Roche Neurology Update

Virtual IR Event

March 11th 2024

Welcome

Bruno Eschli
Head of Investor Relations

Agenda

Welcome
15:00 – 15:05 CET
Bruno Eschli, Head of Investor Relations

Late stage pipeline Neurology
15:05 – 15:15 CET
Paulo Fontoura, SVP and Global Head of Neuroscience, Immunology, Ophthalmology, Cardiometabolic, Infectious and Rare Diseases Clinical Development

Elevidys in Duchenne Muscular Dystrophy (EMBARK) – MDA data presentation
15:15 – 15:30 CET
Alex Murphy, Senior Clinical Director

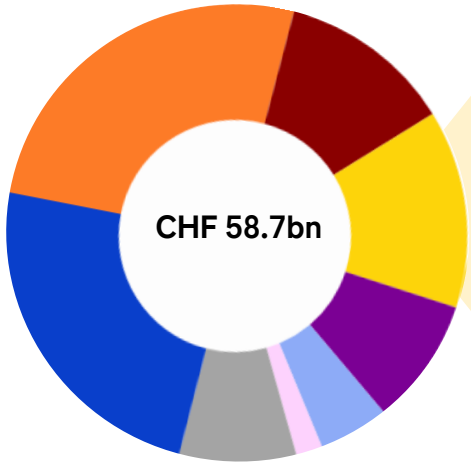
Early stage pipeline Neurology
15:30 – 15:50 CET
Azad Bonni, SVP and Global Head of Neuroscience & Rare Diseases, Roche Pharma Research & Early Development

Q&A
15:50 – 16:30 CET

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

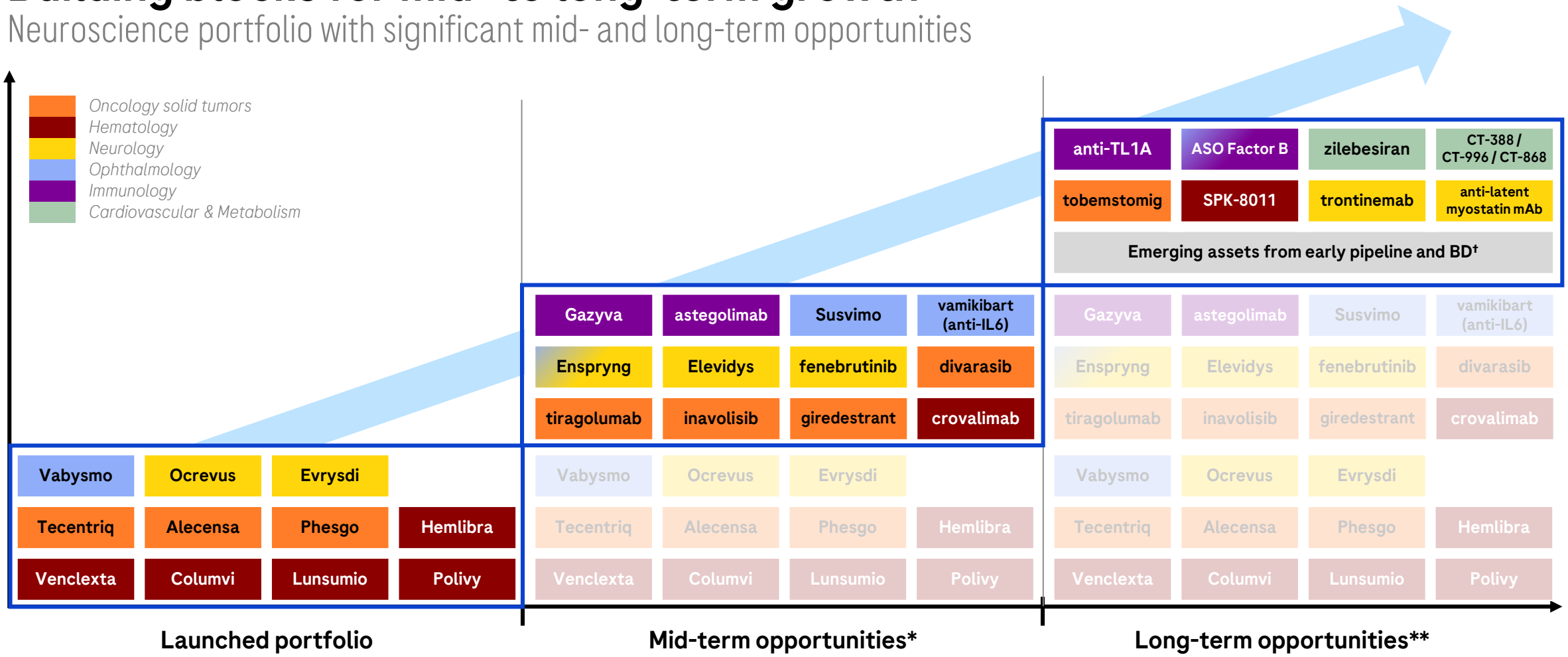
	NME	Indication	Newsflow	Timing
Oncology / Hematology	**tiragolumab**	NSCLC	Final Ph III data	H2 2024
	inavolisib	BC	US/EU filing	2024
	divarasib	NSCLC	Ph I/II readout	2024/25
	giredestrant	BC	Ph III readout	2025
Neurology	**Elevidys**	DMD	Ph III readout	2024/25
	prasinezumab	PD	Ph IIb readout	2024
	Evrysdi + 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)

Neurology late stage pipeline

Paulo Fontoura
SVP and Global Head of Neuroscience, Immunology, Ophthalmology, Cardiometabolic, Infectious and Rare Diseases Clinical Development

Neurology pipeline

Industry leading portfolio differentiated on targets and platform technologies

Ph I (5 NMEs)

RG6035	**Brainshuttle™ CD20** Multiple Sclerosis
RG6182	**MAGLi** Multiple Sclerosis
RG6289	**Gamma-secretase modulator** Alzheimer's
RG6418	**selnoflast** Parkinson's
RG6163	undisclosed psychiatric disorders

Ph II (6 NMEs, 1AI)

RG7935	**prasinezumab** Parkinson's	
RG6100	**bepranemab**[1] Alzheimer's	
RG6102	**trontinemab** Alzheimer's	
RG6042	**tominersen** Huntington's	
RG6237 + RG7916	**GYM329 + Evrysdi** SMA	RD
RG6237	**GYM329** FSHD	RD
RG7816	**alogabat** Autism spectrum disorder	

Ph III (1 NME, 5AI)

RG6168	**Enspryng** gMG	RD
RG6168	**Enspryng** MOG-AD	RD
RG6168	**Enspryng** AIE	RD
RG7845	**fenebrutinib** Multiple Sclerosis	
RG1594	**Ocrevus high dose** Multiple Sclerosis	
RG1594	**Ocrevus SC** Multiple Sclerosis	

Launched (4)

RG1594	**Ocrevus** Multiple Sclerosis		✓
RG6168	**Enspryng** NMOSD	RD	✓
RG7916	**Evrysdi** SMA type 1/2/3	RD	✓
RG6356	**Elevidys**[2] DMD	RD	✓

- Small molecule
- Antibody
- Gene therapy
- Brain shuttle
- Locked nucleic acid / antisense

- Neuro-immunologic disorders
- Neuro-degenerative disorders
- Neuro-developmental disorders
- Neuro-muscular disorders
- Psychiatric disorders
- ✓ FDA approval
- RD = Rare disease

[1]bepranemab in partnership with UCB, studies are currently run by UCB; [2]Elevidys in partnership with Sarepta Therapeutics; NME=new molecular entity; AI=additional indication; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; SMA=spinal muscular atrophy; FSHD=facioscapulohumeral muscular dystrophy; MOG-AD=myelin oligodendrocyte glycoprotein antibody-associated disease; AIE=autoimmune encephalitis; MAGL=monoacylglycerol lipase

Neurology near term key catalysts

	Molecule	Indication	Ph I	Ph II	Ph III	Status
Multiple Sclerosis (MS)	Ocrevus SC	RMS & PPMS			OCARINA II	EU approval: mid-2024; US approval: Sept
	Ocrevus HD	RMS			GAVOTTE	Data expected 2025
		PPMS			MUSETTE	Data expected 2025
	Fenebrutinib	RMS			FENhance 1	Data expected 2025
					FENhance 2	Data expected 2025
		PPMS			FENtrepid	Data expected 2025
Neuromuscular Disease (NMD)	Elevidys	DMD (ambulatory 4-7yrs)			EMBARK	Planned EMA submission mid-year
		DMD (ambulatory 0-3 yrs)			ENVOL	Actively recruiting
		DMD (ambulatory 8-18 yrs; non-ambulatory, all ages)			ENVISION	Actively recruiting
	Enspryng	gMG			LUMINESCE	Data expected H1 2024
	Evrysdi + GYM329	SMA			MANATEE	Ph III enabling data expected 2024
	GYM329	FSHD			MANOEUVRE	Ongoing
Neurodegenerative Disease	Trontinemab	Alzheimer's disease				Ph III enabling data expected 2024
	Prasinezumab	Parkinson's disease			PASADENA	4 year data presented at AD/PD
					PADOVA	Ph III enabling data expected H2 2024

RMS=relapsing multiple sclerosis; PPMS=primary progressive multiple sclerosis; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; SMA=spinal muscular atrophy; FSHD=facioscapulohumeral muscular dystrophy

Neurology diagnostics: Integrated solutions along patient journey

Biomarker tests drive access to disease modifying therapies and support disease management

Diagnostics Day May 22nd

	Screening and triage	Diagnosis	Treatment	Disease monitoring
Alzheimer's Disease	**Elecsys® Amyloid Plasma Panel (pTau181 + APOE4)** *Sensitivity >85%* *Specificity >65%* ***FDA BDD*** Global prospective trial ongoing, filing expected 2025	**Elecsys® CSF AD assay (pTau181 + Aβ42)** *Sensitivity >90%* *Specificity >90%* ✔ Approved by FDA	Anti-amyloid Ab: • Lecanemab (Biogen) • Donanemab (Eli Lily) • Trontinemab*	NfL has the potential to provide patient insights for other neurodegenerative diseases such as Alzheimer's
	Rule-in Test (pTau 217)* Development ongoing			
Multiple Sclerosis			• Ocrevus • Fenebrutinib*	**Elecsys NfL** (blood test detects disease activity)[1] ***FDA BDD***

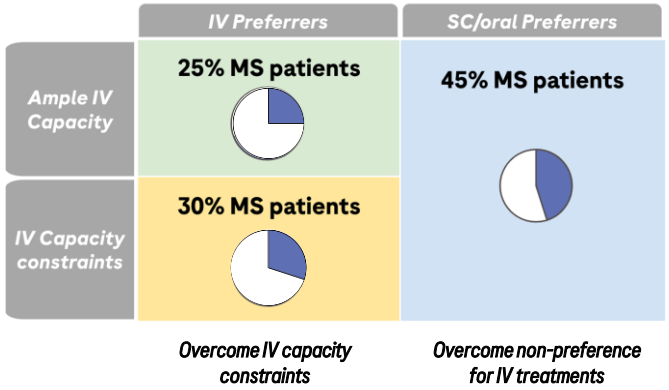
*In development; 1. Research Use Only (RUO) not linked to any specific indication; BDD=breakthrough devices designation; NfL=neuro filament light chain

Ocrevus: SC Q6M dosing approval expected 2024

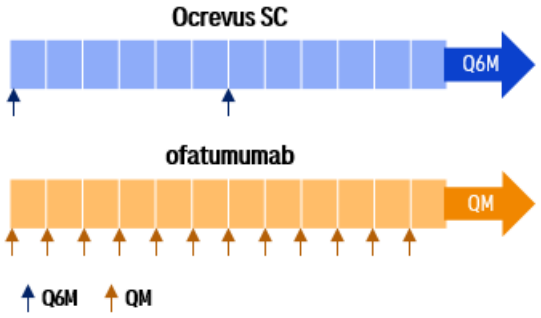
EU approval expected mid-year; FDA PDUFA Sept 2024

Ocrevus SC to deliver significantly reduced time & treatment burden

SC market expansion opportunities



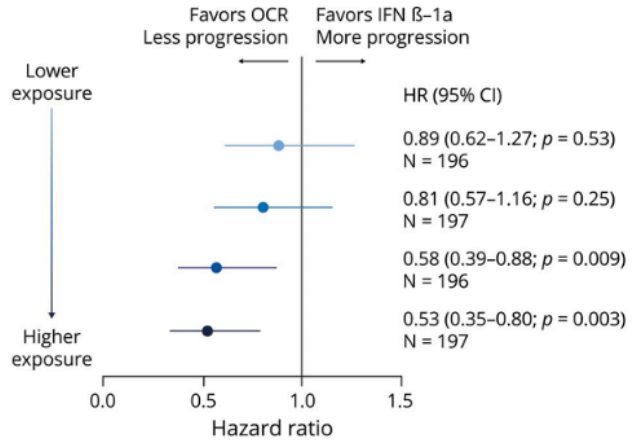
Convenient Q6M dosing frequency



- Ocrevus SC markedly reduces administration time to 10 min
- Retains Q6M dosing that has demonstrated high compliance and strong pt preference
- Ocrevus SC provides a solution to centers without IV infrastructure or with IV capacity constraints and offers expansion opportunities to centers that currently prefer SC over IV treatment options

Ocrevus HD to further improve control of disability progression

CDP by OCR-exposure quartiles in pts with RMS[1]



- Post hoc analysis suggest that a higher dose of Ocrevus could lead to an improved efficacy on disability progression
- Ocrevus HD Ph III trials (MUSETTE & GAVOTTE) in RMS & PPMS recruitment completed and data expected 2025

1. Hauser S et al Neurol Neuroimmunol Neuroinflamm 2023;10:e200094.doi:10.1212; MS=multiple sclerosis; IV=intravenous; SC=Subcutaneous; RMS=relapsing multiple sclerosis; PPMS=primary progressive multiple sclerosis; Q6M=every 6 months; QM=Monthly; HD=high dose; CDP=confirmed disability progression; OCR=ocrelizumab; IFN=interferon; CI=confidence interval

Fenebrutinib: Highly selective, non-covalent, brain-penetrant BTKi

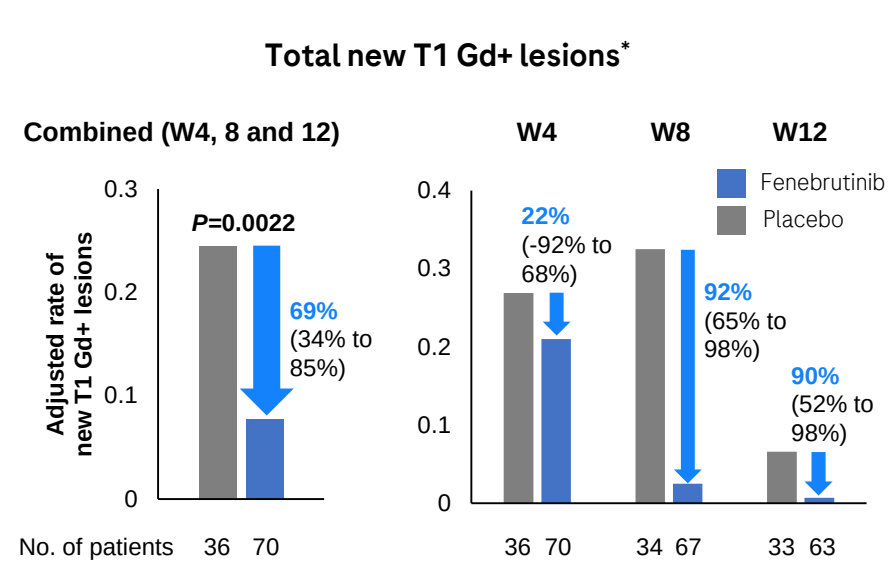
Ph III (FENhance 1&2) in RMS and (FENtrepid) in PPMS data expected 2025

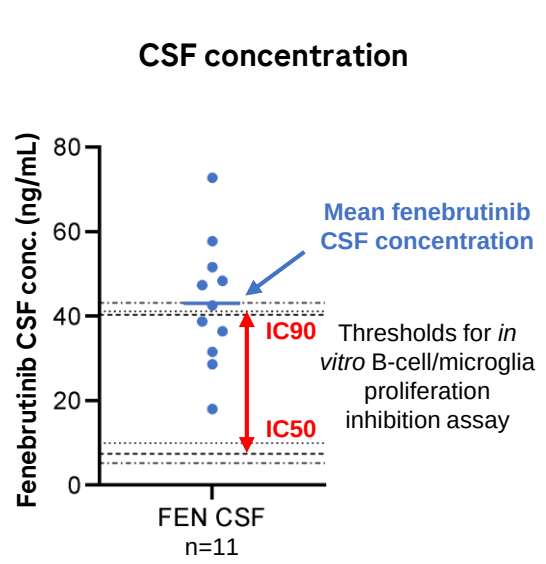
BTKi competitive landscape[1]

Fenebrutinib	Tolebrutinib	Evobrutinib ✘	Remibrutinib
Non-covalent Reversible	Covalent Irreversible	Covalent Irreversible	Covalent Irreversible
WB B cell IC_{50}: 8 nM	10 **nM**	84 **nM**	18 **nM**
WB Myeloid cell IC_{50}: 31 nM	166 **nM**	1660 **nM**	67 **nM**
RMS, PPMS (vs Ocrevus)	RMS, SPMS, PPMS (vs placebo)	RMS	RMS

- Fenebrutinib's dual MoA targets both B cells and myeloid cells
- Fenebrutinib's excellent selectivity limits off-target effects, potential for better safety outcomes: large safety database with >2,500 pts dosed with fenebrutinib

Ph II (FENopta) results in RMS[2]





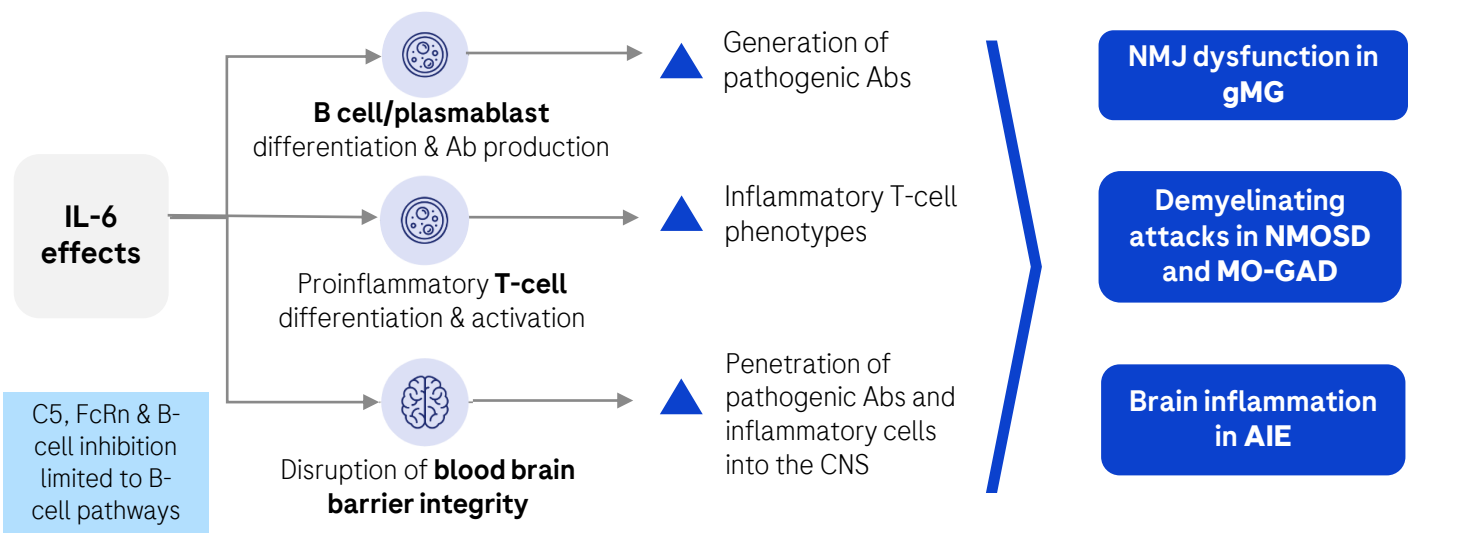
- Ph II (FENopta) showed significant reductions in brain lesions in RMS, meeting all primary and secondary endpoints
- Rapid onset of T1 Gd+ lesion reduction from W4; relative reduction of 92%/90% in W8/12
- CSF concentration levels sufficient to reduce B-cell and microglia activity in vitro
- Safety profile in MS consistent with previous studies in non MS indications[3]

1. Kramer, et al (2023) nature reviews neurology 289-304 ;Crawford, et al.(2018) J Med Chem 61, 2227-2245; Francesco, et al., ACTRIMS-ECTRIMS (2017) 200644. Haselmayer, et al. (2019) J Immunol 202, 2888-2906; Angst D, et al. (2020) J Med Chem 63, 5102-5118; 2. Hua LH et al., EAN 2023; 3. Oh J, et al., ACTRIMS 2024; *Results were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset. Arrows indicate relative reduction (95% CI) of lesions; MS=multiple sclerosis; BTKi=Bruton's tyrosine kinase inhibitor; nM=nanomolar; WB=whole blood; MoA=mechanism of action; CSF=cerebrospinal fluid; RMS=relapsing multiple sclerosis; PPMS=primary progressive multiple sclerosis; SPMS=secondary progressive multiple sclerosis; Gd+=gadolinium-enhancing; MRI=Magnetic Resonance Imaging; CNS=central nervous system

Enspryng in neurological disorders gMG, AIE, and MOG-AD

First-in-class IL-6R inhibitor and best-in-disease potential in gMG

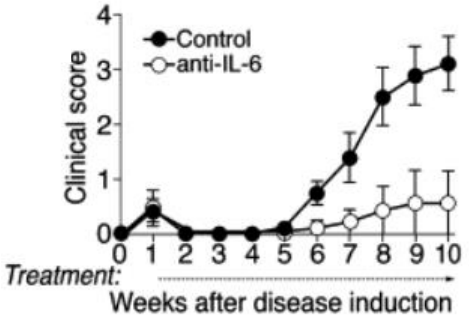
IL-6 has a key role in multiple upstream mechanism which drive autoantibody-mediated neurological diseases



- IL-6 blockade has the potential to reduce auto-antibody-mediated NMJ damage in gMG
- High unmet need remains in gMG: ~10-30% of patients fail SoC therapies; at least 60% of patients on existing biologics do not achieve stable remission[1]
- Enspryng was engineered to provide durable suppression in IL-6 and shown to have a favorable safety profile (9 years of exposure data in NMOSD); simple SC Q4W home administration by patient and caregiver

Preclinical/case study data support use of anti-IL6R mAb in gMG

Suppression of EAMG by anti-IL-6 treatment in rodent model[2]



- Preclinical data have shown treatment with an anti-IL6R antibody in rodent models of AChR+ myasthenia gravis (AChR EAMG) reduced AChR antibody titres and improved clinical outcomes
- Ph III (LUMINESCE) in gMG LPI achieved Aug 2023, results expected H1 2024

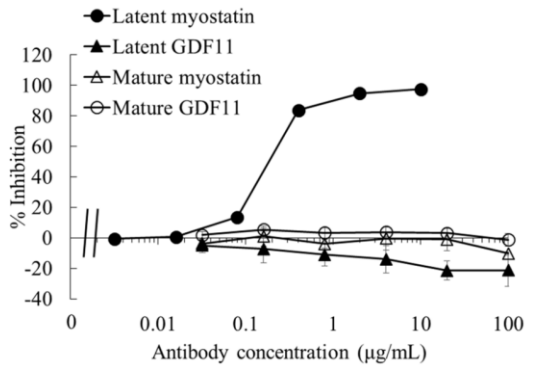
1. Howard JF Jr, et al. Lancet Neurol. 2021; 2. Aricha R et al. J Autoimmune. 2011; IL-6R=interleukin 6 receptor; gMG= generalized myasthenia gravis; AcHR=acetylcholine receptor; NMJ=neuromuscular junction; SC=subcutaneous; Q4W=every 4 weeks; MOG-AD=myelin oligodendrocyte glycoprotein antibody-associated disease; AIE=autoimmune encephalitis; SoC=Standard of care; EAMG= experimental autoimmune myasthenia gravis; mAB= monoclonal antibody; LPI=last patient in; Enspryng in collaboration with Chugai

GYM329 (anti-latent myostatin mAb) in SMA and FSHD

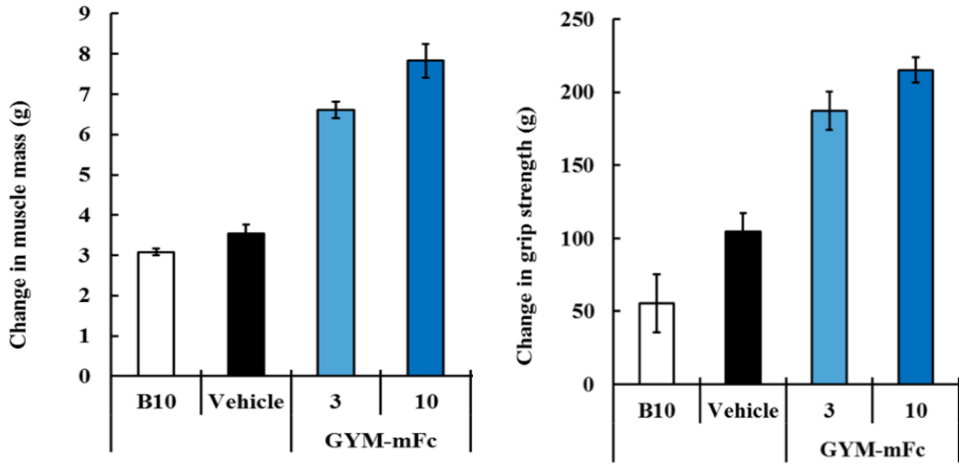
Best-in-disease potential to improve muscle strength in neuromuscular diseases

GYM329 (anti-latent myostatin mAb)

Efficient inhibition of latent myostatin but not GF11[1]

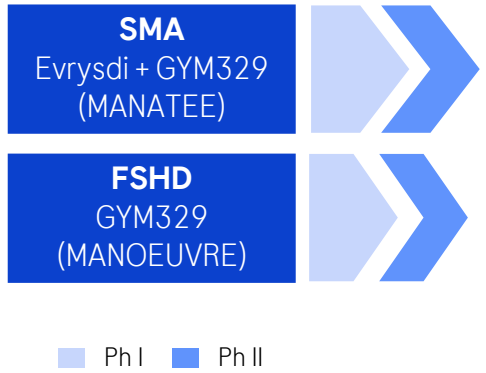


Increase in muscle mass and strength in mouse models[1]



- Preclinical studies showed that GYM329 has higher specificity myostatin inhibition and superior muscle strength-improvement effects in mice compared with other anti-myostatin therapies
- Unique sweeping[2] and recycling technology allows less frequent SC dosing
- In an animal model of SMA, the combination of GYM329 + Evrysdi improved muscle size and strength

Neurology development program



- Ph II (MANATEE) of GYM329 and Evrysdi in SMA ongoing; interim data expected 2024
- Ph II (MANOEUVRE) in FSHD ongoing

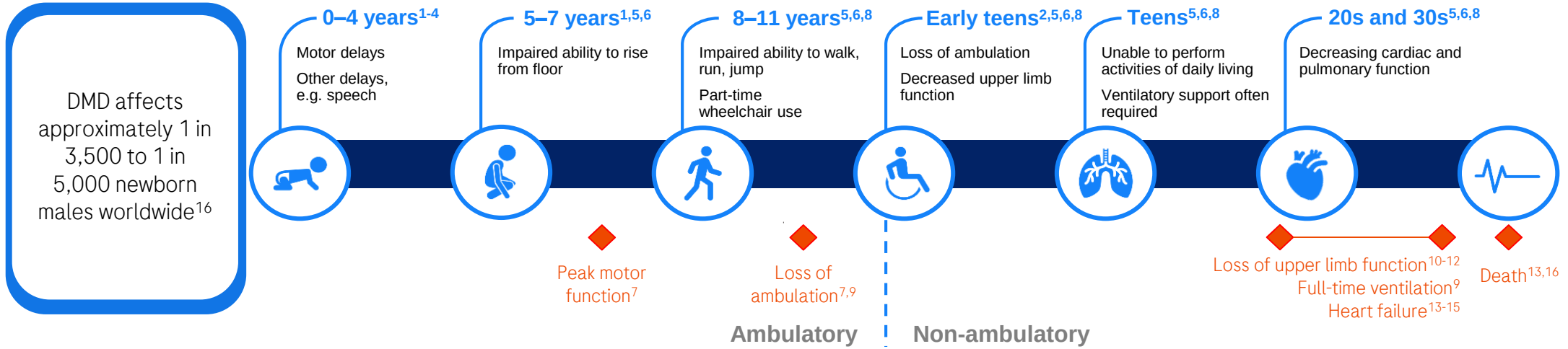
1. Muramatsu H. et al., Nature Scientific Reports. 2021; [2]A sweeping antibody is a recycling antibody that has been further engineered to bind to FcRn at neutral pH; SC=subcutaneous; CNS=central nervous system; mAb=monoclonal antibody; SMA=spinal muscular atrophy; GDF11=growth differentiation factor 11; FSHD=Facioscapulohumeral muscular dystrophy; GYM329 in collaboration with Chugai

Elevidys in Duchenne Muscular Dystrophy (EMBARK) – MDA data presentation

Alex Murphy
Senior Clinical Director

Duchenne muscular dystrophy: Unmet need remains critical

DMD is progressive, irreversible, and 100% fatal



Treatment options are currently limited to slowing progression and improving quality of life; there remains no cure for DMD

Corticosteroids – current SoC

- Does not change the disease course
- Severe side-effects

Exon skipping technologies

- Not applicable or available to all

Other approaches exist but are more about symptom management (e.g., anti-fibrotic)

1. Chen YW, et al. Neurology. 2005; 65:826–834; 2. Peverelli L, et al. Neurology. 2015; 85:1886–1893; 3. Lurio JG, et al. Am Fam Physician. 2015; 91:38–44; 4. Cyrulnik SE, et al. J Pediatr. 2007; 150:474–478; 5. Goemans N, et al. Neuromuscul Disord. 2013; 23:618–623; 6. Bushby K & Connor E. Clin Investig (London). 2011; 1:1217–1235; 7. Muntoni F, et al. PLoS One. 2019; 14:e0221097; 8. Henricson EK, et al. Muscle Nerve. 2013; 48:55–67; 9. Birnkrant DJ, et al. Lancet Neurol. 2018; 17:347–361; 10. Birnkrant et al. Lancet Neurol 2018;17:251-67; 11. Bartels et al. J Rehabil Med 2011;43:770-5; 12. Bushby K et al. Lancet Neurol 2010a;9:77-93; 13. Kieny et al. Ann Phys Rehabil Med 2013;56:443-54; 14. Verhaart et al. Curr Opin Neurol 2012;25:588-96; 15. McNally et al. Circulation. 2015; 131:1590-1598; 16. Birnkrant et al. Pediatr Pulmonol 2016;51:70-6; 16. CDC https://www.cdc.gov/ncbddd/musculardystrophy/data.html

NSAA: A unidimensional functional scale

NSAA may not capture changes in specific functional abilities in certain populations, particularly over 52 weeks

NSAA assess 17 items that measure various functional abilities on a scale of 0, 1, and 2

17 assessments for ambulatory DMD patients

- Stand
- Walk
- Jump
- Run
- Rise from chair
- Gets to sitting
- Stand on right leg
- Stand on left leg
- Climb step (right leg)
- Climb step (left leg)
- Descend box step (right leg)
- Descend box step (left leg)
- Stand on heels
- Rise from floor
- Lift head
- Hop on right leg
- Hop on left leg

Example - Rise from floor: NSAA score of 1

Perform with slight difficulty
4.7 s

Perform with great difficulty
7.3 s

- The heterogeneity of DMD disease progression is a challenge when designing trials of short duration in EMBARK's study population and age range (4–7-year-olds); motor function may still be improving, maintaining, or starting to decline
- A 1-point difference in the NSAA indicates different ranges of function, from inability to do a task, to using compensation, or performing with no compensation. In younger patients, neurodevelopmental maturation might also affect these achievements

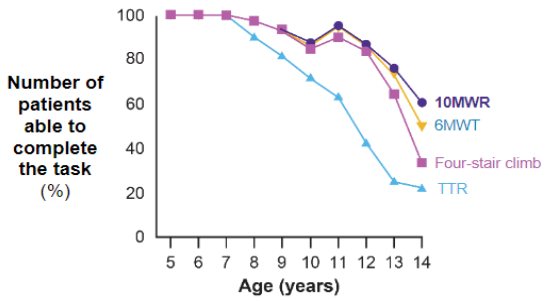
1. Muntoni F. et al. (2019). Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. PLOS ONE, 14(9), e0221097; DMD=Duchenne muscular dystrophy; NSAA=North Star Ambulatory Assessment

Timed function tests (TFT) are more responsive to disease change

Novel digital endpoint (SV95C) enables objective precise measurement of disease progression in the real world

TFTs are lost in a predictable and sequential manner[1-3]

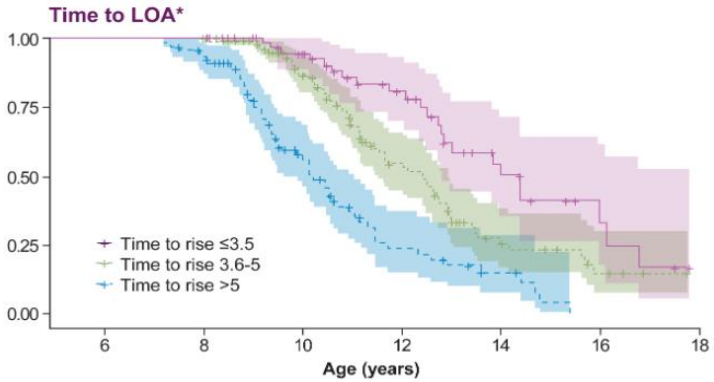
TFT by age in natural history[2]



- TFTs such as TTR and 10MWR may be more sensitive measures of functional change in the age range and study duration of EMBARK

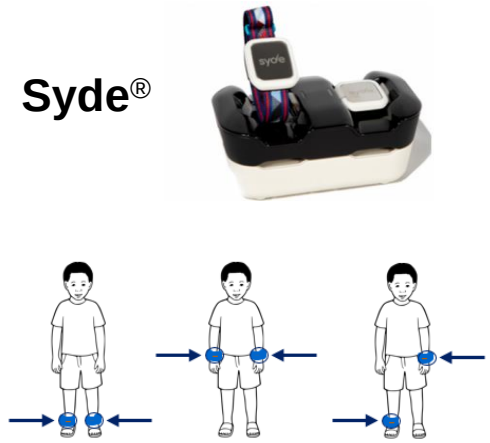
Time to rise (TTR) is strongly predictive of loss of ambulation

Time to loss of ambulation vs. time to rise[4]



- TTR is the most responsive marker of disease progression in earlier stages of disease and has strong prognostic clinical relevance
- Different durations for Time to Rise predict markedly altered trajectories in time to loss of ambulation, according to natural history data

Stride velocity 95th centile (SV95C)



- Novel digital endpoint SV95C measures speed of walking via a wearable device (Syde®); a valuable alternative to the 6 minute walk test (6MWT)
- Qualified by EMA for future use as a primary endpoint in clinical trials

1. McDonald CM. Muscle Nerve. 2018; 58:614–617; 2. Arora H, et al. Muscle Nerve. 2018; 58:631–638; 3. Merlini L & Sabatelli P. BMC Neurol. 2015; 15:153.; 4. Zambon AA, et al. Dev Med Child Neurol. 2022; 64:979–988; *Total of 293 patients in the UK North Star database; LOA=loss of ambulation 10MWR=10-metre walk/run

Safety and efficacy of delandistrogene moxeparvovec versus placebo in Duchenne muscular dystrophy (EMBARK): Pivotal Phase 3 primary results

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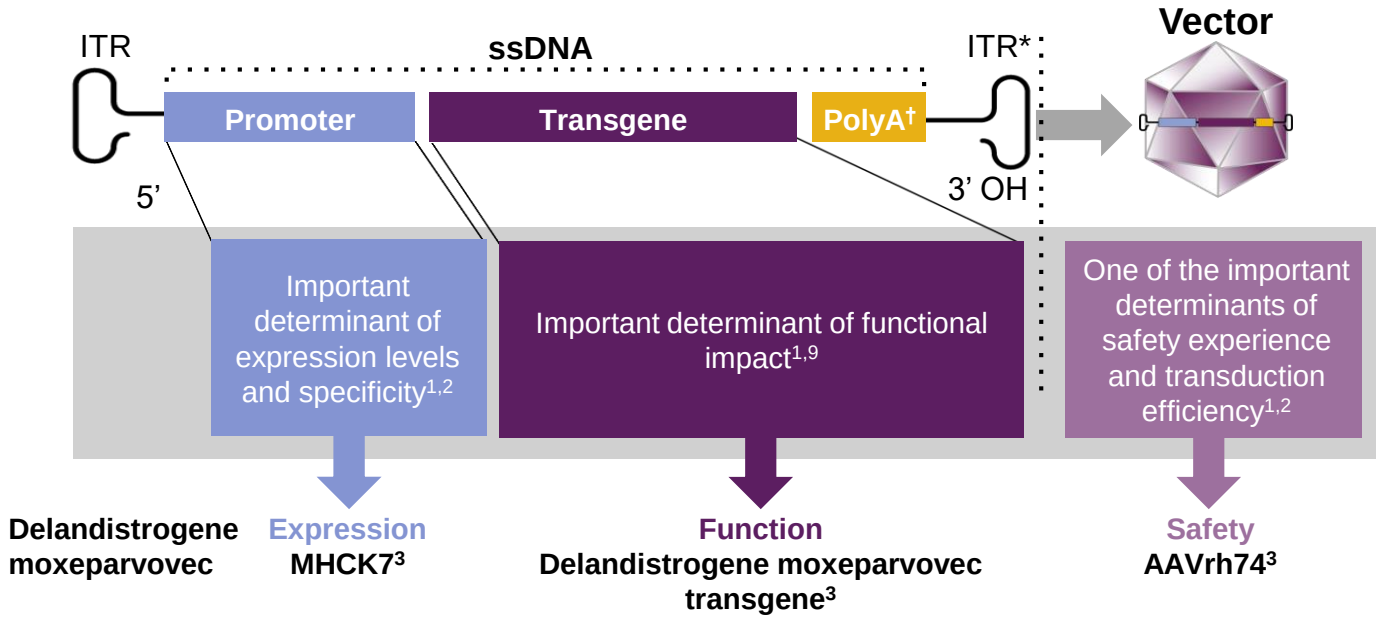
*Presenting on behalf of the author group (email address: medinfo@sarepta.com); †At the time of study.

Background

- Delandistrogene moxeparvovec is a rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered protein that retains key functional domains of the wild-type protein[1–3]
- As of February 2024, delandistrogene moxeparvovec is approved in the USA, UAE, Qatar, and Kuwait for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene. Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene[4–7]

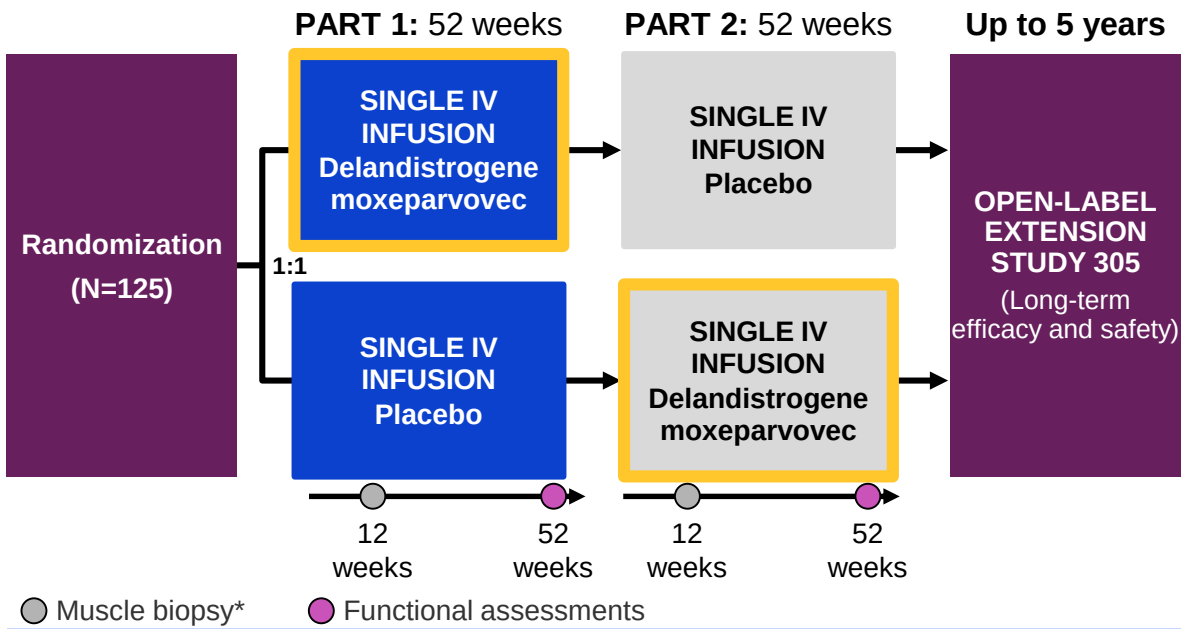
- EMBARK (NCT05096221)[8] is a Phase 3, two-part, multinational, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of delandistrogene moxeparvovec in patients with DMD aged ≥4 to <8 years
- We present an overview of the 1-year safety and functional outcomes from Part 1 of EMBARK



*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.
AAVrh74, adeno-associated virus rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; OH, hydroxide; polyA, polyadenylation; rAAV, recombinant adeno-associated virus; ssDNA, single-stranded DNA.

Study design and endpoints[8]

Stratification based on age at randomization (≥4 to <6 or ≥6 to <8 years) and NSAA total score at screening (≤22 vs >22)



Key inclusion criteria:

- Ambulatory males aged ≥4 to <8 years at randomization
- Confirmed DMD diagnosis (*DMD* mutation fully contained within exons 18–79 [inclusive])
- Ability to cooperate with motor assessment testing
- NSAA total score >16 and <29 points at screening
- TTR <5 seconds at screening
- On a stable daily dose of oral corticosteroids for ≥12 weeks before screening
- rAAVrh74 total binding antibody titers <1:400

Primary endpoint

- Change from baseline to Week 52 in NSAA total score

Key secondary functional endpoints

- Change from baseline to Week 52 in:
  - TTR
  - 10MWR

Other secondary functional endpoints

- Change from baseline to Week 52 in:
  - SV95C as measured by a wearable device (Syde®)
  - 100MWR
  - Time to ascend 4 steps

Safety endpoints

- TEAEs, SAEs, and AEs of special interest
- Clinically significant changes in laboratory assessments

Additional pre-specified efficacy analyses

- GST for totality of evidence analysis on a composite of endpoints through permutations[10,11]

The primary endpoint and secondary endpoints were tested using a statistical hierarchy to control the overall Type I error at a 2-sided level of 0.05†

*Only a subset of patients will receive a muscle biopsy for expression assessments, based on site experience and feasibility. †Additional endpoints were included in the sequential testing, that are not reported in this presentation.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AE, adverse event; DMD, Duchenne muscular dystrophy; GST, global statistical test; IV, intravenous; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SV95C, stride velocity 95th centile; TEAE, treatment-emergent adverse event; TTR, Time to Rise.

Patient demographics (Part 1)

Demographics were balanced between delandistrogene moxeparvovec and placebo groups

Characteristic	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)	All (N=125)
Age, mean (SD), years	5.98 (1.06)	6.08 (1.05)	6.03 (1.05)
4–5 years, n (%)	30 (47.6)	29 (46.8)	59 (47.2)
6–7 years, n (%)	33 (52.4)	33 (53.2)	66 (52.8)
Dosing weight, mean (SD), kg	21.29 (4.62)	22.37 (6.42)	21.83 (5.59)
Time since corticosteroid treatment started, mean (SD), years	1.07 (0.92)	0.97 (0.83)	1.02 (0.88)
Primary and secondary functional endpoints			
NSAA total score, mean (SD), points	23.10 (3.75)	22.82 (3.78)	22.96 (3.75)
TTR, mean (SD), seconds	3.52 (0.81)	3.60 (0.68)	3.56 (0.75)
10MWR, mean (SD), seconds	4.82 (0.79)	4.92 (0.73)	4.87 (0.76)
SV95C, mean (SD), meters/second*	1.82 (0.30)	1.77 (0.29)	1.79 (0.30)
100MWR, mean (SD), seconds†	60.67 (15.55)	63.01 (17.01)	61.80 (16.25)
Time to ascend 4 steps, mean (SD), seconds‡	3.17 (1.01)	3.37 (1.09)	3.27 (1.05)

*SV95C: Delandistrogene moxeparvovec n=61, placebo n=62, total N=123. †100MWR: Delandistrogene moxeparvovec n=63, placebo n=59, total N=122. ‡Time to ascend 4 steps: Delandistrogene moxeparvovec n=63, placebo n=61, total N=124.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SV95C, stride velocity 95th centile; TTR, Time to Rise.

Safety overview

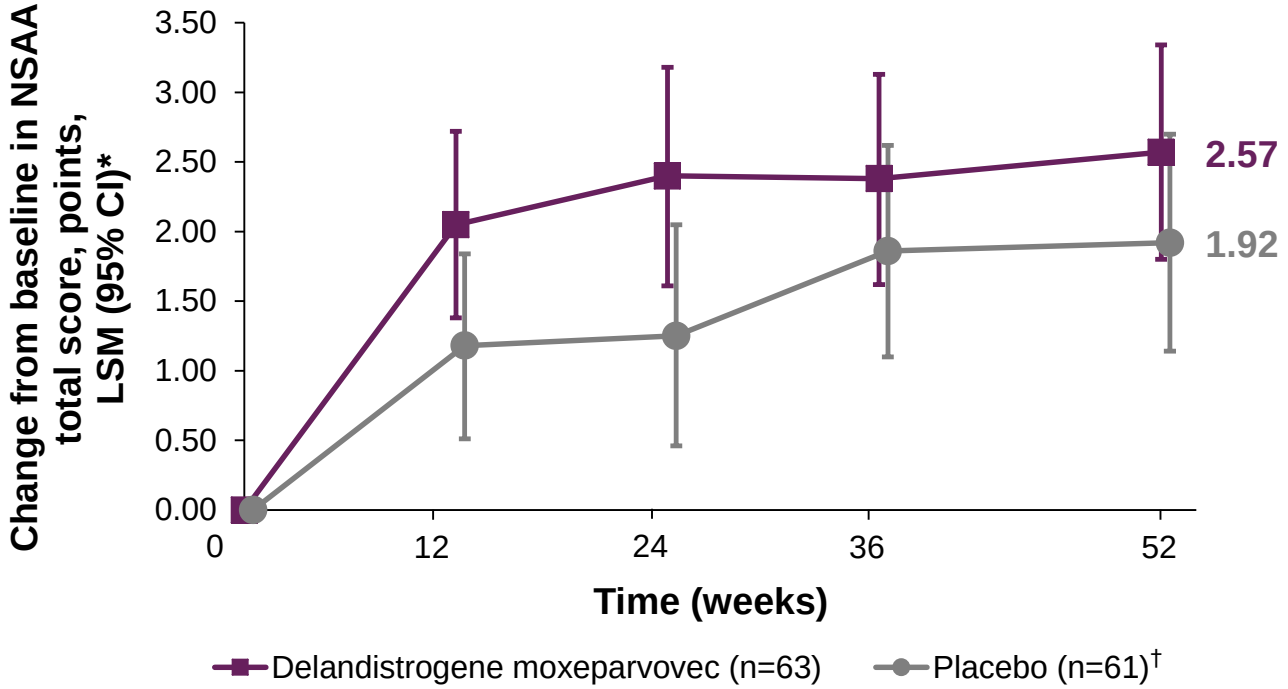
	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)
Patients with any TEAE, n (%)	62 (98.4)	57 (91.9)
TEAEs, n	664	502
Patients with any TR-TEAE, n (%)	48 (76.2)	17 (27.4)
TR-TEAEs, n	235	43
Patients with any TR-SAE, n (%)	7 (11.1)	0
TR-SAEs, n	10	0
Patients with an AE leading to study discontinuation, n (%)	0	0
Deaths, n (%)	0	0

- The safety profile of delandistrogene moxeparvovec in EMBARK was **consistent with experience from early-phase studies**
- AEs were **medically manageable** with appropriate monitoring and treatment
- There were **no clinically relevant complement activation AEs, no deaths,** and **no study discontinuations**

AE, adverse event; TEAE, treatment-emergent adverse event; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event.

Primary endpoint: Change from baseline to Week 52 in NSAA total score

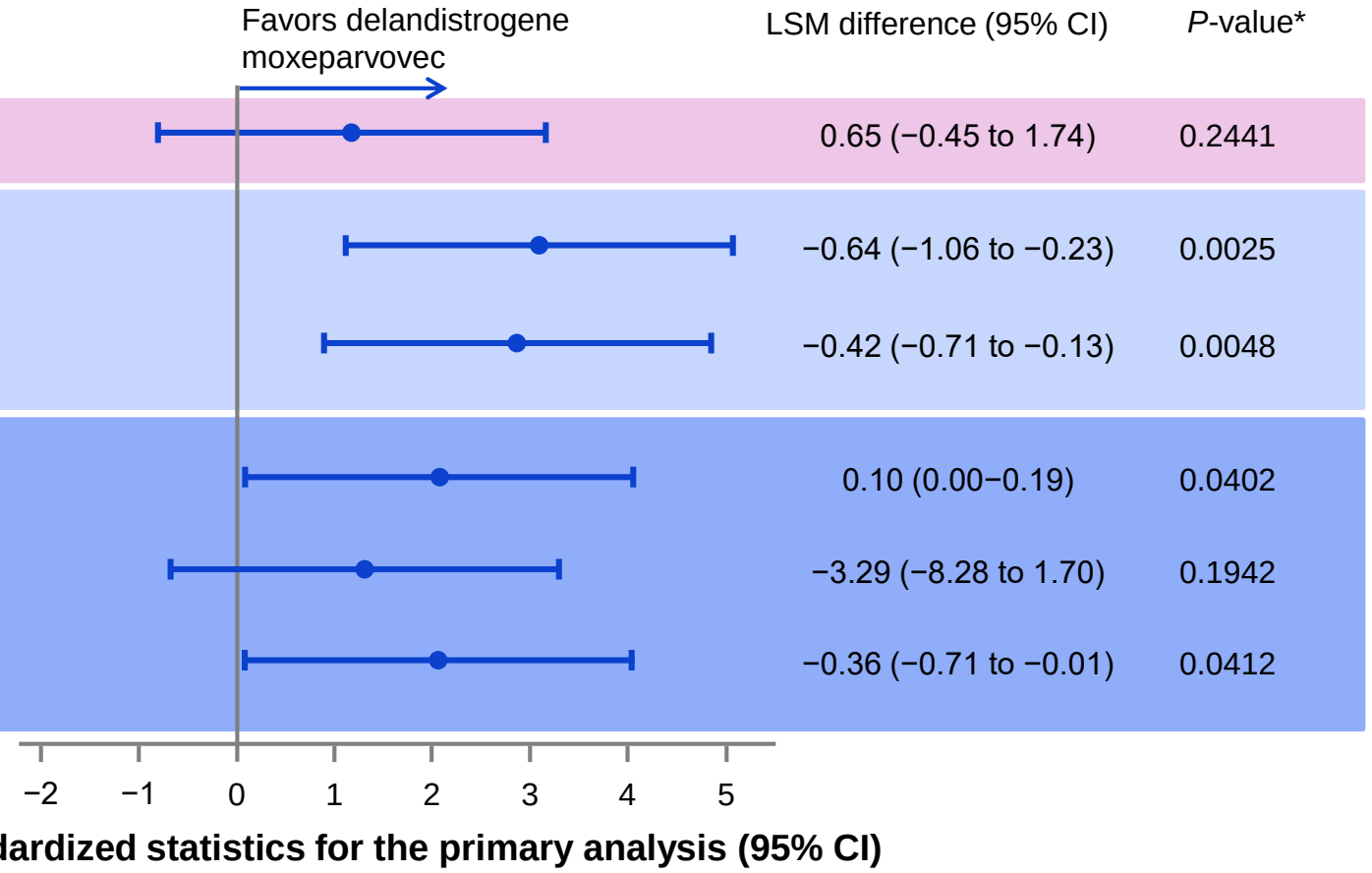
Between-group difference LSM (SE):
0.65 (0.55) points (95% CI −0.45 to 1.74)
***P*=0.2441**



*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †One patient in the placebo group had missing data at Week 52; the patient's functional tests were marked as invalid by the clinical evaluator due to back pain from compression fractures.
CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error.

Functional endpoints at Week 52 in the overall population

		Delandistrogene moxeparvovec	Placebo	LSM difference (95% CI)	*P*-value*
Primary	**NSAA**	63	61	0.65 (−0.45 to 1.74)	0.2441
Key secondary	**TTR**	63	61	−0.64 (−1.06 to −0.23)	0.0025
	10MWR	63	61	−0.42 (−0.71 to −0.13)	0.0048
Other functional	**SV95C**	57	61	0.10 (0.00−0.19)	0.0402
	100MWR	59	57	−3.29 (−8.28 to 1.70)	0.1942
	Time to ascend 4 steps	62	60	−0.36 (−0.71 to −0.01)	0.0412

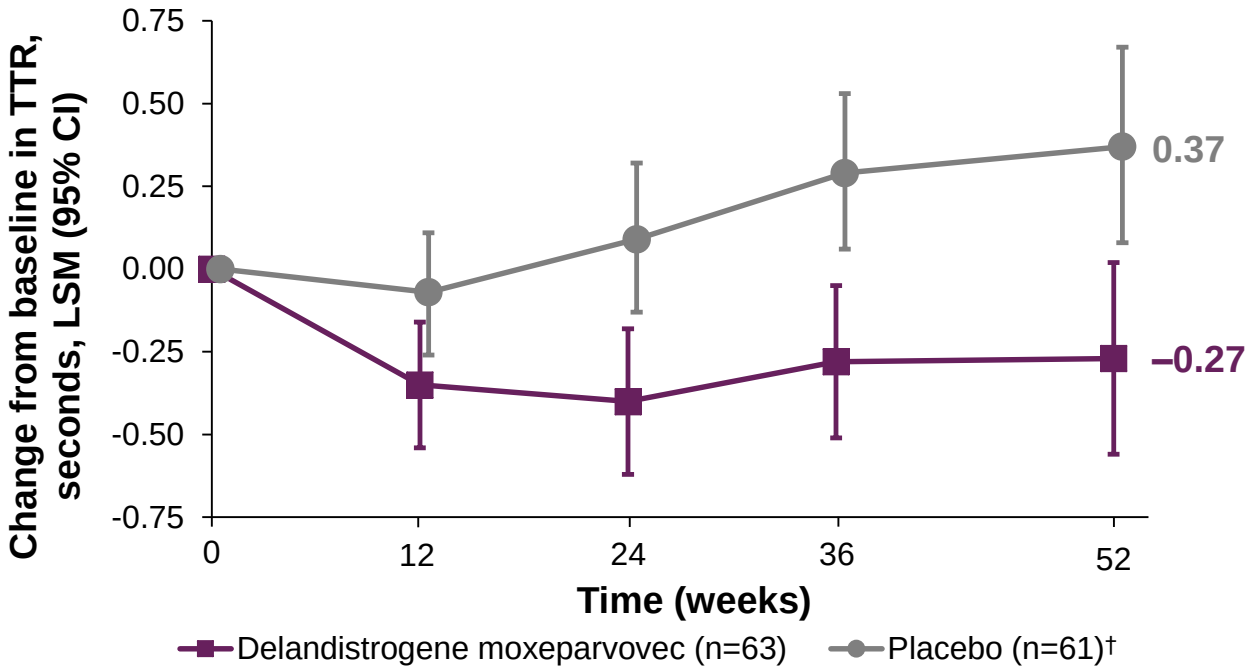


*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects

LSMs (of change from baseline) and CIs were standardized by dividing by the SE. Negative values for timed function tests (TTR, 10MWR, 100MWR, and time to ascend 4 steps) show an improvement in the time taken to achieve these endpoints. LSM differences are on original scale (without SE adjustment). Signs of timed function tests were reversed in the forest plot to align favorable directions among endpoints. Numerical results of LSM difference kept the original signs.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; SV95C, stride velocity 95th centile; TTR, Time to Rise.

Key secondary functional endpoint: Change from baseline to Week 52 in TTR

Between-group difference LSM (SE):
–0.64 (0.21) seconds (95% CI –1.06 to –0.23)
P*=0.0025



- Negative values indicate an improvement in the time taken to achieve this endpoint
- The separation between groups was **clinically relevant**

*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing of endpoints are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †One patient in the placebo group had missing data at Week 52; the patient's functional tests were marked as invalid by the clinical evaluator due to back pain from compression fractures.
CI, confidence interval; LSM, least-squares mean; SE, standard error; TTR, Time to Rise.

Post hoc analyses on TTR

- All patients had a TTR <5 seconds at screening
- With delandistrogene moxeparvovec treatment, **fewer patients progressed to a TTR of >5 seconds** compared with placebo

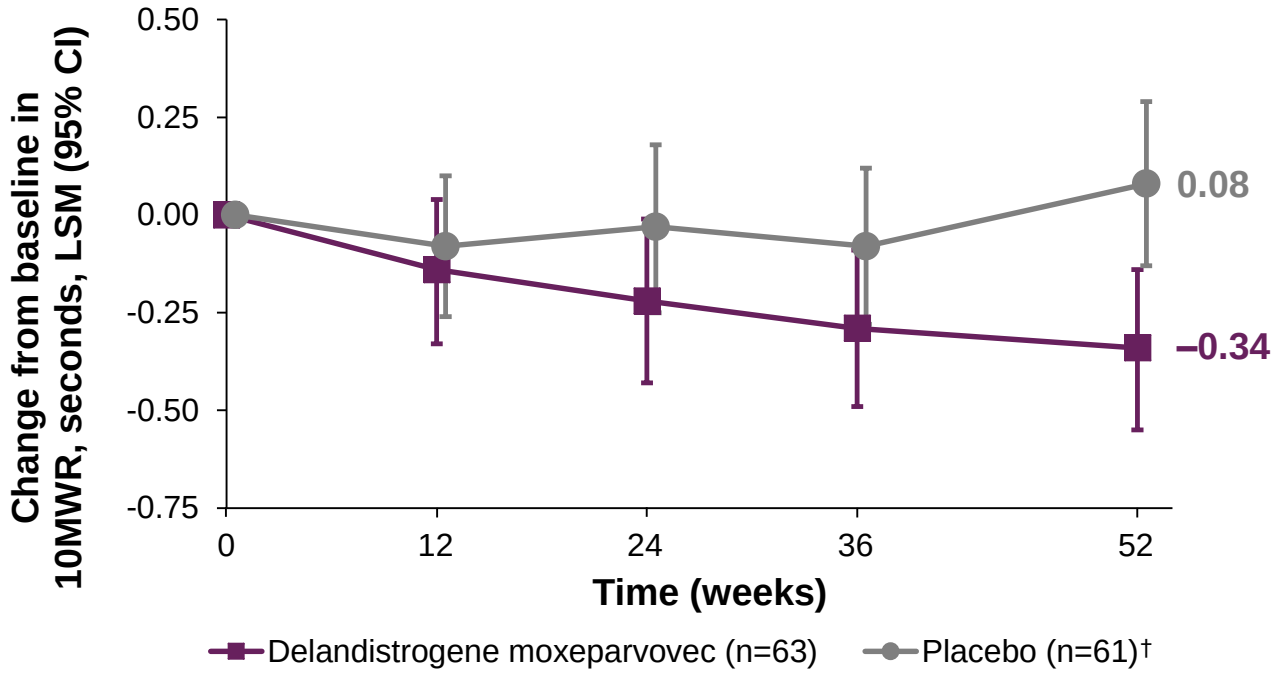
Patients with TTR >5 seconds at Week 52		Reduction in odds
Delandistrogene moxeparvovec (n=63)	Placebo (n=61)	
3%	16%	**91% (*P*=0.0135)**

- A TTR of >5 seconds is a threshold of **prognostic significance for loss of ambulation**[12,13]

TTR, Time to Rise.

Key secondary functional endpoint: Change from baseline to Week 52 in 10MWR

Between-group difference LSM (SE):
–0.42 (0.15) seconds (95% CI –0.71 to –0.13)
P*=0.0048



- Negative values indicate an improvement in the time taken to achieve this endpoint
- The separation between groups was **clinically relevant**

*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing of endpoints are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †One patient in the placebo group had missing data at Week 52; the patient's functional tests were marked as invalid by the clinical evaluator due to back pain from compression fractures.
10MWR, 10-meter Walk/Run; CI, confidence interval; LSM, least-squares mean; SE, standard error.

Conclusions at Week 52

Safety findings demonstrate the manageable benefit–risk profile of delandistrogene moxeparvovec with no new safety signals identified and no deaths, study discontinuations, or clinically relevant complement-mediated AEs

Delandistrogene moxeparvovec did not reach statistical significance compared with placebo in the primary endpoint of NSAA at 52 weeks

Between-group differences favoring delandistrogene moxeparvovec on secondary functional endpoints indicate the potential for long-term disease modification of DMD

A post hoc analysis of TTR showed fewer delandistrogene moxeparvovec-treated patients progressing to a TTR of >5 seconds, a prognostic marker for accelerated disease progression and earlier loss of ambulation

- **The totality of evidence indicates that delandistrogene moxeparvovec produces potential beneficial disease trajectory modification versus placebo with a manageable safety profile**
  - EMBARK Part 2 will provide 2-year data on patients treated in Part 1, allowing progression to be monitored and adding to longer-term data

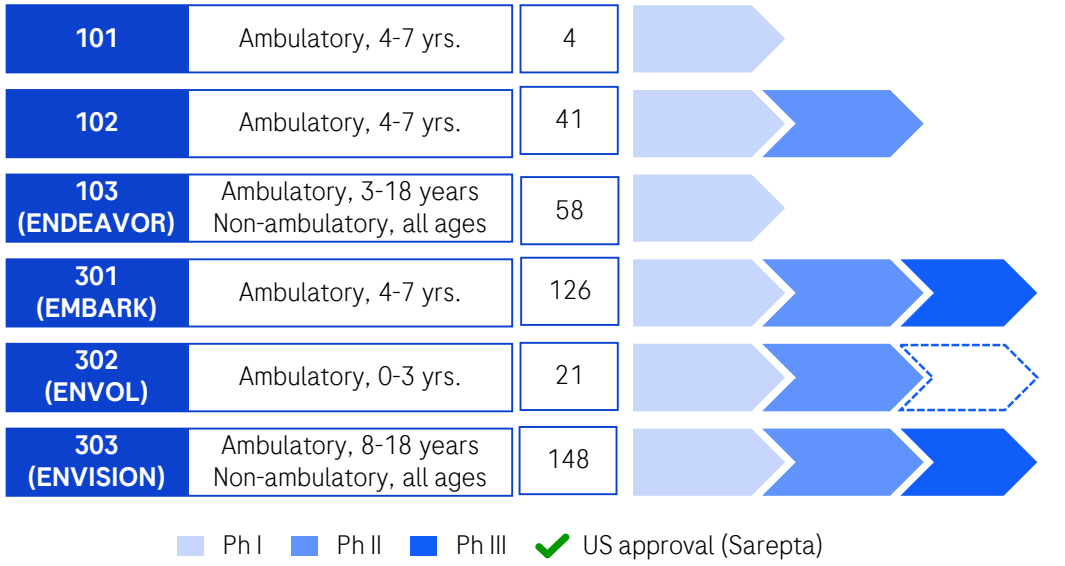
AE, adverse event; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; TTR, Time to Rise.

Elevidys in Duchenne muscular dystrophy

First and only gene therapy approved for the treatment of ambulatory DMD pts 4-5 yrs

Comprehensive development program

Trial	Patient population	N	Development stage	Status
101	Ambulatory, 4-7 yrs.	4		✓
102	Ambulatory, 4-7 yrs.	41		✓
103 (ENDEAVOR)	Ambulatory, 3-18 years Non-ambulatory, all ages	58		✓
301 (EMBARK)	Ambulatory, 4-7 yrs.	126		Planned EMA submission mid-year
302 (ENVOL)	Ambulatory, 0-3 yrs.	21		Actively recruiting
303 (ENVISION)	Ambulatory, 8-18 years Non-ambulatory, all ages	148		Actively recruiting



- Elevidys has the largest clinical trial program to support the broader Duchenne patient populations
- Elevidys is currently approved in the US, UAE, Qatar, and Kuwait for the treatment of ambulatory pediatric patients age 4-5 yrs with DMD
  - Submission are ongoing in up to 9 countries based on Ph I and Ph II data

DMD=Duchenne muscular dystrophy; Elevidys in collaboration with Sarepta

Neurology early stage pipeline

Azad Bonni
SVP and Global Head of Neuroscience & Rare Diseases, Roche Pharma Research & Early Development

Neurology pipeline

Industry leading portfolio differentiated on targets and platform technologies

Ph I (5 NMEs)	
RG6035	**Brainshuttle™ CD20** Multiple Sclerosis
RG6182	**MAGLi** Multiple Sclerosis
RG6289	**Gamma-secretase modulator** Alzheimer's
RG6418	**selnoflast** Parkinson's
RG6163	undisclosed psychiatric disorders

Ph II (6 NMEs, 1AI)		
RG7935	**prasinezumab** Parkinson's	
RG6100	**bepranemab**[1] Alzheimer's	
RG6102	**trontinemab** Alzheimer's	
RG6042	**tominersen** Huntington's	
RG6237 + RG7916	**GYM329 + Evrysdi** SMA	RD
RG6237	**GYM329** FSHD	RD
RG7816	**alogabat** Autism spectrum disorder	

Ph III (1 NME, 5AI)		
RG6168	**Enspryng** gMG	RD
RG6168	**Enspryng** MOG-AD	RD
RG6168	**Enspryng** AIE	RD
RG7845	**fenebrutinib** Multiple Sclerosis	
RG1594	**Ocrevus high dose** Multiple Sclerosis	
RG1594	**Ocrevus SC** Multiple Sclerosis	

Launched (4)			
RG1594	**Ocrevus** Multiple Sclerosis		✓
RG6168	**Enspryng** NMOSD	RD	✓
RG7916	**Evrysdi** SMA type 1/2/3	RD	✓
RG6356	**Elevidys**[2] DMD	RD	✓

- Small molecule
- Antibody
- Gene therapy
- Brain shuttle
- Locked nucleic acid / antisense

- Neuro-immunologic disorders
- Neuro-degenerative disorders
- Neuro-developmental disorders
- Neuro-muscular disorders
- Psychiatric disorders
- ✓ FDA approval
- RD = Rare disease

[1]bepranemab in partnership with UCB, studies are currently run by UCB; [2]Elevidys in partnership with Sarepta Therapeutics; NME=new molecular entity; AI=additional indication; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; SMA=spinal muscular atrophy; FSHD=facioscapulohumeral muscular dystrophy; MOG-AD=myelin oligodendrocyte glycoprotein antibody-associated disease; AIE=autoimmune encephalitis; MAGL=monoacylglycerol lipase

Brainshuttle™ AD

Roche

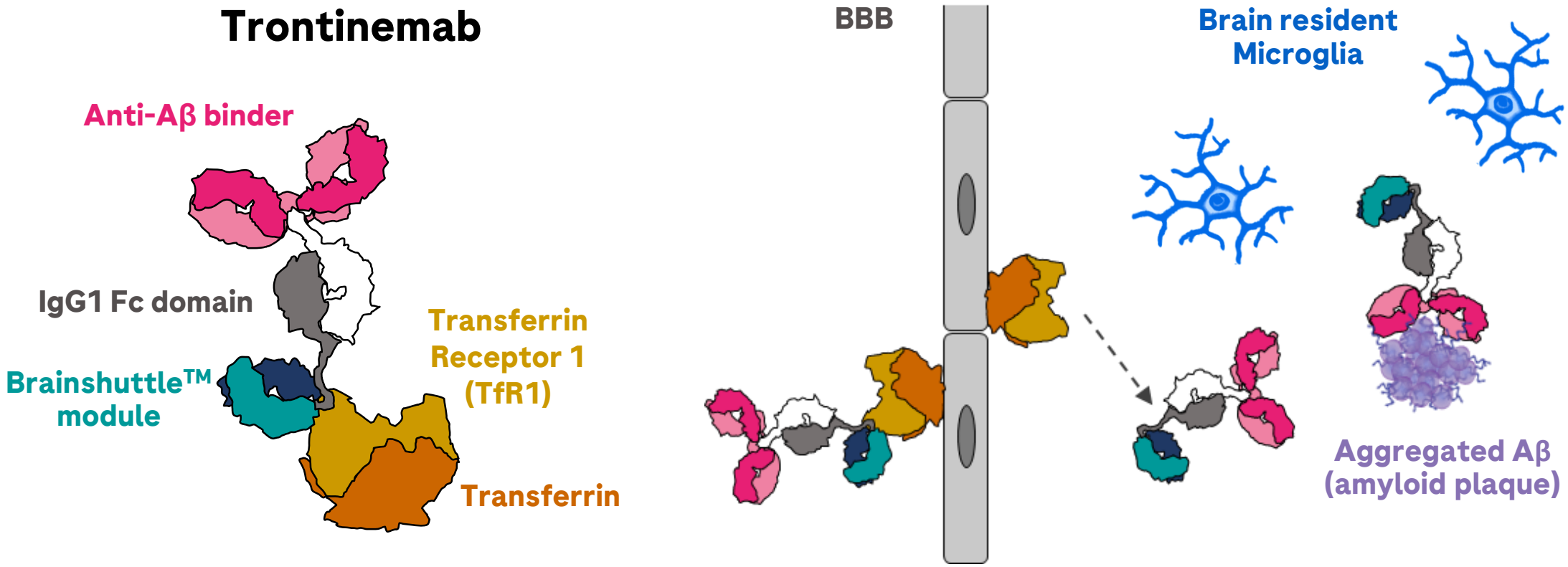
RAPID DOSE-DEPENDENT AMYLOID PLAQUE DEPLETION WITH TRONTINEMAB, A NOVEL BRAINSHUTTLE™ ANTIBODY IN DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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

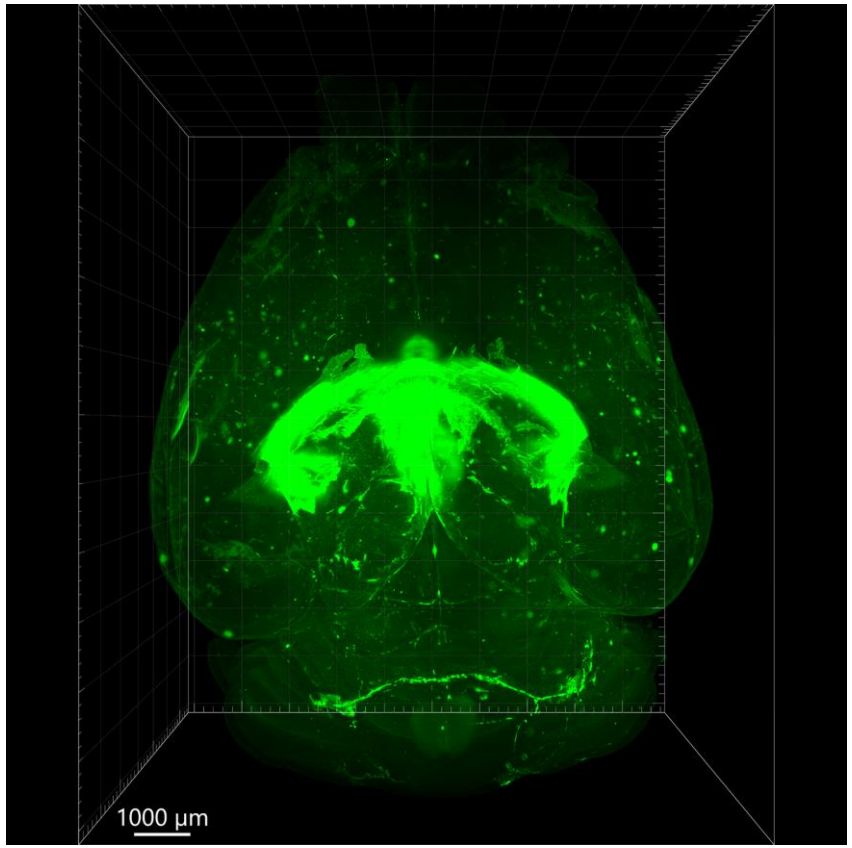


Trontinemab crosses the BBB via TfR1-mediated transcytosis at the capillary level

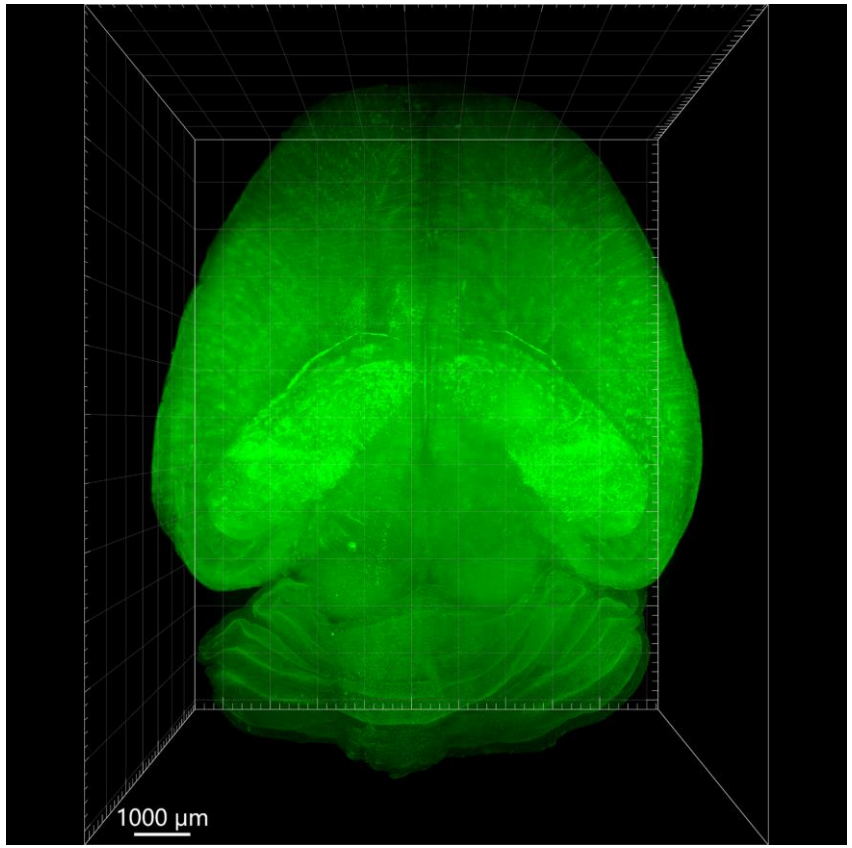
Aβ, amyloid beta; IgG1, immunoglobulin G1; Fc domain, fragment crystallisable domain; BBB, blood brain barrier.

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

Standard IgG[1]



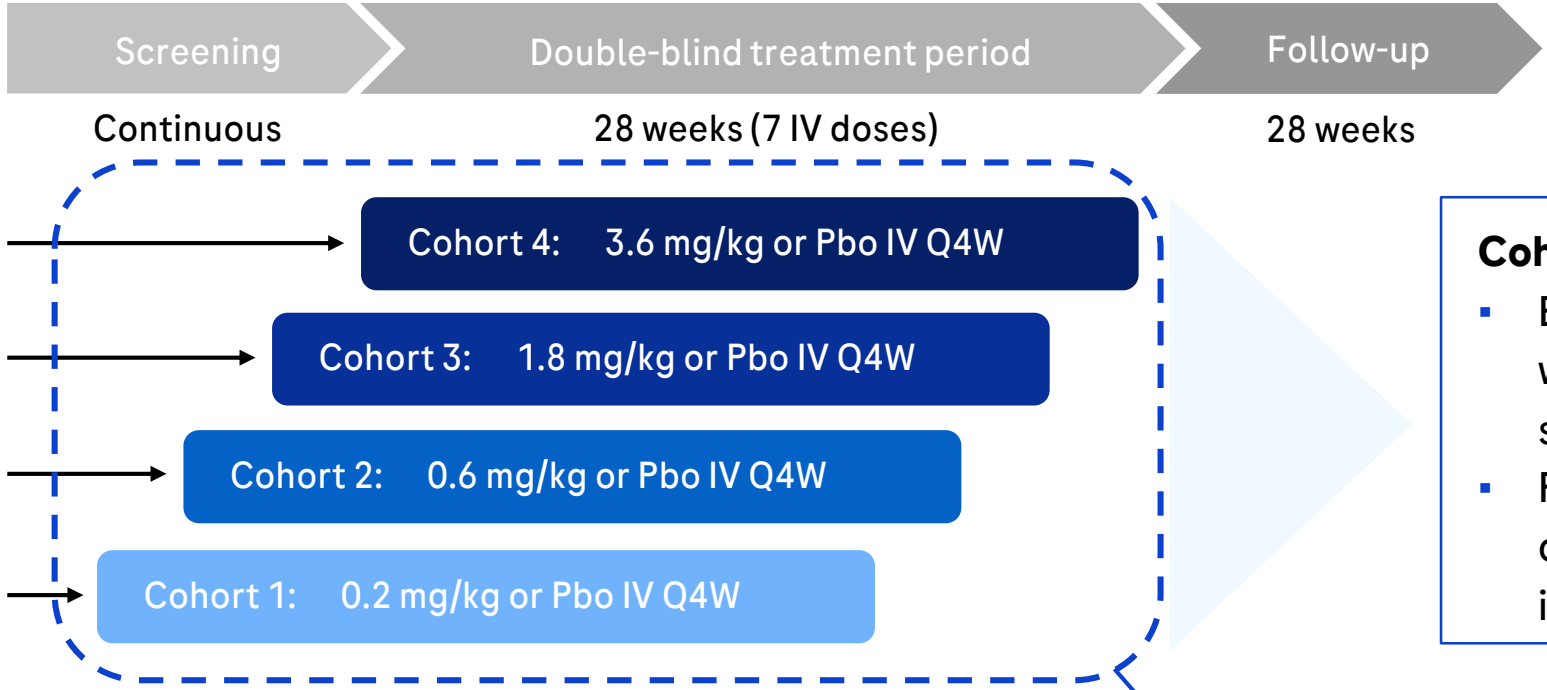
Brainshuttle™ IgG[1]



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

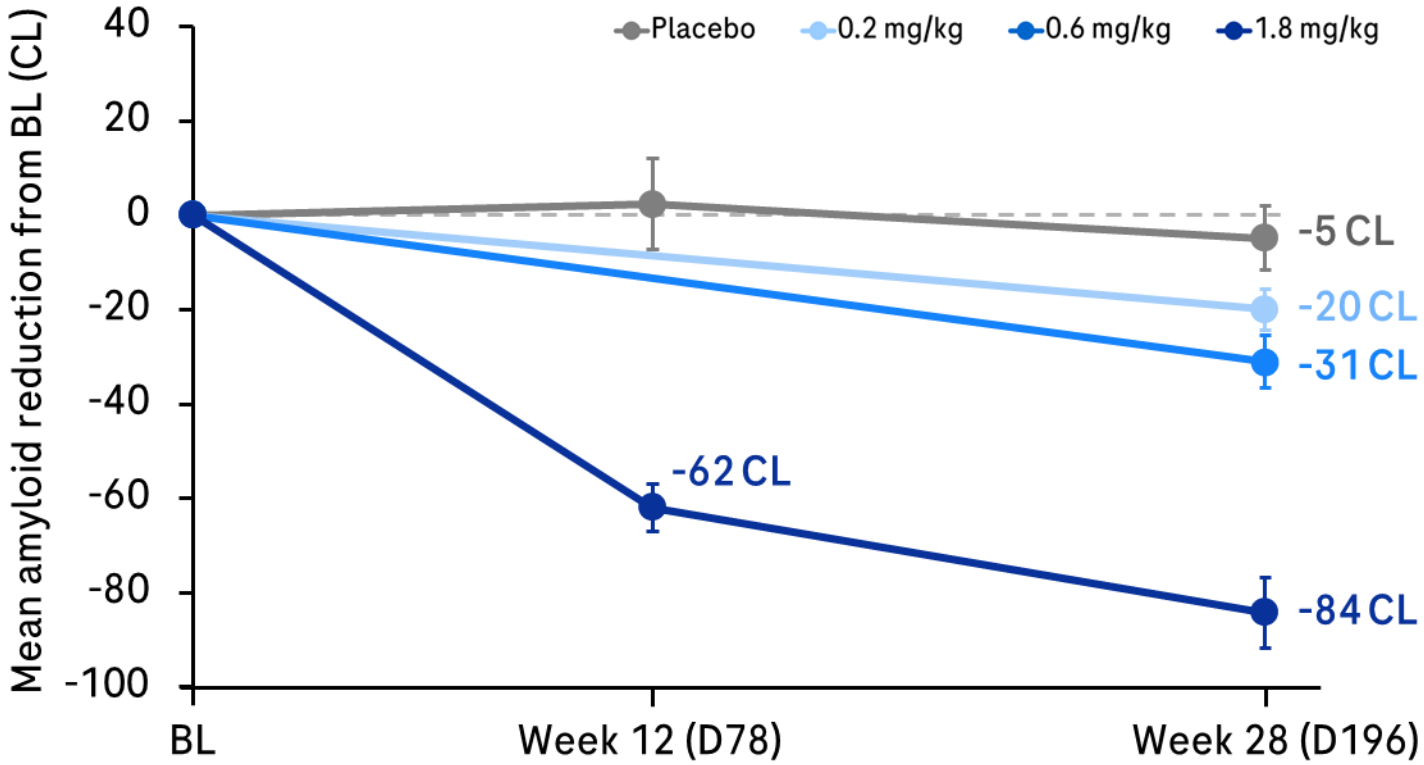
Interim analysis[1] included data from 15 participants in cohort 4 (3.6 mg/kg) at BL[2]

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]

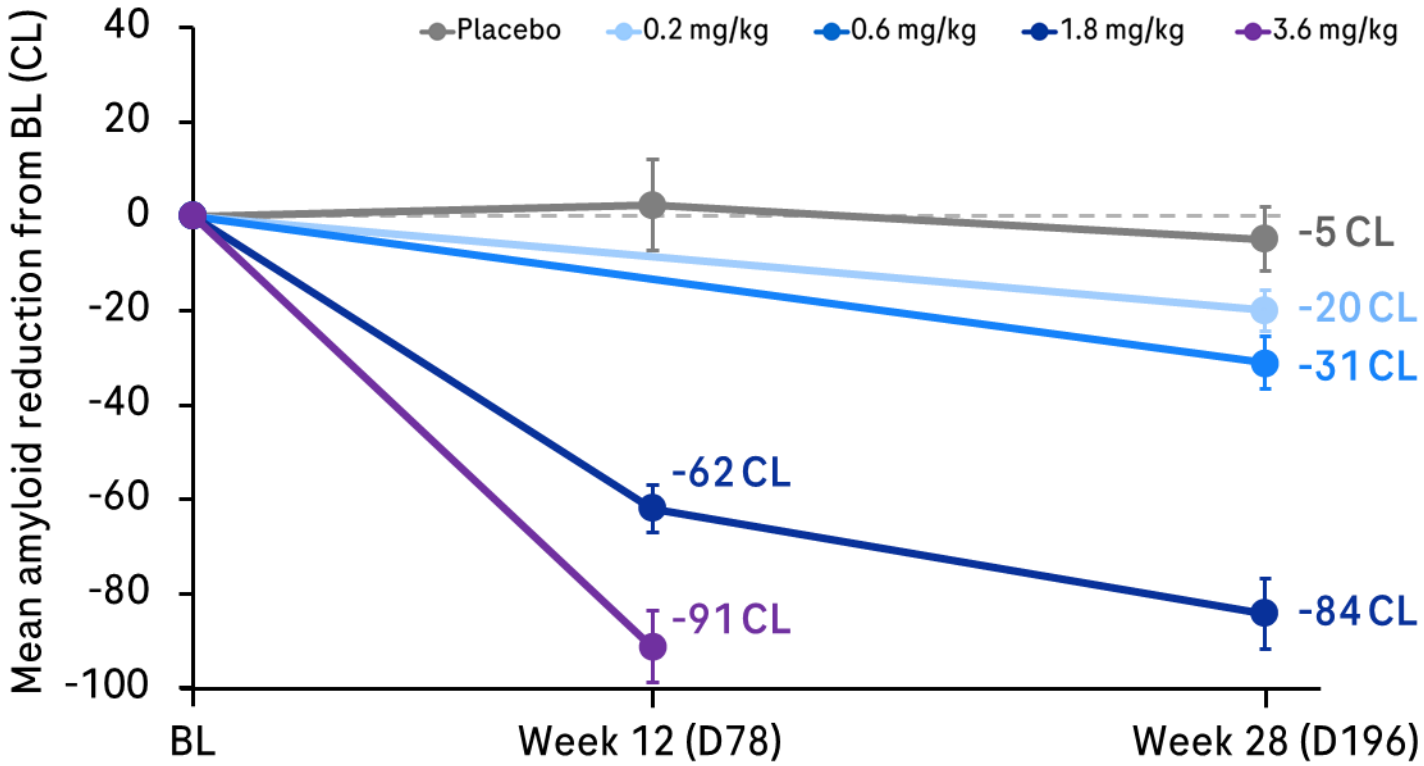


Placebo	n = 12	n = 5	n = 9
0.2 mg/kg	n = 11	-	n = 10
0.6 mg/kg	n = 11	-	n = 10
1.8 mg/kg	n = 13	n = 11	n = 8

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]



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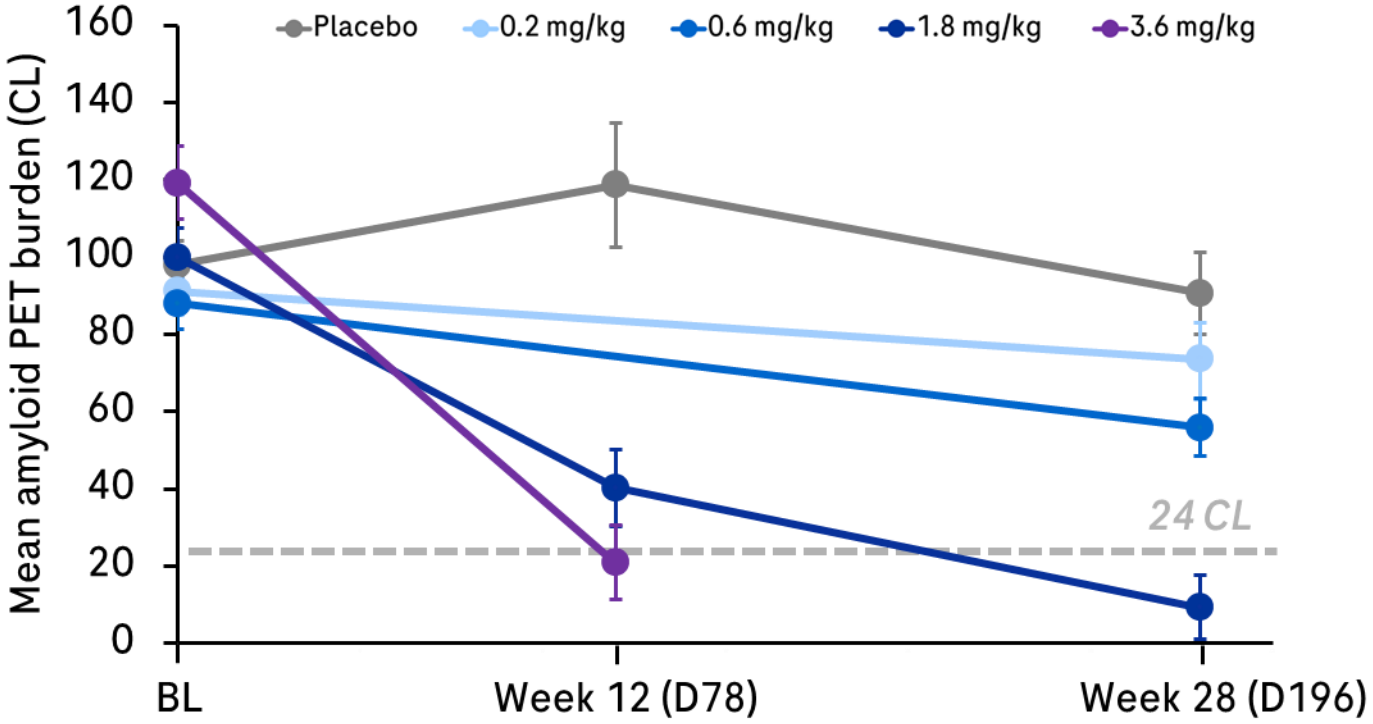
1.8 mg/kg	n = 13	n = 11	n = 8
3.6 mg/kg	**n = 12**	**n = 8**	-

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

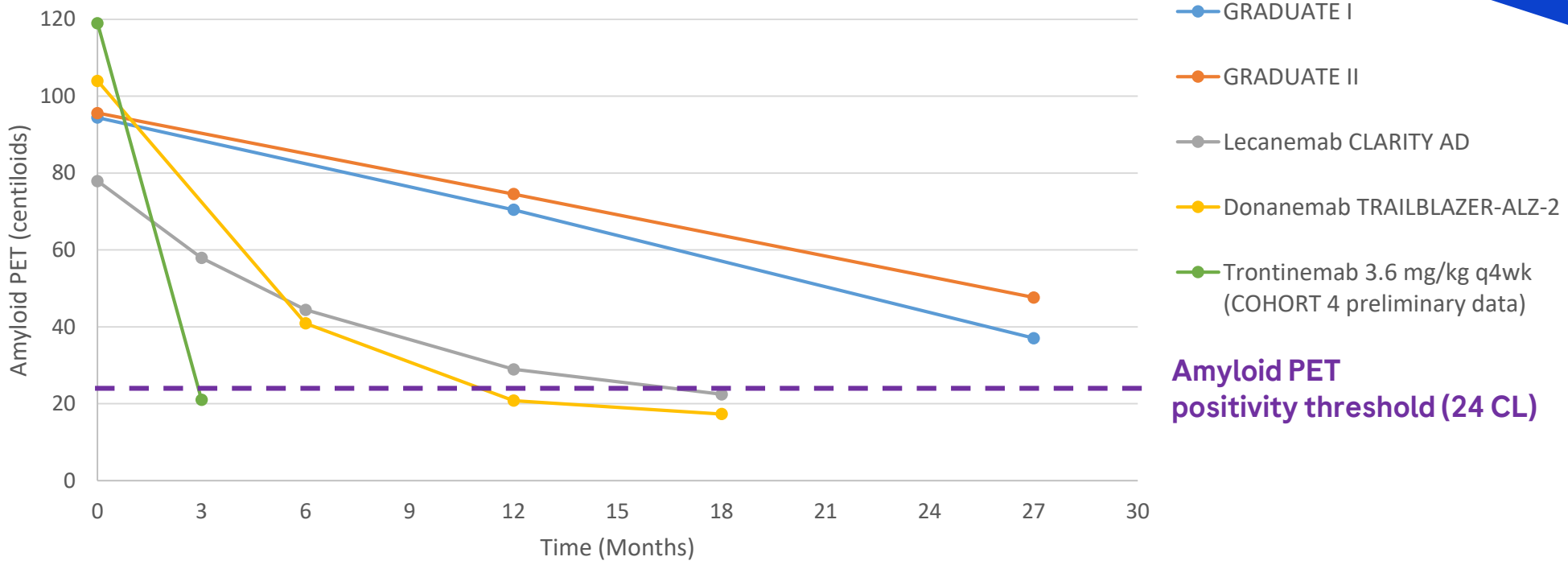
- Trontinemab is a novel Brainshuttle™ Aβ antibody that crosses the blood brain barrier via active TfR1 mediated transcytosis at the capillary level.
- In people with AD, trontinemab demonstrated rapid and robust amyloid plaque reduction at relatively low doses (1.8 and 3.6 mg/kg), compared with standard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

PASADENA long-term open-label extension continue to show reduced motor and functional progression in prasinezumab-treated individuals with early-stage Parkinson's disease compared to a real-world data arm

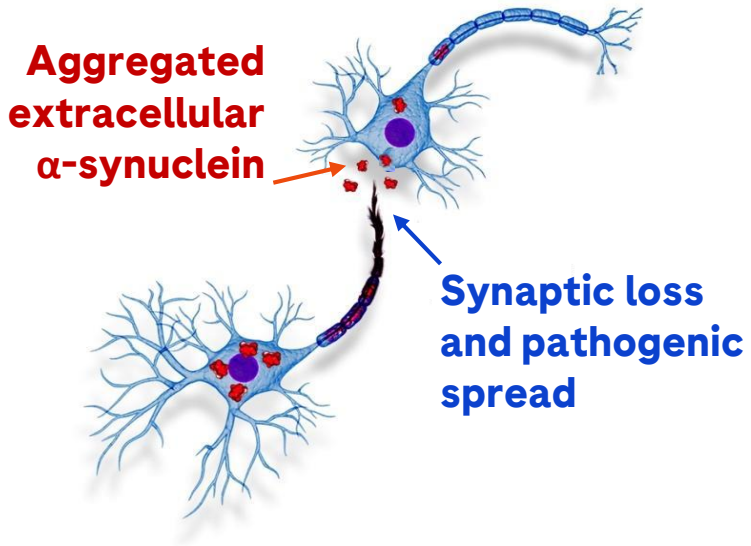
Gennaro Pagano, M.D., Ph.D.,[1,2] Annabelle Monnet, M.Sc.,[3] Adriana Reyes, M.Sc.,[3] Tanya Simuni, M.D.,[4] Ronald B. Postuma, M.D.,[5] Nicola Pavese, M.D., Ph.D.,[6] Fabrizio Stocchi, M.D., Ph.D.,[7] Krzysztof Smigorski, Ph.D.,[1] Valentina Gerbaldo, M.Sc.,[8] Riorge Thomas, M.Sc.,[9] Nima Shariati, Ph.D.,[3] Hanno Svoboda, Ph.D.,[1,10] Paulo Fontoura, M.D., Ph.D.,[11] Rachelle Doody, M.D., Ph.D.,[11] Geoffrey A. Kerchner, M.D., Ph.D.,[1] Patrik Brundin, M.D., Ph.D.,[1] Azad Bonni, M.D., Ph.D.,[1] Kenneth Marek, M.D., Ph.D.,[12] and Tania Nikolcheva, M.D., Ph.D.[11]

5-9 March | ADPD 2024

Prasinezumab is a humanised IgG1 monoclonal antibody that selectively binds aggregated α-synuclein

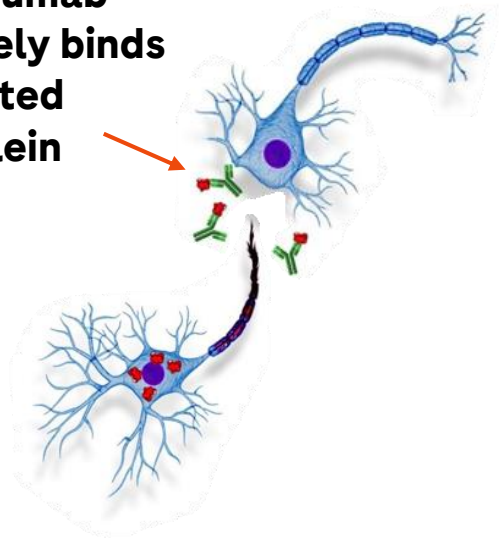
Proposed mode of action of prasinezumab for the treatment of Parkinson's disease[1–13]

Parkinson's disease



Prasinezumab's mode of action

Prasinezumab selectively binds aggregated α-synuclein



Proposed effects:

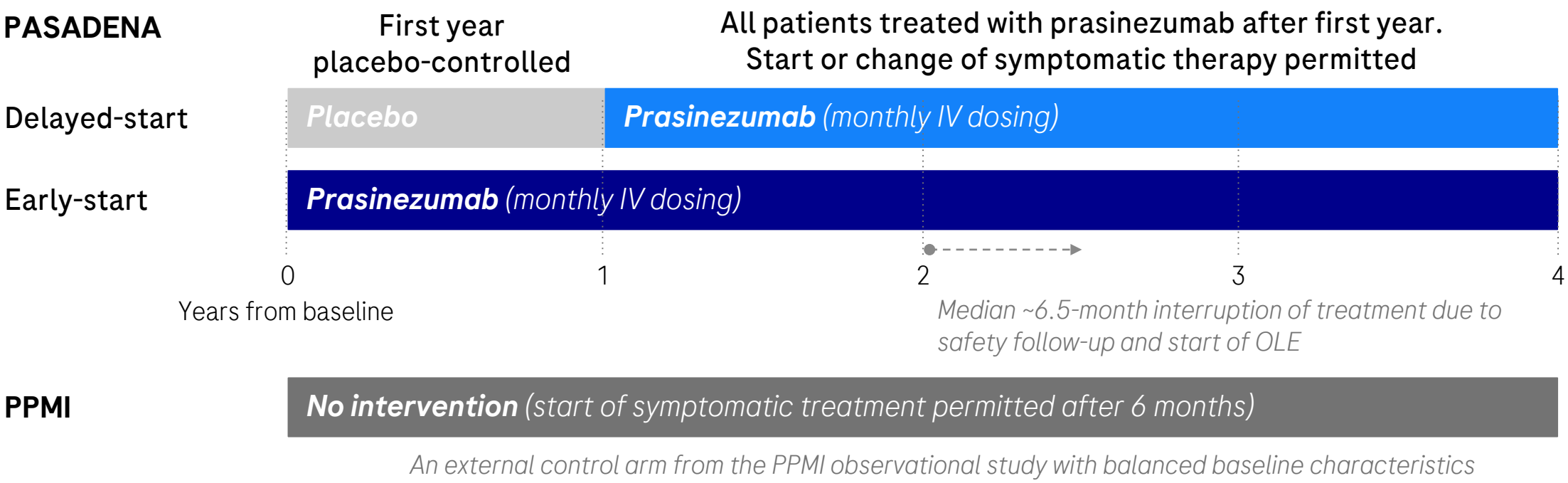
- Reducing neuronal toxicity
- Preventing cell-to-cell transfer of pathogenic α-synuclein aggregates
- Slowing disease progression

IgG, immunoglobulin.

1. Kalia LV & Lang AE. *Lancet*. 2015;386:896–9125; 2. Nakamori M, *et al. Neurotherapeutics*. 2019;16(2):287–98; 3. Benskey MJ, *et al. J Neurochem*. 2016;137:331–59; 4. Braak H, *et al. Neurobiol Aging*. 2003;24:197–211; 4. Mollenhauer B, *et al.* Presented at MDS 2018. Abstract:255; 5. Spillantini MG, *et al. Nature*. 1997;388:839–40. Reviewed by Goedert M, *Science*. 2015; 349:1255555; 6. Braak H, *et al. Neurobiol*. 2003;24:197–211; 7. Ulusoy A, *et al. EMBO Mol Med*. 2013;5:1051–9; 8. Kordower JH, *et al. Neurobiol Dis*. 2011;43:552–7; 9. Games D, *et al. J Neurosci*. 2014; 34:9441–54; 10. Masliah E, *et al. PLoS One*. 2011;6:e19338; 11. Masliah E, *et al. Neuron*. 2005;46:857–68; 12. ClinicalTrials.gov. NCT03100149. PASADENA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03100149 (last accessed February 2024); 13. ClinicalTrials.gov. NCT04777331. PADOVA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT04777331 (last accessed February 2024).

Contextualising the PD progression rate in the PASADENA open-label extension (OLE) vs PPMI cohort after a 4-year follow-up

Objective: To compare progression on MDS-UPDRS in the PASADENA[1,2] prasinezumab population with a propensity score-balanced cohort from the PPMI dataset



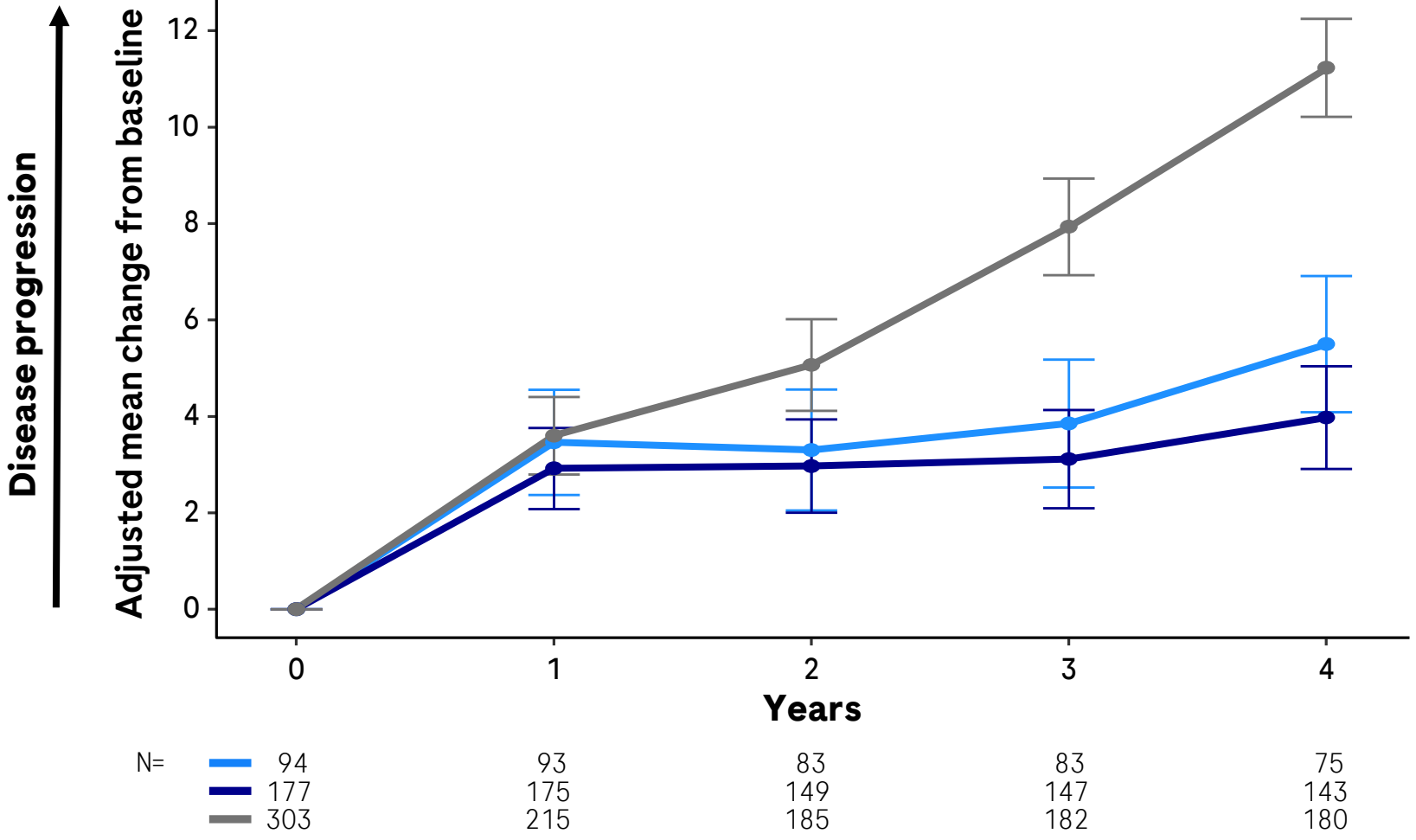
Note: PASADENA is a multicentre, randomised, double-blind, placebo-controlled Phase II study of prasinezumab in individuals with early PD with an OLE phase. Participants received monthly intravenous doses of prasinezumab (1,500 or 4,500 mg) or placebo for a 52-week period (Part 1), followed by a 52-week extension (Part 2) in which all participants received active treatment. Different dose strengths arms of prasinezumab not depicted during year 1 and 2. OLE of PASADENA started after 2 years and a planned 3-month (min 2.80, max 17.70) safety wash-out.
PASADENA: data cut-off 2nd Oct 2023; PPMI: the current study only included the sporadic PD cohort, data cut-off Aug 2021.
MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative.
1. Pagano G, *et al. Front Neurol*. 2021:12:705407; 2. ClinicalTrials.gov. NCT03100149. PASADENA Phase 2 clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03100149 (accessed February 2024).

Baseline characteristics are balanced after weighting with propensity scores

Baseline demographic and disease characteristics	PASADENA N=271	Before propensity score weighting		After propensity score weighting	
		PPMI N=303	SMD	PPMI N=269.88	SMD
Age (years) (mean (SD))	59.98 (9.0)	62.11 (8.53)	0.243	61.20 (9.28)	0.133
Sex = male, n (%)	188 (69.4)	202 (66.7)	0.058	189.3 (70.1)	0.017
MDS-UPDRS Part III (mean (SD))	21.15 (8.96)	21.17 (8.85)	0.003	21.13 (9.71)	0.001
H&Y stage II, n (%)	201 (74.2)	183 (60.4)	0.297	205.7 (76.2)	0.047
PD diagnosis (months) (mean (SD))	9.89 (6.34)	4.87 (5.36)	0.855	9.20 (5.61)	0.115
Years of education ≥12, n (%)	244 (90.0)	279 (92.1)	0.072	236.2 (87.5)	0.080
Montreal Cognitive Assessment (MoCA) (mean (SD))	28.17 (1.79)	27.23 (2.26)	0.462	28.02 (1.89)	0.082
DaT-SPECT putamen bilateral (mean (SD))	0.92 (0.26)	0.81 (0.28)	0.436	0.92 (0.31)	0.018

Note: SMD ≤0.2 indicates balance between groups. PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
DaT-SPECT, dopamine transporter imaging with single photon emission computed tomography; H&Y, modified Hoehn and Yahr stage; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative; SD, standard deviation; SMD, standardised mean difference.

Prasinezumab-treated individuals progress less than PPMI on MDS-UPDRS Part III OFF (motor examination)



Relative progression (80% CI) @ 4yrs

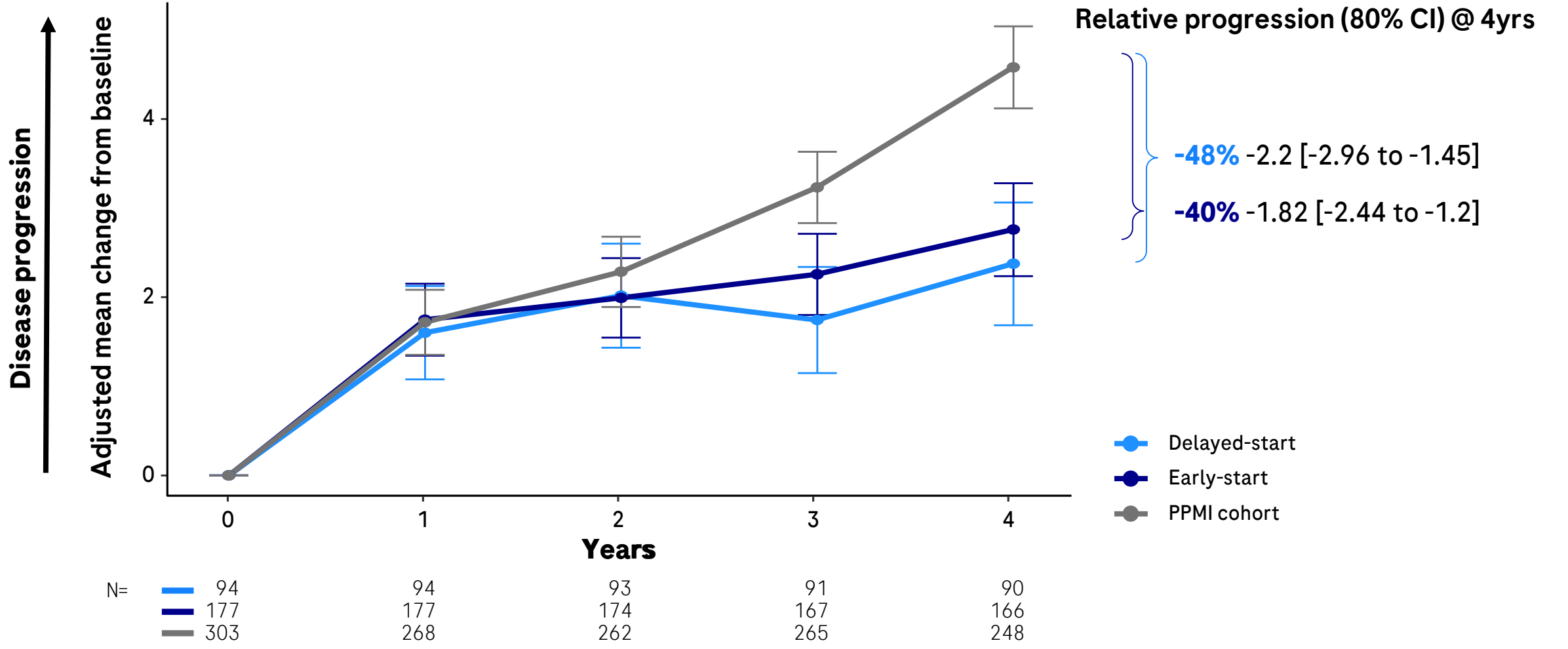
-51% -5.73 [-7.33 to -4.14]

-65% -7.26 [-8.59 to -5.93]

Delayed-start
Early-start
PPMI cohort

Note: Data and analysis is not intended as a delayed-start analysis (compare between PASADENA arms). PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

Prasinezumab-treated individuals progress less than PPMI on MDS-UPDRS Part II (motor experiences of daily living)



Note: Data and analysis is not intended as a delayed-start analysis (compare between PASADENA arms). PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

Summary

The comparison of PASADENA and PPMI data suggests potential benefit in slowing motor progression in favour of prasinezumab on multiple endpoints

- ❑ **Slowing of progression on MDS-UPDRS Part III** (clinician-rated motor examination) OFF and ON symptomatic medication state, **consistent** with previous data analyses
- ❑ **Slowing of progression on MDS-UPDRS Part II** (patient-reported motor experiences of daily living) emerges **after** the effect on Part III

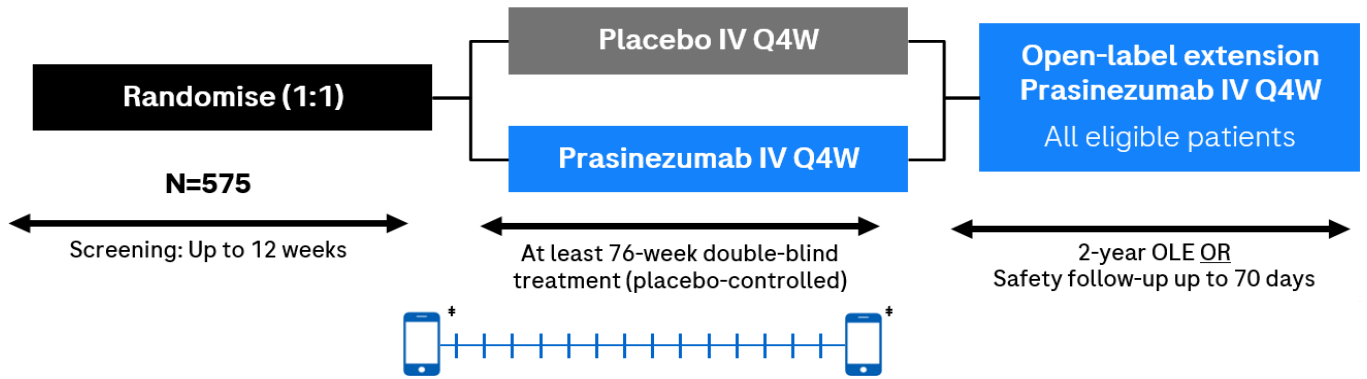
These findings are exploratory and need to be confirmed in an independent trial such as the Phase IIb PADOVA study and its OLE

MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative; OLE, Open Label Extension.

Prasinezumab in Parkinson's disease

Ph IIb (PADOVA) data expected 2H 2024

Ph IIb (PADOVA) trial design



Primary endpoint:
Time to confirmed motor progression event defined as ≥5 points on MDS-UPDRS Part III in OFF medication state at 18 months

- PADOVA was designed to follow up on a signal of slowing of motor progression observed in PASADENA in a population on stable background symptomatic therapy
- A time-to-event design was used to measure the impact of prasinezumab on meaningful motor progression and to mitigate the impact of symptomatic medication
- PADOVA enrolled 586 individuals with early-stage PD, of whom 74.4% were on stable L-DOPA and 25.6% on MAO-Bi therapy at baseline

‡Digital biomarkers (smartphone and wrist-worn wearable assessments); IV=intravenous; Q4W=every 4 week; OLE=open label extension; L-DOPA=levodopa; MAO-Bi=monoamine oxidase type B inhibitor; MDS-UPDRS=Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; OFF=practically defined OFF state, i.e. 12 hours after last dose; PD=Parkinson's disease; In collaboration with Prothena

Doing now what patients need next