Quantifying the growth hormone lowering effect of BIM23B065 after a GH stimulation test

Michiel J. van Esdonk[1,2], J. Stevens[1,3], M. Dehez[4], L. Pons[4], F.E. Stuurman[1], W. de Boon[1], P.H. van der Graaf[2,5], I. Paty[4], J. Burggraaf[1,2]

Universiteit Leiden The Netherlands

Cluster Systems Pharmacology

INTRODUCTION

- BIM23B065 is a novel somatostatin-dopamine chimeric compound designed to reduce excessive growth hormone (GH) secretion in patients with acromegaly.
- Phase I, double-blind, randomized, placebo-controlled study to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of BIM23B065 in healthy male volunteers.
- Growth hormone releasing hormone (GHRH) was administered to monitor the secretion of GH

METHODS

- The study consisted of two parts with 6 active and 2 placebo treated subjects per cohort:
  - SAD: 0.1 mg, 0.4 mg, 0.8 mg, 1.2 mg, and 1.5 mg
  - MAD: 1.2 mg q.d., 0.8 mg b.i.d., and 1.0 mg b.i.d.
- GH stimulation tests were performed on day 8 and day 13 in the MAD study.
- 1 µg/kg GHRH was administered 1 hour after dosing of BIM23B065/placebo to stimulate GH release.
- Population PK/PD modeling was conducted using NONMEM V7.3:
  - A total of 453 BIM23B065, 589 metabolite, and 276 plasma GH concentrations were used for model building.

RESULTS

- The PK of BIM23B065 and its metabolite were best described using 2-compartment models.
- BMI negatively influenced the absorption rate constant of the subcutaneous administration of BIM23B065.
- GHRH stimulates a first-order GH release following an E_{max} relationship **(Figure 2)**.
- Treatment with BIM23B065 gave a **3000** times increase in the $EC_{50\%}$ of the GHRH effect, thereby reducing the GH release after administration of GHRH **(Figure 1)**.
- The inhibition of the GH release was similar after 8 and 13 days of treatment.
- All η-shrinkage were below 25%

RESEARCH OBJECTIVES

- **Quantify the pharmacokinetics of BIM23B065 and its main metabolite (BIM23B133)**
- **Characterize the response to a GH stimulation test after treatment with BIM23B065**

CONCLUSION

- The PK of BIM23B065 and its metabolite (BIM23B133) as well as GH release after GHRH administration were well described by the developed model **(Figure 1,3)**.
- GH release was **significantly** reduced in BIM23B065 treated subjects after a GH stimulation test.
  - No change in GH release between the 3 cohorts was identified

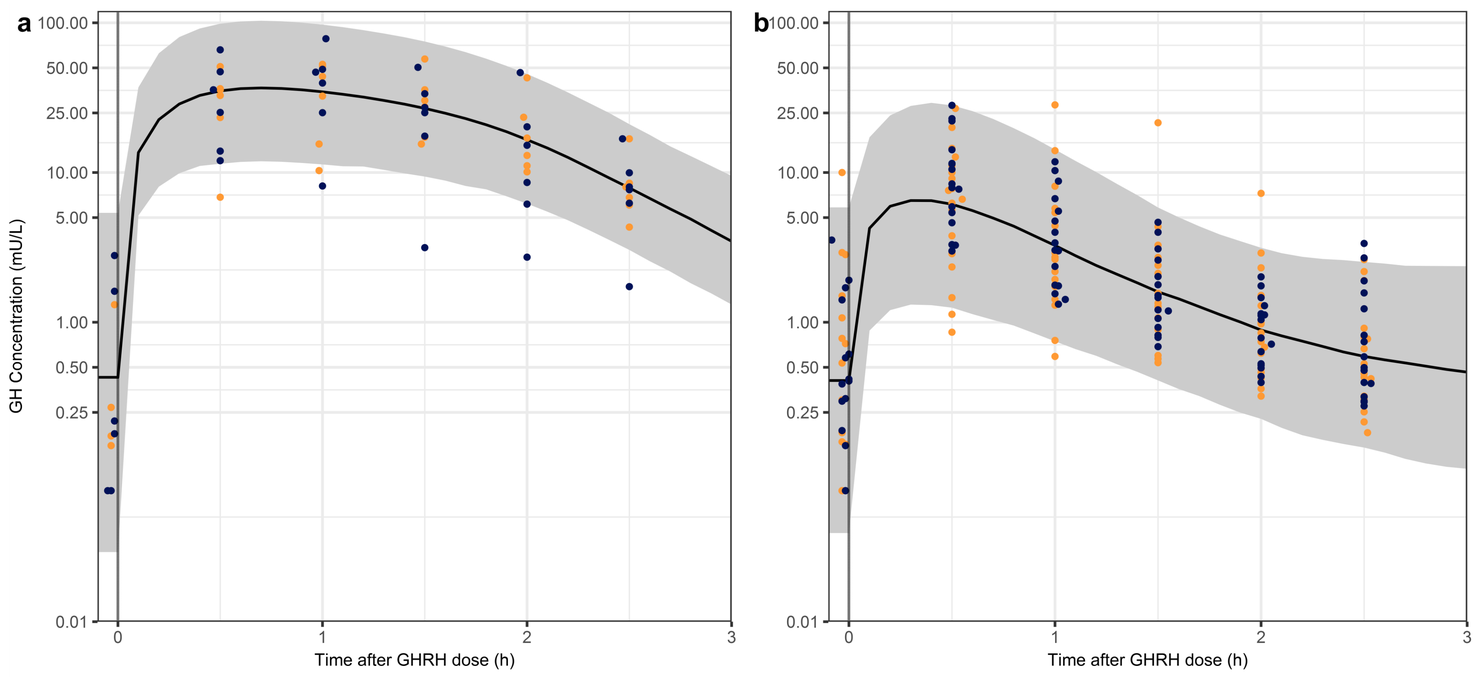

*Figure 1) Median growth hormone concentration (black solid line) and 95%-prediction interval (grey area) of **placebo** (a) and **BIM23B065** treated individuals (b). Orange dots: occasion 1, blue dots: occasion 2.Vertical dotted grey line is time of GHRH administration.*

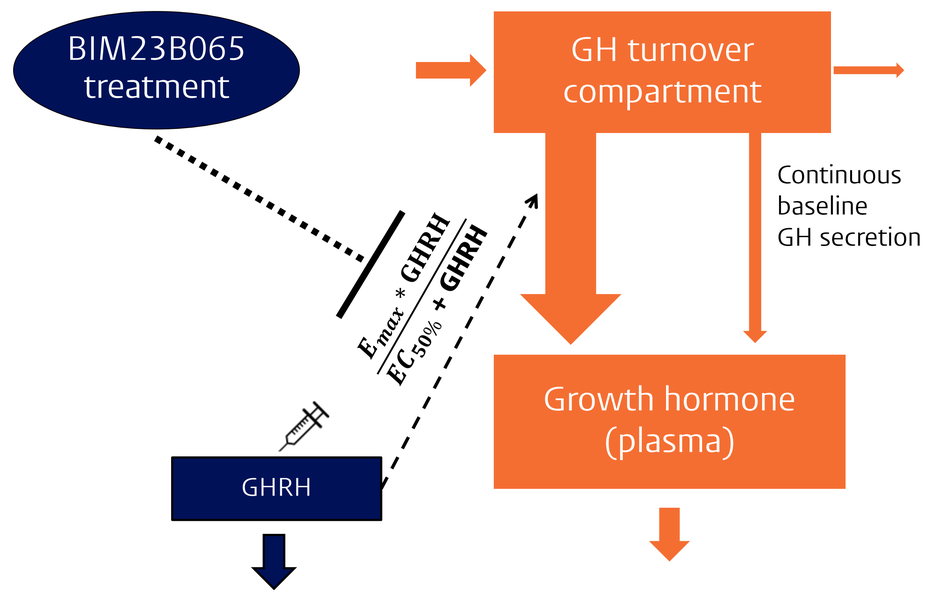

Figure 2)
Top left: Effect of BIM23B065 on the GHRH stimulatory effect
Bottom left: Structural PK model of GHRH
Right: Structural PD model for GH release in a GH stimulation test

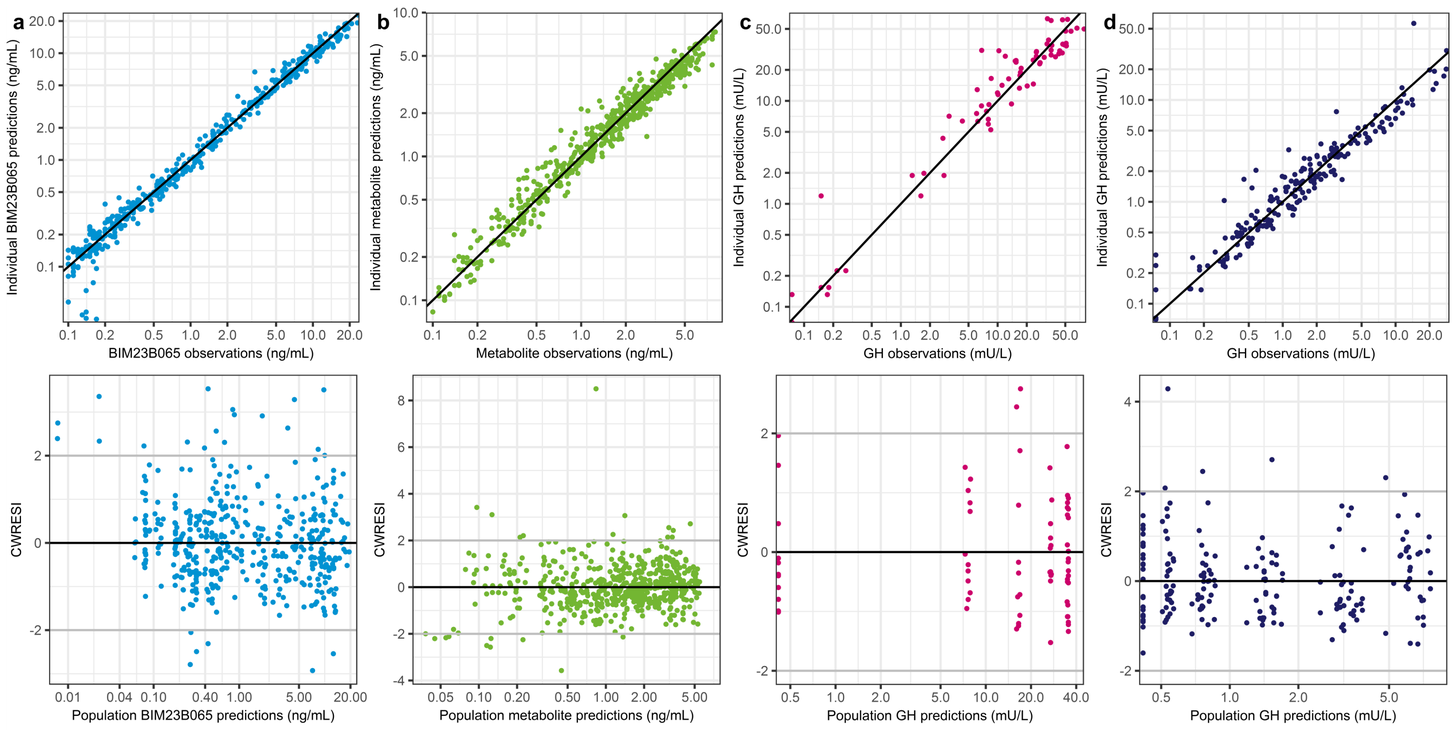

Figure 3) Top: Individual model predictions versus observations for a) BIM23B065, b) metabolite and c+d) GH concentrations (c = placebo, d = BIM23B065 treated). Bottom: Population model predictions versus conditional weighted residuals with interaction.

*Table 1: PK (left) and PD (right) model parameter estimates with relative standard errors (RSE%). * Indicate fixed parameters*

Parameter	Estimate [RSE%]	Parameter	Estimate [RSE%]
$k_{a\text{-intercept}}$ (/h)	2.41 [14]	k_{in} (mU/L/h)	43.3 [26.5]
$k_{a\text{-slope}}$ (/h/23.31kg/m^2)	-1.35 [22.4]	k_{out} (/h)*	0.279
$V_{central\text{-}parent}$ (L)	8.76 [40.7]	Baseline secretion (mU/L/h)	0.916 [23.5]
$V_{peripheral\text{-}parent}$ (L)	334 [22]	$E_{MAX\text{-}GHRH}$ (/h)*	1
Q_{parent} (L/h)	41.5 [11.1]	$EC_{50\%\text{-}GHRH}$ (µg)	0.055 [52.3]
Linear metabolization parent (L/h)	21.8 [45.9]	Proportional effect BIM23B065 on $EC_{50\%}$	3000 [38.5]
$V_{max\text{-}parent}$ (mg/h)	0.0788 [22]	$k_{el\text{-}GH}$ (/h)*	2.2
KM_{parent} (µg/L)	0.673 [28.7]		
Transit $rate_{non\text{-}linear}$(/h)	0.332 [13.3]		
Transit $rate_{linear}$(/h)	0.22 [6.26]		
$V_{central\text{-}metabolite}$ (L)	5.51 [13.7]		
$V_{peripheral\text{-}metabolite}$ (L)	4230 [1.58]		
$Q_{metabolite}$ (L/h)	11.1 [7.61]		
$CL_{SAD\text{-}metabolite}$ (L/h)	10.5 [7.35]		
$CL_{MAD\text{-}metabolite}$ (L/h)	18.5 [8.1]		
$k_{el\text{-}GHRH}$* (/h)	4.16		

AFFILIATIONS

[1]Centre for Human Drug Research, Leiden, The Netherlands.
[2]Division of Pharmacology, Cluster Systems Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.
[3]Department of Clinical Pharmacy and Pharmacology (current affiliation), University Medical Center Groningen, Groningen, The Netherlands.
[4]Ipsen Innovation, Les Ulis, France.
[5]Certara QSP (current affiliation), Canterbury, UK.