TRIAL STATISTICAL ANALYSIS PLAN

c37762870-01

BI Trial No.:	1368-0037
Title:	An open label extension study to assess the long term safety of treatment with BI 655130 administered subcutaneously in adult patients with moderate to severe atopic dermatitis Including Protocol Amendment 1 [c26581385-02]
Investigational Product(s):	BI 655130
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	20 Dec 2021 SIGNED
Version:	1.0

1. TABLE OF CONTENTS

LIST OF TABLES

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
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim-customised MedDRA query
BM-SAP	Biomarker Statistical Analysis Plan
BMI	Body mass index
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CRP	C-reactive protein
CSAP	Cumulative statistical analysis plan
CTP	Clinical trial protocol
CTR	Clinical trial report
DBLM	Database lock meeting
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DV	Protocol deviation
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
EDMS	Electronic document management system
EMA	European Medicines Agency
EoT	End of treatment
EoS	End of study
ES	Enrolled set

Term	Definition / description
FAS	Full analysis set
HLT	High level term
HLGT	High level group term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
iPD	Important protocol deviation
ISF	Investigator site file
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MQRM	Medical quality review meeting
N	Number of observations
NRI	Non-Responder imputation
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
Q1	1st quartile
Q3	3rd quartile
q4w	every 4 weeks
RCTC	Rheumatology common toxicity criteria
RPM	Report planning meeting
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
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

Term	Definition / description
TSAP	Trial statistical analysis plan
UDAEC	User-defined AE concepts
ULN	Upper limit of normal range
VAS	Visual analogue scale

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analyses described in the CTP and its amendments, and to include detailed procedures for executing the statistical analysis of the 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.

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

Pharmacokinetic (PK) parameters are not planned to be analysed nor be the part of the CTR.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), 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 data that will be performed for a final analysis. The specifications of the analyses for the status reviews at the time points within the requested timelines will be defined as requests in the Cumulative Statistical Analysis Plan (CSAP).

The results of the analyses defined in this SAP will be summarised in the abbreviated CTR.

5. ENDPOINT(S)

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.

For all endpoints and unless explicitly specified otherwise, End-of-Study visit refers to V53 (Week 220), using extended time windows as defined in Table 6.7: 1.

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(S)

The primary endpoint is the number (and percentage) of patients with treatment emergent adverse events (AEs) at Week 48. This will be analysed as part of the Safety analysis (see Section 7.8)

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.

- Change from baseline in Eczema Area and Severity Index (EASI) Score at Week 48

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

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 = $(\text{Erythema}_{\text{Head}} + \text{Edema/papulation}_{\text{Head}} + \text{Excoration}_{\text{Head}} + \text{Lichenification}_{\text{Head}}) \times (\text{Head}_{\text{Region Score}}) \times 0.1 +$
$(\text{Erythema}_{\text{Trunk}} + \text{Edema/papulation}_{\text{Trunk}} + \text{Excoration}_{\text{Trunk}} + \text{Lichenification}_{\text{Trunk}}) \times (\text{Trunk}_{\text{Region Score}}) \times 0.3 +$
$(\text{Erythema}_{\text{Upper limb}} + \text{Edema/papulation}_{\text{Upper limb}} + \text{Excoration}_{\text{Upper limb}} + \text{Lichenification}_{\text{Upper limb}}) \times (\text{Upper\_limb}_{\text{Region Score}}) \times 0.2 +$
$(\text{Erythema}_{\text{Upper limb}} + \text{Edema/papulation}_{\text{Lower limb}} + \text{Excoration}_{\text{Lower limb}} + \text{Lichenification}_{\text{Lower limb}}) \times (\text{Lower\_limb}_{\text{Region Score}}) \times 0.4$

- 50% improvement from baseline in EASI (EASI50) at Week 48

  Numbers and percentages will be analysed.

  Achievement of Decrease in EASI ≥ xx% (EASIxx)

  Achieving an improvement 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.

- 75% improvement from baseline in EASI (EASI75) at Week 48

Numbers and percentages will be analysed.

- Change from baseline in SCORing of Atopic Dermatitis (SCORAD) at Week 48

  The actual 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 48

  Numbers and percentages will be analysed.

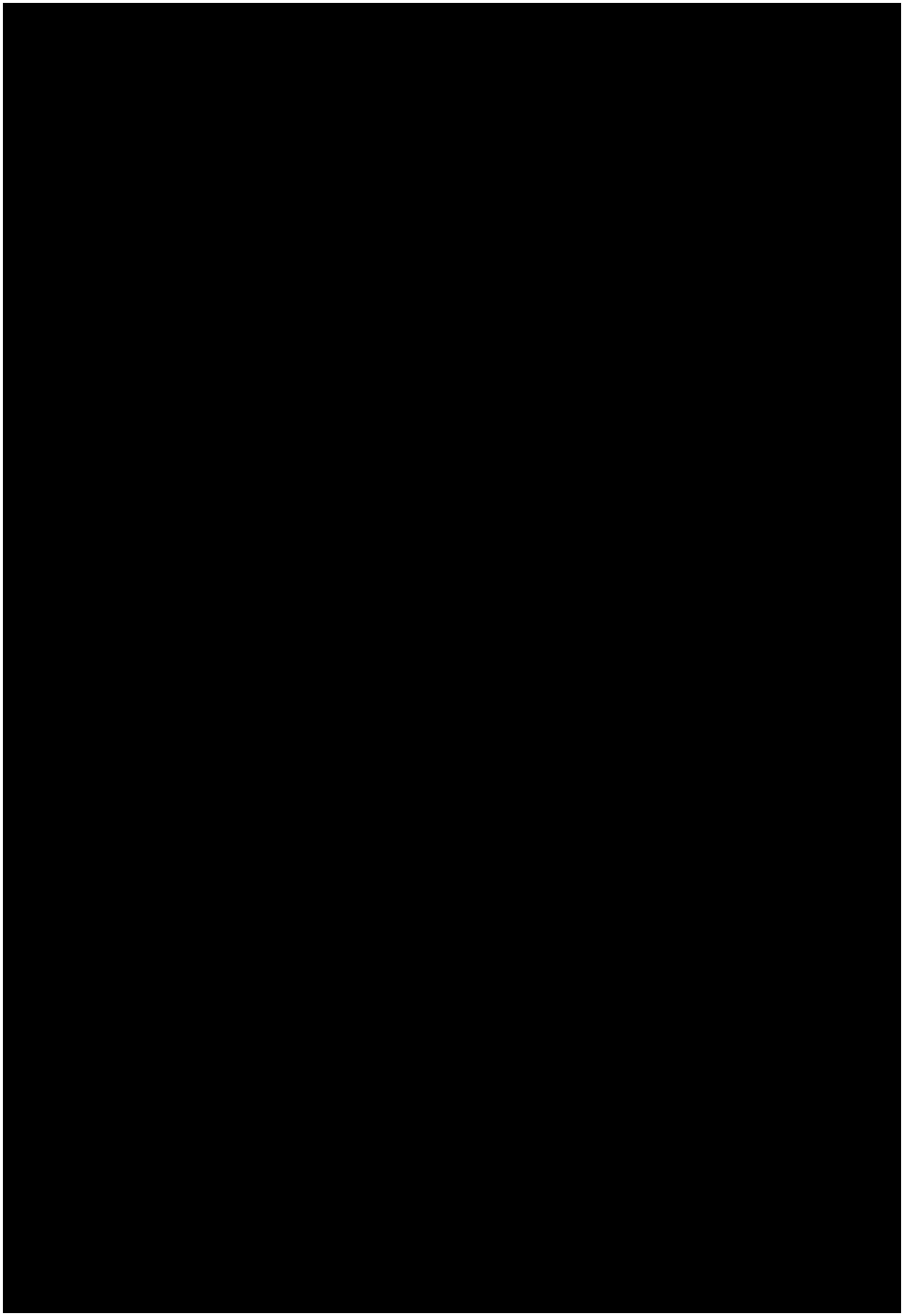
  IGA score allows investigators to assess the overall disease severity at one given time point. It is a 5-point scale with: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. The overall IGA score includes the assessment of erythema, induration/papulation, lichenification, and oozing/crusting. 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."
  The 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.

[redacted]

5.4.1 Safety

Safety will be assessed based on:



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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 subcutaneous doses of 600 mg of BI 655130 solution for SC injection (every four weeks).

The following trial phases are defined:

Table 6.1: 1 Flow chart of trial phases

Trial phase	Description	Start (included)	End (excluded)
Open label Treatment phase	On-treatment period	Date of start of injection of first study drug (Day 1)	EoT visit date + 1 day
Follow-up phase	Off-treatment follow-up period	EoT 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.
EoT = End of treatment; EoS = End of study;

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

The time windows for data presentation in the analysis are described in Table 6.7: 1.

Treatment group will be labelled as follows: **"Speso 600 mg SC q4w"** (i.e., patients receiving BI 655130 600 mg). In addition, the descriptive statistics will be presented for the following groups:

1. By treatment received in the parent trial (1368-0032):

    - **"Placebo" followed by "Speso 600 mg SC q4w"** – patients who were randomised to receive placebo in the double-blind period of the parent trial and received Speso treatment in the open-label period of the parent trial

    - **"Placebo" followed by "no Speso 600 mg SC q4w"** – patients who were randomised to receive placebo in the double-blind period of the parent trial and

didn't receive Speso treatment in the open-label period of the parent trial (but didn't discontinue the parent study prematurely)

- **"Speso 600 mg SC q4w" followed by "Speso 600 mg SC q4w"** – patients who were randomised to receive active treatment (Speso) in the double-blind period of the parent trial and received Speso treatment in the open-label period of the parent trial

- **"Speso 600 mg SC q4w" followed by "no Speso 600 mg SC q4w"** – patients who were randomised to receive active treatment (Speso) in the double-blind period of the parent trial and didn't receive Speso treatment in the open-label period of the parent trial (but didn't discontinue the parent study prematurely)

- **"Overall Total"** – all patients from FAS, regardless of the treatment received in the parent trial.

2. By the response achieved at Week 16 of the parent trial (1368-0032):

    - **"Responders"** – patients who attained at least 75% reduction in EASI score at Week 16 compared to baseline during the parent trial

    - **"Non-responders"** – patients who attained less than 75% reduction in EASI score at Week 16 compared to baseline during the parent trial

    - **"Overall Total"** – all patients from FAS, regardless of the EASI response status at Week 16 in the parent trial.

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).

Handling of iPDs in the analysis is included in the DV domain specifications and stored within the TMF in EDMS.

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.

- 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. In addition, this set will be used for display of baseline and demographic characteristics, and patients with iPDs.

- Full analysis set (FAS)
  This patient set includes all patients in the SAF who had a baseline measurement and at least one post-baseline measurement for the secondary endpoint, EASI Total Score. It will be the main analysis set for presentation of efficacy results.

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 Subject sets analysed

	Subject set		
Class of endpoint	ES	SAF	FAS
Primary and key secondary endpoints			X
(other) Secondary and further endpoints			X
Safety endpoints & treatment exposure		X	
Patients disposition	X		
Demographic/baseline endpoints		X	

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

6.5 POOLING OF CENTRES

Given the low number of patients per centre and the primarily descriptive nature of the statistical analysis, separate analyses by centre are not meaningful and will not be performed.

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, it will be imputed 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 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, no imputation of missing data is planned. Only observed data will be used for analysis.

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 (3)).

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.

6.6.4 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.

Information on the time since first diagnosis will be imported form the database of the parent trial (1368-0032).

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.

There will be two different baseline definitions used in the analyses:

1. Baseline for this extension trial – defined as the last measurement recorded before the first trial medication administration in this study.

2. Baseline for the parent trial (1638-0032) – defined as the measurement recorded at randomisation visit (Visit 2) of the parent trial. If the data at Visit 2 is missing, then the data from Visit 1 of the parent trial will be considered baseline.

Two separate analyses will be conducted, using the baselines as defined above.

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 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

Visit number / name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1	Day 1	Day 1	n/a	1 [A]	1	1 [A]	1
V2	Week 4	Day 29	+/- 14	15	43	2	43
V3	Week 8	Day 57	+/- 14	44	71	44	71
V4	Week 12	Day 85	+/- 14	72	99	72	99
V5	Week 16	Day 113	+/- 14	100	127	100	127
V6	Week 20	Day 141	+/- 14	128	155	128	155
V7	Week 24	Day 169	+/- 14	156	183	156	183
V8	Week 28	Day 197	+/- 14	184	211	184	211
V9	Week 32	Day 225	+/- 14	212	239	212	239
V10	Week 36	Day 253	+/- 14	240	267	240	267
V11	Week 40	Day 281	+/- 14	268	295	268	295
V12	Week 44	Day 309	+/- 14	296	323	296	323
V13	Week 48	Day 337	+/- 14	324	351	324	351
V14	Week 52	Day 365	+/- 14	352	379	352	379
V15	Week 56	Day 393	+/- 14	380	407	380	407
V16	Week 60	Day 421	+/- 14	408	435	408	435
V17	Week 64	Day 449	+/- 14	436	463	436	463
V18	Week 68	Day 477	+/- 14	464	491	464	491
V19	Week 72	Day 505	+/- 14	492	519	492	519
V20	Week 76	Day 533	+/- 14	520	547	520	547
V21	Week 80	Day 561	+/- 14	548	575	548	575
V22	Week 84	Day 589	+/- 14	576	603	576	603
V23	Week 88	Day 617	+/- 14	604	631	604	631
V24	Week 92	Day 645	+/- 14	632	659	632	659
V25	Week 96	Day 673	+/- 14	660	687	660	687
V26	Week 100	Day 701	+/- 14	688	715	688	715
V27	Week 104	Day 729	+/- 14	716	743	716	743
…	…	…	…	…	…	…	…
V52	EoT	Day 1429	+/- 14	1415	1443	1415	1443
V53	EoS	Day 1541	+/- 14	1528	1555	1444	1555/EoT+ 16weeks

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 injection 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.

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.

In addition, separate analyses will be performed using the parent trial baseline. Baseline value will then be defined the same way as in the parent trial (1368-0032) and will be taken from that parent trial.

7. PLANNED ANALYSIS

All efficacy and safety analyses will be purely exploratory in nature. The following analyses are planned throughout the trial.

- **Status review (at the requested timelines)**

The status reviews will be performed periodically and on demand. The analyses will include all data available at the time of the snapshot. The analyses are planned to be defined for each time point as requests in the CSAP, depending on the requirements.

- **Final analysis (Week 220)**

The analysis of the entire efficacy, safety, PK, and biomarker data collected through the full 220 weeks of follow-up will be performed once all entered patients have completed the trial (up to EoS Visit); at that time point, a final database lock will be done and all data through week 220 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] (7) 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

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" (7).

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 (overall) will be summarised by presentation of the frequency of patients entered, treated, entered but not treated, who completed all doses of trial medication as planned (until the trial termination), who prematurely discontinued study drug administration by reason, who completed the observational period as planned, who prematurely discontinued study participation. Disposition will be listed by country.

The frequency of patients with iPDs will be presented for the SAF, overall. 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 overall.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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

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 < 65 years ≥ 65 years
BMI	< 25 kg/m^2 25 to < 30 kg/m^2 ≥ 30 kg/m^2
Time since first diagnosis	≤ 1 year > 1 to ≤ 5 years > 5 to ≤ 10 years > 10 years
Age at disease onset	≤ 12 years old > 12 years old

7.2 CONCOMITANT DISEASES AND MEDICATION

For this extension study, no information on historical medication is collected. For more details on that, please refer to the parent trial (1368-0032) results.

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 summarised overall.

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, overall.

Concomitant use of non-drug therapies will be summarized overall with frequency and percentage.

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 injected (as a % of planned) is defined as the volume injected at a visit (in number of syringes as recorded in the eCRF), divided by 4 (the number of syringes the patient should have received).

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

7.4 PRIMARY ENDPOINT(S)

The primary endpoint for this trial is the number of patients with treatment emergent adverse events at Week 48.

7.4.1 Primary analysis of the primary endpoint(s)

The analysis of the primary endpoint will be descriptive in nature and will be a part of the Safety analyses described in detail in Section 7.8.

The primary analysis will be performed on the SAF.

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

All secondary efficacy endpoints will be analysed descriptively based on the FAS.

For continuous secondary efficacy endpoints (EASI Score and SCORAD Score), standard statistical parameters (as defined in Section 7) will be presented per group defined in Section 6.1. Both absolute and percent change from baseline will be analysed as an outcome as well as the values recorded at the respective time points.

For binary endpoints (EASI50, EASI75, achieving at least 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA), frequency tables will be provided per group defined in Section 6.1.

7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of trial drug will be tabulated. The amount of treatment received will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) per visit and overall. Additionally, number of injections administered (as defined in Section 5.4.4) overall will be displayed.

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.

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] (4) and "Handling of missing and incomplete AE dates" [BI-KMED-BDS-HTG-0035] (3).

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 (6)) and for the class of AESIs.

The following are considered an AESI in this trial:

- Hepatic injury
- Systemic hypersensitivity reactions including anaphylactic reaction
- Severe infections (according to RCTC grading in the ISF)
- 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 (6), 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
Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below (Anaphylactic reaction, Angioedema, Hypersensitivity)
Anaphylactic reaction	Narrow SMQ “Anaphylactic reaction”
Angioedema	Narrow SMQ “Angioedema”
Hypersensitivity	Narrow SMQ “Hypersensitivity”
Infections ALL	Combined search strategy based on the individual UDAECs described below (Severe infections, Opportunistic infections, Tuberculosis infections, and Serious infections); Severe infections investigator-defined will be disregarded for this search.
Severe infections (according to RCTC grading)	SOC Infections and infestations of at least severe RCTC grade, by HLGT
Serious infections	SOC Infections and infestations reported as serious AEs
Opportunistic infections	SMQ Opportunistic Infections (narrow)
Tuberculosis infections	BIcMQ sub-search 8.2 “Tuberculosis related terms”, narrow
Malignant tumours	Narrow Sub-SMQ “Malignant tumours” Narrow Sub-SMQ “Haematological malignant tumours” Narrow Sub-SMQ “Non-Haematological malignant tumours”
Malignant skin tumours	Broad Sub-SMQ “Skin malignant tumours”
Skin melanomas	HLT Skin melanomas (excl. Ocular)
Non-melanoma skin cancer (NMSC)	Broad sub-SMQ “Skin Malignant tumors” excluding HLT skin melanomas (excl. ocular)
Malignancies excluding NMSC	Sub-SMQ “Malignant tumours” excluding NMSC, whereas NMSC is defined above
Torsades de pointes	Broad sub-SMQ “Torsades de pointes/QT prolongation”

Table 7.8.1:1 Project MedRDA dearch criteria for User Defined Adverse Event Concepts (cont.)

DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), narrow	SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome", narrow
DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), broad	Algorithmic SMQ on "Drug reaction with eosinophilia and systemic symptoms syndrome", broad Algorithm: A or (B and C and D) or (B and C and E) or (B and D and E)
Depression	sub-SMQ "Depression (excl suicide and self-injury)", broad
Suicidal ideation and behavior (SIB)	sub-SMQ "Suicide/self-injury"

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 (5). 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 “Handling, Display and Analysis of Laboratory Data” (5). 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 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.

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.

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 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 Others

Injection reactions including anaphylactic reaction

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

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 abbreviated CTR.

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 finalised prior to first patient randomised into the trial. Further details were provided in a DMC charter.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

This is an open-label trial with a single arm and the treatment information will be loaded into the trial database.

9. 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	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON
4	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON
5	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
6	*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
7	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**20-DEC-21**	[redacted]	None	This is the final TSAP