



PHARMACEUTICALS  
Consulting Division

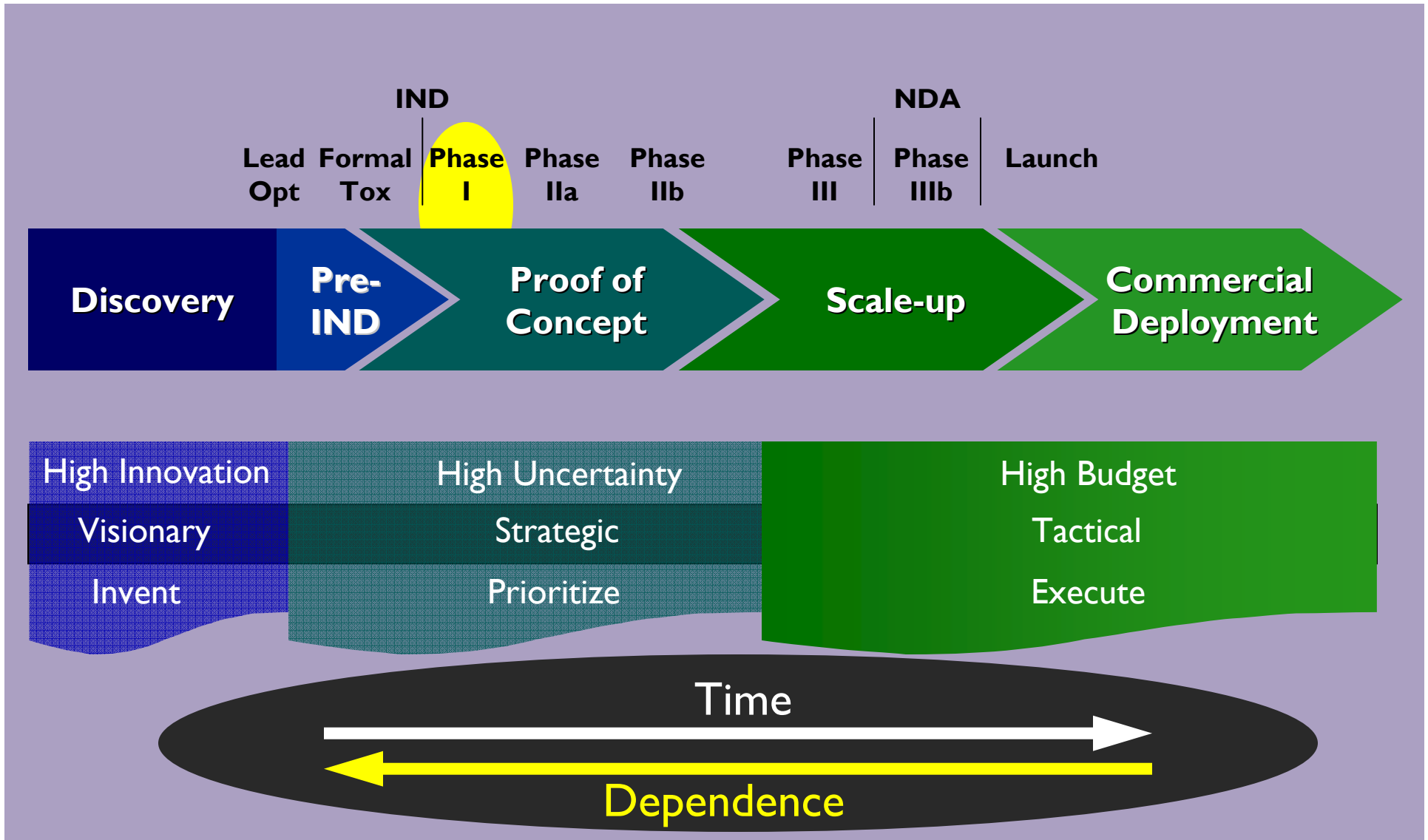
## PhysioPD™ Modeling in Phase I

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Phase I begins a drug's most strategically sensitive development period.



A novel sulfonylurea (SU) type-2 diabetes drug candidate is about to undergo 1<sup>st</sup>-in-human trials<sup>1</sup>.

RP 9487

Increased  
insulin  
secretion

**Lower plasma glucose  
(therapeutically significant)**

**Hypoglycemia**

Effects on heart,  
kidneys, and  
other tissues

- **Hypertension**
- **Ischemia severity**
- **Water retention**
- **Weight gain**
- **Effect erosion over time**

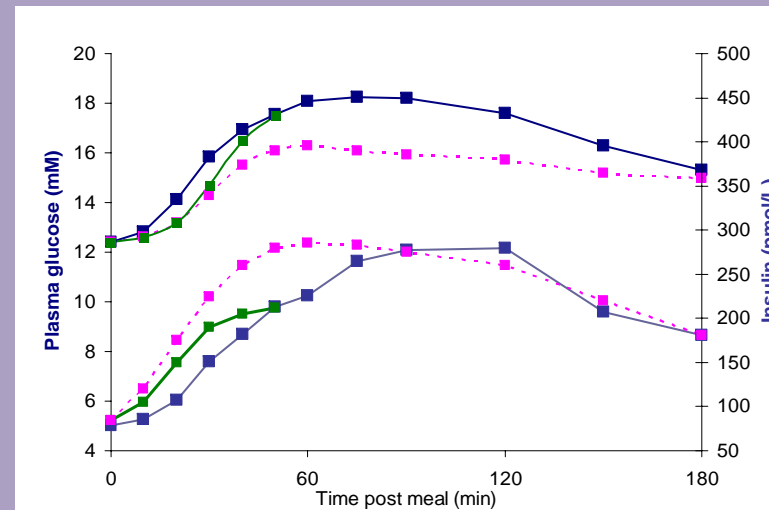
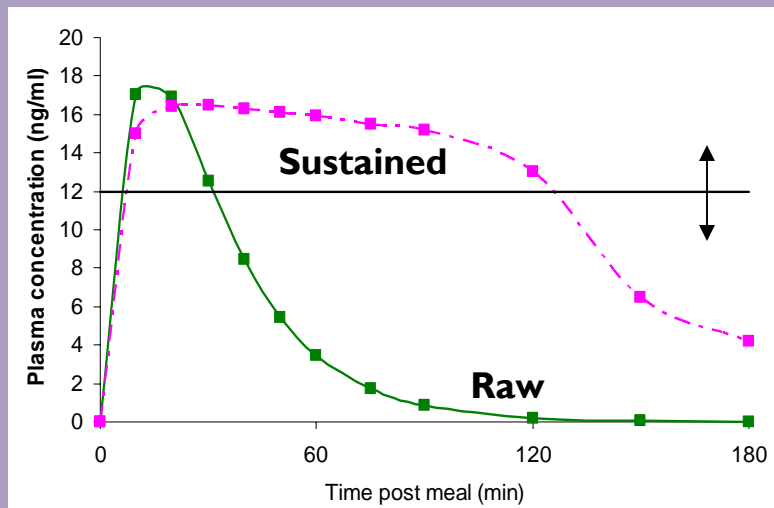
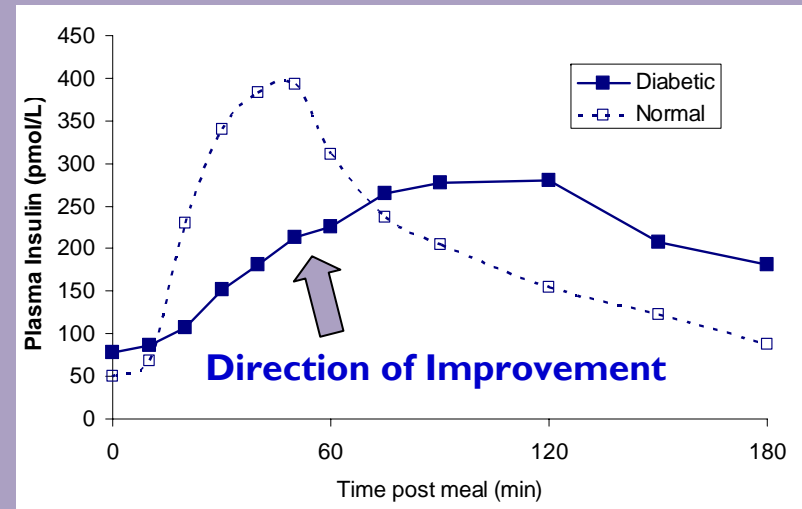
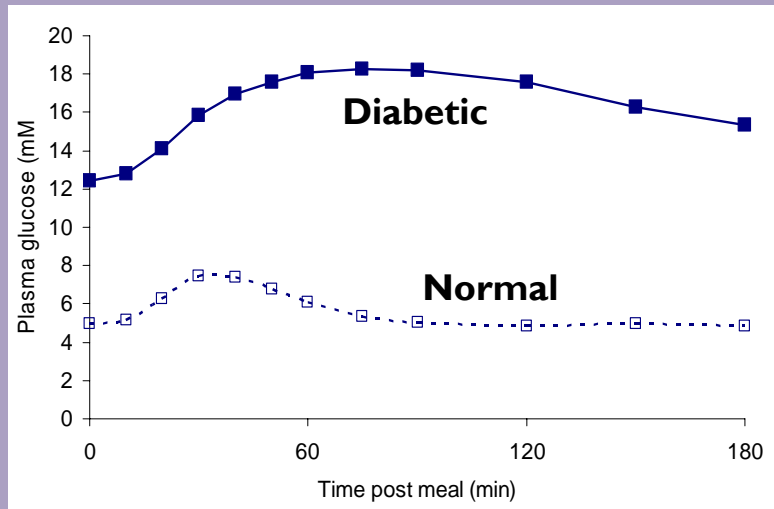
<sup>1</sup> **Disguised, composite case. All data are illustrative. For discussion purposes only.**



## “The drug works too well!”

- Preclinical RP 9487 studies show very high *in vivo* potency compared to SUs in the market.
- Such high potency comes at the cost of a very short half life in plasma and, potentially, hypoglycemia.
- Preclinical RP 9487 data show that controlled release can significantly reduce the likelihood of hypoglycemia and other adverse effect frequency and severity.
- Reflecting market-volume potential, RP 9487 is being formulated for:
  - 3-hour controlled release (TID/QAC)
  - 12-hour controlled release (QD).

# A sustained release RP 9487 can potentially maintain plasma glucose at a healthy level.

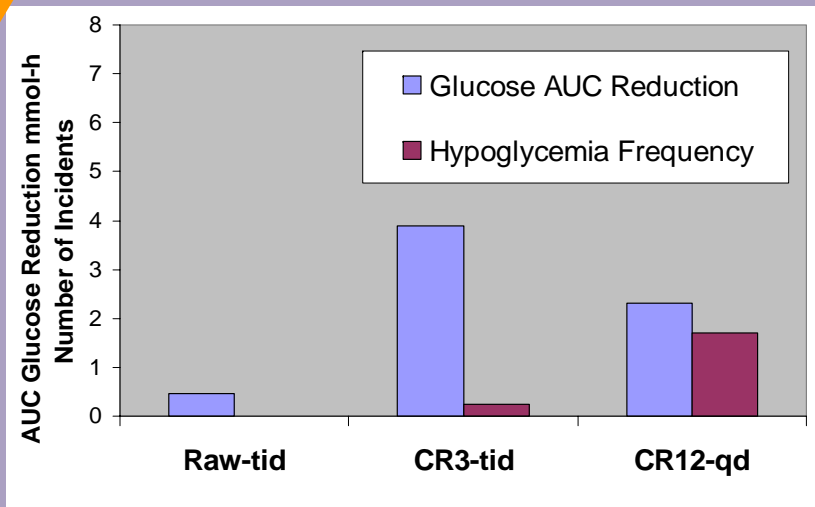
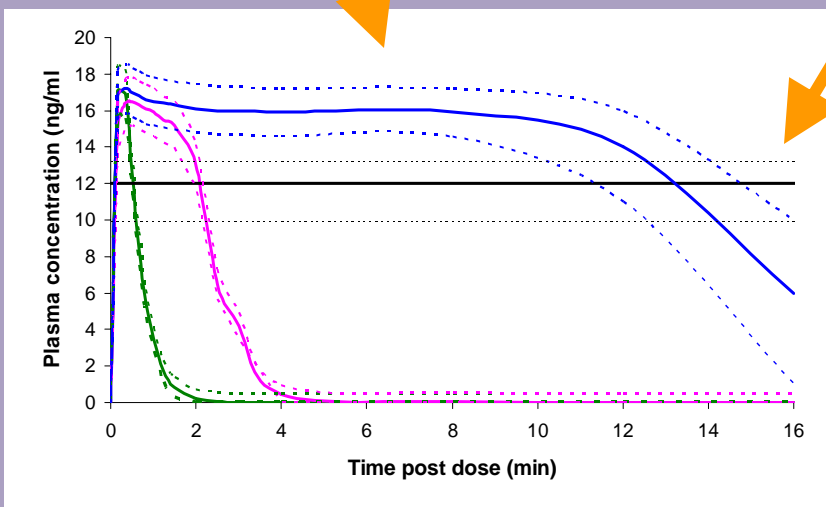
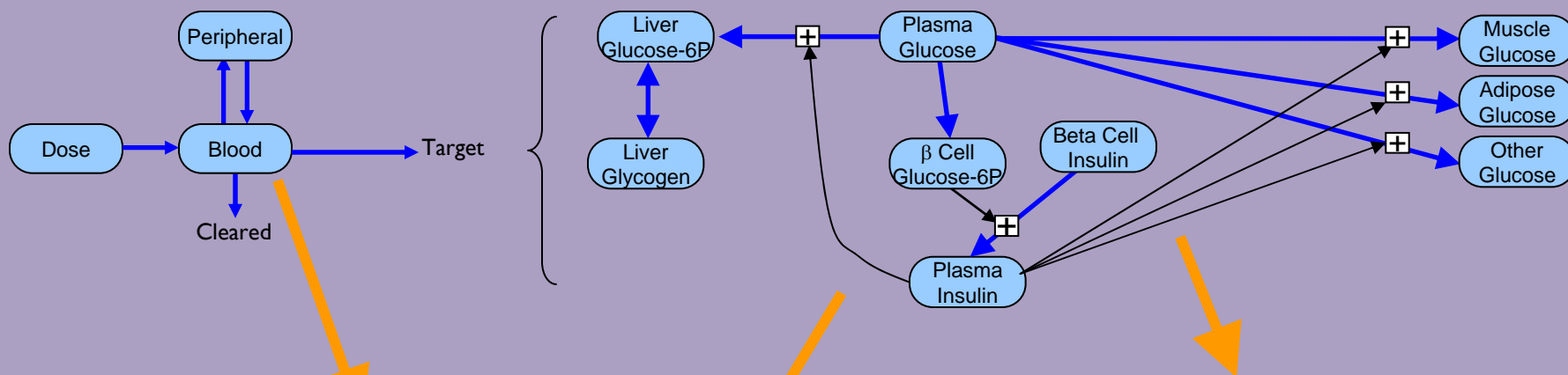


## How do we test RP 9487's PK and safety without breaking the bank?

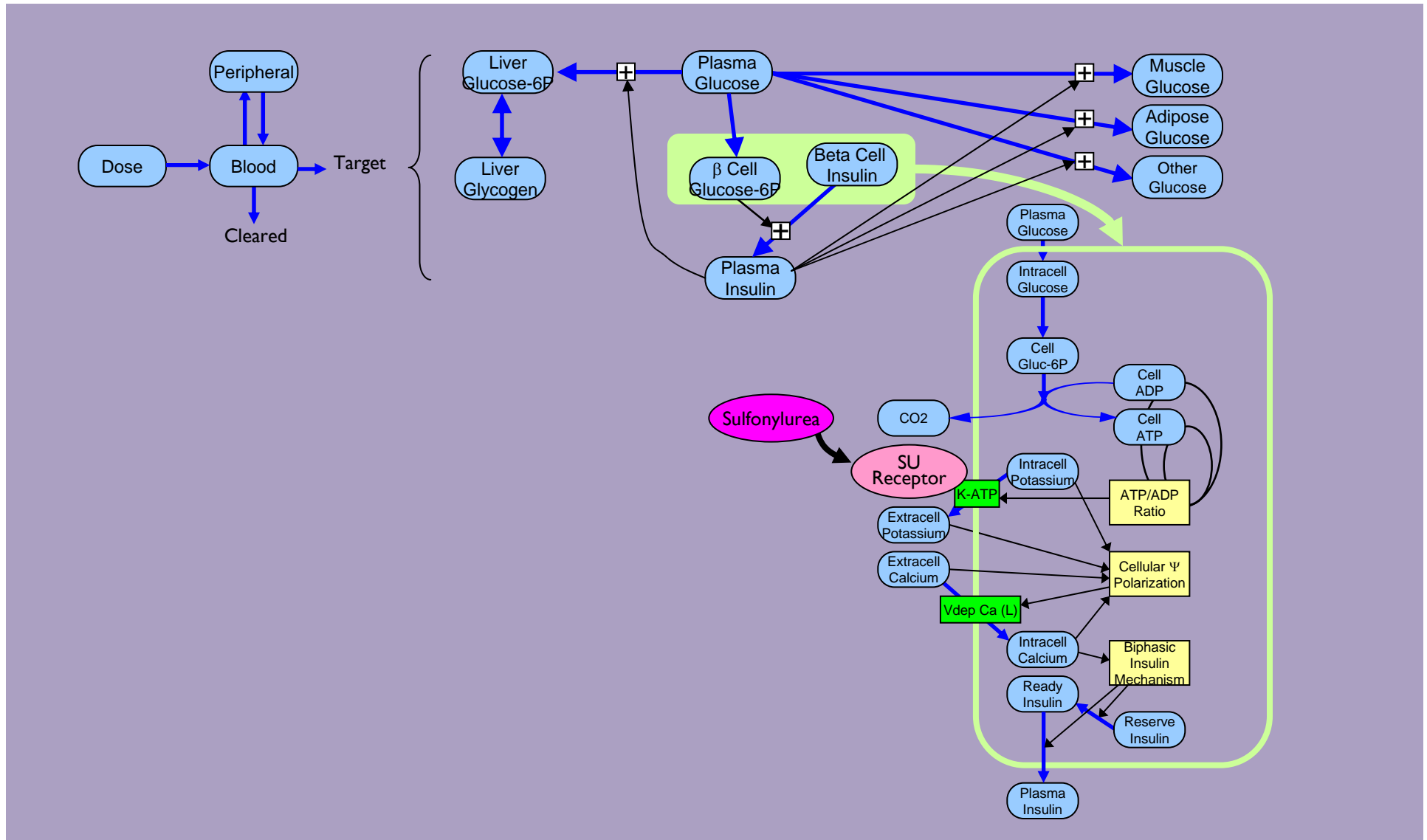
- We have a narrow therapeutic window.
  - If RP 9487 were not so potent, it would have probably been discontinued.
- To design efficient and conclusive I<sup>st</sup>-in-human studies that support future Phase II and III studies, we must reliably estimate RP 9487's therapeutic threshold in humans.
- We also need to select an optimal release form for RP 9487.
- While we could conduct an adaptive sequence of clinical trials to determine the desired parameters, we'd prefer not to because:
  - It would take too long.
  - It would be too expensive.
- Challenge: Peek into the future via modeling and simulation

# Using public and proprietary data, a custom PhysioPD model reliably predicted both PK and PD trial results

## Simplified PhysioPD model schematic

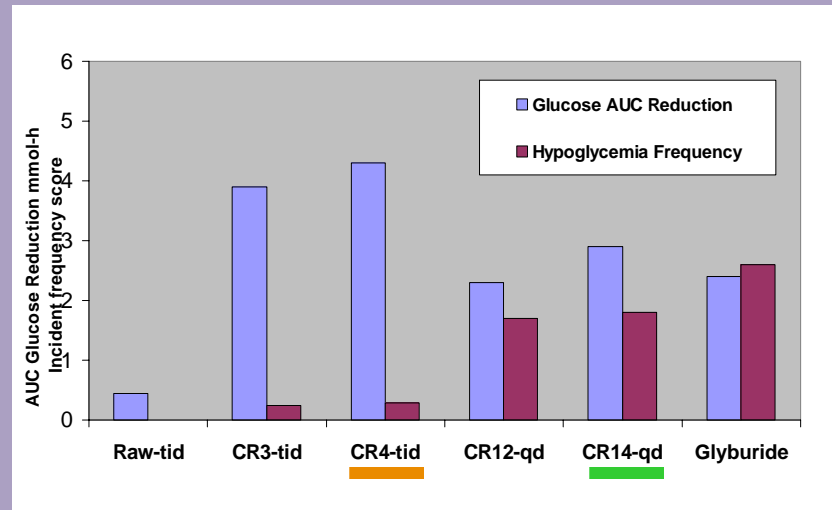
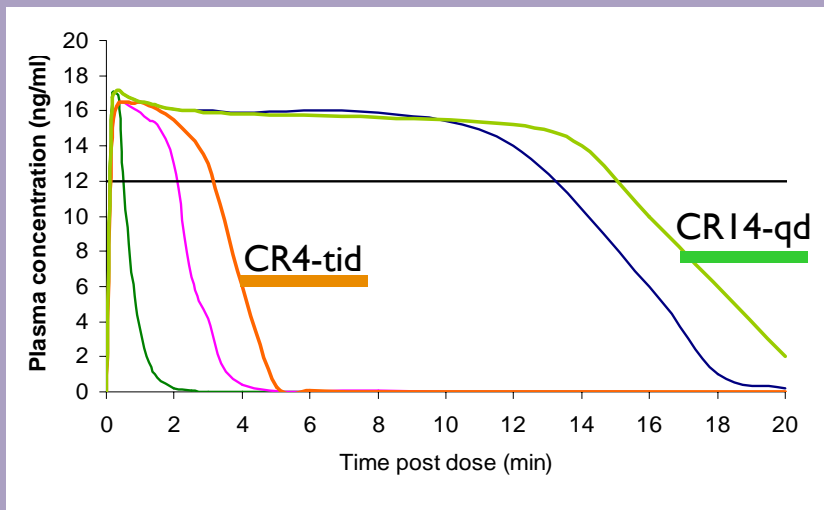


# Accurate glucose and hypoglycemia predictions were made possible by integrating diverse data.

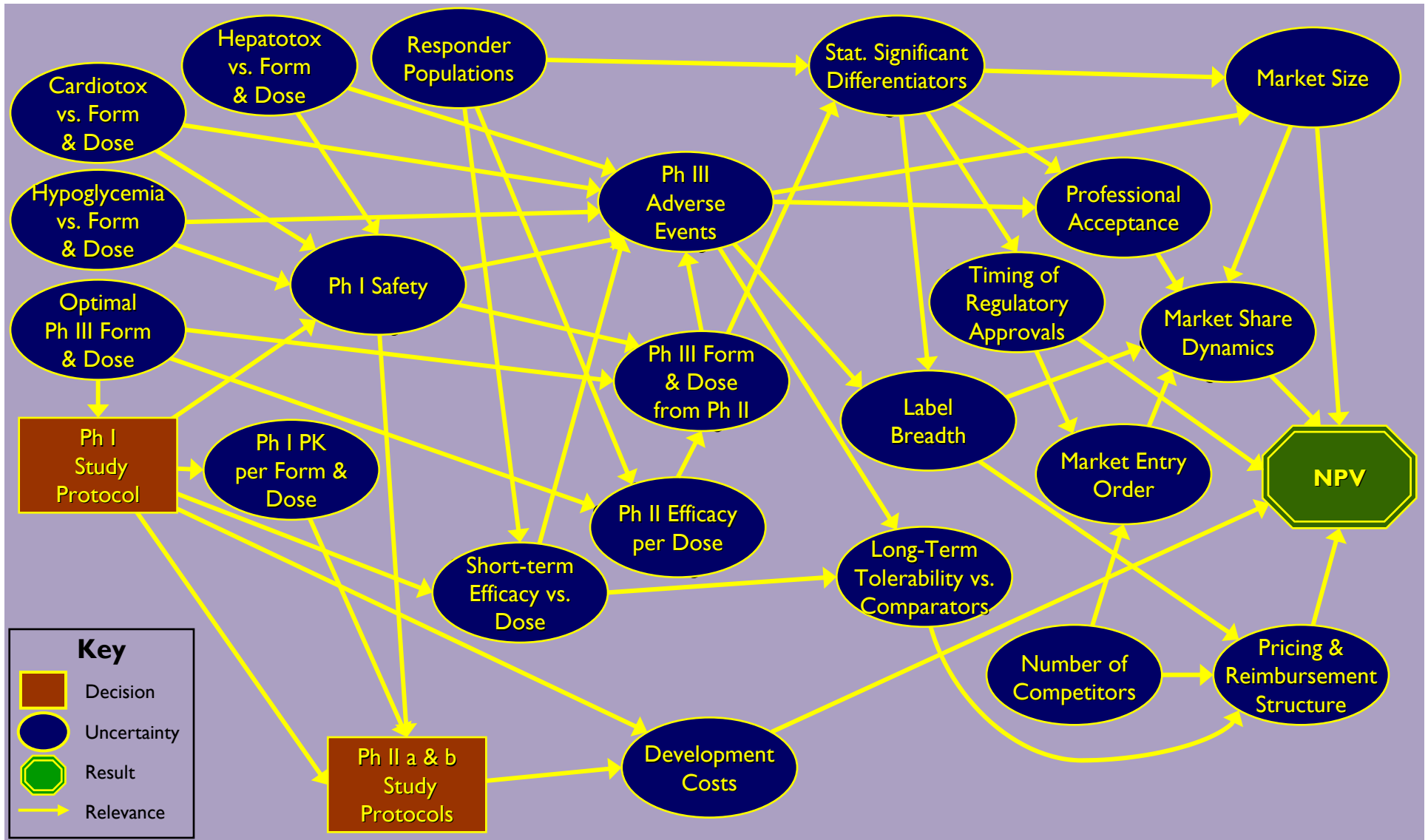


## PhysioPD model results suggested CR formulations with potentially better glycemic control and safety.

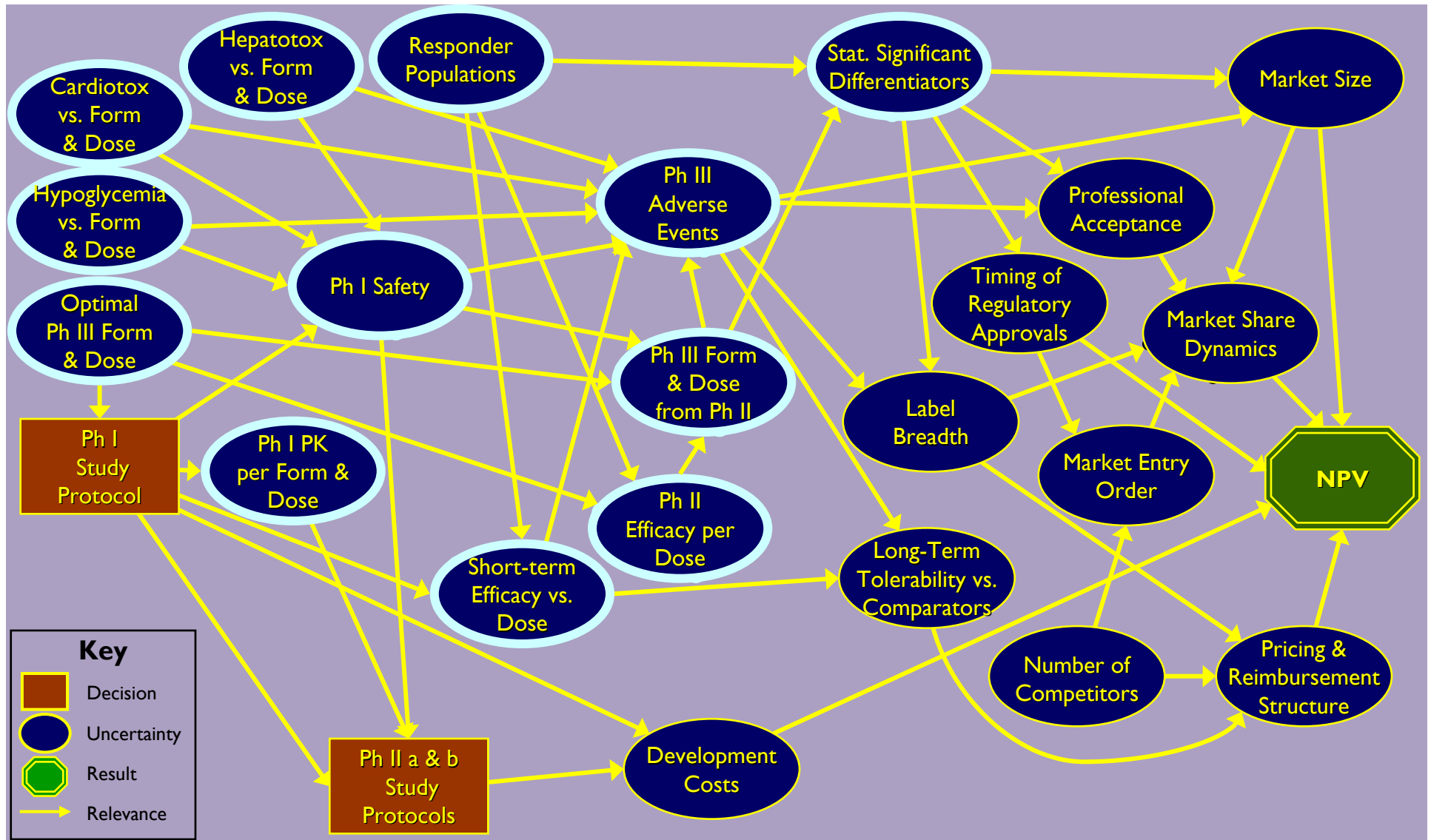
- A** 4-hour formulation giving better glycemic control without significant risk of adverse events
- B** 14-hour qd formulation giving better glycemic control with less risk of adverse events than Glyburide; suitable for some patients
- All four CR formulations were manufacturable.



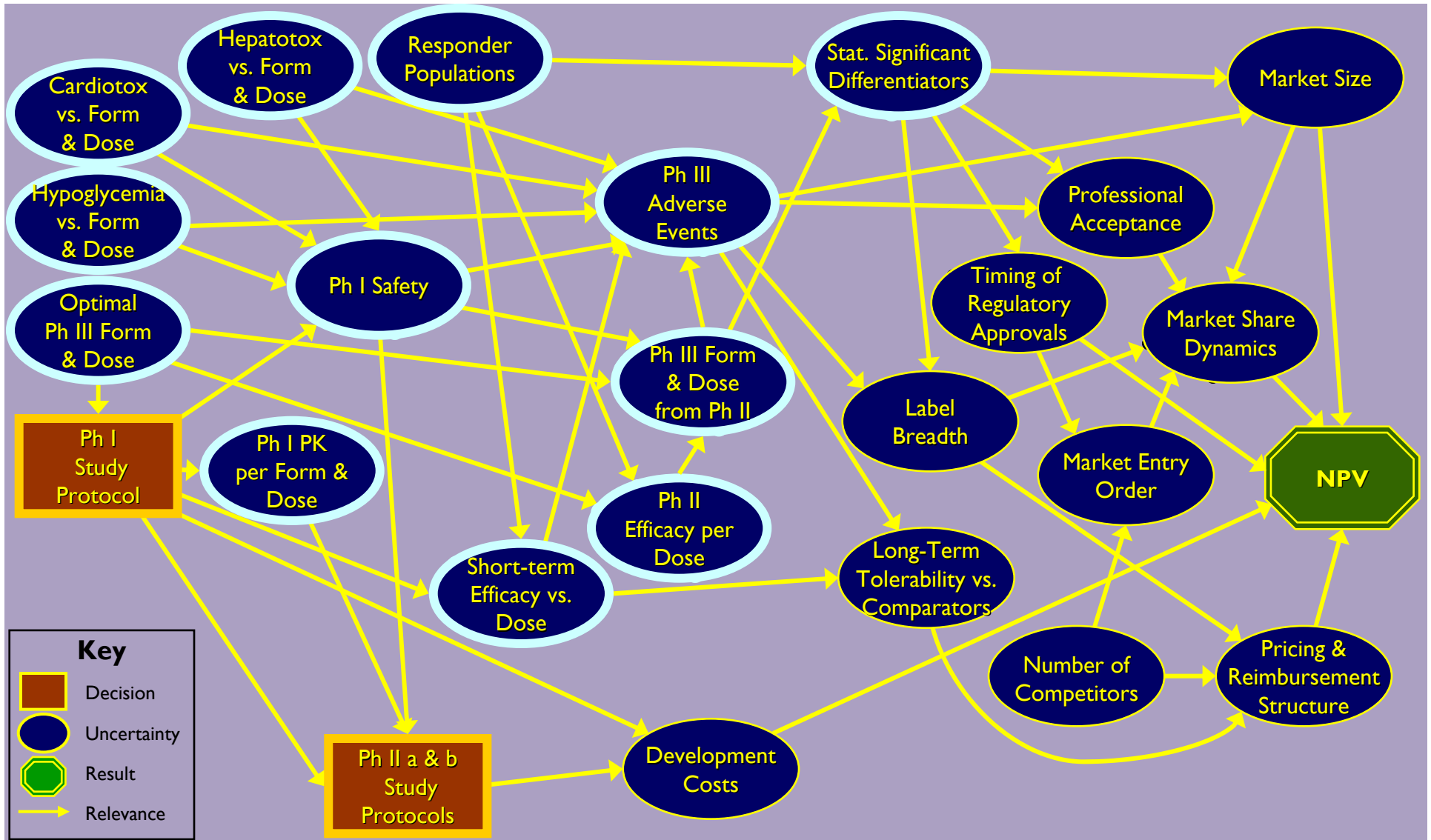
# The choice between formulations and Phase I plans involved expertise from many parts of the organization.



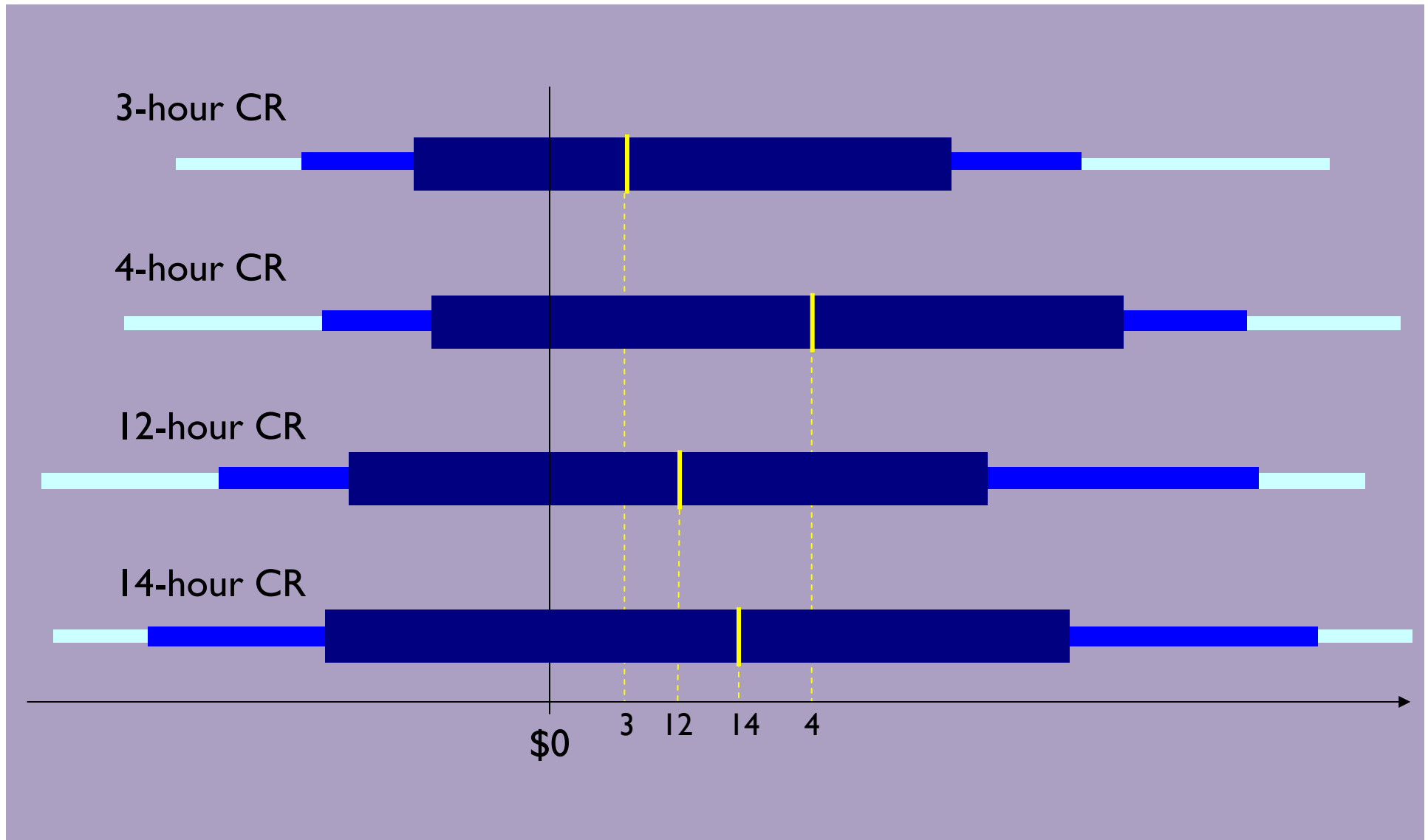
PhysioPD simulations enabled scientists to accurately and reliably assess key uncertainties.



PhysioPD simulations also let the team create and prescreen alternative study protocols.



While all 4 CR formulations seem promising, the 4- and 14-hr forms have superior risk-adjusted value.



PhysioPD model predictions led to very conclusive, informative, and efficient 1<sup>st</sup>-in-human studies.

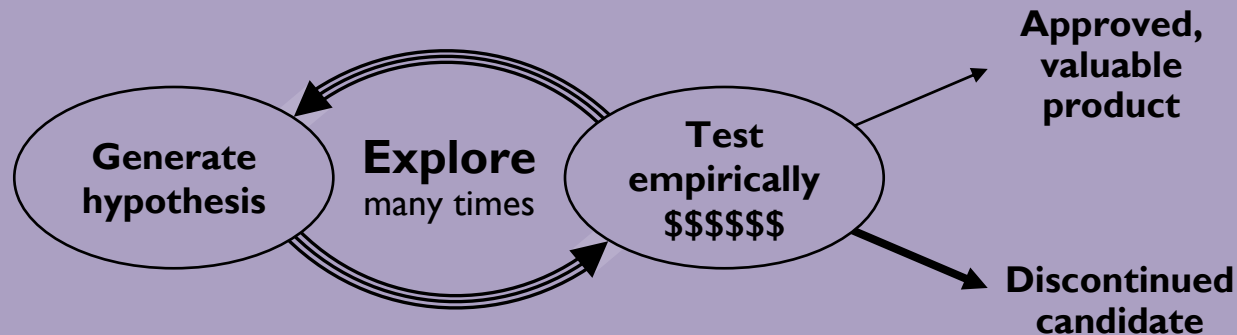


- The 4-hour controlled release form achieves the target SU plasma level with minimal night-time hypoglycemia risk.
- The 14-hour controlled release shows better efficacy than the 12-hour form with similar hypoglycemia risk – both substantially better than Glyburide.
- QD formulations has great commercial promise; and, while somewhat less convenient, TID/QAC regimens work well in diabetes.
- Both 4-hour and 14-hour controlled-release RP 9487 forms entered Phase IIa trials.

# Decision-focused PhysioPD simulation leads to faster, less costly, and more successful development.

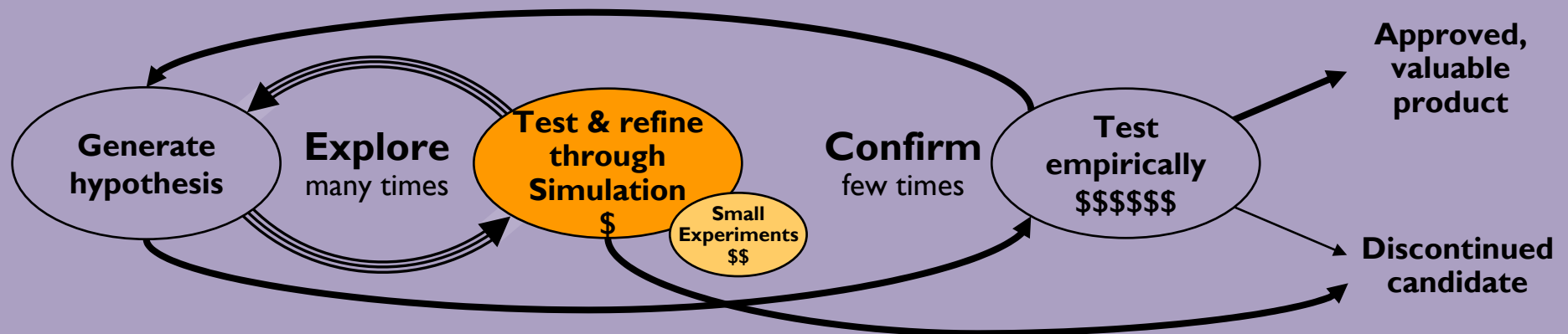
## Standard development method:

Multiple, expensive empirical tests



## Enhanced with simulation:

Better resolution with fewer empirical tests



Simulation informs decisions, improves alternatives, and yields pin-point accuracy.

- Much lower development costs
  - Far fewer repeat studies
- Faster development
- Fewer failed trials
- Much greater learning
- Newer and better alternatives
- Corporate memory

Simulate and refine → Experiment



Pin-point  
Accuracy





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