TRIAL STATISTICAL ANALYSIS PLAN

c17115152-02

BI Trial No.:	1368.15
Title:	Trial Statistical Analysis Plan (including Interim analysis after 75% of patients completed the primary endpoint; Primary analysis at Week 16; and, Final trial analysis). Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP). Including Protocol Amendment 2 [c09935708-03]
Investigational Product:	BI 655130
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	23 May 2018 SIGNED
Version:	2.0 Final

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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 limit of quantification
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BM-SAP	Biomarker Statistical Analysis Plan
BMI	Body mass index
BRAVE	BI RAVE®
BRPM	Blinded Report Planning Meeting
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CTC	Common Terminology Criteria
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

Term	Definition / description
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of trial
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FAS	Full analysis set
F/U	Follow-up
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	Immunohistochemistry
IL	Interleukin
IPV	Important protocol violation
IRT	Interactive response technology
kg	Kilogram
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MQRM	Medical quality review meeting
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NRI	No response imputation
NRI-IR	No response imputation including rescue medication
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
PD	Pharmacodynamic(s)
PG	Pharmacogenomic(s)

Term	Definition / description
PGA	Physician Global Assessment
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPP	Palmoplantar Pustulosis
pppPGA	Palmoplantar Pustulosis Physicians Global Assessment
ppPASI	Palmoplantar Pustular Psoriasis Area and Severity Index
PPS	Per protocol set
psvBSA	Plaque psoriasis vulgaris BSA
PT	Preferred Term
PV	Protocol Violation
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
RS	Randomized set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SMQ	Standardised MedDRA query
SOC	System Organ Class
TCM	Trial Clinical Monitor
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification

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 analyses 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, planning of sample size, randomisation.

A separate Biomarker Statistical Analysis Plan (BM-SAP) will complement this TSAP.

Study data will be stored in a trial database within the 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). SAS calling R version 3.0.2 or later (12) may be used for calculation of Reeve's confidence intervals.

This TSAP will document the features of the primary week 16 analysis (to be performed once all randomized patients have completed through the week 16 visit), as well as the final trial analysis (to be performed once all patients have completed the trial). In addition, details regarding the interim analysis to be performed once 75% of patients have completed through the week 16 visit will also be described. Statistical features of an interim analysis performed once 50% of patients had completed through the week 16 visit are described in a separate SAP which was prepared by an external vendor.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (latest version) will be performed as planned with the following adaptations.

The Safety Set as defined in the CTP is referred to as the SAF in this TSAP. In the CTP, it is stated that patients will be analyzed for safety according to the actual treatment received at the randomization visit. Since at each dosing visit multiple vials will be administered for a single infusion - each vial with its own medication number – it is likely that analysis according to the randomized treatment itself may better reflect the fact that the majority of vials that a patient receives will represent the correct treatment assignment according to the randomization schedule. Hence, the analysis of the safety data will be performed according to the randomized treatment, and not the actual treatment received at the randomization visit.

The CTP states, e.g. Section 7.3.1, that a 95% Wilson confidence interval around the unadjusted absolute risk difference versus Placebo will be provided. This statement must be elaborated because the Wilson confidence interval was originally developed for single proportions (see (16)). Newcombe (17) transferred this method to risk differences. Therefore, the confidence interval for risk differences on binary endpoints used in this trial will be based on Newcombe and may correctly be referred to as a Newcombe confidence interval.
Change in plaque psoriasis BSA is listed as a further endpoint in CTP Section 5.1.3 and, for clarification this refers to the absolute change from baseline.

5. ENDPOINTS

For all endpoints and unless explicitly specified otherwise, Week 16 refers to Visit V11 (PE visit) using extended time windows as defined in .

For all endpoints and unless explicitly specified otherwise, Week 24 refers to Visit V12 (Week 24) using extended time windows as defined in Table 6.7: 1.

For all endpoints and unless explicitly specified otherwise, Week 32 refers to Visit 13 (EOT/Week 32) using extended time windows as defined in Table 6.7: 1.

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

5.1 PRIMARY ENDPOINT(S)

Efficacy: ppPASI50 at Week 16

The achievement of ppPASI50 at Week 16 is the primary efficacy endpoint in this trial.

Derivation of the ppPASI and ppPASI50 is described in Section 9.1.

Safety:

The number of patients with drug-related AEs is the primary safety endpoint in this trial. Further details are provided in Section 7.8.1.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

The secondary endpoints are listed below.

- Treatment success defined as achieving a clinical response of 0 or 1=clear/almost clear via PPP Physicians Global Assessment (pppPGA) at Week 16

Derivation of pppPGA is described in Section 9.2.

- ppPASI75 at Week 16

Derivation of ppPASI and ppPASI75 is described in Section 9.1.

- Percent change from baseline in the ppPASI at Week 16

Derivation of ppPASI is described in Section 9.1.

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 either intravenous doses of 300mg or 900mg of BI 655130 solution for infusion (at weeks 0, 4, 8 and 12), or Placebo.

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 EOT visit (Week 32 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 off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last infusion + 140 days.

For the interim analysis to be performed once 75% of patients have completed the planned first 16 weeks of trial, the following data will be used:

- The 16-week data will be summarized up to the minimum of the (analysis-specific data cut-off; study day 141), unless otherwise specified.
- The 24-week data will be summarized up to the minimum of (the analysis-specific data cut-off; study day 197), unless otherwise specified.

The date of the analysis-specific data cut-off will be presented in a Data Cleaning Plan to be developed for the interim analysis on the week 16 data.

For the primary analysis to be performed once all patients have completed through the planned first 16 weeks of trial, the following data will be used:

- The 16-week data will be summarized up to the minimum of the (analysis-specific data cut-off; study day 141), unless otherwise specified.
- The 24-week data will be summarized up to the minimum of (the analysis-specific data cut-off; study day 197), unless otherwise specified.
- The 32-week (EoS) data will be summarized up to the analysis-specific data cut-off.

The date of the analysis-specific data cut-off will be presented in a Data Cleaning Plan to be developed for the primary analysis on the week 16 data.

For the final analysis of the trial to be performed once all patients have completed through the planned 32 weeks of trial, results will be summarized including applicable data from the on-treatment period (Treatment phase plus REP). The selection of data for presentation in this analysis is described in Table 6.7: 1.

Treatment groups for the analysis will be labelled as follows:

- **"300 mg BI "**
- **"900 mg BI"**
- **"Placebo"**
- **"BI Total"** (i.e., across 300mg and 900mg arms)
- **"Overall Total"** (across treatments), where appropriate.

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 BRPM/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 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 summarised into categories and will be captured in the BRPM/DBLM/MQRM 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 BRPM/DBLM/MQRM. 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 summarised and listed.

Table 6.2: 1 Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
A	**Entrance criteria violated**		
A1	**Inclusion criteria not met**		
A1.01	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.	IC01 (i.e., Inclusion criterion 1) Note that IC obtained late (but available at time of analysis) may not lead to exclusion. See section B "Informed consent" for details.	All analyses
A1.02	18-65 years, males or females at Screening LABEL: Age beyond 18-65, not male or female.	IC02 Also check versus derived age for patient.	None
A1.03	Palmoplantar Pustulosis defined as presence of primary, persistent (> 3 months duration), sterile, macro-scopically visible pustules on the palms and/or soles, without or with plaque psoriasis on less than 10% of the body surface area. LABEL: No presence of PPP.	IC03 Also check versus ppPASI that pustule severity > 0 on at least one region	PPS
A1.04	Presence of active pustulation (yellow pustules) on palms and /or soles. LABEL: No active pustulation on palms/soles.	IC04	PPS
A1.05	A minimum ppPASI score of 12 and pppPGA of at least moderate severity at baseline. LABEL: ppPASI < 12, pppPGA not at least mod.	IC05. Also check versus reported pppPGA and derived ppPASI at baseline.	PPS

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code		Description	Comments	Excluded from[1]
	A1.06	Women of childbearing potential (WOCBP)[a] and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. LABEL: Contraception methods not used.	IC06	None
A2		**Exclusion criteria violated** ***General Exclusion Criteria***		
	A2.01	Patients with associated plaque psoriasis ≥ 10% of the body surface area. LABEL: Plaque psoriasis >= 10% of body surface.	EC01. Also check versus derived psvBSA at screening	PPS
	A2.02	Women who are pregnant, nursing, or who plan to become pregnant while in the trial. LABEL: Pregnant or nursing.	EC02	None
	A2.03	Severe, progressive, or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof. LABEL: Severe or uncontrolled disease.	EC03	PPS

[a] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
A2.04	Presence or known history of anti-TNF-induced PPP-like disease. LABEL: Anti-TNF-induced PPP-like disease.	EC04	PPS
A2.05	Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome. LABEL: SAPHO syndrome.	EC05	PPS
A2.06	Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Prochymal). LABEL: Transplanted organ or cell therapy.	EC06	PPS
A2.07	Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly. LABEL: Lymphoproliferative disease.	EC07	None
A2.08	Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. LABEL: Malignancy within last 5 years.	EC08	None

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
A2.09	Patients who have previously undergone allergy immunotherapy for prevention of anaphylactic reactions. LABEL: Previous Allergy immunotherapy.	EC09	None
A2.10	Use of any restricted medication as specified in CTP Table 4.2.2.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator LABEL: Use of restricted medication.	EC10 – based on tick box only.	PPS
A2.11	Administration of live vaccines during the study period or within 6 weeks prior to randomisation. LABEL: Live vaccine within last 6 weeks.	EC11	None
A2.12	History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients. LABEL: History of allergy/hypersensitivity.	EC12	None
A2.13	Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation, as assessed by the investigator. LABEL: Systemic infections within last 2 weeks.	EC13	None

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
A2.14	Chronic or relevant acute infections including human immunodeficiency virus (HIV), viral hepatitis and (or) active or latent tuberculosis (patients with a positive QuantiFERON TB test are excluded. Patients with suspected false positive or undeterminable QuantiFERON TB result may be re-tested). LABEL: Chronic or relevant acute infections.	EC14	None
A2.15	Major surgery performed within 12 weeks prior to randomisation or planned within 32 weeks after randomisation (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator. LABEL: Recent or planned major surgery.	EC15	None
A2.16	Total white blood count (WBC) < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL, or hemoglobin <8.5 g/dL at screening. LABEL: WBC, PLAT, NEU, HGB below limit.	EC16 Also check versus screen Lab values	None
A2.17	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal, or total bilirubin > 1.5x the upper limit of normal (patients with Gilbert's syndrome are not excluded) at screening. LABEL: AST/ALT/TBIL above limits.	EC17 Also check versus screen Lab values (medical review for Gilbert Syndrome)	None

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code		Description	Comments	Excluded from[1]	
	A2.18	Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s). LABEL: Recent enrollment in other study.	EC18	PPS	
	A2.19	Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial. LABEL: Alcohol or drug abuse.	EC19	PPS	
	A2.20	Previous randomisation in this trial. LABEL: Previous randomisation in this trial.	EC20	PPS	
B		**Informed consent**			
	B1	Informed consent not available LABEL: IC not available.	Based on direct assessment, not simply the tick box (which is A1.01). 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 analyses	#
	B2	Informed consent too late LABEL: IC too late.	Informed consent date was after Visit 1	None	

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code		Description	Comments	Excluded from[1]
C		**Trial medication and randomisation**		
C1		**Incorrect trial medication**		
	C1.01	Study drug medication not taken at all LABEL: Study drug medication not taken at all.		PPS, FAS, SAF
	C1.02	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.	PPS
C2		**Incorrect Dosing**		
	C2.01	Actual administered dose above planned LABEL: Actual dose above planned	Can only be finally judged after DBL since unblinding information is required. <u>Placebo</u> patient who • receives ≥100mg of verum overall • or receives ≥100mg of verum on at least one specific visit will be considered to be an IPV. A <u>BI 300mg</u> patient who jointly fulfils all of the following: • Is randomized to the 300mg group • At least one of the following: o received ≥ 20% above planned amount of verum overall o received ≥ 50% above planned amount of verum on at least one specific visit will be considered to be an IPV. Here, the planned amount of verum on a	PPS

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
		specific visit is 300mg. The planned amount of verum overall is • 300mg if discontinuation before visit V6 • 2*300mg if discontinuation before V8 • 3*300mg if discontinuation before V10 • 4*300mg if discontinuation on or after V10 A <u>BI 900mg</u> patient who jointly fulfills all of the following: • Is randomized to the 900mg group • At least one of the following: o received ≥20% above planned amount of verum overall o received ≥ 20% above planned amount of verum on at least one specific visit will be considered to be an IPV. Here, the planned amount of verum on a specific visit is 900mg. The planned amount of verum overall is • 900mg if discontinuation before visit V6 • 2*900mg if discontinuation before V8 • 3*900mg if discontinuation before V10 • 4*900mg if discontinuation at or after V10	

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code	Description	Comments	Excluded from[1]
C2.02	Actual administered dose below planned LABEL: Actual dose below planned	Can only be finally judged after DBL since unblinding information is required. A Placebo patient can not be below planned. A <u>BI 300mg</u> patient who jointly fulfills all of the following: • Is randomized to the 300mg group • At least one of the following: o received 20% below planned amount of verum overall o received 50% below planned amount of verum on at least one specific visit will be considered to be an IPV. Here, the planned amount of verum on a specific visit is 300mg. The planned amount of verum overall is • 300mg if discontinuation before visit V6 • 2*300mg if discontinuation before V8 • 3*300mg if discontinuation before V10 • 4*300mg if discontinuation on or after V10 A <u>BI 900mg</u> patient who jointly fulfills all of the following: • Is randomized to the 900mg group • At least one of the following: o received ≤ 20% below planned amount of verum	PPS

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code		Description	Comments	Excluded from[1]	
			overall o received ≤ 50% below planned amount of verum on at least one specific visit will be considered to be an IPV. Here, the planned amount of verum on a specific visit is 900mg. The planned amount of verum overall is • 900mg if discontinuation before visit V6 • 2*900mg if discontinuation before V8 • 3*900mg if discontinuation before V10 • 4*900mg if discontinuation at or after V10		
C3		**Randomization not followed**			
	C3.01	Treated without randomisation LABEL: Treated without randomisation.	Patient treated according to eCRF, but not randomised according to IVRS.	RS, SAF, FAS, PPS	
C4		**Medication code broken**			
	C4.01	Medication code broken before week 16 without just cause LABEL: Code broken early without just cause.	Medication code was broken prior to DBL for the week 16 analysis for no valid reason. Final decision at the DBL meeting for the Week 16 analysis based on medical judgment.	PPS	#
	C4.02	Medication code broken after week 16 without just cause LABEL: Code broken late without just cause.	Medication code was broken after DBL for the week 16 analysis for no valid reason. Final decision at final DBL based on medical judgment.	None	#

Table 6.2: 1 (cont'd) Important protocol violations

Category / Code		Description	Comments	Excluded from[1]	
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short LABEL: Washout too short.		PPS	#
D2		**Prohibited medication use**			
	D2.01	Use of restricted medication as per CTP Table 4.2.2.1: 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 16 LABEL: Restricted medication prior to week 16.		PPS	#
D3		**Mandatory medication not taken**	<not applicable>		
E		**Missing data**	<not specified>		
F		**Study specific analysis**	<not specified>		
F1		**Other trial specific violation**			
	F1.01	PE assessment more than 1 week before planned day LABEL: PE assessment > 1 week before planned.		PPS	
F2		**Certain violations of procedures used to measure primary or secondary efficacy data**	<not specified>		
G		**Other safety related violations**			
	G1.01	Pregnancy test not done for woman of child bearing potential LABEL: Pregnancy test not done.	Pregnancy test not done at any visit where such is scheduled and the patient did not yet complete follow-up.	None	

PV will be detected manually; PE = Primary endpoint
Source: BI reference document 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (2).
[1] See Section 6.3 for population definitions

6.3 PATIENT 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 display of patient disposition.

- Randomized set (RS)
  This patient set includes all patients who were randomized into the trial.
  It will be used for display of patient analysis sets and patients with IPVs.

- Safety analysis set (SAF)
  This patient set includes all randomized patients who received at least one dose of study drug. It will be the main analysis set for presentation of safety. Treatment assignment will be as randomized.

For the interim analysis once 75% of patients have completed through the week 16 visit, the following additional patient sets will be defined.

- Full analysis set week 16 - 75 (FAS wk 16 - 75)
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint and who were randomized more than 99 days before the data cut-off date (specific for the 75% interim); qualifying patients who did not provide any primary endpoint data, even partial data of the primary endpoint, for any visit post day 99, and who had not discontinued the trial post day 99, will be excluded. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy up to week 16.

- Full analysis set week 24 - 75 (FAS wk 24 - 75)
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint and who were randomized more than 141 days before the data cut-off date (specific for the 75% interim); qualifying patients who did not provide any primary endpoint data, even partial data of the primary endpoint, for any visit post day 141, and who had not discontinued the trial post day 141, will be excluded. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy data up to week 24.

For the primary analysis to be performed once all patients have completed through the week 16 visit, the following additional patient sets will be defined.

- Full analysis set (FAS)
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy up to week 16.

- Per protocol set (PPS)
  This patient set includes all patients in the FAS who adhered to the CTP without any

IPV which was flagged for exclusion from the PPS in the table above.
This set will be used for sensitivity analysis on the primary efficacy endpoint.

- Full analysis set week 24 (FAS wk 24 - primary)
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint and who were randomized more than 141 days before the data cut-off date (specific for the week 16 primary analysis); qualifying patients who did not provide any primary endpoint data for any visit post day 141, and who had not discontinued the trial post day 141, will be excluded. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy data up to week 24.

- Full analysis set week 32 (FAS wk 32 - primary)
  This patient set includes all patients in the SAF who had a baseline measurement available for the primary endpoint and who were randomized more than 197 days before the data cut-off date (specific for the week 16 primary analysis); qualifying patients who did not provide any primary endpoint data for any visit post day 197, and who had not discontinued the trial post day 141, will be excluded. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy data up to week 32.

For the final trial analysis, the definition of FAS and PPS will be identical to those analysis sets derived for the week 16 primary analysis. Additional analysis sets to be defined for the final trial analysis include:

- Pharmacokinetic parameter set (PKS)
  This patient set includes all patients in the SAF who provide at least one evaluable observation for the BI 655130 concentration, which was not flagged for exclusion.
  This patient set will be used for the display of concentrations.

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 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 analysed

Class of endpoint	Patient set[1]					
	RS	ES	SAF	FAS wk 16 – 75 FAS wk 24 – 75 FAS FAS wk 24 - primary FAS wk 32 - primary	PPS	PKS
Disposition	OR	OR				
Compliance			OR	OR		
Exposure			OR	OR		
IPVs	OR					
Demographic/baseline characteristics			OR	OR		
Primary efficacy endpoint				NRI, NRI-IR, OC, OC-IR, LOCF	NRI, OC	
Primary safety endpoint			OR			
Secondary efficacy endpoints (Binary)				NRI, OC, LOCF		
Secondary efficacy endpoints (Continuous)				LOCF, OC		
Further safety parameters			OR, OC-IR			

[1] Patient set as applicable to the particular time-point of the analysis (75% of patients with week 16, primary analysis on week 16, or final trial analysis).
For explanation of the different approaches with regard to missing data see Section 6.6.
OR = Original results (i.e., ignoring visit windows)
NRI = No Response Imputation
NRI-IR = No Response Imputation including rescue medication
OC = Observed cases
OC-IR = Observed cases including also values after rescue medication
LOCF = Last observation carried forward

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.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 of the CTP describes the handling of missing data.

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows).

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

6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

6.6.2 Efficacy data

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.

Missing data imputations at the interim analysis once 75% of patients have completed the week 16 visit, as well as at the primary analysis of week 16 once all patients have achieved the week 16 visit, will be performed using all available on-treatment data observed up to the respective analysis cut-off date.

Binary efficacy endpoints

The primary endpoint in this study, ppPASI50, is a binary outcome derived from the ppPASI score, which itself is regarded as a continuous endpoint. The ppPASI may be missing (e.g. if one of its components is missing). Imputation approaches as described in this section for the binary endpoints will be applied to impute the binary outcome directly as opposed to imputing on any underlying, i.e. continuous, distribution.

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed as the primary imputation approach (analysis type: No Response Imputation [NRI]):

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits 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

If a patient takes a rescue medication (as defined in Section 5.4.4) for the treatment of PPP, then all data subsequent to the intake of such rescue will be considered to represent a failure to achieve a response.

A sensitivity analysis on this approach will be performed whereby data collected after rescue intake will be included (i.e. not set to failure); analysis type: NRI-IR.

Further approaches to the handling of missing data will be performed as follows:

- Observed cases (analysis type: 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 (analysis type: 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.
- Last observation carried forward (analysis type: LOCF) will be used for selected binary endpoints. For LOCF, carrying forward of baseline information is allowed. Where applicable, LOCF carries last value prior to any use of rescue medication forward within the on-treatment period.

Missing data after premature discontinuation will not be imputed when following the OC and OC-IR approach.

Categorical efficacy endpoints with more than two outcomes

Some endpoints or their subscores are categorical with more than two potential outcomes (e.g. PGA, DLQI). As a general, rule imputation will only be applied on the complete score.

However, if a subscore is presented by itself, application of, e.g., LOCF may be applied within the subscore. Imputed subscores will not be combined to provide a complete score.

Continuous efficacy endpoints

For efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach, if applicable, will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

The primary technique for the handling of missing data of continuous endpoints will therefore be the OC approach (described above for the binary efficacy endpoints). Last observation carried forward (LOCF) may, however, also be used for some continuous secondary or further endpoints (analysis type: LOCF). These endpoints include % change in the ppPASI,

For LOCF, carrying forward of baseline information is allowed.

For sensitivity analysis, an MMRM may be fit after application of the LOCF approach. This approach may be referred to as: LOCF-MMRM.

6.6.3 Safety data

From CTP Section 7.5: *With respect to safety evaluations, it is not planned to impute missing values.*

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

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, rescue, and historical medication for PPP 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 of study medication 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.

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.

6.7 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 either on- or off-treatment values based on the definition 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 for such data.

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.

A graphical analysis of the ALT and total bilirubin will be performed (so called eDISH plot) based on the available data obtained during the on-treatment period.

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 V2). These extended time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs, 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)
V1	Screening	- 28 to -7	n/a				
V2	Day 1	Day 1	n/a	1 [A]	1	1 [A]	1
V3	Day 4	Day 4	+/- 2	2	6	2	5
V4	Day 8	Day 8	+/- 3	5	11	6	11
V5	Week 2	Day 15	+/- 3	12	18	12	22
V6	Week 4	Day 29	+/- 3	26	32	23	36
V7	Week 6	Day 43	+/- 3	40	46	37	50
V8	Week 8	Day 57	+/- 3	54	60	51	64
V9	Week 10	Day 71	+/- 3	68	74	65	78
V10	Week 12	Day 85	+/- 3	82	88	79	99
For 75% Interim analysis and for Primary analysis (Week 16)							
V11	PE	Day 113	+/- 3	110	116	100	Minimum of (cut-off, 141) [B]
V12	Week 24	Day 169	+/- 7	162	176	142	Minimum of (cut-off, 197) [B]
V13 [D]	EOT/Week 32/FU	Day 225	+/- 7	218	232	198	Minimum of (cut-off, LD [C] + 140) [B]
For final trial analysis							
V11	PE/Week 16	Day 113	+/- 3	110	116	100	141
V12	Week 24	Day 169	+/- 7	162	176	142	197
V13	EOT/Week 32/FU	Day 225	+/- 7	218	232	198	LD [C] + 140
For On-/Off- treatment displays (final trial analysis only)							
	EOT/Week 32/FU	Day 225	+/- 7			198	Day of last f-up value [B]

Days are counted relative to the day of first 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 Day 1. Such data will be listed only.

[B] The cut-off date will be specified in the data cleaning plan for the 75% interim analysis or 16-week analysis.

[C] LD = Day of Last dose/infusion received

[D] V13 will additionally be presented for the primary analysis at week 16 (but not for the interim analysis)

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, 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 "NRI" and the "OC" approaches defined in Section 6.6).

For visits without an assigned value based on time windows, a value will thereafter be imputed as defined in Section 6.6. Imputation of efficacy endpoints, when applicable, will be performed based on all available observations obtained during the on-treatment period, irrespective of whether the observation was selected in any time window.

7. PLANNED ANALYSIS

All efficacy analyses will be purely exploratory in nature. The following analyses are planned at different stages throughout the trial.

- **75% Interim analysis (Week 16)**

This analysis is performed when 75% of patients have completed 16 weeks of the study (75% interim analysis).

The cut-off date for inclusion of data into the analysis of efficacy, based upon the planned date of attendance of the 44th patient (i.e. approximately 75% of the 60 planned patients) to the PE visit, will be described in a separate data cleaning plan, which will include details on the degree to which trial data will be cleaned prior to performing the analysis. The individual patient cut-off date for inclusion of data into the analysis is described in Table 6.7: 1.

Main efficacy analyses will display visits up to Week 16 only based on the FAS wk 16 – 75. Additional displays of the efficacy will present data up to week 24 only based on the FAS wk 24 – 75. All available data will be used for imputation purposes prior to data truncation for the analysis.

Selected outputs for the following endpoints will be generated. Details on the planned analyses are provided in Section 9.6:

- Disposition
- Demographic and baseline characteristics
- Concomitant medication use
- Exposure
- ppPASI50
- ppPASI, change from baseline and percent change from baseline

- pppPGA ≤ 1 (yes/no)

No safety data will be analyzed

Details on the 75% interim analysis specified above will be done by an external vendor.

Only selected individuals will be unblinded. Since the study is planned to continue in a blinded manner through Week 32, a logistics (and access) plan will be developed in order to describe the processes to be implemented to protect the integrity of the ongoing trial through the final trial analysis.

No separate report is planned to be written for this analysis.

- **Primary Analysis (Week 16)**

This analysis is performed when all patients have completed 16 weeks of the study (primary analysis).

The cut-off date for inclusion of data into the analysis of efficacy, based upon the planned date of attendance of the last randomized patient to the PE visit, will be described in a separate data cleaning plan, which will include details on the degree to which trial data will be cleaned prior to performing the primary week 16 analysis. The individual patient cut-off date for inclusion of data into the analysis is described in Table 6.7: 1.

Main efficacy analyses will display visits up to Week 16 only based on the FAS. Additional displays of the efficacy will present data up to week 24 only based on the FAS wk 24, and up to week 32 (EoS) based on the FAS wk 32.
All CRF (efficacy and safety) data as well as further data related to safety such as the central Lab data files will be summarized at the time of the week 16 primary analysis. Other selected data that may be displayed at this time includes:

The primary analysis will be performed by the sponsor. Only selected individuals will be unblinded for this analysis. Since the study is planned to continue through an additional 16 weeks of further blinded follow-up, a logistics (and access) plan will be developed in order to describe the processes to be implemented in order to protect the integrity of the ongoing trial through the final analysis.

No separate report is planned to be written for the primary analysis. All analyses are planned to be documented in a clinical trial report which is to be prepared at the end of the trial.

- **Final analysis (Week 32)**

The analysis of the entire efficacy, safety, and biomarker data collected through the full 32 weeks of follow-up will be performed once all entered patients have completed the trial (up to EOT/Week 32 Visit); at that time point, a final database lock will be done and all on-treatment data through week 32 will be reported.

General Remarks

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, including those collected during the off-treatment period. 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 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

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.

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 outputs which include both on- and off-treatment data will also be produced. Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients screened, entered, screened but not entered, treated, entered but not treated, who completed all doses of trial medication as planned, who completed the PE visit (Visit 11), who completed the EOT visit, and who were prematurely discontinued, by reason. Disposition will be listed by country.

The frequency of patients with IPVs will be presented for the RS by treatment. The IPVs will be listed per patient indicating whether or not the IPV led to exclusion from patient sets analyzed.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Descriptive statistics will be presented by treatment for demographic parameters and baseline characteristics, based on the SAF and FAS.

For the continuous variables described below, categories are defined in Table 7.1: 1. These variables will be 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 < 65 years ≥ 65 years < 65 years 65 to < 75 years 75 to < 85 years ≥ 85 years
Weight	≤70 kg >70 to ≤80 kg >80 to ≤ 90 kg >90 kg
BMI	< 25 kg/m2 25 to < 30 kg/m2 ≥ 30 kg/m2
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 SAF.

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.

Concomitant diseases which are present at start of the study, as well as characteristics of the trial disease, will be descriptively summarized by treatment.

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 study analysis phases).

Concomitant medication use (excluding rescue medication) will be summarised with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for

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

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

Use of rescue medication will be summarised separately (see Section 7.6.5).

Concomitant use of non-drug therapies will be summarized with frequency and percentage. Summaries will be presented for

- concomitant non-drug therapies taken any time prior to Day 1 (the day of start of trial treatment)
- 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 and by visit via total volume infused (as a % of planned) for the FAS and SAF using descriptive statistics (N, mean, SD, minimum, median, maximum). The volume infused (as a % of planned) is defined as the volume infused at a visit (in ml as recorded in the eCRF), divided by 60 ml (the volume the patient should have received), times 100.
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 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".

The number of patients who received a dose will be tabulated per visit.

7.4 PRIMARY ENDPOINT

This binary primary efficacy endpoint will be described using patient frequencies and percentages for the FAS (or its derivatives - see Section 6.3).

The analysis of the primary endpoint will be based on Section 7.3.1 of the CTP:

From CTP Section 7.3.1: *The primary analysis of the unadjusted absolute risk difference versus Placebo will be calculated simply as the difference in the observed proportion of patients with ppPASI50 at week 16 for each treatment scenario, for the FAS. A 95% Wilson confidence interval around this difference will also be provided. In addition, a parametric bootstrap 95% confidence interval will be generated by sampling from the binomial distribution on each treatment with number of patients and observed proportion of responders per treatment representing the sampling parameters. A hierarchical approach to the testing of both scenarios for BI 655130 versus Placebo will, however, be performed for the primary analysis in order to control for multiplicity arising as a result of the multiple treatment comparisons.*

The method to provide confidence intervals for single proportions will be based on Wilson (16). The method to provide confidence intervals for unadjusted risk differences is derived from the Wilson method by Newcombe (17).

As described in Section 7.2 of the CTP, there will be no formal hypothesis testing performed in this trial.

From CTP Section 7.3.1: *Exploratory analyses of the primary endpoint will include, in the absence of model convergence issues due to occurrence of low cell frequencies, the difference in the proportion of patients with a ppPASI50 between BI 655130 and placebo being analysed, for the FAS, using a logistic regression approach with a logit link via PROC LOGISTIC in SAS®. Fixed classification effects will include treatment and presence or absence of plaque psoriasis (yes/no).*

The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale.

Confidence intervals to support the logistic regression of the primary endpoint will be calculated using the cumulative distribution function method of Reeve (14), instead of the delta method that was originally proposed in the CTP. More specifically, as suggested in

Reeve (14), a numerical search algorithm will be employed to find the quantiles x_A of the cumulative distribution function, $F_{\widehat{\Delta p}}$, such that $F_{\widehat{\Delta p}}(x_A) = A$, where A = 2.5% and A = 97.5% and $F_{\widehat{\Delta p}}$ is given by equation (10) in Reeve (14). R code that will be used to implement this is provided in Appendix 9.5.

7.5 SECONDARY ENDPOINTS

Analysis of secondary endpoints is described in Section 7.3.2 of the CTP.

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

From CTP Section 7.3.2: *For the secondary binary endpoints, for the FAS, the unadjusted absolute risk difference versus Placebo will be calculated and a 95% Wilson confidence interval around this difference will also be provided. In addition, a parametric bootstrap 95% confidence interval will also be generated.*

As defined for the primary endpoint, the method to provide confidence intervals for single proportions will be based on Wilson (16), and for unadjusted risk differences is derived from the Wilson method by Newcombe (17).

For secondary continuous endpoints, mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach (see [CTP] Section 7.3).

From CTP Section 7.3: *[REML-based] analyses will include the fixed, categorical effects of treatment and visit, presence or absence of plaque psoriasis (yes/no), as well as the treatment-by-visit interaction, and continuous, fixed covariates of baseline "endpoint" and baseline-by-visit interaction. An unstructured covariance structure will be used to model the within-patient measurements. Exploratory confidence intervals will be based on least-squares mean differences to Placebo using a two-sided $\alpha = 0.05$.*

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Patients will be analysed according to the stratum (presence or absence of plaque psoriasis) as indicated on the eCRF.

SAS code for the above model will be based on the following structure:

```
PROC MIXED DATA=alldat cl method=reml;
  CLASS visit trt stratum subject;
  MODEL ept = base visit trt stratum visit*trt base*visit / ddfm=kr s CL;
  REPEATED visit / subject= subject type=un r rcorr;
  LSMEANS visit*trt / pdiff=all om cl alpha=0.05 slice=visit;
RUN;
```

For handling of non-convergence see Section 9.7.

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 summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) per visit and overall.

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the SAF 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) across all treatment arms, or, if a total column across all arms is not foreseen in the table, by total frequency (within system organ class) across the two BI arms.

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. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first BI 655130 administration will be assigned to the on-treatment phase.

An overall summary of AEs will be presented by treatment.

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

The following is considered an AESI in this trial:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- *an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or*
- *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

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 (primary safety endpoint of this trial). Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial, and patients with other significant AEs (as described previously). 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 standardized values and provided by visit, including summaries of the last value on treatment, the minimum value on treatment and maximum value on treatment.

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 standardized 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 or 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, respiratory rate 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, including summaries of the last value during on-treatment period, the minimum value during on-treatment period, and the maximum value during on-treatment period (see Table 6.1: 1 for definition of the 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 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.

7.9 HANDLING OF DMC ANALYSES

A partially external DMC, independent of the trial and project teams, was 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 was produced and finalized prior to first patient randomised into the trial. Further details were provided in a DMC charter.

8. REFERENCES

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9. ADDITIONAL SECTIONS

9.1 ppPASI AND RELATED ENDPOINTS

The Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI) is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. The adaptation from PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis, will be used in this trial (Table 9.1: 1).

This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 to 72. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).

Table 9.1: 1 Palmoplantar Pustulosis Psoriasis Area and Severity Index

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (in%)* (A)	0	<10	10<30	30<50	50<70	70<90	90 - 100

* where area assessed is glabrous skin on the palms/ soles

The Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI)

The ppPASI is calculated as follows as a weighted sum of the scores obtained for E, P, D and A in Table 9.1: 1:

ppPASI = [(E+P+D) x A x 0.2 (right palm)]

+ [(E+P+D) x A x 0.2 (left palm)]

+ [(E+P+D) x A x 0.3 (right sole)]

+ [(E+P+D) x A x 0.3 (left sole)]

Missing values for severity or area of involvement will not be imputed. If at least one of these values is missing, then the ppPASI score will also be considered to be missing. However, individual items and subscores may be presented as applicable.

Achievement of Decrease in ppPASI ≥ xx% (ppPASIxx)

Achieving a response of xx% or larger decrease from baseline in ppPASI score is denoted as ppPASIxx. The ppPASIxx represents a binary variable with values of 0 (= non-response) or 1 (=response).

It is calculated based on the following approach (with xx typically taking a value of 50, 75 or 90):

$$\text{If } \left\{ \frac{ppPASI(BL) - ppPASI(current)}{ppPASI(BL)} \times 100 \right\} \geq xx \text{ then ppPASIxx = 1,}$$

else ppPASIxx = 0.

The modified (precise) ppPASI

A modified ppPASI score (precise ppPASI) will be calculated based on the absolute number/percent affected area rather than using the ranges. Therefore, the calculation will include a factor 0.06 to scale to the same range (0 to 72) as the ppPASI described above. It is based on the following calculation:

Modified ppPASI = [(E+P+D) x (0.06 x Area affected (expressed in %) in right palm) x 0.2]
+ [(E+P+D) x (0.06 x Area affected (expressed in %) in left palm) x 0.2]
+ [(E+P+D) x (0.06 x Area affected (expressed in %) in right sole) x 0.3]
+ [(E+P+D) x (0.06 x Area affected (expressed in %) in left sole) x 0.3]

Missing values for severity or area of involvement will not be imputed. If at least one of these values is missing, then the modified ppPASI score will also be considered to be missing. However, individual items and subscores may be presented as applicable.

ppPASI severity (by component)

Within each component (E, P or D), the mean severity across all body areas (both palms and both soles) is calculated and presented for each component separately. For example, for Erythema, present $(E_{\text{right palm}} + E_{\text{left palm}} + E_{\text{right sole}} + E_{\text{left sole}})/4$.

Within a component, a missing value in one body area leads to a missing value for the component.

Present the results separately "(by component)".

ppPASI severity (by palms or soles)

Among the two palms only, calculate the ppPASI (palms) score via the components E, P, or D as well as the area (A) but replacing the region factor of 0.2 with a factor of 0.5 (total range combining both palms of 0 to 72):

$$\text{ppPASI (palms)} = 0.5 * \{ \ [(E_{\text{right palm}}+P_{\text{right palm}}+D_{\text{right palm}}) \times A_{\text{right palm}}] + [(E_{\text{left palm}}+P_{\text{left palm}}+D_{\text{left palm}}) \times A_{\text{left palm}}] \ \}$$

If at least one of the two palms has a missing value, then the ppPASI (palms) score will be missing.

Repeat for the ppPASI (soles) score but replacing the region factor of 0.3 with a factor of 0.5.

Present results separately for each of "(palms or soles)".

PPSI-proxy (using most severely affected area at baseline)

Within each area (right palm, left palm, right sole, left sole) sum the severities of components E, P and D; select the worst area at baseline among the four (highest score).
If there are more than one body regions with highest severity at baseline, select the first area in following order: Right Sole, Left Sole, Right Palm, Left Palm from these multiple body regions as the worst affected area. The sum score for the worst area represents the PPSI-proxy (range 0 to 12).

9.2 THE PALMOPLANTAR PUSTULOSIS PHYSICIAN GLOBAL ASSESSMENT (pppPGA)

Palmoplantar Pustulosis Physician Global Assessment (pppPGA) relies on clinical assessment of the patient's skin presentation on the palms and soles. The investigator (or qualified site personnel) scores the lesions on the most severely affected palmoplantar surface from 0 – 4 as clear, almost clear, mild, moderate or severe.

Scoring of pppPGA is described in Table 9.2: 1 below.

Table 9.2: 1 PPP Physician Global Assessment (pppPGA)

Score	Wording	Detailed description
0	Clear	No signs of PPP; no scaling or crusts or pustule remains
1	Almost clear	Slight scaling and/or erythema and / or slight crusts; very few new (yellow) and / or old (brown) pustules
2	Mild	Scaling and/or erythema and/or crusts; visible new (yellow) and/or old (brown) pustules of limited number and extent
3	Moderate	Prominent scaling and/or erythema and / or crusting; prominent new (yellow) and / or old (brown) pustules covering most of the area involved
4	Severe	Severe scaling and/or erythema and / or crusting; numerous new (yellow) or old (brown) pustules with and/or without major conflence covering the entire area of at least 2 palmoplantar surfaces

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0 Initial	**24-May-2017**		None	This is the initial TSAP with necessary information for trial conduct. First approved version before first patient in.
2.0 Final	**23-May-2018**		(all)	This is the final TSAP, approved before database snapshot for the 75% interim analysis. It is also intended to be the final TSAP before database lock for the primary analysis.