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Model-Based Development of Gemcabene, a New Lipid-Altering Agent

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ABSTRACT

The purpose of this study was to evaluate the value of model-based, quantitative decision making during the development of gemcabene, a novel lipid-altering agent. The decisions were driven by a model of the likely clinical profile of gemcabene in comparison with its competitors, such as 3-hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), the cholesterol absorption inhibitor ezetimibe, and their combination. Dose-response models were developed for the lipid effects (low-density lipoprotein cholesterol [LDL-C] and high-density lipoprotein cholesterol); adverse effects, such as persistent alanine aminotransferase elevation and myalgia; tolerability issues, such as headache; and risk reduction for coronary artery disease-related events for 5 statins, ezetimibe, gemcabene, and their combinations. The integrated model was based on the joint analysis of publicly available summary-level data and proprietary patient-level data and included information from almost 10,000 patients. The model was made available and accessible to the development team by using the Pharsight Drug Model Explorer model visualization technology. The modeling greatly enhanced the understanding of the clinical profile of gemcabene when given alone or in combination with a statin. The interaction between statins and gemcabene for the LDL-C lowering effect was found to be significantly different from the interaction between statins and ezetimibe. Ezetimibe was found to have a pharmacological-independent interaction resulting in additional LDL-C lowering over the entire statin dose range. The gemcabene interaction was found to be less than independent, resulting in almost no additional LDL-C lowering at high-statin doses, although the drug has a significant LDL-C effect when administered alone or in combination with a low dose of a statin. The quick availability of the model after completion of the first phase II trial in the target patient population and the ability of the team to explore the potential clinical efficacy and safety of gemcabene in comparison with alternative treatment options facilitated a quick decision to stop development.

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INTRODUCTION

Drug development decision making is greatly facilitated by having a model of the likely clinical profile of the new investigational drug (NCE) readily available. The model of the clinical profile should quantify the probability distribution of clinical safety, tolerability, and efficacy as a function of treatment strategy (dose) and patient population attributes. Preferably, the model should include competitors or treatment alternatives so that a quantitative assessment can be made of the clinical benefits and drawbacks of the NCE relative to those competitors. Building, such an integrated model, requires the joint analysis of data from multiple sources, different levels of detail, and potentially different end points. This often includes study-level data from individual patients available for the NCE, as well as summary data on competitors found in the literature.

To support dynamic decision making in an industrial pharmaceutical environment, the model has to be quickly updated after new study data has become available and has to be easily accessible by the development team members and decision makers. Pharsight Corporation has just released a novel software tool called Drug Model Explorer (or DMX for short) to provide nonmodeling experts easy access to the model results, to allow them to explore various aspects of the product profile and to communicate the findings throughout the organization.

The purpose of this study was to assess the value of such an integrated model of the likely clinical profile of the NCE, enabled by a model visualization tool, such as DMX, in making data-driven decisions during the drug development process. The methodology was applied during the development of gemcabene, an investigational new drug that lowers low-density lipoprotein cholesterol (LDL-C), decreases

triglycerides, and raises high-density lipoprotein cholesterol (HDL-C).[1] The most widely used drugs to reduce LDL-C are 3-hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, and 6 statins, atorvastatin, rosuvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin, are currently on the market. A distinguishing feature between the statins is the magnitude by which they lower LDL-C in the available dose range. Recently, ezetimibe, a cholesterol absorption inhibitor, was introduced to the market to be given alone or in combination with statins to additionally reduce LDL-C and achieve the aggressive new target levels that were set by the US National Cholesterol Education Program.[2] Like ezetimibe, gemcabene was intended to be given in combination with a statin. To evaluate the product profile of gemcabene, alone and in combination with a statin, we developed a model for the lipid effects (LDL-C and HDL-C); adverse effects, such as persistent alanine aminotransferase elevation and myalgia; and for tolerability issues, such as headache, for 5 of the currently marketed statins, ezetimibe, gemcabene, and the combination of ezetimibe or gemcabene with a statin. To evaluate the impact of treatment with a combination of a statin with gemcabene or ezetimibe on coronary artery disease, a model was established to predict the risk reduction relative to placebo or compared with other statin treatments on the basis of the lipid effects. Whereas all aspects of the product profile contributed to decision making, the LDL-C effect was an important deciding factor and is the main focus of this article.

MATERIALS AND METHODS

Studies Included

Using Medline, a search was performed for clinical trials that included atorvastatin, rosuvastatin, simvastatin, lovastatin, pravastatin, or ezetimibe. The cut-off date for the retrieval of publications was May 31, 2003. Trials were included if they were randomized, controlled trials investigating treatment with any of the above-listed compounds for at least 4 weeks in patients with hypercholesterolemia. Additional data available in the summary basis of approval for the US Food and Drug Administration were also evaluated. Although most of the published information on ezetimibe was used, the literature search was not meant to be comprehensive, and primarily publications evaluating a dose range of a particular statin or comparative trials between statins were selected. Data for gemcabene was available from 4 Pfizer-sponsored clinical trials. One of the gemcabene trials has since been published.[1]

End point data were extracted for each trial. The primary efficacy end point was the mean percentage of change in LDL-C from pretreatment (baseline) values. The information on potential explanatory variables was collected for each trial to evaluate their potential impact on the trial results. Variables that were collected include treatment duration, baseline LDL-C, location (United States or Europe), and the year the trial was published.

Statistical Analysis

When combining results from different trials, careful attention must be given to the consistency or homogeneity of the outcomes across the trials. Because of potential random, or known, trial-to-trial differences in the patient populations, one cannot simply take the mean of the results across all trials. To appropriately account for such trial-to-trial differences, a random effects regression analysis was used so that an accurate comparison across trials can be made.[3-5]

The following model structure was used to characterize the percentage of change in LDL-C for each of the drugs when administered alone or in a combination of statins and a nonstatin (ezetimibe or gemcabene):

$$Y = E_0 + E_{statin} + E_{non-statin} + 0.01 \cdot \gamma \cdot E_{statin} \cdot E_{non-statin} + \eta + \varepsilon \quad (1)$$

In this equation, Y is the patient's percentage of change in LDL-C, E_0 is the intercept representing the placebo effect; $E_{(non)statin}$ is the dose response relationship for the statin or nonstatin (see below); γ characterizes the type of interaction; η is a trial-specific random effect assumed to be normally distributed with mean 0 and unknown variance ω;[2] and ε reflects the between subject variability, which was assumed to be normally distributed with mean 0 and variance σ.[2] A pharmacologically independent interaction is implied between the statin and nonstatin if γ is 1. A sigmoidal E_{max} model was used to characterize the dose-response relationship for each compound:

$$E_{drug} = \frac{Dose^n \cdot E_{\max}}{Dose^n + ED_{50}^n} \quad (2)$$

In this equation, E_{max} is the maximal drug effect, reflecting the maximal difference in response between placebo and active treatment; *Dose* is the dose of the drug; ED_{50} is the dose of the drug to achieve 50% of E_{max}; and n is the Hill coefficient.

The nonlinear mixed-effects function provided in S-PLUS 6.1 (Insightful Corp.) was used to calculate the maximum likelihood estimates of the model parameters. The impact of trial, location, treatment duration, baseline LDL-C, drug class, and drug on the model parameters (E_0, E_{max}, ED_{50}, and n) was carefully evaluated. Final model selection was done based on the log likelihood criterion ($p < 0.05$). The

difference in −2 times the log of the likelihood between a full and reduced model is approximately asymptotically χ^2 distributed, with degrees of freedom equal to the difference in the number of parameters between the 2 models. A decrease of >3.84 in −2 times the log of the likelihood is significant at the $p < 0.05$ level for 1 additional parameter. SEs of the parameter estimates were approximated using the square roots of the diagonal elements of the asymptotic variance-covariance matrix.

Predictions

The model was used to simulate the expected dose-response relationship and its associated uncertainty for the percentage of change in LDL-C after administration of the individual drugs and their combinations for several different patient populations. The predictive distribution of the dose-response relationships was derived by sampling 5,000 sets of model parameters from the variance matrix of the parameter estimates. For each set of parameters, the dose-response relationship of the drugs was calculated for a typical trial (ie, the trial-specific random effect is zero, yielding the dose-response relationship for a representative patient population). The 90% uncertainty interval is taken between the 5th and 95th percentile of the predictive distribution. The model predictions were published in the DMX and made available to the development team to support decision making. DMX is a simple visual software interface designed to make it easy for the nonmodeler to access the modeling results and to explore the product profile, in this case, gemcabene, relative to its competitors. The DMX interface consists of an input zone containing controls for selecting model, patient, and treatment characteristics, and output zones displaying simulated predictions as plots and tables.

RESULTS

Data

On the basis of literature data, Pfizer internal study reports, and summary basis for approval of NDAs, we created a database of 21 randomized clinical trials that evaluated the lipid-lowering effect of statins, ezetimibe, and their combination in patients with elevated LDL-C. All 21 of the studies were randomized, double-blind, multiple-dose (once-daily regimen), parallel-group studies; among them, 13 studies were placebo controlled, and the majority were multicenter studies. The lipid-lowering effect of gemcabene alone was studied in 3 Pfizer-sponsored trials. A fourth trial was conducted in the target hypercholesterolemic patient population to evaluate the combination of gemcabene and atorvastatin. The first 3 clinical trials were conducted in healthy volunteers, healthy obese subjects, and subjects with low HDL-C and normal or elevated triglycerides. Because the baseline LDL-C levels were much lower in these healthy subject studies, the individual patient data available for gemcabene was used to evaluate the impact of baseline LDL-C and triglycerides on the percentage of LDL-C reduction. An analysis of data (ANOVA) was performed on these 3 trials with factors for dose, trial, baseline LDL-C, and triglycerides. A small impact of baseline LDL-C values <100 mg/dL on the mean percentage of LDL-C reduction was found. No treatment by baseline interaction was found. Based on the ANOVA model, least-squares estimates were obtained for the mean percentage of LDL-C reduction for each treatment group and each trial. The least-squares estimates were used as summary data in the dose-response analysis. Table 1 provides an overview of all of the trials included in the analysis.

LDL-C

The reduction in LDL-C observed after statin treatment was best described by a dose-response model with a common E_{max} (maximal effect) and a different ED_{50} (potency) for each of the statins. No statistically significant difference in E_{max} or Hill coefficient (n) was found between the statins. In fact, none of the statins had a statistically significant effect on E_{max} when tested independently. This suggests that all of the statins share a similar shape of the dose-response relationship with a similar maximal effect of about 79% reduction in LDL-C over placebo (estimated maximum effect at infinite dose). This is consistent with their common mechanism of action. The model parameters for the statins are presented in Table 2. A small but statistically significant difference between North American and European studies was found for the overall placebo effect. An additional 4% reduction in LDL-C was consistently observed in Europeans trials. No statistically significant effect was found for the other explanatory variables on E_0, E_{max}, ED_{50}, and n for the statins. Figure 1 shows the fit of the dose-response model for the LDL-C data for each statin to the data from all of the trials. The figure indicates an adequate summarization of the data by the proposed dose-response model. The symbols represent the observed mean change in LDL-C for specific dose strengths across all of the trials. The vertical line around each of the symbols reflects a 95% confidence interval on the observed mean change in LDL-C.

A simple E_{max} model best described the dose-response relationship for ezetimibe. A Hill coefficient for ezetimibe could not be estimated and was fixed to 1. The maximal LDL-C reduction for ezetimibe (E_{max}) when given alone was only about 20% and is much smaller than the LDL-C reduction observed for the statins. The model parameters for ezetimibe are presented in Table 2. Figure 2 shows the

Table 1. Overview of Studies Used in the Analysis*

Ref.	Year	Population	Drug, Dose (No. of Patients)	Duration (weeks)	N	Baseline LDL-C (mg/dL)
6	1995	Hypercholesterolemia	Pl (12), A2.5 (11), A5 (13), A10 (11), A20 (10), A40 (11), A80 (11)	6	79	188
7	1996	Hypercholesterolemia	Pl (9), A10 (11), A20 (10), A40 (10), A60 (13), A80 (12)	6	65	190
7	1996	Hypercholesterolemia	Pl (51), A10 (55), A40 (53), A80 (52)	16	211	207
8	1997	Hypercholesterolemia	Pl (133), A10 (707), L20 (191)	16	1031	191
9	1998	Hypercholesterolemia	A10 (73), A20 (51), A40 (61), A80 (10), P10 (14), P20 (41), P40 (25), S10 (70), S20 (49), S40 (61), L20 (16), L40 (16), L80 (11)	8	498	217
10	2000	Hypercholesterolemia	Pl (17), E1 (17), E5 (20), E10 (18), E20 (16), E40 (18), L40 (18)	8	124	
11	2001	Hypercholesterolemia	Pl (29), R1 (13), R2.5 (13), R5 (17), R10 (16), R20 (13), R40 (34), R80 (31), A10 (13), A80 (10)	6	189	190
12	2001	Hypercholesterolemia	R5 (119), R10 (111), P20 (136), S20 (139)	12	505	189
10,13	2001	Hypercholesterolemia	Pl (52), E0.25 (47), E1 (49), E5 (49), E10 (46)	12	243	172
10,13	2001	Hypercholesterolemia	Pl (36), E5 (75), E10 (72)	12	183	174
14	2002	Hypercholesterolemia	Pl (132), R5 (128), R10 (129), A10 (127)	12	516	187
15	2002	Hypercholesterolemia	R5 (127), R10 (128), A10 (127)	12	382	186
16	2002	Hypercholesterolemia	R5 (135), R10 (132), A10 (139)	12	408	187
17	2002	Hypercholesterolemia	R5 (121), R10 (115), P20 (116), S20 (120)	12	472	188
18	2002	Hypercholesterolemia	Pl (226), E10 (666)	12	892	167
19	2002	Hypercholesterolemia	Pl (70), E10 (61), S10 (70), S10E10 (67), S20 (61), S20E10 (69), S40 (65), S40E10 (73), S80 (67), S80E10 (65)	12	668	179
20	2003	Hypercholesterolemia	R5 (38), R10 (45), R20 (38), R40 (44), R80 (42), A10 (43), A20 (39), A40 (42), A80 (41)	6	372	190
21	2003	Hypercholesterolemia	Pl (205), E10 (622)	12	827	165
22	2003	hypercholesterolemia	Pl (60), E10 (65), A10 (60), A10E10 (65), A20 (60), A20E10 (62), A40 (66), A40E10 (65), A80 (62), A80E10 (63)	12	628	181
23	2003	Hypercholesterolemia	Pl (65), E10 (64), P10 (66), P10E10 (71), P20 (69), P20E20 (66), P40 (70), P40E40 (67)	12	538	178
24	2003	Hypercholesterolemia	Pl (64), E10 (72), L10 (73), L10E10 (65), L20 (74), L20E10 (62), L40 (73), L40E40 (65)	12	548	178
n.p.	2003	Volunteers	Pl (6), G50 (8), G150 (8), G450 (8), G600 (10), G900 (7)	4	47	120
1	2003	Subjects with low HDL and normal or elevated TG	Pl (32), G150 (33), G300 (31), G600 (29), G900 (30)	4	155	113
n.p.	2003	Nondiabetic healthy obese subjects	Pl (27), G900 (23)	4	50	112
n.p.	2003	Hypercholesterolemia	Pl (157), A10 (17), A40 (17), A80 (16), G300 (13), A10G300 (16), A20G300 (18), A80G300 (18), G600 (15), A10G600 (16), A20G600 (16), A80G600 (17), G900 (15), A10G900 (17), A20G900 (14), A80G900 (15)	8	255	175

*n.p., indicates not published; Pl, placebo; A, atorvastatin; L, lovastatin; P, pravastatin; S, simvastatin; R, rosuvastatin; G, gemcabene; and E, ezetimibe.

Table 2. Estimated Model Parameters and Their 95% Confidence Intervals

Parameters	Mean	95% Confidence Intervals	
E_0	0.802	0.0598	1.54
$E_{max,\ statin}$ (%)	−78.7	−90.7	−66.7
$ED_{50,\ Atorvastatin}$ (mg)	13.1	6.57	26.2
$ED_{50,\ Rosuvastatin}$ (mg)	4.35	2.19	8.62
$ED_{50,\ Simvastatin}$ (mg)	30.5	15	62.1
$ED_{50,\ Lovastatin}$ (mg)	82.8	37.1	185
$ED_{50,\ Pravastatin}$ (mg)	97.3	42.4	223
n_{statin}	0.451	0.366	0.557
$E_{max,Ezetimibe}$ (%)	−19.6	−20.6	−18.6
$ED_{50,Ezetimibe}$ (mg)	0.302	0.151	0.604
$n_{Ezetimibe}$	1		
$\gamma_{Ezetimibe}$	1		
$E_{max,gemcabene}$ (%)	−34.8	−45	−24.6
$ED_{50,gemcabene}$ (mg)	314	220	448
$n_{gemcabene}$	2.27	1.19	4.34
$\gamma_{gemcabene}$	1.69	1.49	1.88

fit of the dose-response model for the reduction in LDL-C data for monotherapy with ezetimibe. Figure 3 shows the impact of 10 mg of ezetimibe on the statin dose-response relationship. A simple pharmacologically independent interaction between statins and ezetimibe was observed. The interaction coefficient (γ) was not statistically significantly different from 1 and was, therefore, fixed to this pharmacological value.

The dose-response relationship for gemcabene for the percentage of LDL-C reduction was well described by a sigmoidal E_{max} model. The E_{max} for gemcabene is about 35%, which is larger than the E_{max} for ezetimibe but smaller than the lipid-lowering effect produced by the statins. The model parameters for gemcabene are presented in Table 2. Figure 4 shows the fit of the dose-response model for the reduction in LDL-C data for monotherapy with gemcabene. Figure 5 shows the impact of different atorvastatin doses on the gemcabene dose-response relationship. The interaction coefficient γ was significantly different from 1 ($p < 0.001$) suggesting a more complex interaction between gemcabene and statins than the simple independent pharmacological interaction that was observed between statins and ezetimibe. The interaction is actually less than independent, with $\gamma = 1.69 \pm 0.10$ (mean ± SE), resulting

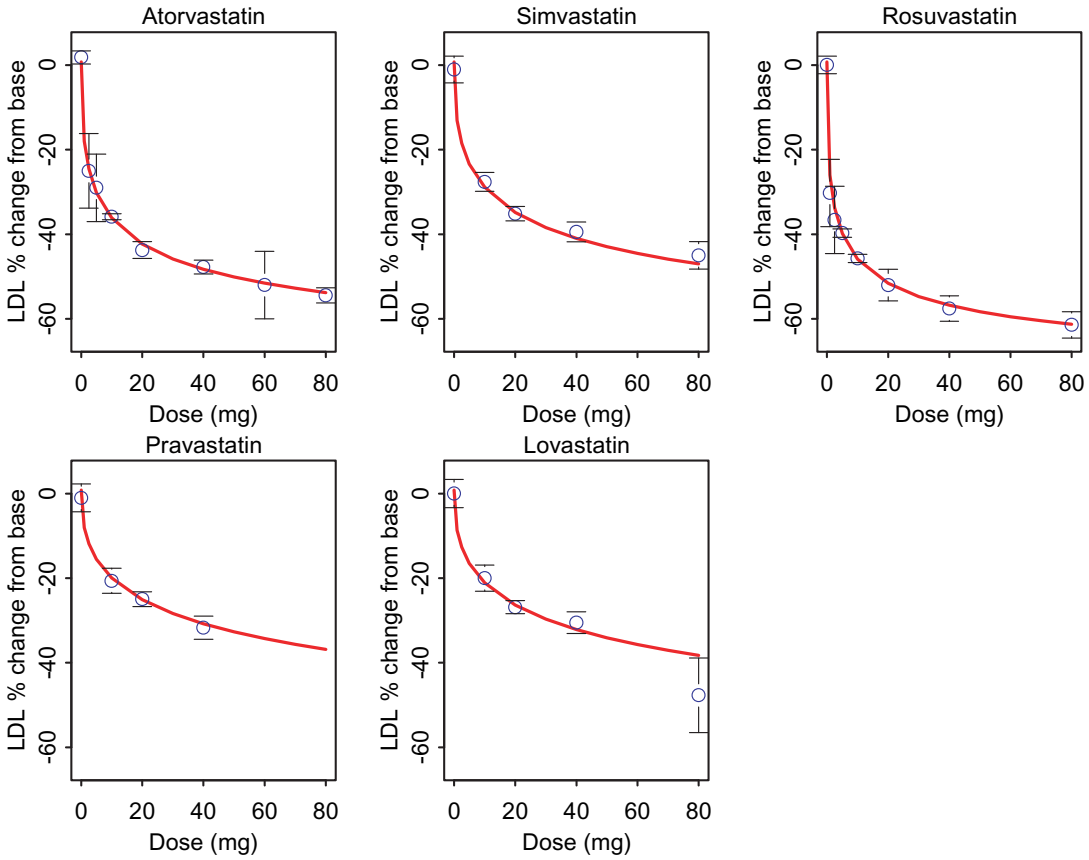

Figure 1. Dose-response relationship for monotherapy with statins. The symbols and bars represent the observed population mean and 95% confidence interval for ther percentage of LDL-C reduction across all monotherapy statin trials. The solid line is the model-predicted mean percentage of LDL-C reduction.

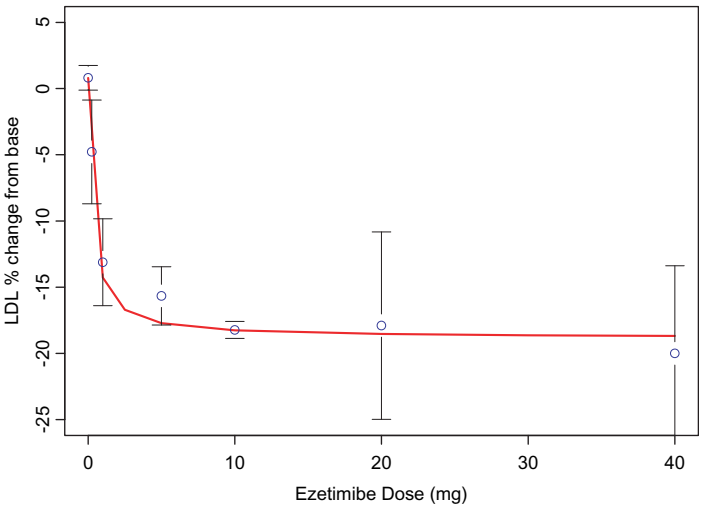

Figure 2. Dose-response relationship for monotherapy with ezetimibe. Each data point represents the observed mean response and 95% confidence interval for a specific dose strength across all trials. The solid line is the model-predicted mean percentage of LDL-C reduction.

in limited additional LDL-C lowering effect of gemcabene when used in combination with high doses of statins. The variance of the trial-specific random effect was found to be not statistically significantly different from zero suggesting homogeneity between studies in the magnitude of LDL-C reduction observed for a specific treatment strategy.

DISCUSSION

The purpose of the integrated model was to understand early in the development cycle the likely efficacy, safety, and tolerability profile of a novel experimental LDL-C lowering compound, gemcabene. Phase I studies had shown that the LDL-C lowering potential of gemcabene was probably not as pronounced as that of a statin, and the compound would have to be coadministered with a statin to be commercially viable. Therefore, a phase IIA study was planned to characterize the effects of gemcabene when coadministered with atorvastatin. The decision to proceed or stop development of gemcabene would not only be based on the ability of the drug to additionally lower LDL-C when compared with atorvastatin but also on how this would compare with other statins and statins that are coadministered with the cholesterol absorption inhibitor ezetimibe. Furthermore, the potential LDL-C lowering benefit should be weighted against safety and tolerability issues. In the absence of randomized, controlled studies comparing all of those treatment options, an indirect comparison through a metaanalysis provides the best quantitative comparative information.

Throughout the development of gemcabene, the modeling results were shared with the development team via a model visualization and exploration tool (DMX). To understand the value and necessity of a visualization tool like DMX, it is important to understand some of the current barriers that

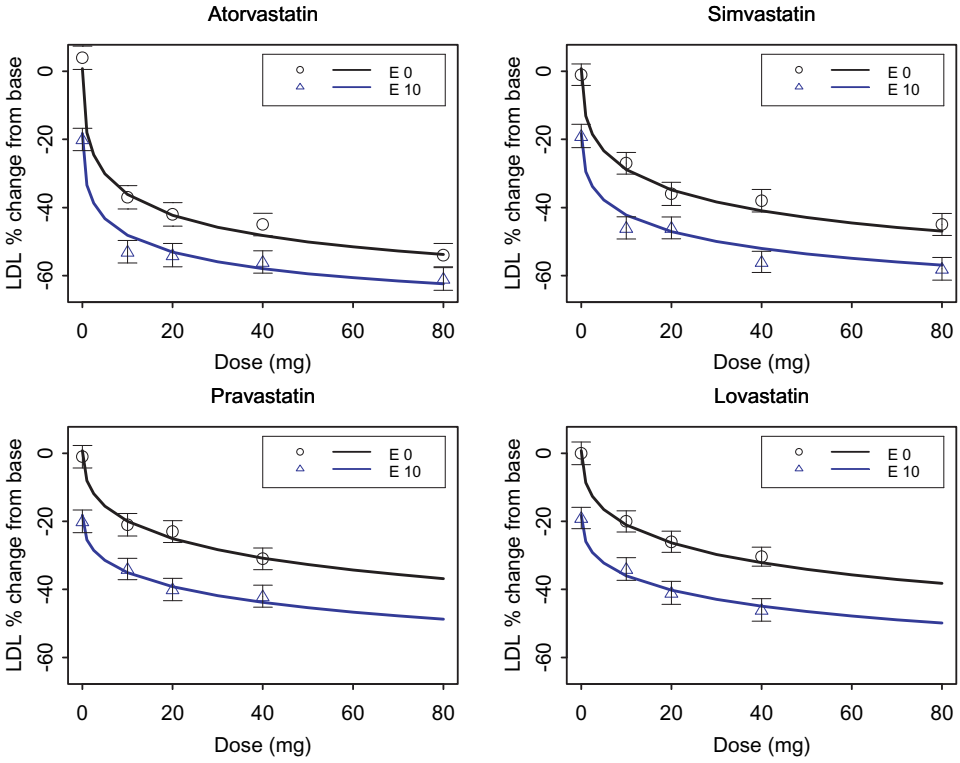

Figure 3. Statin dose-response relationship in the absence (E 0) and presence of 10 mg Ezetimibe (E 10). Each data point represents the observed mean response and 95% confidence interval for a specific treatment strategy across all combination therapy trials. The solid line is the model-predicted mean percentage of LDL-C reduction.

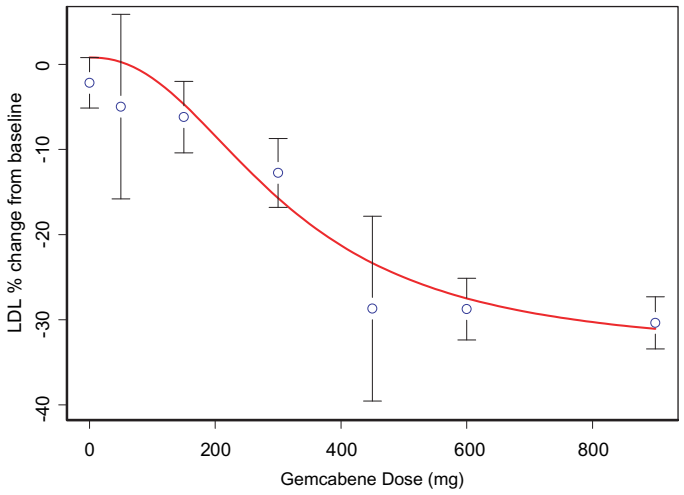

Figure 4. Dose-response relationship for monotherapy with gemcabene in a hypercholesterolemic patient population. Each data point represents the observed mean response and 95% confidence interval for a specific treatment strategy across all trials that evaluated gemcabene monotherapy (including the monotherapy arms of the combination study).

limit the impact of modeling and simulation on drug development decision making. The first barrier is the unfamiliarity of most drug developers with modeling methodologies. Because of this unfamiliarity, the development team members are hesitant to use the findings as part of their decision making. The second barrier is the large number of outputs or "views" that the model can provide. If we consider the probability distribution of a certain clinical response to a certain treatment option in a certain patient population as an output of the model, then for all practical purposes, the gemcabene model had >22,500 outputs. We can easily get to this number if we consider that the model of the product profile contained 8 end points, 5 statins, 2 nonstatins, about 6 dose groups per compound, and a couple of different patient populations. If we additionally consider that we often want to compare different treatment options or different patient populations, the number of potential views becomes staggering. The final barrier is the need to direct modeling requests to the pharmacometric modeling expert. As a result, every update of the model and every request for a different output of the model are funneled through the expert. This creates a bottleneck with respect to timely feedback of results and the ability to have an interactive team discussion around the modeling results. DMX was created to take away these barriers by combining a publishing tool to allow the modeler to quickly and easily publish new model results with a navigation tool to allow the team members to quickly and easily explore the product profile.

To best leverage the available data, a model-based meta-analysis was used, characterizing the dose-response relationship for each of the compounds. The advantage of a dose-response analysis is that comparisons between the compounds can be made across a wide dose range, including doses that have not been studied or for which only limited data are available. Another advantage is that compounds with a similar mechanism of action may share features of the dose-response relationship, such as a similar shape or similar maximal effect. Similarly, it is likely that all statins interact with other compounds in a similar way. The sharing of dose-response and interaction parameters across compounds greatly enhances the precision of the predictions of the model. This is especially true for interactions. For example, to characterize the interaction between a statin and nonstatin across 3 doses of each compound, an ANOVA model would require 9 additional parameters. For 5 statins, that would be a total of 45 parameters. The interaction model used in the current analysis requires only 1 additional parameter to characterize that interaction. A final advantage is that the model-based analysis can easily incorporate placebo and controlled trials.

Previous dose-response analyses have characterized the statin dose-response relationship for LDL-C reduction with a log-linear model.[4,25,26] Although the log-linear model provided a good description of the observations, there are several reasons to consider a more pharmacological E_{max} model. First, extrapolation with the log-linear model results in unrealistic predictions, a decrease in LDL-C of >100% at higher doses and a paradoxical increase in LDL-C at lower doses. Second, estimation of a maximal effect is not possible with a log-linear model. For these reasons, an E_{max}-based model was selected for this analysis.

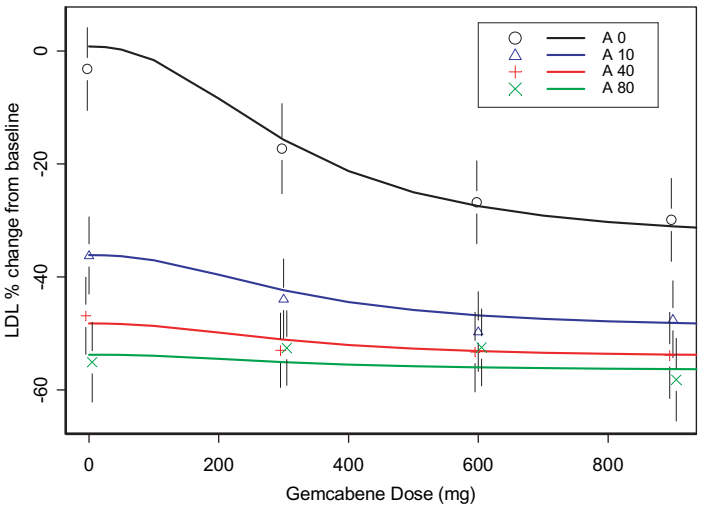

Figure 5. Dose-response relationship for gemcabene when combined with placebo (A 0), 10 mg atorvastatin (A10), 40 mg atorvastatin (A 40), and 80 mg atrovastatin (A 80). Each data point represents the observed mean response and 95% confidence interval for a specific treatment strategy observed in the interaction study between gemcabene and atorvatstatin. The solid line is the model-predicted mean percentage of LDL-C reduction.

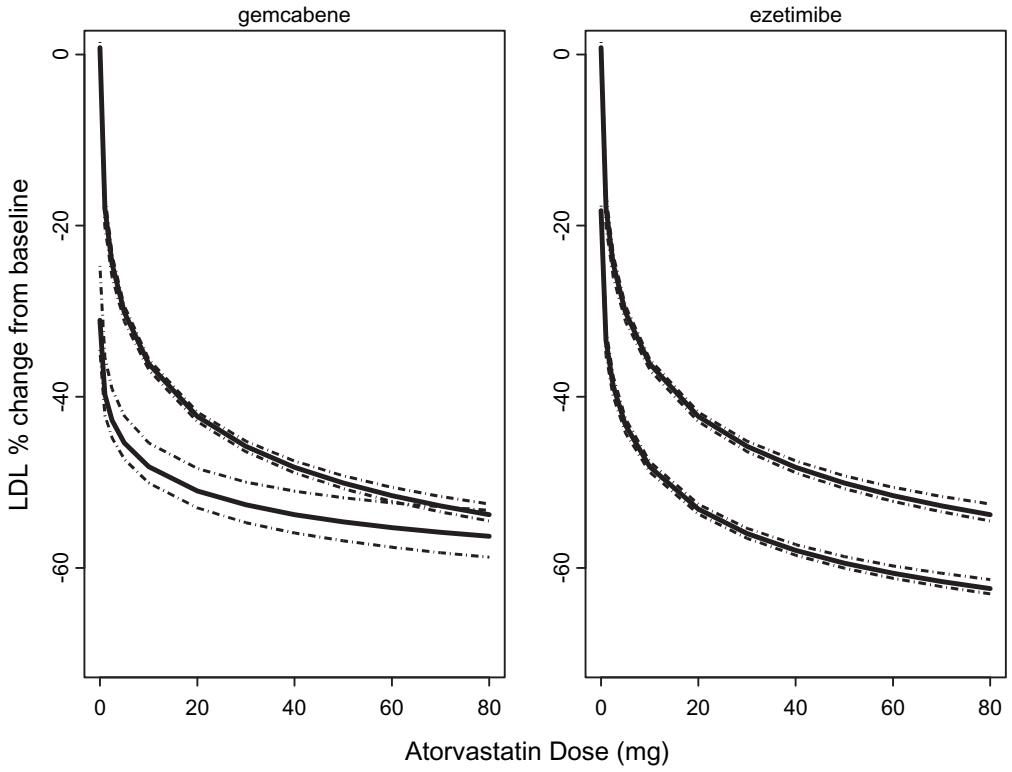

Figure 6. Dose-response relationship of monotherapy with atorvastatin and the combination of atorvastatin with 900 mg gemcabene (left) or 10 mg ezetimibe (right). The predictions are shown for a typical patient population in a typical trial. The solid lines represent the model predictions; the dashed lines span a 90% probability interval for those predictions.

Figure 1 shows that the statin dose-response relationship for LDL-C reduction is well described by a sigmoid E_{max} model. As expected, the statins were found to share a common shape and maximal effect of the dose-response relationship for LDL-C reduction. The evidence for this is strong, because none of the statins were found to have a statistically significant difference on the shape or maximal effect of the dose-response relationship, and the evaluated sample size was quite large. The only difference between the statins with regard to LDL lowering is their potency, ie, the dose required to achieve a certain effect. Using atorvastatin as a reference, the relative potencies of rosuvastatin, simvastatin, lovastatin, and pravastatin are 0.33, 2.3, 6.3, and 7.4, respectively. Hence the percentage of LDL-C reduction by 10 mg of atorvastatin is about equivalent to that of 3.3 mg of rosuvastatin, 23 mg of simvastatin, 63 mg of lovastatin, and 74 mg of pravastatin, respectively. A shallow dose-response relationship (small Hill coefficient) for statins is suggested. For such a dose-response relationship, the maximum efficacy is more difficult to achieve. After an initial steep LDL reduction, there is a prolonged shallow decline in LDL with increasing doses.

The LDL-C dose-response relationship for the cholesterol inhibitor ezetimibe and the investigational drug gemcabene are also well described by a sigmoidal E_{max} model. Both compounds differ from the statins in their ability to lower LDL-C. The maximal LDL-C reduction of ezetimibe is estimated to be only 19.6%. As is apparent from Figure 2 and the low ED_{50} of about 0.3 mg, ezetimibe at 10 mg is given at a relative high dose, resulting in a LDL-C reduction of 19.1% (18.3% to 19.8%, 90% prediction interval) close to the maximal effect. The maximal effect of gemcabene is estimated to be significantly larger than that of ezetimibe but still quite a bit smaller than the LDL-C lowering produced by statins in their therapeutic dose range. Gemcabene 900 mg is predicted to have a LDL-C reduction of 31.9% (25.5% to 35.4%, 90% prediction interval). This would imply that 900 mg of gemcabene produces about the same LDL-C reduction as 5 mg of atorvastatin, clearly at the low end of the potential LDL-C reduction with statins.

Recent guidelines of the US National Cholesterol Education Program have called for even lower target LDL-C levels.[2] To achieve these more stringent guidelines, statins could be combined with compounds that lower LDL-C through a different pharmacologic mechanism. The cholesterol absorption inhibitor ezetimibe is an example of this, and just recently a fixed-dose combination of ezetimibe and simvastatin was introduced to the market. Given the very different mechanism of action of ezetimibe and statins, ezetimibe is expected to add to the effect of the statins across the statin dose range. Ezetimibe blocks the absorption of cholesterol by inhibiting the passage of dietary and biliary cholesterol across the intestinal wall, whereas

Table 3. Predicted Additional Mean Change in LDL-C Reduction Between Combination Therapy of Atrovastatin With 900 mg of Gemcabene or 10 mg of Ezetimibe and Monotherapy With Atorvastatin*

	900 mg Gemcabene			10 mg Ezetimibe		
Atorvastatin (mg)	**Mean**	**5%**	**95%**	**Mean**	**5%**	**95%**
0 mg	−31.9	−35.4	−25.5	−19.1	−19.8	−18.3
10 mg	−12.0	−13.9	−9.1	−12.0	−12.4	−11.5
20 mg	−8.7	−10.7	−6.0	−10.8	−11.2	−10.4
40 mg	−5.5	−7.8	−2.7	−9.7	−10.0	−9.3
80 mg	−2.5	−5.3	0.4	−8.7	−9.0	−8.3

*The expectation and 90% probability interval are shown.

statins modulate only endogenous cholesterol, inhibit biosynthesis of cholesterol, and enhance the removal of LDL-C. Because there is limited overlap between these 2 pathways of cholesterol lowering, a pharmacologically independent interaction is expected between ezetimibe and statins. Pharmacological independence means that when ezetimibe and a statin are combined, the expected LDL-C reduction can be calculated as 1 − (1 − statin fractional LDL-C reduction)*(1 − ezetimibe fractional LDL-C reduction). An independent interaction is represented in the dose-response model by an interaction coefficient γ of 1. Indeed, when estimated, the interaction coefficient γ of ezetimibe was found to be 0.87 (0.70 to 1.04, 95% confidence interval) and was found to be statistically not significantly different from 1.

The interaction between gemcabene and statins was found to be quite different from the interaction of ezetimibe and statins. The interaction coefficient γ was estimated to be 1.69 (1.49 to 1.88, 95% confidence interval) and significantly >1, suggesting a more complex interaction between gemcabene and statins than a simple independent pharmacological interaction. An interaction coefficient >1 means that the interaction is actually less than independent, resulting in a limited additional LDL-C lowering effect of gemcabene when used in combination with high doses of statins. Figure 6 shows the difference between gemcabene and ezetimibe in their interaction with atorvastatin. Whereas gemcabene provides an additional LDL-C lowering benefit at low doses of atorvastatin, the compound provides almost no additional benefit at high doses of atrovastatin. This is quite different from ezetimibe, which provides a benefit across the atorvastatin dose range. Table 3 shows the additional LDL-C lowering effect of 900 mg of gemcabene and 10 mg of ezetimibe when given in combination with atorvastatin versus monotherapy with atorvastatin. The table shows that in combination with 10 mg of atorvastatin, 900 mg of gemcabene provides the same additional LDL-C lowering of about 12% as the combination of atorvastatin with 10 mg of ezetimibe. At 80 mg of atorvastatin, however, the combination with 900 mg of gemcabene only provides an additional 2.5% reduction, which is statistically significantly less than the additional 8.7% provided by 10 mg of ezetimibe. Figure 6 and Table 3 also show that the dose-response relationship of statins and their combination with ezetimibe and gemcabene are well understood, and any decision based on the LDL-C profile can be made with high confidence. The uncertainty in the predictions is small, which implies that it is highly unlikely that gemcabene will add to the effect of a high dose of a statin, although that particular combination has only been studied in 16 to 17 patients.

In conclusion, the availability of the integrated model combined with the model visualization tool (DMX) led to a quick decision to stop the development of gemcabene. The model contributed significantly to this decision, because it provided a quantitative comparison between gemcabene and ezetimibe when administered alone or in combination with a statin. These treatment options were not directly compared in the phase II trial. The integrated model also increased the certainty of the decision to stop development. The analysis of the data on several statins, ezetimibe and gemcabene, with a pharmacological plausible model greatly increased the certainty on the additional effect of gemcabene to a high-dose statin when compared with the analysis of the phase II trial alone. The 90% confidence bounds of the estimate of the additional effect of gemcabene to a high-dose statin on basis of the phase II trial alone actually included the point estimate of the additional effect of ezetimibe to a high-dose statin. The integrated model, however, showed that it was extremely unlikely for gemcabene to equal or beat the additional effect of ezetimibe to a high dose of any statin.

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