INTRODUCTION
BIM23B065 is a novel somatostatin-dopamine chimeric compound designed to reduce excessive growth hormone (GH) secretion in patients with acromegaly.

First-In-Human study to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of BIM23B065.

Phase I, double-blind, randomized, placebo-controlled study.

OBJECTIVES
To quantify the pharmacokinetics of BIM23B065 and its main metabolite (BIM23B133)
To characterize the response to a GH stimulation test after treatment with BIM23B065
To identify covariates that influence the PK and PD of BIM23B065

METHODS
The study consisted of two parts:
1) SAD: 0.1 mg, 0.4 mg, 0.8 mg, 1.2 mg, and 1.5 mg
2) MAD: 1.2 mg q.d., 0.8 mg b.i.d., and 1.0 mg b.i.d.

6 active and 2 placebo treated subjects per cohort.
The duration of the MAD was 13 days, including a 6 day up-titration period.

GH stimulation tests were performed on 2 occasions (day 7 and day 13) in the MAD study.
1 µg/kg growth hormone releasing hormone (GHRH) was administered 1 hour after dosing of BIM23B065/placebo to stimulate GH release.

Population PK/PD modeling was conducted using NONMEM:
- 1/2 compartment models with linear or non-linear absorption and elimination kinetics were explored.
- 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.
BIM2 negatively influenced the absorption rate constant of the subcutaneous administration of BIM23B065.
GHRH stimulates GH release following an $E_{max}$ relationship.
Treatment with BIM23B065 gave a 3000 times increase in the $E_{50}$ of the GHRH effect, thereby reducing the GH release after administration of GHRH.

The inhibition of the GH release was similar after 7 and 13 days of treatment.

CONCLUSIONS
The PK of BIM23B065 and its metabolite as well as GH release were well described by the model.
GH release was significantly reduced in BIM23B065 treated subjects after a GH stimulation test.