

# Communicating the Value of Pharmacodynamic Modelling in Drug Development

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# Traditionally, drug development is a lengthy and costly process.

**Research**  
**\$23 Billion<sup>1</sup>**

**Clinical Development**  
**\$48 Billion<sup>1</sup>**



- High throughput screening
- Combinatorial chemistry
- Genomics
- Rational drug design

Significant increase in investment and productivity

- Long, risky and complex process
- Of 5,000 screened compounds, 250 enter preclinical testing, 5 enter clinical testing, 1 is approved by FDA<sup>2</sup>
- Avg. cost to develop new drug \$802M<sup>2</sup>
- Only 3 out of 10 drugs produce revenues that match or exceed R&D costs<sup>2</sup>

Productivity is declining

*A key problem is separating the winners from the losers early.*

<sup>1</sup> 2002 Estimated Global Pharma and Biotech R&D Spending by Category: BioPharm International, March 2003

<sup>2</sup> PhRMA 2003 Industry Profile, March 2003

# FDA Perspective

There is a clear emerging message from the FDA regarding their view of the importance of Modelling and Simulation (M&S) to reduce the cost, time, and uncertainty in getting new medical products to patients.

## Critical Path White Paper (March, 2004) and Report (March, 2006)\*

- Proposes utilization of model-based approaches to improve knowledge management and decision-making

\*<http://www.fda.gov/oc/initiatives/criticalpath/>

## Guidances

- In 1999, FDA issued “Guidance for Industry | Population Pharmacokinetics”
- In 2003, FDA issued “Guidance for Industry | Exposure-response relationships: Study Design, Data Analysis, and Regulatory Applications”

## New focus on End-of-Phase IIa meetings

- Goal: Reduce unnecessary late stage (IIb, III) failures by
  - Review of dose vs. response models , exposure vs. response models, drug - disease models, simulations of phase IIb and preparation for phase III trial design
  - Review dose adjustment strategies for special populations
  - Review clin pharm and biopharmaceutical issues, as well as newer areas of uncertainty: QT trial design, pharmacogenomic and paediatric considerations

# Reasons for inefficiencies in clinical development ...

## Inefficient decision making processes (poor knowledge management)

- lack of necessary information to make informed decisions
- decisions not based on quantitative inputs
- focus on the wrong areas (e.g., speed to market as opposed to understanding the dose response)
- loss of knowledge due to changes in staff and assignments
- inability to capture information (such as how and why decisions were made, intellectual property, etc.)

## Lack of (efficient) utilization of technology

## .... And What Can Be Done About It?

### Model-Based Drug Development (MBDD)

- Rather than filling in gaps in knowledge, M&S is now being used to better design future studies and drug development programs:
  - Optimize clinical drug development focus on establishing exposure-response relationships to allow correct choice of dose(s)
  - Establish the use of drug-disease models and advanced pharmacometric concepts in early drug development
  - Promote the use of innovative clinical designs early in clinical development to establish proof of concept and exposure-response relationships

# Model-Based Drug Development

## Key Considerations

- Tools for computer assisted trial simulation
- Data repositories
- Standardization of tools, databases and practices
- Communicating outcomes to decision-makers

## Goal

- **SMALLER NUMBER OF FAILED TRIALS**
  - Reduced cost associated with trials
  - Increased certainty in trial designs
  - Lower rate of late-stage attrition
  - Studies in appropriate populations

# Examples of Applications of MBDD

Historically, typical PK/PD applications include:

- What are the important determinants of drug exposure - age, weight, gender, ethnicity, renal function? Which is the most important?
- What is the relationship between exposure and the incidence of adverse events - eg nausea, fatigue, diarrhoea, major bleeds?
- What is the relationship between exposure and clinical outcome - eg change in fasting plasma glucose, LDL reduction, reduction in tumour size?

# Newer focus of MBDD

PK/PD applications in MBDD include:

- **Pre-clinical (In-vitro → in-vivo)**
  - What is the effect of disease progression on PK/PD?
  - Selection of dose ranges for first in man (FIM) studies
- **Early Development**
  - Identify doses and dose escalation steps → evaluate different study designs
  - Identify useful metrics of exposure and identify relationships with safety and efficacy

# PK/PD applications in MBDD

- **Mid-late phase Development**

- What is the optimal number and timing of plasma samples to be drawn in a Phase 2a study to determine exposure-response?
- Competitive positioning - what is the predicted fraction of patients and their characteristics who might achieve a response or develop adverse effects; who does it compare with competitors.
- What dosing regimens should be taken into Phase 3?
- What is the expected difference in response between naïve patients and patients non-naïve to maintenance treatment?
- Evaluation of competing study designs - eg what is the effect of a run-in period of varying lengths (0, 2 or 4 weeks)?

## ... and from a clinical perspective:

What is the expected clinical response for a treatment in a particular patient population?

What is the level of certainty surrounding predicted response?

How do different treatment strategies and target patient sub-populations impact response?

What is the probability that response is less or greater than a specific target?

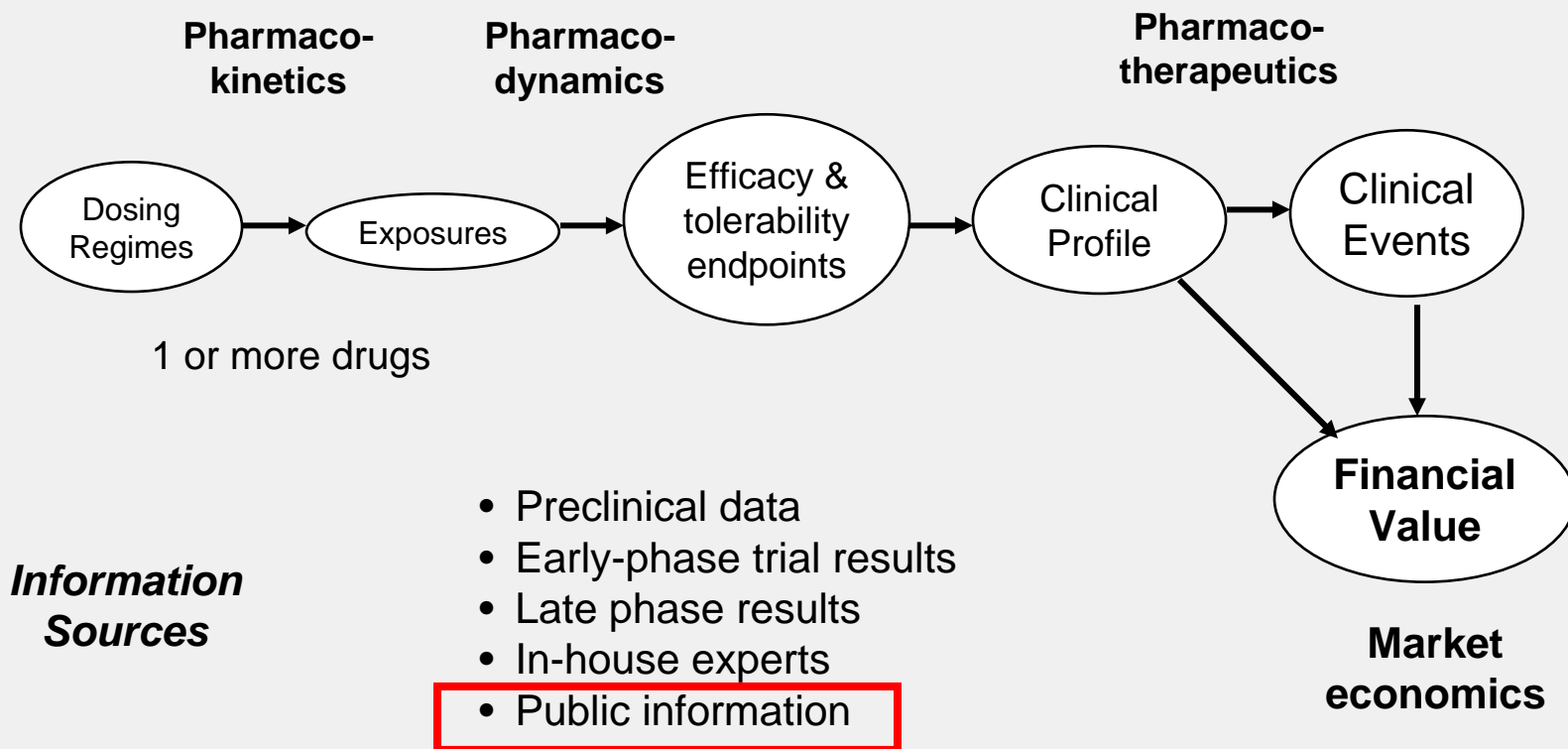
What dose is required to achieve a target response?

What is the probability of achieving a specific efficacy target while keeping probability for adverse events below a certain level?

How do the attributes for the compound compare to competitors?

What is optimal positioning strategy versus competitors to balance safety and efficacy?

To simulate drug development scenarios of interest, a number of sub-models are developed and integrated



## Public-Source Data

Provides rich information to better understand product profiles, competitive positioning, variability and uncertainty in drug development.

### Public data sources include

- journal articles
- regulatory documents (e.g., FDA Summary Basis for Approval)
- package inserts
- published abstracts or poster presentations
- meeting proceedings
- online resources (e.g., press releases about new clinical trial results, online clinical trial registries)

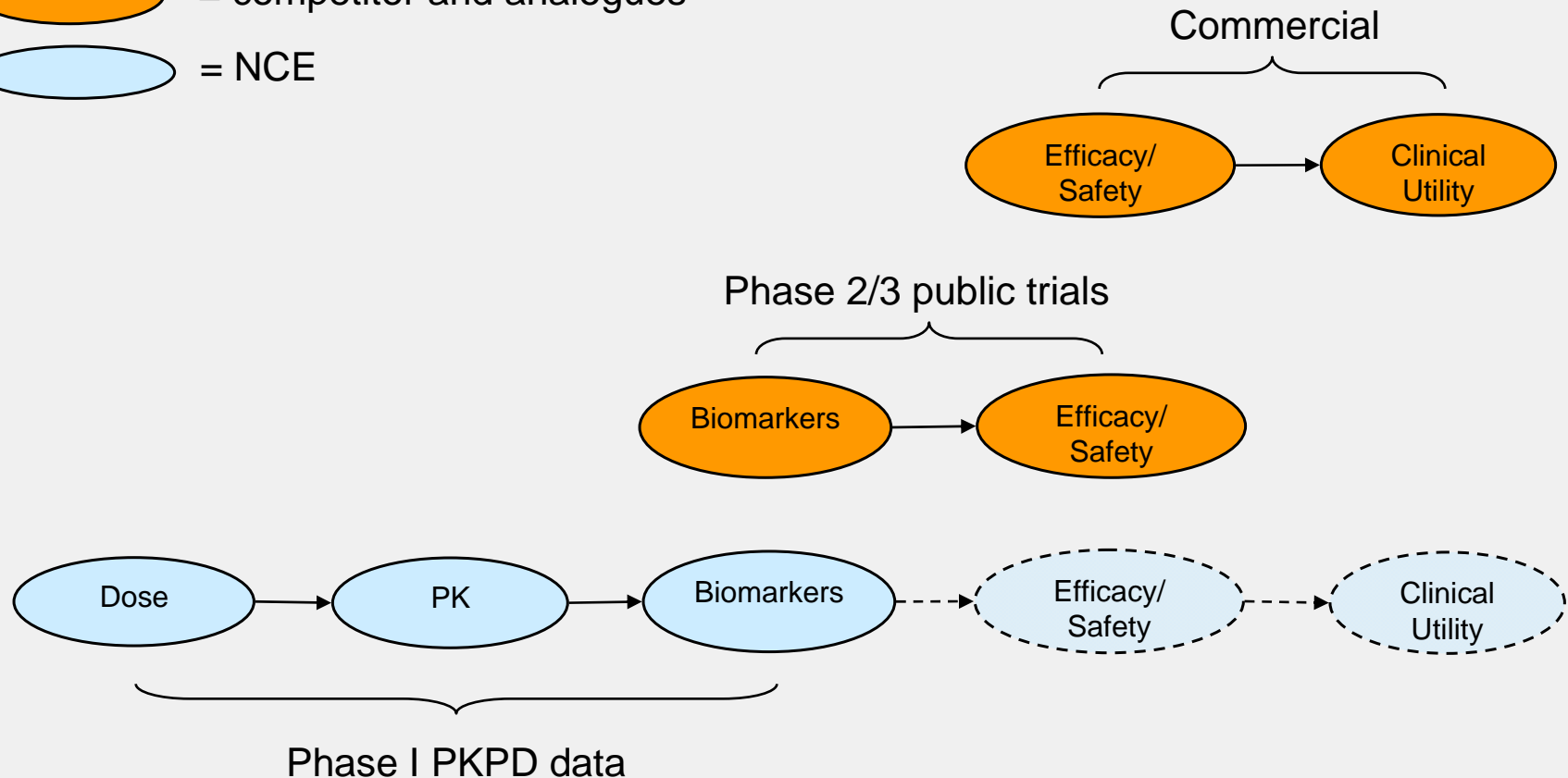
# Public-Source Data

- **Public-source data helps inform:**
  - efficacy/safety profile of established standards of care
  - the likely clinical profile of an entity in the early stages of clinical development
  - the natural progression of disease (model structures, parameter values, boundary conditions, placebo response)
  - effects of different treatment regimens, and potential covariates
  - comparative drug attributes (e.g., relative potencies)
  - trends, relationships between endpoints, treatments
  - provides initial estimates of variability and uncertainty
  - prediction of unobserved clinical outcomes: “borrowing” information, such as response at time points beyond those currently studied

# An example of an approach used to predict dose-response for a new drug using public-source data

 = competitor and analogues

 = NCE



# Case Studies

Example 1. How can preclinical data be used to support dose selection for a FIM study?

Example 2: How can M&S be used to support labelling?

Example 3: What is the product profile of an NCE versus competing therapies ?

## Example 1. How can preclinical data be used to support dose selection for a FIM study?

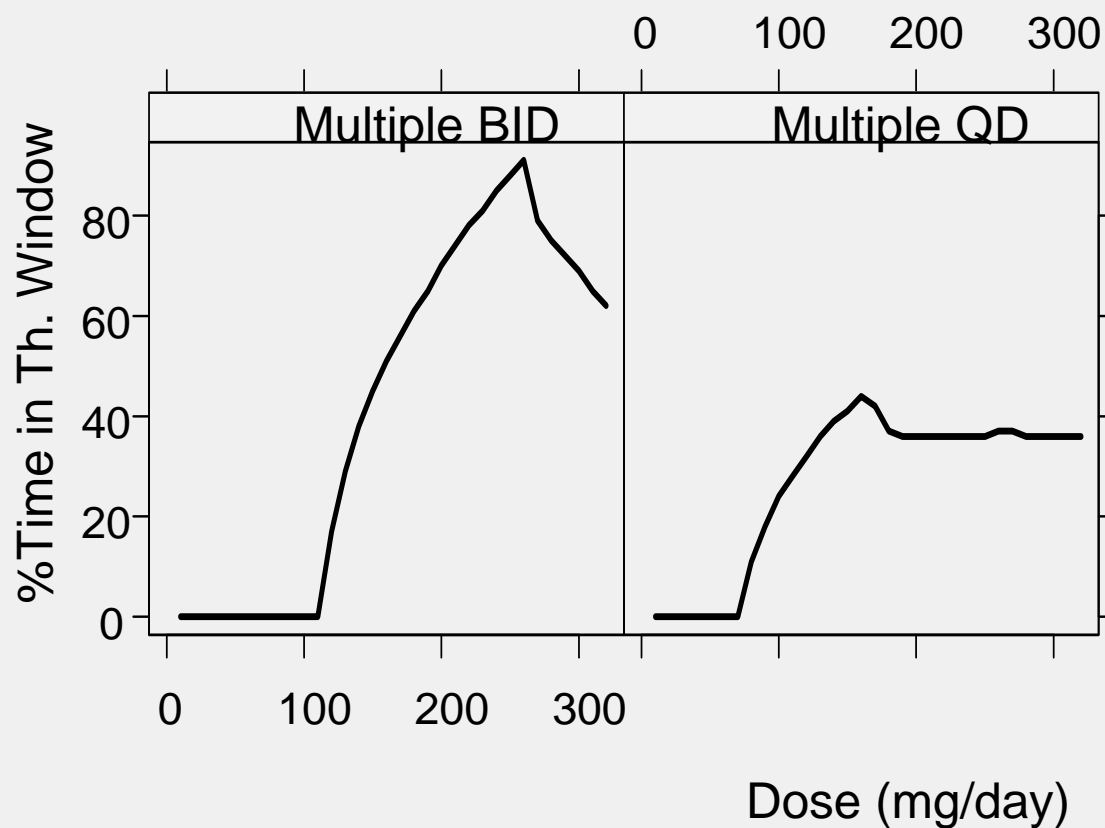
Allometric scaling was used to predict human pharmacokinetics.

Preclinical PK/PD data from cynomolgous monkey, relative potency information and literature data was used for simulation.

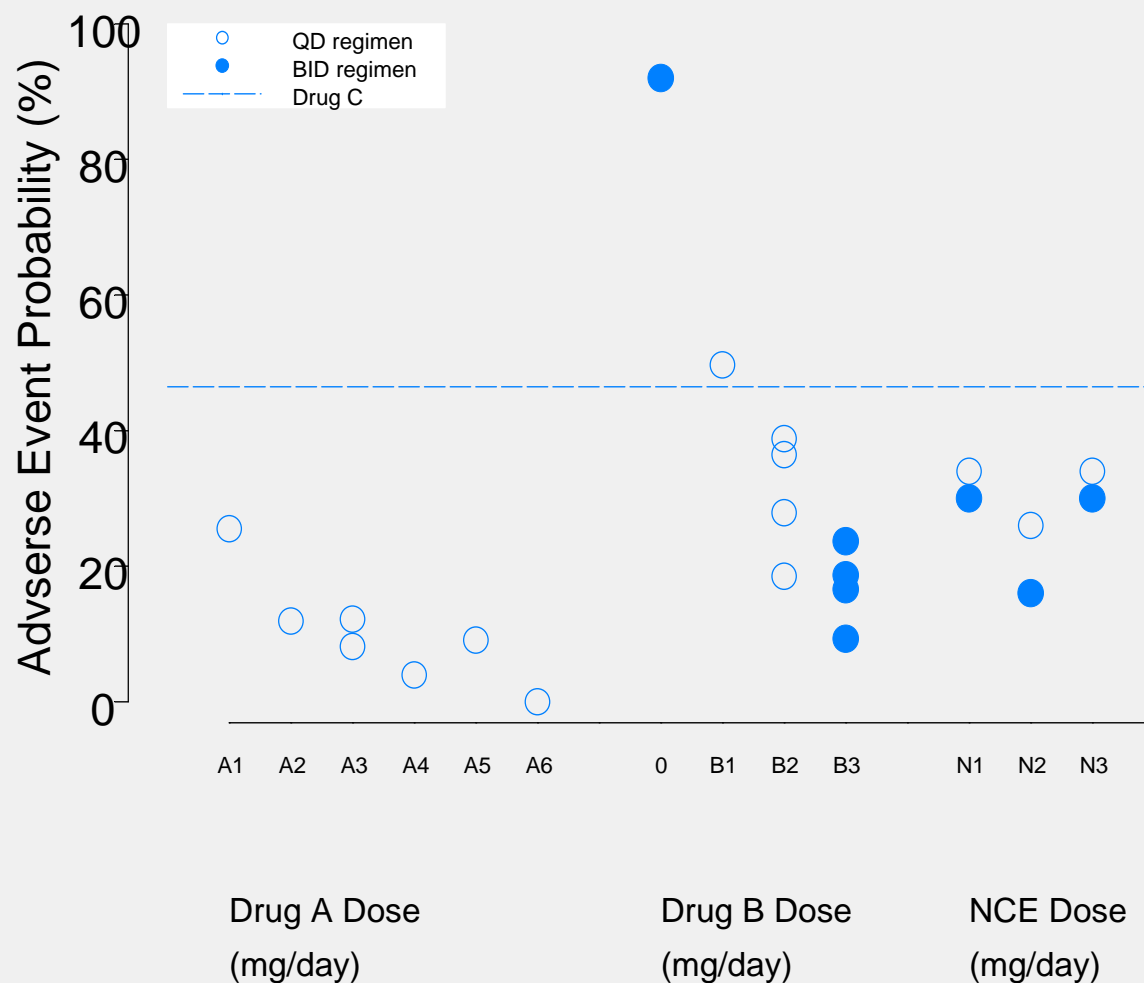
A range of doses (30-fold), regimens (QD and BID) and bioavailability fractions (5 to 50%) were used to project human PK vs. response profiles. The combination of dose and bioavailability ranges was chosen to compensate for any misspecification due to projection method or underlying assumptions.

Target therapeutic range was determined using publicly available literature for three comparators.

# Comparisons across regimens and drugs showed a favourable predicted response



# The response was comparable to competitors



Human projections for the NCE of interest identified a dose which provided a similar safety profile to that of comparators.

# Example 2: How can M&S be used to support labelling?



*Investigational New Drugs* **19**: 163–169, 2001.  
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## **Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel**

René Bruno, Nicole Vivier, Christine Veyrat-Follet, Guy Montay and Gerald R. Rhodes  
*Aventis Pharma Recherche et Developpement, Drug Metabolism and Pharmacokinetics, Antony, France and Collegeville PA*

# Docetaxel exposure-response modeling was performed in 640 patients

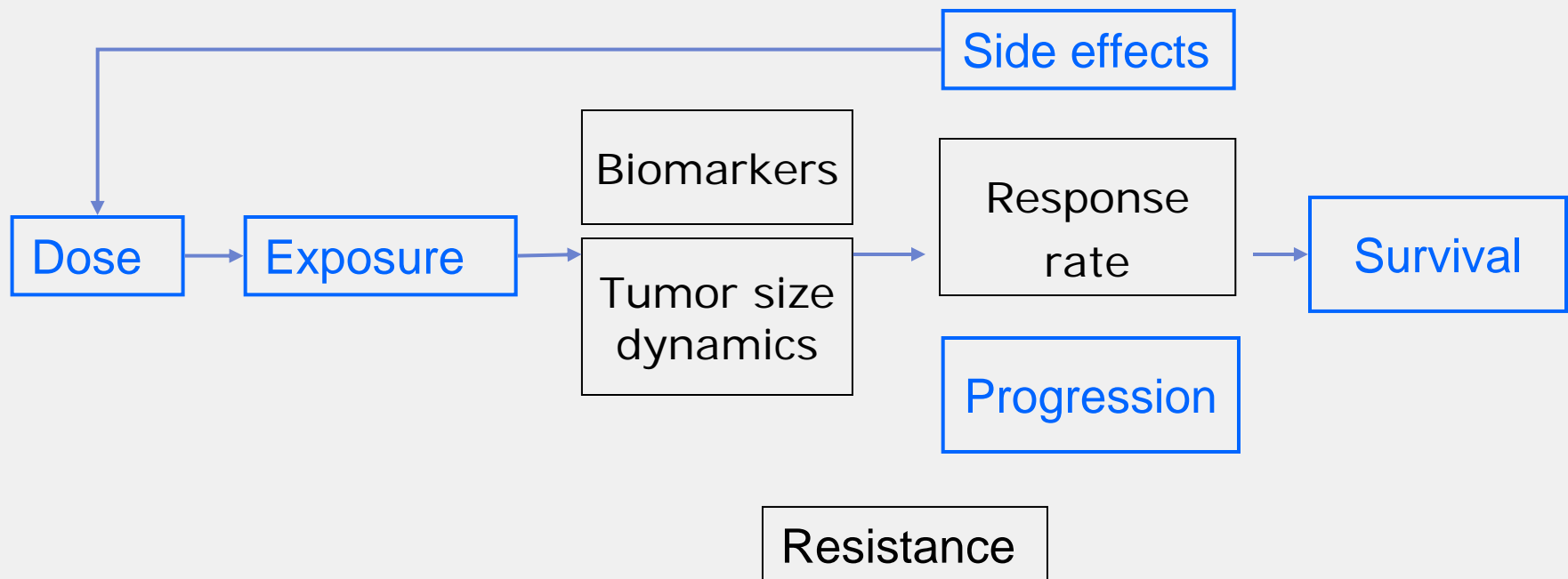
Patients with solid tumor including metastatic breast and non-small cell lung cancer

Docetaxel clearance and AUCs were estimated using population PK

Likelihood of tumor response (CR and PR), time to progression, survival and toxicity (grade 4 neutropenia, febrile neutropenia...) were analyzed

Source: R. Bruno et al. J. Clin. Oncology 16, 187-196, 1998

# Docetaxel model



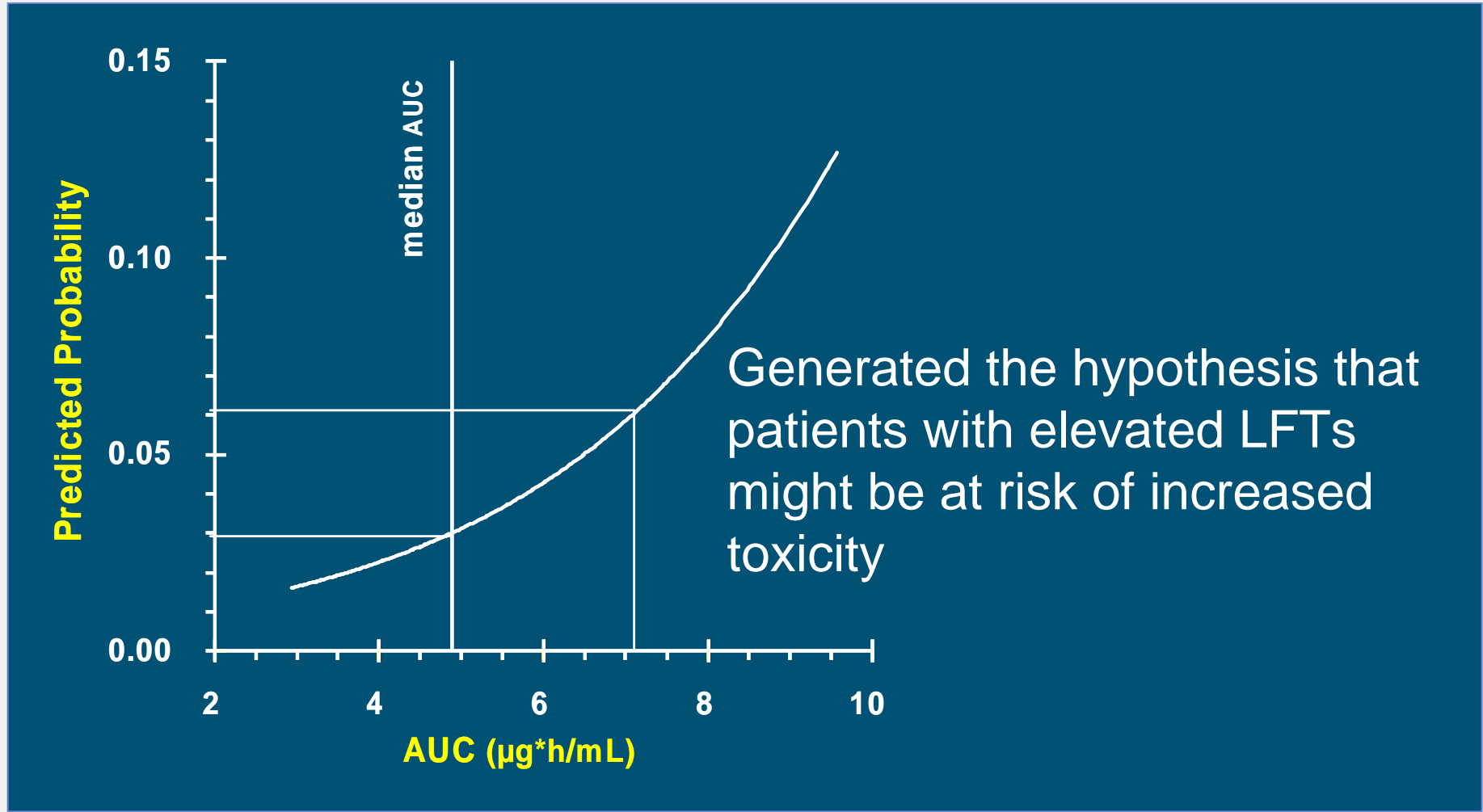
# Adverse events were related to docetaxel exposure

Docetaxel AUC at first cycle was a significant independent predictor of:

- grade 4 neutropenia (n = 582)
- febrile neutropenia (n = 582)
- fluid retention (n = 631)

Source: R. Bruno et al. J. Clin. Oncology 16, 187-196, 1998

There was a clinically meaningful increase in the odds of febrile neutropenia in patients with high exposure



These results justified a safety analysis by liver enzymes that confirmed the risk in patient with elevated LFTs

MBC patients treated at 100 mg/m<sup>2</sup> (Taxotere Package Insert)

Side effects	Normal (n=730)	Elevated (n=18)
Febrile neutropenia	2.4 %	8.6 %
Infection (grade 3-4)	7.1 %	33 %
Stomatitis (grade 3-4)	7.8 %	39 %
Toxic death	2.6 %	17 %

ODAC recommended approval in patients with normal LFTs without waiting for Phase III results.

Patients with elevated LFTs were excluded from Phase III studies.

MBC = metastatic breast cancer; ODAC = Oncology Drugs Advisory Committee to US FDA

# Contribution of this approach to first approval in metastatic breast cancer

“Taxotere: ... the value of nonlinear mixed effects modeling of dose-PK-PD relationships... was demonstrated... PK/PD analysis identified patients at risk for neutropenia, and justified the subsequent safety re-analysis of the clinical database to address questions posed by... regulatory authorities, that allowed the sponsor to confirm the profile of the drug without waiting for Phase 3 data... population PK/PD studies provided many advantages including:

- A scientific and clinical basis by which safety concerns were alleviated...
- Accelerated approval of the drug for market access.
- Provision of key information in the package insert.”

Source: Lesko et al. Eur. J. Pharm. Sci. 10, iv-xiv, 2000

## Example 3: What is the product profile of an NCE versus competing therapies ?

Gemcabene (CI-1027) is a non-statin compound developed as a low-density lipoprotein cholesterol (LDL-C) lowering compound.

Based on a beneficial effect of the drug on LDL-C in several phase I and IIa trials. it was decided to initiate a study in hypercholesterolemia.

Key question: “Given the LDL-C lowering effect of gemcabene in combination with a statin compared with competing therapies, should clinical development continue?”

A second objective was to effectively communicate the critical drug attributes to the clinical team to facilitate decision-making

Source: Hermann D, Wang W, Falcoz C, Hartman D, Mandema J. [Strategies to Improve Model-Based Decision-Making During Clinical Development](#). [poster]. Presented at: Annual Meeting of the Population Approach Group in Europe (PAGE); June 2005; Pamplona, Spain. Reprinted courtesy of PAGE.

# Strategy: Efficient Model-Based Development

A Phase IIA trial was planned to assess gemcabene LDL-C lowering ability, alone and in combination with atorvastatin

To aid decision-making, the team agreed to undertake a dose-response analysis of gemcabene trials as well as statins and ezetimibe (competitor) using literature data

- 21 trials were included (~10000 patients)
- Statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin)
- Nonstatins (gemcabene historical data, ezetimibe, mono- and combination therapy)
- Models were built for 7 efficacy and safety endpoints that drive decision-making, and were updated with the Phase IIA trial results

# Methods: Meta-Dose-Response Analysis

Mono-therapy LDL-C % change dose-response:

Statins and Non-statins: gemcabene, ezetimibe

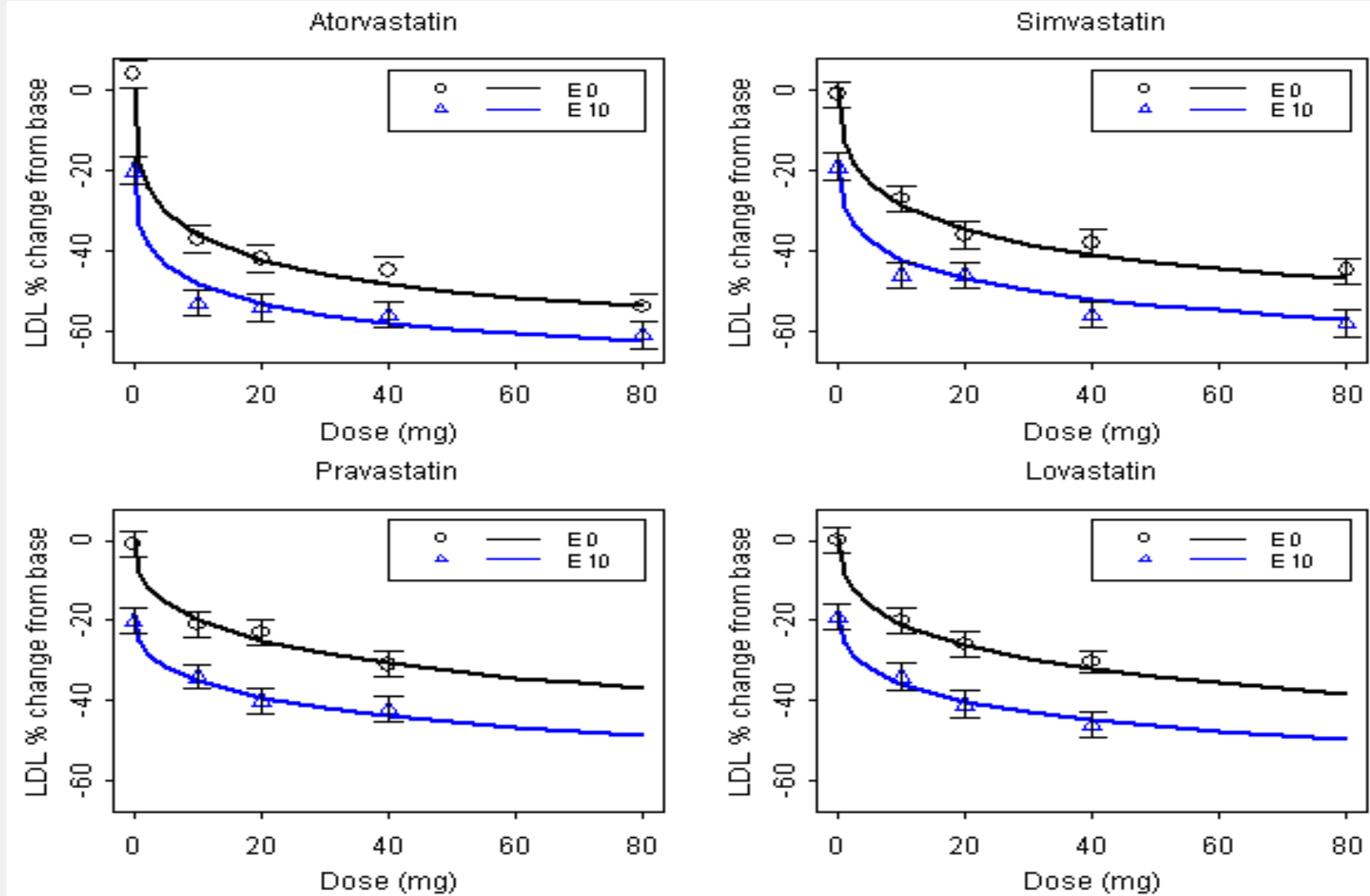
$$E_{drug} = \frac{Dose^n \cdot E_{max}}{Dose^n + ED_{50}^n}$$

Interaction term added to describe combinations

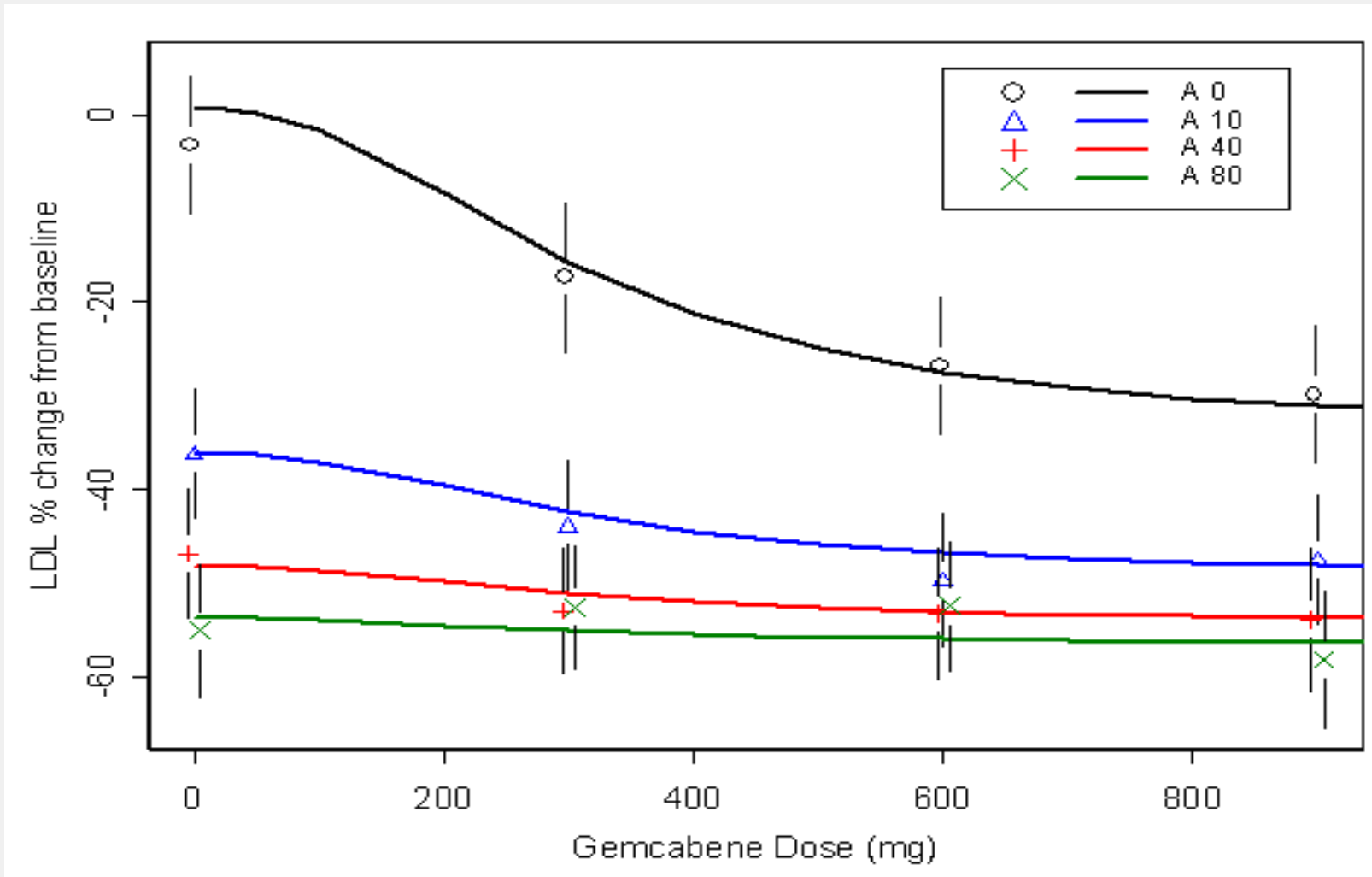
$$LDL\% \text{ change} = E_0 + E_{statin} + E_{non-statin} + \gamma \cdot E_{statin} \cdot E_{non-statin} + \eta + \varepsilon$$

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

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



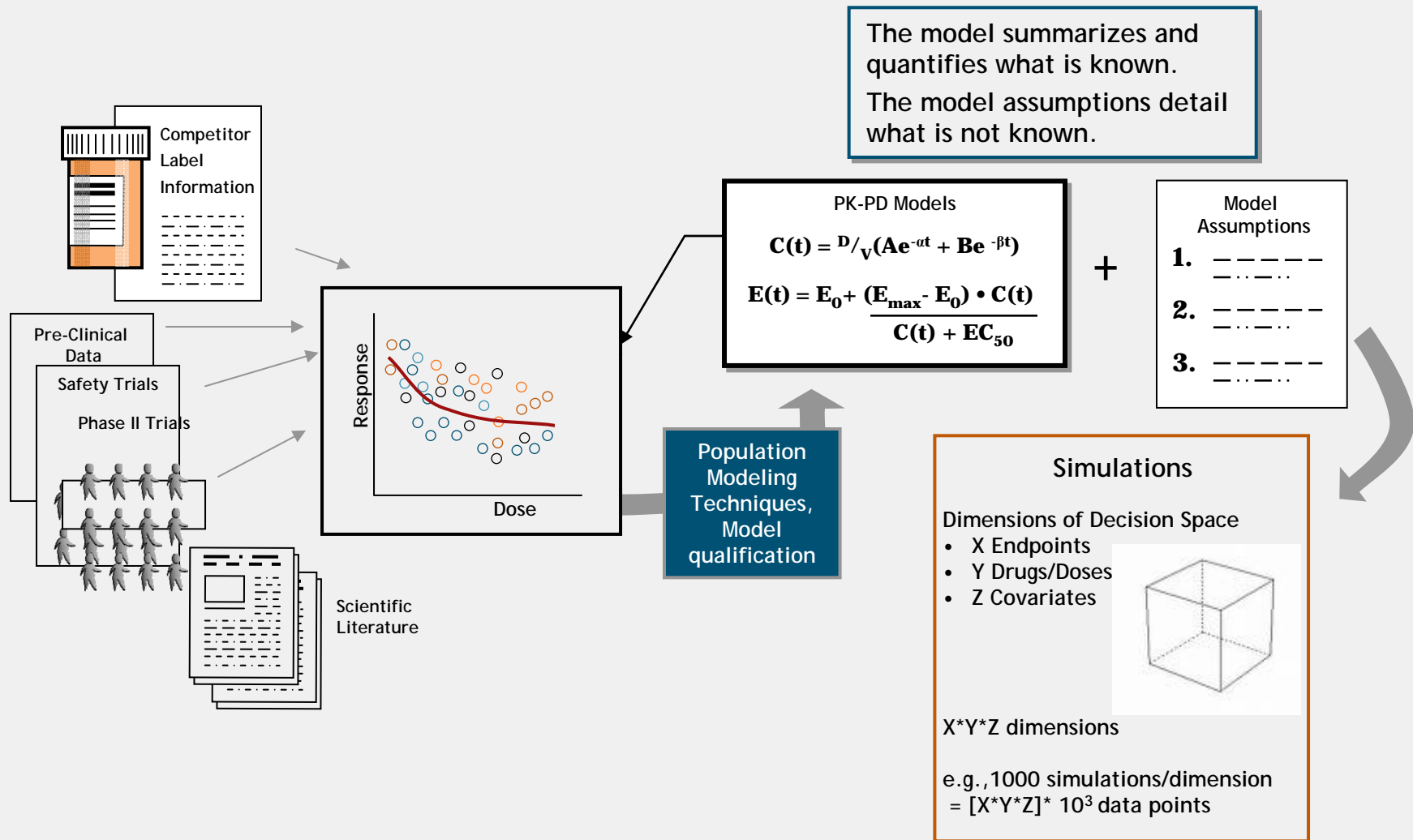
## ... And Gemcabene



**A 0 = gemcabene alone**

**A 10 = gemcabene + atorvastatin 10 mg etc.**

# Summary of process so far ....



# Models provide answers to important clinical questions.

What is the expected clinical response for a treatment in a particular patient population?

What is the level of certainty surrounding predicted response?

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What dose is required to achieve a target response?

What is the probability of achieving a specific efficacy target while keeping probability for adverse events below a certain level?

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# Models provide answers to important clinical questions.

What is the expected clinical response for a treatment in a particular patient population?

What is the level of certainty surrounding predicted response?

But often the challenge is in communicating this information to nonmodellers who lack familiarity with the models, but who need to be informed of the drugs key attributes in order to make clinical development decisions.

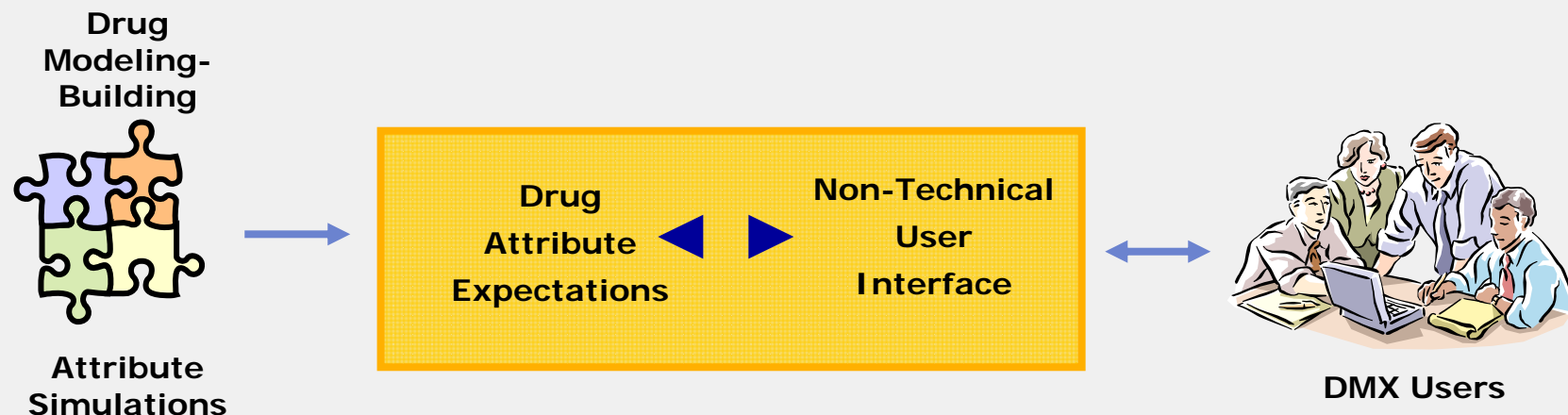
What is optimal positioning strategy versus competitors to balance safety and efficacy?

# Gemcabene: The next step: Effectively Communicate Key Drug Attributes to Decision- Makers

Estimate predictive distribution by re-sampling from model parameter covariance matrix (simulate large multidimensional data set)

Perform simulations and display in Drug Model Explorer® (DMX®)

- A visualization and communication tool to explore M&S results and facilitate quantitative decision-making
- Allows exploration of key drug attributes and their respective uncertainties by the team



Our purpose is to view and query model-based attributes based on simulation of mean responses.

We can achieve detailed exploration of the dose-response curve for many combinations of endpoints, treatments, covariates, and competing products

**Response Selection**

**Covariates, Assumptions**

**Controllable Inputs (Treatments, Competing Therapies & Doses)**

**Output Controls**

**Plots Display Trends**

Shaded area shows prediction interval for expected dose-response or response as a function of other explanatory variables (e.g., dose, time)

Dotted horizontal line(s) show defined success ranges, or "cut points" based on product profiles

Vertical lines show explanatory variables of interest (e.g., dose, time)

**Tables Display Details**

Tables display quantitative estimates of prediction intervals or other information

Alanapine	Inferior	Equivalent	Superior
100.0	70.4%	27.6%	2.0%
150.0	40.3%	41.9%	17.8%
200.0	27.1%	38.3%	34.6%

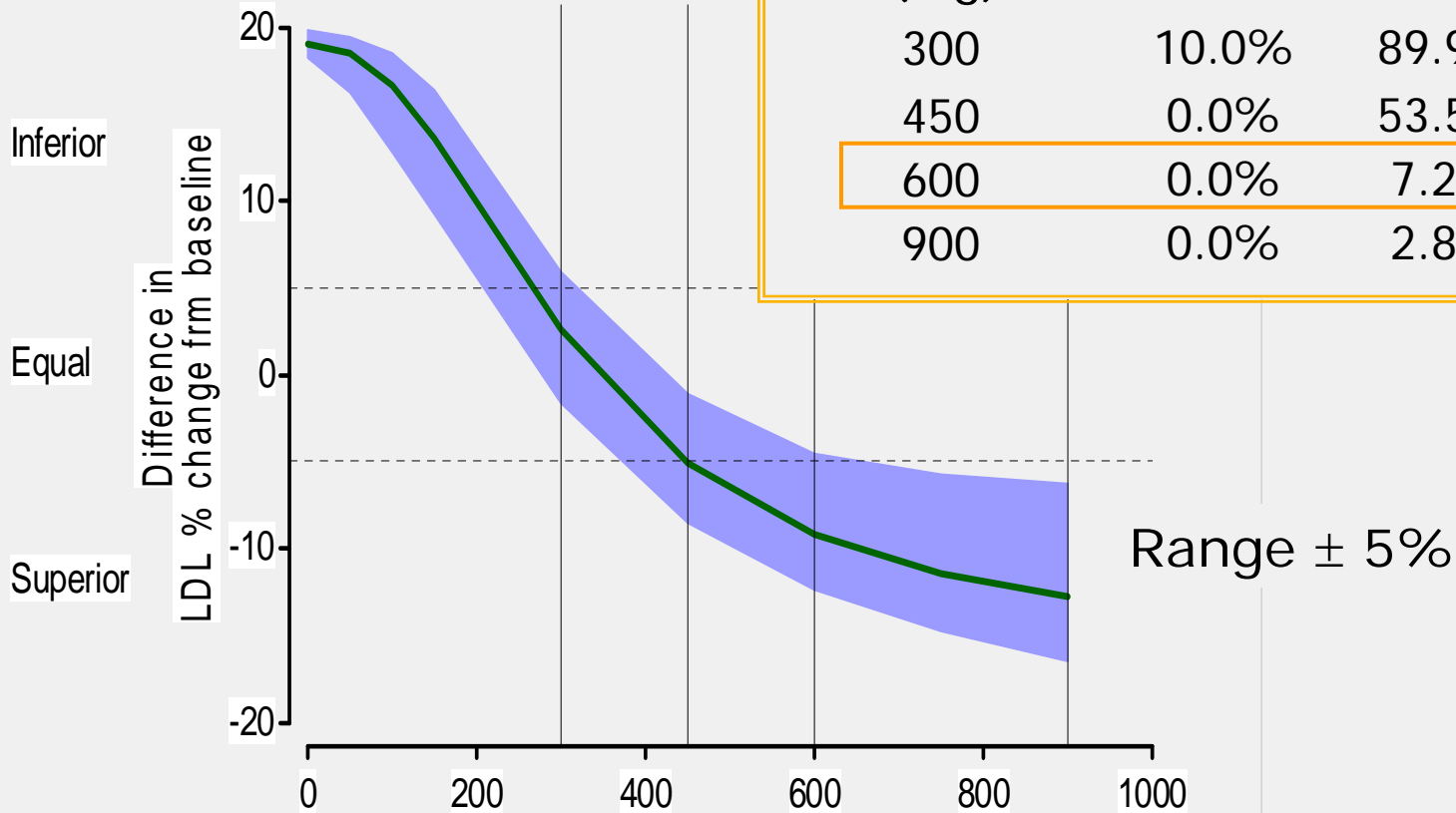
# Q1: What is the probability that gemcabene monotherapy is clinically superior to ezetimibe 10 mg?

## Difference in LDL % change frm baseline vs CI1027

Atorvastatin: 0

Ref: Atorvastatin: 0 + Ezetimibe: 10

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%



# Q1: What is the probability that gemcabene monotherapy is clinically superior to ezetimibe 10 mg?

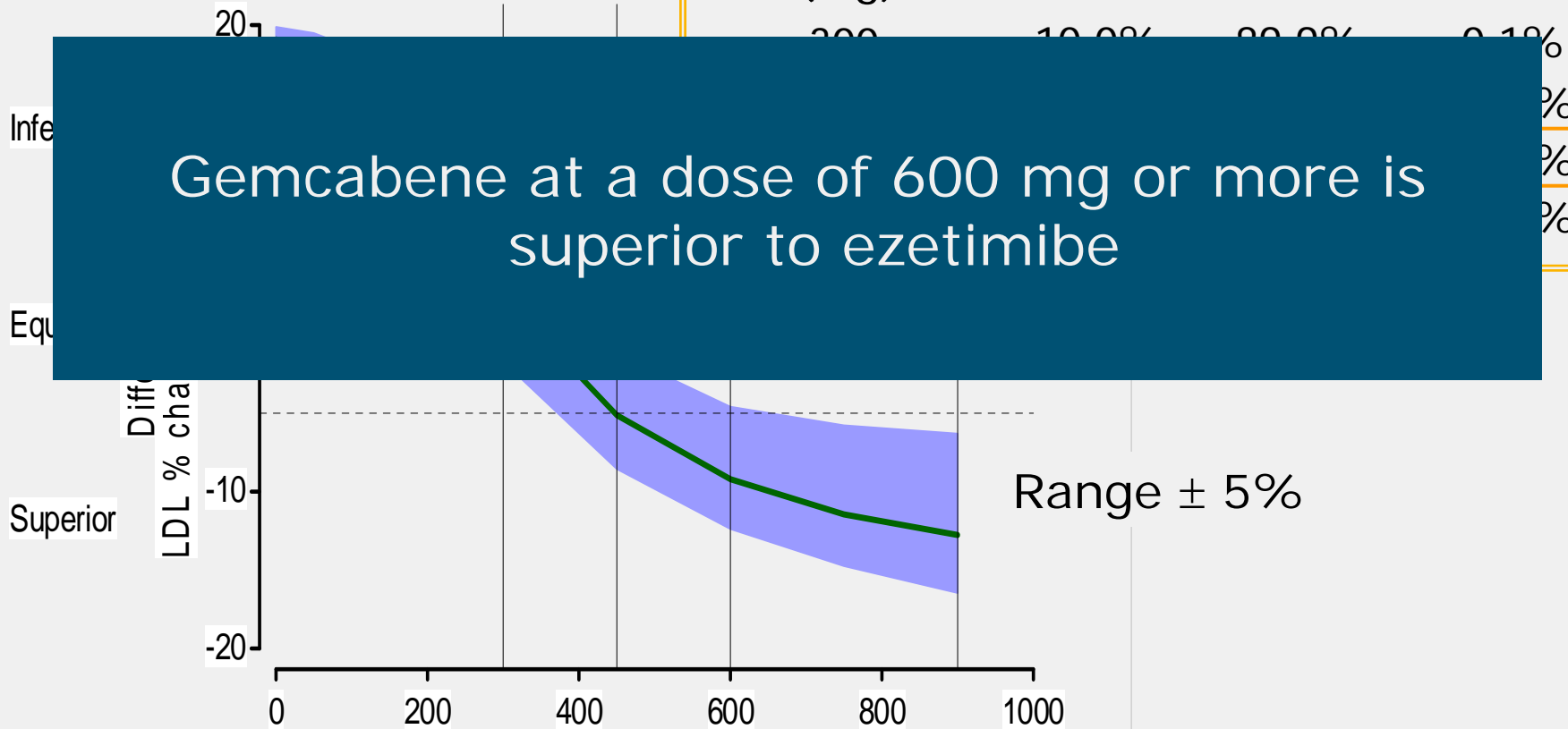
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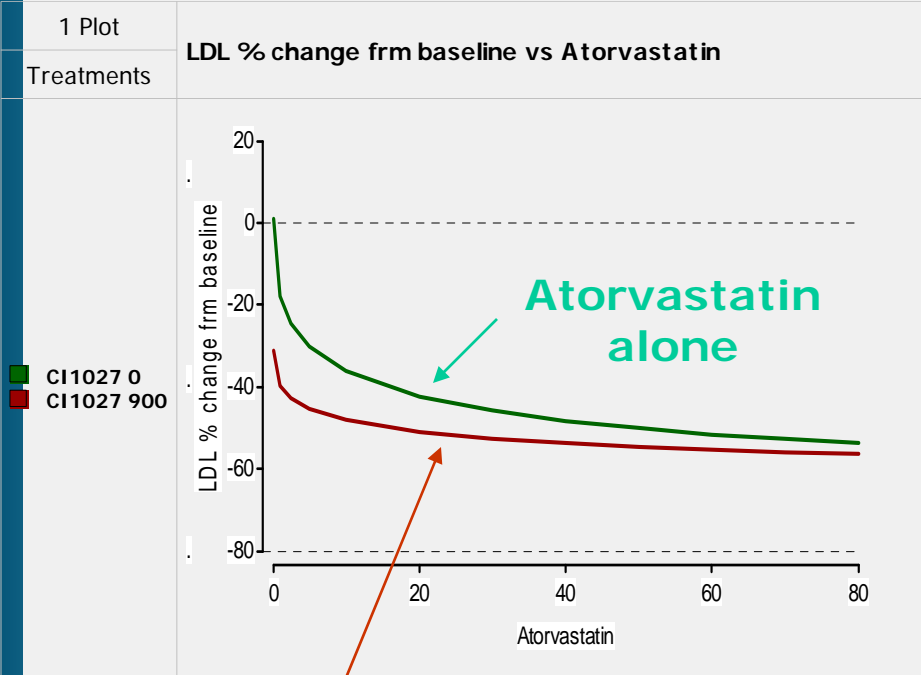
Gemcabene (mg)	Inferior	Equal	Superior
0	10.0%	89.0%	0.1%
200	10.0%	89.0%	0.1%
400	10.0%	89.0%	0.1%
600	10.0%	89.0%	0.1%
800	10.0%	89.0%	0.1%
1000	10.0%	89.0%	0.1%

Gemcabene at a dose of 600 mg or more is superior to ezetimibe

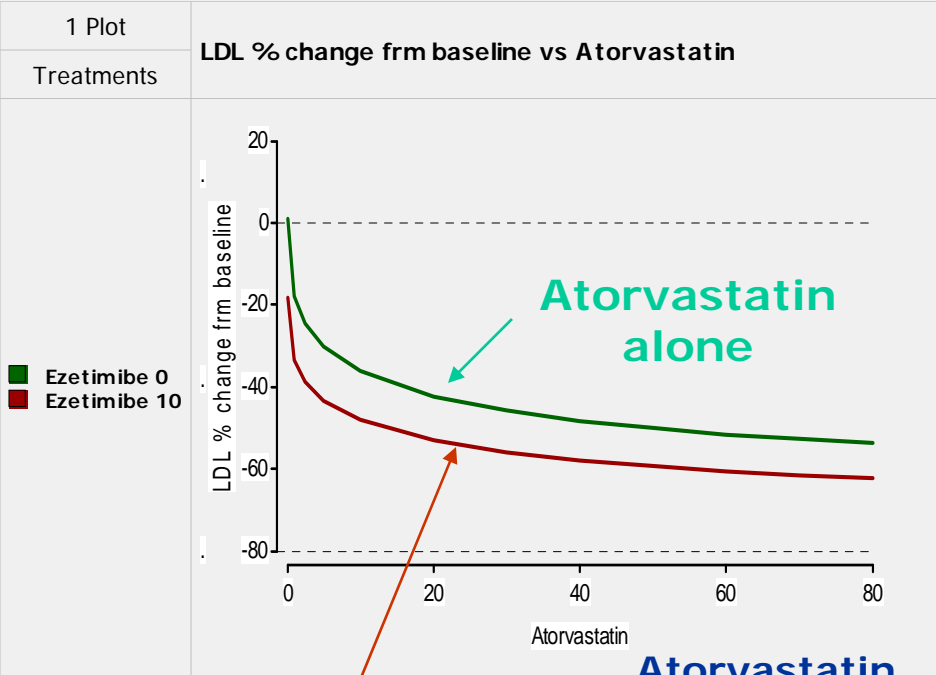


# Q2: What is the probability that, in combination with a statin, gemcabene is clinically superior to ezetimibe?

## LDL % Change from Baseline



+ Gemcabene 900 mg

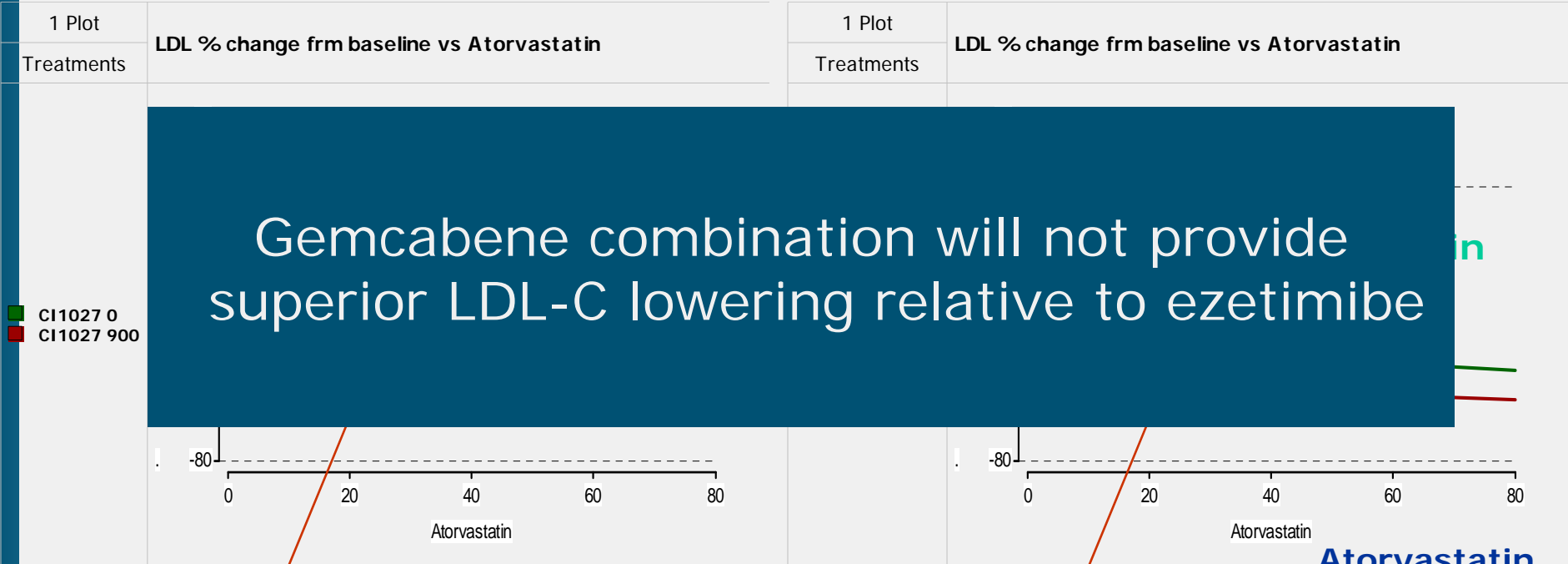


+ Ezetimibe 10 mg

Atorvastatin dose (mg)

# Q2: What is the probability that, in combination with a statin, gemcabene is clinically superior to ezetimibe?

**LDL % Change from Baseline**



**+ Gemcabene 900 mg**

**+ Ezetimibe 10 mg**

**Atorvastatin dose (mg)**

## Q3: Given the magnitude of LDL-C lowering across the gemcabene + statin dose range should clinical development continue?

Data Analysis Method	Data Base	Assumptions	Mean (95% CI)	Comments
			<b>Gemcabene Combo - mono</b>	
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
			<b>Ezetimibe Combo - mono</b>	
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

### Q3: Given the magnitude of LDL-C lowering across the gemcabene + statin dose range should clinical development continue?

Data Analysis Method	Data Base	Assumptions	Mean (95% CI)	Comments
			<b>Gemcabene Combo - mono</b>	
ANCOVA	Phase IIIA trial	Few	4.8	Traditional analysis
M F				1 1/2 al
M F				ion ity
	historic data			competitor level of LDL-C lowering

The gemcabene 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.

### Q3: Given the magnitude of LDL-C lowering across the gemcabene + statin dose range should clinical development continue?

Data Analysis Method	Data Base	Assumptions	Mean (95% CI)	Comments
			<b>Gemcabene Combo - mono</b>	
ANCOVA	Phase IIa trial	Few	4.8	Traditional analysis
M				1/2 al
M				on ty
	historic data			competitor level of LDL-C lowering

Development of gemcabene was discontinued.

# Value of MBDD approach for gemcabene

Application of exposure-response based model allowed the team to extract knowledge from all relevant gemcabene and competitor data, minimizing uncertainty

The availability of integrated dose-response models for gemcabene and competitors guided informed decision-making during early development.

- 7 key efficacy and safety endpoints could be integrated to make trade-offs

Based, in part, on the quantitative knowledge obtained through M&S the development of gemcabene was discontinued after one Phase IIA trial in the target population

This approach resulted in a more confident decision without further investment of time and money.

# Concluding Remarks

Modeling provides the means for integrating knowledge and using it for quantitative decision-making.

Exposure - response models are key to allow extrapolation to other populations and to designing further studies.

Clinical information about previously developed drugs may be exploited to develop models for predicting clinical outcomes.

Such prior knowledge (prior information + models) can be exploited to accelerate clinical development.

M&S can be exploited to answer important clinical questions; appropriate display of the results is critical to information transfer and decision-making within clinical teams.