



# Optimizing clinical diabetes drug development

## *What is the recipe?*

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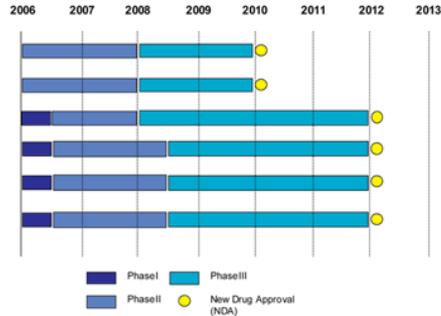
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# Why optimise diabetes drug development?



“Increasing need for safe and effective diabetes medicine”



“More difficult to show improved clinical profile against competitors”



“The risk for late stage failure increases which harms our ability to fund future innovation”

# What is the challenge?

## Phase I

- Safety
- PK
- PD: FPG, GIR
- 1-5 weeks

## Phase II

- Safety
- PK
- PD: FPG, MPG, HbA<sub>1c</sub>
- 10-16 weeks

## Phase III

- Safety
- PK
- PD: FPG, MPG, HbA<sub>1c</sub>
- 6-12 month

Different endpoints and duration make prediction hard!

FPG: Fasting plasma glucose (measured before a meal)

GIR: Glucose infusion rate (from clamp)

MPG: Mean plasma glucose (from 24-h profile)

HbA<sub>1c</sub>: Glycosylated hemoglobin (marker for long-term glucose)

# Key questions for efficacy prediction



5-week data  
(FPG/GIR)

12-week data  
(MPG, HbA<sub>1c</sub>)

Model library that enables  
bridging between different development phases

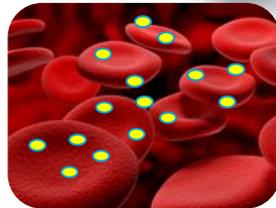


Which dose  
will be  
in phase  
(MPG/HbA<sub>1c</sub>)



The right dose and  
performance  
against  
competitors?  
(HbA<sub>1c</sub> at 26 weeks)

# Ingredients



## Modeling of 24-Hour Glucose and Insulin

Diabetologia (2006) 49:2030–2038  
DOI 10.1007/s00125-006-0327-z

### ARTICLE

Within-patient  
of subcutaneous  
by compartment

W. H. O. Clausen · A. I.

Received: 21 October 2005  
© Springer-Verlag 2006

### Formaliza- tion-based clinical drug mechanistic physiologic reduction

**Abstract**  
Aims/Hypothesis: Pharma-  
sulin preparations have  
descriptive measures such  
peak plasma concentration  
single-be  
ling studies of single-be  
have also appeared, with  
feasibility of insulin pha  
appropriate level of detail  
used compartmental mod  
of biphasic insulin asp

## Integrated model of glucose homeostasis in type 2 diabetes including the effect of exogenous glucose

### Background

- Diabetes is a metabolic disorder characterised by elevated blood glucose levels. Thus the primary treatment is to correct glucose and obtain normal blood glucose. An example using exogenous insulin therapy for diabetes is insulin therapy designed to mimic the insulin response of a normal individual and thereby generate normal blood glucose.
- In order to regulate insulin-treated type 2 diabetes mellitus (T2DM) patients, the effect of exogenous glucose.

### Objective

- To propose a framework for predicting phase 3 end-of-trial HbA<sub>1c</sub> based on phase 2 data.

### Background

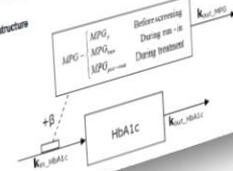
- In late-phase clinical trials, HbA<sub>1c</sub> is used as the main biomarker for efficacy, driven mainly by its strong predictability of long-term complications in diabetes.
- Phase 3 trials within diabetes drug development generally have duration of more than 24 weeks driven by a need for reaching HbA<sub>1c</sub> steady-state to achieve full drug effect.
- On the contrary, phase 2 dose-finding trials may be significantly shorter – sometimes not reaching HbA<sub>1c</sub> steady-state – thus leading to underestimation of the HbA<sub>1c</sub> lowering ability.
- We propose a framework for predicting phase 3 end-of-trial HbA<sub>1c</sub> based on phase 2 data that potentially avoids this issue by quantifying the longitudinal relation between glucose and HbA<sub>1c</sub>.

## ADOPT (A Dynamic HbA<sub>1c</sub> EndPoint Prediction Tool) A framework for predicting primary endpoint in Phase 3 diabetes trials

Table 1 Description of studies

Treatment type	Study name	Study and arm	n	HbA <sub>1c</sub> at baseline	Ref.
Insulin therapy	Insulin glargine comparison	Study 1-arm 1	289	8.8	(1)
	Insulin aspart	Study 1-arm 2	248	8.8	
Novo mix	Novo mix comparison	Study 2-arm 1	89	9.7	(2)
	Novo mix	Study 2-arm 2	110	9.8	
Lipulate 1 (Lipulate/insulin)	Lipulate 1 (Lipulate/insulin) comparison	Study 3-arm 1	176	8.8	(3)
	Lipulate 1 (Lipulate/insulin) comparison	Study 3-arm 2	189	8.8	
Lipulate 2 (Lipulate/insulin)	Lipulate 2 (Lipulate/insulin) comparison	Study 4-arm 1	170	8.8	(4)
	Lipulate 2 (Lipulate/insulin) comparison	Study 4-arm 2	228	8.4	
Lipulate 3 (Lipulate/insulin)	Lipulate 3 (Lipulate/insulin) comparison	Study 5-arm 1	224	8.2	
	Lipulate 3 (Lipulate/insulin) comparison	Study 5-arm 2	212	8.2	
Lipulate 4 (Lipulate/insulin)	Lipulate 4 (Lipulate/insulin) comparison	Study 6-arm 1	116	8.4	
	Lipulate 4 (Lipulate/insulin)	Study 6-arm 2	224	8.4	

Figure 1 Model structure



System and disease

PK/PD

Integration

Biomarker

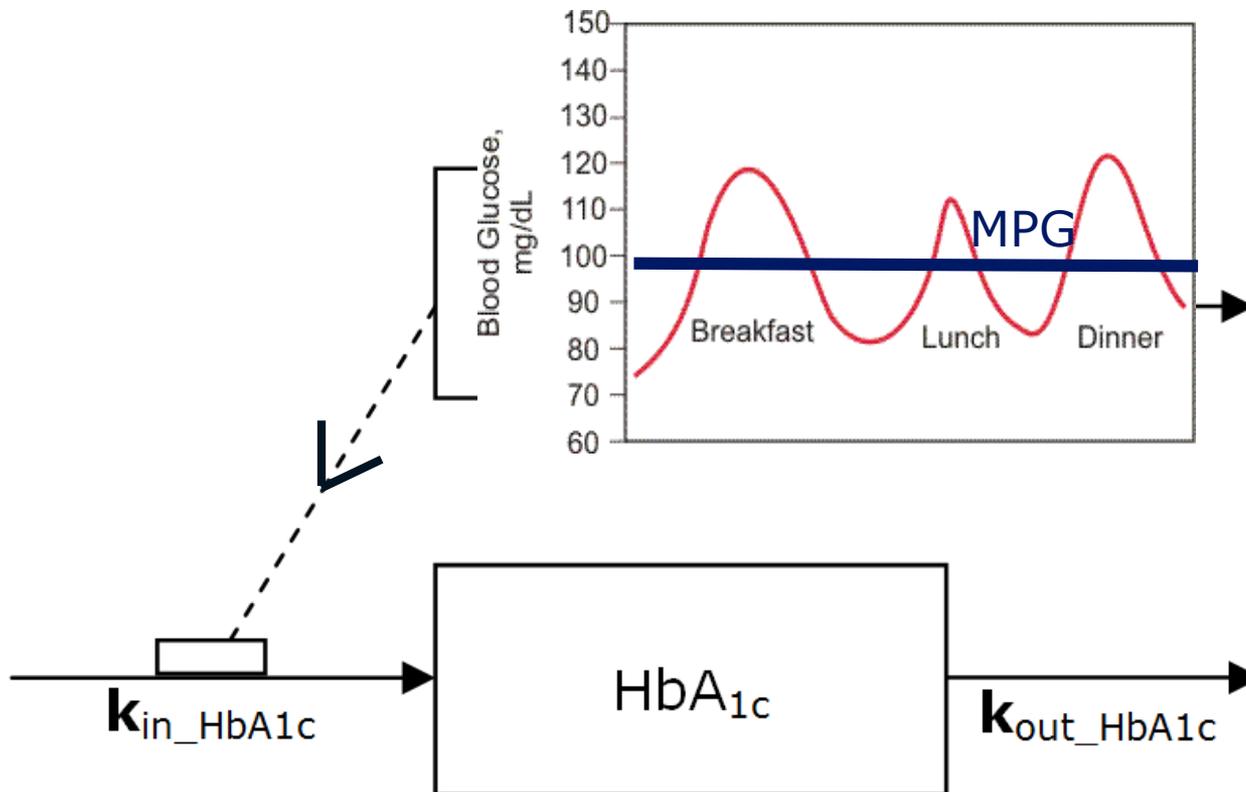
# Question based development of ADOPT

Help answer what we expect in efficacy at end-of-study phase III

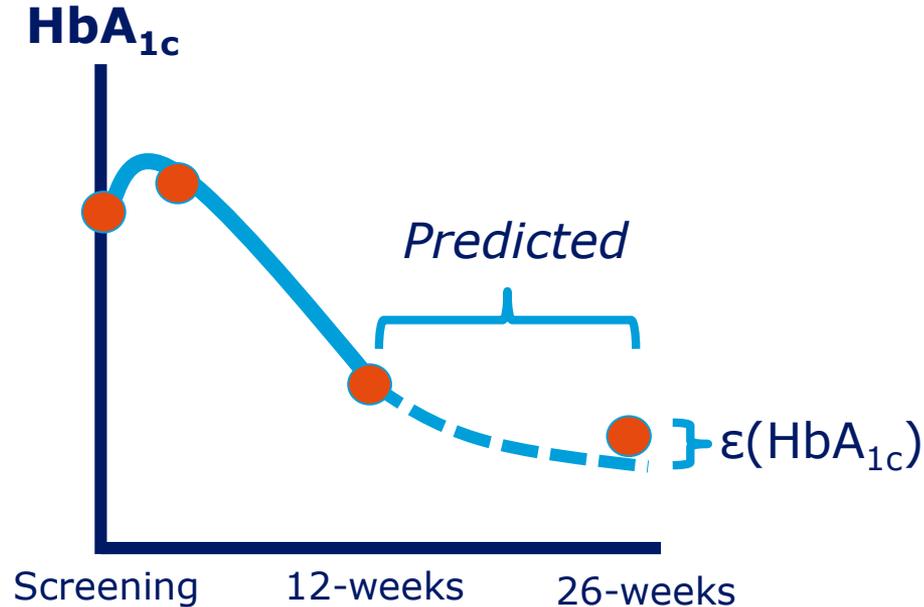
Support the use of 12-week mean/fasting plasma glucose (FPG/MPG) and HbA<sub>1c</sub> data

Must be able to predict HbA<sub>1c</sub> at end-of-study with an accuracy of <0.3%\*

# ADOPT: Basic model structure



# ADOPT: Model performance



## 12 treatment arms

### Insulin glargine

Insulin detemir

Novo mix

### Insulin glargine

Lira 1.8+Metformin+Rosiglitazone

### Metformin+Rosiglitazone

Lira 1.2+Metformin+Rosiglitazone

Lira 0.6+Metformin

Lira 1.8+Metformin

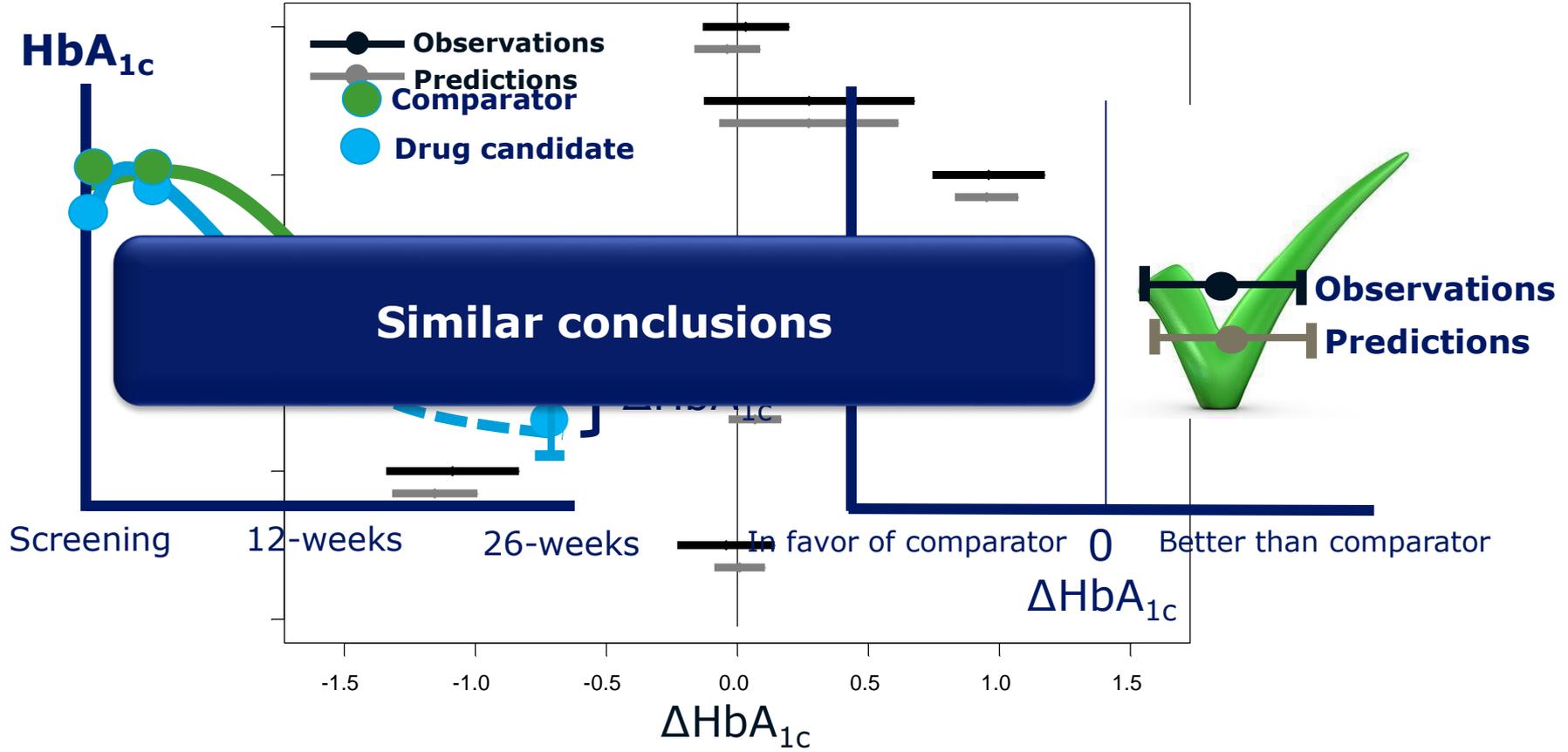
### Glimeperide+Metformin

Metformin

Lira 1.2+Metformin

$$\epsilon(\text{HbA}_{1c}) = 0.14\%$$

# ADOPT: Support decision making?



# Key questions for phase III trial

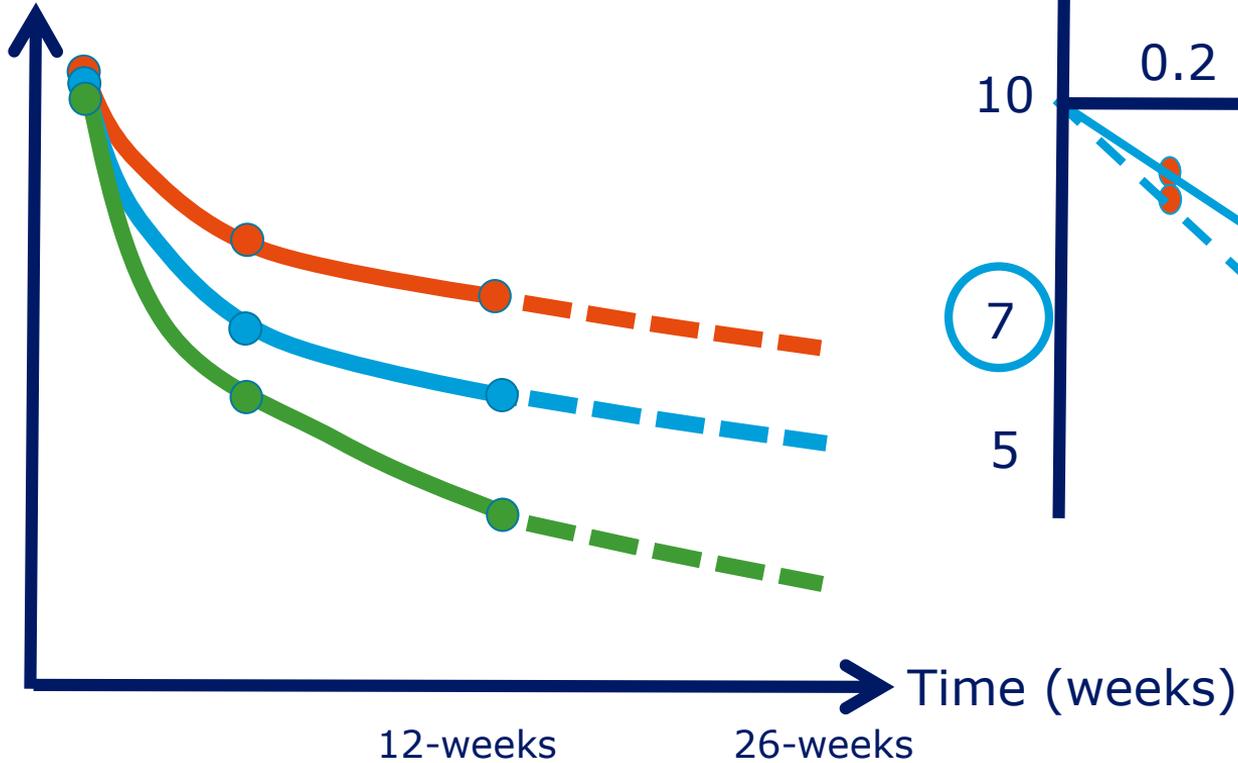


Which dose should be selected?

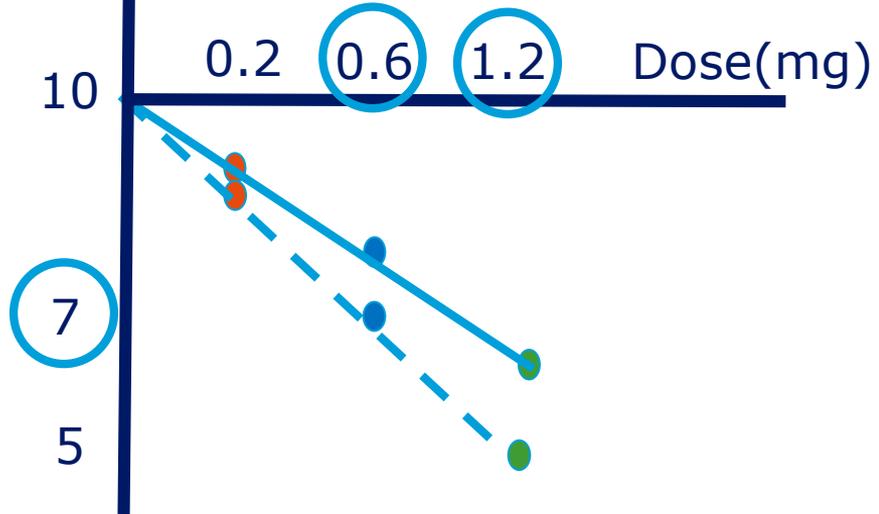
Are we going to show superiority  
against comparator?

# Optimal dose?

HbA<sub>1c</sub>(%)

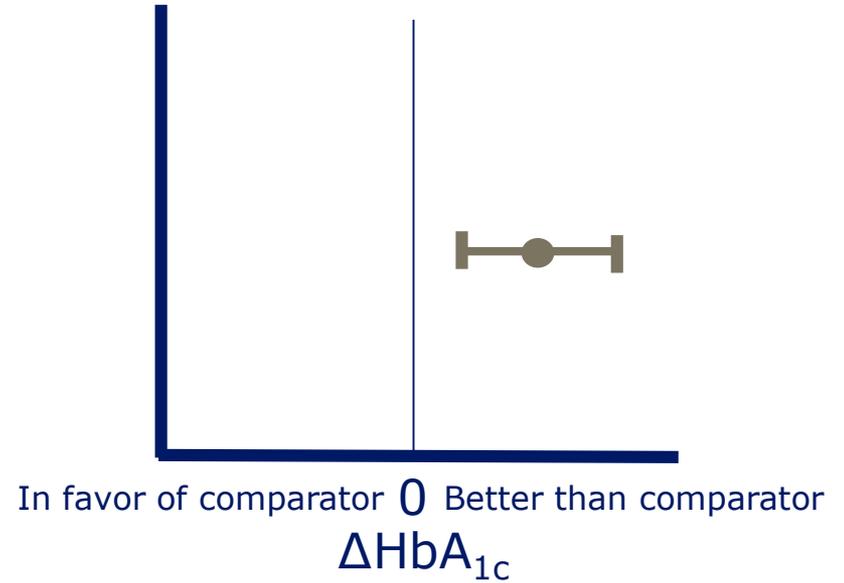
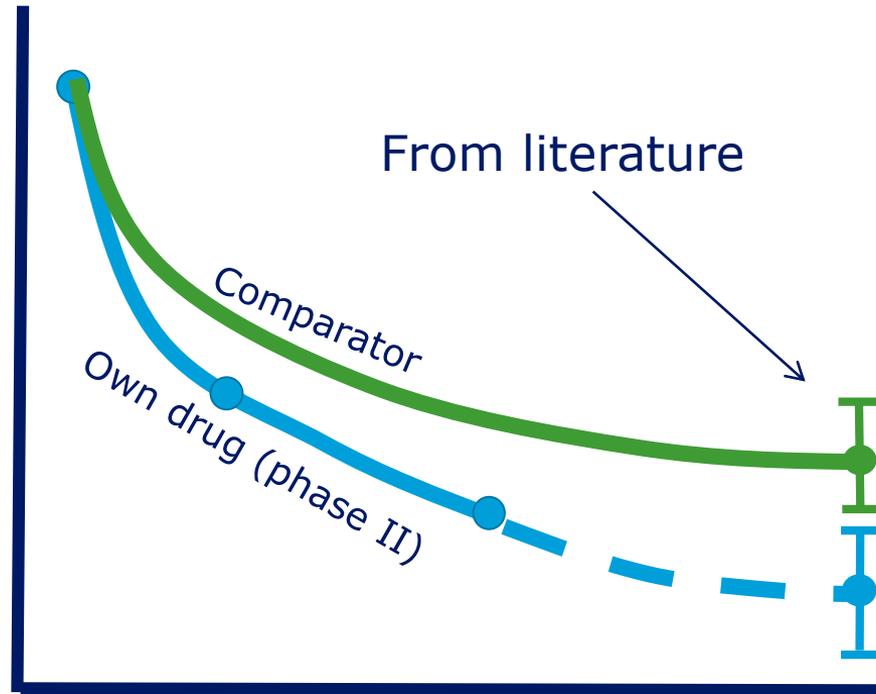


HbA<sub>1c</sub>(%)



# Superiority vs. comparator?

HbA<sub>1c</sub>



# Modeling is an essential part of the recipe

## *We just need to...*



“Take into account the difference in biomarkers measured in each phase”



“Build drug and disease models and frameworks for integrating these”



“Match model development with drug development questions”

# The real chefs!

Uppsala  
university



Novo Nordisk A/S



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**Thanks for  
listening!**

# How do we combine the ingredients and create value?

## Development status

## Key question

Kjellson MC, Cosson VF, Mazer NA et. all, Journal of Clinical Pharmacology, 2013

12-week phase 2 study with glucose profiles and HbA<sub>1c</sub>, but HbA<sub>1c</sub> has not reached steady-state..

What do we expect in steady-state HbA<sub>1c</sub> in a similar phase 3 study?

12-week phase 2 study with glucose profiles and HbA<sub>1c</sub>, but HbA<sub>1c</sub> has not reached steady-state..

Which dose should be selected in our phase 3 study to obtain optimal efficacy?