

# EMBARC: A Phase 3b, open-label, single-arm, safety study to evaluate the long-term safety and efficacy of aducanumab in eligible participants with Alzheimer's disease

Castrillo-Viguera C<sup>1</sup>, Chalkias S<sup>1</sup>, Burkett PR<sup>1</sup>, Wu S<sup>1</sup>, Chen H<sup>1</sup>, Harrison K<sup>1</sup>, Yurgalevitch C<sup>1</sup>, and Budd Haeberlein S<sup>1</sup>

<sup>1</sup>Biogen, Cambridge, MA, USA



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## Statement on aducanumab

- Aducanumab is an investigational drug whose efficacy and safety have not yet been established. It is not approved for use in any country.
- 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.

# Introduction

- EMERGE and ENGAGE are Phase 3 studies that evaluated the safety and efficacy of aducanumab,<sup>1</sup> a human monoclonal antibody that selectively targets aggregated forms of A $\beta$ 
  - 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 **EMBARC (NCT04241068)<sup>2</sup> re-dosing study** was designed to address two fundamental questions:
  - 1) What is the long-term safety and efficacy of aducanumab dosing with the highest dose tested in the Phase 3 trials?
  - 2) What are the changes in clinical and biomarker measures during the treatment gap?

## Study overview<sup>2</sup>

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

<b>Population</b>	Eligible patients with Alzheimer's disease actively enrolled in the aducanumab studies in March 2019 (including EMERGE, ENGAGE, the LTE of the PRIME study, and the EVOLVE safety study)
<b>Dose</b>	Aducanumab 10 mg/kg IV infusion every 4 weeks, with a titration period <sup>a</sup>
<b>Duration</b>	24 months
<b>Sample size</b>	Estimated enrollment of 1800 participants <sup>b</sup>
<b>Primary objective</b>	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
<b>Exploratory objectives</b>	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

### Inclusion Criteria:<sup>2,c</sup>

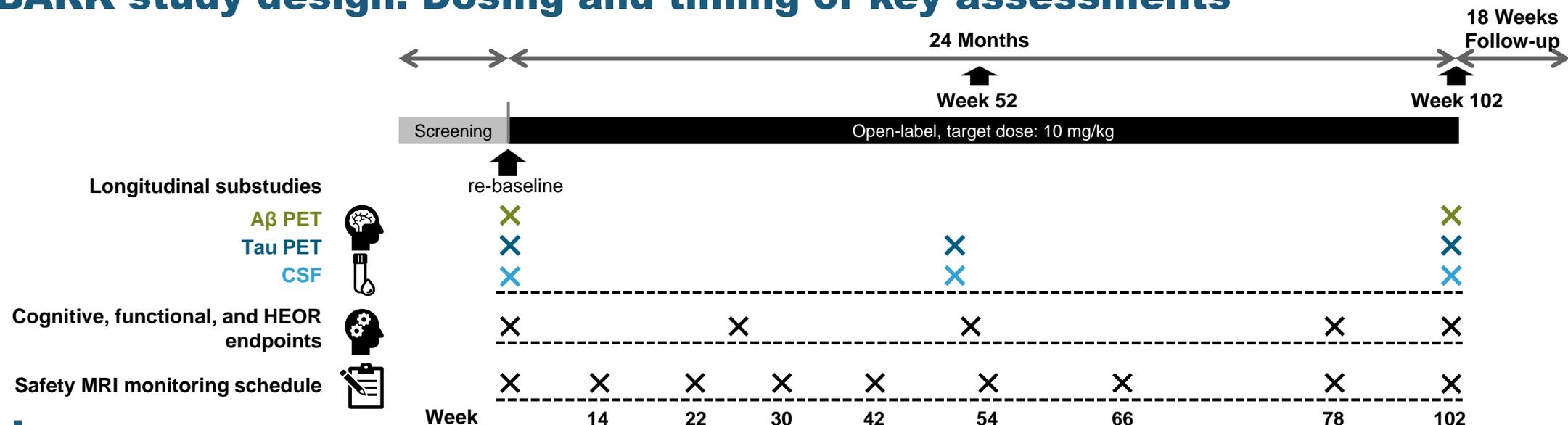
- Participation in an aducanumab clinical study at the time of the announcement of early termination (feeder studies)
- Having a care partner who, in the Investigator's opinion, has adequate contact with the participant as to be able to provide accurate information about the participant's cognitive and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

### Exclusion Criteria:<sup>2,c</sup>

- 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

<sup>a</sup> 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; <sup>b</sup> As of March 9, 2021; <sup>c</sup> EMBARC is an open-label, multicenter, longitudinal, single-arm, global Phase 3b study in participants with Alzheimer's disease who were previously participating in aducanumab studies (ENGAGE; EMERGE; PRIME, and EVOLVE, collectively referred to as feeder studies) at the time of their early termination. 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); 2. ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT04241068> (Accessed March 16, 2021). A $\beta$ , amyloid beta; HIV, human immunodeficiency virus; IV, intravenous; LTE, long-term extension; MRI, magnetic resonance imaging; PK, pharmacokinetics.

# EMBARK study design: Dosing and timing of key assessments



## Analyses

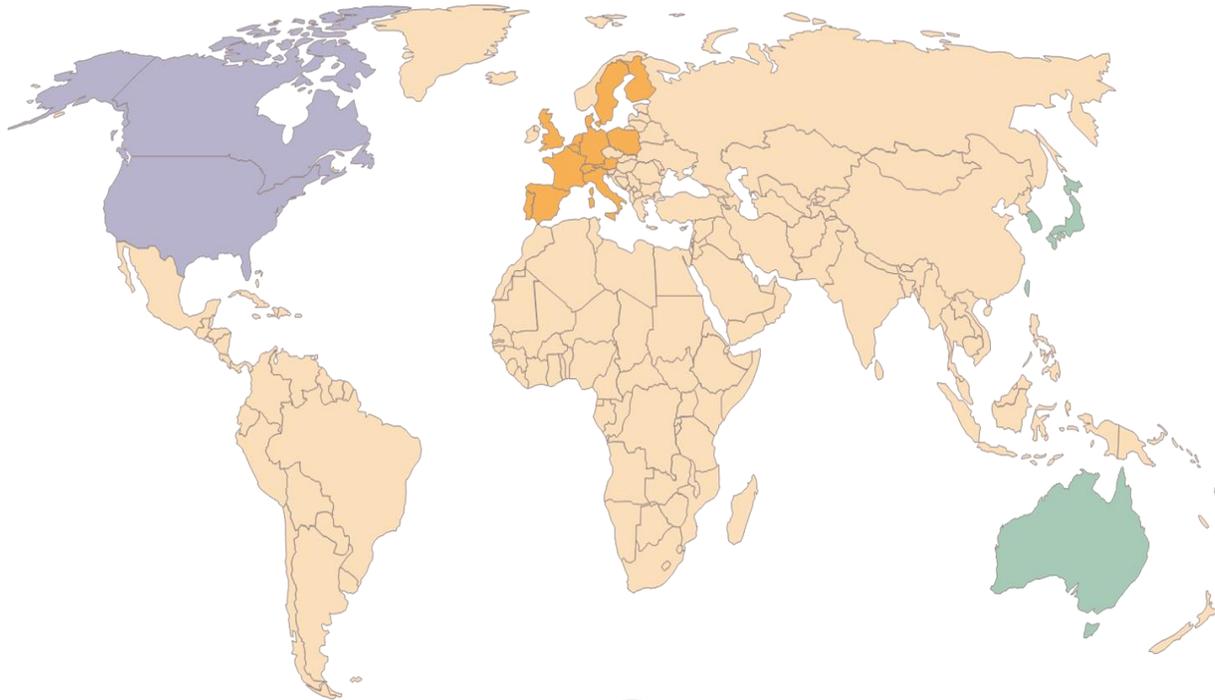
	Safety	Exploratory Efficacy/Pharmacodynamics
<b>Population</b>	<ul style="list-style-type: none"> <li>Safety population: participants who received at least one dose in the EMBARK study</li> <li>Safety MRI population: participants who received at least one dose in the EMBARK study and have at least one follow-up MRI will be used for analyses of ARIA data</li> <li>Safety population will be used for all other safety analyses</li> </ul>	<ul style="list-style-type: none"> <li>Participants who received at least one dose of study treatment in the EMBARK study<sup>a</sup></li> <li>Participants who received at least one dose of study treatment in the EMBARK study and have PET and/or CSF data<sup>a</sup></li> </ul> <p>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</p>
<b>Analyses</b>	<ul style="list-style-type: none"> <li>Incidence of AEs and SAEs for aducanumab-naïve and aducanumab-pre-exposed in the feeder studies patients                             <ul style="list-style-type: none"> <li>ARIA: Radiographical severity and clinical symptomatology</li> <li>Immunogenicity</li> </ul> </li> <li>Changes from EMBARK baseline in vital signs, laboratory measurements, C-SSRS and ECG</li> </ul>	<ul style="list-style-type: none"> <li>Changes from end-score in feeder study to baseline score in re-dosing study for clinical assessments and amyloid PET</li> <li>Changes from re-dosing baseline in clinical assessments, amyloid PET, Tau PET and CSF biomarkers to 24 months by MMRM or ANCOVA</li> </ul>

<sup>a</sup> All screened patients will be considered for changes in clinical and biomarker measures during the treatment gap.

EMBARK protocol. Data on file.

Aβ, amyloid beta; AE, adverse event; ANCOVA, analysis of covariance; ARIA, amyloid-related imaging abnormalities; CSF, cerebrospinal fluid; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; HEOR, health economics and outcomes research; MMRM, mixed model repeated measures; MRI, magnetic resonance imaging; PET, positron emission tomography; SAE, serious adverse event.

# What will we learn from the EMBARK study?



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

**As of March 9, 2021:**

- 20 countries
- 305 sites selected globally
  - 301 active sites
- Participants screened: 1705
- Participants enrolled: 1361



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 effect**



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



Large **imaging and fluid biomarker substudies** 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

## Conclusions



EMBARC 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 enrollment of 1800 participants<sup>a</sup>



The results of EMBARK will provide further information on the long-term safety and efficacy of aducanumab

**We thank the Alzheimer's disease community, all the patients and their family members participating in the aducanumab studies, as well as the investigators, partners, and site staff for their enormous efforts in such a challenging year**

<sup>a</sup> As of March 9, 2021.

ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT04241068> (Accessed March 16, 2021).