

Accelerating profitable CNS compound development

- Pre-clinical to Phase III
- Bayesian Modeling
- Adaptive Trial Design
- Decision Analysis

Neuroscience Drug Commercialization Windhover Therapeutic Alliances Series

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Pharsight Corp.



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Pharsight Corp. Overview

- **Profile**

- Founded in 1995 with IPO in August 2000
- Offices in Mountain View, CA (HQ) and Cary, NC (R&D)
- Global headcount approximately 90
- Stock traded OTCBB: PHST

- **Key Industry Considerations**

- Large pharmaceutical and biotech marketplace
- Outsourcing of development activities escalating
- Rising drug development costs driving need for analytical drug development tools
- FDA focus on modeling & simulation for Critical Path Initiative

- **Key Company Considerations**

- Leading innovator in modeling & simulation
- Largest base of modeling & simulation skills and experience
- Leverageable software and professional service business models
- Industry standard software for PK/PD analysis
- FDA Cooperate Research and Development Agreement (CRADA)



FDA Influence: Critical Path Initiative



FDA Issues Critical Path Paper - June 2004

- The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product.

FDA Unveils Critical Path Opportunities List - March 2006

- #51 Clinical Trial Simulation. Clinical trial simulation can predict efficient designs for development programs that reduce the number of trials and patients, improve decisions on dosing, and increase informativeness. Stakeholders are looking for first steps, such as identification of tools and best practices.

FDA and Pharsight sign CRADA - June 2006

- Pharsight will make available a comprehensive suite of software tools, including: Pharsight[®] Knowledgebase Server[™] (PKS[™]), PKS Validation Suite[™], WinNonlin[®] Validation Suite[™], Trial Simulator[™] and Drug Model Explorer[™] (DMX[™]).
- FDA will use the Pharsight tools to review clinical trial data, especially for clinical pharmacology and clinical safety reviews, and will provide feedback to Pharsight.

Strategic Consulting Services: a Multi-Disciplinary Team



- Over 20 PhD and/or MD scientists
- World-class experts from industry, FDA, academia, and consulting
- Expertise in clinical pharmacology, pharmacostatistics, biostatistics, decision science, genomics, and mathematical modeling & simulation of drugs and diseases
- Service in all major drug development geographies, including US, EU, and Japan

Pharsight's expertise supports global clientele.

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Top 50 Pharma

(Med Ad News, Parexel R&D Sourcebook 2004/5)

Pfizer	Elan
GlaxoSmithKline	Baxter
Johnson & Johnson	Eisai
AstraZeneca	Merck KGaA
Aventis	Daiichi
Novartis	Chugai
Roche	Serono
Merck	Chiron
Bristol Myers Squibb	Alcon
Eli Lilly	Altana
Wyeth	Genzyme
Abbott Laboratories	Mitsubishi
Schering Plough	Amersham
Bayer	Kyowa Hakko
Boehringer Ingelheim	Shionogi
Sanofi-Synthelabo	Solvay
Amgen	Taisho
Takeda	Allergan
Schering AG	Forest
Sankyo	Tanabe
Genentech	Teva
Akzo Nobel	Bausch & Lomb
Yamanouchi/Astellas	3M
Novo Nordisk	Proctor & Gamble
Fujisawa/Astellas	UCB Pharma

Leading Biotech

(SG Cowan, Parexel R&D Sourcebook 2004/5)

- Amgen**
- Biogen Idec**
- Celera Genomics**
- Cephalon**
- Chiron**
- CV Therapeutics**
- Exelexis**
- Genentech**
- Genzyme**
- Gilead**
- Human Genome Sciences**
- ICOS**
- MedImmune**
- Millennium**
- Neurocrine**
- Protein Design Labs**
- Regeneron**
- Transkaryotic Therapies**
- Tularik**
- Vertex**

Experience: 119 Completed Projects in 2005 alone. 24 new consulting clients. Cumulative experience in all phases and all major TA's.



Cumulative Experience by Therapeutic Area and Phase

Therapeutic Area	Phase I	Phase II	Phase III	Phase IV
Anti-Infectives (includes HIV & HCV)	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	
Cardiovascular	✓	✓	✓	✓
Central Nervous System	✓	✓	✓	✓
Dermatology			✓	
Endocrine (includes diabetes & HRT)	✓	✓	✓	
Gastro-intestinal (GI)		✓	✓	
Genito-urinary (GU)	✓	✓	✓	
Immunomodulation (includes allergies)	✓	✓	✓	
Oncology (includes Hematology)	✓	✓	✓	✓
Ophthalmology	✓			
Pain (includes anesthetics)	✓	✓	✓	
Respiratory			✓	

Quantitative decision-making

The key to high quality decisions is decision-focused use of modeling and simulation

Model until you can choose between alternatives, then act

Integrate models:

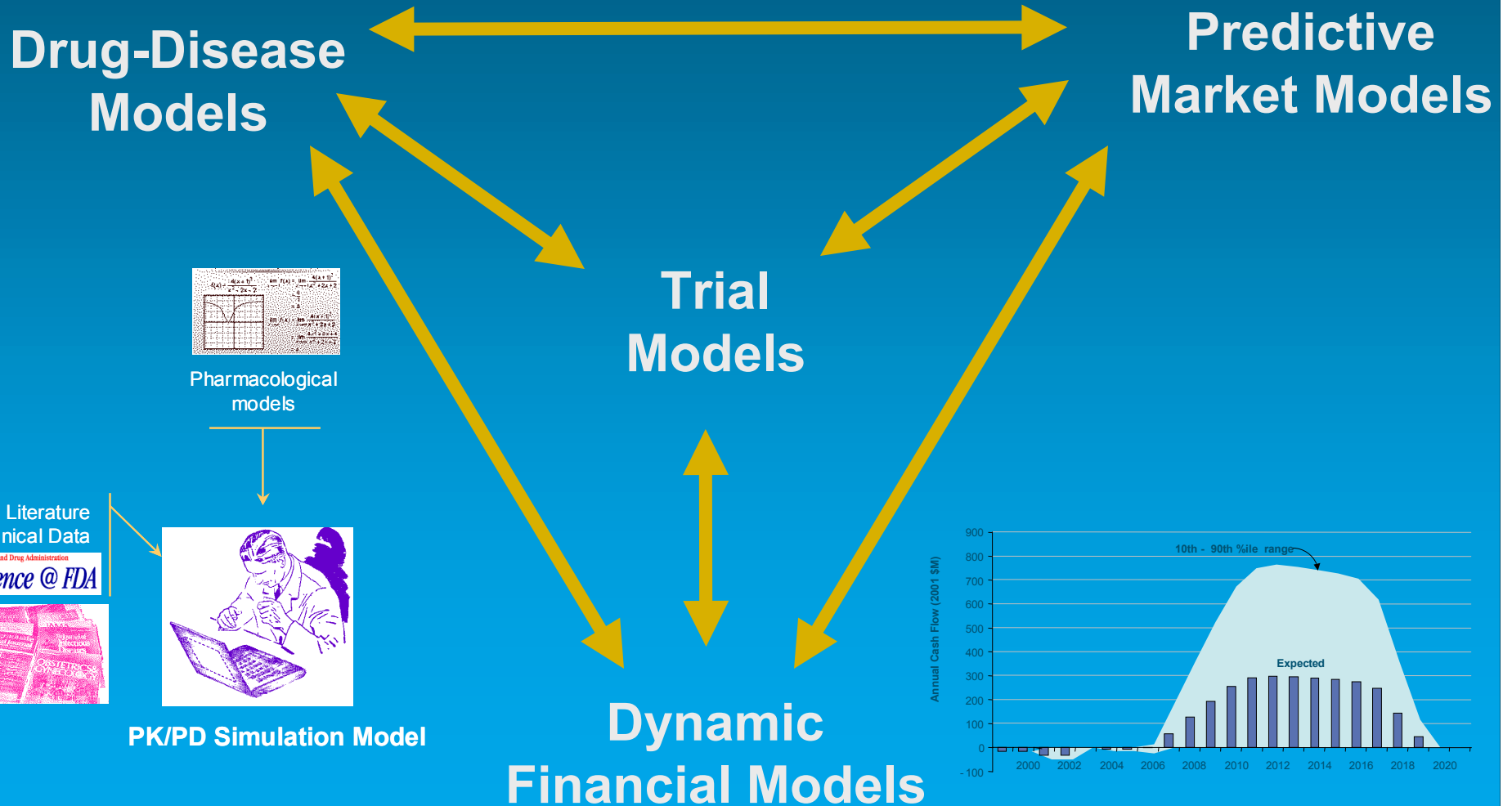
- drug
- disease
- trial
- program
- market and financial



The model-based decision process

- Establish decision criteria (at least identify the key decision-drivers)
- Leverage prior knowledge from all available sources
 - Data on the NCE of interest
 - Preclinical, Phase I safety & biomarkers, clinical safety & efficacy ...
 - Knowledge about the target disease & affected physiologic systems
 - Knowledge/data on related compounds
 - From proprietary or public sources
 - Analogs or competitors
- Build models for all responses key to strategic decisions based on that knowledge
 - Disease model
 - Drug models for the NCE of interest and related or potentially competing drugs
 - Trial models
 - Market and financial models

The foundation of the Pharsight Integrated Decision Process is science-based modeling.



Pharsight brings a wide variety of skills for decision framing, analysis and program implementation to maximize drug value.



- **Decision-Framing Tools**

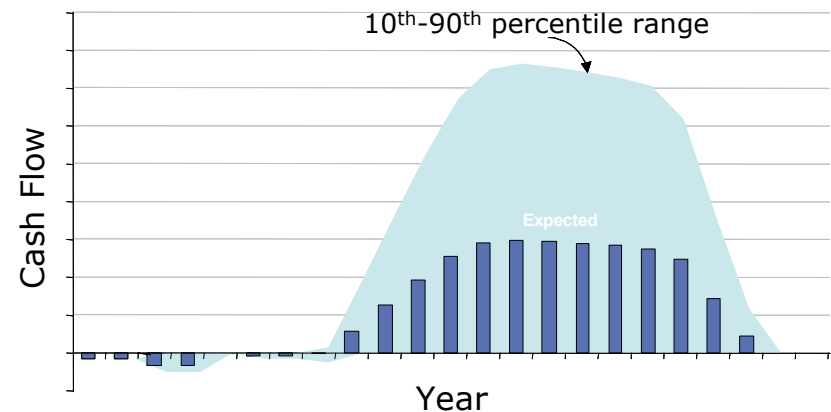
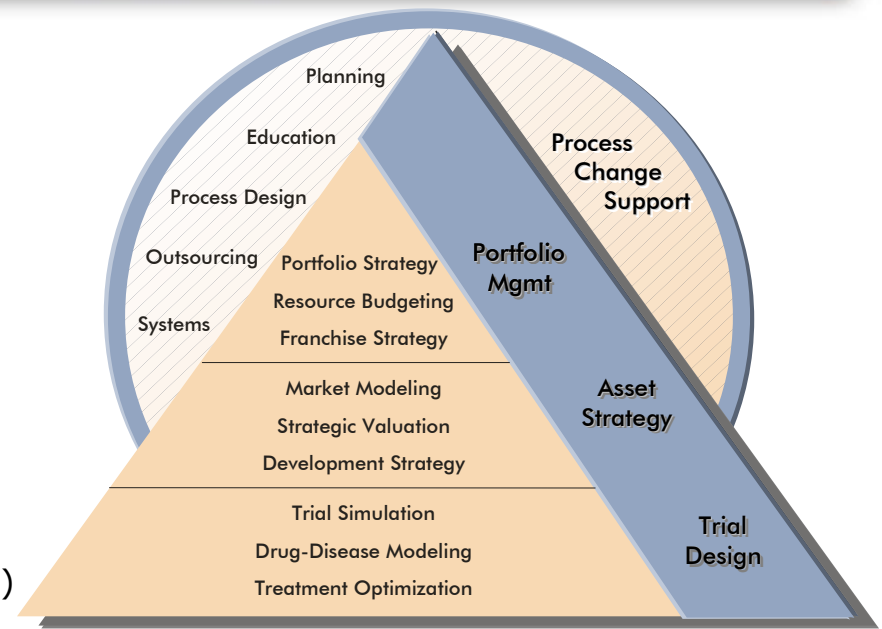
- Strategy Tables
- Objective Hierarchies
- Decision Hierarchies
- Influence Diagrams
- Decision-Risk Timeline

- **Analysis Tools**

- Decision Trees
- Simulation Models
- Cash Flow Models and Cloud Diagrams
- Portfolio Selection
- Tornado Diagrams
- Optimal Ordering Models (Formulation, Indication)

- **Implementation Tools**

- Contingency Planning
- Drug and Disease Modeling
- Adaptive Trial Designs
- Seamless Trial Designs
- Formulation Portfolio Learning & Selection
- Indication Portfolio Learning & Selection
- Trial Simulation and Optimization

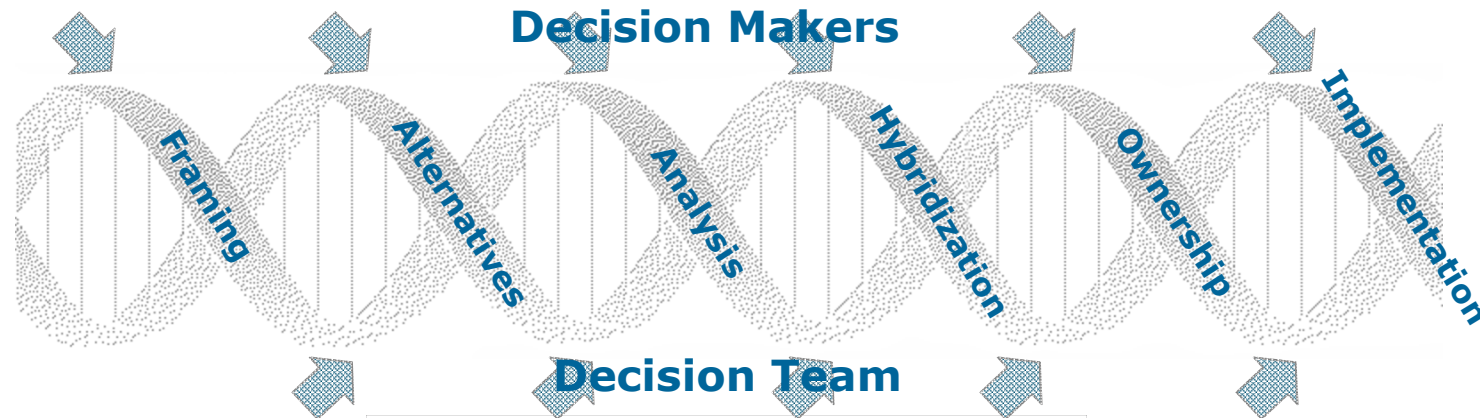


The project DNA consists of management insight, learning, team communication, ownership and implementation.

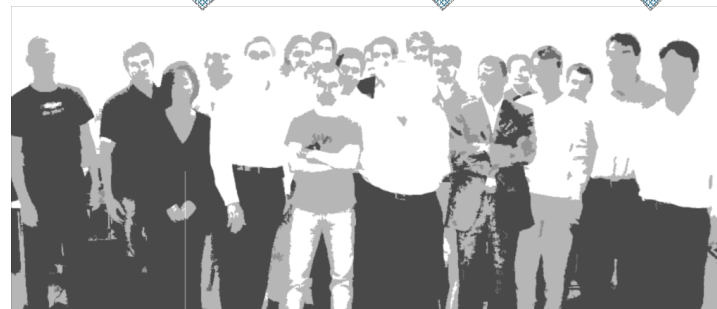
Framing: A dialog about the critical information to encompass just enough scope to lead to a high-quality decision.



Alternatives: A set of alternatives encompassing the opinions and debates across the organization.



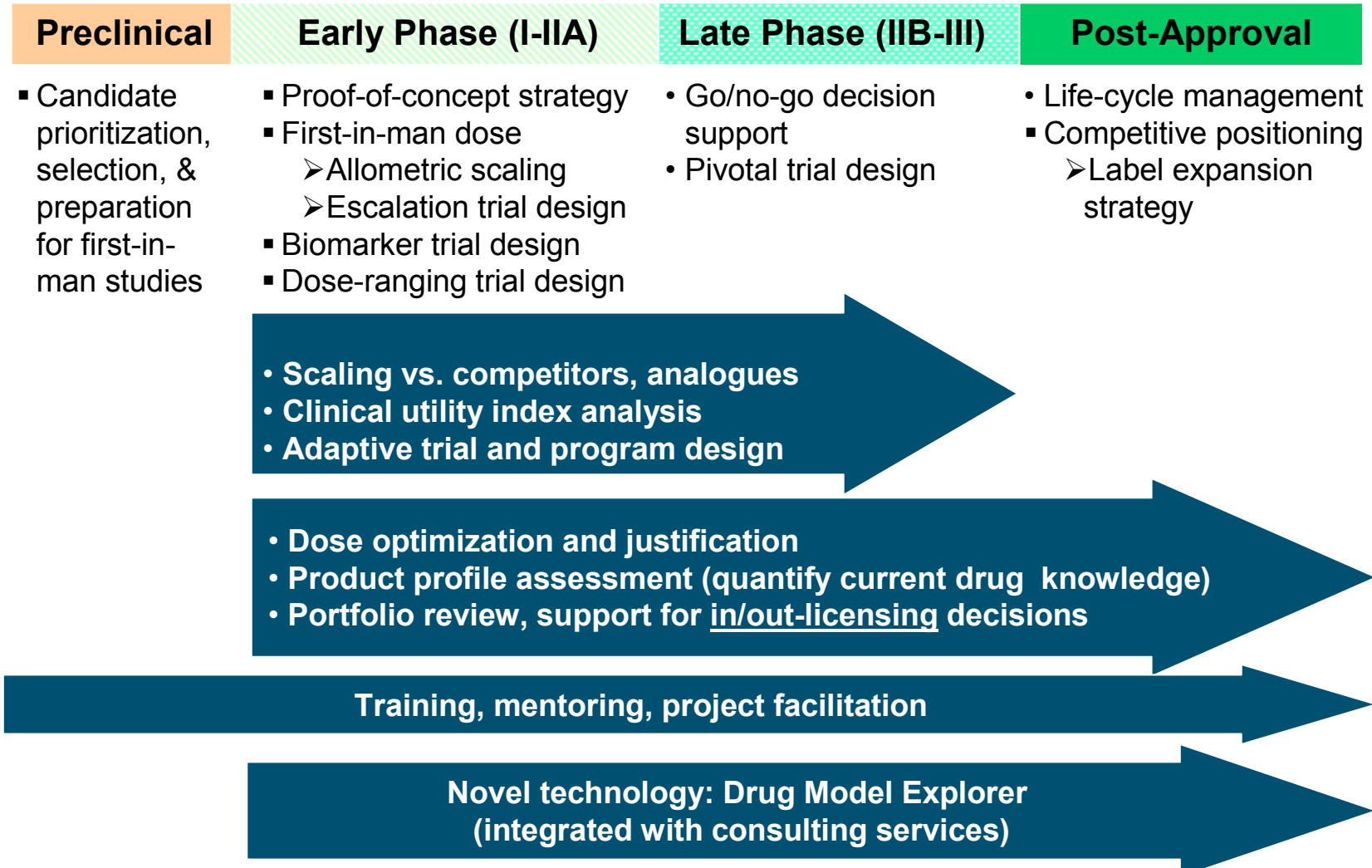
Hybridization: A new “hybrid” alternative(s) incorporating the best elements of the initial alternatives and any new insights gained.



Implementation: The design of development tactics including trial design, regulatory interaction, contingency planning, etc. to maximize the value of learning and speed time to market.

Pharsight facilitates integrated decision making at all development stages.

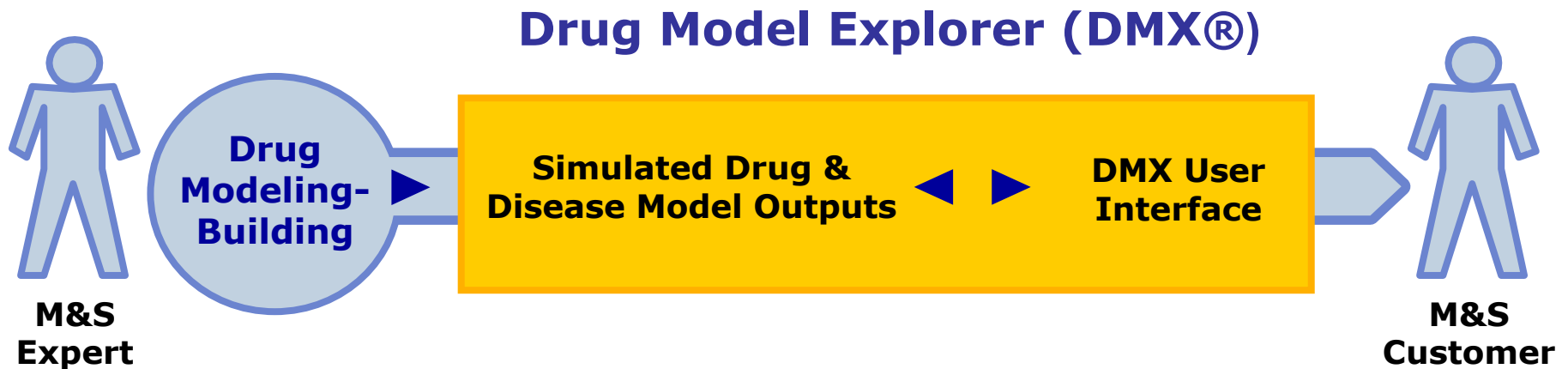
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What Is DMX?

A Tool to Explore Modeling Results in Real Time

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- DMX is a software visualization and communication tool to explore modeling and simulation results
 - Used by modeling experts to make modeling and simulation results available to teams and decision-makers
 - Used by the project team to compare performance vs. competing treatments, evaluate product profiles, and understand trade-offs
 - Used by companies to capture knowledge and update as new information becomes available

DMX is a tool for communicating these modeling and simulation results – it allows team to view and query model-based drug attributes.



Example Question: “What is the likelihood that given doses of my drug are likely to produce a response similar to or better than a competitor?”

DMX CNS Demo Version 1
View Model Documentation

1 Plot, large size
Download Plots in MSOffice Format

Difference in PANSS vs Alanapine
Diagnosis: Population
Alanapine
Reference: Lobotacain: 400.0

Alanapine	No File	Accept
50.0	99.9%	0.1%
100.0	89.6%	10.4%
150.0	64.7%	35.3%
200.0	44.9%	55.1%

Plots Display Trends

Shaded area shows prediction interval for expected dose-response

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

Vertical lines show doses of interest

Tables Display Details

Tables display quantitative estimates of prediction intervals or other information

Response Selection

Covariates, Assumptions

Controllable Inputs (Treatments, Competing Therapies)

Output Controls

DMX in the News: Pfizer Wins *Bio-IT World* 2005 Best Practices Award for Application of DMX and M&S

- Bio-IT World recently announced Pfizer Global R&D as a winner of its 2005 Best Practices Award for the application of DMX and decision-focused modeling strategies on a compound in its cardiovascular franchise

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

David Hermann¹, Wenping Wang², Christine Falcoz³, Daniel Hartman¹, Jaap Mandema⁴

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Acknowledgements: Gemcabene Team, DMX Team

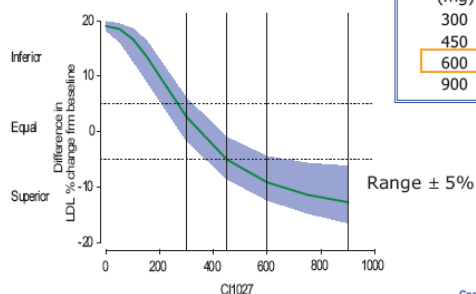
RESULTS (continued)

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.

Difference in LDL % change frm baseline vs C11027

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%

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Case Study # 1

Predicting first human dose with knowable uncertainty



- **Critical Business Issue**

- Identify plausible range of NCI clinical dose for a second-in-class compound that are equi-effective to clinical competitor dose

- **Methods Used**

- Projected human availability and clearance using pre-clinical data and allometric scaling
- Researched literature on competitor receptor occupancy and efficacious dose information
- Constructed model integrating first principle relationships ($\text{Dose} = \text{Clearance} / (F * \text{Potency})$) to project human dose for NCI with knowable uncertainty
- Tornato plots illustrating component of knowledge with most influence on uncertainty

- **Results and Impact**

- The range of possible efficacious doses provides key information to design the Phase Ia safety study
- With Phase Ia data support GO/NO GO decision to Phase Ib

Available preclinical data and model assumptions structure our knowledge.

- Available Preclinical Data
 - **Receptor occupancy (RO) assay**
Dose vs % receptor occupancy
Brain concentration vs % receptor occupancy
 - **Pharmacokinetic & Bioavailability studies**
in rats and dogs
in vitro and po data
brain and plasma data
- Model Assumptions
 - **Identical receptor occupancy (RO) will produce identical effect.**
 - **Relative RO relationship between Comparitor and NCI is similar in rats and humans i.e EC₅₀ ratios are identical**
 - **Brain/Plasma concentration ratios are similar across species.**
 - **Allometric scaling predicts human clearance**

Steady-state assumption

$$RO = \frac{Cb_{nci}^{\gamma}}{Cb_{nci}^{\gamma} + EC_{nci}^{\gamma}} = \frac{Cb_c^{\gamma}}{Cb_c^{\gamma} + EC_c^{\gamma}}$$

Distribution Ratio

$Cb = Kp \cdot Cp$

$$Cp = \frac{Dose / \tau}{CL / F}$$

$$Dose_{nci} = (EC_{50nci} / EC_{50c}) \times (Kp_c / Kp_{nci}) \times [(CL / F_{nci}) / (CL / F_c)] \times \text{Effective Dose}_c$$

Receptor
occupancy
in rats

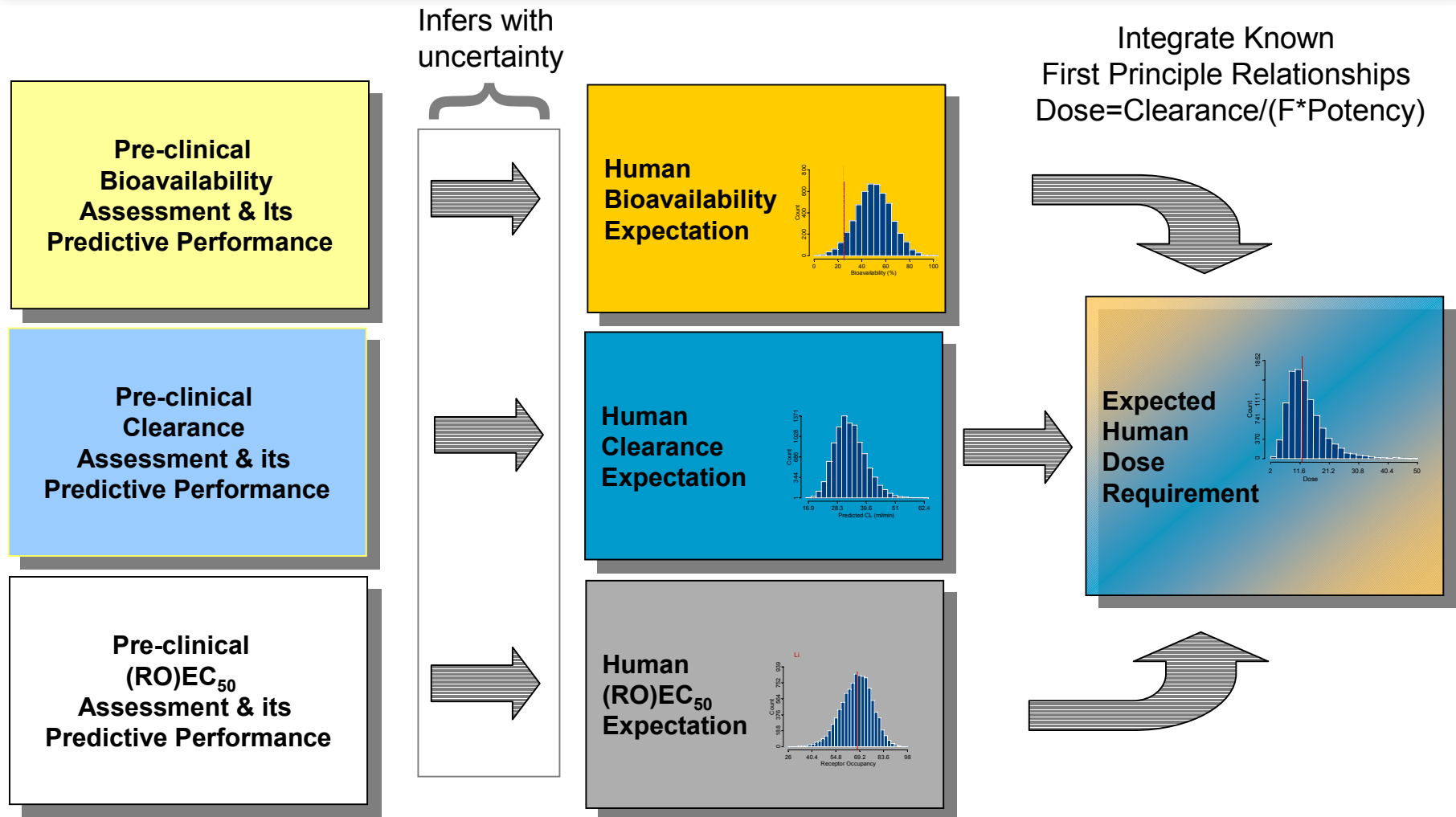
Brain/Plasma
in rats

Allometric
scaling

Literature data

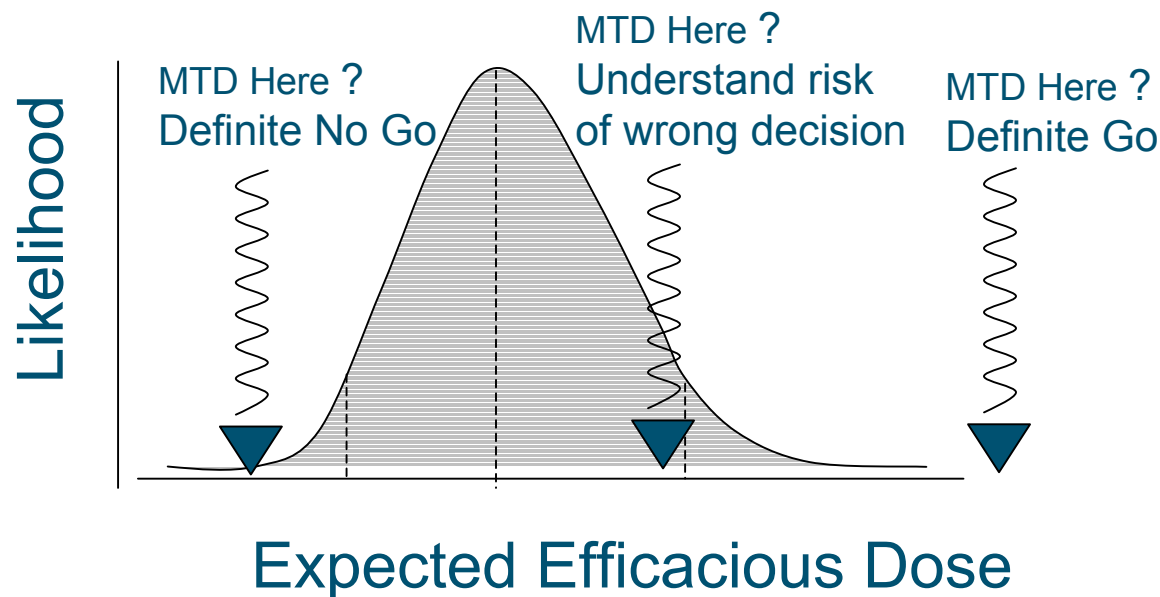
Human dose requirement was calculated with knowable uncertainty

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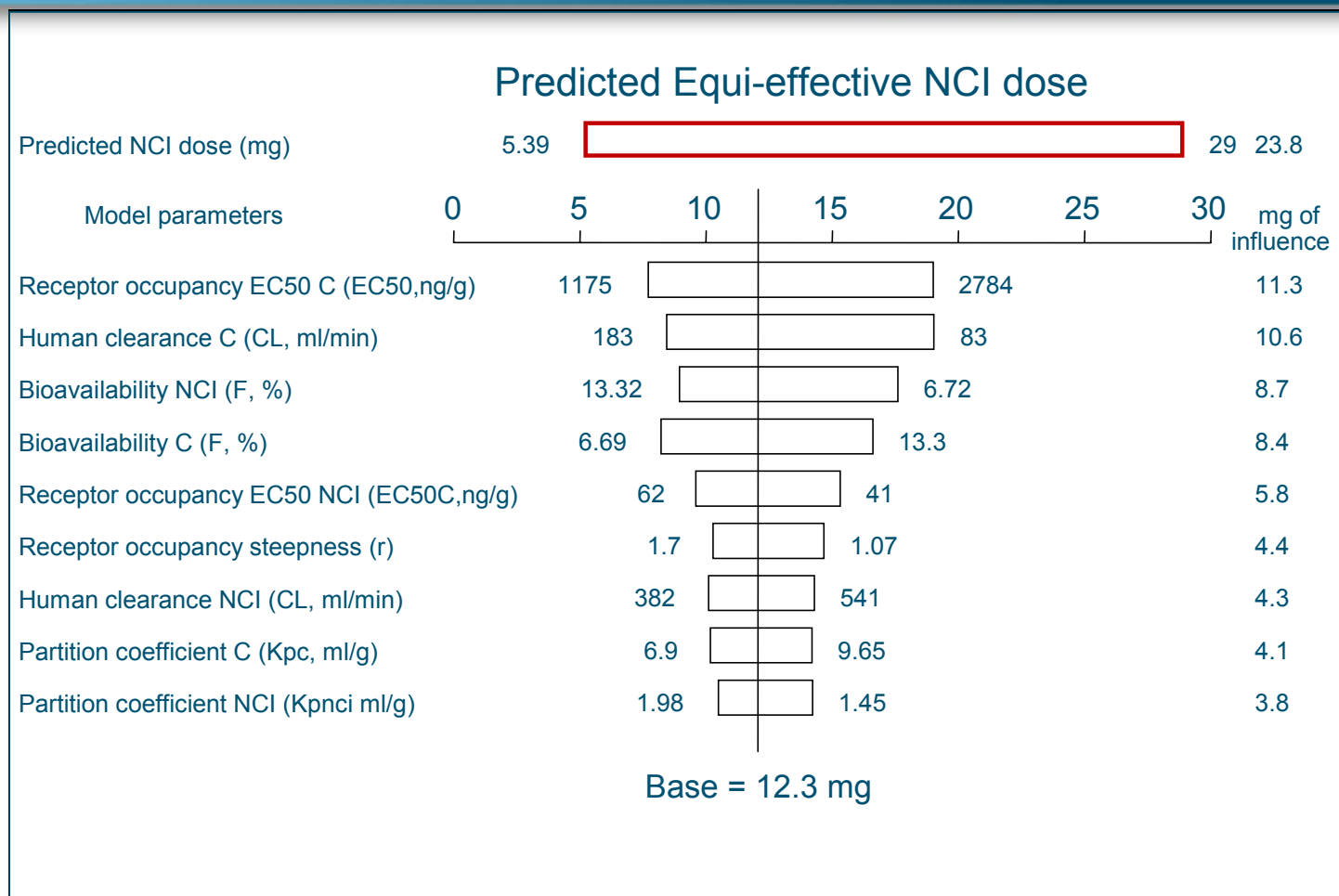


The range of possible efficacious doses informs the design of the phase 1a safety studies

- The start and stop dose in the SDSS span the possible range of efficacious doses.
- The range of doses supports CMC.
- With Phase 1a data support Go/No Go decision to Phase Ib
 - How likely is the MTD to be within range?



Tornado plot illustrates components of knowledge with most influence on uncertainty



Each bar represents the influence of a single variable on the predicted range of nci doses. The most influential variables are at the top. The vertical line is our best estimate of the predicted nci dose . The central tendency of the nci dose range can lie between 6.3 mg and 25.2 mg given the model uncertainty. The most likely value is 12.3 mg.

What questions do you have?

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The Clinical Utility Index or CUI



Clinical Utility provides a context for evaluating treatment; It estimates physician treatment preference or clinical benefit.

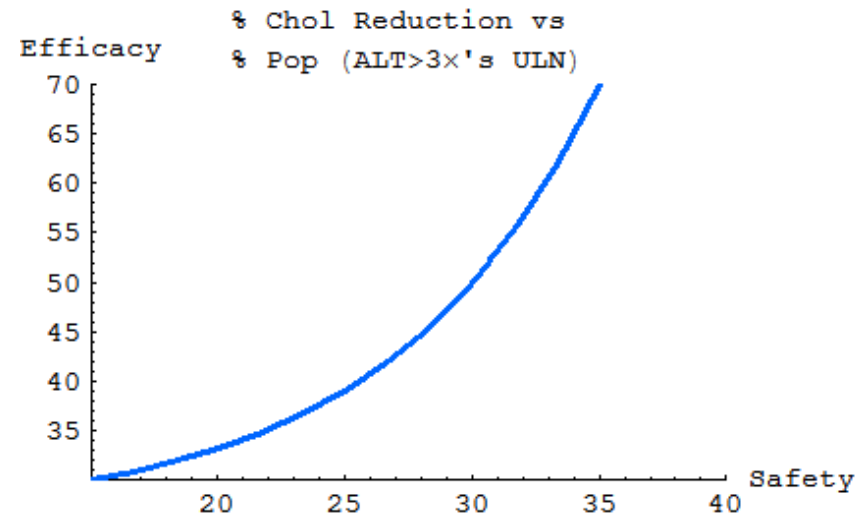
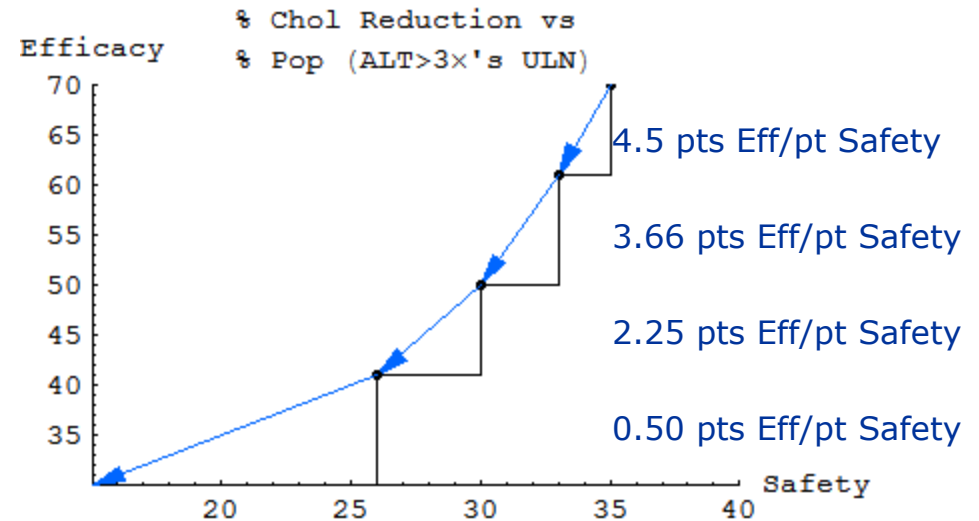
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- Every drug has benefits and risks.
- The relative importance of these characteristics depends on the disease the drug is intended to treat.
- The benefits change with dosage, patient population, etc.
- Tradeoffs must often be made among the drug effects comprising the product profile, balancing the benefits and risks.
- The Clinical Utility Index (CUI) quantifies these tradeoffs by providing a single metric for the multiple dimensions of benefit and risk.
 - **It is...** a **systematic** approach to understanding subjective preferences
a **transparent** way of weighing tradeoffs
knowledge-driven; available data are used; if not rely on expert opinion
 - **It is not** an “**objective**” measure in the sense of a physiological measurement

Example: Indifference in efficacy vs safety

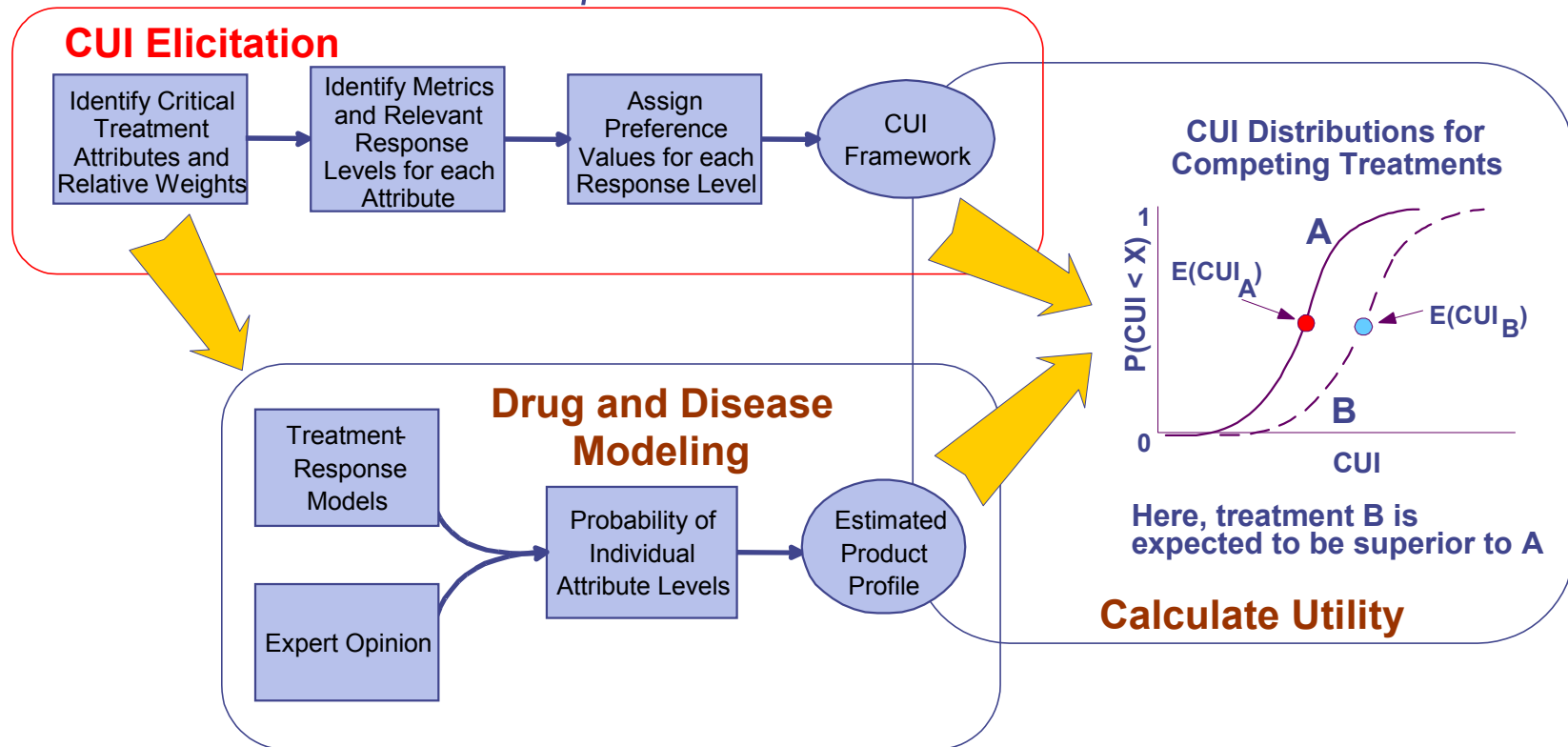
Continuing in this way, we could, in principle, trace out a smooth relationship. This cumbersome process needs to

- Suppose we have a drug
 - that can lower cholesterol by 70%
 - but 35% of the population has ALT in excess of 3 x's ULN
- Most companies would be willing to give up some efficacy to gain safety
- As we gain safety we are willing to give up less and less efficacy for safety
- Tradeoffs of this type are assessed via the CUI



The framework for the CUI is elicited from the project team or “thought leaders.”

When combined with models of response, the CUI provides an estimate of relative patient benefit



The CUI can be validated against marketed competitors. The CUI is an early phase replacement for cost conjoint analyses.

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Validity

- Once constructed, the product profiles of competitive drugs already marketed or in development can be isolated.
- The CUI provides a rank order for these product profiles.
- Current market share of the competitors should be roughly proportional to both CUI ranking and/or CUI value itself.
- This ranking exercise provides a “sanity check” for the internal validity of the constructed scale. If the scale does not preserve market share ranking, the scale must be reassessed to be congruent.

Conjoint or Discrete Choice Analysis

- Both methods model preferences and tradeoffs across different aspects of possible treatments.
- Both methods map all possible product profiles along a single dimension of utility.
- The methods differ based on how and from whom they are constructed.

What questions do you have?

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Case Study #2
CUI in Sleep Maintenance
Insomnia

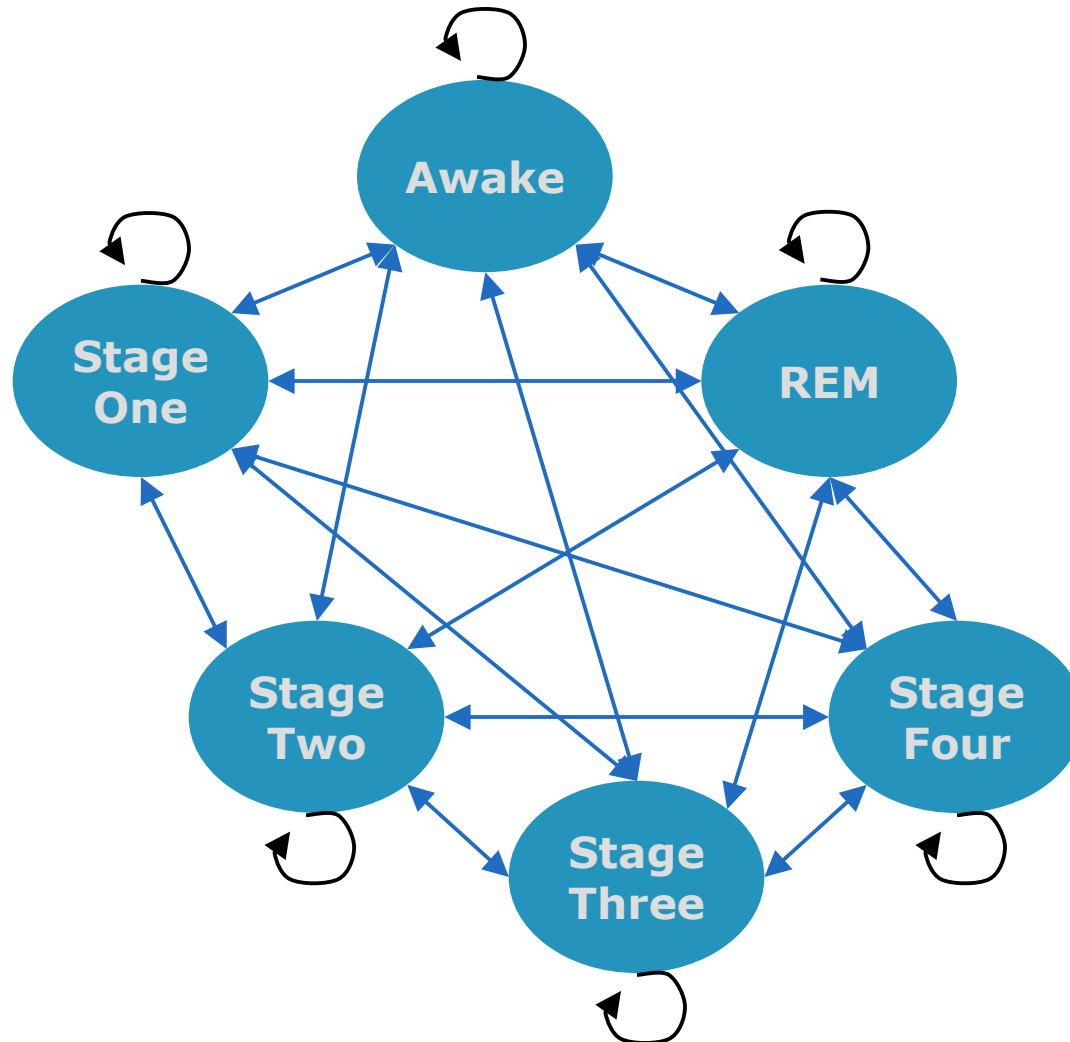


The clinical utility of compounds for sleep maintenance insomnia to prescribing physicians was estimated by the client development team.

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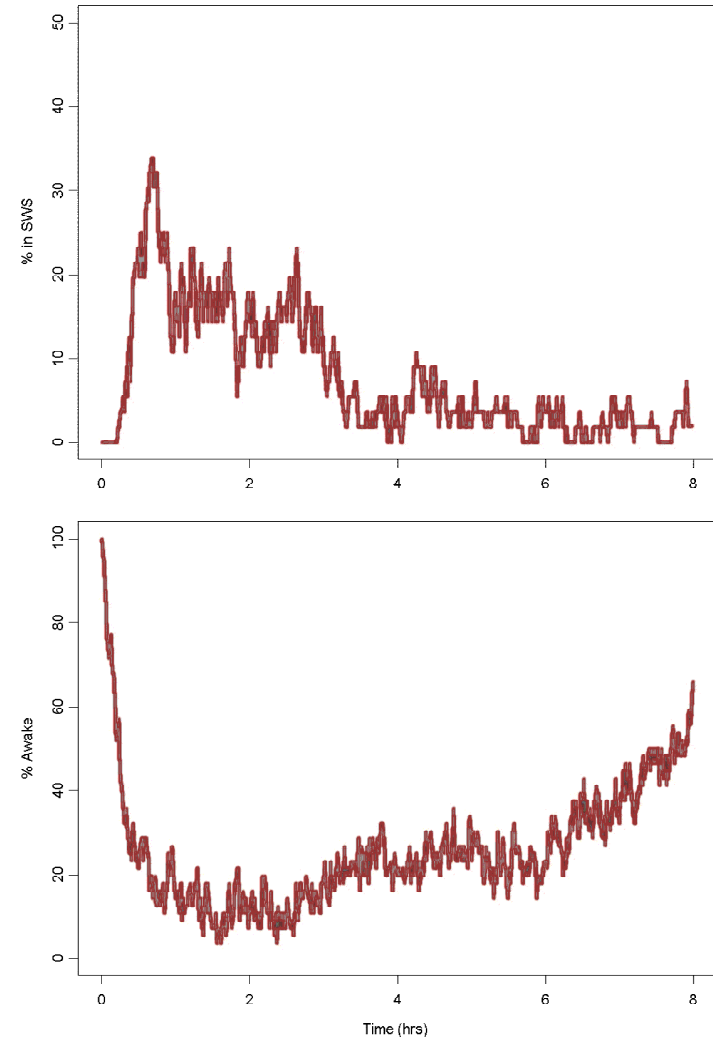
- The CUI is a surrogate marker for the “uptake” by prescribing physicians upon FDA approval
- The clinical utility of the compound has characteristics that are both objective and subjective patient outcomes during the program trials.
- The M&S results are limited to the objective measures of sleep quality in the trials and QTc prolongation.

A six-state, time and drug-dose & disease-state dependent Markov model provided the basis for efficacy and trial design.



The drug disease model showed the efficacy of *Pharsight* the drug during 8 hrs of sleep.

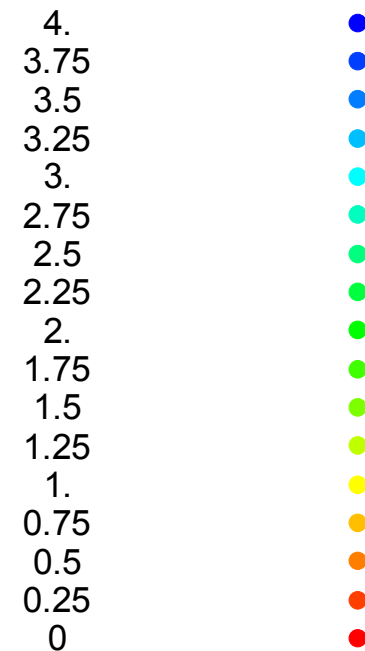
- A dose of 2 mg seemed to fall in the sweet spot and product QTc prolongation less than the FDA limit of 5 ms.
- Slow Wave Sleep increased on drug early during the first half of the night.
- The Percent Time Awake decreased later in the night.
- The drug was progressed to the next phase of development.



Objective measures of WASO, Total Sleep Time and “Vigor” (to a lesser extent) are important to physicians.

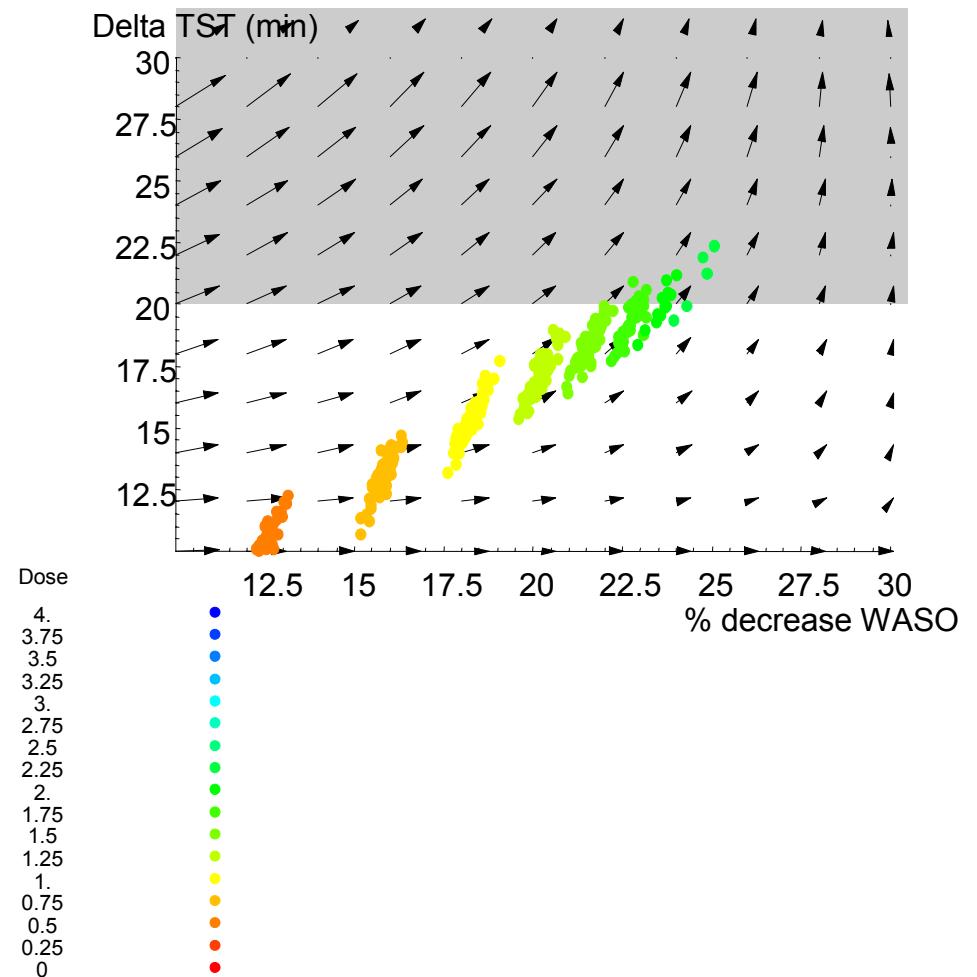
- Pharsight ran the sleep model for various doses (color coded) estimating WASO, SWS and TST on a population basis.
- These simulations were grouped into a low SWS-time (surrogate for Vigor) case and a high SWS-time case. The model shows high correlation among these important outcomes.

Dose



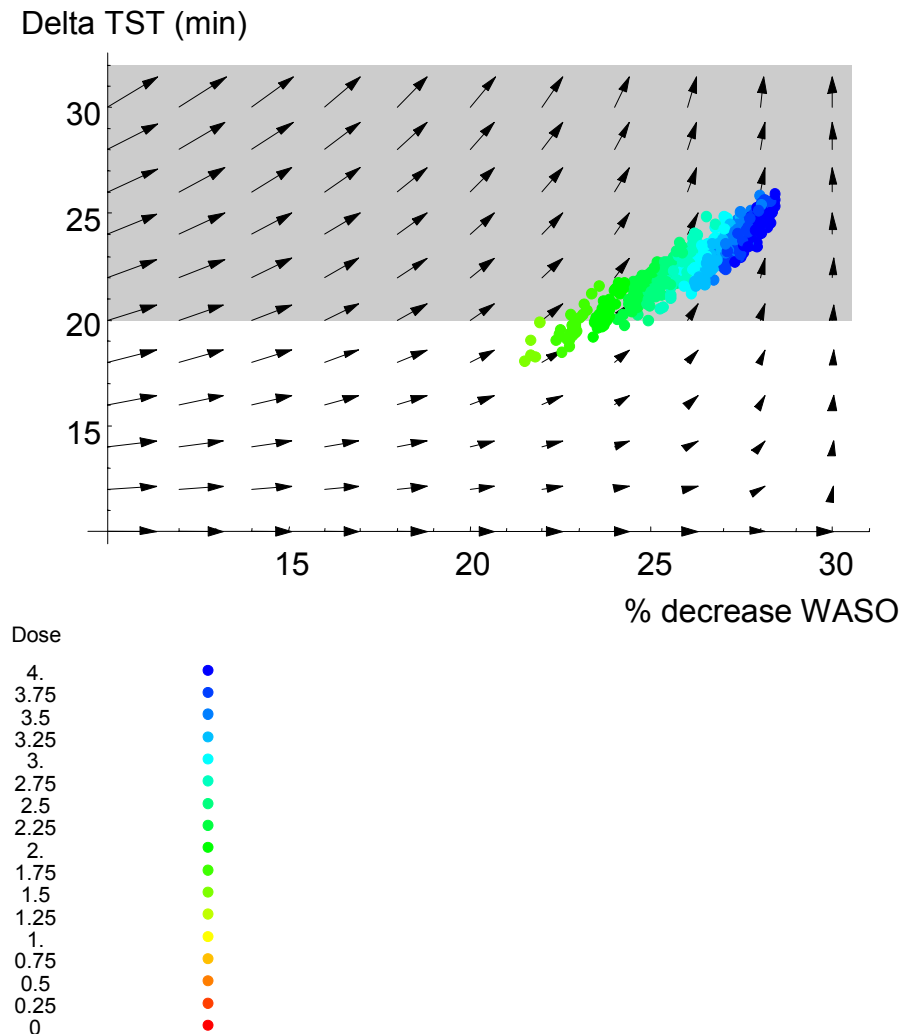
Low SWS times were associated with low doses. There is no chance of hitting the "Sweet Spot" with doses below 1.5 mg.

- Arrows show the direction of increasing clinical utility
- The gray box is the "sweet spot" for the target product profile as established in the CUI
- Almost all doses below 2 mg fall outside the sweet spot.
- Change in TST is relative to placebo.
- % decrease in WASO is relative to placebo.

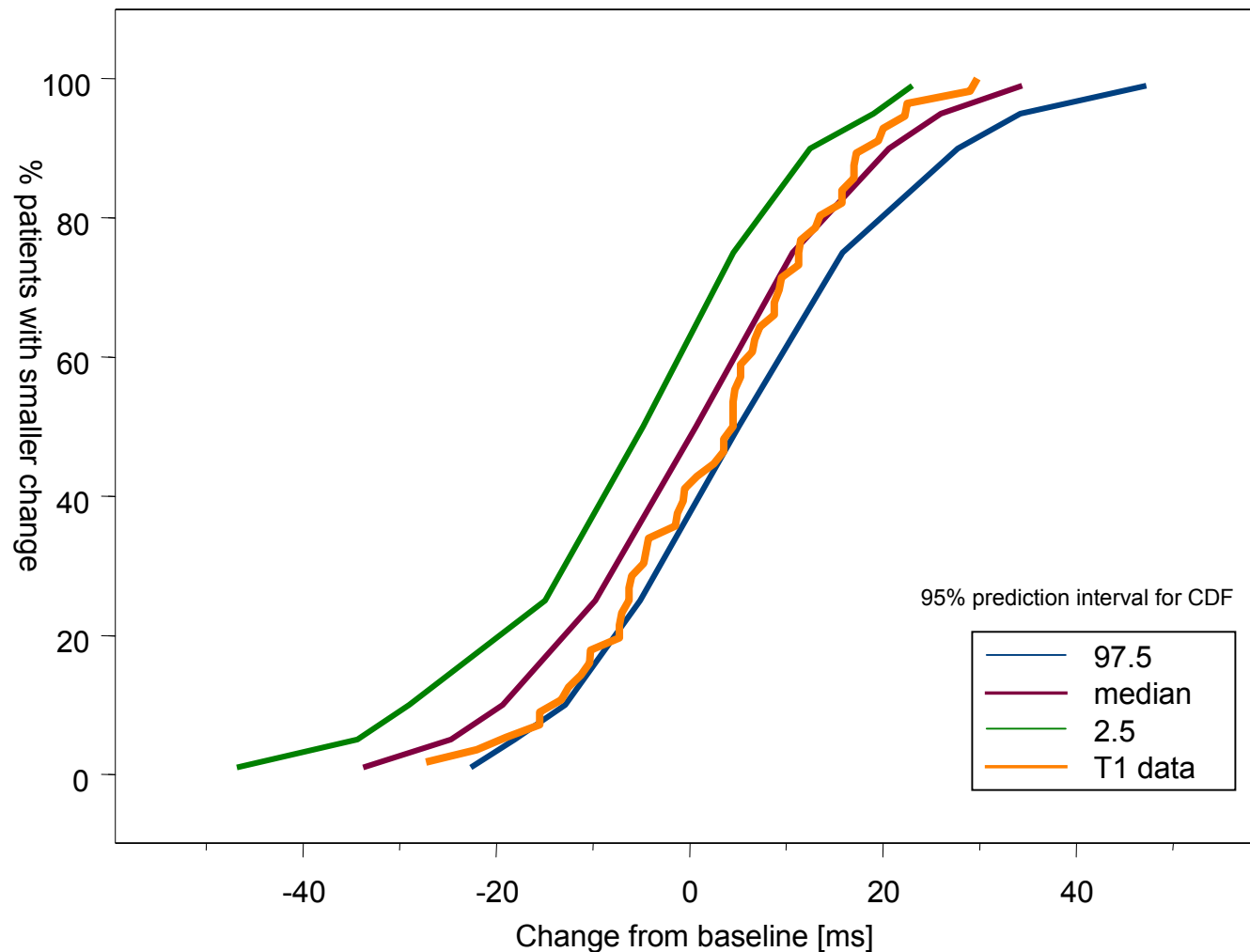


High SWS times were associated with high doses. There is almost no chance of hitting the “Sweet Spot” with doses below 2 mg.

- Arrows show the direction of increasing clinical utility
- The gray box is the “sweet spot” for the target product profile.
- All doses are above 1.5 mg.
- Some 2 mg doses fall outside the “sweet spot”.
- Change in TST is relative to placebo.
- % decrease in WASO is relative to placebo.



M&S predicted observed patient variability.
Trial-1 QTc change from baseline fell within
the model's prediction interval.



Conclusions: A limited dosing interval exists that maximizes the clinical utility and exceeds the Target Product Profile for objective measures of sleep quality.

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- Even if a 1 mg is significantly different from placebo, the combination of efficacy outcomes is highly unlikely to be sufficiently high to meet the target product profile.
- QTc prolongation **is** significant at doses greater than 5mg.
- At doses of 2 mg and below, QTc prolongation is clinically insignificant in a patient population with mean age 65 or younger.
- All trials designed to treat patients significantly older than 65 should be modeled to carefully choose dosing and numbers of EKG measurements. There is a chance that random variation could provoke FDA comments in this sub-population.
- The CUI is maximized at about 2.25-2.5 mg over the subset of items modeled.

What questions do you have?

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Illustration: Adaptively finding optimal dose via the CUI



Illustrative trial of an adaptive dose trial for a cancer agent (simplified actual trial)



Trial Description

- 4 doses : 1/4, 1/2, 3/4, or 1 mg/m²
- 36 patients, in cohorts of size 3
- First cohort treated at 0.25 mg/m²
- $\pi_{\text{Tox}} = 0.40$ = upper limit on Pr(Toxicity)
- $\pi_{\text{Eff}} = 0.20$ = lower limit on Pr(Efficacy)

- How do find the best dose, given

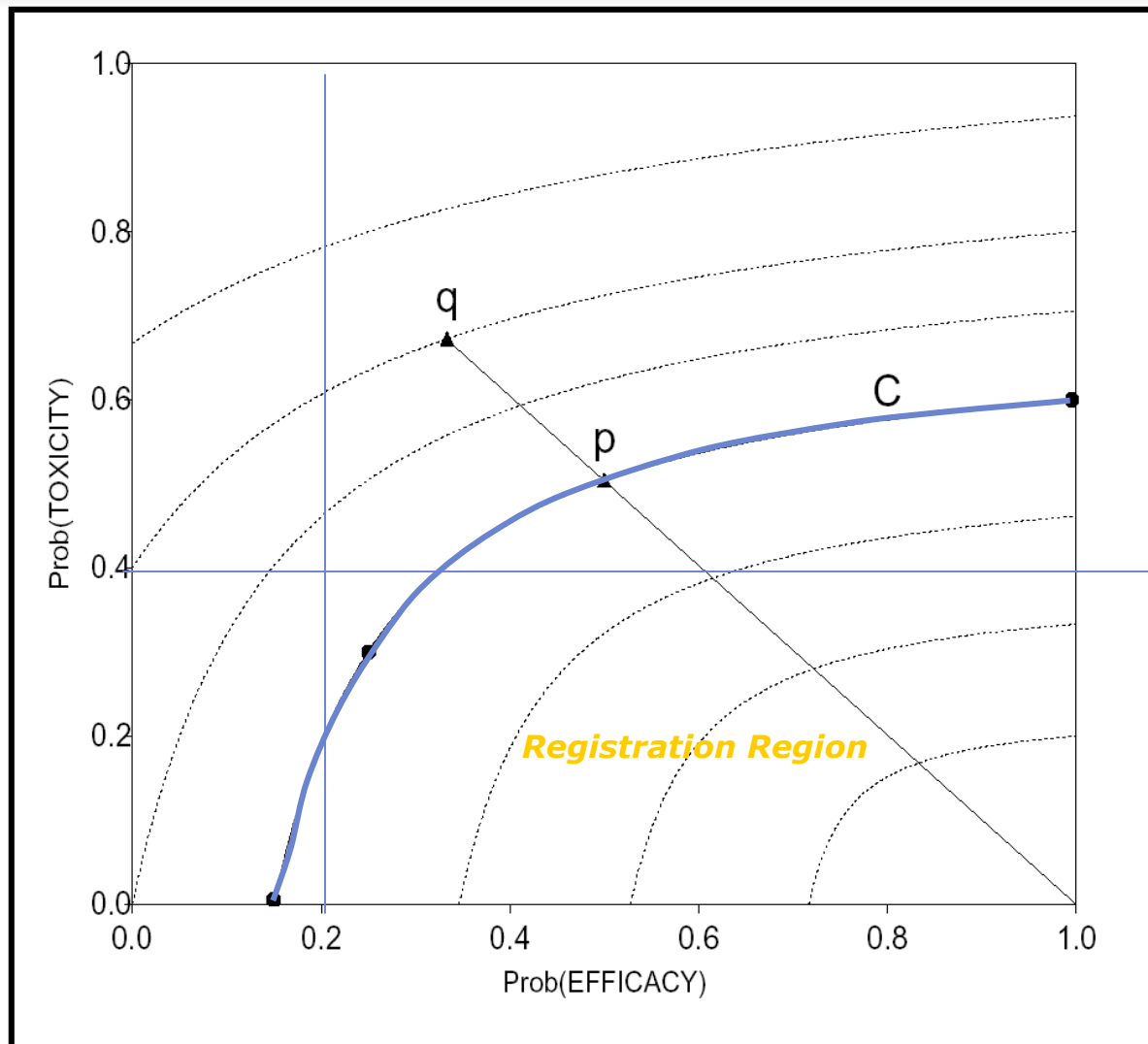
$$\pi_{\text{Eff}} (\text{min}) = .20 \text{ and } \pi_{\text{Tox}} (\text{max}) = .40$$

- and the current data from the trial? We know Dose d is an *Acceptable Dose*
 - if it is not likely that either
- $\pi_{\text{Eff}}(d) < .20$ or $\pi_{\text{Tox}}(d) > .40$
- But, how may one compare acceptable doses in terms of the two-dimensional criterion

$$\{ \pi_{\text{Eff}}(d) , \pi_{\text{Tox}}(d) \} ?$$

Value Space consists of efficacy-toxicity tradeoff contours of the CUI. Given a drug at q , finding a dose along the p - q line maximizes CUI.

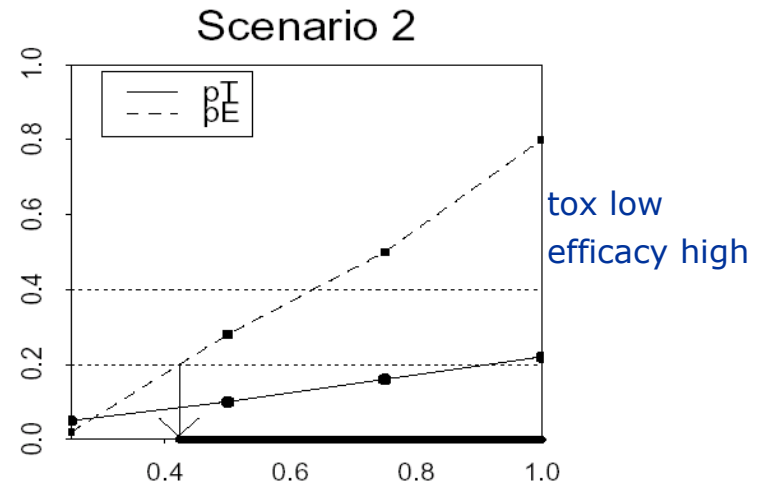
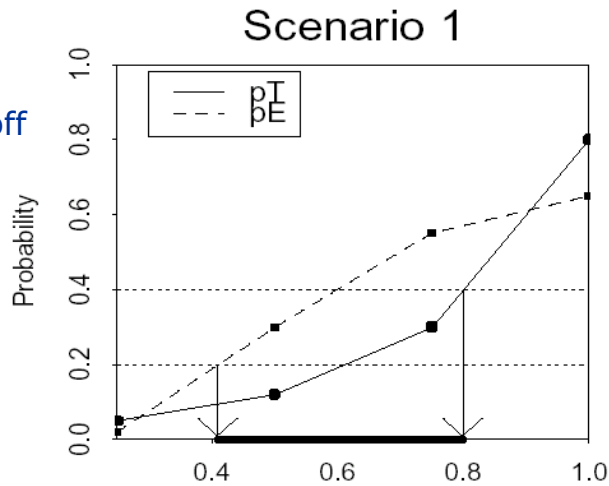
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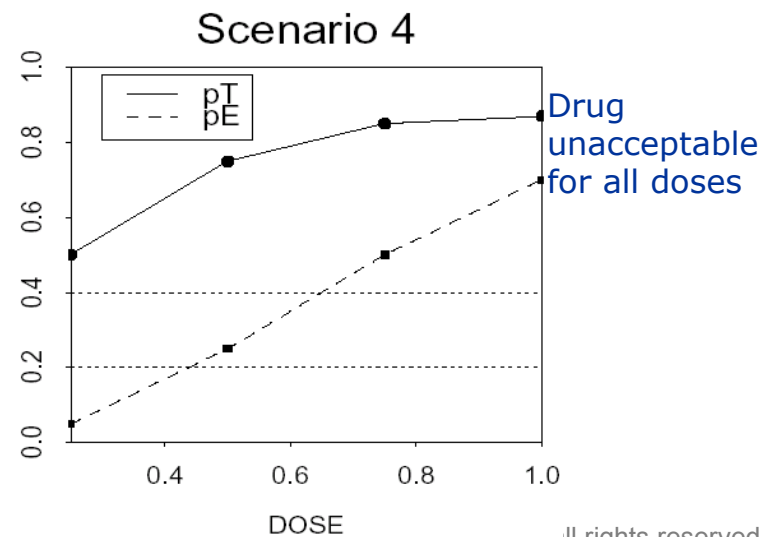
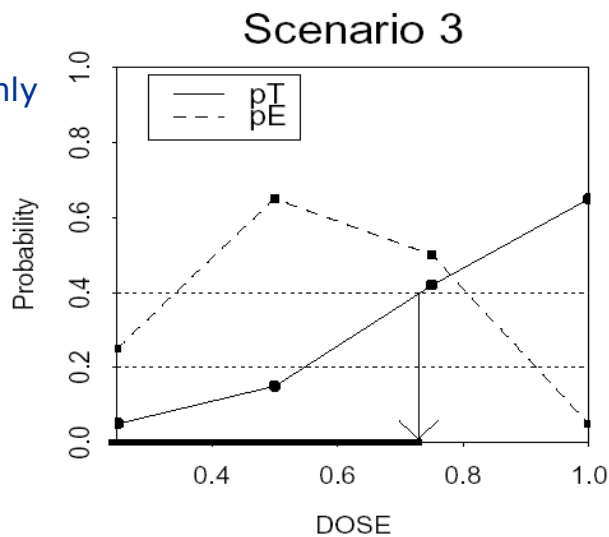
Step to the next dose with expected CUI along the contour line closest to the lower right corner.

Simulation scenarios show four combinations of efficacy and toxicity as a function of dose.

tox increases
narrow tradeoff
range



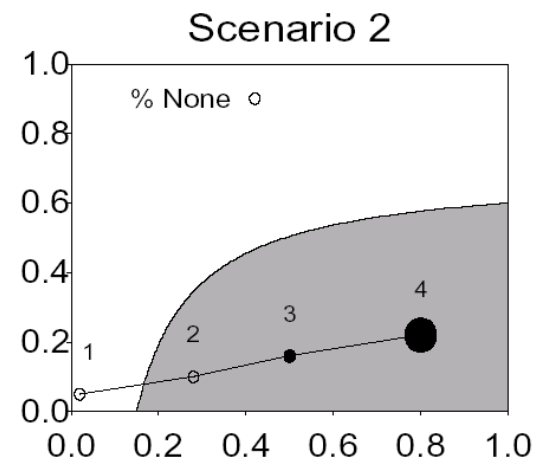
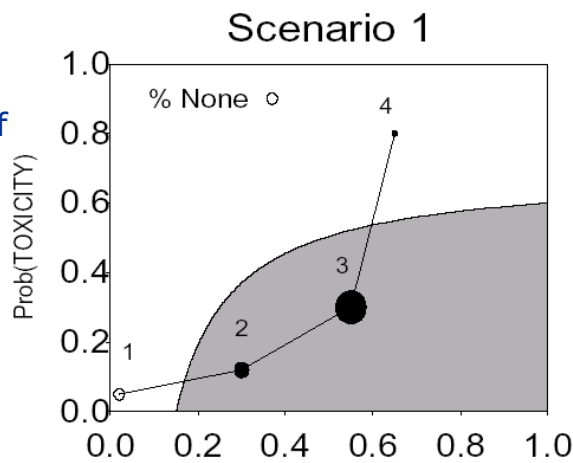
efficacious only
at low doses



The adaptive trial learns the parameters of efficacy and toxicity and finds the highest utility drug most of the time.

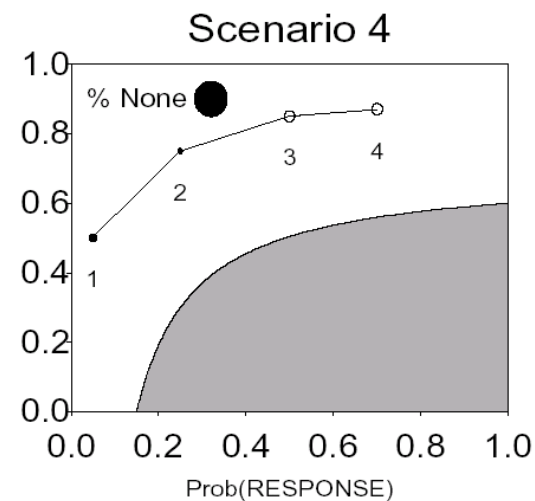
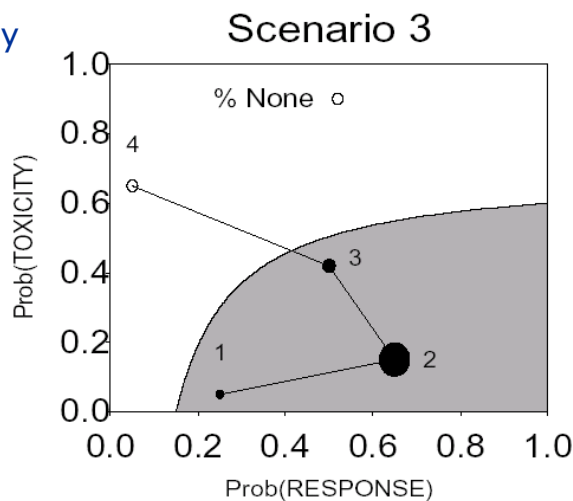
The gray region shows a registerable, efficacious drug. The lower RH corner is a perfect drug. Size of dots is proportional to frequency of final selection.

tox increases
narrow tradeoff
range



tox low
efficacy high

efficacious only
at low doses



Drug
unacceptable
for all doses

- The CUI based adaptive trial methodology reliably:
 - Finds safe doses with high efficacy
 - Stops if no dose is acceptable (all doses are either toxic or not efficacious or both are true)
 - Is likely to find higher doses with higher efficacy than traditional trials
 - Accommodates complex dose-outcome relationships, e.g., biologic agents or learning about multiple models
- Implementation is hard work, but state-of-the-art algorithms and computer programs are available
- Many pharmaceutical companies have developed CUIs for early trials and incorporate conjoint information for later trials
- Modeling and Simulation can demonstrate the operating characteristics of the design (type I, II & III error) under various scenarios (for both management and the FDA)

What questions do you have?

Pharsight



Seamless phase IIa/IIb/III

Bayesian dose selection, futility and seamless phase III go/no go



The client was optimistic about a novel mechanism compound entering phase II in schizophrenia.

Pharsight

- The compound impacted a very specific set of brain receptors
- The compound was very unlikely to produce extrapyramidal symptoms
- Patients taking the drug would likely have higher adherence if the drug exhibited the target product profile
- A subpopulation with negative symptoms were likely to be better treated than available drugs
- Patents protected a truly global market
- The drug could provide blockbuster profits to replace revenue from current blockbusters coming off patent

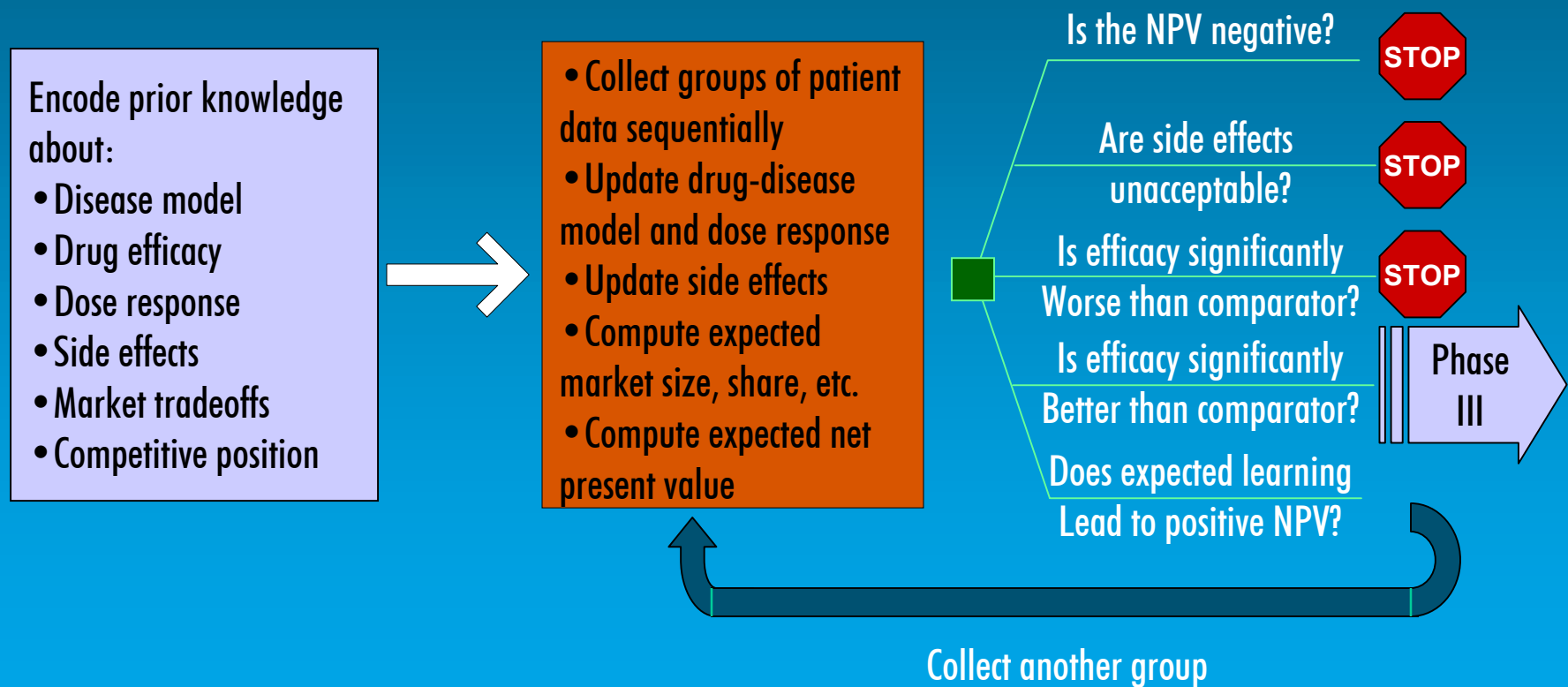
Pharsight's mission was to find a way to improve decision making and phase II/III trial execution.

Pharsight

- Pharsight was blinded by an impartial third party from the results of the trials.
- Pharsight provided a phase II design which we believed would be more effective than the client design
- Pharsight's design was simulated using the actual patient data obtained from the phase II trial
- Pharsight also simulated the clients phase III trials in a blinded fashion
- The phase II results, time and cost were compared for competing designs
- The phase III results were compared with the actual phase III trial outcomes

For phase II, group sequential designs provide multiple learning and decision opportunities.

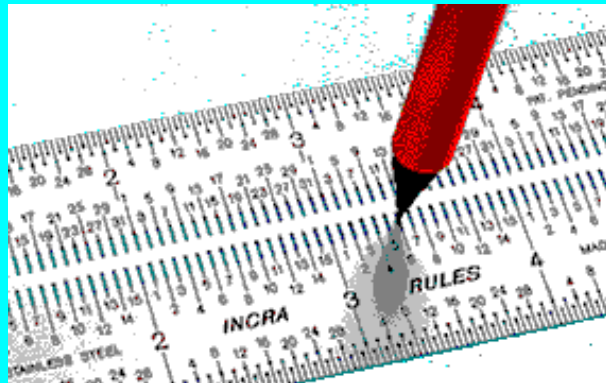
The Pharsight Phase II Design



Pharsight's modeling approach is to model all elements of the product profile, not just efficacy.

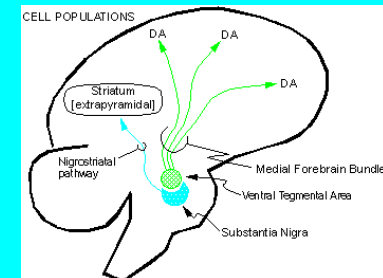
Pharsight

6 week Δ PANSS [Trt-Placebo]

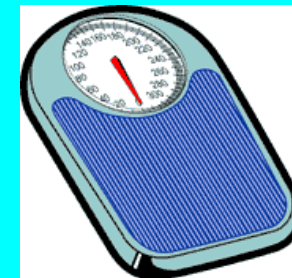


Negative Sub-Score Δ PANSS

EPS Symptoms



Weight Gain

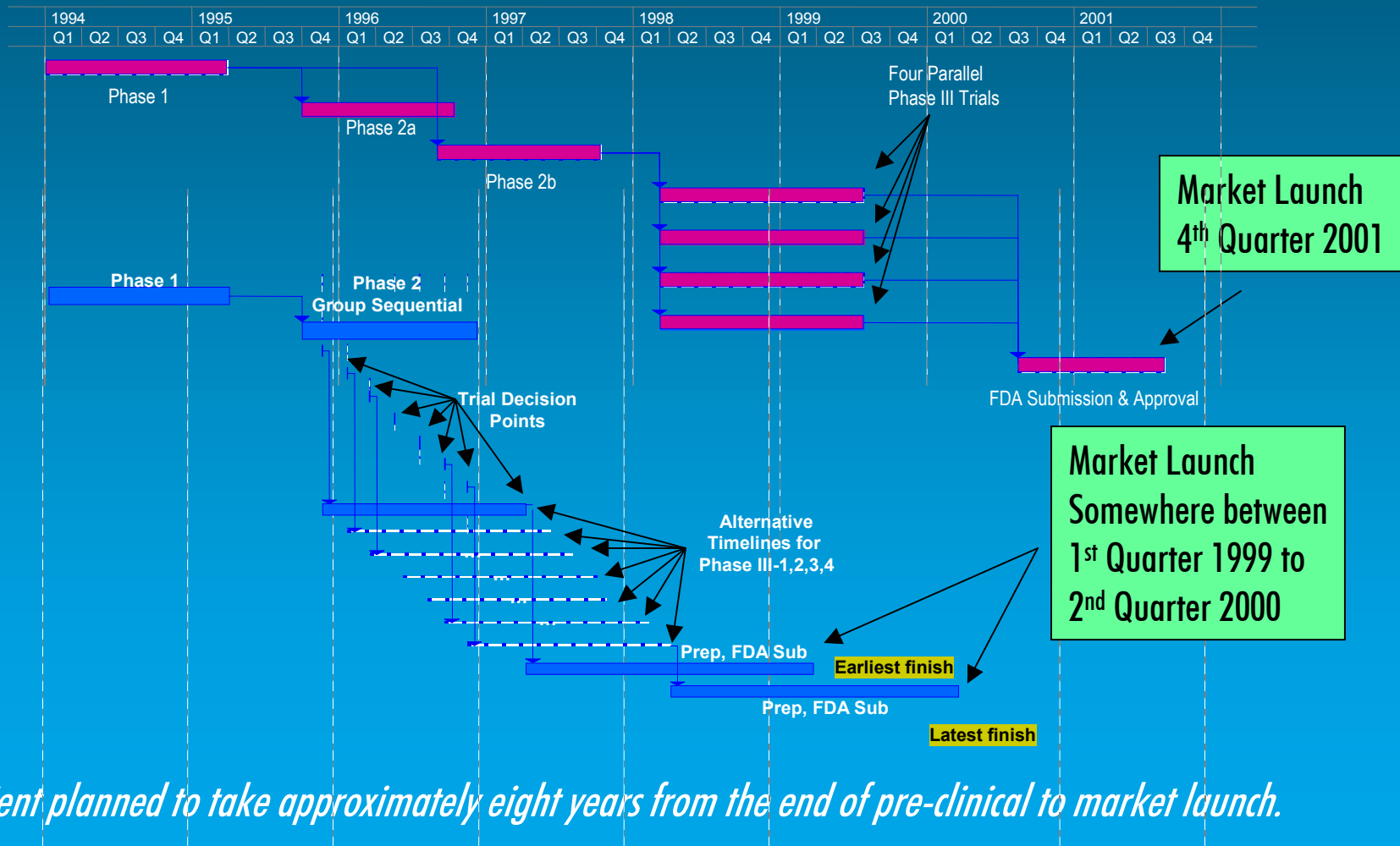


QTc Interval



Five characteristics of the drug define marketing attractiveness to docs (the product profile).

Pharsight's design could save as much as two years compared to the clients original design.



The client planned to take approximately eight years from the end of pre-clinical to market launch.

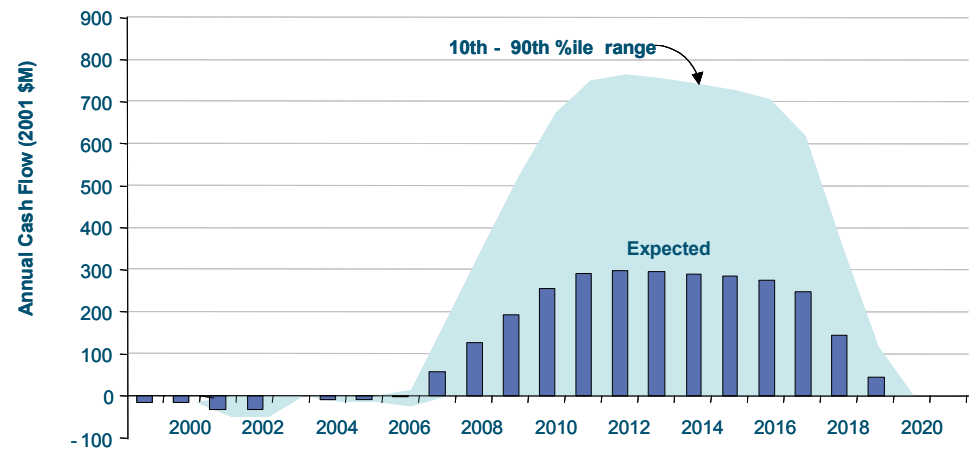
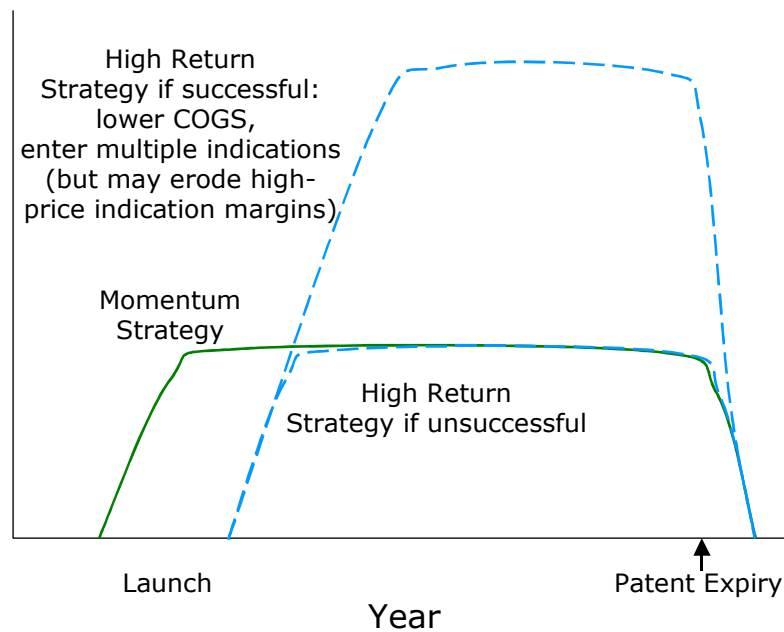
Seventy two market attractiveness ratings mapped into four categories: Blockbuster, Intermediate, Niche and No File.

Competitor drug profiles were used to 'anchor' the market attractiveness rating scale.

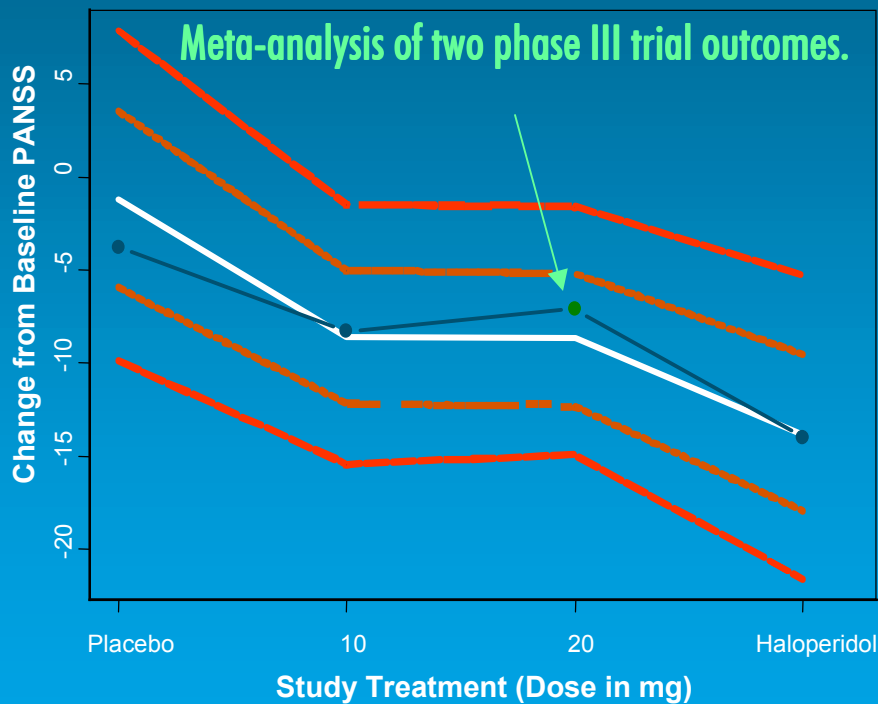
Efficacy	EPS	Neg Symp	Weight	QTc	Mkt Outcome	Rating			
High	Negligible	Outstanding	Low	Don't Worry	Blockbuster	100%	Blockbuster! WOW		
High	Negligible	Outstanding	Low	Fallback	Blockbuster	85%			
High	Negligible	Outstanding	Moderate	Don't Worry	Blockbuster	98%			
High	Negligible	Outstanding	Moderate	Fallback	Blockbuster	83%			
High	Negligible	Outstanding	High	Don't Worry	Blockbuster	96%			
High	Negligible	Outstanding	High	Fallback	Blockbuster	81%			
High	Negligible	Acceptable	Low	Don't Worry	Blockbuster	90%			
High	Negligible	Acceptable	Low	Fallback	Blockbuster	75%			
High	Negligible	Acceptable	Moderate	Don't Worry	Blockbuster	88%			
High	Negligible	Acceptable	Moderate	Fallback	Blockbuster	73%			
High	Negligible	Acceptable	High	Don't Worry	Blockbuster	86%	Blockbuster (this is olanzapine)		
High	Negligible	Acceptable	High	Fallback	Blockbuster	71%			
High	Moderate	Outstanding	Low	Don't Worry	Blockbuster	78%			
High	Moderate	Outstanding	Low	Fallback	Blockbuster	63%			
High	Moderate	Outstanding	Moderate	Don't Worry	Blockbuster	76%			
High	Moderate	Outstanding	Moderate	Fallback	Blockbuster	61%			
High	Moderate	Outstanding	High	Don't Worry	Blockbuster	74%			
High	Moderate	Outstanding	High	Fallback	Intermediate	59%			
High	Moderate	Acceptable	Low	Don't Worry	Blockbuster	68%			
High	Moderate	Acceptable	Low	Fallback	Intermediate	53%			
High	Moderate	Acceptable	Moderate	Don't Worry	Blockbuster	66%	Blockbuster (this is risperidone)		
High	Moderate	Acceptable	Moderate	Fallback	Intermediate	51%			
Low	Negligible	Acceptable	Moderate	Don't Worry	Niche	39%			
Low	Negligible	Acceptable	Moderate	Fallback	No File	24%			
Low	Negligible	Acceptable	High	Don't Worry	Niche	37%			
Low	Negligible	Acceptable	High	Fallback	No File	22%			
Low	Moderate	Outstanding	Low	Don't Worry	Niche	29%			
Low	Moderate	Outstanding	Low	Fallback	No File	14%			
Low	Moderate	Outstanding	Moderate	Don't Worry	Niche	27%			
Low	Moderate	Outstanding	Moderate	Fallback	No File	12%			
Low	Moderate	Outstanding	High	Don't Worry	No File	25%			
Low	Moderate	Outstanding	High	Fallback	No File	10%			
Low	Moderate	Acceptable	Low	Don't Worry	No File	19%			
Low	Moderate	Acceptable	Low	Fallback	No File	4%			
Low	Moderate	Acceptable	Moderate	Don't Worry	No File	17%			
Low	Moderate	Acceptable	Moderate	Fallback	No File	2%			
Low	Moderate	Acceptable	High	Don't Worry	No File	15%			
Low	Moderate	Acceptable	High	Fallback	No File	0%			

The risk-return balance must be considered in a strategy that pursues a high-returns. The uncertainty of a high return strategy is usually larger.

Commercial Cash Flow

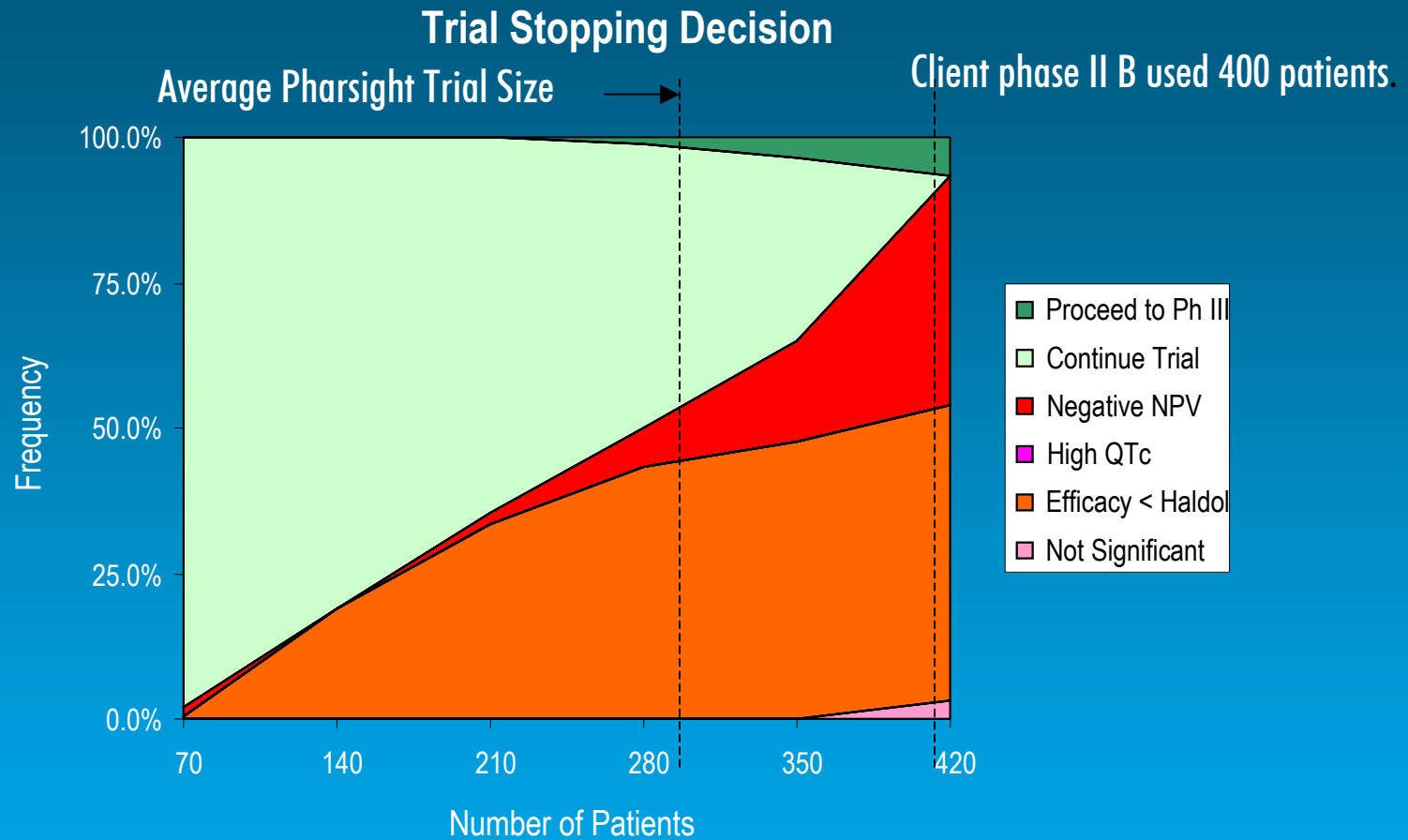


Simulation of the client Phase III trial predicted failure and was an accurate predictor of the unblinded data.



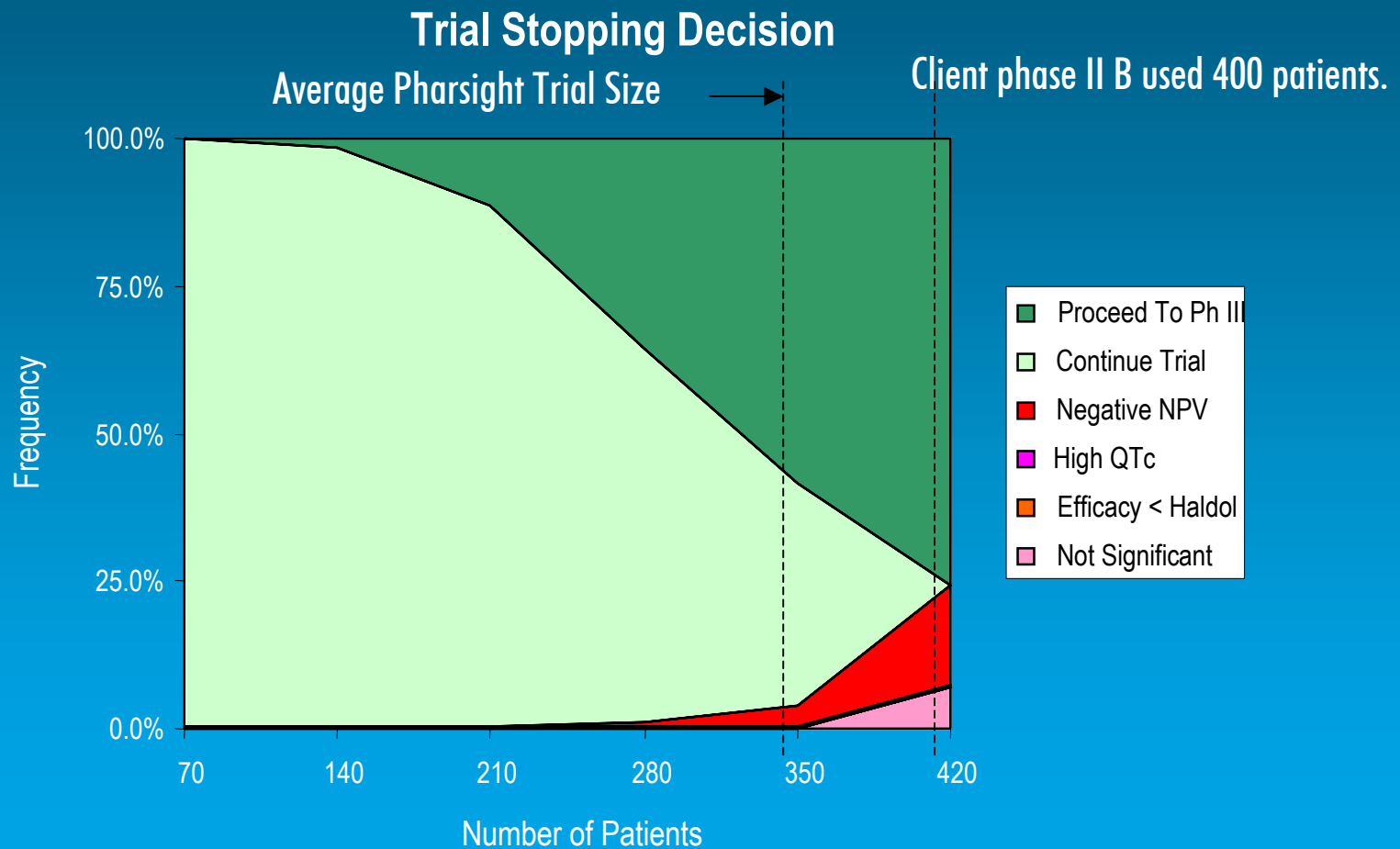
- Inclusion of prior literature data led to improvement in description of Phase III data, especially haldol response
- Included data for placebo from 5 studies with 224 patients
- Prior Haldol data consisted of 1220 patients from 8 studies

Repeated simulations showed that the client drug would have failed in the Pharsight trial design.



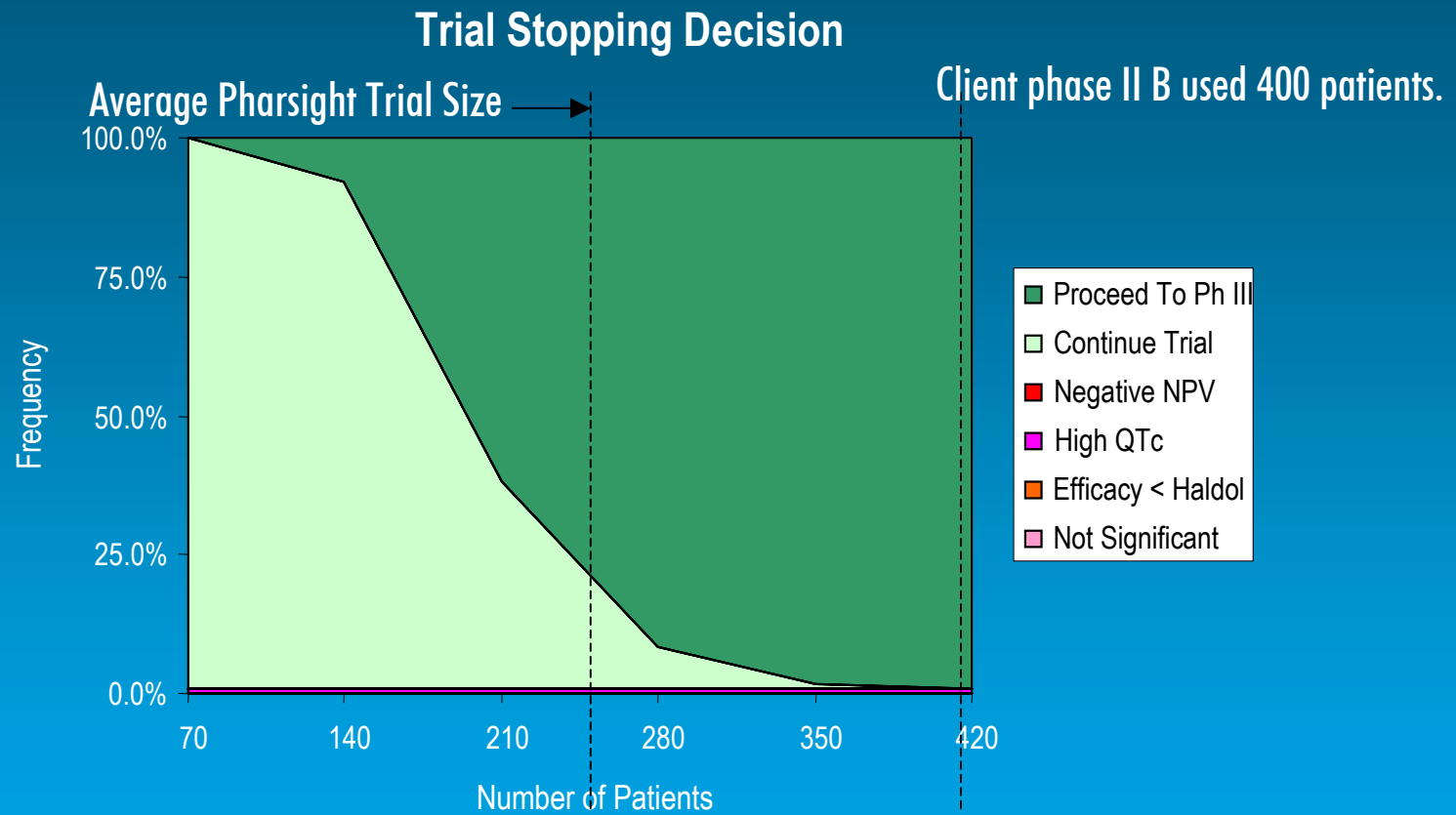
- *Average trial accrued 295 patients in ~10 mo. An erroneous "GO" decision given 6.5% of the time.*
- *The first patient group serves the same purpose at the phase II a.*
- *The client had equivocal results and proceeded to phase III.*

In 76% of the simulations, the Pharsight trial design recommended starting phase III given a drug efficacy profile similar to haldol.



➤ *Average trial accrued 341 patients in ~12 mo.*

With blockbuster efficacy the Pharsight trial recommended starting phase III early.



- *Average trial showed significant efficacy after evaluating 235 patients in ~9 mo.*
- *Compared to the original design the expected value of the compound would increase by 26% due to a quicker time to market.*

Either way we demonstrated significant value 

If the Drug Candidate was...

■ ..."Effective"



+\$500M in earlier revenue

■ ...a "Dud"



+\$55M in cost avoided from earlier "kill"

This design was created 6 years ago. How would we enhance it today?

Pharsight

- The analysis estimated dose-response and used it to select an optimal dose to a seamless confirmatory trial
- The decision strategy focused only on whether the selected dose met PoC criteria and whether there was sufficient value in gaining more data.
- The adaptive stopping method was an ad hoc mix of hypothesis testing for success (alpha spending method) and model-based methods for futility assessments.
- An arguably better approach would be to use a completely Bayesian-decision-analytic method using a loss function that considered the same safety, efficacy, cost and ROI factors.

- Adaptively assign patients to doses that will be most informative about the optimal dose for treating future patients
 - Use decision analysis and dose-response models for multiple safety- & efficacy-related outcomes
 - Further enhances efficiency and informativeness of the trial by selectively assigning more patients to more informative treatments

What questions do you have?

Pharsight



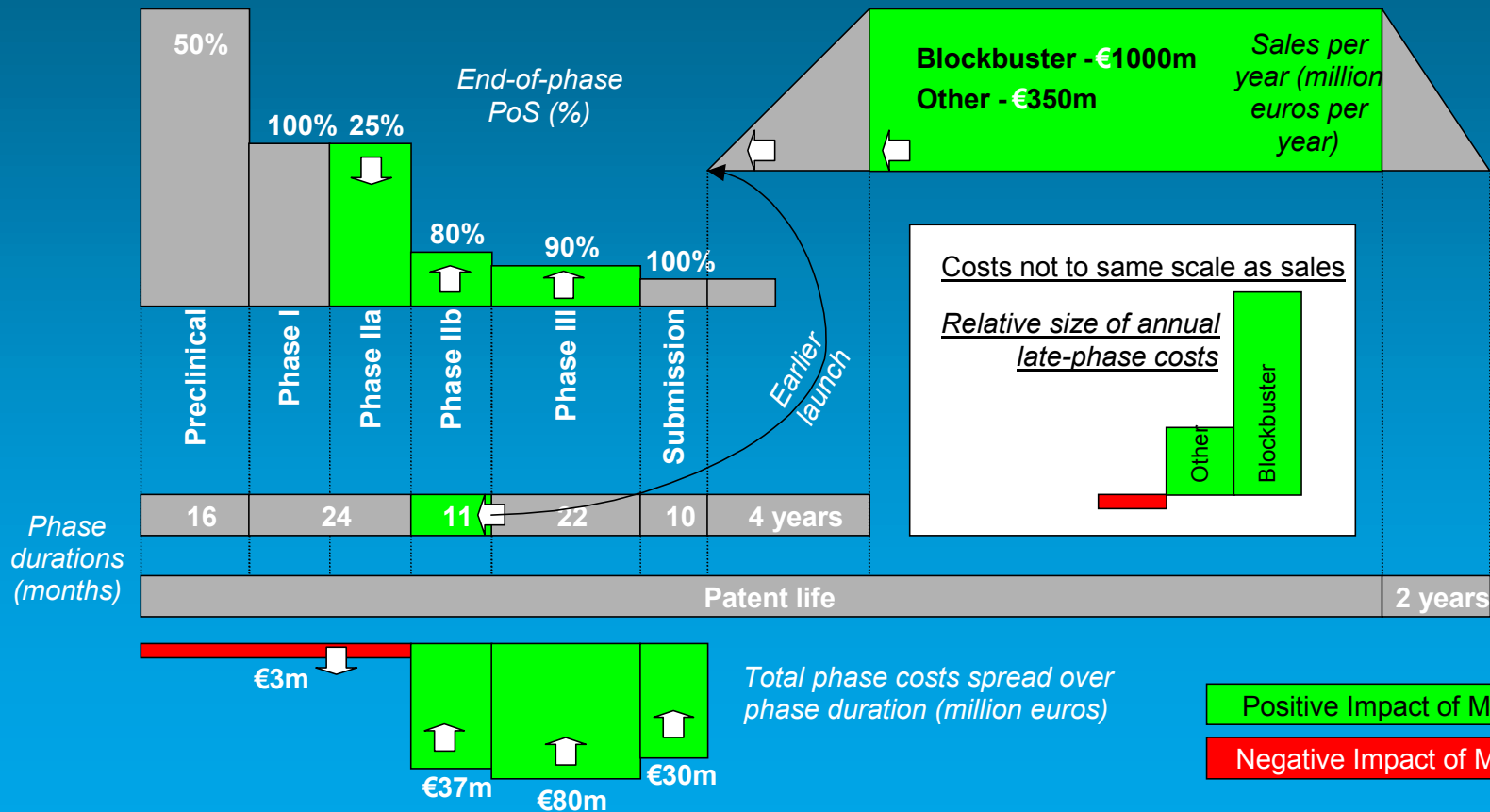
Pharsight

Putting it all together...

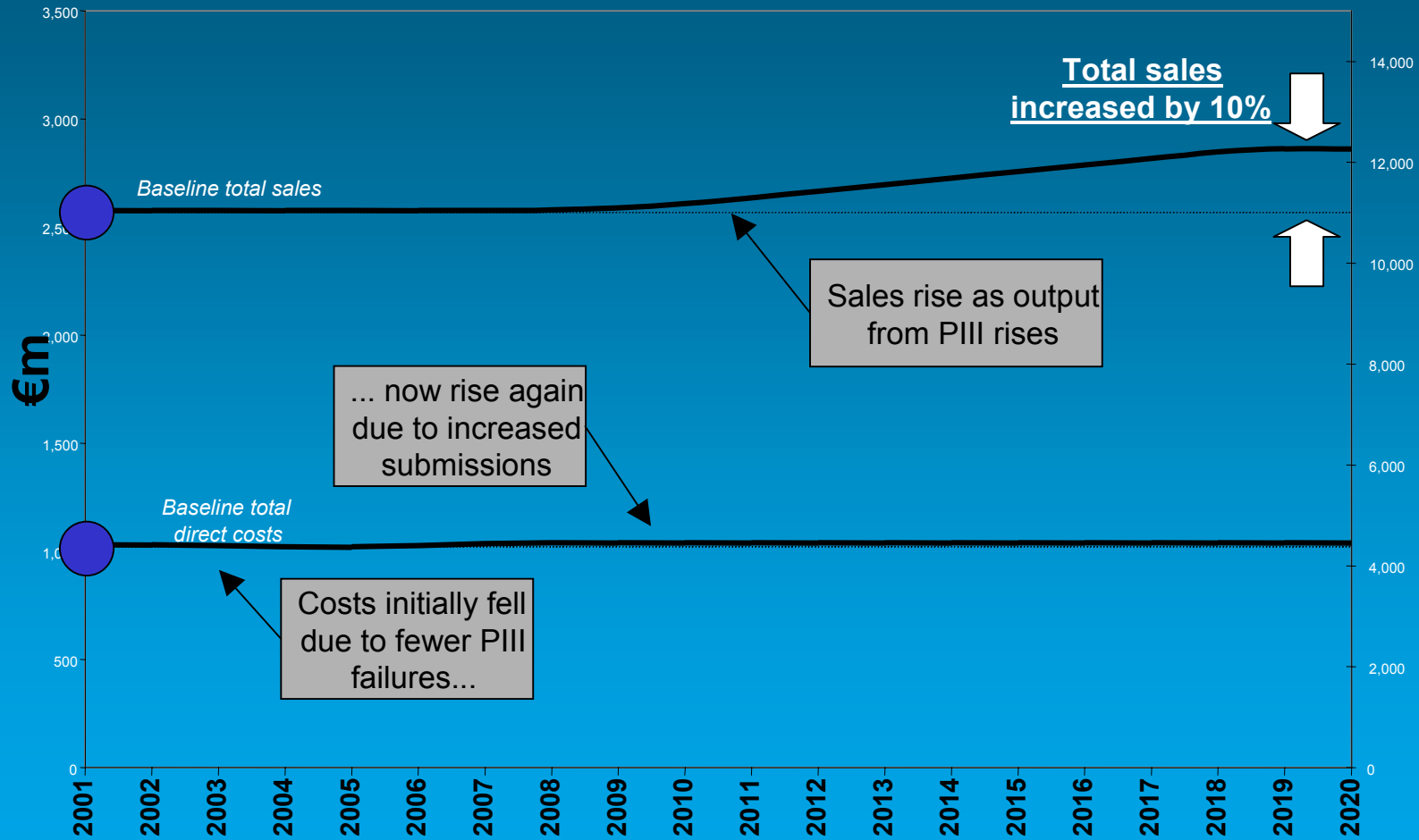
The impact on the bottom line



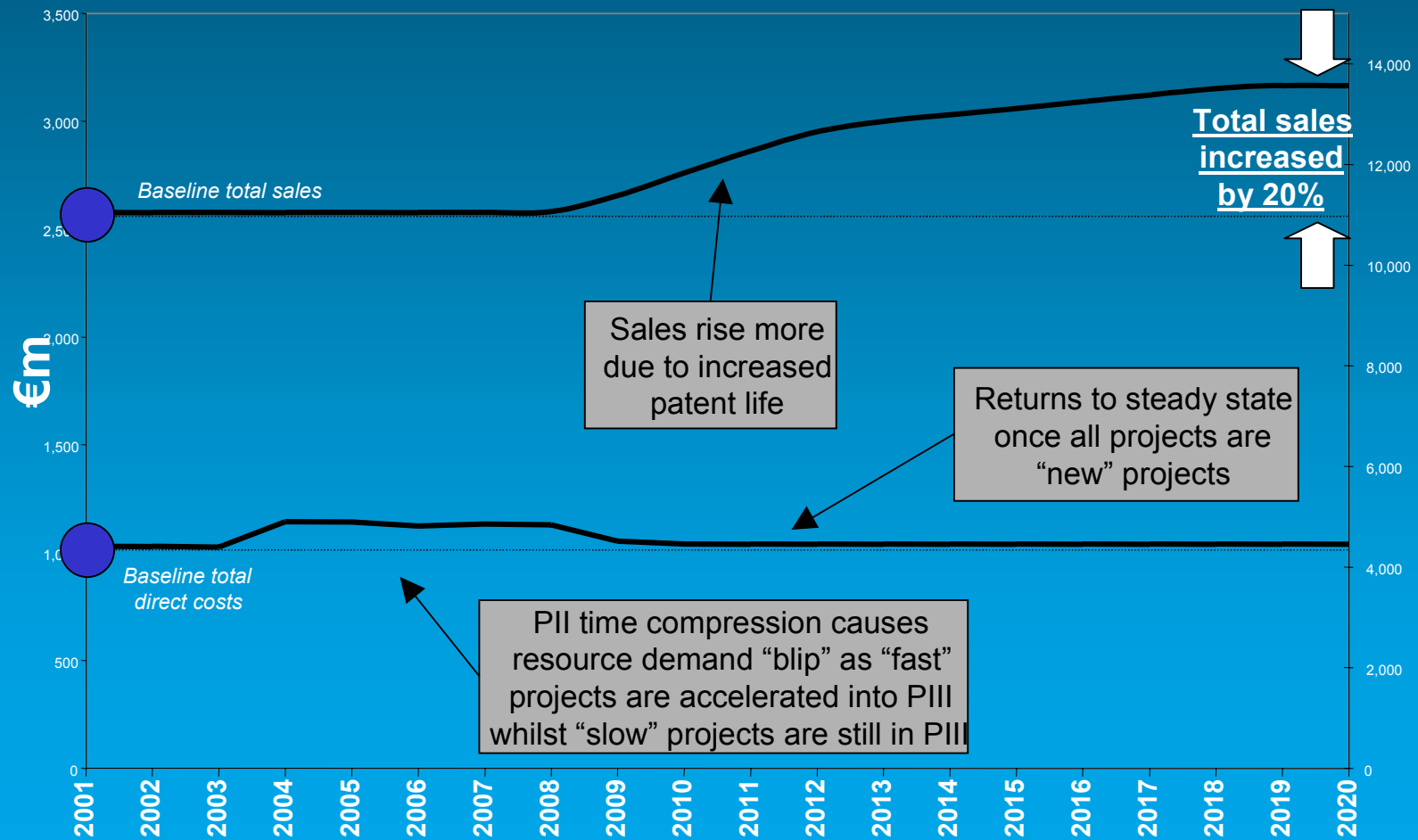
Typical Project Cost and Revenues



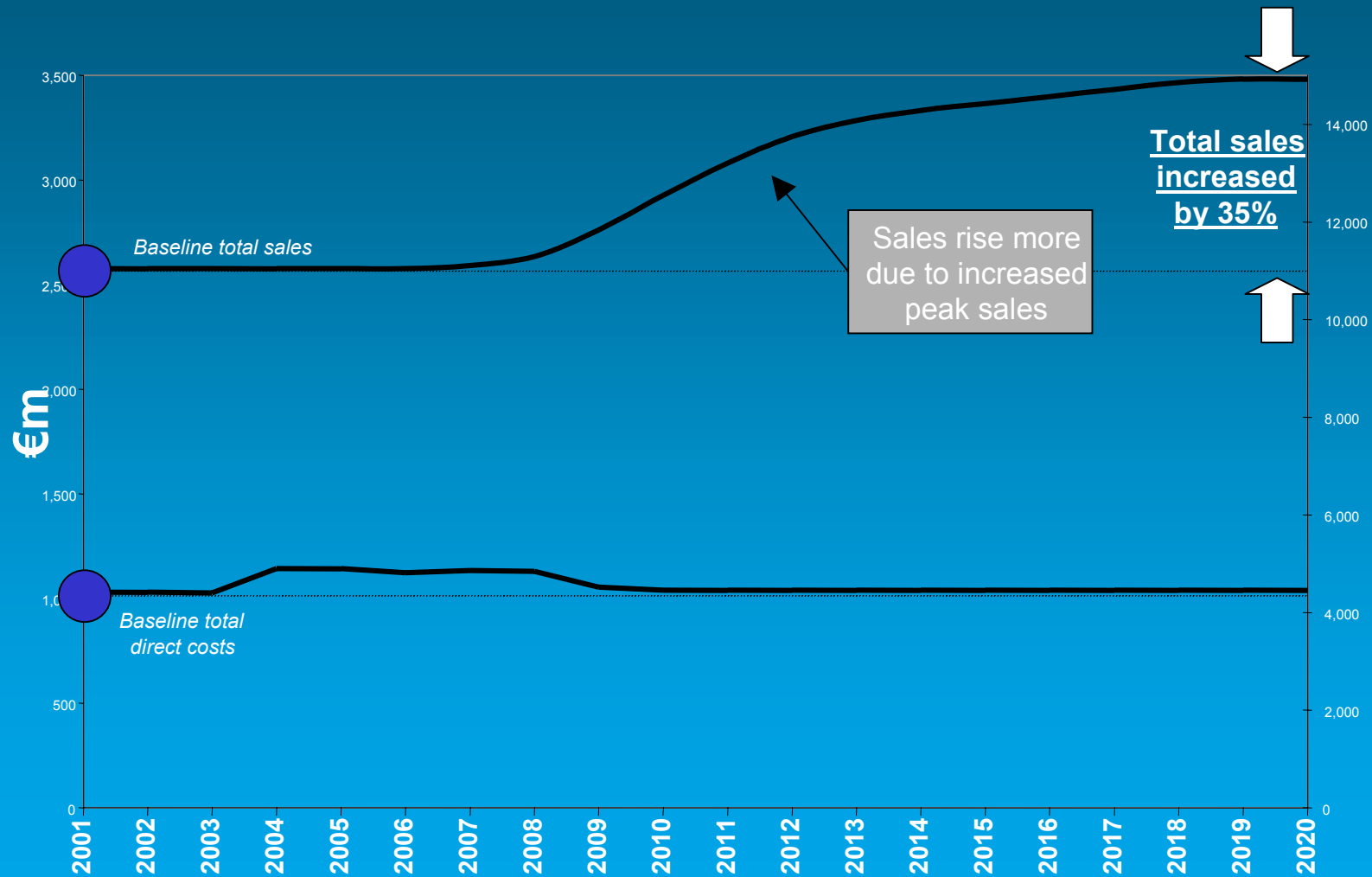
Since you are failing early, successful submissions increase.



Now add adaptive dosing and Phase II time is cut in half.



Finally, improved drug development strategies lead to a 10% increase in peak revenue.



What questions do you have?

Pharsight



Final thoughts



Key points supporting use of modeling, decision analysis and adaptive trials for development

- **Modeling (and simulation) provides the means for:**
 - Leveraging prior information and integrating new information
 - Exploring the performance of competing strategies
 - Low risk exploration of novel strategies
- **Decision analysis:**
 - Permits a flexible definition of PoC that considers safety/efficacy/cost/ROI trade-offs.
 - More flexible basis for trial decisions (interim or final) compared to hypothesis testing
- **Adaptive trials:**
 - Enhance efficiency by learning as the trial progresses and refining elements of the trial design to enhance future learning
 - Reduce the risk of:
 - An inadequately informative trial or
 - A longer or larger trial than necessary

- Adaptive trial designs are complex to design, require investment from the development team and sponsor, and have additional logistic challenges.
- The development benefits are speed to market, better dose selection and better competition for pharmaceutical companies.
- Patients are exposed to fewer inferior treatments and have treatments with better product profiles sooner.
- **Questions?**

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Mr. Korsan is Director of Decision Services. He has over 20 years experience in decision consulting, having worked with some of the largest pharmaceutical, biotech, medical instrumentation and medical-surgical manufacturing companies in the US. In addition to pharmaceutical consulting experience, Mr. Korsan has a broad background in banking, telecommunications, insurance, power generation, and consumer products. Prior to joining Pharsight, Mr. Korsan was a manager at Coopers & Lybrand in their Advanced Technology Group. He founded his own boutique consulting firm in 1985. He was also a senior decision analyst with Strategic Decisions Group and a senior management consultant with SRI International (Stanford Research). Mr. Korsan has a M.S. in electrical engineering from Carnegie Mellon University, an M.A. in mathematics from the University of Pittsburgh, and a B.S. in mathematics and physics from Manhattan College. He is a member of SIAM, INFORMS and a senior member of the IEEE. He is widely published and has research interests in sensitivity analysis, simulation and decision support systems.