TRIAL STATISTICAL ANALYSIS PLAN

c17032121-03

BI Trial No.:	1368-0004
Title:	Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC) including Protocol Amendment 3 [c10710598-04]
Investigational Product:	BI 655130
Responsible trial statisticians:	Phone:+ Fax:
Date of statistical analysis plan:	06-DEC-2019 REVISED
Version:	Version 3.0 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
AP	Alkaline phosphatase
5-ASA	5-Aminosalicylate
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
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
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ELISA	Enzyme Linked Immunosorbent Assay
EoO	End of Observation
EoT	End of trial
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials

Term	Definition / description
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
F/U	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
IL-36R	Interleukin-36 Receptor
IMP	Investigational medicinal product
iPD	important protocol deviation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical quality review meeting
MTX	Methotrexate
6-MP	6-Mercaptopurine
NOA	Not analysed
NOR	No valid result
NOS	No sample available
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
PD	Pharmacodynamic(s)
PG	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RBS	Rectal Bleeding Subscore
REP	Residual effect period

Term	Definition / description
RNA	Ribonucleic Acid
RNAseq	RNA sequencing
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SFS	stool
SI	Système international d'unités
SMQ	Standardised MedDRA query
TGF-β	Transforming Growth Factor beta
TNF	Tumour Necrosis Factor
TS	Treated set
TSAP	Trial statistical analysis plan
UC	Ulcerative Colitis
ULN	Upper limit of normal range
VEGF	Vascular Endothelial Growth Factor

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 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 BRAVE 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).

R version 3.1.2 or later (6), Bioconductor version 2.13 or later, and the DESeq-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 describes the analyses of BMs defined as endpoints and planned to be reported in the CTR.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following changes of endpoints (based on Mayo score) were implemented to be consistent across trials.

The following renamings were conducted:

- The secondary endpoint clinical remission (Mayo Score ≤2 with all subscores ≤1) will be labelled as *total clinical remission*
- The further endpoint Modified clinical remission (Mayo Score ≤2 AND (A) rectal bleeding subscore (RBS) = 0, (B) modified endoscopic subscore ≤1; and (C) stool frequency subscore = 0 or =1 and drop ≥ 1 from baseline) will be labelled as *clinical remission*

See Section 9.1 for details on deriving the efficacy endpoint scores at each visit.

5. ENDPOINTS

For all endpoints and unless explicitly specified otherwise, Week 10 refers to Visit V8 and Week 12 refers to Visit EOT.

For handling of missing data and corresponding sensitivity analyses, see Section 6.6.

5.1 PRIMARY ENDPOINT

The primary endpoint is the total number of deregulated genes comparing baseline to post-treatment, analysed by gene expression of mucosal biopsies via RNA sequencing, per time point up to week 12.

Details on the planned analyses are given in Section 7.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable. No key secondary endpoints have been specified in the CTP.

5.2.2 Secondary endpoints

5.2.2.1 Secondary efficacy endpoints

The following secondary efficacy endpoints will be analysed:

- *Percent change in CRP from baseline to Week 12*
- *Percent change in faecal calprotectin from baseline to Week 12*
- *Percent change in faecal lactoferrin from baseline to Week 12*
- *Total clinical remission (defined as Total Mayo score ≤2 points, and all subscores ≤1 point) at Week 12 (cf. Section 4)*

For details on calculating the total Mayo score at each visit, cf. Section 9.1.

5.2.2.2 Secondary safety endpoints

Secondary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of patients with drug-related AEs (cf. Section 5.3 of the CTP).

5.3.3 Further safety criteria

Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0.

Further safety criteria of interest are:

- AEs
- SAEs

- Safety laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- Physical examination
- Vital signs
- Relevant findings in 12-lead ECG
- IgE and ADA (anti-drug antibodies), as detailed in the lab manual

5.4.1 Demographic and other baseline characteristics

Standard demographic data and baseline characteristics are used as recorded in the eCRF. These include sex, ethnicity, race, age, height, weight, BMI, smoking status. Disease characteristics including time since first diagnosis, previous surgery for UC and extra intestinal manifestations will be collected during screening.

Age [years] will be determined as the difference between year of birth and year of informed consent.

BMI will be calculated as weight [kg] / height $[m]^2$ (based on the last available weight measurement prior to the first dose of BI 655130).

Time since first diagnosis [years] will be calculated as the difference between date of first diagnosis and date of informed consent, divided by 365.25. For calculation in context of incomplete information on the date of first diagnosis, cf. Section 6.6.

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 intravenous doses of 1200mg of BI 655130 solution for infusion (at V2, V5 and V7).

The following study phases are defined:

Table 6.1: 1 Flow chart of analysis phases

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 first study drug minus 1 minute.
Treatment phase & Residual effects period (REP)	On-treatment period	Date/time of start of infusion of first study drug (Day 1)	Date of end of infusion of last study drug + 140 days at 11:59 p.m.
Follow-up[1] phase	Off-treatment period	Date of end of infusion of last study drug + 141 days at 12:00 a.m.	Latest of: i) Date of EoO visit (Week 28 visit); 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 following phase.
[1] The Follow-up phase only exists if the trial completion date is after the date of end of last infusion + 140 days

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

Treatment groups for the analysis will be labelled as follows:

- **"Speso 1200 mg IV BI q4w"**

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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/MQRM. 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 important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

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

iPDs will be summarised and listed for the entered set.

Table 6.2: 1 Important protocol deviations

Category / Code	Description	Comments	Excluded from[1]
A	**Entrance criteria violated**		
A1	**Inclusion criteria not met**		
A1.01	Age out of range LABEL: Age beyond 18-65	Inclusion criterion 1 Also check versus derived age for patient.	None
A1.02	Body weight out of range LABEL: Body weight larger 100 kg	Inclusion criterion 2 Also check versus reported body weight for patient	None
A1.03	Diagnosis of UC <3 months prior to screening LABEL: Diagnosis only recent	Inclusion criterion 3 Also check derived time since diagnosis for patient	None
A1.04	Moderately to severely active UC not confirmed, e.g. Mayo Score ≤ 6 and/or no elevated C-Reactive protein (CRP) or faecal calprotectin at pre-baseline visit. LABEL: Disease activity not moderate or severe	Inclusion criterion 4 Also check derived total MCS,CRP and faecal calprotectin at pre-baseline Manual check in addition.	CAS

PV will be detected manually
Source: BI reference document*:* "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2).
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code	Description	Comments	Excluded from[1]	
A1.05	Receiving conventional, non-biologic therapy for UC. Concurrent UC treatments need to be on stable doses: This therapy could consist of one or more of the following: • Oral 5-ASA compound, with stable dose for at least 4 weeks prior to screening • 6-MP, Methotrexate (MTX) or AZA, with stable dose for at least 8 weeks prior to screening • Oral corticosteroids (≤ 20mg/day per day of prednisone or equivalent), with stable dose for at least 4 weeks prior to screening <u>LABEL:</u> Concurrent UC treatment not on stable dose	Inclusion criterion 5	CAS	#
A1.06	Negative colon cancer screening within the past 12 months prior to screening not available <u>LABEL:</u> Lack of negative colorectal cancer screening	Inclusion criterion 6	None	
A1.07	Patients who are naïve or experienced to TNF antagonists (including infliximab, adalimumab, or golimumab) but have not failed that treatment due to primary non-response or loss of response <u>LABEL:</u> Patient with previous TNF experience (non-response or loss of response)	Inclusion criterion 7	CAS	
A1.08	Women of childbearing potential did not agree to use effective method of birth control; male patients did not agree to use condoms <u>LABEL:</u> Contraception methods not used	Inclusion criterion 8	None	

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code		Description	Comments	Excluded from[1]	
	A1.09	Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial LABEL: IC not in accordance with legislation	Inclusion criterion 9– check for tick box only. Further PVs on informed consent are defined in section B below	All	
A2		**Exclusion criteria violated**			
	A2.01	Pregnancy LABEL: Pregnancy	General exclusion criterion 6	None	
	A2.02	Patients who have previously failed treatment with any TNF antagonist (including infliximab, adalimumab, golimumab) due to primary non-response or loss of response LABEL: Prior failure with any TNF antagonist	Gastrointestinal exclusion criterion 1	CAS	#
	A2.03	Extensive colonic resection, subtotal or total colectomy LABEL: Extensive colonic resection, or colectomy.	Gastrointestinal exclusion criterion 4	None	
	A2.04	Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine LABEL: Ileostomy, colostomy, or stenosis	Gastrointestinal exclusion criterion 5	None	
	A2.05	Patients who must or wish to continue the intake of restricted medications (cf. CTP Table 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial LABEL: Use of restricted medication	Gastrointestinal exclusion criterion 6	CAS	

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code	Description	Comments	Excluded from[1]
A2.06	Evidence of infection with C. difficile or other intestinal pathogen < 30 days prior to screening LABEL: Infection with intestinal pathogen	Gastrointestinal exclusion criterion 7	CAS
A2.07	Currently require or are anticipated to require surgical intervention for UC LABEL: Require surgical intervention for UC	Gastrointestinal exclusion criterion 8	CAS
A2.08	Colonic mucosal dysplasia (moderate or severe) or colonic adenomas LABEL: Colonic mucosal dysplasia	Gastrointestinal exclusion criterion 9, 10	None
A2.09	Primary sclerosing cholangitis LABEL: Primary sclerosing cholangitis	Gastrointestinal exclusion criterion 11	None
A2.10	Faecal transplant ≤ 6 months before screening LABEL: Faecal transplant within 6 months	Gastrointestinal exclusion criterion 12	None
A2.11	Disease limited to the rectum, extending <15 cm past the anal verge (ulcerative proctitis) LABEL: Disease limited to the rectum	Gastrointestinal exclusion criterion 13	CAS

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code	Description	Comments	Excluded from[1]	
A2.12	Relevant infectious disease or increased risk of infectious complications LABEL: Increased risk of infectious complications	Infectious Disease exclusion criterion 14, 15, 16	None	
A2.13	Evidence of a current or previous disease or medical condition other than UC that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data LABEL: Current or previous disease leading to exclusion	General exclusion criterion 15	CAS	
A2.14	Active or suspected malignancy or history of malignancy within 5 years prior to screening visit LABEL: Malignancy within last 5 years	General exclusion criterion 16	None	
A2.15	Major surgery performed within 12 weeks prior to randomization or planned during the trial LABEL: Recent or planned major surgery	General exclusion criterion 17	None	
A2.16	Pathological safety lab parameters LABEL: Pathological safety lab parameters	General exclusion criterion 18	None	#
A2.17	Conflicting other investigational treatment LABEL: Conflicting other treatment	General exclusion criterion 19	CAS	

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code		Description	Comments	Excluded from[1]	
	A2.18	Known hypersensitivity to any component of the IMP LABEL: Known hypersensitivity to IMP	General exclusion criterion 21	None	
	A2.19	Patients who were treated with a TNF antagonist within 8 weeks prior to screening, or 3 half-lives of agent from screening, whichever is longer LABEL: Recent TNF treatment	Gastrointestinal exclusion criterion 2	CAS	#
	A2.20	Prior use of any other biological treatment in the past (e.g. integrin inhibitors, IL12/23 or IL23 inhibitors, any other investigational biological drugs) LABEL: Prior use of any other biologic	Gastrointestinal exclusion criterion 3	CAS	#
B		**Informed consent**			
	B1	Informed consent not available LABEL: IC not available	Based on direct assessment, not simply the tick box (which is A1.08). 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 LABEL: IC too late.	Informed consent date was after Visit 1	None	

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code		Description	Comments	Excluded from[1]	
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication**			
	C1.01	Study drug medication not taken LABEL: Study drug medication not taken at all	Patient entered but no study drug taken	CAS, FAS, SAF	
	C1.02	Incorrect medication overall LABEL: Incorrect medication	Patient who fulfills the following would be considered an iPD: • >= 2 vials (300mg) deviation from planned dose at one visit • >= 3 vials (450mg) deviation from planned dose overall	CAS	
	C1.03	Patient skipped an intermediate dose LABEL: Patient skipped an intermediate dose.	Patient missing a dose at an intermediate visit when dose at a later scheduled visit has been taken.	CAS	
C2		**Non-compliance**			
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short LABEL: Washout too short	Washout period too short -See Table 4.2.2: 1 in CTP.	CAS	#

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code		Description	Comments	Excluded from[1]	
D2		**Prohibited medication use**			
	D2.01	Use of restricted medication as per CTP Table 4.2.2: 1 on or after Screening or during the on-treatment period when not provided as a rescue treatment to stabilize a worsening disease condition- prior to or up to Week 12 LABEL: Restricted medication prior to week 12	If restricted medication is initiated during trial	CAS	#
	D2.02	Use of restricted medication as per CTP Table 4.2.2: 1 when not provided as a rescue treatment to stabilize a worsening disease condition – after Week 12 LABEL: Restricted medication after week 12	If restricted medication is initiated during trial	None	#
D3		**Change in background medication**			
	D3.01	Concurrent UC treatments need to be on stable doses during treatment: Any dose change in background medication on or after Screening or during the on-treatment period unless it is due to rescue use or adverse event– prior to or up to Week 12 LABEL: Concurrent UC treatment not stable prior to Week 12	Medical review	CAS	#
	D3.02	Any dose change in background medication period unless it is due to rescue use or adverse event – after Week 12 LABEL: Concurrent UC treatment not stable after Week 12	Medical review	None	#

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

Table 6.2: 1 Important protocol deviations (continued)

Category / Code		Description	Comments	Excluded from[1]	
E		**Missing data**			
		None	Missing visits, evaluations, and tests will be considered missing data, not protocol deviations		
F		**Study specific analysis**			
F1		**Other trial specific violation**			
	F1.01	Incomplete diagnosis of ulcerative colitis LABEL: Incomplete diagnosis of UC	Medical review	CAS	#
F2		**Certain violations of procedures used to measure primary or secondary efficacy/biomarker data**			
	F2.01	To be defined at the RPM, if applicable	Manual iPDs which have a potentially relevant effect on primary or secondary data	Any exclusion will be defined at the RPM/ DBLM/ MQRM.	#
G		**Other safety related violations**			
	G1	Pregnancy test not done for woman of child bearing potential LABEL: Pregnancy test not done		None	

PV will be detected manually
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [*001-MCS-40-413*] (2)
[1] See Section 6.3 for population definitions

6.3 SUBJECT SETS ANALYSED

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 (ENTS)
  This patient set includes all patients who signed informed consent and entered the trial. It will be used for analyses of patient disposition.

- Safety analysis set (SAF):
  This patient set includes all patients in the ENTS who received at least one dose of study drug. It will be used for analysis of safety, demographic data, baseline characteristics and (certain) biomarkers.

- Completers analysis set (CAS):
  This patient set includes all patients in the SAF who completed trial medication and trial through EOT visit (i.e. a visit date was reported within the time-window of Week 12 visit; cf. Table 6.7: 1) and who had a baseline and at least one post-baseline measurement available for any clinical efficacy endpoint (e.g. Mayo score or Robarts histopathology index) or any biomarker endpoint (e.g. gene expression and/or inflammatory biomarker) without any iPD flagged for exclusion from the CAS in the table above. If a patient has any rescue use on or after Visit 1b but prior to administration of first dose of BI 655130 then this patient will also be excluded from the CAS. This is the main analysis set for presentation of primary endpoint

- Full analysis set (FAS):
  This patient set includes all patients in the SAF who had a baseline and at least one post-baseline measurement available for any clinical efficacy endpoint (e.g. Mayo score or Robarts histopathology index) or any biomarker endpoint (e.g. gene expression or inflammatory biomarker) without any iPD flagged for exclusion from the FAS in the table above (cf. Table 6.2: 1). If a patient has any rescue use on or after Visit 1b but prior to administration of first dose of BI 655130 then this patient will also be excluded from the FAS. This patient set will be used for (sensitivity) analyses of efficacy and biomarkers.

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/MQRM. These decisions will be documented in the RPM decision log (3).

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 analysed

Class of endpoint	ES	ENTS	SAF	CAS	FAS
Disposition	OR	OR			
Compliance			OR		
Exposure			OR		
iPDs		OR			
Demographic/ baseline characteristics			OR		
Primary endpoint				OC	OC
Secondary safety endpoint			OR		
Secondary (and further) clinical efficacy endpoints					OC
Secondary inflammatory endpoints					OC
Further safety parameters		OR, OC-IR			

i) For explanation of the different approaches with regard to missing data see Section 6.6.
OC = observed cases, OC-IR = observed cases including also values after rescue medication, OR = original results.

Note that the number of patients with available data for an endpoint may differ. For details, see section “Handling of missing data”.

6.5 POOLING OF CENTRES

Given the low number of patients per centre and the primarily descriptive nature of the 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

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 not affected by patients’ rescue medication use (e.g. plasma concentration level of BI 655130), or, if it is not meaningful to apply any imputation rule for the replacement of missing values.

6.6.1 Withdrawals

For all patients, the reason for withdrawal from treatment (e.g., adverse event) must be recorded in the eCRF. These data will be included in the trial database and reported. The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

6.6.2 Efficacy data

For the Mayo and RHI 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. It is not planned to impute missing data for any efficacy endpoint in this trial. Cf. Section 9.1 for details regarding the derivation of (clinical) efficacy endpoints.

Data censoring for rescue medication use

Rescue medication use will be identified on the eCRF. For the purpose of data censoring, the following scenarios are considered rescue therapy in this trial:

- Any medication taken (even single use) after first dose of BI 655130 and on or before end of the on-treatment period which is considered by the investigator to be rescue treatment (as per tick in the CRF);
- Any increase in the dose of background medication for UC after first dose of BI 655130 and on or before end of the on-treatment period (i.e. Treatment phase plus REP) which is considered by the investigator to be rescue treatment (as per tick in the CRF)

The following approach will be used to present the efficacy data:

- Observed cases (OC) approach will include all collected data (based on time windows as described in Section 6.7), 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).

6.6.3 Safety data

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 UC 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.

In principle safety data are displayed using the OR approach (meaning the presentation of data exactly as observed). However, for safety data that are displayed by time point (or visit) of measurement, the following approach will be used:

- Observed cases including rescue (OC-IR) approach will include all collected data (based on time windows as described in Section 6.7), with no imputation performed on the missing data and including all values measured after intake of a rescue medication.

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).

6.6.6 RNA sequencing data

The OC approach (cf. Section 6.6.2) will be used to present the RNA sequencing data.

6.6.7 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.

6.7 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 first 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, unless otherwise specified, 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 on-treatment values or off-treatment values, based on the definition of the study analysis phases in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Frequency tables for these data will be using on-treatment data only. Therefore, no assignment to time windows will be necessary.

All other safety, efficacy and biomarker measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment (which is scheduled for Visit 2). 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 /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1a	Screening	-35 to -9	n/a				
V1b	Screening	-8 to -6	n/a				
V2	Baseline	Day 1	+/-0	1[A]	1[A]	≤1 [A]	1 [A]
V3	Week 1, Day 4	Day 4	+/-0	4	4	2[A]	8
V4	Week 2	Day 15	+/- 1	14	16	9	21
V5	Week 4	Day 29	+/- 2	27	31	22	35
V6	Week 6	Day 43	+/- 2	41	45	36	49
V7	Week 8	Day 57	+/- 2	55	59	50	63
V8	Week 10	Day 71	+/- 2	69	73	64	77
EoT	Week 12	Day 85	-6 to +1	79	86	78	99
FU1	Week 18	Day 127	+/- 5	122	132	100	141
EoO[B]	Week 28	V7 +141days[C]	+5			142	Day of last f-up value[B]

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) will not be assigned to Visit 3. Such data will be listed only.
[B] Note that measurements assigned to the Week 28/EoO visit may represent follow-up measurements (off-treatment period; cf. Table 6.1: 1). Both on-treatment and off-treatment data will be included for analysis of this visit.

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 which are both closest to the planned day and were measured on the same day, the worst value will be selected.

Assignment of 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 "OC" approach defined in Section 6.6.2). Visits which were not assigned a value based on time windows will not be imputed in this trial.

For derivation of the last value on treatment, minimum value on treatment, and maximum value on treatment, all on-treatment values (whether or not selected in any time window; see Table 6.1: 1 for definition of the on-treatment period) 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) before the off-treatment period 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 standards "Standards for Reporting of Clinical Trials and Project Summaries"(10).

A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced and handled by the DMC.

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 treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) 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 and some biomarkers, 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 standards "Standards for 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.

Note that for the analysis of all data in this trial, the primary approach is to report only those data that fall within the on-treatment period. However, for selected displays of endpoints presented by-visit, additional ouputs which include both on- and off-treatment data will also be produced.

Disposition of the patient population participating in the trial will be summarised for the ES by presentation of the frequency of patients screened, entered, screened but not entered, treated, entered but not treated, who completed planned visit at Week 12, who completed all

doses of trial medication as planned, who completed planned observation time, and who were prematurely discontinued, by reason. Patients who completed trial through the planned visit at Week 12 must not be considered to have discontinued trial at any time prior to the lower bound of the Week 12 time window. The vital status of prematurely discontinued patients at EoO visit will also be summarised. Disposition will be listed by country.

The frequency of patients with iPDs, also summarised by whether or not the iPD led to exclusion from the CAS or FAS, will be presented for the ENTS.

The frequency of patients in each of the different analysis sets will also be presented.

Unless explicitly specified otherwise 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.

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 to < 75 years ≥ 75 years
Weight	≤70 kg >70 to ≤80 kg >80 to ≤ 90 kg >90 kg
BMI	< 25 kg/m^2 25 to < 30 kg/m^2 ≥ 30 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.

Characteristics of the trial disease, such as the disease diagnosis and the type of extra-intestinal diagnoses which are present at start of the study, as well as the occurrence of any prior surgery for ulcerative colitis will be descriptively summarized. Any changes in the pre-existing extra-intestinal diagnoses (improved or worsened) as well as the development of newly diagnosed extra-intestinal diagnoses will be listed.

A medication will be considered concomitant to treatment, if it

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

Concomitant medication use (excluding rescue medication, historical medication for UC and background medication) will be summarised with frequency and percentage of patients by preferred name. Summaries will be presented for concomitant medication taken during the on-treatment period (cf. Section 6.1).

The frequency and percentage of patients with previous medication for UC treatment will be displayed.

The frequency and percentage of patients taking any background medication for UC will be tabulated by type of background therapy; any increases or decreases in dose of these medications during the on-treatment period will also be displayed.

Rescue medication use (including via background medication dose increase defined for purpose of rescue use) on or after Visit 2 and before end of the on-treatment period will be summarised separately.

Concomitant use of non-drug therapies will be summarised with frequency and percentage. Summaries will be presented for concomitant non-drug therapies taken any time during the on-treatment period (cf. Section 6.1).

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarised overall via total volume infused (as a % of planned) for the FAS using descriptive statistics (N, mean, SD, minimum, median, maximum). For the patients who discontinued the study treatment prematurely only the visits on or before premature discontinuation will be used for the calculation of overall compliance.

The by visit compliance will be listed only.

The number and percentage of patients with the following overall compliance categories will be presented:

- "< 80% of planned",

- "80 to 120% of planned" and
- "> 120% of planned".

7.4 PRIMARY ENDPOINTS

The pre-processing of the raw read count values will be conducted as described in Section 7.3 of the CTP. The primary endpoint will be evaluated for the CAS. The analysis will be performed as defined in Section 7.3.1 of the CTP. The FDR adjusted P-value based on the Wald test and the log2 fold change, are used to identify deregulated genes.

Definition of deregulated genes
A gene is defined as deregulated at time point i if the FDR adjusted P-value of the Wald test is below 0.01 and if |fold change (time point i vs. baseline)| ≥ 1.3.

The total number of deregulated genes per (post-baseline) time point (V2, V3, V4, V7 and EoT) will be reported.

The following sensitivity analyses may be conducted:

- The number of deregulated genes will be evaluated for the FAS in case this analysis set differs (with regard to RNA analyses) from the CAS
- In case the number of identified deregulated genes is very large (> 5000 deregulated genes at all time points) a smaller threshold for the FDR adjusted P-value will be considered
- In case the number of identified deregulated genes is empty (or includes less than 50 genes at all time points) the 50 genes with the smallest FDR adjusted P-values will be listed per (post-baseline) time point

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

7.5.2.1 Secondary efficacy endpoints

The analysis of CRP, FCP and FLFwill be performed as defined in Section 7.3.2 of the CTP and will be based on theSAF.

The CRP, FCP and FLF will be descriptively summarized by visit as continuous variables. For each marker the absolute value and percent change from baseline will be analysed per treatment group via

- Mean, standard deviation, median, Q1, Q3, normalized IQR (0.7413*IQR), minimum, maximum, gMean

- Error bars for the median with Q1 being the lower end and Q3 the upper end of the bars of the respective outcome variable will be calculated for each time point. This information will be displayed graphically in conjunction with the median.

- Line plots presenting individual values of the respective outcome variable over time. Beside the individual patient lines also a median line will be depicted in all plots for a better visual interpretation.

In plots with absolute values reference lines indicating LLOQ and ULOQ may be included. In addition lower and upper limit of the normal range, if a normal range is available, will be presented.

The analysis of secondary efficacy endpoints will be performed as defined in Section 7.3.2 of the CTP and will be based on the FAS.

Total clincal remission at Week 12 will be assessed based on the proportion of patients with Total Mayo score ≤2 points, and all subscores ≤1 point (cf. Section 9.1.1). The proportion of patients with total clinical remission 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 total Mayo scores (resp. partial MCS), as well as for each of the four subscore (SFS, RBS, PGA and mESS; cf. Section 9.1.1) will also be produced. Furthermore line plots will be produced presenting Mayo score (resp. the Mayo subscores SFS, RBS, PGA and mESS) over time.

7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of trial drug will be tabulated. The duration of infusion [in minutes], the amount of treatment received (actual and weight based), as well as the volume infused [% of planned] will be listed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the SAF and following BI standards. No hypothesis testing is planned.

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 "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (4).

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, on-treatment period or off-treatment period (i.e. follow-up) 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 first BI 655130 administration will be assigned to the on-treatment phase.

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of other significant AEs (sponsor definition based on ICH E3) according to ICH E3 (9) and for the class of AESIs.

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

The following is considered an AESI (cf. CTP section 5.3.5.1):

- Infusion reactions including anaphylactic reaction
- Cytokine release syndrome
- Opportunistic and mycobacterium tuberculosis infections
- Hepatic injury

The investigator identified AESI will be captured from the eCRF and reported as "Investigator reported AESI" table. In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (cf. Table 7.8.1:1).

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Event Concepts

Adverse event of special interest	**Categories**
Infusion/Systemic hypersensitivity reactions including anaphylactic reactions	**Narrow SMQ "Anaphylactic reaction"** **Narrow SMQ "Angioedema"** **Narrow SMQ "Hypersensitivity"**
Severe infections (according to RCTC grading)	**SOC Infections and infestations of at least severe RCTC grade, by HLGT**
Opportunistic and mycobacterium tuberculosis infections	**BIcMQ "Infections":** **Narrow sub-search 8 "Opportunistic infections including Tuberculosis related terms"**
Tuberculosis related terms	**BIcMQ "Infections":** **Narrow sub-search 8.2 "Tuberculosis related terms"** **HLT "Tuberculosis infections"**
Malignant tumours	**(SMQ "Malignancies" – not for display)** **(Sub-SMQ "Malignant or unspecified tumours" – not for display)** **Narrow Sub-SMQ "Malignant tumours"** **Sub-SMQ "Haematological malignant tumours"** **Sub-SMQ "Non-Haematological malignant tumours"**

Based on the specification provided in ICH E3 (9), the sponsor has defined AEs which are to be classified as 'other significant'. For the current trial, these will include those non-serious AEs which were reported with 'action taken = Drug withdrawn' or 'action taken = Dose reduced'.

The frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, drug related SAEs, patients with AESIs, patients with AEs leading to trial discontinuation, and patients with other significant AEs (as described previously) and User-defined Adverse Event Concepts (UDAEC) per SSAP (cf. Table 7.8.1: 1). 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 summarised by treatment, primary system organ class and preferred term. The frequency of patients with SAEs will also be summarised.

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 summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalized values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, 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 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 based upon normalized values and provided by visit(including follow up), including summaries of the last value on treatment, the minimum value on treatment and maximum value on treatment. Graphical displays via box plots will be produced to present each continuous laboratory endpoint over time.

Laboratory values will be compared to their reference ranges; shift tables will be provided for the number of patients with a specific RCTC grade at baseline versus the grade at the last

measurement on treatment, as well as the worst grade on treatment. These analyses will be based on normalized laboratory values.

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 patient's 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 combined with a total bilirubin ≥ 2xULN 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 the ALT and total bilirubin during the on-treatment period will also 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 by treatment using on-treatment data only, including summaries of and will include the last value during on-treatment period, the minimum value during on-treatment period, and the maximum value during on-treatment period.

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 analysed 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 analysed as such. No separate listing or analysis of ECG data will be prepared.

7.8.5 Others

Immunogenicity

The frequency and percentage of patients with ADAs to BI 655130 will be presented, by visit.

ADA will be analyzed descriptively. A potential effect of ADA on PK and safety may be evaluated.

7.9 HANDLING OF DMC ANALYSES

A fully external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details will be provided in a DMC charter.

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-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*001-MCS-50-415_RD-03: "Clinical Trial Analysis Decision Log (template with annotations)", current version; IDEA for CON*
4	*KM Asset* BI-KMED-BDS-HTG-0035 : "Handling of missing and incomplete AE dates", current version; KMED
5	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
6	*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
7	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED
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	*KM Asset BI-KMED-BDS-HTG-0045:*"Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

This is a revised TSAP including the following modifications to the final TSAP

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
Initial	**19-MAY-17**		None	This is the initial TSAP with necessary information for trial conduct
Final	**16-MAY-18**		All	This is the final TSAP
Revised (Version 3.0)	**06-DEC-19**		All	Changes with respect to biomarker analyses and changes due to updated project standards are implemented.