The Estimands Academy for Trial Teams

"Bringing estimands to *life* through real case studies"

Webinar 5: Estimands framework in action, the Alzheimer's disease case

2nd July 2024 2-3:30 pm UK /3-4:30 pm CET/10-11:30 am EST

EFSPI European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe

efpia European Federation of Pharmaceutical Industries and Associations

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Introductions

 Marcel Wolbers	Since completing his PhD in mathematical statistics in 2002, Marcel Wolbers has spent half of his career as an academic biostatistician and the other half as a statistician in the pharmaceutical industry. Between 2009 and 2016, he was the head of biostatistics at the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam. Since 2016, he has been an expert statistician working in the Methods, Collaboration, and Outreach group (MCO) of Roche's data sciences and statistics department. His research interests include the design and analysis of innovative clinical trials, estimands, missing data, prognostic models, and competing risks.	Data Science, Product Development, F. Hoffmann-La Roche Ltd,, Switzerland
 Rachid Abbas	Rachid Abbas is a statistician in Roche's Product Development department since 2020. With a medical degree in public health and a Master's in biostatistics, he has a strong interest in statistical issues in drug development. Rachid has held academic positions at Paris Diderot University and Gustave Roussy, contributing to clinical trials in geriatrics and neuro-oncology. At Roche, he supports late-phase Alzheimer's Disease programs. His research interests include the design and analysis of innovative clinical trials, including adaptive designs, estimands, and trial emulation	Data Science, Product Development, F. Hoffmann-La Roche Ltd,, Switzerland
 Angeliki Thanasopoulou	Senior Clinical Scientist in the Alzheimer's Disease & Neurodegeneration Franchise at Roche since 2019. She has previously worked in clinical development in a small size biotech focusing on rare diseases in neuromuscular, neurodegenerative and respiratory indications, across Phase 1 up to Phase 4 studies. Prior to joining the Pharmaceutical Industry she completed a postdoctoral position in the University Hospital Basel working on translational research and Investigator Initiated Trials. Angeliki is a biologist in training with a masters and PhD in in molecular and cellular biology.	Clinical Science, Product Development, F. Hoffmann-La Roche Ltd,, Switzerland

Disclosures

Marcel Wolbers, Rachid Abbas and Angeliki Thanasopoulou are employees of, and owns stocks or stock options in, F. Hoffmann-La Roche Ltd.

Disclaimer

Gantenerumab is an investigational drug that has not been approved by any health authority.

The intent of this presentation is to provide scientific information on gantenerumab and the information included should not be interpreted as a recommendation for the use of the product for non-approved uses.

EFPIA / EFSPI Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

Estimand Implementation Working Group (EIWG) Members

The EIWG consists of 43 members representing 26 companies and institutions.

Name	Company	Name	Company	Name	Company
Mary Elliott-Davey	Amgen	Stefan Englert	J&J/Janssen	Nikolay Stoyanov	PPD (C)
Antonia Morga	Astellas	Mette Krog Josiassen	Lundbeck	Sue McKendrick	PPD
Amel Besseghir*	Fresenius	Nanco Hefting*(C)	Lundbeck	Judith Anzures-Cabrera	Roche
David Wright	AstraZeneca	Michael Tribanek	Medac	Estelle Lambert	Servier
Vivian Lanius	Bayer	Armin Schueler	Morphosys	Christian Loesch	UCB
James Bell	BI	Ngoc-Thuy Ha	Merck	Katsumi Yoshida	UCB
Stefano Vezzoli	Chiesi	Volker Schoder	Metronomia	Brennan Kahan	UCL
Rob Hemmings	Consilium	Khadija Rantell	MHRA	Ian White	UCL
Lorenzo Guizzaro	EMA	Nick Manamley	Mundi Pharma	Pepa Polavieja	Novo Nordisk
Chrissie Fletcher*	GSK	Melanie Wright	Novartis	Zara Ghodsi	Pfizer
Millie Wang (C)	GSK	Helle Lynggaard	Novo Nordisk	Chun-Hang Tang	GSK
Carrie Li	Ironwoodpharma	Rikke Mette Agesen	Novo Nordisk (C)	Beatrice Panico	Scendea
Oliver Keene	Independent	Christian Bressen Pipper	Novo Nordisk	Anna Robertson	Pfizer
Paul Terrill	Independent	Maria Dilleen	Pfizer	*: Co-Lead of Working Group C: Clinician	
Maria Efstathiou	IQVIA	Rod Junor	Pfizer (C)		

Acknowledgements

Our sincere thanks to:

- Roche for allowing us to use the Graduate case study.
- To EFPIA/EFSPI for sponsoring and promoting the webinar.
- To EIWG members for the lively discussion and comments on the slides.

Agenda

Introduction and Acknowledgements	Marcel
Overview of the estimand framework	Rachid
Introducing the Graduate studies	Angeliki
Graduate studies analysis plan	Rachid
The adjudication committee	Angeliki
Conclusion	Rachid
Wrap up learning outcomes	Rachid
Q & A	Marcel

Learning Objectives

- Core elements of the estimand framework
- Real case study in early Alzheimer’s disease
- Cross functional workflow
- Reconsidering the design of study protocols, data collection, and analysis plans

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The estimand framework: fostering communication

The ICH-E9(R1) addendum, released on July 30, 2020

Language to ease agreement between Sponsor and Regulator:

- Align on clinical trial's objective
- Promote transparency on the design, conduct, analysis and interpretation of a clinical trial

A precise description of the treatment effect

“Why are we running a trial?”

details

assess treatment effect…

… difference between IMP and placebo

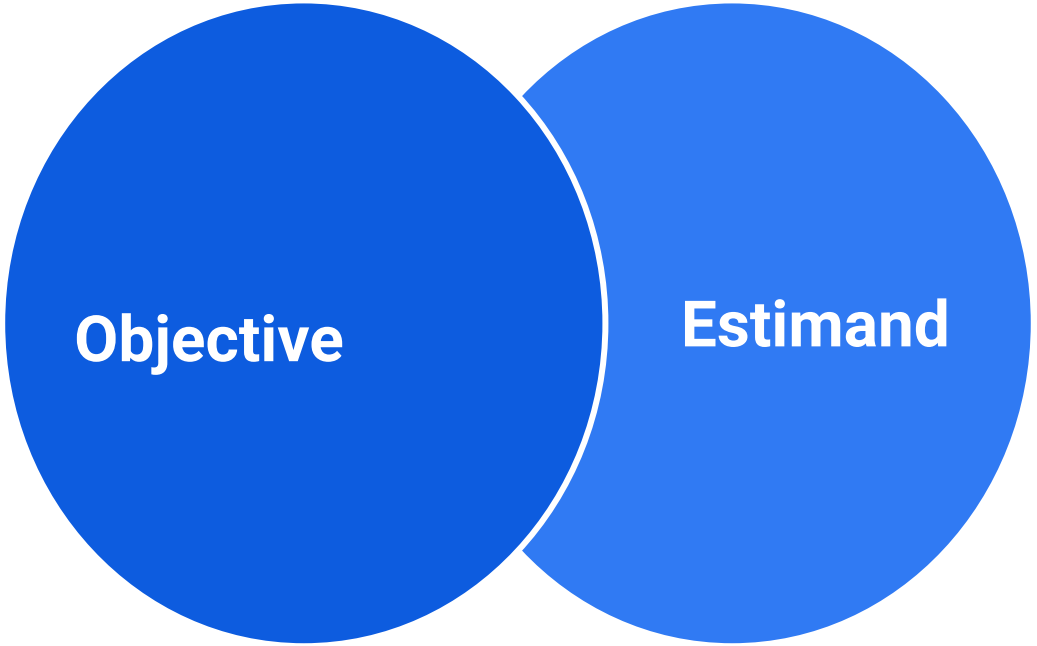
… on disease progression

… at 2 years

… irrespective of symptomatic medication

… in the absence of COVID-19 pandemic

…



State the treatment effect of interest

Determines all subsequent elements of the ‘chain’

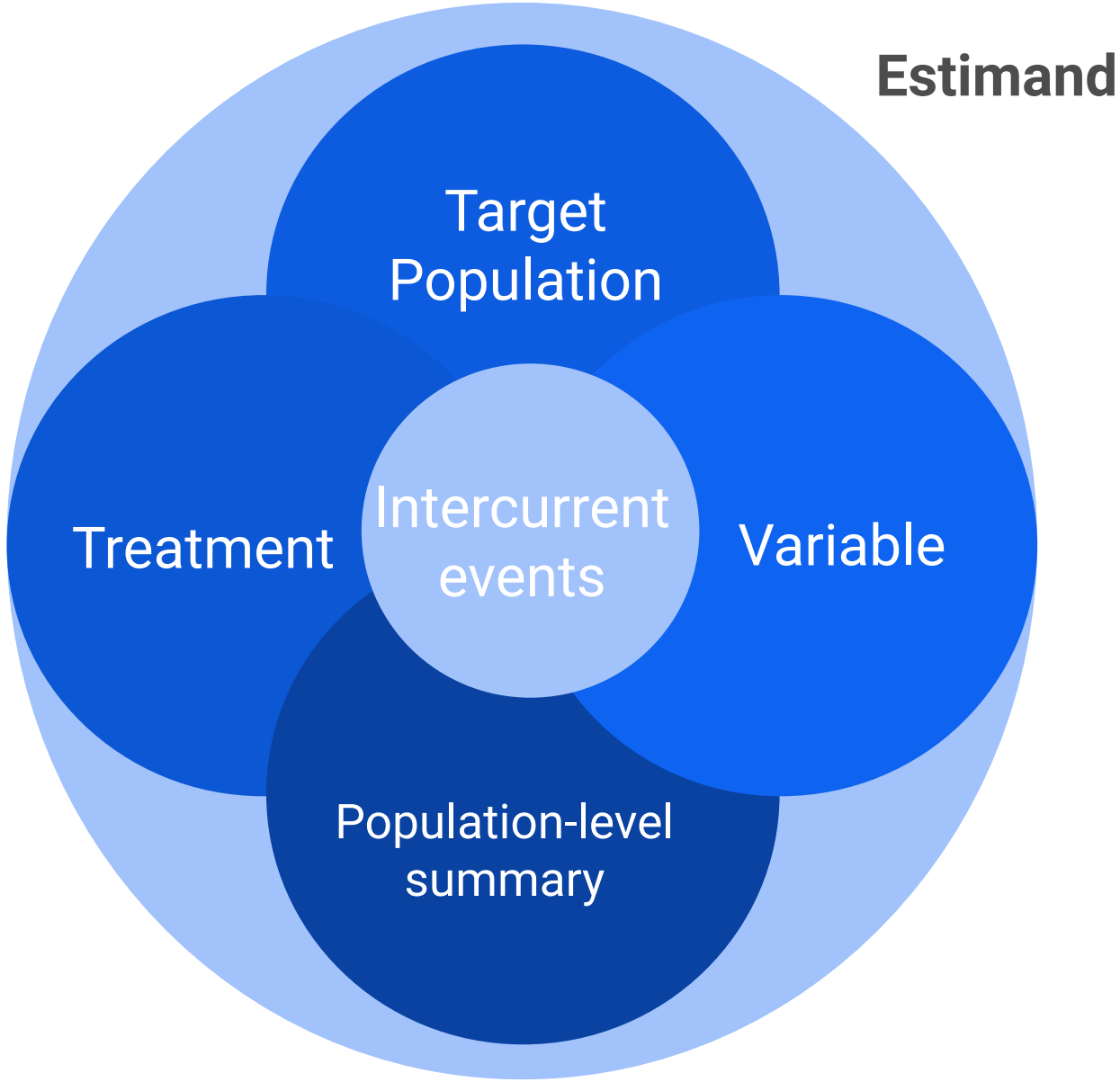
A pillar of the clinical trial protocol

“What are we trying to estimate?”

Estimand: the target of estimation

- Defined at trial design stage
- Attributes
- Reflects clinical considerations
- Cross-functional effort

Accounts for intercurrent events



Which events might affect our ability to interpret the data?

Intercurrent events

> Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

European Medicines Agency. ICH E9 (R1) addendum. 2020.

An integral part of to the estimand definition

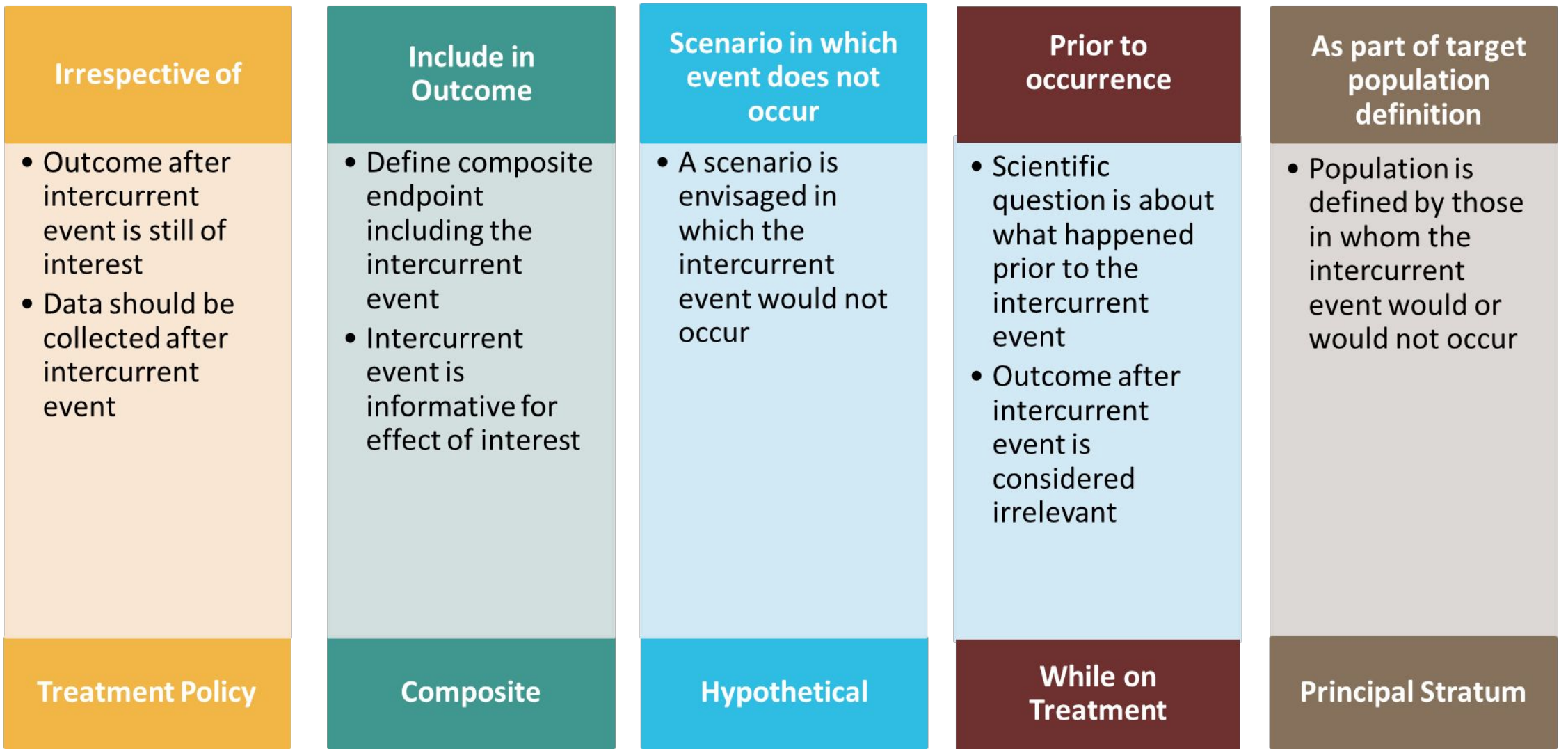
Need precision:

- discontinue study drug…
  … due to an adverse event
- use of a rescue medication…
  … due to lack of efficacy

Contrast with missing data:

- missing data: data relevant to the analysis which was not collected
- intercurrent event: events affecting the interpretation or existence of subsequent data

5 analysis strategies for intercurrent events



European Medicines Agency. ICH E9 (R1) addendum. 2020.

Quiz #1

Which of the following statements about the estimand is true?

A. the estimand must be described in a language that is flexible enough to adapt to circumstances

B. the estimand is independent of the estimator

C. the estimand reflects the clinical question posed by the trial objective

D. the description of an estimand involves attributes based on clinical considerations and how intercurrent events should be addressed

Quiz #1

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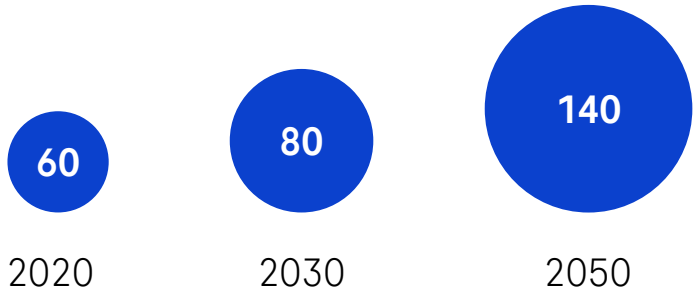
Alzheimer's disease is one the world's most significant health challenges

Health threat

Predicted global manifested AD prevalence (patients, million)



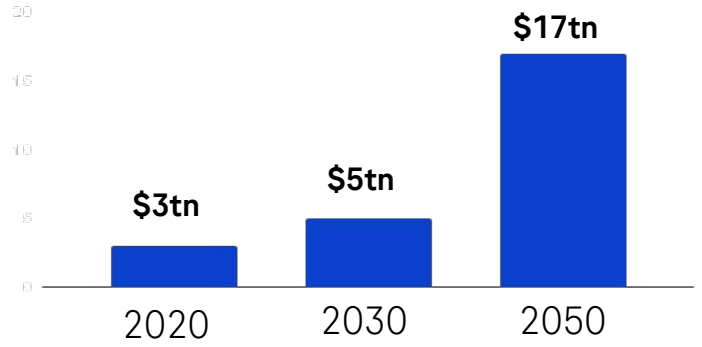
Prevalence of AD to increase due to population growth and ageing.

Today in the US, **one in three elderly individuals** dies with AD or dementias.

AD ranks **7th leading cause of death** and is a WHO public health priority.

Economic burden

Value of a Statistical Life Year burden of AD and related dementia (USD, trillion)

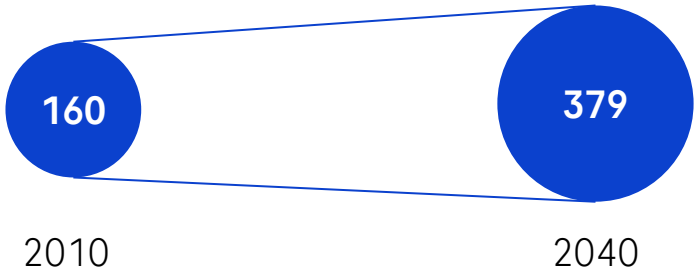


The cost to society of AD is growing due to **direct medical costs** (e.g., treatment, hospital visits) but also **indirect costs.**

Public AD research funding is only 10% of oncology funding for example in the US.

Humanistic burden

Cost of informal caregiving in the US (USD, billion)



People living with AD: Impacts patient's health-related quality of life and activities of daily living.

Caregiver burden: Hundreds of millions of caregivers and families suffer emotionally, physically and financially, disproportionally women.

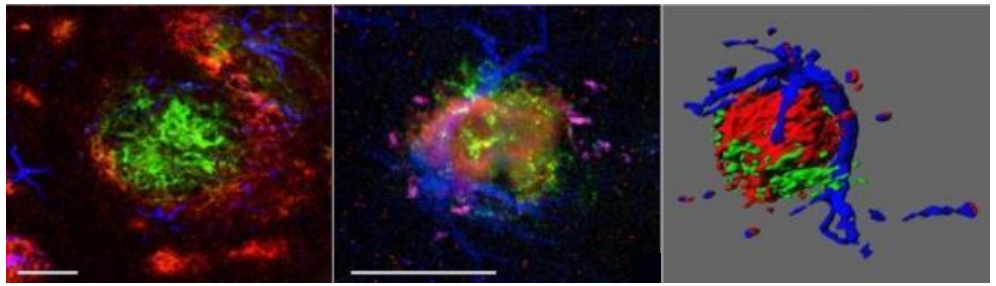
AD = Alzheimer's Disease, VSL = value of statistical life; USD = United States Dollar; Source: Deb A et al., Expert Review of Pharmacoeconomics and Outcomes Research 2017; Nandi A et al., The Lancet 2022; World Health Organization

Development of subcutaneous gantenerumab, a fully human anti-Aβ monoclonal antibody targeting Alzheimer's disease

Highest affinity for aggregated Aβ, including oligomers, fibrils, and plaques[2,3]

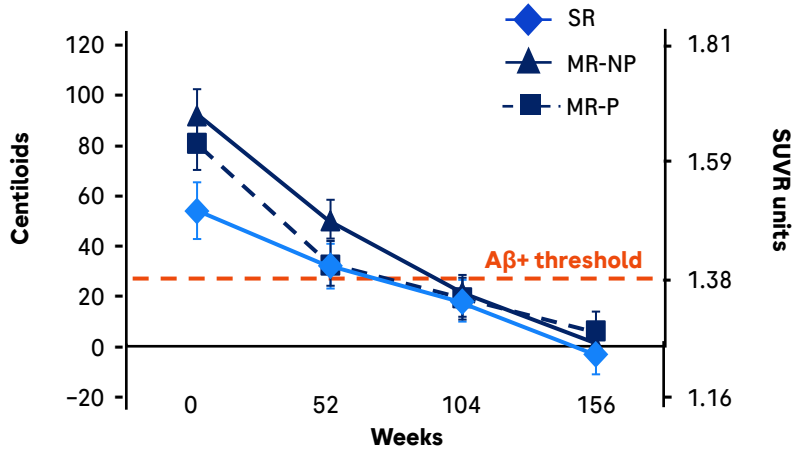
Clearance of aggregated Aβ

Microglia-mediated phagocytosis[2]



Triple labeling of microglia (blue) adjacent to gantenerumab (red) bound to Aβ deposits (green)

SR & MR OLE amyloid plaque removal[4,a]



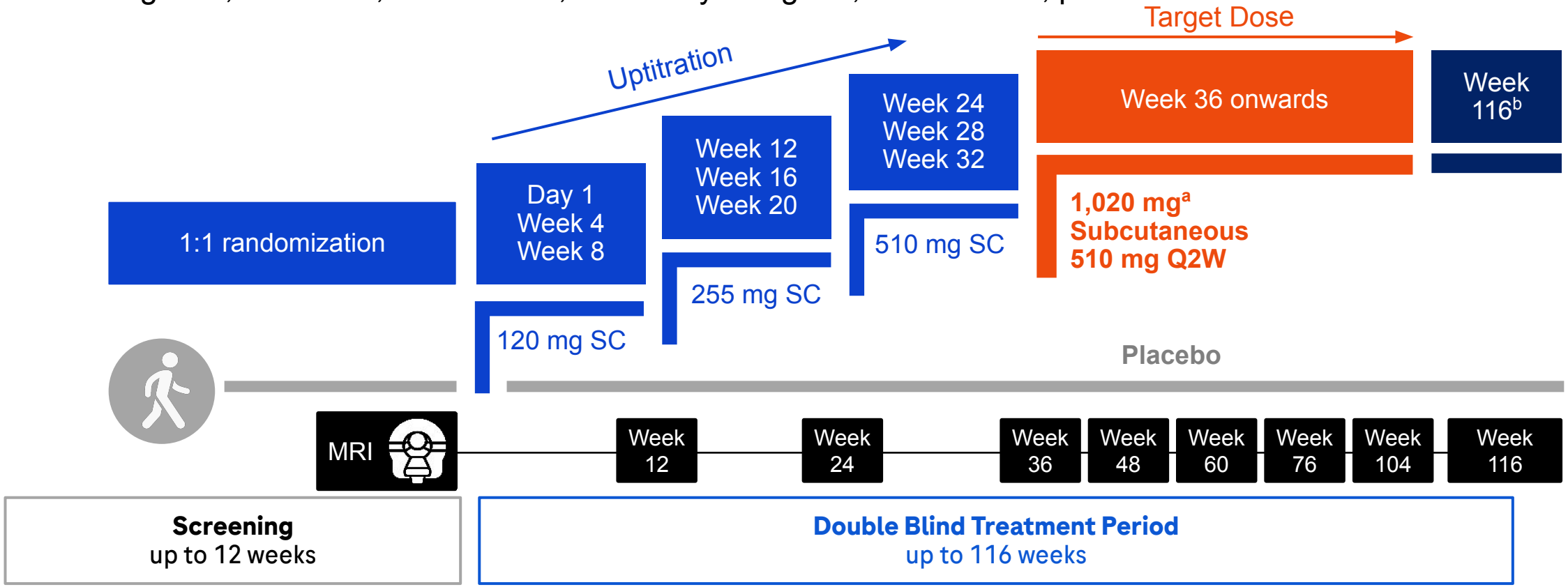
Below positivity threshold reached by 52% of participants with a decrease of 70 CL vs baseline at Week 104

Gantenerumab has shown downstream effects on multiple biomarkers of AD pathology and neurodegeneration in clinical trials[5,6]

[a]Data from SR and MR OLE PET substudies. Aβ, amyloid-beta; AD, Alzheimer's disease; CL, centiloid; MR, Marguerite RoAD; MR-NP, Marguerite RoAD – non-placebo; MR-P, Marguerite RoAD – placebo; OLE, open-label extension; PET, positron emission tomography; SR, SCarlet RoAD; SUVR, standardized uptake value ratio.1. Doody R. J Prev Alzheimers Dis 2017;4:264–272; 2. Bohrmann B, et al. J Alzheimers Dis 2012;28:49–69; 3. Chen Y, et al. ACS Chem Neurosci 2020;11:3233–3244; 4. Klein G, et al. J Prev Alzheimers Dis 2021;8:3–6; 5. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 6. Salloway S, et al. Nat Med 2021;27:1187–1196. Left-hand images from J Alzheimers Dis, 28, Bohrmann B, et al. Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β, p. 49-69, ©2012, with permission from IOS Press.

GRADUATE I and II studies assessed the efficacy and safety of subcutaneous gantenerumab in early symptomatic AD

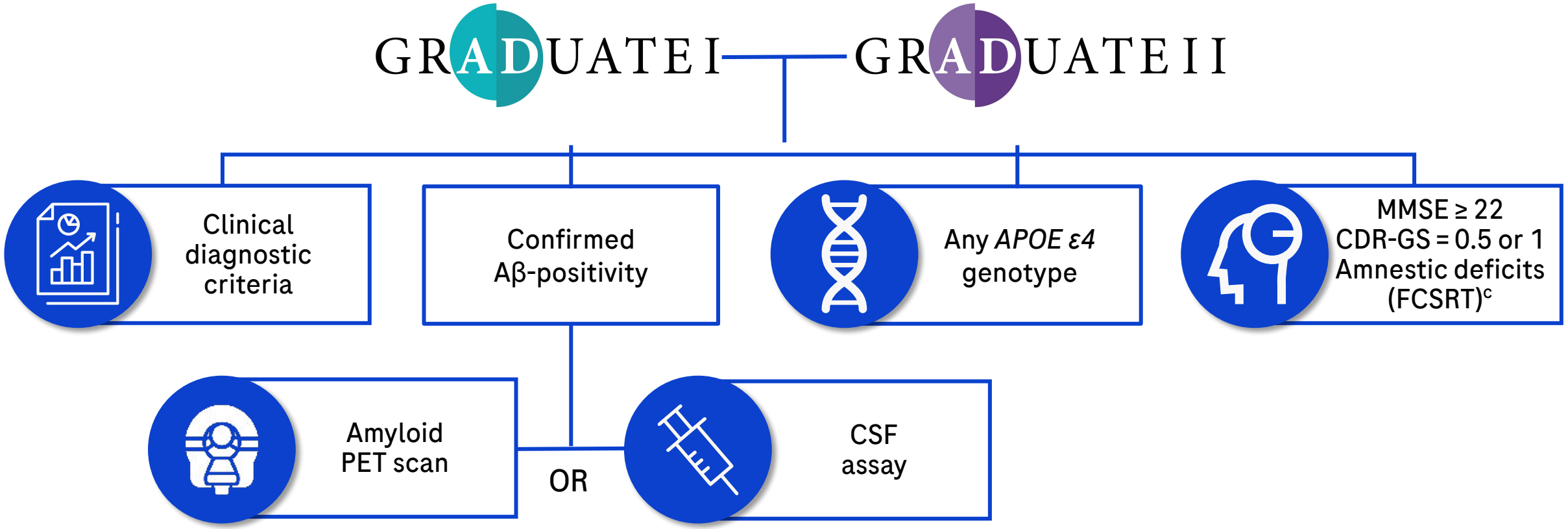
Two global, 27-month, randomized, identically designed, double-blind, placebo-controlled studies



- ➔ Uptitration was implemented to mitigate the safety risk of ARIA which is an identified risk for anti-Aβ immunotherapies (gantenerumab included)
- ➔ A brain MRI scan was performed before each uptitration step and at target dose and in case of ARIA, treatment would either continue, be temporarily interrupted or withdrawn depending on the severity and type of the ARIA event
- ➔ Efficacy assessments were performed approx. every 6 months

A Q2W, every 2 weeks; SC, subcutaneous;1. ClinicalTrials.gov. ID: NCT03444870. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03444870 on November 24, 2022; 2. ClinicalTrials.gov. ID: NCT03443973. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03443973 on November 24, 2022; 3. Pross N, et al. Presented at AD/PD 2019, Lisbon, Portugal; 4. Lane C, et al. Presented at CTAD 2021, Boston, MA, USA; 5. F. Hoffmann-La Roche Ltd. data on file.

Studies enrolled people living with MCI or mild dementia due to AD

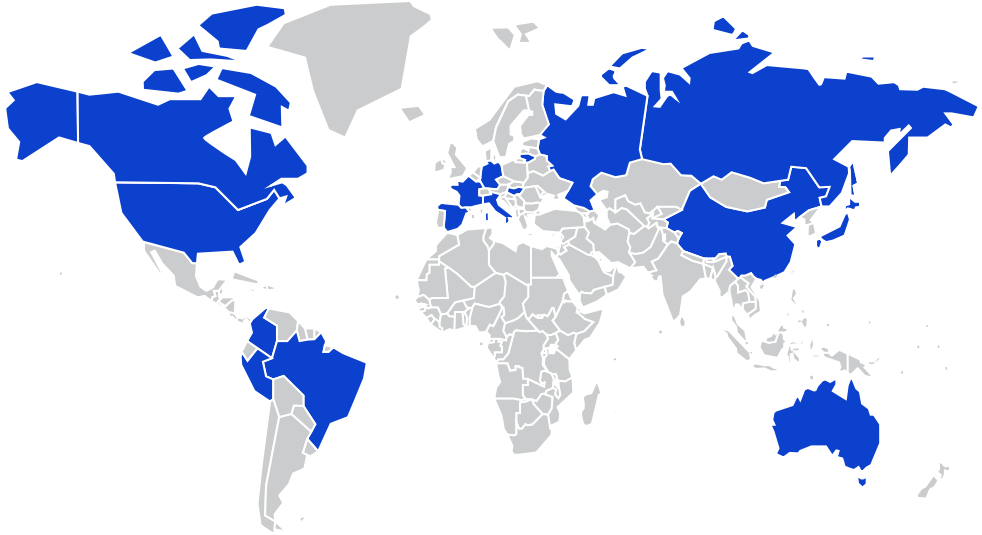


Aβ, amyloid-beta; AD, Alzheimer's disease; *APOE ε4*, apolipoprotein E ε4 allele; CDR-GS, Clinical Dementia Rating – Global Score; CSF, cerebrospinal fluid; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; pTau, phosphorylated tau. Lane C, et al. Presented at CTAD 2021, Boston, MA, USA.

Global reach of GRADUATE I and II

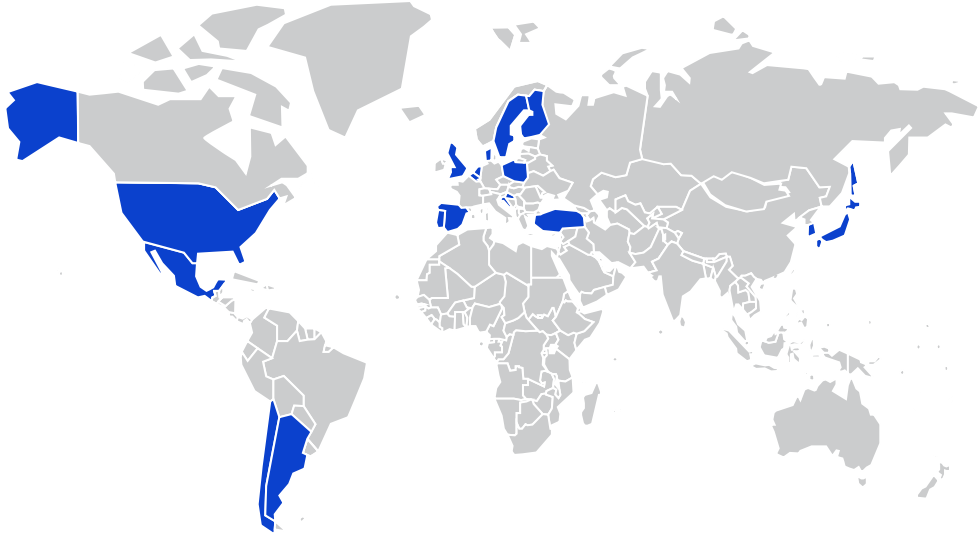
Two independent studies recruited participants in 288 sites across 30 countries, with no overlapping sites

GRADUATE I (N = 985)



- Australia
- Brazil
- Canada
- Mainland China
- Republic of China
- Colombia
- France
- Germany
- Hungary
- Italy
- Japan
- Lithuania
- Peru
- Russian Federation
- Spain
- United States of America

GRADUATE II (N = 980)



- Argentina
- Belgium
- Chile
- Croatia
- Denmark
- Finland
- Japan
- South Korea
- Mexico
- Netherlands
- Poland
- Portugal
- Singapore
- Spain
- Sweden
- Turkey
- United Kingdom
- United States of America

GRADUATE I and II had a wide range of efficacy and biomarker endpoints

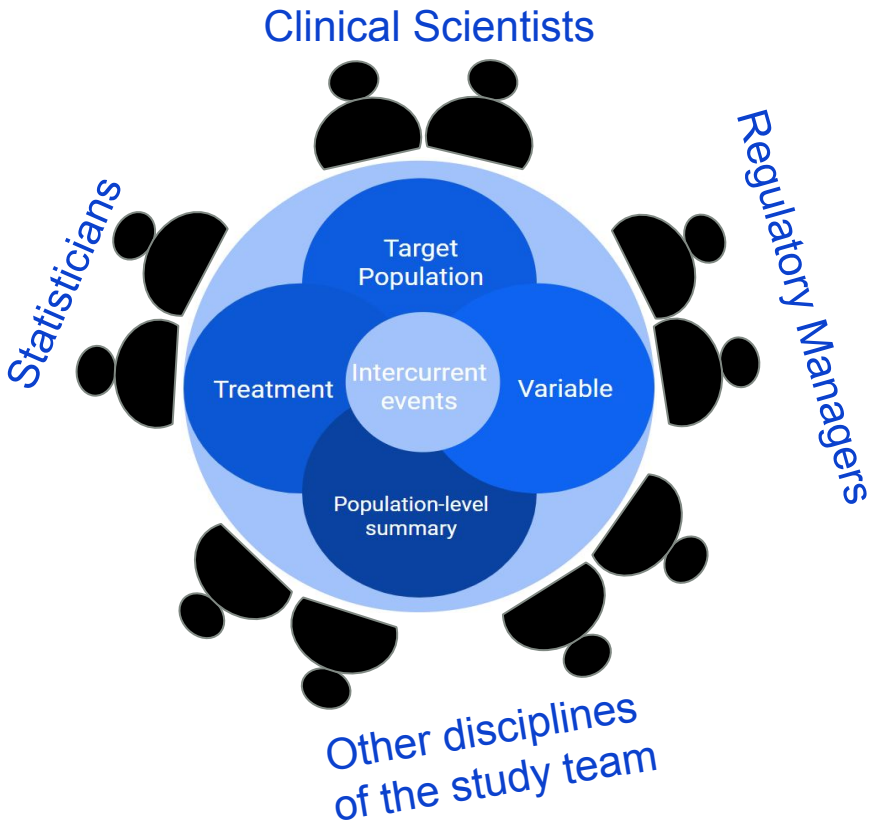
Change from baseline (Day 1) to Week 116

- ClinRO measure used to stage the severity of AD dementia based on a semi-structured interview with the participant and a reliable informant
- Assesses level of cognitive and functional impairment across six domains
- The sum of the ratings across each of the six domains is the CDR-SOB score

Efficacy endpoints							
	Primary endpoint	**CDR-SB**					
	Secondary endpoints	ADAS-Cog13	ADCS-ADL	FAQ	MMSE	Verbal fluency	Coding
	Exploratory	NPI-Q	ZCI-AD	QoL-AD	EQ-5D	RUD-Lite	
	Biomarker	Amyloid PET	Tau PET	CSF	Plasma	MRI	

ADAS-Cog 13, Alzheimer's Disease Assessment Scale – Cognitive Subscale 13; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE, adverse event; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CSF, cerebrospinal fluid; ClinRO, Clinical Reported Outcome; EQ-5D, EuroQoL – Five Dimensions; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination;; NPI-Q, Neuropsychiatric Inventory Questionnaire; PET, positron emission tomography; PK, pharmacokinetic; QoL, Quality of Life; RUD, Resource Utilization in Dementia; ZCI-AD, Zarit Caregiver Interview – AD.

Cross-functional team was formed to align with the estimands framework



Estimands

Regulatory Bodies

FDA
Food and Drug Administration

EMA
European Medicines Agency

GRADUATE I and II primary estimand

Target Population

Early symptomatic AD (MCI and mild AD dementia due to AD) population as identified by the inclusion and exclusion criteria

Treatment

Study drug (gantenerumab or placebo) administered during uptitration Q4W at the respective dose for each step and at target dose Q2W

- including safety-related dose modifications
- irrespective of the use or initiation of symptomatic treatment for AD

Variable

Change from baseline to Week 116 in CDR-SB

Population-level summary

Difference in variable means between treatment arms

Intercurrent events

Create a list of intercurrent events for this study

Protocol design and study conduct in the era of estimands

Study design and data collection approach should be developed having the estimands in mind

Predefine the targeted study population and the clinical question of interest	This will guide the definition of the ICEs early on in the process
Think of the Intercurrent Events of the study in advance	This will ensure that necessary processes exist: ◆ Data collection to capture the majority of the ICEs in the study ◆ Data Review Plan to ensure data quality ◆ Site Training and Monitoring focusing on critical variables
Treatment Discontinuations	Whenever a study participant that discontinues treatment, study data collection should continue until the end of the study if possible ◆ EDC system has to be designed accordingly to capture this data
Reason for treatment discontinuation	Important to capture an informative reason for each ICE of treatment discontinuation that occurs in the study

EDC = Electronic Data Capture, ICE = intercurrent event

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Q & A	Marcel

Analysis plan under the estimand framework

Design a statistical analysis plan aligned on

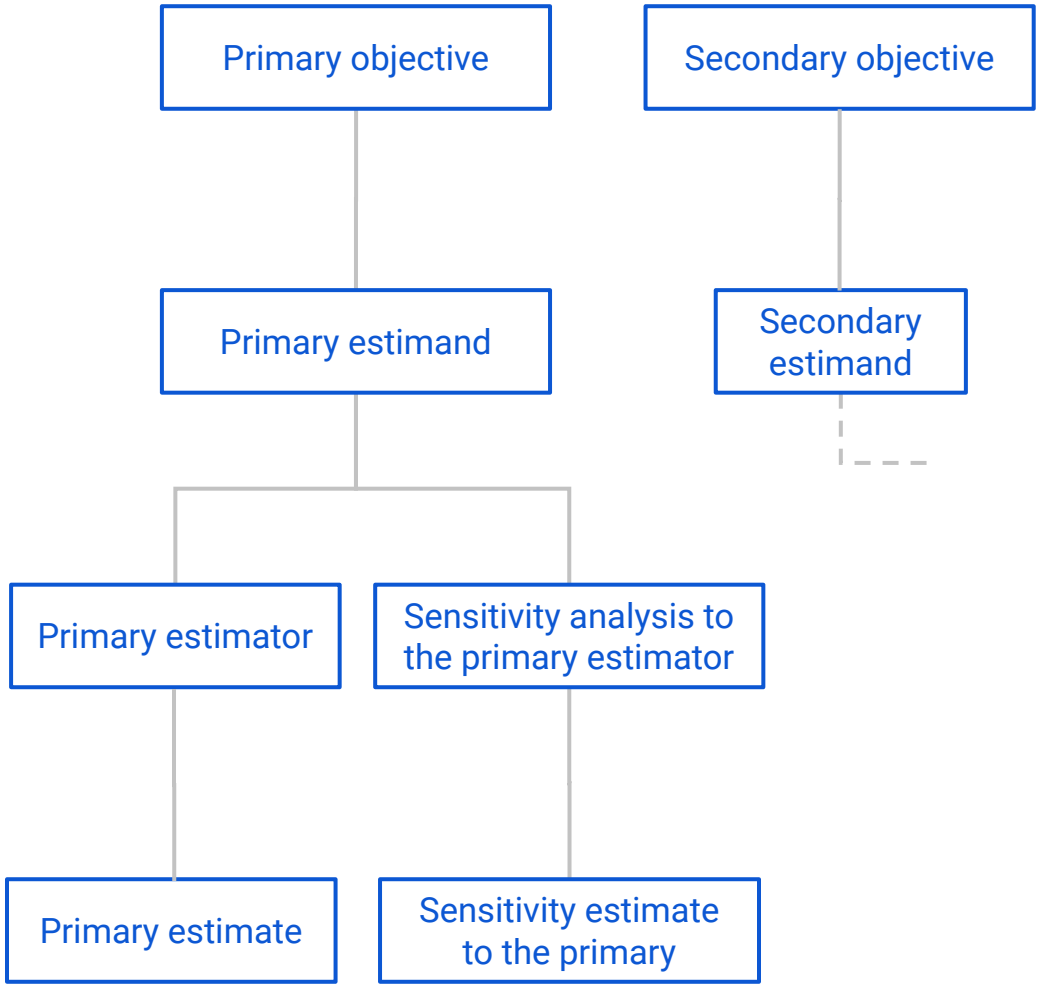
- the clinical question of interest
- and estimand

as defined in the protocol

Emphasis on the estimator: management of ICEs and missing data based on assumptions

Sensitivity analyses: robustness of inference to deviation from assumptions

Primary / secondary estimand



Intercurrent event related to primary estimand

Workflow:

1. List
2. Capture
3. Categorize
4. Set an analysis strategy

Cross functional input

Clinical science
Safety science
Operations
Regulatory

Intercurrent Event
Withdrawal from study treatment due to lack of efficacy
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuation due to AE, incl. suspected or confirmed COVID-19 AEs)
Withdrawal from study treatment with no informative reason given
Withdrawal from study treatment due to the COVID-19 pandemic
Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months)
Withdrawal from study treatment due to purely administrative reason
Death
Withdrawal from study treatment due to use or initiation of protocol prohibited medication
Withdrawal from study treatment due to other SDCR ICEs

Intercurrent event related to primary estimand

Workflow:

1. List
2. Capture
3. Categorize
4. Set an analysis strategy

Cross functional input

Ensure that the data collected inform on the occurrence of an intercurrent event

Intercurrent Event
Withdrawal from study treatment due to lack of efficacy
Withdrawal from study treatment due to safety or tolerability reason
(NOTE: This will include discontinuation due to AE, incl. suspected or confirmed COVID-19 AEs)
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Death
Withdrawal from study treatment due to use or initiation of protocol prohibited medication
Withdrawal from study treatment due to other SDCR ICEs

Intercurrent event related to primary estimand

Workflow:

1. List
2. Capture
3. Categorize
4. Set an analysis strategy

Cross functional input

For each ICE, pre-specify whether or not the ICE is related to the study drug or the condition

Intercurrent Event
Withdrawal from study treatment due to lack of efficacy
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuation due to AE, incl. suspected or confirmed COVID-19 AEs)
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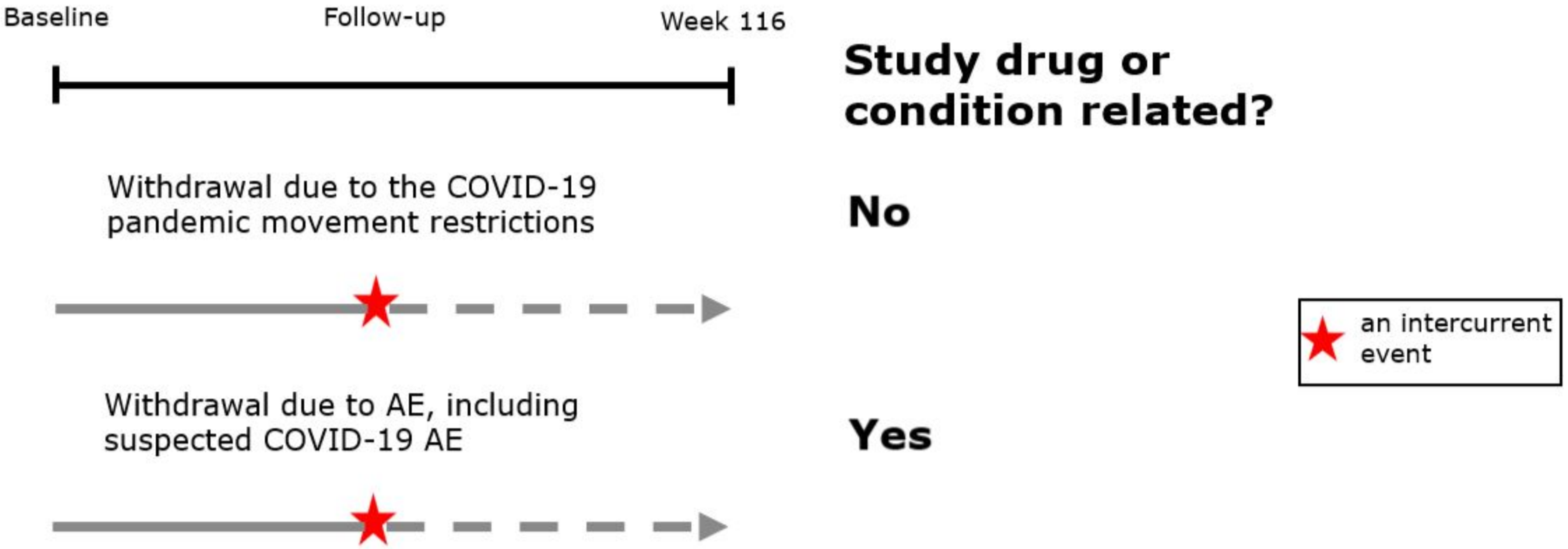
Withdrawal from study treatment due to other SDCR ICEs

Intercurrent event categories



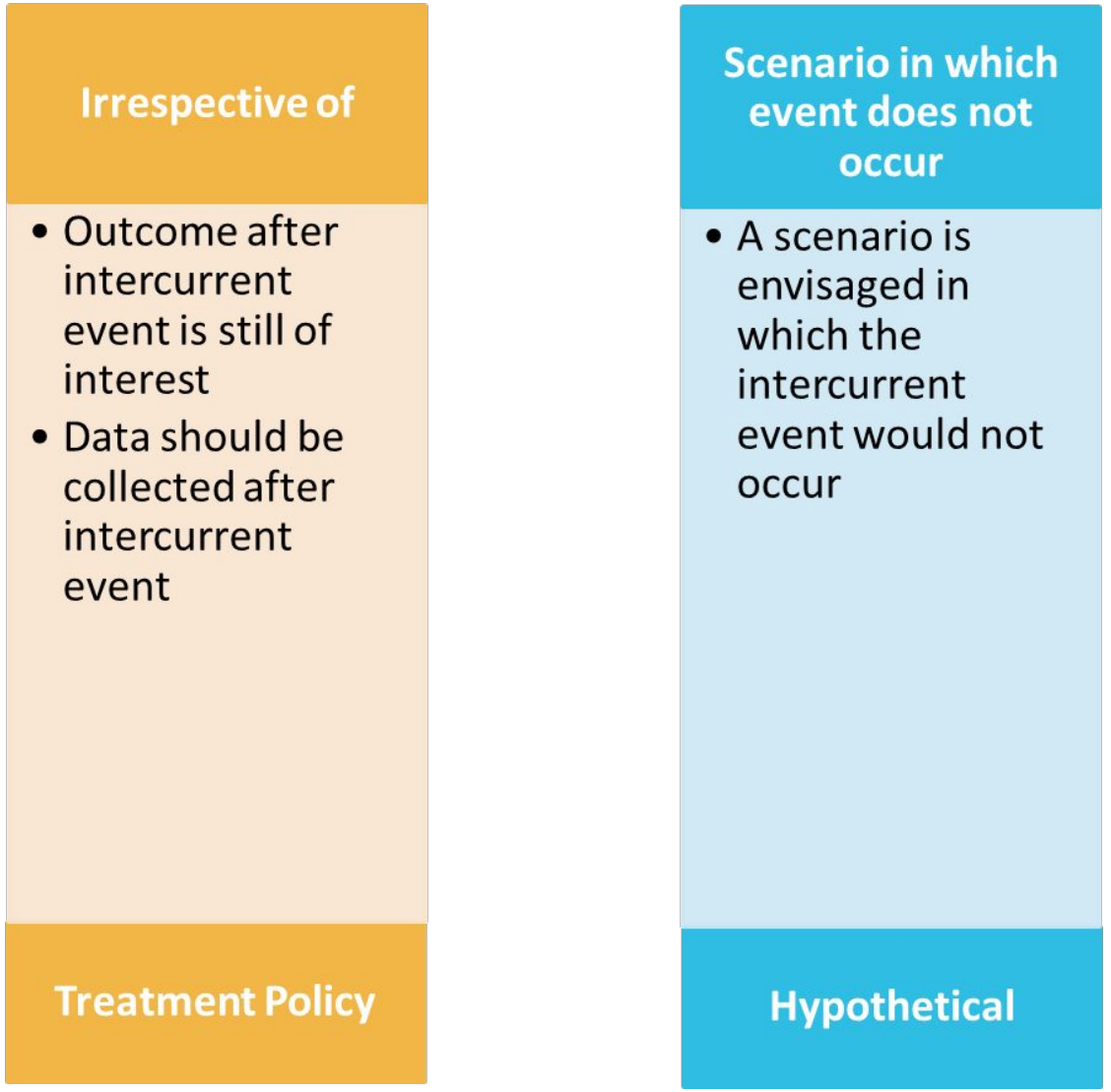
Intercurrent event related to primary estimand

Workflow:

1. List
2. Capture
3. Categorize
4. Set an analysis strategy

Dual handling strategy
Treatment policy
Hypothetical

Regulatory body alignment (briefing package)



European Medicines Agency. ICH E9 (R1) addendum. 2020.

Intercurrent event related to primary estimand

Workflow:

1. List
2. Capture
3. Categorize
4. Set an analysis strategy

Dual handling strategy depending on the ICE's category

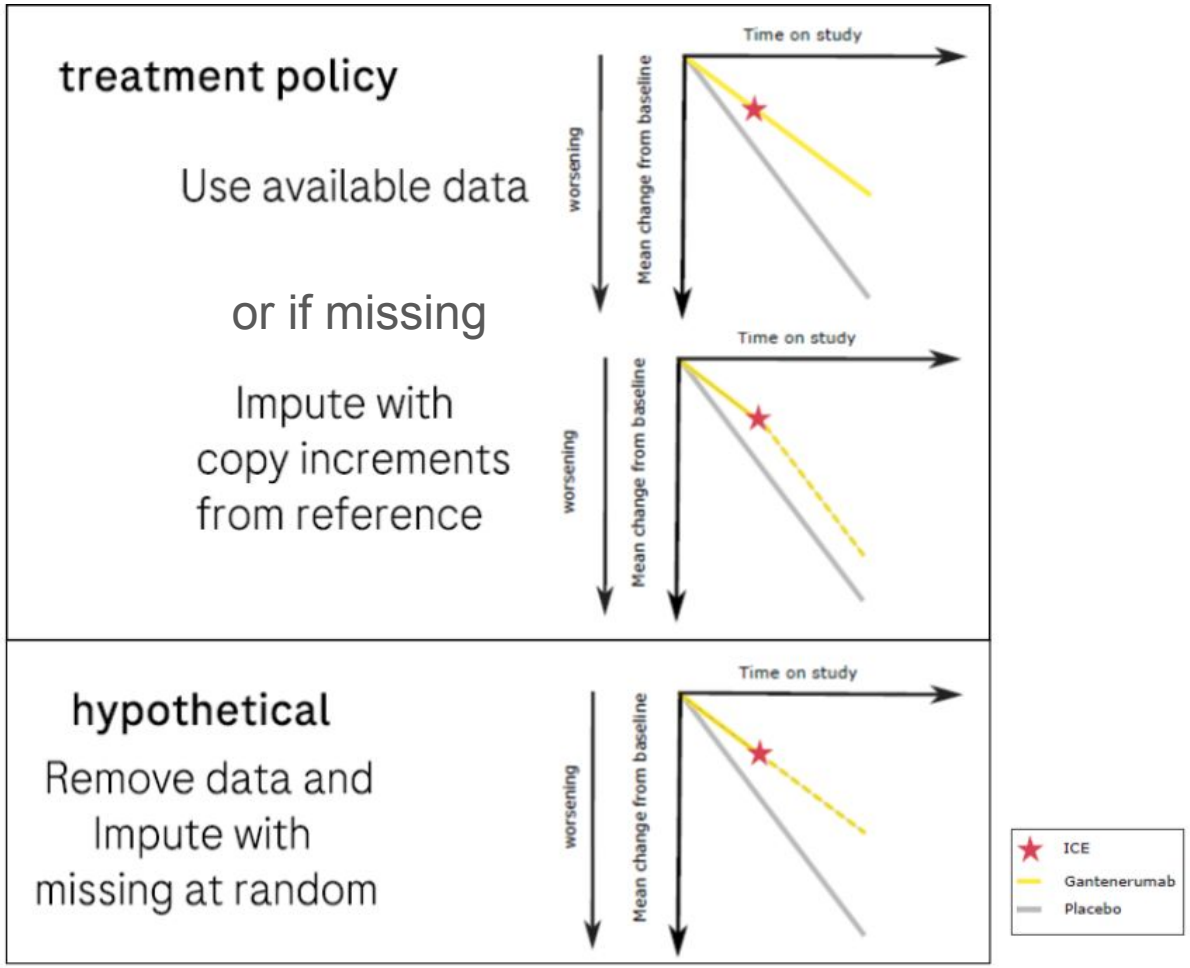
Assumptions:

- copy increments from reference
- missing at random

Study drug or condition related?

Yes

No



Quiz #2

Which of the following ICEs would be considered as SDCR (study drug or condition related) for the analysis strategy in GRADUATE?

A. discontinuation due to a SAE not related to the study drug
B. intolerability of the drug administration
C. withdrawal of consent without any further justification provided
D. move to another country

Quiz #2

Which of the following ICEs would be considered as SDCR (study drug or condition related) for the analysis strategy in GRADUATE?

A. discontinuation due to a SAE not related to the study drug

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C. withdrawal of consent without any further justification provided

D. move to another country

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How to deal with ICEs of **non informative** treatment discontinuations?

Independent ICE adjudication committee

The Committee was provided and reviewed the ICEs related to study treatment discontinuations where ambiguity existed about the reason they occurred when captured in the eCRF

Non Informative treatment discontinuation ICEs:

- Due to withdrawal of consent
- Due to PI's judgement
- Due to other reasons
- Due to Protocol deviation

Informative treatment discontinuation ICEs:

- Due to AE
- Due to death
- Due to lack of efficacy
- Due to COVID-19

The role of the committee was to categorise these ICEs of non-informative treatment discontinuations to NSDCR or SDCR

Committee Members:

Cross-functional composition:

- Clinical Scientist
- Medical Director
- Statistician

Independent members with no knowledge or access to the study data

➔ The Adjudication Committee supported GRADUATE Study Team to achieve the classification of ICEs of non-informative treatment discontinuations as SDCR or NSDCR in a controlled and unbiased manner

Agenda

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Q & A	Marcel

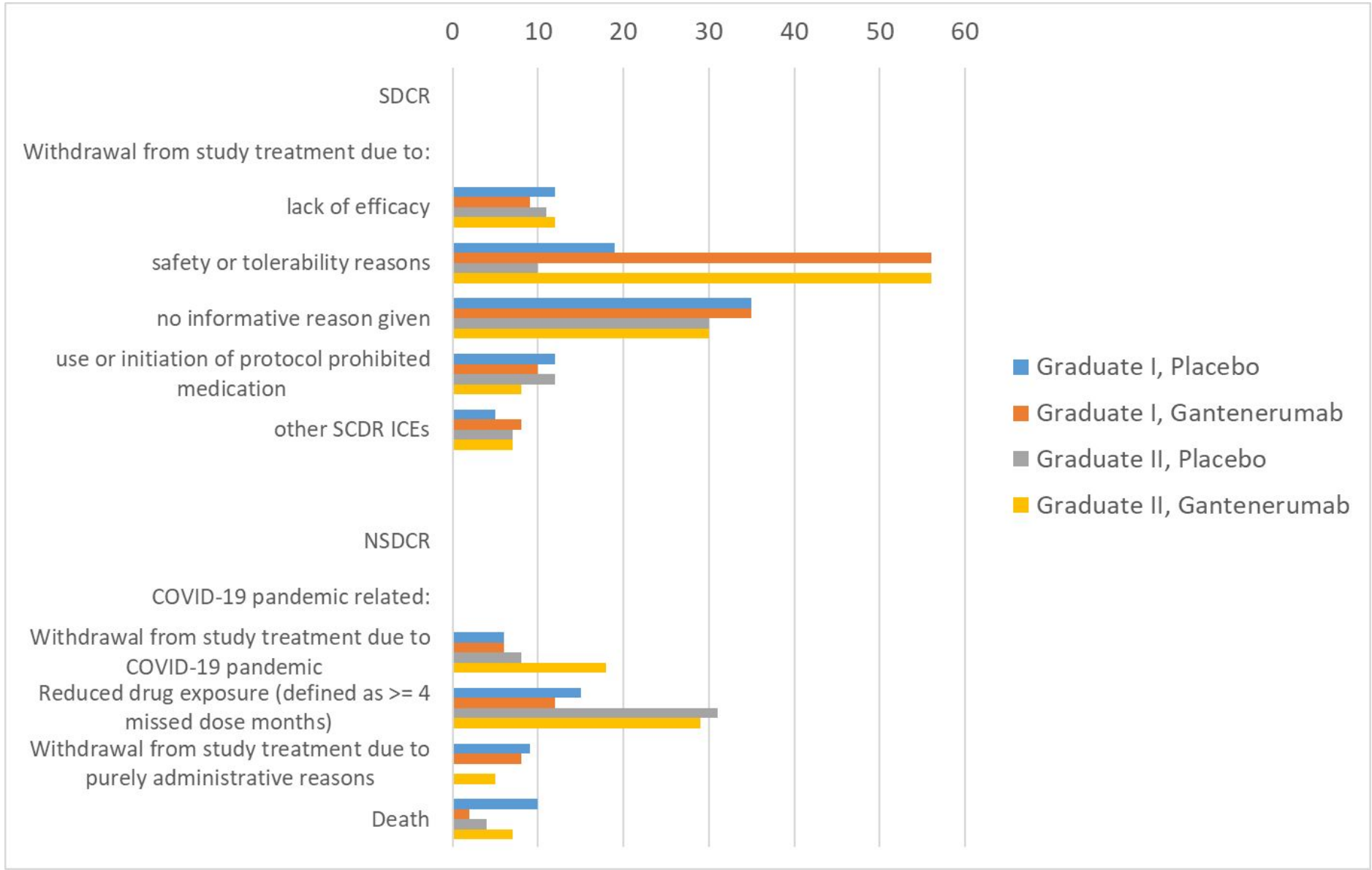
A total of 546 (28%) participants had at least 1 ICE

ICEs were mainly:

- SDCR, 384 participants
- Safety related, including COVID-19
- Experimental arm

Adjudicated ICEs:

- 330 cases adjudicated
- 82% were SDCR
- ‘No informative reason’



Key Takeaways

The GRADUATE studies set a reference point for the implementation of the estimand framework in future pivotal clinical trials in early Alzheimer's disease

Important insights for the future:

Cross functional input early in the process is critical to clarify the clinical question of interest, the estimand and its attributes, and the intercurrent events

The estimand framework drives a paradigm shift, compelling study teams to reconsider the design of:

- **Study protocol**, centered on the clinical question of interest and the primary estimand
- **Data Collection,** set up (eg. EDC) to capture and classify intercurrent events
- **Statistical Analysis Plan**, aligning the estimator with the estimand and clarifying assumptions related to intercurrent events analysis strategy

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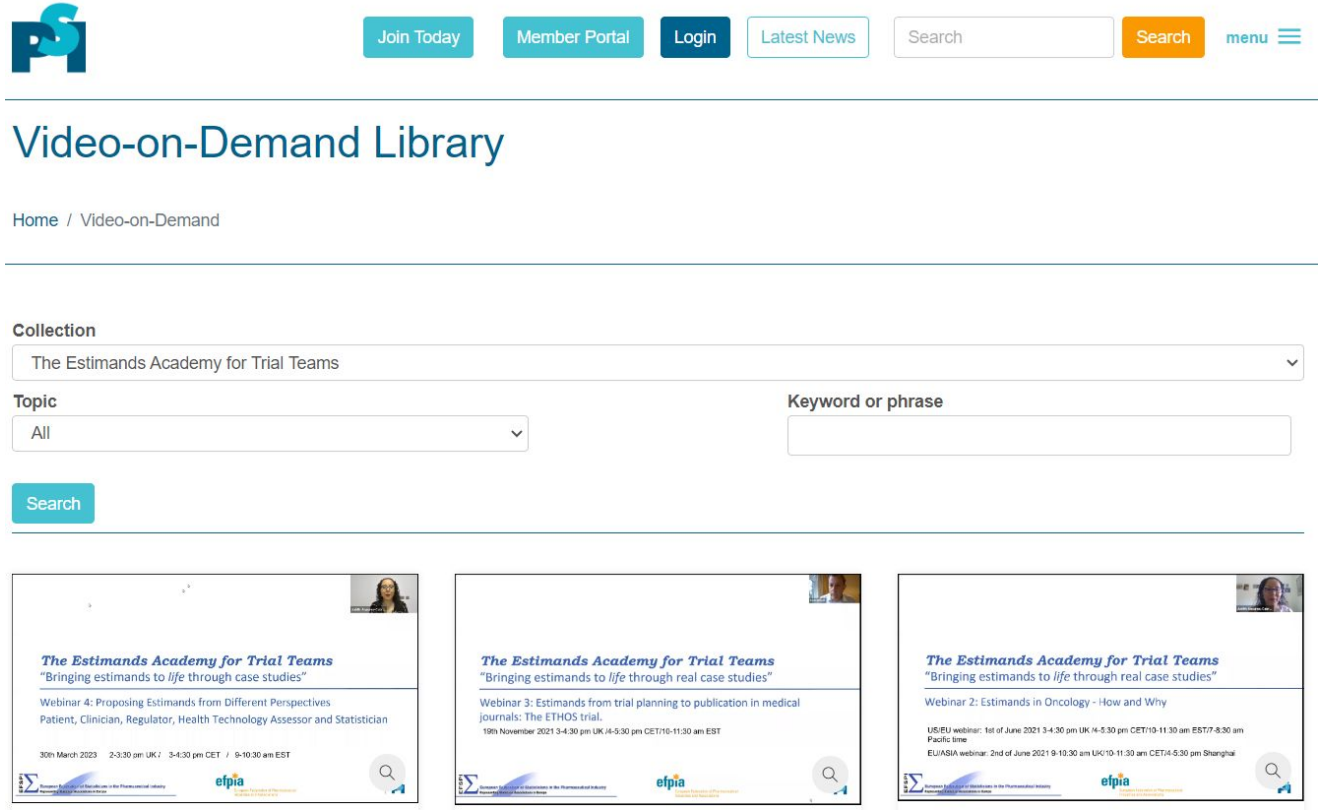
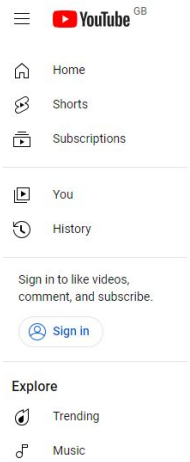
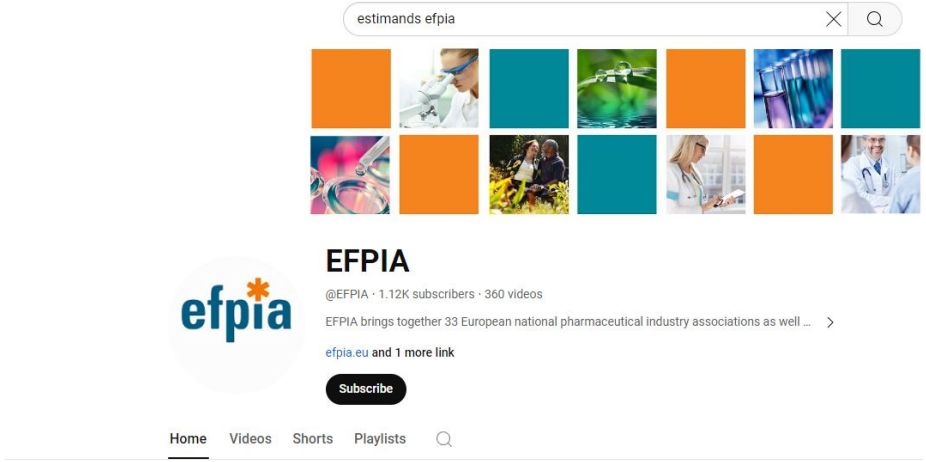
Link to previous webinars

- PSI Video on Demand Library - The Estimands for Trial Teams Collection (https://www.psiweb.org/vod/Index/)
- EFPIA YouTube Channel (https://www.youtube.com/@EFPIA)







Thank you

The Estimands Academy for Trial Teams

"Bringing estimands to *life* through real case studies"