TRIAL STATISTICAL ANALYSIS PLAN

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Title:	Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Investigational Product(s):	Brigimadlin
Responsible trial statistician(s):	[redacted] Email: [redacted]
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TABLE OF CONTENTS

TITLE PAGE....1
TABLE OF CONTENTS....2
1. LIST OF TABLES....3
2. LIST OF ABBREVIATIONS....4
3. INTRODUCTION....6
4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY....7
5. ENDPOINTS(S)....8
5.1 PRIMARY ENDPOINT(S)....8
5.2 SECONDARY ENDPOINT(S)....8
[redacted]
6. GENERAL ANALYSIS DEFINITIONS....9
6.1 TREATMENT(S)....9
6.2 IMPORTANT PROTOCOL DEVIATIONS....9
6.3 SUBJECT SETS ANALYSED....9
6.4 HANDLING OF MISSING DATA AND OUTLIERS....10
6.5 BASELINE, TIME WINDOWS AND CALCULATED VISITS....10
7 PLANNED ANALYSIS....12
7.1 DISPOSITION OF SUBJECTS....12
7.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS....12
7.3 CONCOMITANT MEDICATION....13
7.4 TREATMENT COMPLIANCE....13
7.5 PRIMARY OBJECTIVE ANALYSIS....13
7.6 SECONDARY OBJECTIVE ANALYSIS....14
7.6.1 Secondary objective analysis....14
7.8 EXTENT OF EXPOSURE....19
7.9 SAFETY ANALYSIS....20
7.9.1 Adverse Events....20
7.9.2 Laboratory data....23
8 TIMEPOINT OF RELEASE OF TREATMENT INFORMATION....24
9 REFERENCES....25
10 HISTORY TABLE....26

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1. LIST OF TABLES

Table 1 Rules for imputations of missing or incomplete dates 10
Table 2 Nominal time points and windows for imaging 11
Table 3 Details of best overall response confirmation rules 13
Table 4 Censoring rules for DOR 16
Table 5 Censoring rules for PFS 17
Table 6 Censoring rules for OS 19
Table 7 User-defined AE categories (UDAECs) 20
Table 8 History table 26

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Plasma Concentration-time Curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
DOR	Duration of Objective Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Regulatory Activities
MDM2	Murine Double Minute 2
NE	Not Evaluable
OR	Objective Response
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression-Free Survival
PD	Progressive Disease
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Preferred Term
REP	Residual Effect Period

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Term	Definition / description
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
StD	Standard Deviation
SD	Stable Disease
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBILI	Total Bilirubin
TP53	Tumor Protein P53
TS	Treated Set
TSTAT	Trial Statistician
ULN	Upper Limit of Normal

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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) will be used for all analyses.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In November 2024, Boehringer Ingelheim decided to discontinue future development of brigimadlin.

As per CTP, recruitment in 1403-0011 and further expansion of the study, including Cohort-1-CN has been discontinued as of 26 Nov 2024.

All available primary and secondary endpoints will be reported in the final analysis in CTR. Further endpoints will not be analyzed. Hypothesis testing will no longer be conducted as a result of the decision to discontinue development of brigimadlin. Efficacy set will no longer be used.

The assessment of efficacy will continue, except all imaging-related endpoints will no longer be assessed by central independent review.

Patients will be followed up for safety but will no longer be followed up for disease progression and overall survival.

Sampling and analyses for pharmacokinetics of brigimadlin, exploratory analyses of biomarkers, and patient-reported outcome questionnaires will be discontinued.

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5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the trial is objective response (OR) based on central independent review. OR is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 from the date of treatment start until the earliest date of disease progression, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent.

5.2 SECONDARY ENDPOINT(S)

Secondary endpoints of the trial are:

- Duration of objective response (DOR) based on central independent review. DOR is defined as the time from first documented confirmed objective response (OR) until the earliest date of disease progression or death among patients with confirmed objective response.
- Progression-free survival (PFS) based on central independent review. PFS is defined as the time from treatment start until the earliest date of tumour progression according to RECIST version 1.1 or death from any cause, whichever occurs first.
- Overall survival (OS), defined as the time from treatment start until death from any cause.
- Disease control (DC) based on central independent review. DC is defined as a best overall response of CR, PR, or stable disease (SD) where best overall response is defined according to RECIST version 1.1.
- Occurrence of treatment-emergent adverse events (AEs) during the on-treatment period.
- Occurrence of treatment-emergent AEs leading to trial drug discontinuation during the on-treatment period.
- The following endpoints reflecting patient-reported outcomes (PRO) will be assessed with the following PRO measures (PROMs), for Cohorts 1 and 1-CN only:
- Change from baseline in EORTC QLQ-C30 physical functioning domain score
- Change from baseline in EORTC QLQ-C30 fatigue domain score
- Change from baseline in EORTC QLQ-C30 role functioning domain score
- Change from baseline in EORTC QLQ-BIL21 tiredness domain score.

[redacted]

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

All treated patients will be classified into brigimadlin 45 mg q3w.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A summary of violations of inclusion/exclusion criteria and all other important protocol deviations will be provided.

6.3 SUBJECT SETS ANALYSED

Screened Set (SS):

This patient set will include all patients screened.

Treated Set (TS):

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This patient set includes all patients who were dispensed trial medication and were documented to have taken at least one dose of trial medication.

All safety, efficacy, demographics and baseline characteristics are based on the TS. Screened Set will be used for disposition.

No per protocol set will be used in the analysis for this trial. However, important protocol deviations will be identified and listed based on TS.

6.4 HANDLING OF MISSING DATA AND OUTLIERS

Unless otherwise specified, missing data for any presentation of efficacy data will not be imputed. Missing or incomplete AE dates are imputed according to BI standards. Missing dates that affect the evaluation of endpoints specified in previous sections of this SAP will be imputed utilizing a "worst case" approach, which will be applied on a case-by case basis (depending on the affected endpoint).
The rule in Table 1 will be used in this trial, if applicable.

Table 1 Rules for imputations of missing or incomplete dates

Date	Imputation rule
Date of death	Date last known to be alive + 1, if month is the same as month of last known alive date; Else if only year and month are given, this will be imputed with 1st of the month
Date of first appearance or recurrence of metastasis	1st of the month if day is missing January if month also missing
Date of start of concomitant medication	1st of the month if day is missing January if month also missing
Date of end of concomitant medication	Last day of the month if day is missing December if month also missing
Date of start of subsequent anti-cancer therapy (imputation required only for censoring of PFS)	If the day (respectively day and month) of the start date of subsequent anti-cancer therapy is missing, then the first of the month (respectively 1st January) will be imputed unless this date leads to a date before the stop date of study medications.

6.5 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, baseline is defined as the last value prior to first administration of trial medication. For efficacy presented by visit, labs and vital signs, visits will be presented as collected.

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Study days and visits will be labelled according to the Flowcharts in the CTP.

Laboratory values
Baseline is defined as the last time point before the first administration of trial medication. For laboratory assessments, time is recorded in addition to examination date; therefore, examination time must also be taken into account when defining baseline. A laboratory value on the same date as the first administration of trial medication is considered to be a baseline value if the time of the laboratory value is before or the same as the time of first administration of trial medication.
If any of these times are missing, and the date of the laboratory assessment is equal to the date of first administration of trial medication, then the laboratory assessment will be considered as according to protocol, i.e., as prior to first administration of trial medication.

Imaging time windows
To identify whether consecutive imaging time points are missing for a given patient, a nominal time point (e.g., 6 weeks, 12 weeks, 18 weeks, 24 weeks, etc.) will be assigned to each image. This is achieved by creating windows for every radiological disease assessment. The windows are defined in Table 2.

Table 2 Nominal time points and windows for imaging

Nominal time point [weeks from Cycle 1 Day 1]	**Due date of scans [days from Cycle 1 Day 1]**	**Window [days]**
6-week interval until Week 48		
0 weeks	1 day	≤ 1 day
6 weeks	43 days	2 to ≤ 64 days
12 weeks	85 days	65 to ≤ 106 days
18 weeks	127 days	107 to ≤ 148 days
24 weeks	169 days	149 to ≤ 190 days
30 weeks	211 days	191 to ≤ 232 days
36 weeks	253 days	233 to ≤ 274 days
42 weeks	295 days	275 to ≤ 316 days
48 weeks	337 days	317 to ≤ 379 days
From Week 48 onwards, 12-week interval		
60 weeks	421 days	380 to ≤ 463 days
72 weeks	505 days	464 to ≤ 547 days
Etc.	Etc.	Etc.

If a patient does not have an image in one of the windows described in Table 2, then the patient will be said to have “missed an assessment” for that time point.

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7 PLANNED ANALYSIS

Descriptive statistics for continuous variables will generally be n (number of patients with non-missing values), mean, standard deviation (StD), minimum, median, and maximum. In general, means, medians, and StDs will be presented to one more decimal place than the raw data. Minimums and maximums will be presented to the same number of decimal places as the raw data.

Tabulations of frequencies for categorical data will include all possible categories, unless otherwise specified (e.g. adverse event terms) and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. A missing category will be displayed if and only if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

Time-to-event endpoints will be summarized in months to one decimal place. The set of summary statistics is: number of patients [N (%)], number of patients with event [N (%)], number of patients censored [N (%)], <Time to event> [<Unit>] followed by Min / P25 (25th percentile) / Median / P75 (75th percentile) / Max.

7.1 DISPOSITION OF SUBJECTS

The number of patients screened but not treated in the study will be presented. The number of patients prematurely discontinuing their study treatment during the study treatment period or prematurely discontinuing from the study will be presented with the categorization of the reasons for discontinuation of either treatment or study, where the corresponding percentages will be shown using number of treated patients as denominator.

The disposition of all patients screened in the study will be listed, showing the country, center, patient number, date of end of treatment, treatment discontinuation reason, date of end of study and study discontinuation reason.

7.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided for demographics and baseline disease characteristics of treated patients. The tables will show the relevant statistics (number and percent within categories of the relevant variables; other descriptive statistics for the continuous measured variables) for treated patients.

Baseline demographics will include age, sex, race, weight, BMI and ECOG PS. Additionally, baseline disease characteristics will be summarized including tumor classification, anatomical site, diagnosis, time from first diagnosis, tumor characteristics, prior radiotherapy, prior surgery, MDM2 status, presence of TP53 mutation.

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7.3 CONCOMITANT MEDICATION

Concomitant medications taken concomitantly while on treatment will be summarized. This includes medications with start date prior to start of treatment but end date missing or after start of treatment.

7.4 TREATMENT COMPLIANCE

Compliance to treatment will not be presented however Exposure to drug is included in addition to any changes to planned regimen (reductions or delays) will be presented.

7.5 PRIMARY OBJECTIVE ANALYSIS

The primary endpoint of the trial is objective response (OR) based on central independent review. OR is defined as a best overall response (as detailed for OR based on central independent review) of complete response (CR) or partial response (PR) according to RECIST version 1.1 based on central independent review.

A best overall response of CR or PR must be confirmed by a subsequent tumor assessment (based on central independent review), i.e., a confirmed response requires a repeat observation at least 4 weeks apart.

Unconfirmed PR or CR will be presented as a sub-category of SD. SD must last for at least 35 days to be presented as SD. SD lasting less than 35 days and followed by PD will be presented as a sub-category of PD. SD lasting less than 35 days and without evaluable response thereafter will be listed as “Not evaluable”. Any assessments done in compliance with the pre-specified (-)7 day assessment window will also be accounted for as within the 35-day duration.

Confirmation rules for best overall response are shown below in Table 3.

Table 3 Details of best overall response confirmation rules

Overall response (first time point)	**Overall response (subsequent time point)**	**Confirmed best overall response**
CR	CR	CR
CR	PR	SD, PD or PR[$]
CR	SD	SD as long as ≥ 35 days, otherwise PD
CR	PD	SD as long as ≥ 35days, otherwise PD
CR	NE/Missing*	SD as long as ≥ 35 days, otherwise NE
PR	CR	PR

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Overall response (first time point)	Overall response (subsequent time point)	Confirmed best overall response
PR	PR	PR
PR	SD	SD
PR	PD	SD as long as ≥ 35 days, otherwise PD
PR	NE/Missing*	SD as long as ≥ 35 days, otherwise NE
SD	SD	SD
SD	PD	SD as long as ≥ 35 days, otherwise PD
SD	NE/Missing	SD as long as ≥ 35 days, otherwise NE
NE	NE/Missing	NE

[$] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
* If a patient has an overall response sequence of CR, NE/Missing, CR, then the patient's confirmed best overall response is CR. If a patient has an overall response sequence of PR, NE/Missing, PR, then the patient's confirmed best overall response is PR.

7.6 SECONDARY OBJECTIVE ANALYSIS

7.6.1 Secondary objective analysis

As per CTP version 6.0 following secondary endpoints will be analyzed:
DOR, PFS, DC and OS.

Duration of Objective Response (DOR)

DOR is defined as the time interval from first documented confirmed OR based on central independent review until disease progression (based on central independent review) or death among patients with confirmed OR based on central independent review, whichever occurs first.

DOR can only be calculated for patients with confirmed OR (based on central independent review). Derivations below are described in days. However, the endpoints below will be presented in months in the statistical tables.

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For patients with confirmed OR and disease progression (based on central independent review) or death:

- DOR [days] = date of outcome – date of first assessment indicating OR (based on central independent review) + 1.

For patients with confirmed OR and without disease progression (based on central independent review) or death:

- DOR (censored) [days] = date of outcome – date of first assessment indicating OR (based on central independent review) + 1.

As described in the CTP, patients administered a subsequent anti-cancer therapy recorded in the case report form (CRF) but not presenting with progressive disease (PD) based on central independent review before the start of the new anti-cancer therapy will be censored at the date of imaging before the new anti-cancer therapy started.

If a patient has a radiological examination take place over a number of days, i.e., target lesions assessed on day x and non-target lesions assessed on day y, a single date for the derivation of PFS for each patient is still required. The following rules will be applied:

- If the overall response is PD, the earliest date of multiple assessments will be taken.
- If the overall response is SD, PR, or CR, the latest of multiple assessment dates will be taken, i.e., in the case of SD, PR, or CR, the latest of multiple dates will be used to censor the patient.

If a patient does not have an image in one of the time windows described in Table 2, then the patient will be considered to have “missed an assessment” for that time point.

An image where an overall response of NE (not evaluable) has been assigned is not considered evaluable. Images for which NE is assigned as the overall response at an imaging time point are considered to be missed assessments. It cannot be assumed that NE indicates progression has not occurred.

Rules to determine events and censoring for DOR are provided in Table 4.

Only radiological assessments after first assessment indicating OR (based on central independent review) should be taken into consideration.

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Table 4 Censoring rules for DOR

Situation	Outcome (Event or Censored)	Date of outcome
No other anti-cancer therapy		
Alive and not progressed, and no more than one consecutively missed radiological assessment	Censored	Date of last radiological assessment
Alive and not progressed, and two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, and zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, and two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression, and zero or one missed radiological assessment prior to death	Event	Date of death
Death but no progression, and two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death, and no more than one consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

Progression Free Survival (PFS)

PFS is defined as the time interval from first treatment until the earliest of tumor progression according to RECIST version 1.1 (based on central independent review) or death from any cause, whichever occurs first.

For patients with known date of progression (based on central independent review) or death:

- PFS [days] = earlier date of progression (based on central independent review) or death – date of first treatment + 1.

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For patients who will be censored:

- PFS (censored) [days] = date of last imaging assessment without disease progression (based on central independent review) – date of first treatment + 1.

As described in the CTP, patients administered a subsequent anti-cancer therapy recorded in the case report form (CRF) but not presenting with progressive disease (PD) based on central independent review before the start of the new anti-cancer therapy will be censored at the date of imaging before the new anti-cancer therapy started.

If a patient has a radiological examination take place over a number of days, i.e., target lesions assessed on day x and non-target lesions assessed on day y, a single date for the derivation of PFS for each patient is still required. The following rules will be applied:

- If the overall response is PD, the earliest date of multiple assessments will be taken.
- If the overall response is SD, PR, or CR, the latest of multiple assessment dates will be taken, i.e., in the case of SD, PR, or CR, the latest of multiple dates will be used to censor the patient.

If a patient does not have an image in one of the time windows described in Table 2, then the patient will be considered to have "missed an assessment" for that time point.

An image where an overall response of NE (not evaluable) has been assigned is not considered evaluable. Images for which NE is assigned as the overall response at an imaging time point are considered to be missed assessments. It cannot be assumed that NE indicates progression has not occurred.

Rules to determine events and censoring for PFS are provided in Table 5.

Table 5 Censoring rules for PFS

Situation	Outcome	Date of outcome
No baseline radiological assessment		
Patient with death on or before the second planned radiological assessment	Event	Date of death
Patient without death or patient with death after second performed radiological assessment	Censored	Date of first treatment
Without post-baseline radiological assessments		
Vital status is unknown, or patient is known to be alive	Censored	Date of first treatment
Death prior to or on the second planned radiological assessment	Event	Date of death
Death beyond the second planned radiological assessment	Censored	Date of first treatment

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Situation	Outcome	Date of outcome
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed, and no more than 1 consecutively missed radiological assessment	Censored	Date of last radiological assessment
Alive and not progressed, and 2 or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, and 0 or 1 missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but 2 or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessment
Death but no progression, and 0 or 1 missed radiological assessment prior to death	Event	Date of death
Death without progression, but 2 or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to death	Censored	Date of first treatment

Disease Control (DC)

Disease control is defined as best overall response of CR, PR, or stable disease (SD) where best overall response is defined according to RECIST version 1.1.

Overall Survival (OS)

OS is defined as the time interval from first treatment until death from any cause.

For patients with known date of death of any cause:

- OS [days] = date of death – date of first treatment + 1.

For patients who will be censored:

- OS (censored) [days] = date of last contact when the patient is known to be alive – date of first treatment + 1.

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Date of last contact when the patient is known to be alive may be derived using the following data sources:

- Patient follow-up in eCRF: date of patient status obtained, last date patient known to be alive (in case patient is lost to follow-up), date of refusal (in case of patient's refusal for follow-up)
- Tumor response (date of imaging target lesions, date of imaging non-target lesions, date of detection of new lesion)
- Administration page of brigimadlin (including termination of trial medication page)
- Start date of subsequent anti-cancer therapy
- Start date of subsequent radiotherapy
- Date of first treatment
- Onset and/or end dates of AEs
- Vital signs and/or physical examination dates

Rules to determine events and censoring for OS are provided in Table 6 below.

Partial death dates will be imputed as described in section 6.4 .

Table 6 Censoring rules for OS

Status at time of analysis	Outcome (Event or Censored)	Date of outcome
Patient died, and the date of death is known	Event	Date of death
Patient died, and the date of death is unknown	Event	Date of last contact when the patient is known to be alive + 1 day
Patient alive	Censored	Date of last contact when the patient is known to be alive
Unknown	Censored	Date of last contact when the patient is known to be alive

As per CTP version 6.0 endpoints based on patient-reported outcome questionnaires will not be analyzed.

7.8 EXTENT OF EXPOSURE

Exposure will be presented as total number of cycles and Exposure period, where Exposure period is defined as the time interval from the date of first treatment administration to last

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treatment administration date. Breakouts by months of treatment received will be presented. Additionally, patients with dose reductions and dose delays will be summarized.

7.9 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.9.1 Adverse Events

Unless otherwise specified, 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 emergent AEs. AEs occurring from the start of treatment until stop of treatment + residual effect period (REP = 30 days) will be considered on-treatment. AEs occurring prior to the start of treatment will be assigned to 'screening' and all AEs occurring after last drug intake + 30 days (REP) will be assigned to 'follow-up' (for listings only).

An overall summary of AEs will be presented. The frequency of patients with AEs will be summarized in following 2 ways.

- By treatment, highest CTCAE grade, primary SOC, and PT. The SOCs will be sorted alphabetically. PTs will be sorted by decreasing frequency (within SOC).

- By treatment, highest CTCAE grade, (grouped) preferred term (with the latest version defined in Table 7) and preferred term. The (grouped) preferred terms will be sorted by decreasing frequency, and preferred terms within the (grouped) preferred terms are sorted by decreasing frequency.

AEs with a missing CTCAE grade will be displayed under the category of "All Grades", and an explanatory footnote will be added. No "Missing Grade" category will be displayed.

Table 7 User-defined AE categories (UDAECs)

User-defined AE categories	MedDRA Preferred Terms	Use as grouped PT in standard AE tables
Haematological AEs		
Thrombocytopenia+	- Include PTs under SMQ 20000031 Haematopoietic thrombocytopenia (Narrow)	Yes
Anaemia+	- Include PTs under SMQ 20000029 Haematopoietic erythropenia (Narrow) - Anaemia - Haemoglobin decreased - Leukoerythroblastic anaemia - Normochromic anaemia	Yes

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User-defined AE categories	MedDRA Preferred Terms	Use as grouped PT in standard AE tables
	- Normochromic normocytic anaemia - Normocytic anaemia	
Neutropenia+	- Febrile neutropenia - Neutropenia - Neutropenic infection - Neutropenic sepsis - Neutrophil count decreased - Radiation neutropenia - Band neutrophil count decreased - Cyclic neutropenia - Idiopathic neutropenia	Yes
Lymphopenia+	- Lymphocyte count decreased - Lymphopenia - B-lymphocyte count decreased - T-lymphocyte count decreased - CD19 lymphocytes decreased	Yes
Other Leukopenia+	- Include PTs under SMQ 20000030 Haematopoietic leukopenia (Narrow) - Exclude PTs already in Neutropenia+ and Lymphopenia+	Yes
Other Cytopenias+	- Include PTs under SMQ 20000028 Haematopoietic cytopenias affecting more than one type of blood cell (Narrow)	Yes
Gastrointestinal AEs		
Nausea	- Nausea	No
Vomiting+	- Vomiting - Vomiting projectile - Retching	Yes
Diarrhoea	- Diarrhoea	No
Other Gastrointestinal AEs	- Includes PTs under SMQ: 20000137 Gastrointestinal nonspecific inflammation and dysfunctional conditions (Narrow) - Exclude PTs already in Nausea, Vomiting+ and Diarrhoea - Exclude PT Non-cardiac chest pain	No
Haemorrhage		

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User-defined AE categories	MedDRA Preferred Terms	Use as grouped PT in standard AE tables
Haemorrhage	- Blood urine - Blood urine present - Gastric occult blood positive - Occult blood positive - Urinary occult blood - Urinary occult blood positive - Include PTs under SMQ: 20000039 Haemorrhage terms (excl laboratory terms) (Narrow)	No
Infections		
Infections	- Include PTs under SOC: Infections and infestations	No
Fatigue		
Fatigue+	- Fatigue - Cancer fatigue - Asthenia - Lethargy - Malaise	Yes

+ indicates grouped PTs.

The following tables/listings will be produced for AEs with an onset during the on-treatment period by worst CTCAE grade:

- Patients with AEs
- Patients with drug-related AEs
- Patients with SAEs
- Patients with drug-related SAEs
- Patients with AEs of Special Interest
- Patients with AEs leading to death (no CTCAE grade required)
- Patients with AEs leading to dose reduction of trial medication
- Patients with AEs leading to dose delay of trial medication
- Patients with AEs leading to permanent discontinuation of trial medication

7.9.1.1 Groupings of adverse events and adverse events of special interest

The following adverse events of special interest (AESI) are defined in the CTP.

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1. Hepatic injury (refer section 5.2.6.1.4 of CTP)

2. Hematological AEs
   - Thrombocytopenia of CTCAE Grade 3 associated with bleeding
   - Thrombocytopenia of CTCAE Grade 4
   - Neutropenia of CTCAE Grade 3 with documented infection
   - Neutropenia of CTCAE Grade 4 lasting >7 days
   - Febrile neutropenia CTCAE Grade ≥3
   - Thrombocytopenia or anemia requiring transfusion per local or international guidelines

3. Gastrointestinal AEs
   - Nausea of CTCAE Grade ≥3
   - Vomiting of CTCAE Grade ≥3
   - Diarrhea/colitis of CTCAE Grade ≥3

7.9.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards. The number and percentage of patients with possibly clinically significant on-treatment abnormalities as identified by use of clinically significant ranges for each laboratory parameter collected will be presented. The patients with possible clinically significant abnormalities will be identified within the on-treatment period by study treatment.

Vital signs and ECG data observed at baseline, during the trial and at the end-of-trial will also be presented. The tables will show the relevant statistics (number and percent within categories of the relevant variables; other descriptive statistics for the continuous measured variables) for treated patients.

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8 TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

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9 REFERENCES

9.1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.2	*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.
9.3	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.
9.4	*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.

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10 HISTORY TABLE

Table 8 History table

Version	Date	Author	Sections changed	Brief description of change
1.0	18-FEB-2025	[redacted]	None	This is the final TSAP.