ACCELSIORS

STATISTICAL ANALYSIS PLAN (SAP)

A phase IIA, open-label, single-arm, two stage, multi-centre study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of repeated subcutaneous administration of BIM23B065 in subjects with acromegaly

Protocol version 2.0

		Signature	Date
Author:	PPD *Biostatistician II*	PPD	02 FEB 2017
Reviewed by:	PPD *Manager, Biostatistics*	PPD	02-FEB-2017
	PPD *Project Statistician, ClinBAY Limited*	PPD	02 FEB 2017
Approved by:	PPD *Chief Scientific Officer, Scientific Strategy*	PPD	02-FEB-2017
	PPD *Clinical Statistics Manager, IPSEN Pharma, SAS*	PPD	02 Feb 2017

Effective Date: *10-FEB-2017*	**Version:** **1.0**

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1. HISTORY OF CHANGES

All versions of the document have to be documented in the table of history of changes. The owner of the document has to act in accordance with the latest version of the document.

Status	Version	Effective Date (10-FEB-2017)	Change description
Current version	1.0		First version

2. ABBREVIATIONS

Acronyms, Abbreviations, Initials	Description / Explanation
ACC	Accelsiors CRO and Consultancy Services
ACTH	Adrenocorticotrophic Hormone
ADA	Anti-Drug Antibodies
AE	Adverse Event
BID	Bis in die (twice a day)
BP	Blood Pressure
BS	Biostatistics
CBC	Complete Blood Count
Core Review Team	Consists of Project Manager, Head of Drug Safety Unit, Clinical Data Manager, Biostatistician
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicities
DM	Data Management
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
DSMB	Data and Safety Monitoring Board
D_2	Dopamine Receptor Sub-type 2
ED	Early Discontinuation
EE	Efficacy Evaluable

Acronyms, Abbreviations, Initials	Description / Explanation
EoS	End of Study
FDA	United States Food and Drug Administration
FSH	Follicle Stimulating Hormone
FT4	Free Thyroxine
FU	Follow Up
GCP	Good Clinical Practice
GH	Growth Hormone
HR	Heart Rate
ICU	Intensive Care Unit
IGF-1	Insulin-like Growth Factor-1
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat Population
LH	Luteinizing Hormone
mITT	Modified Intent to Treat
NA	Not Applicable
PD	Pharmacodynamics
PK	Pharmacokinetics
PM	Project Manager
PP	Per-Protocol Population
PRL	Prolactin
QA	Quality Assurance
QC	Quality Control
RA	Regulatory Authority

Acronyms, Abbreviations, Initials	Description / Explanation
RNA	Ribonucleic Acid
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SMP	Study Management Plan
SOP	Standard Operating Procedure
$SSTR_2$	Somatostatin Receptor 2
$SSTR_5$	Somatostatin Receptor 5
TEAE	Treatment-emergent AE
TID	Ter in die (Three times a day)
TSH	Thyroid Stimulating Hormone
WIN	Work Specific Instruction

3. GENERAL

3.1. Distribution list

Statistical Analysis Plan is an Accelsiors confidential document.

Accelsiors: Complete SAP is distributed to Project Management.

IPSEN/Aepodia: Complete SAP is made available for Aepodia S.A. and Ipsen Pharma SAS for internal distribution.

3.1.1. Contact Details of Accelsiors Biostatistics team

Biostatistician	PPD Háros u. 103. 1222 Budapest Hungary	**Phone:** PPD **Fax:** PPD **E-Mail:** PPD
SAS Programmer	PPD Háros u. 103. 1222 Budapest Hungary	**Phone:** PPD **Fax:** PPD **E-Mail:** PPD

3.1.2. Contact Details of Vendors

Laboratory for PD Parameters	Institut für Laboratoriumsmedizin, Klinische Chemie und Molekulare Diagnostik Paul-List-Str. 13/15 04103 Leipzig	**Phone:** PPD **Fax:** PPD
Laboratory for PK Parameters	Kymos Pharma Services S.L. Parc Tecnològic del Vallès Ronda Can Fatjó, 7B 08290 - Cerdanyola del Vallès Barcelona	**Phone:** PPD
Laboratory for Immunogenicity Testing	Bertin Pharma Parc d'Activités du Pas du Lac 10 bis avenue Ampère 78180 Montigny le Bretonne - France	**Phone:** PPD

Supporter of Cardiac Safety Assessments	Biomedical Systems SA/NV Waversesteenweg 1945 Chaussée de Wavre 1160 Brussels, Belgium	**Phone:** PPD **Fax:** PPD

3.2. Scope

This SAP applies to all planned statistical analyses performed by Accelsiors Biometrics. Details regarding PK and PK/PD modelling will be described in a separate Pharmacometric Analysis Plan. Any other statistical tasks, which are not analysis-related (e.g. Protocol and CRF Review) are out of the scope of this plan. These tasks are described in detail in the applicable BS SOPs and WINs.

Activity/Task	*Sponsor/ 3rd Party Vendor*	*ACC*	*N/A*
Interim statistical analyses		X	
Final statistical analyses		X	
PK analysis	X		
PK/PD analysis	X		

3.3. Purpose

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-FR-10380-002. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analysis not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned analysis not identified in this SAP will be clearly identified in the respective CSR.

3.4. Preparation, Review and Changes to the SAP

The SAP will be prepared by ACC Biostatistician for submission to ACC PM and to the Aepodia S.A. and Ipsen Pharma SAS study team for review and input. Final approval is given by the ACC Chief Scientific Officer and by the head of statistics of Ipsen Pharma SAS. The SAP needs to be finalized before the first patient first visit.

SAP is subject to the periodic review as appropriate in relation to the trial status. The authoring, review and approval of SAP revisions will follow the same process as for the initial version. Review may result in possible extension, modification or replacement in the form of an Appendix, Amendment, or Revision.

The core review team is responsible for ensuring that after any changes all sections of the Statistical Analysis Plan will be harmonised.

3.5. Changes to the Protocol

In case the clinical study protocol undergoes a major amendment affecting statistical analyses procedures then a new version of the SAP will be issued.

Authoring, review and approval process of new SAP versions will be the same as for the initial version.

4. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Ipsen Pharma SAS protocol D-FR-10380-002 (A phase IIA, open-label, single-arm, two stage, multi-centre study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of repeated subcutaneous administration of BIM23B065 in subjects with acromegaly). This phase IIA study is being carried out to assess pharmacodynamics, safety and tolerability of BIM23B065 for the treatment of acromegaly. The structure and content of this SAP provides sufficient details to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol D-FR-10380-002 issued 27 July 2016.
- Clinical Study Protocol version 2, D-FR-10380-002 issued 14 September 2016.
- CRF Module Plan 1.1. for Protocol D-FR-10380-002.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

- To assess the pharmacodynamics (PD) of repeated administration of BIM23B065 in reducing growth hormone (GH) in subjects with acromegaly.

5.1.2. Secondary Objectives

- 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 (BP) and heart rate (HR).

5.1.3. Exploratory Objectives

- To correlate GH, Insulin-like Growth Factor-1 (IGF-1) and Prolactin (PRL) responses with expression of Somatostatin Receptor 2 ($SSTR_2$), Somatostatin Receptor 5 ($SSTR_5$) and Dopamine receptor sub-type 2 (D_2) in pituitary tumour tissues, when available.
- To assess anti-drug antibodies (ADA).

5.1.4. 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).

5.2. Study Endpoints

PD endpoints are primary and PK and safety are secondary endpoints in this study. PD and safety endpoints are further described below. PK endpoints, PK and PK/PD analyses are detailed in a separate Pharmacometrics Analysis Plan document.

5.2.1. Primary Endpoints and Evaluations

- The proportion of subjects with GH ≤2.5µg/l or >50% reduction from mean baseline GH (measured over 6 hours on Day -1) after 6-day titration plus 8-day treatment with BIM23B065 measured by mean serum concentration of GH over 6-hours on Day 14.

5.2.2. Secondary Endpoints and Evaluations

- Assessment of safety and tolerability.
- Assessment of 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.
- Determination of 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.

5.2.3. Exploratory Endpoints and Evaluations

- Assessment of ADA.
- Exploration of the relationship between response to BIM23B065 and the expression of SSTR2, SSTR5 and D2 in those subjects with available tumour tissue.

5.2.4. Safety Endpoints and Evaluations

- Adverse Events.
- Vital signs (supine and standing BP 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.

5.2.5. Pharmacodynamics and Pharmacokinetics Endpoints and Evaluations

- PD Assessments:

  - Mean serum concentration of GH over 6 hours at baseline (Day -1), 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.

5.2.6. 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).

6. STUDY METHODS

6.1. Overall Study Design and Plan

This is an open-label, non-randomised, multi-centre, 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. 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.

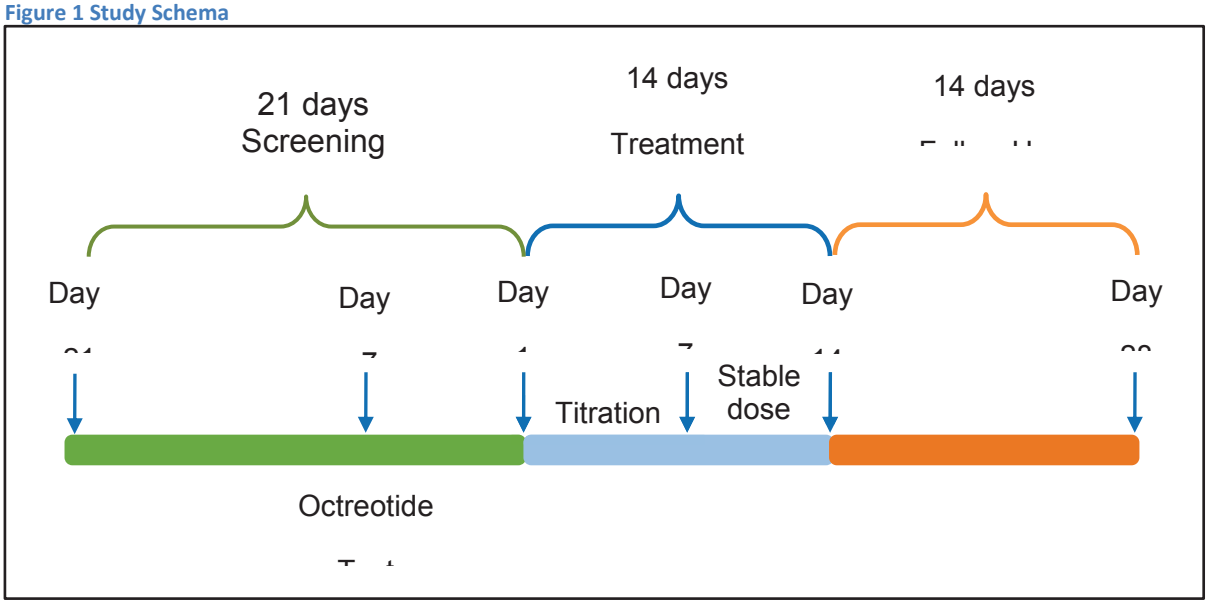
Any subjects who withdraw prior to the Day 14 end of treatment visit may be replaced except for early withdrawal due to safety and tolerability reasons. As soon as 12 subjects (out of which at least 8 are Octreotide responders as tested during the screening period) reach Visit 8, withdrawn subjects will 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 (for detailed description see Table 1 of the Protocol), they may have their dose reduced to the prior dose. The minimum dose allowed for the treatment period is 0.6mg BID or TID.
- If during the titration period, the subject experiences any cardiovascular events that meet the protocol determined criteria (for detailed description see Table2 of the Protocol), 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.

Figure 1 Study Schema



6.2. Selection of Study Population

The detailed description of the inclusion and exclusion criteria can be found in the study Protocol.

6.3. Method of Treatment Assignment and Randomization

No randomisation list will be required for this open-label study. Enrolled subjects will be identified throughout the study with the unique subject number assigned at screening.

7. SEQUENCE OF PLANNED ANALYSIS

7.1. Data Review Committee (DRC)

Details of the DRC set up, membership, management and responsibilities will be provided in the DRC charter and archived in the TMF. Safety and efficacy data will be summarised and presented to the DRC according to analyses planned in the DRC charter.

7.2. Interim Analysis

During Stage 1, two interim analyses are planned after 6 and 8 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 defined in the DRC charter.

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 2 below).

- If there are less than 3 out of 6 (3/6) 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 2).

If there is at least 3/6 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 evaluable 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 2).

If there are 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 (out of 12 subjects) then the Stage 2 will be initiated, where new enrolled subjects will follow the TID administration part (Option 3 in
- Figure 2).

If there are at least 8/12 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 as the primay objective is met with the BID regimen.

At any time during Stage 1 if at least 3 subjects experienced at least one dose limiting toxicity (DLT) (the definition of DLT can be found in the study protocol Table 3.) then the DRC will stop the recruitment and no TID administration part will be conducted.

During Stage 2, two interim analyses are planned after the first 6 and 8 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 below).

If there are less than 3/6 responders, then no new subjects will be enrolled into the TID administration part and the study will stop (Option 1 in Figure).

If there are 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).

If there are at least 4 responders, then 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).

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

Figure 2 BID administration part (Stage 1)

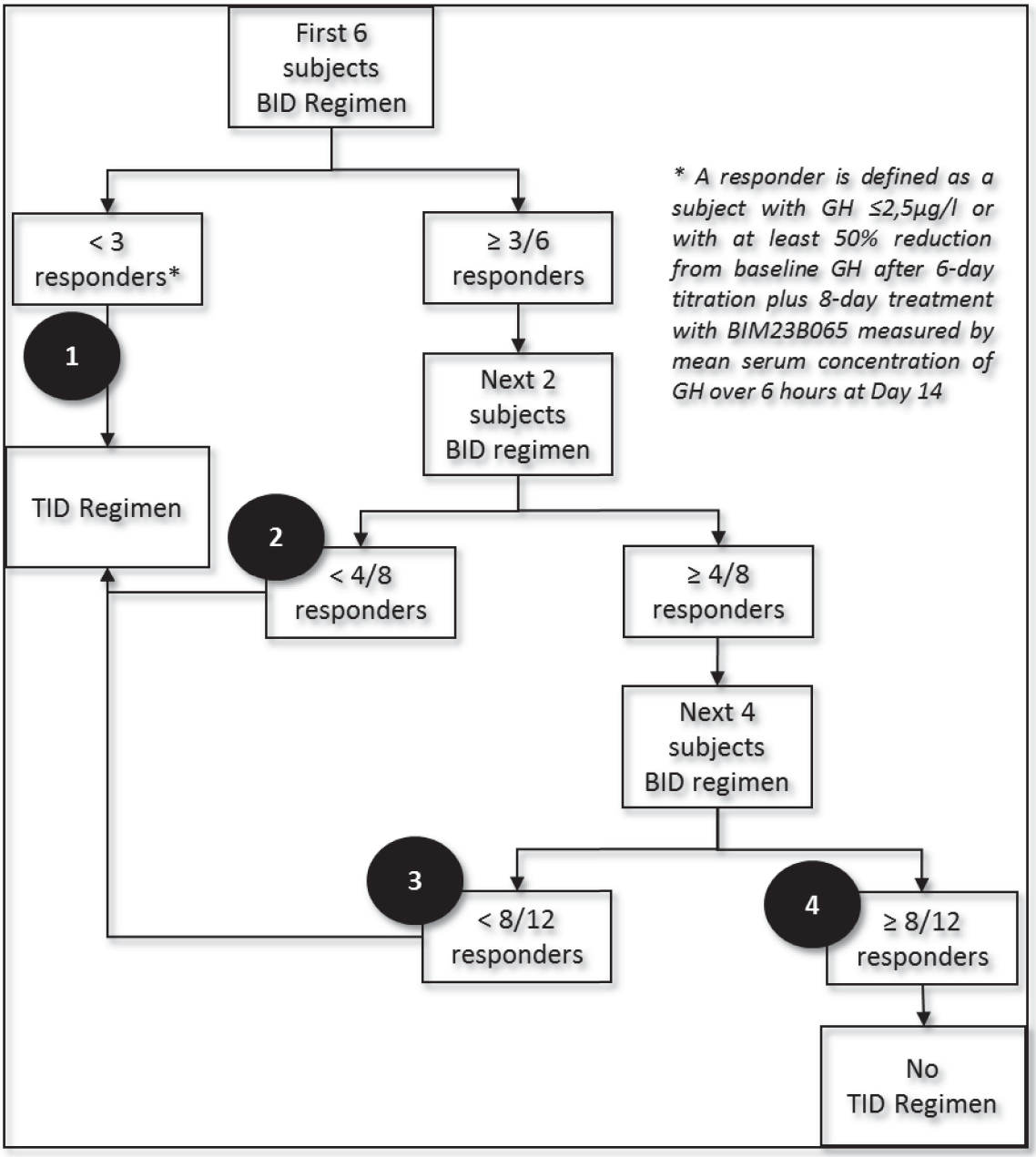
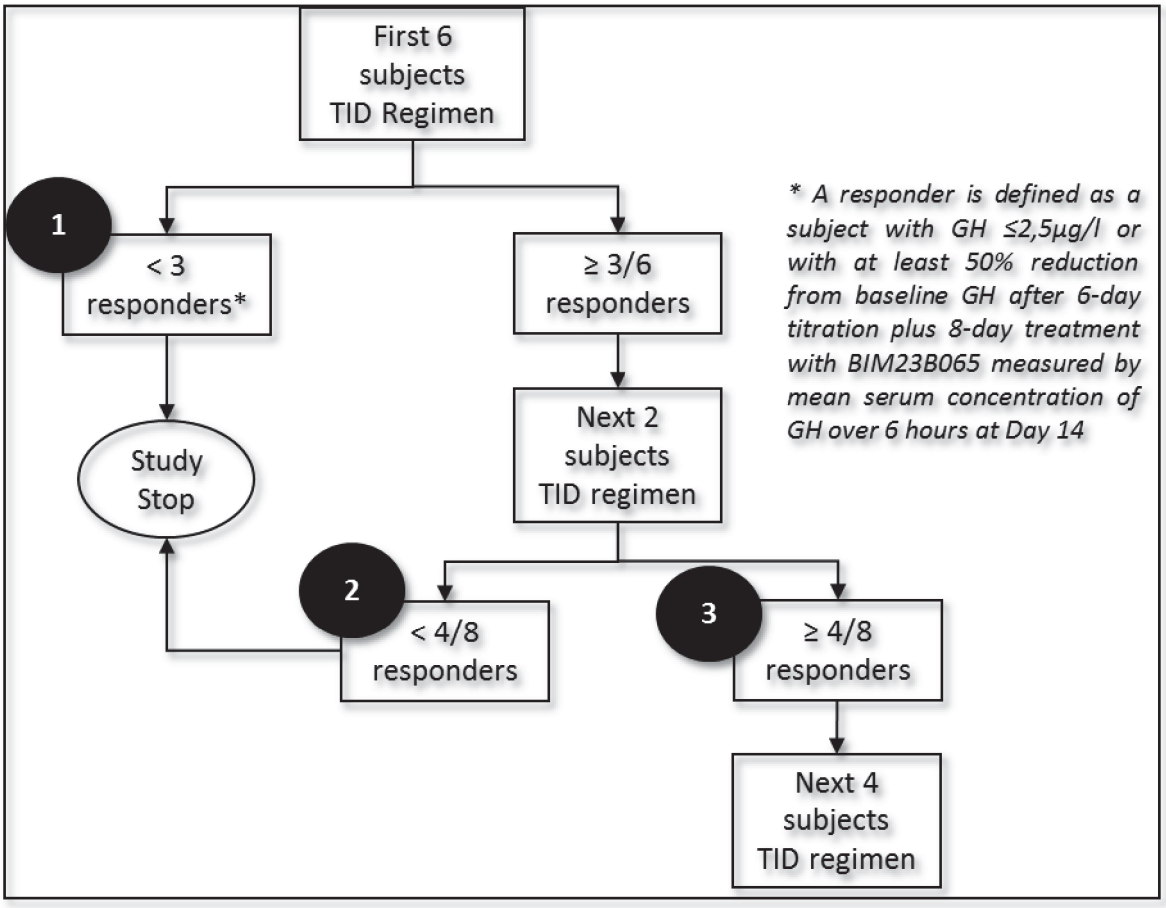


Figure 3 TID administration part (Stage 2)



7.3. Monthly blood pressure and 12-lead ECG report

On the second week of each month a report will be created presenting the blood pressure and ECG parameters for all subjects enrolled until the beginning of the month.

Systolic blood pressure, diastolic blood pressure and heart rate will be listed with visit days and time-points. The time-matched change from baseline (the same time-point on Day -1) will be calculated, and listed. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for the scheduled values and changes from baseline at each time point.

ECG parameters (RR interval, PR/PQ interval, QRS interval, QT interval, QTc interval (calculated according to the Fridericia method), and HR) will be listed at each visit and time point, along with their change from the time-matched baseline of Day-1. Descriptive statistics will be provided about the measured values and the calculated change of baseline.

Number and proportion of subjects with absolute QTc values above 460, 480 and 500 msec and subjects with a QTc change more than 30 and 60 msec from baseline will be presented at each time point.

7.4. Final Analyses

The study can be discontinued prematurely at any time if the Sponsor judges it for any appropriate reason, and for safety reasons, patients will not be dosed further.

In the final analyses all data will be listed for the BID (Stage 1) and TID (Stage 2) treatment regimen separately and summary tables will be created including the results of both stages.

8. SAMPLE SIZE DETERMINATION

A sufficient number of subject will be enrolled so that there is a maximum of 24 evaluable subjects for the primary analysis (12 per stage). Enrolled subjects who drop out of the study prior to Day 14 GH evaluation may be replaced so that 12 are evaluable per Stage. (Replacement strategy is detailed in Section 10.1.).

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 mean 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%.

9. ANALYSIS POPULATIONS

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 (EE) population: All subjects in the mITT population with an evaluable primary efficacy endpoint (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 (EE) population who complete the study and for whom no major protocol violations/deviations occurred.

9.1. Use of analysis populations in different analyses

Analyses	Safety population/ Intent to Treat Population	Modified Intent to Treat Population	Efficacy Evaluable Population	Per Protocol Population
Baseline Assessments (including demographics, disease characteristics, prior therapies)	✓		✓	
Compliance and exposure	✓	✓	✓	✓
PD Assessments		✓	✓	
Efficacy: Primary endpoint			✓	✓
Efficacy: Secondary endpoints			✓	✓
Safety (including concomitant therapies)	✓			

10. GENERAL ISSUES FOR STATISTICAL ANALYSIS

10.1. Definition of Treatment Arms

It is a single-arm study, all subjects will receive the same IMP, BIM23B065. Patients with the different dosing regimens (BID and TID) will be presented as “BID” and “TID” subjects.

10.2. Definition of Baseline

Most baseline assessments will be performed on Day -1 (Visit 3) with some exceptions. In case the data of the planned baseline assessment is not available, the last assessment which precedes the first administration of the IMP will be used as a baseline.

- For the GH and PRL calculations the mean serum concentration will be used as baseline, collected over 6 hours on the Day -1. The baseline IGF-1 will be measured on Day -1.
- For antibodies anti-BIM23B065 the baseline will be the serum concentration taken prior to octreotide test dose, on V2.
- For other laboratory assessments (all endocrine and clinical laboratory assessments, parameters of glucose metabolism etc.) baseline will be the measurement of Day -1. At the parameters of glucose metabolism more baseline values will be used in accordance to the fasting condition or the relative time from meals (the fasting condition on Day -1 will be compared with the fasting condition of the studied day, while the assessment one hour after meal will be compared to the baseline (Day -1) one hour after meal measurement etc.).
- For BP and HR, orthostatic hypotonia, and ECG, the baseline will be the corresponding measurements on Day -1 at the same time points (i.e. time-matched). For Holter the baseline will be the assessment on Day -1.
- For gallbladder echography, the baseline will be the assessment during the screening period.
- For other results of the physical examination (body weight, body temperature etc.) the D-1 assessments will be the baseline.

10.3. Definition of Visit Windows

There will be two stages. During Stage 1, the subjects will be enrolled to receive BIM23B065 BID, and during Stage 2, TID.

Both the BID and TID regimen parts will consist of 3 periods: screening, treatment, and follow up.

Screening period will start on the date of signing the informed consent and ends on the Day -1, the day preceding the first dose of IMP on Day 1. Treatment phase will start on Day 1 and ends with the Visit 8. Follow up phase starts on the following day of the Visit 8 and ends with the End of Study/Early Discontinuation visit.

Throughout the study 9 visits are planned (please see Study Schedule of Events in the Protocol). During the analysis visits will not be re-defined, eCRF visits will be used. Visits will be presented with the following labels: SCR (screening) D-1 (first day of Visit 3, pre-dose day), D1 – D14 (Day 1 is the first dosing day), EOS (End of Study day), ED (Early Discontinuation).

10.4. Multicentre Study

This is a multicentre study planned to be conducted in multiple centres from approximately 6 countries. No subgroup analyses are planned by country, the data of the sites will be pooled.

10.5. Planned Subgroup Analyses

Two age categories will be defined: subjects with 18-64 years age at baseline, and subjects with 65-75 years age at baseline. Descriptive statistics for the disposition, demographics, baseline characteristics, AE, primary and secondary endpoints will be prepared by age category and by octreotide responder category (responders/non responders).

10.6. Analysis Software

All analysis will be performed using SAS® Software version 9.3 or above.

10.7. Derived and Computed Variables

The following derived and computed variables have been initially identified. It is expected that additional variables could be required. The SAP will not be amended for additional variables unless they are directly related to the primary endpoint or key secondary efficacy variables. Any additional derived or computed variables will be identified and documented in the ADaM requirement documentation and/or in the footnotes of the outputs, where appropriate.

Variable Name	Description	Valid values (Ranges)	Computation methods, Notes or equation(s)
OTPDMEN	Mean GH over 6 hours after octreotide dosing during Octreotide Test	0-200 ug/L	= [SUM(GH measurements 1, 2, 3, 4, 5, 6 hours post octreotide dose)]/number of valid GH measurements
OTRBL	Reduction from Baseline in GH level during Octreotide Test	0-100 %	= [1- (OTPDMEN/ Baseline GH level)] x 100
GHMDX	Mean GH over 6 hours measured on DayX	0-200ug/L	= [SUM(GH measurements 1, 2, 3, 4, 5, 6)]/number of valid GH measurements over 6 hours on DayX]

Variable Name	Description	Valid values (Ranges)	Computation methods, Notes or equation(s)
GHRGL	Reduction from Baseline in GH level on DayX	0-100 %	= [1- (GHMDX/GHM(D-1))] x 100

As a general rule mean will be calculated by summarizing the available valid (non-missing) measurements and divided by the number of measurements. Percent change from baseline will be calculated according to the following: [1- (present value/baseline value)] x 100.

10.1. Methods for Missing Data

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 may be replaced. If the withdrawal is due to safety and tolerability reasons no replacement will be performed, but otherwise the subject will 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 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.

No substitution of missing values will be performed, an observed case approach will be used.

In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered. For example, if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data (e.g. stop date) indicates differently.
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on

31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

If the severity or the relationship to the IMP is not available for an AE it will be marked as 'unknown'.

11. STUDY SUBJECTS

Information on subjects of Stage BID and Stage TID will be presented in separately in lists and in the same tables.

11.1. Disposition of Subjects and Withdrawals

Disposition data will be listed for all subjects who entered this study.

A frequency table will be created displaying disposition of patients including:

- Total number of subjects entered (subjects who gave informed consent);
- Number of screening failures/withdrawals before enrolment
- Number of enrolled subjects
- Number of subjects in the ITT set (subjects who received at least one IMP administration);
- Number of subjects withdrawn after the treatment start date;
- Number of subjects completed the treatment phase;
- Number of subjects completing the study (including follow up);

Withdrawals/Discontinuations during the treatment period will be summarized by the coded term for main reason of withdrawal (patients with a reason recorded as "other" will have an own category). Subjects withdrawn will be listed along with the reason and date of discontinuation.

11.2. Protocol Deviations

Protocol deviations will be assessed from medical aspect during a data review meeting before database lock in order to decide on subject's eligibility to PP, EE and mITT populations. Protocol deviations will be classified as either minor or major. Details of protocol deviation evaluation will be provided in the study specific Protocol Deviation Handling Plan.

Protocol deviations per subjects will be listed along with the description of the deviation and 'minor' or 'major' evaluation flags.

11.3. Study Participant Disposition

The numbers and percentages of enrolled subjects included in the ITT, mITT, EE and PP populations will be tabulated. The reasons for subject exclusions from the populations will also be listed.

12. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

12.1. Demographics

Demographics will be presented descriptively for the ITT set.

Descriptive statistics for continuous variable (age at baseline in years) will comprise N, arithmetic mean, standard deviation, minimum value, median, maximum value and number of non-missing values. Age (in integer, years) will be calculated from the difference between the recorded exact or rounded date of birth and the date of informed consent.

Descriptive statistics for categorical variables (gender, race, ethnicity, age category) will comprise numbers of subjects and percentages in each category.

12.2. Drug Exposure

Incidence tables will present the actual doses per day. The descriptive statistics of the final and cumulative doses at the end of the titration and treatment periods will be presented. Total daily doses will be summarized and tabulated by day.

The administered and planned total daily doses of each day will be listed with the cumulative doses at the end of the titration and treatment periods.

Exposure time being the number of days when the subject received IMP will be summarized.

12.3. Prior and Concomitant Medications

Prior/concomitant medications will be coded using WHO Drug Dictionary (June 2016 Version or higher). These therapeutics will be listed by subject and by the second level of Anatomical Therapeutic Chemical (ATC) classification system code and ATC4 terms. Prior medication is defined as medication with a start date prior to the date of the first administration of the study medication.

12.4. Baseline and Screening Conditions

Ideally, in general, baseline control assessments will be performed on Day -1 (Visit 3), for detailed description please see Section 10.2.

12.4.1. Baseline Medical History

Medical history/current medical condition events will be coded using MedDRA 19.1 or higher. These events will be listed by subject and by system organ class (SOC) and preferred terms (PT).

The history of acromegaly will be detailed. Subjects will be listed with the date of acromegaly diagnosis, disease duration, the number of pituitary surgeries, the date, time since and the type of the last surgery and whether the patient is treatment naïve or not. Descriptive summaries will be presented for the main acromegaly characteristics.

12.4.2. Baseline Octreotide Test

Number and percentage of enrolled octreotide responders and non-responders will be presented.

All enrolled subjects will be listed along with their octreotide test results. The baseline GH level, the mean GH in the 6 hours after a single sub-cutaneous injection of 100ug octreotide, the reduction from baseline (in %) and the responder status will be presented. An octreotide responder is defined as having a >50% reduction from baseline in mean GH in the 6 hours.

12.4.3. Baseline Body Temperature, Height and Weight

Descriptive statistics for baseline vital signs (body weight, body height, body temperature along with the location of the measurement and D1 (predose) will be presented and the results will be listed.

12.5. Measurement of Treatment Compliance

Compliance factor will be determined for BIM23B065 on each day according to the following equation:

$$\text{Compliance (\%) (on a day)} = \frac{\text{Amount of BIM23B065 Administered}}{\text{Amount of BIM23B065 Expected to be Administered}} \text{ x } 100$$

$$\text{Overall compliance (\%)} = \frac{\text{Cumulative administerd BIM23B065}}{\text{Cumulative BIM23B065 Expected to be Administered}} \text{ x } 100$$

A subject will be considered as compliant on a day if its compliance rate is between 80 and 120%. It will be overall compliant if the overall compliance rate is within 80-120%.

The descriptive statistics of the compliance percentages and rates on each day and overall will be presented.

A by-patient listing will be created to display the compliance on each day and overall along with the presentation of any specific action that was applied during the dosing and the description of the reason for dose administration not occurred as planned.

13. EFFICACY ANALYSIS

13.1. Primary Efficacy Variable Analyses

The primary efficacy variable is the percentage of subjects who are GH responders on Day 14. GH response is defined as having a mean GH ≤ 2.5 µg/l at Visit 8 (Day 14, after 6-day titration plus 8-day treatment with BIM23B065) or at least a 50% reduction in the mean GH change from baseline on Day 14. The mean serum concentration of GH is calculated at baseline and on Day14 from the non-missing serum concentrations of GH recorded over 6 hours on these days. The number and 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 (i.e. <=33%) will be tested at the one-sided 5% significance level. The exact p-value will be reported. The test will be rejected if the lower 90% confidence limit is larger than 33%. Primary efficacy analysis will be based on the Efficacy Evaluable population.

13.1.1. Sensitivity and Supportive Analyses for the Primary Efficacy Variable

The primary efficacy analysis will be repeated on the Per Protocol Population, if the populations are different.

13.1.2. Subgroup Analyses

The number and proportion (%) of GH responders will be presented by age categories and by octreotide responders/non-responders. Confidence intervals will only be calculated for subgroups where the sample size N>2.

13.2. Secondary Efficacy Variable Analysis

The secondary efficacy endpoint analyses will be based on the Efficacy Evaluable and on the Per Protocol population.

13.2.1. GH responders

The following secondary GH response criteria will be defined on Day 7 and Day 14 based on the GH profiles:

- Mean GH ≤ 1.0 ug/l
- Mean GH ≤ 2.5 ug/l
- Mean GH reduction from baseline ≥ 50%

The GH measurements, their mean by visit, the mean percent changes from baseline and the various GH responder criteria will be listed by patient and visit. The number and proportion (90% CI calculated by the Clopper-Pearson method) of GH responders on Day 7 and Day14 will be reported.

Descriptive summaries will be presented for the measured GH values and for the calculated percent changes from baseline. Mean (+ SE) profiles over time will be displayed graphically.

13.2.2. PD endpoints

The IGF-1 and PRL measurements and the mean of the PRL concentration will be listed by patients and by visits along their change from baseline in percent.

Descriptive summaries will be presented for the measured concentration values and for the calculated percent change from baseline in the mITT set. Mean (+ SE) profiles over time will be displayed graphically.

The number and proportion (%) of subjects with IGF-1 < age normalized ULN, will be presented by visit along with the 90% Clopper-Pearson CI.

14. SAFETY AND TOLERABILITY ANALYSES

The safety analyses will be performed based upon the ITT population.

14.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 19.1 or higher version.

Only treatment-emergent AEs (i.e. AEs which occurred or worsened in severity during or after the first administration of a study drug) will be presented in tables. AEs occurred before the first administration of the study drug will be listed separately.

14.1.1. Summary of AEs

An overview AE summary table will be prepared presenting the number and proportion of subjects in the following categories:

- subjects reporting any adverse events
- subjects with Serious AEs (SAEs)
- deaths
- subjects with AEs leading to early withdrawal
- subject with severe AEs
- subjects with IMP-related AEs

A data listing of SAEs will be provided, displaying details of the event(s) captured on the eCRF. Serious adverse event narratives will be written by Accelsiors PV team and reviewed then by Aepodia S.A. and Ipsen Pharma SAS prior to be inserted in the CSR.

14.1.2. Deaths

The details of the event(s) captured on the eCRF will be supplied and narratives will be written by Accelsiors PV team and reviewed the by Aepodia S.A. and Ipsen Pharma SAS.

14.1.3. AE listings

All treatment-emergent AEs (TEAEs) will be listed by subject ID, presenting the start and end date of AE, the duration, as well as the period in which it occurred (titration/treatment), the last dose received prior to AE occurrence, classification by SOC and PT, severity, outcome, concomitant treatment, relationship to study medication (i.e. related or not related) and action taken.

AEs occurred before the first study drug administration will be listed separately.

A listing of AEs leading to withdrawal, SAEs, deaths will be provided, displaying details of the event(s) captured on the eCRF.

14.1.4. AE tables

Summary tables of number of subjects with TEAEs will be provided by PT in decreasing frequency, by SOC and PT and by SOC, PT and maximum severity. If a patient experiences more

than one AE within a preferred term, only the AE with the greatest intensity will be included in the summaries.

14.2. Cardiovascular Vital Signs

14.2.1. Blood Pressure and Heart Rate

All available measurements (i.e. systolic blood pressure, diastolic blood pressure and heart rate) will be listed with visit days and time-points. Abnormal values will be marked by bolding. The normality range for systolic blood pressure is 100-140mmHg, for diastolic blood pressure 60-90mmHg and for the heart rate from blood pressure measurements 60-100mmHg (inclusive of the borders).

The time-matched change from baseline will be calculated for all post-baseline scheduled measurements after D1 T0 that has corresponding measurement at the same time point on Day -1.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for the scheduled values and changes from baseline at each time point.

14.2.2. Orthostatic hypotonia

The diagnosis of orthostatic hypotension can be set if there is a decrease between the measurement in a supine position and standing position of ≥20 mmHg in SBP or a ≥10 mmHg in DBP or an increase ≥30 bpm in heart rate. By patient listing will be provided with the measurement pairs (supine – standing), the position how they were measured, the calculated difference between the supine and standing measurement. The values will be flagged if any criteria of orthostatic hypotonia was fulfilled.

Frequency tables will be created to present the proportion of subjects with orthostatic hypotension by visit, for each time point and overall. The number and proportion of orthostatic hypotension episodes will be summarized by visit.

14.2.3. 12-lead ECG

Detailed listing will be provided with all available data at each time point. Abnormal values will be marked by bolding, based on the normality ranges, provided by BMS. Normality range is 60-100 beat/minutes for heart rate, 120-200 ms for PR, ≤ 110 ms for QRS. For males the normal value for QTcF is between 360 and 450 ms, while for females 360 and 470 ms.

The mean of the ECG assessments will be calculated from the triplicates. The time-matched and predose changes from baseline will be calculated as follows:

- Time-matched changes: The time-matched mean replicated measurements of the Day-1 will be used as baseline.
- Predose changes: the mean of the triplicates of the pre-dose measurements (time point -1hour) on Day 1 will be used as baseline.

Descriptive summaries will be presented for the each ECG parameter on the mean replicated values and the changes from baseline (time-matched and predose) of RR interval, PR/PQ interval, QRS interval, QT interval, QTc interval (calculated according to the Fridericia method), and HR at each visit and time point.

A listing will be prepared for the interpretation of the ECG measurements recorded on the eCRF by visits and time points.

Subjects with clinically significant findings will be listed additionally along with the critical ECG parameter.

Number and proportion of subjects with absolute QTc values above 460, 480 and 500 msec and subjects with a QTc change more than 30 and 60 msec from baseline will be presented at each time point.

14.2.4. 3-lead Holter

All provided data (the start and stop time of the assessments, the recorded electrocardiographic measurements (ventricular rate, number of single VE beats, number of paired VE beats, number of VE runs of 3+ beats, total number of VE beats, number of single SVE beats, number of paired SVE beats, number of SVE runs of 3+ beats, total number of SVE beats, pauses (total pauses > 2 seconds) atrial fibrillation – Atrial Flutter, Second degree AV-block, Third degree AV-block), interpretation of clinical significance provided by the investigator) will be listed by patients and visit days. The interpretation will be summarized and presented in frequency tables by visit days, and in a shift table to present the change from baseline.

14.3. Clinical Laboratory Assessments

14.3.1. Haematology, Clinical Chemistry, Coagulation, Urinalysis

By patient lists will be provided with all measurements along with the unit, normal range, any deviation from it (High/Low/Abnormal values), and the relevance of being outside the normal range, identified by the investigator. Measurement results will only be presented in standard units.

Descriptive summaries will be presented for continuous clinical laboratory values. Categorical laboratory parameters will be summarized in frequency tables.

Laboratory measurements of patients with clinically significant abnormalities will be listed separately.

14.3.2. Parameters of the Glucose Metabolism

By patient lists will be provided with all measurements (HbA_1c, insulin, glucagon, concurrent glucose) along with the unit, normal range, any deviation from it, and the relevance of being outside the normal range, identified by the investigator. Visit labels will be provided describing the timing of the sampling to the dosing and to the meals.

Descriptive statistics will be presented (mean, SD, median, minimum, and maximum) by time points.

The change from the baseline value, measured pre-dose on Day-1 will be calculated and summarized in tabular and graphical formats for HbA_1c.

The time- and food status-matched change from baseline at insulin, glucagon and concurrent glucose will be calculated in the following way: every time point on Day 1 and Day 14 will have the own baseline value from Day -1, considering fasting conditions or their timing to meals.

Additional list will be created of patients with clinically significant abnormal values along with the abnormal parameter.

14.3.3. Antibodies to BIM23B065

A by-patient listing will be created containing the results of antibody assessments by visits.

A frequency table will be created to present the number and percentage of subjects developing antibodies, by visits.

14.3.4. Endocrine Parameters

By patient lists will be provided with all measurements along with the unit, normal range, any deviation from it, and the relevance of being outside the normal range, identified by the investigator.

Descriptive summaries will be presented from the measured values and from the calculated change from baseline (Day -1).

Additional list will be created of patients with clinically significant abnormal values along with the abnormal parameter.

14.4. Gallbladder Echocardiography

By patient list will be provided with all assessments and all time points. The presence of lithiasis and sludge, the result and the description of abnormality will be presented. The number and percentage of patient with lithiasis and sludge will be.

14.5. Physical Examination

Physical examination data will be presented in a by-patient listing along the reason if it was not done at each time point.

14.6. Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Subjects are to be discontinued from the study if they become pregnant.

15. OTHER PLANNED ANALYSIS

15.1. Pharmacometrics

Details regarding PK, and PK/PD modelling will be described in a separate Pharmacometric Analysis Plan.

15.2. Tumour tissue receptor expression and drug response

Subjects with available tumour tissue specimen will be categorized according to the SSTR2, SSTR5 and D2 receptor expression status. Incidence tables for tumour tissue categories will be presented.

The number and proportion of GH responders, subjects with an IGF-1<ULN (age normalized) on Day 14, and subjects with a PRL<ULN (gender normalized) on Day 14 will be presented by the receptor expression status.

15.3. Biobanking

Subjects who consented for biobanking will listed along the blood sampling date, time and type of collected sample (serum, DNA, RNA).

16. DEPARTURES FROM THE ANALYSIS PLANNED IN THE PROTOCOL

As a per protocol secondary endpoint the efficacy of BIM23B065 in reducing IGF-1 to <ULN (age normalized) will be assessed after 6 day-titration and 8-day treatment period at Day 14. A minor change will be implemented in SAP in the IGF-1 profile assessment, since it won't be assessed on Day 7. As a secondary response criteria IGF-1 profiles will be defined on Day 14 to be in accordance with the per protocol determined endpoints and with the collected laboratory data determined in the Study Schedule of Events.

17. LIST OF APPLICABLE QUALITY DOCUMENTS

17.1. List of Relevant SOPs and WINs

Document Code	Title	Effective Date
SOP-BS-004	Sample Size Determination	03Dec2014
SOP-BS-005	Statistical Analysis Plan	12Nov2015
SOP-BS-008	Statistical Analysis and Programming	12Nov2015
WIN-BS-030	Conventions for Statistical Programming	03Dec2014

18. REFERENCES

No.	Designation/ Code/Appendix	Title
1.	ICH E9	ICH Harmonised tripartite Guideline: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS E9
2.	ICH E3	ICH Harmonised tripartite Guideline: STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS E3

No.	Designation/ Code/Appendix	Title
3.	ICH E14	ICH Harmonised tripartite Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
4.	ASA	Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999 http://www.amstat.org/committees/ethics/index.html
5.	RSS	The Royal Statistical Society: Code of Conduct, August 1993. http://www.rss.org.uk/main.asp?page=1875
Comments:		