NOVARTIS

Clinical Development

VAY736

CVAY736Y2102 / NCT03400176

Phase Ib open-label study of VAY736 and ibrutinib in patients with chronic lymphocytic leukemia (CLL) on ibrutinib therapy

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Feb-2024	Prior to DB Lock	Creation of Amendment 1	Changes to dose expansion arm and study design [redacted]	Section 1.1 Study design Section 2.1 Data analysis and information Section 1.1 Study design Section 1.2 Study objectives and endpoints Section 2.3.2 Demographic and background data Section 2.8.1 Efficacy analysis [redacted] Section 3.1.2 Dose-expansion part
			Update secondary efficacy objective to include CRi in rate of CR/CRi at C9	Section 1.2 Study objectives and endpoints Section 2.8.1 Efficacy analysis Section 3.1.2 Dose-expansion part
			Update imputation rule for prior antineoplastic therapies	Section 2.3.4.4 Partial-date imputation rules for prior antineoplastic therapies
			Add section for diagnosis and extent of cancer imputation	Section 5.1.5 Diagnosis and extent of cancer imputation
			Remove statement regarding TTP analysis with censoring rules	Section 2.8.1 Efficacy analysis
			Clarify summaries and listings for lab parameters	Section 2.8.2.3.3 Data analysis
			Update PK analysis set to observing vomit after ibrutinib	Section 2.2.1 Analysis sets Table 2-1 Classification based on PDs and non-PD criteria

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			dosing to 4 hours from 8 hours	
			Add clarifications for visits/timepoints to be used in efficacy analyses	Section 2.8.1 Efficacy analysis
			[redacted]	Section 1.2 Study objectives and endpoints [redacted]
			Add AESI reporting criteria	Section 2.8.2.2
			[redacted]	[redacted]
			Add definitions for immunogenicity	Section 2.2.1 Analysis sets Section 2.2.2 Subject classification Section 2.8.4.5.1 Sample ADA Status Section 2.8.4.5.2 Patient ADA Status
			Remove histological grade, predominant and additional histology/cytology summary and listing	Section 2.3.5 Diagnosis and extent of cancer
			Update to include new guidelines for IWCLL for disease response assessments for CLL and censoring rules	Section 5.2 Guidelines for efficacy analysis for chronic lymphocytic leukemia (CLL) studies
			Update and add literature cited in SAP to reference section	Section 2.6.1.1 Statistical hypothesis, model, and method of analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.8.4.4 Dose proportionality
				Section 5.2 Guidelines for NCI CLL Working Group 2018 (IWCLL)
				Section 6 References
			Add changes to protocol specified analyses	Section 4 Change to protocol specified analyses
			Add missing acronyms	List of Abbreviations
			Correct minor typographical errors	All

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List of abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
[redacted]	[redacted]
[redacted]	[redacted]
BLRM	Bayesian Logistic Regression Model
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug Administration Record
DDI	Drug-Drug Interaction
DDS	Dose Determining Set
DI	Dose Intensity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
HR	Heart Rate
IB	Investigator’s Brochure
IG	Immunogenicity
IGHV	Immunoglobulin Heavy Chain
IGIS	Immunogenicity Incidence Set

IGPS	Immunogenicity Prevalence Set
IV	Intravenous(ly)
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
JAGS	Just Another Gibbs Sampler
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRD	Minimum Residual Disease
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
[redacted]	[redacted]
ORR	Overall Response Rate
OS	Overall Survival
Q2W	Once Every Two Weeks
Q4W	Once Every Four Weeks
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic(s)
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PR	Pulse Rate
PT	Preferred Term
qd	Qua'que di'e / once a day
RAP	Report and Analysis Process
RD	Recommended Dose
RDE	Recommended Dose for Expansion
RDI	Relative Dose Intensity
[redacted]	[redacted]
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SCr	Serum Creatinine
SOC	System Organ Class

SS	Safety Set
SSD	Study Specifications Document
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study VAY736Y2102 that will be presented in the Clinical Study Report (CSR). The output shells accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variables and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on the Protocol Version 06 released on 20-Oct-2021.

All required changes to the planned analysis described in this document will be made through an amendment or addendum, depending on whether the change is made before or after database lock (DBL), respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document, without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., maximum-tolerated dose (MTD) or recommended dose for expansion (RDE) declaration, Investigator's Brochure (IB) updates, abstracts, posters, presentations, manuscripts, and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

The CVAY736Y2102 trial has been endorsed for early termination by the ICDB on 22-Sep-2023, due to business purposes and not safety concerns.

1.1 Study design

This Phase Ib, multi-center, open-label study has two parts: a dose-escalation part and a dose-expansion part. The purpose of the dose-escalation part is to characterize the safety and tolerability of VAY736 in combination with ibrutinib in patients with relapsed, refractory chronic lymphocytic leukemia (CLL). The dose-escalation part will be guided by a Bayesian Logistic Regression Model (BLRM) to estimate the MTD and/or RDE of the combination.

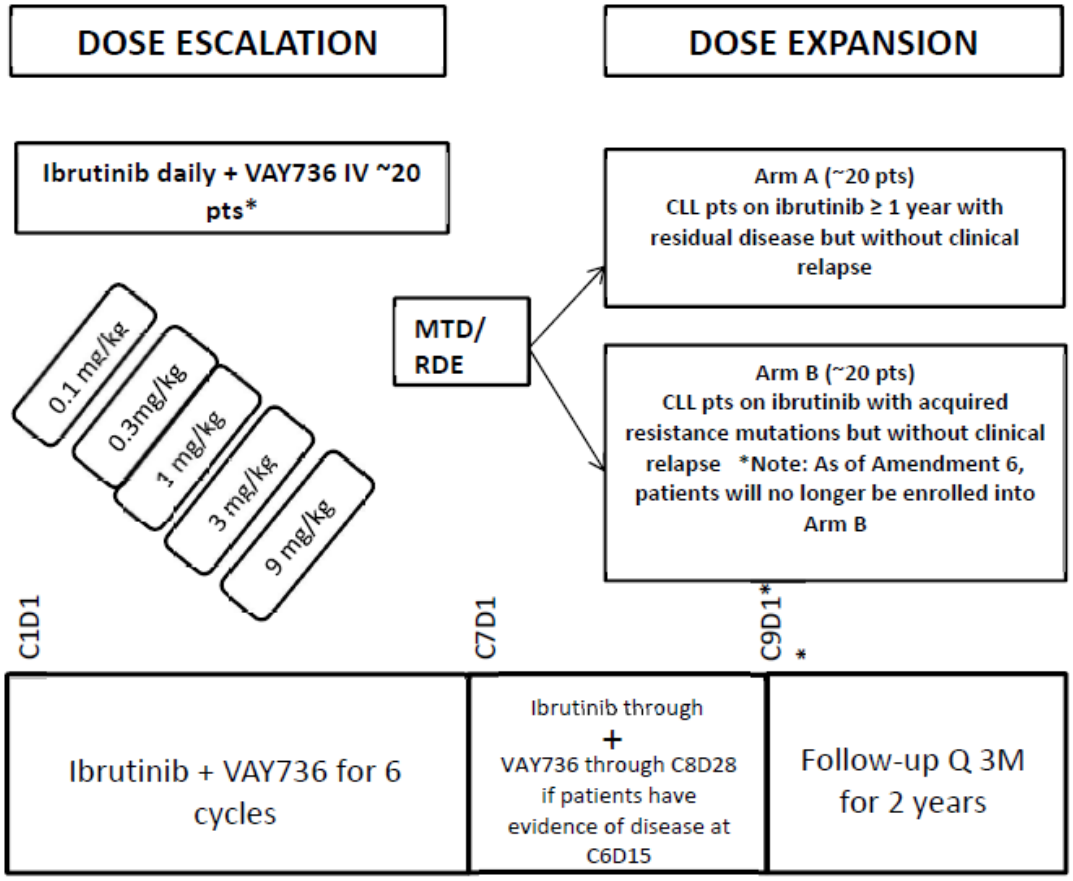
Upon identification of the MTD or RDE, a dose-expansion part will be opened to patient enrollment to further characterize the safety, pharmacokinetics (PK), and pharmacodynamics (PD), if available, and preliminary anti-tumor efficacy of the combination.

Both the dose escalation and dose expansion parts will enroll patients with CLL who are currently receiving ibrutinib therapy following relapse on another approved therapy AND have either failed to achieve a CR after > 1 year of ibrutinib treatment OR who have developed a resistance mutation to ibrutinib without clinical relapse at any time during treatment. The dose expansion part of the study will also include patients who have received ibrutinib either alone or in combination (or have received ibrutinib continuously with multiple sequential combination partners) as first-line therapy and have either failed to achieve a complete response after 1 year of therapy or have developed a resistance mutation to ibrutinib. Approximately 15-20 patients will be enrolled to the dose escalation part of the study. In the expansion part, approximately 40 patients will be enrolled to two arms (approximately 20 patients in each arm). One arm will enroll patients who have been on ibrutinib treatment for more than one year with evidence of residual disease which places them at risk for clinical relapse; the other arm will enroll patients with acquired resistance mutations to ibrutinib who have not yet demonstrated

clinical relapse, see Figure 1-1. All patients with acquired resistance mutations will be enrolled in Arm B, irrespective of ibrutinib treatment duration.

As of Protocol Version 06, enrollment to Arm B (patients with BTK inhibitor resistance mutation) is closed due to slower than anticipated enrollment.

Figure 1-1 Study design



*Combination administered for either 6 cycles or 8 cycles, ibrutinib continued through C8D28. For patients who achieve a CR at the primary endpoint (C9D1), investigators may consider discontinuing ibrutinib.

**Patients will be evaluated for the final disease assessment on C9D1 (± 7 days) in accordance with IWCLL guidelines.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 2.6
To determine the MTD and/or RD of the combination of VAY736 with ibrutinib To characterize the safety and tolerability of the combination of VAY736 and ibrutinib	**Safety** Escalation only: • Incidence of DLTs in cycle 1 (28 days) Escalation and expansion: • Incidence and severity of AEs and SAEs, including changes in laboratory parameters and vital signs **Tolerability** Dose interruptions, reduction, and dose intensity	
Secondary		Refer to Section 2.8
To assess any preliminary antitumor activity of the combination	Rate of patients with CR/CRi assessed by investigators per IWCLL at cycle 9 day 1 Overall response rate (ORR) assessed by investigators per IWCLL criteria and Time To Progression (TTP) Clearance of ibrutinib resistance mutations (BTKC481 and/or PCLγ2 hotspot), defined as less than 1% mutation bearing alleles (Arm B only).	
To characterize the PK of VAY736 and ibrutinib when used in combination therapy	Plasma concentration of VAY736 and ibrutinib, and derived parameters	
To assess immunogenicity (IG) following one or more intravenous infusions of VAY736	Presence of anti-VAY736 antibodies	
[redacted]		

Objective	Endpoint	Analysis
[redacted]		

2 Statistical methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version in the GPS environment. For Bayesian modeling, R (version 3.2.3) and/or JAGS (version 4.6.0) will be used. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 8.3 (or latter version if available).

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patients' data from the dose escalation and dose expansion parts up to the time when all patients have completed at least six cycles of combined treatment with VAY736 and ibrutinib and two cycles of ibrutinib alone or have discontinued the study. The primary CSR will include all outputs planned within the TFL shell document. Additional data for patients continuing to receive study treatment past the data cutoff date of the primary CSR, as allowed by the protocol, will be reported once all patients have discontinued the study. However, only a selection of key outputs (indicated in the TFL shell document) for which additional data was collected will be provided for the final report.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements. All relevant pharmacokinetic (PK) measurements will also be summarized. The summaries will use descriptive statistics for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

In case of intra-subject dose escalation, patient's data from before and after the change in dose will be listed and summarized together under the originally intended dose level/treatment group.

A treatment is defined by the dose level (corresponding to a single combination of doses of VAY736 and ibrutinib) and regimen. During the initial dose-escalation phase of the study, in which the dose of VAY736 will be escalated in combination with a fixed dose of ibrutinib, cohorts of patients with the same treatment will be pooled into one single *treatment group*. Thus, a treatment group may consist of more than one cohort. Patients receiving the same dose of VAY736 under different regimens, Q2W or Q4W, belong to different treatment groups. Specific plans regarding a change in dosing regimen are discussed in Section 2.6.1.1 of the SAP.

Patients treated with the same dose level and schedule of VAY736 will be pooled, for all safety analyses including PK and ADA, into a single treatment group (which may include patients from both the dose-escalation and dose-expansion parts).

For efficacy analyses, data will also be summarized by study part, and within each study arm of the dose expansion part. If multiple dose regimens are observed, summaries will also be produced within each treatment regimen as follows:

- Study parts: dose escalation, dose expansion
- Study arms:

- Dose expansion part:
  - Study arm A (~20 pts): patients with advanced CLL who have been on ibrutinib treatment for more than one year with evidence of residual disease and which places them at risk for clinical relapse.
  - Study arm B (~20 pts): patients with acquired resistance mutations to ibrutinib who have not yet demonstrated clinical relapse.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Investigational treatment will refer to the combination *VAY736 + ibrutinib*. The term investigational treatment may also be referred to as **study treatment**. For consistency across studies, the term study treatment will be used throughout this document.

The expression ***combination therapy*** may also be used to refer to the investigational treatment VAY736+ibrutinib, as defined in the protocol.

Investigational drug will refer to VAY736 and ibrutinib. The terms **investigational drug** and **study drug** are used interchangeably. For consistency across studies, the term study drug will be used throughout this document.

2.1.1.2 Date of first/last administration of study treatment

In the combination arm, the date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of either VAY736 or ibrutinib was administered and recorded on the Dose Administration Record (DAR) eCRFs.

- First and last dose of VAY736 will be as recorded on the Study Treatment - VAY736) eCRF.
- First dose of ibrutinib will be as recorded on the Study Treatment - PK - Ibrutinib eCRF, and
- Last dose of ibrutinib will be as recorded on the Study Treatment – Ibrutinib eCRF.

2.1.1.3 Study day

The study day for ***safety assessments*** (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5. For safety assessments before start of study treatment, the study day is negative and derived by (date of event – start date of study treatment). For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0.

The study day for **other assessments** (e.g., efficacy, [redacted] etc.) will be calculated the same way as safety assessments.

2.1.1.4 Baseline

Baseline is the result of an investigation describing the "true" state before start of study treatment administration.

The last available assessment on or before the date of start of study treatment is taken as "baseline" assessment, unless specified otherwise. Assessments should be done within 21 days prior to the start of study treatment apart from baseline efficacy assessments which can be conducted within 28 days the date of start of study treatment. Height and virology assessments (including HBV and HCV) may also be performed outside of the 21-day window. Other assessments taken outside of the above specified assessment window, will not be considered for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

For the purpose of VAY736 immunogenicity analysis, the baseline assessment will be defined with respect to the date of the first administration of VAY736.

If patients have no measurement meeting the above criteria, the baseline result will be missing.

2.1.1.5 On-treatment assessments

Safety summaries (tables, figures) include only data from the on-treatment period defined below, with the exception of baseline data, which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death, including on-treatment and post-treatment deaths, will be provided. Summary tables for AEs will include only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs), as discussed in Section 2.8.2.1.2.

The overall observation period will be divided, for safety assessments, into three mutually exclusive segments as follows:

Pre-treatment period: from the day of patient's first informed consent to the day before first administration of the study treatment.

On-treatment period: from date of first administration of study treatment to 30 days after the date of last actual administration of VAY736 (including start and stop date).

Post-treatment period: starting at day 31 after last administration of VAY736.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Note that these observational period definitions do not impact the reporting of efficacy assessments; all completed efficacy assessments will be summarized, irrespective of their timing with regard to the above definitions.

2.1.1.6 Date of last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the last complete date reported among the following as seen in Table 2-1:

Table 2-1 Last contact derivation

Source data	Conditions
Last contact date/last date patient was known to be alive from Safety Follow-up page	Patient status is reported to be alive, lost to follow-up, or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from treatment page	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Efficacy assessment date if available	Evaluation is marked as 'done'
Laboratory/Concomitant medication collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g., the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

2.1.1.7 Date of start of alternative cancer therapy

The date of start of alternative cancer therapy is the Start Date of Dose as recorded on the Antineoplastic Therapy Since Discontinuation of Study Treatment – Medication eCRF. Note: The start date of Ibrutinib is not considered as the start of alternative cancer therapy.

2.2 Analysis Set/ Subject Classification/ Withdrawal of ICF/ Subgroups

2.2.1 Analysis sets

Full Analysis Set (FAS)

The Full Analysis Set (FAS) and Safety Set (SS) are defined in the same way and comprise all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received where treatment received is defined as the treatment most frequently taken between Study Day 1 and the end of cycle 1 (the first 28 days of dosing), the onset of a DLT, or treatment discontinuation, whichever occurs first.

Safety Set (SS)

Same as definition of FAS.

Per-Protocol Set (PPS)

Not applicable

Dose-Determining Set (DDS)

The Dose-Determining Set (DDS) includes all patients from the FAS (escalation part) who met the minimum exposure criterion and had sufficient safety evaluations or experienced a dose limiting toxicity (DLT) during cycle 1 (the first 28 days of dosing).

A patient has met the minimum exposure criterion if the patient takes, during the first 28 days, all planned doses of VAY736 and 75% of the planned doses of ibrutinib (i.e., two doses of VAY736 Q2W or one dose of VAY736 Q4W, and ≥ 21 of 28 daily doses of ibrutinib).

Patients who do not experience a DLT during cycle 1 (the first 28 days of dosing) are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur. Patients will be analyzed according to the study treatment received as defined for FAS.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS and an additional patient may be recruited (see VAY736Y2102-CSP-Section 7.1.3.1).

Pharmacokinetic Analysis Set (PAS)

The Pharmacokinetic Analysis Set (PAS) includes all Patients who provide an evaluable PK profile. A profile is considered evaluable if all the following conditions are satisfied:

- Patient receives one of the planned treatments.
- Patient provides at least one primary PK parameter (see Table 2-7 for a listing)
- Patient did not vomit within 4 hours after the dosing of ibrutinib.

Immunogenicity Prevalence Set (IGPS)

he IGPS includes all patients in the FAS with a non-missing baseline IG sample **or** at least one non-missing post-baseline IG sample (applicable for VAY736 only)

Immunogenicity Incidence Set (IGIS)

The IGIS includes all patients in the IGPS with a non-missing baseline IG sample **and** at least one non-missing post-baseline IG sample (applicable for VAY736 only).

See Section 2.8.4.5.2 for further definitions.

2.2.2 Subject Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations (PD) entered in the database and/or on specific classification rules defined in Table 2-2 Classification based on PDs and non-PD criteria.

Table 2-2 Classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Full analysis set	No written informed consent (INCL01)	Patient didn't receive at least one dose of study treatment
Safety set	No written informed consent (INCL01)	Patient didn't receive at least one dose of study treatment
Dose-determining set	No written informed consent (INCL01)	1. The patient does not experience a DLT during the first cycle and does not meet the minimum exposure criterion. 2. The patient does not experience a DLT during the first cycle but has no sufficient safety evaluation (i.e. he has not been observed for the full duration of the first cycle of treatment, and/or is considered by both Novartis and Investigators to have not enough safety data to conclude that a DLT did not occur).
PK Analysis set	No written informed consent (INCL01)	1. Patient didn't receive at least one of the planned treatments 2. Patient didn't provide at least one primary PK parameter 3. Patient vomited within 4 hours after the dosing of ibrutinib
Immunogenicity prevalence set	No written informed consent (INCL01)	Patients without a determinant baseline IG sample or at least one

		determinant post-baseline IG sample
Immunogenicity incidence set	No written informed consent (INCL01)	Patients without a determinant baseline IG sample and at least one determinant post-baseline IG sample

2.2.3 Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g., PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.4 Subgroup of interest

Not applicable.

2.3 Subject Disposition / Demographics / Other Baseline Characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Subject disposition

The following will be tabulated:

- Treatment 1 Disposition/VAY736 Disposition (C1-C6):
  - Number (%) of patients who discontinued treatment with VAY736 and primary reasons for discontinuation
- Treatment 2 Disposition/Ibrutinib Disposition (C1-C9)
  - Number (%) of patients who discontinued treatment with Ibrutinib and primary reasons for discontinuation
- Treatment 3 Disposition/VAY736 Disposition (C7-C9)
  - Number (%) of patients who discontinued treatment with VAY736 and primary reasons for discontinuation
- Post-treatment follow-up
  - Number (%) of patients who discontinued post-treatment follow-up and reasons for discontinuation

2.3.2 Demographic and background data

Demographic data including age, sex, race, ethnicity, height, weight, and ECOG performance status will be listed and summarized. In addition, following age categories will be summarized: 18- <65 years, 65- < 85 years, and ≥ 85 years. Additional baseline characteristics data will be included: ibrutinib resistance mutation, the time (in months) from the start of ibrutinib therapy to the first study treatment, and the results of direct and indirect Coombs tests.

2.3.3 Medical History

A listing of medical history and current medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

2.3.4 Prior antineoplastic therapy

All prior antineoplastic medication, radiotherapy and surgery will be listed. The number (%) of patients who received any prior antineoplastic medication will be summarized.

2.3.4.1 Prior antineoplastic medications

The summary of prior antineoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting at last treatment, time (in months) from last treatment to progression, best hematological response per IWCLL at last treatment (defined to be the best response during the last treatment regimens recorded), and reason for discontinuation at last treatment. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

2.3.4.2 Prior antineoplastic radiotherapy

The listing of prior antineoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each patient).

2.3.4.3 Prior antineoplastic surgery

Data collected on prior antineoplastic surgery will be listed.

2.3.4.4 Partial-date imputation rules for prior antineoplastic therapies

The following partial-date imputation rules will apply:

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used, with the exception of the imputation rule in scenario (B) of Table 2-4, which will be replaced by TRTSTD-1. See Section 2.8.2.1.1.

End Date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

2.3.5 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include stage at initial diagnosis, stage at time of study entry, time (in months) since initial diagnosis, time (in months) from initial diagnosis to first relapse, time (in months) since most recent recurrence/relapse, current extent of disease (metastatic sites).

2.4 Protocol deviations

The full list of protocol deviations will be documented in the Study Specification Document (SSD).

2.5 Treatments (study treatment, concomitant therapies, compliance)

2.5.1 Study treatment

The safety set will be used for all summaries and listings of study treatment.

2.5.1.1 Data handling

2.5.1.1.1 Data analysis

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for each component of study treatment in ***combination therapy***. The duration of exposure will also be presented for the study treatment (VAY736+ibrutinib). Duration of exposure will be categorized into mutually exclusive time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval.

The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment.

Patient-level listings of all doses administered on treatment along with dose change reasons will be produced.

2.5.1.2 Duration of exposure to study treatment

Duration of exposure to study treatment refers to exposure to the combination of ibrutinib and the investigational therapy VAY736. The following exposure durations will be calculated:

(A) Duration of exposure to VAY736 (*days*) = (last date of exposure to VAY736) – (date of first administration of VAY736) + 1

(B) Duration of exposure to ibrutinib (*days*) = (last date of exposure to ibrutinib) – (date of first administration of ibrutinib) + 1

(C) Duration of exposure to study treatment (days) = max(last date of exposure to ibrutinib or VAY736) – (date of first administration of ibrutinib) + 1 will be used for the duration of exposure to study treatment

The last date of exposure to ibrutinib is the last date of dose administration.

The last date of exposure to VAY736 administered Q2W is the last date of administration +13 days.

The last date of exposure to VAY736 administered Q4W is the last date of administration +27 days.

Table 2-2 Definition of last date of exposure of investigational drug

Scenario	Definition of last date of exposure of investigational drug	Example
Scenario 1: Investigational drug with a cyclic administration	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered. Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.	**Example 1:** In a once-a-week administration of an investigational drug, the last date of exposure is the date of administration in the last cycle + 6 days. **Example 2:** In a 21-day cycle with one or several infusions in the beginning of the cycle (e.g., 2 weeks on 1 week off), the last date of exposure is the date of first infusion in the last cycle + 20 days.
Scenario 2: Daily administration of the investigational drug	Date of last administration of a non-zero dose of the investigational drug.	**Example 3**: A patient had a permanent discontinuation of the investigational drug 06-Jan-2013 after being put on a temporary interruption since 01-Jan-2013. In this case the last date of exposure is 31-Dec-2012.

2.5.1.3 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components, VAY736 and ibrutinib, respectively.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment. For VAY736, this is documented in the VAY736 Dose Administration eCRF.

For ibrutinib, **the planned and actual dose** is the first non-zero dose as recorded on the Study treatment – PK - Ibrutinib eCRF. Any periods of dose interruption or reduction are be recorded in the change log.

For patients who did not take any drug, the actual cumulative dose is equal to zero for that drug.

For VAY736, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period, and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For ibrutinib, the actual cumulative dose is calculated as the planned dose, multiplied by the duration of exposure to ibrutinib, accounting for any periods of dose interruptions. The planned cumulative dose is the dose is calculated as the planned dose multiplied by duration of exposure to ibrutinib.

2.5.1.4 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*dosing unit / unit of time*) = Actual Cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

For example, the dosing unit for VAY736 is mg/kg and the unit of time is 14 days:

*DI (mg/kg/14 days) = 14 * Actual Cumulative dose (mg/kg) / Actual duration of exposure*

*= 14 * Actual cumulative dose (mg/kg) / [Last dosing date – First dosing date + Dose interval (14 days)]*

For Ibrutinib the dosing unit is mg, and the unit of time is day (mg/day):

DI (mg/day) = Actual Cumulative dose (mg) / Actual duration of exposure (day)

= Actual cumulative dose (mg) / [Last dosing date – First dosing date + Dose interval (1 day)]

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (dosing unit / unit of time) = Planned Cumulative dose (dosing unit) / Duration of exposure (unit of time).

For example, the dosing unit for VAY736 is mg/kg and the unit of time is 14 days:

*DI (mg/kg/14 days) = 14 * Planned Cumulative dose (mg/kg) / Duration of exposure*

For Ibrutinib the dosing unit is mg, and the unit of time is day (mg/day):

DI (mg/day) = Planned Cumulative dose (mg) / Duration of exposure (day)

Relative dose intensity (RDI) is defined as follows:

RDI = DI (*dosing unit / unit of time*) / PDI (*dosing unit / unit of time*).

As an example, the RDI for VAY736 is defined as:

RDI = DI (mg/kg/14 days) / PDI (mg/kg/14 days)

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. The duration of exposure considered for the derivation of the DI and the RDI will be derived from the start date of study treatment to the end of the last cycle initiated irrespective of date of death, last contact date for withdraw consent and cut-off date.

RDI will be summarized as a percentage. Summary of RDI may include categorical summaries, based on clinically meaningful intervals; see SAP Section 2.5.3.

2.5.1.5 Dose reductions, interruptions, or permanent discontinuations

The number of patients who have dose reductions or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted' and 'Dose changed' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions and dose changes, respectively.

Dose reduction: a dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered is lower than the prescribed dose. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on dose change flag and the change and the direction of the change. Dose reduction will be reported for VAY736 only.

Dose interruption: Actual dose administered equal to zero, between the first and last non-zero doses, following a non-zero actual dose administered. Dose interruption is collected as such in the treatment page eCRF. Number of dose interruptions and corresponding reason will be summarized.

- For VAY736, 'Dose interrupted' field from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions.
- For ibrutinib, dose interruptions will be captured in the dose change log.

The corresponding fields 'Reason for dose change/dose interrupted' will be used to summarize the reasons. For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive doses with different reasons, they will be counted as separate interruptions. However, if the reason is the same in these mentioned multiple entries on consecutive doses, then it will be counted as one interruption.

2.5.2 Prior, concomitant and post therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and

blood transfusions) administered in the study and are recorded in the Concomitant Medications and Prior or Concomitant non-drug therapies/procedures eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Significant non-drug therapies will use MedDRA coding.

Any concomitant therapies starting prior to or after the start of study treatment will be listed.

A separate listing will be provided for instances of concomitant, limited-field palliative radiotherapy to non-target lesion(s). Per protocol VAY736Y2102-CSP-Section 6.4, such concomitant therapies are allowed, and will be recorded on the Concomitant radiotherapy/surgery case report form (CRF) page.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.8.2.1.1 for AE date imputation rules). No imputation will be performed for concomitant medication end dates.

2.5.3 Compliance

Compliance to the study treatment will be summarized in terms of the RDI. The predefined RDI categories are < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients falling in each category will be presented.

2.6 Analysis of the primary objective

The primary objective is to characterize the safety and tolerability of the combination of VAY736 with ibrutinib, and to determine the MTD or RDE for the combination.

The following primary endpoints are of interest in both the dose-escalation and dose-expansion parts of the study.

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Changes in laboratory parameters and vital signs
- Dose interruptions, reductions, and dose intensity

The dose-escalation part will study an additional endpoint:

- Incidence of DLTs during the first treatment cycle of the investigational treatment.

For the analysis of safety and tolerability endpoints see VAY736Y2102-CSP-Section 10.5.3, in addition to analysis of the DLT rate as below.

2.6.1 Reports of DLT analysis

A dose-limiting toxicity (DLT) is defined as a clinically relevant adverse event or abnormal laboratory value or dose reduction due to AE which occur ≤ 28 days following the first administration of study treatment as defined in VAY736Y2102-CSP-Section 6.2.4, Table 6-3.

The MTD (or RD) will be estimated in the dose-escalation part of the study by modeling the probability of DLT occurrence in Cycle 1 for patients in the dose-determining set (DDS). This probability is estimated by the statistical models in Section 2.6.1.1.

The following reports will be produced based on the dose determining set:

- A plot of posterior interval probabilities will be presented in the body of the CSR;
- Summary of the DLTs with onset during the evaluation period (dose escalation part only) by primary system organ class, preferred term: recommendations at the time of database lock will be included in the body of the CSR. Summaries of recommendations from each dose escalation meeting (DEM) will be included in Appendix 16.1.9 of the CSR;
- Listing of inferential results from the BLRM at the time of database lock, will be included in Appendix 16.1.9.

The Bayesian model for DLT rates is described in the next section.

2.6.1.1 Statistical hypothesis, model, and method of analysis

Identification of a recommended dose

Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in cycle 1 for patients in the DDS. A recommended dose below the MTD may be identified based on other safety, clinical, PK, and PD data (see VAY736Y2102-CSP-Section 6.2.3).

Bayesian adaptive approach

The dose escalation part of this study will be guided by a Bayesian analysis of Cycle 1 dose limiting toxicity (DLT) data for VAY736 and ibrutinib. The Bayesian analysis will be based on a model with three parts, representing:

- Single agent VAY736 toxicity
- Single agent ibrutinib toxicity
- Interaction

The single-agent toxicities are modeled as follows. Let $\pi_1(d_1)$ be the risk of DLT of the first cycle for VAY736 given as a single agent at total cycle 1 dose d_1 (Q2W VAY736 dose mg/kg $*$ 2); $\pi_2(d_2)$ be the risk of DLT of the first cycle for ibrutinib given as a single agent at daily dose d_2 (mg) . These single agent dose-DLT models are logistic:

$$\text{VAY736:} \quad \text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*) \qquad (1)$$

$$\text{Ibrutinib:} \quad \text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*) \qquad (2)$$

where $d_1^* = 3.0$ mg/kg total cycle 1 dose (1.5mg/kg $*$ 2) and $d_2^* = 420$ mg daily are used to scale the doses of VAY736 and ibrutinib, respectively. Hence, α_1 and α_2(>0) are the single-agent odds of a DLT of the cycle 1 at 3.0 mg/kg total cycle 1 dose and 420 mg daily, respectively; and β_1 and β_2 (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

Under no interaction, the risk of a DLT at dose d_1 of VAY736 and dose d_2 of ibrutinib is:

$$\pi_{12}^0(d_1, d_2) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)$$

To allow for interaction between VAY736 and dose d_2 of ibrutinib, an odds multiplier is introduced. The risk of DLT for combination dose (d_1, d_2) is then given by:

$$\text{odds}\left(\pi_{12}(d_1, d_2)\right) = \exp(\eta \times d_1/d_1^* \times d_2/d_2^*) \times \text{odds}\left(\pi_{12}^0(d_1, d_2)\right)$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; and η is the log-odds ratio between the interaction and no interaction model at the reference doses. i.e., 3.0 mg/kg(1.5 mg/kg $*$ 2) of total cycle 1 VAY736 and 420 mg of daily ibrutinib. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity, respectively.

Specifications of the prior distributions for $\alpha_1, \alpha_2, \beta_1, \beta_2$, and η are given in VAY736Y2102-CSP-Section 14.2.2.

Assessment of patient risk

After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principle (Rogatko et al 2007). A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 25%.

Dose recommendations

At each dose-escalation meeting, summaries of the posterior distribution of DLT rate will be listed for each dose. In particular, the posterior probabilities of the three toxicity intervals will be listed for each provisional dose level. Complete guidelines for dose-escalation decision making are given in VAY736Y2102-CSP-Section 6.2.3.

Change in dose schedule

In the case that additional dosing schedules for VAY736Y are explored during dose-escalation, a BLRM of the same functional form will be used to estimate the dose-DLT relationship for each new schedule. Data from previous or concurrently explored schedules will be used to inform the dose escalation for the new schedule. At each time the decision is taken to explore a new schedule, the model to be used to guide escalation in that schedule will be constructed. The model will be finalized prior to first patient treated under the new schedule and will be documented in full in CSR Section 16.1.9. The details may refer to VAY736Y2102-CSP-Section 14.2.

In addition, in case VAY736Y Q2W dosing schedule continues, and a new dosing schedule is explored during dose-escalation, a BLRM of the same functional form described in VAY736Y2102-CSP-Section 14.2 will be used to estimate the dose-DLT relationship for each schedule based on a newly derived prior incorporating the historical trial data and the on-study data from previous schedule.

2.6.2 Handling of missing values/censoring/discontinuations

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

Patients with unknown or missing response and who are treated in the study but provide no information on response at the end of treatment will be treated as non-responders and will be included in the denominator when calculating CR/CRi rate or ORR.

2.6.3 Supportive and sensitivity analyses

Additional [redacted] supportive analyses will be conducted, if appropriate, [redacted]

2.7 Analysis of the key secondary objective

Not applicable.

2.8 Analysis of other secondary objective(s)

2.8.1 Efficacy analysis

Evaluation of anti-tumor activity will be based on investigators' assessment per IWCLL criteria (see VAY736Y2102-CSP-Appendix 1 for details) as documented in the eCRF. The variables used to evaluate anti-tumor activity are CR/CRi rate, clearance of ibrutinib resistance mutations, overall response rate (ORR), and time to progression (TTP). Analyses of these variables will use the FAS, including patients from both the escalation and expansion parts. All analyses will be provided by dose level in dose escalation and by two arms in dose expansion.

Rate of CR/CRi at C9 for expansion arm A and arm B: The proportion of patients with CR or CRi assessed by investigators per IWCLL criteria (see VAY736Y2102-CSP-Appendix 1 for details) at C9 will be provided. The rate of CR/CRi at C9 is the primary endpoint for the evaluation of anti-tumor activity and will be analyzed for each expansion arm using a Bayesian modeling approach.

A minimally informative beta distribution is used as prior distribution with parameters a=0.25 and b=1. This assumes, *a priori*, that the response rate is 20%.

Posterior summaries for CR/CRi rate (posterior mean, including 90% credible intervals and the posterior probability that the true CR/CRi rate falls in the activity intervals defined below) will be provided:

Posterior probability of response rate intervals:

- [0, 20%) – clinically not meaningful
- [20%, 40%) – moderate clinical benefit
- [40%, 100%] – superior clinical benefit

In addition, exact confidence interval (90% CI) also will be provided.

To determine which response assessments occurred at C9, response assessment dates within a window of +/- 3 days of patient's Cycle 9 visit start date or end date will be considered as C9 responses.

Clearance of ibrutinib resistance mutation for expansion arm B is defined as less than 1% mutation bearing alleles (BTKC481 and/or PCLγ2) during treatment (up to C9). The proportion of patients with negative mutation, where negative mutation is defined as having clearance of the baseline ibrutinib resistance mutation, will be provided along with corresponding 90% exact confidence interval (CI). Note that only R665, S707, A708 and L845 variants will be considered as functional PLCγ2 mutations. Other PLC γ2 variants will not be considered for this analysis.

Overall response rate (ORR) is defined as the proportion of patients with best overall response (BOR) of complete response (CR), complete response with incomplete marrow recovery (CRi), or partial response (PR), as assessed by investigators per IWCLL criteria (see VAY736Y2102-CSP-Appendix 1 for details) and will be calculated based on all response evaluations. The ORR will be calculated by dose level in dose escalation and by arm in dose expansion, and overall, and will be presented along with corresponding 90% exact confidence intervals (CI). Assessments taken after the start of alternative cancer therapy will be excluded.

Time to progression (TTP) is the time from start of treatment to the date of event which is defined as the first documented progression (defined as overall disease response assessment of PD) or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate disease assessment. Assessments taken after the start of alternative cancer therapy will be excluded.

Median TTP (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (TTP rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (3, 6, 12, 18 and 24 months) will be presented. The number (%) of progressions, deaths and patients censored will also be summarized.

2.8.2 Safety analyses

The Safety Set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

2.8.2.1 Adverse events (AEs)

2.8.2.1.1 Data handling and AE date imputation rules

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

A missing AE start date will be imputed using the following logic matrix described in Table 2-3.

Table 2-3 Imputation rules for a partially missing AE start date

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started
TRTM: Month treatment started; TRTY: Year treatment started

Table 2-4 is the legend to the logic matrix shown in Table 2-3 and details the relationship of AE start date to study treatment start date.

Table 2-4 Imputation legend and AE/treatment start date relationship

	AE start date relationship	Imputation
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B)	Uncertain	TRTSTD+1
(C)	Before treatment start	15MONYYYY
(D)	Before treatment start	01JULYYYY
(E)	After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for AE end dates.

All events with a start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing. The same rule will be applied to adverse events starting before or on the cut-off date and not having a documented end date. No imputation will be performed for missing/incomplete AE end dates.

2.8.2.1.2 Data analysis

AE Summaries (CSR outputs)

AE summaries will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. All AEs collected in the AE (e)CRF page will be listed along with

the information collected on those AEs e.g., AE relationship to study drug, AE outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational arm.

The following adverse event summaries will be produced by treatment:

- Overview of adverse events (number and % of patients with any AE, any SAE any fatal SAE, any dose reductions/interruptions, AE leading to discontinuation, AE requiring additional therapy);

The following adverse event summaries will be produced by treatment and maximum grade (All grades and Grade >=3):

- AEs by SOC and PT, regardless of relationship to study treatment and suspected to be related to study treatment;
- Serious adverse events by SOC and PT, regardless of relationship to study treatment and suspected to be related to study treatment Leading to treatment discontinuation;
- AEs leading to dose interruption/adjustment;
- AEs Requiring additional therapy;
- Dose limiting toxicities by SOC and PT;

The following listings will be produced:

- All adverse events (safety set)

Deaths (CSR Outputs)

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment arm, system organ class (SOC) and preferred term (PT).

All deaths will be listed for the safety set, and post-treatment deaths will be flagged.

The death summaries cover patients from the Safety Set.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables treatment-emergent adverse events (30 days after the administration of last study treatment, for definition of last study treatment, see Section 2.1.1.2) which are not serious adverse events with an incidence greater than 5% and treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a single subject, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Only disclosure to clinicaltrials.gov is applicable for this trial. As there are no study sites based in the European Union (EU), no disclosure to EudraCT will be made.

DSUR – Development Safety Update Report

For the purpose of Development Safety Update Report (DSUR) reporting, estimates of overall cumulative patient exposure to study treatment by sex and age will be provided for the Safety Set, as required.

2.8.2.2 Adverse events of special interest/ grouping of AEs

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to investigational drug(s) VAY736.

These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), high level group terms, high level terms, and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on-treatment period will be summarized.

Selected AEs are described in the VAY736 electronic Case Retrieval Sheet (eCRS) – indication: Waiha, itp, cll, nhl. Summaries of these AESIs will be provided by safety topic.

A listing of all grouping levels down to the MedDRA PTs, based on the electronic Case Retrieval Strategy, used to define each AESI will be generated.

2.8.2.3 Laboratory data

2.8.2.3.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory

CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in the Appendix 5.3 of the SAP, Section 5.3. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 4.03 results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

The following summaries will be produced separately for hematology and chemistry:

- For parameters with CTC grades: Shifts from baseline to the worst post-baseline CTC grade,
- For parameters with no CTC grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications,

The following listings will be produced:

- Any laboratory observations with CTCAE grade of 3 or 4.

Table 2-3 below lists all hematology and chemistry laboratory parameters that will be summarized.

Table 2-3 Local clinical laboratory parameters to be summarized

Test category	Test Name
Hematology	Hematocrit, Hemoglobin (Hemoglobin increments will not be presented), MCV, Platelets, White blood cells, Differential (Basophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Bicarbonate, Corrected Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN), Uric Acid, Amylase, Lipase, Non-fasting Glucose

2.8.2.3.2 Imputation rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

The following rules will be applied to derive the WBC differential counts and associated normal ranges when only percentages are available for Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, or other differential:

xxx count = (WBC count) * (xxx %value / 100)

If normal ranges are not available for certain differentials, then these differentials will not be presented.

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

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

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

2.8.3 Other safety data

2.8.3.1 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Notable vital signs collected during the on-treatment period will be summarized. Values measured during the post-treatment period will be flagged in the listings. The number and percentage of patients with notable vital sign values (high/low) as seen in Table 2-6 below will be presented by treatment arm.

Table 2-6 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase >= 10% from baseline	decrease >= 10% from baseline
Systolic blood pressure (mmHg)	>=180 and increase from baseline of >=20	<=90 and decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 and increase from baseline of >=15	<=50 and decrease from baseline of >=15
Pulse rate (bpm)	>=100 and increase from baseline of >25%	<=50 and decrease from baseline of >25%
Body temperature (°C)	>= 39.1	--

2.8.4 Pharmacokinetic analysis

PK parameters will be determined using non-compartmental method(s) for VAY736 and ibrutinib. PK parameters such as those listed in Table 2-7 will be estimated and reported, when applicable. For ibrutinib, PK parameters determined will be only AUClast, Cmax, Tmax, Tlast, and if applicable other PK parameters (eg AUC0-t). The PAS subset of patients will be used in all pharmacokinetic data analysis and summary statistics.

Table 2-7 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) after first dose and at steady-state (amount x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time^{-1})
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)
Racc	Accumulation ratio should be calculated using AUC values obtained from a dosing interval

2.8.4.1 Data handling principles

All concentrations below the lower limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters, unless otherwise stated under the Pharmacokinetic Analysis Set.

At the time of analysis, concentration data from patients may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These patients and concentration data points will be identified at the time of analysis.

2.8.4.2 Data analysis set

All pharmacokinetic data analyses and PK summary statistics will be based on PAS. Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.

2.8.4.3 Basic tables, figures, and listing

Descriptive statistics will be presented for all pharmacokinetic parameters, as described below.Table 2-8 Descriptive analysis

Parameters	Descriptive statistics
AUC(1), Cmax, CL/F, Vz/F, $T_{1/2,}$ Racc	Mean, standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
$T_{max,}$ Tlast	Median, minimum, and maximum.
(1) Includes AUCtau, AUClast (or all AUC parameters) CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100 Note: For ibrutinib, PK parameters determined will be only AUClast, Cmax, Tmax, Tlast, and if applicable other PK parameters (eg AUC0-t).	

Zero concentrations will not be included in the geometric mean calculations. Tmax will be summarized in terms of median values and ranges. Missing concentrations or PK parameter values will not be imputed. A listing of derived PK parameters per subject will be produced by treatment group.

2.8.4.4 Dose proportionality

The analysis of dose proportionality may be conducted for AUCtau and Cmax of VAY736 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in the summary table.

Cmax and AUC will be used for dose proportionality analysis using the power model (Gough 1995). The power model empirical relationship between a PK parameter and dose is of the form

$$PK = Exp(\alpha)(dose)^{\beta},$$

where "PK" represents the PK parameter AUC or Cmax. For analysis, this equation is log-transformed (natural log), obtaining the equation

$$\log_e(PK) = \alpha + \beta \log_e(Dose),$$

The slope beta measures the dose-proportionality between Dose and the PK parameter.

To test for dose proportionality, the confidence interval criteria for assessment of dose proportionality from Smith et al. (2000) will be used. The a *priori* acceptance range for the slope, according to Smith, is given by:

$$1 + \frac{Ln(0.8)}{Ln(dose\_ratio)} < \beta < 1 + \frac{Ln(1.25)}{Ln(dose\_ratio)}$$

Where 1.25 and 0.8 are the critical *a priori* values suggested by regulatory authorities for any bioequivalence problem after a data log transformation, and "*dose_ratio*" is the ratio of the largest to the smallest dose. Dose proportionality can be claimed if the 90% confidence interval for the slope is entirely contained within this a *priori* range.

2.8.4.5 Immunogenicity

The presence and/or concentration of anti-VAY736 antibodies (Anti-Drug Antibody) will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics to assess IG following one or more intravenous infusion of VAY736.

2.8.4.5.1 Sample ADA Status

Each IG sample is assessed in a three-tiered anti-drug antibody (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for VAY736 (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered as ADA positive. Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut-point: ADA positive (yes) or ADA negative (no), or 'NOT REPORTABLE'.
- Titer (for positive samples): Numerical representation of the magnitude of ADA response.

Fold titer change (i.e., 4-fold): threshold for determining treatment boosted
The following definitions apply only to non-missing samples:

- ADA-negative sample: sample where assay is ADA negative
- ADA-positive sample: sample where assay is ADA positive.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding non-missing baseline sample. To be classified as treatment-boosted or treatment-unaffected, both the post-baseline and baseline titer must be non-missing:

- treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline.
- treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with titer that is at least x-fold greater than the ADA-positive baseline titer.
- treatment-unaffected ADA-positive sample: ADA-positive sample post-baseline with titer that is less than x-fold greater than the ADA-positive baseline titer.

The following summaries of ADA sample status (n and %) will be provided using Immunogenicity prevalence set:

- ADA-positive samples (i.e., ADA prevalence), overall and by time point (including baseline). For summaries by time point, the denominator is the number of patients at that time point with a non-missing sample.

2.8.4.5.2 Patient ADA Status

Any IG sample collected after 140 days of the last dose of VAY736 will not be used for summaries or derivations and will only be included in the listing.

Patient ADA status is defined as follows:

- Treatment-induced ADA-positive patient: patient with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- Treatment-boosted ADA-positive patient: patient with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- Treatment-unaffected ADA-positive patient: patient with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- Treatment-reduced ADA-positive patient: patient with ADA-positive sample at baseline and at least one post baseline sample, all of which are ADA-negative samples.
- ADA-negative patient: patient with ADA-negative sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify for any of the above definitions

Listings will be provided for patient ADA status using the IGIS.

The following summaries of ADA patient status (n and %) will be provided using the IGIS:

- Patients with ADA-negative sample at baseline
- Patients with ADA-positive sample at baseline
- ADA-negative Patients
- Treatment-boosted ADA-positive patients; denominator is the number of patients with ADA-positive sample at baseline.
- Treatment-induced ADA-positive patients; denominator is the number of patients with ADA-negative sample at baseline.
- ADA-negative patients: denominator is the number of patients in Immunogenicity incidence set.
- ADA-inconclusive patients
- ADA-positive patients (i.e., ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive patients; denominator is the number of patients in Immunogenicity incidence set.

[redacted].

2.9 Interim analysis

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose of VAY736 in combination with ibrutinib has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in VAY736Y2102-CSP-Section 6.2.3.

3 Sample size calculation

3.1.1 Dose-escalation part

No formal statistical power calculations to determine sample size were performed for this study.

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD/RDE level, as described in VAY736Y2102-CSP-Section 6.2. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RDE for further elaboration of safety and pharmacokinetic parameters as required. Minimum of fifteen patients are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

3.1.2 Dose-expansion part

During dose expansion, additional patients will be enrolled to gain more information about the safety and tolerability of VAY736 in combination with ibrutinib, to obtain additional PK/PD data and to obtain preliminary anti-tumor activity for two expansion arms.

VAY736 in combination with ibrutinib will enroll two groups of approximately 20 patients each receiving the MTD or RDE study treatment, the probability to detect AEs with a true incidence rate of 10% is 87.8% with 20 patients or 98.5% with 40 patients (Table 3-1).

Table 3-1 Probability to detect at least one special adverse event of interest

Special AE of interest incidence rate			
	20	30	40
2.5%	0.397	0.532	0.637
5%	0.642	0.785	0.871
10%	0.878	0.958	0.985
15%	0.961	0.992	0.998

In addition, evaluation of CR/CRi rate at Cycle 9 as defined by IWCLL guidelines is the secondary objective in dose expansion part.

Table 3-2 below shows the 90% credible intervals for N=20 for the arm A/arm B in expansion, with different response rates using a minimally informative beta distribution as prior distribution with parameters a=0.25 and b=1. This assumes *a priori* response rate of 20%. Note that the final interval will depend on the final sample size.

8 responses observed out of 20 patients will provide 3%, 53%, 44% chance that there is no clinical benefit, moderate clinical benefit, and superior clinical benefit as defined above, respectively.

Table 3-2 Posterior summaries based on assumed observed responses (CR/CRi at C9) and 20% prior assumption

Observed CR/CRi (x/N)	Posterior mean (90% credible interval)	Probability of no clinical benefit [0% - 20%]	Probability of moderate clinical benefit (20% - 40%]	Probability of superior clinical benefit (40%-100%]
3/20	.153 (.048,.295)	.756	.240	.005
4/20	.200 (.078,.354)	.544	.436	.020
6/20	.294 (.147,.464)	.170	.687	.143
8/20	.388 (.224,.565)	.026	.530	.443
10/20	.482 (.309,.658)	.002	.223	.775

4 Change to protocol specified analyses

1. In protocol v06, one secondary efficacy objective as outlined in Section 10.5.2 is Rate of CR at C9 for expansion arm A and arm B.
   - In SAP Sections 2.8.1, 3.1.2,
2. In protocol v06 Section 10.5.2: Overall response rate (ORR) is defined as best overall response (BOR) of complete response (CR) or partial response (PR), assessed by investigators per IWCLL criteria (see Appendix 1 for details). ORR for each expansion arm along with corresponding 90% exact confidence interval (CI) will be provided.
   - In SAP Section 2.8.1, based on clinical team discussion, overall response rate (ORR) is updated and now defined as the proportion of patients with an overall disease response at C9 of complete response (CR), complete response with incomplete marrow recovery (CRi), or partial response (PR), as assessed by investigators per IWCLL criteria. The rationale is to include the additional response assessment category, CRi.
3. In protocol v06 Section 10.5.4, immunogenicity analyses are discussed to study the presence and/or concentration of anti-VAY736 antibodies (Anti-Drug Antibody).
   - SAP Sections 2.2.1, 2.2.2, 2.8.4.5.1 and 2.8.4.5.2 were added and/or modified to include the standard definitions for immunogenicity analysis sets, ADA sample status and ADA patient status, so that the immunogenicity analyses can be properly defined and performed.
4. [redacted]
   - In SAP Section 2.9.5, based on clinical team discussion, the definition of [redacted] so this is additionally updated.
5. In protocol v06 Section 14.1 Appendix 1 – Guidelines for NCI CLL Working Group 2018 (IWCLL), the guidelines consist of four response categories: CR, PR, SD, and PD.

- In SAP Section 5.2, the guidelines for efficacy evaluations for CLL studies were added. This includes updating the response categories have been updated to include two additional responses: complete response with incomplete marrow recovery (CRi) and Unknown, because the 2018 IWCLL criteria guidelines specify CRi and Unknown as possible responses. The new appendix aligns with TCO standard language. It also now specifies TTP censoring rules that were not previously detailed in the SAP.

6. In Protocol v06, Sections 6.6.1.1, 7.2.3.1, and 10.1.5, vomiting within 8 hours of ibrutinib administration should be collected, and the time (using the 24-hour clock) of vomiting should be recorded in the adverse events eCRF.
   - In SAP, after discussions with clinical and PKS line functions, we have updated this to vomiting within 4 hours of ibrutinib administration. The eCRF was not per-protocol for unknown reasons and instead collected vomiting with 4 hours of dosing. PKS confirmed that 4 hours of monitoring should be sufficient for ibrutinib based on Tmax half-life and standards.
7. In Protocol v06, Section 10.1.4, the definition of the Dose-determining analysis set (DDS) includes patients from the FAS from both the expansion and escalation parts of the study.
   - In SAP, patients from the expansion parts of the study will not be included as part of the definition of the DDS to align with Section 6.2.4 and Section 10.4.1 in the Protocol which clearly specify that DLTs will be reported for the escalation part of the study.
8. In Protocol v06, Section 10.4.1, changes in electrocardiograms are considered as part of the primary objective.
   - In SAP, reference to ECG monitoring and analysis as part of the primary objective was removed to align with Table 3-1 Objectives and related endpoints of the Protocol.
9. In Protocol v06, Section 10.5.3.4 a listing of ECG evaluations for all patients with at least one abnormality should be presented.
   - In SAP, as ECG is not considered part of the study objectives, no ECG data will be listed.

5 Appendix

5.1 Imputation rules

All imputation rules were defined in previous sections of the SAP, as referenced below.

5.1.1 Study drug

See Section 2.5.1.1.

5.1.2 AE date imputation

See Section 2.8.2.1.1.

5.1.3 Concomitant medication date imputation

Same as AE date imputation; see Section 2.5.2 for discussion of concomitant medication summaries, and Section 2.8.2.1.1 for the imputation rule.

5.1.4 Prior and post antineoplastic therapies date imputation

See Section 2.3.4.

5.1.5 Other imputation

When a date of diagnosis or date of relapse/recurrence/progression or previous progression is recorded as a partial date, the missing day is imputed to the 1st of the month (e.g., DEC2021 imputed to 01DEC2021) and if the day and month are both missing then the missing date is imputed to 1st of January of that year (e.g., 2021 imputed to 01JAN2021).

If the imputed date of relapse/recurrence/progression or previous progression is less than the date of diagnosis or prior antineoplastic therapy, use the date of diagnosis or the start of prior antineoplastic therapy as the imputed date of relapse/recurrence/progression or previous progression, respectively. Instances where time to progression is before last antineoplastic therapy will not be included in the summary tables.

5.2 Guidelines for efficacy evaluation in chronic lymphocytic leukemia (CLL) studies1

5.2.1 Introduction

This document provides the working definitions and specifications for a consistent and efficient analysis of efficacy for VAY736 clinical studies in chronic lymphocytic leukemia (CLL). The current document is written primarily for the relapse and refractory disease setting. Modifications may be indicated for earlier disease settings.

This document is based on the updated National Cancer Institute (NCI) sponsored response guidelines of CLL authored by the International Workshop on CLL (iwCLL) (Hallek et al 2018).

The objectives of this document are to:

- Ensure that the definitions of responses in a clinical study protocol correctly reflect the above-mentioned guidelines.
- Provide guidance for the response assessment and clinical monitoring to ensure consistency in applying the guidelines.

Moreover, this document describes data handling and derivation rules. Respective sections may be used in the statistical analysis plan (SAP) to provide further details. Relevant sections of this document will be copied into individual clinical trial protocols as appendix to the protocol.

5.2.2 Efficacy assessment

5.2.2.1 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following are recorded:

5.2.2.1.1 Lymphadenopathy

Throughout this document, a nodal lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and the long axis is ≥ 1.5 cm, regardless of the length of the short axis. A measurable nodal lesion must become < 1.5 cm in long axis to be considered normalized.

Index nodal lesions are selected from the measurable nodal lesions. A minimum of one measurable index nodal lesion and maximum of six of the largest dominant nodal lesions should be documented at baseline and assessed throughout the study. If a patient has no measurable nodal disease at baseline, then it would be acceptable that no index nodal lesions be identified. Index nodal lesions should be from disparate regions of the body (e.g., neck, chest, abdomen, and pelvis) including mediastinal and retroperitoneal areas of disease whenever these sites are involved. Two perpendicular dimensions must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion. The response of lymphadenopathy is based the sum of the products of diameters (SPD) of all index lesions (up to 6) assessed by image and the sum of the longest diameters of all index lesions (up to 6) assessed by physical exam. One CT scan should be performed before randomization/enrollment/start of treatment as baseline and a second CT scan at time of establishing response for lymphadenopathy, if abnormal at baseline. Additional CT scan may

be required in the protocol. When both CT and physical exam measurements are available for a lesion, CT result overrules physical exam measurement.

5.2.2.1.2 Hepatomegaly and spenomegaly

The presence of enlarged spleen or liver before randomization/enrollment/start of treatment on the basis of CT scan and physical exam should be recorded on the corresponding CRF at baseline. If there is hepatomegaly or splenomegaly at baseline, CT scan of the abdomen with liver and spleen measurements should be performed at time of establishing complete remission. Post-baseline CT may not be needed if no hepatomegaly and/or splenomegaly is detected at baseline. Additional CT scan maybe required in the protocol. The radiological responses of hepatomegaly and splenomegaly are based on the measurement of the largest diameter.

5.2.2.1.3 Blood lymphocytes

Blood lymphocytes will be recorded before randomization/enrollment/start of treatment (baseline) and reevaluated at every assessment of response as well as at the end of study.

5.2.2.1.4 Marrow

Status of bone marrow involvement by CLL before randomization/enrollment/start of treatment will be assessed and collected and subsequent samples can be obtained for comparison (as specified in the protocol or as clinically indicated) as well as for confirmation of CR/CRi if CR/CRi is indicated by clinical and laboratory evaluations. Bone marrow reports will be recorded on the corresponding CRF and should describe cellularity, lymphocyte infiltration, and [redacted]. MRD assessments by flow cytometry and/or next generation sequencing may be recommended in the protocol.

5.2.2.1.5 Platelet count, hemoglobin and neutrophils

Platelet count, hemoglobin and neutrophils will be recorded before randomization/enrollment/start of treatment (baseline) and reevaluated at every assessment of response as well as at the end of study.

5.2.2.1.6 Other (Constitutional symptoms, transfusions, disease transformation)

Constitutional symptoms should resolve completely in patients who have achieved CR/CRi. Constitutional symptoms in patients with CLL are CLL disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

Constitutional symptoms are defined as any of the following disease-related symptoms as assessed and reported (present vs. absent) by the Investigator:

a. Unintentional weight loss of 10% or more within the previous 6 months;
b. Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities);
c. For patients who are not neutropenic with ANC > 500, fevers equal or higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
d. Night sweats for 1 month or more without evidence of infection.

Constitutional symptoms will be recorded before randomization/enrollment/start of treatment (baseline) and reevaluated at every assessment of response as well as at the end of study.

Transfusions (red blood cells, platelets, plasma) received by the patient within 7 days of blood response assessments will be noted in the CRF.

In patients with evidence of transformation, histological evaluation (biopsy of the involved lesion) may be recommended for confirmation in the protocol.

5.2.2.2 Baseline evaluation

The following assessments are mandatory at baseline:

- Peripheral blood for lymphocytes, platelet, hemoglobin, and neutrophils, including evaluation of minimal residual disease (Section 5.2.2.1.1 and Section 5.2.2.1.5)
- Lymphadenopathy (CT plus physical exam) (Section 5.2.2.1.1)
- Hepatomegaly (CT plus physical exam) (Section 5.2.2.1.2)
- Splenomegaly (CT plus physical exam) (Section 5.2.2.1.2)
- Bone marrow aspirate and/or biopsy (Section 5.2.2.1.4)
- Constitutional symptoms (Section 5.2.2.1.6)
- [redacted]

For disease status at baseline, the most current disease assessment for lymph node, liver, spleen, bone marrow, constitutional symptoms and blood count within the protocol specified window should be used as the baseline reference.

5.2.2.3 Post-baseline overall disease response evaluation

The post-baseline evaluation of overall disease response is a composite of the individual responses from peripheral blood count, lymph node, spleen, liver, bone marrow and constitutional symptoms etc.

Treatment discontinuation for any reason not related to new antineoplastic therapy will be handled using the treatment policy strategy: Tumor assessment data collected after discontinuation of study treatment will be used to derive BOR.

5.2.2.3.1 Component and timing of overall disease response evaluation

An overall disease response evaluation must consist of all of the following components:

- Peripheral blood for lymphocytes, platelet, hemoglobin and neutrophils (Section 5.2.2.1.3 and Section 5.2.2.1.5).
- Lymphadenopathy (Section 5.2.2.1.1)
- Hepatomegaly (Section 5.2.2.1.2)
- Splenomegaly (Section 5.2.2.1.2)

Please note post-baseline CT scans for lymph node are required at time of establishing response if these sites are abnormal at baseline or as specified per individual protocol. If there is hepatomegaly or splenomegaly at baseline, CT scan of the abdomen with liver and spleen measurements should be performed at time of establishing complete remission.

In addition,

- Post-baseline bone marrow aspirate and/or biopsies (Section 5.2.2.1.4) for morphologic assessment of cellularity, lymphocytic infiltration and [redacted] are required to demonstrate that a patient has achieved response in bone marrow for the first time. Following initial achievement of response, a bone marrow biopsy or aspirate will not be required unless it is clinically indicated (e.g. improvement from initial response, progression, cytopenia of uncertain cause etc.) or as specified per individual protocol. [redacted]
- Evaluation of constitutional symptoms (Section 5.2.2.1.6) is required to demonstrate that a patient has achieved CR/CRi without disease-related constitutional symptoms or as specified per individual protocol.
- Lymph node biopsy can be performed to assess the disease transformation to a more aggressive histology (e.g., Richter syndrome).

In order for all components of disease assessments to be qualified as the same response evaluation, peripheral blood sample collection, physical exam, CT scan (if needed), bone marrow biopsy/aspirate (if needed) and constitutional symptom assessment (if needed) must be performed, in general, within 14 days of each other, unless specified otherwise in the protocol.

In case of a missing measurement of a required component to qualify for a certain response category, the overall response at that assessment will be "Unknown", unless progression was seen.

5.2.2.3.2 Overall disease response criteria

The general principle of overall disease response determination at a given evaluation is described in Table 5-1. Also refer to Hallek et al 2018 for a detailed explanation of each response criteria.

Table 5-1 Overall disease response classification at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria in Group A and Group B must be met and patients don't have disease-related constitutional symptoms: **Group A** **Lymphadenopathy** • None ≥ 1.5 cm (CT is required at time of establishing CR/CRi if abnormal at baseline) **Hepatomegaly** • Liver size normal (CT is required at time of establishing CR/CRi if abnormal at baseline) **Splenomegaly** • Spleen size normal (CT is required at time of establishing CR/CRi if abnormal at baseline) **Blood lymphocytes**

Response category	Definition
	• < 4000 /µL **Group B** **Platelet count** • ≥ 100,000 /µL **Hemoglobin** • ≥ 11.0 g/dL (without red blood cell transfusions or erythropoietin support within 7 days) **Neutrophils** • ≥ 1500 /µL **Marrow** • Normocellular, no CLL cells, no B-lymphoid nodules
Complete remission with incomplete marrow recovery (CRi)	All criteria for CR as defined above are met, except a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL.
Partial remission (PR)	At least two of the criteria of Group A plus one of the criteria of Group B below must be met if abnormal at baseline. If only one parameter of both groups A and B is abnormal prior to therapy, only 1 needs to improve. **Group A** **Lymphadenopathy** • Decrease ≥ 50% from baseline (CT is required at time of establishing PR if abnormal at baseline) or meet CR criteria. **Hepatomegaly** • Decrease ≥ 50% from baseline of enlargement of liver below the costal margin by physical exam or meet CR criteria. **Splenomegaly** • Decrease ≥ 50% from baseline of enlargement of spleen below the costal margin by physical exam or meet CR criteria. **Blood lymphocytes** • Decrease ≥ 50% from baseline or meet CR criteria. **Group B** **Platelet count** • ≥ 100,000 /µL or increase ≥ 50% from baseline **Hemoglobin** • ≥ 11.0 g/dL or increase ≥ 50% from baseline (without transfusions within 7 days)
Progressive disease (PD)	At least one of the criteria in Group A, Group B or Others group is met **Group A** **Lymphadenopathy** • Increase ≥ 50% from baseline or from response in greatest determined diameter of any previous site, only applicable if abnormal at baseline

Response category	Definition
	Hepatomegaly • Increase ≥ 50% from baseline or from response, only applicable if abnormal at baseline **Splenomegaly** • Increase ≥ 50% from baseline or from response , only applicable if abnormal at baseline **Blood lymphocytes** • Increase ≥ 50% over the course of 2 months from baseline or from response with at least 5000 /µL **Group B** **Platelet count** • Decrease ≥ 50% over baseline or best response secondary to CLL and unrelated to autoimmune cytopenias **Hemoglobin** • Decrease of ≥ 2 g/dL from baseline or best response secondary to CLL and unrelated to autoimmune cytopenias **Marrow** • Increase of CLL cells by ≥ 50% over the nadir **Others:** **New lesion** • Appearance of any new lesion such as enlarged lymph nodes (≥1.5cm), splenomegaly, hepatomegaly or other organ infiltration **Disease transformation** • Transformation to a more aggressive histology (e.g., Richter syndrome) as documented by lymph node biopsy.
Stable disease (SD)	Failure to meet the criteria for CR, PR or PD. SD is equivalent to no response (NR)
Unknown	"Unknown" is assigned in case the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame (VAY736Y2101-CSP-Section 16.1.2.2 and Section 16.1.2.3.1). However, if there is any evidence of PD, the overall response will considered as PD.

The overall disease responses of CR/CRi must stay the same until PD, with the exception of an UNK status. A patient who had a CR/CRi cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more disease component reappearing, in which case the status would become a PD.

Once an overall disease response of PR is observed, the PR response status must be maintained or improved over time until PD, with the exception of an UNK status. That is, after a single PR

the overall disease response should still be considered PR (or UNK) until PD is documented or the disease totally disappears in which case a CR/CRi assignment is applicable.

5.2.2.3.3 Establishing CR, CRi, PR and subsequent maintenance of CR, CRi, PR with no clinical evidence of progression

A full response evaluation, including assessments of peripheral blood, bone marrow, lymph node, liver, spleen and constitutional symptom, is required at the first time a CR or CRi is demonstrated (Section 5.2.2.3.1). Based on iwCLL response guidance, bone marrow aspirate/biopsy is not a required criterion for establishing PR. Additional bone marrow biopsies/aspirates may be recommended in the protocol.

Following initial achievement of CR, CRi or PR, if the patient has no evidence of PD as assessed on peripheral blood, lymph node, liver, spleen and constitutional symptoms, patients will be considered to have maintained a clinical CR, CRi or PR. The maintenance assessment of lymph node, liver and spleen can be done via physical exam or CT.

In order for the best overall disease response to be categorized as CR, CRi or PR, there must be no evidence of PD at a minimum of 8 weeks (56 days) after the initial achievement of CR, CRi or PR. Please note, if additional assessments (e.g. bone marrow, CT scan or lymph node biopsy/aspirate) are performed (Section 5.2.2.3.1) in the same evaluation for disease response evaluation purpose, they will also need to show remission status.

The onset date of CR, CRi or PR will then be derived as the evaluation date of the initial CR, CRi or PR assessment. If a patient satisfied CRi at one evaluation and later confirmed as a CR in the next evaluation, the patient will be considered as having confirmed CR.

5.2.2.3.4 Date of overall disease response evaluation

A complete evaluation of response includes at the minimum the assessments of peripheral blood, lymph node, liver and spleen. In addition, bone marrow aspirate/biopsy, constitutional symptoms and lymph nodal biopsy/aspirate may be required. All components of disease assessments must be performed within the specified time frame (Section 5.2.2.3.1) to be qualified as the same response evaluation.

If the overall disease response is CR, CRi, PR, SD, or Unknown, the evaluation date (i.e. for one evaluation number) is defined as the latest of all dates of required measurements at that evaluation number. This rule applies also in case of multiple measurements of the same variable.

PD can be assessed based on a partial evaluation (e.g. a PD is assessed from blood alone). The assessment date for PD is calculated as the earliest date of all assessments that reveal a PD.

5.2.3 Data collection

5.2.3.1 Data sources

The summary of data sources refers to disease-specific (e)CRF standard modules or data transfer specification (DTS) modules. It is not appropriate to deviate from these specifications in Table 5-2.

Table 5-2 Data sources

(e)CRF module	Specification
Overall disease response	Overall disease response and assessments of individual components for • Lymphadenopathy; • Hepatomegaly; • Splenomegaly • Bone marrow; • Blood lymphocyte; • Platelet count • Hemoglobin • Neutrophils • B-symptoms • Disease transformation (e.g., Richter syndrome)
Nodal lesion (index and new lesion)	Lesion index number, location, evaluation method (CT , Physical exam), dimension
Liver and Spleen assessment	Evaluation method (CT, Physical exam), result
Bone marrow biopsy / aspirate	Cellularity, lymphocyte, B-lymphoid nodule, marrow infiltration
Blood response	Blood lymphocyte, platelet, hemoglobin and neutrophils
B-symptom	To assess if there are any constitutional symptoms attributable to CLL
Blood component transfusion	Type and volume of transfusions, timing with respect to disease assessment
Lymph node biopsy/aspirate	To assess whether disease has transformed to a more aggressive histology (e.g., Richter syndrome)
DTS module	Specification
[redacted]	[redacted]

5.2.3.2 Recording response evaluation on the (e)CRFs

The components and timing needed to adequately assess overall disease response is outlined in Section 5.2.2.3.1. In practice, disease response evaluation (either a complete assessment or only some components) may be performed on both scheduled and unscheduled time points. Also, it is not uncommon in oncology trials that disease responses are sometimes assessed at time points not matching the scheduled time points. For example, when a patient's condition prevents certain assessments, the scheduled evaluation will have to be delayed to a later time point.

As a result, the recording of response evaluation is aligned using the "Evaluation number" on the (e)CRFs. A new evaluation number should be assigned whenever a scheduled or unscheduled disease response assessment is performed, and hence is not necessarily aligned with the study visits.

When progressive disease (PD) can be judge based on any component, e.g., if a PD is observed from blood sample alone without bone marrow assessment etc. at any time, it will be recorded on the (e)CRFs, with all other assessments as "not done" or "unknown". See also Section 5.2.2.3.4 regarding assigning date of the overall response.

5.2.4 Derivation of efficacy endpoints

5.2.4.1 Best overall response

Best overall response will be calculated by patient based on all evaluations.

The best overall disease response is the best disease response recorded from the start of the treatment until PD, death, start of new therapy, withdrawal of consent or end of study, whatever comes first. Best response will be assigned according to the following order:

1. CR
2. CRi
3. PR
4. SD
5. PD
6. Unknown

In case no post-baseline assessment is available or assessments with only unknown response status are available, the category "unknown" will be assigned as best overall response.

Based on the patients' best overall response during the study, the following rate is calculated:

Overall response rate (ORR) is the proportion of patients with best overall response of PR or better. For the calculation of the ORR, the denominator should include all patients in the targeted patient population. Additional analysis sets can be defined in the study protocol.

5.2.4.2 Time-to-event endpoints

General rule for the calculation of the time to event interval is:

Time to event = end date - start date + 1 (in days)

When no post-baseline response assessment is available, the date of *randomization/start of the treatment* will be used as end date (duration = 1 day), i.e., time to event variables will never be negative.

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than "not done" or "unknown".

5.2.4.2.1 Overall survival

Overall survival (OS) is defined as the time from date of *randomization/start of the treatment* to the date of death due to any cause.

If a patient is alive or his/her survival status is unknown, OS will be censored at the date of last contact. The derivation of the last contact date, e.g., the variables and data panels to be used, should be clearly specified in the statistical analysis plan.

5.2.4.2.2 Progression-free survival

Progression-free survival (PFS) is defined as time from date of *randomization/start of the treatment* to date of (1) death due to any cause or (2) PD.

If a patient has not had an event, PFS is censored at the last adequate response assessment date.

5.2.4.2.3 Duration of response

Duration of response (DOR) is defined as the duration from the first documented onset of PR or better response to the date of PD or death due to disease progression.

In case a patient does not have PD or death due to disease progression, DOR will be censored at the date of the last adequate assessment.

5.2.4.2.4 Time to response

Time to response (TTR) is defined as the time between date of *randomization/start of the treatment* to the date of first onset of PR or better response.

Patients without experiencing any PR or better response will be censored according to the following events:

- Patients experiencing a PD or death will be censored at maximum follow-up (i.e. date of last visit)
- Patients not experiencing PD/death will be censored at their last adequate response assessment date

5.2.4.3 Event and censoring date, sensitivity analysis

This section outlines the possible event and censoring dates for PD (Table 5-3), as well as addresses the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed. Using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 5-3 Options for event dates used in TTP

Situation	Options **(1) = default unless specified differently in the protocol or analysis plan**	Outcome
A No baseline or post-baseline assessment	(1) Date of randomization/start of treatment	Censor
B PD or death at scheduled assessment date or before next scheduled assessment	(1) Date of PD (or death)	Event
	(2) Date of next scheduled assessment	Event
C1 PD or death after **exactly one** missing assessment	(1) Date of PD (or death)	Event
	(2) Date of next scheduled assessment[1]	Event
C2 PD or death after **two or more** missing assessments	(1) Date of last adequate assessment[1]	Censor
	(2) Date of next scheduled assessment[2]	Event
	(3) Date of PD (or death)	Event

D	No PD and no death	(1) Date of last adequate assessment	Censor
E	Discontinuation of study treatment due to PD without documented PD, i.e. clinical PD based on investigator claim	(1) N/A	Ignored
		(2) Date of discontinuation (visit date at which clinical PD was determined)	Event
F	New anti-cancer therapy given	(1) Date of last adequate assessment prior to start of new anti-cancer therapy	Censor
		(2) Date of new anti-cancer therapy	Censor
		(3) Date of new anti-cancer therapy	Event
		(4) N/A	Ignored

[1] Date of the last adequate tumor assessment, is the date the last tumor assessment with overall lesion response of CR, PR, or SD before an event or censoring occurred.

[2] Date of next scheduled assessment is defined as the date of last adequate tumor assessment plus the protocol specified time interval for assessments.

The primary analysis and the sensitivity analyses must be specified in the Study Protocol. Clearly define if and why options (1) are not used for situations C,E, and (if applicable) F.

Situations C (C1 and C2): PD or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual PD or death date, in the case of only one missing assessment.

- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or more missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Discontinuation of study treatment due to 'PD' without documented PD: By default, option (1) is used for situation E as patients without documented PD should be followed for PD after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If PD is claimed based on clinical deterioration instead of response assessment, option (2) may be used for indications with high early PD rate or difficulties to assess response due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

5.3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010)

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L	< 3.0 – 2.0 x 10^9/L	< 2.0 – 1.0 x 10^9/L	< 1.0 x 10^9/L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB			Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9/L	< 2.0 - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 x 10^9/L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB - CTC grades in Novartis Oncology (26Oct15)

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.
(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.
(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**
(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

LAB - CTC grades in Novartis Oncology (26Oct15)

Note: For non-fasting glucose Grade 1 and 2 is not assessed.

6 References

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