TRIAL STATISTICAL ANALYSIS PLAN

c17409411-02

BI Trial No.:	1351.1
Title:	An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients Including revised Protocol Amendment c02587386-04
Investigational Product:	BI 836909
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	07 Sep., 2018 SIGNED
Version:	Revised

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the tSAP

Term	Definition / description
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCMA	B-cell maturation antigen
BI	Boehringer Ingelheim
BRPM	Blinded Report Planning Meeting
CR	Complete response
CRS	Cytokine release syndrome
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLT	Dose limiting toxicity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DOR	Duration of response
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMWG	International Myeloma Working Group
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MRD	Minimal residual disease
MTD	Maximum tolerated dose
PD	Progressive disease

Term	Definition / description
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
PD	Protocol deviation
Q1	Lower quartile
Q3	Upper quartile
RPM	Report planning meeting
SC	Safety committee
sCR	Stringent complete response
SOC	System organ class
TSAP	Trial statistical analysis plan
VGPR	Very good partial response

3. INTRODUCTION

As per ICH E9 [1], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 or newer version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary objective is to assess the safety of BI 836909 in humans and to determine the maximum tolerated dose (MTD). The primary endpoints are the following:

- MTD of BI 836909: MTD is defined as the highest dose of the dose level tested where ≤ 1 patient out of 6 develops dose limiting toxicity (DLT)

- Number of patients with DLTs

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

This section is not applicable as no key secondary endpoints have been specified in the protocol.

5.2.2 Secondary endpoints

- Objective response rate (percentage of patients with stringent complete response (sCR), complete response (CR), partial response (PR) and very good partial response (VGPR))
- Duration of response (DOR)
- Minimal residual disease (MRD)
- Duration of MRD response
- Progression-free survival (PFS)

Secondary pharmacokinetic endpoint is:
- Serum concentration at steady state (C_{ss}) for c.i.v.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Patients are administered BI 836909 as a continuous 4-week infusion followed by a 2-week break for 5 cycles or until progression, unacceptable adverse events or other reason necessitating withdrawal. In case of ongoing clinical benefit a maximum of 5 additional treatment cycles can be given.

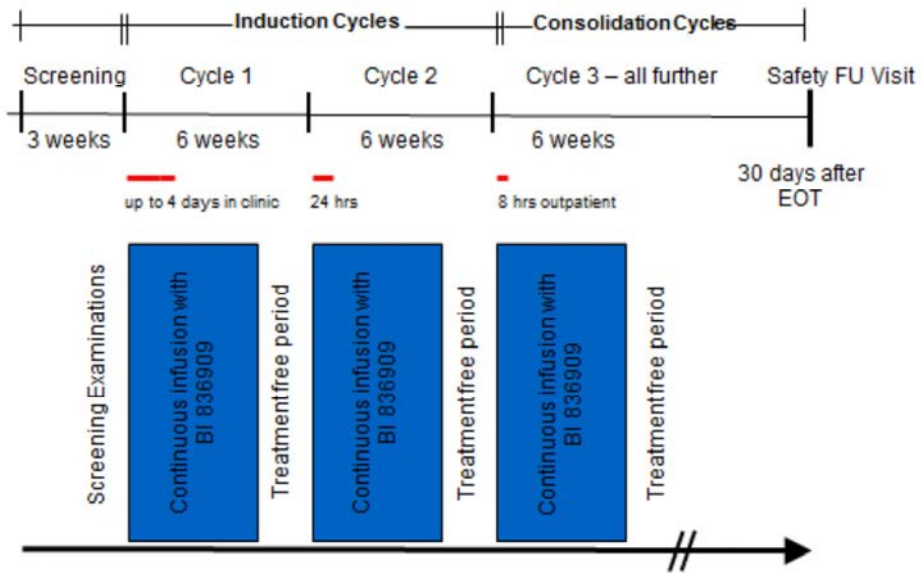


Figure 6.1:1 Overall study design

For all analyses, statistics will be tabulated by treatment dose group (see Table 6.1: 1).

Table 6.1: 1 Treatment labels for use in the CTR

Treatment label	Short label
BI 836909, 0.2 µg/d, c.i.v.[1]	0.2 µg/d civ
BI 836909, 0.4 µg/d, c.i.v. [1]	0.4 µg/d civ
BI 836909, 0.8 µg/d, c.i.v. [1]	0.8 µg/d civ
BI 836909, 1.6 µg/d, c.i.v. [1]	1.6 µg/d civ
BI 836909, 3.2 µg/d, c.i.v.	3.2 µg/d civ
BI 836909, 6.5 µg/d, c.i.v.	6.5 µg/d civ
BI 836909, 13 µg/d, c.i.v.	13 µg/d civ
BI 836909, 25 µg/d, c.i.v.	25 µg/d civ
BI 836909, 50 µg/d, c.i.v.	50 µg/d civ
BI 836909, 100 µg/d, c.i.v.	100 µg/d civ
BI 836909, 200 µg/d, c.i.v.	200 µg/d civ
BI 836909, 400 µg/d, c.i.v.	400 µg/d civ
BI 836909, 800 µg/d, c.i.v.[2]	800 µg/d civ

[1] The 1st four treatment label (0.2 – 1.6 µg/d) may be combined into one column for selected displays.

[2] Further doses will be tested in case that MTD could not be confirmed at a dose level of 800 µg/day. Intermediate doses cohorts will be entered if determined by the safety committee, for example, in case that the dose cohort 400 µg/day exceeds MTD (>1 patients out of 6 with DLT) and no DLT is observed on 200 µg/day, 300 µg/day might be considered.

The purpose of the definition below is to describe the different study interval in this trial.

The treatment periods of the study are:

- Screening period:
  The screening period starts from the date of informed consent and ends at the date of the first administration of study drug.

- Treatment period:

Treatment period starts from the date of the first administration of study drug and ends at the date of the last administration of study drug.

- Residual effect period:

  Residual effect period starts from the date of the last administration of study drug + 1, and ends at the date of the last administration of study drug + 30 days .

- Follow-up period;

  The Follow-up period starts from the last administration of study drug + 30 days.

Please see Table 6.1:2 below, for a definition of treatment periods. The purpose of the definitions below is to describe the treatment periods in this trial.

Table 6.1: 2 Definition of treatment periods

Analyzing Treatment Period	Start Date	Start Time	End Date
Screening	Date of informed consent		Date of the first administration of BI 836909
Treatment	Date of the first administration of BI 836909	Time of the first administration of BI 836909	Date of the last administration of BI 836909
Residual effect period	Date of the last administration of BI 836909 + 1 day		Date of the last administration of BI 836909 + 30 day
Post-treatment	Date of the last administration of BI 836909 + 31 day		Not applicable

For safety analyses, adverse events (AEs) will be classified to one of the following time periods: “Screening”, “Treatment”, or “Post-treatment”. Section 5.2.2 of the protocol specifies that all AE reported within 30 days of the last trial medication will be considered on treatment. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date of first administration of BI 836909, then the AE is assigned to “Screening”;

- If date of first administration of BI 836909 ≤ AE onset date ≤ date of last administration of BI 836909 + 30 days, then the AE is assigned to “Treatment”;

- If AE onset date > date of last administration of BI 836909 + 30 days, then the AE is assigned to “Post-treatment”.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurements in a non-negligible way. Patients with important PDs that could potentially impact the evaluation of the primary endpoints will be excluded (Refer to Section 6.3 Table 6.3:1).

A list of important PDs is given in Table 6.2: 1 below. Important PDs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will be discussed at the Blinded Report Planning Meeting (BRPM).

If the data show other important PDs, this table will be supplemented accordingly at MQRMs or RPMs or through team review of the manual PD log. The decision whether a patient will be excluded from the analysis will be made at the final BRPM prior to DBL.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1	**Inclusion criteria not met**		
	A1.1	Disease severity for MM not met	Inclusion criteria (IN) 1 or 3 not met.	None
	A1.2	Disease measurability not met	IN 2	None
	A1.3	Requirements on ECOG status, age, ability to adhere to study visit schedule not met	IN 5 or 6 not met	None
	A2	**Exclusion criteria met**		
	A2.1	Certain prior or current disease conditions.	Exclusion criteria (EX) 1, 2, 3, 23, 24 or 25 met	None
	A2.2	Last anticancer or investigational treatment, transplantation	EX 4, 6, 7 or 21 met	None
	A2.3	Pregnancy / breast feeding / contraception related	EX 17, 18 or 19 met	None
	A2.4	Clinical relevant concurrent medical disease, infections or conditions	EX 9, 10, 11, 12, 13,14, 15 or 16 met	None
	A2.5	Hypersensitivity to investigational drug	EX 22 met	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after Screening Visit date	None
	B3	Outdated informed consent signed	e.g., Outdated version of informed consent with major change	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Medication kit assigned not matching IVRS assignment	None

Table 6.2: 1 (continued) Important protocol deviations

Category / Code		Description	Requirements	Excluded from
	C2	Non-compliance with BI 836909	Any patients with non-compliance issues as defined in Section 5.4.2 or other issue related such as manipulation of bump by patients.	None
	C3	Improper preparation or administration of BI 836909 for IV infusion	Create listing, decision at MQRM / RPM, see CTP Section 4.1.4 for drug preparations and mandatory pre-medications. Check comment in the eCRF.	None
D		**Concomitant medication**		
	D2	Prohibited medication use concomitantly with study medication	• Chronic oral use of NSAIDs • Chronic systemic use of corticosteroids • Quinidine • Cytotoxic/myelosuppressive, immunologic drugs or radiation therapy	None
F		**Other category**		
	F1	Other trial specific	Other protocol deviations deemed to be IPD from manual PD log, e.g., multiple procedures not performed correctly.	None

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations. All final decisions as to whether any deviation is relevant will be taken at the RPM.

6.3 SUBJECT SETS ANALYSED

All entered subjects who received trial medication will be included in the safety analysis and in the pharmacokinetic analysis set depending on the availability of measurement values and on their adherence to the CTP. The criteria for inclusion into these populations are defined as follows:

Populations: Please see below for the specified populations.

Treated set (TS): all patients who were administered study medication. This set of patients is used for all analyses except for analysis of PK data.

MTD evaluation set (MTDS): all patients in the TS who were not replaced for the MTD determination. Rules for replacement of patients were defined in CTP, Section 4.1.4.5. In addition safety committee will decide the replacement of patients.

PK Analysis Set (PKS): all evaluable patients in the treated set which provide at least one evaluable observation for at least one PK endpoint.

The TS will be used for all efficacy and safety analyses. In addition, the MTDS represent the populated used for MTD determination. The primary analyses of DLTs during 1st cycle will be based upon the MTDS. PK analyses will be based on the PKS. Refer to Protocol Section 7.3.5 on handling PK endpoints.

Table 6.3: 1 Subject sets analysed

		Subject set	
Class of endpoint	Treated set	MTDS	PKS
Primary and key secondary endpoints	X	primary analysis	
Other secondary and further endpoints	X		
Safety endpoints	X		
Demographic/baseline endpoints	X		
PK endpoints			X

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Safety data and other data

In general, missing data will not be imputed and all reasonable efforts will be taken during the study conduct to obtain such data. Only observed values will be analysed. Data of subjects who withdrew after the screening examination or were not treated will be only listed.

6.6.2 AE dates and times

Missing or incomplete AE dates will be imputed according to BI standards (see DM&SM "Handling of missing and incomplete AE dates"). [3]

6.6.3 Missing plasma concentrations and pharmacokinetic parameters

Missing data and outliers of PK data are handled according to BI standards (see "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics") [2].

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, baseline values will be the measurements taken most recently prior to the first administration of study drug. If this value is not available, the measurement at screening visit will be used. If the lab is repeated at screening, then the last one should be used.

For efficacy analyses, baseline is defined as the pre-treatment observation at C1V1. If C1V1 is missing, then Screening will be used for baseline.

Visit will be labelled according to the flow chart in the protocol: Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'; therefore 'Day 0' will not be used.

Clinical disease status will be assessed at screening and at the start of each new cycle (e.g., before Cycle 2, 3, 4 and 5, etc.) as well as EOT.

While nominal times listed in this section should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

7. PLANNED ANALYSIS

For all the analyses in this open label phase I trial, patients will be included in the dose cohorts they were originally assigned to.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. The category "missing" will be displayed where applicable (i.e., if and only if there are actually missing values in the data).

For in-text tables, the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD), median, Q1 (lower quartile), Q3 (upper quartile), depending on the data.

For end-of-text tables, the set of summary statistics is: N/Mean/SD/Q1/Median/Q3. For appendix tables, the set of summary statistics is: N/Mean/SD/Min/Q1/Median/Q3/Max.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristics collected and to be presented include

- Gender *(Male/Female)*
- Age [*years*]
- Race (as defined in the eCRF)
- Body height [*cm*]
- Body weight [*kg*]
- Body mass index at baseline [kg/m^2]
- Body surface area at baseline [m^2]
- Smoking status (as defined in the eCRF)
- Alcohol status (as defined in the eCRF)
- ECOG performance score (*0/1/2*)
- Baseline cytogenetics
- Time since first diagnosis [*months*]
- ISS stage at screening (*I/II/III*)
- Site of tumor manifestation at screening (Bone/CNS/Soft tissue plasmacytoma/Other)
- Number of bony lesions (*None/<10/≥10*)
- Sum of longest diameters of plasmacytomas if present [*mm*]

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

7.3 TREATMENT COMPLIANCE

Non-compliance is defined by any patients who are administered study medication less than 14 days in any cycle (excluding those who discontinued per protocol, e.g., due to AE, or PD). Number of non-compliant patients will be summarized by descriptive statistics.

7.4 PRIMARY ENDPOINTS

In order to identify the MTD, the number of patients with DLTs during Cycle 1 at each dose level will be displayed descriptively by dose level with the lowest 4 doses pooled. In addition, the number of patients with DLTs during any treatment course will be analysed.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other Secondary endpoints

Objective response rate (ORR)

Objective response rate is defined as the percentage of patients achieving a sCR, CR, PR and VGPR as evaluated by the investigator according to the response criteria of the International Myeloma Working Group. The objective response rate will be presented as the proportion of responders, with the exact 95% Clopper-Pearson confidence intervals. The best response (sCR > CR > PR > VGPR) across all assessment will be used and presented.

Duration of response (DOR)

For patients with objective response, the duration of response is calculated from the time of first recorded achievement of a response until documented progression or death. DOR will be summarized descriptively by quartiles if applicable.

Minimal residual disease (MRD) response

MRD response is defined as <1 tumour cell within 10^4 normal cells in bone marrow using FACS analysis. MRD response rate will be calculated as the proportion of patients achieving MRD response with the exact 95% Clopper-Pearson confidence interval.

Duration of MRD response

For patients with MRD response, the duration of MRD response is calculated from the time of first recorded achievement of a MRD response until documented progression or death. Duration of MRD response will be summarized descriptively by quartiles if applicable.

Progression free survival (PFS)

PFS is defined as the time from first treatment with BI 836909 until disease progression or death. For patients who did not have any event (e.g., alive without progression), their PFS will be censored at date of last documented disease assessment. For patients without any events and no disease assessment performed post-baseline, their PFS will be censored at the date of treatment start. PFS will be summarized descriptively by quartiles with 95% confidence interval calculated from Kaplan-Meier estimate.

Pharmacokinetic analyses

The secondary pharmacokinetic endpoints C_{ss}, [redacted] will be descriptively explored, [redacted]

Refer to CTP Section 5.5.1 for pharmacokinetic parameters to be calculated. The derivation of the parameters will be according to BI's standard operating procedures. Pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program (Phoenix Winnonlin, version 6.3). The analysis of standard PK parameters is performed according to BI standards (see "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics") [2].

[redacted]

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarized descriptively by total treatment time (days and number of courses), number of cycles initiated, average number of days of infusion per cycle, number of cycles with at least 14 days of infusion will be calculated; off-drug periods due to non-compliance or toxicity prior to permanent discontinuation will be included as treatment time. Standard descriptive summaries, by treatment group, of these data will be provided for the treated set.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). In addition, DLT occurred during course 1 will be tabulated based on the MTD evaluation set (MTDS).

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to [3, 4].
The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till last drug intake + residual effect period will be assigned to the treatment. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period will be assigned to ‘post-treatment’ (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 [5], AEs classified as ‘other significant’ needs to be reported and will include those non-serious adverse events leading to treatment discontinuation or non-serious AEs leading to dose reduction.

An overall summary of adverse events will be presented. This summary will include the first 6 categories from the list below and AEs by highest intensity graded according to CTCAE (version 4.03).

The frequency of subjects with adverse events will be summarised by treatment, primary system organ class and preferred term (mention MedDRA levels to be displayed in the tables).

Separate tables will be provided for patients with each of the following AE categories:

- All AEs,
- DLTs (Course 1 only[1]),
- DLTs (All courses),
- AEs leading to dose reduction,

- AEs leading to treatment discontinuation,
- Serious AEs,
- Drug related AEs,
- Drug related serious AEs,
- CTCAE Grade 3 or higher AEs,
- AEs leading to death,

[1]: Course 1 defined by from start of treatment to start of Cycle 2 or the last dose administration of BI 836909 during Cycle 1 + 30 days, whichever occurs earlier.

Separate tables will be provided for subjects with other significant adverse events according to ICH E3 [5], for subjects with adverse events of special interest (only if defined) and for subjects with serious adverse events.

The system organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

Additional AE tables will be produced for adverse events of special interest (AESIs):

- Infusion-related reactions (CTCAE grade 3 or higher),
- Cytokine release syndromes (CTCAE grade 3 or higher),
- Tumour lysis syndrome,
- CNS adverse events (CTCAE grade 2 or higher),
- DLT,
- Hepatic injury (defined in CTP Section 5.2.2.1).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards “Handling, Display and Analysis of Laboratory Data” [6]. The following analyses will be presented for all applicable laboratory parameters:

- Descriptive statistics,
- Frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment,
- Frequency of patients with possible clinically significant abnormalities.

CTCAE version 4.03 grades will be applied to laboratory parameters using the current BI oncology standard [6]. Possible clinically significant abnormalities are defined as CTCAE grade of 2 or greater, with an increase of at least one grade from baseline.

Baseline is defined by the last available measurement before study drug administration. In cases of repeated measurements performed for the same visit the last observation will be used for tabulations.

7.8.3 Vital signs

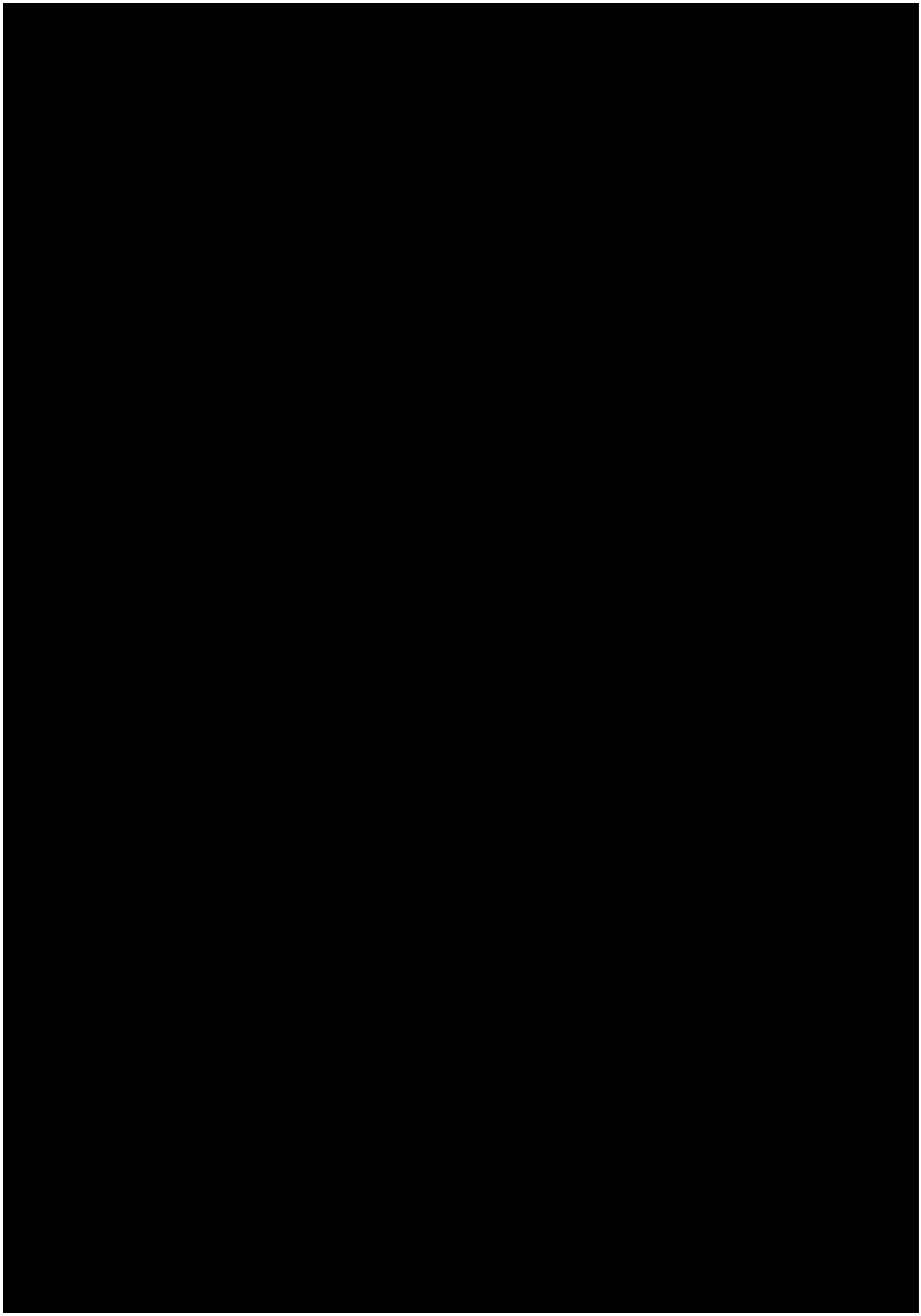
Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

ECGs were collected with an adverse event recorded if the readout was associated with any clinical finding.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5.	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
6.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**18-MAY-2017**	[redacted]	None	This is the final TSAP
Revised	**07-SEP-2018**		Title page	Delete "subcutaneous dose" from the title since that part is not included in the study any more. Change of responsible trial statistician.
			4	The cut-off date for interim analysis and the interim last patient out (LPO) have been adjusted. The analysis content for the interim CTR has also been modified.
			6.1	Update the overall study design scheme since part B and the long-term follow up is deleted from the study design. Add one more row for the dose level of "800 µg/d, c.i.v" into Table 6.1:1. Wording for the definition of "Residual effect period" has been updated to avoid confusion.
			6.2	Change the terminology of 'protocol violation' to 'protocol deviation' per latest SOP 001-MCS-40-413. Delete "or SC injection" from the description for the C3 category of iPD and delete two duplicated rows for C2 and C3 types of iPD in Table 6.2:1.
			7.8.1	Revise the definition of "Other significant AEs" based on the discussion during BRPM on July 24, 2018.
			[redacted]	

APPROVAL / SIGNATURE PAGE

Document Number: c17409411 **Technical Version Number:2.0**

Document Name: 8-01-tsap

Title: An open label, phase I, dose escalation study to characterize the safety,

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Medical Writer	[redacted]	10 Sep 2018 16:03 CEST
Approval-Clinical Trial Leader		10 Sep 2018 16:13 CEST
Author-Trial Statistician		10 Sep 2018 20:28 CEST
Author-Trial Clinical Pharmacokineticist		11 Sep 2018 16:15 CEST
Approval-Project Statistician		12 Sep 2018 21:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed