How predictive is **short-term body-weight loss** in the **longer term** for **decision making** during clinical drug development?

W-001

Franziska Kluwe[1,2], Monika Maas[3], Anita Hennige[4], Benjamin Weber[5], Charlotte Kloft[1]

[1]Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany
[2]Graduate Research Training Program PharMetrX, Berlin/Potsdam, Germany
[3]Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
[4]Therapeutic Area Metabolism Medicine, Boehringer Ingelheim International GmbH, Biberach an der Riss, Germany
[5]Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA

Motivation

Why is research in the area of obesity of interest and highly relevant?

- **Worldwide prevalence of obesity** has **tripled** since 1975 and is **still rising (Fig. 1)** [1]
- **Adults:** 39% overweight and **13% obese** (2016) [2]
- **2.8 million deaths/year** resulting from **overweight/obesity**
- Obesity is **major risk factor** for **chronic diseases**

→ **Weight loss can significantly improve these outcomes**

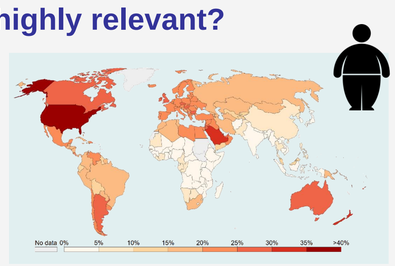

Figure 1. Percentage of population classified as "obese" by country (2016) [2]. Obesity defined as BMI >30 kg/m^2.

What are the key challenges?

- High **unmet medical need** for **effective** and **safe therapy** of patients with overweight or obesity and with/without type 2 diabetes (T2D)
- **Few** approved weight-loss compounds with **limited efficacy** (3%-7% body-weight loss)
- Clinical trials in T2D/obesity are **time-consuming** and **expensive**

Objectives

What are the objectives of this work?

- Make use of **publicly-available (summary-level) clinical trial data** to:
  - Quantify and characterise the relationship between **short-term (e.g. 4 weeks)** and **longer term (e.g. 12, 24, 52 weeks) mean body-weight loss** (WT, %) for different **incretin-based therapies** in **adult patients** with **obesity** and/or **T2D**
  - Investigate if this relationship is **consistent across compounds** and **populations**
  - Evaluate the effect of potential **predictors** (e.g. indication) on this relationship

What is the clinical significance?

- Assess **potential** of **shorter Phase I studies (typically 12 weeks)** or **interim data analyses,** after only e.g. **4 weeks of treatment**, on expected outcomes
- Facilitate **decision-making** and **selection of promising drug candidates** and **streamline clinical development** of new anti-obesity compounds/combination therapies

Methods

(1) Clinical database specifications

- **Published randomised, controlled Phase I-IV clinical trials:**
  - **Adult patients** with **obesity +/- T2D**
  - Receiving **incretin-based therapies** (GLP-1 agonists, DPP-4 inhibitors, dual GIP/GLP-1 agonists)
  - Weight-loss endpoints (incl. baseline)
  - Published **from 01/2010 until 11/2018**

GLP-1: Glucagon-like peptide-1; *DPP-4:* Dipeptidyl peptidase 4, *GIP:* Glucose-dependent insulinotropic polypeptide

(2) Clinical database

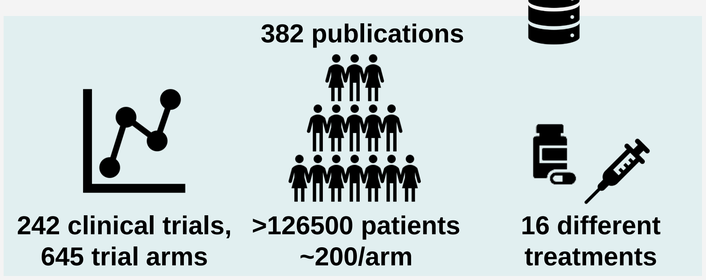

Figure 2. Schematic representation of "clinical weight loss database" developed from systematic literature research according to [3,4].

(3) Data analysis

- **Exploratory** and **statistical data analysis**
- **Regression-based meta analysis [5]:**
  - Evaluation of relation between **short-term** and **long-term** reduction in mean body weight relative to baseline (ΔWT) for incretin-based therapies and placebo
- **Internal** and **external model evaluation**
- **Software:** R v3.4.3, RStudio 1.1.447 [6,7]

Results

Clinical database

- Mainly **parallel, double-blind phase 3 studies** in peer-reviewed journals
- **Reported weight-loss endpoints:** Absolute weight loss or relative change from baseline (including baseline weight)
- Patients ≤18 years were excluded (n_{arm}=9)
- Baseline trial arm characteristics stratified by indication reveled distinct **differences** between patients with/without T2D (**Tab. 1**)
- Trial arms comprised (in descending order) **GLP-1 agonists**, placebo, DPP4 inhibitors and dual agonists

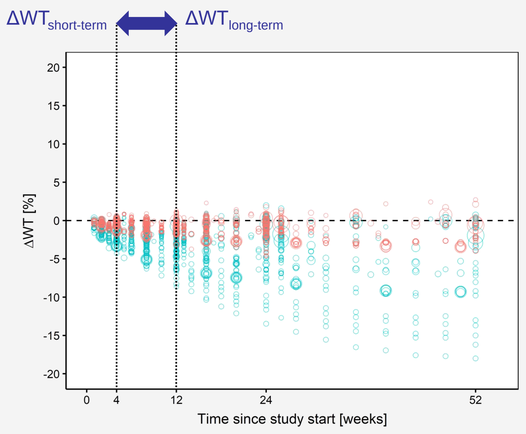

Figure 2. Mean body-weight change from baseline (ΔWT, %) versus time since study start (weeks) for all trial arms (n=636). Data point size corresponds to trial arm size. *Horizontal dashed line:* No change from baseline; *Vertical dotted lines:* Time after treatment start; *Green dots:* Treatment arms; *Red dots:* Placebo arms.

Table 1. Characteristics of trials arms stratified by indication at baseline (mean, standard deviation).

Characteristic	T2D (n_{arm}=572)	Non-T2D (n_{arm}=63)
Continuous		
Age [years]	56.9 (4.19)	41.9 (8.62)
Weight [kg]	86.5 (10.4)	101 (10.9)
Height [cm]	169 (3.07)	169 (2.30)
BMI [kg/m^2]	30.7 (3.09)	36.1 (3.59)
Categorical		
Sex (male,%)	61.9	35.0
BMI >30 kg/m^2 (%)	59.6	96.3

Abbreviations:
BMI: Body mass index; *T2D*: Type 2 diabetes.

Exploratory analysis

- Key aspect is **reduction in mean body weight relative to baseline** (ΔWT, %) after 12, 24 or 52 weeks (**Fig. 2**)
- Most data available up to 24-26 weeks
- Pronounced differences between placebo and treatment arms (**Fig. 2**)
- For trial arms comprising placebo and DPP4-inhibitors, ΔWT was relatively small, but for GLP-1 and dual GIP/GLP-1 agonists maximum ΔWT was ~10%-20%
- Linear relation between short-term $\Delta WT_{4\text{-}6\ weeks}$ versus long-term $\Delta WT_{10\text{-}14\ weeks}$ was identified (**Fig. 3**)
- In the following, exemplary for the applied workflow, the analysis of $\Delta WT_{4\text{-}6\ weeks}$ versus $\Delta WT_{10\text{-}14\ weeks}$ is shown:

Regression-based meta analysis

- **Regression-based meta analysis** [5] was performed **on summary-level data** (using 90% of available data → "development dataset"); influence of **potential additional predictors** (baseline WT/BMI/age, indication, drug class) was tested
- To account for differences in trial sizes, **weighting according to trial arm size** was used
- Strong correlation between of $\Delta WT_{4\text{-}6\ weeks}$ and $\Delta WT_{10\text{-}14\ weeks}$ was identified (**Fig. 3**, r=0.87, with 95% confidence interval 0.84-0.89)
- Evaluation of predictors revealed statistically significant influence of **trial arm baseline WT** (P = .0005), additional predictors were not significant (BMI, age, indication, drug class)
- External model evaluation showed **good model performance** using "test dataset", i.e. the remaining 10% of available data (**Fig. 4,** red data points)
- Using the developed model, $\Delta WT_{short\text{-}term}$ **of -2.0%** for studies with mean baseline WT of **90 kg** and **110 kg** would translate into typical $\Delta WT_{long\text{-}term}$ of **-4.38%** and **-5.02%**

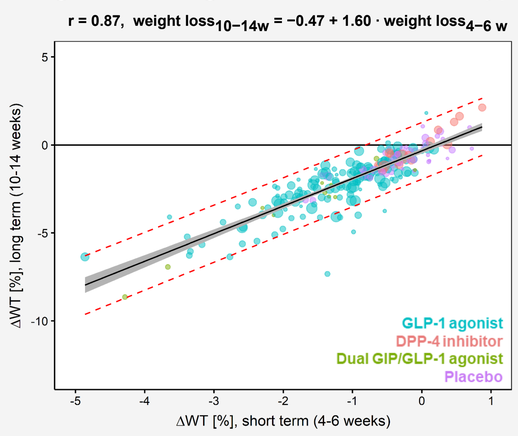

Figure 3. Short-term (4-6 weeks) body-weight change from baseline (ΔWT, %) versus long-term (10-14 weeks) body-weight change from baseline for all trial arms. Data point size corresponds to trial arm size. *Black line:* Regression line; *Shaded grey area:* 95% confidence interval; *Dashed red line:* 95% prediction interval.

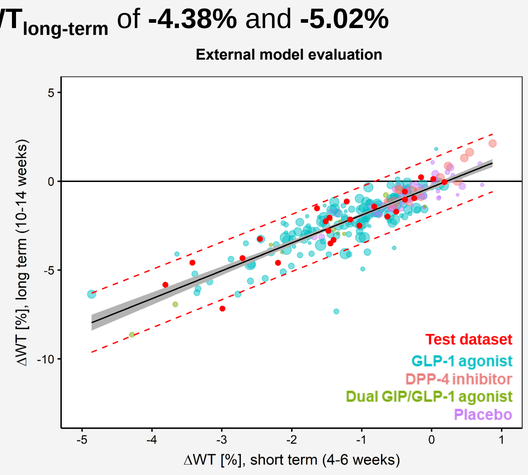

Figure 4. External model evaluation. Data point size corresponds to trial arm size. *Red data points:* Belonging to "test dataset"; *Black line:* Regression line (with data from "development dataset"); *Shaded grey area:* 95% confidence interval; *Dashed red line:* 95% prediction interval.

Conclusions and Perspectives

- Analysis revealed **high correlation between $\Delta WT_{short\text{-}term}$** and **$\Delta WT_{long\text{-}term}$** for all investigated treatments **independent** of mechanism of action or dosing regimen
- Further exploration of correlations including potential predictors, e.g. baseline WT/BMI/age, indication or drug class, revealed significant influence of **trial arm baseline WT**, which was illustrated using 50th (90 kg) and 95th percentile (110 kg) of baseline WT distribution
- Results of this analysis can be easily visualised, interpreted and communicated
- **Strong relation** between **$\Delta WT_{short\text{-}term}$** and **$\Delta WT_{long\text{-}term}$** can be used to **inform** and **optimise clinical trial design,** e.g. perform early interim data analyses or reduce trial length
- The presented workflow was successfully applied and integrated into a clinical project
- Present limitations and **future optimisations, i.e. next steps**:
  - **Descriptive character** of regression model, hence rather limited in use for predictions
  - Due to nature of analysis, currently **no differentiation** between (i) different drug classes/placebo detected or (ii) evaluation of different doses/dosing regimens possible
  - **Longitudinal evaluation** shall be performed, e.g. longitudinal model-based meta analysis (MBMA) (clinical data up to 5 years available)
  - **MBMA** can improve model **predictivity** (**explain variability** by **incorporating differences** between drug classes, doses or dosing regimens and **integrating significant covariates**) and can be used for **clinical trial simulations**

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References:

[1] NCD Risk Factor Collaboration. Lancet 387: 1377–1396 (2016).
[2] WHO. Fact sheet on obesity and overweight (2018). Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
[3] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd. (2008).
[4] D. Moher, A. Liberati, J. Tetzlaff et al. PLoS Med. 6: e1000097 (2009).
[5] N. Plock, L. Bax, D. Lee et al. J. Clin. Pharmacol. 57: 52–63 (2017).
[6] R Core Team. R Foundation for Statistical Computing, Vienna, Austria (2019).
[7] RStudio Team. RStudio, Inc., Boston, MA, USA (2019).

For additional information, please contact:
Franziska Kluwe
franziska.kluwe@fu-berlin.de

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