TRIAL STATISTICAL ANALYSIS PLAN

c30136303-02

BI Trial No.:	1368-0007
Title:	An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials. Including Protocol Amendment 2 [include c27319443-05]
Investigational Product(s):	Spesolimab, (BI 655130)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	October 28 2022
Version:	2.0

1. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above limit of quantification
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	BI customized MedDRA queries
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
CR	Clinical remission
CRF	Case report form
[redacted]	[redacted]
CTC	Common Terminology Criteria
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of treatment
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
[redacted]	[redacted]
F/U	Follow-up
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin

Term	Definition / description
IPD	Important protocol deviation
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
SAE	Serious adverse event
SAF	Safety Analysis Set
SD	Standard deviation
SDL	Subject data listing
SMQ	Standardised MedDRA query
SOC	System Organ Class
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification

3. INTRODUCTION

As per ICH E9, 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 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, and planning of sample size.

[redacted]

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 statistical analysis plan describes the final analysis of this discontinued trial.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As a consequence of the early termination of this open-label, long-term extension trial, the following changes in the planned analyses have been implemented:

1) Due to limitations in the data capture of the current eCRF, the secondary endpoints specified in the protocol, "Proportion of patients with perianal fistula remission at weeks 48, 96, 144, 192, 240, 288, and 336" and "Proportion of patients with perianal fistula response at weeks 48, 96, 144, 192, 240, 288, and 336", cannot be fully derived, and thus the planned analyses for these secondary endpoints cannot be performed. A listing at the individual patient level showing the status of fistulas for each treated patient will instead be prepared.

[redacted]

5. ENDPOINTS

For handling of missing data see Section 6.6, unless otherwise specified.

Note that, unless otherwise stated in Section 7, for the specification of efficacy endpoints below, the baseline is defined as the last non-missing value reported prior to the first dose of the study drug in the preceding induction study, i.e., the efficacy baseline definition from the parent trial.

For the summary of all efficacy data, only those observations which were collected during the on-treatment period (i.e. first dose of spesolimab through to the last dose of spesolimab + 16 weeks) will be used.

5.1 PRIMARY ENDPOINT

The primary endpoint for this trial is a safety endpoint: the exposure-adjusted incidence rate of patients reporting a treatment emergent adverse event (TEAE) up to week 336 of the maintenance treatment. For this endpoint, time-at-risk begins at the study drug start date of the current study, and not of the parent trial.

Please refer to Section 7.2.2 of the CTP for a more thorough discussion of the primary endpoint.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable. No key secondary endpoints have been specified for this trial.

5.2.2 Secondary endpoints

- Proportion of patients with perianal fistula remission at week 48, 96, 44, 192, 240, 288, and 336
- Proportion of patients with perianal fistula response at week 48, 96, 44, 192, 240, 288, and 336

Please refer to Table 2.1:1 of the CTP for a complete description of the secondary endpoints.

As described in Section 4, due to limitations in the CRF collection of data, it is not feasible to calculate either of these two secondary endpoints. Nonetheless, the derivation algorithms for these two endpoints, as originally proposed, are maintained and described below.

The derivations of perianal fistula remission and response are Boolean functions based on the following, where a fistula refers to an external opening:

Let
- v indicate a given analysis visit;
- $o(v)$ indicate the count of open fistulas (± drainage/discharge upon gentle finger compression) at v;
- $\epsilon(v)$ be the number of newly emerged fistulas (± drainage/discharge upon gentle finger compression) from the baseline of the parent trial to v;
- BL be the number of open and draining fistulas at the baseline of the parent trial.

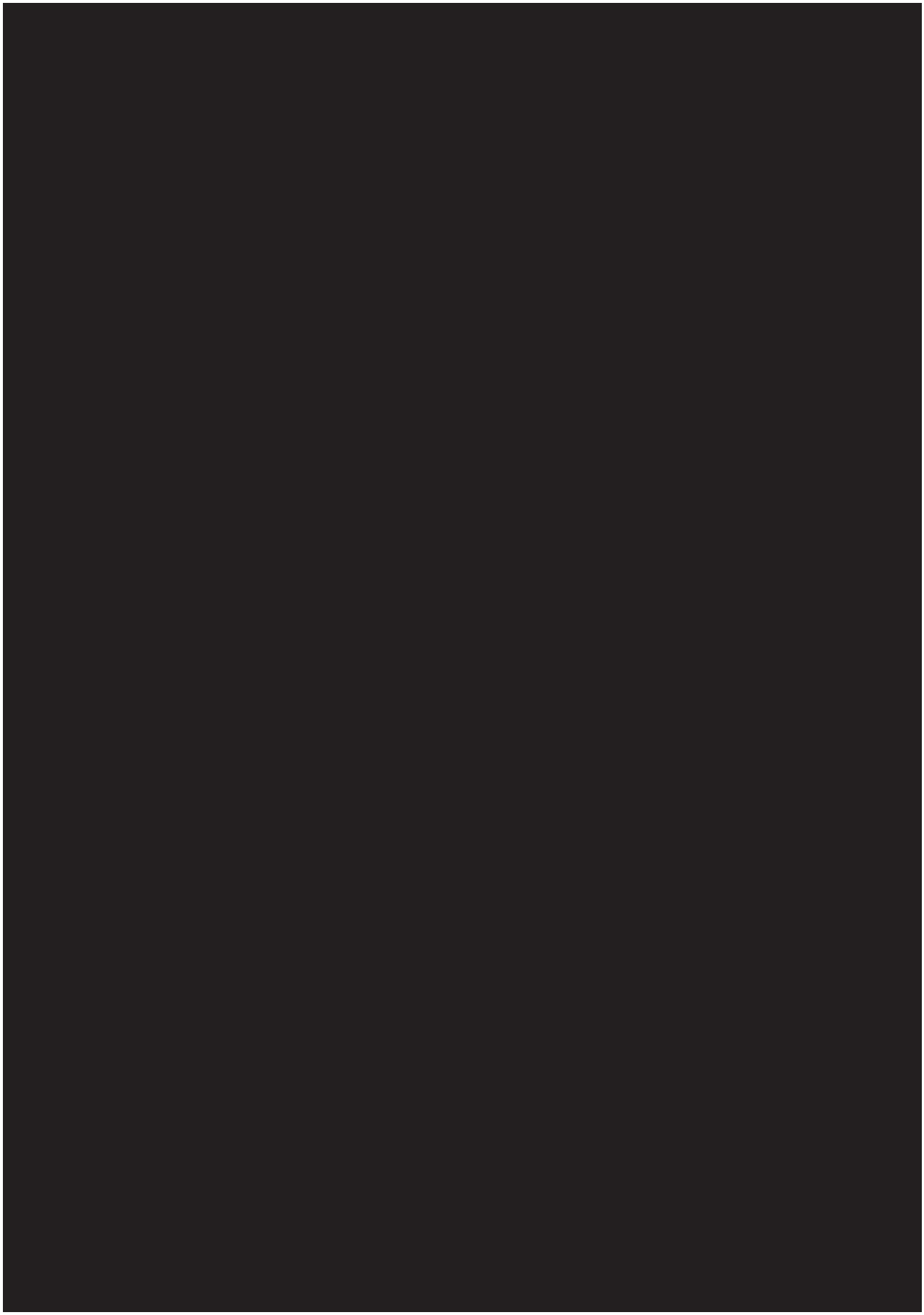
Then, perianal fistula remission (PFM) for a given patient x is

$$PFM(x) = \begin{cases} 0, & if \ \dfrac{o(v)}{BL + \epsilon} > 0 \\ 1, & if \ \dfrac{o(v)}{BL + \epsilon} = 0 \end{cases}$$

, and perianal fistula response (PFR) for a given patient x is

$$PFR(x) = \begin{cases} 0, & if \ \dfrac{o(v)}{BL} > 0.5 \\ 1, & if \ \dfrac{o(v)}{BL} \leq 0.5 \end{cases}$$

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, refer to CTP Section 4.

Patients who experience a fistula relapse during the maintenance treatment (as defined in CTP Table 2.1: 1) will be administered a single intravenous dose of spesolimab 1200 mg followed by an intensified subcutaneous maintenance dosing schedule with 600 mg q4w.

The following study periods are defined:

Table 6.1: 1 Flow chart of analysis periods which apply to all patients.

Analysis period	On-/off-treatment	Start (included)	End (included)
Screening period (Approx.. 1-2wks)	Off-treatment	Earliest of (Date of informed consent, first screening procedure)	Date/time of injection of first s.c. maintenance study drug minus 1 minute.
Overall maintenance period[1] (Approx... 336 wks)	On-treatment	Date/time of first s.c. maintenance study drug.	Date of last administered spesolimab (irrespective of formulation) + 112 days at 11:59pm.
Follow-up period[2]	Off-treatment	Date of last study drug administration (irrespective of formulation) + 113 days at 12:00 AM.	Latest of: i) Date of EOS visit (Week 352 visit); ii) last contact date on End of Study page at 11:59 p m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
[1] The overall maintenance treatment period applies to all patients taking at least one dose of maintenance treatment regardless of flare occurrence. This period will be considered to understand long-term efficacy and safety of spesolimab.
[2] The follow-up period only exists if the trial completion date is after the date of end of last injection/infusion plus REP.

The on-treatment period is defined as the overall maintenance period (including REP).

For all analysis periods, assessments done on the same day as the first maintenance treatment dose will be assigned to the appropriate analysis phase based on the assessment of date/time. If time is not collected for an assessment, then assignment will be to the previous analysis phase, e.g., to the screening phase.

Treatment Labels

Treatments will be labelled as follows:

- “Overall Speso”

[redacted]

6.3 SUBJECT SETS ANALYSED

The following patient sets are defined for analysis.

[redacted]

Safety Set (SAF)
This patient set includes all patients who received at least one dose of study drug in the overall maintenance period. This set will be the main analysis set used for presentation of efficacy and safety data. This set was formally called the Treated Set in the CTP.

Table 6.3:1 illustrates the data sets that are to be used for each category class of endpoints. For explanation of the different methods of handling missing data, see Section 6.6.

Table 6.3:1 Patient sets analyzed

Class of endpoints	ES	SAF
[redacted]		
[redacted]		
[redacted]		
[redacted]		
Primary endpoint		X
Secondary endpoint		X
[redacted]		
[redacted]		

[redacted]

6.5 POOLING OF CENTRES

All patients from all centers will be pooled for statistical analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.3 of the CTP describes the handling of missing data.

Based on the different reasons for patients' data missing, different approaches will be used to assess the impact of missing data on the endpoints of this trial, depending upon the type of the endpoint. [redacted]

[redacted]

6.6.1 Withdrawals

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

6.6.2 Efficacy endpoints

Refer to Section 7.3 of the CTP for a description of the handling of missing data for efficacy endpoints.
As described in Section 4, due to limitations in the CRF collection of data, it is not feasible to calculate either of the two secondary efficacy endpoints; [redacted]

6.6.3 Safety endpoints

For safety data, including the primary endpoint, no missing data imputations are planned.

The only exceptions where imputation might be necessary for safety evaluation are AE dates, [redacted]. Missing or incomplete AE dates are imputed according to BI standards (see KM Asset BI-KMED-BDS-HTG-0035 (3)).

[redacted]

- 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 last contact 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 last contact 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 the first day of the month.
- If the day and month of the start date are missing then the start date is set to the 1st of 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]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Measurements reported with date and time and taken prior to the start of administration of trial treatment are pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment are assigned as 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.

Refer to Section 5.2 for baseline definitions for each applicable efficacy endpoint in this trial.

For safety endpoints, the baseline is defined as the last value prior to initiation of the maintenance treatment (Visit M1).

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.

[redacted]

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day, but which are not measured on the same day, the later value will be selected. If there are two observations on the same day, the later value will be selected.

For derivation of the last value on treatment, minimum value on treatment, and maximum value on treatment, all on-treatment values (whether selected in any time window or not; see Table 6.1: 1 for definition of the on-treatment period) will be considered. These will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether selected in any time window or not) within the on-treatment period will be considered.

7. PLANNED ANALYSIS

General Remarks

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (7).

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). (see Section 7.8.1 below for details).

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	lower quartile
Median	median
Q3	upper quartile
Max	maximum

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of clinical trials and project summaries" (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 patient set (unless otherwise specified, all patients in the patient set irrespective of whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category "missing" will be displayed only if there are actually missing values.

Considering the early termination of this long-term extension trial and the use of an abbreviated CTR (aCTR) for trial results reporting, part of the planned trial analyses will not be performed. For details, please refer to section 4.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report by using the SAF only. The presentation of EIM is defined in Section 7.8.5.1.

Concomitant diseases (i.e., baseline conditions) will be coded according to the most recent version of MedDRA. Baseline here refers to the baseline of this current long-term safety trial.

Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Concomitant non-drug therapy will be coded according to the most recent version of MedDRA.

A medication/non-drug therapy will be considered concomitant to treatment, if it is ongoing at the start of this trial's treatment or starts within the on-treatment period (see Section 6.1 for a definition of study analysis periods).

7.3 TREATMENT COMPLIANCE

As described in section 4, reporting of treatment compliance is not required for an aCTR.

7.4 PRIMARY ENDPOINT(S)

The primary endpoint for this open label, long-term safety trial is a safety endpoint.

7.4.1 Primary analysis of the primary endpoint(s)

Refer to TSAP, Section 7.8.1.

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

None specified.

7.5.2 (Other) Secondary endpoints

Refer to TSAP, Section 5.2.2. for a description of the secondary endpoints.
As described in Section 4, due to limitations in the CRF collection of data, it is not feasible to calculate either of the two secondary endpoints. A listing at the individual patient level showing the status of fistulas for each treated patient will instead be prepared.

[redacted]

7.7 EXTENT OF EXPOSURE

A table of total treatment exposure [mg] across the overall maintenance period will be summarized for the SAF for spesolimab s.c. and spesolimab i.v., respectively. For the time at risk, and for the total duration of exposure(weeks), data will also be tabulated as a frequency table with categorized treatment duration, (i.e., >0 to 48 weeks, >48 to 96 weeks, >96 to 144 weeks) for the SAF for 'Overall Speso' only.

7.8 SAFETY ANALYSIS

All safety analyses will be performed 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 analysis of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA. Preferred terms (if applicable) will be sorted by total frequency (within system organ class).

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (4) [*KM Asset BI-KMED-BDS-HTG-0041*] and "Handling of missing and incomplete AE dates" (3) [*KM Asset* BI-KMED-BDS-HTG-0035].

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to either the screening period, the applicable on-treatment period, or the off-treatment period (i.e. follow-up) as defined in Section 6.1. Since only the start date of an AE is collected (without start time), any AE which occurs on the same day as the first maintenance treatment will be assigned to the respective on-treatment period.

Refer to CTP Section 7.2.2 for a description of the calculation of exposure-adjusted adverse event incidence rates (per the primary endpoint).

The AE summaries described below will be produced for the following treatment periods:

- The overall maintenance period [based on the SAF]

An overall summary of AEs will be presented. This overall summary will include the class of AESIs. Refer to CTP Section 5.2.6.1.4 for a description of what is considered as an AESI.

The investigator identified AESI will be captured from the eCRF and reported in the "Investigator reported AESI" table. In addition, user defined adverse event categories (UDAEC) identified through specific search criteria will be reported separately; the UDAEC applicable to this trial are stored centrally and will be referenced for this presentation.

Adverse Events classified as 'other significant' will be reported using an adaptation of the ICH E3 (6) and will include those non-serious and non-significant AEs which were reported with 'action taken = drug withdrawn' or 'action taken = reduced'.

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Categories (UDAEC)

User-defined AE category	
Label	**Description**
Infections ALL	Combined search strategy based on the individual UDAECs for infections described below
- 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
Hypersensitivity ALL	Combined search strategy based on the individual UDAECs for hypersensitivity described below
- Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
- Angioedema	Narrow SMQ "Angioedema"
- Hypersensitivity	Narrow SMQ "Hypersensitivity"

User-defined AE category	
Label	**Description**
- 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 ALL	
- Malignant tumours	Narrow Sub-SMQ "Malignant tumours" (Display also - Narrow Sub-SMQ "Haematological malignant tumours" - Narrow Sub-SMQ "Non-Haematological malignant tumours")
- Malignancies excluding non-melanoma skin cancer (NMSC)	Sub-SMQ "Malignant tumours" excluding NMSC, where NMSC is defined as broad Sub-SMQ "Skin malignant tumours" excluding HLT Skin melanomas (excl. Ocular)-
Peripheral Neuropathy ALL	
- Guillain-Barré Syndrome	Narrow SMQ "Guillain-Barré syndrome" (SMQ code 20000131)
- Peripheral Neuropathy	Narrow SMQ "Peripheral Neuropathy" (SMQ code 20000034)

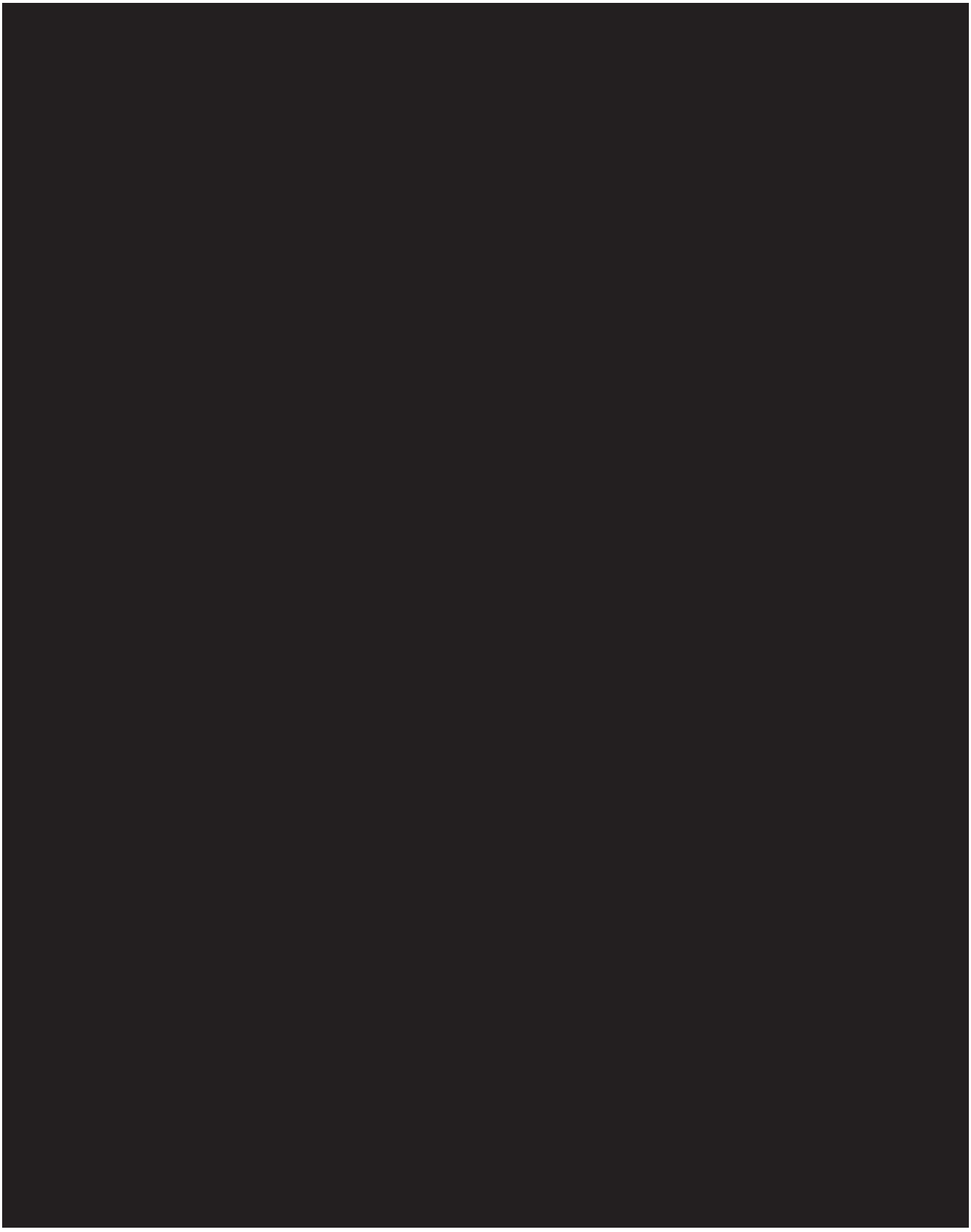
User-defined AE category	
Label	**Description**
- Demyelination	Narrow SMQ "Demyelination" (SMQ code 20000154)

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term.

AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial, patients with other significant AEs and User-defined Adverse Event Categories (UDAEC) (see Table 7.8.1: 1). AEs will also be summarized by maximum or worst intensity based on the RCTC measure (see Section 5.4.1).

Listings for AEs by Primary System Organ Class and Preferred Term and SARS-Cov-2 infections at each individual level will be provided.

[redacted]



8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version
2	*001-MCS-40-413:* " Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset* BI-KMED-BDS-HTG-0035 : "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
5	*001-MCS-36-472:* " Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", 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	*001-MCG-159*: "Reporting of clinical trials and project summaries", current version; IDEA for CON
8	*KM Asset BI-KMED-BDS-HTG-0042:* “Handling, Display and Analysis of Laboratory Data”, current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**DD-MMM-YY**	[redacted]	None	This is the final TSAP
Final	**02-Feb-22**		None	This is the final TSAP prior to first interim analysis
2.0	**28-OCT-22**		All sections	After the sponsor's decision of early termination of this long-term safety trial due to non-promising efficacy results from the parent trial, and before final database lock, revisions and necessary updates are made through this TSAP.