CERTARA

Understanding Drug-drug Interactions with a Self-inhibiting Compound

Using physiologically-based pharmacokinetic (PBPK) modeling and simulation, researchers predicted multiple-dose exposure levels and optimized the design of a drug-drug interaction study for a compound exhibiting auto-inhibition

Background

A small biotechnology company had begun early clinical development of a candidate therapy with promise in multiple indications. The drug was metabolized and eliminated primarily through the cytochrome P-450 3A4 (CYP3A4) pathway.

Challenge

In vitro studies had indicated the possibility of complex drug-drug interactions (DDI). The candidate exhibited both competitive and time-dependent inhibition of CYP3A4, the key enzyme in its own metabolism. In Phase I trials, non-linear pharmacokinetics observed following multiple oral dosing were attributable to the study drug's ability to inhibit its own metabolism (auto-inhibition), increasing exposure levels over time.

The drug's sponsor needed to quickly and efficiently evaluate the candidate's potential for DDIs mediated via the CYP3A4 pathway, to support the design of a DDI study.

Solution

The sponsor partnered with Certara to gain further understanding of the relative contributions of underlying determinants of the drug's disposition. Certara and the sponsor would use that understanding to optimize the design for a DDI study to evaluate the potential impact of co-administration of the drug with ketoconazole, a recognized potent inhibitor of CYP3A4, on the drug's pharmacokinetics.

Having identified that the study drug inhibited its own metabolism through CYP3A4 antagonism, Certara scientists developed a PBPK model. They used the model in simulations to evaluate

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Solution

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Benefit

The PBPK modeling and simulation results elucidated the mechanisms determining drug exposure and interactions with other CYP3A4 inhibitors.

competing clinical study designs for a ketoconazole DDI investigation. The best design would enable the sponsor to identify the maximum DDI potential, and to better understand the mechanism for this interaction.

PBPK modeling and simulation demonstrated that the greatest magnitude of DDI, as quantified by the increase in study drug exposure, was observed when a single dose—as opposed to repeat doses—of the study drug was given with multiple doses of ketoconazole.

The result at first sight may seem counter-intuitive. A greater degree of enzymatic inhibition might be expected when the study drug, which inhibits its own metabolism, is given repetitively and then together with ketoconazole, which also inhibits the study drug's metabolism. Instead, repeated administration of the study drug decreases availability of CYP3A4, making less of the enzyme available for inhibition by ketoconazole and reducing the magnitude of the DDI.

Benefit

The PBPK modeling and simulation results provided the sponsor with a greater understanding of the mechanisms determining drug exposure and interactions with other CYP3A4 inhibitors.

Impact

The sponsor was able to demonstrate to regulatory authorities a mechanistic understanding of the basis of CYP3A4 mediated DDIs, providing an evidence-based justification for their clinical study designs.

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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