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

Michiel J. van Esdonk1,2, J. Stevens1,3, M. Deheer1, L. Pons4, F.E. Stuurman1, W. de Boon1, P.H. van der Graaf2,3, I. Paty4, J. Burggraaf2,3

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

RESEARCH OBJECTIVES

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

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 Emax relationship (Figure 7).
- Treatment with BIM23B065 gave a 3000 times increase in the Emax of the GHRH effect, thereby reducing the GH release after administration of GHRH (Figure 7).
- The inhibition of the GH release was similar after 8 and 13 days of treatment.
- All n-shrinkage were below 25%

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).
- 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 3: Nocturnal growth hormone concentration (black solid line) and 95% prediction interval (gray area) of placebo (a) and BIM23B065 treated individuals (b). Change dose: occasion 1. Blue date: occasion 2. Vertical dashed grey line: time of GHRH administration.

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

<table>
<thead>
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<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
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Figure 4: Top left: Effect of BIM23B065 on the GH-stimulatory effect. Bottom left: Structural PK model of GHRH. Right: Structural PD model for GH release in a GH-stimulation test.

Figure 5: Top: Individual model predictions versus observations for a) BIM23B065, b) metabolite and c+d) GH concentrations (a = placebo, d = BIM23B065 treated). Bottom: Population model predictions versus conditional weighted residuals with interaction.

AFFILIATIONS

1Centre for Human Drug Research, Leiden, The Netherlands
2Department of Clinical Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, The Netherlands
3Department of Clinical Pharmacology and Pharmacy (current affiliation), University Medical Center Groningen, Groningen, The Netherlands
4NovoNordisk, LetiLife, France
5Central QSP (current affiliation), Canterbury, UK

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