EMBARK: A Phase 3b, Open-label, Single-arm, Study to Evaluate the Long-term Safety and Efficacy of Aducanumab in Eligible Participants with Alzheimer's Disease

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Clinical Trials on Alzheimer's Disease

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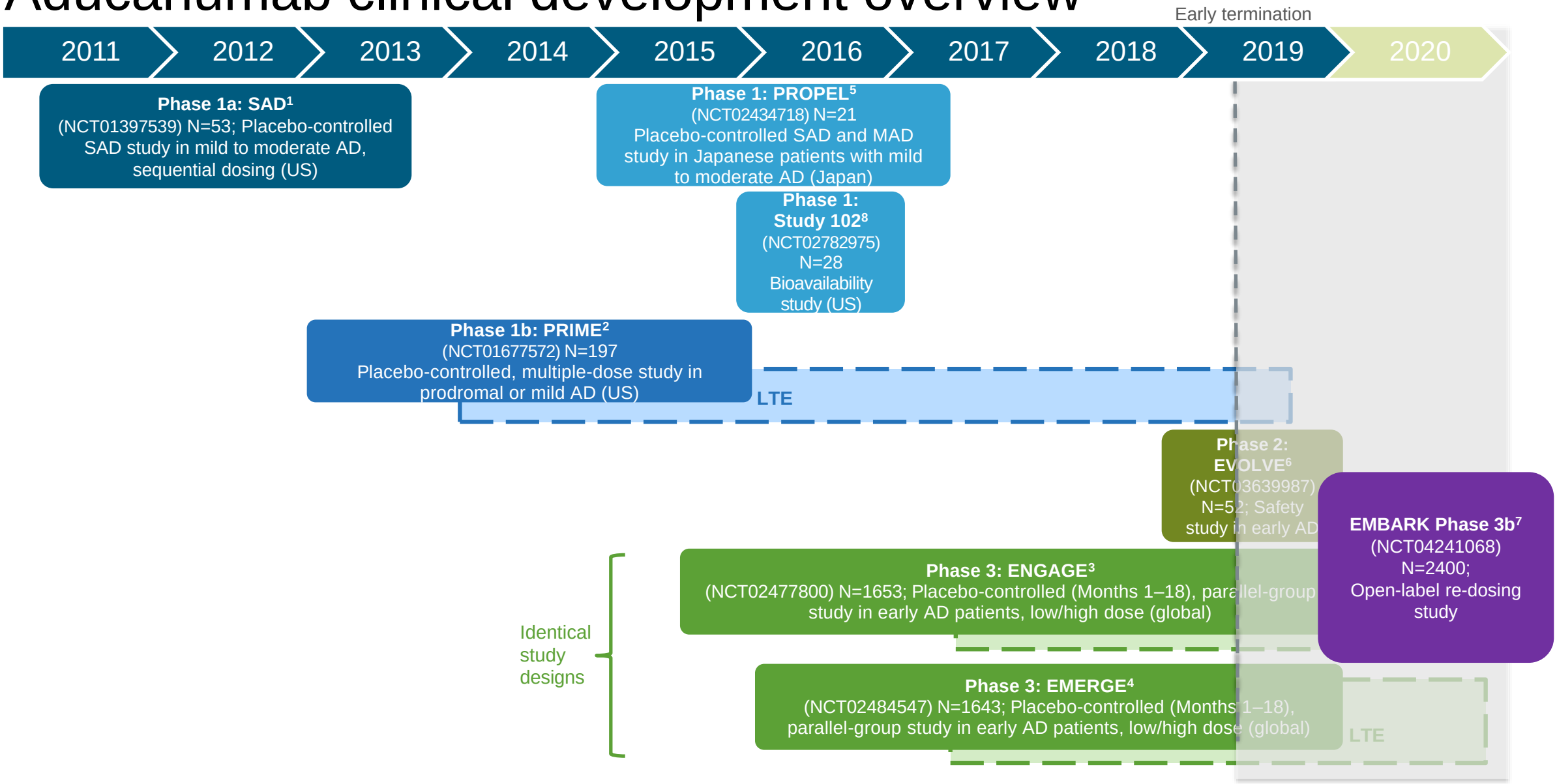
Legal disclaimer

- Aducanumab is an investigational compound and is not yet approved
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and commercialization
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally

Aducanumab clinical development overview



1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT01397539 (Accessed August 23, 2020); 2. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT01677572 (Accessed August 23, 2020); 3. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT02477800 (Accessed August 23, 2020); 4. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT02484547 (Accessed August 23, 2020); 5. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT02434718 (Accessed August 23, 2020); 6. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT03639987 (Accessed August 23, 2020); 7. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020); 8. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02782975. AD, Alzheimer's disease; LTE, long-term extension; MAD, multiple ascending doses; SAD, single ascending dose.

Rationale for the EMBARK study

- In EMERGE, **treatment with high-dose aducanumab significantly reduced clinical decline** compared with placebo on the pre-specified primary and secondary endpoints; this finding was supported by biomarker results

- ENGAGE did not meet its primary endpoint; however, participants who received adequate exposure to high-dose aducanumab **had outcomes similar to those** observed in EMERGE

- The EMBARK (NCT04241068) re-dosing study was designed to address two fundamental questions:
  - What is the long-term safety and efficacy of aducanumab dosing with the highest dose tested in the Phase 3 trials?
  - What are the changes in clinical and biomarker measures during the treatment gap?

Budd Haeberlein, et al. Data presented at CTAD 2019.

Overview of EMBARK study design

EMBARK is a global open-label, multicenter, longitudinal, single-arm, global Phase 3b study in participants with Alzheimer's disease (AD) who were previously participating in aducanumab studies at the time of their early termination (ENGAGE; EMERGE; PRIME, and EVOLVE, collectively referred to as feeder studies)	
Population	Eligible patients actively enrolled in the aducanumab studies in March 2019 (including ENGAGE, EMERGE, the LTE of the PRIME study, and the EVOLVE safety study)
Dose	Aducanumab 10 mg/kg IV infusion every 4 weeks, with a titration period*
Duration	24 months
Sample size	N~2400 patients
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 long-term efficacy and biomarker effects

*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.
1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020).
IV, intravenous; LTE, long-term extension.

Inclusion and exclusion criteria

Inclusion:*

- Was **participating in an aducanumab clinical study** at the time of the announcement of early termination (feeder studies)
- Has one **care partner** who, in the Investigator's opinion, has adequate contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities

Exclusion:*

- Any **medical or neurological condition** (other than Alzheimer’s disease) that might be a contributing cause of the patient’s **cognitive impairment**
- **Stroke** or any unexplained **loss of consciousness** within **1 year prior** to Screening
- Clinically significant **unstable psychiatric illness** in past **6 months**
- History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities within 1 year prior to Screening
- A **seizure event** that occurred after the last visit of the feeder study and before Screening for this study
- Evidence of impaired liver function as shown by an abnormal liver function profile at Screening
- History of or known seropositivity for HIV
- Clinically significant systemic illness or serious infection within 30 days prior to or during Screening
- Contraindications to having a brain MRI

*Other protocol defined Inclusion/Exclusion criteria may apply
ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020).
HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

Study objectives

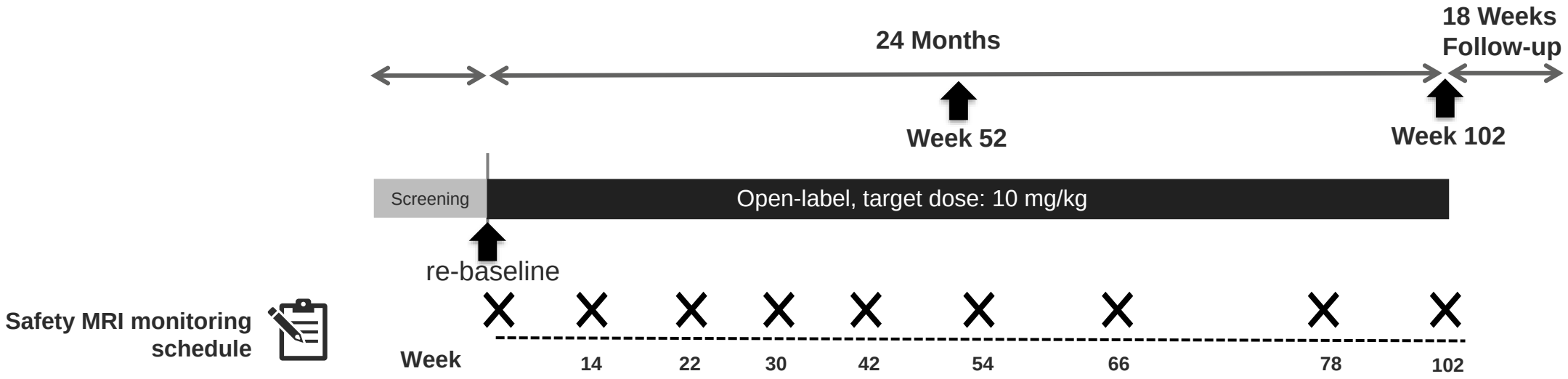
Objectives
Primary
• To evaluate the long-term safety and tolerability of a monthly dose (10 mg/kg) of aducanumab after a gap period imposed by discontinuation of feeder studies
Exploratory
• To evaluate the long-term efficacy of aducanumab using clinical endpoints
• To evaluate the long-term effect of aducanumab on biomarker endpoints
• To evaluate the long-term effect of aducanumab on PK endpoints

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020).
PK, pharmacokinetics.

Objectives and endpoints (1/3)

Objective	Endpoint
Primary	

To evaluate the long-term safety and tolerability of a monthly dose (10 mg/kg) of aducanumab after a gap period	• Incidence of AEs, SAEs, ARIA and immunogenicity with long-term treatment and/or re-exposure to aducanumab
	• Safety and tolerability parameters including:
	  • Incidence of all AEs; AEs leading to treatment discontinuation or study withdrawal, and all SAEs
	  • Incidence of ARIA-E and ARIA-H
	  • Incidence of anti-aducanumab antibodies in serum

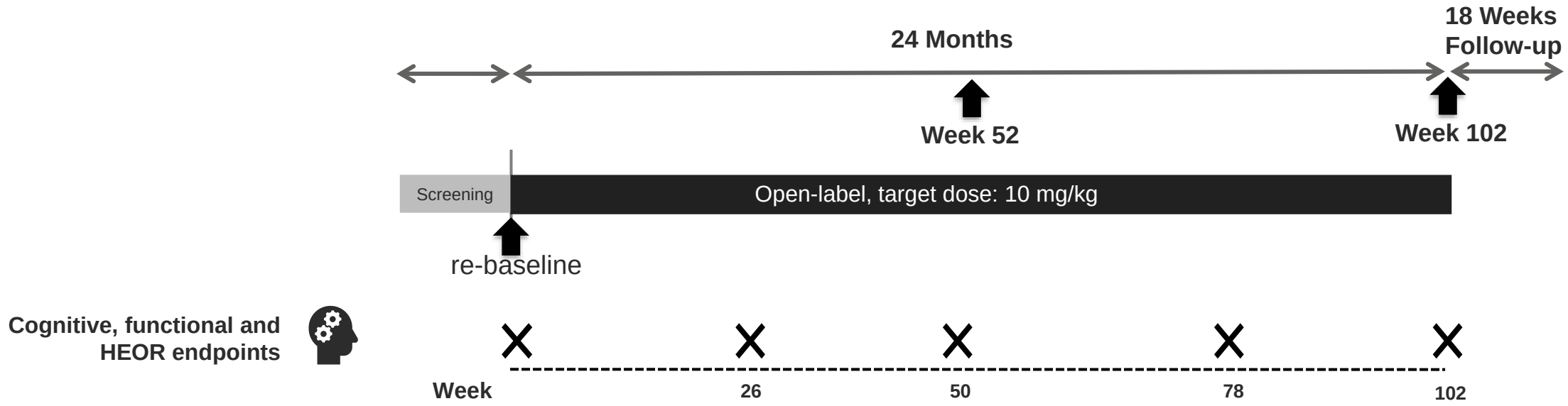


1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020).

AE, adverse event; ARIA, amyloid related imaging abnormalities; ARIA-E, ARIA-edema, ARIA-H, ARIA-hemorrhage; SAE, serious adverse event.

Objectives and endpoints (2/3)

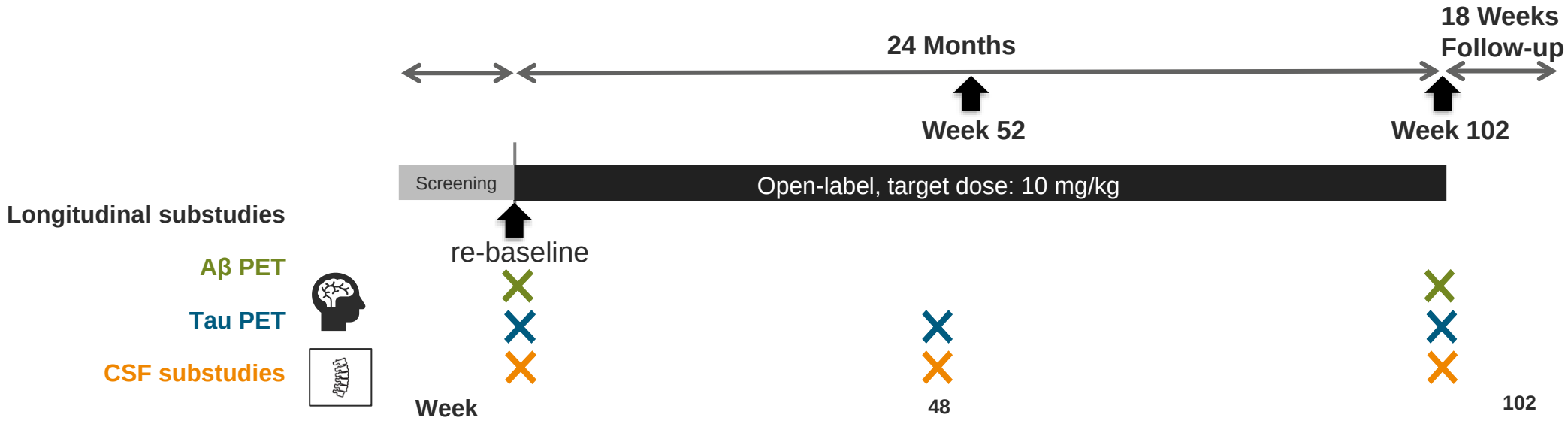
Objective	Endpoint
Exploratory	
To evaluate the long-term efficacy of aducanumab	Changes in cognition, neuropsychiatric status, function, and quality of life as measured by: • CDR-SB score, ADAS-Cog 13 score, ADCS-ADL-MCI score, MMSE score, MOCA score, NPI-10 total score • Health economics and outcome research measures of EQ-5D (SR); EQ-5D (IR-S); EQ-5D (IR-I); mPDQ-20, CAM and ADCS-MCI-CGIC



1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020).
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; CAM, confusion assessment method; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CGIC, Caregiver Global Impression of Change; MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; NPI-10, neuropsychiatric inventory-10.

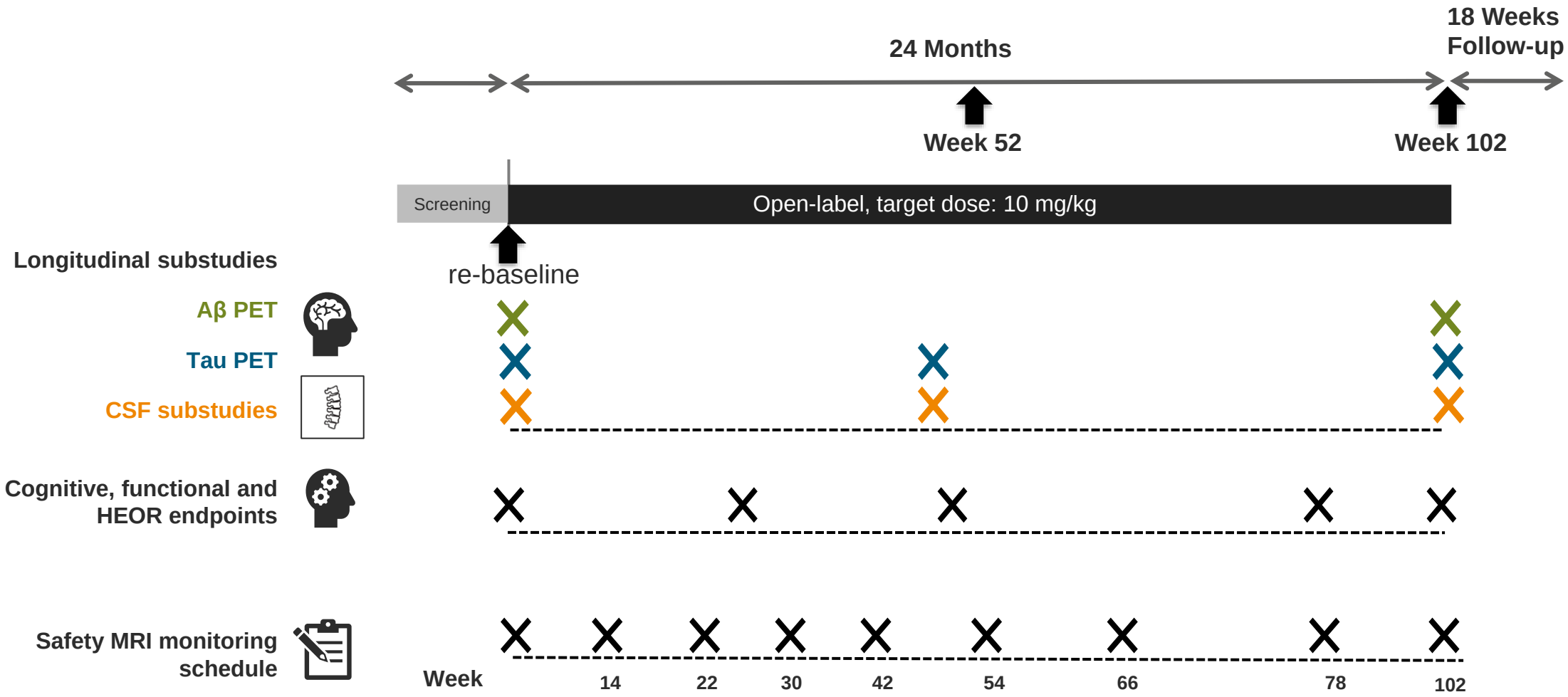
Objectives and endpoints (3/3)

Objective	Endpoint
Exploratory	
To evaluate the long-term effect of aducanumab on biomarker endpoints	<u>PET Imaging</u> Change in: • Amyloid PET signal (in a subset of sites and participants) • Tau PET signal (in a subset of sites and participants) <u>Fluid biomarkers (blood and optional CSF)</u> • Change in levels of fluid biomarkers related to disease which may include, but are not limited to, amyloid and tau proteins (in a subset of participants) <u>MRI Imaging</u> • Change in MRI morphometric measures of regional brain volume



1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show//NCT04241068 (Accessed August 23, 2020). CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.

EMBARK study design: Dosing and key assessments



1. EMBARK protocol. Data on file.

Aβ, amyloid beta; CSF, cerebrospinal fluid; HEOR, health economics and outcomes research; MRI, magnetic resonance imaging; PET, positron emission tomography.

Statistical analyses: Safety

Analyses:

- Incidence of AEs and SAEs for treatment-naïve and treatment-experienced patients
  - ARIA: radiographical severity and clinical symptomatology
  - Immunogenicity
- Changes from EMBARK baseline in vital signs, laboratory measurements, C-SSRS and ECG

Populations for analysis:

- Safety population: participants who received at least one dose in the EMBARK study
- Safety MRI population: participants who received at least one dose in the EMBARK study and have at least one follow-up MRI will be used for analyses of ARIA data
- Safety population will be used for all other safety analyses

1. EMBARK protocol. Data on file.

AE, adverse event; ARIA, amyloid-related imaging abnormalities; C-SSRS, Columbia Suicide Severity Rating Scale; ECG; electrocardiogram; MRI, magnetic resonance imaging; SAE, serious adverse event.

Statistical analyses: Exploratory efficacy/PD

Analyses:

- Changes from end-score in feeder study to baseline score in re-dosing study for clinical assessments and amyloid PET
- Changes from re-dosing baseline in clinical assessments, amyloid PET, Tau PET and CSF biomarkers to 24 months by MMRM or ANCOVA

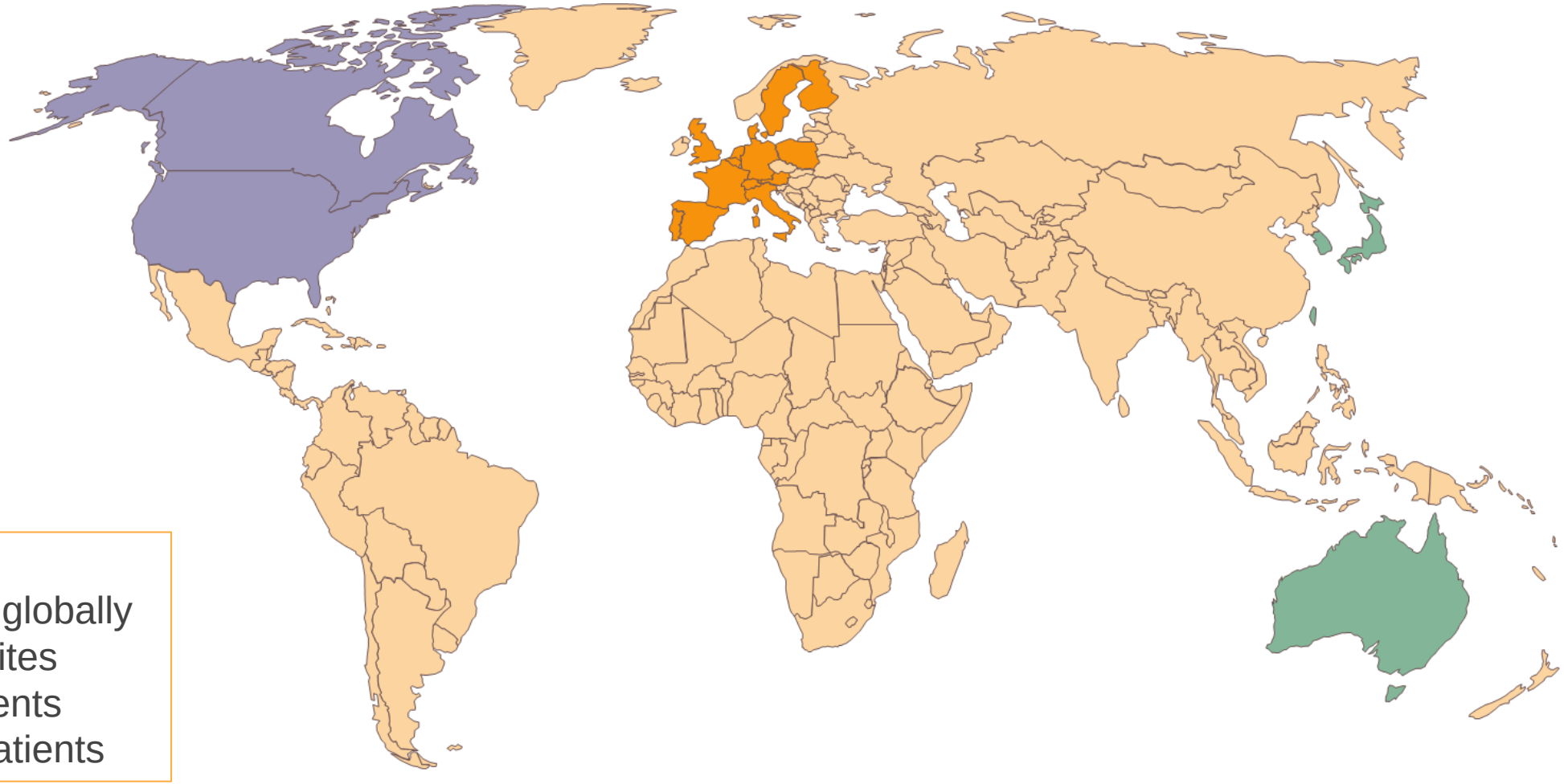
Populations for analysis:*

- Participants who received at least one dose of study treatment in the EMBARK study
- Participants who received at least one dose of study treatment in the EMBARK study and have PET and/or CSF

Efficacy analyses will consider the prior exposure to aducanumab (length and dose level), the length of wash-out period, and participants' demographics and other disease characteristics

*All screened patients will be considered for changes in clinical and biomarker measures during the treatment gap.
1. EMBARK protocol. Data on file.
ANCOVA, analysis of covariance; CSF, cerebrospinal fluid, MMRM, mixed model repeated measures, PET, positron emission tomography.

EMBARK is expected to be one of the largest clinical trials in Alzheimer's disease



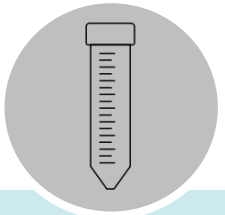
- 20 countries
- 312 sites selected globally
  - 163 activate sites
- 880 screened patients
- 531 randomized patients

What will we learn from the EMBARK study?

EMBARK will provide a **deeper understanding** of:
1) the occurrence of ARIA after a long treatment gap and re-exposure to aducanumab
and
2) the long-term safety of 10 mg/kg aducanumab

EMBARK will shed light on the **effect of prolonged treatment interruption** and improve our understanding of **the durability of treatment effects**

EMBARK will **inform the effect of aducanumab** on treatment-naïve patients who **initiate treatment at a more advanced stage of Alzheimer's disease**



A **large substudy of imaging and fluid biomarkers** will provide a deeper understanding of the **durability of aducanumab effect** following a treatment gap, after prolonged exposure and, potentially, the correlation between biomarkers and clinical outcomes

ARIA, amyloid related imaging abnormalities.

Summary

- EMBARK is a global open-label, single-arm clinical study assessing the long-term safety and efficacy of aducanumab in participants with Alzheimer’s disease who were actively participating in the aducanumab clinical studies at the time of their early termination (March 21, 2019)
- The primary objective of EMBARK is to evaluate the long-term safety and tolerability of aducanumab
- The EMBARK study is currently enrolling, and is expect to be one of the largest clinical trials in Alzheimer’s disease, with an estimated total enrollment of 2400 participants
- The results of EMBARK will provide further information on the long-term safety and efficacy of aducanumab

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