Strategies to Improve Model-based Decision-making During Clinical Development

David Hermann1, Wenping Wang2, Christine Falcoz3, Daniel Hartman4, Jaap Mandema5

1(Pfizer Global Research and Development, Ann Arbor, USA; 2 formerly with Pharsight Corporation, now at JNJ PRD; 3 Pharsight Corporation; 4 formerly with Pharsight Corporation, now at Quantitative Solutions

ABSTRACT

Objectives: To assess the utility of a novel PK/PD-based modeling and simulation tool as well as the utility of the Pharsight Corporation’s Drug Model Explorer™(DMX™) software for decision-making during early clinical development after CI-1027 (gemcabene).

Background: CI-1027 was developed as a low-density lipoprotein cholesterol (LDL-C) lowering compound. The team was interested in assessing early the effect of CI-1027 plus statin combination compared with statin monotherapy or a key competitor plus statin combination. Given the LDL-C lowering effect across the CI-1027 plus statin dose range, should clinical development continue?

Strategy: A single Phase IIA trial was planned along with a dose-response surface meta-analysis of literature data on key competitors and CI-1027 data for several efficacy and safety endpoints. DMX software provided the team an interactive, easy to use, query tool to compare treatments and make trade-offs based on all endpoints.

Methods: The Phase IIA trial was a single 8-week, double-blind, study in hypercholesterolemic patients with randomization to one of three CI-1027 doses, three ezetimibe doses, and their respective combination. Summary data from the trial were combined with CI-1027 Phase I data and literature data from ezetimibe and statin trials. A nonlinear mixed effects regression analysis was undertaken to describe (1) the mono-therapy dose-response for the non-statins, CI-1027, and ezetimibe, and (2) the dose-response for 5 statins as mono-therapy and in combination with a non-statin. Summary data from 21 clinical trials (~10,000 patients) were included for LDL-C. Emak models described the relationship between percent change in LDL-C and CI-1027, ezetimibe, and statin (mono-therapy) dose. Combinations were well described by adding a simple interaction term to the model.

Results: The predictive distribution of the dose-response surface was obtained from the models covariance matrix and uploaded into DMX. After selecting an endpoint, population, and treatment of interest the DMX system immediately displayed the corresponding quantitative result, including likely differences between CI-1027 and competitors. For LDL-C, the CI from the ANCOVA analysis of the Phase IIA trial overlapped that of ezetimibe. The CI from the meta-analysis does not overlap the ezetimibe CI clearly suggesting that CI-1027 is unlikely to lower LDL-C sufficiently to compete with ezetimibe.

Conclusion: In this case, the availability of integrated dose-response models for CI-1027 and competitors guided informed decision-making during early development. Based, in part, on the quantitative knowledge obtained through modeling all relevant data and made accessible via DMX, the development of CI-1027 was discontinued after one Phase IIA trial in the target population.

INTRODUCTION

The issue in clinical drug development is... attrition & productivity. One effective way to manage this is to model exposure-response based on all relevant data including prior knowledge on competitors. It is also important to effectively communicate to the clinical team the critical drug attributes (dose-response, differences between treatments, response in a target population, response at a given dose, dose-range to achieve a target response, response vs. comparators etc.).

For gemcabene (CI-1027), a non-statin compound:
• Phase I single & multiple dose PK dose trials, and three phase IIA trials were completed. These studies showed a beneficial effect on LDL-C and it was decided to initiate a LDL-C project in hypercholesterolemia.
• The team was interested in addressing early the key question: “Given the LDL-C lowering effect across the gemcabene doses in combination with statins, vs. the competition, should clinical development continue?”

STRATEGY: Efficient Model-Based Development

• Minimum Number of Studies: A Phase IIA trial was planned to assess gemcabene LDL-C lowering ability.

• Integrated Analysis: To aid decision-making, the team agreed to undertake a complementary dose-response analysis of study drug trials and considerable historic data on statins and ezetimibe (competition):
  - Rational approach to pooling data from trials with different drugs, doses, patient types, durations, etc.
  - Models were built ahead for 7 efficacy and safety endpoints that drive the project.

• Effective Communication: DMX software provided the clinical team ... with relevant historic data ... from the continually updated exposure-response analysis.

• Decision-Making: At the level of the program (data pooled across trials) and the competitive environment ... and early.

METHODS

1) Collect Relevant Data
• Summary & individual patient
• 21 trials (~10,000 patients)
  - Literature, SDBs
  - Statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin)
  - Non-statins
  - Gemcabene historic data (different populations)
  - Ezetimibe (non-competing cholesterol absorption inhibitor)

• Combination therapy with statins
• Update when new data rolled in from the Phase IIA gemcabene+atorvastatin dose-response surface study

2) Meta-Dose-Response Analysis

• Mono-therapy LDL-C % change dose-response:
  - Non-statins: gemcabene, ezetimibe
  - Statins: atorvastatin, rosvavastatin, simvastatin, pravastatin, lovastatin

• Combination therapy with statins
• Update when new data rolled in from the Phase IIA gemcabene+atorvastatin dose-response surface study

RESULTS

• Question 1: What is the probability that gemcabene mono-therapy is clinically superior to ezetimibe? Gemcabene is superior to ezetimibe from 600 mg.

• Question 2: What is the probability that, in combination with a statin, gemcabene is clinically superior to ezetimibe? Gemcabene combination will not provide superior LDL-C lowering relative to competitor.

• Question 3: Given the magnitude of LDL-C lowering across the gemcabene + statin dose range should clinical development continue? The CI from the meta-analysis does not overlap ezetimibe CI clearly suggesting that gemcabene is unlikely to lower LDL-C to the extent necessary to compete with ezetimibe.

CONCLUSION: Interpreting/Communicating Beyond the Trial...

- Application of exposure-response based model allowed the full team to extract confidence from all relevant gemcabene and competitor data, minimizing attrition & productivity.
- DMX provided quantitative information in easy to understand graphs that put new data into context.
  - This added informed decision making by the clinical team during early development.
- The predictive distribution of the dose-response surface was obtained from the models covariance matrix and uploaded into DMX. After selecting an endpoint, population, and treatment of interest the DMX system immediately displayed the corresponding quantitative result, including likely differences between CI-1027 and competitors. For LDL-C, the CI from the ANCOVA analysis of the Phase IIA trial overlapped that of ezetimibe. The CI from the meta-analysis does not overlap the ezetimibe CI clearly suggesting that CI-1027 is unlikely to lower LDL-C sufficiently to compete with ezetimibe.

Shaaded area show doses of interest... and early.