CID Case Study: A Study in Patients with Epilepsy with Myoclonic-Atonic Seizures

Study Design:

The proposed study is a multisite, double-blind, randomized, placebo-controlled, parallel group study in children and adolescents with epilepsy with myoclonic-atonic seizures (EMAS). The primary endpoint is EMAS-associated seizure frequency over the treatment period.

Based on the need for therapeutic treatments in the EMAS population, the difficulty of enrollment in this rare population, and the consistent treatment effect across related indications, the sponsor proposed Bayesian methodologies to formally incorporate the study results from related populations into the primary analysis of the proposed study in the EMAS population. A Bayesian hierarchical model is specified for the treatment effects across populations, in which each study-specific treatment effect has a normal distribution centered on an overall treatment effect. A prior on the variance parameter of this distribution is specified to induce dynamic borrowing of the data from the historical studies of the related populations. The degree of similarity of the EMAS observed data relative to the historical data influences the magnitude of borrowing.

The sample size will be updated via unblinded interim analyses based on the Goldilocks methodology using Bayesian predictive probabilities according to a prespecified algorithm.

Innovative Characteristics:

FDA considers the following trial design features to be innovative:

• Borrowing of treatment effect information from historical studies of the same drug for different indications.

• Goldilocks methodology using Bayesian predictive probabilities to make sample size decisions.

Potential Benefits of Design:

• The borrowed information and adaptive sample size can reduce the number of patients that would be needed in the study, making the program more feasible.

• The dynamic borrowing approach 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 is the impact of the borrowed information?

• Is the proposed approach for borrowing appropriate and interpretable?

• Is the proposed design robust to deviations from the model assumptions?

• What are the statistical properties and performance of the design under various plausible deviations from these model assumptions?

• What is the impact of the Goldilocks adaptation on the operating characteristics in the setting of dynamic borrowing?

Simulations:

The Sponsor conducted simulations to:

1. Investigate a wide range of prior informative distributions and choose a single prior distribution prospectively that provides acceptable operating characteristics.

2. Evaluate the operating characteristics of the selected design in the context of a smaller sample size and Bayesian borrowing of external data and under a wide set of assumptions regarding treatment effects and endpoint variability.

3. Investigate the behavior of the Bayesian borrowing for single virtual studies, i.e., understand how much influence the borrowing can have on the interpretation of results in a single observed EMAS data set.

4. Evaluate the performance of the proposed Goldilocks approach.

The sponsor conducted preliminary simulations using the initial set of assumptions based on observed data from a historical trial. FDA requested further simulations to assess the operating characteristics of the model under a variety of scenarios and deviations from the various model assumptions. FDA also sought clarification on 1) how the prior distributions for the variance parameter of the treatment effect dynamically determined the amount of borrowing and 2) the operating characteristics of the Goldilocks approach.

Discussion:

A key assumption underlying the Bayesian hierarchical model is the exchangeability of treatment effects between the different studies, i.e., the probability of observing any particular set of treatment effects on those studies is invariant to the re-ordering of the studies. This assumption is considered justifiable based on clinical rationale as well as the consistency of results seen in the historical trials.

FDA suggested that the sponsor explore additional choices of informative prior distributions or other approaches to reduce the amount of borrowing when there is prior-data conflict. The sponsor explored other approaches including a frequentist test at a higher nominal significance level, a Bayesian power prior, and additional versions of a Bayesian hierarchical model and demonstrated that the operating characteristics were similar to those under the proposed two-level hierarchical model. The sponsor also explored the Bayesian effective sample size when there is prior-data conflict, which aided in understanding the impact of borrowed information under worst-case scenarios. FDA emphasized a need to pre-specify sensitivity analyses that allow examination of the robustness of the interpretation of the analyses.

The sponsor also explored alternative strategies separating the effect of the Bayesian analysis and the adaptive sample size to aid in understanding the impact of the proposed Goldilocks approach on operating characteristics.

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

Kristine R. Broglio, Jason T. Connor & Scott M. Berry (2014) Not Too Big, Not Too Small: A Goldilocks Approach To Sample Size Selection, Journal of Biopharmaceutical Statistics, 24:3, 685-705, DOI: 10.1080/10543406.2014.888569