TRIAL STATISTICAL ANALYSIS PLAN

c27696306-02

BI Trial No.:	1368-0032
Title:	Phase IIa multicentre, randomized, double-blind, placebo controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis Including Revised Protocol Amendment #3 [c23806995-04]
Investigational Product:	BI 655130
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	20 Aug 2020 SIGNED
Version:	2.0

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AD	Atopic dermatitis
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALQ	Above limit of quantification
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim-customised MedDRA query
BLQ	Below the lower limit of quantification
BM-SAP	Biomarker Statistical Analysis Plan
BMI	Body mass index
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
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
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency

Term	Definition / description
EoS	End of study
ES	Enrolled set
EX	Exclusion
FAS	Full analysis set
FAS-C	Full analysis set including completers
gCV	Geometric coefficient of variation
gMean	Geometric mean
HIV	Human immunodeficiency virus
HLT	High level term
HLGT	High level group term
IC	Informed consent
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IN	Inclusion
iPD	Important protocol deviation
IQR	Interquartile range
IQRMP	Integrated Quality and Risk Management Plan
IRT	Interactive response technology
LD	Last dose
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model Repeated Measures
MQRM	Medical quality review meeting
N	Number of observations
NA	Not applicable
NR	Non-Responder
OL	Open label
PD	Pharmacodynamic(s)
PE	Primary endpoint

Term	Definition / description
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set
Q1	1st quartile
Q3	3rd quartile
R	Responder
RAGe	Report appendix generator
RCTC	Rheumatology common toxicity criteria
REML	Restricted maximum likelihood
RPM	Report planning meeting
RS	Randomized set
SAE	Serious adverse event
SAF	Safety analysis set
SAF-OL	Safety analysis set in the open-label treatment period
SAP	Statistical analysis plan
SCORAD	SCORing of Atopic Dermatitis
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SMQ	Standardised MedDRA query
SOC	System Organ Class
TB	Tuberculosis
TSAP	Trial statistical analysis plan
UDAEC	User-defined AE concepts
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the 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 trial statistical analysis plan (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.

[redacted]

Pharmacokinetic (PK) parameters will be calculated using WinNonlinTM software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

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).

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 including data beyond week 16 (to be performed once all patients have completed the trial). A separate Interim Statistical Analysis Plan describes the analyses that were performed once 75% of patients had completed at least 4 weeks of treatment.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

NA

5. ENDPOINTS

For all endpoints and unless explicitly specified otherwise, Week numbers refer to specific Visit numbers using extended time windows as defined in Table 6.7: 1 and Table 6.7:2.

For all endpoints and unless explicitly specified otherwise, End-of-Study visit refers to V10 (Week 28) for Responders and V11 (Week 44) for Non-Responders, using extended time windows as defined in Table 6.7: 1 and Table 6.7:2.
Responders are defined as patients who attain at least 75% reduction in Eczema Area and Severity Index (EASI) score compared to baseline at Week 16. Non-Responders are defined as patients who do not achieve at least 75% improvement from baseline in EASI score at Week 16.

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

Definition of baseline is provided in Section 6.7.

5.1 PRIMARY ENDPOINT

The primary efficacy endpoint is change from baseline in EASI Score at Week 16.

The absolute and percent change from baseline will be analysed as well as the absolute values at visits.
The EASI total score assesses the extent of disease (area affected) at four body regions: head, trunk, upper limb, and lower limb for which the following scoring will be used:

% involvement	0	1 to <10%	10 to <30%	30 to <50%	50 to <70%	70 to <90%	90 to 100%
Region score	0	1	2	3	4	5	6

The severity of each of the four clinical signs: erythema, induration/papulation, excoriation, and lichenification using the following severity scale for each body region:

- 0 for “None”
- 0.5 for “None to Mild”
- 1 for “Mild”
- 1.5 for “Mild to Moderate”
- 2 for “Moderate”
- 2.5 for “Moderate to Severe”
- 3 for “Severe”

The following formula will be used to derive the EASI Total Score:

EASI Total Score = ($Erythema_{Head}$ + $Edema/papulation_{Head}$ + $Excoration_{Head}$ + $Lichenification_{Head}$)×($Head_{Region\ Score}$)×0.1 + ($Erythema_{Trunk}$ + $Edema/papulation_{Trunk}$ + $Excoration_{Trunk}$ + $Lichenification_{Trunk}$)×($Trunk_{Region\ Score}$)×0.3 + ($Erythema_{Upper\ limb}$ + $Edema/papulation_{Upper\ limb}$ + $Excoration_{Upper\ limb}$ + $Lichenification_{Upper\ limb}$)×($Upper\_limb_{Region\ Score}$)×0.2 + ($Erythema_{Upper\ limb}$ + $Edema/papulation_{Lower\ limb}$ + $Excoration_{Lower\ limb}$ + $Lichenification_{Lower\ limb}$)×($Lower\_limb_{Region\ Score}$)×0.4

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

The secondary endpoints are listed below.

- Drug-related Adverse Events (AEs)

  Numbers and percentages of patients with drug-related AEs will be presented.

- Change from baseline in EASI Score at Week 4

  The absolute and percent change from baseline as well as the absolute values at visits will be analysed.

- EASI50/75 responders at Week 4 and 16

  Numbers and percentages will be analysed.

  Achievement of Decrease in EASI ≥ xx% (EASIxx)

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

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

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

  else EASIxx = 0.

- Change from baseline in SCORing of Atopic Dermatitis (SCORAD) at Week 4 and 16

  The absolute and percent change from baseline as well as the absolute values at visits will be analysed.

  The SCORAD consists of three elements: extent of disease, intensity of disease, and subjective symptoms (Pruritus and Sleep Loss). It sums up to a maximum of 103 points. Two of the SCORAD items are subjective symptoms (C) assessed on Visual Analog Scales (VAS) from 0 to 10: Pruritus VAS and Sleep Loss VAS.

  The following formula will be used to calculate the SCORAD element assessing the Extent of the disease:

  $$\underline{\textit{Extent Score(A)}} = (Face_{Front}\times 4.5 + Upper\_Limbs_{Front}\times 9 + Trunk_{Front}\times 18 + Lower\_limbs_{Front}\times 18 + Genitals_{Front}\times 1 + Head_{Back}\times 4.5 + Upper\_limbs_{Back}\times 9 + Trunk_{Back}\times 18 + Lower\_limbs_{Back}\times 18)/100$$

  In the SCORAD element assessing the Intensity of the disease the following scoring will be used:

  - 0 for “Absence”
  - 1 for “Mild”
  - 2 for “Moderate”
  - 3 for ”Severe”

  The SCORAD Intensity score element will be derived using the formula below:

  $$\underline{\textit{Intensity Score(B)}} = (Erythema\_Score + Edema/Papulation\_Score + Oozing/crusts\_Score + Excoriations\_Score + Lichenification\_Score + Dryness\_Score)$$

  For the SCORAD element subjective symptoms the following formula will be used:

  $$\underline{\textit{Subjective symptoms(C)}} = Pruritus\_VAS + Sleep\_Loss\_VAS$$

  The following formula will be used to calculate the SCORAD Total Score:

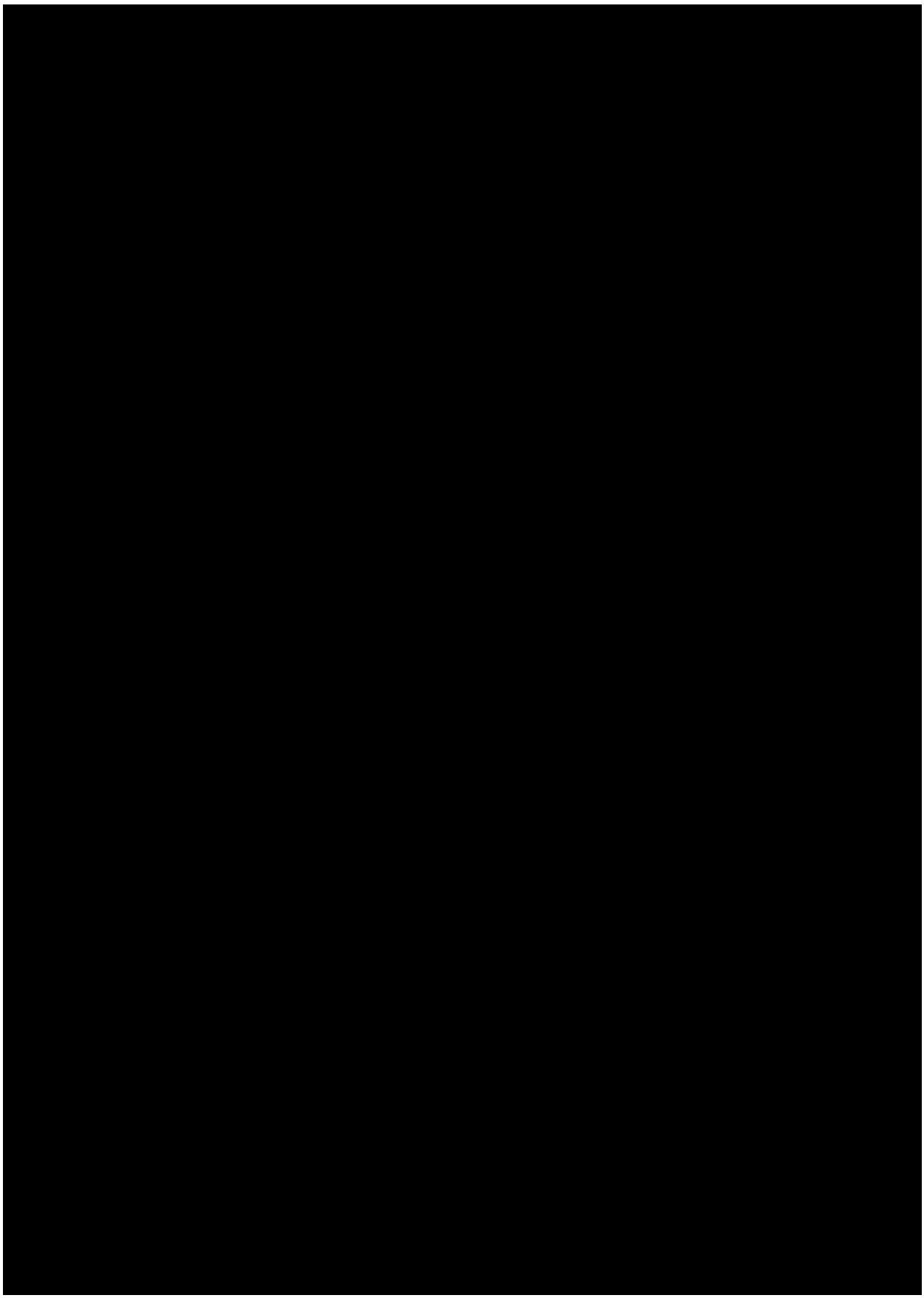
  $$\underline{\textbf{SCORAD Total Score}} = (A/5) + (B\times 7/2) + C$$

- Patients achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in the Investigator's Global Assessment (IGA) at Week 4 and 16

  Numbers and percentages will be analysed.

  IGA score allows investigators to assess the overall disease severity at one given time point. It is a 5-point scale with: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. The overall IGA score includes the assessment of erythema, induration/papulation, lichenification, and oozing/crusting. For the first three sections the following scale will be used:
  - "None"
  - "Barely Perceptible" ("Minimal" for lichenification)
  - "Slight but Definite"
  - "Clearly Perceptible"
  - "Marked"

  For oozing/crusting the available answers are "None" or "Present."
  Following instructions will be used to derive the **IGA Score**:
  - IGA Score = 0 if the answers in all sections are "None".
  - IGA Score = 1 if any of the following occurred: (erythema is barely perceptible OR induration/papulation is barely perceptible OR lichenification is minimal) AND no oozing/crusting is observed.
  - IGA Score = 2 if any of the following occurred: (erythema is slight but definite (pink) OR induration/papulation is slight but definite OR lichenification is slight but definite), AND no oozing/crusting is observed.
  - IGA Score = 3 if any of the following occurred: erythema is clearly perceptible (dull red) OR induration/papulation is clearly perceptible OR lichenification is clearly perceptible OR oozing/crusting is present.
  - IGA Score = 4 if any of the following occurred: erythema is marked (deep or bright red) OR induration/papulation is marked OR lichenification is marked. Note: For IGA score of 4, the oozing/crusting may be present.



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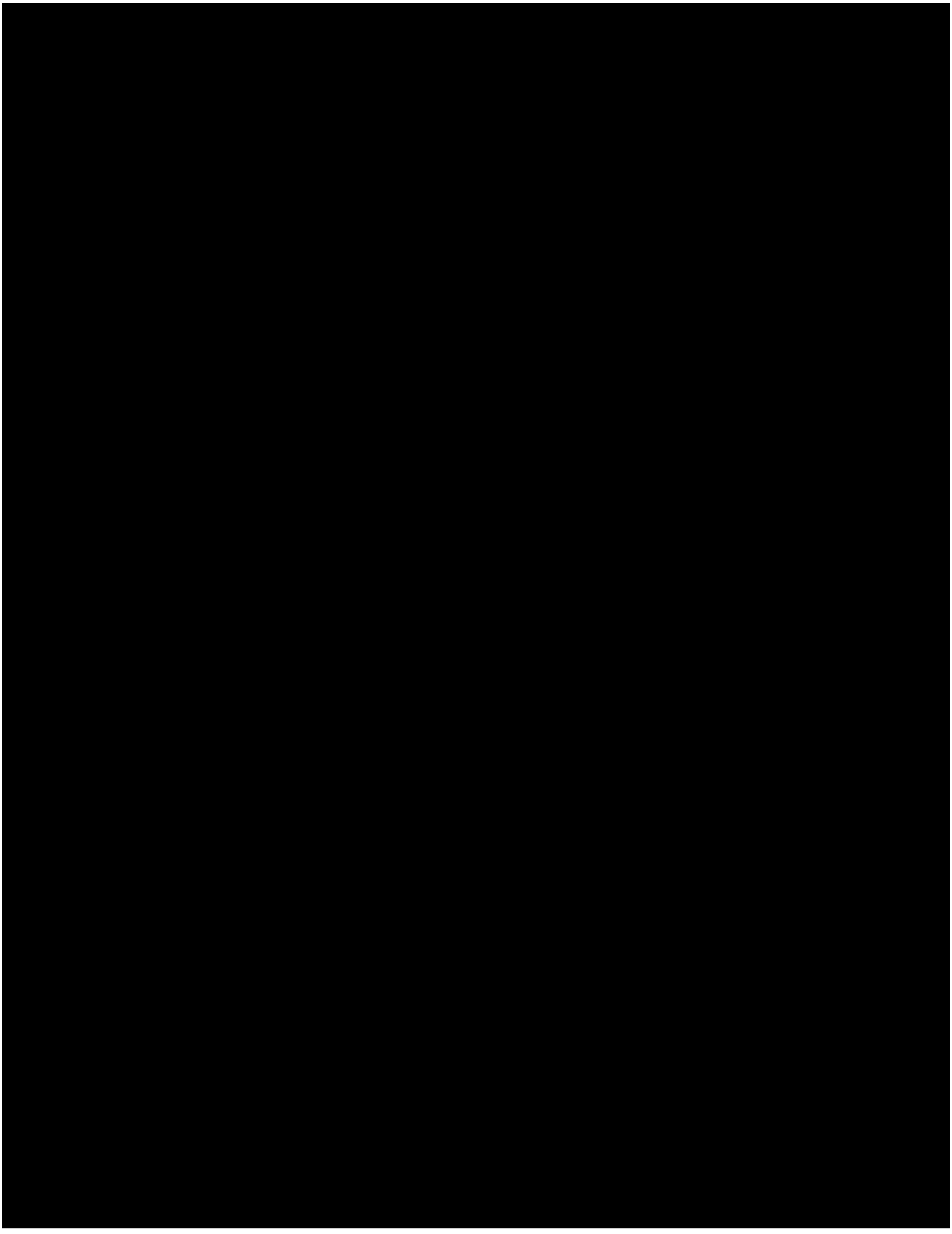
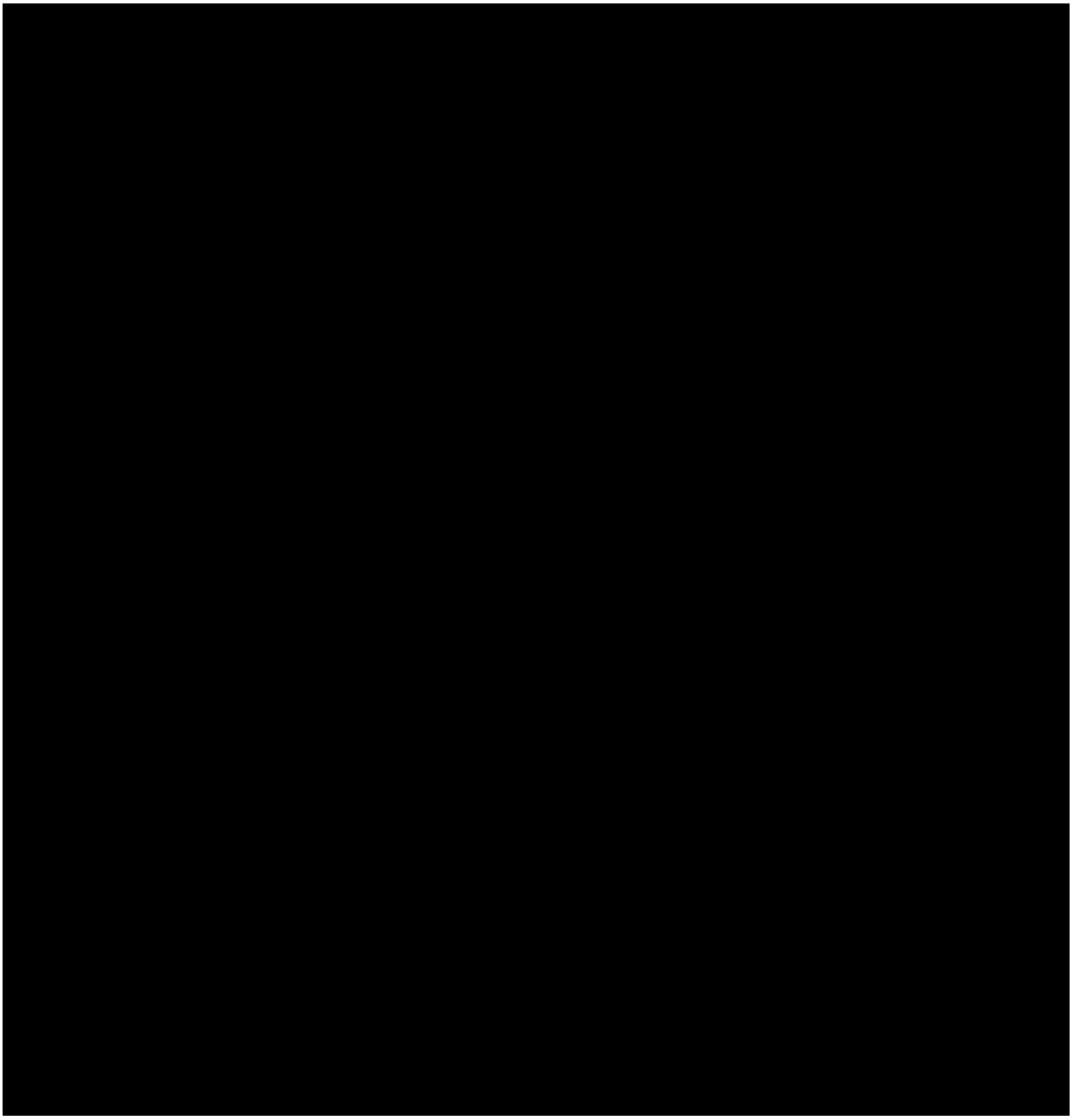
Safety will be assessed based on:

- Adverse events
- Serious adverse events (SAEs)

[redacted]





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.

In the blinded treatment phase, all patients will receive either intravenous doses of 600mg of BI 655130 solution for infusion (at weeks 0, 4, 8, and 12), or Placebo.

At Week 16, all patients will be evaluated with the EASI Score. Non-responders (EASI < 75) will be re-allocated to receive BI open label trial drug from Week 16 through Week 28; they will be followed until Week 44. Responders (EASI >= 75) will be re-assigned to receive no further trial treatment but will be expected to come to all visits up to Week 28, when EOS visit is planned.

The following trial periods/phases are defined:

Table 6.1: 1 Flow chart of trial period/phases

Trial phase	Description	Start (included)	End (excluded)
Screening phase	Screening	Date of informed consent	Date of start of first infusion of study drug (day 1).
Blinded Treatment phase	Randomised On-treatment period	Date of start of infusion of first study drug (Day 1)	Week 16 visit date + 1 day
Open label Treatment phase[1]	Re-allocation period (Either open label BI655130 or No treatment)	Week 16 visit date + 1 day	Date of EoS Participation visit + 1 day

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] Non-responders (i.e. EASI<75) at Week 16 will be re-allocated to BI655130 600mg IV open label and will continue in the trial until Week 44. Responders (EASI>=75) at Week 16 will be re-allocated to no treatment and will be observed until Week 28 or the day when they return to a 50% reduction in EASI score (EASI50) and start the treatment in the extension trial.

Patients who discontinue the treatment but will continue on trial visits will be included in analyses with the available data. For patients who discontinue trial prematurely only available data will be used in the analyses.

For the final analysis of the trial to be performed once all patients have completed through the planned period, results will be summarized including the data from the reallocation period (Open-label Treatment phase). Results will be presented separately and in descriptive manner. The time windows for data presentation in this analysis are described in Table 6.7: 1. In addition, analyses including the data from the double-blind period (initially used for the Primary Analysis) will be re-run after the final database lock.

To distinguish between assignment to trial periods/phases and AE assignments, please, refer to Table 6.1:2.

Table 6.1: 2 AE assignment to analysis treatment groups

Randomised treatment	**EASI75 response at Week 16**	**Open-label period**	**AE assignment to analysis treatment group**
PLACEBO	Responder	No Treatment	AE that occurred between first randomised study drug intake and min[(EoS visit date), (last randomised study drug administration date + 112 days)] will be analysed under PLACEBO. AEs occurring later will be listed only.
PLACEBO	Non-Responder	BI 655130 Treatment	AE that occurred between first randomised study drug intake and Week 16 visit date (excluding) will be analysed under PLACEBO. AEs occurring later will be analysed under Open-label BI Treatment.
BI 655130	Responder	No Treatment	AE that occurred between first randomised study drug intake and min[(EoS visit date), (last randomised study drug administration date + 112 days)] will be analysed under BI 655130. AEs occurring later will be listed only.
BI 655130	Non-Responder	BI 655130 Treatment	AE that occurred between first randomised study drug intake and Week 16 visit date (excluding) will be analysed under BI 655130. AEs occurring later will be analysed under Open-label BI Treatment.

Treatment groups up to Week 16 will be labelled as follows:

- **"Speso 600 mg IV q4w"** (i.e., patients randomised to BI 655130 600 mg)
- **"Placebo"** (i.e., patients randomised to Placebo)
- **"Overall Total"** (across treatments: Placebo and BI 655130 600 mg), where appropriate.

Treatment groups for the efficacy analysis after week 16 will be labelled as follows:

- **"Open-label treatment: No Treatment"**
  - **“Placebo”** (i.e., patients randomised to Placebo in the double-blind treatment period and who did not receive an open-label BI 655130 treatment starting from Week 16 (V7))
  - **“Speso 600 mg IV q4w”** (i.e., patients randomised to BI 655130 in the double-blind treatment period and who did not receive and open-label BI 655130 treatment starting from Week 16 (V7))
  - **“Total”** (i.e., patients randomised either to Placebo or BI 655130 in the double-blind treatment period and who did not receive an open-label BI 655130 treatment starting from Week 16 (V7))
- **"Open-label treatment: Speso 600 mg IV q4w"**
  - **“Placebo”** (i.e., patients randomised to Placebo in the double-blind treatment period and received an open-label BI 655130 treatment starting from Week 16 (V7))
  - **“Speso 600 mg IV q4w”** (i.e., patients randomised to BI 655130 in the double-blind treatment period and received and open-label BI 655130 treatment starting from Week 16 (V7))
  - **“Total”** (i.e., patients randomised either to Placebo or BI 655130 in the double-blind treatment period and received an open-label BI 655130 treatment starting from Week 16 (V7))

Treatment groups for the safety analysis for the whole trial will be labelled as follows:

- **"Speso 600 mg IV q4w"** (i.e., patients randomised to BI 655130 600 mg)
- **"Placebo"** (i.e., patients randomised to Placebo)
- **"Total Speso 600 mg IV q4w OL"** (i.e., patients randomised either to Placebo or BI 655130 600mg and assigned to BI 655130 600 mg open-label treatment at Week 16)

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 meetings, 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 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 Integrated Quality and Risk Management Plan (IQRMP) (3). The following table 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 are indicated as such in Table 6.2: 1.

iPDs will be summarised and listed.

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 < 18	IN02 Also check versus derived age for patient.	None
	A1.01a	Age out of range LABEL: Age > 75	IN02 Also check versus derived age for patient.	None
	A1.02	Moderate to severe atopic dermatitis per CTP not confirmed, ie.: BSA of atopic dermatitis involvement at screening < 10% OR BSA of atopic dermatitis involvement at baseline < 10% OR EASI at screening < 7.1 (12 in the CTP as inclusion criterion) OR EASI at baseline < 16 OR IGA at screening < 3 OR IGA at baseline < 3 LABEL: Disease severity out of range (moderate-severe).	IN04 Also check versus BSA, IGA, and EASI	None

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

Category / Code		Description	Comments	Excluded from[1]
	A1.03	Diagnosis of AD for less than 1 year. LABEL: Disease duration too short.	IN03 Also check versus derived disease duration	None
	A1.04	History of inadequate response to topical corticosteroid as judged by the investigator not documented or documented response to topical corticosteroid. LABEL: Lack of inadequate response to topical corticosteroid	IN05 Also manual review versus listing of concomitant therapies (eCRF page, form: Atopic Dermatitis Therapy History (Topical)) and listing of reasons for discontinuation	None
	A1.05	Patient is not willing to use a standard emollient for the duration of the study LABEL: Lack of willingness to use an emollient	IN06	None
	A1.06	Women of childbearing potential are not ready or able to 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. LABEL: Not sufficient or no contraception method used	IN07	None
A2		**Exclusion criteria violated** ***General Exclusion Criteria***		
	A2.03	Use of topical corticosteroids (or agent) for atopic dermatitis within 7 days prior to first dose of trial treatment LABEL: Use of topical corticosteroids – wash-out period too short.	EX01 Also manual review versus listing of concomitant therapy used	None

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

Category / Code	Description	Comments	Excluded from[1]
A2.04	Use of systemic corticosteroids (or agent) for atopic dermatitis within 4 weeks prior to first dose of trial treatment. LABEL: Use of systemic corticosteroids – wash-out period too short.	EX02 Also manual review versus listing of concomitant therapy used	None
A2.05	Women who are pregnant or plan to become pregnant while in the trial. LABEL: Pregnancy.	EX03	None
A2.06	Currently enrolled or less than 30 days or 5half lives since participation in another investigational device or drug trial, or receiving other investigational treatment(s). LABEL: Participation in another drug development program.	EX11	None
A2.07	Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy. LABEL: History of transplantation or stem cell therapy.	EX04	None
A2.08	Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. LABEL: Malignancy.	EX05 Also manual review versus listing of AEs and listing of medical history	None

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

Category / Code	Description	Comments	Excluded from[1]
A2.09	Use of any restricted medication as specified in CTP, Table 4.2.3.1:1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator. LABEL: Restricted medication use.	EX06 Also manual review versus listing of concomitant therapy	None
A2.10	History of allergy/hypersensitivity to the systematically administered trial medication agent or its excipients. LABEL: History of allergy/hypersensitivity	EX07 Also manual review versus listing of medical history	None
A2.11	Active systemic infections (Fungal and bacterial disease) during the last 2 weeks prior to first drug administration, per investigator assessment. LABEL: Washout after systemic infection too short.	EX08 Also manual review versus listing of AEs and listing of medical history	None
A2.12	Relevant chronic or acute infections (exception: common cold) including HIV or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection. LABEL: Chronic or acute infection.	EX09 Also manual review versus listing of medical history	None

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

Category / Code	Description	Comments	Excluded from[1]
A2.13	Patients with active TB. Patients with a positive QuantiFERON TB test during screening, if patient had previous diagnosis of active or latent TB and has not completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion). Patients with suspected false positive or indeterminate QuantiFERON TB result may be retested once. If the QuantiFERON TB test result is not available or provides indeterminate results after repeat testing: A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive. LABEL: Tuberculosis.	EX10 Also manual review versus listing of medical history	None
A2.14	Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than AD, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and ECG), or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of data. LABEL: General health condition.	EX12 Also manual review versus listing of medical history, vital signs, laboratory results	None

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

Category / Code		Description	Comments	Excluded from[1]	
	A2.15	Major surgery (major according to the investigator) performed within 12 weeks prior to first study drug administration or planned during the study. LABEL: Time since major surgery <12 weeks before start of treatment or planned during the study.	EX13 Also manual review versus listing of medical history and AEs	None	
	A2.16	Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold ULN elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin. LABEL: Hepatic disease.	EX14 Also manual review versus listing of AEs and laboratory results	None	
B		**Informed consent**			
	B1	Date of informed consent missing OR No signature available LABEL: IC not available.	IN01 In this case: Patient's data will not be used for the reporting in CTR	All analyses	#
	B2	Informed consent too late. LABEL: IC too late.	Informed consent date was after V1	None	

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

Category / Code		Description	Comments	Excluded from[1]	
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication**			
	C1.01	Randomisation order not followed Different medication administered at randomization visit, than the patient was randomised to (i.e. drug kit recorded in eCRF is from a different treatment group than the drug kit assigned by IRT) LABEL: Wrong treatment dispensed at randomisation visit.	Usually in this case patient should continue with the first medication administered for the whole trial.	None	
	C1.02	Wrong kit assigned to the patient. LABEL: Wrong medication assigned.	After unblinding check the numbers of kits assigned by IRT system versus the randomised treatment.	None	
	C1.03	Patient treated without randomisation. LABEL: Treatment without randomisation.	Patient treated according to eCRF, but not randomised according to IRT.	None	
C2		**Non-compliance**			
	C2.01	Non-compliance with study drug administration - administered dose too high LABEL: Too high dose taken	The dose administered above 600 mg	None	#
	C2.02	Non-compliance with study drug administration - administered dose too low LABEL: Too low dose taken	The dose administered below 600 mg Check versus total infusion volume reported on the eCRF	None	

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

Category / Code		Description	Comments	Excluded from[1]	
C3		**Incorrect trial medication dispensed**			
	C3.01	Incorrect trial medication dispensed	This could be e.g. the case if wrong medication was dispensed by investigator at any visit after randomisation visit. After unblinding it needs to be checked whether this is an iPD.	None	
		LABEL: Incorrect trial medication dispensed			
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short	Check versus concomitant medication end date	None	#
		LABEL: Washout too short.			
D2		**Prohibited medication use**			
	D2.01a	Use of restricted medication (other than steroid) with potential influence on efficacy data	Manual review versus listing of concomitant medication	None	#
		LABEL: Restricted medication other than steroid.			
	D2.01b	Use of restricted medication (systemic steroid) with potential influence on efficacy data	Manual review versus listing of concomitant medication	None	#
		LABEL: Restricted medication (systemic steroid).			
	D2.01c	Use of restricted medication (skin-related steroid) with potential influence on efficacy data	Manual review versus listing of concomitant medication	None	#
		LABEL: Restricted medication (skin-related steroid).			

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

Category / Code		Description	Comments	Excluded from[1]	
F		**Study specific analysis**			
F1		**Other trial specific violation**			
	F1.01	Study drug intake too early (i.e., <14 days after the previous intake) LABEL: Study drug intake outside time window (<14 days)	Check actual visit dates	None	
	F1.02	Primary endpoint (PE) assessment more than 1 week before planned day LABEL: PE assessment >1 week before planned.	Check actual visit dates versus the scheduled ones	None	
F2		**Certain violations of procedures used to measure primary or secondary efficacy data**			
	F2.01	Missing data entries of EASI for Week 4. LABEL: Missing EASI at Week 4.	Missing data for EASI Score– interim analysis.	None	
	F2.02	Missing data entries of EASI for Week 16. LABEL: Missing EASI at Week 16.	Missing data for PE.	None	
	F2.03	Patient incorrectly assigned as responder/non-responder for EASI at V7 (in IRT system)	Manual review vs. data entered into the IRT system	None	#

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

Category / Code		Description	Comments	Excluded from[1]	
G		**Other safety related violations**			
	G1.01	Pregnancy test not done for woman of child bearing potential per CTP flowchart 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	
	G1.02	Pregnancy or nursing LABEL: Pregnancy or nursing.	Medical review: Pregnancy or nursing during the trial up to 16 weeks after the last study drug administration	None	#

PD will be detected manually; PE = Primary endpoint; IC = Informed consent; IN = Inclusion criterion; EX = Exclusion criterion
Source: BI reference document: "Identify and Manage Important Protocol Deviations (iPD)" [001-MCS-40-413] (2).
[1] See Section 6.3 for population definitions
* tick box on eCRF page and derived data will be checked.

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 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 disposition, baseline and demographic characteristics, and patients with IPDs.

- 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 based on the actual treatment administered. Actual treatment refers to the actual treatment administered at the first dosing. This treatment should be followed through the whole trial, regardless of the initially randomised treatment.

- Safety analysis set in the open-label treatment period (SAF-OL)
  This patient set includes all randomized patients who received at least one dose of study drug and received study medication after re-allocation visit (i.e., after Week 16 visit). Treatment assignment will be based on the actual treatment administered starting from Week 16 visit. This analysis set will the main set for presentation of the safety data for the treatment re-allocation period.

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

- Full analysis set including completers (FAS-C)

  This analysis set includes all patients in the FAS who completed double-blind treatment, i.e., did not prematurely discontinue treatment up to (and including) Week 12.

- 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.

Handling of Treatment Misallocations in Analysis Sets

If a patient was administered incorrect treatment during the study, then for safety the following will be used in addition:

- If a patient is planned to receive multiple dose administrations of BI 655130 (i.e. randomized to BI 655130 600 mg IV every 4 weeks), then patients will be reported under their actual treatment from the randomisation visit for safety analyses because the overall safety profile is expected to be driven by the amount of drug received in totality over the entire treatment duration. It is not expected that the safety profile will deviate from the planned treatment regimen if the subject receives only one or two vials of the incorrect medication at only some dosing occasions.

- If a patient is planned to receive multiple dose administrations of placebo, then patients will be reported under their randomized treatment group for safety analysis if the patient was administered no vials of BI 655130 at any visit. If the patient was administered at least one vial of BI 655130 during the treatment period, then the patient will be assigned to BI 655130 600 mg IV treatment group.

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.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Withdrawals

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

6.6.2 Efficacy data

Binary efficacy endpoints

The primary imputation approach for binary endpoints will be No Response Imputation (NRI) described below.

1. If a patient prematurely discontinues study medication administration for any reason, then all data subsequent to the discontinuation will be considered to be missing. The cut-off date to be used is the last dose of study medication administration + 4 weeks (including the extended time windows).
2. For endpoints which are measured at multiple visits, if there are data at visits both before and after the visit with a missing outcome, then impute as success (a responder) 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).

For all patients with a missing visit outcome, impute as a failure to achieve a response (non-responder).
In addition, for all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), frequency tables with observed data will be presented.

Categorical efficacy endpoints with more than two outcomes

Some endpoints or their subscores are categorical with more than two potential outcomes (e.g. IGA, DLQI). As a general rule, imputation will only be applied on the complete score. In case if a categorical subscore is analysed separately, no imputation will be applied (only observed data will be analysed).

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.

6.6.3 Safety data

From CTP Section 7.5: *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 BI-KMED-BDS-HTG-0035 (4)).

Partial start and stop dates for concomitant medications 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.
- If the day and month of the start date are missing then the start date is set to 1st January of the year.
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

[redacted]

6.6.6 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. Note: Every effort should be made to have at least data on year of the first diagnosis populated.
- 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. For definitions used in Safety analyses, refer to Section 7.8.

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 will not be based on visits. 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 in the trial phase, all values from the relevant phase (whether or not collected in any time window; see Table 6.1: 1 for definition of the trial periods/phases) 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 date of EoS Participation visit 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, and biomarker measurements to visits for statistical analysis of the double-blind treatment period

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			-∞	0
V2	Day 1	Day 1	n/a	1 [A]	1	1 [A]	1
V3	Week 2	Day 15	+/- 3	12	18	2	21
V4	Week 4	Day 29	+/- 3	26	32	22	42
V5	Week 8	Day 57	+/- 3	54	60	43	70
V6	Week 12	Day 85	+/- 3	82	88	71	98
V7	Week 16	Day 113	+/- 3	110	116	99	Week 16 visit date

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.

Table 6.7:1 needs to be taken only when the measurement occurs between randomisation date and primary endpoint visit date (Week 16 visit date). Any unscheduled visits after Week 16 visit date will not be taken into account in Table 6.7:1.

For measurements after the primary endpoint visit date (Week 16 visit date), including unscheduled visits, refer to the Table 6.7:2.

Table 6.7: 2 Time windows for assignment of efficacy, safety lab, vital signs, and biomarker measurements to visits for statistical analysis after Week 16 visit date

Visit number/ name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V7.1*	Week 16OL					Week 16 visit date+1	126
V8	Week 20	Day 141	+/- 3	138	144	127	154
V9	Week 24	Day 169	+/- 3	166	172	155	182
V10**	EoS for R	Day 197	+/- 3	194	200	183	210/ LD+16 weeks/EoS visit date
V11a***	EoS for NR	Day 228	+/- 3	225	231	211	238/ LD+16weeks /EoS visit date
V11b***	EoS for NR	Day 309	+/- 3	306	312	239	LD+16weeks /EoS visit date

Days are counted relative to the day of first treatment, which is defined as Day 1.
LD = Last dose of treatment
EoS = End of Study
R = Responder
NR = Non-Responder
* For vital signs, measurements after EASI responder-non-responder assessment are assigned to Week 16 (V7), after first open-label (OL) treatment
** V10 EoS applies to patients who responded at Week 16 (up to LD+16 weeks); Non-responders receive the last dose of the BI655130 at that Week 28 visit (up to day 252)
*** V11a and V11b apply to patients who did not respond at Week 16 and were re-allocated to BI655130 treatment

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.

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.

- **Primary Analysis (Week 16)**

The primary analysis is planned to be performed when all patients complete week 16 visit of the trial.
A memorandum is planned to summarize the results of the primary analysis at Week 16.

- **Final analysis (Week 44)**

The analysis of the entire efficacy, safety, PK, and biomarker data collected through the full 44 weeks of follow-up will be performed once all entered patients have completed the trial (up to EoS for Non-Responders/Week 44 Visit); at that time point, a final database lock will be done and all data through week 44 will be reported. The majority of biomarkers will be reported outside the CTR.

General Remarks
The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" [BI-KMED-BDS-HTG-0045] (10) with the exception of those generated for PK.
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

For PK analyte concentrations, the following descriptive statistics will additionally be calculated:

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

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "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.

Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients screened, entered/randomised, screened but not entered, treated, entered but not treated, who completed all doses of trial medication as planned (overall, in the double-blind treatment period, and in the BI open-label treatment period), who prematurely discontinued study drug administration by reason (overall, in the double-blind treatment period, and in the BI open-label treatment period), patients still on-going in the study, those, who completed the observational period as planned, who prematurely discontinued study participation, who completed Week 4 visit (V4), who completed the re-allocation visit at Week 16 (V7), number of patients reallocated to BI open-label treatment. Disposition will be listed by country.

The frequency of patients with iPDs will be presented for the RS by treatment. The IPDs will be listed per patient indicating whether or not the iPD led to exclusion from patient sets analysed.

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 RS.

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	< 30 years ≥ 30 years < 50 years 50 to < 65 years 65 to < 75 years ≥ 75 years < 65 years ≥ 65 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
Disease severity based on EASI total score	>7 to ≤ 21 (moderate) >21 (severe)
Disease severity based on IGA score	= 3 (moderate) = 4 (severe)
Age at disease onset	≤12 years old >12 years old <18 years old ≥18 years old

7.2 CONCOMITANT DISEASES AND MEDICATION

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

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 will be summarised with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for:

- historical medication taken before the first study drug administration of the double-blind period (i.e., the start and stop dates are before the date of the first study medication infusion)
- concomitant medication that started before the double-blind treatment (i.e., concomitant medication start date was prior to first study treatment administration)
- concomitant medication started and taken within the double-blind period (from the day of the first treatment administration to the date of the Week 16 visit – 1 day)
- concomitant medication that started on or after the Week 16 (V7) visit date (i.e., concomitant medication start date was on the Week 16 visit date or thereafter)

The frequency and percentage of patients with previous medication for AD will be displayed as per data collected in the eCRF (i.e., separately for topical, non-topical, and non-topical/non-drug therapies). Frequencies by preferred name and treatment arm will be displayed.

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

- historical non-drug therapies taken before the first study drug administration of the double-blind period (i.e., the start and stop dates are before the date of the first study medication infusion)
- concomitant non-drug therapies that started before the double-blind treatment (i.e., concomitant non-drug therapy start date was prior to first study treatment administration)
- concomitant non-drug therapies started and taken within the double-blind period (from the day of the first treatment administration to the date of the Week 16 visit – 1 day)
- concomitant non-drug therapies that started on or after the Week 16 (V7) visit date (i.e., concomitant non-drug therapy start date was on the Week 16 visit date or thereafter)

In addition, the frequency and percentages of patients with concomitant AD medication used during the double-blind period (i.e., starting at baseline visit or thereafter) will be displayed by ATC3 and preferred name and by treatment.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarised overall via total volume infused (as a % of planned) for the 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 100 ml (the volume the patient should have received).
In case the total volume administered (including saline) is greater than 100 mL (including flushing volume), 100mL i.e., full infusion will be used in the analysis.

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 100% of planned"

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

7.4 PRIMARY ENDPOINT

The primary endpoint for this trial is the percentage change from baseline in EASI Score at Week 16.

7.4.1 Primary analysis of the primary endpoint

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 is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the percent change from baseline of EASI score after 16 weeks of treatment.*

The analysis will include the fixed, categorical effects of treatment-by-visit interaction, stratification factor Asian/Non-Asian, and the fixed continuous effects of baseline-by-visit interaction. Visits will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α=0.10 (two-sided

90% confidence intervals (CI)). The primary treatment comparison will be the contrast between treatments at Week 16.

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=0.10 slice=visit;
RUN;
```

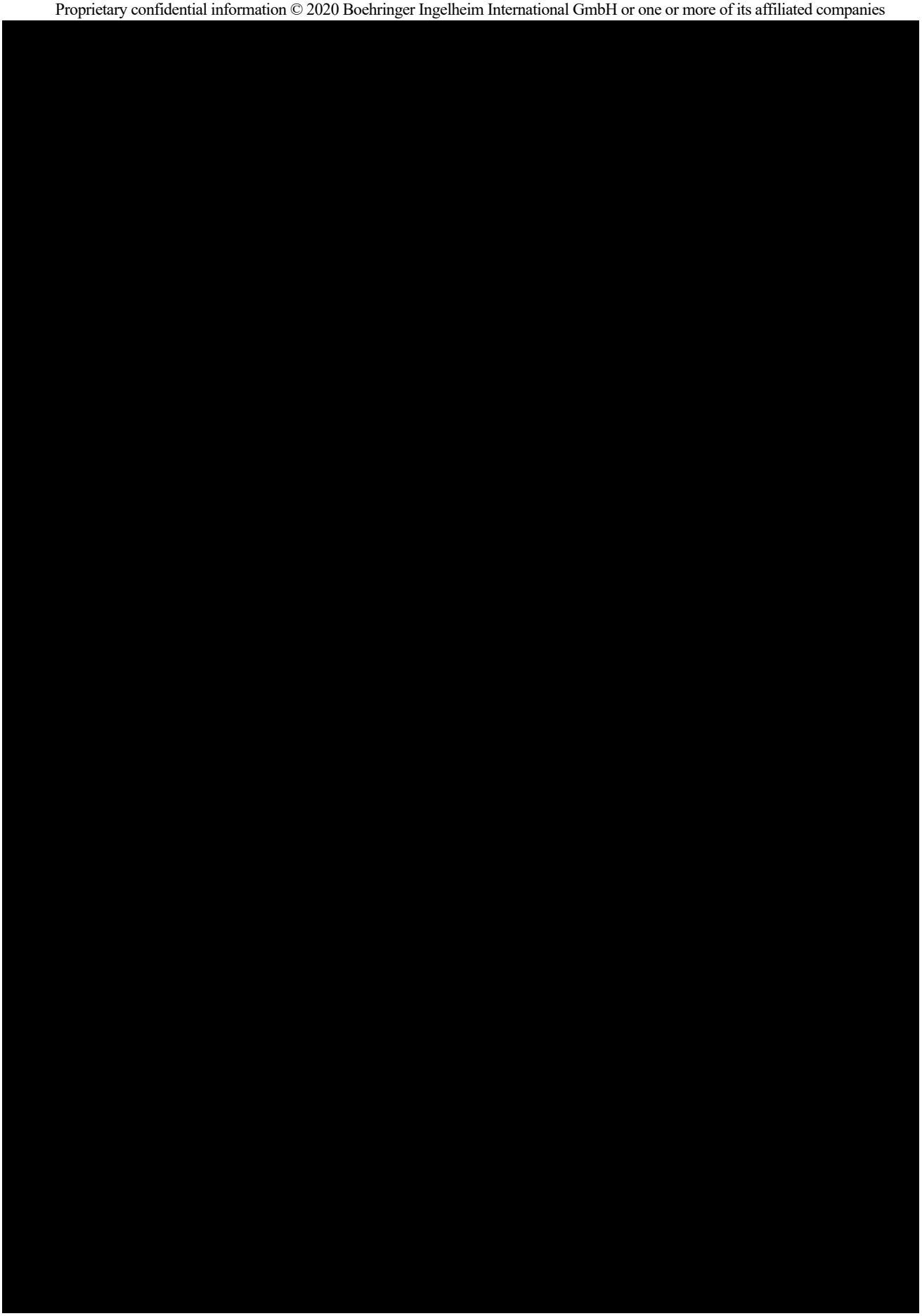
For handling of non-convergence see Section 9.1.

The following hypothesis testing will be performed having an alpha level of 10% (two-sided) or 5% (one-sided):

H_0: Mean percent change from baseline in EASI score at Week 16 (BI 655130)
≤ Mean percent change from baseline in EASI score at Week 16 (Placebo)

H_1: Mean percent change from baseline in EASI score at Week 16 (BI 655130)
> Mean percent change from baseline in EASI score at Week 16 (Placebo)

The primary analysis will be performed on the FAS with patients analysed according to the stratum to which they belong (regardless of any miss-assignment to treatment based on identification of the wrong stratum).



[redacted]

7.5 SECONDARY ENDPOINTS

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

All secondary efficacy endpoints will be analysed on FAS.

The continuous secondary efficacy endpoints (change from baseline in EASI at Week 4 and change from baseline in SCORAD at Week 4 and 16) will be analysed using the same MMRM model as defined for the primary endpoint. Both absolute and percent change from baseline will be analysed as an outcome.

A responder analysis based on the EASI Score will be performed at Week 4 and 16.

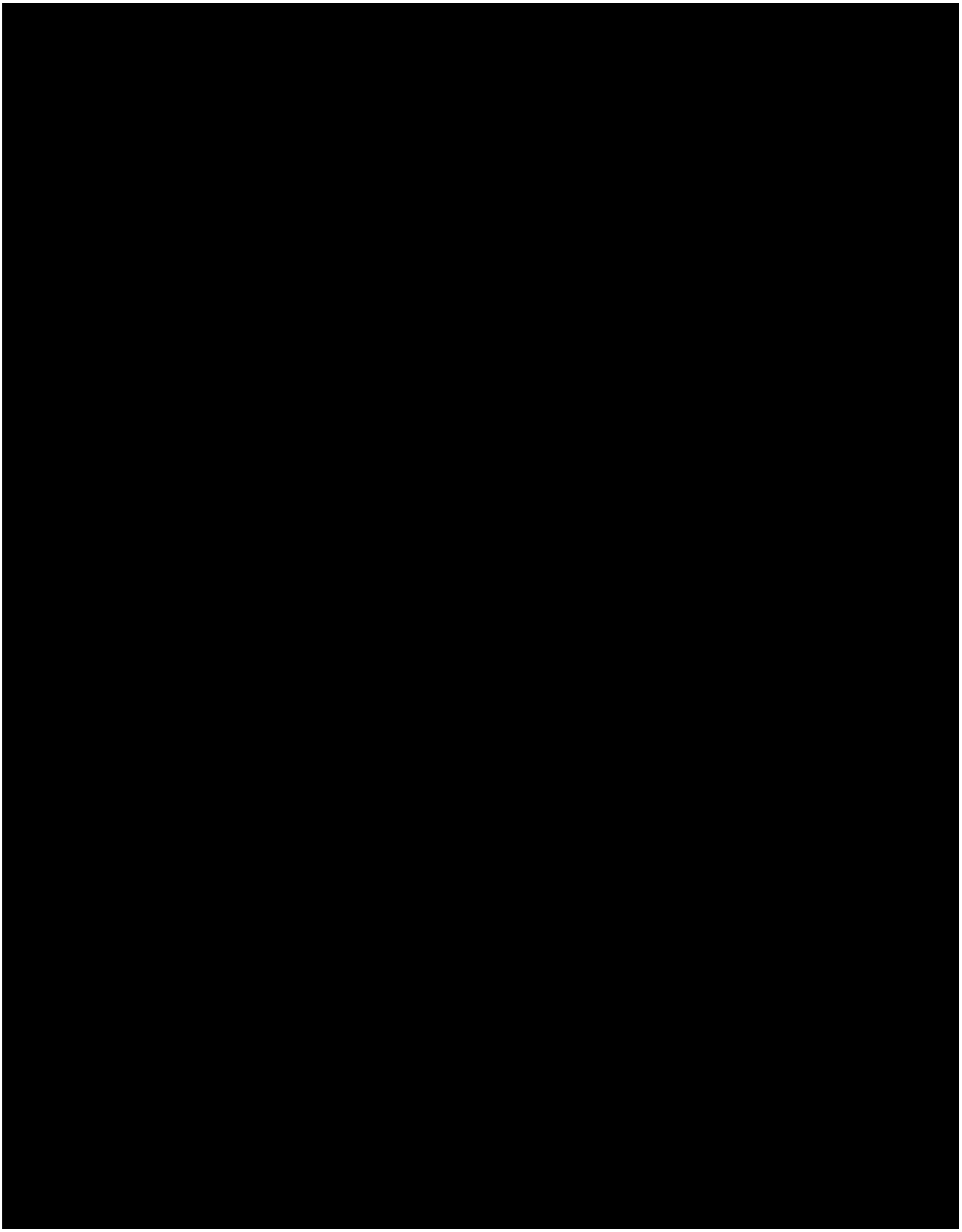
The binary endpoints defined above will be analysed with a logistic regression model including treatment and Asian/Non-Asian as explanatory variables. Risk difference for BI655130 versus placebo will be obtained as well as the response rates for the treatment groups.
As a sensitivity analyses, the Cochran-Mantel-Haenszel (CMH) test adjusted by Asian/Non-Asian will be performed.

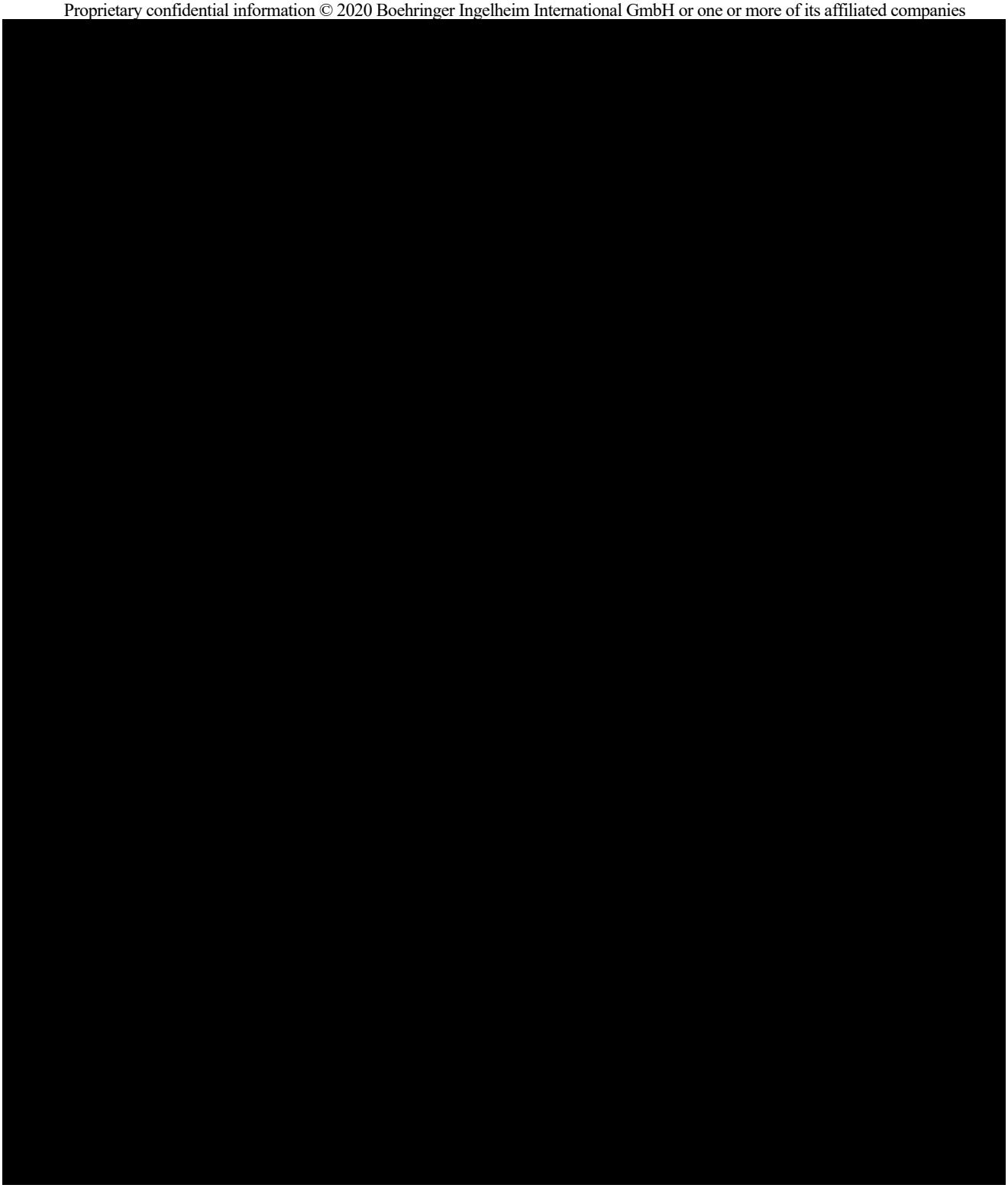
The proportion of patients who achieved at least a 2-grade reduction from baseline in IGA to clear (0) or almost clear (1) at Week 4 and 16 will be analysed with CMH test.

7.5.2.2 Secondary safety endpoints

The secondary safety endpoint is defined as the number of patients with drug related adverse events (AEs). This will be a part of the Safety analyses described in detail in Section 7.8.

[redacted]





[redacted]

7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of trial drug will be tabulated. The amount of treatment received (actual and weight based) will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) per visit and overall. Additionally, number of infusions administered overall per treatment arm will be displayed. Also, the duration of the infusion will be provided for each visit.

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the SAF following BI standards. No hypothesis testing is planned.
In addition, overall AE table and the frequency table of patients with at least one AE by MedDRA System Ogran Class and Preferred Term will be prepared for AEs occurring between start date of study medication and Week 16 visit data (not including residual effect period).

All safety data analyses beyond Week 16 (for patients not receiving BI open-label treatment) will be based on SAF-OL.

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.

The analyses of AEs will be performed for double-blind period and for the re-allocation period separately.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event data from Clinical Trials" [BI-KMED-BDS-HTG-0066] (7) and "Handling of missing and incomplete AE dates" [BI-KMED-BDS-HTG-0035] (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. If 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 (9)) and for the class of AESIs.

The following is considered an AESI in this trial:

- Hepatic injury
- Infusion reactions including anaphylactic reaction
- Severe infections
- Opportunistic and mycobacterium tuberculosis infections

The investigator has to classify on the eCRF whether an observed AE was an AESI or not. Only those AEs that are indicated by the investigator as AESI in the eCRF will be analysed in this category.

Based on the specification provided in ICH E3 (9), the sponsor has defined AEs which are to be classified as 'other significant'. 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 (secondary safety endpoint of this trial). Separate tables will also be provided for patients with SAEs, patients with drug-related 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 RCTC grade.

A summary of user-defined AE concepts (UDAEC) will be presented by treatment group. The UDAEC are presented in the table below.

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

User Defined AE Concepts	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 infections	MedDRA SMQ Opportunistic Infections (narrow)
Hepatic injuries	See Section 7.8.2
Tuberculosis infections	BIcMQ sub-search 8.2 "Tuberculosis related terms"
Malignant tumours	(SMQ "Malignancies") (Sub-SMQ "Malignant or unspecified tumours") Narrow Sub-SMQ "Malignant tumours" Narrow Sub-SMQ "Haematological malignant tumours" Narrow Sub-SMQ "Non-Haematological malignant tumours"
Torsades de pointes	Broad SMQ "Torsades de pointes/QT prolongation"
Malignant skin tumours	(SMQ "Skin neoplasms, malignant and unspecified") Broad Sub-SMQ "Skin malignant tumours"
Skin melanomas	HLT Skin melanomas (excl. Ocular)
Non-melanoma skin cancer (NMSC)	Broad Sub-BIcMQ "Skin Malignancies excluding melanomas"
Malignancies excluding NMSC	Sub-SMQ "Malignant tumours" excluding broad sub-BIcMQ "Skin Malignancies excluding melanomas"

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.

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.

The analyses of safety laboratory parameters will be performed for the double-blind period and re-allocation period separately.

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 "Handling, 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 normalised values and provided by visit, including summaries of the last value on treatment, the minimum value on treatment and maximum value in the respective period (double-blind or re-allocation).

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.

In addition, box and whiskers plots will be presented for the laboratory parameters.

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.

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 analysed 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 and will be performed for double-blind period and re-allocation period separately.

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 the respective period (double-blind or re-allocation), the minimum value during respective period, and the maximum value during respective period (see Table 6.1: 1 for definition of the trial periods/phases).

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

7.8.5.1 Infusion reactions including anaphylactic reaction

Infusion reactions will be summarized overall, with the frequency and percentage of patients who experienced any infusion reaction, both overall and specifying anaphylactic reaction as part of the table presenting patients with adverse events of special interest (AESI).

7.8.5.2 Immunogenicity

The frequency and percentage of patients with ADAs to BI 655130 will be presented by treatment by visit and overall, if sufficient data is available.

Further exploratory assessments of the ADA data (e.g. relationship between ADA and PK) might be performed once data is available and these will be described, if done, in the CTR.

7.8.5.3 Handling of DMC Analyses

A partially external DMC, independent of the trial and project teams, was set-up on project level to review all available safety data as well as selected efficacy data in an unblinded manner 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

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; Group “Clinical Operations”, IDEA for CON
3	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version; Group “Clinical Operations”, IDEA for CON
4	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON
5	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
6	*001-MCS-36-472_RD-03*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON
7	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON
8	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
9	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
10	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON
11	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**12-Feb-20**	[redacted]		This is the first version of the TSAP
2.0	**20-Aug-20**	[redacted]		This is the second version of the TSAP, including CTP Amendment 3 The following changes to the TSAP were made:
			[redacted]	[redacted]
			7.1	Disease severity based on EASI Score, disease severity based on IGA Score, and age at disease onset were added as part of the baseline characteristics
			6.2	"Nursing" iPD (G1.02) was changed to "Pregnancy or nursing"
			[redacted] 7.4.2	[redacted]
			6.7	Time windows for visit 11 were updated as per CTP amendment (Table 6.7:2)
			7.8	Additional outputs for AEs occurring between study treatment start date and Week 16 visit date (not including REP) were added.
			7.8.1	List of user-defined AE concepts was updated as per new MedDRA version (Table 7.8.7:1). Information on disclosure in EudraCT was removed since it is not applicable in this study.