Trial Statistical Analysis Plan

c06878240-02

BI Trial No.:	1270.11
Title:	An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- in combination with GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/ progressed after autologous/ allogeneic stem cell transplant Including protocol amendments 1 to 5 (c02102551-08)
Investigational Product(s):	BI 836826
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	30 JAN 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALKP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical, Therapeutic, Chemical (Classification System)
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
BS	Biomarker Set
BSA	Body Surface Area
C_{max}	Maximum measured plasma concentration
CR	Complete Remission
CT	Computer Tomography
CTh	Concomitant Therapy
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
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) Case Report Form
EOT	End of Treatment
FISH	Fluorescence In Situ Hybridization
GemOx	Gemcitabine and Oxaliplatin

Term	Definition / description
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
IRR	Infusion Related Reaction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's Lymphoma
OR	Objective Response
PET	Positron Emission Tomography
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PR	Partial Remission
PT	Preferred Term
R	Rituximab
REP	Residual Effect Period
SCR	Screened Set
StD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SPD	Sum of Products of Diameter
TLS	Tumour Lysis Syndrome
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation E9 (ICH E9) (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, and definition of measurements and variables.

The study is a multicentre study initially planned with two study parts. Part 1 is an open-label, (Phase 1b) dose-escalation according to a standard 3+3 design. Part 2 was to be a randomised parallel study comparing BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) to rituximab (R-) in combination with GemOx.

The primary objective of part 1 of the study is to determine the maximum tolerated dose (MTD) of BI 836826 in combination GemOx. The secondary objective of part 1 is to evaluate the pharmacokinetics (PK) of BI 836826 when administered in combination with GemOx.

The primary objective of part 2 of the study was to investigate efficacy by means of the overall response rate based on central review assessment of BI 836826-GemOx compared with R-GemOx. The secondary objective was to compare the efficacy of the two combinations by means of the complete remission (CR) rate based on central review assessment.

Due to the strategical decision to stop the project, the part 2 of the trial will not be conducted. The trial will be stopped after the dose escalation phase (or earlier). Therefore, this TSAP only describes the analysis of part 1 of the trial.

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

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints of this trial are:

- The number of evaluable patients with dose-limiting toxicities (DLTs) in the MTD evaluation period (cycle 1)
- The MTD of BI 836826 with GemOx based on the number of evaluable patients with DLTs in cycle 1. The MTD of BI 836826 with GemOx is defined as the highest dose studied for which the number of evaluable patients with dose-limiting toxicity is 17% or less (i.e., 0-1/6 patients) during the MTD evaluation period.

For the definition of DLT, refer to CTP Section 5.3.8.
Patients who have been replaced are not considered evaluable for MTD determination.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other secondary endpoints

The secondary endpoints are:

- The pharmacokinetic parameters AUC_t and C_{max} of BI 836826 when administered in combination with GemOx.
- OR by investigator assessment

5.4.3 Pharmacokinetic parameters

The PK parameters will be calculated as defined in Section 5.5.1 of the CTP using the processes detailed in (4).

5.4.4 Adverse Events

Severity of adverse events (AEs) is scaled according to Common Terminology Criteria of Adverse Events (CTCAE) version 4.03 (5).

5.4.4.1 Adverse events of special interest

DLTs, Infusion related reactions (IRRs), late onset infections and drug-induced liver injury (DILI) are considered as adverse events of special interest (AESI) in this study, for details see CTP Section 5.3.6.1 and 5.3.8.

5.4.4.3 Other significant adverse events

Other significant AEs are all serious and non-serious AEs leading to treatment discontinuation or dose reduction of any study medication.

5.4.5 Laboratory parameters

Original values will be converted into standard units and the CTCAE grades will be assigned to parameters which have a CTCAE definition.

Primary List: Tables and figures for these laboratory values and urine measurement will be displayed in Section 15 of the clinical trial report (CTR).

Table 5.4.5: 1 Primary laboratory parameters

Worsening direction	Laboratory	Measurement
low value	Haematology	white blood cell count (WBC, total leukocyte count)
		platelets (thrombocytes, PLTCT)
	Differentials	neutrophils (NEUABS)
	Biochemistry	inorganic phosphate (P)
high value	Substrates	creatinine (CRE)
		total bilirubin (TBILI)
	Enzymes	aspartate transaminase (AST)
		alanine transaminase (ALT)
	Biochemistry	lactate dehydrogenase (LDH)
		uric acid (URIC)
high and low value	Electrolytes	potassium (K)
		calcium (CA)
		Corrected calcium
	Differentials	lymphocytes (lymphopenia) (LYMPABS)
	Haematology	haemoglobin (HGB)
	Flow cytometry	TBNK (CD3, CD4, CD8, CD19, CD56)

Corrected calcium:
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.

5.4.5.1 Laboratory values of special interest

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. If however the baseline value is missing, then 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 CTCAE criteria, the BI default rules for clinical significance should be applied (6).

Tumour lysis syndrome (TLS)/Laboratory signs of cell destruction
In patients with a high tumour burden who are exposed to a highly effective therapy, there is a risk of rapid tumour destruction resulting in TLS. The presence of TLS will be mainly investigated via adverse event reporting and the respective UDAEC. 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 5.4.5.1: 1 below. In addition, it will be investigated whether an adverse event episode of the UDAEC "Tumour lysis syndrome" started in the same time window in which potential laboratory signs of cell destruction have been observed.

Table 5.4.5.1: 1 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%

Derivation of "relative baseline" for the laboratory values uric acid, potassium, inorganic phosphate and creatinine: relative baseline is derived for each BI 836826 infusion as the last respective value prior to BI 836826 infusion. Relative baseline will be derived independently for the four parameters, i.e. the four baseline values do not necessarily have to be derived from the same laboratory assessment.

Around each infusion of BI 836826, a time window is constructed. This time window starts at the day and start time of BI 836826 infusion until the end of the 6th day after BI 836826 infusion (end of the day, i.e. 23.59h), i.e. the day of BI infusion and the following 6 days will be considered for evaluation of potential laboratory signs of cell destruction.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this trial, treatment is not randomised (open-label, dose-escalation). Different dose levels of BI 836826 in combination with GemOx can arise. All planned analyses will be presented by initial treatment group, i.e. for all dose cohorts separately and in total over all dose cohorts. To justify the MTD determination of BI 836826 with GemOx, DLTs occurring during the MTD evaluation period (first treatment cycle) will be presented separately from those occurring during the complete on-treatment period. Patients where treatment group assignment has not been followed will be handled on a case-by-case basis and will be agreed upon latest at the last report planning meeting before DBL.

For safety summaries, events that start from the first administration of any trial medication until 30 days (residual effect period (REP)) after the last administration of any trial medication will be considered as having occurred “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 period will be displayed in separate listings from those occurred during the on-treatment period.

Labels of each analysis treatment period, analysis numbers, the labels used for displays in the tables and listings in the CTR, as well as codes, decodes, sort order and labels for each trial medication are provided in the TSAP technical document “ADS plan”.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol set (PPS) analysis will be performed for this study, hence no patient will be excluded from the analyses. However patients with important protocol violations (IPVs) will be documented. The following table defines the different categories of potential IPVs.

Table 6.2: 1 Important protocol violations

Category/Code		Description	Requirement	Excluded from
A		**Entrance criteria not met**		
	A1*	Efficacy related entrance criteria not met	In4, In 5 Missing bone marrow biopsy at screening	None
	A2*	Patient has condition that may cause additional risk from study medication	In 9, Ex 6, Ex 7, Ex 8, Ex 9, Ex 10	None
	A3*	Patient has laboratory assessments that may cause additional risk.	In 8	None
	A4*	Patient is unable to comply with the protocol	Ex 11	None
	A5*	Patient does not have trial diagnosis or is not part of the target population	In1, In 2, In 3, In 6 Ex 1, Ex 2, Ex 3, Ex 4, Ex 5, Ex 12	None
B		**Informed consent**		
	B1*	Informed consent not given or too late	In 7	None
C		**Trial medication and randomisation**		
	C1*§	Incorrect treatment taken	Study drugs dispensing error leading to change in actual treatment	None
	C2*§	Drug not administered according to the protocol	Infusion schedule followed=”No” and medical review of associated comments (e.g. no IPV if volume and duration of infusion are according to local standards)	None

Table 6.2: 1 Important protocol violations (cont.)

Category/Code	Description	Requirement	Excluded from	None
D		**Concomitant medication**		
	D1 *§	Prohibited medication	• Any other anti-lymphoma therapy • Systemic immune-suppressive therapy other than corticosteroids • Concomitant anti-neoplastic therapy • Long term (>5 days) daily oral steroid treatment at doses higher to prednisolone 20mg per day	None
	D2 *§	Pre-medication not administered according to protocol	Did the subject receive standard pre-medication? ="No" to any standard pre-medication and medical review of associated comments (e.g. no IPV if patient receives a combination of premedication according to local standards)	None

* Automatic IPV
§ Manual IPV

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 MTD evaluation set (MS) includes all patients who were documented to have received at least one dose of BI 836826 and were not replaced for the MTD evaluation. The MTD evaluation set will be used for the primary analysis of DLTs and MTD determination.

Rules for replacement of patients are defined in the CTP. The list of replaced patients will be provided by the Trial Clinical Monitor no later than at the last report planning meeting and will be stored in the TMF.

Treated set (TS) includes all patients who received at least one dose of any study medication. The TS will be used for all planned safety and efficacy analyses besides the MTD determination.

Pharmacokinetic set (PKS) includes all patients in the TS who have at least one drug plasma concentration available. The PKS is used for the pharmacokinetic analyses.

No PPS will be used for analysis.

6.5 POOLING OF CENTRES

This section is not applicable because there are no inferential statistics, and therefore no statistical model in which centre/country could be included.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (7).
Missing data and outliers of PK data are handled according to (4).

In general, missing data not discussed in (4, 7) will not be imputed, unless required for the following analyses and definitions. Then the rules as described below apply.

1) Change of laboratory values from baseline

Laboratory values at baseline: For missing laboratory data at visit 1 (before the very first administration of any study medication) the data of preceding visits will be used.

2) Definition of on-treatment period and actual treatment

Date of permanent discontinuation of last study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of last study medication. However, if the date of the very last intake is partially missing this will be imputed with

- If only month and year are given, the last day of the month will be used for imputation
- If only year is given, the 31st of December of this year will be used for imputation

If the imputed date leads to a date that is later than the date of the EOT visit, then the imputed date is the date of the EOT visit. If the imputed date leads to a date that is later than the death date, then the imputed date will be the date of death.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

Unless otherwise specified, baseline is defined as the latest time-point before the very first administration of any study medication in the first cycle. 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 the very first administration of any 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 first study drug administration.

If any of these times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / standard deviation [StD] / Minimum [Min] / Median / Maximum [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.

If not otherwise specified, the abbreviation Pxx should be used for displaying of the xx^{th} percentiles.

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.

Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversions 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

Only descriptive statistics are planned for this section.

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 summary table (or listing) with the number of patients with protocol violations by initial treatment will be created in Section 15 of the CTR.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version.

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 CThs started after the administration of first trial medication. Transfusions will be displayed separately. Separate summaries will be presented for concomitant medications with missing or incomplete start dates.

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 ENDPOINTS

The primary endpoint of part 1 is the MTD of BI 836826 in combination with GemOx, analysed via the number of patients with DLTs during the MTD evaluation period (for definition of DLT see CTP Section 5.3.8, for definition of the MTD evaluation period see Section 6.1). In order to identify the MTD, the number of patients with DLTs at each dose level will be presented.

Patients in TS who were replaced during the MTD evaluation period will be excluded from the determination of the MTD, i.e. the MS will be used for the analysis of the primary endpoints.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Other secondary endpoints

The analysis of PK parameters AUC_t and C_{max} of BI 836826 when administered in combination with GemOx will be performed according to (4).

Further standard PK parameters will be evaluated if feasible.

OR by investigator assessment will be analysed descriptively for all patients in the TS in terms of the OR rate.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS besides the analysis of the MTD, this will be performed on the MS.

The primary analysis of the study 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 the MTD.

7.8.1 Adverse events

7.8.1.1 Maximum tolerated dose and dose limiting toxicities

A table displaying DLTs by primary system organ class (SOC) and preferred term (PT) will be provided by initial treatment for the MTD evaluation period for the MS. The same table will additionally be displayed for all treatment courses of the on-treatment period for the TS.

A summary of the number of patients with DLT within the MTD evaluation period and within the on-treatment period will be given by initial treatment for the TS.

7.8.1.2 Adverse events

Unless otherwise specified, adverse events analysis will be performed for the on-treatment period.

The analyses of AEs will be descriptive in nature and will follow the standard procedure laid down in (9). AEs will be coded with the most recent version of MedDRA. The version number will be displayed as a footnote in the respective tables and listings.

The SOCs will be sorted alphabetically. In tables displaying AEs by dose cohort 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 AEs 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 and 30 days 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 + 30 days will be assigned to “post-study”. The actual planned dosages of BI 836826 and GemOx 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 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", "missing Grade", "Grade 1", "Grade 2", "Grade 3", "Grade 4" and "Grade 5", but the "missing grade" column should only be displayed in case AEs with a missing CTCAE grade occurred. A separate table will show AEs leading to death. In this table no CTCAE grades will be shown.

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

7.8.1.3 Protocol-specified adverse events of special interest

Protocol-specified AESIs are defined in the CTP, Section 5.3.6.1.

Any event that qualifies for DLT

Please refer to Section 5.3.8 of the CTP and to Section 7.8.1.1 of this TSAP.

Infusion-related reactions (IRR)

IRRs will be analysed as AEs by UDAEC as defined in Section 7.8.1.4. To help analysing these terms, a by-patient listing with patients with an IRR as defined by the UDAEC categories will be produced. Additionally, IRRs will be analysed separately using the associated symptoms as indicated in the eCRF.

Frequency of patients with IRRs will be tabulated by treatment and infusion number. Summary statistics will be provided for the "Duration of IRR [h]" and the "Time since start of treatment (in the respective infusion) [min]" (until IRR).
For the *All Infusions* column, "Duration of IRR [h]" and "Time since start of treatment (in the respective inf) [min]" will be based on all reported infusions and hence patients with more than one infusion accompanied by an IRR will contribute more than once.

Late onset infections

Frequencies of these AESIs will be displayed.

Hepatic injury

The frequency of this AESI will be displayed in the CTR.

7.8.1.5 Other significant AEs

Frequency tables of patients with

- AEs leading to dose reduction of BI 836826
- AEs leading to dose reduction of oxaliplatin
- AEs leading to overall permanent discontinuation of last study medication
- AEs leading to discontinuation of BI 836826
- AEs leading to discontinuation of gemcitabine
- AEs leading to discontinuation of oxaliplatin

will be provided by dose cohort and total, worst CTCAE grade, primary SOC and PT for the on-treatment period.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow (8). 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, CD4 T-cell count and platelets

Differentials: neutrophils (absolute count), and absolute lymphocyte count

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:

- 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 parameters. 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.

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.

Patients with hepatic enzyme elevation will be tabulated. Additionally, laboratory values of special interest as described in Section 5.4.5 will be analysed.

Neutropenia and infections:

Special attention will be paid to neutropenia episodes of CTCAE grade 3/4 for ≥ 7 days as well as neutropenia episodes for CTCAE grade 4 for ≥ 7 days. The number of patients with such episodes, number of episodes, number of episodes per patient, duration of episodes as well as exposure adjusted number of durations (number of episodes per patient divided by number of infusions per patient), mean and median duration of episodes per patient will be summarised.

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.

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 (same for neutropenia episode Grade 3 and 4 and concomitant infection).

Time profiles for neutrophils will be prepared on patient level as well as displaying the mean and 95% CI for neutrophil counts over time for each cycle separately

Thrombocytopenia and bleeding:

Thrombocytopenia based on low platelets counts will be analysed the same way as neutropenia. A frequency table displaying number of patients with episode of platelets 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. In this context, concomitant AE is defined as AE with onset date within the thrombocytopenia episode (same for thrombocytopenia episodes of Grade 3 and 4 and concomitant bleeding).

Time profiles of platelets will be prepared as for neutrophils.

Low CD4+ T-cell count and infections:

Low CD4+ T-cell counts will be analysed the same way as neutropenia. A frequency table displaying number of patients with episode of low CD4+ T-cell counts Grade 4 and concomitant AEs in the UDAEC Infection 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 CD4+ T-cell episode (same for low CD 4+ T-cell count episodes of Grade 3 and 4 and concomitant infections).

Laboratory signs of cell destruction:

Potential laboratory signs of cell destruction may be considered present if two or more of the four laboratory parameters of interest are considered abnormal simultaneously. Abnormality is defined in Table 5.4.5.1: 1. Simultaneously means that abnormality of these ≥2 lab parameters occurs within 24 hours within the 7 day window described above.

In case a patient has potential laboratory signs of cell destruction as defined above observed, it will be checked whether a clinical symptom in terms of an AE episode from the UDAEC "Tumour lysis syndrome" has been reported within the same time window as the potential laboratory sign of cell destruction. Since only start dates but not start times of AEs are captured in the eCRF, the time window for UDAEC screening will be from the day of BI 836826 infusion until the following 6 days.

A listing will show all four laboratory values for all patients, including a flag whether the value is considered abnormal with regard to the definitions from Table 5.4.5.1: 1. A second listing will show all patients who have potential laboratory signs of cell destruction and

indicate whether an AE episode from the UDAEC "Tumour lysis syndrome" has been reported in the same time window. The number of patients with laboratory signs of cell destruction and clinical symptoms will be also reported in a table.

7.8.3 Vital signs

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

7.8.4 ECG

No separate analyses are planned. Newly emergent abnormalities will be recorded and analysed as AEs.

8. REFERENCES

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4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
5	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.pd f 2010 (BI Literature database R10-4848)
6	*001-MCG-157_RD-02:* "Standard Clinical Evaluation Criteria", current version; IDEA for CON.
7	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
8	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
9	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
10	Choi WWL, et al A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 15 (17), 5494 - 5502 (2009) BI Literature database P14-15474

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**03-NOV-16**		None	This is the initial TSAP with necessary information for trial conduct
Final	**30-JAN-18**		1-9	This is the final TSAP