Protocol Title:

A PHASE IIA, OPEN-LABEL, SINGLE-ARM, TWO STAGE, MULTI-CENTRE STUDY TO INVESTIGATE THE PHARMACODYNAMICS, PHARMACOKINETICS, SAFETY AND TOLERABILITY OF REPEATED SUB-CUTANEOUS ADMINISTRATION OF BIM23B065 IN SUBJECTS WITH ACROMEGALY

Protocol D-FR-10380-002

Protocol Amendment #1, Version 2.0, dated 14-SEPTEMBER-2016

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Agreement on Protocol – Signature Page

Protocol Title: A phase IIa, open-label, single-arm, Two stage, multi-centre study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of repeated sub-cutaneous administration of BIM23B065 in Subjects with acromegaly

Protocol Version Number: 2.0

Protocol Version Date: 14-SEPTEMBER-2016

By signing below, I hereby confirm that I have read, discussed and understood the above mentioned version of the protocol **D-FR-10380-002** and the background information concerning the study drug. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Investigator	**Sponsor**
Name	Name:
Title:	Title:
Date:	Date:
Signature:	Signature

SYNOPSIS

Title	A phase IIa, open-label, single-arm, Two stage, multi-centre study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of repeated sub-cutaneous administration of BIM23B065 in Subjects with acromegaly
Study Alias	D-FR-10380-002
EudraCT Number	**2015-003868-37**
Investigational Product	BIM23B065
Type of Study	Phase IIa open-label single-arm
Investigational Site	The study will be performed in multiple investigational sites in multiple countries.
Study Duration	The overall study duration is expected to be approximately two years from first subject screened to last subject discharged from the study. Each subject will be in the study for approximately 7 weeks, including 3 weeks for screening activities, 2 weeks treatment and 2 weeks of post-study follow-up.
Objectives	Primary: • To assess the pharmacodynamics of repeated administration of BIM23B065 in reducing growth hormone (GH) in subjects with acromegaly Secondary: • To assess the safety and tolerability of repeated administration of BIM23B065 in subjects with acromegaly • To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of repeated administration of BIM23B065 • To investigate the PK of BIM23B133 which is the major metabolite of BIM23B065 • To assess the correlation of BIM23B065 exposure with blood pressure and heart rate (HR). Exploratory: • To correlate GH, Insulin-like Growth Factor-1 (IGF-1) and prolactin (PRL) responses with expression of somatostatin receptor 2 (SSTR2), somatostatin receptor 5 (SSTR5) and dopamine receptor sub-type 2 (D2) in pituitary tumour tissues, when available • To assess anti-drug antibodies (ADA) Biobanking: • To explore potential utility of biomarkers for association with drug activity, adverse events (AEs), to explore drug mechanism of action and/or disease understanding. Serum/plasma, whole blood samples will be collected for deoxyribonucleic acid (DNA) and whole blood samples for ribonucleic acid (RNA).
Endpoint	Primary Endpoints: • The proportion of subjects with GH ≤2.5µg/l or >50% reduction from mean baseline GH after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6-hours at Day 14. Secondary Endpoints: • To assess the safety and tolerability of BIM23B065 • To assess the proportion of subjects with GH <1.0µg/l after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6-hours at Day 14. • To investigate the PK profile of BIM23B065

	• To correlate the PK with changes in GH, IGF-1 and PRL • To determine the efficacy of BIM23B065 in reducing IGF-1 to <Upper Limit of Normal (ULN) (age normalised) after 6-day titration and 8-day treatment period at Day 14 and Day 28. • To investigate the PK profile of BIM23B133 • To assess the correlation of exposure of BIM23B065 with blood pressure and HR. Exploratory: • To correlate GH and IGF-1 responses with expression of SSTR2, SSTR5 and D2 in pituitary tumour tissue • To assess anti-drug antibodies Biobanking: • To biobank whole blood samples for DNA at baseline pre-dose (Day -1), serum/plasma and whole blood samples for RNA at baseline pre-dose (Day -1), at Day 14 and Day 28 (EoS/ED)
Study Design	This is a open-label, non randomised, multi-centres, adaptive two-stage phase II study. During stage 1, up to 12 subjects will be enrolled to receive BIM23B065 twice a day (BID) for two weeks. The primary endpoint will be the proportion of subjects with GH ≤2.5 µg/l or >50% reduction from baseline GH on Day 14. The mean serum concentration of GH collected over 6 hours will be used for the baseline (Day -1) and endpoint (Day 14) GH determination. Several sequential analyses will occur during Stage 1. The Stage 1 arm (BID administration) may be terminated early for futility during each of these interim analyses if the responder rate does not exceed some pre-determined minimum efficacy criteria. In that case, a stage 2 arm will be initiated during which up to 12 subjects will be recruited to receive BIM23B065 three times a day (TID) for 14 days. The same sequential analysis and early termination rule for futility will apply during stage 2 as for stage 1. If the primary endpoint is met after the stage 1 BID cohort, the TID cohort 2 will not be started. Any subject who withdraws prior to the Day 14 end of treatment visit may be replaced except for early withdrawal due to safety and tolerability reasons. As soon as 12 subjects (out of which at least 8 are Octreotide responders) reach Visit 8, withdrawn subjects will not be replaced.. Both the BID and TID regimen parts will consist of 3 periods: • A screening period of 21 days maximum during which the eligibility criteria will be assessed. An Octreotide test will be also performed at the latest 7 days prior to first Investigational Medicinal Product (IMP) administration. • A treatment period that will consist of twice or three times daily administrations of BIM23B065. This period will last 14 days. The first 6 days will be a titration of BIM23B065 (0.4 mg/0.6 mg/0.8 mg BID or TID). Then a stable target dose (1.0 mg) of BIM23B065 will be BID or TID administered from Day 7 to Day 14. • If a subject experiences any safety or laboratory events that meet the criteria in Table 1, they may have their dose reduced to the prior dose. The minimum dose allowed for the treatment period is 0.6mg BID or TID. o If the criteria for dose reduction are met when a subject is taking 1.0mg BID or TID, they may be dose reduced to 0.8mg BID or TID. o If the criteria for dose reduction are met when a subject is taking 0.8mg BID or TID, they may be dose reduced to 0.6mg BID or TID. o A subject may be dose reduced more than once and at anytime during the study. For example, from 1.0mg BID or TID to 0.8mg BID or TID and if safety/tolerability issues persist, they may be further dose reduced to 0.6mg BID or TID.

	• If the subject experiences any cardiovascular events that meet the criteria in Table 2 during the titration period, they must remain on their current dose and not be dose escalated. • A follow up period that will last for 14 days during which the subjects will not be administered BIM23B065.
Number of Subjects	This study will enrol approximately 15 subjects so that 12 subjects will be evaluable per stage. A drop-out rate of 20% is expected requiring approximately 15 subjects to be treated per stage.
Treatment: route, strength, regimen	BIM23B065 will be administered twice a day (morning and evening) or three times a day (every 8 hours ± 1 hour). The doses administered will be : 0.4mg; 0.6mg, 0.8mg and 1.0 mg by subcutaneous (sc) injection.
Reference/Control Treatment: route, strength, regimen	NA
Drug administration	BIM23B065 will be administered by subcutaneous injection in the abdomen. There should be a rotation of the injection sites between left and right sides.
Main Inclusion/Exclusion Criteria	Male and female subjects between 18 and 75 years old with a confirmed diagnosis of acromegaly, with or without a history of pituitary surgery, will be included into this study. Subjects can be either treatment naïve or have received prior treatment for their acromegaly.
Study Evaluation Criteria: Safety Efficacy Pharmacokinetic Pharmacodynamic	<u>Pharmacodynamic Assessments</u> • Mean serum concentration of GH over 6 hours at baseline, Day 7 and Day 14, • IGF-1 levels at baseline, Day 14 and Day 28, • PRL cycle 6 hours at baseline, Day7 and Day 14 <u>Pharmacokinetic Assessments:</u> • Time points will follow a sparse PK sampling approach. On Day 7 (first day of 1.0mg) pre-dose, 0.5h, 1h, 2h, 4h and 6h post-morning dose. On Day 14 (last day of 1.0mg) pre-dose, 0.5h, 1h, 2h, 4h and 6h post-morning dose. • One random sampling for PK analysis will also be taken at further routine study visits (Day 10) to co-ordinate with safety and PD assessments. • BIM23B065 and its major metabolite BIM23B133 <u>Safety</u>: • Adverse Events. • Physical examination • Vital signs (supine and standing blood pressure and HR) • 12-lead ECG and ECG monitoring by 3-lead holter device at specific timepoints, corrected QT interval (QTc) will be calculated using Fridericia methodology • Clinical laboratory assessments: haematology, coagulation, clinical biochemistry including glucose, glucagon and insulin measurements, urinalysis • Putative antibodies to BIM23B065 • Endocrine parameters: Adrenocorticotrophic Hormone (ACTH), Cortisol, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Free Thyroxine (FT_4), Thyroid Stimulating Hormone (TSH) and Testosterone (for males only). • Gallbladder echography
Pharmacokinetic Methodology	Plasma samples will be analysed to determine concentrations of BIM23B065 and BIM23B133 using a validated, specific and sensitive LC MS/MS method.
Statistical Methodology:	The maximum sample size will be 24 evaluable subjects (12 per stage). Enrolled subjects who drop out of the study prior to Day 14 GH evaluation may be replaced. If 12 evaluable subjects have already completed visit 8 (day 14) any subsequent

	withdrawn subjects will not be replaced. A minimum of 8 of the 12 evaluable subjects must be responsive to a single test dose of octreotide pre-study defined as a >50% reduction in GH. Per the primary endpoint, a subject is defined as a responder if the median concentration of GH over 6 hours is ≤2.5µg/l or if there is at least 50% reduction from mean baseline in GH at Day 14 (after 6 days titration plus 8 days treatment). Based on the exact test for single proportion, twelve evaluable subjects per stage would be sufficient to have over 84% power, at a significance level of 0.05 (one sided) to reject the null hypothesis that there is no indication of efficacy of BIM23B065 if the GH responder rate is at most 33%, assuming that the GH responder rate is equal to 75%.

RATIONALE FOR PROTOCOL AMENDMENT #1

The overall changes and rationale for the changes made to this protocol are to address Ethics Committee request as follows:

- To exclude patients with unsubstituted/untreated hypoadrenalism (addition of one exclusion criteria)
- To add serum cortisol as safety endocrine parameter

In addition, the following modifications have been performed:

- To modify a mistake in calculation of the total blood volume in the Attachment 3.
- Modifications of the Global Patient Safety contact details.

All modifications are presented in the Attachment 6.

PROTOCOL HISTORY

Protocol version	Rationale for amendment
V.1.0, 27JUL2016	NA – initial version
V.2.0, 14SEPT2016, Amendment #1	See rationale for Protocol amendment #1 (above)

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LIST OF DEFINITIONS AND ABBREVIATIONS

DEFINITIONS

Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOP), good clinical practices, and the applicable regulatory requirement(s).
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, GCP requirements and the applicable regulatory requirements.
End of Study	End of study (EoS) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
Enrol / Randomise	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter/Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed- or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document (ICD) directly or through their legally acceptable representatives.
Ethics Committee	A board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
Investigator	A physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Preliminary (interim) analysis	Any analysis intended at any time prior to the formal completion of a study.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves [invasive or diagnostic procedures and/or tests (for example, blood draws)]. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be ether a healthy human or a patient.

ABBREVIATION	Wording Definition
ABP	Automated blood pressure
ACTH	Adrenocorticotrophic hormone
ADA	Anti Drug Antibodies
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the (plasma concentration vs. time) curve
$AUC_{0-\infty}$	Area under the (plasma concentration vs. time) curve from time 0 to infinity
AUC_{0-X}	Area under the (plasma concentration vs. time) curve from 0 to time X
AUC_t	Area under the serum concentration time curve from time 0 to last quantifiable timepoint
ADA	Anti-Drug Antibodies
BID	Bis in die (twice a day)
BP	Blood pressure
CA	Competent Authority
Cl	Clearance
Cl/F	Apparent total clearance (from plasma)
C_{max}	Observed maximal (peak) concentration
CMC-SC	Chemistry Manufacturing and Control- Supply Chain
CRF	Case report form: a printed or electronic form for recording study subjects' data during a clinical study, as required by the protocol.
CRO	Contract research organisation
CTCAE	Common Terminology Criteria for Adverse Event
CVM	Cytomegalovirus
DA	Dopamine agonist
DNA	Deoxyribonucleic acid
D_2	Dopamine receptor sub-type 2
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicities
DRC	Data Review Committee
EBV	Epstein–Barr virus
EC	Ethics Committee

ABBREVIATION	Wording Definition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ED	Early Discontinuation
EoS	End of Study
FDA	Food and Drug Administration
FIM	First in man
FSH	Follicle stimulating hormone
FT4	Free Thyroxine
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GH	Growth Hormone
GHRH	Growth Hormone Releasing Hormone
HbA1c	Haemoglobin A1c
HCG	Human chorionic gonadotrophin
HCP	Healthcare Professional
HCV	Hepatitis C virus
HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's brochure
ICD	Informed consent document
ICH	International conference on harmonisation
IEC	Independent Ethic Committee
IGF-1	Insulin-like Growth Factor-1
IMP	Investigational Medicinal Product
INR	International normalised ratio
IRB	Institutional Review Board
ISF	Interim Storage Facility
ITT	Intention to treat
IUD	Intra-Uterin device
IUS	Intra-uterin hormone-releasing system
LAR	Long acting release
LC-MS	Liquid chromatography - Mass spectrometry
LH	Luteinising hormone

ABBREVIATION	Wording Definition
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
NA	Not applicable
ND	Not done
PD	Pharmacodynamics
PDM	Pharmacokinetics and Drug Metabolism
PP	Per protocol
PRL	Prolactin
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
QD	Quaque die (once a day)
QTc	Corrected QT interval
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious Adverse Events
SBP	Systolic blood pressure
sc	subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
SSA	Somatostatin Analogues
SST	Somatostatin
$SSTR_2$	Somatostatin Receptor 2
$SSTR_5$	Somatostatin Receptor 5
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
t_{max}	Time of observed C_{max}
TEAE	Treatment Emergent Adverse Event
TID	Ter in die (Three times a day)
TMF	Trial master file
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
V	Volume of distribution

ABBREVIATION	Wording Definition
V/F	Apparent volume of distribution
WHO	World Health Organisation
WOCBP	Women Of Childbearing Potential

1 STUDY DRUG BACKGROUND INFORMATION

1.1 Investigational Medicinal Product Name

BIM23B065 consists of one molecule of dopamine bound to one molecule of a peptidic somatostatin (SST) analogue. It is a chimera of a Dopamine receptor sub-type 2 (D_2) and an Somatostatin Receptor 2 ($SSTR_2$) agonist. Its theoretical molecular formula is $C_{77}H_{101}N_{17}O_{10}S$ corresponding to a molecular weight of 1456.8 g/mol (as free base), and the structural sequence is: (D-6-methyl-8β-Ergolinylmethyl)-thioethyl-cyclic [DLysyl-Arginyl-Phenylalanyl-4-Aminophenylalanyl-DTryptophyl-Lysyl-Threonyl-Tyrosyl].

The single molecule is hypothesised to bridge the two receptors, bringing them physically together. An interaction and heterodimerisation between the two receptors has been proposed, resulting in stronger downstream post-receptor signalling than is observed with agonist of each receptor alone or in combination, suggesting a potential synergistic benefit from the combined targeting of these receptors.

The original rationale for the development of BIM23B065 came from clinical literature indicating greater suppression of Growth Hormone (GH) in patients with acromegaly with a combination of SST and Dopamine agonist (DA) analogues than with either alone. Ipsen began the development program with the idea of building this combined activity into a single molecule. The Ipsen team subsequently found that *in vitro* combined SST and DA analogues provided no greater suppression than SST analogues alone; however, the prototype chimeric molecule showed increased efficacy and 100-1000 fold increased potency (1)(2). Ipsen optimised the ratio of the SST and DA activities to achieve a first-generation compound with consistently improved efficacy/potency in suppressing GH in acromegalic tumours, as compared with the current clinical SST analogues (3). CCI

[redacted]

1.2 Findings from Nonclinical and Clinical Studies

1.2.1 Non Clinical Studies

Non-clinical safety findings are summarised in the BIM23B065 Investigator's Brochure (IB) (4).

1.2.2 Clinical Studies

A phase I study of BIM23B065 has been conducted in 71 healthy male subjects.

No Serious Adverse Events (SAEs) were reported following single ascending dose (SAD) or multiple ascending dose (MAD) administrations of BIM23B065 for 14 days in this population. The most frequent treatment emergent adverse events (TEAEs) were injection site reactions, and after multiple administrations hypotension. Cases of liver transaminases increases were also reported. All TEAEs after multiple administrations were of mild severity.

Typical injection site reactions were described as localised erythema at the injection site (of 4 cm to 5 cm diameter for the higher doses), of mild, not associated with pain, that spread outwards as it resolves. Reactions typically resolve within 2 hours post dose and can be managed without treatment. Hypotension, postural hypotension and HR decrease also occurred at 1.0 mg twice a day (BID) in this population of healthy young male subjects. To mitigate this risk a 6-day dose titration period prior to the starting of the maintenance dose was included in the MAD part of the study. Of note, decrease in HR never reached dose limiting toxicity (DLT) level. Subjects should be warned of the potential for the development of postural hypotension**.** Measures are outlined in this protocol which are designed to minimise the risk of hypotensive episodes.

In the MAD part of the study, elevations of hepatic transaminases were seen in subjects who received BIM23B065. Increases were in the range >ULN to ≤3.0×ULN. They resolved spontaneously and were not accompanied by elevations of bilirubin.

In addition, after multiple dosing of BIM23B065 there were no abnormalities in fasting blood glucose levels.

Upper gastrointestinal symptoms, such as abdominal pain, upper abdominal pain, nausea, cramps or discomfort was observed in this first-in-man study. Nausea and abdominal discomfort were more common after the evening dose of BIM23B065 when the drug was administered in the fed state. These gastrointestinal TEAEs were all mild severity.

Isolated cases of raised amylase and lipase (1 volunteer) and neutropenia (1 volunteer) which were regarded as DLTs were seen during repeated dosing with BIM23B065. All events resolved before the end of the study.

Additional information regarding safety profile of BIM23B065 may be found in the IB (4).

With regards to Pharmacodynamics (PD) findings, in the MAD part of the Phase I study, GH cycles were assessed up to 11 hours postdose. Spontaneous peak in GH levels were observed in subjects who received placebo, which were notably reduced in subjects receiving BIM23B065.

In both single and multiple ascending dose parts of the study, dosing with BIM23B065 led to reductions in mean plasma prolactin (PRL) concentrations, with greater and longer lasting reductions in PRL concentration observed with higher individual doses.

Finally, suppression of GH concentrations was demonstrated during the growth hormone releasing hormone (GHRH) stimulation test in the multiple ascending dose part of the study. Mean exposure to GH after GHRH stimulation was considerably lower in subjects receiving BIM23B065 compared to those receiving placebo.

1.3 Known and Potential Risks

To date, BIM23B065 has been studied in one phase I study in healthy male subjects. Single doses of up to 1.5 mg and multiple doses of 1.2 mg once a day (QD) and up to 1.0 mg BID have been administered to healthy male subjects in a single and multiple dose escalation and multiple dose titration study.

Hypotension

Hypotension and postural hypotension occurred very commonly in healthy male subjects (starting half an hour after investigational medicinal product (IMP) administration with acute

effect at 2 hours after IMP administration), particularly with multiple dosing of BIM23B065. Subjects should be warned of the potential for the development of postural. Measures are outlined in this protocol which are designed to minimise the risk of hypotensive episodes.

Heart rate decrease

During the phase 1 study, hypotension, postural hypotension and heart rate (HR) decrease commonly occurred in this population of healthy young male subjects, particularly following multiple dosing of BIM23B065 at 1.0 mg BID. Subjects should be warned of the potential for the development of postural hypotension. Blood pressure and HR will be closely monitored during the present study.

Increase ALT and AST

Increases in mean alanine aminotransferase (ALT) concentration were observed during treatment in all dosing groups with greater increases noted with higher daily BIM23B065 doses. All increases in ALT and aspartate aminotransferase (AST) were of mild intensity and resolved before the end of the study and were not accompanied by elevations in bilirubin. Investigators should comply with laboratory safety testing requirements and guidance on the management of abnormalities of liver function tests as detailed in this current study protocol.

1.4 Selection of Investigational Medicinal Product Doses and Dose Regimen

The stage 1 starting dose has been selected to allow a titration period and will consist of a BID administration of 0.4mg at Days 1 and 2, 0.6 mg at Days 3 and 4, then 0.8 mg at Days 5 and 6 with 1.0 mg from day 7.

This titration schedule has been validated during the phase I study in healthy male subjects (with the aim of reducing the occurrence of known side-effects of dopamine agonists; primarily hypotension).

Then from Day 7 to Day 14 a stable target dose of 1.0 mg will be administered BID.

This 1.0 mg BID dose was estimated to be the maximal tolerated dose during the multiple ascending dose part of the Phase I study. In addition this dose level was associated with robust PD effects in GH and PRL.

If during the study, a subject is unable to tolerate 1.0mg BID and meets the criteria for dose reduction in Table 1 (please see page 23), dose may be reduced to 0.8mg BID. If the safety or tolerability issue persists, the dose may be further reduced to 0.6mg BID. This decision will be taken in agreement with the Investigator. The dose of 0.6mg is the lowest dose permitted for the treatment phase and any subject unable to tolerate this dose level of 0.6mg will be withdrawn from the study.

If a subject experiences changes in blood pressure or bradycardia as described in Table 2 (please see page 23) during the titration phase, they will not have their dose increased further and they will remain on their current dose.

Following an algorithm described in Figure 3 (please see page 32), a stage 2 with three times a day (TID) administration of the IMP with new subjects will be conducted with the same above described design.

1.5 Study Population

Both gender subjects aged between 18 and 75 years with a confirmed diagnosis of acromegaly, with or without a history of pituitary surgery, will be included into this study. Subjects can be either treatment naïve or have received prior treatment(s) for their acromegaly. (See Sections 4.4 and 4.5).

1.6 Potential Benefits to Participants

The study participants will not have a therapeutic benefit. The study is part of a global development plan for BIM23B065 and the compound is at early stage of development. This study is designed to increase the understanding of the PD effects and safety after a short duration of treatment. Future studies may demonstrate a potential benefit to patients with acromegaly.

1.7 Rationale for the Study

The development program of BIM23B065 is designed to provide evidence that the chimeric dual agonist peptide BIM23B065, as a single entity, is effective in treating GH-secreting pituitary adenomas that involve $SSTR_2$ and D_2. The purpose of this second clinical study with BIM23B065 is to evaluate the effect of repeated administration of BIM23B065 on the secretion of GH in patients with acromegaly. Results obtained in the First in man (FIM) trial performed in healthy subjects confirmed the pharmacological activity properties of BIM23B065 in reducing efficiently spontaneous GH secretion as well as GHRH induced secretion. The proposed study aims to confirm this pharmacological activity but in patients with acromegaly, as well as evaluate further the safety profile of BIM23B065 after multiple administrations over 14 days. The half-life ($t_{1/2}$) of BIM23B065 with the current formulation is relatively short and therefore suggest the need of more than one injection per day. The first study in healthy subject assessed a twice-a-day dose regimen and provided robust data on GH reduction as well as optimise the safety and tolerability profile in respect to a single dose as well as by a dose increase titration approach. However in respect to the optimal scheme of administration, three injections per day could provide, potentially, an even better sustained reduction in GH over dosing interval. The proposed study will start with a BID dose regimen (stage 1) and if the results obtained after this first part are not satisfactory in terms of GH reduction, and provided that there are no safety and tolerability issues, the second stage will test a TID dose regimen. Thus at the end of this study, data will be obtained about the potential for BIM23B065 to effectively reduce GH secretion in patient with acromegaly as well as the safety and tolerability after multiple administrations of the compound. CCI [redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- To assess the PD of repeated administration of BIM23B065 in reducing GH in subjects with acromegaly.

2.2 Secondary Objective(s)

- To assess the safety and tolerability of repeated administration of BIM23B065 in subjects with acromegaly.
- To assess the pharmacokinetics (PK) and PD of repeated administration of BIM23B065.
- To investigate the PK of BIM23B133 which is the major metabolite of BIM23B065.
- To assess the correlation of BIM23B065 exposure with blood pressure and HR.

2.3 Exploratory Objective(s)

- To correlate GH, IGF-1 and PRL responses with expression of $SSTR_2$, $SSTR_5$ and D_2 in pituitary tumour tissues, when available.
- To assess anti-drug antibodies (ADA).

2.4 Biobanking

- To explore potential utility of biomarkers for association with drug activity, adverse events (AEs), to explore drug mechanism of action and/or disease understanding. Serum/plasma, whole blood samples will be collected for deoxyribonucleic acid (DNA) and whole blood samples for ribonucleic acid (RNA).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, non randomised, multi-centres, adaptive two-stage phase II study.

During stage 1, up to 12 subjects will be enrolled to receive BIM23B065 BID for two weeks. The primary endpoint will be the proportion of subjects with GH ≤2.5 µg/l or >50% reduction from baseline GH on Day 14. The mean serum concentration of GH collected over 6 hours will be used for the baseline (Day -1) and endpoint (Day 14) GH determination.

Several sequential analyses will occur during Stage 1. The Stage 1 arm (BID administration) may be terminated early for futility during each of these interim analyses if the responder rate does not exceed the pre-determined minimum efficacy criteria (see details in section 4.3 and section 8.2). In that case, a stage 2 arm will be initiated during which up to 12 subjects will be recruited to receive BIM23B065 three times a day (TID) for 14 days. The same sequential analysis and early termination rule for futility will apply during stage 2 as for stage 1.

Any subjects who withdraw prior to the Day 14 end of treatment visit may be replaced except for early withdrawal due to safety and tolerability reasons. As soon as 12 subjects (out of which at least 8 are Octreotide responders as tested during the screening period) reach Visit 8, withdrawn subjects will not be replaced.

Both the BID and TID regimen parts will consist of 3 periods (See Figure 1):

- A screening period of 21 days maximum during which the eligibility criteria will be assessed. An Octreotide test will be also performed at the latest 7 days prior to first IMP administration.
- A treatment period that will consist of twice or three times daily administrations of BIM23B065. This period will last for 14 days. The first 6 days will be a titration of BIM23B065 (0.4 mg/0.6 mg/0.8 mg BID or TID). Then a stable target dose (1.0 mg) of BIM23B065 will be BID or TID administered from Day 7 to Day 14.
- If during the study, a subject experiences any safety or laboratory events that meet the criteria in Table 1, they may have their dose reduced to the prior dose (See Figure 2). The minimum dose allowed for the treatment period is 0.6mg BID or TID.
  - For example, if the criteria for dose reduction are met when a subject is taking 1.0mg BID or TID, they may be dose reduced to 0.8mg BID or TID.
  - If the criteria for dose reduction are met when a subject is taking 0.8mg BID or TID, they may be dose reduced to 0.6mg BID or TID.
  - A subject may be dose reduced more than once and at anytime during the study. For example, from 1.0mg BID or TID to 0.8mg BID or TID and if safety/tolerability issues persist, they may be further dose reduced to 0.6mg BID or TID.
- If during the titration period, the subject experiences any cardiovascular events that meet the criteria in Table 2, they must remain on their current dose and not be dose escalated.
- A follow up period that will last for 14 days during which the subjects will not be administered BIM23B065.

Table 1 Criteria for dose reduction

Body System	Criteria
Cardiovascular	Any symptomatic hypotensive event that does not meet the criteria for drug withdrawal (please see Table 3) but in the opinion of the Investigator requires dose reduction. For example, severe dizziness requiring the subject to sit or lie down post-dose on 2 or more occasions

Table 2 Criteria for not dose escalating

Body System	Criteria for not dose escalating: If at any time point with a given dose the subject has:
Cardiovascular	Systolic hypotension <100 mmHg for supine SBP Postural hypotension (drop in either SBP or more than 25 mmHg or DBP of more than 10 mmHg) Bradycardia <50 beats/min and decrease from baseline exceeding 20 beats/min (assuming supine position)

Criteria should be confirmed by a repeat assessment (3 measurements over 1 hour) after 10-15 minutes rest in supine position.

SBP=systolic blood pressure, DBP=diastolic blood pressure,

Table 3 Criteria for Discontinuation of BIM23B065 administration and for definition of Dose Limiting Toxicity

Body System	Criteria
Cardiovascular	Systolic hypotension <80 mmHg for supine SBP or symptomatic Postural hypotension (drop in either SBP or more than 30 mmHg or DBP of more than 15 mmHg), symptomatic and/or requiring treatment Bradycardia <40 beats/min and decrease from baseline exceeding 20 beats/min (assuming supine position) and associated with symptoms QTcF interval >500 ms or QTcF over 460 ms and increase exceeding 60 ms as compared to baseline value
Hepatic	AST/ALT ≥ 5xULN Bilirubin ≥2xULN AST/ALT > 3xULN and Bilirubin > 2x ULN and ALP > 2xULN
Renal	Serum creatinine ≥1.5xULN
Other AEs	In the view of the Investigator, any other unacceptable toxicity or clinically significant abnormality in laboratory tests, vital signs or ECG

Cardiovascular criteria should be confirmed by a repeat assessment after 10-15 minutes rest in supine position

SBP=systolic blood pressure, DBP=diastolic blood pressure, AST=aspartate aminotransferase, ALT=alanine aminotransferase, ULN=upper limit of normal range, QTcF=QT interval corrected for HR according to Fredericia, ECG=electrocardiogram

Figure 1 Study Schema

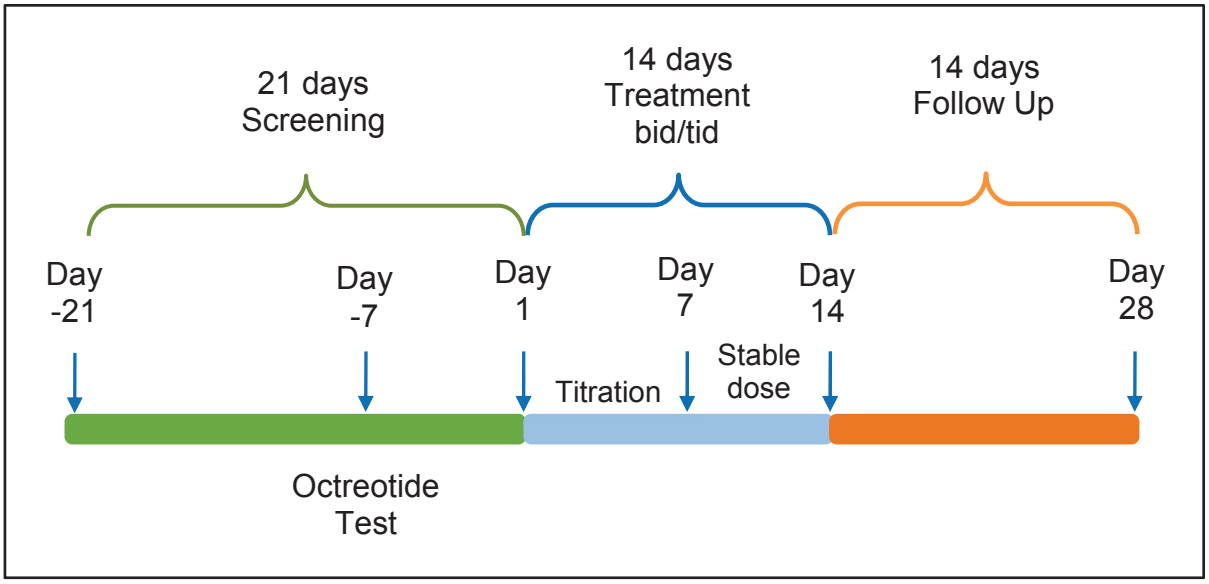
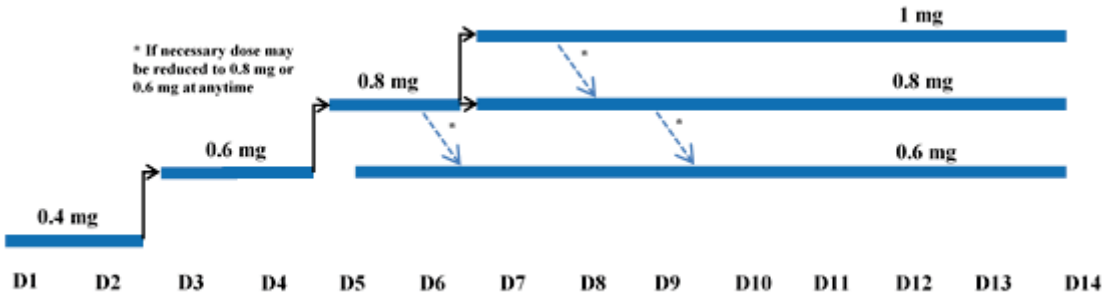


Figure 2 Treatment Period; Cohort 1 is BID dosing and a possible cohort 2 is TID dosing



3.2 Primary and Secondary Endpoints and Evaluations

Pharmacokinetic and Pharmacodynamic endpoints are primary and secondary endpoints in this study and are further described below.

3.2.1 Primary Endpoints and Evaluations

- The proportion of subjects with GH ≤2.5µg/l or >50% reduction from mean baseline GH after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6-hours at Day 14.

3.2.2 Secondary Endpoints and Evaluations

- To assess safety and tolerability.
- To assess the proportion of subjects with GH <1.0µg/l after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6-hours at Day 14.
- To investigate the PK profile of BIM23B065.
- To correlate the PK with changes in GH, IGF-1 and PRL.
- To determine the efficacy of BIM23B065 in reducing IGF-1 to <ULN (age normalised) after 6 day-titration and 8-day treatment period at Day 14 and Day 28.
- To investigate the PK profile of BIM23B133.
- To assess the correlation of exposure of BIM23B065 with blood pressure and HR.

3.2.3 Exploratory Endpoints and Evaluations

- To assess anti-drug antibodies.
- To explore the relationship between drug concentrations and potential changes in PD markers (PK/PD relationship).
- To explore the relationship between response to BIM23B065 and the expression of SSTR2, SSTR5 and D2 in those subjects with available tumour tissue.

3.2.4 Safety Endpoints and Evaluations

- Adverse Events.
- Vital signs (supine and standing blood pressure and HR).
- 12-lead ECG and ECG monitoring by 3-lead Holter device at specific timepoints, QTc interval will be calculated using Fridericia methodology.
- Clinical laboratory assessments: haematology, coagulation, clinical biochemistry including glucose, glucagon and insulin measurements, urinalysis.
- Putative antibodies to BIM23B065.
- Endocrine parameters: Adrenocorticotrophic Hormone (ACTH), Cortisol, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Free Thyroxine (FT4), Thyroid Stimulating Hormone (TSH) and Testosterone (for males only).
- Gallbladder echography.

3.2.5 Pharmacokinetics and Pharmacodynamics Endpoints and Evaluations

- PD Assessments
  - Mean serum concentration of GH over 6 hours at baseline, Day 7 and Day 14.
  - IGF-1 levels at baseline, Day 14 and Day 28.
  - PRL levels over 6 hours at baseline, Day 7 and Day 14.
- PK Assessments:

- Time points will follow a sparse PK sampling approach. On day 7 (first day of 1.0mg) pre-dose, 0.5h, 1h, 2h, 4h and 6h post-morning dose. On day 14 (last day of 1.0mg) pre-dose, 0.5h, 1h 2h, 4h and 6h post-morning dose.
- One random sampling for PK analysis will also be taken at further routine study visits (Day 10) to co-ordinate with safety and PD assessments.
- Drug (BIM23B065) and its major metabolite BIM23B133.

3.2.6 Biobanking Endpoints and Evaluations

- To biobank whole blood samples for DNA at baseline pre-dose (Day -1), serum/plasma and whole blood samples for RNA at baseline pre-dose (Day -1), at Day 14 and Day 28 (EoS/ED).

3.3 Subjects Managements

3.3.1 Study Visits and Procedures

Study visits and procedures are described in the Study Schedule of Events (see Section 15.1).

3.3.1.1 Screening Period

After a subject has received explanations and response(s) to his/her potential questions about the study by the Investigator (or designee) and has been given reasonable time to think about it, a signed and dated informed consent form will be obtained prior to any study procedures.

Once informed consent is obtained, subjects will be allocated a study-specific subject number which must comply with formatting specifications provided by the Sponsor (see Section 3.3.2).

The screening tests and assessments will then be performed to check compliance with Inclusion/Exclusion criteria and study restrictions (Visit 1). The results must be obtained and confirm subject's eligibility within 21 days prior to dosing on Day 1.

In parallel of the completion of the initial screening assessments, subjects will undergo on an octreotide test dose to assess their response to somatostatin analogues (SSA) (Visit 2 performed at the latest on Day -7). An octreotide responder is defined as having a >50% reduction from baseline in mean GH in the 6 hours after a single sub-cutaneous injection of 100µg octreotide (sampling at -15 minutes, 1, 2, 3, 4, 5 and 6 hours).

The subjects will be hospitalised 24h prior to first IMP administration and baseline control assessments will be performed on Day-1 (Visit 3). Subjects will be hospitalized at the latest in the morning of on Day -1

If a subject has undergone pituitary surgery, and if the subject consents (subject will sign a separate and specific consent form), any paraffin-fixed tumour tissue will be analysed for $SSTR_2$, $SSTR_5$ and D_2 receptor expression. This will either be done at the investigational site with a methodology protocol and reagents provided by Ipsen or at a central laboratory using the same methodology protocol. Given the difficulties in obtaining tumour blocks it is expected that very few will be retrieved and evaluated so this will be an exploratory objective. Subjects who do not have tumour tissue available are equally eligible for the study.

Re-screening; due to the inherent variability of the assays for both GH and IGF-1 measurement, a subject may be re-screened on one occasion should the GH or IGF-1 value (as measured by central laboratory) be outside of the inclusion criteria. The decision to rescreen is taken at the Investigator's discretion and the Sponsor must be informed.

Subject who participated to the stage 1 of the study (BID administration) cannot participate to the stage 2 (TID administration).

3.3.1.2 Study Treatment Period

Subjects will receive administration of the IMP on the morning of Day 1 (Visit 3). Subject will remain hospitalised at least until Day 2 post morning dose assessments. BIM23B065 will be administered twice a day or three times a day s.c. injection in the abdominal region with a rotation of injection sites between left and right sides. In addition to IMP administration, safety, PD and PK assessments will be performed during Visit 3.

The first 6 days will be a titration of BIM23B065, with the aim of reducing the occurrence of known side-effects of dopamine agonists; primarily hypotension. Due to the need for all injections of BIM23B065 to be given by a healthcare professional (HCP) and for the close monitoring of side-effects and safety, subjects will have the option of either:

- Being admitted to hospital for the whole duration of the treatment period of the study irrespective of the IMP administration regimen (i.e. BID or TID administration).
- Only for the BID administration regimen: being admitted for the titration week (up to first dose of 1.0mg) and then having a HCP visiting them twice a day to administer subsequent doses in-between 3 further visits to the hospital for full study assessments.
- Only for the BID administration regimen: being admitted for 24 hours on Day 1, returning to the site for the first injection of each dose increase (every 2 days) during the titration week (up to and including 1.0mg) and having a HCP visiting them twice a day to administer subsequent doses and complete study assessments. The subject would return to hospital for the remaining study visits.
- For the TID administration regimen: due to the frequent injections, the subjects will be hospitalised for the treatment period duration.

Titration of BIM23B065 will be in 4 steps with dose increases every 2 days until the target dose is reached at Day 7. The doses will be 0.4mg BID or TID (Day 1 and Day 2), 0.6mg BID or TID (Day 3 and Day 4), 0.8mg BID or TID (Day 5 and Day 6) and 1.0mg BID or TID (starting at Day 7). The concentration of BIM23B065 will be constant (1.0mg/ml) and the required dose will be achieved by adjusting the volume administered (0.4mL, 0.6ml, 0.8ml or 1.0 ml). Study visits will occur every day that BIM23B065 is uptitrated (Visit 4 on Day 3, Visit 5 on Day 5 and Visit 6 on Day 7). Safety will be assessed at all visits, PD during Visits 6 and 8 and PK assessments will be performed during Visits 6, 7 and 8.

Subjects will be administered a target dose of 1.0 mg BID or TID from Day 7 until the morning of Day 14. The morning dose on Day 14 will be the final dose. Safety assessments will be performed during Visit 7 on Day 10. The criteria for either not increasing the dose or dose escalation are described in this protocol in Table 1 and Table 2.

If during the study, a subject experiences any safety or laboratory events that meet the criteria in Table 1 on page 23, they may have their dose reduced to the prior dose.

- For example, if the criteria for dose reduction are met when a subject is taking 1.0mg BID or TID, they may be dose reduced to 0.8mg BID or TID.
- If the criteria for dose reduction are met when a subject is taking 0.8mg BID or TID, they may be dose reduced to 0.6mg BID or TID.
- A subject may be dose reduced more than once and at anytime during the study. For example, from 1.0mg BID or TID to 0.8mg BID or TID and if safety/tolerability issues persist, they may be further dose reduced to 0.6mg BID or TID.
- 0.6mg BID or TID is the minimum allowable dose for the treatment period and if a subject is unable to tolerate 0.6mg BID or TID, they will be withdrawn from the study.

Last visit of the treatment period will be Visit 8 and will occur on Day 14. Safety, PD and PK assessments will be performed.

As this is a first-in-patient study, the recruitment rate will be as follows for both IMP administration regimen parts (i.e. BID or TID);

For the first 3 subjects for both BID and TID cohorts, no more than 1 subject per 8 days may be treated (perform Visit3 - Day1). The Data Review Committee (DRC) will review the first 7 days safety data of the first 3 subjects including blood biochemistry, blood pressure and ECG data. Once the DRC has approved the study to continue, subjects may be enrolled at a rate of a maximum of 3 treated subjects per week (in other terms, a maximum of 3 subjects attending visit 3 per week).

3.3.1.3 End of Study/Early Discontinuation Visit

Subjects will be discharged from the study after completion of the End of Study (EoS) visit (Visit 9) for follow-up assessments which will happen 2 weeks after the last dosing day (Visit 8), or earlier in case of early treatment discontinuation.

3.3.2 Subjects Disposition

At screening, subjects will be allocated an 11-digit subject number. It will consist of the combination of the country number (three digits), centre number (three digits) and the sequential order of entry of the subject in the unit (five digits).

A minimum of 8 octreotide responders must be evaluable in the final analysis. If an octreotide responder withdraws prematurely, he/she will be replaced by another octreotide responder. If an octreotide non-responder withdraws, they can be replaced by either a responder or non-responder.

The minimum evaluable number of subjects is 12 per stage of either BID or TID administration.

A subject is considered evaluable if he or she completes the 14-day treatment period (with 6 hours GH samples collected). Subjects who withdraw from the study before reaching the point of being evaluable will be replaced except for withdrawal due to safety and tolerability reasons. If 12 evaluable subjects have already completed visit 8 (day 14) any subsequent withdrawn subjects will not be replaced.

3.3.3 Study Duration

For each individual subject, the study is expected to last a maximum of 7 weeks, including up to 3 weeks for screening assessments, 2 weeks of study treatment and a 2 weeks safety follow-up.

3.4 Study Conduct

All screened subjects must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names (i.e. Subject Identification Log – to be kept on site(s)) and a list of all subjects screened (and potentially enrolled) into the study (i.e. Screening and Enrolment Log – to be shared with the Sponsor or designee) to enable reconciliation of records at a later date if required.

For screened failure subjects, data collection will be limited to demography, informed consent signature date, eligibility and visit status (that includes reason for screen failure).

The study is planned to be conducted in more than one country. Depending on the recruitment rate, number of countries involved may vary.

3.5 Rationale for the Study Design

Discussion of Design

This study will be the first in an acromegaly subject population with a planned 14-day treatment period which includes up-titration. There will be a 2 week safety follow-up period during which the subject will not receive BIM23B065. The study treatment is this duration for a number of reasons;

- Due to the short $t_{1/2}$ (5-7 hours), steady state will be reached in a couple of days. This is true for both BIM23B065 and the major metabolite. This is sufficient time for the required PK analysis.
- The primary endpoint is % subjects with a reduction of mean GH to mean GH≤2.5µg/l or a >50% reduction from mean baseline. GH can respond rapidly to therapy and a 6-day titration plus 8-day treatment is considered sufficient to see any GH response.
- The 2-stage adaptive design of the trial permits to evaluate two dosage regimen (BID and TID) in a maximum of 24 subjects. During Stage 1, the BID regimen will be tested in up to 12 subjects. Futility analyses will occur several times during Stage 1. The BID regimen will be stopped for futility if it does not meet the primary objective. Then, a TID regimen will be initiated in a Stage 2 cohort. The same interim and final futility analyses will occur for Stage 2 as for Stage 1 cohort.
- If the BID regimen meets the primary objective of the study at the end of Stage 1, Stage 2 will not be initiated.

4 POPULATION RECRUITMENT, ENROLMENT AND WITHDRAWAL

4.1 Definitions

Screened Subject:

A screened subject is a subject who signed the Informed Consent and could potentially be enrolled into the study.

Screening Failure:

A subject is considered as a screening failure when he/she is not enrolled in the study after signing the Informed Consent.

Subject Enrolment:

A subject is considered as enrolled in the study when he/she has received a least one IMP administration.

Subject Drop-out:

A subject will be considered as drop-out when, for any reason, he/she withdraws from the study after the 1st IMP administration.

4.2 Recruitment of Population

The Study will start with the BID administration cohort (Stage 1). The first 3 subjects will have to be dosed at least 8 days apart. This is to ensure that safety data can be reviewed by the DRC after the titration period before the next subject receives their first dose. If no related SAE is reported or unless the first 3 subjects experienced at least one DLT, remaining subjects can be dosed at a maximum rate of 3 per week. After the stage 1, the study may continue with the TID administration cohort (please see next Section for more details). Again the first 3 subjects will have to be dosed at least 8 days apart. This is to ensure that safety data can be reviewed by the DRC after the titration period before the next subject receives their first dose. If no related SAE is reported or unless the first 3 subjects experienced at least one DLT, remaining subjects can be dosed at anytime.

As described in Section 3.3.1, and for both IMP administration regimen (BID and TID), subjects will be screened within 3 weeks before dosing on a voluntary basis. The criteria for enrolment must be followed explicitly.

As illustrated in the Study Schedule of Events (see Section 15.1), eligibility of subjects in the study will be based on the results of a screening medical history (including any pre-existing conditions, and previous/concomitant medication(s)), physical examination, clinical laboratory tests (including PD assessments), GH levels, vital signs, electrocardiogram (ECG) and gallbladder echography. These tests / assessments may be performed at any time during the screening period (Day -21 to Day -7, included) after Informed Consent signature. Results of tests and assessments required at screening should be available to confirm subject's eligibility prior D-7 – when octreotide test will be performed – and prior dosing on Day 1.

4.3 Interim Analyses during Stage 1 and Stage 2

During Stage 1, one interim analysis is planned after 6 subjects complete the Day 14 GH assessment. The DRC will meet and review the number of GH responders on Day 14 (i.e. a GH responder is defined as a subject with GH ≤2.5µg/l or with at least 50% reduction from baseline GH after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6 hours at Day 14) as well as the safety and tolerability data. Based on the safety and efficacy data of these subjects, the DRC will decide if the BID cohort may be continued or stopped, and if stopped, if a TID cohort (Stage 2) may be initiated, according to the following criteria (please see Figure 3 below).

- If there are less than 3 responders then the BID regimen (Stage 1) will be stopped for futility and Stage 2 will be initiated, where new enrolled subjects will follow the TID administration part (Option 1 in Figure 3).

If there is at least 3 responders, then the Stage 1 will continue: the next 2 subjects will follow the BID administration part and DRC will review the safety and efficacy data once 8 subjects will have completed stage 1.

- If there are less than 4 responders (out of 8 subjects) then the BID regimen (Stage 1) will be stopped for futility and Stage 2 will be initiated, where new enrolled subjects will follow the TID administration part (Option 2 in Figure 3).

If there is at least 4 responders (out of 8 subjects), then the Stage 1 will continue: the next 4 subjects will follow the BID administration part and DRC will review the safety and efficacy data once 12 subjects will have completed stage 1.

- If there are less than 8 responders then the Stage 2 will be initiated, where new enrolled subjects will follow the TID administration part (Option 3 in Figure 3).

If there is at least 8 responders, then no new subjects will be enrolled into the BID administration part, no TID administration part will be conducted and the study will be stopped.

At any time of the stage 1 if at least 3 subjects experienced at least one DLT, then the DRC will stop the recruitment and no TID administration part will be conducted.

During Stage 2, one interim analysis is planned after the first 6 subjects will have completed the GH Day 14 assessment. The DRC will review safety and efficacy data of these subjects in order to decide if the trial may be stopped early for futility or not (please see Figure 4 below).

If there are less than 3 responders, then no new subjects will be enrolled into the TID administration part and the study will stop (Option 1 in Figure 4).

If there is at least 3 responders (out of 6 subjects), then the next 2 subjects will follow the TID administration part and DRC will review the safety and efficacy data once 8 subjects will have completed stage 2.

If there are less than 4 responders (out of 8 subjects) then the TID regimen (Stage 2) will be stopped for futility, no new subjects will be enrolled into the TID administration part and the study will stop (Option 2 in Figure 4).

If there is at least 4 responders, then the Stage 2 will continue: the next 4 subjects will follow the TID administration part once 12 subjects will have completed stage 2 and the study will be stopped (Option 3 in Figure 4).

Again, at any time of the stage 2 if at least 3 subjects experienced at least one DLT, then the DRC will stop the recruitment.

Figure 3 BID administration part

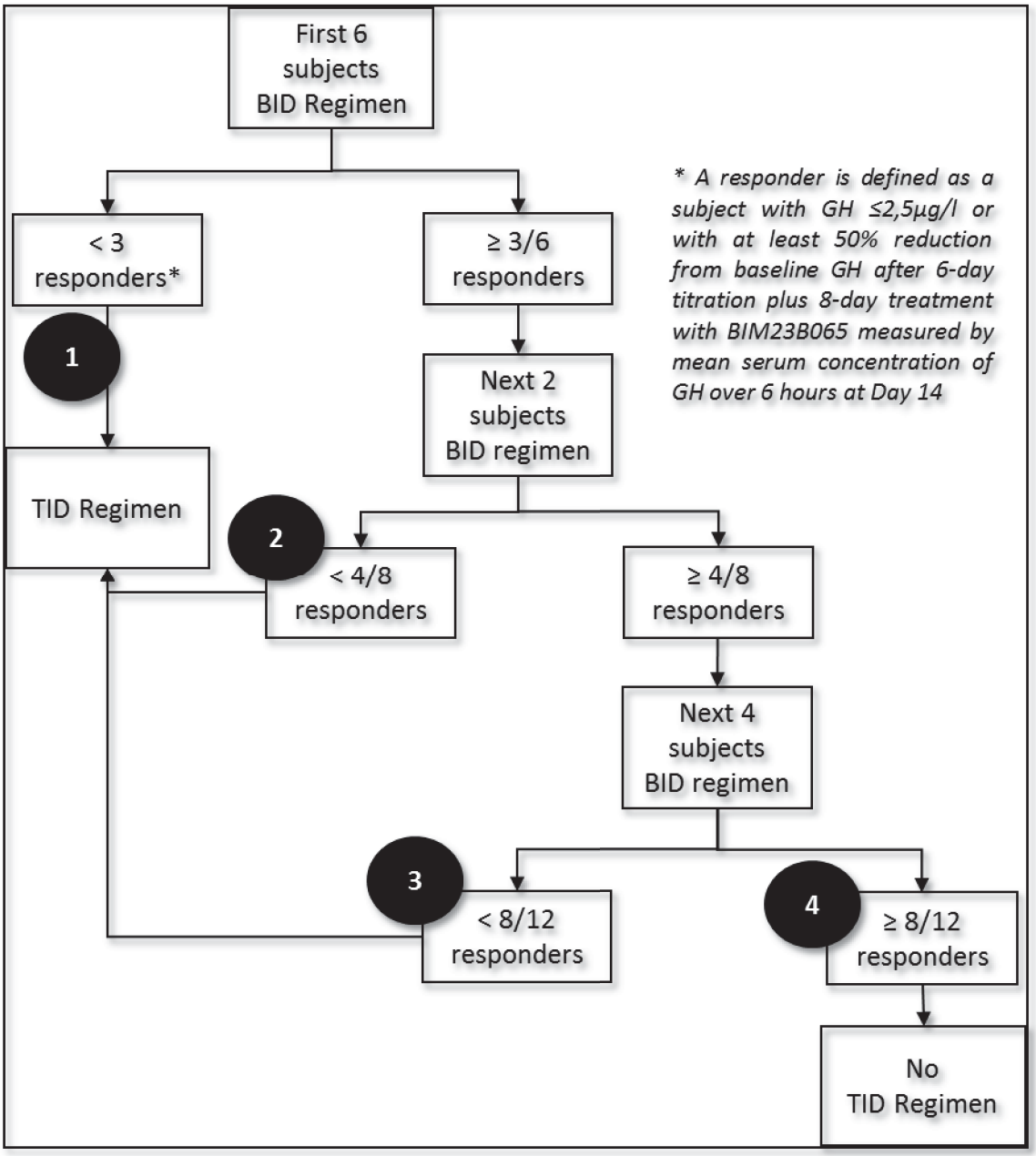
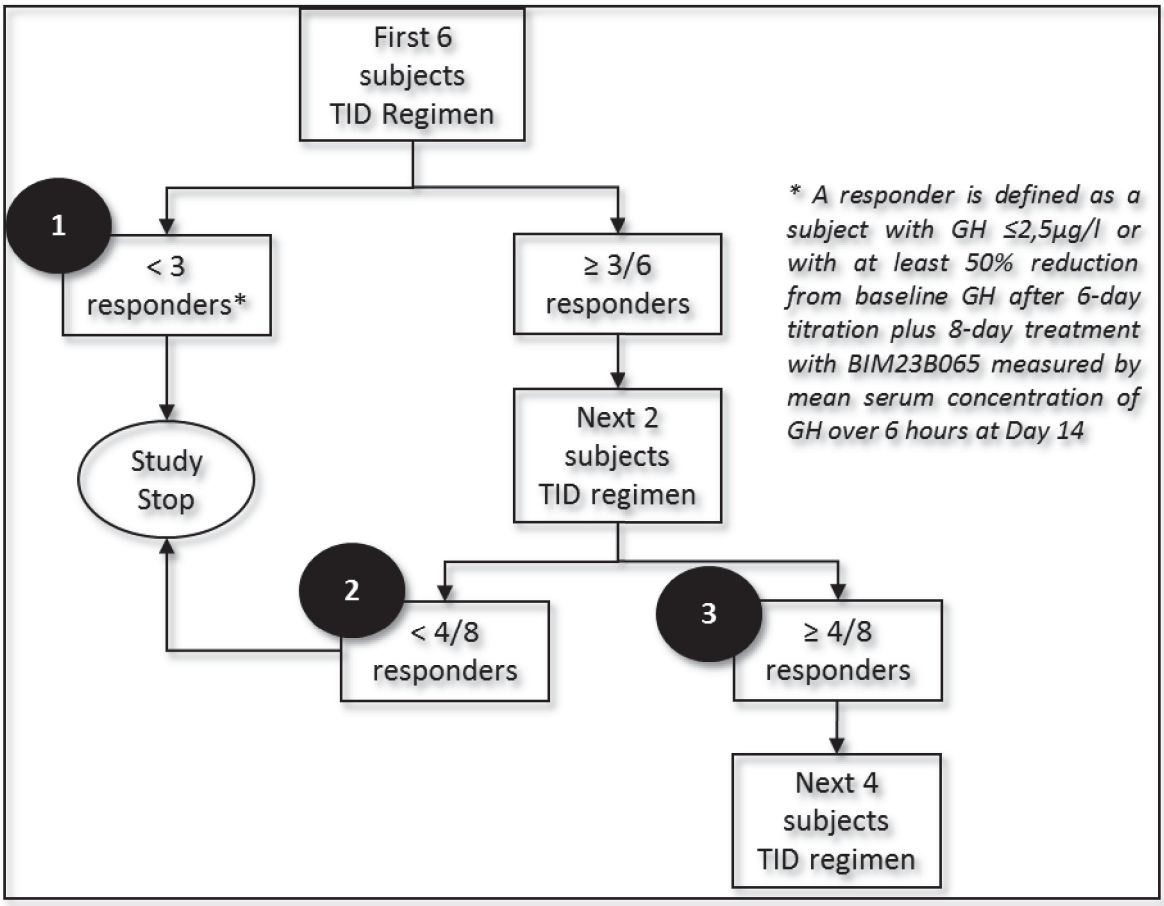


Figure 4 TID administration part



4.4 Inclusion Criteria

Potential study subjects may be entered in the study if they meet all of the following criteria:

(1) Provided written informed consent prior to any study related procedures.

(2) Subjects will have a documented diagnosis of acromegaly.

(3) Subjects will have active acromegaly confirmed by a mean serum concentration of GH over 2 hours > 2.5 µg/l at screening analysed by central laboratory.

(4) Subjects who have had pituitary surgery must be >8 weeks post-surgery.

(5) 18 to 75 years of age.

(6) Negative pregnancy test (female subjects).

(7) Female who is either of non-childbearing potential or who is not pregnant at screening and agrees to use highly effective contraception during whole duration of the study. Non-childbearing potential is defined as being postmenopausal for at least 1 year, or women with documented infertility (natural or acquired).

(8) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the treatment period of the study.

(9) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow up evaluation as specified in the protocol.

4.5 Exclusion Criteria

Potential study subjects may not be entered into the study if any of the following apply:

(1) The subject has received long-acting SSA within 12 weeks prior screening (e.g. octreotide long acting release (LAR), lanreotide Autogel, pasireotide LAR).

(2) The subject has received short-acting SSA within 1 week (e.g. octreotide s.c.) prior to screening.

(3) The subject has received a dopamine agonist within 6 weeks (e.g. bromocriptine or cabergoline) prior to screening.

(4) The subject has received GH antagonist within 12 weeks prior to screening (e.g. pegvisomant).

(5) The subject had undergone radiotherapy to the pituitary gland at any time prior to study entry.

(6) It is anticipated that the subject will undergo pituitary surgery or radiation to the pituitary gland during the study, or will require additional medical therapy for acromegaly (including SSA, pegvisomant, or dopamine agonists) during the study.

(7) The subject has unsubstituted/untreated adrenal insufficiency.

(8) If the subject has any history of postural hypotension or evidence of postural hypotension at screening (>= 20 mm Hg decrease in SBP, >= 10 mm Hg decrease in DBP, or >=30 bpm increases in pulse rate, after standing for 2 minutes from resting supine position of at least 10 min).

(9) Subject with poorly controlled diabetes mellitus (presence of ketoacidosis or a glycosylated haemoglobin level >10%).

(10) Subject with diabetes treated with insulin for less than 6 weeks prior to study entry, or with an unstable insulin dose in the 6 weeks prior to study entry or Haemoglobin A1c (HbA1c) >10%.

(11) Subject is taking beta-blockers (which can inhibit compensatory increases in HR during hypotensive episodes).

(12) Subject is taking Clonidine, Alpha-blockers, Verapamil and Diltiazem, Amiodarone, Ivabradine and Anti-cholinesterase drugs.

(13) Subject is being treated for hypertension and in the opinion of the Investigator their antihypertensive medication puts them at increased risk of postural hypotension.

(14) Subject is hypotensive at screening as defined as systolic < 90 mmHg and/or diastolic <60 mmHg.

(15) Subject has clinically significant hepatic abnormalities and/or ALT and/or AST ≥2 x ULN and/or alkaline phosphatase (ALP) ≥2 x ULN and/or total bilirubin ≥1.5 x ULN and gamma-glutamyl transferase (GGT) ≥2.5 x ULN during the screening period (local laboratory results).

(16) Subject has a compression of the optic chiasm causing visual-field defects.

(17) Subject with a life expectancy of < 1 year.

(18) Subject is receiving any oestrogen-containing Hormone Replacement Therapy (HRT).

(19) Subject is receiving neuroleptic antipsychotic/antiemetic drugs.

(20) Subject has clinically significant pancreatic abnormalities and/or amylase and/or lipase ≥2 x ULN during the Screening period (local laboratory results).

(21) Any significant renal abnormalities, including confirmed proteinuria and/or creatinine ≥1.5x ULN during screening assessed by the local laboratory.

(22) Subject has any known uncontrolled cardiovascular disease or any of the following within 6 months of Screening: ventricular or atrial dysrhythmia ≥ common terminology criteria for adverse event (CTCAE) grade 2, bradycardia ≥ CTCAE grade 2, electrocardiogram (ECG), QTc prolonged ≥ CTCAE grade 2, myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, hypertension not adequately controlled by current medications.

(23) Subject with history of, or known current, problems with alcohol or drug abuse.

(24) Subject with any mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

(25) Subject with uncontrolled hypothyroidism.

(26) Subject with abnormal coagulation.

(27) Subject with previously known immune compromise.

(28) Subject with history of gallstones or any gallstones/sludge observed at screening gallbladder echography (local assessment).

(29) Subject has been treated with any other IMP prior to the first study visit without undergoing a washout period of seven times the elimination $t_{1/2}$ of the investigational compound.

(30) Subject has a known hypersensitivity to any of the test materials or related compounds.

(31) Subject had abnormal findings during the screening period, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety or ability to complete the study.

(32) Blood donation within the last 3 months.

4.6 Randomisation

No randomisation list will be required for this open-label study. Subjects will be identified throughout the study with the subject number assigned at screening (see Section 3.3.2).

4.7 Discontinuation of an Individual Subject

4.7.1 Discontinuation / Withdrawal Criteria

All subjects are free to interrupt or withdraw their consent to participate in the study at any time, for any reason, specified or non-specified, and without penalty.

A subject may also be discontinued from the study upon Sponsor's and/or Investigator's decision for any appropriate reason, such as safety related to an adverse event or concomitant therapy, major protocol violation or deviation, noncompliance with protocol restrictions, etc.

The Sponsor and its representatives must be informed of all cases of discontinuation.

The criteria described in Table 3 on page 23 are for the discontinuation of study drug administration for reasons of safety.

For studies, with optional biobanking Subjects participating to the optional research biobanking program have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which the sample is kept). If a subject wishes to withdraw his consent for biobanking and the samples are still at the Investigator site at this time, the Investigator must inform the study monitor in writing of the subject's decision and destroy the samples. The study monitor will forward confirmation of the destruction to the repository leader in the Biomarker team.

If the samples are at the Sponsor's repository (central lab or the biobanking vendor), the Investigator must inform directly the Sponsor using following e-mail address PPD who will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the withdrawal, which will be forwarded to the Investigator.

4.7.2 Follow-up Procedures for Drop-out Subjects

In case a subject who has already taken study medication(s) drops out or is discontinued from the study earlier than study end, the end of study/early discontinuation (ED) visit (Visit 9) should preferably be done within 14 days of the last IMP administration. It is preferred not for it to be done on the day of discontinuation so that all safety events are captured that occur in the days after the last IMP administration and before the EoS/ED visit. However, if there is no option but to complete the EoS/ED visit on the day of discontinuation, then this is acceptable. The reason and date for drop-out should be documented.

Drop-out subjects will have completed their study participation when they have undergone all assessments of this last study visit (EoS/ED), and electronic case report form (eCRF) should be completed up to these last assessments.

Data collected prior to subject discontinuation may be kept in study records and shared with the Sponsor for study analyses (see Section 9) unless a subject formally specifies his/her decision to withdraw his consent for using data already collected before discontinuation.

4.7.3 Replacement Strategy

Subjects who drop-out from the study after IMP administration but before reaching last IMP administration on day 14 and its associated assessments will be replaced. The exception is if the drop-out is due to a safety or tolerability reason. As soon as 12 subjects (out of which at least 8 are Octreotide responders) reach Visit 8, withdrawn subjects will not be replaced.

4.8 Discontinuation of Study Site(s)

Study site participation may be discontinued if the Sponsor, the Investigator, or the ethics committee (EC) of the study site judges it necessary for any reason.

4.9 Discontinuation of Subject's Recruitment

Subjects' recruitment in the study may be stopped at any time upon Sponsor's decision, e.g. if actual data indicate that a sufficient number of subjects have already been enrolled in the study or for any other appropriate reason.

4.10 Study Termination

The study can be discontinued prematurely at any time if the Sponsor judges it for any appropriate reason. In that case, all scheduled procedures and assessment for subjects who are still in the study will be performed.

5 STUDY TREATMENT

5.1 Study Drug and Treatment of Subjects

5.1.1 Investigational Drug Formulation

Chemical Identity

BIM23B065 consists of one molecule of dopamine bound to one molecule of a peptidic SST analogue. It is a chimera of a D_2 and an SST2 receptor agonist.

Laboratory code: BIM23B065

INN: Not Applicable

Chemical formula: D-6-methyl-8β-Ergolinylmethyl)-thioethyl-cyclic [DLysyl-Arginyl-Phenylalanyl-4-Aminophenylalanyl-DTryptophyl-Lysyl-Threonyl-Tyrosyl]

Empirical formula: $C_{77}H_{101}N_{17}O_{10}S$

Molecular weight: 1456.8 g/mol

Dosage Form and Strength of BIM23B065

The IMP, BIM23B065, is an immediate release formulation to be administered by a bolus s.c. injection. The drug product is a clear to slightly opalescent and colourless to slightly coloured sterile solution filled in a clear glass vial with a rubber stopper.

The dosage strength is 1.0 mg/ml.

Investigational Medicinal Product Packaging and Release and Labelling

The Investigational Medicinal Product BIM23B065 will be packaged and released by the Beaufour Ipsen Industrie, Chemistry, Manufacturing and Control Supply Chain (CMC-SC) and delivered to the investigational sites or deposited in an Interim Storage Facility (ISF). A sufficient quantity of BIM23B065 will be supplied as well as an acknowledgement of receipt form. The Sponsor's representative will receive a Certificate of Analysis for the IMP batches of the study, and the Certificate of Compliance which reflects the product release statement and will provide them to the sites according to local requirements.

The core text for all packaging units will be translated and/or adjusted, to be in compliance with applicable regulatory requirements (e.g. Good Manufacturing Practice guidelines (Volume 4 Annex 13)), national laws in force and in accordance with the local languages. A non-exhaustive description of the core text of the IMP labels is displayed below:

- Sponsor name, address and telephone number (the main contact for information on the product and the clinical study),
- Study Number,
- Pharmaceutical dosage form,
- Route of administration,
- Quantity of dose units,
- Batch number,
- Treatment number,
- Subject Number,
- Investigator Name,
- Direction for use,
- "Keep out of reach of children",
- "For clinical trial use only",
- Storage conditions,
- Expiry date.

Storage

The Investigator, or designee (e.g. Pharmacist), will ensure that IMPs will be stored, and returned or destroyed according to applicable regulations. The IMP will be stored in a secured and locked area, under monitored conditions and at the recommended temperature (between +2°C and +8°C), in accordance with applicable regulatory requirements and any other specific instructions provided by the Sponsor. If IMP is taken home by the subjects, they will be instructed to keep the IMP in a refrigerator. All IMP will be administered by qualified staff members at the investigational site, or by a HCP outside the investigational site.

Supplies for this study will not be stored in such a way that they may be confounded with supplies being used for another study.

Investigational Drug Accountability

BIM23B065 will be provided to the Investigator, or designee (e.g. Pharmacist), and administered to subjects by appropriately trained study staff as described in Section 5.1.2.

The Pharmacist or assignee will record drug movement and accountability on specific drug accountability forms/logs. Study medication allocation, preparation and disposition records, as well as shipping, dispensing and returned drug records, and inventory logs must be maintained at the investigational site.

The dispensing for each subject will also be documented in the eCRF.

It is essential that all used and unused supplies are retained for verification by the Sponsor or designee who will ensure that BIM23B065 administration in the eCRF, the accountability forms/logs and the number of remaining used/unused treatments are consistent.

At the end of the study, all remaining IMPs will be preferably destroyed at the investigational site or return to CMC-SC (Beaufour Ipsen Industry – Dreux) for destruction (only if site is not able to do it). The destruction of used and unused BIM23B065 should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted by the Sponsor or designee.

5.1.2 Study Drug Administration

The Investigator, or designee, will only administer BIM23B065 to subjects enrolled in this study.

Each dose of IMP will be prepared and allocated to subject(s) according to the pre-determined dosing schedule agreed upfront with the Sponsor or designee.

Preparation Procedure

BIM23B065 will be supplied as a sterile solution in vials for s.c. injection, in one dosage strength at 1.0 mg/ml.

Administration Procedure

The Investigator, or an approved representative (e.g. pharmacist), will ensure that all BIM23B065 is administered by qualified staff members.

The study drug will be administered to the subject via s.c. injection in the abdominal region (intended volume of administration will be 0.4 ml, 0.6 ml, 0.8 ml and 1.0 ml). There will be a rotation of the injection sites in the abdomen between the left and right sides. BIM23B065 will be administered BID (morning dose and evening dose) or TID (morning dose, mid-day dose and evening dose) for the whole duration of the treatment period except on Day 14 when only the morning dose will be administered.

When the IMP is administered twice a day, there should be an interval of 12 hours (± 1 hour) between the morning and the evening doses.

When the IMP is administered three times a day, IMP should be administered every 8 hours ± 1 hour. First IMP administration in the morning should be around 8 a.m., second IMP administration should be around 4 pm and third IMP administration will be around midnight.

Section 6.1 has details of when BIM23B065 should be administered regarding food intake.

5.2 Blinding

Not applicable (open label study).

5.3 Product Complaint

Sponsor collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

The Investigator is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose.
- Faxing the completed product complaint form within 24 hours to Sponsor or designee.

If the Investigator is asked to return the product for investigation, they will return a copy of the product complaint form with the product.

6 STUDY RESTRICTIONS

6.1 Study Drug Administration

No food effect on IMP exposure has been demonstrated so far in the development of BIM23B065. In the interest of keeping food intake constant in case of effect on GH secretion/levels, breakfast is to be eaten within 1 hour of the morning dose – either 1 hour before or 1 hour after. Nevertheless, for each subjects, breakfast intake with regards to morning dosing should remain the same for the whole treatment period.

For the evening dose (BID administration) and for the afternoon and night dose (TID administration), there are no specific restrictions regarding food intake related to IMP administration. In the phase I healthy volunteer study, there were reports of abdominal pain in some subjects after the evening dose which was given in a fed state. There was less abdominal pain reported after the morning dose which was given in a fasted state. As a result, if a subject reports abdominal pain post-administration of BIM23B065, the evening injection (BID administration) or the afternoon and the night injection (TID administration) can be given when the subject is in a fasted state.

Episodes of hypotension were reported after IMP administration during the phase I study in healthy volunteers. It is recommended to ask the subject to remain lying down or sitting in a reclined chair for approximately 30 minutes after each dose before standing in order to minimise the risk of episodes of dizziness or syncope. After 30 minutes in supine/reclined position, the subject should be sitting for at least two minutes before standing.

6.2 Concomitant Therapy(ies)

Concomitant drugs or therapies are to be avoided during the study unless required to treat an AE or an ongoing medical condition.

Concomitant administration of bradycardia inducing drugs (e.g. beta-blocker) is not allowed, as it may inhibit compensatory increases in HR during any hypotensive episodes.

Clonidine, Alpha-blockers, Verapamil and Diltiazem, Amiodarone, Ivabradine and Anti-cholinesterase drugs should also not be allowed.

During the study, the Investigator should regularly check if the subject has received any concomitant medication/therapy that is not permitted at study entry.

Subjects will provide information about all previous medication taken over the last 3 months and investigational drug taken over the last year, and this information will be recorded on the appropriate eCRF.

Contraception

The inclusion of Women Of ChildBearing Potential (WOCBP) requires use of a highly effective contraceptive measure (5)

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
  - intravaginal
  - transdermal
- intra-uterin device (IUD)
- Intra-uterin hormone-releasing system (IUS) with no oestrogen

- bilateral tubal occlusion
- vasectomised partner[1]
- sexual abstinence[2]

One of the contraceptive methods is required for women with childbearing potential for the duration of the study, i.e. from enrolment until discharge from the study. In addition, subject will be asked to continue to use contraceptive method 3 months following the last dose of study drug.

6.3 Lifestyle Restrictions

Non Applicable for this study

1 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
2 Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

7 STUDY ASSESSMENTS

Timing of safety assessments, PD and PK sampling collection, and any other tests is specified in the attached study schedule of events table. Maximum blood volume for all tests and assays is also documented for each of the tests in the attached summary of blood collection volumes (See Section 15.3).

7.1 Safety Assessments

The Investigator is responsible for monitoring the safety of the subjects who have entered the study and to take appropriate action during the study concerning any event that seems unusual, as well as to alert the Sponsor or its assigned representative.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

The Investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the set up of a discharge plan if needed.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical study records throughout the study.

Safety Parameters

The following safety parameters will be collected during this study at specific time points described in the study schedule of events:

- Adverse events;
- Physical examination with oral/body temperature and body weight/height
- Vital signs, including HR, SBP and DBP
- 12-Lead ECG and 3-lead Holter
- Clinical safety laboratories, including clinical chemistry, haematology, HbA1c, insulin, glucagon and concurrent glucose.
- Endocrine parameters including, ACTH, Cortisol, LH, FSH, FT4, TSH and Testosterone (for male subjects only);
- Gallbladder echography,
- Anti-BIM23B065 Antibodies.

Further routine medical assessments or any additional safety procedures may be performed during the study, if warranted and agreed upon between the Sponsor and Investigator, or when clinically indicated.

Any clinically significant findings that result in a diagnosis should be recorded and commented on appropriate document.

7.1.1 Adverse Events

7.1.1.1 Definition

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

An AE can include an undesirable medical condition occurring at any time, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the EoS/ED.

7.1.1.2 Adverse Event Collection

AEs will be monitored from the time that a subject gives informed consent and throughout the study, and will be elicited by direct, nonleading questioning or by spontaneous reports.

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF.

Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the Investigator.
- The management of elevations in AST/ALT and/or bilirubin is detailed in the algorithm in Attachment 4 (Section 15.4). Should such elevations be detected during the study, the subject management algorithm is to be followed. The parameters in the algorithm in Attachment 4 correlate with the guidance in Table 3 in Section 3.1.

Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

Other Investigation Abnormal Findings

Abnormal test findings as judged by the Investigator as clinically significant (e.g. electrocardiogram changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

7.1.1.3 Adverse Events Assessment

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. IMP or other illness). The Investigator is required to assess causality and record that assessment in the eCRF.

Adverse events will be classified by the Investigator as mild, moderate or severe according to the following criteria:

- **Mild**: Symptoms do not alter the subject's normal functioning,
- **Moderate**: Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject,
- **Severe**: Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

If in the duration of an AE there is a change in intensity, each change will be recorded as a new episode of the AE.

The relationship of an AE to IMP administration will be classified by the Investigator according to the following:

- **Related**: Reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: Reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

The expectedness of an AE shall be determined by the Sponsor according to the current version of the IB.

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

If a subject's treatment is discontinued or changed as a result of an AE, study site personnel must clearly report to the Sponsor or its designee the circumstances and data leading to such decision.

7.1.1.4 Adverse Event Follow-up

If an AE is still present at the end of the study, reasonable follow-up clinical monitoring should be managed by the Investigator or any appropriate physician until event is resolved or stabilised at an acceptable level, as judged by the Investigator. The frequency of follow-up evaluation is left to his/her discretion.

7.1.1.5 Clinical Evaluation of Safety

All study drug and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the Investigator. Symptoms reported to occur prior to dosing will be distinguished from those reported as new or increased in severity during or after IMP administration. Each symptom will be classified by the most suitable term from a version of a medical regulatory dictionary agreed by the Sponsor and other parties involved in the study.

7.1.1.6 Serious Adverse Event Assessment

Definition

A SAE is defined as any adverse event that either:

(1) Results in death,

(2) Is life-threatening, that is any event that places the subject at immediate risk of death from the event as it occurs. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons,

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP,

(6) Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

(7) Other medically important conditions

In addition to the above criteria, any additional AE that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.

Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

SAE Collection and Reporting

Study site personnel must immediately (within 24 hours) report any SAE to the Sponsor using the contact details specified on the front page of the current document, independent of the circumstances, together with the Investigator's opinion of causality, as soon as it occurs or comes to the attention of the Investigator at any time during the study period.

Any SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the Sponsor:

- Study number,
- Investigational site identification,
- Subject number,
- AE,
- Investigator's name and contact details.

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. The Investigator should always provide an assessment of causality for each event reported to the Sponsor. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

7.1.1.7 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to IMP or procedure.

7.1.1.8 Pregnancy

Pregnancy tests will be performed in all female subjects of childbearing potential as specified in the schedule of assessments (See Section 15.1).

Information regarding pregnancies with a conception date either during the study period or within 3 months after dosing must be collected in the eCRF and reported to the Sponsor on a Standard Pregnancy Outcome Report Form.

The Investigator must instruct all female subjects to inform him/her immediately should they become pregnant. The Investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy. The Sponsor will request further information from the Investigator as to the course and outcome of the pregnancy using a Standard Pregnancy Outcome Report Form. Adverse consequences of a pregnancy will be regarded as SAEs.

If the Investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, this should be reported to the Sponsor. After the partner has given informed consent, she should be counselled and monitored until conclusion of the pregnancy.

7.1.1.9 Death

All AEs resulting in death either during the study period or within 1 months after dosing must be reported as a SAE.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction),
- Outcome: fatal.

The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be “death” or “sudden death”.

7.1.1.10 Reporting to Competent Authorities, IECs/IRBs and other Investigators

The Sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the Competent Authorities (CAs), Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and other Investigators concerned by the IMP.

Reporting will be done in accordance with the applicable regulatory requirements. The Sponsor must report all SUSARs to EMA’s EudraVigilance database within 15 days.

Fatal and life-threatening SUSARs should be reported within 7 calendar days, with another 8 days for completion of the report.

The Sponsor can prepare additional reports for other authorities (e.g. Food and Drug Administration (FDA)).

7.1.2 Physical Examination

Physical examinations will be conducted as presented in the Study Schedule of Events (see Section 15.1).

Clinically significant changes, in the judgement of the Investigator, in physical examination findings will be recorded as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

7.1.3 Vital Signs Assessments

Systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) will be assessed with an automated device so that measurements are independent of the observer. Body

Weight and body temperature will also be assessed and recorded as part of vital signs assessments. Height will be measured at Screening Visit only.

Blood pressures and HR will be measured as follows:

Automated blood pressure (ABP) will consist of a 5-hour post-dose period recording and should be started at least 1 hour pre-dose in the morning of the visit (recordings every 30 minutes). Recordings should be taken every 30 minutes for the first hour post-dose, then every 15 minutes for the second hour post-dose and every 30 minutes for the next 2 hours. ABP will be taken at visit 3 (Day -1 as baseline assessment and Day 1: to include the morning dose), visit 4 (Day 3: to include the morning dose), visit 5 (Day 5: to include the morning dose), visit 6 (Day 7: to include the morning dose), visit 7 (Day 10: to include the morning dose) and visit 8 (Day 14: to include the morning dose). The machine used for ABP measurements will be standardised across study sites with evidence of recent calibration. Recordings will be stored with the ABP machine and will be transferred to central reader as specified in a specific study manual.

At the times stipulated in the Study Schedule of Events (see Section 15.1), single measurement of supine blood pressure will be recorded on the hospital subject file and reported onto the eCRF. Single BP measurement will be obtained with the same machine used for ABP measurement. All BP assessments will be taken in triplicate.

Measurements of orthostatic blood pressure will consist of BP measurements of subject being standing for 2 minutes after at least 10 minutes supine. Orthostatic blood pressure timepoints are stipulated in the Study Schedule of Events (see Section 15.1).

Orthostatic hypotension will be defined as a decrease of 20 mmHg or more in SBP or 10 mmHg or more in diastolic blood pressure (DBP) from supine to standing or more than 30 bpm increases in pulse rate, after standing for 2 minutes from resting supine position of at least 10 minutes.

7.1.4 Electrocardiograms Assessments

A 3 lead Holter device will be used at visit 3 (Day -1 as baseline assessment and Day 1), visit 6 (Day 7) and visit 7 (Day 10). A continuous 24-hour post-dose period will be recorded and should be started at least 15 minutes pre-dose in the morning of the visit. The 24-hour period will cover two or three administrations of IMP (except for Day -1 where there will be no IMP administration, this assessment will be the baseline assessment). The Holter device can be removed immediately prior to the third (when BID administration) or fourth (when TID administration) scheduled administration of IMP.

At the times stipulated in the Study Schedule of Events (see Section 15.1), , 3 consecutive twelve-lead computerised standard ECGs, with paper printout, will be obtained whilst the subject is in resting supine position for at least 10 minutes. At Visits when IMP is administered, this assessment will be performed post-dose. ECG machines will be standardised between sites and ECG data analysed by a central reader in addition to the local analysis described below. All assessments will be performed in triplicate.

For each timepoint, computerised standard ECGs will be recorded so that the following parameters can be automatically calculated and reported on the ECG paper printout:

- Sinus rhythm,
- RR interval duration or HR,
- PR interval duration,
- QRS interval duration,

- QT interval duration,
- QT interval corrected by the Fridericia correction method.

Automated ECG interval data will be interpreted by a qualified physician at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, for immediate subject management. The qualified physician will document his/her review and interpretation (including evaluation of clinical significance in case of abnormality) on every ECG printout.

The paper printouts will be kept in the source documents at site. Only the interpretation and abnormalities after central review will be reported in the eCRFs for integration with other clinical study data. These paper ECGs may be subject to further review, if appropriate.

ECG analysis will be included as a safety evaluation/endpoint in this study.

Any clinically significant abnormalities will be recorded as AEs.

7.1.5 Clinical Safety Laboratory Tests

Blood will be collected for standard clinical laboratory tests, including biochemistry, haematology, as well as specific tests such as urine/serum pregnancy tests for women of childbearing potential) at timepoints indicated in the Study Schedule of Events (see Section 15.1).

The exact lists of parameters to be assessed are given in Section 15.2.

7.1.5.1 Urinalysis

Freshly voided urine samples (at least 10 mL) will be collected to perform a dipstick assessment of the parameters described in Section 15.2.

Microscopy will be performed, if indicated. If in the opinion of the Investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

7.1.5.2 Pregnancy Test

Human chorionic gonadotrophin (HCG) urine test will be performed for all female subjects of childbearing potential at Screening (visit 1), pre-dose (visit 3) and EoS (visit 9). It may be repeated at any time during the study according to Investigator's judgement.

In case of a positive urine test, a Beta-human chorionic gonadotrophin (ßHCG) serum test will be performed and if clinically indicated thereafter.

Any subject becoming pregnant during the study will be withdrawn from treatment. All pregnancies that occur during the study are to be reported as described in Section 7.1.1.8.

7.1.5.3 Investigator's Review

Investigators must document their review of each laboratory report by signing or initialling and dating each report. Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values will be evaluated.

When multiple laboratory values are out of range but not clinically significant, "all labs NCS" or a general comment may be written on the laboratory page. However, all clinically significant laboratory values must be individually marked with CS.

The Investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 7.1.1 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the

Investigator and the Sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

7.1.5.4 Sample Handling, Storage and Destruction

Full details related to the samples processing, labelling, storage, shipment, destruction procedures, methodology and reference ranges will be provided to the Investigator via separate instructions and archived in the Trial Master File (TMF).

Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards. Clinical laboratory tests will be performed by local laboratories (apart for urine pregnancy test).

7.1.6 Additional Definitions or Special Procedures

7.1.6.1 Gallbladder Echography

A Gallbladder echography will be conducted according to study site procedures for the evaluation of presence or absence of lithiasis or sludge as illustrated in the Study Schedule of Events (see Section 15.1). The results will be recorded in the eCRF specifically the presence or absence of biliary sludge or stones.

7.1.6.2 Anti-BIM23B065 Antibodies

Blood samples will be collected for the assay of anti-BIM23B065 antibodies timepoints illustrated in the Study Schedule of Events (see Section 15.1).

- Collect 2 mL of blood into a Silica clot activator collection tube at each time point.
- Allow the blood to clot for at least 30 minutes but no longer than 60 minutes at room temperature.
- Centrifuge blood samples at room temperature within 60 minutes of collection at 1300g for 10 minutes
- Transfer 2 times 500µl of separated serum immediately to 2x 1 ml Sarstedt-storage tube Store the samples within 1 hour at -20°C or below
- All study samples will be collected by a central laboratory and sent to BERTIN PHARMA.

Full details regarding the requirements for processing, labelling and shipment of these samples will be provided in separate instructions and archived in the TMF.

All samples collected for anti-BIM23B065 antibodies assessment may be stored for up to 3 months following the finalisation of the Clinical Study Report at the Sponsor designated laboratory in Europe. Any samples left 5 years after all subjects have finished the study will be destroyed with prior approval by the Sponsor.

7.2 Efficacy Assessment(s)

For this study, the primary PD and efficacy parameter will be GH.

Blood samples will be collected at timepoints indicated in the Study Schedule of Events (see Section 15.1).

Mean serum concentration of GH over 6 hours at Day -1, Day 7 and Day 14 will be calculated.

7.3 Pharmacokinetics Assessments

7.3.1 Pharmacokinetics Sampling Schedule

BIM23B065 and BIM23B133 serum concentrations at timepoints illustrated in the Study Schedule of Events (see Section 15.1).

7.3.2 Sampling Method for Pharmacokinetic Measurements

Sampling method will be as follow:

- Collect 7 mL of blood into a Li-Heparin containing collection tube at each time point.
- Blood samples will be placed immediately on melting ice.
- Centrifuge blood samples at 4°C within 60 minutes of collection at 2000g for 15 minutes at 4°C.
- Transfer 3 times at least 900µl of separated plasma immediately to 3x 2 ml Sarstedt-storage tube.
- Store plasma samples at -80°C.
- Sarstedt tube will be collected by a central laboratory and sent to Kymos
- There will be 2 separate shipments for primary (2 tubes) and backup (1 tube). The backup will be sent after the main have been received.

Specific details of labelling, sampling, storing and shipping procedures will be described in separate documentation, and provided by the Sponsor.

7.3.3 Bio-analytical Method

Plasma samples will be analysed to determine concentrations of BIM23B065 and BIM23B133 using a validated, specific and sensitive LC-MS/MS methods.

7.3.4 Pharmacokinetic Parameter Estimation

Analysis of PK data by noncompartmental approach will be documented by a separate analysis plan. Individual plasma concentrations for BIM23B065 and BIM23B133 will be listed and summarised by timepoints and dose level using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation assuming log-normally distributed data). Linear and semilogarithmics- plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

The following, but not limited to, PK parameters may be calculated on Day 7 and Day 14:

- C_{max}: Empirical peak plasma concentration after first dose.
- tmax: Empirical time of Cmax.
- AUCt: Area under the plasma concentration time curve within a dosage interval (0 to last measurable concentration) after the first dose.
- AUCτ: Area under the plasma concentration time curve within a dosage interval (0 to 24 hours) after the first dose.
- AUCinf: Area under the plasma concentration time curve extrapolated to infinity.
- AUC%ext: Percentage of AUC extrapolated.
- t½: Terminal elimination half-life.
- λz: Elimination rate constant.
- CL/F: Apparent total clearance of the drug from plasma after s.c. administration.
- Vz/F: Apparent volume of distribution during terminal phase after s.c. administration.

Additional exploratory model-based analysis using non-linear mixed effects model (population PK analysis) might also be conducted using specific software (e.g. NONMEM).

7.4 Pharmacodynamic Assessment(s)

For this study, the primary PD parameter will be GH.

The other PD parameters, IGF-1 and PRL concentrations will be regarded as secondary endpoints and used as supportive information to complete the efficacy evaluation.

Blood samples will be collected at timepoints indicated in the Study Schedule of Events (see Section 15.1).

All PD parameters will be assessed in a central laboratory. All details of sample collection, handling and shipment will be provided in the laboratory manual. Details of methodology and reference ranges will be provided in the TMF.

7.5 Pharmacokinetics/Pharmacodynamics Evaluation

To investigate the relationship between PD/safety variables (GH, IGF-1, PRL, blood pressure, HR) and PK exposure, exploratory PK/PD modeling might be performed if a relationship between BIM23B065 exposure and PD effect can be defined. Details regarding PK and PK/PD modeling will be described in a separate Pharmacometric Analysis Plan and results will be reported in a standalone report.

7.6 Optional Exploratory Assessment(s)

7.6.1 Tumour Tissue Receptors Profile

For subjects who have undergone pituitary surgery and who consent (on a separate and specific consent) paraffin-fixed tumour tissue (when available and in accordance with local regulations) will be collected for further analyses on correlation of the GH, IGF-1 and PRL responses with the expression of $SSTR_2$, $SSTR_5$ and D_2.

7.6.2 Biobanking

Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

Serum and plasma, whole blood samples for RNA and whole blood samples for DNA, are biobanked for future analysis of circulating markers, including proteins, pharmacogenetic and pharmacogenomic biomarkers and will only be collected for those subjects who have agreed to it by signing the specific informed consent form for the optional exploratory part of the study.

The biobanked samples will be stored for up to 15 years from the end of the study, to be made available for future research towards further understanding of (i) treatment response including, but not limited to, the safety profile, (ii) drug treatment mode of actions and (iii) disease understanding.

Instructions for collection, processing, handling and shipment of the samples banking are outlined in Section 15.5 and will be detailed in the laboratory manual.

Samples to be used for serum, plasma and whole blood for DNA, and whole blood for RNA, will be at timepoints indicated in the Study Schedule of Events (see Section 15.1).

Serum/Plasma Biobank for Biomarker Assessment

Total blood will be collected on specific dry tubes for serum isolation and frozen for storage. Further details of sample collection, coding and analysis will be provided in a laboratory manual.

Blood for DNA and RNA for Biobank

Blood will be collected in PAXgene DNA and RNA tubes, which have proprietary materials in them to preserve the integrity of the nucleic acids so only the recommended volume should be collected.

Further details of sample collection, coding and analysis will be provided in a laboratory manual.

7.7 Compliance to Study Procedures

7.7.1 Compliance to Protocol

Every attempt will be made to select subjects who have the ability to understand and comply with instructions. Noncompliant subjects may be discontinued from the study. The time and day of drug administration may be recorded. Drug accountability records will be maintained by the study site.

7.7.2 Compliance to Timing of Procedures

The specifications in this protocol for the timings and dates of primary tests are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor deviations within the allowed time windows specified in the Study Schedule of Events (see Section 15.1); however, the actual time must always be correctly recorded in the eCRF and other relevant source documents. Any excursion outside of these allowed time windows might be regarded as protocol violation.

Modifications may be made by the Sponsor to the time points based upon the safety/tolerability and PK information obtained. Any major modification that might affect the conduct of the study, subject safety, and/or data integrity will be detailed in a protocol amendment.

8 STATISTICAL ANALYSES

8.1 Data Analysis Plan

8.1.1 General Considerations

Statistical analysis will be performed by the Sponsor or designee selected Contract Research Organisation (CRO) according to ICH E9 guidelines and using SAS version 9.3 or higher. Further details of the statistical analyses will be available in a Statistical Analysis Plan developed by the CRO per Sponsor agreement and approval. All data will be listed and summarised for the BID (Stage 1) and TID (Stage 2) treatment regimen separately.

8.1.2 Analyses Population

The following populations will be used during statistical analyses:

- Safety population/Intent to treat (ITT): All subjects with at least one IMP administration
- Modified Intent to treat (mITT) population: All subjects in the Safety population with available pharmacodynamic data and no protocol deviations with relevant impact on PD data.
- Efficacy Evaluable population: All subjects in the mITT population with non missing evaluations of the primary efficacy criterion (mean concentration of GH over 6 hours) at baseline and V8 (+14 days post baseline).
- Per protocol (PP) population: All subjects in the efficacy evaluable population who complete the study and for whom no major protocol violations/deviations occurred.

8.1.3 Determination of Sample Size

The maximum sample size will be 24 evaluable subjects (12 per stage). Enrolled subjects who drop out of the study prior to Day 14 GH evaluation may be replaced. If 12 evaluable subjects have already completed visit 8 (Day 14) any subsequent withdrawn subjects will not be replaced.

A minimum of 8 of the 12 evaluable subjects must be responsive to a single test dose of octreotide pre-study defined as a >50% reduction in GH.

Per the primary endpoint, a subject is defined as a responder if the median concentration of GH over 6 hours is ≤2.5µg/l or if there is at least 50% reduction from mean baseline in GH at Day 14 (after 6 days titration plus 8 days treatment).

Based on the exact test for single proportion, twelve evaluable subjects per stage would be sufficient to have over 84% power, at a significance level of 0.05 (one sided) to reject the

- null hypothesis that there is no indication of efficacy of BIM23B065 if the GH responder rate is at most 33%, assuming that the GH responder rate is equal to 75%.

8.1.4 Primary Analysis

The primary efficacy variable is the percentage of subjects with mean GH ≤ 2.5 µg/l at V8 or at least 50% reduction in the mean change from baseline at V8 (14 days after first IMP administration) i.e. % GH responders. The mean serum concentration of GH is obtained for baseline and V8 from the non-missing serum concentrations of GH recorded over 6 hours on these days. The proportion of GH responders will be reported with its 90% confidence interval calculated using the exact Clopper-Pearson method. The null hypothesis that the GH responder rate is not clinically relevant will be rejected if the lower 90% confidence boundary is larger than 33%. Primary efficacy analysis will be based on the Efficacy evaluable population.

8.1.5 Study Participant Disposition

The numbers and percentages of subjects enrolled and included in the safety, ITT, mITT and efficacy evaluable populations will be tabulated. The reasons for subject exclusions from the populations will also be tabulated. In addition, the numbers of subjects who were treated, discontinued and completed will be tabulated.

Primary reasons for discontinuation of study treatment will be tabulated.

8.1.6 Study Participant Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographics including age categories 18-64 yrs and 65-75 yrs and baseline data (medical history, concomitant medications, etc.) will be presented by overall for the safety population(s).

8.1.7 Statistical Evaluation of Safety

Safety analyses and summary tables will be based on the safety population. Adverse events reported by investigators will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19 or higher Version).

All safety data will be included in the subject data listings. Listings of AEs will be presented by subject, system organ class and preferred term as well as whether the AE occurred during up titration or after and the corresponding dose at the time of AE occurrence.

All AEs and SAEs occurring during the Screening period will be reported;

A TEAE is defined as any AE that occurs during the active phase of the study if:

- it was not present prior to receiving the dose of BIM23B065, or
- it was present prior to receiving the dose of BIM23B065 but the intensity increased during the active phase of the study.

All TEAEs will be flagged in the AEs listings. The incidence of all reported TEAEs and SAEs as well as non SAEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

Concomitant medication will be coded by using the World Health Organisation (WHO) Drug Dictionary (December 2015 Version or higher) and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs (blood pressure and HR) and clinical laboratory tests at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. For the ECG parameters, clinically significant findings will be listed.

8.1.8 Pharmacokinetic Analyses and Statistical Inference

The PK data analysis will be performed independently by a CRO under the supervision of Ipsen's Pharmacokinetics and Drug Metabolism (PDM) Department as described in Section 7.3.4.

Individual listings and summary tables of BIM23B065 concentrations will be provided.

8.1.9 Pharmacodynamics Analysis

All PD data will be included in the subject data listings and summarised separately for the BID and TID regimen in the mITT set.

The following secondary response criteria will be defined on Day 7 and Day 14 based on the GH and IGF-1 profiles and their change from baseline:

- Mean GH ≤ 1.0 µg/l
- Mean GH ≤ 2.5 µg/l
- Mean GH reduction from baseline ≥ 50%
- Mean IGF-1 to <ULN (age normalised)

For all secondary responses, the number and proportion of responders will be summarised over time by BIM23B065 actual dose level and overall.

Individual profiles of GH, IGF-1 and PRL over time and their percent change from baseline will be summarised for each day separately in tabular and graphical formats.

Individual profiles and % change from baseline in other PD parameters such as ACTH, Cortisol, LH, FSH, FT4 TSH and testosterone will be also be summarised.

8.2 Preliminary and/or Interim Analysis

During each stage, interim and final analyses will occur after the number of subjects as presented in the table below complete their GH assessment on Day 14. The corresponding dosing arm (i.e. BID or TID) will be stopped for futility if the number of GH responders is not superior to the preset maxima, as defined in the Table 4.

Table 4 Maximum Number of GH responders to declare futility

Analysis occurs after # subjects with evaluable GH responder endpoint	Maximum number of GH responders to declare futility
6 (interim1)	2
8 (interim2)	3
12 (final)	7

If Stage 1 (BID) arm is stopped for futility, Stage 2 (TID) arm may be initiated, if warranted based on safety and tolerability. If final Stage 1 (BID) data show efficacy, Stage 2 will not be initiated. If Stage 2 arm is stopped for futility, the study will be terminated.

The maximum threshold of 2 for the interim futility stop after 6 subjects and the threshold of 3 after 8 subjects were determined based on the calculation of the predictive probability of failure at study end (6). Indeed, given the observed responders at interim time, we calculate the probability that the study will be a failure at the end of the stage, when 12 subjects will be available. Failure is when the lower bound for the Clopper-Pearson 90% confidence interval on GH responder rate does not exceed 33%. The distribution of responder rates for the 6 or 4 subjects yet to be recruited after the interim analysis 1 and 2, respectively, was estimated using a beta-binomial distribution with probability equal to the observed responder rate in the interim set and beta prior with parameters (a=0.5, b=0.5). The predictive probability of failure was at least 95% at both interims.

After 12 subjects, the threshold of 7 was set to the maximum number of responders so that the test would not be significant at the one-sided 5% level.

Ongoing DRC are planned during the study. Data review will be documented in a data/medical review plan. See description of DRC in Section 12.3.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Capture

The following source data may be generated and handled for further data basing process:

- Paper-based or electronic data captured in Case Report Forms
- Paper-based or electronic data captured systems, other than the case Report Forms
- Paper or electronic data from local or external vendors.

To ensure accurate, complete, and reliable data, the Sponsor or its representative will provide instructional material to the study site(s), as appropriate. Training session will be given during a start-up/initiation meeting for instructions on the completion/data entry of any source data documents and Case Report Forms.

The Investigators or their designees must verify that all data entries in the eCRFs are accurate and correct. If certain information is not available for a particular timepoint and/or subject, specific instructions should be followed, e.g. to document that the procedure was either not done (ND) or not applicable (NA).

Every effort should be made to ensure that all safety evaluations are completed by the same individual who made the initial baseline determination.

9.2 Data Handling

All or part of the data will be monitored at periodic visit to the study site, according to a monitoring plan. All entries in the eCRFs, corrections and alterations are to be made by the responsible Investigator or his/her designee.

Once monitored and cleaned, the paper-based data (either source or transcribed data) that have been selected for populating the database will follow a single entry process. Electronic data will be directly entered in the database.

Details of all data management procedures, from the initial planning to the archiving of final datasets / documents following database freeze/lock will be documented in appropriate data management and validation plan(s). Among others, these procedures will also describe quality control (QC) checks, data handling process for any missing, unused or spurious data, as well as coding procedures for AE's, medical history, non drug therapy and medications.

9.3 Record Keeping

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes.

Depending on the data collected and the type(s) of data, records will be kept following storage, and archiving procedures agreed by the Sponsor/Investigator site involved in this study, and in accordance to any regulations that are applicable in the country(ies) where the study is conducted.

10 REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. The Electronic Data Capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all local regulatory requirements.

10.1 Subject Information Sheet and Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

The subject information sheet and consent document will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the study and desires to participate.

The Investigator is ultimately responsible for ensuring that the EC-approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

10.2 Ethical Review Considerations

The following documents should be submitted to the relevant Ethics Committee(s) (EC's) for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the Sponsor,
- Currently applicable IB or package labelling,
- Relevant Investigator's curriculum vitae,
- Subject information and ICD(s) and form(s),
- Subject emergency study contact cards
- Recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the Investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the Investigator site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the Ethics Committee will be notified about the study completion.

10.3 Regulatory Considerations

This study will be conducted in accordance with applicable laws and regulations, GCPs, and the ethical principles that have their origin in the Declaration of Helsinki.

All or some of the obligations of the Sponsor will be assigned to a (CRO).

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

10.4 Final Report Signature

The Investigator or designee will proposed to review and sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusion of the report.

11 INSURANCE AND FINANCE

11.1 Insurance

The Sponsor declares that it has taken out a product liability insurance covering all subjects screened and enrolled in this study in respect to risks involved in the study.

11.2 Financial Agreement

Since this study is to be performed in partnership with a Contract Research Organisation (the CRO) in charge of project management and other CROs (third parties), separate financial agreements between the Sponsor and the CRO on one side, the CRO and third parties and the Investigator site(s) and the third party on the other side, will be signed prior to initiating the study, outlining overall Sponsor and Investigators responsibilities in relation to the study.

12 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will provide instructional material to the study sites, as appropriate. A start-up training session will be done prior to screening start to instruct the Investigators and investigational site staff. This session will give instruction on the protocol, the completion of the eCRFs, and all study procedures.

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal Investigator and the Sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations and Exceptions

Protocol deviations are defined and classified either Major or Minor for a given study. Major deviations (or combination of minor becoming major) may impact or not the analysis Population. All minor and major protocol deviations will be identified and recorded by clinical unit personnel and should be traceable

Major Protocol Deviation definition:

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC/IRB and which may affect the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Minor Protocol Deviation definition

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC/IRB but do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

As a matter of policy, the Sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the Sponsor and the responsible IRB/IEC is required before the subject will be allowed to enter the study.

If investigative clinical unit personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (Eligibility criteria deviation), they must immediately inform the Sponsor. Such subjects will be discontinued from the study treatment, except in an exceptional instance, following review and written approval by the Sponsor and the responsible IRB/IEC.

12.1.3 Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved).

The Investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members

must be listed on the clinical unit authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the Investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the Investigator or the study monitor.

12.2 Monitoring

The Investigator is responsible for the validity of all data collected at the site.

The Sponsor is responsible for monitoring these data to verify that the rights and well-being of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements.

Before the study initiation visit, the Sponsor assigned CRO will write a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed.

Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set up to ensure the Sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel.

Adequate time and space for monitoring visits should be made available by the Investigator.

The Investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested.

Quality of the paper-based or electronic data will be reviewed to detect errors in data collection and, if necessary, to verify the quality of the data.

The eCRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject's personal data (e.g. name, address, phone…) is present on a document required by the Sponsor (e.g. laboratory print outs) these data must be blacked out permanently by the site personnel, leaving the date of birth visible (or only the year of birth depending on local regulation), and annotated with the subject number as identification.

12.3 Data Review Committee

The DRC will be composed of the coordinating Investigator, the Sponsor drug safety physicians, the Sponsor medical director, the Sponsor clinical pharmacology representant and a statistician. Ad hoc members may be part of the DRC if required by the permanent members. A specific charter will be developed to define roles and responsibilities. Safety and efficacy data will be summarised and presented to the DRC.

For both the BID and the TID cohorts and for the first 3 subjects, the DRC will review the first 7 days safety data including blood biochemistry, blood pressure and ECG data. Once the DRC has approved the study to continue, subjects may be enrolled at a rate of a maximum of 3 subjects completing visit 3 per week.

During each stage (i.e. BID and TID cohorts), DRC will meet for interim and final analyses after the 6, 8 and 12 subjects have completed their GH assessment on Day 14.

Details of the DRC set up, membership, management and responsibilities will be provided in the DRC charter and archived in the TMF.

12.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a Quality Assurance (QA) personnel designated by the Sponsor, or by regulatory bodies. The Investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable Ethics Committee with direct access to any original source documents.

The Investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the Sponsor. The Sponsor should be notified of any projected delays, which may impact the completion of the study.

12.4.1 Audit and Inspection

Authorised personnel from external CAs and the Sponsor's authorised QA personnel may carry out inspections and audits.

12.4.2 Data Quality Assurance

All data Monitored will be reviewed (secondary monitoring) for completeness, consistency, and protocol compliance by the assigned data management group.

Reasons should be given in the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13 PUBLICATION POLICY

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a steering committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

14 REFERENCES

1. Alexandru Saveanu, Rakesh Datta, Shengwen Zhang, Yeelana Shen, Jesse Z Dong, Thomas Graillon, Celine Desfilles, Tanya Landsman, Heather A Halem, Alain Enjalbert, Anne Barlier and Michael D Culler. Novel Somatostatin-Dopamine Chimeric Compound Demonstrates Superior Efficacy in Suppressing Growth Hormone Secretion from Human Acromegalic Tumors Partially Responsive to Current Somatostatin and Dopamine Therapies. Poster Endocrine Society's 98th Annual Meeting and Expo, April 1–4, 2016.
2. Heather A. Halem, Shengwen Zhang, Rakesh Datta, Amy Bastille, Jeremy Beech, Marilyn Marques, Shraddha Patel, Yeelana Shen, Jesse Z. Dong and Michael D. Culler. A Novel Somatostatin-Dopamine Chimeric Compound Induces Dose-Related Suppression of GHRH-Stimulated Growth Hormone Secretion and Increases Insulin Sensitivity in Normal Rats. Poster Endocrine Society's 98th Annual Meeting and Expo, April 1–4, 2016.
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4. Investigator’s Brochure BIM23B065, Final Version No. 2.0, Dated 08 April 2016.
5. Guidance Clinical Trial Facilitation Group, Recommendations related to contraception and pregnancy testing in clinical trials, September 2014.
6. J Jack Lee and Diane D Liu. A predictive probability design for phase II cancer clinical trials. Clinical Trials 2008; 5: 93–106.

15 ATTACHMENTS

15.1 Attachment 1 – Study Schedule

Study Schedule of Events - Protocol D-FR-10380-002

	Screening			Treatment						End of Study
	V1	V2	V3	V3	V4	V5	V6	V7	V8	V9
Procedures and assessments	Screening	Octreotide test dose	Baseline Pre-dose	Post-1st dose	Up-titration	Up-titration	**Up-titration**		Primary endpoints	EOS/ED
Week	-3 to -1	-3 to -1	-1	1	1	1	2	2	2	4
Day	-21 to -7	-21 to -7	-1	1 and 2	3	5	7	10	14	28 ± 2
Informed consent	x									
Urine pregnancy test	x		x							x
Hospitalisation[1]			x	x						
Adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Demographic data	x									
Medical history	x									
Eligibility criteria	x	x	x							
Octreotide test dose		x[2]								
IMP administration[3]				x[4]	x[5]	x[5]	x[5]	x[5]	x[6]	
Gallbladder echography	x[7]									x
Physical exam[8]	x		x		x	x	x	x	x	x
12-lead ECG[9]	x		x	x	x	x	x	x	x	x
3-lead Holter ECG[10]			x	x			x	x		
Vital signs	x		x	x	x	x	x	x	x	x
Body Temperature			x							
Body Height, Body Weight[11]	x		x							x
ABP[12]			x[13]	x	x	x	x	x	x	
Blood Pressure (non automated) and HR	x		x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x
Orthostatic BP	x		x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	
Clinical Laboratory tests	x		x		x[16]	x[16]	x[17]	x[16]	x[16]	x
PK assessments							x[18]	x	x[18]	
PD assessments										
GH and PRL cycle	x[19]		x[20]				x[20]		x[20]	
IGF-1	x		x						x	x
Safety endocrine assessments										
ACTH, Cortisol[23], FSH, FT4, TSH, LH, Testo[21]			x[22]	x[22]			x[22]		x[22]	x

Procedures and assessments	Screening			Treatment						End of Study
	V1	V2	V3	V3	V4	V5	V6	V7	V8	V9
	Screening	Octreotide test dose	Baseline Pre-dose	Post-1st dose	Up-titration	Up-titration	Up-titration		Primary endpoints	EOS/ED
Week	-3 to -1	-3 to -1	-1	1	1	1	2	2	2	4
Day	-21 to -7	-21 to -7	-1	1 and 2	3	5	7	10	14	28 ± 2
HbA_1c	x		x						x	x
Insulin, glucagon and concurrent glucose[24]			x	x					x	
Pituitary tumour tissue collection[25]	x									
Biobanking[26]			x						x	x
Antibodies anti-BIM23B065		x[27]								x

1. Hospitalisation for 24 hours to include at a minimum pre-first dose baseline assessments up to the morning dose on Day 2 and post-dose assessments. For TID cohort hospitalisation will last the whole treatment period
2. Octreotide test dose with 100µg octreotide with 6 hours with GH sampling at -15 min, 1, 2, 3, 4, 5 and 6 hours post-octreotide dose
3. IMP will be administered twice a day (with an interval of 12 hours ± 1 hour between the morning and the evening administration) or three times a day (every 8 hours ± 1hour with first IMP administration around 8 am, second one around 4 pm and third one around midnight)
4. Both doses on Day 1 and morning dose on Day 2 (for BID regimen, if the subject returns home, evening dose of Day 2 to be administered by HCP at subject's home)
5. For BID regimen, morning dose only during visit and evening dose at home (if the subject returns home). For TID regimen all doses will be performed at hospital.
6. Final study IMP dose to be given in the morning at study visit. No evening dose will be administered (BID) nor the afternoon and the night dose for TID
7. Gallbladder echography performed at screening between Day -21 and Day -7
8. Physical examinations are to be performed prior to IMP injection
9. Twelve-lead computerised standard ECG whilst the subject is in resting supine position for at least 10 minutes. 3 consecutive ECGs will be obtained. At Visit 3 (at Day -1 and at Day 1), Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8, ECGs will be performed within 1 hour pre-dose and 30 minutes and 2 hours post-dose. At Visit 1 and Visit 9, only 1 set of 3 consecutive ECG will be obtained.
10. Three lead holter ECG will be recorded for 24 hour period starting at least 15 minutes pre-dose. The 24 hour period will cover two or three IMP administrations (BID in stage 1 and TID in stage 2). Assessment to be performed at Day -1 (for baseline assessment) Day 1, Day 7 and Day 10.
11. Body height only at screening. Body weight at screening, Day 1 pre-dose and Day 28.
12. Automated blood pressure will be taken starting at least 1 hour before the morning dose and will last for 4 hours post dose. Recordings should be taken every 30 minutes for the first hour pre and post-dose, then every 15 minutes for the second hour post-dose and every 30 minutes for the next 2 hours post-dose.
13. Automated blood pressure will be performed twice at Visit 3 at Day -1 (as baseline assessment) and at Day 1.
14. Supine blood pressure. At Visit 3 (both at Day -1 as baseline assessment and at Day 1), Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8, Blood pressure will be recorded 1 hour pre-dose then post-dose at : 30 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes and 2 hours.

15. Orthostatic BP At Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8, Blood pressure will be recorded 1 hour pre-dose then post-dose at : 30 minutes, 1 hour, and 2 hours. For Visit 5 and Visit 6 additional Orthostatic BP will be recorded on Day 4 and Day 6 respectively at the following timepoints; 1 hour pre and post evening (for BID) or 1 hour pre and post night (for TID) dose of Day 4 and Day 6
16. Clinical laboratory tests (including urine samples) at visits 4, 5, 7 and 8 should be done pre-dose in the morning
17. Clinical laboratory tests (including urine samples) at visits 6 should be done pre-dose in the morning and 6 hours post-dose (morning dose)
18. PK samples for BIM23B065 will be taken at visits 6 and 8 at pre-dose (-15 minutes), 0.5h, 1h, 2h, 4h and 6h post-morning IMP dose
19. PRL and Mean concentration of GH over 2 hours (5 samples at T0 then every half an hour up to 2 hours)
20. PRL and Mean concentration of GH over 6 hours means will be obtained with PRL and GH samples pre-dose (-15 minutes) and at 0.5h, 1h, 2h, 4h and 6h. For Visit 3 PRL and mean GH over 6 hours will be obtained at Day -1 (as baseline assessment)
21. Testosterone will be assessed for males only
22. Blood samples for ACTH, FT4, TSH, LH, FSH and testosterone will be taken at baseline pre-dose on Day -1, 1 hour post dose in the morning of Day 2 and 1 hour post. dose in the morning of Day 7 and Day 14.
23. Serum Cortisol will be assessed at baseline on Day -1 and and at Visit 9 (EOS/ED). Samples should be withdrawn at 8 am.
24. Samples at morning pre-dose in fasting condition, 2 h after first dose, 1 sample just before lunch and 1 sample 1h and 2h after lunch on Day -1, Day 1 and Day 14.
25. If tumour tissue is available and subject consents
26. Serum/plasma and whole blood for RNA (at Baseline (Day-1), Visit 8 (Day 14) and Visit 9 (Day 28) and whole blood for DNA (only at Baseline (Day -1))
27. Antibody sample to be taken prior to octreotide test dose

15.2 Attachment 2 –Clinical Laboratory Tests

	Scre	Main		Scre	Main
Haematology			**Clinical Chemistry**		
Haematocrit	x	x	Sodium	x	x
Haemoglobin	x	x	Potassium	x	x
Erythrocyte count (RBC)	x	x	Bicarbonate	x	x
Mean cell volume (MCV)	x	x	Chloride	x	x
Mean cell haemoglobin (MCH)	x	x	Calcium	x	x
Mean cell haemoglobin concentration (MCHC)	x	x	Phosphorus	x	x
Leukocytes (WBC)	x	x	Glucose (fasting) [a]		
Absolute counts of:			Amylase	x	x
Neutrophils	x	x	Lipase	x	x
Lymphocytes	x	x	Urea	x	x
Monocytes	x	x	Total cholesterol	x	x
Eosinophils	x	x	Total protein	x	x
Basophils	x	x	Albumin	x	x
Platelets	x	x	Total bilirubin	x	x
			Conjugated bilirubin	x	x
Coagulation			Alkaline phosphatase (ALP)	x	x
Activated partial thromboplastin time	x	x	Aspartate aminotransferase (AST)	x	x
Prothrombin time and derived measures of prothrombin ratio	x	x	Alanine aminotransferase (ALT)	x	x
International normalised ratio (INR)	x	x	Creatinine	x	x
			Gamma-glutamyl transferase (GGT)	x	x
Urinalysis [f]			Triglycerids (TG)	x	x
pH	x	x	Total creatine kinase	x	x
Protein	x	x	Glycated Haemoglobin (A1C)	x	x
Glucose	x	x	Insulin, concurrent Glucose and Glucagon	x	x
Ketones	x	x			
Bilirubin	x	x	**Endocrine**		
Urobilinogen	x	x	TSH	x	x
Blood	x	x	FT4	x	x
Nitrite	x	x	FSH	x	x
Microscopic examination of sediment (if indicated) [b]	Opt.	Opt.	ACTH	x	x
Pregnancy test[c]			Testosterone [g]	x	x
			Cortisol		
			LH	x	x

Scre = Screening visit(s), Main = Treatment Study Part and EoS/ED, Opt. = Optional

a Glucose measured in fasting

b will not be collected in the eCRF unless abnormal

c Urine pregnancy test at least at screening, predose and discharge from the study (EoS/ED). Serum pregnancy test will be performed only in case of positive urine pregnancy test.

f Urinalysis performed via dipstick.

G Only male

15.3 Attachment 3 – Blood Sampling Summary

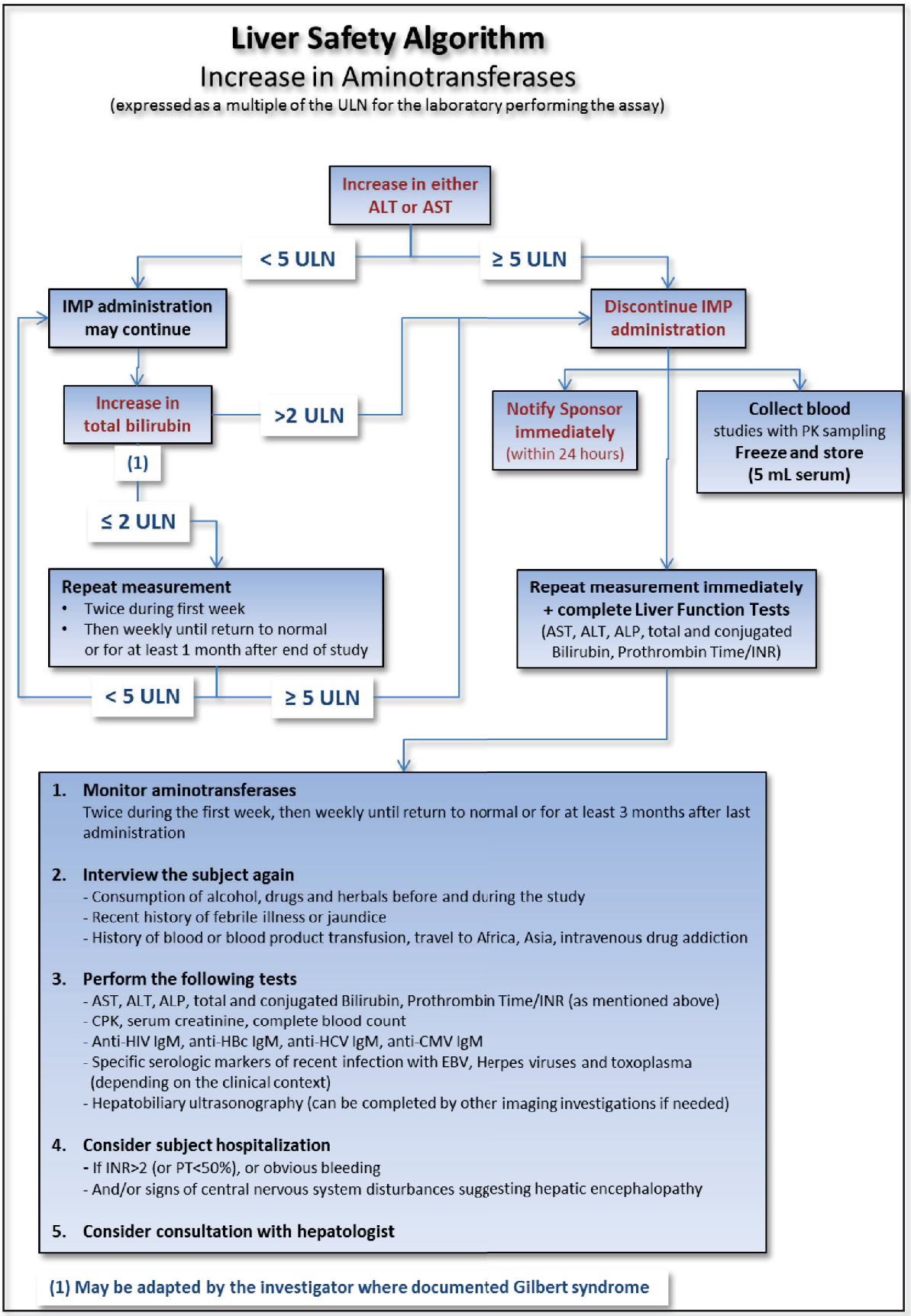
This table summarises the maximum number of (veni) punctures and blood volumes for all blood sampling (screening, safety laboratories and bio-analytical assays) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

Category	Description	Volume tube (mL)	Number of Samples	Total Volume (mL)
Safety	Haematology	4	9	36
	Biochemistry	8.5	9	76.5
	Coagulation	4.5	9	40.5
	HbA1c	3	4	12
	ACTH	2	5	10
	Cortisol, FT4, TSH, FSH, LH, Testosterone	3	5	15
	Insulin, glucose	2	15	30
	Glucagon	2	15	30
	BIM23B065 Antibodies	2	2	4
Biobank	Biobank serum	5	3	15
	Biobank DNA	8.5	1	8.5
	Biobank RNA	2.5	6	15
PK	PK	7	13	91
PD	GH, PRL	2	30	60
	IGF-1	2	4	8
Total volume				**451.5**

HbA1c = Haemoglobin A1c, FT4 = Free thyroxine, TSH = thyroid stimulating hormone, FSH = follicular stimulating hormone, LH = luteinising hormone, DNA = Deoxyribonucleic acid, RNA = Ribonucleic acid, PK = Pharmacokinetics, GH = Growth Hormone, IGF-1 = Insulin-like Growth Factor 1, PRL = Prolactin, ACTH = Adrenocorticotropic hormone

15.4 Attachment 4 – Liver Safety Algorithm



15.5 Attachment 5 - Biobanking

Biobanking involves the collection of blood samples. Blood samples will be collected only in subjects who have signed consent for the exploratory part, particularly for the biobank samples, during specific time points described in Section 15.1 (Attachment 1 – Study Schedule). One of the four blood samples will be centrifuged (serum sample); the three others will not be centrifuged (two blood samples in RNA PAXgene and one blood sample in DNA PAXgene tubes). The samples should be clearly and appropriately labelled with the following minimum information: study code, subject number, and visit name.

The samples will be stored at -80°C at the site or a central laboratory. The samples will then be shipped regularly to the biobanking central laboratory, FISHER, on dry ice. Upon receipt of each shipment with samples, an acknowledgment of receipt made out by the contact person will be sent to the site or the central laboratory. The samples will then be stored at the biobanking central laboratory, FISHER, for future exploratory biomarker analysis.

Samples will be stored for up to 15 years at the biobanking central laboratory, FISHER. After 15 years of storage any remaining samples will be destroyed. Samples may be destroyed earlier if subjects withdraw consent from the biobanking programme.

All the detailed procedures will be described in a separate laboratory manual.

Shipment contact and addresses FISHER (biobanking central laboratory)

Address: Fisher BioServices, 1 Woodside, Bishops Stortford, Herts, CM23 5RG, England

Phone: PPD

Fax: PPD

E-mail: PPD

15.6 Attachment 6 – Protocol Amendment Summary

All additions have been identified by the use of underline and all deletions by ~~strikethroughs~~.

Front page

Pharmacovigilance contact details:

PPD, Ipsen Biopharm Ltd

EU Qualified Person for Pharmacovigilance

102 Park Drive, Milton Park, Oxfordshire, OX14 4RY, England

Tel: PPD

Mob: PPD

Synopsis

- Endocrine parameters: Adrenocorticotrophic Hormone (ACTH), Cortisol, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Free Thyroxine (FT_4), Thyroid Stimulating Hormone (TSH) and Testosterone (for males only).

3.2.4 Safety Endpoints and Evaluations

• Endocrine parameters: Adrenocorticotrophic Hormone (ACTH), Cortisol, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Free Thyroxine (FT4), Thyroid Stimulating Hormone (TSH) and Testosterone (for males only).

4.5 Exclusion Criteria

Potential study subjects may not be entered into the study if any of the following apply:

…

(6) It is anticipated that the subject will undergo pituitary surgery or radiation to the pituitary gland during the study, or will require additional medical therapy for acromegaly (including SSA, pegvisomant, or dopamine agonists) during the study.

(7) The subject has unsubstituted/untreated adrenal insufficiency.

(8) If the subject has any history of postural hypotension or evidence of postural hypotension at screening (>= 20 mm Hg decrease in SBP, >= 10 mm Hg decrease in DBP, or >=30 bpm increases in pulse rate, after standing for 2 minutes from resting supine position of at least 10 min).

7.1 Safety Assessments

…

• Clinical safety laboratories, including clinical chemistry, haematology, HbA1c, insulin, glucagon and concurrent glucose.

• Endocrine parameters including, ACTH, Cortisol, LH, FSH, FT4, TSH and Testosterone (for male subjects only);

• Gallbladder echography,

8.1.9 Pharmacodynamics Analysis

…

For all secondary responses, the number and proportion of responders will be summarised over time by BIM23B065 actual dose level and overall.

Individual profiles of GH, IGF-1 and PRL over time and their percent change from baseline will be summarised for each day separately in tabular and graphical formats.

Individual profiles and % change from baseline in other PD parameters such as ACTH, Cortisol, LH, FSH, FT4 TSH and testosterone will be also be summarised.

Study Schedule of Events - Protocol D-FR-10380-002

	Screening			Treatment						End of Study
	V1	V2	V3	V3	V4	V5	V6	V7	V8	V9
Procedures and assessments	Screening	Octreotide test dose	Baseline Pre-dose	Post-1st dose	Up-titration	Up-titration	Up-titration		Primary endpoints	EOS/ED
Week	-3 to -1	-3 to -1	-1	1	1	1	2	2	2	4
Day	-21 to -7	-21 to -7	-1	1 and 2	3	5	7	10	14	28 ± 2
Informed consent	x									
Urine pregnancy test	x		x							x
Hospitalisation[1]			x	x						
Adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Demographic data	x									
Medical history	x									
Eligibility criteria	x	x	x							
Octreotide test dose		x[2]								
IMP administration[3]				x[4]	x[5]	x[5]	x[5]	x[5]	x[6]	
Gallbladder echography	x[7]									x
Physical exam[8]	x		x		x	x	x	x	x	x
12-lead ECG[9]	x		x	x	x	x	x	x	x	x
3-lead Holter ECG[10]			x	x			x	x		
Vital signs	x		x	x	x	x	x	x	x	x
Body Temperature			x							
Body Height, Body Weight[11]	x		x							x
ABP[12]			x[13]	x	x	x	x	x	x	
Blood Pressure (non automated) and HR	x		x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x
Orthostatic BP	x		x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	x[15]	
Clinical Laboratory tests	x		x		x[16]	x[16]	x[17]	x[16]	x[16]	x
PK assessments							x[18]	x	x[18]	
PD assessments										
GH and PRL cycle	x[19]		x[20]				x[20]		x[20]	
IGF-1	x		x						x	x
Safety endocrine assessments										
ACTH, Cortisol[23], FSH, FT4, TSH, LH, Testo[21]			x[22]	x[22]			x[22]		x[22]	x

Procedures and assessments	Screening			Treatment						End of Study
	V1	**V2**	**V3**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
	Screening	Octreotide test dose	Baseline Pre-dose	Post-1st dose	Up-titration	Up-titration	**Up-titration**		Primary endpoints	EOS/ED
Week	-3 to -1	-3 to -1	-1	1	1	1	2	2	2	4
Day	-21 to -7	-21 to -7	-1	1 and 2	3	5	7	10	14	28 ± 2
HbA_1c	x		x						x	x
Insulin, glucagon and concurrent glucose[24]			x	x					x	
Pituitary tumour tissue collection[25]	x									
Biobanking[26]			x						x	x
Antibodies anti-BIM23B065		x[27]								x

….

23. Serum Cortisol will be assessed at baseline on Day -1 and and at Visit 9 (EOS/ED). Samples should be withdrawn at 8 am.

15.2 Attachment 2 –Clinical Laboratory Tests

…

Microscopic examination of sediment (if indicated) [b]	Opt.	Opt.	ACTH	x	x
Pregnancy test[c]			Testosterone [g]	x	x
			Cortisol		
			LH	x	x

15.3 Attachment 3 – Blood Sampling Summary

Category	Description	Volume tube (mL)	Number of Samples	Total Volume (mL)
Safety	Haematology	4	9	36
	Biochemistry	8.5	9	76.5
	Coagulation	4.5	9	40.5
	HbA1c	3	4	12
	ACTH	2	5	10
	Cortisol, FT4, TSH, FSH, LH, Testosterone	3	5	15
	Insulin, glucose	2	15	30
	Glucagon	2	15	30
	BIM23B065 Antibodies	2	2	4
Biobank	Biobank serum	5	3	15
	Biobank DNA	8.5	1	8.5
	Biobank RNA	2.5	6	15
PK	PK	7	13	91
PD	GH, PRL	2	30	~~46~~60
	IGF-1	2	4	8
Total volume				**~~437.5~~451.5**

HbA1c = Haemoglobin A1c, FT4 = Free thyroxine, TSH = thyroid stimulating hormone, FSH = follicular stimulating hormone, LH = luteinising hormone, DNA = Deoxyribonucleic acid, RNA = Ribonucleic acid, PK = Pharmacokinetics, GH = Growth Hormone, IGF-1 = Insulin-like Growth Factor 1, PRL = Prolactin, ACTH = Adrenocorticotropic hormone