# Trial Statistical Analysis Plan

**c02204387-02**

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| **BI Trial No.:** | 1270.2 |
| **Title:** | A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin (including protocol amendments 1 to 5 [c02158149-09]) |
| **Investigational Product(s):** | BI 836826 |
| **Responsible trial statistician(s):** | Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 28 AUG 2017 REVISED |
| **Version:** | Revised |

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# 2. LIST OF ABBREVIATION

| Term | Definition / description |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALB | Albumin |
| ALKP | Alkaline phosphatase |
| ALT | Alanine amino transferase |
| aPTT | Activated artial thromboplastin time |
| AST | Aspartate amino transferase |
| ATC classification | Anatomical, Therapeutic, Chemical classification |
| BAS | Basophils |
| BMI | Body Mass Index |
| BRPM | Blinded Report Planning Metting |
| BSA | Body Surface Area |
| CA | Calcium |
| COOMB | Direct antiglobulin test |
| CR | Complete remission |
| CRu | Complete remission unconfirmed |
| CRE | Creatinine |
| CT | Computer tomography |
| CTh | Concomitant therapy |
| CTC | Common Terminology Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| DBL | Database lock |
| DILI | Drug-induced liver injury |
| DLT | Dose limiting toxicity |
| DM&SM | Boehringer Ingelheim Data Management and Statistics Manual |
| ECOG | Eastern Cooperative Oncology group |
| eCRF | Electronic case report form |
| EMEA | European Agency for the Evaluation of Medicinal Products |

| Term | Definition / description |
|---|---|
| EOS | Eosinophils |
| EoT | End-of-text |
| FFS | Failure free survival |
| GLU | Glucose |
| HCT | Haematocrit |
| HGB | Haemoglobin |
| ICH | International Conference on Harmonisation |
| IGA | Immunoglobulin A |
| IGG | Immunoglobulin G |
| IGM | Immunoglobulin M |
| INR | International normalised ratio of prothromin time (INR) |
| IRR | Infusion related reaction |
| K | Potassium |
| LDH | Lactate dehydrogenase |
| LYMPH | Lymphocytes |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MONO | Monocytes |
| MRT | Mean residence time |
| MTD | Maximum tolerated dose |
| NA | Sodium |
| NE | Not evaluable |
| NEUT | Neutrophils |
| NHL | Non-Hodgkin Lymphoma |
| NK cells | Natural Killer cells |
| OBD | Optimal biological dose |
| O*C | Oracle Clinical |
| P | Inorganic phosphate |
| PD | Progressive disease |
| PFS | Progression free survival |

| Term | Definition / description |
|---|---|
| PLT | Platelets |
| PR | Partial remission |
| PRT | Prothrombin time |
| PT | Preferred term |
| PV | Protocol violation |
| RBD | Red blood cell count |
| RD | Relapsed disease |
| RET | Reticulocytes |
| SAE | Serious adverse event |
| SCR | Screened set |
| SD | Stable disease |
| StD | Standard deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SPD | Sum of products of diameter |
| TBILI | Total bilirubin |
| TCM | Trial Clinical Monitor |
| TLS | Tumour lysis syndrome |
| ToC | Table of contents |
| TPRO | Total protein |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| WBC | White blood cells |

# 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, randomisation. This TSAP follows the Boehringer Ingelheim (BI) internal reference (1).

The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836826 in patients with non-Hodgkin lymphoma (NHL) of B-cell origin. BI 836826 is a new biological entity and the maximum planned single dose is 1400 mg. If the MTD is not reached with this dose, an optimal biological dose (OBD) may be defined instead.

The MTD of BI 836826 was defined as 100 mg in this trial for Caucasian patients. This dose was declared based on safety demonstrated during the dose escalation which was performed in 37 Caucasian patients. The results have been reported in the "CTR – Phase I Safety Analysis Report" (8).

The planned additional expansion phase enrolled 4 patients (all 4 in Korea). After 3 of these 4 Korean patients developed significant toxicities (ie. infections associated with Grade 4 neutropenia), the protocol was amended for the need of exploring lower dose levels (50 mg and 75 mg) in a designated escalation cohort of Korean patients, with the aim of defining a MTD in Korean patients. Thus, the expansion phase on 100 mg had been stopped. Secondary objectives are the collection of overall safety and anti-tumour efficacy data and the determination of the profile of BI 836826.

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

SAS® Version 9.2 (or higher) will be used for all analyses.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

The primary endpoints of this trial are the MTD and the number of dose limiting toxicities (DLTs) during the MTD evaluation period. Instead of the MTD, an OBD might be defined instead.

Maximum tolerated dose (MTD):

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

The MTD evaluation period is defined as the time from the first administration of study medication to 7 days after the second administration.

Note that in case of administration of split dose during course 1, both infusions on consecutive Days 1 and 2 of Course 1 are considered as the first administration.

Additionally, all information, including adverse events (AEs) qualifying for a DLT from later times, will be considered in the final determination of the dose recommended for Phase II.

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

Not applicable.

### 5.2.2 Other Secondary endpoints

Tumour size reduction (indicator lesions, spleen and liver nodules)

Tumour size reduction of indicator lesions, spleen nodules and liver nodules will be analysed separately as secondary endpoints as follows:

Tumour size reduction of indicator lesions will be analysed as secondary endpoint “Best % change from baseline in SPD” from imaging data.

Tumour size reduction of liver nodules will be analysed as secondary endpoint “Best % change from baseline in SPD” from imaging data.

Tumour size reduction of spleen nodules will be analysed as secondary endpoint “Best % change from baseline in SPD” from imaging data. Best overall response (according to investigator assessment):

Response will be assessed according to the Standardized or Revised Response Criteria for Malignant Lymphoma from 1999 ([R04-1585]). Each patient will be assigned to one of the

following categories:

- complete remission (CR)
- complete remission unconfirmed (CRu)
- partial remission (PR)
- stable disease (SD)

progressive disease (PD)

Best overall response (CR, CRu, PR, SD, PD in this order) is defined as the best overall response obtained since the start of study treatment. Best overall response will be evaluated in two different ways: first, all responses as documented by the investigator (independent of the assessment procedure) will be evaluated. In a further analysis, only disease evaluations for which imaging data are available in the eCRF will be evaluated. In case PD is captured by the investigator, the response PD will be always considered as PD, independent whether imaging data is available at this timepoint or not. For both evaluations only response assessments prior to any further NHL therapy and until PD will be taken into account.
For the calculation of the date of response: if patients would have their examinations contributing to the disease assessment over a number of days, the earliest date of the multiple examinations will be considered.

Progression free survival (PFS):

PFS is defined as the time from first administration of study medication until disease progression or death, whatever occurs first.

Patients administered a new additional therapy for NHL recorded in the electronic case report form (eCRF) but not presenting with disease progression before the start of this new NHL therapy will be censored at the date of last response assessment during which the patient was evaluable and did not have the event before the new NHL therapy has started.

Patients not administered another NHL therapy and not presenting with disease progression or death during the trial will be censored at the date of the last response assessment during which the patient was evaluable and did not have the event.

A patient is said to have an evaluable response assessment if a response of CR, CRu, PR, SD or PD has been assigned.

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

Table 5.2.2:1 Derivation rules for progression-free survival

| **Situation** | **Outcome (event or censored)** | **Date of outcome** |
|---|---|---|
| Baseline and post-baseline disease assessment: disease progression or death without prior additional NHL therapy | Event | Date of first disease progression or death |
| Baseline and post-baseline disease assessment: disease progression or death and prior additional NHL therapy | Censored | Date of last response assessment before start of new NHL therapy |
| Baseline and post-baseline disease assessment: No disease progression or death without additional NHL therapy | Censored | Date of last response assessment |
| Baseline and post-baseline disease assessment: No disease progression or death with additional NHL therapy | Censored | Date of last response assessment before start of new NHL therapy |
| No baseline or post-baseline disease assessment: without death | Censored | Date of first administration of BI 836826 |
| No baseline or post-baseline disease assessment: death on or before the first planned disease assessment (i.e. at week 4 assessment) | Event | Date of death |
| No baseline or post-baseline disease assessment: death after first planned disease assessment (i.e. at week 4 assessment) | Censored | Date of first administration of BI 836826 |

Remark: determination of the response status via disease assessment refers to any disease assessment via imaging or via physical assessment

Progression free survival (PFS) [in days] is therefore the time from first administration of study medication to the earlier date of disease progression or death (minimum date of disease progression or death – date of first administration of study medication + 1).

Progression free survival (PFS) censored [in days] is therefore the time from first administration of study medication to the date of last response assessment (date of last response assessment – date of first administration of study medication + 1).

Failure free survival (FFS):

FFS is defined as the time from first administration of study medication until disease progression or death or start of next NHL therapy.

Patients not administered another NHL therapy and not presenting with disease progression or death during the trial will be censored at the date of the last response assessment during which the patient was evaluable and did not have the event.

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

Table 5.2.2:2 Derivation rules for failure-free survival

| **Situation** | **Outcome (event or censored)** | **Date of outcome** |
|---|---|---|
| Baseline and post-baseline disease assessment: disease progression or death or start of next NHL therapy | Event | Date of first disease progression or death or start of next NHL therapy |
| Baseline and post-baseline disease assessment: No disease progression, death or new NHL therapy | Censored | Date of last response assessment |
| No baseline or post-baseline disease assessment: no death or new NHL therapy | Censored | Date of first administration of BI 836826 |
| No baseline or post-baseline disease assessment: death/next NHL therapy on or before the first planned disease assessment (i.e. week 4 assessment) | Event | Date of death/next NHL therapy |
| No baseline or post-baseline disease assessment: death/next NHL therapy after the first planned disease assessment (i.e. week 4 assessment) | Censored | Date of first administration of BI 836826 |

Remark: determination of the response status via disease assessment refers to any disease assessment via imaging or via physical assessment

Failure free survival (FFS) [in days] is therefore the time from first administration of study medication to the earlier of disease progression or death or start date of next NHL therapy. (minimum date of disease progression, death or start of next NHL therapy – date of first administration of study medication + 1).

Failure free survival (FFS) censored [in days] is therefore the time from first administration of study medication to the date of last response assessment (date of last response assessment – date of first administration of study medication + 1).

### 5.4.4 Adverse events

Severity of AEs is scaled according to Common Terminology Criteria of Adverse Event (CTCAE version 4.0, [R10-4848]).
Besides analysis with regard to primary system organ class and preferred term, AEs by user-defined AE categories (UDAEC) will be analysed. Definitions of user-defined categores in terms of MEdDRA codes and subsearches can be found in Section 9.4 of this TSAP.

### 5.4.5 Laboratory parameters

#### 5.4.5.1 General safety laboratory parameters

In this trial the original laboratory values will be converted into standard units and the CTCAE grades will be assigned to all parameters which have a CTCAE definition. For this study, the laboratory parameters and their functional groups, together with the direction of concern are:

Haematology: Haemoglobin (HGB) (-), haematocrit (HCT) (-), red blood cell count (RBC) (-), white blood cells (WBC) (-), platelets (PLT) (-) and reticulocytes (RET) (-),

Differential: Neutrophils (NEUT) (-), lymphocytes (LYMPH) (+ and -), monocytes (MONO) (-), basophils (BAS) (+) and eosinophils (EOS) (+), CD3+ T cell count (CD3V) (-), CD4+ T cell count (CD4V) (-), CD8 T cell count (CD8V) (-), CD56+ natural killer cell count (CD56V) (-), CD 19+ B cell count (+ and-)

Electrolytes: Sodium (NA) (+ and -) and potassium (K) (+ and -)

Enzymes: Aspartate amino transferase (AST) (+), alanine amino transferase (ALT) (+), alkaline phosphatase (ALKP) (+)

Substrates: Total bilirubin (TBILI) (+), glucose (GLU) (+ and -) and creatinine (CRE) (+)

Coagulation: International normalised ratio of prothromin time (INR) (+), activated artial thromboplastin time (aPTT) (+) and prothrombin time (PRT) (+)

Urine (measured by dipstick): pH, glucose, erythrocytes, leukocytes, protein, nitrite

Biochemistry: Calcium (CA) (+ and -), corrected calcium (+ and -), inorganic phosphate (P) (-), lactate dehydrogenase (LDH) (+), urea (UREA) (+), total protein (TPRO) (-),
albumin (ALB) (-), uric acid (URIC) (+), Immunoglobulin A (IGA) (+ and - ),Immunoglobulin M (IGM) (-), Immunoglobulin G (IGG) (-), direct antiglobulin test (COOMB), CMV DNA (qual.)

The signs + (-) means the above (below) the reference ranges. For the parameters TPRO, ALB, URIC, IGA, IGM, IGG, and direct antiglobulin test, no CTCAE grade definition is

available. The direction of concern will be investigated with regard to their respective reference ranges.

Urine measurement (based on dipsticks with 0, +, ++, and +++; the more + the worse) will be displayed if available. For urine measurement based on dipsticks conversion rules can be found in Section 9.3.

The grading of hypocalcemia is based on corrected calcium as calcium can be falsely low if hypoalbuminemia is present. The following corrective calculation will be performed:

Corrected calcium (mg/dL) = Total Calcium (mg/dL) – 0.8[Albumin (g/dL)-4)

No correction of the reference range has to be done. The reported reference range of total calcium should be used for analyses.

Corrected calcium can be only derived at a certain time point in case both laboratory values, total calcium and albumin, have been reported for the patient in the same laboratory sample.

The following laboratory parameters are considered as prioritized laboratory values as defined on project level: Haemoglobin, WBC, neutrophils, lymphocytes, platelets, ALT, AST, total bilirubin, LDH, creatinine, uric acid, potassium, inorganic phosphate, calcium, corrected calcium, albumin,CD4+ T cell count. Prioritized laboratory values will be presented in Section 15 of the CTR, while all other laboratory parameters of concern will be displayed in Appendix 16.1.9.2.

#### 5.4.5.2 Tumour lysis syndrome (TLS)/Laboratory signs of cell destruction

The presence of TLS will be mainly investigated via adverse event reporting (see Section 7.8). In addition, laboratory signs of cell destruction will be investigated based on the laboratory values uric acid, potassium, inorganic phosphate and creatinine. Laboratory signs of cell destruction may be considered present if within the time window of the day of BI 836826 infusion and the following 6 days two or more of these laboratory parameters are considered abnormal simultaneously. Simultaneously means that abnormality of these ≥2 lab parameters occurs within 24 hours within the 7 day window after BI 836826 infusion. The definition of abnormal laboratory values is given in Table 5.4.5.2: 1 below. .In case laboratory signs of cell destruction are observed, it will be checked whether an AE episode that may indicate clinical TLS is reported within the 7 day time window after BI 836826 infusion. For the respective UDAEC see Section 7.8.

Table 5.4.5.2:1 Definition of abnormal lab values for laboratory signs of cell destruction

| Laboratory parameter | abnormal value |
|---|---|
| Uric acid | ≥476 µmol/L AND increase from relative baseline by ≥25% |
| Potassium | Only if relative baseline is < 6.0 mmol/L: value ≥ 6.0 mmol/L |
| Inorganic phosphate | ≥1.45 mmol/L AND increase from relative baseline by by ≥25% |
| Creatinine | Absolute increase from relative baseline by 26.5 µmol/L AND increase from relative baseline by ≥50% |

Definition of relative baseline: relative baseline is the last laboratory value prior to BI 836826 infusion, ie. it will be derived for the four laboratory values separately for each infusion.

# 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 can arise. The data will be presented for all dose cohorts separately, where Korean patients will be presented as a separate dose cohort from Caucasian patients.

In addition, the results for all patients in total, all Caucasian patients in total, and all Korean patients in total will be presented.

To justify the MTD determination, DLTs occurring during the MTD evaluation period (very first infusion of BI 836826 until the day of second infusion in Course 1 + seven days) will be presented separately from those occurring during the complete on-treatment period.

"Analysing treatment" will be used for reporting of treatment emergent AEs and to differentiate between screening, on-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.

For the on-treatment period and the MTD evaluation period, the initial trial medication assigned at the beginning of the first treatment course will be used as the label of the analysing treatment.

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.

The actual planned dose of trial 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.

The following table defines the different categories of important PVs. If the data show other important PVs, this table will be supplemented accordingly latest at the blinded report planning meeting (BRPM).

Table 6.2:1 Important protocol violations

| Category /Code | | Description | Example/Comment | Excluded from |
|---|---|---|---|---|
| **A** | | **Entrance criteria not met** | | |
| | A1 | Patient has condition that may cause additional risk from study medication | Ex 16 - 21,23,24 | None |
| | A2 | Patient has laboratory assessments that may cause additional risk. | Ex 9 – 14, | None |
| | A3 | Patient is unable to comply with the protocol | Ex 22, 25 | None |
| | A4 | Patient does not have trial diagnosis or is not part of the target population | In 1 - 2, 4, 6-7, Ex 1 – 7, Ex 8 | None |
| **B** | | **Informed consent** | | |
| | B1 | Informed consent not given or too late | In 8 | None |
| **C** | | **Trial medication and randomisation** | | |
| | C1 | Drug not administered according to the protocol | Administration according to protocol="No" and medical review of associated comments | None |
| | C2 | Drug not administered according to protocol | Individual pre-medication taken="No" and medical review whether premedication would have been required according to protocol | None |

## 6.3 PATIENT SETS ANALYSED

The Screened Set (SCR) includes all patients who signed 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 analyses.

Replacement of patients is defined in Section 3.3.4.1 in the CTP. The final list of replaced patients is supplied by the Trial Clinical Monitor (TCM) no later than at the last BRPM before the DBL.

No per protocol population will be used for analyses.

Study medication is defined as BI 836826.

First administration of study medication is defined as date of first administration of BI 836826.

## 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 (5)).
Missing data and outliers are handled according to 001-MCS-36-472 (2).

If the day of birth is missing, then the imputed days will be the 15$^{th}$. If start of new NHL therapy date is incomplete (only month given), then the start date will be imputed with the 1$^{st}$ of month 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 trial medication in the first treatment phase, where the first administration

of trial medication is defined in Section 6.3 above. If this criterion is not fulfilled, then no baseline will be derived.

For laboratories where not only the examination date but also time is 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 date and 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.

The definition of relative baseline for the investigation of laboratory signs of cell destruction is given in Section 5.4.5.2.

# 7. PLANNED ANALYSIS

For end-of-text (EoT) tables, the set of summary statistics is: N / Mean / standard deviation [StD] / Minimum [min] / Median / Maximum [max].

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 days 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.

### 7.1.2 Important protocol violations

A listing with the number of patients with protocol violations by initial treatment will be created in Section 15 of the CTR.

### 7.1.3 Demographic and other baseline

Standard descriptive analysis and summary tables for all patients treated by initial treatment will be created for demography, smoking/alcohol status, previous therapies, physical

examination, disease evaluation at baseline, virology screening, ECOG and oncological history.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant therapies will be coded according to World Health Organisation Drug Dictionary (WHO DD). Concomitant therapies (CTh) 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.

A summary of the most frequently used concomitant medications (drug classes and generic name) during the treatment and before starting of treatment will be reported. Separate listings/tables will be provided for therapy starting before therapy and those therapies starting after first administration of the trial drug as well as for therapies with missing or incomplete start dates. A summary of concomitant therapy will be given.

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.

## 7.3 TREATMENT COMPLIANCE

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

The numbers of patients complying with the administration of trial medication according to protocol (yes/no) will be listed.

For patients with administration "not according to the protocol" a listing with comments will be presented.

Furthermore, a listing will show all administrations of trial drug including also the administration of premedication acetaminophen/paracetamol, antihistamine and glucocorticoid.

## 7.4 PRIMARY ENDPOINTS

The primary endpoints of this trial are the MTD and the number of DLTs during the MTD evaluation period. The MTD is determined from the occurrences of DLTs during the MTD evaluation period, which is from treatment start until the second infusion of BI 836826 plus 7 days. 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. Patients, if any, who did not complete at least two administrations of BI 836826 for reasons other than DLT will be excluded from the analysis of the primary endpoint. These patients will be replaced at the same dose level.

At the end of the dose escalation phase, a brief interim safety analysis was performed and reported to further describe the dose escalation steps actually occurred and to justify the determination of MTD, see also Section 9.1 and "CTR – Phase I Safety Analysis Report" (8).

## 7.5 SECONDARY ENDPOINTS

### 7.5.1 Key secondary endpoint

Not applicable.

### 7.5.2 Secondary endpoints

Tumour size of target lesions, spleen nodules and liver nodules (from imaging data) will be analysed in terms of their SPD best percentage change from baseline. Summary statistics will be presented for all cohorts. A waterfall plot will also be generated to summarise tumour size reduction graphically for the SPD of the indicator lesions identified at baseline imaging. Furthermore, the tumour size of indicator lesions, liver nodules and spleen nodules and the change with respect to baseline will be listed by time point (for imaging data as well as for data from physical assessment).

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

PFS and FFS will be analysed exploratory using Kaplan-Meier methods.

## 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 by dose group. The purpose of these tables is to summarize and document the data that led to the selection of the MTD. With regard to the final CTR, no selected MTD analyses for Caucasian patients will be displayed since the determination of the MTD for Caucasian patients has been already described in the "CTR – Phase I Safety Analysis Report" see (8)).

### 7.8.1 Adverse events

7.8.1.1 Maximum tolerated dose and dose limiting toxicity

A summary of the number of patients with DLT within the MTD evaluation period will be given by initial treatment.

In order to explore the behaviour of DLTs with respect to the actual dose of BI 836826, we will examine descriptively the dose response relationship, using DLTs in the MTD evaluation period and DLTs up to the end of the on treatment phase, in separate analyses. Still, the determination of the MTD of Caucasian patients had been already described in the "CTR – Phase I Safety Analysis Report" (8) and will thus not be described again in the final CTR.

#### 7.8.1.2 Adverse events

AE analysis will be performed for all treatment periods and selected analyses for the MTD evaluation period.

The analyses of AEs will be descriptive in nature and will follow the standard procedure laid down in the Data Management and Statistics Manual (DM & SM) (including all required tables and listings) (current guideline 'Handling and Summarization of AE Data for CTR and Integrated Summaries' (6)). 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 SOC will be sorted alphabetically, and PTs 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 AEs occurring between the first administration of BI 836826 until 8 weeks after last administration of BI 836826 will be assigned to the on-treatment period. AEs will be distinguished for the treatment course in which the subjects are on-treatment as well as for screening, and post-study. 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.

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 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.

CTCAE grading within AE tables is displayed as “all Grades”, “Grade 1”, “Grade 2”, “Grade 3”, “Grade 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 separate categories 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 grades”, “Grade 1/2”, “Grade 3/4” and “Grade 5” is used, but the “missing grade” column should only be displayed in case AEs with a missing CTCAE grade occured.

AE attributes

AE attributes "CTCAE Grade 3/4 combined with drug relation" and “CTCAE Grade 5 combined with drug relation” 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” is needed similarly to the AE attribute "CTCAE Grade 3/4 combined with drug relation" and “CTCAE Grade 5 combined with drug relation”, respectively, as described above.

Frequency of patients with AEs will be summarised by treatment, highest CTCAE grade, primary SOC and PT. Tables will be provided for patients with related AEs, with serious adverse events (SAEs), with non-serious AEs, with DLTs, with protocol-specified significant AEs, with other significant AEs, with Adverse events of special interest (AESIs), AEs by user-defined AE category, with Infusion-related reactions (IRRs), with AEs leading to permanent discontinuation of study medication, with AEs leading to dose reduction, and with AEs leading to death.

7.8.1.3 Protocol-specified significant AEs and AEs by user-defined category (UDAEC)

Protocol-specified significant AEs as defined in the CTP, Section 5.2.2.1, will be summarized..

AEs by UDAEC will be displayed in a frequency table of AEs by user-defined category, preferred term and worst CTCAE grade as well as in a frequency table by user-defined category and worst CTCAE grade. UDAEC categories are described in Section 9.4.

7.8.1.4 Other significant AEs

Other significant AEs are serious and non-serious AEs leading to treatment discontinuation and/or serious and non-serious AEs leading to dose reduction. Respective frequency tables by worst CTCAE grade, primary system organ class and preferred term will be provided.

7.8.1.5 Infusion-related reactions (IRR)

Frequency of IRRs 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 50 mg dose cohort (enrolment before April 2013)), the symptoms of an IRR are reported as AEs but not captured explicitly as symptoms of an IRR. For these patients, potential symptoms of an IRR can be only identified by pre-defined AE preferred terms as given by the user-defined category . For patients from following dose cohorts (including some patients of the 50mg cohort), not only IRRs are reported with the AE term “Infusion-related reaction” but also its symptoms which are

additionally marked as symptoms of an IRR. IRR tables capturing IRR symptoms can be only displayed for these patients. 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.

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 based on the preferred MedDRA term will be displayed by administration visit together with its CTCAE grade for all patients.

#### 7.8.1.6 Tumour lysis syndrome

Potential clinical tumour lysis syndrome will be analysed via the UDAECs for TLS as defined in Section 9.4.

In addition, screening for laboratory signs of cell destruction based on the laboratory values of uric acid, potassium, phosphorus and creatinine will be done as described in Section 5.4.5.2.

### 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 DM & SM (Guideline 'Display and Analysis of Laboratory Data' (7)).

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.

Single time courses by initial treatment will be used to display laboratory values over time. The graphs may be truncated if sufficient data is not available. These graphs will be displayed in Chapter 16.1.9.2 of the CTR for the following parameters, using the BI standardized values for haematology and differentials.

Haematology: haemoglobin, WBC count and platelets

Differentials: neutrophils (absolute count), absolute lymphocyte count, absolute Monocyte count and Natural Killer (NK) cells, CD 4 T-cell count

Biochemistry: LDH.

Clinically relevant abnormalities (as defined in Section 9.2) will also be summarised.

The change of the laboratory value will be calculated for all laboratory parameters from baseline to the end of the treatment for the whole treatment duration. No post-study laboratory values will be considered.

Worst laboratory value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter.

The change of the CTCAE grade of the lab value will be calculated

- from baseline to the last laboratory value on treatment
- from baseline to the worst value on treatment
- from worst value on treatment to last value on treatment

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 inititally. 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.

Patients with possibly clinically significant laboratory values will be tabulated (see Section 9.2).

The prioritized laboratory values (see Section 5.4.5.1) will be displayed in Section 15 of the final CTR while all other laboratory parameters will be displayed in the Appendix of the CTR.

Neutropenia, thrombocytopenia and leukopenia

Episodes of low neutrophil, platelet and WBC counts are of special interest. Episodes with CTCAE grade 3/4 as well as episodes with CTCAE grade 4 lasting 7 or more days will be analysed separately.

An episode of low blood counts of grade 4 starts with the first occurrence of a CTCAE grade 4 and lasts until the first time the CTCAE grade falls back to <=3 (analogously for an episode of CTCAE grade 3/4) .

In case the episode starts during the EOT or Follow-up, the duration of this episode is defined to be missing. The reason for this approach is that after the EOT laboratory data is only

captured infrequently and therefore the duration of an episode would be overestimated due to lack of data.

If an episode starts before EOT and the CTCAE grade of the respective parameter does not fall back to the respective grade that ends the episode 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.

Number of patients with respective episodes, number of episodes, episodes per patient, duration of individual episode, number of episodes divided by number of infusion per patient, mean and median duration of episode per patient will be displayed.

Additionally, a frequency table displaying number of patients with episode of neutropenia Grade 4 and concomitant AEs in the UDAEC Infections (incl. respiratory infections and sepsis) of any grade as well as only for Grade 3 or 4 infections will be provided. In this context, concomitant AE is defined as AE with onset date within the neutropenia episode. This will be also done for CD4+ T-cell count Grade 4 and concomitant CD4 related specific infections from the UDAEC CD4 related specific infections.

The same way, a frequency table displaying number of patients with episode of thrombocytopenia Grade 4 and concomitant AEs in the UDAEC bleeding of any grade as well as only for Grade 3 or 4 bleeding will be provided.

### 7.8.3 Vital signs

Descriptive statistics of absolute values for vital signs (including body weight) will be provided by initial treatment and planned time or visit over all treatment courses.

### 7.8.4 ECG

No analyses are planned.

### 7.8.5 Others

Not applicable.

# 8. REFERENCES


| | |
|---|---|
| 1 | *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON. |
| 2 | *001-MCS-36-472* "Standards and processes for analyses performed within clinical Pharmacodynamics", current version; IDEA for CON. |
| 3 | *001-MCS-36-472_RD-01* "Noncompartmental Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON. |
| 4 | *001-MCS-36-472_RD-03* "Description of Analytical Transfer Files and PD Data Files", current version; IDEA for CON. |
| 5 | *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON. |
| 6 | *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON. |
| 7 | *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON. |
| 8 | *c02337389-01 "Clinical Trial Report – Phase I Safety Analysis Report"* |
| [R04-1585] | Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17 (4), 1244-1253, 1999. |
| [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. |
| [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). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf 2010 |
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# 9. ADDITIONAL SECTIONS

## 9.1 INTERIM SAFETY ANALYSIS

After the MTD (or, if applicable, the OBD) has been defined, an interim safety analysis was performed and the results were consolidated in in the "CTR – Phase I Safety Analysis Report" (8).

### 9.1.1 Time point and general content

After all patients treated in the dose finding phase of this trial have either completed the MTD evaluation period or dropped out of the study, safety analyses were performed to justify the dose to be used in the expansion phase of this trial. For this purpose, a database snapshot was performed. This snapshot has not been done following the process of an interim DBL. The safety analyses summarized results regarding safety of patients and did contain the determination of the MTD of BI 836826 as well as a recommendation for the dose of BI 836826 to be used in the expansion phase of this study. No efficacy and PK analyses were performed for the safety analyses.

A version of the TSAP was signed and archived before the snapshot of the safety analyses has been performed.

### 9.1.2 Tables and eCRF pages to be cleaned

Selected tables and listings from trial patients with regard to the safety evaluation were provided for the safety analyses.

The tables and listings that are contained in the report for the safety analyses were specified more precisely in the table of contents (ToC). The Oracle Clinical (O*C) database was as clean as possible before the snapshot was taken. Nevertheless, it was considered that the data might be unclean at that time point. eCRF pages that were particularly focused on in the cleaning process were the following:

- pages related to AEs
- pages related to laboratory data (note: only the prioritized laboratory values, see Section 5.4.5.1, will be displayed in the safety update report)
- administration of study medication pages
- pages related to patient disposition

# 10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10:1 History table

| Version | Date (DD-Mmm-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| Final | **28-Apr-14** | | None | This is the final TSAP without any modification |
| Revised | **28-Aug-17** | | All | Correction of spelling and grammar mistakes |
| | | | 3 | Explanation that the expansion phase of the trial was cancelled |
| | | | 4 | Clarifications deleted since these points have been already clarified in the CTP amendment |
| | | | 5.2.2 | Wording changes to clarify that SPD will be calculated based on indicator lesions<br><br>Deletion of liver and spleen endpoints (have been deleted in CTP amendment)<br><br>Clarification that response endpoints will be evaluated separately: based on imaging data only and based on all response assessments by the investigator<br><br>Clarification of derivation of date of response assessment<br><br>Censoring rules for PFS added<br>Censoring rules for FFS added |

Table 10:1 History table (cont.)

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| | | | 5.4.5 | Further safetly lab parameters added<br>Derivation of corrected calcium added<br>Corrected calcium, albumin and CD4+ T-cell count added as prioritized lab values<br><br>Analysis of TLS/laboratory signs of cell destruction revised after PVWG decision |
| | | | 6.1 | Clarification that Korean patients will be presented separately |
| | | | 6.2 | IPV table revised |
| | | | 6.3 | |
| | | | | |
| | | | 6.7 | Clarification of laboratory baseline values |
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Table 10:1 History table (cont.)

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|---|---|---|---|---|
| | | | 7.8.1 | Specific DLT analyses deleted (lack of data for analysis)<br><br>Display of CTCAE poolings clarified<br><br>Analysis of TLS/laboratory signs of cell destruction revised |
| | | | 7.8.2 | Handling of -1 and -9 lab values revised<br><br>Analyses with regard to neutropenia, thrombocytopenia, leukopenia nd low CD4+ T-cell count added |
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