TRIAL STATISTICAL ANALYSIS PLAN

c40843858-02

BI Trial No.:	1368-0077
Title:	Multi-centre, open-label, expanded access program of 900mg intravenous (i.v.) spesolimab in patients with generalized pustular psoriasis (GPP) presenting with a flare Including Revised Protocol # 2 [c39436286-01]
Investigational Product(s):	Spesolimab, BI 655130
Responsible trial statistician(s):	[redacted] Tel.: [redacted] Fax:
Date of statistical analysis plan:	17 Aug 2023
Version:	2 Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body mass index
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ES	Enrolled set
GPP	Generalized pustular psoriasis
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
i.v.	intravenous
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
iPD	important protocol deviation
IQR	Interquartile range
MedDRA	Medical dictionary for regulatory activities
OR	Original results
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
REP	Residual effect period
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software

Term	Definition / description
[redacted]	[redacted] dose
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined adverse event categories
WHO-DD	World health organisation – drug dictionary

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 [redacted]. 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, randomization.

SAS® Version 9.4 or higher will be used for all analyses.

Note that this TSAP applies to trial 1368-0073 (including Revised Protocol # 2 [c36703857-02]), 1368-0077 (including Revised Protocol # 2 [c39436286-01]), 1368-0109 under the Expanded Access Program.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Not applicable.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is defined in CTP Section 2.1.2.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Secondary endpoints are listed in CTP Section 2.1.3.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The following treatment option is planned in the study:

- [redacted] Dose [redacted]: spesolimab [redacted]
- [redacted] Dose [redacted]: spesolimab [redacted] at Day [redacted] and Day [redacted]

The study phases are defined relative to spesolimab at Day 1 as below:

Table 6.1: 1 Flow chart of analysis phases of the study for each flare

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of i) Date of informed consent, ii) first screening procedure	Date/time of start of [redacted] minus 1 minute
Treatment phase (including REP if applicable)	On-treatment period	Date/time of start of [redacted] (Day 1)	Earliest of: i) Date of end of last [redacted] + 112 days at 23:59, ii) Date of end of study visit, iii) Date/time of start of screening for next flare
Follow-up phase[1]	Off-treatment period	Date of end of [redacted] of last study treatment + 113 days at 0:00 a.m.	Latest of: i) Date of EOS visit; ii) Last contact date on End of Study page at 23:59

Dates are defined individually per patient. REP represents the residual effect period. An analysis phase will not extend beyond the start date of the following phase. [1] The follow-up phase only exists if the last contact date is after the date of [redacted] of last study drug + 112 days.

Note that in the trial, a patient experiencing a new GPP flare may re-enter the study within/after the [redacted]-week follow-up period, starting from screening again. For details, refer to section 3.1 in CTP. Therefore, a patient may have more than one screening/flare treatment/follow-up period.

Data across all flare treatment periods will be pooled and handled per patient, with "Overall Speso [redacted]" to label the treatment group.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS (2).

In addition, all COVID-19 related protocol deviations, regardless of important or non-important PDs will be included in the DV domain as well.

6.3 SUBJECT SETS ANALYSED

The following analysis set will be defined for this trial:

- Enrolled Set (ES):
  This patient set includes all patients who signed informed consent. It will be used for analyses of patient disposition.
- Treated Set (TS):
  This patient set includes all patients who received at least one dose of study drug. It will be used for all other analyses.

[redacted]

6.5 POOLING OF CENTRES

All patients from all centres will be pooled for descriptive analyses.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

[redacted]

Safety data

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

For safety data not by visit such as AE and possibly clinically significant laboratory abnormalities, OR approach will be used for the descriptive reporting for corresponding treatment periods.

The only exceptions where imputation might be necessary for safety evaluation are AE dates and AE start time and, start and stop dates for concomitant medications.

Missing or incomplete AE dates are imputed according to BI standards (4).

Partial start and stop dates for concomitant medications and historical medication use 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 then the start date is set to first day of the month (except for escape medication, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing then the start date is set to 1st January of the year.
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

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

Time since first diagnosis

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

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

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is N / Mean / SD / Min / Q1 / Median / Q3 / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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 group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category "missing" will be displayed only if there are actually missing values.

Disposition of the patient population participating in the trial will be summarised by the presentation of the frequency of patients enrolled, enrolled but not treated, enrolled and treated, who completed participation in the trial, and who were prematurely discontinued from trial, by reason. The iPDs, baseline conditions/medical history, demographic/baseline characteristics, concomitant medications, concomitant non-drug therapies, exposure will be presented based on TS for the entire trial duration. In addition, the number of flares will also be summarized based on TS.

For safety data, per patient analysis based on patient will be used for the analysis, whose denominator will be the number of patients or time at risk per patient for all applicable periods.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report:

Sex, ethnicity, race, age, height, weight, BMI, mutation status of the IL36RN, CARD14 and AP1S3, disease characteristics for current flare, time since first diagnosis.

Age [years] will be determined as the difference between year of birth and year of informed consent. BMI will be calculated as weight [kg] / height $[m]^2$

Medical History for GPP includes mutation status (IL36RN, CARD14 and AP1S3), as well as the details, if any, on the presence of chronic plaque psoriasis or chronic erythrodermic psoriasis will be summarized. The method by which diagnosis of GPP was confirmed is also collected.

Disease characteristics will include details on current flare.

Time since first diagnosis [years] will be calculated as the difference between date of first diagnosis and date of informed consent, divided by 365.25.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases (i.e. baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

A medication/non-drug therapy will be considered concomitant to treatment, if it

- is ongoing at the start of that treatment period or
- starts within that treatment period (see Section 6.1 for the definition).

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of that treatment period.

Concomitant medication use will be summarized with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

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

Historical medication for GPP will be summarised with frequency and percentage of patients, including presentation by type of historical medication (preferred name), and by reason for discontinuation.

7.3 TREATMENT COMPLIANCE

Not applicable.

7.4 PRIMARY ENDPOINT(S)

Refer to section 7.8.1 for the description of adverse events including the primary endpoint.

7.5 SECONDARY ENDPOINT(S)

Refer to section 7.8.1 for the description of adverse events including the secondary endpoint.

[redacted]

7.7 EXTENT OF EXPOSURE

Treatment exposure is defined as the total dose of randomized spesolimab [mg] received per patient. In general, the total dose of spesolimab [mg] received per [redacted] is calculated as the

total [redacted] volume [mL], as documented on the eCRF, times the strength prepared in the [redacted]

Strength in [redacted]

[redacted]

The duration of the [redacted] trial treatment [minutes] at each visit will be calculated as the end of the [redacted] date/time minus the start of the [redacted] date/time.

The number of doses will be calculated, which is based upon the number of visits at which doses of study drug were administered.

Time at risk will be assessed in months per definition in Section 7.8.1, where the end date will be the end of each flare treatment period in Table 6.1: 1.

The duration of [redacted], the number of doses, time at risk and the total dose [mg] will be summarised by descriptive statistics (N, mean, SD, minimum, Q1, median, Q3, maximum), using per patient analysis for all flare treatment period.

7.8 SAFETY ANALYSIS

All safety analyses will be performed following BI standards. No hypothesis testing is planned.

For all flare treatment period (all flares for a patient combined) based on TS, the AE data and possibly clinically significant laboratory abnormalities will be analysed under OR (as defined in Section 6.6)

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA. Patients will be analyzed according to the actual treatment received.

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, treatment phase or follow-up phase as defined in Section 6.1. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as spesolimab at Day 1 will be assigned to the on-treatment period.

The primary endpoint of occurrence of treatment emergent adverse events (TEAE), will be analysed as the exposure-adjusted adverse event incidence rates in all flare treatment period based on TS by using per patient analysis for TEAE.

Per patient analysis for TEAE

1) The exposure adjusted incidence rate (per 100 patient years) of a selected treatment emergent adverse event is defined as the number of patients experiencing the adverse event per treatment group during time at risk divided by the total time of patients at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 patient years).

   Time at risk [patient years] = (date of onset of AE– first treatment start date within that treatment period + 1) / 365.25

   For all flare treatment period on a patient level, each flare treatment period is combined with the previous flare treatment period as defined in Section 6.1.

2) If, for a patient, the selected treatment emergent adverse event didn't occur during the above defined treatment period (per Section 6.1) then the time at risk will be censored at the earliest of date of death, last contact date per EoS page, or the end of the above defined treatment period.

   For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

   Incidence rate [1/100 Patient years (pt-yrs)] = 100 * number of patients with TEAE / Total TEAE-specific time at risk [patient years].

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the exposure adjusted incidence rates (per 100 patient years or per 100 flare treatment period years), as well as the number of patients with AEs and the number of flare treatment periods with AEs. System organ classes (SOCs) (if applicable) will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms (PTs) (if applicable) will be sorted by total frequency (within SOC).

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (3) and "Handling of missing and incomplete AE dates" (4).

An overall summary of AEs will be described in all flare treatment period based on TS by per patient analysis. The exposure-adjusted incidence rate and frequency will be summarized by treatment, primary SOC and PT for the following AEs: drug-related AEs considered by the investigator, AEs leading to treatment discontinuation, other significant AEs, SAEs, drug-related SAEs, AESIs, and user-defined adverse event categories (UDAEC) and serious UDAEC (cf. Table 7.8.1: 1). AEs will also be summarized by the maximum intensity.

According to ICH E3 (5), the sponsor has defined AEs which are to be classified as 'other significant'. For the current trial, these will include those non-serious AEs which were reported with 'action taken = Drug Withdrawn' or 'action taken = Dose Reduced'.

The following are considered as AESIs (see Sec 5.2.4.1.4 of CTP):

- Potential Severe Drug Induced Liver Injury (DILI)
- Systemic hypersensitivity reactions including [redacted] reactions and anaphylactic reaction
- Severe infections (according to RCTC grading in the ISF)
- Opportunistic and mycobacterium tuberculosis infections
- Peripheral neuropathy

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

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

Table 7.8.1: 1 Project MedDRA search criteria for User Defined Adverse Event Categories

User-defined AE category		
	Label	Description
Infections (serious/severe, opportunistic)	Infections ALL	Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search
	Opportunistic infections	Narrow SMQ "Opportunistic infections"
	Tuberculosis infections	BIcMQ "Infections": Narrow sub-search 8.2 "Tuberculosis related terms"
	Serious infections	all serious events in SOC "Infections and infestations"
	Severe infections	all events in SOC "Infections and infestations" of at least severe RCTC grade, by HLGT
Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the individual UDAECs described below
	Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
	Angioedema	Narrow SMQ "Angioedema"
	Hypersensitivity	Narrow SMQ "Hypersensitivity"
	DRESS, algorithmic	Based on broad SMQ "Drug reaction with eosinophilia and systemic symptoms" (SMQ code 20000225), defined using algorithm as follows: A or (B and C and D) or (B and C and E) or (B and D and E) where the categories A, B, C, D and E are defined categorisations of the PTs of the SMQ. For PTs of category A only narrow scope is used, for all other categories broad scope is used. For identification of potential DRESS through the combination of adverse event occurrences within each of the categories B, C, D and E, adverse event start and end dates will be used. For the latter, potential DRESS is then identified if, within a 7-day period after occurrence of a relevant contributing event (assessed on each day between start and end date [inclusive] of the initiating event), there is at least one adverse event reported (based on start date only) from each of the other applicable categories within a specific combination of categories as described above (in parentheses). If the end date is missing, the event is considered to be ongoing, and end date will be the last day of the applicable treatment period
	DRESS, narrow	Narrow SMQ "Drug reaction with eosinophilia and systemic symptoms", any event within category A only

Malignancies	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 tumours” excluding HLT Skin melanomas (excl. Ocular)
	Malignancies excluding NMSC	Sub-SMQ “Malignant tumours” excluding NMSC, whereas NMSC is defined above
3-point MACE	3-point MACE	BIcMQ “Major Adverse Cardiovascular Events” with Narrow sub-search 1.1 “3-Point MACE (part 1/2)” Narrow sub-search 1.2 “3-Point MACE (part 2/2)”*
Torsades de Pointes	Torsades de Pointes	Broad sub-SMQ “Torsade de pointes/QT prolongation”
Peripheral neuropathy	Peripheral neuropathy	Narrow SMQ "Demyelination” Narrow SMQ "Guillain-Barre syndrome" Narrow SMQ "Peripheral neuropathy”

*this is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094

7.8.2 Laboratory data

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 investigator, and will be analyzed as such.

7.8.3 Vital signs

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

7.8.4 ECG

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

7.8.5 Others

Local Tolerability will be summarized at Day 1 and Day 8, with the frequency and percentage of patients/flare treatment periods who experienced any reaction presented by symptom and severity of reaction.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

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.	*KM Asset BI-KMED-BDS-HTG-0041: "Handling and Summarization of Adverse Event Data for Clinical Trial Reports and Integrated Summaries", current version, KMED.*
4.	*KM Asset BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version, KMED.
5.	*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, EMA webpage.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**06-Dec-22**	[redacted]	None	This is the final TSAP
2	**17-Aug-23**		Section 3	Added clarifications of this TSAP.
			Section 7	Updated disposition to remove trial medication.
			Section 7.8.1	Added AE for disclosure and revised AE analyses to focus on per patient analysis.