Clinical Trial Simulation to Compare Adaptive and Fixed Designs for a Phase 3 Clinical Trial of Nacystelyn® (L-Lysine-N-acetyl-L-cysteine) for Cystic Fibrosis

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Abstract

Background: Nacystelyn® (L-Lysine-N-acetyl-L-cysteine) is being developed as a mucolytic and/or anti-inflammatory agent to use in Cystic Fibrosis. Objective for the phase 3 clinical trial of Nacystelyn includes dose selection as well as determination of efficacy and safety at the selected dose.

Methods: Objective was to compare adaptive and two-stage adaptive designs with dose selection as a binary outcome to the classical phase 3 trial design with the same binary outcome to evaluate the relative merits of the different candidate designs with respect to operating characteristics related to dose selection and selection of patients.

Results: Results of the simulation studies are essentially unaltered with respect to overall power, however the fixed design had a clear advantage with respect to the probability of rejecting the null hypothesis for the suitability defined best dose.

Conclusions: Based on estimated primary endpoint rates and assumed recruit- ment rate, dose selection is unlikely to occur prior to full enrollment of a trial. A single fixed design including placebo and 5 active Nacystelyn doses (10, 20, 40, 60, and 80 mg BID) is therefore the most efficient strategy for selecting an appropriate dose and demonstrating efficacy of the drug.

Operating Characteristics

The two operating characteristics identified to be of primary interest were overall power to reject the null hypothesis (or stage 1 dose rejection rate) and the probability of selecting the true null dose. Adaptive designs were evaluated with respect to a fixed “best case” (i.e., a version of the adaptive design presumed to have the best possible chance of outper- forming a fixed design with respect to key operating characteristics, whereas:

1) A stage 1 rejection was defined to continue until at least one of the following had occurred:
- ≥50 patients enrolled
- ≥50 pulmonary exacerbation events observed
- 12 months elapsed since first patient was enrolled.

2) At the end of stage 1, a stage 2 dose selection strategy described above is applied to select a single active dose which is carried forward with placebo to stage two. The number of subjects enrolled in the second stage of the trial is fixed at 200.

3) The design was evaluated under various scenarios as assessed in the context of a dose-response model for time to first respiratory infection (estimated from a Cox proportional hazards model) and the following base-case scenarios were considered:
- Drug treatment protocol
- Background treatment status (binary indicator for use of rhDNase 2.5 mg QD), 
- Event rate
- Situation in which the low dose is carried forward

4) The dose selection strategy for adaptive designs was then to:
• Use a Bayesian model fitting procedure to compute the estimated dose response function
• Use to compute the derived values
• Select the estimated utility-defined dose as the dose to carry forward to the second stage of the trial.

Figure 1: Dose response and utility under various scenarios. The vertical dashed line in each panel represents the “best dose” with respect to the utility function.

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Event Rates, Covariates, and Atrribution

Table 2: Operating Characteristics

Results

Event Rates, Covariates, and Atrribution

Model-based estimates used in the simulations included the following:
- PK event rate was estimated at approximately 30% for each patient per year, with a 5% chance of withdrawing due to safety concerns.
- The age (covariate) was modeled using a logistic distribution with a probability of rejection increasing with age.
- Drug x patient interaction was also modeled as a logistic distribution.
- Each event rate was estimated using Monte Carlo simulation, with 10,000 replicates of the model.

Dose-Response

Based on data from the phase 3 NAL-96-12 trial, an approximate 30% and 50% hazard reduction relative to placebo was estimated for 8 mg BID and 16 mg BID NAL treatment, respectively. The final design was selected to be a good fit for the data from the phase 3 trial.

Risk: The “best dose” may not be selected, and, conditioned on not selecting the “best” dose, there is of course zero probability of obtaining a significant result for that dose.

Conclusion

In general, the fixed and adaptive designs were essentially unaltered with respect to sample size for the candidate designs with respect to the probability of rejecting the null hypothesis for the best dose. Conditional on selecting the “best dose”, the probability of selecting the correct “best dose” was generally sufficiently high (approximately 60% and 80% under scenarios of primary interest for fixed and adaptive designs, respectively) such that the information available from a 6-month phase 2 study with 524 patients. Thus, even if a stable phase 2 study were conducted, it may not be possible to statistically demonstrate the superiority of the Nacystelyn® fixed dose design, vitamin C, or other interventions.

References