CERTARA

Safe Dosing for Organ Impairment

A model-enhanced view into exposure levels supported high-confidence dose selection and opened the way for study in patients with organ impairment

Background

A small virtual pharmaceutical company achieved clinical proof-of-concept for a new formulation of an approved drug, which it hoped would overcome a contraindication to use the drug in a key patient population.

In early-phase trials, the drug candidate showed promise to fill an unmet need by making the oral treatment safe for patients with organ impairment, a contraindication for the approved formulation. Due to its limited absorption into the bloodstream, the new drug was expected to reach therapeutic concentrations at its target in the gastrointestinal tract while avoiding high systemic exposures in patients with reduced drug clearance.

Challenge

In order to move ahead with large-scale trials, the drug sponsor sought a stronger understanding of the dose-exposure relationship. In particular, they needed compelling evidence that they would achieve safe exposures in patients with organ impairment to convince regulators to remove a partial clinical hold in that population.

Solution

An integrated team of modeling and simulation scientists from Certara Consulting Services took on the challenge. At the initial meeting with client scientists, the consulting team gained the background information they needed. The consultants prepared a strategic "road map" forward from Phase II through new drug application submission, and met regularly with the sponsor as work progressed.

Through a combination of non-compartmental analysis (NCA) and population pharmacokinetic (PopPK) modeling, the team built a model of the new drug formulation's complex dose-exposure relationship. By combining data from early trials of the new and marketed formulations in subjects

Challenge

A small pharmaceutical company sought to understand the dose-exposure relationship for a new drug formulation in order to proceed with Phase III trials in patients with organ impairment.

Solution

A team of scientists from Certara Consulting Services used a combination of NCA and PopPK modeling and simulation to predict the effects of organ impairment on exposure.

Benefit

Simulations demonstrated that target doses of the new formulation in organ-impaired patients produced plasma concentrations similar to safe exposures observed in healthy subjects taking the approved formulations.

with normal organ function and a small number of organ-impaired patients, the scientists were able to model the impact of organ impairment on pharmacokinetics of the new drug. The team applied the models to perform Monte Carlo simulations of plasma concentrations at a variety of dose levels and frequencies for the different formulations, predicting the effects of organ impairment on exposure.

Benefit

The comprehensive approach combining NCA, PopPK modeling and simulation enabled the sponsor to predict single- and multiple-dosing exposures across a variety of clinical scenarios. Simulations demonstrated that target doses of the new formulation in organ-impaired patients produced plasma concentrations similar to safe exposures observed in healthy subjects taking the approved formulation.

Impact

The model-based analysis provided scientific support for a key end-of-phase-II meeting with the Food and Drug Administration. The predicted exposures convincingly illustrated safe dosing in patients with organ impairment.

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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