

## Learning from One Indication to the Next

### Application of modeling and simulation to support the regulatory approval of a monoclonal antibody based on small clinical trials and evidence from a previous indication

#### Background

In some cases, information gained during developing a drug for one indication can be leveraged to support approval for a different indication. PNH (paroxysmal nocturnal hemoglobinuria) is a rare, progressive, and life-threatening disease. It is characterized by rampant destruction of red blood cells (hemolysis) and excessive blood clotting.<sup>1</sup> Likewise, aHUS (atypical hemolytic uremic syndrome) is an ultra-rare genetic disease that causes abnormal blood clots to form in small blood vessels throughout the body. The sequelae of aHUS include kidney failure, damage to other organs, and premature death. There were no FDA-approved treatments for this rare disease.

Both aHUS and PNH are caused by chronic, uncontrolled activation of the complement system. During activation of the complement system, the terminal protein C5 is cleaved to C5a and C5b. C5a and C5b have been implicated in causing the terminal complement-mediated events that are characteristic of both aHUS and PNH. Eculizumab is a humanized monoclonal antibody (mAb) that binds C5, thereby inhibiting its cleavage. In 2007, Certara Strategic Consulting developed a pharmacokinetic/pharmacodynamic (PK/PD) model that supported the approval of this mAb for treatment of PNH based on evidence of effectiveness from clinical studies.<sup>2</sup>

#### Challenge

Diagnosed in only a few thousand patients each year, aHUS proved extremely difficult to study in the clinic due to very low trial recruitment. Though very few patients were available for study, some additional data were available from PNH clinical studies. The drug sponsor needed to optimize dosing of eculizumab for both adult and pediatric aHUS patients, making best use of all available data.

#### Solution

The sponsor again turned to Certara Strategic Consulting. As the sponsor's resource for model-based development strategy for PNH, Certara's scientific experts were already familiar with the drug's PK

#### Challenge

The drug sponsor needed to optimize dosing for a ground-breaking drug for an ultra-rare, life-threatening genetic disorder affecting both adult and pediatric patients. Though very few patients were available for study in the target indication, some additional data were available from a previously approved indication for the same compound.

#### Solution

Certara Strategic Consulting scientists performed PK/PD modeling of data from three small trials in the new indication to elucidate the dose-response-effect relationships for two surrogate endpoints. Trial simulations based on the models were used to explore the best dosing for pediatric and adult patients, using body weight to adjust the dosage for younger patients.

#### Benefit

Using the model-based and observed efficacy and safety profiles, the consultants recommended dosing regimens for adult and pediatric patients in the new indication.

and safety profile to date. Their starting point was a population PK model that had been previously constructed in adult patients with PNH.<sup>3</sup> This model was customized and used to develop optimal dosing strategies for adult and pediatric aHUS patients.

Comparing the case of adults with PNH to pediatric aHUS, it became apparent that children may require lower levels of medication. The PK/PD relationship in PNH was leveraged to measure the drug's exposure and inform pediatric dosing for aHUS. Knowledge about eculizumab's mechanism of action for PNH also suggested that optimal binding to the pharmacological target (C5) should translate into a clinical benefit.

Identification of the therapeutic dosing window for a mAb in pediatric patients with a rare disease involved several steps. First, to ensure patient safety, the upper exposure limit needed to be determined. As a safeguard against toxicity, the upper exposure limit was capped at what had been previously observed in adults.

To ensure efficacy, the minimum drug exposure also had to be determined. Using the predicted concentration of the soluble target and the binding characteristics of the mAb to its target, a minimum concentration threshold was set to obtain close to full inhibition of the target. Then, trial simulations using a population PK model were performed to determine which doses would optimize the probability of obtaining the mAb within the window of target engagement in neonates, children, adolescents, and adult patients.

The clinical program for aHUS involved two Phase II studies and a retrospective observational study. A total of 57 patients with aHUS participated in these studies (35 adult, 22 pediatric patients). Two different biomarkers were used to assess the efficacy of treatment. The proximal biomarker, free C5, showed complete suppression upon treatment with the mAb. Likewise, the mAb caused full inhibition of hemolytic activity (the distal biomarker).<sup>3</sup> The primary endpoint indicated that the response to interventions across all age groups was very high.

## Benefit

Using the model-based and observed efficacy and safety profiles, the consultants were able to recommend dosing regimens for adult and pediatric aHUS patients.<sup>3</sup>

## Impact

Patients treated with the mAb experienced several benefits including improvement in platelet counts and other blood parameters and better kidney function, even eliminating the requirement for plasmapheresis in some patients. Soliris® (eculizumab) received FDA approval to treat aHUS adult and pediatric patients.<sup>4</sup>

## References

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## 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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