Trial Statistical Analysis Plan

C13709701-02

BI Trial No.:	1368.11
Title:	Multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis Final Protocol (including protocol revision 1 (c08910926-02))
Investigational Product:	BI 655130
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	06 NOV 2017 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALQ	Above the upper limit of quantification
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BMS	Biomarker set
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CGI	Clinical Global Impression
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ES	Enrolled set

Term	Definition / description
EudraCT	European union drug regulating authorities clinical trials
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
gCV	Geometric coefficient of variation
gMean	Geometric mean
GPP	Generalized pustular psoriasis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
IPV	Important protocol violation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NRI	No response imputation
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set

Term	Definition / description
PSS	Psoriasis symptom scale
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
REP	Residual effect period
RNA	Ribonucleic acid
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
VAS	Visual analogue scale

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 CTP and its amendments, 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 revised CTP. 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, and planning of sample size.

Study data will be stored in a trial database within the Oracle Clinical™ system.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

PK parameters will be calculated using WinNonlin™ software (professional Network version 5.2, Pharsight Corporation, Mountain View, CA 94041-1530, USA).

R version 3.0.2 or later (12), Biconductor version 2.13 or later, and the limma-package version 3.18.13 or later will be used in the analyses of gene expression data. Genome version hg38/GRCh38 will be used in conjunction with Ensembl version 84 or later.

This TSAP fully specifies the planned analyses for the analysis of the 4-week data. It also specifies the planned analyses for the complete trial data through Week 20 as far as possible; prior to the final DBL, updates will be required for the analyses of further endpoints related to biomarker and RNA sequencing data.

Final Analysis of the 4-week data

It is planned to keep sites open through at least the end of September 2017 in order to potentially achieve a total of 8 to 10 patients who are treated with BI 655130. Once a decision

has been made to stop further recruitment into the study then steps will be taken to prepare for the final analysis of the 4-week data.

The final analysis of the efficacy and safety data collected up to Week 4 will be performed once all entered patients have completed the first 4 weeks of study (i.e. through Visit 12); at that time point, a database lock will be done. The individual patient cut-off date for inclusion of data into the 4-week analysis will be the minimum of (actual cut-off date; date of dosing plus 38 days [representing the upper boundary of the time window for the Week 4 visit]); the actual cut-off date used for data cleaning purposes will be specified in the data cleaning plan for the 4-week analysis and will typically represent the date of attendance of the last patient to the Week 4 visit (i.e. date of performance of last Visit 12). Since the final analysis of the efficacy and safety data up to week 4 in this open-label trial will be complete, and because no further patient dosing visits are planned, the week 4 results may be made available and published to support enrolment into subsequent trials in this and potentially other indications of BI 655130. Analyses of the data described in the sections listed below will be performed at the time of database lock for the 4-week data:

- Section 7 (Analyses of disposition, IPVs and analysis sets, up to Week 4)
- Section 7.1 (Demographics and other baseline characteristics)
- Section 7.2 (Historical medications, background medications, concomitant medication use, and medical/disease history)
- Section 7.5.2.1 (Secondary efficacy endpoints up to Week 4, based on FAS and PPS)
- Section 7.6.1 (Further efficacy endpoints up to Week 4, based on FAS)
- Section 7.6.4 (Use of rescue medication up to Week 4, based on TS)
- Section 7.7 (Extent of exposure)
- Section 7.8.1 (Adverse events up to Week 4)
- Section 7.8.2 (Laboratory data up to Week 4)
- Section 7.8.3 (Vital signs including body temperature up to Week 4)
- Section 7.8.5 (Injection site reactions)

Other selected data that will be displayed at time of the 4-week database lock includes:

- Plasma concentrations data

Some of the analyses performed at the time of the 4-week database lock may also be repeated following database lock for the entire trial (once all patients have completed the trial). The results for such endpoints obtained following the 4-week database lock should be considered the main source for interpretation on treatment effects over the first 4 weeks of study for the CTR; any differences in the outcomes obtained following the final database lock, if applicable, should be described.

Analysis of the complete trial data through Week 20

The analysis of the entire efficacy and safety, as well as biomarker, data including those data collected through the full 20 weeks of follow-up will be performed once all entered patients have completed the trial (up to Visit 14); at that time point, a final database lock will be done and all trial data will be reported.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following analyses described in this TSAP are new/adapted analyses from those specified in the revised CTP.

- For secondary efficacy endpoints of a continuous nature, it was specified in the CTP that exact 95% confidence intervals around the mean will be produced. Per specification in Section 7.5.2.1, the 95% confidence intervals for continuous data will be based on the t-distribution.

In the CTP it is stated that analyses of immunohistochemistry and flow cytometry will be conducted. These analyses will not be carried out for the CTR, but may be done at a later time point (depending on the obtained results). In case they are performed at a later time point, the analysis details will be described in a separate document.

In the CTP, it was noted that a logistics plan will be developed to protect the integrity of the trial data once the week 4 analyses has been performed. However, since at this time the final analysis of the efficacy and safety data up to week 4 will be complete, and because no further patient dosing visits are planned, the week 4 results may be made available and published to support enrolment into subsequent trials in this and potentially other indications of BI 655130.

The following analyses described in this TSAP are new/adapted analyses from those specified in the signed version of the TSAP, dated 4 OCT 2017:

- Section 6.2
  Definition of IPV: exclusion criteria 8 (i.e. use of restricted medication prior to the study) was modified from a programmatic to a manual assessment. This was done in order to ensure that medical decision could be made on whether such occurrence of an IPV would or would not affect the assessment on efficacy.

  Same consideration was also applied to IPV D2.01 (and D2.02) representing prohibited medication use during the study.

- Section 6.6.2
  LOCF imputation was clarified to confirm that the baseline value would be carried forward in the event of no available post-baseline data (and not just in the case when missing post-baseline data was driven by rescue medication taken immediately after the first dose).

- Section 6.6.9
  Additional imputation strategies, for summary reporting only, are presented for the handling of cases where incomplete data are reported for previous GPP flare occurrences.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

CTP: *Primary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of patients with adverse reactions, defined as drug-related AEs.*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

5.2.2.1 Secondary efficacy endpoints

CTP: *Secondary efficacy endpoints will be:*

- *Percent change* [calculated as "reduction"] *from baseline in GPPASI total score at Week 2*
- *Proportion of patients with GPPGA total score of 0 (clear) or 1 (almost clear) at Week 2*
- *Change from baseline in FACIT-Fatigue scale score at Week 2*
- *Change from baseline in Pain VAS score at Week 2*

For details on calculating these scores at each visit, cf. Section 9.1.

5.2.2.2 Secondary pharmacokinetic endpoints

Secondary PK endpoints are $AUC_{0-\infty}$ and C_{max} of BI 655130 in plasma, as defined in Section 5.5.1.1 of the CTP.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, cf. Section 4 of the CTP.

All patients will receive one intravenous dose of 10 mg/kg of BI 655130 solution for infusion.

The following separate study phases are defined for analyses of efficacy, biochemical and cellular biomarkers, AEs, laboratory tests and vital signs:

Table 6.1: 1 Flow chart of analysis phases for efficacy, biochemical and cellular biomarkers, AEs, laboratory tests and vital signs

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of infusion of study drug minus 1 minute
Treatment phase[1]	On-treatment period	Date/time of start of infusion of study drug (Day 1)	Date of end of infusion of study drug + 28 days at 11:59 p.m.
REP	On-treatment period	Date of end of infusion of study drug + 29 days at 12:00 a.m.	Date of end of infusion of study drug +140 days at 11:59 p.m.
Follow-up[2] phase	Off-treatment period	Date of end of infusion of study drug + 141 days at 12:00 a.m.	Latest of: i) Date of End-of-Trial visit (Week 20); ii) end date on trial termination page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the subsequent phase.

[1] For the analysis of AEs, any AE occurrence on the same day as start of infusion of study drug will be assigned to the treatment phase.

[2] The follow-up phase only exists if the trial completion date is after the date of end of infusion + 140 days.

For the final analysis to be performed once all patients have completed through the planned first 4 weeks of trial, results will be summarized for the on-treatment period, unless otherwise specified. The selection of data for presentation in this analysis is described in Table 6.7: 1.

For the entire analysis of the trial to be performed once all patients have completed through the planned 20 weeks of trial, results will be summarized for the on-treatment period, as well as for the off-treatment period, if applicable.

Analysis phases will be labelled as follows in statistical analyses:

- Screening phase: **Screening**
- On-treatment period: **BI 655130**
- Follow-up: **Follow-up**
- Total over the screening, on-treatment and follow-up periods: **Total**

CTR Section 15, Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE displays will present results for the on-treatment period. Screening and follow-up phases will not be included in this analysis.

CTR Appendix 16.1.9.2.8.1 displays will present results for the screening phase, on-treatment period, follow-up period, and total.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled patients). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be queried in the clinical database. Each protocol deviation must be assessed to determine whether it is an IPV. For definition of IPVs, and for the process of identification of these, refer to the BI reference document "Protocol Violation Handling Definitions" (2).

If any IPVs are identified, they are to be summarized into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be IPVs in this trial. If the data show other IPVs, this table will be supplemented accordingly by the time of the RPM/DBLM. Not all IPVs will lead to exclusion from analysis sets. IPVs leading to exclusion from analysis sets are indicated as such in Table 6.2: 1.

IPVs will be summarized and listed.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Comments	Excluded from
A		**Entrance criteria violated**		
A1		**Inclusion criteria not met**		
	A1.01	Age out of range	Inclusion criterion 1, also check versus derived age	None
	A1.02	"A known and documented history of GPP" not confirmed	Inclusion criterion 2	PPS, PKS, BMS, DSS, RSS
	A1.03	"Presenting with a flare of GPP with at least 10% of BSA with erythema and pustules" not confirmed	Inclusion criterion 3	PPS
	A1.04	GPPGA score showing a severity less than moderate	Inclusion criterion 4, also check calculated GPPGA at Visit 3	PPS
	A1.05	For GPP patients receiving maintenance treatment with retinoids and/or methotrexate: maintenance treatment was received for less than 4 weeks prior to Visit 2. For other GPP patients: patient received any maintenance therapy other than retinoids and methotrexate at Visit 2.	Inclusion criterion 5	PPS
	A1.07	Women of childbearing potential did not agree to use effective method of birth control; male patients did not agree to use condoms	Inclusion criterion 7	None
A2		**Exclusion criteria violated**		
	A2.01	Pregnancy	Exclusion criterion 1	None
	A2.02	Immediate, life-threatening flare of GPP	Exclusion criterion 2	None
	A2.03	Identified, ongoing serious/severe infection	Exclusion criterion 3	PPS
	A2.04	Acute generalized exanthematous pustulosis (AGEP)	Exclusion criterion 4	PPS, PKS, BMS, DSS, RSS
	A2.05	Differential diagnosis of toxic epidermal necrosis or Stevens-Johnson syndrome	Exclusion criterion 5	PPS, PKS, BMS, DSS, RSS
	A2.06	Involved in or intending to participate in another investigational study during the course of this trial	Exclusion criterion 6	PPS, PKS, BMS, DSS, RSS

PV will be detected manually.
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).

Table 6.2: 1 Important protocol violations (continued)

Category / Code	Description	Comments	Excluded from	
A2.07	Previous enrolment in this trial	Exclusion criterion 7	FAS[1], PPS[1], PKS, BMS[1], DSS[1], RSS[1]	
A2.08a	Use of restricted medication with potential influence on efficacy data	Exclusion criterion 8, manual assessment of potential influence at RPM/DBLM	PPS, PKS, BMS, DSS, RSS	#
A2.08b	Use of restricted medication without potential influence on efficacy data	Exclusion criterion 8, manual assessment of potential influence at RPM/DBLM	None	#
A2.09	Patients with dose escalation of their maintenance therapy with methotrexate and/or retinoids within the 4 weeks preceding Visit 2	Exclusion criterion 9	PPS	
A2.10	Background therapy with ciclosporin within the last 30 days preceding Visit 2	Exclusion criterion 10	PPS	
A2.11	Previous exposure to an IL36R inhibitor	Exclusion criterion 11	PPS, PKS, BMS, DSS, RSS	
A2.12	Severe, progressive or uncontrolled disease	Exclusion criterion 12	PPS	
A2.13	Chronic or relevant acute infections	Exclusion criterion 13	PPS	
A2.14	Patients with transplanted organ or who have ever received stem cell therapy	Exclusion criterion 14	PPS	
A2.15	History of lymphoproliferative disease	Exclusion criterion 15	PPS	
A2.16	Active or suspected malignancy or history of malignancy within 5 years prior to Visit 2	Exclusion criterion 16	PPS	
A2.17	Evidence of a current or previous disease or medical condition other than GPP	Exclusion criterion 17	PPS	
A2.18	History of allergy/hypersensitivity to a systemically administered biologic agent	Exclusion criterion 18	PPS	
A2.19	Refusal to be hospitalized for 4 days following the infusion	Exclusion criterion 19	None	

[1] The data reported during the second enrolment of the patient in the trial will be excluded.
PV will be detected manually.
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comments	Excluded from	
B		**Informed consent**			
	B1	Informed consent not available	Date of informed consent missing or no signature on patient's "Declaration of Informed Consent" In this case: Patient's data will not be used at all.	All	
	B2	Informed consent too late	Informed consent date was after Visit 1	None	
C		**Trial medication**			
C1		**Incorrect trial medication**			
	C1.01	Study drug medication not taken	Patient entered but no study drug taken	TS, FAS, PPS, PKS, BMS, DSS, RSS	
C2		**Non-compliance**			
	C2.01	Non-compliance with study drug intake- - administered dose too high	Study medication dose is greater than 120% of the planned dose	PPS	
	C2.02	Non-compliance with study drug intake- - administered dose too low	Study medication dose is less than 70% of the planned dose	PPS, BMS, DSS, RSS	
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short	Washout period too short - See Table 4.2.2.1: 1 in CTP	PPS, PKS	#
	D1.02	Rescue use on or after Visit 2 but prior to administration of study drug	Rescue medication taken on the day of Visit 2 or on the day of Visit 3 (clock time will not be reported)	FAS, PPS	
D2		**Prohibited medication use**			
	D2.01a	Use of prohibited med. on or after V2 or during the on-trt. period, unless rescue trt. to stabilize a worsening disease cond. – prior to or on D14, with potential influence on eff. data	See the list of restricted medication in CTP, Table 4.2.2.1: 1, manual assessment of potential influence at RPM/DBLM	PPS, PKS, BMS, DSS, RSS	#

PV will be detected manually.
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comments	Excluded from	
	D2.01b	Use of prohibited med. on or after V2 or during the on-trt period, unless rescue trt. to stabilize a worsening disease cond. - prior to or on D14, without potential infl. on eff. data	See the list of restricted medication in CTP, Table 4.2.2.1: 1, manual assessment of potential influence at RPM/DBLM	None	#
	D2.02	Use of prohibited medication during treatment period when not provided as a rescue treatment to stabilize a worsening disease condition – after Day 14	See the list of restricted medication in CTP, Table 4.2.2.1: 1	None	#
D3		**Mandatory medication not taken**			
	D3.01	Any dose change in background medication on or after Visit 2 – prior to or on Day 14	Dose escalation of background therapy (methotrexate or retinoids) is not allowed within 4 weeks before Visit 2 (dose decrease is permitted). From Visit 2 to Visit 14 no change in dose of retinoids or methotrexate is allowed.	PPS, PKS, BMS, DSS, RSS	
	D3.02	Any dose change in background medication – after Day 14	Dose escalation of background therapy (methotrexate or retinoids) is not allowed within 4 weeks before Visit 2 (dose decrease is permitted). From Visit 2 to Visit 14 no change in dose of retinoids or methotrexate is allowed.	None	
E		**Missing data**			
		None	Missing visits, evaluations, and tests will be considered missing data, not protocol violations		
F		**Study specific analysis**			
F1		**Other trial specific violation**			
	F1.01	Study drug intake outside time window	Infusion period takes longer than 240 minutes.	None	

PV will be detected manually.
Violations F2.01 and F2.02 can only be detected at the trial site.
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comments	Excluded from	
F2		**Certain violations of procedures used to measure secondary efficacy data**			
	F2.01	Evaluation of GPPASI or GPPGA for a given patient not performed by the same physician up to Week 2	GPPASI, GPPGA assessments up to Week 2 for a given patient are not performed by the same physician.	PPS	#
	F2.02	Evaluation of GPPASI or GPPGA for a given patient not performed by the same physician throughout the study	GPPASI, GPPGA for a given patient is not performed by the same physician throughout the study.	None	#
	F2.03	Temperature recordings for a given patient not made at the same area throughout the study	Not all recordings for a given patient made in ear or oral cavity, respectively.	None	
G		**Other safety related violations**			
	G1	Pregnancy test not done for woman of child bearing potential at Visit 12, 12pc, 13, 13pc, or 14		None	#

PV will be detected manually.
Violations F2.01 and F2.02 can only be detected at the trial site.
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).

6.3 PATIENT SETS ANALYZED

The following analysis sets will be defined for this trial:

- Enrolled set (ES)
  This patient set includes all patients who signed informed consent.
  It will be used for analyses of patient disposition.

- Entered set (ENT-S):
  This patient set includes all entered patients (as identified by the investigator in the eCRF), whether treated or not.
  It will also be used for analyses of patient disposition.

- Treated set (TS):
  This patient set includes all patients in the ENT-S who received study drug at Visit 3.
  It will be used for analysis of safety data.

- Full analysis set (FAS):
  This patient set includes all patients in the TS who had a baseline and at least one post-baseline measurement available for GPPASI or GPPGA without any IPV flagged for exclusion from the FAS in the table above.
  This is the main analysis set for presentation of efficacy.

- Per protocol set (PPS):
  This patient set includes all patients in the FAS who adhered to the CTP without any IPVs which are flagged for exclusion from the PPS in the table above.
  The PPS will be used for sensitivity analysis of secondary efficacy endpoints.

- Pharmacokinetic parameter set (PKS):
  This patient set includes all patients in the TS who provide at least one observation for at least one secondary PK endpoint, which was not flagged for exclusion. PK parameters (and blood and plasma concentrations) can be flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a patient's data will be documented in the CTR.
  Relevant IPVs are documented in Table 6.2: 1 above.
  Plasma and blood concentrations and/or parameters will be considered as non-evaluable, if e.g. a pre-dose concentration is >5% of the C_{max} value of that patient, or if relevant time deviations occurred (as identified no later than in the RPM), or due to use of restricted medications (as identified no later than in the RPM).
  CTP: *It will be decided in the Report Planning Meeting which patients are to be included in the PKS.*
  This patient set will be used for the descriptive analysis of concentrations and PK parameters.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at latest at the RPM/DBLM.

Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints, and the approaches used with regard to missing data. For explanation of the different methods of handling missing data, cf. Section 6.6.

Table 6.3: 1 Patient sets analyzed

	Patient set					
Class of endpoint	ES	ENT-S	TS	FAS	PPS	PKS
Disposition	OR	OR	OR			
Compliance and exposure			OR	OR		
IPVs		OR				
Demographic/ baseline characteristics				OR		
Primary endpoint			OR			
Secondary efficacy endpoints				LOCF[1], NRI[1], OC-IR[2], OC[2]	LOCF[2], NRI[2],OC[2]	
Secondary PK endpoints						OR

[1] secondary analysis
[2] sensitivity analysis
[3] only for percent reduction from baseline in GPPASI total score, change from baseline in FACIT-Fatigue scale score and change from baseline in Pain VAS
[4] only for proportion of patients with GPPGA total score of 0 or 1
For explanation of the different approaches with regard to missing data see Section 6.6.
"LOCF" and "NRI" means analyses involving imputed data, cf. Section 6.6.2.
OC = observed cases, OC-IR = observed cases including also values after rescue medication, OR = original results.

6.5 POOLING OF CENTRES

It is planned that up to 10 patients in approx. 7 centres in 7 countries will be entered in this trial, i.e., it can be expected that 1 or 2 patients only will be entered per centre. All endpoints will be evaluated by descriptive statistical methods, unless otherwise specified.

Given the low number of patients per centre and the primarily descriptive nature of statistical analysis, separate analyses by centre are not meaningful and not desirable. All patients from all centres will be pooled for statistical analysis.

Listings, sorted by centre, will however be displayed.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Withdrawals

CTP: *If a patient is removed from or withdraws from the trial prior to the administration of trial medication, the reason for withdrawal will be entered in the case report form (CRF) and trial database and will be reported in the clinical trial report (CTR). If a patient is removed from or withdraws from the trial after the administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. The data will be included in the CRF/trial database and will be reported in the CTR.*

6.6.2 Efficacy data

Handling of missing item scores for the FACIT will be based on FACIT Administration and Scoring Guidelines (Version 4): If there are missing items in the FACIT-Fatigue, the FACIT-Fatigue scale score can be prorated. This is done by multiplying the sum of the FACIT-Fatigue scores by 13 (i.e. the number of items in the FACIT-Fatigue scale), then dividing by the number of items actually answered. When there are missing data, prorating in this way is acceptable as long as more than 50% of the items were answered, i.e., if the number of answered questions is 7 or higher. Cf. Section 9.1 for details regarding the derivation of the FACIT-Fatigue scale score.

For the GPPASI, GPPGA and PSS total scores, a missing item or component score will lead to a missing total score. However, individual items and subscores may be presented as applicable. Cf. Section 9.1 for further details regarding the derivation of efficacy endpoints.

Based on the different reasons for patients' data missing for different endpoints, various approaches will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint (cf. Table 6.3: 1). Approaches to be applied are described below.

Note that Visit 14 (i.e. the Week 20 (follow-up)) is intended to report follow-up data, i.e., data collected after the end of the on-treatment period (as defined in Table 6.1: 1). Therefore, no imputation based on data from the on-treatment period will be used to impute missing data at Visit 14 in order to avoid the mixing of on- with off-treatment data.

For the final analysis on the 4-week data, missing data imputations will be performed using only the data cleaned and planned to be reported at this time (Table 6.7: 1); data from later time-points will be excluded.

Binary efficacy endpoints

Some efficacy endpoints are defined in terms of the proportion of patients with a particular binary outcome, i.e. achievement of a GPPGA total score of 0 or 1. For those binary outcomes, the different methods for handling of missing data, presented below, will be performed as presented in Table 6.3: 1. Please note that some of these binary outcomes are derived from other parameters, but imputation is planned to take place only at the binary level, i.e., the GPPGA total score itself will not be imputed, but the binary endpoints derived based on these scores will be imputed.

- The following primary imputation strategy ("NRI") will be performed:
  - If there are data at the visits both immediately before and immediately after the visit with a missing outcome, then impute as success only if both the preceding and the following observations also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7);
  - Otherwise, impute as a failure to achieve a response (i.e. no response imputation [NRI]).

  For patients who take a rescue medication (as defined in Section 5.3.4) during the course of the study, all efficacy outcomes measured after the day of first use of rescue medication will be set to missing and, during the on-treatment period, will be imputed using the steps described above.

- Observed cases (OC) approach will be used as a sensitivity analysis and will include all collected data, with no imputation performed on the missing data. Such an OC approach will exclude all values measured after intake of a rescue medication (i.e. such values will be set to missing).
- Observed cases including rescue (OC-IR) approach will be used as a further sensitivity analysis and is an extension of the OC approach which includes additionally all values which were measured after rescue medication intake.

Continuous efficacy endpoints

For continuous efficacy endpoints, such as the pain VAS, FACIT-Fatigue scale score, and GPPASI total score, the different methods for handling of missing data, presented below, will be performed as presented in Table 6.3: 1:

- Imputation technique ("LOCF"): Under the assumption that the disease is self-limiting and will gradually improve over time, the LOCF approach will be used as the primary imputation strategy to replace missing values either at intermediate visits or due to early withdrawal from the trial. The last available value, including baseline, will be carried forward to all subsequent visits within the on-treatment period at which a measurement is missing. Values measured after the day of first rescue medication intake (as defined in Section 5.3.4) will be set to missing and the missing values within the on-treatment period will be imputed by LOCF.

- In addition, as sensitivity approaches, the OC and OC-IR will also be performed.

Rescue medication use

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows as described in Section 6.7 and not setting values to missing).

OR analysis will be performed on parameters and endpoints that are either not affected by patients' rescue medication use (e.g. plasma concentration level of BI 655130, rescue

medication use itself), or, if it is not meaningful to apply any imputation rule for the replacement of missing values.

6.6.3 Safety data

CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

The only exceptions where imputation might be necessary for safety evaluation are AE dates and start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Partial start and stop dates for concomitant medications and historical medication for GPP will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing then the end date is set to 31st of December of the year (or to the patient's trial completion date, if it is earlier than the 31st of December of the year).
- If the day of the start date is missing the start date is set to first day of the month (except for rescue medication, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing then the start date is set to 1st January of the year (except for rescue medication, where the first dosing day/month will be used if first dosing happened in the same year).
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

If a concomitant medication or historical medication was ticked to be ongoing, it is expected that the end date is missing and will not be imputed for display purposes.

For safety data that are displayed by time point (or visit) of measurement, the OC-IR approach will be used.

6.6.4 PK data

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5). **CTP**: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies […] to the lag phase, including the predose values).*

CTP: *For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be set to*

missing. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

PK data will be presented using the OR approach described in Section 6.6.2.

6.6.8 Time since first diagnosis

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the 30th June of that year.
- If only the day of the first diagnosis is unknown, time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

6.6.9 Disease characteristics

Incomplete information regarding disease characteristics will be imputed as follows:

- If the "number of flares of GPP that resolved spontaneously without treatment" is >0 and equal the "number of resolved flares of GPP (total)" in previous 12 months, and information is missing whether the shortest flare resolved spontaneously without treatment, this information will be imputed with "Yes". This will be analogously done for the longest flare, but only if "number of resolved flares of GPP (total)" in previous 12 months is reported to be > 1.

- For calculation of "time since start of last flare of GPP before the trial to Visit 2", partial dates for "start date of symptoms of last flare" will be replaced with the first day of the month (if month and year are available). Otherwise, the dates will not be replaced. Replacement will only be done for calculation; the "start date of symptoms of last flare" will not be imputed.

- If the actual "start date of symptoms of last flare" is unknown but "before the 12 months that precede the trial", then the "time since start of last flare of GPP before the trial to Visit 2" will be set to "> 1 year" for the statistical summary of disease characteristics.

- If the actual "start date of symptoms of last flare" is unknown but "during the 12 months that precede the trial", then the "time since start of last flare of GPP before the trial to Visit 2" will be set to "<= 1 year" for the statistical summary of disease characteristics. If additionally no information was provided regarding the date of resolution of last flare of GPP before the trial (i.e. no date and no time interval relative to start of trial), this will be imputed with the information that the flare stopped "during the 12 months that precede the trial".

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Measurements reported with date and time and taken prior to start of administration of trial treatment will be considered pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of administration of trial treatment will also be considered pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

Baseline is defined as the last measurement collected prior to the start of administration of the trial treatment.

Measurements taken after start of administration of trial treatment will be considered values of the on-treatment period or follow-up values, based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

The assessment of injection site reactions (scheduled for Visit 3 and Visit 4) will be handled differently to other by-visit endpoints, because the Visit 3 assessment is not a pre-treatment assessment, but is planned after injection of trial treatment, therefore representing an on-treatment measurement (i.e., both assessments are on-treatment assessments). Assessments at or after start of administration of trial treatment will be assigned to the nominal visit number as recorded on the eCRF, i.e. no time windows will be applied for analysis of this data.

Analysis of AE data and of rescue use will not be based on visits, therefore, no assignment to time windows will be necessary.

All other safety, efficacy and biomarker measurements will be assigned to visits based on time windows around the planned visit dates, defined relative to the day of trial treatment (which is scheduled for Visit 3). These time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs, biomarker, and RNA sequencing measurements to visits for statistical analysis

Visit number	Visit label	Planned day	Time window		
			Window	Start (inclusive)	End (inclusive)
4	Week 1, Day 2	Day 2	exact day	Day 2[A]	Day 2
5	Week 1, Day 3	Day 3	exact day	Day 3	Day 3
6	Week 1, Day 4	Day 4	exact day	Day 4	Day 4
7	Week 1, Day 5	Day 5	exact day	Day 5	Day 5
8	Week 1, Day 6	Day 6	exact day	Day 6	Day 6
9	Week 1, Day 7	Day 7	+ 3 days	Day 7	Day 10
10	Week 2	Day 14	+/- 3 days	Day 11	Day 17
11	Week 3	Day 21	+/- 3 days	Day 18	Day 24
For final Week 4 analysis					
12	Week 4	Day 28	- 3 days/+ 10 days	Day 25	Minimum of (cut-off[B]; Day 38)
For final analysis of entire trial					
12	Week 4	Day 28	- 3 days/+ 10 days	Day 25	Day 38
13	Week 12	Day 84	+/- 14 days	Day 70	Day 98
14	Week 20 (follow-up)	Day 142[D]	exact day to last value	Day 142	Day of last value[C]

All days are counted relative to the day of treatment, which is defined as Day 1.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory, GPPASI, GPPGA) will not be assigned to Visit 4. Such data will be listed only.
[B] The cut-off date will be specified in the data cleaning plan for the 4-week analysis.
[C] Note that measurements assigned to the Week 20 (follow-up) visit are intended to represent follow-up measurements, i.e., made after the end of the on-treatment period (as defined in Table 6.1: 1).
[D] Planned day per CTP is Day 140, which would still be during the on-treatment period, as REP is defined to be 140 days.

Repeated and unscheduled efficacy, safety and biomarker measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day, but which are not measured on the same day, the later value will be selected. If there are two observations on the same day, the worst value will be selected.

Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data after setting values after rescue medication intake to missing (if applicable, i.e. for the "LOCF" and "NRI" approaches and the "OC" approach defined in Section 6.6.2). Visits which were not assigned a value based on time windows will thereafter be imputed for the NRI and LOCF approaches defined in Section 6.6.2. Imputation of efficacy endpoints (binary as well as continuous) will be performed based on all available observations, irrespective of whether the observation was selected in any time window. For example, for LOCF imputation, the last observed value during the on-treatment period will be carried forward, whether or not it was the selected value in a time window. For more details on LOCF refer to Section 6.6.2.

For derivation of the last value during the on–treatment period, the minimum value during the on–treatment period, and the maximum value during the on–treatment period, all values during the on-treatment period (whether or not selected in any time window) will be considered; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether or not selected in any time window) will be considered.

Tables and figures with results of the statistical analysis will only display visits at which the respective parameter was planned to be collected according to the CTP.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (10).

The individual values of all patients will be listed. Listings will generally be sorted by country, centre number, patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

Analyses of secondary and further PK endpoints will be performed by BI and presented in Section 15.6 of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	lower quartile
Median	median
Q3	upper quartile
Max	maximum

For plasma concentrations as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of clinical trials and project summaries" (10).

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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

Disposition of the patient population participating in the trial will be summarized by presentation of the frequency of patients screened, entered, screened but not entered, treated, entered but not treated, who completed the trial through planned visit at Week 4, who completed planned observation time, who completed trial medication, and who were prematurely discontinued, by reason. A patient is defined to have completed the trial through the planned visit at Week 4 if the patient did not discontinue the trial at any time prior to the lower bound of the week 4 time window (cf. Table 6.7: 1). The vital status of prematurely

discontinued patients at Week 20 will also be summarized. Disposition will be listed by country.

The frequency of patients with IPVs, also summarized by whether or not the IPV led to exclusion from the FAS, PPS, PKS, BMS, DSS or RSS, will be presented for the ENT-S. The frequency of patients in each of the different analysis sets will also be presented.

Baseline, for applicable analyses, refers to the last measurement collected prior to the start of administration of the trial treatment.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Descriptive statistics will be presented for demographic parameters and baseline characteristics, based on the FAS. The presence of IL36RN mutation, as recorded in the eCRF at Visit 1 based on historical data, will only be listed.

For the continuous variables described below, the following categories will be defined and presented according to the number and percentage of patients in each category:

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age	< 50 years 50 to < 65 years ≥ 65 years
Weight	≤70 kg >70 to ≤80 kg >80 to ≤ 90 kg >90 kg
BMI	< 25 kg/m^2 25 to < 35 kg/m^2 ≥ 35 kg/m^2
Time since first diagnosis	≤ 1 year > 1 to ≤ 5 years > 5 to ≤ 10 years > 10 years

7.2 CONCOMITANT DISEASES AND MEDICATION

Analyses of concomitant diseases and medication will be based on the FAS.

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Signs/symptoms of the trial disease (as identified on the eCRF) will be summarized separately from other concomitant diseases, by system organ class and preferred term.

Other characteristics of the trial disease, such as the frequency and percentage of resolved flares within the last 12 months, as well as details on the shortest, longest, and last GPP flare which occurred prior to admission into this trial, will be displayed. The duration (up to start of treatment) and likely cause of the current flare of GPP will also be presented. The "number of flares of GPP that resolved with treatment" will be calculated as the number of resolved flares of GPP in previous 12 months minus the number which resolved spontaneously without treatment.

A medication will be considered concomitant to treatment, if it

- is ongoing at the start of trial treatment or
- starts within the analysis phase of the trial treatment (see Section 6.1 for a definition of treatments and analysis phases).

Concomitant medication use (excluding rescue medication on or after Visit 2 and before end of the on-treatment period, historical medication for GPP and background medication) will be summarized with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for

- concomitant therapies taken any time prior to Day 1 (the day of start of trial treatment),
- concomitant therapies initiated on Day 1, and
- concomitant therapies taken any time during the on-treatment period (cf. Section 6.1).

The frequency and percentage of patients with previous treatment on methotrexate, retinoids, ciclosporin, and other historical medication for GPP will be displayed, and will include an assessment of those patients who continue to take methotrexate or retinoids as background medication in this trial. Here, background medication is defined as any administration of methotrexate or retinoids which is ongoing on the day of administration of BI 655130. In addition, the time since last dose relative to Visit 2 for patients who have discontinued prior methotrexate or retinoid use will be listed.

Rescue medication use on or after Visit 2 and before end of the on-treatment period will be summarized separately, as described in Section 7.6.4.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarized for the FAS by descriptive statistics (N, mean, SD, minimum, median, maximum) for the amount of medication taken [% of planned], and by the number and percentage of patients with

- "< 70% of planned",
- "70 to 120% of planned" and
- "> 120% of planned".

7.4 PRIMARY ENDPOINTS

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the number [N (%)] of patients with adverse reactions, defined as drug-related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

7.5.2.1 Secondary efficacy endpoints

Analysis of secondary efficacy endpoints will be based on the FAS; an analysis based on the PPS will be performed as a sensitivity analysis. The analysis of imputed values (cf. Section 6.6.2) will be considered the main approach for secondary efficacy analyses of this trial. Other analysis approaches based on the FAS (and on the PPS) will be considered sensitivity analyses to assess the impact of missing data, intake of rescue medication, and IPVs on the efficacy outcomes.

The GPPASI total score and the percent reduction from baseline in GPPASI total score will be summarized descriptively by visit as will the FACIT-Fatigue scale total score and pain VAS score; the changes from baseline at each post-baseline visit will also be displayed. For the percent reduction from baseline in GPPASI total score as well as the change from baseline in FACIT-Fatigue scale total score and pain VAS at each visit, 95% confidence intervals around the mean will be presented and are calculated as follows:

$$\left(mean - t_{n-1;\,0.975}\frac{SD}{\sqrt{n}};\; mean + t_{n-1;\,0.975}\frac{SD}{\sqrt{n}}\right),$$

where "*mean*" denotes the sample mean, "*SD*" denotes the sample standard deviation, "*n*" denotes the number of non-missing values in the sample, and "$t_{n-1;\,0.975}$" denotes the 0.975 quantile of the t-distribution with *n-1* degrees of freedom.

Graphical presentations of the mean and 95% confidence interval by visit will be provided for percent reduction from baseline in GPPASI total score, change from baseline in FACIT-Fatigue scale total score and change from baseline in pain VAS score. Additionally, for percent reduction from baseline in GPPASI total score, 95% confidence intervals for the median will be calculated based on the SAS procedure PROC UNIVARIATE with option CIPCTLDF, and graphical presentations of the median and 95% confidence interval by visit will be provided.

For the FACIT-Fatigue scale, frequencies of patients with each score for each of the individual questions will additionally be summarized by visit.

The proportion of patients with a GPPGA total score of 0 (clear) or 1 (almost clear) will be summarized descriptively by visit, presenting patient frequencies and proportions together with exact 95% Wilson score confidence intervals. Additional displays of the patient frequencies and percentages for the individual GPPGA total scores (0, 1, 2, 3, 4), as well as for each subscore on the underlying characteristics ('erythema', 'pustules', and 'scaling/crusting'), will also be produced. Bar charts over time will be displayed.

The time of first achievement of a GPPGA total score of 0 (clear) or 1 (almost clear), relative to the day of start of infusion of trial treatment, will be summarized with patient frequencies and percentages for the following categories:

- No response
- Response on or after Visit 2 but prior to treatment start
- Response from treatment start to Day 4
- Response from Day 5 to Day 7
- Response from Day 8 to Day 14 (Week 2)
- Response from Day 15 to Day 28 (Weeks 3 and 4).

7.5.2.2 Secondary pharmacokinetic endpoints

CTP: *The secondary PK parameters (refer to* [CTP] *Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472* [(11)]*). Analyses will be performed for parent drug.*

Descriptive statistics will be presented for secondary PK endpoints, based on the PKS.

Exclusion of PK parameters

The ADS "ADPP" contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, i.e. APEXC is equal to "Included".

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to "ALL CALC", the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to "DESC STATS" the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION", the value can be used for further analyses based on actual times. If ACEXCO is set to "HALF LIFE" the value will be excluded from half-life calculation only; the value is included for all other analyses.

Excluded concentrations, and concentrations and parameters of excluded patients will be listed in the clinical trial report, associated with an appropriate flag.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.7 EXTENT OF EXPOSURE

Exposure [as amount administered in mg/kg as well as in mg] and duration of infusion [in minutes], for the TS, will be summarized by descriptive statistics (N, mean, SD, minimum, median, maximum) and by the number and percentage of patients classified according to the following categories:

Exposure [mg] categories

- Exposure "< 500 mg" BI 655130,
- Exposure "500 mg to < 700 mg" BI 655130,
- Exposure ">= 700 mg" BI 655130,

Duration of infusion [min] categories

- Duration "< 60 min",
- Duration ">=60 min to < 120 min",
- Duration ">=120 min to < 240 min",
- Duration ">= 240 min".

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the TS.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA, preferred terms (if applicable) will be sorted by total frequency (within system organ class).

For analysis, multiple AE occurrence data on the eCRF will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the start date of the second, later occurrence is the same or one day later than the end date of the first occurrence)

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) [001-MCG-156] and "Handling of missing and incomplete AE dates" (4) [001-MCG-156_RD-01].

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, treatment phase or follow-up phase as defined in Section 6.1. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as BI 655130 administration will be assigned to the on-treatment period.

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of other significant AEs according to ICH E3 and for the class of AESIs.

CTP: *The following are defined as protocol-specified AESIs in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*
  - *an elevation of AST and/or ALT and/or AP ≥3-fold ULN plus 2 times the baseline, combined with an elevation of total bilirubin ≥2-fold ULN plus 1.5 time the baseline, measured in the same blood sample.*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (9), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant AEs
(i) which are marked hematological or other lab abnormalities, or
(ii) which were reported with 'action taken = discontinuation' or 'action taken = reduced', or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of patients with AEs will be summarized by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarized separately (primary endpoint of this trial). Separate tables will also be provided for patients with SAEs, patients with AEs leading to study drug discontinuation, patients with AESIs and patients with other significant AEs (according to ICH E3 (9)). AEs will also be summarized by maximum intensity.

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarized by treatment, primary system organ class and preferred term. The frequency of patients with SAEs will also be summarized.

For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). For continuous safety laboratory parameters, normalized values will be derived. Normalization means transformation to a standard unit and to a standard reference range. The process of normalization, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (8). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline (see Section 6.7) will be calculated.

Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided by visit (including follow-up), including the last value on treatment, the minimum value on treatment, and maximum value on treatment. Since safety laboratory tests will be performed at the local laboratory of each site, this analysis will be based on normalized laboratory values only.

Laboratory values will be compared to their reference ranges; a shift table will be provided for the number of patients within and outside the reference range at baseline and at the last

measurement on treatment. This analysis will be based on standardized laboratory values and reference ranges as provided by the local laboratory of each site.

Values of categorical laboratory parameters will only be listed.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on normalized converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group all patients' lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardized laboratory values.

To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN plus 2 times the baseline with concomitant or subsequent total bilirubin ≥ 2xULN plus 1.5 times the baseline in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values.

A graphical analysis of ALT and total bilirubin during the on-treatment period will be performed; the so-called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate), body temperature, and body weight will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided, including the last value on treatment, the minimum value on treatment, and the maximum value on treatment.

The number and percentage of patients with a body temperature of ≥ 37.5 degree C will be presented by means of shift tables for post-baseline visits vs. baseline.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such. No separate listing or analysis of ECG data will be prepared.

7.8.5 Injection site reactions

Injection site reactions will be summarized, by visit as well as overall, with the frequency and percentage of patients who experienced any injection site reaction, both overall and by type of reaction.

Frequency and percentage of patients will also be summarized, by visit, for the intensity of each injection site reaction (mild, moderate, severe), and for the maximum intensity across all types of reaction.

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-50-413_RD-01:* "Protocol Violation Handling Definitions", current version; IDEA for CON

3 *001-MCS-50-413_RD-02:* "Important Manual Protocol Violations Spreadsheet", current version; IDEA for CON

4 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON

5 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON

6 *001-MCS-36-472_RD-03*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON

7 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON

8 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version; IDEA for CON

9 *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

10 *001-MCG-159:* "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON

11 *001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON

12 *R Development Core Team (2013)*: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (2013); website: R-project.org

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**04-OCT-2017**		None	This is the final TSAP without any modification
Revised	**06-NOV-2017**		6.2	Split important protocol violation regarding "use of restricted medication" (acc. to exclusion criterion 8) into such violations with and without potential influence on secondary efficacy data. Split important protocol violation regarding "use of prohibited medication on or after Visit 2 or during the on-treatment period when not provided as a rescue treatment to stabilize a worsening disease condition – prior to or on Day 14" into such violations with and without potential influence on secondary efficacy data.
			6.6.2	Clarified regarding LOCF approach that baseline value can be carried forward into the on-treatment period in case of missing data, irrespective of whether the data is missing or was set to missing due to intake of rescue medication.
			6.6.9 (new)	Added imputation rules for disease characteristics data.

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Meaning of Signature	Signed by	Date Signed
Approval-Project Statistician		06 Nov 2017 16:45 CET
Approval-Trial Clinical Monitor		06 Nov 2017 16:49 CET
Approval-Medical Writer		07 Nov 2017 16:11 CET
Approval-Biostatistics		08 Nov 2017 12:51 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed