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STATISTICAL SOFTWARE & SERVICES

Optimizing Clinical Outcomes Using Simulations In Modern Drug Development

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Overview

- Need for Simulations of Development Program Scenarios
- Drug Development Optimization
- Case Study 1; Use of Biomarkers for decisions making in Early Drug Development
- Case Study 2; Optimization at the program level - Diabetes Development
- Case Study 3 – Portfolio Optimization

Need for Simulations of Development Program Scenarios

Pharma Status

- Diminishing returns
  - End of Blockbuster era, same class drugs (statins, Cox-2 inhibitors, SSRIs).
  - Affordable Care Act. Reimbursement, differentiation
- Increased costs
  - Safety issues with some Blockbusters (Vioxx, Avandia…). Demand for larger safety databases (Diabetes, Obesity…)
  - Failures contribute to estimated costs (Andy Witty, GSK)

Pharma Decision Making

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- Historically decision making easier
  - Same class drugs - straightforward development
  - Blockbusters - large revenues
  - Most common decision criteria: “gut feeling”
- Current, future
  - More emphasis on PoS, differentiation, then on speed of development
  - Differentiation: dose selection, biomarkers
  - **Optimization**; program, portfolio level
  - **Quantification** and **scenario comparisons** necessary

Changes Necessary

- Lack of Quantitative Decision Making in the Pharmaceutical Industry
  - Decision Analysis not Utilized
  - Inadequate use of Statistical Resource
  - Lack of Utilization of Modeling and Simulations (M&S)

- FDA's March 2006 "Critical Path Opportunities List" calls for Advancing Innovative Trial Designs, including
  - #36 greater use of Adaptive Trial Designs; more use of Bayesian methods in drug development
  - #51 clinical trials simulation

Simulations

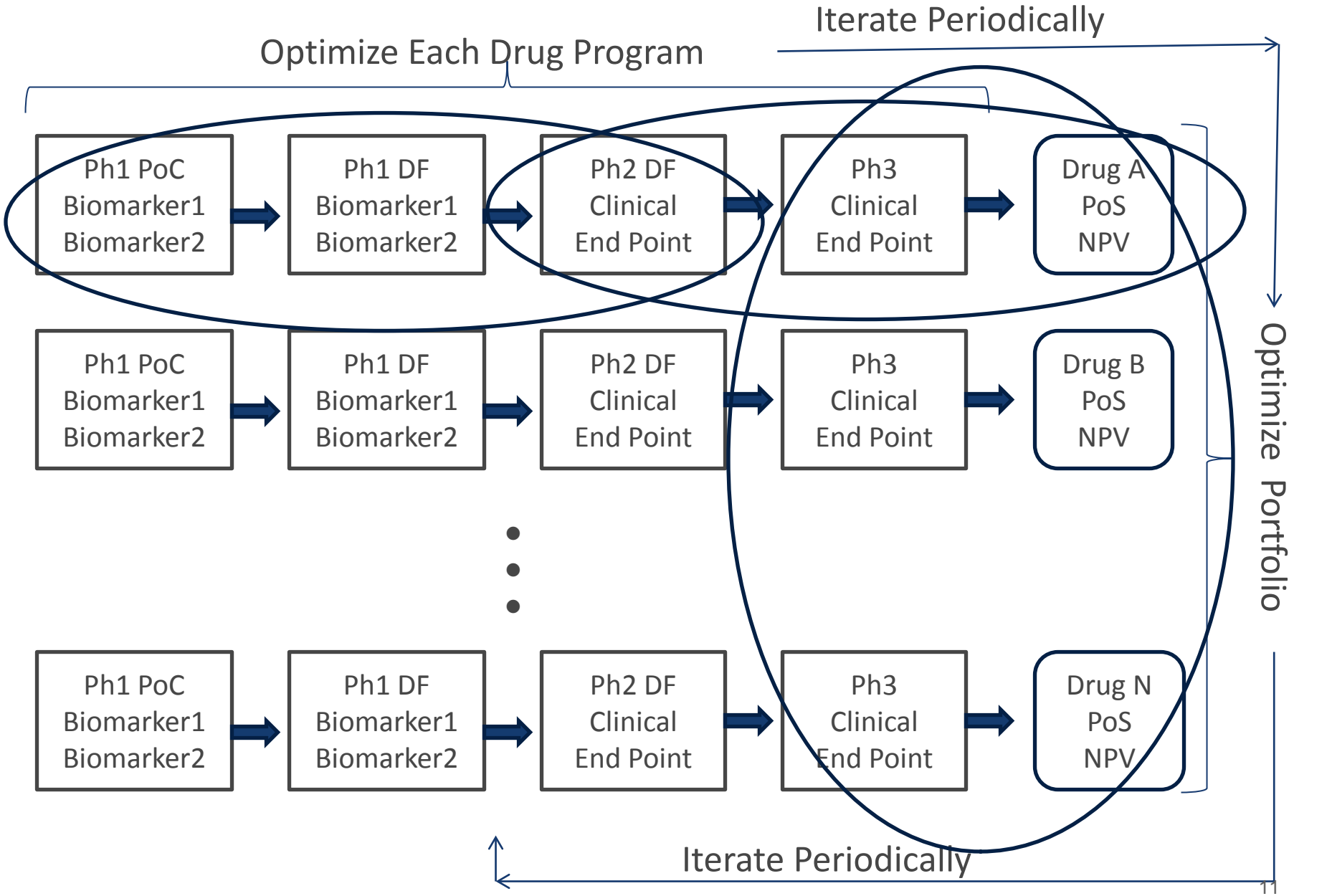
- Integration of information from multiple areas, from pre-clinical development, through the submission stage, to commercial.
  - Outputs from earlier stages can be used to define assumptions for simulation parameters.
- Assessing multiple scenarios such as differing study designs and endpoints
  - Even more diverse inputs such as cost of study start-up, accrual rates, and per-subject costs
- Offer an approach to deal with the computational complexity
- Accounting for uncertainty
  - Distributional output

Drug Development Optimization

Drug Development Optimization

- *Trial level* by application of adaptive design. Examples are: early stopping for efficacy or futility, de-risking development by increase in power an interim analysis as needed, or adaptive population enrichment.
- *Program level*. More effective dose-finding leads to higher success rates in Phase 3 and an improved efficacy/safety profile
- *Portfolio level*. Improved allocation of a fixed budget into individual trials leads to an improved value of the portfolio.

Drug Program & Portfolio Optimization



Case Study 1
Use of Biomarkers
in Early Development

Motivation

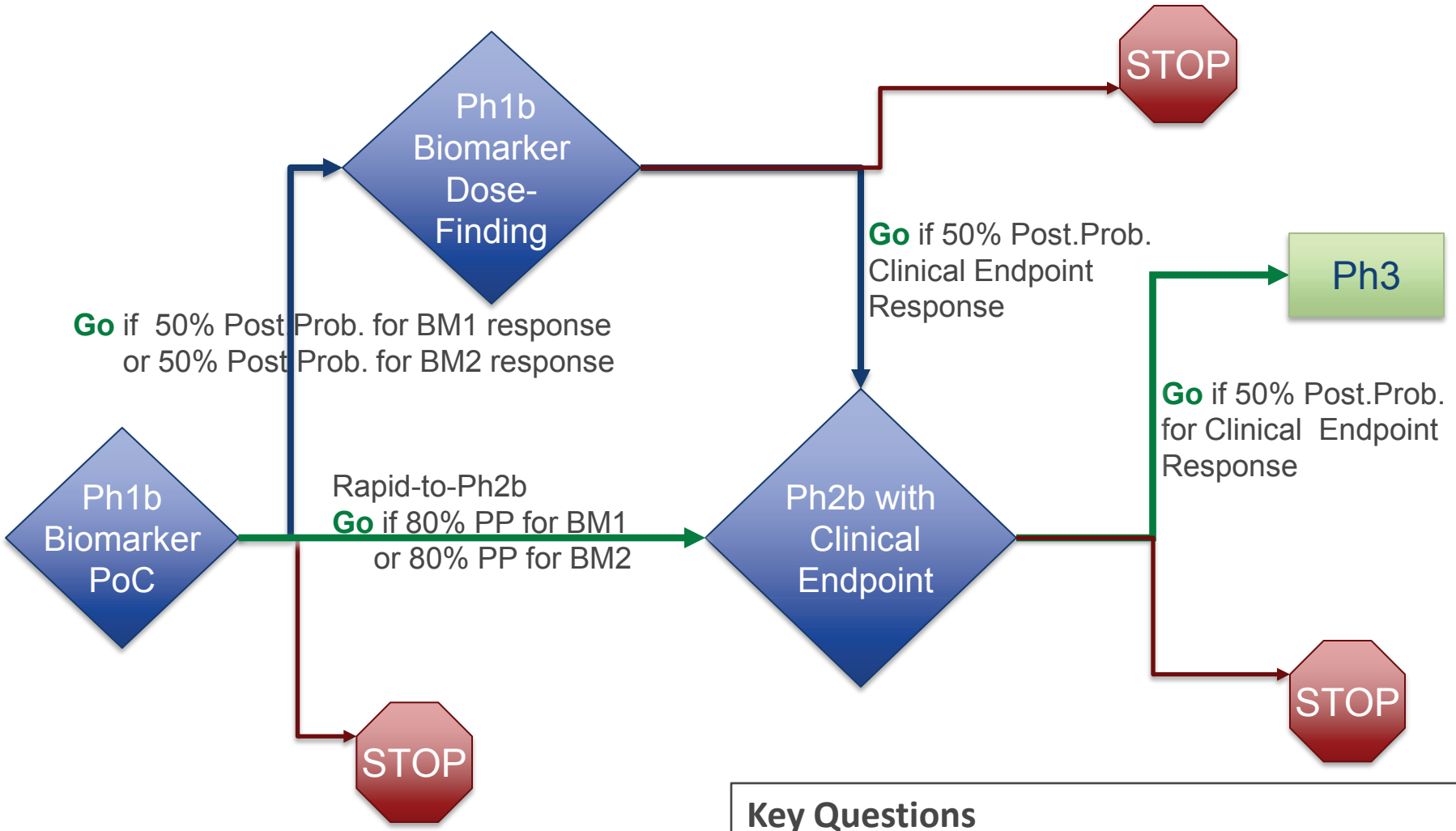
As Sponsor was preparing Early Development Plan, posed these questions:

- How can the relationship between early biomarkers and clinical endpoints be leveraged to optimize Phase 1 - 2 plans? (improve quality of information or speed development time)
  - How can different designs for Ph1b (PoC and Dose-Finding with biomarkers) improve design of Ph2b?
  - Can we use Ph1b data to optimize dose selection for a Ph2b study, allowing reduced Ph2b sample size and/or improved chance of picking correct Ph3 dose?

Drug Program Simulation
Phase 1 → Phase 2

- Optimize biomarker Phase 1 → Phase 2b to improve probability of correct Phase 3 dose choice
  1. Ph1b biomarker PoC trial (high dose vs. pbo)
  2. Ph1b biomarker Dose-Finding trial (low & mid doses vs. pbo)
  3. Pooled analysis (pbo, low, mid, high doses) to select Ph2b doses
  4. Ph2b Dose-Selection trial (chosen doses vs. pbo) using target clinically relevant endpoint
  5. Ph3 Dose Choice

Ph1b-Ph2b Simulation System



Key Questions

Did we make the right decision - stop or go?

If go, did we get the Ph3 dose-choice right?

Drug Program Simulation
Phase 2 → Phase 3

- Optimize Phase 2 → Phase 3 for improving overall program success probability (PoS) and product net present value (NPV) beyond Ph3
  - Antonijevic Z, et al. (2010): Dose Selection Strategies from Phase 2 for Phase 3
  - DIA Adaptive Program Working Group Case Studies
    - Patel N, et al. (2012): Neuropathic pain
    - Antonijevic Z, et al. (2013): Diabetes
    - Marchenko O, et al. (2013) Oncology

Key Decisions / Metrics From Simulation

- Rate (% of simulations) that choose correct dose for Phase 3
  - "Correct dose" defined as the dose with a target level of response for the clinical endpoint

Summary of Selected Findings

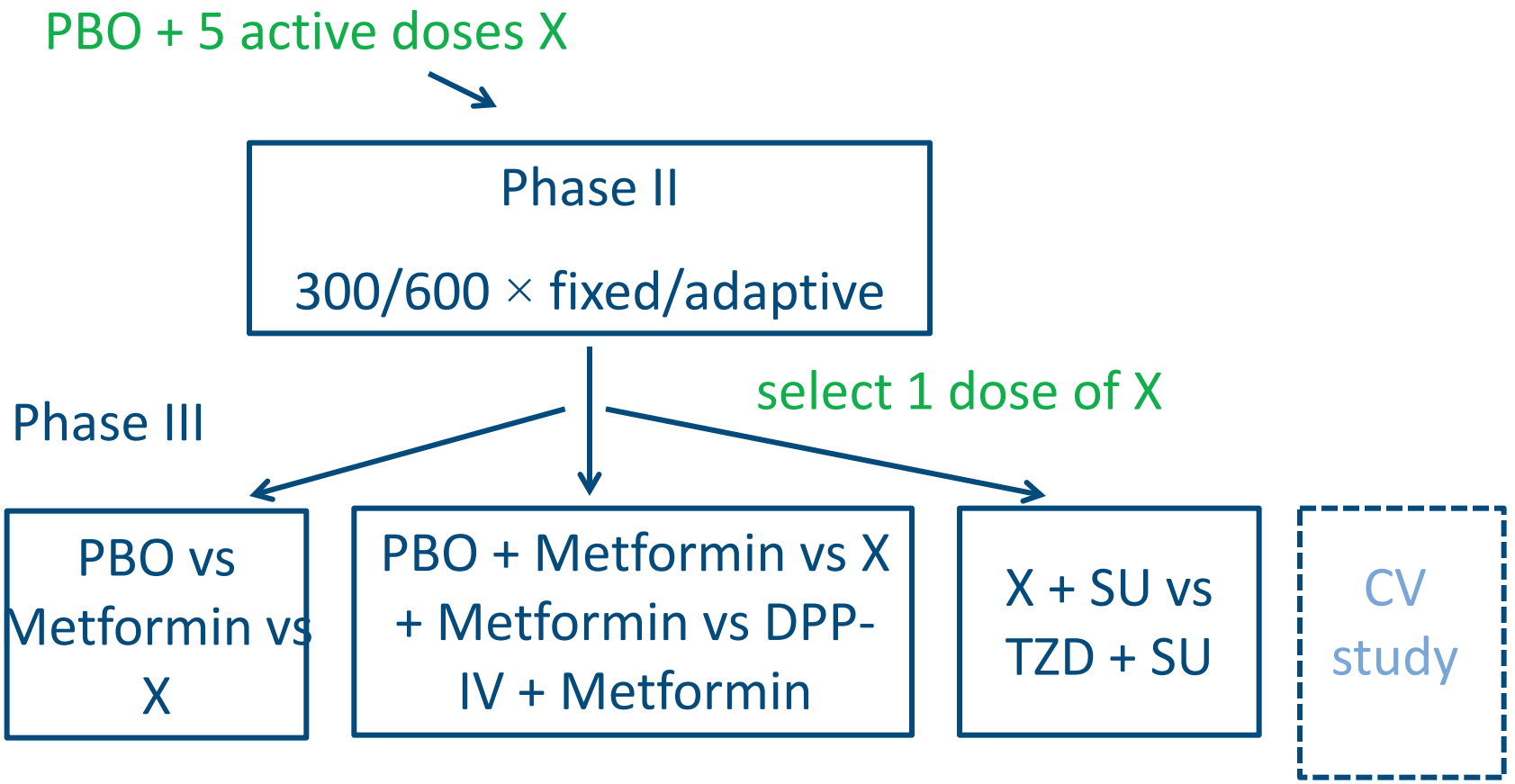
Question	Summary of results
Duration of Phase Ib studies (PoC and Dose-Finding)	2 days is sufficient for making go/no-go decision.
Can we use Phase Ib results for dose selection?	Relationships between biomarkers are too variable to drive decision making
Can we use informative priors to make Phase 2B study more efficient?	Informative priors did not help much
What is optimal design for Phase 2B?	Fixed design with N=100 has limited ability to discriminate between active doses and to select Ph3 dose; consider increasing sample size to 250 per dose

What Sponsor learned about use of biomarkers to optimize Ph2b

- Biomarkers useful for PoC, but not for Clinical Endpoint Dose-Finding
- From an efficacy dose-selection point of view, fastest path should be to move into Phase 2b right after Ph1b PoC
  - Dose-response profile from Ph1b PoC+DF would not impact Phase 3 dose selection
- Ph1b DF could be **skipped**, saving substantial resources and time, OR repurposed to address other key questions, e.g.
  - Dose regimen
  - Dose-response of mechanism of action

Case Study 2
Diabetes Development

Adaptive Program – Phase 2b and 3

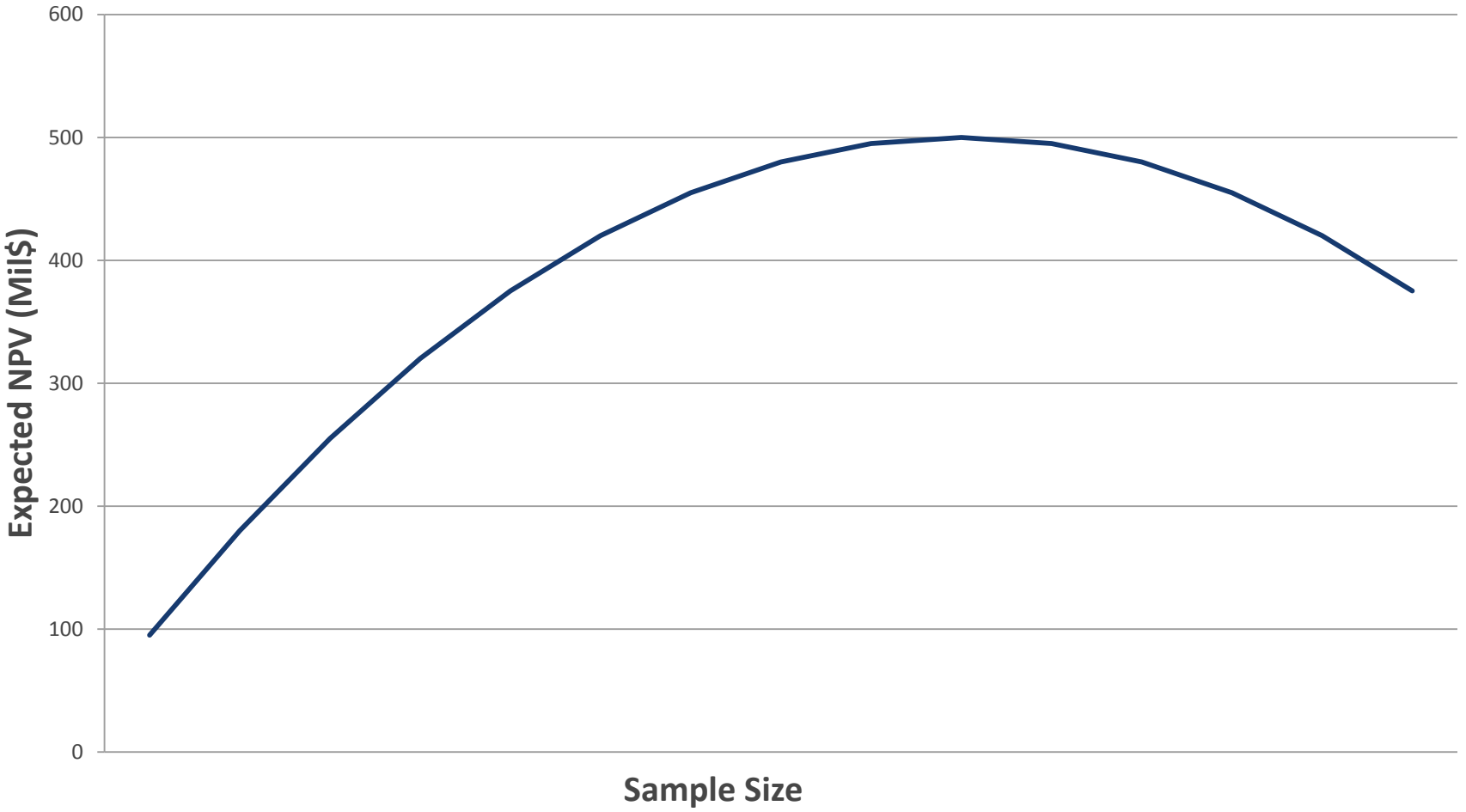


n_3 = 200, 300, 400, 600 per arm

Design Parameters to be Investigated

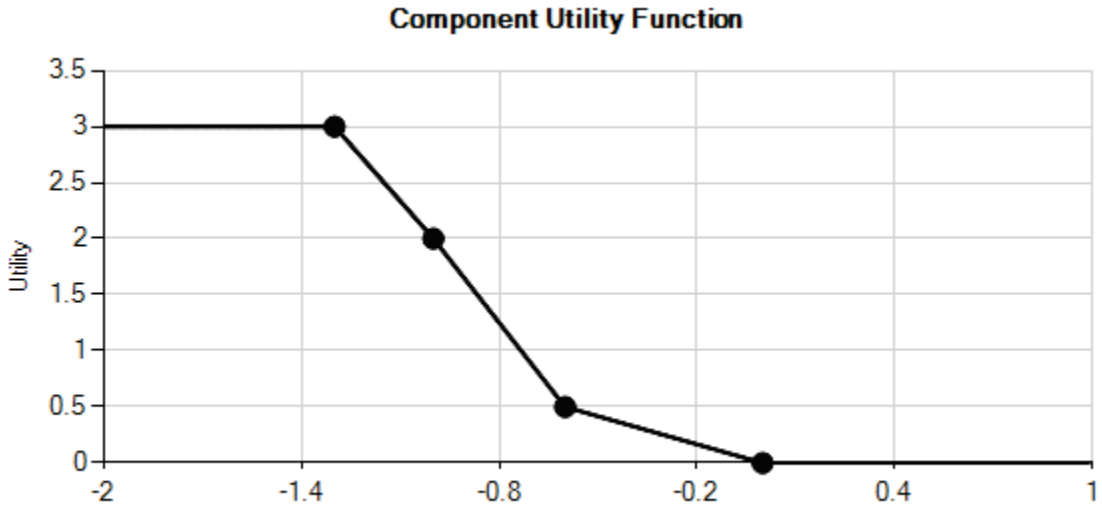
- Phase II Design (adaptive vs. non-adaptive)
- Phase II Sample size (300 vs. 600)
- Phase II follow-up time (12 vs. 24 weeks)
- Phase III Sample size (200, 300, 400, 600 per arm)

Outcome - eNPV



Dose Selection Clinical Utility Function

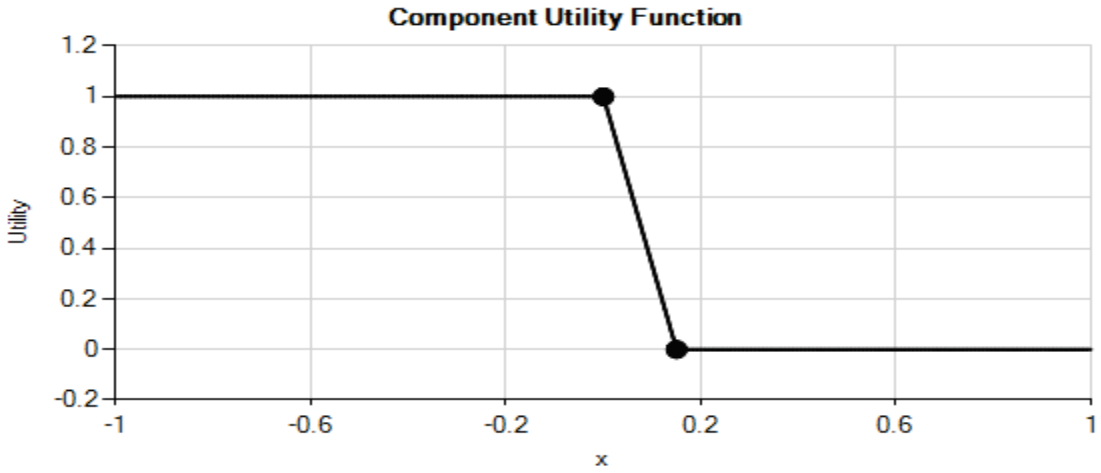
Select dose, and adaptively allocate towards dose with max utility



← HbA1c

×

Probability of hypoglycemic event(s) →



Regulatory Success Criteria

- ≥ 2 trials with statistical significance for efficacy (one of these studies has to be Study #1 showing superiority vs. Placebo)
- The safety requirement is that the upper bound of two-sided 95% confidence interval of the risk ratio of treatment over control is less than 1.8.
- For a program to be successful, both safety and efficacy criteria have to be met.
- Each indication (monotherapy, add-on to metformin, add-on to sulphonylurea) is approved if general approval is received + statistical significance in the trial for that indication
- For Study #2 (previous slide), DPP-IV's currently not accepted as an active comparator, but this will likely change in future, so keep DPP-IV as active comparator.
- For HbA1c use Non-inferiority margins of 0.3

Revenue Function

- Drug has to beat pbo as the entry ticket to the market. Then:

Percent of max NPV for different probabilities of AE									
Drug	**Test**	**Max NPV B$US**	**% Adverse event (hypoglycemic events)**						
			1	2	4	8	16	32	64
TZD	N.I.	1	100	66.7	33.3	0	0	0	0
	Sup	10	100	90	80	70	35	0	0
DPP-IV	N.I.	1	100	50	0	0	0	0	0
	Sup	3	100	80	60	40	20	0	0

Findings

- Larger sample sizes in Phase 2b and Phase 3 studies provide more precise dose selection, and reduce the positive treatment effect bias and uncertainty in estimated ENPV, within the range of sample sizes studied.
- Similar improvements are seen with implementation of an adaptive design over a fixed design in Phase 2b.
- Larger adaptive trials have identified the dose with the maximum utility dose most often, while smaller fixed designs identified this dose least often.
- Larger number of the patients were assigned to the highest utility doses using an adaptive design compared to a fixed design for three different scenarios.
- Dose selection criteria have to be consistent with developers' objectives. It is a very common situation that dose selection criteria are defined by R&D teams, while one of the key objectives is to maximize the expected revenues.
  - We recommend closer collaboration of R&D clinical and commercial groups earlier in development

Case Study 3
Portfolio Optimization

Portfolio

Individual Trials	
A1	T1: Cancer Type I
	T2: Cancer Type II
	T3: Cancer Type III
A2	T1: Cancer Type I
	T2: Cancer Type II
A3	T1: Cancer Type I
	T2: Cancer Type II
A4	T1: Cancer Type I
	T2: Cancer Type II
A5	T1: Cancer Type I

How to Allocate Sample Size in Phase III?

- Strategy 1: Determine sample size for each trial and calculate POS and NPV; do a naive selection among trials with highest eNPV to fit within budget limits.

- Strategy 2: Start all trials with sample size=0. Compare trials for the benefit gained from an incremental increase in sample size; increase the sample size for the best trial. Repeat this procedure until the budget limit is met.

Selected Messages

- Optimization at trial, program, or portfolio level should always be considered in drug development
- Simulations necessary for development scenario comparisons
- A number of things need to be considered when making decisions:
  - Which parameters are of most importance?
  - What are most likely scenarios?
- Optimized development plans across a portfolio could be combined with portfolio optimization to assist senior management with resource allocation across the drug portfolio

- Specific findings:
- Biomarkers useful for PoC, but may be of limited use for dose-finding
- Larger sample sizes in Phase 2b and Phase 3 studies and inclusion of an adaptive design improve outcomes of development programs

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