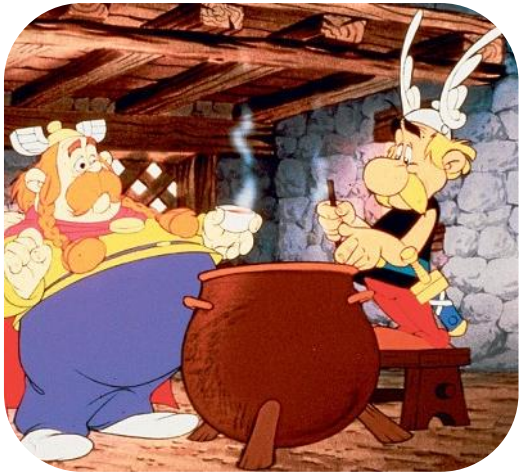


Optimizing clinical diabetes drug development

What is the recipe?

[1]Jonas Bech Møller, PhD, MSc

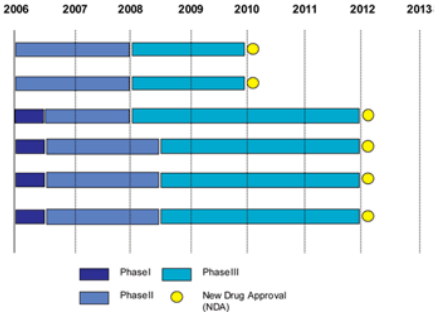
Co-authors: Rune V Overgaard[1], Maria C Kjellsson[2], Niels R Kristensen[1], Søren Klim[1], Steen H Ingwersen[1], Mats Karlsson[2]

Institutions: [1]Quantitative Clinical Pharmacology, Novo Nordisk A/S, Søborg, Denmark; [2]The Pharmacometrics Group, Uppsala University, Uppsala, Sweden;

Drug Disease Model Resources
ddmore

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?

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

- Safety
- PK
- PD: FPG, MPG, HbA_{1c}
- 10-16 weeks

- Safety
- PK
- PD: FPG, MPG, HbA_{1c}
- 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_{1c}: Glycosylated hemoglobin (marker for long-term glucose)

Key questions for efficacy prediction

5-week data
(FPG/GIR)

12-week data
(MPG, HbA_{1c})

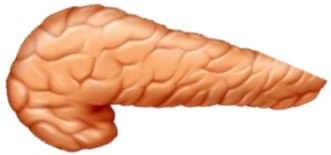
Model library that enables
bridging between different development phases

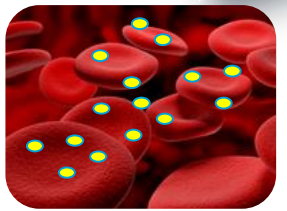
Which d
be
in p
(MPG/HbA_{1c})

Drug Diseas

The right dose and
performance
against
competitors?
(HbA_{1c} at 26 weeks)

Ingredients





System and disease

PK/PD

Integration

Biomarker

Question based development of ADOPT

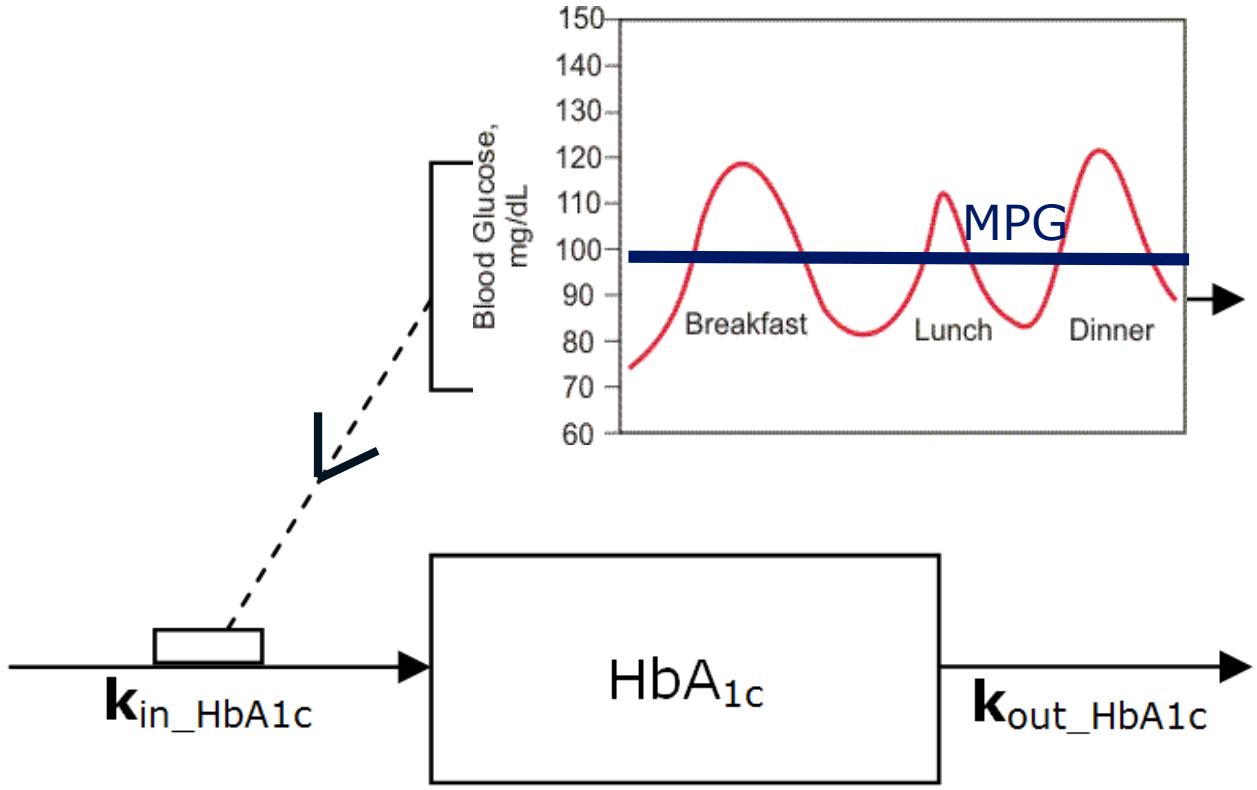
Help answer what we expect in efficacy at end-of-study phase III

Support the use of 12-week mean/fasting plasma glucose (FPG/MPG) and HbA_{1c} data

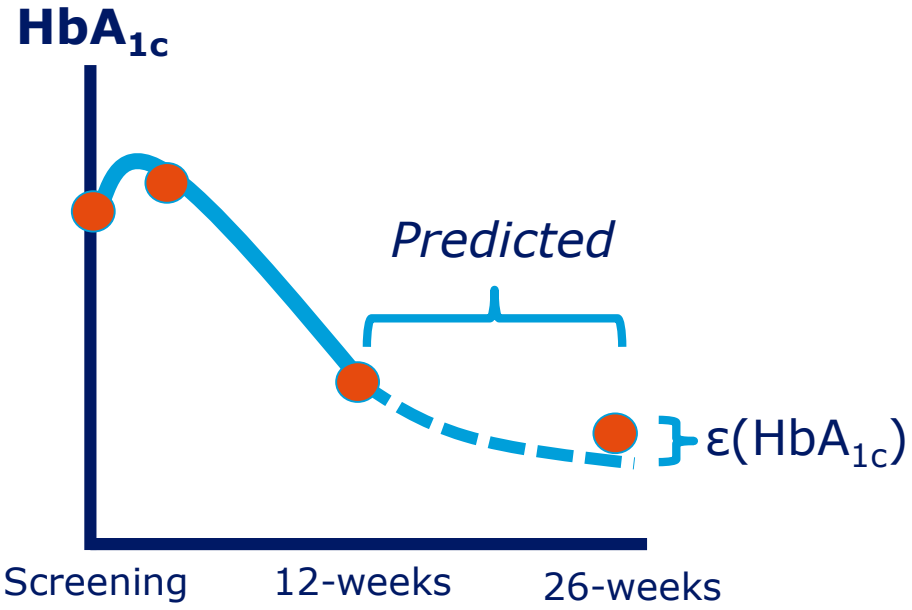
Must be able to predict HbA_{1c} at end-of-study with an accuracy of <0.3%*

*criteria for inferiority FDA/EMA

ADOPT: Basic model structure



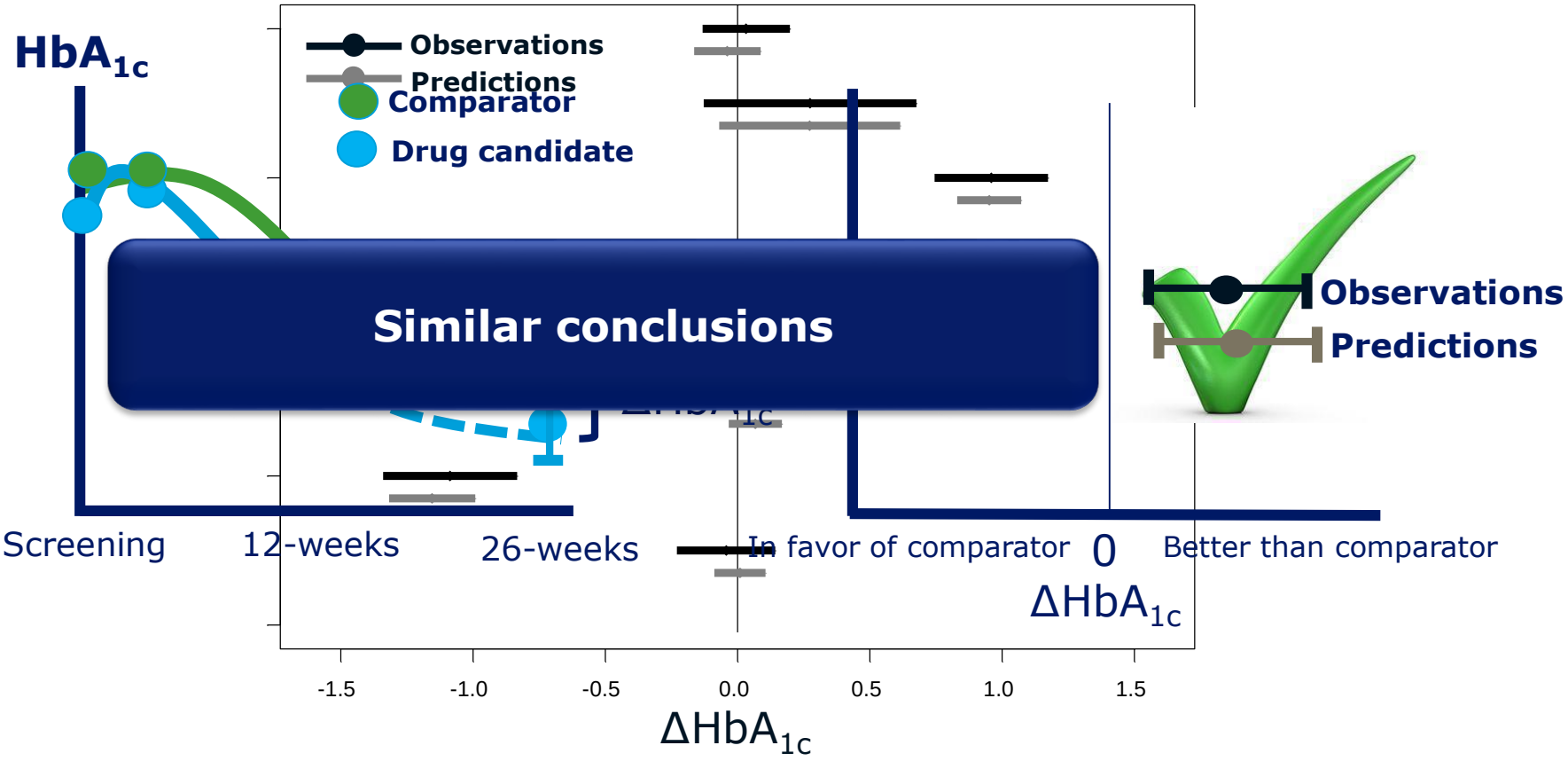
ADOPT: Model performance



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

$$\varepsilon(HbA_{1c}) = 0.14\%$$

ADOPT: Support decision making?

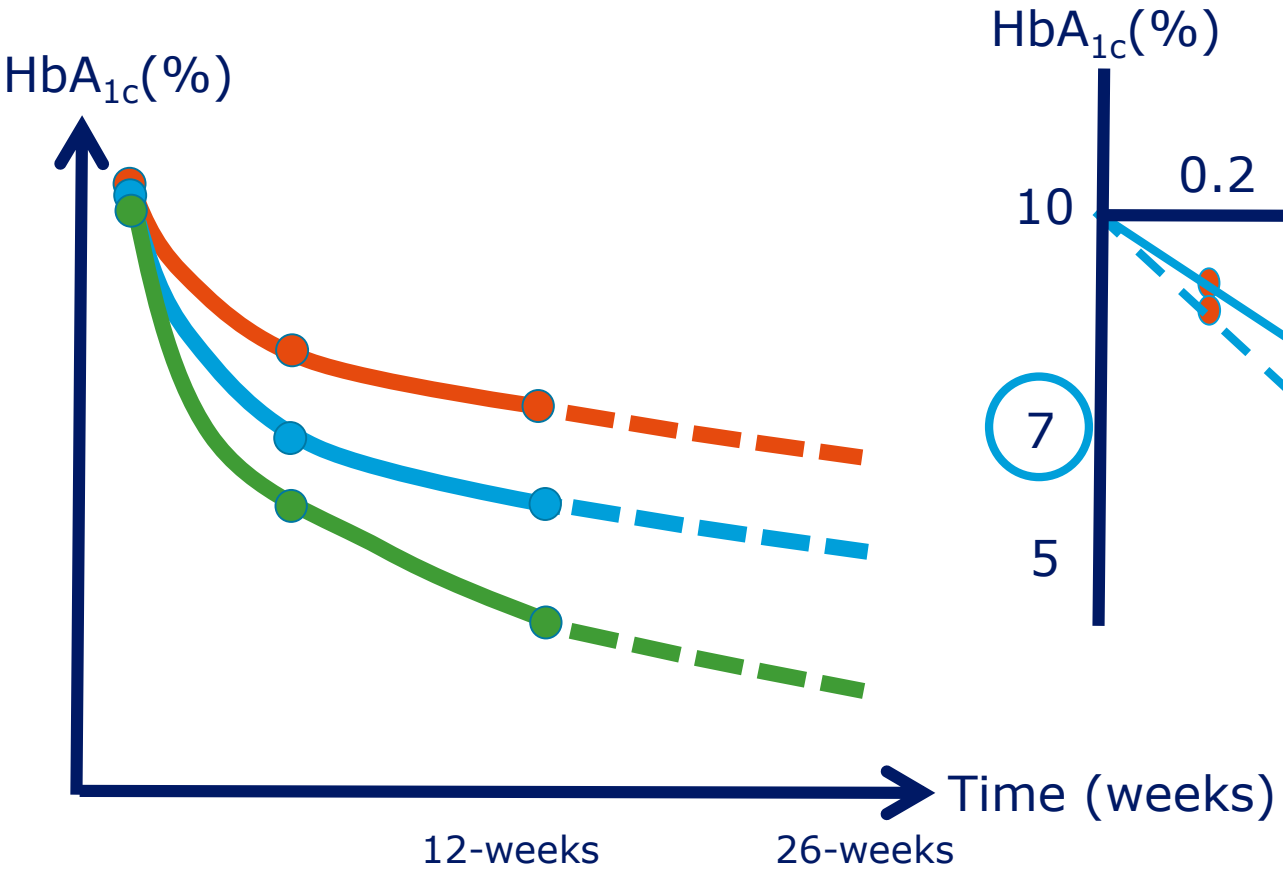


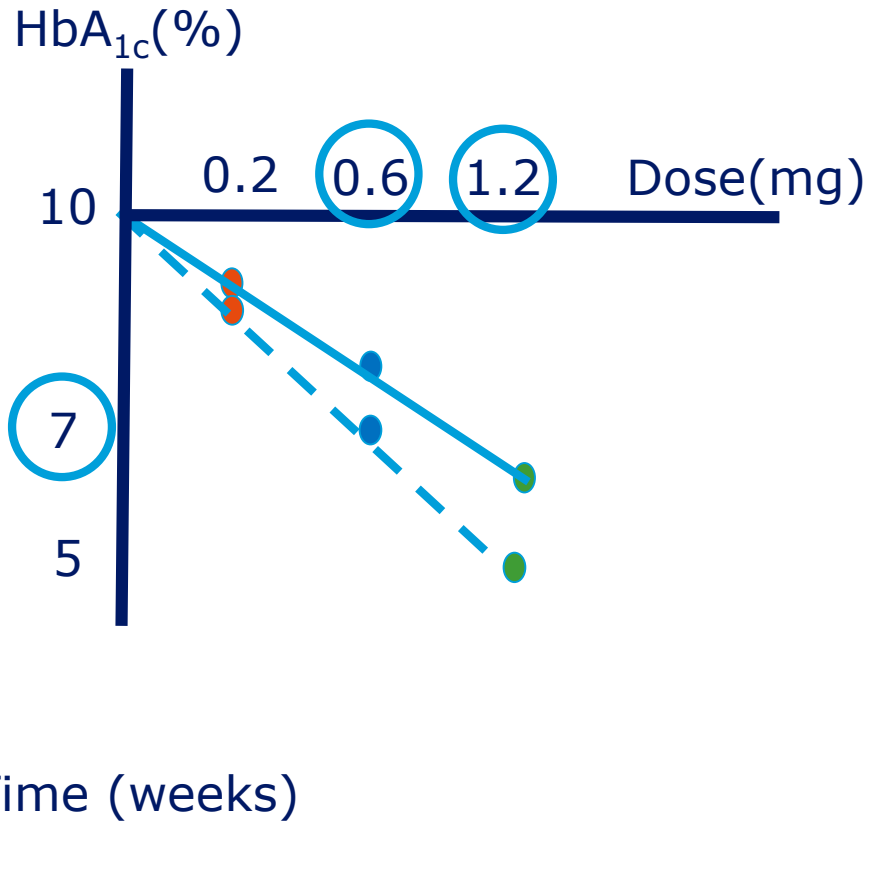
Key questions for phase III trial

Which dose should be selected?

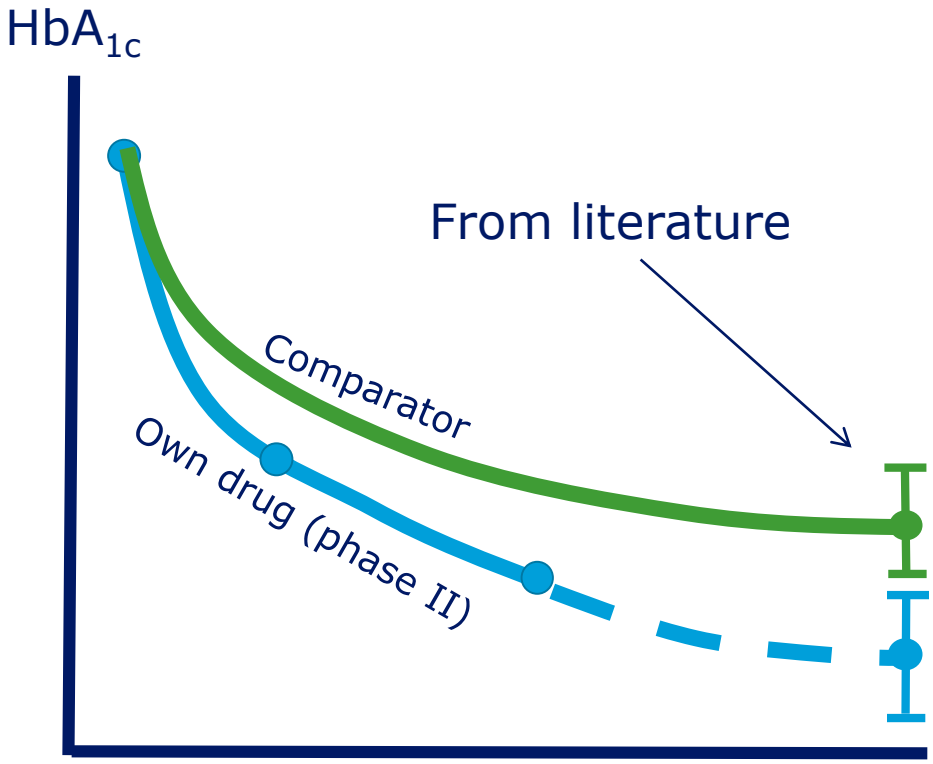
Are we going to show superiority against comparator?

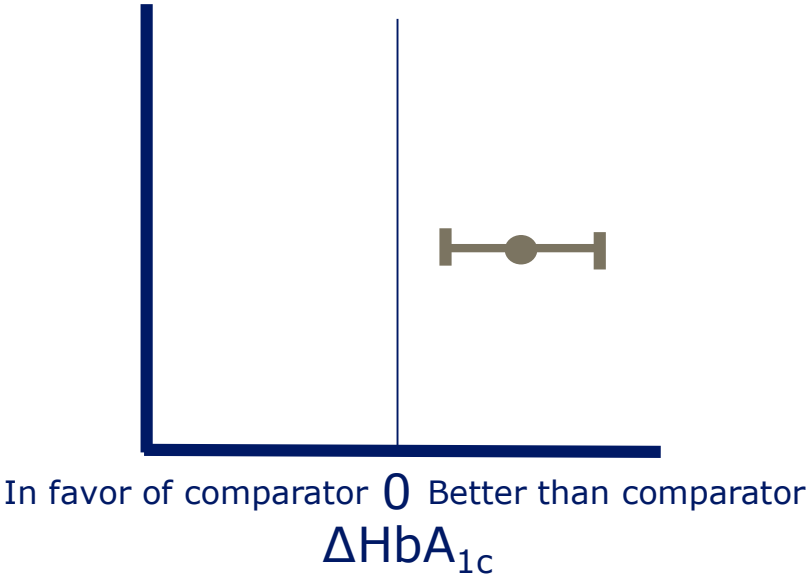
Optimal dose?





Superiority vs. comparator?





Modeling is an essentiel part of the recipe

We just need to…

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

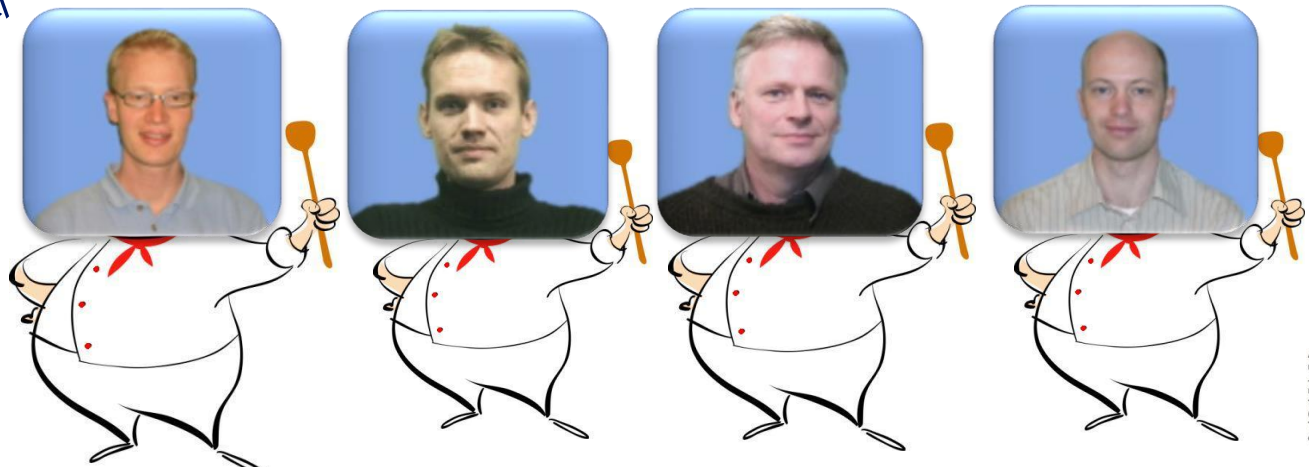
”Build drug and disease models and frameworks for integrating these”

”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_{1c}, but HbA_{1c} has not reached steady-state..	What do we expect in steady-state HbA_{1c} in a similar phase 3 study?
12-week phase 2 study with glucose profiles and HbA_{1c}, but HbA_{1c} has not reached steady-state..	Which dose should be selected in our phase 3 study to obtain optimal efficacy?