CERTARA

Optimizing the Regulatory Strategy for a New Anti-cancer Drug

Certara scientists performed gap analysis to help a small biotech company create a pressure-tested clinical pharmacology package for their first NDA submission for a novel oncology drug.

Background

A small US biotech company was developing a novel targeted anti-cancer drug to treat patients with advanced hematologic or solid tumors that possess a specific genetic mutation. The sponsor sought to file their first new drug application (NDA) for accelerated approval from the FDA. At the time that they engaged Certara, they had interim results from the efficacy arm of their Phase 1 study and had completed discussions with the FDA regarding content of an initial NDA.

Challenge

The sponsor needed to integrate results across studies and analyses to form sound justifications in their NDA to support their starting dose, planned administration with food, and dose modifications for drug interactions. They sought to identify potential gaps in their clinical pharmacology development program and quantitative analysis approach to determine potential risks for the NDA review cycle. In addition, they wanted to optimize their interactions with the Agency for the submission and NDA review while minimizing potential post-marketing requirements.

Solution

A team of Certara scientists performed a clinical pharmacology NDA gap analysis, which then informed developing a strategic roadmap for their approach to the NDA Summary of Clinical Pharmacology Module 2.7.2. Certara Strategic Consulting and Simcyp experts supported this roadmap with quantitative pharmacology analyses using state-of-the-art modeling and simulation tools.

The gap analysis began with evaluating all available data and information on the compound, including Investigator's Brochures, clinical study reports, any regulatory meeting minutes, and all available pre-clinical and clinical data, including modeling and simulation analysis plans and reports.

Challenge

The sponsor needed to develop integrated clinical pharmacology and regulatory arguments to support their NDA filing for a novel targeted anti-cancer drug.

Solution

A team of Certara scientists performed a clinical pharmacology NDA gap analysis, which then informed strategic positions for the NDA submission.

Benefit

The NDA gap analysis provided the sponsor with a risk assessment for the gaps in the data package, which allowed them to prepare for potential NDA review cycle information requests and post-marketing requirements/commitments.

A gap analysis report was then written which outlined the expectations and arguments for the Module 2.7.2 and specifically outlined studies and analyses that needed to be combined to support justifications for dosing and labeling. Some of the quantitative methods that Certara used to support this sponsor included Phoenix WinNonlin non-compartmental analysis (NCA), Phoenix NLME population pharmacokinetic modeling (popPK), and physiologically-based pharmacokinetic (PBPK) modeling with the Simcyp Simulator. As part of the gap analysis, these plans were pressure tested for regulatory acceptance and risk.
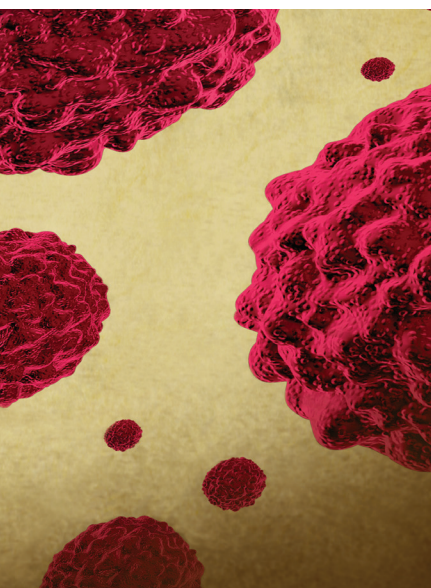
Benefit

The NDA gap analysis and strategy provided this sponsor with several benefits. First, the gap analysis summary report provided the sponsor with a review of potential gaps with their NDA submission. It de-risked the need for the sponsor to conduct a bioequivalence (BE) study prior to NDA submission, and instead, a biowaiver plus robust comparative dissolution was recommended and was successful. In addition, modeling and simulation approaches were used to expedite timelines, reduce cost, and minimize clinical studies wherever possible. For example, Simcyp PBPK modeling was used to eliminate the need for clinical drug-drug interaction (DDI) studies for moderate and weak CYP3A4 inhibitors, strong CYP3A4 inducers, and sensitive substrates of CYP3A4 and CYP2B6. The PBPK modeling was also used to simulate multiple-dose scenarios based on single-dose drug interaction results. Based on the PBPK results, the gap analysis report recommended how to justify dose modifications for co-administration of these drugs. Additionally, the impact of ethnicity on drug exposure was assessed, and our analysis suggested that dose adjustments were not needed for Japanese subjects.

Next, it recommended strategies for submitting the data package for regulatory approval. The recommendations included both advice on addressing potential NDA review cycle information requests and the likelihood of various post-marketing requirements/commitments (see Table 1).

Table 1: Identified Potential Information Requests and Potential Post-marketing Requirements/Commitments

NDA Review Cycle Information Requests	Risk
Update PopPK model with additional study	Moderate-high
Include Study 2 in ER safety analysis	Moderate-low
Update cQT analysis to remove study effect on slope	Moderate-low
PMR/PMC	**Risk**
Hepatic impairment study	High
Renal impairment study	Moderate-low
Study with a strong CYP3A inducer	High
Study with a sensitive CYP3A4 substrate	High
Study with gut pH-altering agents	Moderate-low
Study evaluating an optimal dose of dose regimen	Low

Lastly, to achieve approval, the clinical pharmacology submission package and NDA Module 2.7.2 must convince reviewers of the safety and efficacy of the drug not only for its intended patient population but also for special populations and drug-interactions that may require dose modifications. Thus, justifications and rationales for various drug development decisions and dose modifications are often required. The gap analysis report also included advice on what scientific evidence to include in these justifications and where to place this information within the eCTD submission format for greatest impact and to facilitate FDA review.
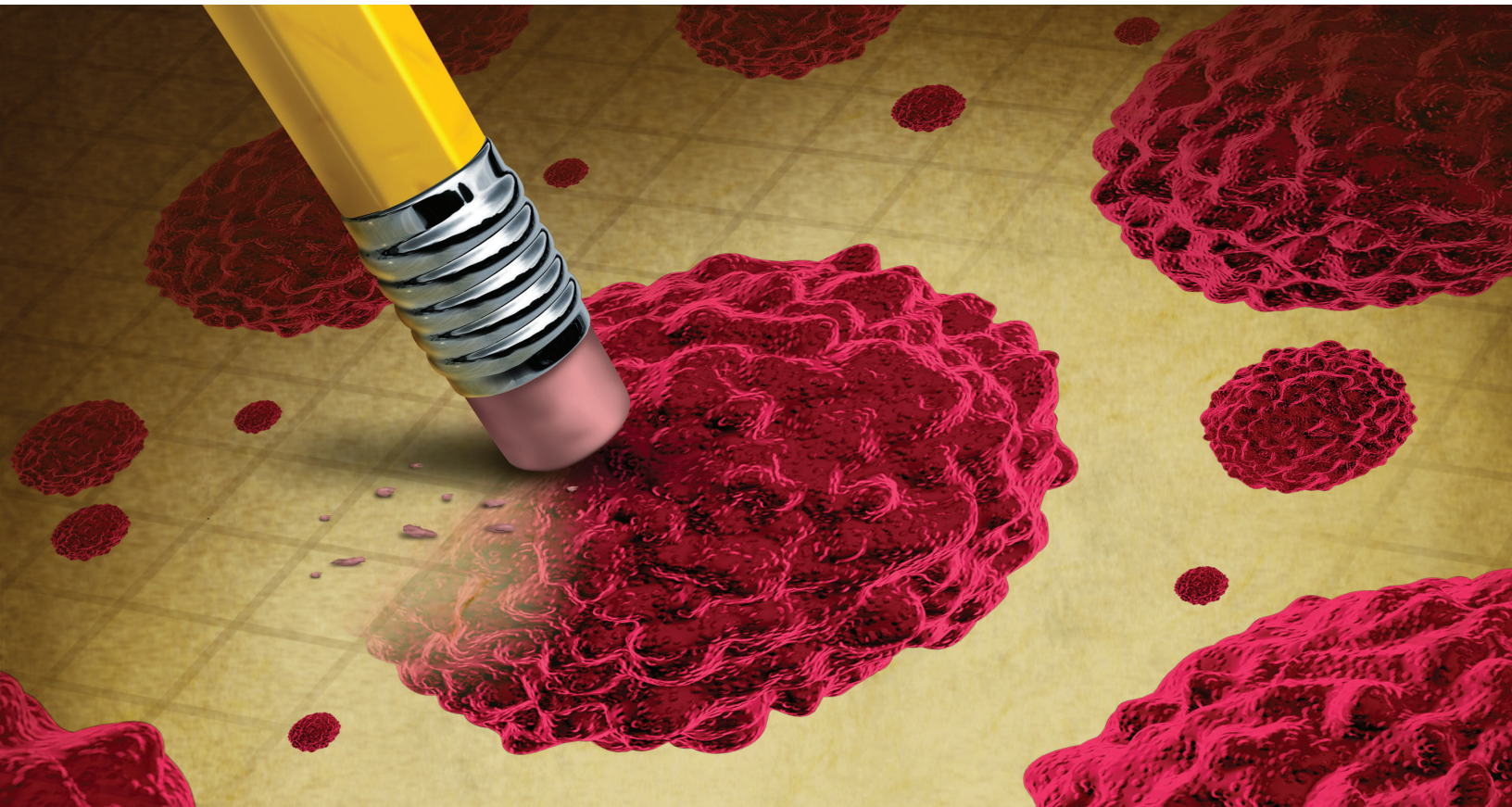
Impact

Undergoing a clinical pharmacology gap analysis supported multiple business goals. The sponsor can file their submission confident that the clinical pharmacology program and modeling and simulation analysis plans will be deemed suitable by FDA reviewers.

They have also gained reassurance that their proposed dosing strategy is well supported by the available safety, efficacy, pharmacodynamic (PD), and exposure-response (ER) analyses.

Moreover, the approved product will have an optimized label in terms of allowing the drug to be taken with food and guidance on co-administration of CYP3A4 inhibitors. In addition, they were able to forward-plan for post-marketing requirements because they've considered potential protocols and timelines for these studies.

The client was optimally positioned for their NDA submission and was able to predict and answer the FDA reviewer's questions. This roadmap prioritized their drug development needs, provided strategic direction, identified potential gaps, assessed risks/benefits, helped position the sponsor for successful interactions with regulators and other partners, and created value. In 2018, the FDA granted approval to this drug product.

Using integrated analyses and strategic reviews, a clinical pharmacology gap analysis can bring value to patients and sponsors by eliminating multiple, dedicated studies, and increasing the likelihood of regulatory and commercial success.

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.

For more information visit www.certara.com or email sales@certara.com.