Model-based Drug Development in Neurodegenerative Diseases: Regulatory Perspectives

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Disclaimer

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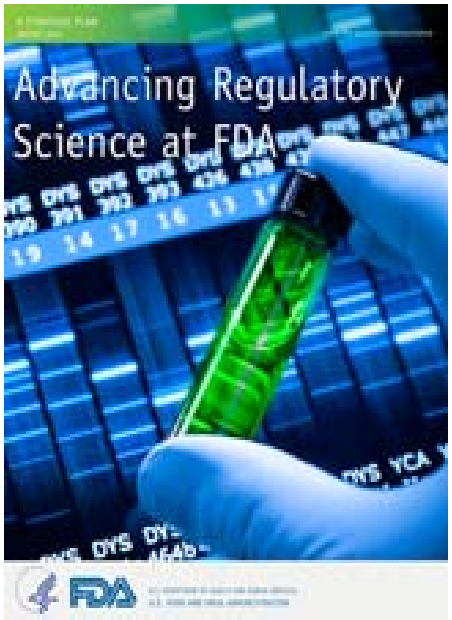
Outline

1. Role of Model Informed Drug Development at the FDA
2. Quantifying Disease Progression
3. Drug Development Tool in Alzheimers' Disease

Advancing Regulatory Science at FDA

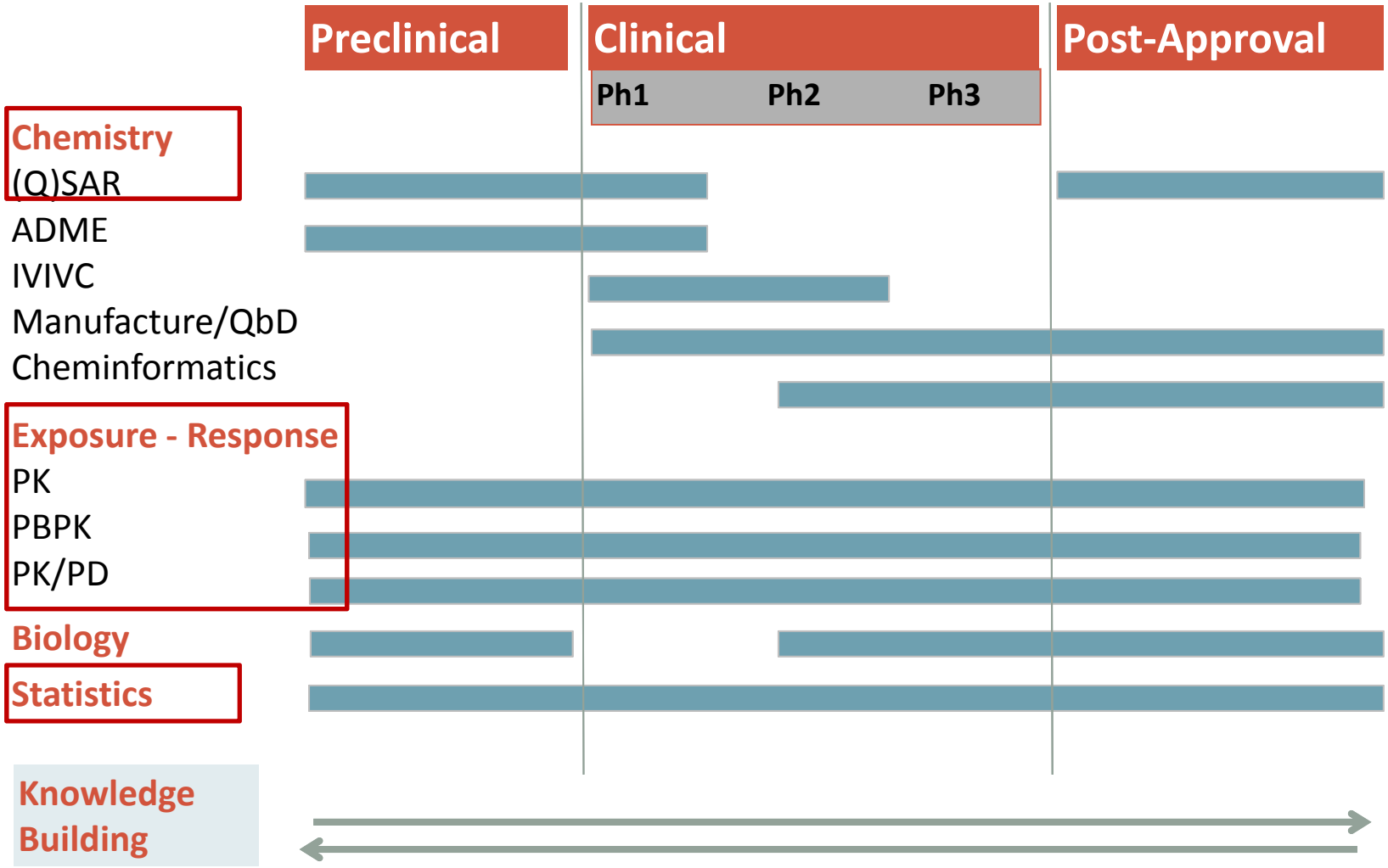
FDA has identified an important role for modeling and simulation (M&S) in its strategic priorities



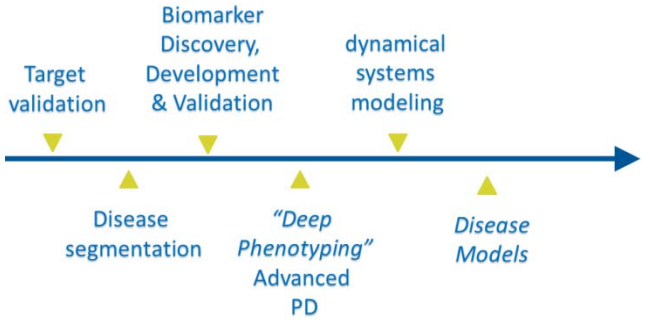
- (Q)SAR models to predict human risk
- Computer models of cells, organs, and systems to better predict product safety and efficacy
- Virtual physiologic patients for testing medical products
- Clinical trial simulations that reveal interactions between therapeutic effects, patient characteristics, and disease variables
- Knowledge building tools
- Methods to verify, store, share

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf

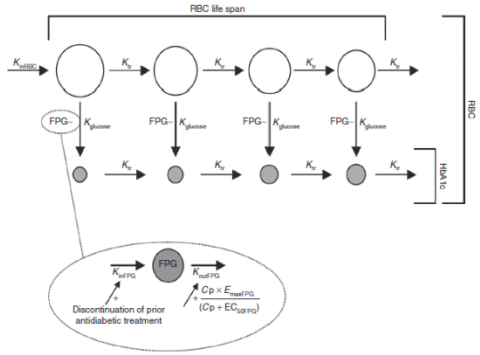
Model Based Development and CDER



New Drug Development: Steps for Changing the Paradigm



Translational research/mechanistic biomarker strategies related to target engagement, MOA and clinical endpoint



Pharmacometric/model-based approaches for mechanistic interpretation of trial results (dose-PK-Response) and clinical trial simulation

Early meetings (e.g. EOP2A) for input on decisions regarding dose selection (E/R) and clinical trial design (POC, effect size, N)

Challenges in Clinical Development: Neurodegenerative Diseases

- Different hypothesized expected effects
- Long duration trial
- Large sample size
- No short-term benefit expected
- Cumulative informative drop-outs
- Convincing biomarker evidence of disease modification

FDA Guidance: Clinical Measures for AD Trials (Feb, 2013)

- Primary endpoints that combine assessments of cognition and function
  - Clinical Dementia Rating Sum of Boxes (CDR-SB) score

- Isolated cognitive measures
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)
  - Mental State Examination (MMSE) classifies the severity of cognitive impairment

FDA Guidance: Design of AD Trials (Feb, 2013)

- Parallel design
  - comparison of the rate of change in key clinical efficacy parameters (based on slopes) between treatment and control groups

- Randomized-start design
  - more convincing means of demonstrating a disease modifying effect

Understanding Disease Progression

= **Disease Progress + Drug Action[1]**

$$E = E0 + \frac{E\max \cdot Conc}{EC50 + Conc}$$

- A disease progression model is a quantitative model that accounts for the time course of disease status,

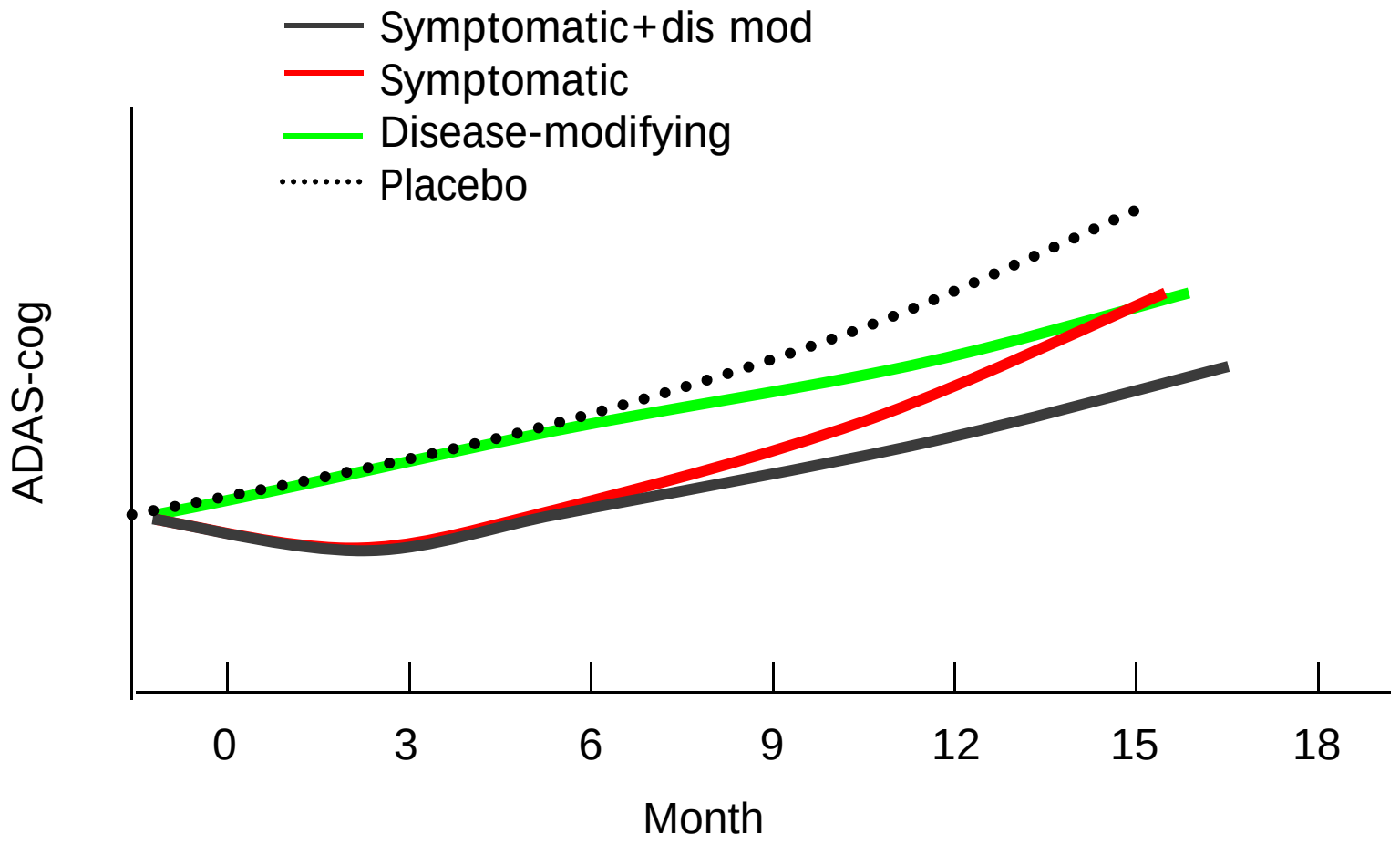
– "clinical outcome" • Survival - Dead or alive (or had a stroke or not, etc.)

- Symptoms - measure of how a patient feels or functions – "biomarkers"

- Signs - physiological or biological measurements of disease activity

- [1] Holford NHG et al, Disease progress models. Principles of Clinical Pharmacology. 2nd ed. San Diego: Academic Press; 2007. p. 313-21.

Drug Effects



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In its "Critical Path Opportunities Report and List", the FDA included a call for the creation of natural history databases to support model-based drug development. Major pharmaceutical companies also contribute to share their placebo/control data from clinical trials.

A Drug Development Tool (DDT) for Simulating Cognitive Trials in Mild to Moderate Alzheimer's Disease (AD)

The submitted drug development tool was found to be scientifically supported and suitable for the purpose of aiding in the design of future clinical trials in patients with mild to moderate AD. This model can be used to explore the effect of important design features such as trial duration, patient evaluation frequency, endpoint selection, and sample size. (June 2013)

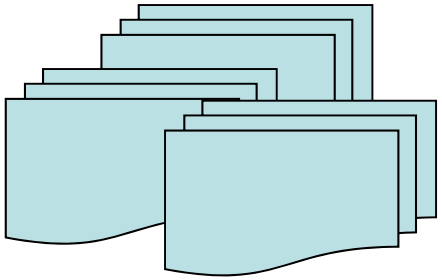
Purpose of DDT

- Understanding AD natural history data, literature-meta-data and pooled data from controls in industry clinical trials.

- Providing a quantitative rationale for selection of a specific trial design.

- Defining common data element standards (Clinical Data Interchange Standards Consortium [CDISC]) for neurodegenerative diseases.

Summary of DDT



Prior information
(data from 3 sources)

CAMD

9 trials (n=3179)

ADNI

3 populations (n=817)

Literature

Summary level data (52 Trials)

ADAS-Cog Model

Drop-out Model

DDT

10,000 Trial Simulations

Power Calculation

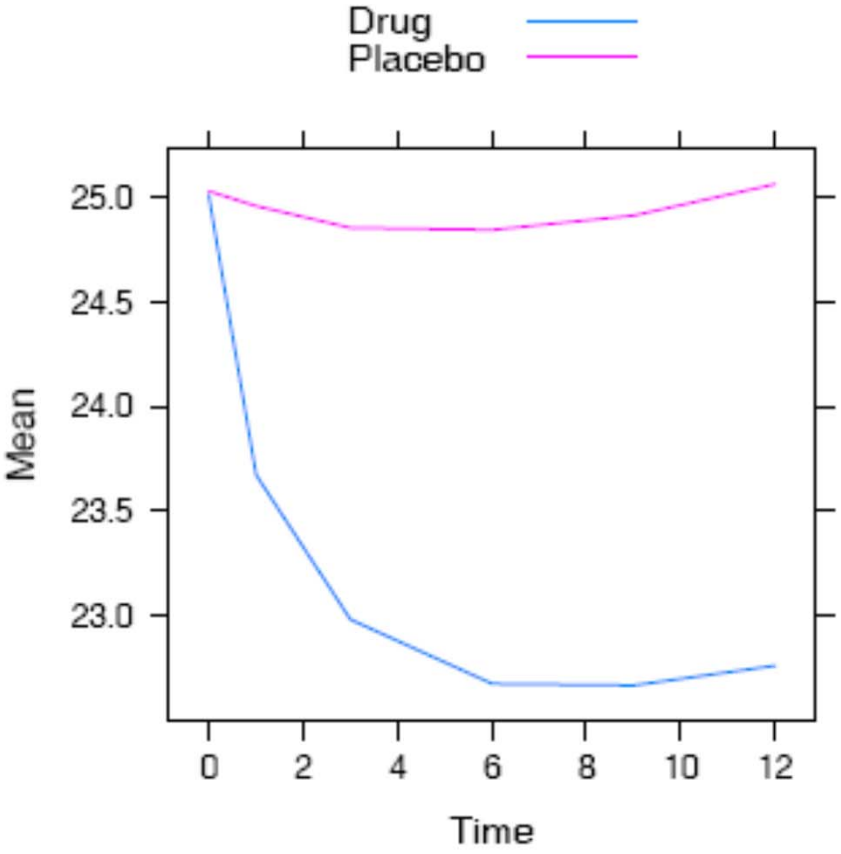
Trial Design (I)

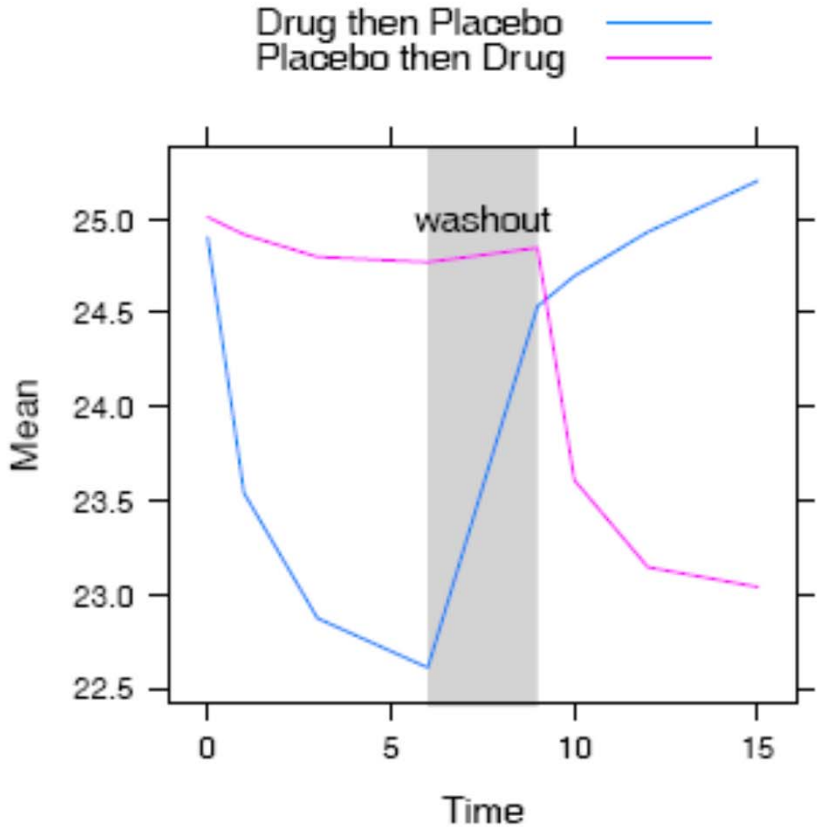
- Symptomatic drug effect scenario: drug properties assumed qualitatively similar to Cholinesterase Inhibitors

  - Parallel design: 75 patients per arm, 12w, assessments at weeks 0, 1, 3, 6, 9, and 12.
  - Cross-over design: 30 patients per arm, with two 6 w treatment durations and a 3w washout period in between, assessments within treatment period at weeks 0, 1, 3, and 6.

- Purpose: Proof of concept study.

Cross-over Design Reduces Sample Size While Maintains Power



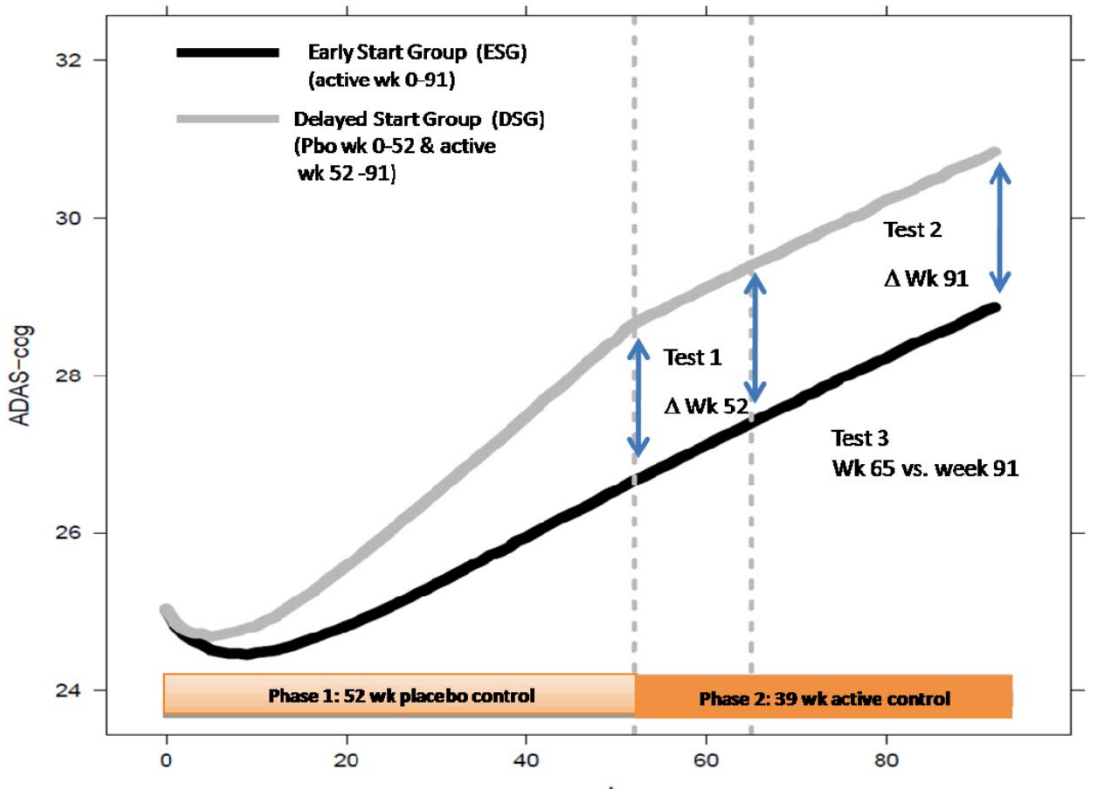


Design	Power
6 week cross-over, n=30/arm	0.85
12 week parallel, n=75/arm	0.77

Trial Design (II)

- Disease modifying drug effect scenarios: disease progression rate 5%, 10%, 20%, 30%, 40%, and 50%.
  - Parallel design: 600 patients per arm, 78 week treatment duration and assessments at weeks 0, 26, 52, and 78.
  - Randomized-start design: assessments at weeks 0, 26, 52, 65, 78, and 91.

Hypothesis tested:
1) Comparing difference from baseline to 52W.
2). Comparing difference in change from baseline at 91W.
3). Comparing the change from 65W to 91W.



Summary

- ADAS-cog is the primary endpoint used for cognition in all previous and ongoing studies. Data selected span the entire range of the ADAS-cog and from a broad range of geographical locations.

- Model provides reasonable description of the data.

- The proposed tool can be used in drug development to assess and compare different trial designs.

Opportunities for Regulators, Industry and Academia Drug Disease Trial Models

Disease–drug–trial models allow learning and integration from prior experience and summarize the knowledge with an ultimate goal to apply models to future development and regulatory decisions, and ultimately share them with the public.

- FDA encourages the use of such approaches and sees its role as identifying the key questions from a regulatory perspective and providing a framework for the utility of the model.
- DDT "Qualification" when there is a precise and clear "Context of Use"

Additional considerations are:

- Areas of unmet medical need; heterogeneity in trial design resulting in 'failed" and uninformative clinical trials; standardizing trial design can potentially increase the burden on effectiveness
- Methodology has heterogeneity within the industry/scientific community with an opportunity to standardize methods, review and reporting
- Align a perspective within a regulatory agency that may result in a change in policy and/or a guidance

Acknowledgements

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