

Early Clinical Development Planning Via Biomarkers, Clinical Endpoints, and Simulation: A Case Study to Optimize for Phase 3 Dose Selection

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Motivation

In developing the strategy for a compound in early clinical development, we posed the following questions:

- How can the relationship between early biomarkers and clinical endpoints be leveraged to optimize Phase 1-2 plans? To 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 the correct Ph3 dose?

Clinical Trial Simulation

- Define true underlying scenario(s) for endpoint(s), study design(s), decision rule(s)
- Generate many repetitions
- Summarize results
- Use to choose and justify trial design
 - Demonstrates design performance for a span of potential true scenarios

Trial simulations are widely used in drug development

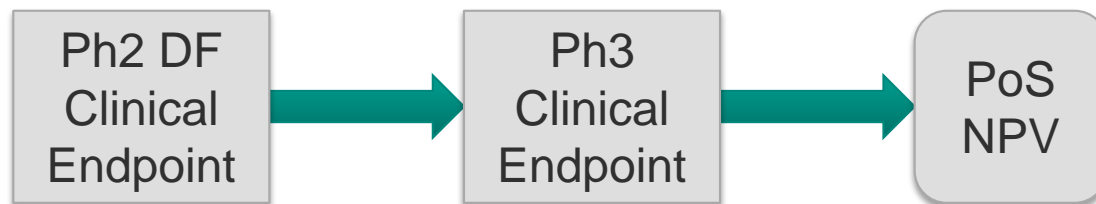
Drug Program Simulation

- Define a *sequence* of clinical trial simulations, including decision rules and design options for moving from one trial to the next
- Aim to optimize the sequence of trials for a particular set of drug program objectives

Drug Program Simulation

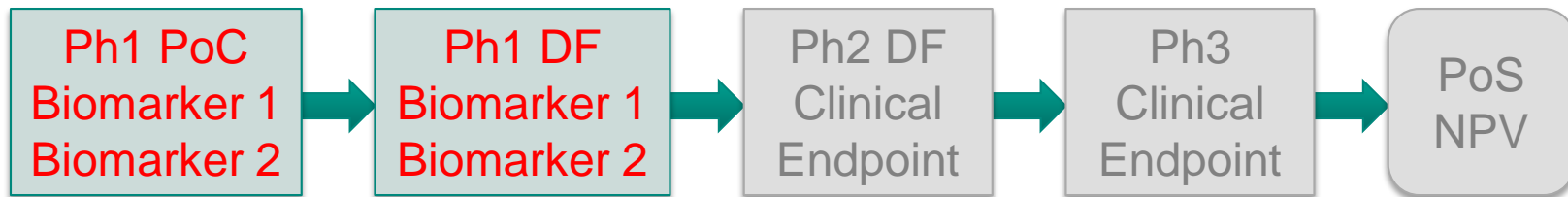
Phase 2 → Phase 3

- Typically, drug program simulations have linked Phase 2 and Phase 3 studies
- *Adaptive program design* has focused on optimizing Ph2b/Ph3 development



- Can we extend this paradigm into *early clinical development*?
 - Is there an opportunity to improve late-stage program success through the design of Ph1 biomarker studies?
 - Biomarkers already commonly used for go/no-go

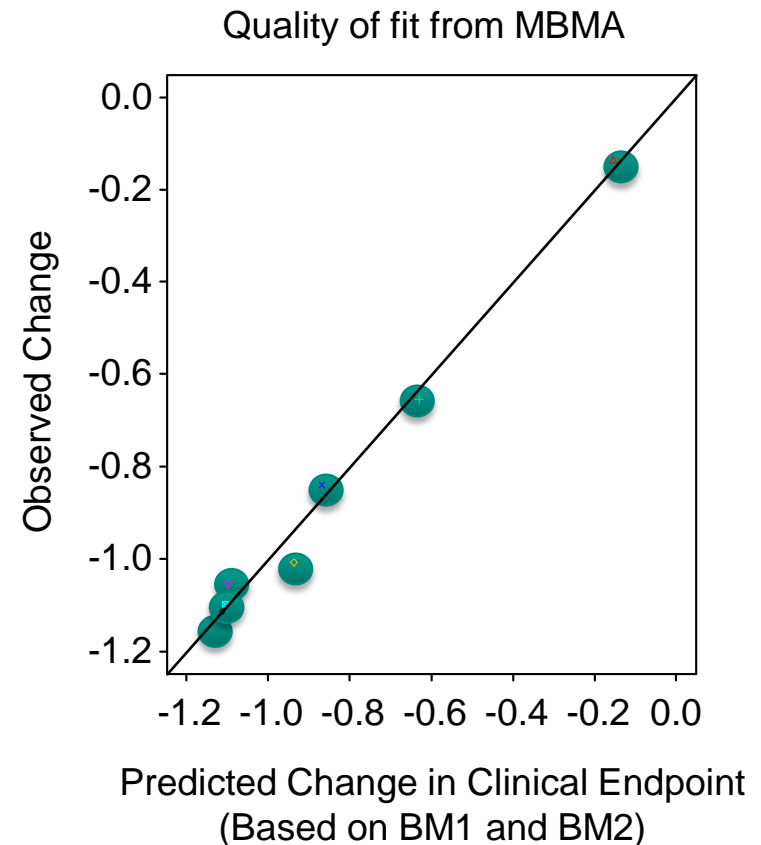
Extending the Drug Program Simulation to Use Phase 1 Studies and Biomarkers



- Benefits of adaptive program design can easily be extended to include Phase 1
- Ph2b study design options that could be informed by a biomarker study
 - Better dose selection
 - Fewer doses
 - Smaller sample size
- Can a dose-response design in Ph1 (using biomarkers) be used to improve the efficiency of a Ph2b study?
 - Can we use Ph1 results to build an informative prior for Ph2b?
 - What is the accuracy of selecting Ph2b doses using biomarkers?
 - What is the impact of using biomarkers on choosing final Ph3 dose?

Simulation Scenario: Endpoints

- Clinical endpoint typically measured in chronic setting (12-24 weeks)
 - Possible to measure earlier as a third biomarker but with smaller effect size
 - Typical Ph2b study size is ~100 patients per group
- Biomarkers BM1 and BM2 can be measured in short-term Ph1 studies
 - Model-based meta-analysis (MBMA) suggested linear relationship to Ph2/3 clinical endpoint
 - Could also utilize mechanistic models without loss of generality
 - Measurements taken later in time have higher correlation to clinical endpoint



Simulation Scenario: Endpoint Model

- Two models used in the simulations
 - Model of “truth” used to simulate trial responses
 - Bayesian model, based on MBMA, used to interpret trial responses as if “truth” not known
- Trial responses were simulated using an Emax model between dose/exposure and biomarker/endpoint response
 - For presentation, endpoints standardized to SD of 1 and desired response is 0.4
- Bayesian predictive model built using MBMA
 - Bayesian calculation of posterior probability of exceeding threshold in clinical endpoint used for go/no-go decision
 - Bayesian model also used to predict efficacy

$$E(y_{ijk}) = \beta_k + \frac{1}{(1 + e^{\log \theta_k - \log c_{ijk}})} \delta_k$$

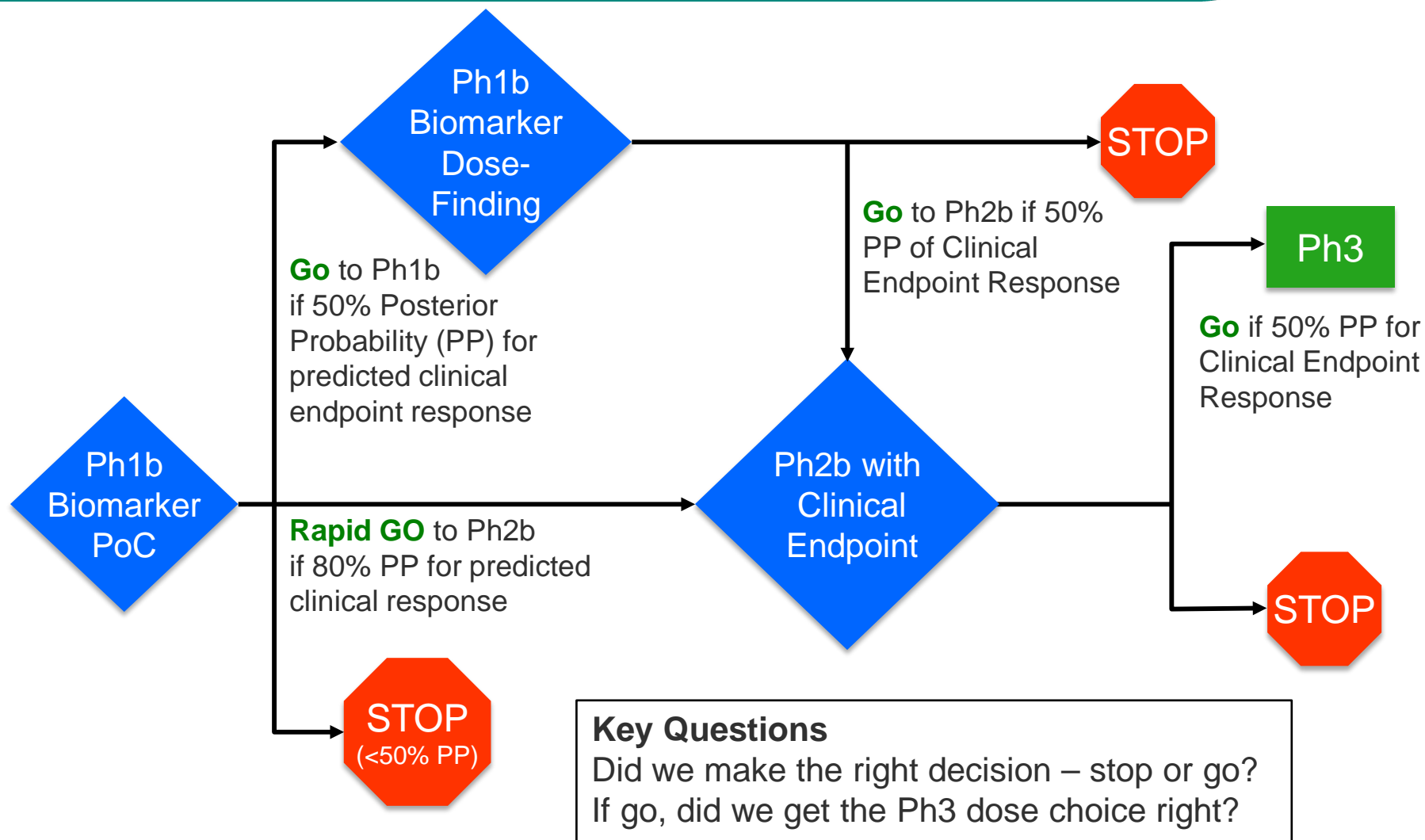
Assumed Parameters

Marker (k)	E0 β	Ed50 Θ	Emax δ	Slope (fixed)
BM1	0	20 mg	1	1
BM2	0	20 mg	1	1
Endpoint	0	20 mg	0.5	1

Covariance Matrix

Marker	BM1	BM2	Endpoint
BM1	1	.8	.4
BM2		1	.3
Endpoint			1

Ph1b-Ph2b Decision Making



Simulation Scenario

Three Potential Clinical Studies

Study	
Ph1 PoC study (biomarker)	Go/no-go based on posterior probability of exceeding desired clinical endpoint threshold, based on Bayesian model linking biomarker to endpoint response
Ph1 DRF study (biomarker)	Bayesian dose-response model informs on dose range for Ph2b Doses chosen to bracket clinically desired effect unless bounded by maximum feasible dose
Ph2b DRF study (“definitive” DRF based on clinical endpoint)	Go/no-go to Ph3 based on posterior probability of exceeding threshold Ph3 dose taken as lowest dose predicted to exceed clinical efficacy threshold with certain probability, so long as it does not exceed maximum feasible dose

Notes:

Focusing on decisions for entering Phase 3, assuming that registration requirements that define Phase 3 are relatively fixed

Simulations here focus only on efficacy biomarkers but could easily be generalized to any biomarker with a dose/exposure-response relationship

Simulation Scenario: Study Options

Study	Fixed Design Elements	Simulated Options
Phase 1 Biomarker PoC trial	Parallel group High dose vs placebo N=20 active, N=10 placebo	<ul style="list-style-type: none"> • Shorter duration – biomarkers A and B only • Longer duration – A, B, early clinical endpoint
Phase 1b Biomarker dose-finding	Parallel group Placebo, low, mid, high dose N=20 active, N=10 placebo	Note: duration to match biomarker PoC trial
Phase 2b trial	Parallel group Placebo, low, mid, high dose	N=25, 50, 100/dose Potential 4th active dose

Other Elements of the Simulation:

Two different prior distributions for Ph2b DR Emax model

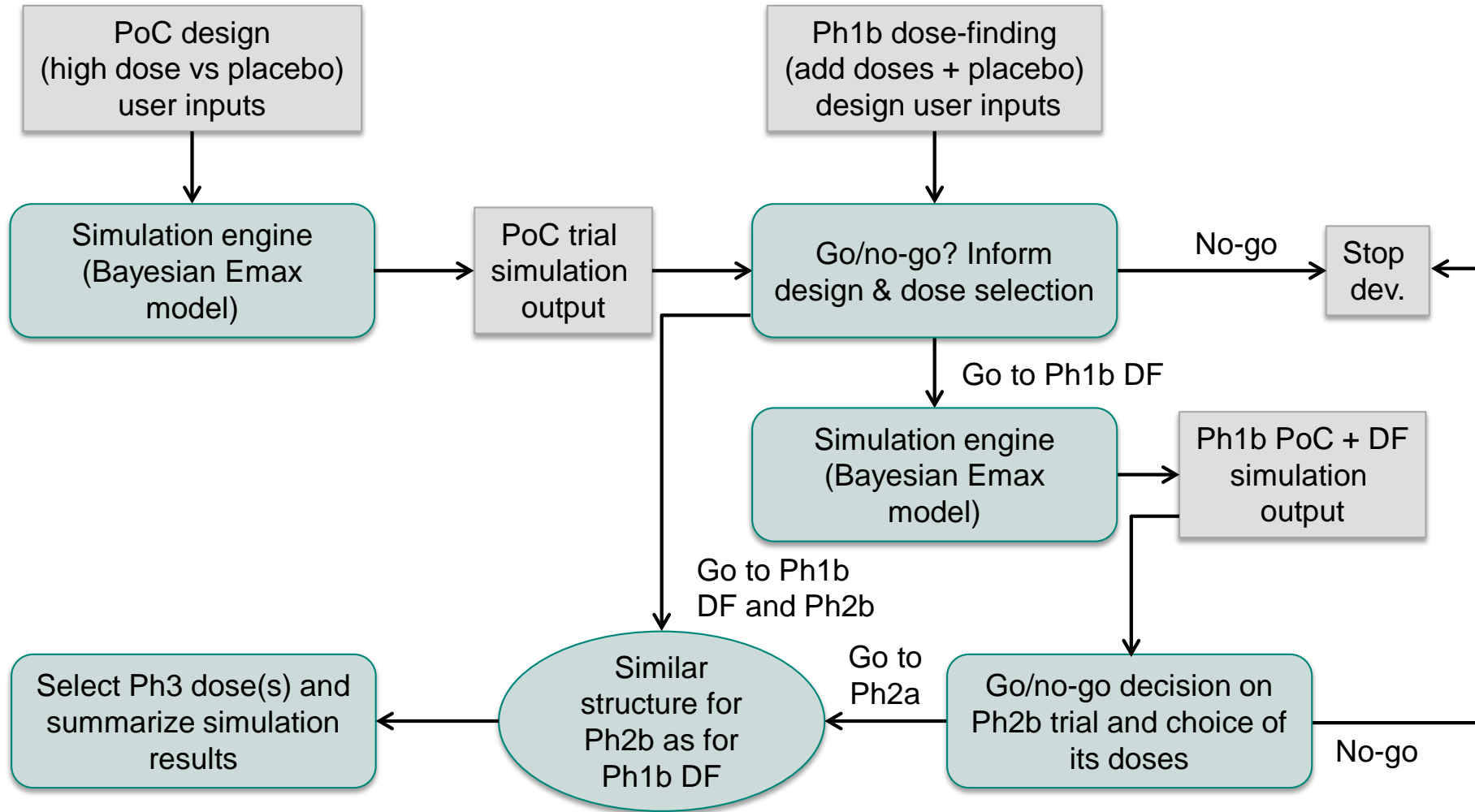
Uninformative

Or informed by early use of clinical endpoint in longer-duration study (“BM3”)

Phase 2 Dose Selection Algorithm

- Want up to 3 doses in Phase 2 with separation between active doses and placebo, and among the active doses
- Two constraints applied:
 - Dose could not exceed “Maximum feasible dose” (MFD)
 - Dose selection constrained to a limited set of feasible doses
- Model is used to predict effect of each dose, based on Ph1 results +/- biomarker study
- Want at least a 0.4 difference from placebo for Ph2 – if no feasible dose is predicted to give this much efficacy, stop
- Choose doses as follows
 - D1: difference of 0.4 more than placebo
 - D2: difference of 0.6 more than placebo and 25% higher than D1
 - D3: twice D2 if less than MFD or 0.15 higher than placebo

Schematic of Ph1b-Ph2b Simulation System

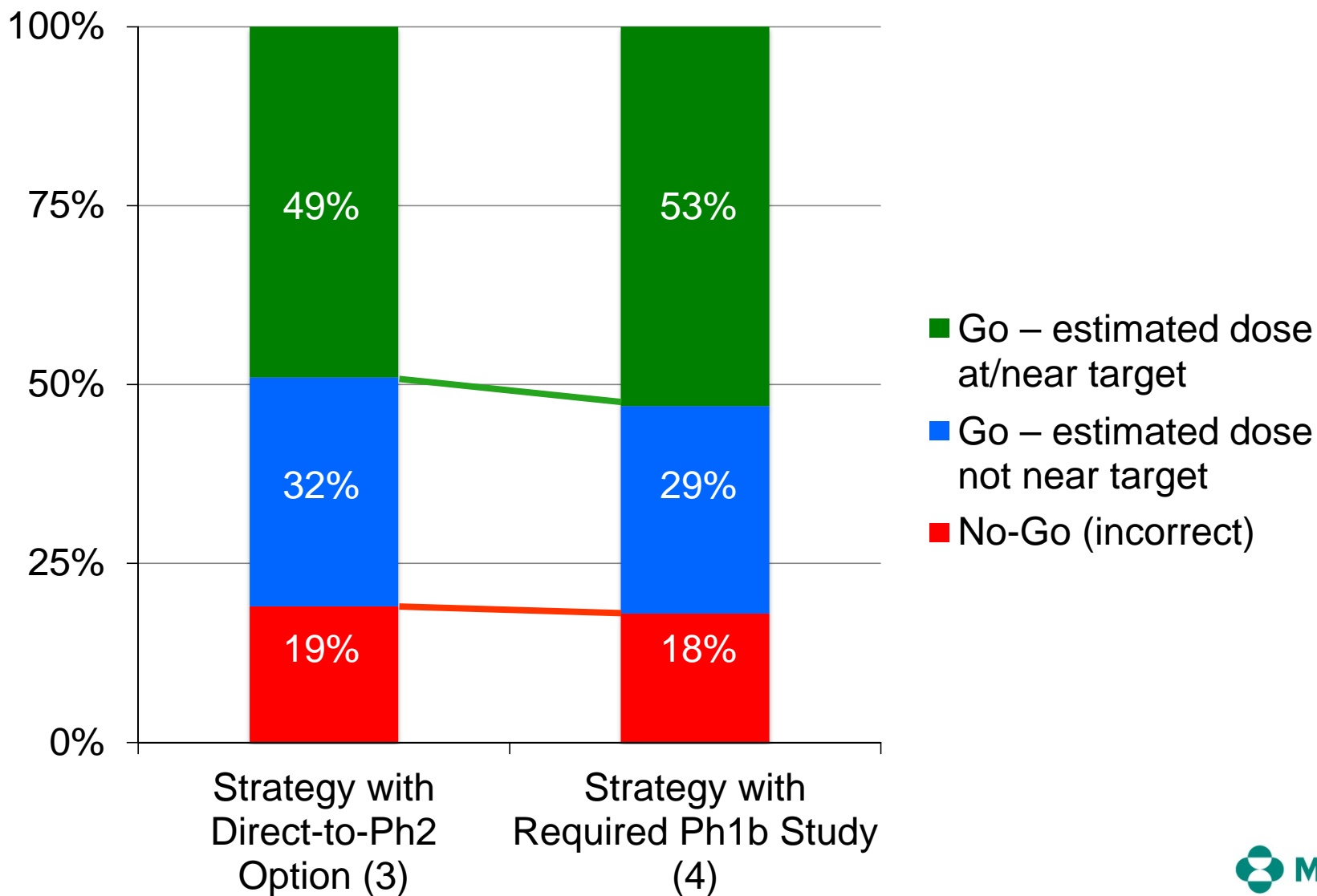


Simulation Results

- Two metrics presented
 - Rate of GO to Ph2b (based on posterior probability criterion)
 - Rate of “correct” dose decisions for Ph3
 - “Correct” defined as exceeding certain threshold of efficacy
 - Aim to be “at” or adjacent to true dose that exceeds threshold
- Selected sets of results to review
 - Impact of allowing direct-to-Ph2b strategy
 - Informative vs. uninformative prior for Ph2b study interpretation
 - Shorter vs longer duration of Ph1 studies
 - Impact of sample size in Ph2b on Ph3 dose selection

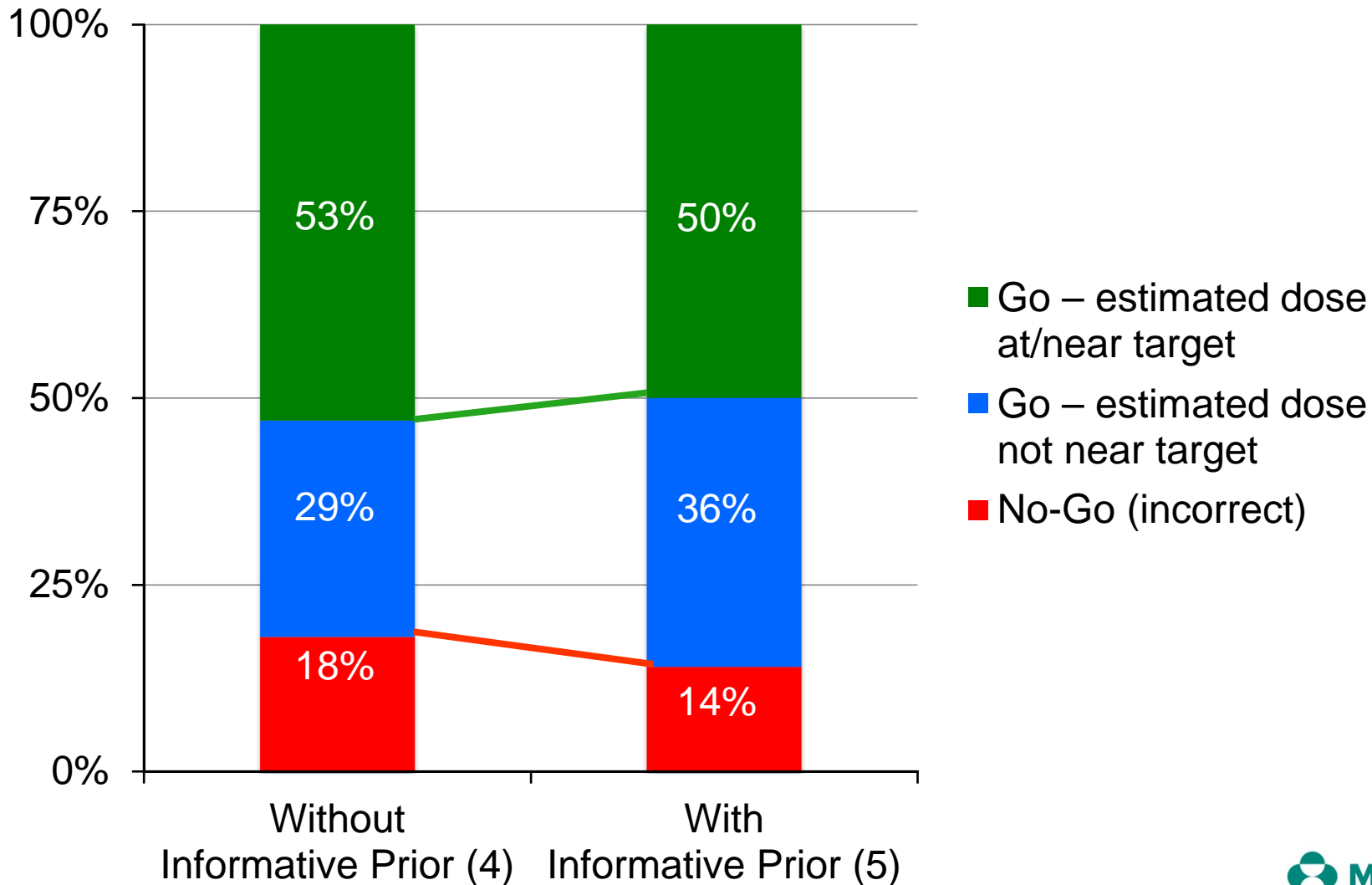
Note: 500-1000 simulations run per scenario (error 3%-5%)

Development strategy with accelerated direct-to-Ph2b option generally similar to requiring Ph1b

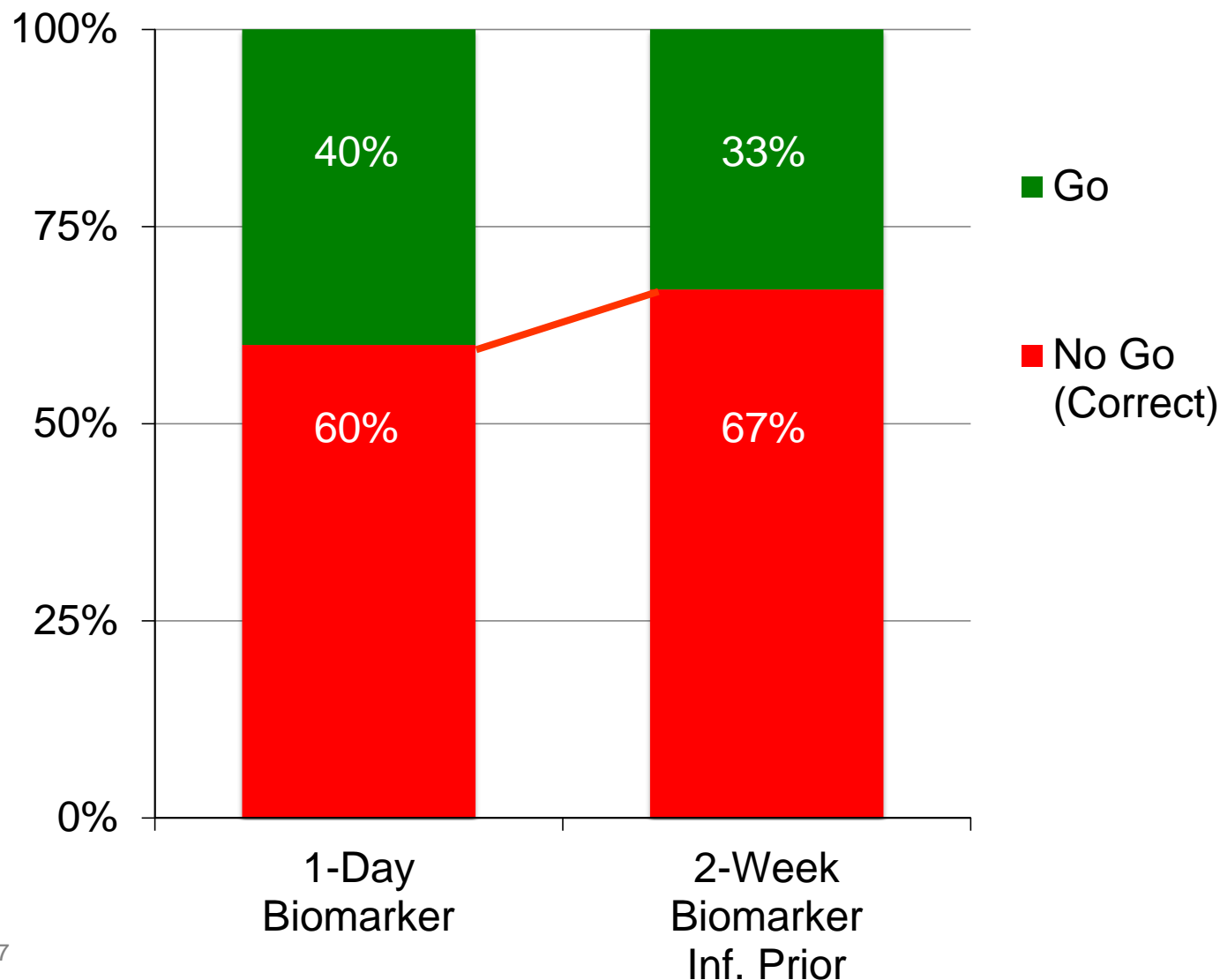


Informative prior reduces rate of incorrect “no go” but dose selection not improved

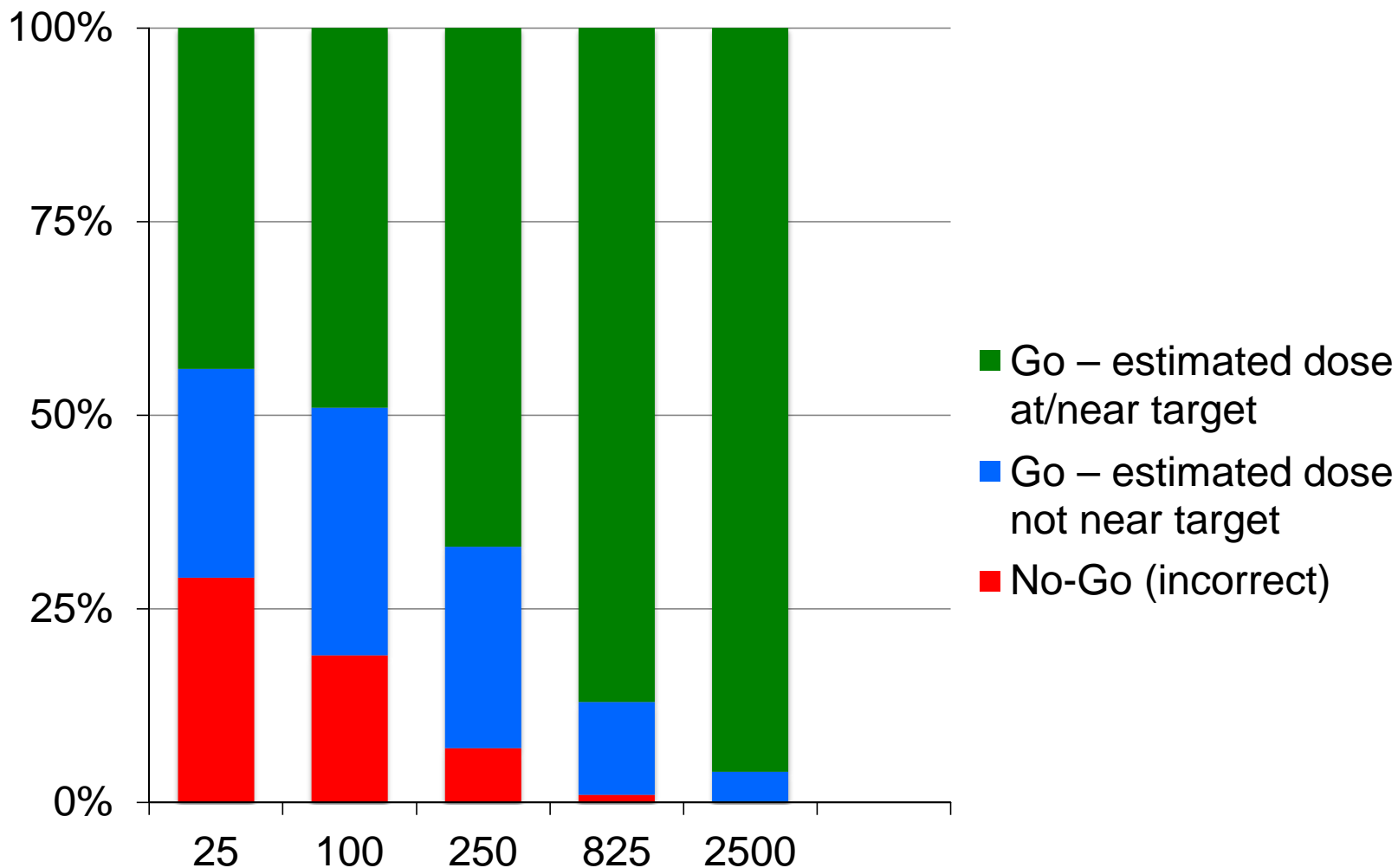
Scenarios both use a modest-sized Ph2b study (n=100)



When desired efficacy is unattainable, longer biomarker study with inf. prior improves rate of correct “no go”



Ph3 dose selection improved by larger Ph2b studies



Conclusions from These Scenarios: Impact on Clinical Development Program

- Simulation framework allowed for an assessment of different scenarios for structuring the clinical program
- Biomarkers used in typical Ph1b study designs enabled better go/no-go decision making
 - Bayesian framework useful for leveraging biomarker results to make posterior probability calculations for exceeding threshold of desired clinical efficacy
 - Longer-duration biomarker was more informative for determining lack of attainable efficacy – better go/no-go decisions
- Biomarkers did not meaningfully improve dose selection
 - Relationships between proposed biomarkers and endpoint were too variable to drive dose decisions
- Dose selection best resolved in Ph2b

Summary: Tool Enables Exploration of More Informative Ph1 Program Designs

- A Bayesian simulation framework was established to assess the impact of biomarkers in a clinical development program
 - Framework allows us to assess utility of different biomarkers, multiple biomarkers, different length studies, Ph1 sample size, and use of informative priors for guiding decision making for Ph2b/Ph3
- Simulation framework drove an understanding of the potential for the models to link endpoints across studies and drive decision making
 - In the motivating example, allowed the team to discuss the value of the Ph1b biomarker study
 - Stimulated the team to think about improving how Ph1b biomarkers could be used to drive decision making
 - Different models that relate biomarkers to clinical endpoints
 - Consider using biomarkers to address different questions, such as
 - Dose regimen
 - Understanding mechanism of action rather than directly correlating Ph1b endpoints to Ph2b endpoints

Future/Related Work

- Consider time/cost tradeoffs more explicitly in the framework
 - What is the cost of each strategy, given similar results in selecting a Ph3 dose?
 - Combine with Ph2 → Ph3 simulations to optimize the entire drug development program
 - Relative costs can provide NPV of different paradigms
- Include constraints in the simulation when optimizing the strategy?
 - What is the maximum value that can be achieved given limited drug supplies? Is it better to wait for larger study or get tentative answer sooner?
- Assess other response models
 - Leverage drug-concentration-to-biomarker relationship and mechanistic models of biomarkers to clinical response? How good do the models have to be to improve Ph3 dose selection?
 - Early findings presented at ASCPT 2015 by Mathangi Gopalakrishnan, University of Maryland
- Incorporate adaptive designs and other design considerations (e.g., varying the number of doses)

- Special Interest Group (SIG) cosponsored by the American Statistical Association and the ISoP
<http://community.amstat.org/sxp/home>
- SIG promotes collaboration between statisticians and pharmacometricians to enable each discipline to learn and grow from the other and to develop innovative approaches to model informed drug development
- Membership open to everyone – neither ASA nor ISOP membership is required



Donald J. Trump

@realDonaldTrump

Just watched ASCPT. Trial simulations can make drug development great again! Biomarkers helped with Go-No-GO but not dose selection. So sad!

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