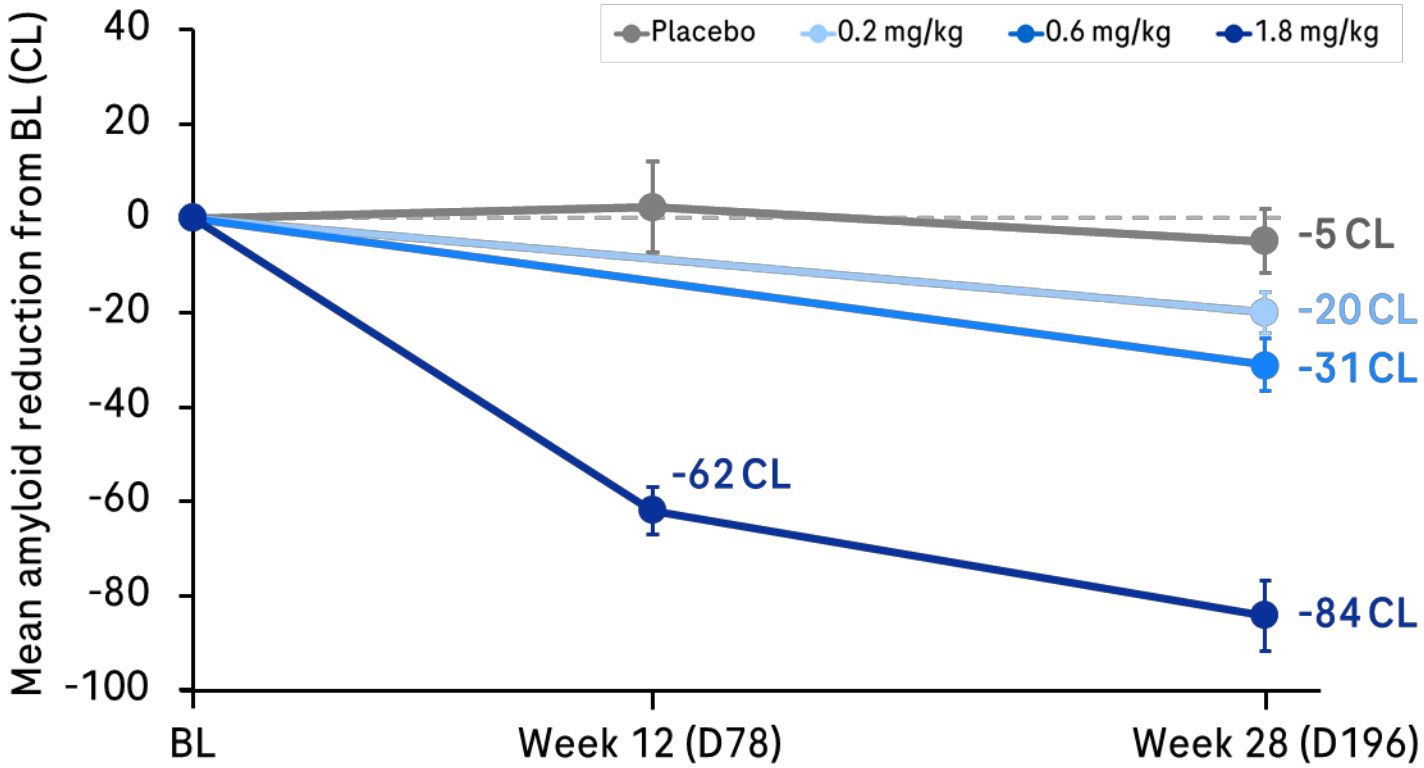
Interim analysis[1] included data from 15 participants in cohort 4 (3.6 mg/kg) at BL[2]

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.

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

Mean amyloid PET change from baseline[1]

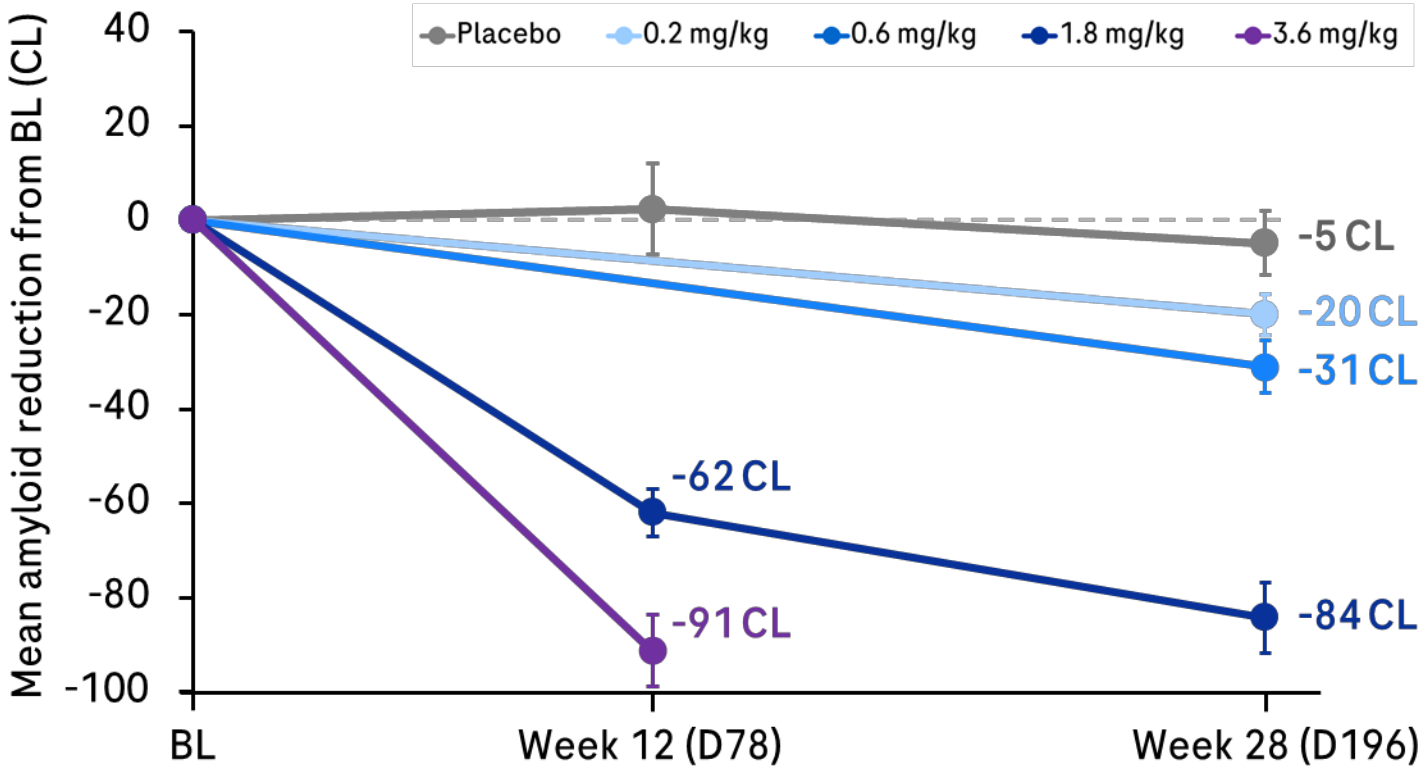


Placebo	n = 12	n = 5	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8

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]

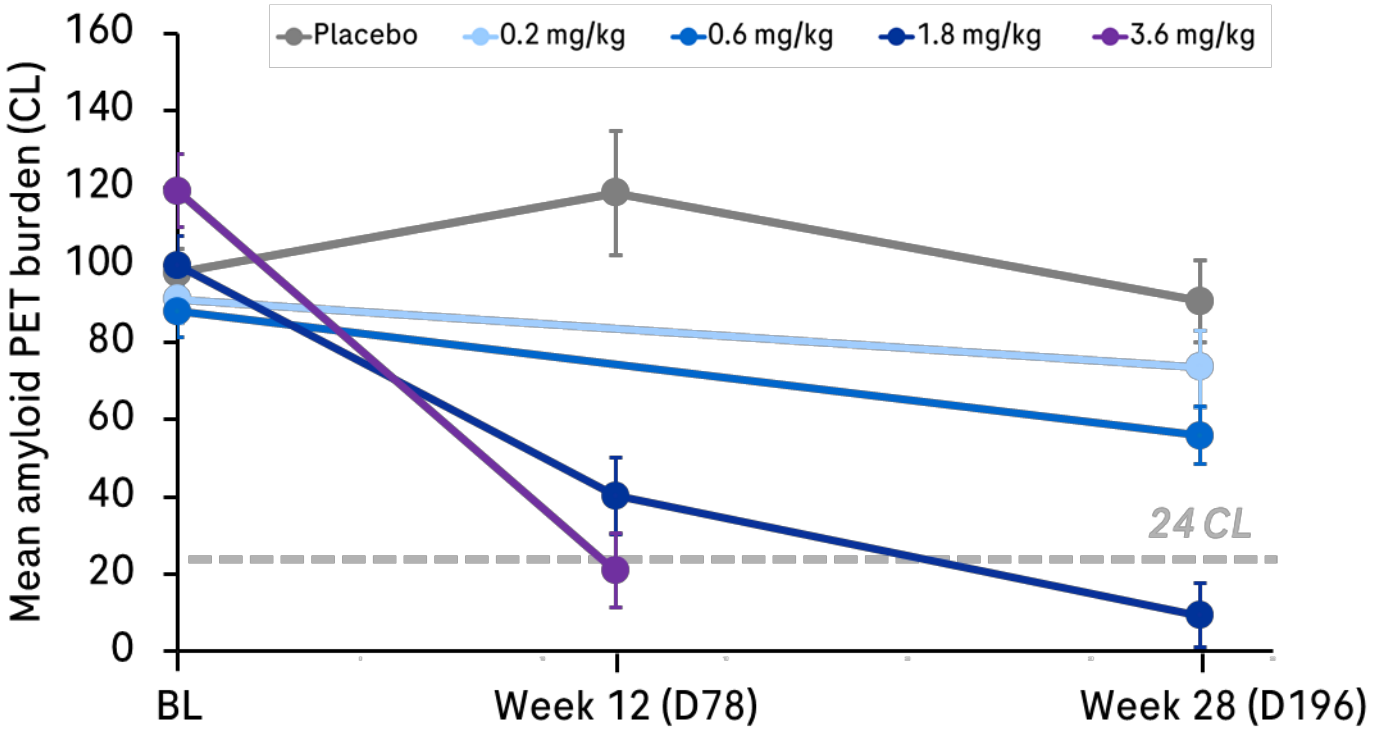


Placebo	n = 12	n = 5	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8
3.6 mg/kg	**n = 12**	**n = 8**	-

Snapshot date: 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).

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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1.8 mg/kg	n = 13	n = 11	n = 8
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

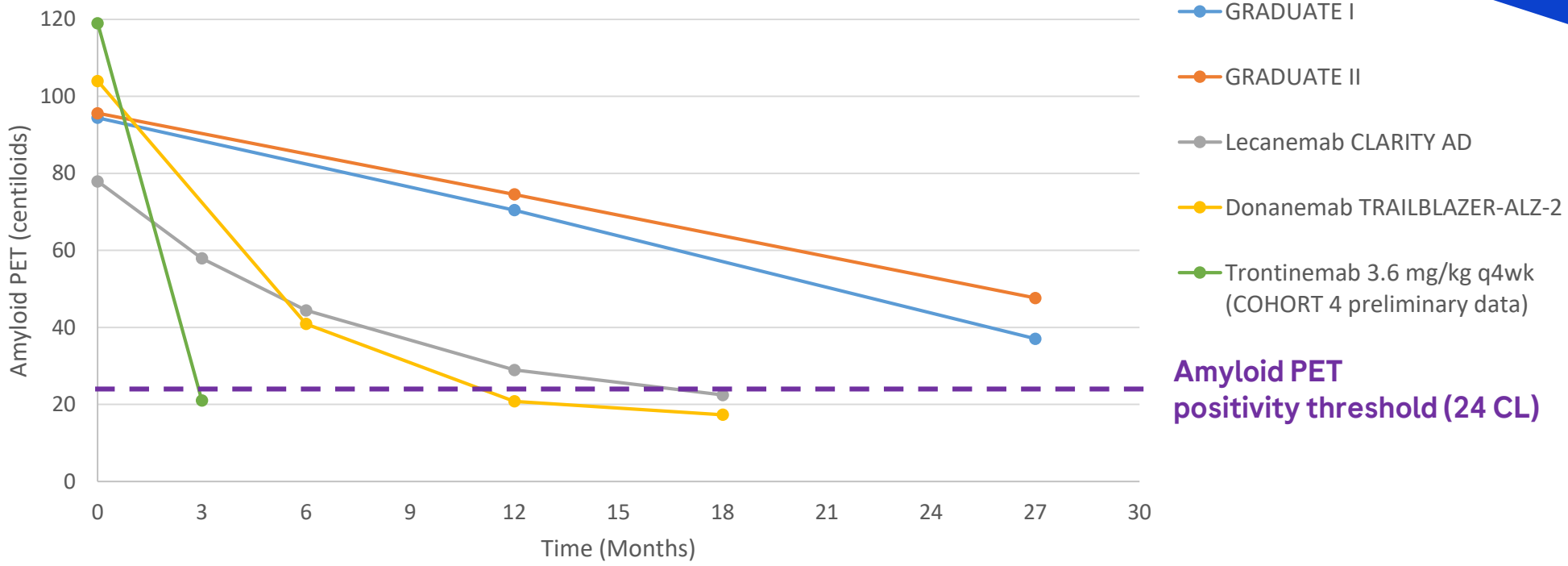
- Trontinemab is a novel Brainshuttle™ Aβ antibody that crosses the blood brain barrier via active TfR1 mediated transcytosis at the capillary level.
- In people with AD, trontinemab demonstrated rapid and robust amyloid plaque reduction at relatively low doses (1.8 and 3.6 mg/kg), compared with standard 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.

Trontinemab in Alzheimer's disease

Best-in-class potential: fast and highly efficient plaque removal

Trontinemab clears amyloid more rapidly than conventional mAbs

For reference - based on published data



GRADUATE I /II: presentation at CTAD 2022, publication in preparation; Lecanemab CLARITY AD: N Engl J Med 2023; 388:9-21; Donanemab TRAILBLAZER-ALZ-2: JAMA. 2023;330(6):512-527; AD=Alzheimer's disease; CL=Centiloid unit; PET=Positron Emission Tomography; mAb=Monoclonal antibody; Aβ=Amyloid β; q4w=Every 4 weeks