Trial Statistical Analysis Plan

c02100724-03

BI Trial No.:	1270.1
Title:	A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia (including Protocol Amendments 1 to 5 [c01568809])
Investigational Product(s):	BI 836826
Responsible trial statistician(s):	[redacted] [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	13-OCT-2016 REVISED
Version:	Revised

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2. LIST OF ABBREVIATION

AE	Adverse Event
ADA	Anti-Drug-Antibodies
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BRPM	Blind Report Planning Meeting
BSA	Body Surface Area
CR	Complete Remission
CTP	Clinical Trial Protocol
CRi	Complete Remission with incomplete marrow recovery
CLL	Chronic Lymphocytic Leukaemia
CL	Clearance
CTCAE	Common Terminology Criteria of Adverse Event
CTh	Concomitant therapies
DBL	Database Lock
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
[redacted]	[redacted]
eCRF	electronic Case Report Form
EOT	End Of Treatment
[redacted]	[redacted]
FFS	Failure Free Survival
G-CSF	Granulocyte-Colony Stimulating Factor
ICH	International Conference of Harmonization
IRR	Infusion Related Reaction
IPV	Important Protocol Violation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
MRT	Mean Residence Time

NE	Not Evaluable
OBD	Optimal Biological Dose
O*C	Oracle Clinical
[redacted]	[redacted]
PR	Partial Remission
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PV	Protocol Violation
PK/PD	Pharmacokinetic/Pharmacodynamic
PT	Preferred Term
REP	Residual Effect Period
SAE	Serious Adverse Event
SCR	Screened Set
SD	Stable Disease
SPD	Sum of Product Diameter
SOC	System Organ Class
SOP	Standard Operating Procedure
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
TLS	Tumour Lysis Syndrome
UDAEC	User-Defined Adverse Event Category
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per International Conference of Harmonisation, statistical principles for clinical trials, E9 (ICH E9), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analyses described in the Clinical Trial Protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the protocol, including protocol amendments. In particular, the TSAP is based on the planned analysis specifications 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. This TSAP follows the Boehringer Ingelheim (BI) internal guideline for developing a TSAP (1).

The primary objective of this trial is to determine the Maximum Tolerated Dose (MTD) or Optimal Biological Dose (OBD) of BI 836826 in patients with advanced chronic lymphocytic leukaemia. Secondary objectives are the collection of overall safety and anti-tumour efficacy data and the determination of the pharmacokinetic profile of BI 836826.

In the following, study medication always refers to BI 836826.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 CLARIFICATIONS

As this trial is the first in human use of BI 836826, the primary objective as defined by the Clinical Trial Protocol (CTP) is to determine the maximum tolerated dose (MTD) of BI 836826. The MTD is determined via the number of dose limiting toxicities (DLTs). The CTP does not contain any definition of primary endpoint. But to follow the definition of the primary objective of the trial as defined by the CTP, the MTD and the number of patients with DLTs during the MTD evaluation period are defined as primary endpoints (see Section 5.1).

During the course of the trial it was decided to change the definition of some of the secondary and further endpoints:

1. Number of lymphocytes in the peripheral blood

The definition of this endpoint was changed from “Number of lymphocytes in the peripheral blood” to “Best % change from baseline in number of lymphocytes in the peripheral blood”.

2. Blood counts (haemoglobin, platelets, neutrophils, red blood cells)

The definition of this endpoint was changed from “Blood counts (haemoglobin, platelets, neutrophils, red blood cells)” to “number of patients with improved haemoglobin count for at least two subsequent response assessments”, “number of patients with improved platelet count for at least two subsequent response assessments” and “number of patients with improved neutrophil count for at least two subsequent response assessments”. It was decided to abandon the definition of a separate secondary endpoint for red blood cells, since red blood cells are highly correlated with haemoglobin count and are thus reflected in this endpoint.

[redacted]

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary objective of this study is the tolerability and safety of BI836826 as reflected by the MTD. Thus, primary endpoints of this trial are the MTD and the number of patients with DLTs during the MTD evaluation period. Instead of the MTD, an optimal biological dose (OBD) might be defined instead.

Maximum tolerated dose (MTD):

The MTD is defined as the highest dose studied for which the incidence of DLT is no more than 17% (i.e., 1/6 patients) during the MTD evaluation period.

The MTD evaluation period is defined as the duration of the first treatment course (i.e. 14 days after first administration of BI 836826).

For the definition of DLT please refer to the CTP Section 5.2.1.1. Please note that the definition of DLT was changed during the trial by amendments of the CTP. With CTP version 6 (04 March 2015), the following additional haematologic AEs were considered DLT:

- Grade 4 neutropenia lasting more than 7 days
- Febrile neutropenia not resolving within 48 hrs with appropriate treatment (antibiotics, antivirals, antifungals, growth factor support)
- Grade 4 thrombocytopenia lasting more than 7 days, or grade 3-4 thrombocytopenia with clinically significant bleeding
- Grade 4 anemia

The respective definition of DLT included in the CTP effective at the start time of the Adverse Event (AE) qualifying for a DLT was used.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other Secondary endpoints

Note: For the response/efficacy analyses with respect to overall response assessment by investigator used: If patients would have their examinations contributing to the disease assessment over a number of days, the earliest date of the multiple examinations should be considered.

For the response/efficacy analyses with respect to lymphocytes and blood counts only laboratory data assessed >= 8 days after the last infusion and with reported laboratory response assessment on-treatment and before start of new Chronic Lymphocytic Leukaemia (CLL) therapy is used. The reason for this approach is that otherwise the respective values of lymphocytes and blood counts would be biased due to the infusion after which an immediate change in values of the respective blood parameters is observed. This change though does not reflect an efficacy effect.

Number of lymphocytes in the peripheral blood

The secondary endpoint with respect to number of lymphocytes in the peripheral blood is defined as "Best % change from baseline in number of lymphocytes in the peripheral blood".

Blood counts (haemoglobin, platelets, neutrophils)

The secondary endpoints with respect to blood counts are defined as

- "Number of patients with improved haemoglobin count for at least two subsequent response assessments"

- "Number of patients with improved platelet count for at least two subsequent response assessments"

- "Number of patients with improved neutrophil count for at least two subsequent response assessments"

An improvement is indicated by the fulfilment of the criteria for "Complete Remission" or "Partial Remission", i.e.

- Haemoglobin count: Greater than 11g/dL or increase of 50% or more compared to baseline if haemoglobin is less than or equal to 11g/dL

- Platelet count: Greater than 100 000/µL or increase of 50% or more compared to baseline if platelets are less than or equal to 100 000/µL

- Neutrophil count: Greater than 1500/ µL or increase of more than 50% compared to baseline if neutrophil count is less than or equal to 1500/µL

Best overall response:

Response will be assessed according to the NCIWG guidelines (R10-4429) based on laboratory data from the peripheral blood and clinical examination by the investigator. Each patient will be assigned to one of the following categories:

- complete remission (CR)
- complete remission with incomplete marrow recovery (CRi)
- partial remission (PR)
- stable disease (SD)

- progressive disease (PD)
- not evaluable (NE)

Best overall response (CR, CRi, PR, SD, PD or NE in this order) is defined as the best overall response obtained since the start of study treatment until PD or start of next CLL therapy. Post-treatment assessments will be considered for the evaluation of best overall response as long as no further CLL therapy has started.

Progression free survival (PFS):

PFS is defined as the time from first treatment with BI 836826 until disease progression or death, whichever occurs first. A patient has an evaluable response assessment if either CR, CRi, PR, SD or PD has been assigned by the investigator.

Derivation of PFS is defined as PFS [days] = date of outcome – date of first administration of BI 836826 + 1.

The censoring rules and the applicable dates of outcome for PFS are given following table.

Table 5.2.2: 1 Derivation rules for progression-free survival

Situation	**Outcome (event or censored)**	**Date of outcome**
Disease progression or death	Event	Date of first disease progression or death
No disease progression or death without additional CLL therapy	Censored	Date of last response assessment
No disease progression or death with additional CLL therapy	Censored	Date of last response assessment before start of new CLL therapy
No baseline or post-baseline disease assessment and without death	Censored	Date of first administration of BI 836826
No baseline or post-baseline disease assessment and death on or before second planned disease assessment (i.e. 28 days after first administration of BI 836826)	Event	Date of death
No baseline or post-baseline disease assessment and death after second planned disease assessment (i.e. 28 days after first administration of BI 836826)	Censored	Date of first administration of BI 836826

Failure free survival (FFS):

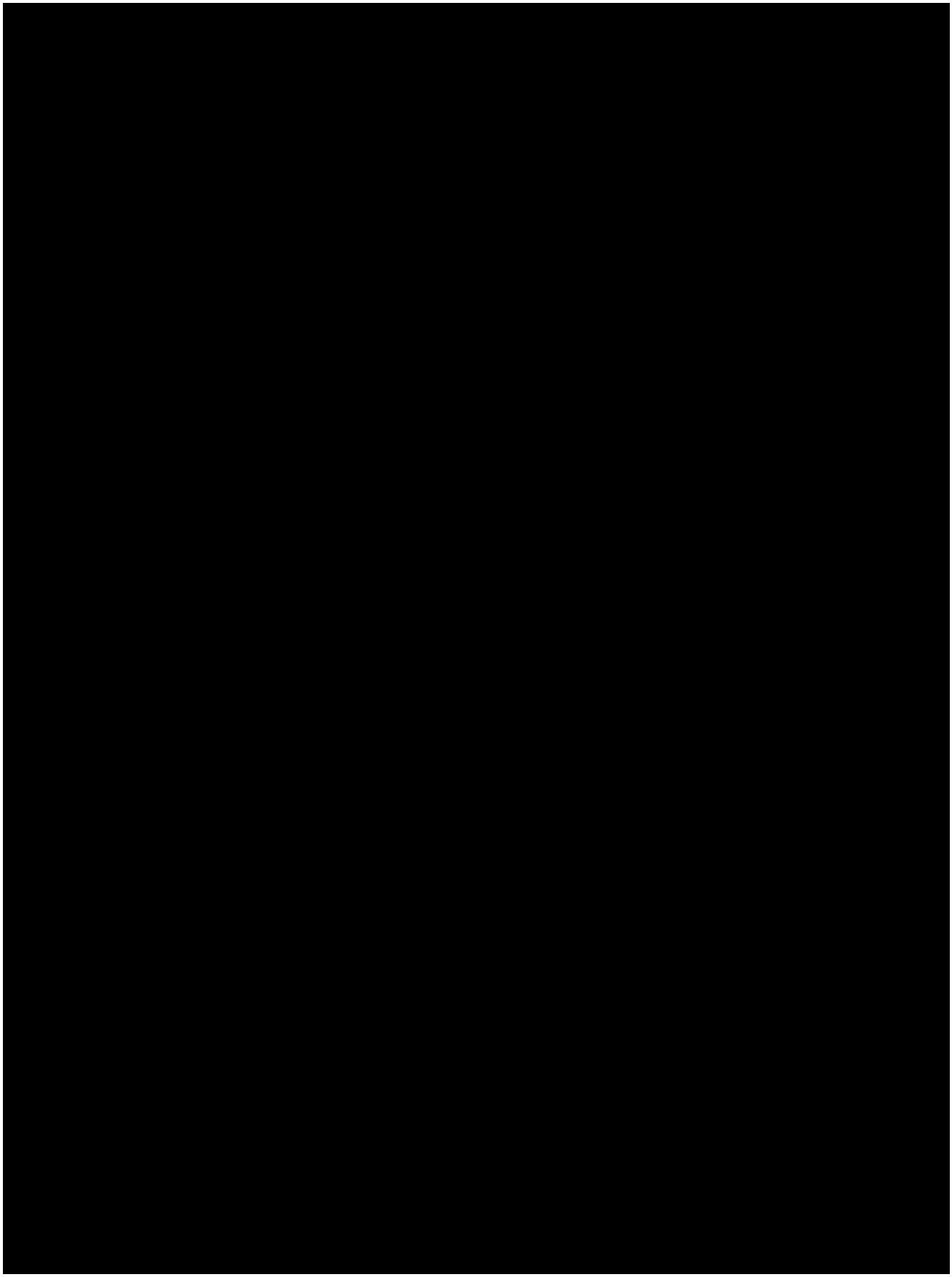
FFS is defined as the time from first administration of BI 836826 until disease progression or death or start of next CLL therapy.

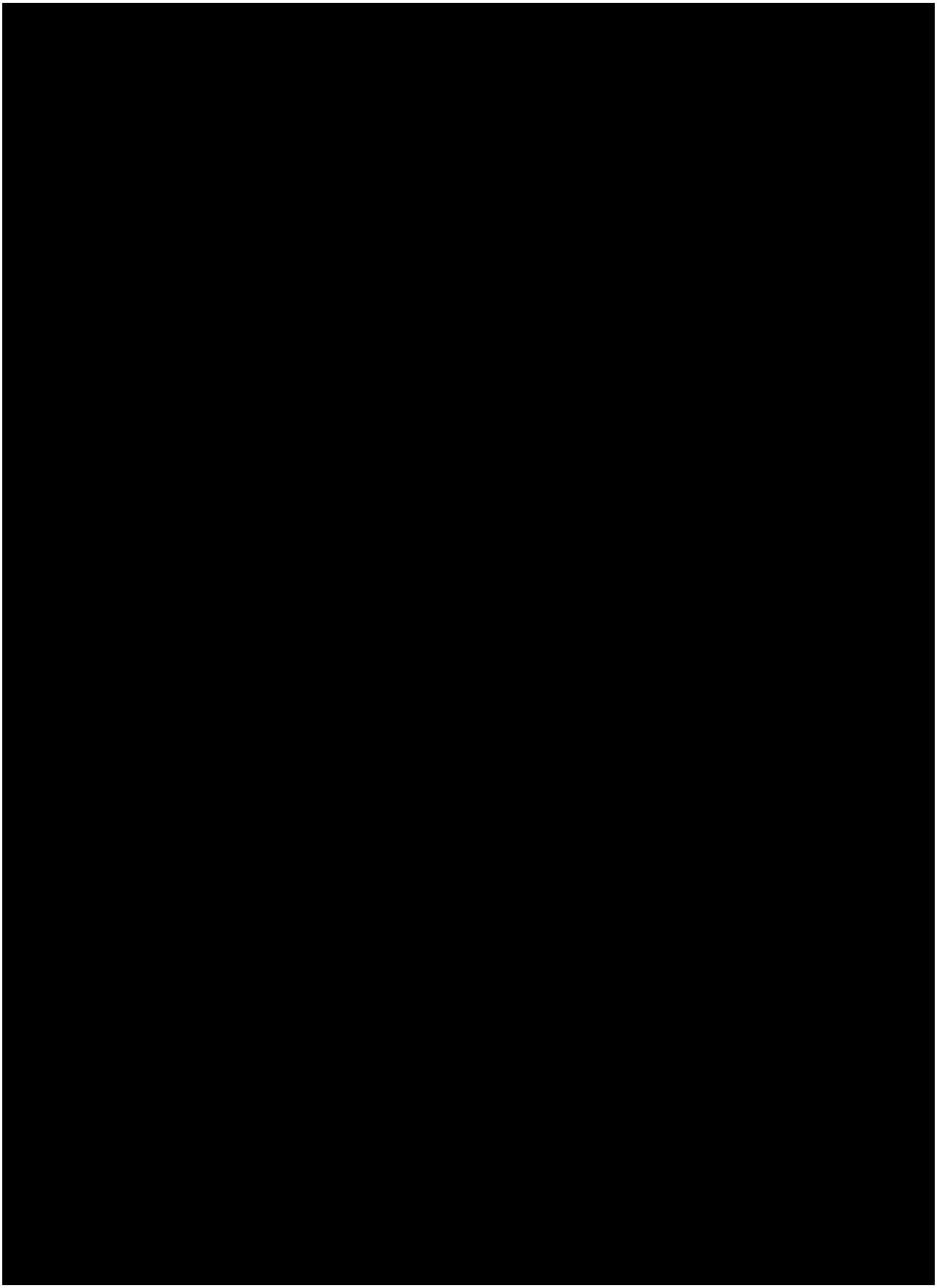
Derivation of FFS is defined as FFS [days] = date of outcome – date of first administration of BI 836826 + 1.

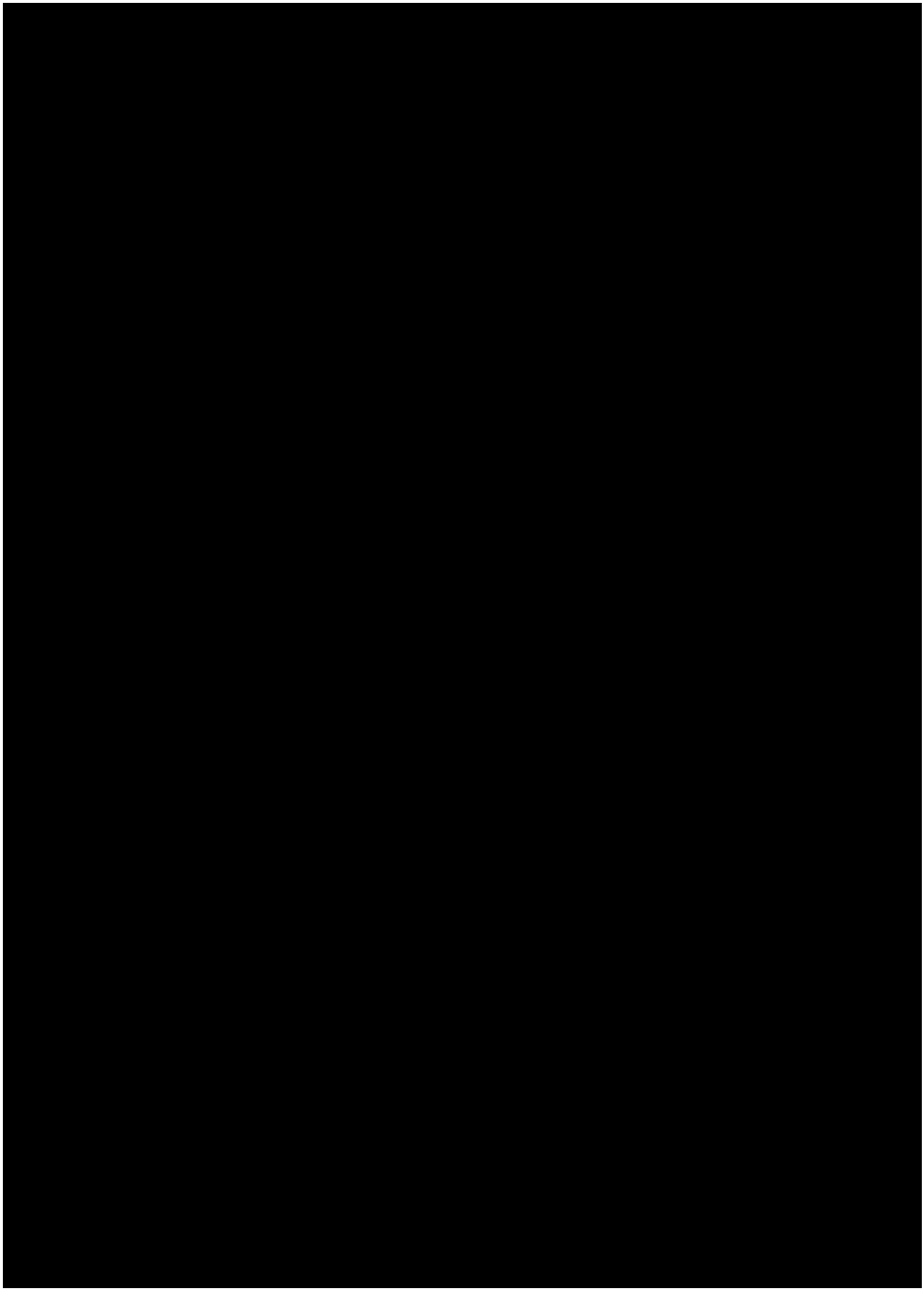
The censoring rules and the applicable dates of outcome for FFS are given in following table.

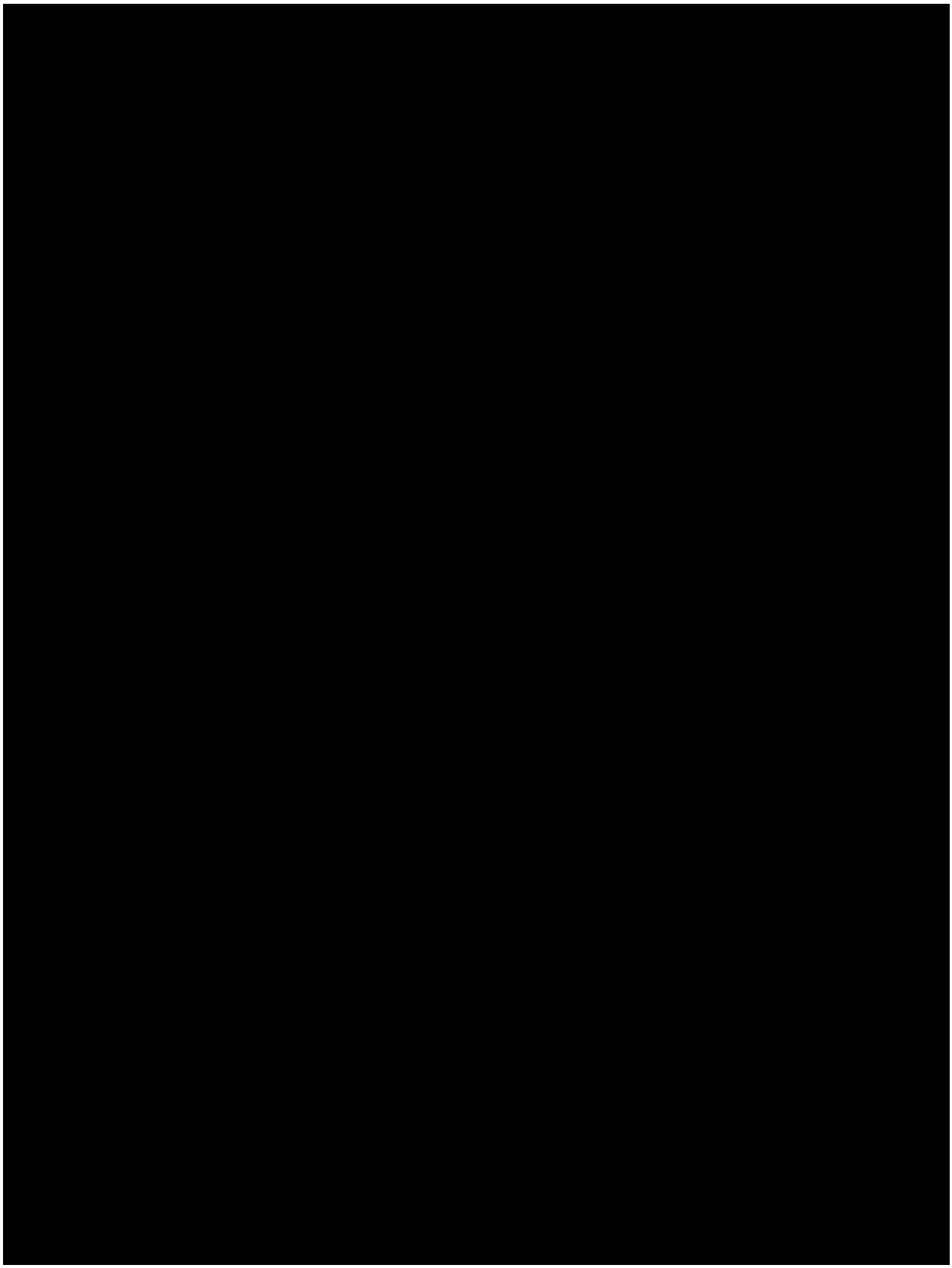
Table 5.2.2: 2 Derivation rules for failure-free survival

Situation	**Outcome (event or censored)**	**Date of outcome**
Disease progression or death or start of next CLL therapy	Event	Date of first disease progression or death or start of next CLL therapy
No disease progression, death or new CLL therapy	Censored	Date of last response assessment
No baseline or post-baseline disease assessment and without death or new CLL therapy	Censored	Date of first administration of BI 836826
No baseline or post-baseline disease assessment and death on or before second planned disease assessment (i.e. 28 days after first administration of BI 836826)	Event	Date of death
No baseline or post-baseline disease assessment and death after second planned disease assessment (i.e. 28 days after first administration of BI 836826)	Censored	Date of first administration of BI 836826









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5.4.4 Adverse events

Severity of adverse events is rated according to Common Terminology Criteria of Adverse Event (CTCAE version 4.0; R10-4848)

In the CTP, protocol-specified significant adverse events were defined as AEs which were of particular concern for safety monitoring within the trial. These AEs needed to be handled by the investigator according to the rules defined for SAE reporting (see CTP Section 5.2.2.2). The following protocol-specified significant adverse events were defined:

- Infusion-related reactions (IRR) (CTCAE grade 3 or higher)
- Tumour lysis syndrome (TLS)
- any event that qualifies for DLT
- Drug-induced liver injury (DILI)

For the definition of hepatic injury inducing alterations of liver parameters refer to the CTP Section 5.2.2.1.

Definitions of AEs by user-defined categories in terms of MedDRA codes and sub-searches can be found in Section 9.4 of this TSAP.

Other significant AEs are all serious or non-serious AEs leading to treatment discontinuation or dose reduction.

5.4.5 Laboratory parameters

5.4.5.1 General safety laboratory parameters

Original values will be converted into standard units and the CTCAE grades will be assigned to parameters which have a CTCAE definition (CTCAE version 4.0) (R10-4848)

Primary List: Tables and figures for these laboratory values and urine measurement will be displayed in Section 15 of the CTRs, if applicable.

Table 5.4.5.1: 1 List of primary laboratory parameters

Worsening direction	Laboratory	Parameter
low value	Haematology	haemoglobin (HGB)
		white blood cell count (WBC, total leukocyte count)
		platelets (thrombocytes, PLTCT)
	Differentials	neutrophils (NEUT)
	Biochemistry	inorganic phosphate (P)
high value	Enzymes	aspartate amino transferase (AST)
		alanine amino transferase (ALT)
	Substrates	creatinine (CRE)
		total bilirubin (TBILI)
	Biochemistry	lactate dehydrogenase (LDH)
		uric acid (URIC)
high and low value	Electrolytes	potassium (K)
		calcium (CA)
	Differentials	lymphocytes (lymphopenia) (LYMPH)

Secondary List: Tables for these laboratory values and urine measurement will be displayed in Appendix 16.1.9.2 of CTRs, if applicable. All laboratory values other than those in the primary list will be considered as secondary, including but not limited to the parameters listed in the following table. Urine measurement (based on dipsticks with 0, +, ++, and +++; the

more + the worse) will be displayed if needed. For urine measurement based on dipsticks conversion rules can be found in Section 9.3.

Table 5.4.5.1: 2 List of secondary laboratory parameters

Worsening direction	Laboratory	Parameter
low value	Haematology	red blood cell count (RBC)
	Differentials	CD3+ T cell count (CD3V)
		CD4+ T cell count (CD4V)
		CD8+ T cell count (CD8V)
		CD56+ natural killer cell count (CD56V)
	Biochemistry	total protein (TPRO)
		albumin (ALB)
		immunoglobulin M (IGM)
		immunoglobulin G (IGG)
	Urine	urine PH (UPH)
high value	Enzymes	alkaline phosphatase (ALKP)
	Coagulation	international normalised ratio of prothromin time (INR)
		activated partial thromboplastin time (aPTTs)
		prothrombin time (PRTsec)
	Biochemistry	urea (UREA)
		direct bilirubin (BILID)
	Urine	urine glucose (UGLU)
		urine nitrite (UNIT)
		urine protein (UPROZ)
		urine erythrocytes (URBCZ)
		urine leukocytes (UWBCZ)
high and low value	Haematology	reticulocytes (RET)
		haematocrit (HCT)
	Differentials	CD19+ B cell count (CD19V)

Table 5.4.5.1: 2 List of secondary laboratory parameters (cont.)

Worsening direction	Laboratory	Parameter
	Differentials	monocytes (MONO)
		basophils (BAS)
		eosinophils (EOS)
	Electrolytes	sodium (NA)
	Substrates	glucose (GLUA, GLUB)
	Biochemistry	immunoglobulin A (IGA)

5.4.5.2 Laboratory values of special interest

Neutropenia, thrombocytopenia and leukopenia

Episodes of low neutrophil, platelets and WBC counts are of special interest. Episodes with CTCAE grade 3 and 4 and CTCAE grade 4 lasting 7 or more days will be analyzed.

An episode of e.g. low neutrophils starts with the first occurrence of a CTCAE grade ≥ 3 and lasts until the first time the CTCAE grade falls back to ≤ 2.

In case the episode starts during EOT or Follow-up, the duration of this episode is defined to be missing. The reason for this approach is that after EOT laboratory data is only captured infrequently and therefore the duration of an episode would be overestimated due to lack of data.

If the episode starts before EOT and the CTCAE grade of the respective parameter does not fall back to grade ≤ 2 and the patient dies, the end of the episode is defined by the date of death. If the episode starts before EOT and lasts during Follow-up the episode is censored with the date of DBL.

Hepatic enzyme elevations (potential Hy's law cases)

Special attention will be paid to patients fulfilling the criteria for potential Hy's law cases. These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3 times upper limit of normal (3 x ULN) with total bilirubin ≥2 x ULN and ALKP < 2 x ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event.

Possible clinically significant abnormal lab values

Possible clinical significance based on CTCAE grading is defined as CTCAE grade 2 or higher with an increase of at least one CTCAE grade from baseline, please refer to Section 9.2. for further details. If the baseline value is missing, all post-baseline values with CTCAE

grade 2 or higher will be classified as possibly clinically significant. For the laboratory parameters recorded that do not have a CTCAE grading defined, the BI default rules for clinical significance should be applied (5).

Tumour lysis syndrome (TLS)

The presence of laboratory TLS will be considered according to Cairo-Bishop classification. Under this system, laboratory TLS is investigated based on the serum values of uric acid, potassium, inorganic phosphate, and calcium. TLS is considered to be present if within the time window of 3 days before until 7 days after administration of BI 836826, two or more of these laboratory parameters are abnormal, or change from baseline by ≥25%.

Table 5.4.5.2: 1 Definition of abnormal laboratory values according to Cairo Bishop

Laboratory parameter	abnormal Value	Change from baseline
Uric acid	≥476 µmol/L or 8 mg/dL	≥25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	≥25% increase
Inorganic phosphate	≥1.45 mmol/L	≥25% increase
Calcium	≤1.75 mmol/L	≥25% decrease

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this Phase I trial, treatments are not randomised (open-label, dose escalation). Different dose levels of BI 836826 are being administered. The data will be presented for all dose cohorts separately and in total over all dose cohorts. To justify the MTD determination, DLTs occurring during the MTD evaluation period (during the first treatment course) will be presented separately from those occurring during the complete on-treatment period.

"Analysing treatment" will be used for reporting of treatment emergent adverse events (AE) and to differentiate between screening, on-treatment, post-treatment and post-study safety data. The inequalities start date ≤ onset date of AE < end date will determine whether the AE will be assigned to the "analysing treatment" or not. Table 6.1:1 defines the "analysing treatment period" which will be used for reporting of treatment emergent AEs and safety laboratory parameters. Safety data recorded during the Residual Effect Period (REP) will be considered as on-treatment.

If not specified otherwise, all safety tables will be based on the on-treatment period. AEs that have an onset date during the screening or post-study periods will be displayed in separate listings from those occurred during the on-treatment period.

Table 6.1: 1 Definition of analysing treatment period(s)

Analysing treatment period	**Start date (including)**	**Stop date (excluding)**
Screening	Date of informed consent	Date of first administration of study medication
On-treatment	Date of first administration of study medication	Start date of 'Follow-up'
Follow-up	Date of end of REP +1	Start date of 'Post-study'
Post-study	Last date patient status obtained / last date patient known to be alive + 1 (if patient is lost to follow-up) / date of refusal + 1 day / the date patient died + 1	During the trial: open / empty; after database lock (DBL): DBL + 1 day

The initial study medication assigned at the beginning of the first treatment course will be used as the label of the analysing treatment.

The actual dose of study medication administered on the day each AE started will also be derived. This will be presented in patient listings, but will not be used for defining treatments for analysis.

Labels of each analysing treatment period, analysis numbers, the labels used for display in the tables and listings in the CTR, as well as codes, decodes, sort order and labels for each trial medication used in this trial are provided in the TSAP technical document "ADS Plan".

6.2 IMPORTANT PROTOCOL VIOLATIONS

Due to the fact that this is a phase I study, no per protocol population is needed, however important protocol violations (PV) should be identified for patients in the treated set (see Section 6.3). Any PV which may affect safety, efficacy or the patient's rights will be determined.

PVs are summarised into categories and are coded in O*C. The following table defines the different categories of important PVs.

Table 6.2: 1 Important protocol violations

Category /Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1[1]	Patient has condition that may cause additional risk from study medication	In 5, Ex 3 - 4, 15 - 20	None
	A2[1]	Patient has laboratory assessments that may cause additional risk.	Ex 8 - 13	None
	A3 [1]	Patient is unable to comply with the protocol	Ex 21, 24	None
	A4[1]	Patient does not have trial diagnosis or is not part of the target population	In 1 - 4, Ex 1 - 2, 5 - 7	None
	A5[1]	HIV test not done at screening	See Ex 17	None
B		**Informed consent**		
	B1[1]	Informed consent not given or too late	In 7	All
C		**Trial medication and randomisation**		
	C1[2]	Drug not administered according to the protocol	Administration according to protocol="No" and medical review of associated comments	None
	C2[2]	Drug not administered according to the protocol	Individual pre-medication taken="No" and medical review whether premedication would have been required according to protocol	None

[1] IPV will be derived automatically

[2] IPV will be identified via individual review at MQRM/BRPM/DBL

6.3 PATIENT SETS ANALYSED

The Screened Set (SCR) includes all patients who signed the informed consent form and will be used to summarize patient disposition.

The Treated Set (TS): consists of all patients who received at least one application of the BI drug BI 836826. The TS will be used for all planned safety and efficacy analyses.

The MTD evaluation set: This patient set includes all patients who were documented to have received at least one dose of study medication and were not replaced for the MTD evaluation. The MTD evaluation set will be used for the primary analyses of DLTs and MTD determination.

Rules for replacement of patients are defined in Section 3.3.4.1 of the CTP. The list of replaced patients will be provided by the Trial Clinical Monitor no later than the last BRPM and should be attached to the BRPM minutes.

[redacted]

No per protocol population will be used for analyses.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

If not stated otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates" (2))

[redacted]

If the day of birth date is missing then the imputed day will be the 15th. If start of new CLL therapy date is incomplete (only month given), then the start date will be imputed with the 1st of months unless the first day leads to a date before the stop date of study medication, then the study medication stop date + 1 will be imputed. If more than only the day is missing, dates will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow chart of the CTP.

Unless otherwise specified, baseline is defined as the time-point closest to but prior to first administration of study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise.

Laboratory values: Baseline is defined as the latest time-point before start of the very first administration of study medication. For laboratories where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first study drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of the start of first study drug administration.

If any of these times are missing (either no time of start of first study drug administration or no lab sample stating that it was taken prior to start of first study drug administration) and so it cannot be concluded whether the blood sampling was done before or at the same time of the start of first study drug administration, the last available laboratory assessment before first study drug administration will be taken (Screening laboratory) .

For graphical presentations of laboratory data, baseline will be coded as Day = 1.

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / standard deviation [StD] / Min / Median / Max. Efficacy data are presented by dose cohort. Displays of safety data will be presented by dose cohort and in total.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, StD, min and max.

For time-to-event analysis tables, the set of statistics is: number of patients [N(%)], Number of patients with event [N(%)], <Time to event> [months] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile), Number of patients censored [N(%)]. If not specified otherwise, the duration as well as the time to event will be displayed in months and a final decision will be made at the last BRPM.

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). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be intended and "[N(%)]" will be displayed only for the main category. If a table includes only categorical data, "[N(%)]" is to be displayed in the column header.

If 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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1.1 Disposition of patients

For patient disposition the standard descriptive table will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed. An overview table with respect to analysis sets (as defined in Section 6.3) together with the primary reason for exclusion will be provided.

7.1.2 Important protocol violations

A listing with protocol violations by patient will be created in Section 15 of the CTR.

7.1.3 Demographic and other baseline characteristics

Standard descriptive analysis and summary tables for all patients treated by initial treatment will be created for demography, alcohol status, ECOG performance score, previous therapies, baseline values of haemoglobin, neutrophil, platelet, lymphocyte count, tumour size, virology and oncology history.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant therapies (CTh) will be coded according to World Health Organisation Drug Dictionary (WHO DD). They will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CThs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CThs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

Summaries will be presented for previous and concomitant medications started at baseline and for concomitant therapies started after first administration of the trial medication. Separate summaries will be presented for concomitant medications with missing or incomplete start dates.

Listings of the data will present the concomitant therapy PT and verbatim text as well as the verbatim text of the indication. In addition the listings will include study day for start and stop dates and duration of therapy. Patients with no concomitant therapy will not be included in the listing. A separate listing will be provided for patients receiving Granulocyte-Colony Stimulating Factor (G-CSF) and transfusions (ATC Codes L03AA, B05AA, B05AX).

7.3 TREATMENT COMPLIANCE

Compliance will be evaluated by whether or not the medication was always administered according to protocol for BI 836826.

A listing will show all administrations of trial drug including the comment if administration was not according to protocol and also the administration of premedication acetaminophen/paracetamol, antihistamine and glucocorticoid will be included.

7.4 PRIMARY ENDPOINT(S)

The primary endpoints of this trial are the MTD and the number of patients with DLTs during the MTD evaluation period. The MTD is determined from the occurrences of DLTs during the MTD evaluation period, i.e. the number of patients with DLTs during the first course. An overall summary of the DLTs (see CTP Section 5.2.1.1 for definitions of DLT) which occurred during the MTD evaluation period will be provided for each dose cohort of the MTD evaluation set. Patients, if any, who did not complete the first treatment course with BI 836826 for reasons other than DLT will be excluded from the analysis of the primary

endpoint, since they are by definition not part of the MTD evaluation set. These patients were replaced at the same dose level. A summary of the number of patients with DLTs overall in any course will be also given by initial treatment and displayed in a similar format to the summary of DLTs occurring in the MTD evaluation period.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Not applicable.

7.5.2 Secondary endpoints

Number of lymphocytes in the peripheral blood

The number of lymphocytes in the peripheral blood will be analyzed in terms of the best percentage change from baseline until start of subsequent CLL therapy or PD. Best percent change is thereby derived by taking the difference between the baseline value and the minimum of all observed values over time. For the primary analysis of this endpoint, summary statistics will be presented for all patients of the TS by dose cohort and in total. In addition, summary statistics will be presented separately for patients of the TS with an abnormal and normal lymphocyte count at baseline. An abnormal baseline count is defined as a lymphocyte count > 4*10^9/L. In addition, the following will be analysed:

Summary statistics will additionally be presented for minimum values of certain lymphocyte types (CD19+ B-cells, CD3+ T-cells, CD4+ T-cells, CD8+ T-cells and CD56+ NK-cells).

For CD4+ T-cells and CD19+ B-cells, the lowest count since start of treatment (nadir) and the time point of occurrence of (nadir) will be derived and described by summary statistics for all dose cohort together and separated by dose cohort. The association of values at baseline and values at nadir will be displayed graphically.

A waterfall plot will also be generated to summarise reduction of lymphocytes graphically and lymphocyte values will be graphically displayed over time for patients of the Treated Set. Furthermore, the number of lymphocytes and the change in lymphocyte count from baseline will be listed by time point.

Blood counts (haemoglobin, platelets, neutrophils)

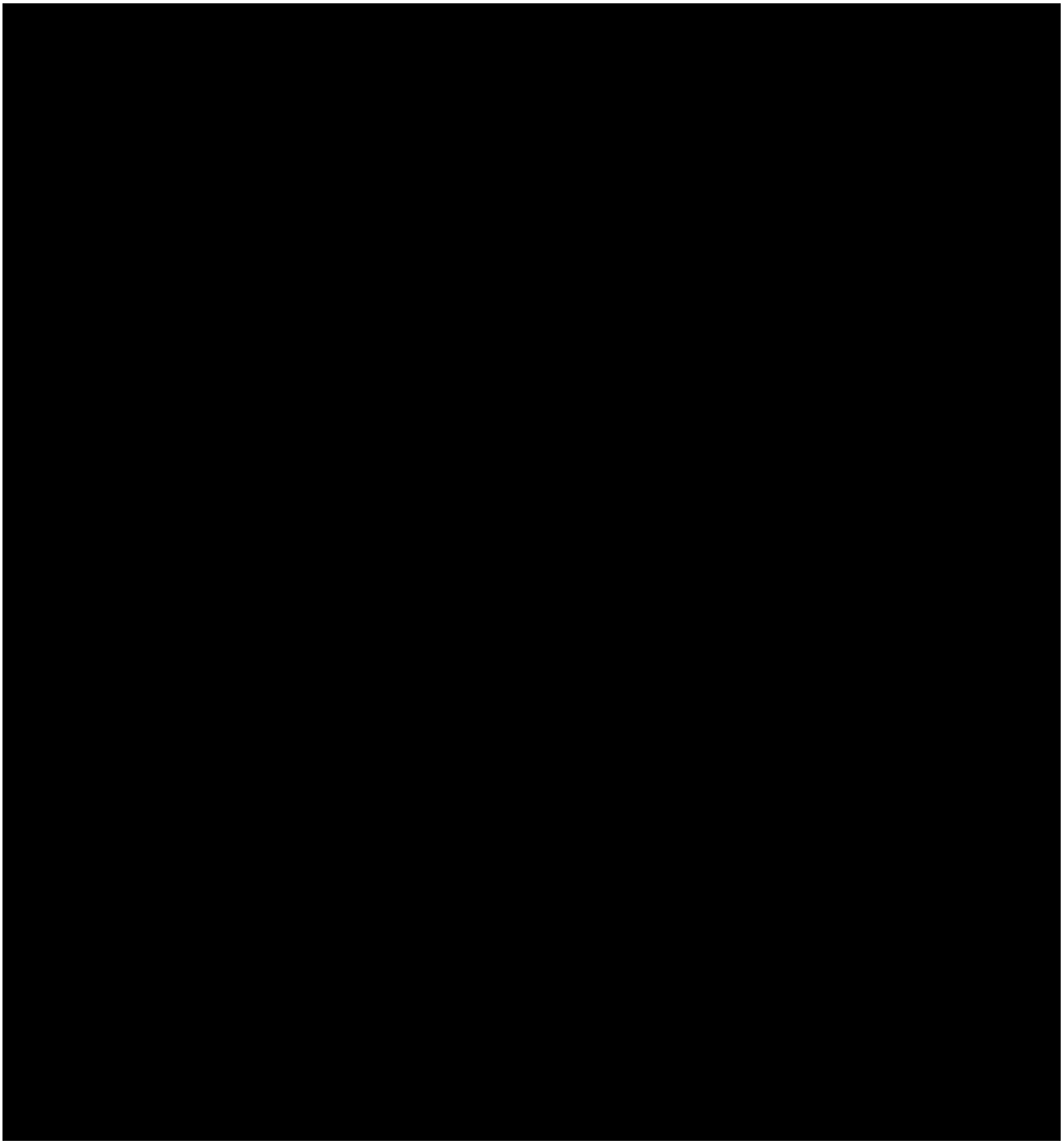
A frequency table will be given for the endpoints “Number of patients with improved haemoglobin / platelet / neutrophil count for at least 2 subsequent response assessments” for all patients of the Treated Set. Additionally, graphical presentations of mean values of haemoglobin, platelet and neutrophil counts over time will be provided by dose cohorts. For neutrophils, the nadir and the time point of occurrence of nadir will be derived and described by summary statistics for all dose groups together and separated by dose group. The association of values at baseline and at time to nadir will be displayed graphically.

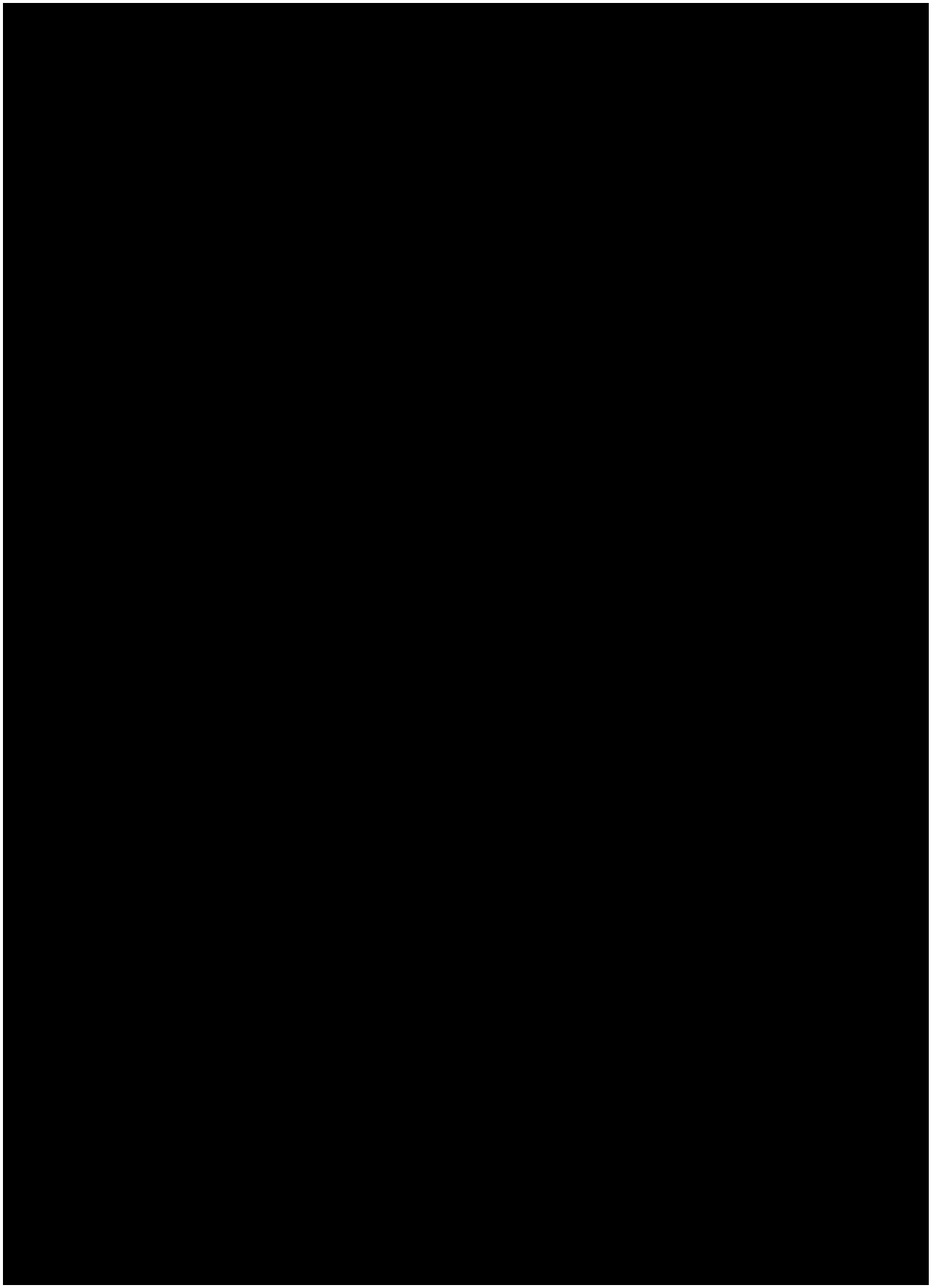
Best overall response

Best overall response will be analysed descriptively. Frequency distributions will be used to examine this endpoint. The number of patients that have either CR, CRi or PR as best overall response will be tabulated separately (to determine the remission rate).

Progression-free and Failure-free survival

PFS and FFS will be analysed exploratory using Kaplan-Meier methods for all patients of the Treated Set.





7.7 EXTENT OF EXPOSURE

Standard descriptive analyses over all treatment courses will be performed. This will include a summary of the variables already described in Section 5.4.2. This descriptive analysis will comprise a mixture of frequency and percentages, as well as summary statistics.

For the sequence of doses, there will be a listing of each dose taken at each treatment course for all patients.

7.8 SAFETY ANALYSIS

The primary analysis is for determination of MTD. No statistical model is foreseen allowing assessment of MTD; descriptive analysis is confined to a listing and descriptive table by dose group. The purpose of these tables is to summarize and document the data that led to the selection of MTD.

7.8.1 Adverse events

7.8.1.1 Maximum tolerated dose and dose limiting toxicity

A table displaying DLTs by primary system organ class and preferred term will be provided by initial treatment for the MTD evaluation period for the MTD evaluation set as well as for the treated set. The same table will additionally be displayed for all treatment courses of the on-treatment period for the treated set.

A summary of the number of patients with DLT within the MTD evaluation period (treatment course 1) and for all treatment courses of the on-treatment period will be given by initial treatment for the treated set.

In order to explore the behaviour of DLTs with respect to the actual dose of BI 836826, the dose response relationship will be examined descriptively, using DLTs in the MTD evaluation period and DLTs up to the end of the on treatment phase, in separate analyses.

[redacted]

[redacted]

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}$$

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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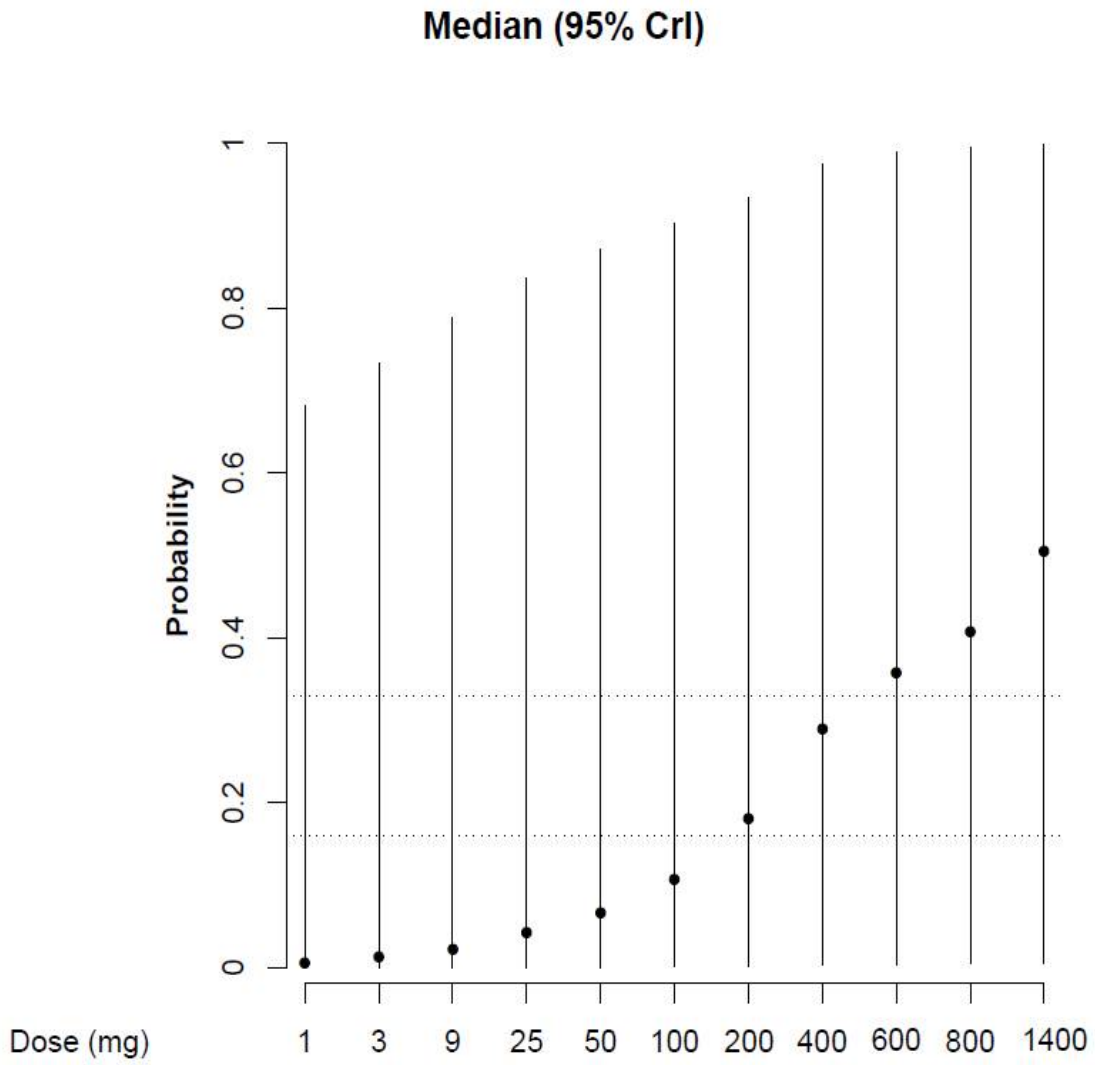


[redacted]

7.8.1.2 Adverse events

Unless otherwise specified, adverse events analysis will be performed for on-treatment periods. Selected analyses (e.g. summary of AEs) will be repeated for the MTD evaluation period.

The analyses of AEs will be descriptive in nature and will follow the standard procedure laid down in the DM & SM (including all required tables and listings; guideline 'Handling and Summarization of AE Data for CTR and Integrated Summaries' (4). AEs will be coded with the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The version number will be displayed as a footnote in the respective tables and listings.

The system organ classes will be sorted alphabetically. In tables displaying AEs by dose cohort preferred terms will be sorted by descending frequency of adverse events in the "Total" BI 836826 group.

Each patient can be observed during the trial under several doses. Analysing the AE of all treatment courses will be carried out under the initial treatment. No formal statistical analysis is planned for the safety comparison.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all adverse events occurring between first administration of BI 836826 until 6 weeks after last administration of BI 836826 will be assigned to the on-treatment period. All adverse events occurring before first administration of BI 836826 will be assigned to "Screening" and all adverse events occurring after last administration of BI 836826 + 6 weeks will be assigned to "post-study (for listings only). The actual planned dosage of BI 836826 administered on the day each AE starts will also be derived and will be included in the listing. Listings of screening events will not be sorted by initial treatment. Post-study listings will be sorted by initial treatment. For details on the treatment definition please refer to Section 6.1.

According to the BI standards, multiple recordings of AEs will be collapsed to episodes on the lowest level term and multiple episodes will be condensed to records on the PT and system organ class (SOC) level. CTCAE grade will be an additional criterion for collapsing and condensing AEs. The maximum CTCAE grade will be assigned to episodes and records. CTCAE grade and DLT information will be displayed in AE listings. MedDRA levels for condensing will be SOC and PT.

An overall summary of adverse events will be presented.

Reporting of CTCAE grades

CTCAE grading within AE tables is displayed as "all grades", "Grade 1/2", "Grade 3/4" and "Grade 5". AEs with missing CTCAE or CTCAE grades not equal to 1 to 5 will be displayed under the category "all grades", but no category "missing grade" is displayed. A footnote is explaining that AEs with missing CTCAE or CTCAE grades not equal to 1 to 5 will be displayed under the category "all grades" and therefore the categories "Grade 1/2", "Grade 3/4" and "Grade 5" might not sum up to the category "all grades". A separate table will show

AEs leading to death. In this table no CTCAE grades will be shown. In the appendix (Section 16.1.9.2), the categorization “all Grades”, “missing Grade”, “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4” and “Grade 5” are used, but the “missing grade” column should only be displayed in case AEs with a missing CTCAE grade occured.

AE attributes “CTCAE Grade 1/2", "CTCAE Grade 3/4” and “CTCAE Grade 5” combined with drug relationship will be derived to avoid incorrect condensing. Consider, for instance, a patient with coincident drug-related abdominal pain with CTCAE Grade 1, and non-related vomiting with CTCAE Grade 3. Without the new attribute these AEs would be reported as drug-related Grade 3/4 under the SOC Gastrointestinal Disorder. With the new AE attribute these AEs would be excluded.

Additional AE attributes “Drug relationship combined with seriousness of the AE” and “Drug relationship combined with seriousness of the AE and CTCAE grade” is needed similarly to the AE attribute “CTCAE Grade 1/2", "CTCAE Grade 3/4" and “CTCAE Grade 5” combined with drug relationship respectively, as described above.

Frequencies of patients with AEs will be summarised by treatment, highest CTCAE grade, primary SOC and PT. Tables will be provided for patients with AEs of incidence > 10%, with drug-related AEs, with serious AEs (SAEs), with drug-related SAEs, with AEs leading to treatment discontinuation, with AEs leading to dose reduction, with protocol-specified significant AEs, with AEs leading to death, and with infusion-related reactions (IRRs).

7.8.1.3 Protocol-specified significant adverse events

Protocol-specified significant AEs are defined in the CTP, Section 5.2.2.1.

Infusion-related reactions (IRR)

Frequency of IRRs with CTCAE grade 3 or higher will be displayed in separate listings and tables where it will be differentiated between the reported AE term “Infusion-related reaction” and the symptoms of an IRR that are reported as AEs.

For patients at the beginning of this trial (up to the 9 mg dose cohort), the term IRR only or the symptoms of an IRR reported as AEs but not captured explicitly as symptoms of an IRR. For these patients, potential symptoms of an IRR can be only identified over pre-defined AE preferred terms (refer to Table 9.4:1).

For patients from following dose cohorts (including some patients of the 9 mg cohort), not only IRRs are reported with the AE term “Infusion-related reaction” but also their symptoms which are additionally marked as symptoms of an IRR.

A listing will show all patients with IRR episodes as well as reported symptoms of these IRRs. Furthermore symptoms of IRRs will also be displayed where it will be distinguished between symptoms marked as such and potential symptoms of an IRR (up to the 9mg dose cohort only).

The number of episodes of IRRs as well as the frequency of its symptoms and CTCAE grades will be displayed graphically for those patients where the symptoms of an IRR are reported as such.

The frequency of the AE "Infusion-related reaction" episodes will be displayed graphically by administration visit together with its CTCAE grade for all patients.

Tumour lysis syndrome

A frequency table displaying patients with clinical TLS (TLS reported as protocol-specified significant AE) will be provided. Additionally to cases of clinical TLS, laboratory TLS will be analysed (please refer to Section 7.8.2).

Any event that qualifies for DLT

Please refer to Section 5.2.1.1 of the CTP.

Drug-induced liver injury (DILI)

Please refer to Section 5.4.4. The frequencies of these protocol-specified significant AEs will be displayed in the CTR.

7.8.1.4 Adverse events by user-defined categories

A frequency table of AEs by user-defined categories,worst CTCAE grade, and preferred term as well as a frequency table of AEs by user-defined categories and worst CTCAE grade for the on-treatment period will be displayed.

7.8.1.5 Other significant AEs

Frequency tables of patients with AEs leading to dose reduction and AEs leading to treatment discontinuation will be provided by dose cohort and total, worst CTCAE grade, primary system organ class and preferred term for the on-treatment period.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow the standard procedure laid down in the SOP "Display and Analysis of Laboratory Data" (5). Patients will be counted under the initial treatment. The analysis of laboratory data will use the same 'analysing treatments' as described for the AEs, except for that the baseline laboratory value (as defined in Section 6.7) will be included in the 'on treatment' period. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline laboratory values will be displayed in the category "Missing CTCAE grade at baseline"

Single time courses by initial treatment will be used to display converted laboratory values over time by dose cohort. The graphs may be truncated if sufficient data is not available. These graphs will be displayed in Chapter 16.1.9.2 for the following parameters.

Haematology: haemoglobin, WBC count and platelets

Differentials: neutrophils (absolute count), absolute lymphocyte count, and natural killer (NK) cells

Enzymes: LDH

Clinically relevant abnormalities (as defined in Section 5.4.5.1) will also be summarised.

Descriptive statistics, including change from baseline, frequency of patients with transitions relative to the references range, will be provided. No post-study laboratory values will be considered. CTCAE grade for applicable laboratory parameters will be calculated according to CTCAE v4.0. The following outputs will be presented:

- Baseline, last value and difference from baseline
- Worst CTCAE grade experienced during the on-treatment period
- Transitions of the CTCAE grade from baseline to the worst lab values, from baseline to the last lab values, and from the worst to last values during the on-treatment period
- Possible clinically significant laboratory values

Note: For calculating the change in CTCAE grade from baseline, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be treated as a CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade is displayed as -9.

For Uric Acid and Hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of -1 will be assigned initially. Patients with a CTCAE grade of -1 will be treated as

- Grade 1 for Uric Acid
- Grade 1 for Hypokalemia

for all analyses. In laboratory listings, the CTCAE grade will be displayed as -1.

Patients with hepatic enzyme elevation will be tabulated. With respect to neutropenia, thrombocytopenia and leukopenia episodes the number of episodes and mean and median duration will be displayed. Additionally, laboratory values of special interest as described in Section 5.4.5 will be analyzed.

Additionally, a frequency table displaying number of patients with episodes of grade 4 neutropenia and concomitant AEs in the user-defined AE category (UDAEC) [redacted] of any grade and grade 3/4 will be provided. In this context, concomitant AE is defined as AE with onset date within the neutropenia episode. The same table will be done for grade 3/4 episodes of neutropenia and concomitant AEs in the UDAEC [redacted] of any grade and grade 3/4 will be done. The same applies for the display of patients with thrombocytopenia and bleeding events. For the definitions of neutropenia, thrombocytopenia and leukopenia episodes please refer to Section 5.2.5.2.

The prioritized laboratory values (see Section 5.4.5) will be displayed in Section 15 of the final CTR while all other laboratory parameters will be displayed in the Appendix of the CTR.

7.8.3 Vital signs

A summary table and a listing of vital signs at each planned time will be provided for the treated set.

7.8.4 ECG

No analyses are planned.

[redacted]

7.8.6 Others

Not applicable.

8. REFERENCES

1 *001-MCG-160*: "Guideline for Developing a Trial Statistical Analysis Plan", current version; IDEA for CON.

2 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

[redacted]

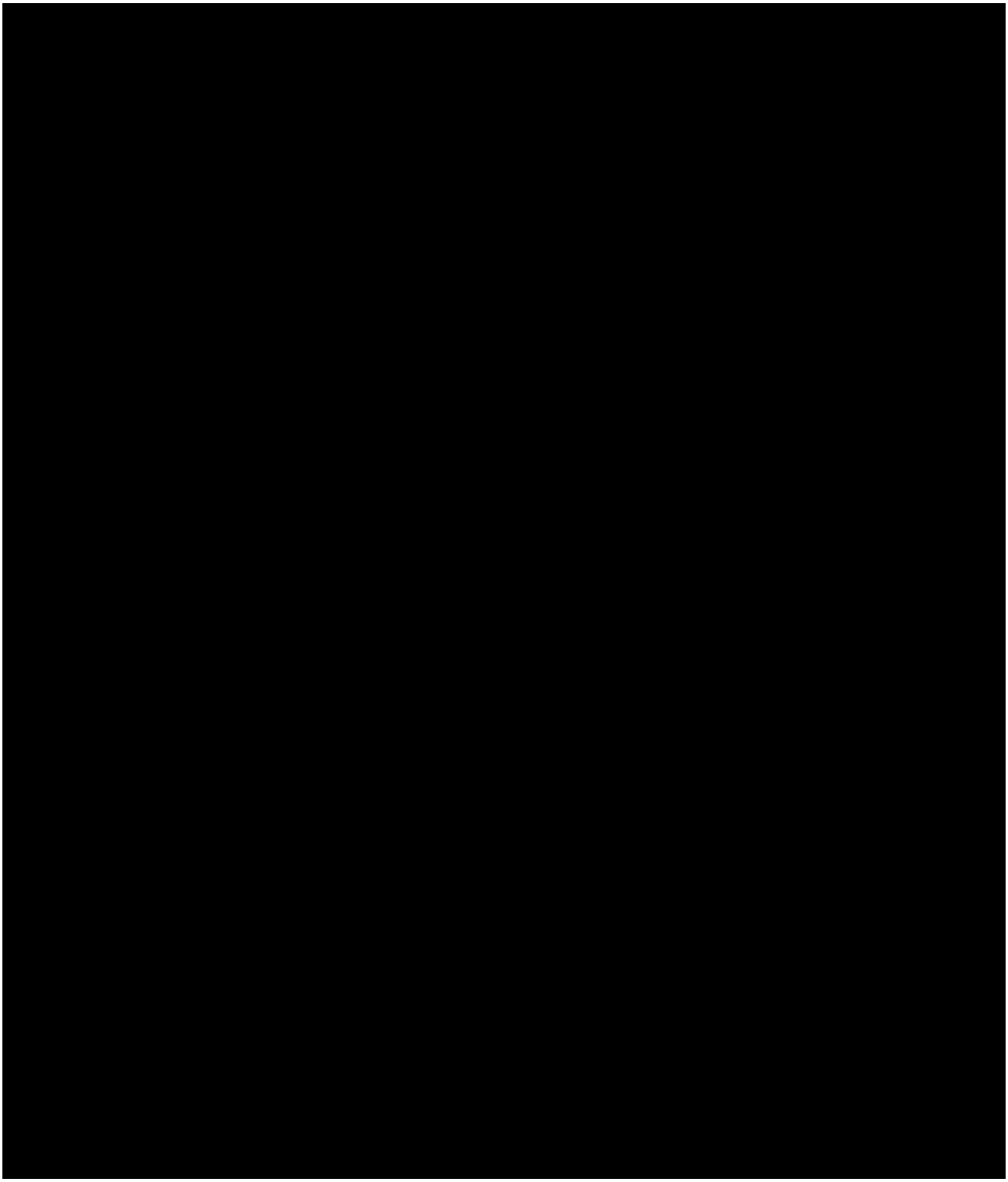
4 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", version 5.0; IDEA for CON.

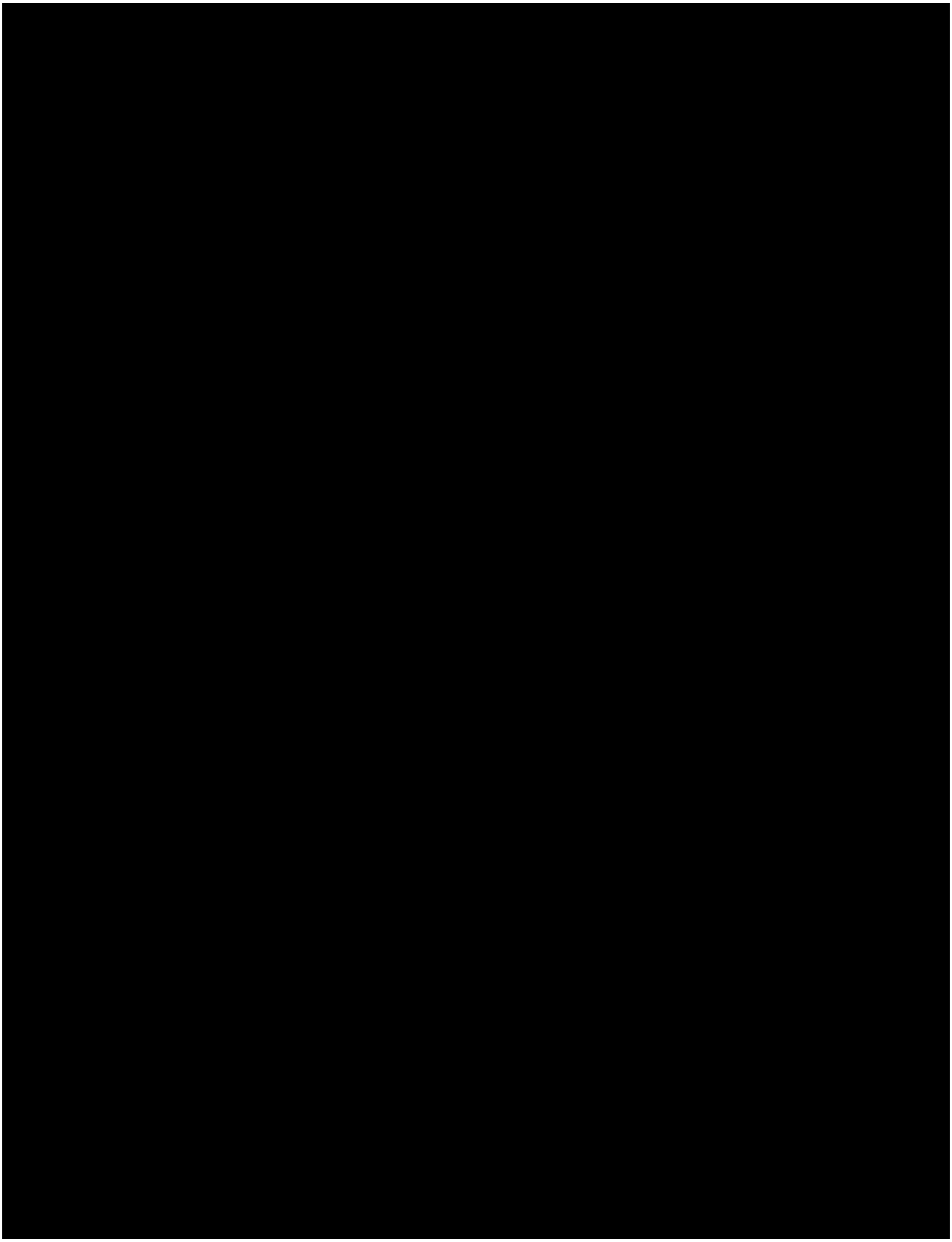
5 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

R10-4429 Hallek M., Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Doehner H, Hillmen P, Keating MJ, Montserrat E, Rai KR, Kipps TJ. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 111 (12), 5446 - 5456 (2008)

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010).

R01-0787 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol (5), 649 - 655 (1982).





10. HISTORY TABLE

Table 10:1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**19-JUL-2016**	[redacted]	None	This is the final TSAP without any modification
Revised	**13-OCT-2016**	[redacted]	All Sections	Correction of typos.
			[redacted]	[redacted]
			[redacted]	[redacted]
			5.2.2	Clarification that if patients would have their examinations contributing to the overall response assessment over a number of days, the earliest date of the multiple examinations should be considered.
			[redacted]	[redacted]
			5.4.4	Deleting sentence about further in-depth analyses for AEs by user-defined categories as text was misleading.
			5.4.5	Correction of laboratory parameters to be displayed in section 15.3 and 16.1.9.2 of the report.
			[redacted]	[redacted]
			7.3	No summary table for treatment compliance will be done as as often investigator said administration was not according to protocol because of an AE, but actually it is according to

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
				protocol to interrupt because of AEs. Instead only a listing of administration of study drug including the comment about administrations not according to protocol will be done.
			[redacted]	[redacted]
			7.7	Clarification that a listing of each dose taken at each treatment course will be provided for all patients and not just patients treated with different doses.
			7.8.1.1	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			7.8.1.5	Clarification which analyses will be done for other significant AEs.
			7.8.2	Converted values will be used for all laboratory plots instead of normalised values for some plots. Deletion of rule for GFR as this parameter is not assessed in the study. No possible clinically significant abnormal laboratory values and tumour lysis syndrome frequency tables will be provided for patients with hepatic enzyme elevations. If needed the information can be extracted from patient listings. Clarification what analyses will be done for neutropenia and thrombocytopenia and how terms are defined.
			[redacted]	[redacted]
			[redacted]	

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
				[redacted]
			[redacted]	
			[redacted]	