TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**228892_3705863_4818193**
BI Trial No.:	**1505-0001**
Title:	A first-in-human open label Phase Ia/Ib, multicenter/multiregional, dose escalation study of BI 765883 administered as monotherapy and in combination with gemcitabine and nab-paclitaxel in unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) or patients with PDAC who have relapsed after post-surgery adjuvant therapy
Investigational Product(s):	BI 765883
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	04 AUG 2025
Version:	1.0 Final
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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse Event
AUC_{0-t}	Area Under the Concentration-time Curve of the Analyte in Plasma Over the Time Interval from 0 to the Last Quantifiable Data Point
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
C_{max}	Maximum Measured Concentration of the Analyte In Plasma
CR	Complete Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DLT	Dose Limiting Toxicity
DV	Deviation Domain
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EWOC	Escalation With Overdose Control
FIH	First-in-Human
ICH	International Conference For Harmonisation
iPD	Important Protocol Deviation
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
mPDAC	Metastatic Pancreatic Ductal Adenocarcinoma
MTD	Maximum Tolerated Dose
MTDS	Maximum-tolerated Dose Set
N	Number of Non-missing Observations
OR	Objective Response

Term	Definition / description
PD	Progressive Disease
PDAC	Pancreatic Ductal Adenocarcinoma
PK	Pharmacokinetics
PKS	PK Parameter Analysis Set
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
PT	Preferred Term
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
StD	Standard Deviation
TS	Treated set
TSAP	Trial Statistical Analysis Plan

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, planning of sample size, randomization.

SAS® Version 9.4 (or later version) will be used for all analyses.

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlinTM software (version 8.1 or higher, [redacted] or SAS Version 9.4 (or later version).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable as this is the first version of the TSAP. This TSAP reflects all amendments in CTP up to and including Amendment 3.

As of May 2025, the study was terminated due to safety issue, and it was decided to produce an abbreviated report for CTR. The abbreviated CTR would include limited primary and secondary endpoint analyses. There would be limited analyses provided for PK and biomarkers as detailed in Section 7.2.5 of the CTP.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoints are defined in Section 2.1.2 of CTP. Since the study is terminated very early due to safety issue during the dose escalation phase (Phase Ia) and MTD was not reached, only the occurrence of DLTs will be summarized for Phase 1a part of the study.

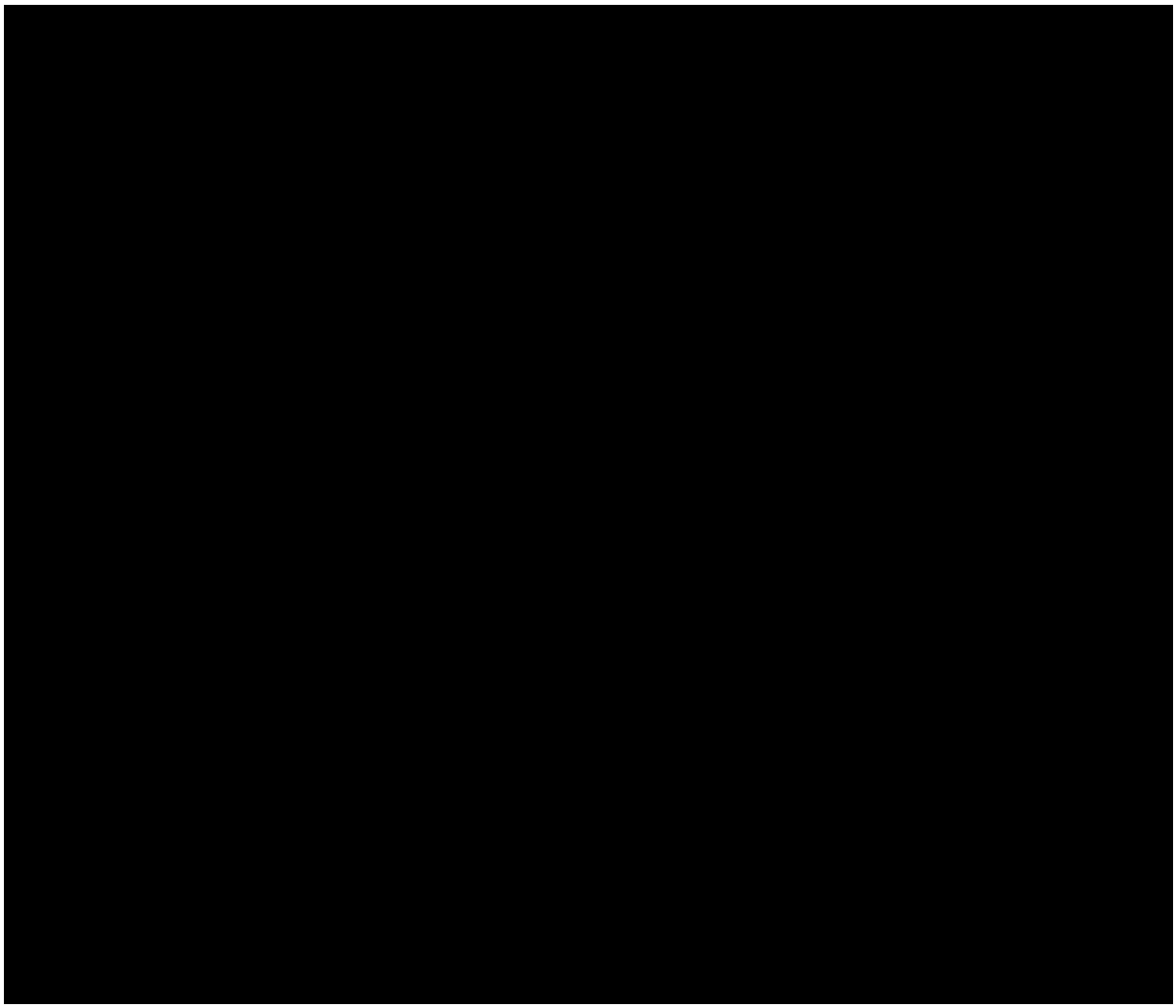
5.2 SECONDARY ENDPOINT(S)

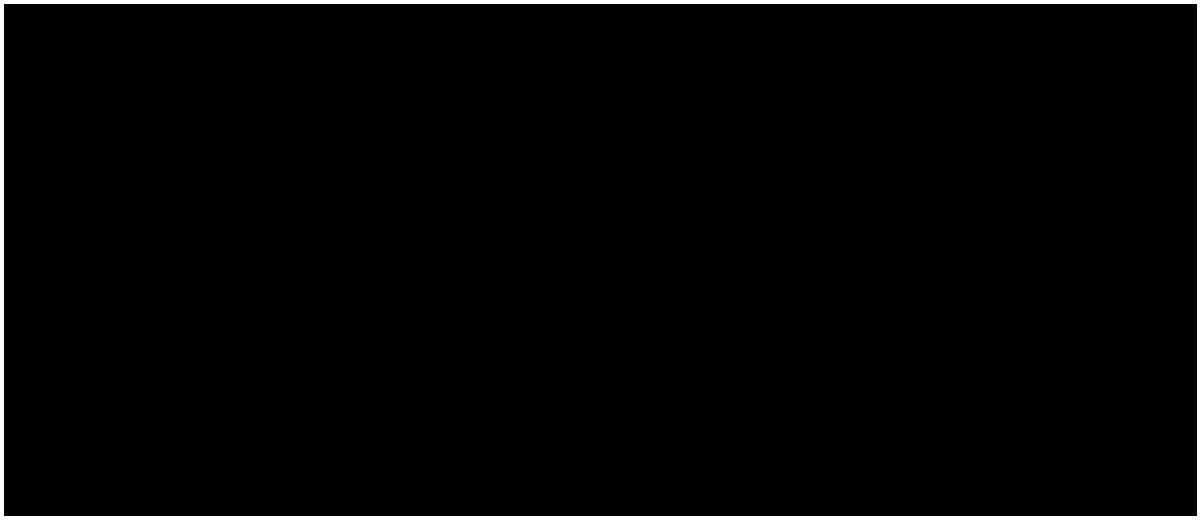
5.2.1 Key secondary endpoint(s)

No key secondary endpoint has been specified for this study.

5.2.2 Secondary endpoint(s)

The secondary endpoints are defined in Section 2.1.3 of CTP. Only safety, tumor response and PK parameter listings will be provided as the study is terminated with a few patients in treatment groups.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is an open-label, Phase Ia/Ib, FIH, multicenter, dose escalation trial of BI 765883 as monotherapy and in combination with gemcitabine and nab-paclitaxel followed by dose expansion cohorts in patients with mPDAC. The study will consist of 2 phases: the dose escalation phase (Phase Ia) and the dose expansion phase (Phase Ib). Since the study is terminated very early due to safety signal during the dose escalation phase (Phase Ia), all the Phase Ia analyses will be performed for the abbreviated CTR.

The following "analyzing treatment" (Table 6.1:1) will be used for reporting treatment emergent AEs and safety laboratory variables and the timeline criteria "start date ≤ onset date of AE < stop date" will be used to determine if an AE will be assigned to be "analyzing treatment" or not. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date/time of the first administration of BI 765883, then the AE is assigned to "Screening";
- If the date/time of the first administration of BI 765883 ≤ AE onset date < min{date of the late administration of BI 765883 + 35 days, DBL date}, then the AE is assigned to "On-treatment";
- If AE onset date ≥ date of the last administration of BI 765883 + 35 days, then the AE is assigned to "Follow-up".

AEs that have onset date during the screening or follow-up periods will be displayed in subject listings from those occurred during the on-treatment period. For the on-treatment period, AE frequency tabulations will contain a "total" column, representing all doses of BI 765883. Subject data listings of AEs will not have a "total" column.

Table 6.1:1 Analyzing Treatments

Analyzing Treatment Period	Start Date (including)	Stop Date (excluding)
Screening	Date of informed consent	Date of the first administration of BI 765883
On-treatment	Date of the first administration of BI 765883	Date of the last administration of BI 765883 + 35 days (for discontinued patients); or DBL date (for on-going patients)
Follow-up	Date of the last administration of BI 765883 + 35 days Note: on-going patients do not have follow-up periods	Date of the last per protocol visit or DBL date, whichever comes first

Note: a 35-day REP is defined for this study. DBL = database lock, REP = Residual effect period.

The actual treatment codes and decodes, the labels for the analyzing treatment, and the analysis numbers are defined in the technical TSAP document of ADS Plan and Data Guide and stored in the same location with this document in Veeva Clinical.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Refer to Identify and Manage Important Protocol Deviations (iPD) (9.6).

The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain specifications, which is stored within the Veeva Clinical. Important PDs will be documented in the DV template domain with input from clinical. The DV template domain will then be sent to data management that will be converted to a database for analysis.

6.3 INTERCURRENT EVENTS

The intercurrent event handling strategies are provided in section 7.2.2 of the CTP. Since this study is terminated very early due to excessive DLTs during first dose of the combination therapy, the analysis of primary endpoint will not be completed as planned.

6.4 SUBJECT SETS ANALYSED

- Screened set: This patient set includes all subjects who have signed the informed consent. The screened set will be used for patient disposition tables.
- Treated set (TS): This includes all subjects who were dispensed study medication and were documented to have been treated with at least one dose of BI 765883. This TS is used for both safety and efficacy analyses.
- MTD evaluation set (MTDS): This includes all patients in the TS who were not replaced for the MTD determination. The MTDS is used for the primary analyses of DLTs and MTD determination. Rules for replacement of patients are defined in the CTP Section 3.3.4.4. The list of replaced patients will be provided by the Trial Clinical Monitor no later than the last RPM and should be documented in the RPM minutes.
- Pharmacokinetic parameter analysis set (PKS): This includes all subjects in the treated set (TS) who provide at least one PK endpoint and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection Pharmacokinetics). Descriptive and potential model based analyses of PK parameters will be based on the PKS.

The subject sets analysed are shown in Table 6.4:1.

Table 6.4: 1 Subject sets analysed

	Subject set		
Class of analysis	Treated set	MTD set	PK Set
Efficacy	X		
Safety & treatment exposure	X		
Demographic & baseline	X		
DLTs & BLRM Analysis		X	
Pharmacokinetic parameter analysis			X

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort was made to collect complete data at each visit for each patient. If not specified otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates and concomitant non-drug therapy/medication dates are imputed according to BI standards (BI-KMED-BDS-HTG-0035 (v1.0): “Handling of missing and incomplete AE dates”).

Missing data and outliers of PK data are handled according to BI standards (BI-KMED-TMCP-MAN-0009: Manual for Noncompartmental Pharmacokinetic/-dynamic Analysis in TMCP). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to CTP’s flow chart.

Unless otherwise specified, baseline is defined as the time point closest to and prior to the first administration of study treatment. Note that for some study procedures (e.g. body weight, vital signs, laboratory tests), baseline may be the measurement made on the same day the study treatment was started. In such cases, these measurements will be assumed to have been taken according to the CTP, i.e. prior to the first administration of BI 765883.

For laboratory parameters for which not only the examination date but also the sampling time was recorded, examination time should be taken into consideration when defining baseline. That is a laboratory measurement on the same date as the first administration of BI 765883 is considered as baseline if and only if, the examination time of the laboratory measurement is before the first administration of BI 765883.

7. PLANNED ANALYSIS

The following standards for End-Of-Text tables are defined:

- The set of summary statistics for continuous data is: N / Mean / StD / Min / Median / Max. For tables that are provided for endpoints with some extreme data, median, should be preferred to mean, StD, Min, and Max .. Other than the Min and Max, all statistics will be presented to one more decimal place than the raw data.

- 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 will be one decimal place. The category "missing" will be displayed only if there are actually missing values.

Where applicable, conversion from days to weeks, months, and years will be as follows:

- Weeks = days ÷ 7
- Months = (days × 12) ÷ 365.25
- Years = days ÷ 365.25.

General aspects for PK

Descriptive data analysis of PK endpoints and concentrations will be performed according to BI procedures.

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example:

- Missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics by dose group and separated by mono and combo treatments are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only listings are planned for this section of the report.

7.3 TREATMENT COMPLIANCE

Due to very short treatment period, the compliance listing is not planned for this section of the report.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

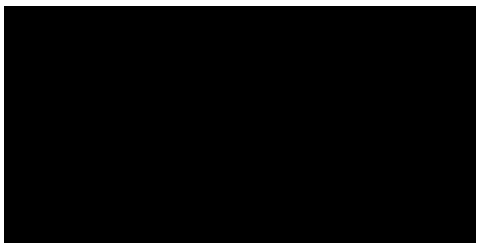
The primary analysis for Phase Ia:

In order to identify the MTD of the trial, the number of patients at each dose level that had DLT evaluation period will be presented. The BLRM as described in Section 7.1 of the CTP will be analyzed using the number of patients at each dose that had DLTs during the evaluation period among the patients in the MTD set. The prior probabilities defined in Table 11 of the CTP will be used for the analysis. The resulting posterior distribution of the DLT rates of the doses tested during the trial will be summarized using their mean, StD, 2.5% quantile, median, and 97.5% quantile. Additionally, the posterior probabilities of the DLT rate lying in the intervals [0, 0.16) (under toxicity), [0.16, 0.33) (target toxicity), and [0.33, 1] (over toxicity) will be computed and listed for each dose. The posterior probabilities of under dosing, target dosing, and overdosing of the tested dose levels will additionally be visualized in a bar diagram that further displays which of the dose levels satisfy the EWOC criterion.

The number of patients with DLTs that occurred during the entire treatment period will be summarized at each level separately for Mono and combination therapies.

The primary analyses for Phase Ib:

As the study is terminated very early due to safety issue during the dose escalation phase (Phase Ia), this section of the report is not applicable for the abbreviated CTR.



[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

The secondary endpoint of the confirmed OR is outlined in Section 2.1.3 of the CTP. Since the study is terminated very early due to safety issue during the dose escalation phase (Phase Ia), the OR analysis is limited to summaries of RECIST 1.1 determinations for CR, PR, SD, and PD.

Descriptive analysis of the following PK parameters will be performed for BI 765883 in phase Ia as outlined in Section 2.1.3 in CTP and according to BI standards (BI-KMED-TMCP-MAN-0009: Manual for Noncompartmental Pharmacokinetic/-dynamic Analysis in TMCP) if applicable and feasible:

- C_{max}: maximum measured concentration of the analyte in serum
- AUC_{0-t}: area under the serum concentration time curve of the analyte

All the summaries will be presented by dose groups and treatment therapies (Mono and Combination).

[redacted]

7.7 EXTENT OF EXPOSURE

Treatment exposure parameters has been defined in Section 5.4.2 of this TSAP. The summaries for number of treatment cycles initiated and total duration of study treatment will be presented by dose groups and treatment therapies (Mono and Combination).

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse Events

As the study is terminated very early during the dose escalation phase (Phase Ia), only Phase 1a AE data will be presented for Phase 1a. The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The analysis of AEs will be based on the concept of treatment of emergent AEs. That means that all AEs occurring between first drug intake till 35 days after last drug intake will be assigned to the treatment assigned. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after the last drug intake + 35 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

The frequency of subjects with AEs will be summarized by dose groups and treatment therapies (Mono and Combination), primary SOC and PT (MedDRA levels to be displayed in the tables). Separate tables will be provided for subjects with SAEs, AEs leading to treatment discontinuation, related AEs, related SAEs, related AEs leading to treatment discontinuation, and AESIs. The Overall AE Summary will be provided by dose groups and treatment therapies (Mono and Combination)..

The system organ classes will be sorted by default alphabetically; PTs will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g. SOC sorted by frequency.

The AEs of Special Interest (AESI) are defined in Section 5.2.6.1.4 of the CTP. The following listings will be provided for the AESIs:

- Listing of patients meeting Drug-induced liver injury (DILI) criteria in Section 5.2.6.1.4 of the CTP by dose groups and treatment therapies (Mono and Combination).
- Listing of patients with Infusion-related reactions (IRR) by dose groups and treatment therapies (Mono and Combination).
- Listing of patients with Dose-limiting toxicities (DLTs) by dose groups (separates for Mono and Combination therapies), primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be provided in listings. The listings will be separated by dose groups and treatment therapies (Mono and Combination).

7.8.3 Vital signs

Only listings are planned for this section of the report. The listings will be separated by dose groups and treatment therapies (Mono and Combination).

7.8.4 ECG

Electrocardiogram (ECG) results will only be listed in the final CTR; Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs.

7.9 OTHER ANALYSIS

Since this study is terminated very early due to excessive DLTs during first dose of the combination therapy, no other analyses will be done.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Since this is an open label study, this section is not applicable.

9. REFERENCES

9.1	*BI-VQD-23790-S-G_50-415_AD-02:* "Project Analysis Dataset (PADS) Template (template)", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.2	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.3	*BI-VQD-12682-S-G_50-415_AD-03:* "Clinical Trial Analysis Decision Log (template)", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.4	*BI-VQD-12177_40-106_AD-03:* "Clinical Trial Protocol general template for Phase I-IV", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents.
9.5	*001-MCS-80-606*: "Management of Non-Compliances, Audit and Inspection Responses", current version, group / owning department "Med Quality Medicine", DMS for controlled documents.
9.6	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents.
9.7	REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, European Commission webpage.
9.8	*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.
9.9	*001-MCS-30-475_RD-01*: "Biomarker: Intended Use & Implementation Statement (IUIS) (template)", current version, group / owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	10-JUL-25	[redacted]	None	This is the final TSAP.
1.0 Final	04-AUG-25	[redacted]	Various	Updated with comments and simplified the analysis outputs for abbreviated CTR after team agreement