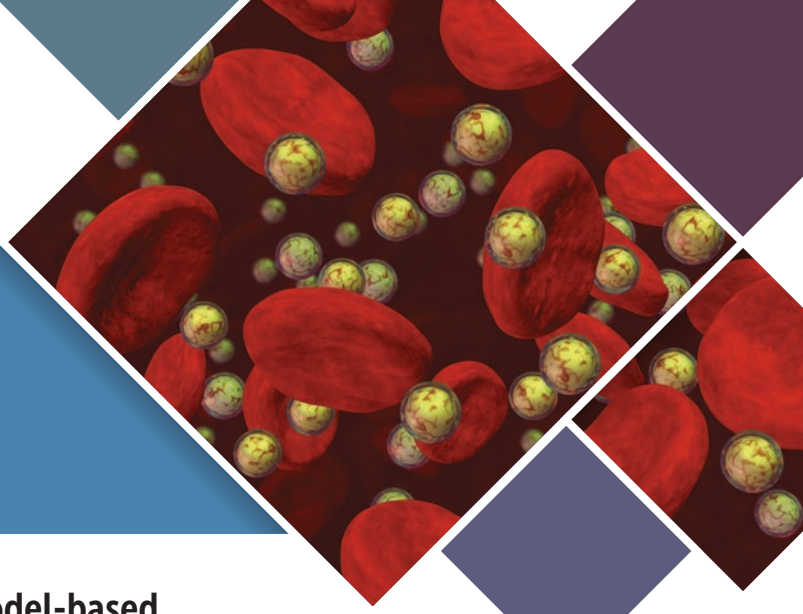
CERTARA



Leveraging Competitor Information to Predict Efficacy of a Novel Drug Formulation

Certara Strategic Consulting scientists used model-based meta-analysis (MBMA) to support developing a fixed-dose combination of ezetimibe and atorvastatin.

Background

Ezetimibe and atorvastatin are both used to treat dyslipidemia—an abnormally high level of lipids in the blood—by lowering levels of low-density-lipoprotein cholesterol (LDL-C). The sponsor wanted to develop a fixed-dose combination (FDC) of two previously approved drugs, ezetimibe and atorvastatin.[1]

Challenge

In bioequivalence (BE) trials conducted across a combined dose range of ezetimibe/atorvastatin, all parameters met traditional BE bounds except atorvastatin C_{max} at two intermediate doses. The FDA uses BE data as the gold standard for regulatory decisions on providing a clinical bridge for drug quality, efficacy, and safety for other similar FDCs. Thus, the agency requested data from clinical equivalence (CE) trials to evaluate the two doses that did not meet atorvastatin BE.

Solution

Model-based meta-analysis (MBMA) analyses were conducted to understand the impact of dosing regimen and formulation on low-density-lipoprotein cholesterol (LDL-C) levels, to predict the impact of changes in exposure for ezetimibe+atorvastatin FDC on efficacy, and inform the design of CE trials. Previously, a dose-response model for statin LDL-C reduction as a monotherapy and in combination with ezetimibe was developed based on publicly-available trial data.[2] This model was updated with published clinical data from over 200 statin trials involving greater than 100,000 patients.

Benefit

The model-based meta-analysis predicted that the observed difference in C_{max} between an ezetimibe+atorvastatin FDC and co-administration of these drugs translated to a clinically insignificant change in lowering of LDL-C (Figure 1). Indeed, the reduction in LDL-C associated

Challenge

The sponsor needed to determine the optimal design for clinical equivalence (CE) trials to evaluate a fixed-dose combination (FDC) of two previously approved drugs, ezetimibe and atorvastatin.

Solution

Certara Strategic Consulting scientists used model-based meta-analysis to understand the impact of dosing regimen and formulation on low-density-lipoprotein cholesterol (LDL-C) levels, to predict the impact of changes in exposure for ezetimibe+atorvastatin FDC on efficacy, and inform the design of CE trials.

Benefit

Insights from the model's predictions from simulations supported reducing the sample size for the CE trials by 17% while still maintaining a 90% probability of success thus saving time and decreasing cost.

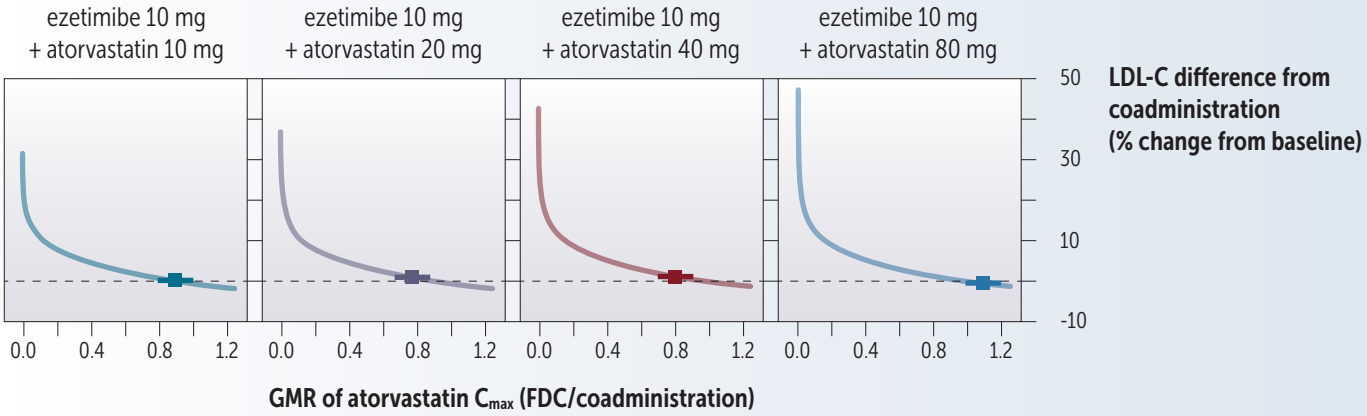
with atorvastatin administration was more highly correlated with total daily atorvastatin dose than with the measurement of peak atorvastatin exposure. This is consistent with the biological processes regulating changes in LDL-C levels which occur over weeks and months, whereas plasma concentrations of atorvastatin peak within an hour of dosing.

The model's predictions from simulations using the BE studies and dose-exposure analysis also allowed more accurate estimation of the treatment difference. These insights were leveraged to design the CE trials. The sample size for the CE trials was able to be reduced by 17% while still maintaining a 90% probability of success resulting in significant time and cost savings. Both doses were found to be clinically equivalent in the CE trials.

Impact

The results of the two CE trials were submitted to the FDA. The FDC attained FDA approval in 2013.[3] In the future, MBMA leveraging relevant competitor information may negate the need for dedicated CE trials after near-miss BE, thus enabling sponsors to accelerate developing new drugs.

Figure 1. The impact of the differences in C_{max} between the FDCs and coadministration of individual atorvastatin and ezetimibe tablets was predicted to result in an insignificant change in efficacy



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