Quantitative Tools Development Update

CPAD Annual Meeting – October 29, 2019

Klaus Romero MD MS FCP

Executive Director, Clinical Pharmacology and Quantitative Medicine

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A Clear and Successful Pathway for Regulatory Endorsement of QDDTs

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C-Path pioneered the pathway for Regulatory endorsement (Fit For Purpose) of Quantitative DDTs

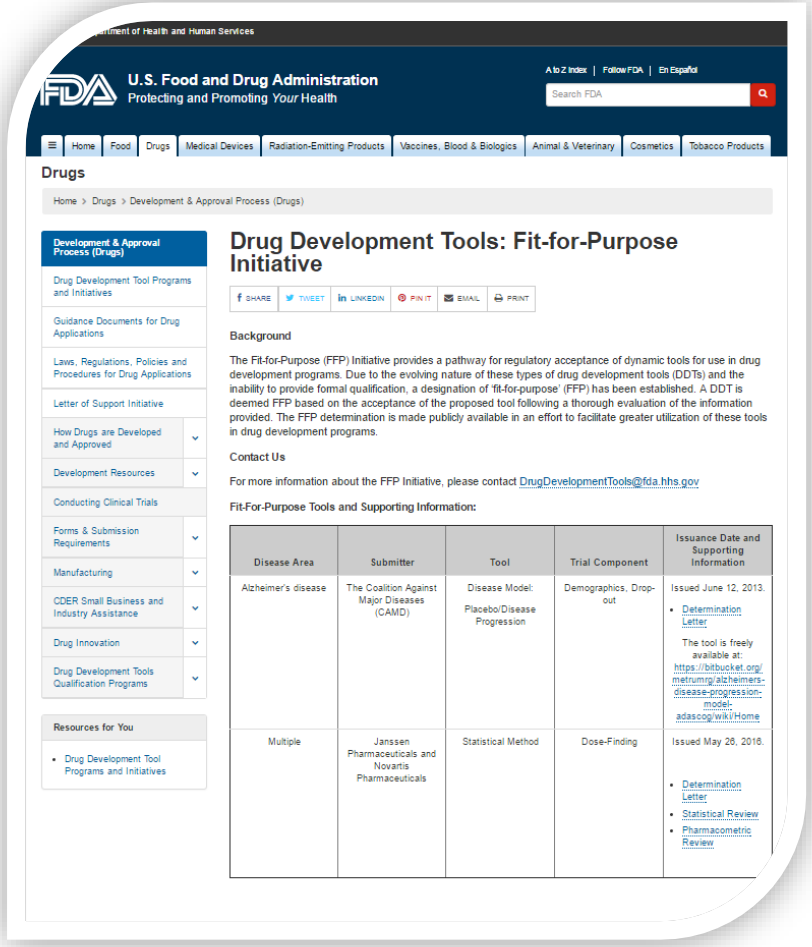
FDA CRITICAL PATH INSTITUTE ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS

Modeling & Simulation for Medical Products Workshop
September 26, 2013

SHORT REPORT

Modeling and simulation for medical product development and evaluation: highlights from the FDA-C-Path-ISOP 2013 workshop

Klaus Romero · Vikram Sinha · Sandra Allerheiligen · Meindert Danhof · Jose Pinheiro · Naomi Kruhlak · Yaning Wang · Sue-Jane Wang · John-Michael Sauer · J. F. Marier · Brian Corrigan · James Rogers · H. J. Lambers Heerspink · Tawanda Gumbo · Peter Vis · Paul Watkins · Tina Morrison · William Gillespie · Mark Forrest Gordon · Diane Stephenson · Debra Hanna · Marc Pfister · Richard Lalonde · Thomas Colatsky



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm

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SCIENCE MEDICINES HEALTH

19 September 2013
EMA/CHMP/SAWP/567188/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease

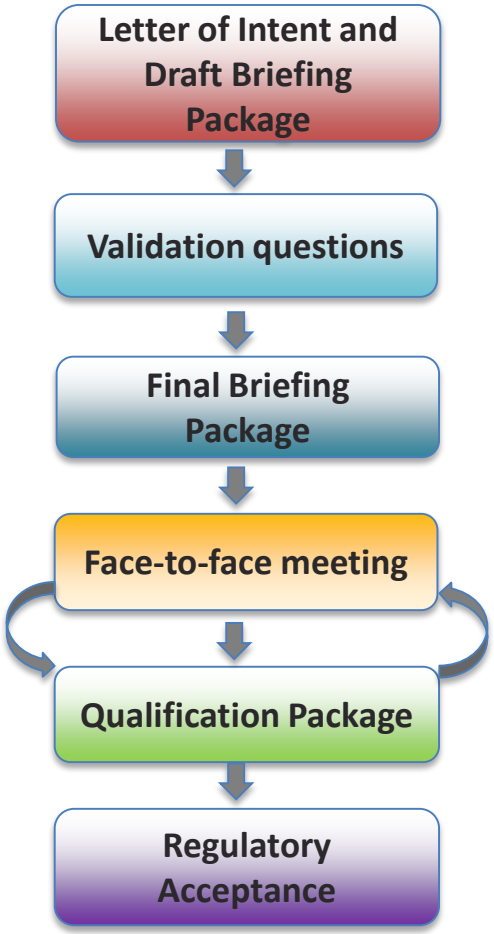
Draft agreed by Scientific Advice Working Party	6 June 2013
Adopted by CHMP for release for consultation	27 June 2013[1]
Start of public consultation	19 July 2013[2]
End of consultation (deadline for comments)	27 August 2013[3]
Adoption by CHMP	19 September 2013

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/10/WC500151309.pdf

Romero K, et al. The future is now: Model-based clinical trial design for Alzheimer's disease. Clin Pharmacol Ther. 2015;97(3):210-4.

Regulatory Pathway Strategy (EMA)

Qualification of novel methodologies steps



Triggers the formal start of the process, and the formation of the specific scientific advice working party (SAWP)

Opportunity to optimize briefing document (tight timelines)

Triggers the first deep-dive regulatory review

Formal checkpoint to finalize the analysis plan for execution

Triggers the final deep-dive regulatory review

Final decision

Briefing Document

- Summary
- Regulatory history
- COU
- Modeling analysis plan:
  - Data sources and management
  - Data analytics
- Q&A:
  - Questions to the Agency
  - Consortium position on the questions

Mild-to-Moderate AD Clinical Trial Simulator

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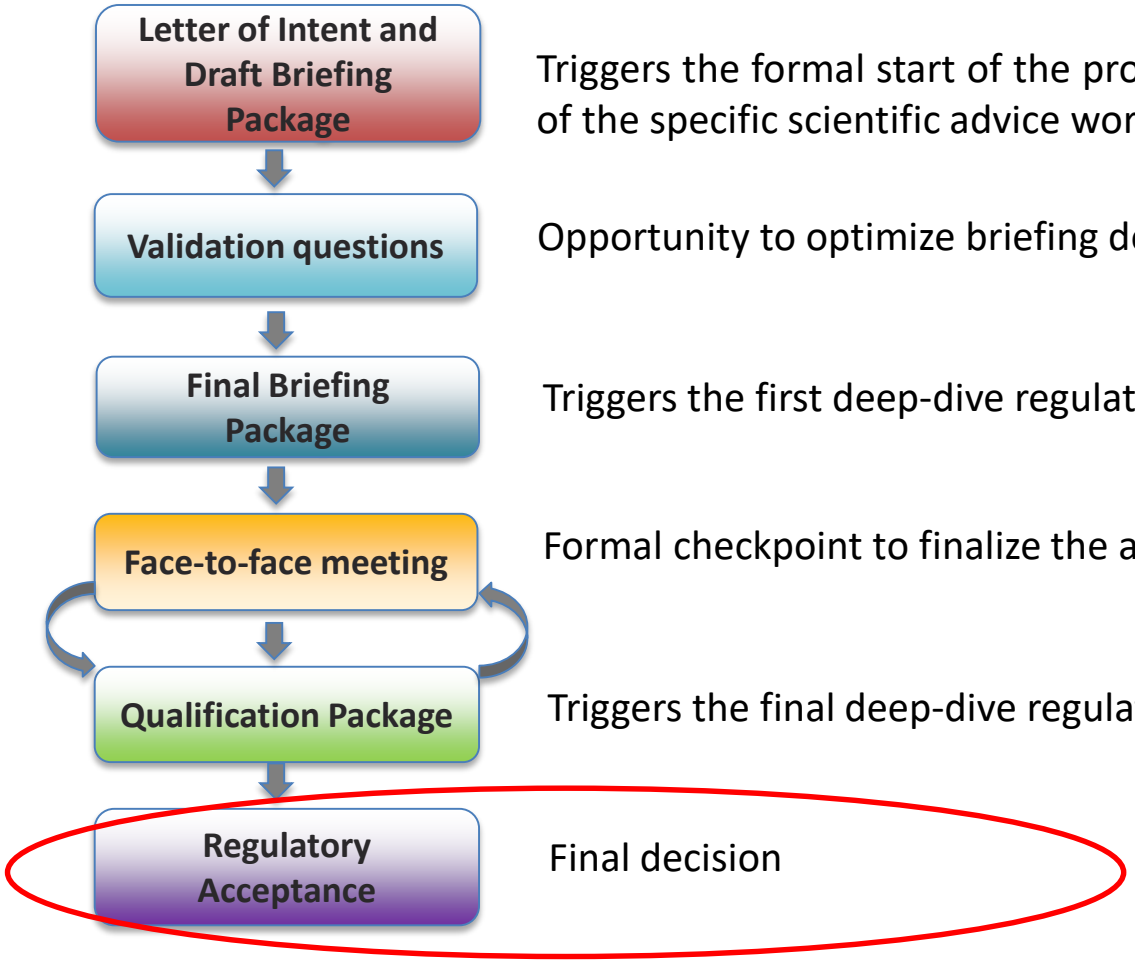
Qualification of novel methodologies steps



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Predementia disease progression model with baseline HV

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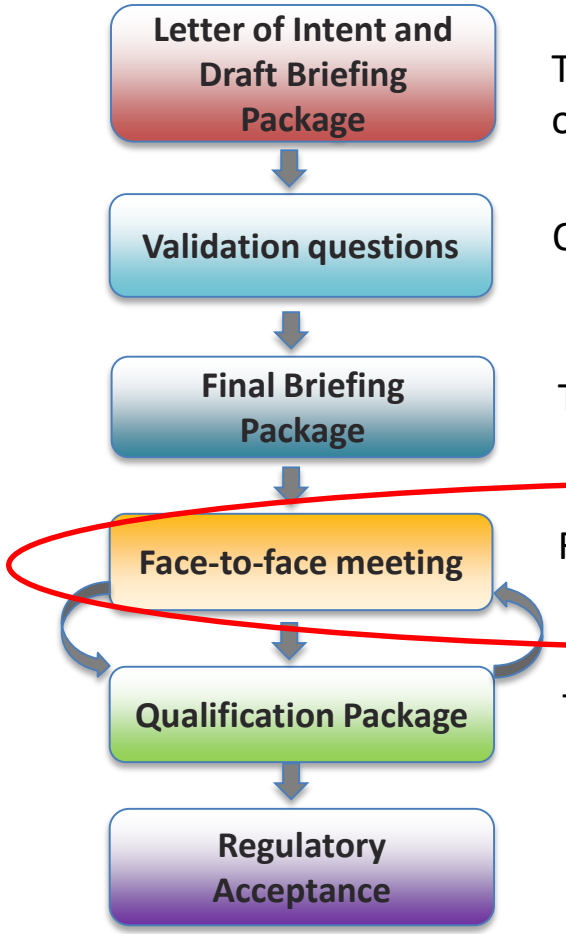

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18 October 2018
EMA/693969/2018
Executive Director

Letter of support for Model-based CT enrichment tool for CTs in aMCI

- **The EMA supports the primary objectives of the applicant and has decided to issue a Letter of Support to the CPAD Consortium**
- **To encourage industry sponsors to share the patient-level data from completed phase II and III clinical trials in the intended target population as defined in the COU statement, including active and control arms, with CPAD**
- **To encourage the CPAD team to disseminate and provide access to the current version of the model for implementation by sponsors actively designing clinical trials**

Regulatory Pathway Strategy (FDA)

Fit-for-Purpose Initiative

Triggers the formal start of the process, and the formation of the regulatory review team

Formal green light to proceed. Provides an opportunity to get early feedback. Opportunity to optimize the briefing document

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Mild-to-Moderate AD Clinical Trial Simulator

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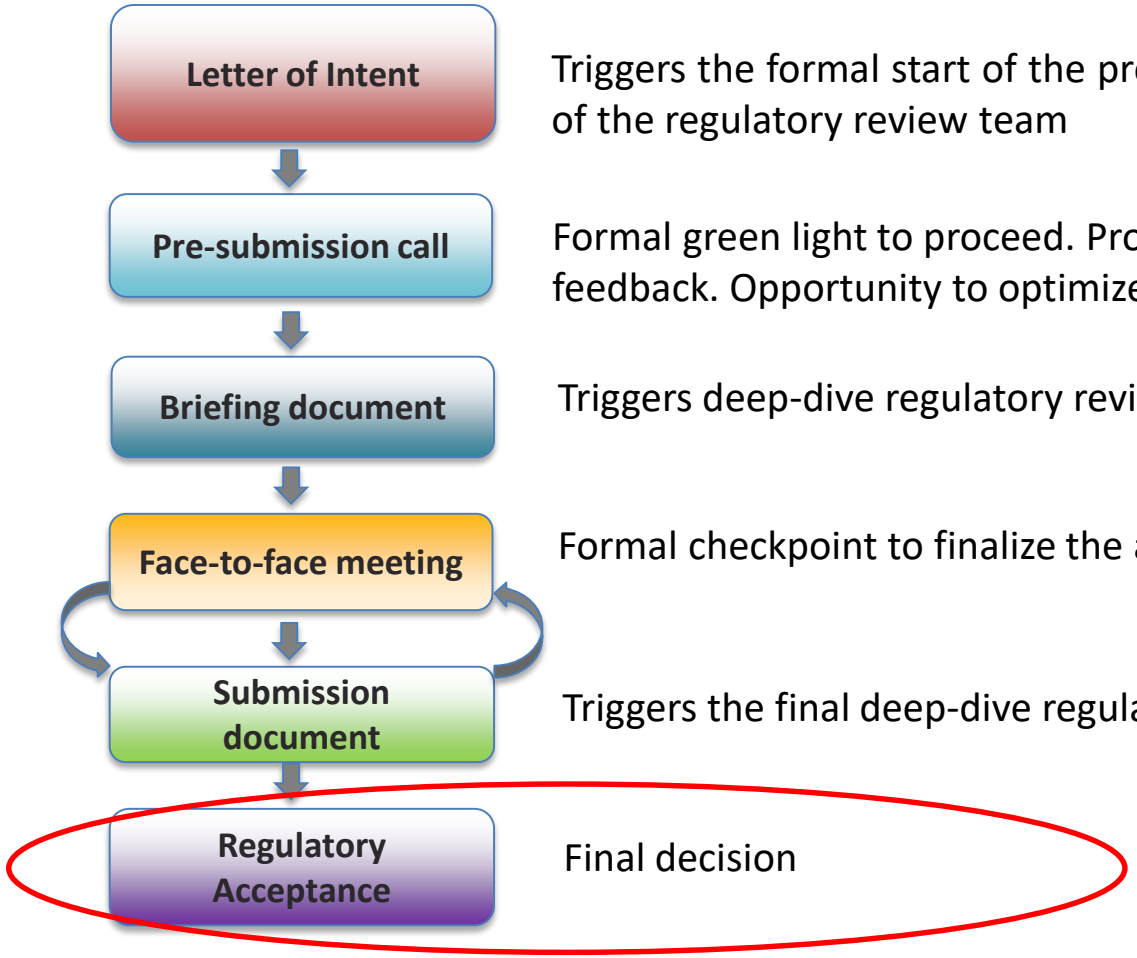
Fit-for-Purpose Initiative



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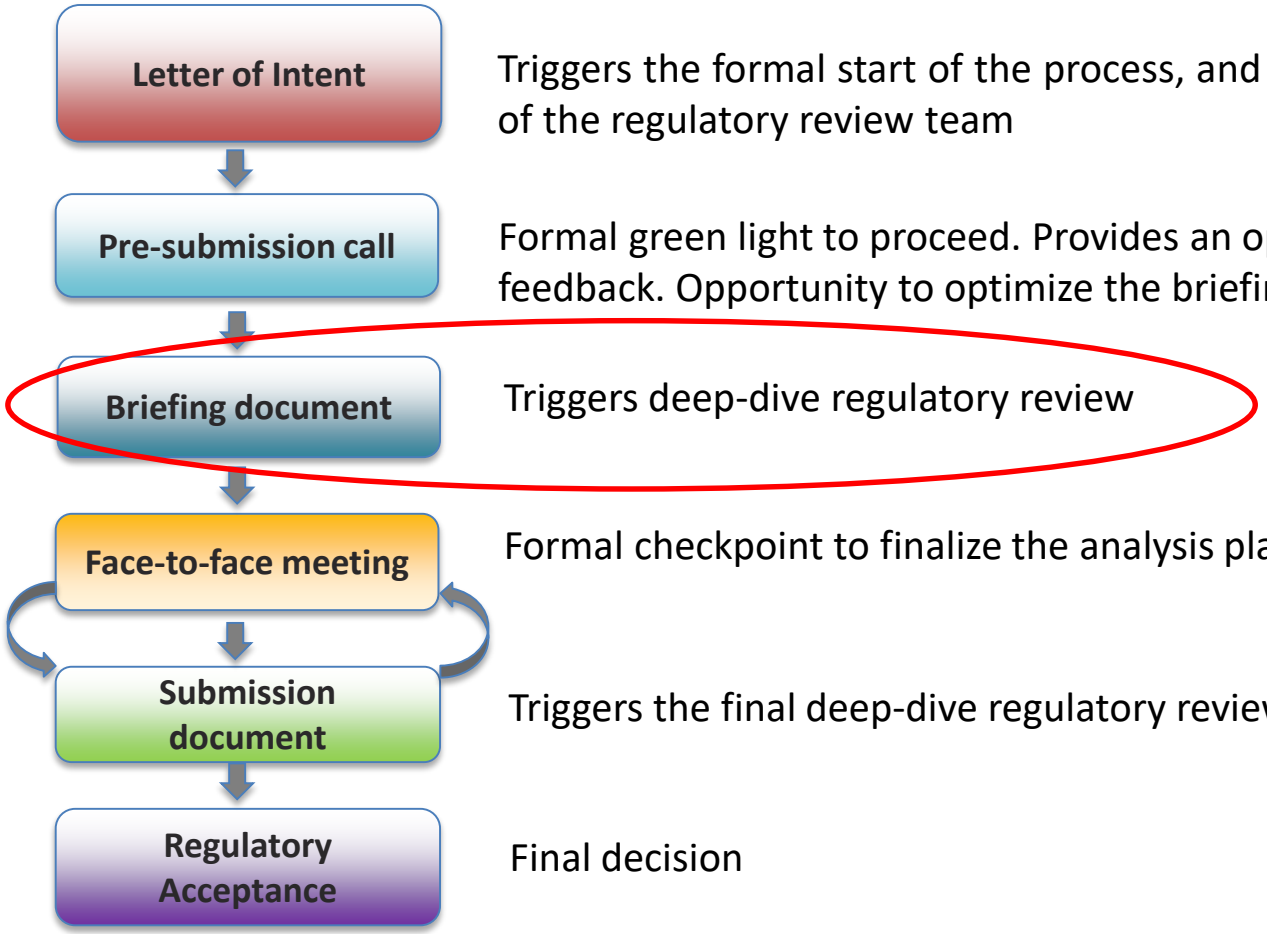

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AD CTS: n=50

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Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 50

Baseline MMSE: 18 – 22 (10–30)

% with 1 APOE4 allele: 45 (0–100)

% with 2 APOE4 alleles: 0 (0–55)

% on stable background medication: 75 (50–100)

Trial Design: Parallel

Include Patient dropout rate? (•) Yes ( ) No

Include Bayesian uncertainty? (•) Yes ( ) No

Duration: 52

Assessment: 4

% of patients in Treatment Arm: 50 (1–100)

Drug effect (% reduction on slope): 30 (0–100)

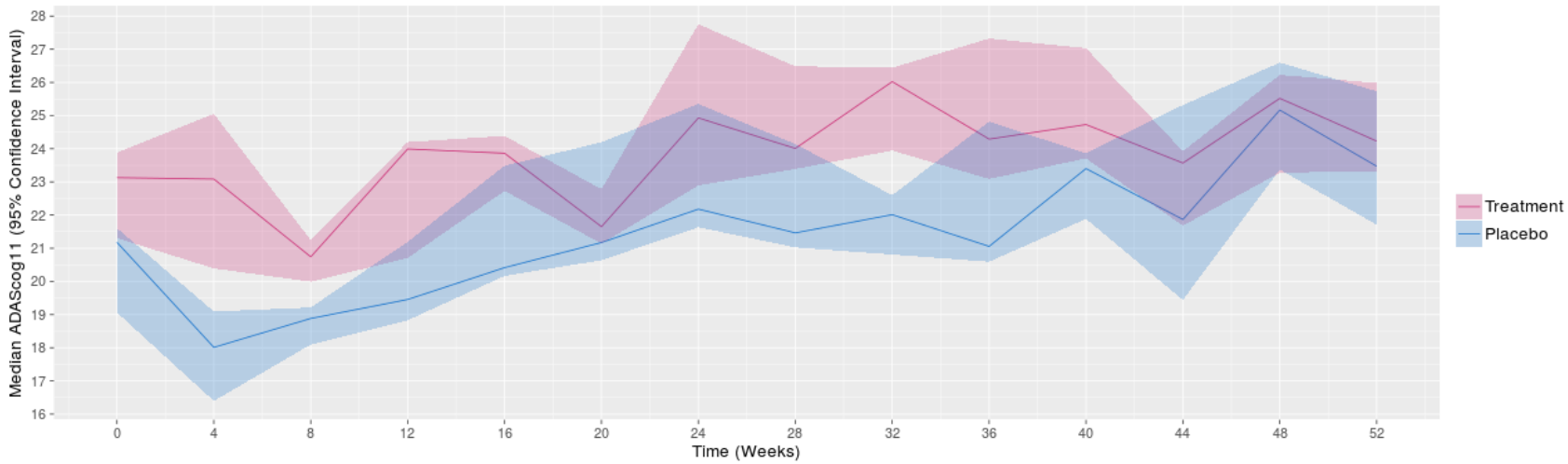
# of simulations: 3

Seed: 1

Alpha (slope difference): 95 (80–100)

Confidence Interval (%): 95 (80–100)

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	4
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Sample size	50
Age, (mean,sd)	(74.57,1.04)
Percentage of Male (mean,sd)	(0.43,0.06)
Number of APOE e4 alleles (%)	0 (54), 1 (44)
Baseline MMSE, median (range)	(18,22)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(47.71,0.84)
Trial Power (%)	0
Monte Carlo Error (%)	0
Confidence Interval of Monte Carlo Error	(0,0)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

AD CTS: n=200

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Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 200

Baseline MMSE: 18 – 22 (10 – 30)

% with 1 APOE4 allele: 45 (0 – 100)

% with 2 APOE4 alleles: 0 (0 – 55)

% on stable background medication: 75 (50 – 100)

Trial Design: Parallel

Include Patient dropout rate? (•) Yes ( ) No

Include Bayesian uncertainty? (•) Yes ( ) No

Duration: 52

Assessment: 4

% of patients in Treatment Arm: 50 (1 – 100)

Drug effect (% reduction on slope): 30 (0 – 100)

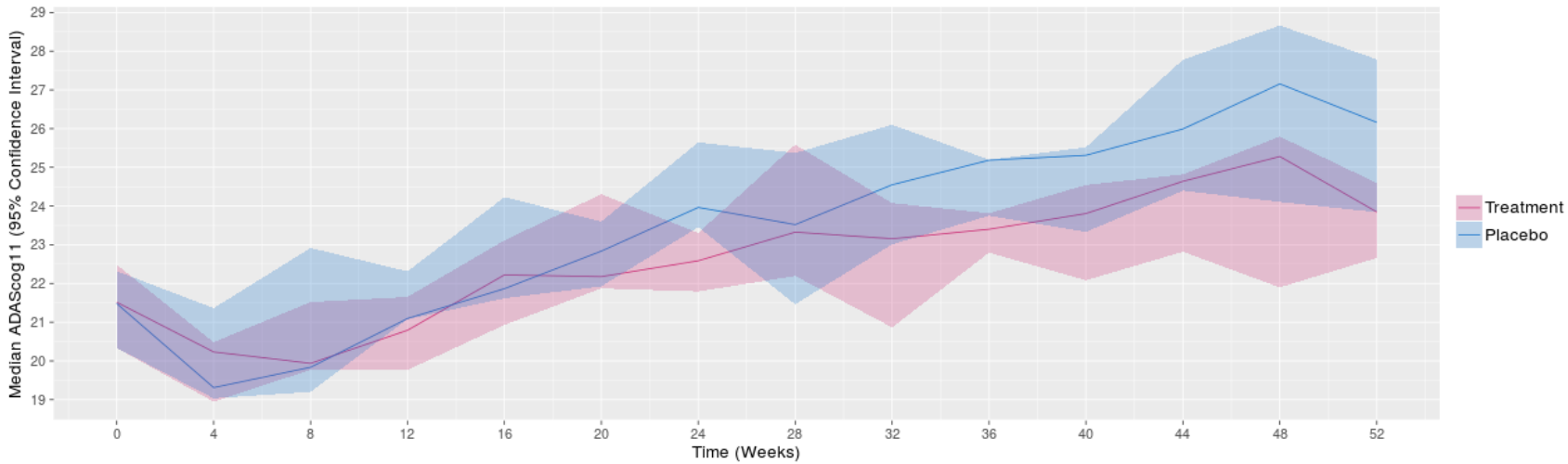
# of simulations: 3

Seed: 1

Alpha (slope difference): 95 (80 – 100)

Confidence Interval (%): 95 (80 – 100)

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	4
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Sample size	200
Age, (mean,sd)	(75.01,0.63)
Percentage of Male (mean,sd)	(0.45,0.03)
Number of APOE e4 alleles (%)	0 (55), 1 (45)
Baseline MMSE, median (range)	(18,22)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(48.96,0.43)
Trial Power (%)	67
Monte Carlo Error (%)	27
Confidence Interval of Monte Carlo Error	(14,120)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

AD CTS: genetic enrichment

Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 200

Baseline MMSE: 18 – 22 (10 – 30)

% with 1 APOE4 allele: 45 (0 – 100)

% with 2 APOE4 alleles: 11 (0 – 55)

% on stable background medication: 75 (50 – 100)

Trial Design: Parallel

Include Patient dropout rate? (•) Yes ( ) No

Include Bayesian uncertainty? (•) Yes ( ) No

Duration: 52

Assessment: 4

% of patients in Treatment Arm: 50 (1 – 100)

Drug effect (% reduction on slope): 30 (0 – 100)

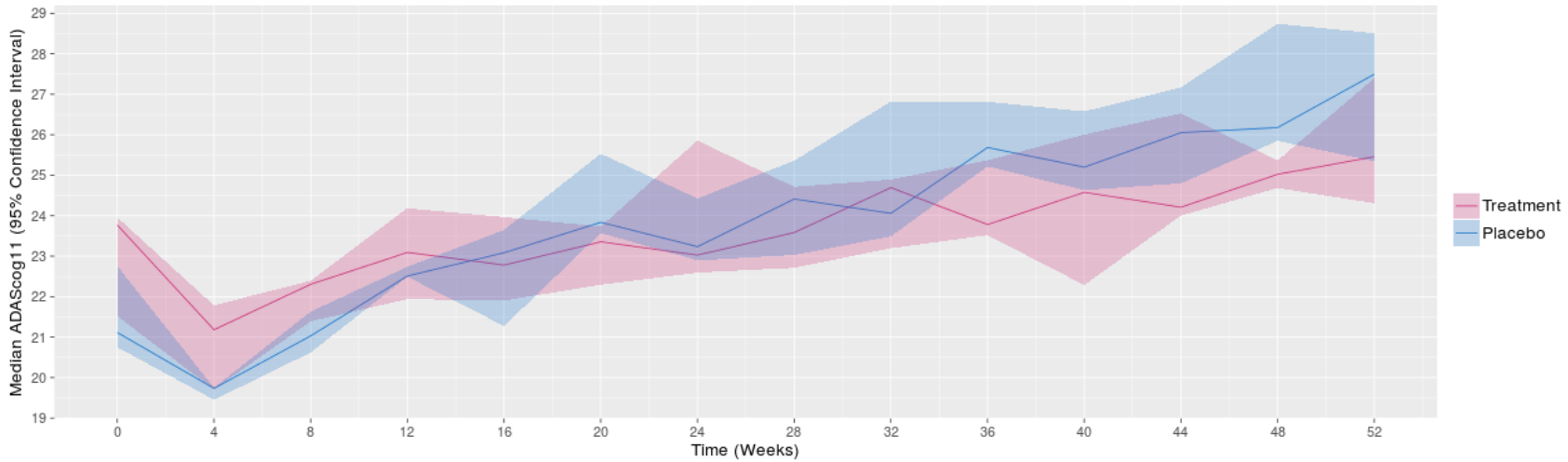
# of simulations: 3

Seed: 1

Alpha (slope difference): 95 (80 – 100)

Confidence Interval (%): 95 (80 – 100)

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	4
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Sample size	200
Age, (mean,sd)	(74.27,0.59)
Percentage of Male (mean,sd)	(0.42,0.02)
Number of APOE e4 alleles (%)	0 (44), 1 (45), 2 (11)
Baseline MMSE, median (range)	(18,22)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(49.11,0.59)
Trial Power (%)	33
Monte Carlo Error (%)	27
Confidence Interval of Monte Carlo Error	(-20,86)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

AD CTS: baseline severity!

Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 200

Baseline MMSE: 19 – 23 (10–30)

% with 1 APOE4 allele: 45 (0–100)

% with 2 APOE4 alleles: 11 (0–55)

% on stable background medication: 75 (50–100)

Trial Design: Parallel

Include Patient dropout rate? (•) Yes ( ) No

Include Bayesian uncertainty? (•) Yes ( ) No

Duration: 52

Assessment: 4

% of patients in Treatment Arm: 50 (1–100)

Drug effect (% reduction on slope): 30 (0–100)

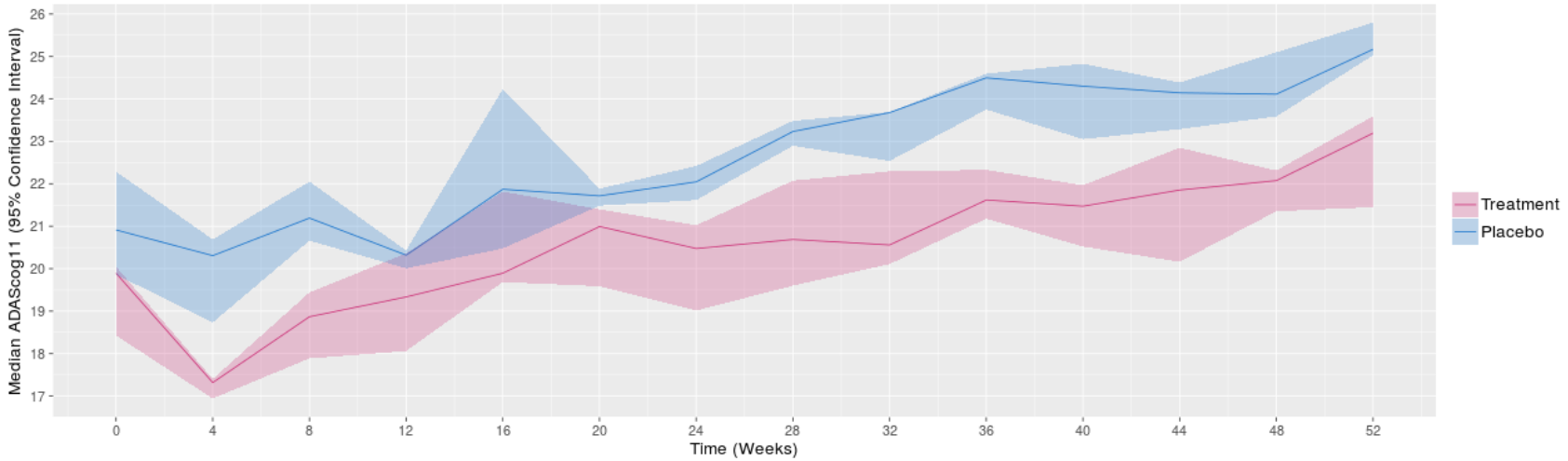
# of simulations: 3

Seed: 1

Alpha (slope difference): 95 (80–100)

Confidence Interval (%): 95 (80–100)

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	4
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Sample size	200
Age, (mean,sd)	(74.34,0.67)
Percentage of Male (mean,sd)	(0.39,0.02)
Number of APOE e4 alleles (%)	0 (44), 1 (45), 2 (11)
Baseline MMSE, median (range)	(19,23)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(49.19,0.17)
Trial Power (%)	0
Monte Carlo Error (%)	0
Confidence Interval of Monte Carlo Error	(0,0)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

MCI/HV CTS: n=400

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Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

Simulate clinical trials on patients with amnestic mild cognitive impairment

Number of Subjects per Arm: 400

Trial Duration (Months): 3 — 24 — 48

Assessment Interval (Months): 1 — 6 — 24

Proportion of Females (%): 35 — 50 — 60

Range of MMSE Scores at Baseline: 24 — 30

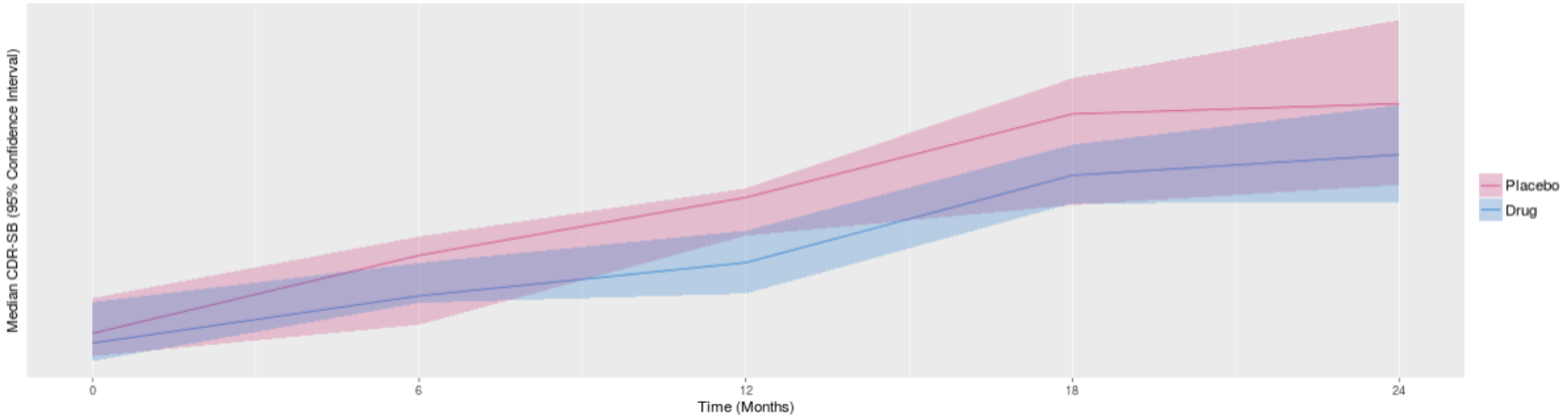
Proportion of APOE-e4 Noncarriers (%): 0 — 50 — 70

Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (LEAP, cm3): 3 — 8.5

Effect of Drug on Rate of Disease Progression (% Reduction): 0 — 30 — 100

Number of Simulations: 4

Simulate Trials



Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	800
Study Duration (Months)	24
Assessment Interval (Months)	6
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Proportion of Female (%)	50
Range of MMSE Scores at Baseline	[24, 30]
Proportion of APOE-e4 Noncarrier (%)	50
Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3)	[3, 8.5]
Median Age at Baseline (95% Confidence Interval) (Years)	73 (72, 73)
Median MMSE Score at Baseline (95% Confidence Interval) (Points)	28 (28, 28)
Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3)	5.3 (5.3, 5.3)
Number of Simulations	4
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	25
Statistical Power (%, 95% Confidence Interval)	50 (6.8, 93.2)

By Daniela Conrado (Model and App Developer) and Jackson Burton (App Developer) on behalf of the Critical Path for Alzheimer's Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

MCI/HV CTS: baseline severity

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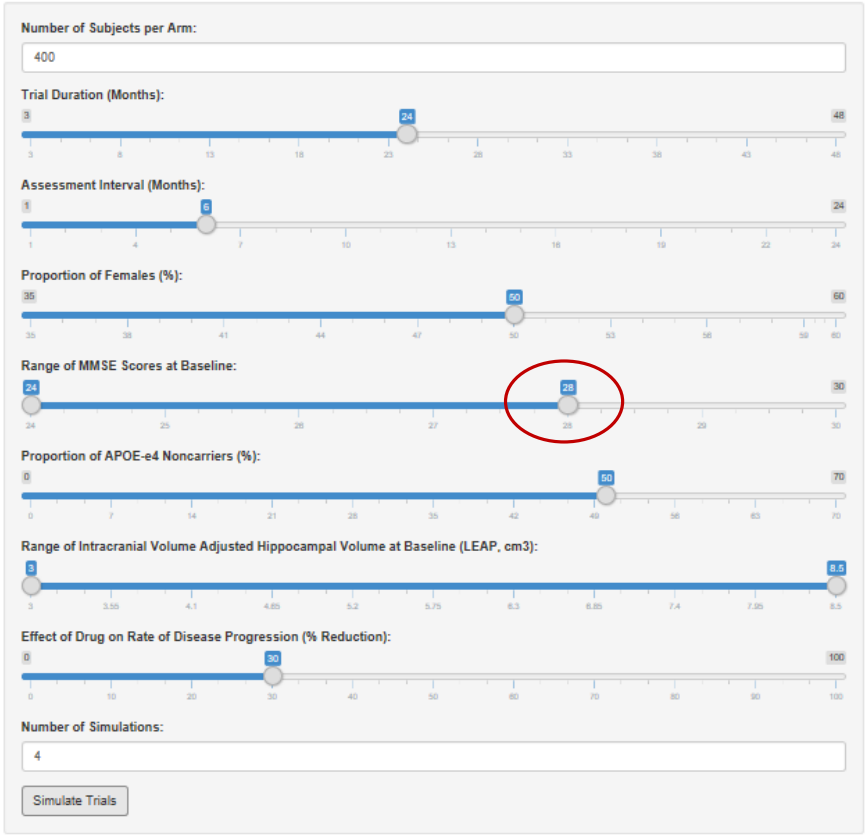

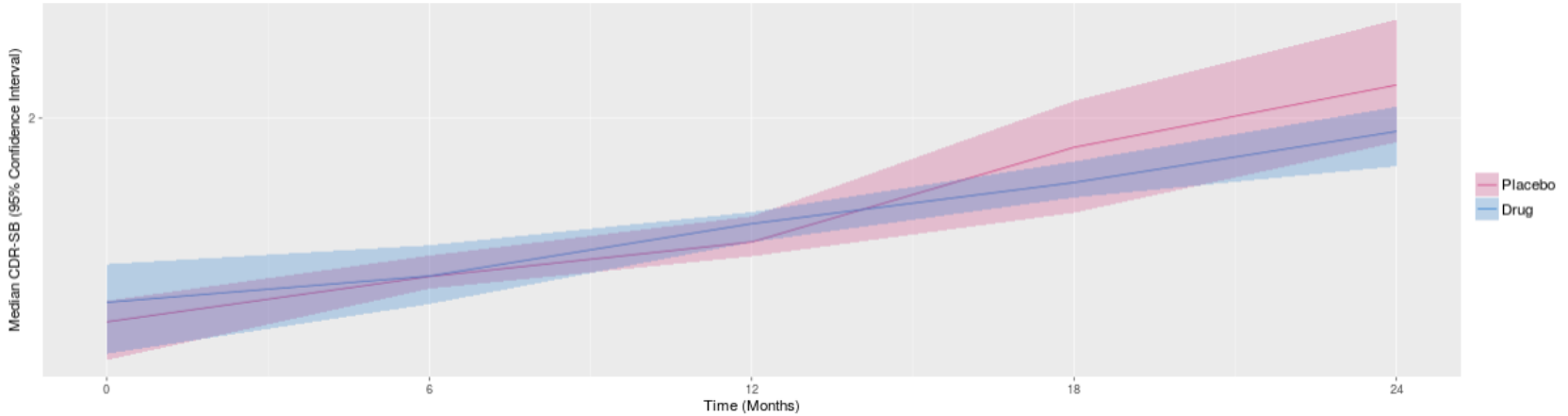

Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	800
Study Duration (Months)	24
Assessment Interval (Months)	6
Effect of Drug on Rate of Disease Progression (% Reduction)	30
Proportion of Female (%)	50
Range of MMSE Scores at Baseline	[24, 28]
Proportion of APOE-e4 Noncarrier (%)	50
Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3)	[3, 8.5]
Median Age at Baseline (95% Confidence Interval) (Years)	75 (75, 75)
Median MMSE Score at Baseline (95% Confidence Interval) (Points)	27 (27, 27)
Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3)	5.1 (5, 5.1)
Number of Simulations	4
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	21.7
Statistical Power (%, 95% Confidence Interval)	75 (19.4, 99.4)

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MCI/HV CTS: biomarker enrichment!

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Number of Subjects per Arm: 400

Trial Duration (Months): 3 — 24 — 48

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Proportion of Females (%): 35 — 50 — 60

Range of MMSE Scores at Baseline: 24 — 28 — 30

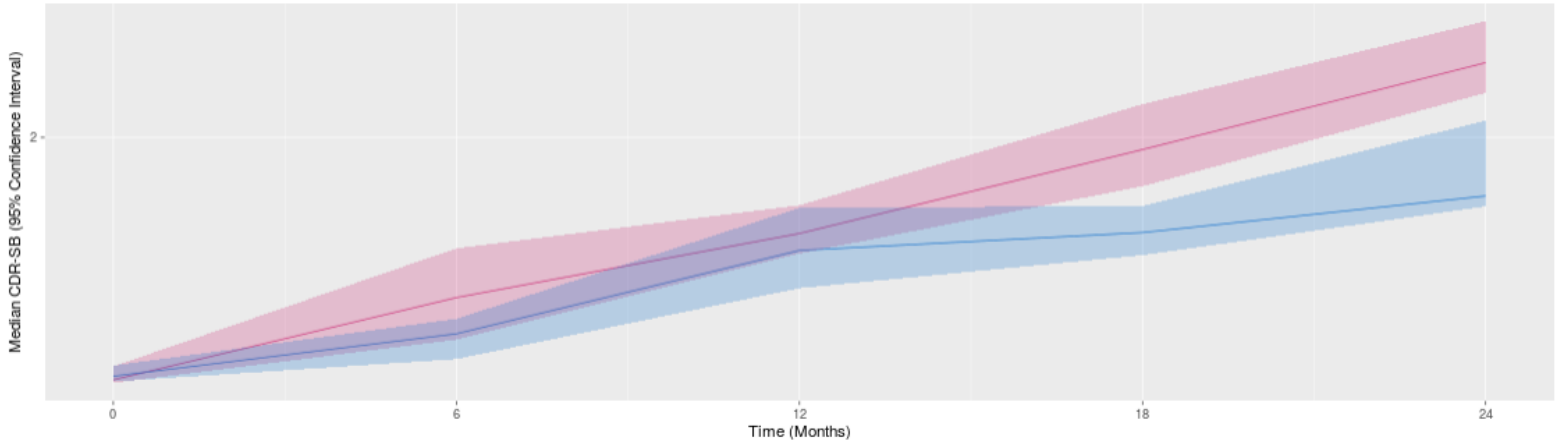
Proportion of APOE-e4 Noncarriers (%): 0 — 50 — 70

Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (LEAP, cm3): 3 — 3.7 — 6.25 — 8.5

Effect of Drug on Rate of Disease Progression (% Reduction): 0 — 30 — 100

Number of Simulations: 4

Simulate Trials



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Proportion of Female (%)	50
Range of MMSE Scores at Baseline	[24, 28]
Proportion of APOE-e4 Noncarrier (%)	50
Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3)	[3.7, 6.25]
Median Age at Baseline (95% Confidence Interval) (Years)	75 (75, 75)
Median MMSE Score at Baseline (95% Confidence Interval) (Points)	27 (27, 27)
Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3)	5 (5, 5)
Number of Simulations	4
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	0
Statistical Power (%, 95% Confidence Interval)	100 (39.8, 100)

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SO…

- There is a pressing need for a better-informed basis on which to design clinical trials in neuroscience
- Science is directing us to conduct trials in even earlier stages of progressive neurological disease – the information upon which to do so is limited

VISION IN ALZHEIMER'S DISEASE AS A TEMPLATE FOR PROGRESSIVE NEUROLOGICAL DISEASES

- To provide a disease progression model across the entire continuum of Alzheimer's disease (AD) – from the earliest stages to severe AD – providing an invaluable tool that will aid in optimizing trial design & execution, reduction of cost & time, and reduced patient burden

Thank you!

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