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

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Acknowledgements:
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ABSTRACT

Objectives
To assess the utility of a novel PK/PD-based modeling and simulation strategy as well as the utility of the Pharsight Corporation's Drug Model Explorer™ (DMX™) software for decision-making during early clinical development of 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 doses 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 to 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 placebo, three CI-1027 doses, three atorvastatin 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. Emax 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 surfaces 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, the CI from the ANCOVA analysis of the Phase IIA trial overlaps 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 managing uncertainty and helping decision-making 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 (competitor).
  - 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 decision-making, and updated very quickly with the Phase IIA trial results.
- **Effective Communication**
  DMX software provided the clinical team ... with an interactive, easy to use, query tool to compare treatments and make trade-offs based on all endpoints ... 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, SBAs
  - Statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin)
  - Non-statins
  - Gemcabene historic data (different populations)
  - Ezetimibe (non-statin competitor; cholesterol absorption inhibitor)
  - Mono-therapy
  - 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: atorva, rosuva, simva, prava, lova

$$E_{drug} = \frac{Dose^{n} \; E_{max}}{Dose^{n} + ED_{50}{}^{n}}$$

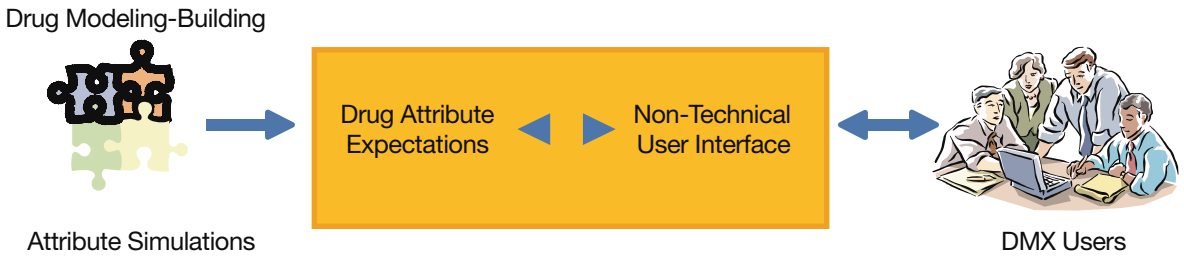
- Interaction term added to describe combination

$$LDL\%change = E_0 + E_{statin} + E_{non\text{-}statin} + \gamma \cdot E_{statin} \cdot E_{non\text{-}statin} + \eta + \varepsilon$$

- Weighted (by variance) non-linear mixed effects (study level random effect) regression to estimate model parameters.

3) Effectively Communicate Key Drug Attributes to Decision Makers

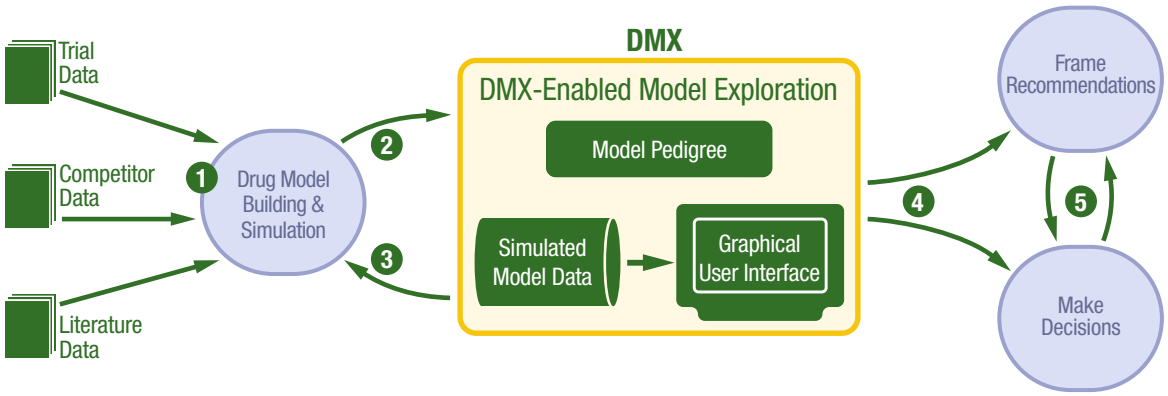
- Estimate predictive distribution by re-sampling from model parameter covariance matrix (simulate large multidimensional data set).
- Upload results into Pharsight Corporation's Drug Model Explorer™ (DMX™) software.



- DMX is a software-based technology for interactive communication, visualization, and exploration of key drug attributes and their respective uncertainties by the team.
- Powerful, user-friendly interface. DMX users can easily view and directly query pre-generated drug and disease model responses within a given input 'decision' space.
- Designed to facilitate quantitative decision-making.

Collaborative Team Workflows Using DMX

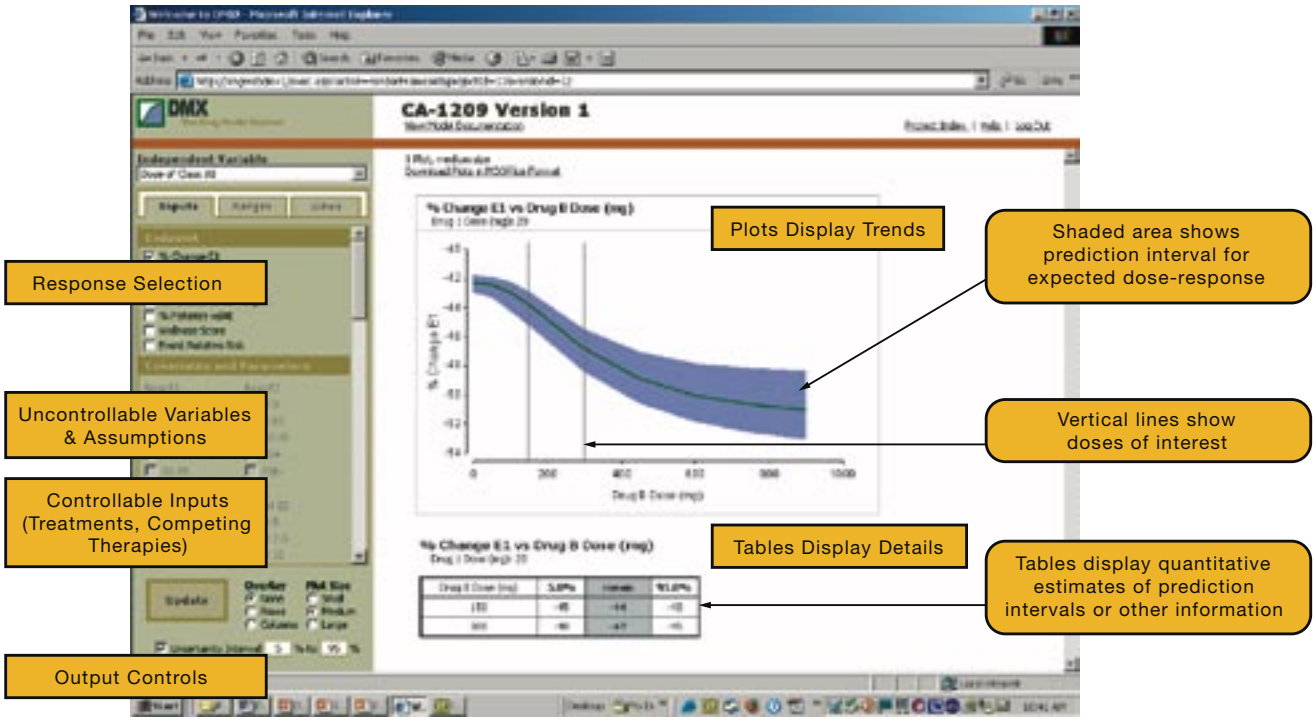
- DMX is used by the project team to compare drug attribute expectations vs. competing treatments.
- DMX is used by modeling experts to make M&S results available to teams and decision-makers.



1. Drug Modeling & Simulation
2. Publish Drug Model Results to DMX
3. Team DMX Exploration, Model Refinement & Feedback
4. Frame Insights & Recommendations
5. Communication & Decision-Making

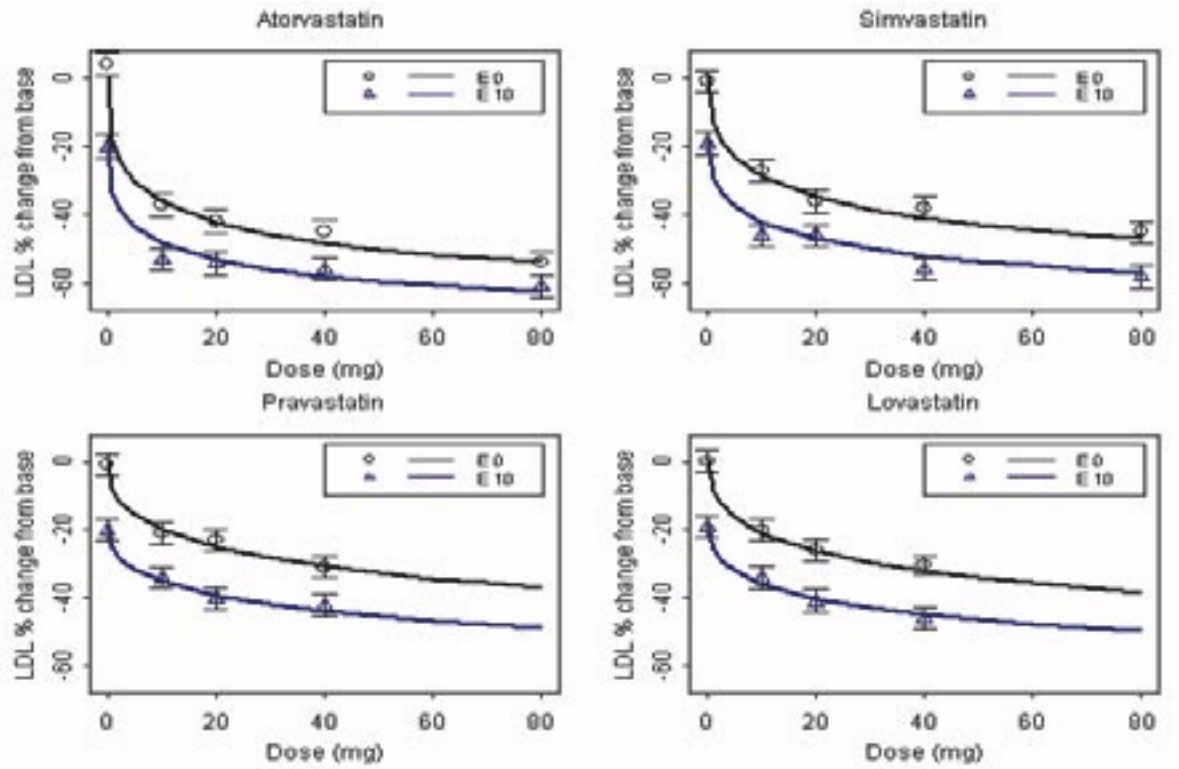
Example of DMX Output: Allows Team to View and Query Drug Model

Example Display: Predicted effect and uncertainty for hypothetical endpoint "% Change E1" vs. dose of Drug B



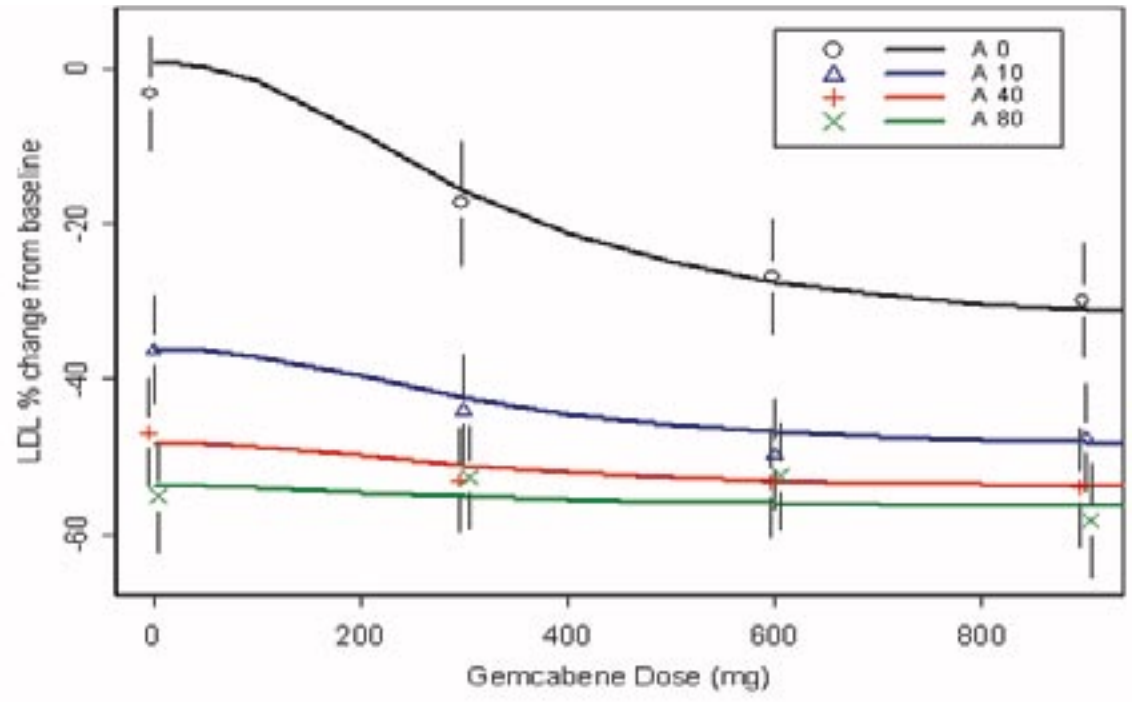
RESULTS

The Model Described Mono- and Combination Dose-Response Well for Ezetimibe ...



E 0 = statin alone *E 10 = + ezetimibe 10 mg*

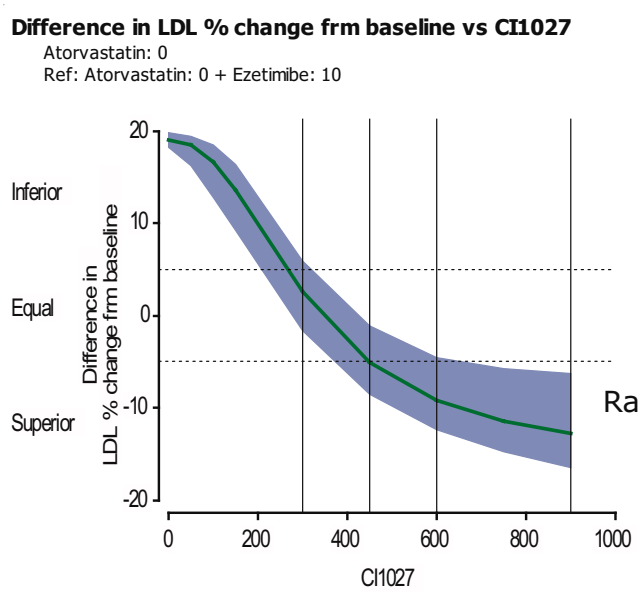
... And Gemcabene



RESULTS (continued)

Question 1:

What is the probability that gemcabene mono-therapy is clinically superior to ezetimibe 10 mg? Gemcabene is superior to ezetimibe from 600 mg.



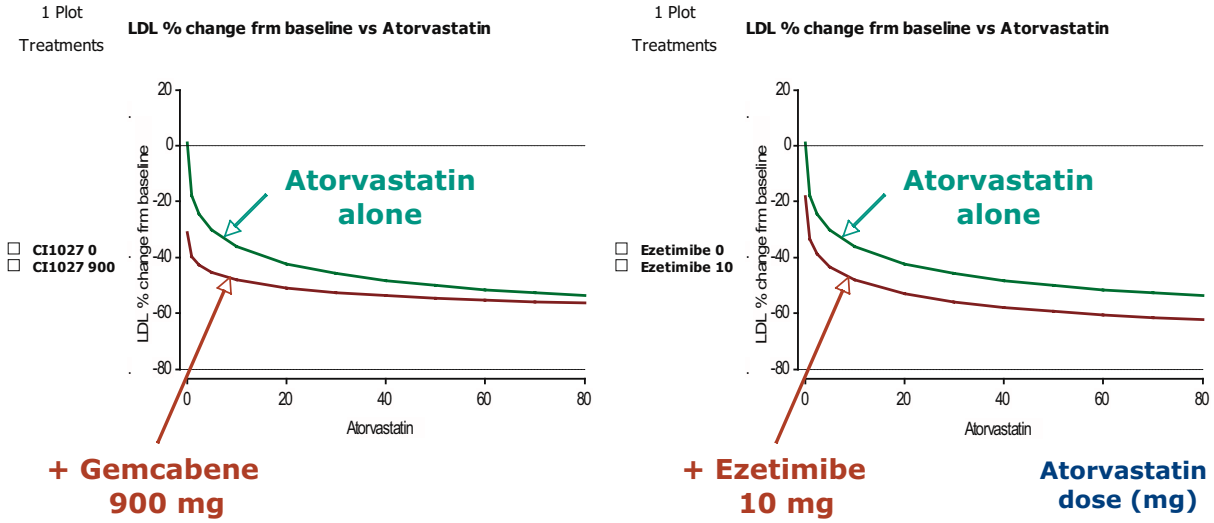
Gemcabene (mg)	Inferior	Equal	Superior
300	10.0%	89.9%	0.1%
450	0.0%	53.5%	46.5%
600	0.0%	7.2%	92.8%
900	0.0%	2.8%	97.3%

Range ± 5%

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.

LDL % Change from Baseline



Question 3:

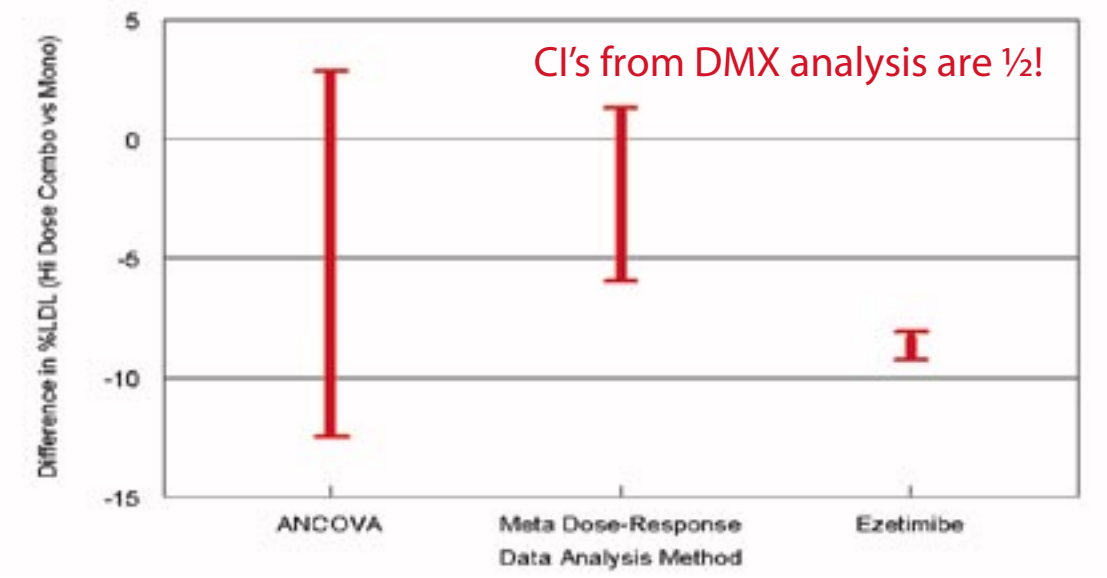
Given the magnitude of LDL-C lowering across the gemcabene + statin dose range should clinical development continue? The CI from the meta-analysis does not overlap ezetimibe CI, clearly suggesting that gemcabene is unlikely to lower LDL-C to the extent necessary to compete with ezetimibe.

Data Analysis Method	Data Base	Assumptions	Mean (95% CI)	Comments
			Gemcabene Combo-mono	
ANCOVA	Phase IIA trial only (n=255)	Few	-4.8 (-12.3 to 2.7)	Traditional analysis
Meta-Dose-Response	Phase IIA trial pooled with relevant historic data	Many	-2.5 (-5.8 to 1.2)	Width of CI decreased ½ compared to traditional analysis
			Ezetimibe Combo-mono	
Meta-Dose-Response	Phase IIA trial pooled with relevant historic data	Many	-8.6 (-9.1 to -8.3)	Gemcabene combination has very low probability of reaching target competitor level of LDL-C lowering

RESULTS (continued)

The CI from the ANCOVA analysis overlaps that of the key competitor, ezetimibe, leaving the project team with an inability to take a clear go / no go decision. The CI from the meta-analysis does not.

95% CI's on benefit of combination over statin mono-therapy



——— Gemcabene ——— Ezetimibe

CONCLUSION Interpreting/Communicating Beyond the Trial...

- Application of exposure-response based model allowed the full team to extract knowledge from all relevant gemcabene and competitor data, minimizing uncertainty.
- DMX provided quantitative information in easy to understand graphs that put new data into context.
  - This aided informed decision making by the clinical team during early development.
  - 7 key efficacy and safety endpoints (LDL-C, % patients to NCEP target LDL-C, hs-CRP, etc...) could be integrated to make trade-offs.
- It resulted in a more confident decision without further investment of approximately $2M and 4-6 months to perform an additional Phase IIA trial.* The development of gemcabene was discontinued after only one Phase IIA clinical trial in the target population.
- Unanimous – team members want same type of analysis and tool for next project.

** numbers based on industry-average benchmarks*