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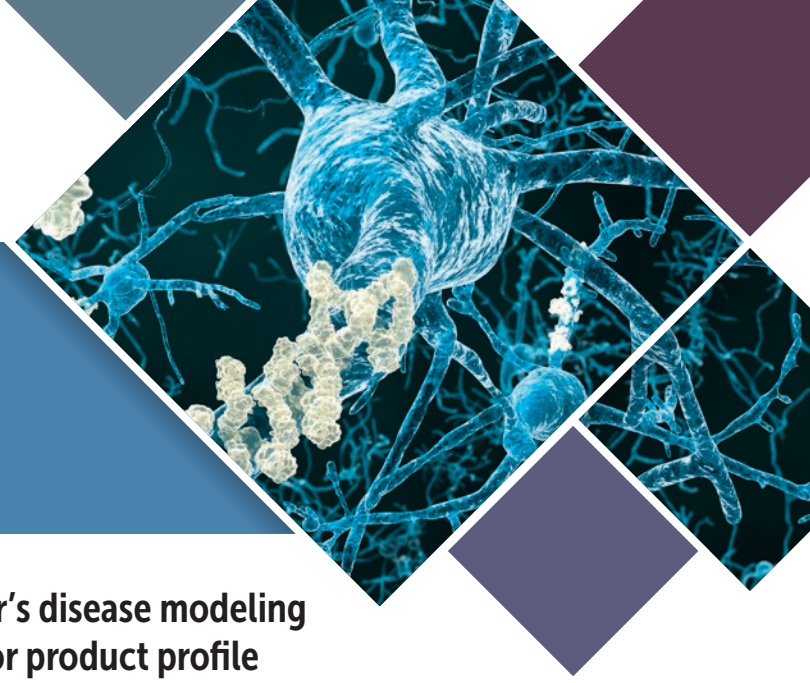

Modeling and Simulation Supports Competitive Dose

Assessment and go/no go decision in Alzheimer's disease modeling strategy provided sponsor with rational basis for product profile evaluation to avoid placing non-competitive dose into Phase III, saving $85 million and redirecting resources towards other programs

Background

A global pharmaceutical company was seeking to advance its drug candidate, indicated for symptomatic treatment for Alzheimer's disease (AD), into pivotal Phase III trials. Data from Phase I and II studies were available on the drug candidate, including Phase IIa and IIb safety and efficacy studies in AD patients.

Challenge

As the sponsor prepared its pivotal trial strategy, it became critical to provide a rational basis for Phase III dose selection and to establish a comprehensive picture of the drug candidate's efficacy profile versus Aricept® (donepezil), the "gold standard" treatment for AD.

Solution

Certara took an integrated approach for its model-based assessment of the sponsor's compound. First, Certara created predictive models of drug response based on the sponsor's Phase I/II data in order to describe the important efficacy (eg, ADAS-cog), safety and tolerability endpoints for the new chemical entity. Certara then built and tested additional models of Aricept dose-response from publicly available Aricept data (14 trials, 3000+ patients) and information from the scientific literature. These data enabled refined modeling of the timing and components of ADAS-cog response, and the resulting pooled models offered a more precise basis for distinguishing between disease progression (time course), placebo effect, treatment effect and the effects of other explanatory variables such as patient characteristics.

Challenge

It was critical to provide a rational basis for Phase III dose selection and to establish a comprehensive picture of the drug candidate's efficacy profile.

Solution

Certara created predictive models of drug response.

Benefit

In addition to the direct cost savings of a potential failed Phase III program, the sponsor was able to redirect valuable resources to other clinical programs in their portfolio.

Finally, Certara constructed a Clinical Utility Index (CUI)® that provided a single metric for multiple dimensions of benefit and risk for AD treatments and captured expert opinion on the therapeutic importance of the NCE's product characteristics.

Combined with drug-disease models, the CUI allowed an estimate of net patient benefit of the NCE relative to Aricept, along with the uncertainty in this comparison, and offered a basis for performing 'what-if' analysis on the benefit of candidate Phase III doses. Simulated dose-response and CUI results, along with a sensitivity analysis of risk-benefit attributes, were viewed using Certara's Drug Model Explorer (DMX) software to enable team communication and decision-making.

Benefit

The model-based meta-analysis and CUI predictions offered compelling evidence to demonstrate an extremely low probability of any dose of the NCE beating Aricept. Additionally, marginal increases in the drug candidate's efficacy were more than offset by increasing incidence of adverse events. Based on the weight of the model-based approach, the sponsor was unable to justify advancing their compound into pivotal Phase III trials.

Impact

The sponsor discontinued development, avoiding further direct investment of $85 million and two years required to conduct a pivotal Phase III trial.[1] In addition to the direct cost savings of a failed Phase III program, the sponsor was able to redirect valuable resources to other clinical programs in their portfolio. The modeling and simulation strategy helped the sponsor establish a comprehensive, quantitative picture of the drug's efficacy profile and competitive prospects to justify dose selection and support a critical go/no go decision.

References

1. Mean out-of-pocket clinical period costs for Phase III investigational compounds. DiMasi, Hansen, Grabowski. The Price of Innovation: New Estimates of Drug Development Costs. Estimates of Phase III trial length for selected therapeutic categories from Pharmaprojects, January 2008. Published in PAREXEL's R&D Statistical Sourcebook, 2008/2009.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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