Evaluation of aducanumab safety in early Alzheimer's disease

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Disclosures

- SC, PB, FF, YT, KU, KS, PS, and SBH are employees of Biogen and may be stockholders
- 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
- 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 and is a consultant to Eisai, Novartis, Genentech, Roche, Avid, and Lilly
- FB was supported by NIHR Biomedical Research Centre at UCLH. He receives personal fees for consultancy from Bayer, Biogen, Roche, IXICO Ltd, Novartis and Combinostics
- JB, DP, and JS are employees of Bioclinica

Forward-looking statements

- This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to additional results from the Phase 3 clinical studies of aducanumab; the potential clinical effects of aducanumab; the potential benefits, safety, and efficacy of aducanumab; potential regulatory discussions, submissions, and approvals and the timing thereof; clinical development programs, clinical trials, data readouts, and presentations related to aducanumab; the enrollment of any future clinical studies of aducanumab; the treatment of Alzheimer's disease; the potential of Biogen's commercial business and pipeline programs, including aducanumab; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai Co, Ltd; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later-stage or larger-scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.
- These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including actual timing and content of submissions to and decisions made by the regulatory authorities regarding aducanumab; regulatory submissions may take longer or be more difficult to complete than expected; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including aducanumab; actual timing and enrollment of future studies of aducanumab; the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis; risks of unexpected costs or delays; the risks of other unexpected hurdles; uncertainty of success in the development and potential commercialization of aducanumab; failure to protect and enforce Biogen's data, intellectual property, and other proprietary rights and uncertainties relating to intellectual property claims and challenges; risks relating to the potential launch of aducanumab, including preparedness of healthcare providers to treat patients, the ability to obtain and maintain adequate reimbursement for aducanumab, and other unexpected difficulties or hurdles; product liability claims; third-party collaboration risks; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments, or otherwise.

Statement on aducanumab

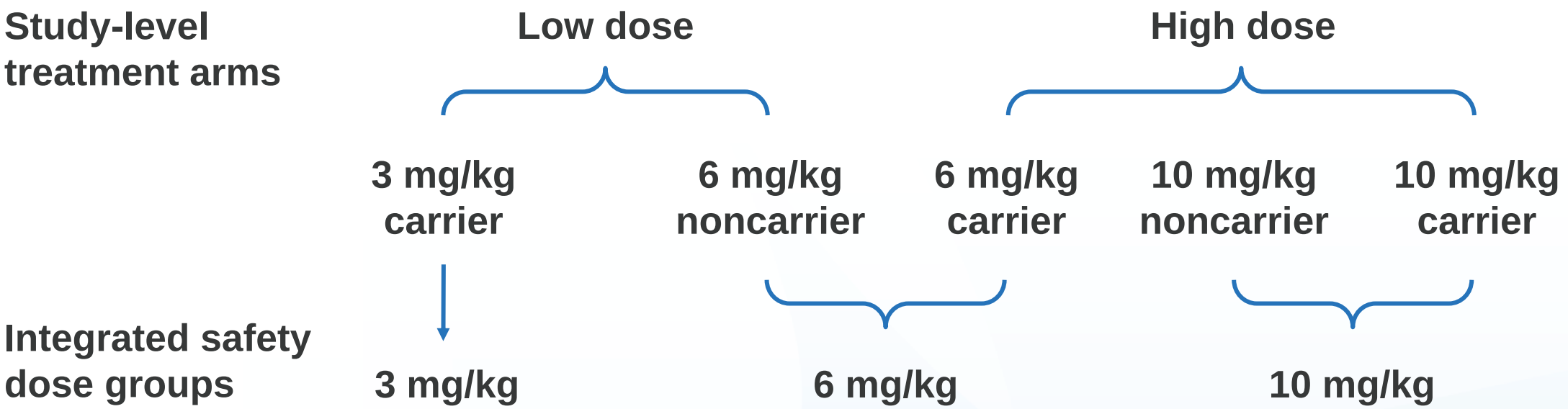
- Aducanumab is an investigational drug whose efficacy and safety have not yet been established. It is not approved for use in any country.
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and commercialization.
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally.

Summary of aducanumab exposure and follow-up

		Aducanumab 10 mg/kg	Total aducanumab (all doses combined)
Placebo-controlled period of EMERGE and ENGAGE	Number dosed	1033	2198
	Exposure, person-years	1295	2752
	Follow-up, person-years	1479	3136
Combined placebo and long-term extension periods of multiple dose studies[a]	Number dosed	1414	2959
	Exposure, person-years	2106	4520
	Follow-up, person-years	2492	5319

[a] Includes PRIME, PROPEL, EMERGE, and ENGAGE. Does not include EVOLVE.

Safety analysis by target dose



Carrier and non-carrier status refers to ApoE ε4 allele.
ApoE ε4, apolipoprotein E ε4.

Amyloid-related imaging abnormalities (ARIA)

ARIA refers to radiographic abnormalities observed with anti-Aβ antibodies

- ARIA-Edema (ARIA-E) refers to brain vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H) refers to brain microhemorrhages or localized superficial siderosis

ARIA may result from increased cerebrovascular permeability as a consequence of antibody binding to deposited Aβ

Greenberg SM, et al. *Nature Rev Neurol* 2020;16:30–42.
Aβ, amyloid beta.

Summary of adverse events

EMERGE and ENGAGE placebo-controlled period

	Patients, n (%)				
		Aducanumab			
	Placebo n=1087	3 mg/kg n=760	6 mg/kg n=405	10 mg/kg n=1033	Total aducanumab (all doses combined) N=2198
Adverse events	**945 (86.9)**	**700 (92.1)**	**347 (85.7)**	**946 (91.6)**	**1993 (90.7)**
ARIA-E	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
Serious adverse events	**151 (13.9)**	**105 (13.8)**	**54 (13.3)**	**141 (13.6)**	**300 (13.6)**
Serious ARIA-E	1 (<0.1)	6 (0.8)	3 (0.7)	13 (1.3)	22 (1.0)
AE leading to discontinuation	45 (4.1)	65 (8.6)	45 (11.1)	91 (8.8)	201 (9.1)
Due to ARIA*	6 (0.6)	47 (6.2)	21 (5.4)	64 (6.2)	132 (6.1)
Fatal adverse events	**5 (0.5)**	**3 (0.4)**	**0 (0)**	**8 (0.8)**	**11 (0.5)**

* Percentages for this row based on the number of patients with at least one postbaseline MRI.

AE, adverse event; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

Adverse events with ≥5% incidence in aducanumab 10 mg/kg group and with ≥2% difference from placebo group

EMERGE and ENGAGE placebo-controlled period

	Patients, n (%)	
	Placebo n=1087	Aducanumab 10 mg/kg n=1033
Adverse events	**945 (86.9)**	**946 (91.6)**
ARIA-E	29 (2.7)	362 (35.0)
Headache	165 (15.2)	212 (20.5)
ARIA-H brain microhemorrhage	71 (6.5)	197 (19.1)
Fall	128 (11.8)	155 (15.0)
ARIA-H superficial siderosis	24 (2.2)	151 (14.6)
Diarrhea	74 (6.8)	92 (8.9)

ARIA-E, amyloid-related imaging abnormalities edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis.

ARIA-E incidence

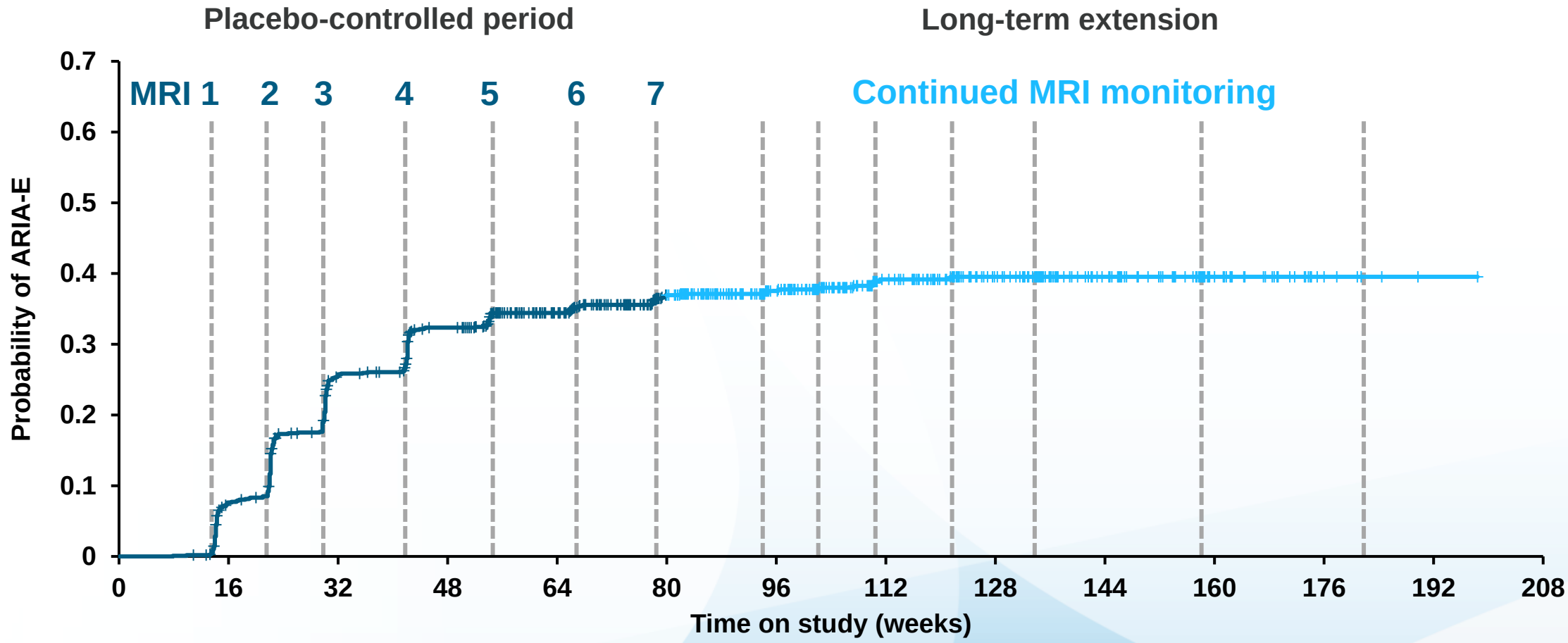
EMERGE and ENGAGE placebo-controlled period

	Patients,[a] n (%)	
	Placebo n=1076	Aducanumab 10 mg/kg n=1029
ARIA-E	29 (2.7)	362 (35.2)
ApoE ε4 carriers	16/742 (2.2)	290/674 (43.0)
ApoE ε4 non-carriers	13/334 (3.9)	72/355 (20.3)

[a] Analyses specific to ARIA are based on patients with at least 1 post-baseline MRI.
ApoE ε4, apolipoprotein E ε4; ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

Kaplan-Meier analysis of time to first ARIA-E

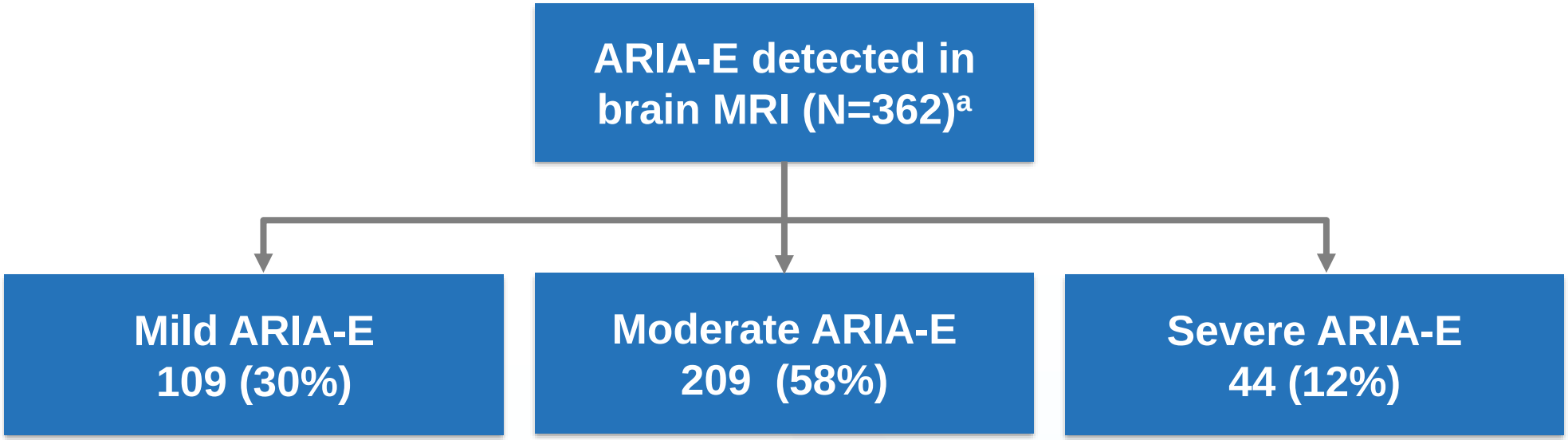
EMERGE and ENGAGE, 10 mg/kg



ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

ARIA-E MRI severity

EMERGE and ENGAGE placebo-controlled period, 10 mg/kg



98% of ARIA-E events resolved on study

- 69% resolved within 12 weeks
- 83% resolved within 16 weeks

[a] Each participant counted once, at maximum radiographic severity.
ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

Symptomatic ARIA-E

EMERGE and ENGAGE placebo-controlled period

	Patients, n (%)	
	Placebo n=1076	Aducanumab 10 mg/kg n=1029
Patients with ARIA-E	29	362
Asymptomatic	26 (89.7)	268 (74.0)
Symptomatic	3 (10.3)	94 (26.0)

- The most common symptoms were headache, confusion, dizziness, and nausea
- Most symptoms during ARIA were mild (67.7%) or moderate (28.3%) in clinical severity
- Severe symptoms were uncommon and included rare reports of seizures

Each participant counted once, at maximum symptomatic status and severity.
ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

ARIA-H incidence

EMERGE and ENGAGE placebo-controlled period

	Patients, n (%)	
	Placebo n=1076	Aducanumab 10 mg/kg n=1029
ARIA-H	94 (8.7)	291 (28.3)
Brain microhemorrhage	71 (6.6)	197 (19.1)
Localized superficial siderosis	24 (2.2)	151 (14.7)
Macrohemorrhage	4 (0.4)	3 (0.3)

ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis.

Relationship between ARIA-E and ARIA-H

EMERGE and ENGAGE placebo-controlled period

	Patients, n (%)	
	Placebo n=1076	**Aducanumab 10 mg/kg n=1029**
Patients with ARIA-E	29	362
ARIA-H subtype		
Brain microhemorrhage	4 (13.8)	146 (40.3)
Localized superficial siderosis	9 (31.0)	140 (38.7)
Patients without ARIA-E	1047	667
ARIA-H subtype		
Brain microhemorrhage	67 (6.4)	51 (7.6)
Localized superficial siderosis	15 (1.4)	11 (1.6)

ARIA-E, amyloid-related imaging abnormalities edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis.

Aducanumab safety summary

The safety profile of aducanumab is well characterized

- More than 5300 person-years of follow-up for aducanumab-treated patients

ARIA-E is most common adverse event among aducanumab-treated patients

- Mainly mild or moderate MRI severity and transient
- Asymptomatic in majority of patients
- Can be mitigated with routine MRI monitoring and dosing management

ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.