PRECISION for medicine

CASE STUDY

Biostatistical analysis leads the FDA to change an orphan drug ruling

Project synopsis

In rare inherited metabolic disorders, predefining the best endpoint to demonstrate efficacy of a new treatment can be challenging. We worked with one sponsor who was developing such a treatment. When results from the placebo-controlled clinical trial proved unimpressive, the contract research organization (CRO) that conducted the trial, satisfied it had followed the established statistical analysis plan, concluded there was nothing further to be done.

The sponsor then turned to Precision for Medicine to see what could be salvaged from the data. We recognized immediately that the study's established primary endpoint simply was not the best metric by which to judge success. Our task was to secure FDA approval for the drug based on the new proposed efficacy endpoint.

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Challenges

The task was straightforward, though extremely difficult: Get the FDA to consider a different efficacy endpoint for approval by showing that the initial primary endpoint was not appropriate for the subset of the patient population studied.

- The trial's primary endpoint was a percent reduction of a substrate found in the kidney. It had been chosen originally because it was similar to the primary endpoint of a successful trial by another sponsor
- Because the baseline number varies depending on the health of the population being studied, the percentage reduction is higher in more seriously ill patients. The population in the previous trial was quite ill, whereas the population in this trial was moderately ill

- In the subset population for this metabolic disease, the more physiologically relevant measure is the absolute difference in the substrate measurement, not the ratio
- Large, traditional CROs are often absorbed by process and less likely to recognize the need to pivot mid-trial

Solutions

The sponsor counted on our superlative biostatistical analytic expertise to show the FDA that the treatment is, in fact, effective.

Typically in a phase 3 trial, the protocol, primary endpoint, and analysis plan are established before the trial begins—the success or failure of the trial is clear-cut. Harnessing our specialization in rare disease, our expertise in biostatical analysis, and our ability to communicate with regulatory agencies, we were able to present the FDA with compelling reasons to accept a retrospective change in the primary endpoint.

We drafted a briefing document that bridged statistical and clinical considerations, then accompanied the sponsor to present our rationale. In meetings with the FDA, we:

- Maintained that the primary endpoint should be altered to reflect the absolute change from baseline versus a percentage change
- Provided output justification from a statistical perspective that demonstrated the original endpoint did not adequately describe the clinical results
- Explained how the sponsor could not have understood the statistical differences at the start of the study

Results

Because this metabolic disease is an orphan indication, the FDA was more willing to consider the modification to the efficacy analysis. With continued, focused conversation, the FDA accepted the revised data and approved the new drug, saving the sponsor many years and millions of dollars that would have been spent on a new study.

As a CRO focusing on rare disease, we're more likely to notice abnormal results during the conduct of a study, so we can suggest other ways of analyzing the data—before the study is concluded and results are provided.

Rarefied Thinking