



Model-based Meta-analysis Supports Pivotal Trial Strategy and Accelerates Clinical Development

Modeling of Phase II and literature data enabled the sponsor to provide the FDA with a convincing efficacy profile and avoided a costly Phase III trial, saving \$60 million and 24 months. The FDA approved the drug in the target indication

Background

A global pharmaceutical company was seeking to optimize the design of pivotal Phase III studies for its central nervous system drug candidate. Data from more than 10 Phase II studies was available on the drug candidate, along with data from an initial Phase III confirmatory trial.

Challenge

As the sponsor prepared for meetings with FDA to finalize the requirements of its confirmatory studies, it became critical to establish a comprehensive picture of the drug candidate's efficacy profile, given the varied nature of primary and secondary endpoints for the indication and the many different designs of existing clinical studies that would support a submission.

Solution

Certara performed a meta-analysis that combined the sponsor's in-house Phase II data with relevant summary-level data published in the scientific literature. The sponsor's existing Phase III trial results were also incorporated in the analysis. Based on these pooled data, models of key response endpoints were built and tested. The models accounted for the differences in response due to different clinical measures, dose, and patient characteristics.

The development team then used the models to perform simulations of expected treatment response, in order to quantify variations and uncertainty of drug effects with greater precision. Finally, the models were used to simulate various Phase III pivotal trial designs and to calculate probability of Phase III study success, estimated as a function of key study attributes such as dose, study duration, number of study arms and number of patients per arm.

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Benefit

Avoided further direct investment of \$60-80 million and 24-30 months required to perform a new Phase III Trial.

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The sponsor presented the modeling and simulation results to the FDA, as part of its meeting with the agency to review the Phase III protocol. The FDA's review found that the model-based meta-analysis, consisting of the pooled Phase II/III and literature data, offered a sufficiently compelling case to support registration without running an additional pivotal Phase III trial. The FDA encouraged the sponsor to file the drug candidate for approval based on the existing clinical database and supporting model-based analysis.

Impact

The sponsor commenced filing its new drug application submission, avoiding further direct investment of \$60-80 million and 24-30 months required to perform a new pivotal Phase III trial.^{1,2} The FDA recently approved the drug candidate in the target indication. In addition to the direct cost savings of an avoided Phase III study, the time-to-market savings from an earlier approval offered the promise of providing a beneficial treatment to patients much sooner, which could be worth tens of millions of dollars to the commercial value of the drug over its patent life. The modeling and simulation strategy helped the sponsor establish a comprehensive picture of the drug's efficacy profile to accelerate clinical development.

References

1. Mean out-of-pocket Phase III costs for investigational CNS drugs. DiMasi et al. *Drug Information Journal* 2004; 38(3):211-223. DiMasi, Hansen, Grabowski. The Price of Innovation: New Estimates of Drug Development Costs. Published in PAREXEL's R&D Statistical Sourcebook, 2008/2009.
2. Estimates of Phase III trial length from Pharmaprojects December 2007, DiMasi et al, *Cutting Edge Information* 2004. 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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