Baseline EMBARK data from EMERGE, ENGAGE, and PRIME participants in the EMBARK re-dosing study

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Disclosures

- SC was an ENGAGE trial site investigator and an Aducanumab Steering Committee member; she is a consultant to Biogen, Cassava Sciences, Cogstate, INmune Bio, ProMIS Neuroscience, and RetiSpec (no personal fees) and receives research support (paid to institution) from AgeneBio, Anavex, Biogen, Cassava Sciences, Eisai, Genentech, Eli Lilly, Janssen, RetiSpec, Roche, and Vielight
- CVD was an EMERGE trial site investigator; he is a consultant to Roche and Eisai and receives research support from Biogen, Eisai, Roche, Genentech, Eli Lilly, Janssen, Merck, Novartis, and Biohaven
- CJM was an ENGAGE trial site investigator and an Aducanumab Steering Committee member; she is supported by NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, and IONIS
- AP reports personal fees from Acadia Pharmaceuticals, Alzheon, Avanir, Biogen, Cadent Therapeutics, Eisai, Functional Neuromodulation, Merck, Novartis, and ONO Pharmaceuticals, and grants to his institution from Alector, Athira, Avanir, Biogen, Biohaven, Eisai, Eli Lilly, Genentech/Roche, and Vaccinex
- JK, RM, AR, JO, and SBH are employees and shareholders of Biogen
- SS was a site investigator and co-chair of the Investigator Steering Committee for the ENGAGE study and is a consultant to Biogen; he also receives research support from and is a consultant to Eisai, Novartis, Genentech, Roche, Avid, and Lilly
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Background

- Insoluble Aβ aggregates are a defining pathophysiological feature of Alzheimer's disease
- Aducanumab is a human immunoglobulin gamma 1 monoclonal antibody targeting soluble and insoluble Aβ aggregates
- Aducanumab was approved for the treatment of MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease by the US Food and Drug Administration under the accelerated approval pathway; this approval was based on the reduction of Aβ plaques observed in treated patients

Aβ, amyloid beta; MCI, mild cognitive impairment.

EMBARK study overview

EMBARK is an open-label, multicenter, longitudinal, single-arm, global Phase 3b study in participants with Alzheimer's disease

Population	Eligible patients with Alzheimer's disease actively enrolled in the aducanumab studies[a] in March 2019
Dose	Aducanumab 10 mg/kg IV infusion every 4 weeks, with a titration period[b]
Duration	24 months
Sample size	This study screened 1856 participants (1694 enrolled)[c] from the former aducanumab studies, which were terminated following Phase 3 futility analysis[1]
Primary objective	To evaluate the long-term safety and tolerability of a monthly dose (10 mg/kg) of aducanumab after a gap period imposed by discontinuation of feeder studies
Exploratory objectives	To evaluate the long-term efficacy of aducanumab using clinical endpoints
	To evaluate the long-term effect of aducanumab on biomarker endpoints
	To evaluate the long-term effect of aducanumab on PK endpoints

[a]EMERGE, ENGAGE, the LTE of the PRIME study, or the EVOLVE safety study. [b] 1mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter. [c] As of July 15, 2021.

1. Combined FDA and applicant PCNS Drugs Advisory Committee briefing document. US Food and Drug Administration website. Published November 6, 2020 (Accessed March 16, 2021). IV, intravenous; LTE, long-term extension; PK, pharmacokinetics.

EMBARK key inclusion and exclusion criteria

Key Inclusion Criteria:[1]

- Participation in an aducanumab clinical study when early termination was announced
- MMSE score above 10 at Screening
- Care partner who can provide accurate information about the participant's cognitive and functional abilities

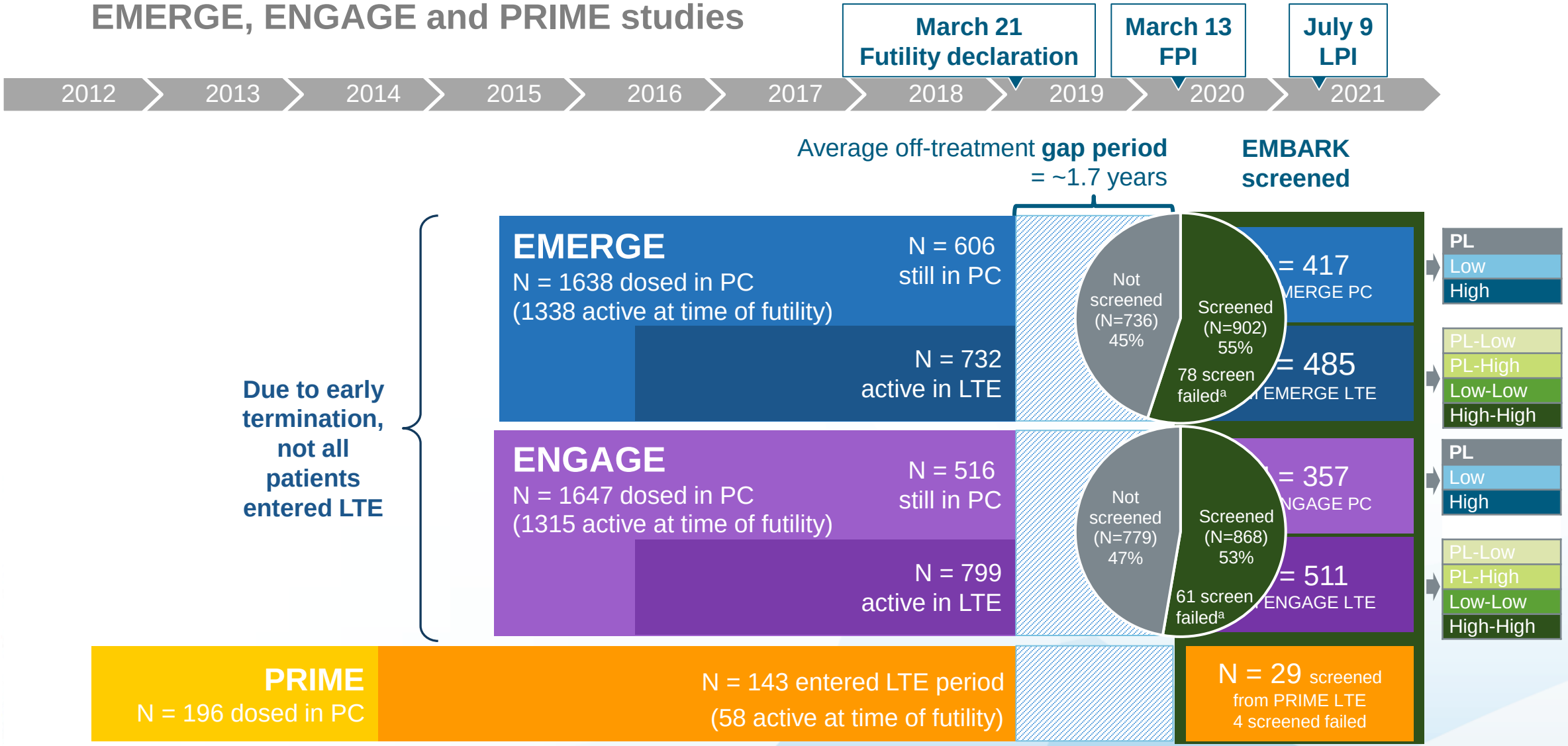
Key Exclusion Criteria:[1]

- A **medical or neurological condition** (other than Alzheimer's disease) that may contribute to **cognitive impairment**
- **Stroke** or unexplained **loss of consciousness** within **1 year** before Screening
- Brain MRI evidence of: acute or subacute hemorrhage; prior macro-hemorrhage or subarachnoid hemorrhage not due to underlying structural or vascular abnormality; >4 (for treatment-naïve participants) or ≥10 (for aducanumab-treated participants) micro-hemorrhages; cortical infarct; superficial siderosis
- Clinically significant, **unstable psychiatric illness** in the past **6 months**
- Medical conditions that are not stable or controlled, or, which in the opinion of the Investigator, could affect the participant's safety or interfere with the study assessments

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04241068 (Accessed October 6, 2021). MMSE, Mini-Mental State Examination.

EMBARK study population

EMERGE, ENGAGE and PRIME studies



EMERGE and ENGAGE had an optional amyloid PET substudy. For EMERGE, 488 enrolled, 392 were active at the time of futility, and 263 were screened in EMBARK. For ENGAGE, 585 enrolled, 455 were active at the time of futility, and 282 were screened in EMBARK [a] The most common reasons for screen failure were brain MRI evidence of acute or subacute hemorrhage (EMERGE: 1.8%; ENGAGE: 1%) and inability to comply with protocol-related tests and procedures (EMERGE: 1%; ENGAGE: 1%). FPI, first patient in; LPI, last patient in; LTE, long-term extension period; PC, placebo-controlled; PL, placebo.

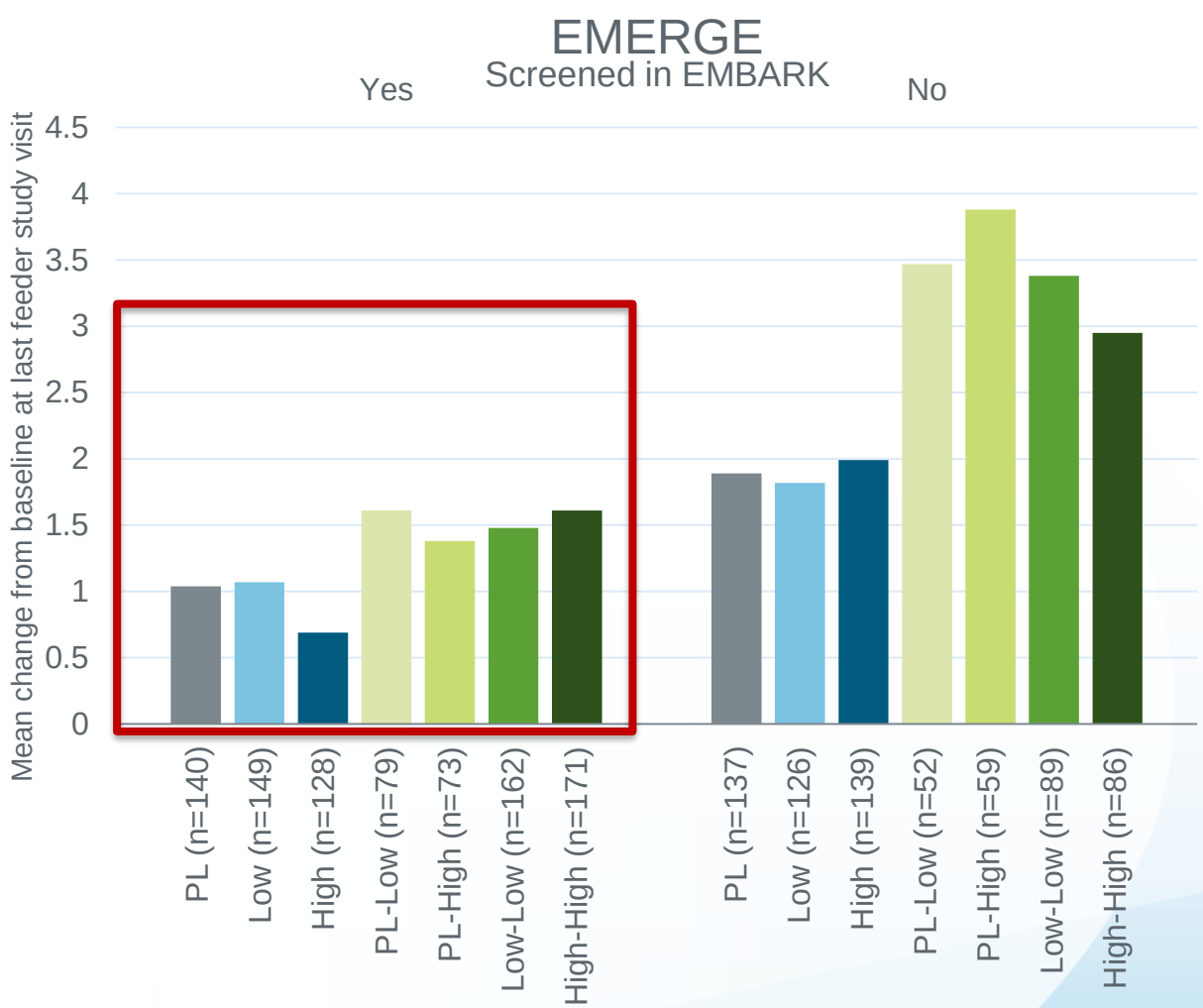
Population in EMBARK is heterogeneous

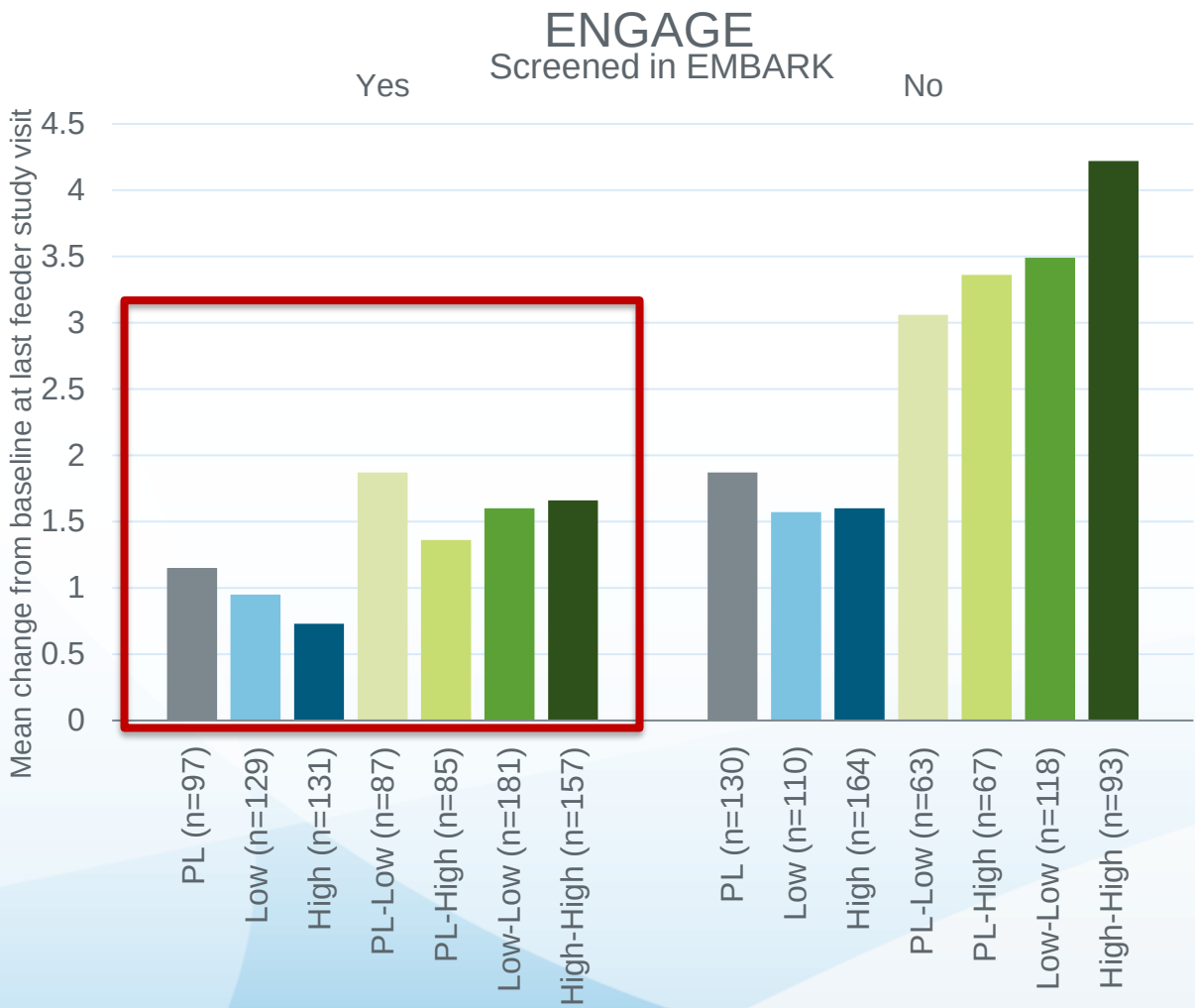
- Not a randomized study
- Patients come from different studies
- Different doses
- Different duration of exposure
- Different treatment gap periods

EMBARK study key limitations

- There may be selection bias for the participants who entered EMBARK
- Impact of constraints imposed by the COVID-19 pandemic on lifestyle, cognition, and behavior of patients and caregivers cannot be adequately assessed

Participants returning for EMBARK showed less clinical progression on CDR-SB in EMERGE/ENGAGE than subjects who did not return





At the time of the E/E futility announcement, the PL, Low and High groups in the PC cohort were active in the PC period and the PL-Low, PL-High, Low-Low and High-High were active in the LTE period. CDR-SB, Clinical Dementia Rating–Sum of Boxes; E/E, EMERGE/ENGAGE; High, high-dose aducanumab; Low, low-dose aducanumab; LTE, long-term extension; PL, placebo.

What can we learn from EMBARK baseline data in conjunction with data from feeder studies?

1. What is the clinical change during the treatment gap period?

2. What is the change in amyloid levels during the treatment gap period?

Demographic and disease characteristics at EMERGE/ENGAGE baseline and EMBARK baseline

	EMERGE/ENGAGE Baseline	EMBARK Baseline
Number of participants (N)	3285	1770
Mean age	70.4	73.1
Lab ApoE ε4 status – n (%)		
Carrier	2240 (68.2)	1197 (67.6)
Non-carrier	1036 (31.5)	567 (32.0)
Mean years since AD diagnosis	1.24	4.63
Symptomatic AD medication (%)	1777 (54.1)	1086 (67.4)
Clinical stage – n (%)		
MCI	2661 (81.0)	532 (30.1)
Mild AD	624 (19.0)	745 (42.1)
Moderate AD	-	408 (23.1)
Severe AD	-	68 (3.8)
Unknown	-	17 (1.0)
Mean CDR-SB ± SD	2.45±1.02	5.32±3.23
Mean MMSE ± SD	26.4±1.74	20.9±5.95
Mean ADAS-Cog 13 ± SD	22.3±6.66	33.1±13.01
Mean ADCS-ADL-MCI ± SD	42.8±5.67	35.4±10.31

AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.

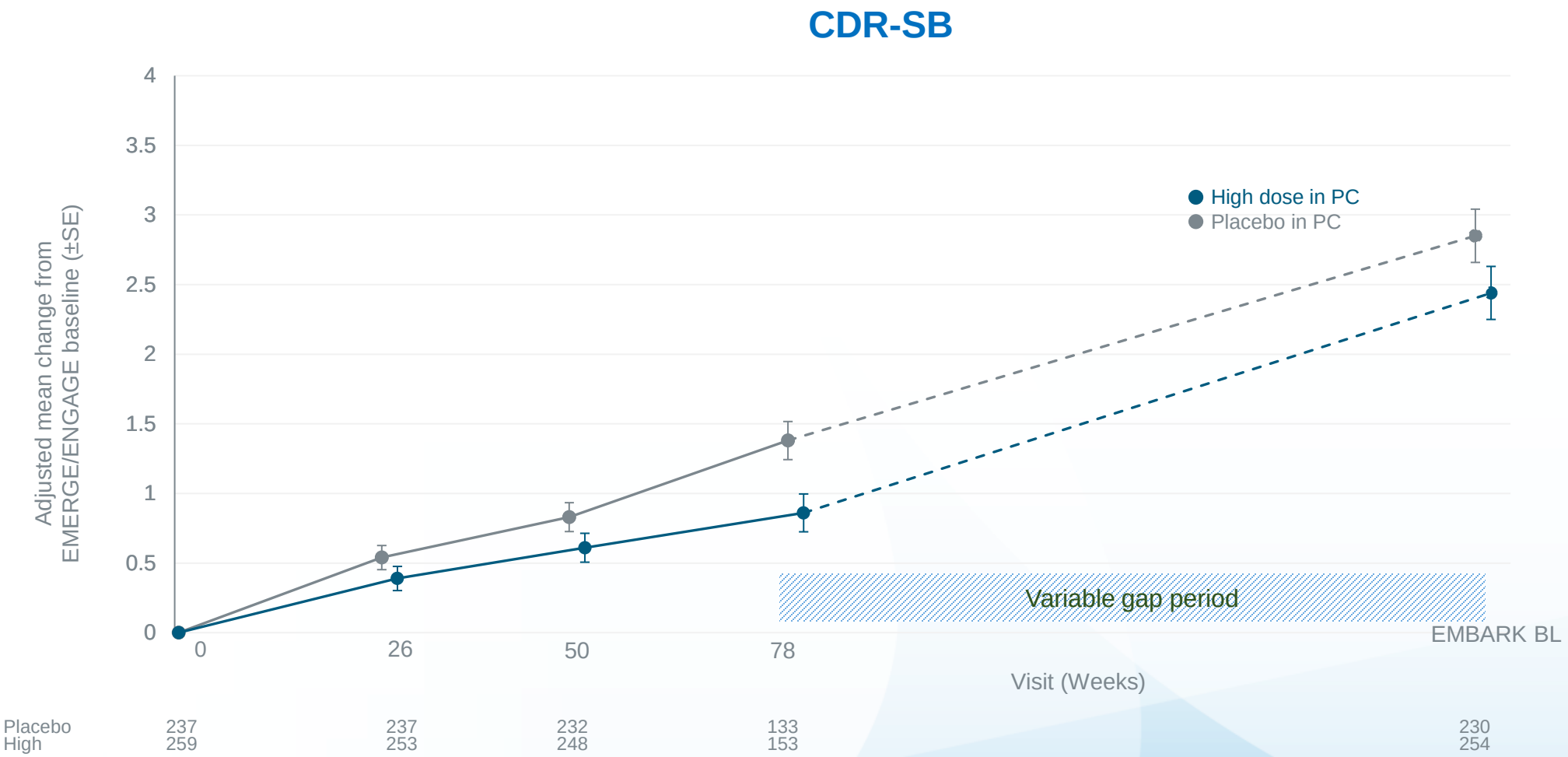
EMERGE and ENGAGE study period durations and exposure: PC cohort[a]

EMERGE			
Treatment group	Placebo (N=140)	Low (N=149)	High (N=128)
Study duration, median years (min, max)	1.1 (0.5, 1.5)	1.1 (0.6, 1.5)	1.1 (0.5, 1.5)
Aducanumab doses, median (min, max)	NA	14 (7,20)	14 (7, 20)
Gap period, median years (min, max)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.8 (1.1, 2.3)
ENGAGE			
	Placebo (N=97)	Low (N=129)	High (N=131)
Study duration, median years (min, max)	1.0 (0.7, 1.5)	1.1 (0.6, 1.5)	1.1 (0.5, 1.5)
Aducanumab doses, median number (min, max)	NA	15.0 (7, 20)	14.0 (6, 20)
Gap period, median years (min, max)	1.8 (1.1, 2.2)	1.8 (1.1, 3.1)	1.8 (1.1, 2.7)

- Across the treatment groups, the study duration ranged from 0.5-1.5 years in both EMERGE and in ENGAGE
- Across the treatment groups in EMERGE and ENGAGE, the gap period ranged from 1.1 to 3.1 years
- The number of aducanumab doses ranged from 7-20 in EMERGE and 6-20 in ENGAGE

[a]At the time of the E/E futility announcement, the PL, Low and High groups in the PC cohort were active in the PC period. E/E, EMERGE/ENGAGE; NA, not applicable; PC, placebo-controlled; PL, placebo.

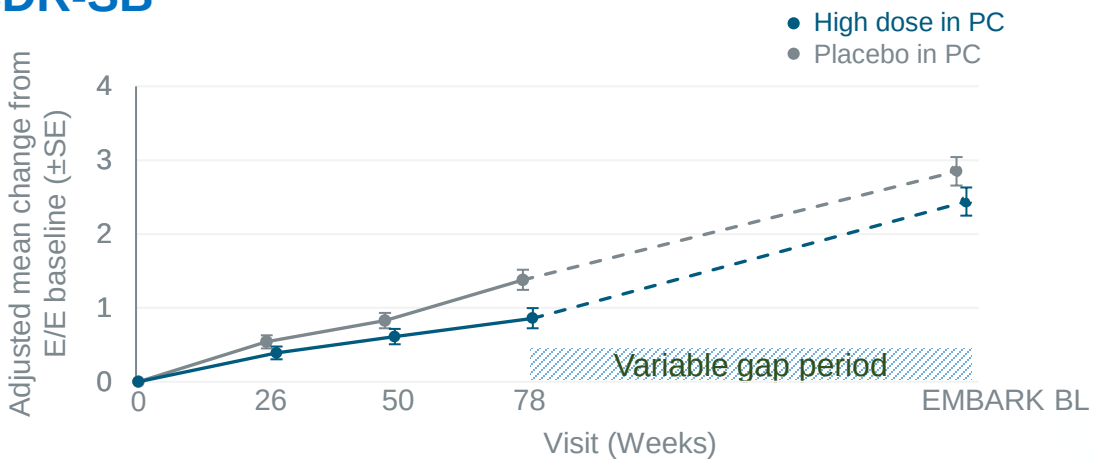
Numerical differences for CDR-SB at the end of the PC period are maintained during the treatment gap from the end of EMERGE and ENGAGE to EMBARK baseline: Pooled PC cohort



Adjusted mean and standard errors at each time point were based on an MMRM, with change from feeder-study baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, feeder-study baseline CDR-SB, feeder-study baseline CDR-SB by visit interaction, feeder-study baseline MMSE, AD symptomatic medication use at feeder-study baseline, region, and laboratory ApoE status. AD, Alzheimer's disease; ApoE, apolipoprotein E; BL, baseline; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; SE, standard error.

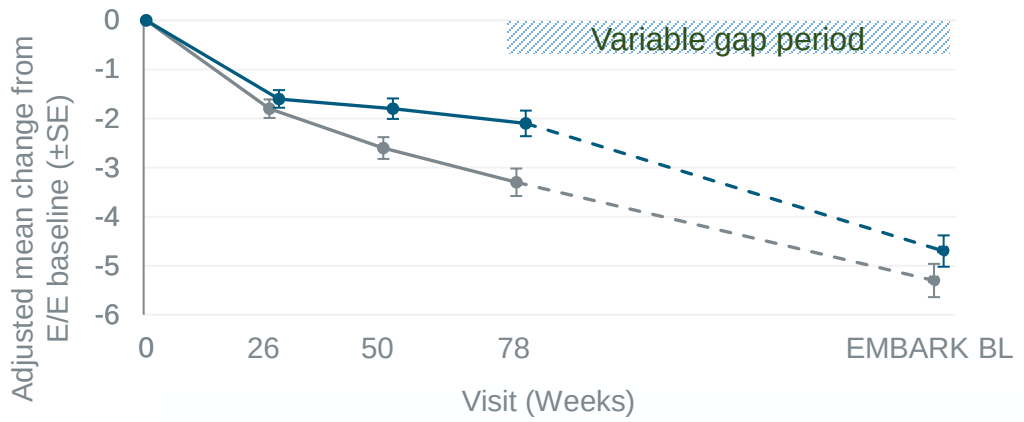
Numerical differences for clinical endpoints at the end of the PC period are generally maintained during the treatment gap from the end of EMERGE and ENGAGE to EMBARK baseline: Pooled PC cohort

CDR-SB



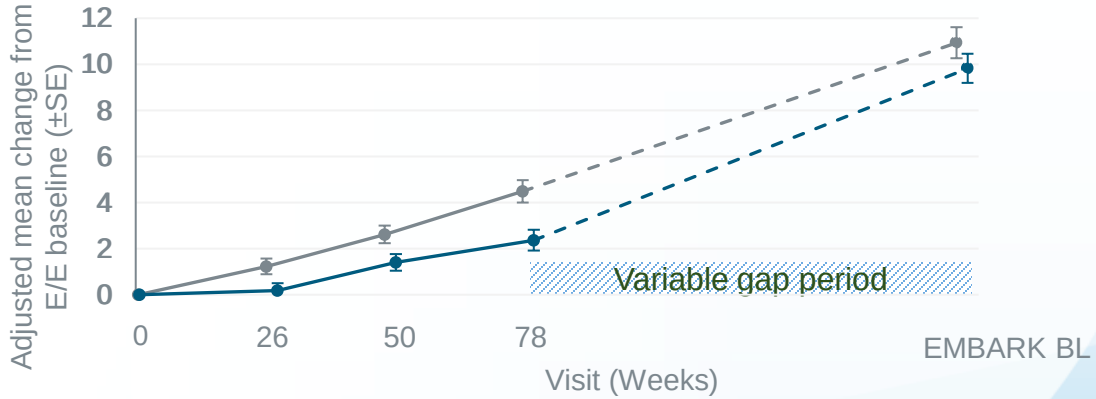
Placebo	237	237	232	133	230
High	259	253	248	153	254

MMSE



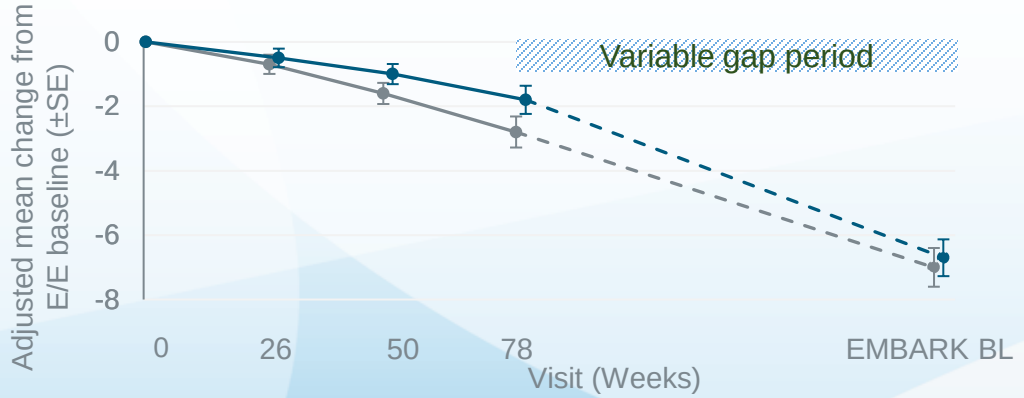
Placebo	237	236	231	134	232
High	259	257	253	156	255

ADAS-Cog 13



Placebo	234	234	229	130	225
High	257	254	250	154	253

ADCS-ADL-MCI



Placebo	234	233	229	127	227
High	258	256	250	155	253

Adjusted mean and standard errors at each time point were based on an MMRM, with change from feeder-study baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, feeder-study baseline CDR-SB, feeder-study baseline CDR-SB by visit interaction, feeder-study baseline MMSE, AD symptomatic medication use at feeder-study baseline, region, and laboratory ApoE status. ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; E/E, EMERGE/ENGAGE; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; SE, standard error.

What can we learn from EMBARK baseline data in conjunction with data from feeder studies?

- ☑ What is the clinical change during the treatment gap period?

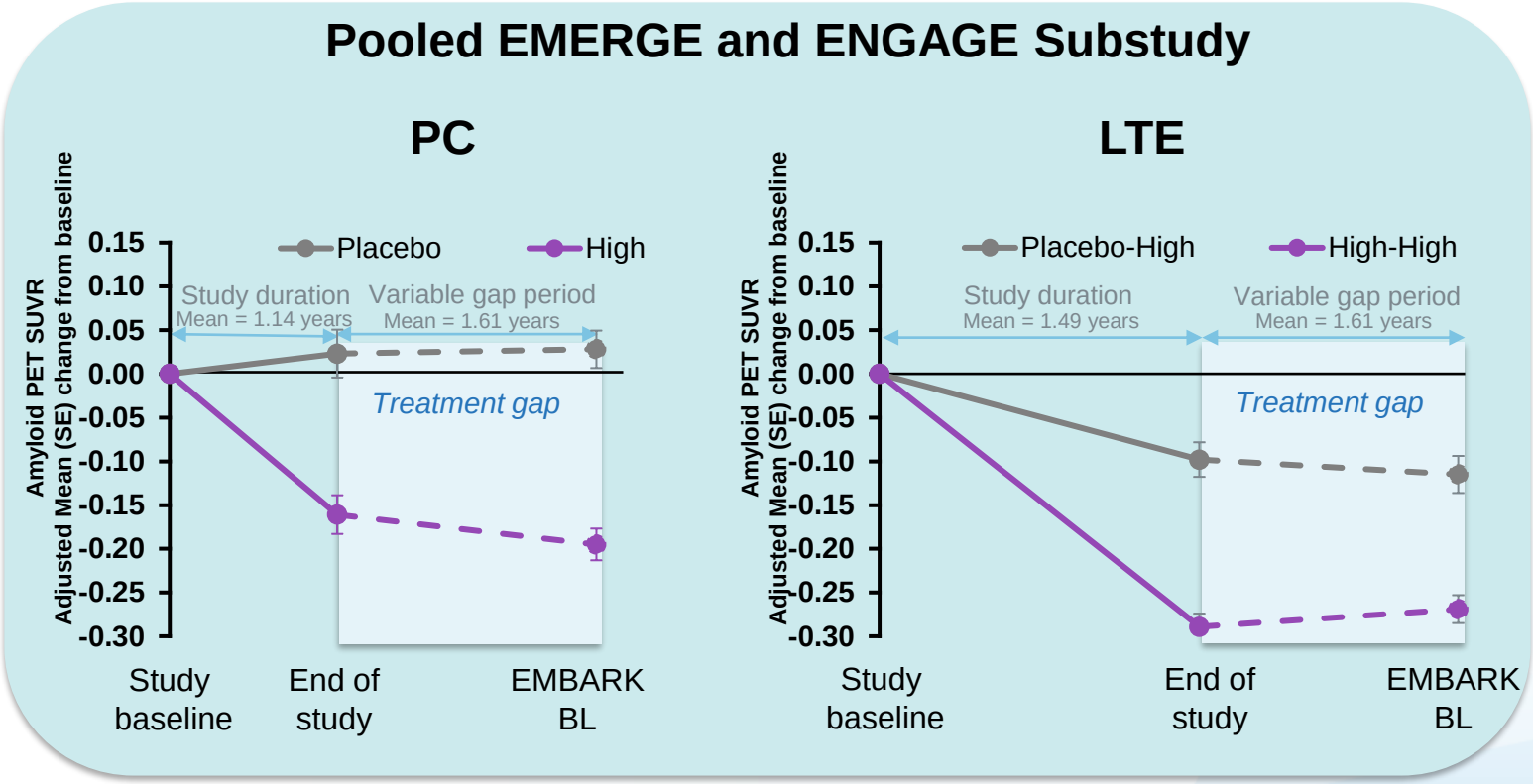
2. What is the change in amyloid levels during the treatment gap period?

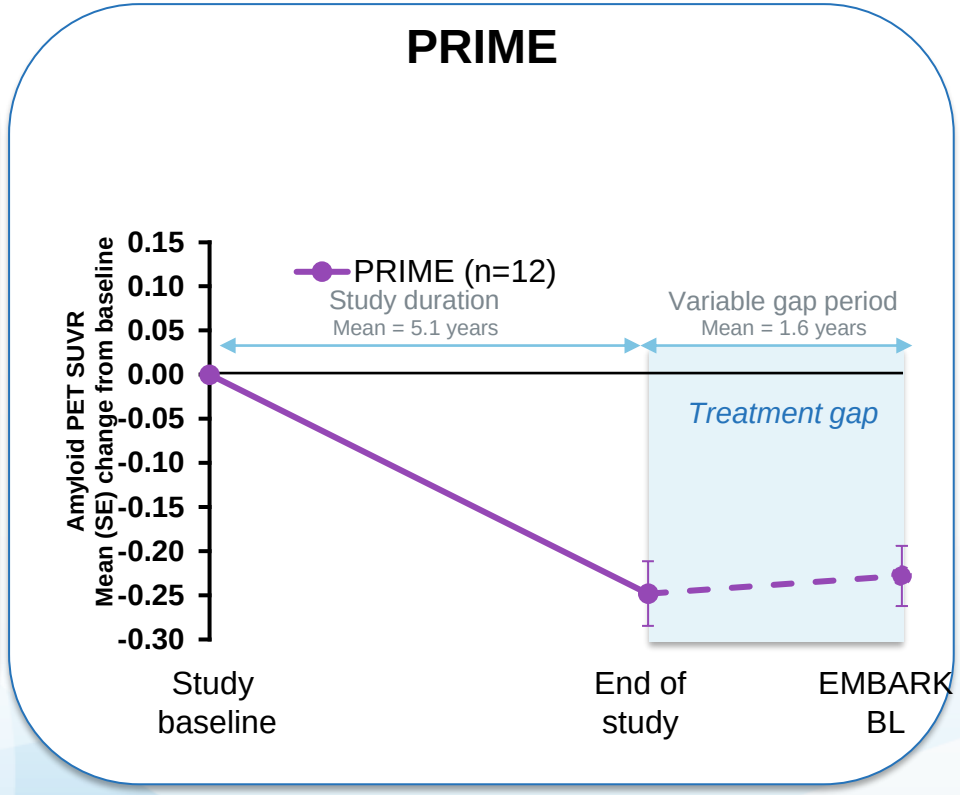
Amyloid PET substudies

- Cerebral Aβ plaque levels were measured by amyloid PET in the PRIME study and a subset of participants who took part in the optional longitudinal amyloid PET substudies in EMERGE and ENGAGE
  - A subset of those participants are participating in an optional longitudinal amyloid PET substudy in EMBARK
- For pooled EMERGE and ENGAGE data, analyses based on an MMRM for change from feeder study baseline amyloid PET composite SUVR were performed
- For PRIME, summary statistics for change from feeder study baseline amyloid PET composite SUVR were calculated for data pooled across all treatment groups

Aβ, amyloid beta; MMRM, mixed model for repeated measures; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Reduction of amyloid plaque levels was maintained during the treatment gap from the end of feeder studies to EMBARK baseline: Pooled EMERGE/ENGAGE substudy data and PRIME data





Placebo	18	16	18	Placebo-High	37	37	37	12	12	12
High	24	23	24	High-High	64	64	64			

The end-of-feeder-study amyloid PET SUVR was defined as the last non-missing post-baseline amyloid PET SUVR in the feeder study. Some subjects may receive aducanumab doses after the date of the last post-baseline amyloid PET in the feeder study. For the pooled EMERGE/ENGAGE analyses, adjusted mean changes were based on an MMRM with change from feeder-study baseline amyloid PET composite SUVR as outcomes using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, feeder-study baseline SUVR value, feeder-study baseline SUVR value by time interaction, feeder-study baseline MMSE, feeder-study baseline age, and laboratory ApoE status (carrier/noncarrier). ApoE, apolipoprotein E; BL, baseline; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Summary

- The EMBARK baseline data can shed light on the effect of the extended aducanumab treatment gap in enrolling patients; however, EMBARK is not a randomized study and there may be selection bias for the subjects who returned for EMBARK
  - Interpretation of these data must weigh the potential influence of the heterogeneity of dose, duration of exposure, and treatment gap periods
- Disease progressed in the treatment gap period, however, numerical differences on clinical endpoints between high-dose aducanumab and placebo at the end of EMERGE and ENGAGE were maintained
- In the PET substudy, brain amyloid plaque reduction in PET SUVR persisted after treatment discontinuation of high-dose aducanumab; a similar result was observed across pooled doses in PRIME
- Other underlying pathological processes may have a role in disease progression despite the maintenance of amyloid plaque reduction during the gap period
- Further efforts are needed to understand the impact of a treatment gap period and the overall duration of treatment

PET, positron emission tomography; SUVR, standardized uptake value ratio.

Acknowledgments

We thank the Alzheimer’s disease community, all the patients and their family members participating in the aducanumab studies, as well as the investigators and their staff conducting these studies