CID Case Study: A Study in Pediatric Patients with Multiple Sclerosis

Study Design:

The proposed study is a randomized, double-blind, Bayesian, group sequential, non-inferiority (NI) trial comparing an investigational treatment to an active control in pediatric patients with multiple sclerosis (MS), borrowing strength from external data in adults and children. The primary endpoint is the annualized relapse rate (ARR). One interim analysis for efficacy is planned.

The available external studies consist of a completed trial in pediatric MS patients and several trials in adult MS patients. A Bayesian framework will be used to incorporate the information from these studies using informative meta-analytic predictive (MAP) priors for the parameters of the statistical model. This MAP prior is combined with a non-informative prior component to produce a robust meta-analytic predictive (RMAP) prior that adapts the amount of information being borrowed based on the compatibility between the prior and observed data.

Innovative Characteristics:

FDA considers the following trial design features to be innovative:

• Use of an active-controlled non-inferiority design that has not been previously used in this setting

• Borrowing information from historical studies to increase the study power and increase the probability of stopping the trial at the interim analysis

• Model-based extrapolation from adults to the pediatric population

Potential Benefits of Design:

• The proposed non-inferiority trial uses an FDA-approved effective comparator, which can be appealing to patients and their families and can improve recruitment and retention.

• The Bayesian framework allows for the incorporation of prior knowledge and can make the trial more efficient.

• Historical information is incorporated using RMAP priors with a 2-component normal distribution and a robust non-informative component which may mitigate the risk of borrowing patient data that is not compatible with that observed in the proposed trial.

Considerations for the Proposed Design:

• What are the advantages of the proposed complex, innovative trial design?

• Is the proposed non-inferiority margin well justified?

• What is the impact of using historical information for both priors and the NI margin?

• Is the proposed approach for borrowing using MAP informative priors appropriate and interpretable?

Simulations:

The sponsor conducted simulations to evaluate operating characteristics varying five parameters including the ARR on the active comparator, the ARR-ratio of the investigational treatment to the active

control, the length of the recruitment period, the maximum follow-up time and the amount of weight placed on the informative MAP components in the RMAP approach. The simulations showed that under the main scenario, where similar relapse rates to the historical information were assumed, a trial that does not borrow information would require 34% more pediatric patients to achieve the same power as the proposed design. A goal of the simulations was to evaluate the impact of departure from the main scenario; thus, additional relapse rate scenarios were explored. The simulations found that the Bayesian design introduced bias that is approximately between a -30% and +10% difference on the ARR-ratio for the primary and sensitivity analyses, while the frequentist analysis had the smallest amount of bias. The precision of the estimates -- as measured using the root mean-squared error of ARR-ratio estimate -- was also explored for the additional scenarios and was found to be better for the Bayesian analyses than the frequentist analysis in most scenarios, indicating that the historical information improves the precision in the ARR-ratio estimates even with some departure from the historical rates.

The impact of using historical information to inform both the margin and priors was also assessed by simulations.

Discussion:

A topic of the discussion involved the benefit of the current NI design over a superiority trial given the treatment landscape of pediatric multiple sclerosis, a rare disease with an unmet need. A non-inferiority design would not expose pediatric MS patients to placebo, given the existence of an approved treatment. The sponsor and Agency acknowledged that a NI trial may be more attractive to pediatricians and patients and may potentially minimize patient burden.

The discussion also centered on a feasible and appropriate margin. The Agency requested a comprehensive and systematic literature review to justify the non-inferiority margin taking between-trial heterogeneity into account. The Agency recommended that a cautious approach to NI margin selection was warranted given that only a single historical trial was conducted in the pediatric MS population and there was uncertainty about using adult study findings for extrapolation. The FDA also suggested exploration of a modeling strategy incorporating additional, relevant data and accounting for the differential treatment effect by age. Moreover, estimation of the effect of the active comparator should incorporate data from controlled studies and between-study variability should be modeled. The FDA indicated the importance of consistency in the effect between trials. Additionally, FDA stated that the sponsor should adequately address the statistical implications of using the same historical data to inform both the NI margin and the prior. The Agency requested extensive simulations regarding the proposed priors and operating characteristics of the planned design.

Reference:

Guidance for Industry: Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products https://www.fda.gov/media/130897/download

Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness https://www.fda.gov/media/78504/download

Schmidli, Heinz, et al. "Beyond randomized clinical trials: Use of external controls." *Clinical Pharmacology & Therapeutics* 107.4 (2020): 806-816