NOVARTIS

Novartis Research and Development

VAY736

Clinical Trial Protocol CVAY736Y2102 / NCT03400176

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

Document type	Amended Protocol Version
EUDRACT number	Not applicable
Version number	v06 (Clean)
Clinical Trial Phase	Ib
Document status	Final
Release Date	20-Oct-2021

Template version 06-Apr-2017

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

ADA	Anti-Drug Antibody
ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine aminotransferase/Glutamic pyruvic transaminase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST/SGOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BP	Blood Pressure
BTK	Bruton's Tyrosine Kinase
BTKi	Bruton's Tyrosine Kinase inhibitor
BUN	Blood Urea Nitrogen
BVN	Bivariate Normal
CI	Confidence Interval
CK	Creatinine Kinase
CL	Clearance
CLL	Chronic Lymphocytic Leukemia
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DBL	Database Lock
DDI	Drug-Drug Interaction
DDS	Dose-determining analysis set
DLT	Dose Limiting Toxicity
DMSO	Dimethyl Sulfoxide
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked ImmunoSorbant Assay
EOT	End Of Treatment

[redacted]

EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
G-CSF	Granulocyte Colony Stimulating Factor
GFP	Green Fluorescent Protein
GLP	Good Laboratory Practice
GVHD	Graft vs. Host Disease
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN	Interferon
IFNR	Interferon Receptor
Ig	Immunogenicity
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgM	Immunoglobulin M
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
i.v.	Intravenous(ly)
IWCLL	International Working Group - CLL
JAGS	Just Another Gibbs Sampler
LC-MS/	Liquid Chromatography Mass Spectrometry Assays
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit Of Quantification
mAb	Monoclonal antibody
MAP	Meta-Analytic-Predictive
MCH	Mean Corpuscular Hemoglobin
MCL	Mantle Cell Lymphoma
MCMC	Markov Chain Monte Carlo
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute

[redacted]

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NYHA	New York Heart Association
OCP DDI	Oncology Clinical Pharmacology Drug-Drug Interaction
ORR	Overall Response Rate
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PFS	Progression-Free Survival
PHI	Protected Health Information
PK	Pharmacokinetics
PLT	Platelets
PR	Partial Response
PR-L	PR with lymphocytosis
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PXR	Pregnane X Receptor
Q2W	Once Every Two Weeks
Q4W	Once Every Four Weeks
RA	Rheumatoid Arthritis
RD	Recommended dose
REB	Research Ethics Board
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SDS	Sodium Dodecyl Sulfate
SLL	Small Lymphocytic Lymphoma
SUSARs	Suspected Unexpected Serious Adverse Reactions
TK	Toxicokinetic
TLS	Tumor Lysis Syndrome
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
WHO	World Health Organization
WM	Waldenstrom’s Macroglobulinemia

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.

[redacted]

Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

Amendment 06 (20-Oct-2021)

Amendment rationale

The purpose of this amendment is primarily three fold: [redacted] 3) allow for the closure of Arm B (patients with BTK inhibitor resistance mutations) due to slower than anticipated enrollment.

[redacted]

3) The decision to close Arm B is not based on any safety concerns. Patients currently enrolled may continue on study as long as they are tolerating study treatment and will continue to be followed per protocol.

Other changes that have been incorporated into the amendment are as follows:

- Update Exclusion Criteria # 3 to modify the washout period (from 30 days to 2 weeks or 5 half- lives, whichever is shorter) for drugs used in combination with ibrutinib as first line treatment or as a sequential combination partner. For subjects that received antibodies, the washout period is 4 weeks prior to study treatment. This will allow patients who are in need of urgent therapy for leukemia control to commence the study treatment as soon as possible.
- Update Exclusion Criteria # 6 to modify the timeframe for administration of live vaccines prior to VAY736 treatment based on practice guidelines in order to prevent potential risks associated with a live vaccine. A $\geq$ 4 week period is recommended for patients who will be receiving B-cell depleting agents including an anti-CD20 monoclonal antibody (Furer et al 2020). Further information is available in the current version of the VAY736 Investigator Brochure.

[redacted]

Study status

At the time of this amendment, dose escalation has been completed with 15 patients enrolled (none ongoing) and dose expansion is ongoing with 11 patients receiving study treatment.

Changes to the protocol

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 05 (11-May-2020)

Amendment rationale

The purpose of this amendment is to:

[redacted]

In addition, the amendment will:

1. [redacted]
2. Increase the time between CT scans from every 3 months to every 6 months during the time-to-progression (TTP) efficacy assessment as there is no clear benefit demonstrated to perform frequent radiographic assessments, in addition to avoiding the unnecessary exposure to radiation for the patient.
3. Update the guidelines for determination of MTD to the most current standard. The change in the guidance language was necessary to clarify that listed conditions only apply to MTD declaration, as RDE has already been assessed.
4. [redacted]
5. Correct minor inconsistencies and typographical errors throughout the document.

Study status

At the time of this amendment, dose escalation is ongoing and a total of 15 patients have been enrolled.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track change version of the [redacted]

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 04 (November 2019)

Amendment rationale

The purpose of this amendment is to address the following health authority requests:

- Clarify that treatment decisions will be solely made based on radiological and clinical response following IWCLL response criteria.
- Revise the study protocol to state that treatment decisions will not be made based on the minimal residual disease (MRD) assessment. The statistical analysis plan will reflect this change. [redacted]
- Clarify that a MRD assay implemented in the current study is multicolor flow cytometry and provide a method description of the MRD assay.
- Investigators may consider discontinuation of ibrutinib for patients who achieve a CR at the primary endpoint (C9D1) and be followed every 3 months for two years for TTP unless the patient experiences disease progression or the administration of a new therapy.
- Allow investigators to treat patients with 2 additional cycles of VAY736 therapy in combination with ibrutinib through Cycle 8 if the patient shows evidence of disease in radiological assessment or abnormal blood counts, defined by IWCLL response criteria, at the Cycle 6 Day 15 time point. Based on the preliminary efficacy data that 3 out of 5 patients had evidence of disease at the primary endpoint (C9D1), the addition of 2 more cycles of VAY736 therapy in combination with ibrutinib through Cycle 8 will help determine if further VAY736 therapy has an enhanced effect on clinical response at C9D1.
- Minor inconsistencies and typographical errors have been corrected throughout the document.

Study status

At the time of this amendment, this study has enrolled 14 patients.

Changes to the protocol

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 03 (21-Aug-2019)

The primary purpose of this amendment is to:

- Expand study eligibility for dose expansion to include CLL patients who have received ibrutinib either alone or in combination as first-line CLL therapy and have either not achieved a complete response after 1 year of therapy or have developed a resistance mutation to ibrutinib at any time.

  Even though ibrutinib is approved for all lines of CLL therapy, recent results from 2 phase III US Oncology cooperative group studies have demonstrated the superiority of ibrutinib or ibrutinib and rituximab combination as initial therapy in chemoimmunotherapy naive patients with improved progression-free survival and decreased toxicity compared to bendamustine and rituximab (BR) in older (≥65) patients and fludarabine, cyclophosphamide, and rituximab (FCR) in younger patients (<70) (Woyach et al 2018, Shanafelt et al 2018). There was an overall survival advantage with ibrutinib and rituximab in younger patients (Shanafelt et al 2018). These studies have definitively set ibrutinib or ibrutinib and rituximab as the standard first-line therapy in all patients with CLL without contraindications. Despite its remarkable clinical activity, the limitations of ibrutinib therapy include intolerance in a subset of patients who experience adverse events, emergence of resistance mutations, and absence of deep complete remissions which necessitates indefinite continuous therapy (Byrd et al 2014, O'Brien at al 2018). Indefinite therapy with extended dosing for years is a major limitation of ibrutinib, as it puts patients at risk for chronic toxicities, such as hypertension, atrial fibrillation, and cardiovascular events (Wiczer et al 2017). In addition, the cost of ibrutinib is substantial and indefinite ibrutinib treatment will be costly for both patients and the healthcare system as a whole (Shanafelt et al 2015). As ibrutinib is now the standard frontline therapy for CLL, these issues will affect a growing number of people.

  In the current study, the addition of 6 cycles of [redacted], antibody VAY736 (12 doses) to ibrutinib for patients who are receiving ibrutinib after progression on a prior line of therapy and have either not achieved a complete response (CR) or have developed a resistance mutation has now been shown to be safe. Eleven patients have been treated at 3 dose levels and demonstrated improved clinical activity with 1 patient achieving a minimal residual disease (MRD) negative CR and one patient achieving a MRD positive CR at 9 months (time of the final response) at the initial dose level. The other 3 patients to reach the 9-month assessment had stable disease. The study treatment has been shown to be safe, without dose limiting toxicities (DLTs). Five of eleven patients experienced adverse events related to study treatment. The most common adverse events related to study drug have been constipation (G1), hypertriglyceridemia (G1), abdominal distension (G2), blood alkaline phosphatase increased (G1), diarrhea (G2) and an infusion-related reaction (G2).

- Recommend that investigators consider discontinuation of ibrutinib for patients who achieve [redacted]. This will allow investigators to follow patients for durability of response and minimize intolerance and toxicities associated with continuous ibrutinib therapy while maximizing patient quality of life. Patients will discontinue all therapy and be observed off therapy for progression.

[redacted]

- Allow investigators to treat patients with 2 additional cycles of VAY736 therapy in combination with ibrutinib through Cycle 8 if the patient does not achieve a [redacted] status in the blood at the Cycle 6 Day 15 time point. Based on the preliminary efficacy data and MRD positivity seen in 4 out of 5 patients that have reached the primary endpoint (C9D1), the addition of 2 more cycles of VAY736 therapy in combination with ibrutinib through Cycle 8 will help determine if prolonged VAY736 therapy has an effect on [redacted]
- [redacted]
- [redacted]
- Minor inconsistencies and typographical errors have been corrected throughout the document.

Study Status

- At the time of this amendment, dose escalation is ongoing and a total of 11 patients have been enrolled.

Changes to the Protocol

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 02 (03-Dec-2018)

Amendment rationale

The purpose of this amendment is to address the following changes:

- Clarify that subjects enrolled in the study may receive either ibrutinib tablets or capsules as these formulations are bioequivalent.
- [redacted]
- [redacted]
- [redacted]
- Update Table 14-11 in Appendix 3 based on the Novartis PK Sciences DDI List (v01 released in 2018 January).
- Provide other minor changes/corrections for consistency and/or clarification.

Study status

At the time of this amendment, dose escalation is ongoing and 7 patients have been enrolled.

Changes to the protocol

[redacted]

[redacted]

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 01 (02-Nov-2017)

Amendment rationale

The purpose of this amendment is to address the following health authority requests:

- Clarify that patients will not be enrolled based on lack of MRD (-) CR after > 1 year of treatment with ibrutinib
- Revise the study protocol to only enroll patients with CLL in both the dose escalation and expansion parts who are receiving ibrutinib in the relapsed setting
- Revise the dose limiting toxicity (DLT) definitions to remove previously listed exceptions
- Add direct and indirect Coomb's testing at baseline and as clinically indicated

Study status

At the time of this amendment, this study has not been opened for recruitment.

Changes to the protocol

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Protocol summary:

Title	Phase Ib open-label study of VAY736 and ibrutinib in patients with chronic lymphocytic leukemia (CLL) on ibrutinib therapy
Brief title	Phase Ib study of VAY736 and ibrutinib in patients with CLL
Sponsor and Clinical Phase	Novartis Phase Ib
Investigation type	Drug, Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of the combination of VAY736 with ibrutinib.
Primary Objective(s) and Key Secondary Objective	To determine the maximum tolerated dose (MTD) and/or RD (recommended dose) of the combination of VAY736 and ibrutinib. To characterize the safety and tolerability of the combination of VAY736 and ibrutinib
Secondary Objectives	To assess any preliminary antitumor activity of the combination of VAY736 and ibrutinib To characterize the PK of VAY736 and ibrutinib when used in combination therapy To assess the immunogenicity (IG) following one or more intravenous infusions of VAY736
Study design	This is a Phase Ib, open-label study to characterize the safety, tolerability, PK, PD, and preliminary anti-tumor activity of the combination of VAY736 with ibrutinib in patients with CLL who have been receiving ibrutinib for more than one year and who have not achieved a complete response to ibrutinib or who have developed a resistance mutation to ibrutinib. The study has two parts, dose escalation and dose expansion. The dose escalation part will determine the maximum tolerated dose (MTD) or the recommended dose (RD) for expansion of the combination of VAY736 with ibrutinib. In the expansion part, patients will be enrolled to one of two arms to further explore the safety, tolerability, and preliminary efficacy of the combination. As of Amendment 6, patients will no longer be enrolled into Arm B (expansion).
Population	Adults with CLL who have been receiving ibrutinib following relapse on another approved therapy and either have not had a complete response after 1 year of treatment or 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.
Inclusion criteria	Written informed consent Ibrutinib dose Escalation: Patients must be receiving 420 mg ibrutinib Expansion: Patients may be on a dose of ibrutinib lower than 420 mg. Any dose must have been stable for 2 months prior to the start of study treatment. Diagnosis of CLL as per World Health Organization (WHO) classification Lack of a complete response after receiving ibrutinib for > 1 year OR presence of known ibrutinib resistance mutation Platelets ≥ 25 x 10^9/L without transfusion support within 7 days of the first dose of VAY736 Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

[redacted]

Exclusion criteria	Receipt of live vaccine within 4 weeks of starting VAY736 Known history of HIV Active hepatitis B or C infection
Investigational and reference therapy	VAY736 Ibrutinib
Efficacy assessments	Rate of patients with CR (complete response) as 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 PLCγ2 hotspot), defined as less than 1% mutation bearing alleles (Arm B only). [redacted]
Safety assessments	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, reductions, and dose intensity
Other assessments	Plasma concentrations of VAY736 and ibrutinib and derived parameters Presence of anti-VAY736 antibodies [redacted]
Data analysis	The study data will be analyzed and reported based on patient's data from the dose escalation and dose expansion parts of the study up to the time when all patients have completed the treatment period and follow-up for disease progression or discontinued the study for any reason. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK and PD measures. The Bayesian logistic regression model with overdose control will be used to assess safety for new patients treated at the dose levels that will be used for dose cohorts that occur after the initial dose cohort.
Key words	Chronic lymphocytic leukemia, CLL, VAY736, ibrutinib, [redacted], ibrutinib resistance mutation, BTK (Bruton's tyrosine kinase), Phase Ib

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

CLL is the most prevalent adult leukemia in the Western hemisphere. Patients with early stage disease have a greater than 10 year life expectancy. However, patients with more advanced disease have a median survival of only 18 months to 3 years (Rai et al 1975). The development of chemoimmunotherapy regimens combining cytotoxic agents such as alkylating agents and purine nucleoside analogs with monoclonal antibodies such as rituximab have attained overall response (OR) rates of over 90% and CR rates of over 70% in patients with previously untreated CLL, with similar improvement in progression free survival (PFS). Notwithstanding the therapeutic advance represented by chemoimmunotherapy combinations, these treatments are not curative in the majority of cases (Nabhan and Rosen 2014). Additionally, several features of CLL are predictive of poor response to chemoimmunotherapy treatments as measured by response duration and shortened survival. These include [redacted] resulting in [redacted] (Dohner et al 2000, Damle et al 1999, Chen et al 2002). Patients with [redacted] treated with fludarabine, fludarabine and rituximab, fludarabine plus cyclophosphamide, or fludarabine, cyclophosphamide, and rituximab have a shorter duration of progression-free survival and overall survival compared to patients without this finding (Badoux et al 2009, Tam et al 2014).

Ibrutinib, an inhibitor of BTK in the B-cell receptor signaling cascade, is a disease-altering therapy in chronic lymphocytic leukemia and has the advantage of effecting responses in patients with these characteristics associated with poor responses to chemoimmunotherapy. Ibrutinib additionally provides a progression free and overall survival advantage over other standard therapies (Byrd et al 2013, Woyach et al 2015, Byrd et al 2015). At the 5-year follow up time from the initial ibrutinib studies, 92% of untreated and 43% of previously heavily treated patients maintain a durable remission (O'Brien et al 2016) Ibrutinib is approved by the US FDA for all patients with CLL and is widely prescribed as a new standard of care for CLL patients.

However, patients in both untreated and previously treated settings typically have small detectable clonal disease leading to their being classified as minimal residual disease positive (MRD+) CR or PR (partial response). To date, combination studies of BTKi (Bruton's tyrosine kinase inhibitor) with rituximab, ofatumumab, bendamustine + rituximab, and venetoclax + obinutuzumab have not demonstrated elimination of these residual cells in the majority of patients (Burger et al 2014, Jaglowski et al 2015, Chanan-Khan et al 2016). This long-term persisting MRD+ disease has significant implications for individual patients and the health care system because continuation of ibrutinib is required in this setting.

Additionally, many patients with CLL will stop responding to ibrutinib either by developing transformation to a large-cell lymphoma (Richter's syndrome) or as progressive CLL, the risk of which increases over time (Maddocks et al 2015, Woyach et al 2017). As ibrutinib is dosed indefinitely, the number of patients with progressive CLL during ibrutinib therapy is expected to increase. Furthermore, survival for patients discontinuing ibrutinib due to CLL progression [redacted] y aggressive disease

phenotype (Woyach et al 2017). It is imperative to develop novel treatments for CLL that address lack of MRD (-) CRs and resistance as major limitations of ibrutinib therapy.

1.2 Introduction to investigational treatment and other study treatment

1.2.1 [redacted]

VAY736 is a fully human monoclonal IgG1 antibody [redacted] VAY736 is currently being developed for the treatment of human autoimmune diseases and B cell malignancies.

[redacted]

[redacted]

[redacted]

1.2.3 VAY736 clinical experience

1.2.3.1 Clinical safety

As of 24-Mar-2021, a total of 495 patients have been enrolled in 11 clinical studies, 9 of which were single blinded or double blinded, randomized, controlled trials .It is estimated that 455 patients have been treated with VAY736 across these 11 studies. Data from patients in 7 studies have been analyzed as of 24-Mar-2021 and summaries of safety data can be found in the VAY736 Investigator Brochure.

CLL

Three patients with refractory, relapsing CLL were enrolled to the dose escalation part of the CVAY736Y2101 clinical trial. Each patient received 0.002 mg/kg of VAY736 per iv infusion, with four infusions planned per 28 day cycle. The first patient enrolled received 3 doses of VAY736 prior to being hospitalized due to grade 3 autoimmune hemolytic anemia and eventually discontinued treatment. This patient had a positive Coombs test before enrolling in the trial and the event of hemolytic anemia was considered related to disease. The second patient enrolled received 5 doses of VAY736, and the third patient received 8 doses of study medication. Both of these patients were discontinued due to progressive disease. Grade 3 events that were reported regardless of relation to study treatment were anemia, anemia hemolytic autoimmune, and neutropenia. The study was terminated early for non-safety related concerns and there was no formal efficacy analysis.

As of15-May-2021, in the ongoing CVAY736Y2102 clinical trial, a total of 15 patients have received VAY736 at various doses, including 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 9 mg/kg IV every 2 weeks in the escalation part of the study. No DLTs were observed. Of the 9 patients who reached the primary endpoint (C9D1), three treated in the 0.3 mg/kg cohort, two treated in the 1.0 mg/kg cohort and 4 treated in the 3.0 mg/kg cohort, four patients have achieved a complete response. As of 15-May-2021 a total of 15 patients received study treatment in the expansion part of the study. 11 patients are ongoing.

Other indications

There is considerable safety data available for use of VAY736 in humans from ongoing and completed trials in autoimmune indications such as RA, primary Sjögren's syndrome, multiple sclerosis and pemphigus vulgaris. The most common adverse events attributable to VAY736 in these studies were lymphopenia, upper respiratory tract infections and infusion related reactions. There were no treatment related serious adverse effects. Mild-moderate infusion reactions occurred that were fully reversible with or without treatment within the first 24 hours after VAY736 administration. Detailed summaries of safety data from the individual studies with VAY736 can be found in the [VAY736 Investigator Brochure].

1.2.3.2 Clinical Pharmacokinetics of VAY736

[redacted] There was moderate between-subject variability with individual profiles overlapping across two consecutive doses. VAY736 showed a relatively short T1/2 of ~10 days

[redacted]

after single i.v. administration for the four highest doses (0.3 to 10 mg/kg), whereas it was around 7 days for the subcutaneous (s.c.) route following single dose and around 9 days following repeated doses. Based on trough concentrations following repeated administration of 60 mg s.c., the steady state of the concentrations occurs around the third-fourth doses. Additional information is available in the [VAY736 Investigator Brochure].

[redacted]

1.2.3.2.2 Immunogenicity of VAY736 in human studies

Immunogenicity was analyzed as part of the CVAY736X2101 clinical trial. A total of five patients (all receiving 10 mg/kg VAY736) out of 23 VAY736-treated patients had at least one sample (post dose) with confirmed anti-drug antibody (ADA) against VAY736. No SAE and no hypersensitivity reaction occurred to any of these five patients. No hypersensitivity reaction, AEs or reduced efficacy was observed in these five patients.

1.2.4 Overview of ibrutinib

Ibrutinib (PCI-32765, Imbruvica™) is a first-in-class, orally-administered, covalently-binding small molecule inhibitor of BTK. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.

Ibrutinib is currently under development for the treatment of B-cell malignancies (Janssen Research & Development, 2016). Ibrutinib is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Waldenstrom's Macroglobulinemia (WM), and marginal zone lymphoma (MZL).

[redacted]

1.2.4.1 Ibrutinib clinical experience

For detailed information on use of ibrutinib in CLL, refer to locally approved ibrutinib prescribing information.

1.2.4.1.1 Clinical pharmacokinetics of ibrutinib

Ibrutinib exposure increases with doses up to 840 mg. Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Absolute bioavailability in fasted condition was 2.9%. Administration with food increased ibrutinib Cmax and AUC. Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence. The volume of distribution (Vd) was 683 L. Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. The half-life of ibrutinib is 4 to 6 hours. For further details refer to the ibrutinib product insert and prescribing information.

1.2.4.1.2 Clinical trial data with ibrutinib in CLL

The safety and efficacy of ibrutinib in patients with CLL/SLL were demonstrated in one uncontrolled trial and three randomized, controlled trials. The most commonly occurring adverse reactions (≥ 20%) in patients with CLL/SLL receiving ibrutinib were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving ibrutinib in patients with CLL/SLL discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients. In an open-label, multi-center trial conducted in 48 previously treated CLL patients, the ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median duration of response (DOR) was not reached (de Claro et al 2015).

PCYC-1102/1103

The phase 1b/2 PCYC-1102 study included 85 patients with relapsed or refractory CLL or SLL and 31 symptomatic treatment naïve patients with CLL or SLL aged ≥65 years. Patients who completed a minimum of 6 treatment cycles with no evidence of disease progression could enroll in a long-term extension study (PCYC-1103) to continue ibrutinib therapy. Treatment consisted of 420 or 840 mg/day ibrutinib administered orally until progressive disease or poor tolerance (Byrd et al 2013, Byrd et al 2015).

After a median follow-up of 22.1 months, 22 (71%) of the 31 symptomatic treatment naïve patients achieved an objective response (95% CI 52·0–85·8); four patients (13%) had a complete response, one patient (3%) had a nodular partial response, and 17 (55%) patients had a partial response (O'brien et al 2014). When these data were updated at median 30 months of follow-up, ORR had improved to 84%, with 23% attaining CR, 55% PR, and 6% PR with lymphocytosis (PR-L). The estimated PFS rates was 96% (95% CI, 76.5-99.5%) at 30 months (Bryd et al, 2015). Five-year follow-up data were recently presented (O'Brien et al 2016). 65% of patients remained on active treatment, and 92% were progression free. Notably, with continued treatment, the CR rate had further improved to 29%.

[redacted]

PCYC-1115

PCYC-1115 (RESONATE-2) was a randomized phase 3 study comparing ibrutinib versus chlorambucil for treatment-naive non-del (17p) CLL in patients aged 65 years or older (Byrd et al 2013). Enrolled patients were randomized to receive either oral ibrutinib (at a dose of 420 mg once daily) until disease progression or development of unacceptable toxicity or up to 12 cycles of chlorambucil. At median follow-up 18.4 months, 86% of patients in the ibrutinib arm (versus 35% in the chlorambucil arm) had achieved an objective response (CR + PR + PR-L). At the time of this initial report, complete responses (including those in patients with incomplete blood-count recovery) had occurred in 4% of patients. Further, the majority of ibrutinib-treated patients with baseline anemia or thrombocytopenia experienced sustained improvement in the hemoglobin level and platelet count (84% and 77%, respectively). Among patients treated in the ibrutinib arm, the median PFS had not been reached, and ibrutinib was associated with a nearly 83% reduced risk of disease progression or death (Hazard Ratio (HR) 0.161, 95%CI 0.091, 0.283). Overall survival was also similarly improved after ibrutinib treatment versus chlorambucil (HR 0.162, 95% CI 0.048, 0.558).

Updated efficacy and safety data from this study were recently presented (Barr 2016). At median follow-up of 29 months, 92% of ibrutinib-treated patients had achieved an objective response. Ibrutinib CR rates likewise continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months. Most Grade ≥ AEs, as well as dose reductions and discontinuations due to AEs decreased over time. 79% of patients continue on ibrutinib treatment on study and 83% of patients had received at least 2 years of treatment. 24-month PFS and OS were 89% v. 24% and 95% v. 84% in the ibrutinib and chlorambucil arms, respectively.

1.2.4.2 Ibrutinib Resistance in CLL

A major limitation of ibrutinib as a CLL therapy is that many patients with CLL will stop responding to ibrutinib either by developing transformation to large-cell lymphoma (Richter's syndrome) or by progressive disease due to resistance to ibrutinib therapy. Relapses as Richter's syndrome tend to occur early and are rare after >2 years of ibrutinib treatment but the risk of progressive CLL increases over time (Maddocks et al 2015, Woyach et al 2017). An analysis of 308 patients who received ibrutinib as participants in clinical trials and followed for a median of 33 months (range 4-61), revealed a cumulative incidence of ibrutinib discontinuation for progressive CLL of 0.7% (95% CI: 0-1.6%) at 1 year and 19.1% (95% CI: 13.9-24.3%) at 4 years (Woyach et al 2017).. As ibrutinib is dosed indefinitely, the number of patients with progressive CLL during ibrutinib therapy is expected to increase over time.

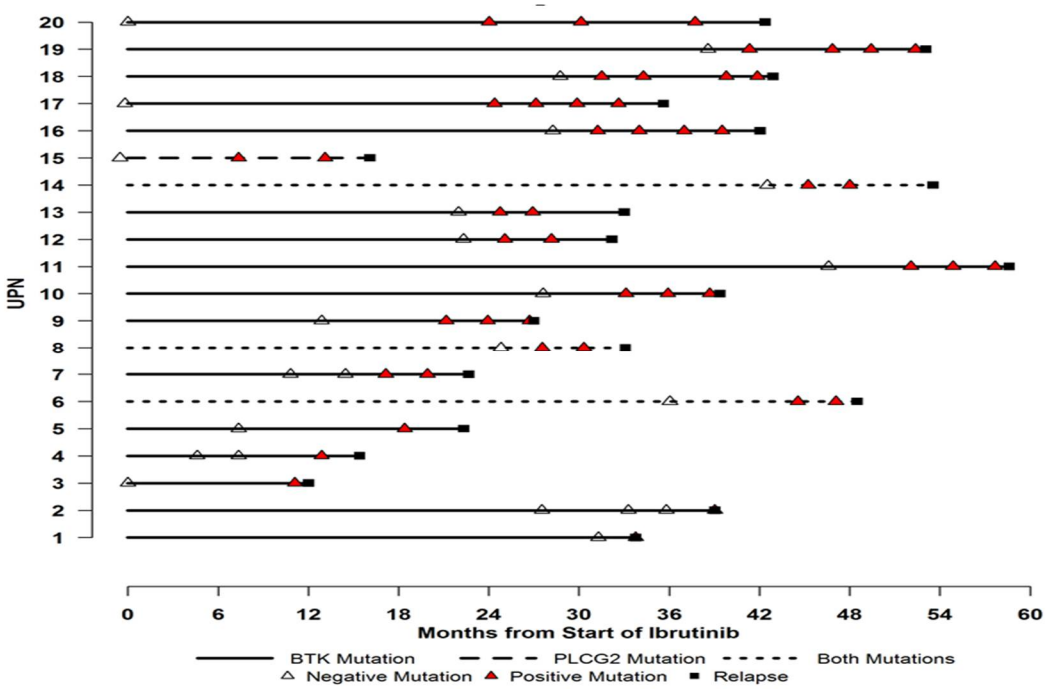
Furthermore, survival for patients discontinuing ibrutinib due to CLL progression was short 22.7 months (95% CI 13.5-NR) and associated with a clinically aggressive disease phenotype (Woyach et al 2017).

CLL progression due to ibrutinib resistance can be mediated by at least two separate mechanisms: mutations in BTK (BTK^{C481S}) which decreases the affinity of ibrutinib for BTK and changes its binding from irreversible to reversible, and mutations in the immediate downstream target of BTK, PLCγ2 (Woyach et al 2014b). These mutations appear during the course of treatment and are not seen in patients who were never exposed to ibrutinib. Once they

[redacted]

are detected on two separate occasions they do not disappear and patients invariably relapse (Maddocks et al 2015, Albitar et al 2015, Albitar et al 2017, Liu et al 2015, Woyach et al 2014b). In ibrutinib-treated patients with a detectable mutation in BTK or PLCγ2 at time of relapse, a clone with the mutation could be detected in 18/20 patients prior to clinical relapse at a median of 9.3 (95% CI: 7.6-11.7) months before clinical progression (Figure 1-1).

Figure 1-1 Ibrutinib resistance mutations can be detected prior to clinical relapse



These patients can be identified by screening and in a cohort of 112 patients that were followed with testing for BTK and PLCγ2 mutations every three months during ibrutinib treatment, 8 developed the BTK^{C481S} mutation and all went on to clinically relapse (Woyach et al 2014b). Once these mutations are detected they do not decrease in allelic frequency or become undetectable and patients invariably develop clinical relapse.

1.3 Overview of the combination of VAY736 and ibrutinib

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3.2 Clinical experience

There are no clinical data or ongoing trials for the combination of VAY736 and ibrutinib.

1.3.3 Potential drug-drug interactions between VAY736 and ibrutinib

Specific studies to investigate drug-drug interactions (DDI) have not been conducted. The likelihood of DDI between VAY736 and ibrutinib is low since VAY736 is a monoclonal antibody and will likely be degraded to small peptides and amino acids by proteases. Therefore, VAY736, will not share a common clearance pathway with ibrutinib that is metabolized by the cytochrome P450 enzymes, CYP3A4 and CYP2D6. Additionally, there is no evidence that [redacted] and/or [redacted] ligand are involved in the regulation of the expression of drug metabolizing enzymes for ibrutinib. However, ibrutinib and VAY736 PK will be monitored in this study.

[redacted]

1.3.4 Expected overlapping toxicities

Combination toxicology studies have not been conducted. Preclinical and preliminary clinical data available from ongoing studies with VAY736 and ibrutinib monotherapy do not indicate a risk for overlapping toxicities. The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) treated with ibrutinib were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia (see ibrutinib package insert). The most common adverse events attributable to VAY736 were lymphopenia, upper respiratory tract infections and infusion related reactions.

An increased number of infusion reactions occurred in the VAY736-treated patients compared to placebo treated patients despite pre-treatment with paracetamol. All infusion-related reactions were mild to moderate in severity. Symptoms all resolved within 24 hours, either spontaneously or with additional paracetamol treatment (for more information please refer to [VAY736 Investigators Brochure]).

No evidence of VAY736-driven reduction in neutrophil counts or hemoglobin levels have been seen to date in ongoing studies. Significant, but transient and reversible, reductions in lymphocyte and NK cell counts were observed in patients treated with VAY736. These reductions are consistent with the intended PD of the compound and activation and redistribution of these cell types in the process of killing of B cells by ADCC. The transient lowering in these cell counts were resolved in all affected patients by the next scheduled evaluation at study day 7.

2 Rationale

2.1 Study rationale and purpose

[redacted]

Ibrutinib has become the standard treatment for many advanced CLL patients. Although most patients benefit from ibrutinib treatment, only a small percentage (7% at one year) achieve complete response and acquired resistance leads to disease progression over time. Combination of VAY736 and ibrutinib has potential to deepen the response to ibrutinib, eliminate the CLL cells with acquired resistance to ibrutinib, and potentially allow for discontinuation of long-term therapy.

[redacted]

The purpose of this study is to determine the safe and tolerable dose of VAY736 for use in combination with ibrutinib and explore preliminary efficacy of the combination. After the safe and tolerable dose of VAY736 is determined in dose escalation, two expansion arms will enroll CLL patients currently taking ibrutinib who have either failed to achieve a CR after >1 year of treatment or who have developed a mutation known to confer molecular resistance to ibrutinib and predict relapse. The purpose of the expansion arms is to gather preliminary efficacy data in these specific groups and will test whether addition of VAY736 to ibrutinib can deepen responses and increase the complete response rate.

2.2 Rationale for the study design

This open label, phase 1b study has two parts. 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 CLL. The dose escalation part of the study will be guided by a Bayesian Logistic Regression Model (BLRM).

The BLRM is a well-established method to estimate the MTD/RD in cancer patients. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA (Guidelines on clinical trials in small populations", February 2007) and endorsed by numerous publications (Babb et al 1998, Neuenschwander et al 2008, Neuenschwander et al 2010, Neuenschwander et al 2014) and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The decision on new dose combinations are made by the Investigators and Sponsor and will be based upon the assessment of risk to new patients as estimated by the BLRM, patient tolerability and safety (including lower grade and later cycle AEs). [redacted]

The dose expansion part of the study will further evaluate safety, tolerability, as well as PK, PD (if available), and preliminary anti-tumor efficacy of the drug combination in specific populations.

2.3 Rationale for dose and regimen selection

This is the first trial that will evaluate the combination of VAY736 with ibrutinib. Drug-drug interactions are not expected; overlapping toxicities are not anticipated but are possible. See Section 1.3.3 and Section 1.3.4.

2.3.1 Rationale for ibrutinib dose and schedule

Ibrutinib will be administered at the standard approved dose in CLL, 420 mg orally administered daily. See ibrutinib package insert for additional information.

[redacted]

2.3.2 Rationale for VAY736 dose and schedule

Based on PK/PD modeling developed for RA patients and simulation adjusted for B cell baseline and dynamics in CLL patients, the proposed starting dose of VAY736 is 0.3 mg/kg i.v. Q2W. [redacted]. Additionally, 90% B cell depletion is associated with the mitigation of neutropenia risk and the recovery of absolute neutrophil counts, as described in Section 1.2.2.3. A dose-escalation approach will be undertaken in order to determine the appropriate dose in combination with ibrutinib. The dose of VAY736 will be escalated in sequential cohorts guided by a BLRM and following clinical review of available data as described in Section 2.2.

2.4 Rationale for choice of combination drugs

See Section 2.1.

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules, are included in this protocol. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. There may be unforeseen risks with the combination of VAY736 with ibrutinib which could be serious. Refer to the latest version of the [VAY736 Investigators Brochure] and the ibrutinib package insert for more information.

[redacted]

2.7 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
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 10.5
To assess any preliminary antitumor activity of the combination	Rate of patients with CR as 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 PLCγ2 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]

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

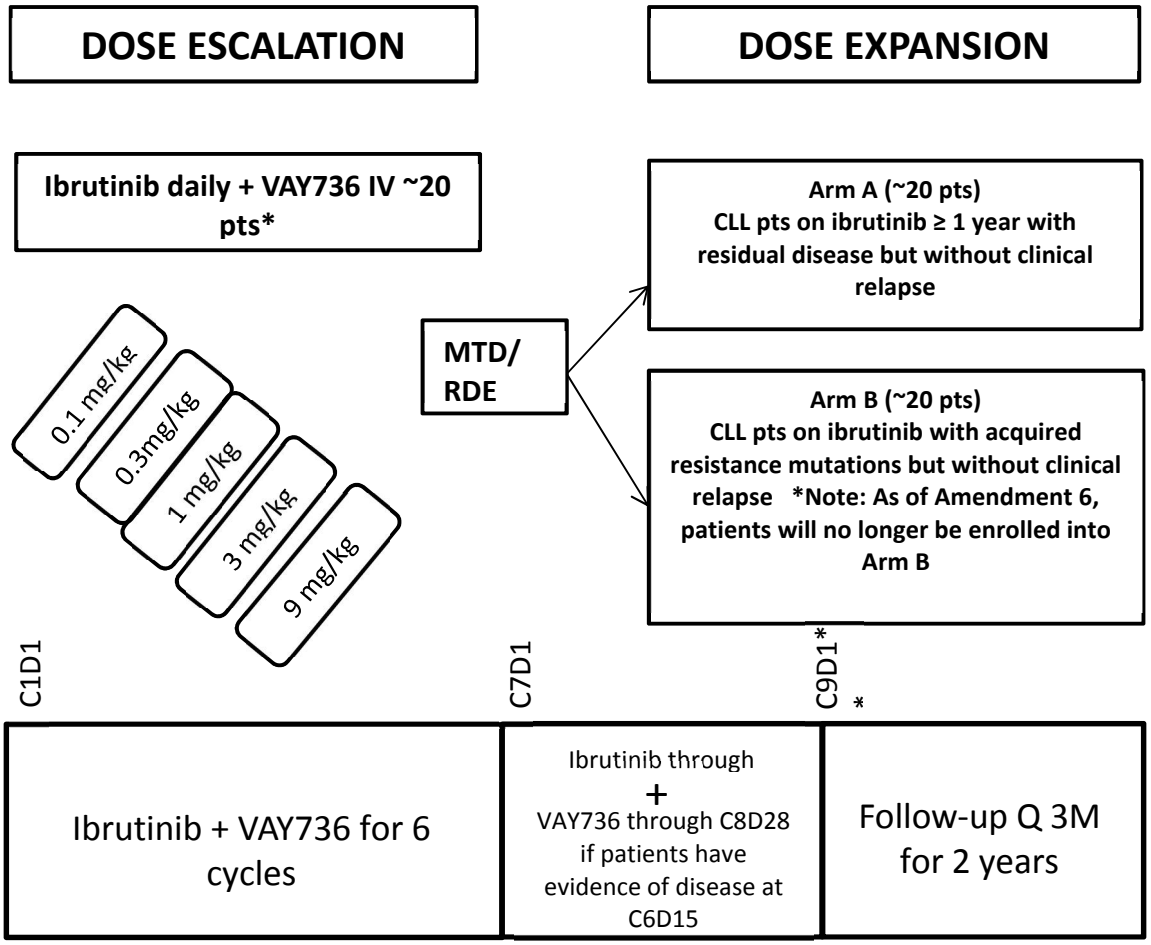
The MTD and/or RDE of the combination of VAY736 with ibrutinib will be determined in this open-label phase Ib dose escalation trial. Upon identification of the MTD or RDE, an expansion part will be opened to patient enrollment to further characterize the safety, PK, and pharmacodynamics (PD) of the combination.

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 and 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 4-1. All patients with acquired resistance mutations who are enrolled to the dose expansion part of the study will be enrolled in Arm B, irrespective of ibrutinib treatment duration.

Patients will receive the combination of VAY736 and ibrutinib for 6 cycles. Starting with C7D1, VAY736 will be discontinued if the patient has achieved a CR per IWCLL response criteria with no evidence of disease per radiological assessment and normal blood counts at C6D15. Ibrutinib will be administered per protocol for an additional two cycles (through C8D28). If a patient has not achieved a CR per IWCLL response criteria at C6D15, VAY736 and ibrutinib will be continued for 2 additional cycles (Cycle 7 and Cycle 8). At C9D1 (±7 days), patients will have their final disease assessment [redacted] of the study. All patients who have remained on study, including those who have discontinued treatment due to reasons other than disease progression, will be assessed at this time point. For patients who achieve a complete response at this assessment, investigators may consider discontinuing ibrutinib in order to follow patients for durability of response and minimize intolerance and toxicity associated with continuous ibrutinib therapy while maximizing patient quality of life.

[redacted]

Figure 4-1 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.

4.2 Timing of interim analyses and design

The dose-escalation design foresees that decisions on future dose levels based on available data are taken at the end of each cohort. These are described in Section 6.2.3 and Section 10.7.

The RD will be selected based on a review by Novartis study personnel and Investigators of available safety and tolerability information (including the DLT risk assessment from the BLRM using EWOC) along with PK, PD and efficacy data. The expansion part will then begin as specified in Section 4.1.

Details about the timing and interim analysis decisions can be found in Section 10.7.

[redacted]

4.3 Definition of end of study

The study will end when all patients have completed the treatment period, safety period and two-year efficacy follow-up or have been lost to follow-up, discontinued the study for any reason, or the study is terminated early.

See Section 10 for details of timing of the primary analysis and final reporting of data.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed by the sponsor of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will enroll patients with CLL who are currently taking ibrutinib therapy following relapse from 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 failed to achieve a complete response after 1 year of therapy or have developed a resistance mutation to ibrutinib. Patients must be taking and tolerating ibrutinib at time of enrollment with no limits to their continued ibrutinib use.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

Patient must meet the following laboratory values at the screening visit unless cytopenias are related to CLL:

1. Diagnosis of chronic lymphocytic leukemia (CLL) meeting criteria established in the World Health Organization (WHO) classification of hematologic disorders or International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (Hallek et al 2018). Variant immunophenotype and prolymphocytic morphology change after diagnosis of CLL is allowed.
2. Age ≥ 18 years
3. [redacted]
4. Male patients agree to avoid fathering a child as per the ibrutinib package insert

[redacted]

5. Dose escalation:
   a. On ibrutinib > 1 year following relapse from another approved therapy without achieving a complete response

   OR

   b. On ibrutinib following relapse with another approved therapy and the presence of a known ibrutinib resistance mutation (BTK or PLCγ2) at ≥1 variant allele frequency OR <1% with two separate measurements at least 4 weeks apart with increasing variant allele frequency.
6. Dose expansion:
   a. Arm A: On ibrutinib > 1 year following relapse from another approved therapy without achieving a complete response and 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 failed to achieve a complete response after 1 year.

b. Arm B: On ibrutinib following relapse with another approved therapy and 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 the presence of a known ibrutinib resistance mutation at ≥1% variant allele frequency OR <1% with two separate measurements at least 4 weeks apart with increasing variant allele frequency. *Note: As of Amendment 6, patients will no longer be enrolled into Arm B.

7. Ibrutinib dose:
   - Escalation: Patients must be receiving 420 mg ibrutinib
   - Expansion: Patients may be on a dose of ibrutinib lower than 420 mg. Any dose must have been stable for 2 months prior to the start of study treatment.
8. Absolute Neutrophil Count ≥ 750 cells/μL (0.75×10^9/L) independent of growth factor support within 7 days of the first dose of VAY736
9. Platelets ≥25×10^9/L without transfusion support within 7 days of the first dose of study drug. Patients with transfusion dependent thrombocytopenia are excluded.
10. Hemoglobin (Hgb) ≥8 g/dL without transfusion support within 7 days prior to the first dose of VAY736.
11. Creatinine Clearance ≥ 30 mL/min using Cockcroft-Gault formula (or similar institutional standard) or creatinine < 2x ULN
12. Total bilirubin ≤1.5 x ULN (For patients with Gilbert's Syndrome: total bilirubin < 3.0 x ULN with direct bilirubin < 1.5 x ULN)
13. Aspartate transaminase (AST) ≤ 3.0 x ULN
14. Alanine transaminase (ALT) ≤ 3.0 x ULN
15. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
16. Written informed consent must be obtained prior to any screening procedures.
17. Patients with relapsed disease after prior allogeneic stem cell transplant (myeloablative or nonmyeloablative) will be eligible if they meet all other inclusion criteria and:
    a. Do not have active (chronic or acute) GVHD and no immunosuppression
    b. Are more than 6 months from transplant

[redacted]

5.3 Exclusion criteria

1. History of transformation to aggressive disease histology (Large cell lymphoma) within 2 years prior to enrollment.
2. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study entry; completely resected basal cell and squamous cell skin cancers, superficial bladder cancer, and completely resected carcinoma in situ of any type.

3a. Received cytotoxic or small molecule targeted anti-neoplastics, any experimental therapy in combination with ibrutinib as first line therapy or as a sequential combination partner, within 14-days or 5 half-lives whichever is shorter before the first dose of study treatment. For subjects that received antibodies or immunotherapies, the washout period is 4 weeks prior to study treatment. Patient must have recovered from any adverse effects of prior treatment prior to enrollment.

Protocol amendment 06 exclusion criterion #3a (denotes the first change to criterion #3)

4. Non-palliative radiotherapy within 2 weeks prior to the first dose of study drug. Palliative radiotherapy to a limited field, such as for the treatment of bone pain or focally painful tumor mass is allowed. To allow for assessment of response to treatment, patients must have remained measurable disease that has not been irradiated
5. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., mAb of IgG1 class)
6. Receipt of live vaccine within a two month period before VAY736 treatment. As of Amendment 6, patients who received live vaccine within 4 weeks before VAY736 will be excluded.
7. All acute toxic effects of any prior antitumor therapy (including ibrutinib) resolved to ≤ Grade 1 before study enrollment (with the exception of alopecia, grade 2 neurotoxicity, or grade 2 or 3 bone marrow parameters)
8. Presence of active CNS disease
9. Known history of HIV infection
10. [redacted]
11. Active, uncontrolled autoimmune cytopenias (including autoimmune hemolytic anemia or immune thrombocytopenia)
12. Current treatment with medications or consuming foods that are strong/moderate inhibitors or strong inducers of CYP3A that cannot be discontinued at least one week

[redacted]

prior to the start of treatment. Refer to Section 6.4.3 for guidance on prohibited medication.

13. Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
14. Impaired cardiac function or clinically significant cardiac disease, including any of the following:

- Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
- Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry

15. Patients with impaired hepatic function as defined by Childs-Pugh class B or C.
16. History of stroke or intracranial hemorrhage within 6 months prior to start of study drug
17. Evidence of active ongoing systemic bacterial, mycobacterial, fungal, or viral infection at the time of study enrollment. Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator.
18. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs, with the exception of prior gastrectomy (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
19. Unable or unwilling to swallow the oral drug as per dosing schedule
20. Two weeks since major surgery treatment (mediastinoscopy, insertion of a central venous access device and insertion of a feeding tube are not considered major surgery)
21. Current use of therapeutic doses of warfarin sodium or any other Coumadin-derivative anticoagulants.
22. Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of CLL. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions and low-dose systemic corticosteroids (≤25 mg/day of prednisone or equivalent) for endocrine or rheumatologic conditions. During study participation, subjects may receive systemic or other corticosteroids as pretreatment for VAY736 infusions or as needed for treatment-emergent comorbid conditions.
23. Life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at undue risk

24a. [redacted]

[redacted]

Protocol amendment 06 exclusion criterion #24a (denotes the first change to criterion #24)

6 Treatment

6.1 Study treatment

The investigational drug VAY736 will be used in combination with the marketed drug ibrutinib.

6.1.1 Dosing regimen

The dosing cycle is 28 days. Patients will receive ibrutinib once daily continuously and VAY736 by i.v. once every 2 weeks (Days 1 and 15). During the dose escalation part of the study, the dose of ibrutinib will be 420 mg. During the dose expansion part of the study, ibrutinib will be continued at the same dose schedule as tolerated before study enrollment, see exclusion criteria in Section 5.2 for additional information on dose level.

A Q4W dosing schedule may also be evaluated if supported by emerging clinical data (e.g., safety or PK/PD or activity). The escalation of the Q4W dosing schedule will be guided by a separate BLRM. The DLT data available from VAY736 Q2W will be used to derive a MAP prior distribution for the Q4W dosing schedule as described in Section 10.4.2. This decision will be formally documented in dose-escalation meeting minutes and distributed to all study sites.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
VAY736	Powder for solution for infusion	As assigned	Once every 2 weeks or every 4 weeks, as assigned
Ibrutinib	Solid dose (tablet or capsule) for oral use	Dose escalation: 420 mg Dose expansion: 420 mg or highest tolerated dose	Daily (28 day cycles)

6.1.1.1 Instructions for ibrutinib administration

- Patients should be instructed to take their dose at approximately the same time on the appropriate days.
- On days when blood for PK samples needs to be collected, the patient should take the dose in the clinic.
- Each dose should be taken with a glass of water and consumed over as short a time as possible unless otherwise instructed.
- Patients should be instructed to swallow capsules/tablets whole and to not chew or open them unless otherwise instructed. Patients may take either tablets or capsules as they are bioequivalent (Please see latest version of the ibrutinib Package Insert)
- Grapefruit, grapefruit juice and Seville oranges should be avoided during the treatment period of the study
- On days of PK/PD sampling, every effort must be made to capture the time of any vomiting within 8 hours of drug administration.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.
- If the patient forgets to take his/her daily dose of ibrutinib, then he/she should take the dose within 8 hours after the missed dose. If more than 8 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose.
- Refer to the ibrutinib package insert for additional information.

Patients should inform the investigational site staff of any missed or delayed doses.

6.1.1.2 Instructions for VAY736 administration

Refer to VAY736 pharmacy manual for information.

6.1.2 Ancillary treatments

Mild to moderate infusion related reactions have been reported in VAY736 clinical trials of autoimmune diseases. For the first two infusions, premedication for the risk of infusion reactions is required. Premedications should be administered 30 minutes to 2 hours prior to each of the first two infusions of VAY736 and should include oral acetaminophen 1,000 mg (or equivalent), oral or intravenous antihistamine, and intravenous corticosteroid (prednisolone 100 mg or equivalent) or similar prophylaxis based on institutional guidelines. For subsequent infusions

[redacted]

(infusions three and beyond), premedication may be administered if deemed appropriate by the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade ≥3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study. The CTCAE category of "Infusion related reaction" should be used to describe study treatment related infusion reactions, unless the investigator considers another category, such as "Allergic reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Refer to Section 6.3 and Section 6.3.2 and Table 6-4

6.1.5 Treatment duration

Patients will receive VAY736 and ibrutinib in combination for up to a total of six cycles. Patients will continue on VAY736 and ibrutinib therapy for Cycle 7 and Cycle 8 if the patient has evidence of disease at the radiological assessment or abnormal blood counts defined by IWCLL response criteria at C6D15. Starting with C7D1, VAY736 will be discontinued if the patient has no evidence of disease in radiological assessment and normal blood at C6D15 and ibrutinib will be administered for the next two cycles. [redacted] Further treatment with ibrutinib is dependent upon the outcome of the assessment that is conducted at C9D1 (see Section 7.1.2).

Patients may be discontinued from treatment with the study drug(s) earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient. Patients, who discontinue VAY736 for reasons other than disease progression prior to 6 cycles of treatment, may continue with ibrutinib through the C9D1 assessment. Patients who discontinue ibrutinib for reasons other than disease progression prior to 6 cycles of treatment may continue with VAY736 through cycle 6 and have a disease assessment at C9D1. Patients who have disease progression and who have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with the agent(s) being administered at the time disease progression is recorded. In addition, treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator.

A patient who has experienced an interruption of more than 28 days of either one or both drugs may remain on study if the patient has experienced clinical benefit and the investigator believes it is in the best interest of the patient to remain on study and such action is agreed to by Novartis. Both the decision and documentation of the discussion with Novartis, must be available in the source documentation and described as an investigator comment in the eCRF.

[redacted]

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

6.2.1.1 Starting dose rationale for ibrutinib

Patients will be treated with the standard, approved dose of ibrutinib (420 mg). Ibrutinib will be taken orally continuously on 28- day cycles. This ibrutinib dose will not be escalated. See Section 1.2, Section 2.3 and Section 6.1 as well as the ibrutinib package insert for additional information.

6.2.1.2 Starting dose rationale for VAY736

The starting dose of VAY736 is 0.3 mg/kg i.v. Q2W on a 28-day cycle. The selection of the starting dose for this study in CLL patients was determined based on the available PK/PD modeling developed for a single agent study in RA. Differences between RA and CLL patients were considered for the simulations, including higher B cell baseline due to the presence of leukemia, lower [redacted] density (Rogier van Gent et al 2008, Defoiche et al 2008, Mihalcik et al 2010), and potentially compromised ADCC effect due to long-term pre-treatment of ibrutinib (Kohrt et al 2014, Ysebaert et al 2014). Simulations suggest that VAY736 at 0.3 mg/kg i.v. [redacted]

The DLT data available from VAY736 Q2W will be used to derive a MAP prior distribution for the Q4W dosing schedule and separate BLRM will be set up for Q4W schedule. The starting dose for Q4W will not exceed the highest tolerated dose evaluated using the Q2W schedule and satisfies the EWOC criteria for Q4W.

6.2.1.3 VAY736 in combination with ibrutinib

No DDI is expected, and minimal overlapping toxicity is predicted (see Section 1.3.3 and Section 1.3.4). Based on these prior safety data and the assumptions for DDI, the starting dose combination satisfies the EWOC criteria within BLRM (see Section 14.2)

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels of VAY736 that may be evaluated during this trial. Ibrutinib will be administered at 420 mg daily during dose escalation. During the dose expansion part of the study, ibrutinib will be continued at the same dose schedule as tolerated before study enrollment.

[redacted]

Table 6-2 VAY736 provisional dose levels

Dose level	Proposed dose of VAY736*
-1**	0.1 mg/kg
1	0.3 mg/kg
2	1 mg/kg
3***	3 mg/kg

*Proposed dose regardless of whether Q2W or Q4W regimen is used. It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK, or PD.

**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

***If clinically indicated, dose levels higher than 3.0 mg/kg may be investigated.

6.2.3 Guidelines for dose escalation and determination of MTD/RD

The MTD is defined as the highest combination drug doses not expected to cause DLT in 33% or more of the treated patients in the first cycle of treatment. Adverse events and laboratory abnormalities considered to be DLTs are defined in Table 6-3. This MTDs or a lower dose combination will then be selected as the RD(s).

The BLRM provides an estimate of the combination of VAY736 and ibrutinib not exceeding the MTD. Typically the MTD is the highest tested combination with less than 25% risk of excessive toxicity (see Section 10.4.2).

The Recommended Dose (RD) will be a dose that is less than or equal to MTD and has, in the view of the investigators and Novartis study personnel, the most appropriate benefit-risk assessment based on the review of safety and tolerability, PK, PD, and activity information. Note, that it is possible that the MTD may not be reached in some situations.

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of 0.3 mg/kg i.v. Q2W of VAY736 in combination with 420 mg of ibrutinib daily.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria and a minimum of three patients are determined to be evaluable. If only 2 patients in a cohort are evaluable and neither subject has experienced a treatment-related clinically significant non hematological toxicity > CTCAE grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade $\geq$ 2 toxicity data during Cycle 1, PK, and PD data from evaluable patients. The recommended dose for the next cohort of subjects will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle.

[redacted]

The adaptive Bayesian methodology provides an estimate of all dose levels of VAY736 in combination with 420 mg daily ibrutinib that does not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle. In all cases, following the half log principle for dose escalation of biologic agents, the dose for the next cohort will not exceed a 3.16 fold increase from the previous dose of VAY736. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

Any dose escalation decisions made by investigators and Novartis personnel will not exceed the dose level recommended by the BLRM using the EWOC principle. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLT observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose cohort only if the combination still meets the EWOC criteria and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose combination as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose combination to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC criteria are satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for expansion. The MTD declaration will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
   b. minimum of 15 patients have already been treated on the trial.
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

[redacted]

6.2.3.1 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.2 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first two cycles of treatment. After the second cycle is completed, individual patients may be considered for treatment at a dose of VAY736 that is higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of VAY736, he or she must have tolerated the lower dose of VAY736 for at least two cycles of therapy (e.g., he or she must not have experienced at the lower dose pair originally assigned a toxicity of non-hematological CTCAE grade ≥ 2 for which relationship to study drug cannot be ruled out). Moreover, the new, higher dose level of VAY736 with which the patient is to be treated must be a dose that has completed evaluation in a dose-escalation meeting and that has not exceeded the MTD estimated by the Bayesian model given all available data.

Documented consultation with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record CRF.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with the combination of VAY736 and ibrutinib and meets any of the criteria included in Table 6-3. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

[redacted]

Table 6-3 Criteria for defining dose-limiting toxicities

For the purpose of dose escalation, DLT is defined as:	
Any Grade 4 AEs are DLTs with the exception of:	
	Neutropenia lasting ≤ 7 days (G-CSF may be used to treat patients who have developed dose-limiting neutropenia, as per institutional guidelines)
	Lymphopenia or Leukopenia unless clinically significant
	Electrolyte abnormalities that are not associated with clinical sequelae or deemed to be not clinically significant and are corrected with appropriate management or supplementation within 72 hours of the onset.
	Platelet count CTCAE grade 4 lasting ≤ 7 days
	Thrombocytopenia not associated with clinically significant bleeding
	Infection without neutropenia lasting for ≤ 7 days
	Tumor lysis syndrome (TLS) persisting for ≤ 7 days despite optimal treatment
Any Grade 3 AEs are DLTs with the exception of:	
	Lymphopenia or leukopenia unless clinically significant
	Infusion reaction that resolves to ≤ Grade 1 within 6 hours.
	Infection without neutropenia lasting for ≤ 7 days
	Febrile neutropenia CTCAE grade 3
	Serum lipase and/or serum amylase (asymptomatic) ≤ 7 consecutive days
	Nausea and vomiting that resolves within 2 days after starting optimal anti-emetic therapy.
	Thrombocytopenia without significant bleeding.
	Anemia that resolves within 7 days in the absence of transfusion
	Isolated AST or ALT for ≤ 7 days
	Diarrhea that resolves within 2 days after starting optimal anti-diarrhea treatment.
	Rash or photosensitivity lasting ≤ 7 days despite skin toxicity treatment
	Fatigue that resolves within 7 days
	Hypertension lasting ≤ 7 days despite treatment
	TLS persisting for ≤ 7 days despite optimal treatment
	Electrolyte abnormalities that are not associated with clinical sequelae and are corrected with appropriate management or supplementation within 72 hours of the onset
	Clinically insignificant abnormal laboratory values lasting ≤ 7 days
	Hyperglycemia ≤ 7 days
The following Grade 2 AEs are considered DLTs:	
	Newly emerging total bilirubin ≥ 2 x ULN with ≥ CTCAE Grade 2 AST/ALT.
	Total bilirubin lasting longer than 7 days
Other AEs	
	Any AE that leads to a dose reduction during the DLT observation period will be considered as a DLT.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Dose delays or adjustments are permitted in order to allow the patient to continue study treatment. If during the first cycle of treatment, a patient experiences an AE meeting the criteria for DLT as outlined in Table 6-3, treatment should be held. Following interruption, treatment may resume at a reduced level if the toxicities resolve to grade 1 or to the patient's baseline

[redacted]

value within the timeframes outlined in Table 6-4. If the AE recurs any time after treatment is restarted, treatment must be discontinued. Adverse events that occur outside the first cycle of treatment should be managed as outlined below and in Table 6-4.

6.3.1.1 VAY736

Dose interruptions and/or reductions for VAY736 are recommended in order to allow patients to continue the study treatment. Upon the first dose adjustment, the dose of VAY736 should be reduced to the next lowest safe dose (or the -1 dose if toxicity occurs in the first cohort) as described in Table 6-2. Dose reduction below -1 dose level is not permitted. These dose modifications are summarized in Table 6-4. Each patient is allowed only 2 dose reductions of VAY736. Further dose reduction may be permitted for patients who have benefitted from treatment upon documented agreement by Novartis. A patient must discontinue treatment if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

6.3.1.2 Ibrutinib

For patients who do not tolerate treatment with ibrutinib, dose interruptions and/or reductions should be undertaken as directed in the package insert and per institutional standard. Ibrutinib dose should be held if VAY736 is interrupted for toxicity that is not related to infusion reactions and resumed as per package insert following resolution of toxicity.

6.3.1.3 VAY736 and ibrutinib

Any dose changes must be recorded on the Dosage Administration Record eCRF.

If a patient requires a dose interruption of > 28 days of either VAY736 or ibrutinib from the intended day of the next scheduled dose, then the patient must be discontinued from the study unless otherwise specified in Section 6.1.5. Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 6.3.2.

[redacted]

Table 6-4 Criteria for dose reduction / interruption and re-initiation of VAY736 treatment for adverse drug reactions.

Dose modifications for VAY736	
Worst toxicity CTCAE Grade[a] (value) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grades 1 -3	Maintain dose level
Grade 4 (ANC < 500/mm3)	Hold VAY736 until ANC ≥ 0.5 x 10^9/L, then resume VAY736 at same dose levels (with G-CSF support) or lower dose levels at investigator discretion.
Thrombocytopenia	
Grade 4 (PLT < 25,000/mm3)	Hold VAY736 until ≤ Grade 3 then resume VAY736 at same dose levels or lower dose levels at investigator discretion
Febrile neutropenia (ANC < 1.0 x 109/L, fever ≥ 38.5°C)	Hold VAY736 until ANC ≥ 0.75 x 109/L, then resume VAY736 at same dose levels (with G-CSF support) or lower dose levels at investigator discretion.
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Delay study treatment until resolved to Grade 1 or baseline If resolved by ≤ 7 days maintain dose level If resolved ≥ 7 days reduce one dose level
Grade 3 (> 3.0 - 6.0 x ULN)	Delay study treatment until resolved to Grade 1 or baseline If resolved by ≤ 7 days maintain dose level If resolved ≥ 7 days reduce dose of VAY736
Grade 4 (> 6.0 x ULN)	Omit dose and discontinue patient from study drug treatments
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN	Omit dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level

[redacted]

> 3.0 - 10.0 x ULN*	Omit dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 7 days, then ↓ 1 dose level If resolved in > 7 days, then discontinue patient from study drug treatments. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN*	Discontinue patient from study drug treatments The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN > 3.0 - 5.0 x ULN For patients with baseline value ≤ 3.0 x ULN	Maintain dose levels Maintain dose levels. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose levels
> 5.0 - 10.0 x ULN For patients with baseline value ≤ 3.0 x ULN	Omit doses. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, ↓ 1 dose level
For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
> 10.0 - 20.0 x ULN	Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then↓ 1 dose level.
> 20.0 x ULN	Discontinue patient from study drug treatment Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.

[redacted]

Combined [c] elevations of AST or ALT and total bilirubin	
AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d]	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grades 1-2	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose until resolved to Grade ≤,1 or baseline then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN)	Omit dose and discontinue patient from study drug treatment.
Vascular disorders	
Hypertension	
CTCAE Grade 3	Omit dose until resolved to Grade ≤,1 or baseline then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
CTCAE Grade 4	Omit dose and discontinue patient from study drug treatment
Gastro intestinal	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Omit dose and discontinue patient from study drug treatment
Diarrhea**	
Grade 1	Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3	Omit dose until resolved to Grade ≤ 1, then:

[redacted]

	If resolved in ≤ 7 days, then↓ 1 dose level If resolved in > 7 days (despite appropriate therapy), then discontinue patient from study drug treatment
Grade 4	Omit dose Discontinue patient from study drug treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	Maintain dose level. Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	Omit dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	Omit dose Discontinue patient from study drug treament
Infusion Reaction	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting – pre-medicate as outlined in Section 6.1.2. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s) If the AE recurs at the reinitiated slow rate of infusion, and despite pre-medication, then discontinue patient from study
Grade 3 or 4	Discontinue treatment
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3 or 4	Hold VAY736 until resolved to ≤ Grade 1 or baseline. If toxicity resolves within 7 days, resume at the same dose. If treatment delay is > 7 days and ≤ 28 days, restart at lower dose level of the VAY736. If delay is greater than 28 days, discontinue treatment.

All dose modifications should be based on the worst preceding toxicity.

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03)

[redacted]

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)

[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

[d] "Cholestasis" defined as ALP elevation (>2.0 xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.

** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

Table 6-5 outlines the follow-up evaluation recommended for toxicities of specific types and CTCAE grades.

Table 6-5 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
Blood and lymphatic system disorders	If CTCAE Grade 4 neutropenia, thrombocytopenia or anemia, or febrile neutropenia occurs, test pertinent labs at least weekly until resolution to baseline or stabilization.
Hepatic	If a hepatic adverse event occurs, ALT, AST and total bilirubin must be measured at least once a week until resolution to CTCAE Grade ≤ 1 or baseline. In patients with total bilirubin Grade ≥ 2 (any duration) bilirubin should be fractionated into total/direct or indirect/direct components and any additional evaluation as clinically indicated by these results should be performed
Investigations (metabolic) Amylase or lipase ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2, continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver disease. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Cardiac disorders QT and ECG ECG changes indicative of ischemic event	Twice weekly ECGs until normalization or stabilization of ECG findings

[redacted]

[redacted]

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

The use of growth-factor support (e.g. filgrastim, pegfilgrastim, erythropoietin, or darbepoetin) should follow standard practice according to product information and per institutional guidelines. Growth factors should not be administered to allow for patient eligibility at screening. Blood/platelet transfusions, the use of bisphosphonates and topical steroid products, and daily corticosteroid use of $\leq$ 10 mg/day prednisone (or equivalent) is permitted at the discretion of the treating physician. Therapeutic doses of anticoagulant will not be permitted. Low doses of warfarin for line patency are allowable.

Limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy following a documented discussion with Novartis. Such local therapies administrated during the study treatment must be listed on the Concomitant radiotherapy/surgery case report form (CRF) page.

6.4.2 Permitted concomitant therapy requiring caution

Not Applicable

6.4.3 Prohibited concomitant therapy

Ibrutinib is primarily metabolized by CYP3A. The concomitant use of CYP3A inhibitors or inducers is likely to alter the exposure of ibrutinib, therefore moderate to strong CYP3A inhibitors and strong CYP3A inducers should not be used during this study. Please refer to the ibrutinib package insert for additional information.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable.

[redacted]

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the clinical database.

6.5.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort will be coordinated by Novartis or designee.

6.5.3 Treatment blinding

Not applicable

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take ibrutinib as per protocol. Ibrutinib will be dispensed to the patient by authorized site personnel only. VAY736 will be given as an IV infusion at the study center. For specifics on the administration of VAY736, see the Pharmacy Manual. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Instructions for the preparation and storage conditions are described in the pharmacy manual.

6.6.1 Study treatment packaging and labeling

VAY736, will be provided as open label bulk medication and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Ibrutinib, will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength) or randomization number if appropriate.

The storage conditions for study drug will be provided on the label.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

[redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (VAY736 and ibrutinib) in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list all of the assessments and indicate with an “X”, the visits when they are performed. Unscheduled testing may be conducted as necessary to address safety concerns. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which assessment produce data to be entered into the database (D) or remain in source documentation only (S) (Category column). No CRF will be used as a source document.

C1D1 assessments can be conducted within 3 days prior to C1D1. On treatment assessments can be conducted within 3 days prior to the planned assessment. If screening assessments are conducted within 3 days of C1D1, they do not need to be repeated for C1D1.

[redacted]

After C1D1, tests and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for assessments except imaging and PK. For PK samples, with the exception of collection(s) made on Day 1 (corresponding with dosing), if PK assessment must be delayed for scheduling purposes, it is mandatory that the correct date and time of the collection are captured in the eCRF. On PK collection days, the time windows are provided in Table 7-6, Table 7-7, and Table 7-8. In situations when dosing is delayed, PK collections should also be delayed until the subsequent dose is given. See Section 7.2.1 for windows on imaging.

[redacted]

Table 7-1 Visit evaluation schedule for Q2W VAY736 dosing regimen

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4		Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**15**			
Obtain Informed Consent	D	7.1.1.1	X																			
Demography	D	7.1.1.2	X																			
Inclusion/exclusion criteria	D	5	X																			
Relevant medical history/current medical conditions	D	7.1.1.2	X																			
[redacted]																						
Diagnosis and extent of cancer	D	7.1.1.2	X																			
Prior antineoplastic therapy	D	7.1.1.2	X																			
Antineoplastic therapies since discontinuation of study treatment	D	7.1.2																			X	X
Prior/concomitant medications	D	7.1.1.2	X	Continuous																		

[redacted]

Physical examination	S	7.2.2.1	X	X				X	X		X					X		X (Q3M after C9)				
Performance status	D	7.2.2.4	X	X					X		X					X		X (Q3M after C9)		X		
Height	D	7.2.2.3	X																			
Weight	D	7.2.2.3	X	X				X	X		X					X		X (through C6 or through C8 if continuing VAY736 treatment)				
Vital signs	D	7.2.2.2	X	X					X		X					X		X				
[redacted]																						
Laboratory assessments		7.2.2.5																				
Hematology	D	7.2.2.5.1	X	X	X	X		X	X	X	X				X	X	X	X (Q3M after C9)	X (C5&C6) (Additionally C7&C8 if continuing VAY736 treatment)	X		
Chemistry	D	7.2.2.5.2	X	X	X	X		X	X	X	X				X	X	X	X (Q3M after C9)	X (C5&C6) (Additionally C7&C8 if continuing VAY736 treatment)	X		
Direct and indirect Coomb's test	D	7.2.2.5	X																			
B2-microglobulin	D	7.2.2.5	X																			
Quantitative immunoglobulins	D	7.2.2.5	X								X							X (C6& C9)				

Thyroid Panel	D	7.2.2.5	X																		
Coagulation	D	7.2.2.5	X	X																X	
Urinalysis	D	7.2.2.5.3	X																		
[redacted]																					
Efficacy assessment																					
Radiologic[1] evaluation	D	7.2.1	X													X		X (C9)	X(C6)			X
[redacted]																					
[redacted]	D	[redacted]																			
Ibrutinib resistance mutation	D	7.2.2.7	X													X		X (C7 & C9)				X
ECG	D	7.2.2.6.1	X																	X		
Safety																						
Adverse events	D	8	X	Continuous																		
[redacted]																						

[redacted]

[redacted]

VAY736 administration	D	6.1.1		X				X	X	X	X				X	X	X	X (through C6 if the patient has no evidence of disease at the radiological assessment and normal blood counts at C6D15 or through C8 if there is evidence of disease at the radiological assessment or abnormal blood counts at C6D15)	X (through C6 if the patient has no evidence of disease at the radiological assessment and normal blood counts at C6D15 or through C8 if there is evidence of disease at the radiological assessment or abnormal blood counts at C6D15)			
Ibrutinib administration	D	6.1.1 & 7.1.2		Continuous daily dosing through C9D1																	
PK sampling (VAY736)	D	7.2.3.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (C5, C6 only) (Additionally C7, C8 if continuing VAY736 treatment)	X (C5 & C6 only) (Additionally C7, C8 if continuing VAY736 treatment)	X		

[redacted]

PK sampling (ibrutinib)	D	7.2.3.1		X	X		X		X		X					X		X (through C6 or through C8 if continuing VAY736 treatment)		X		
VAY736 Ig	D	7.2.3.1		X				X	X		X					X		X (through C6 or through C8 if continuing VAY736 treatment)		X		
[redacted]																						
End of study	D	7.1.5																			X	X

Note: [1]. During TTP efficacy follow up (every 3 months), radiological evaluations will be performed every 6 months

[2] [redacted]

[redacted]

Table 7-2 Visit evaluation schedule for Q4W VAY736 dosing regimen

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4	Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**1**	**15**			
Obtain Informed Consent	D	7.1.1.1	X																		
Demography	D	7.1.1.2	X																		
Inclusion/exclusion criteria	D	5	X																		
Relevant medical history/current medical conditions	D	7.1.1.2	X																		
[redacted]																					
Diagnosis and extent of cancer	D	7.1.1.2	X																		
Prior antineoplastic therapy	D	7.1.1.2	X																		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.2																		X	X
Prior/concomitant medications	D	7.1.1.2	X	Continuous																	

[redacted]

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4	Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**1**	**15**			
Physical examination	S	7.2.2.1	X	X				X	X		X					X	X (Q3M after C9)				
Performance status	D	7.2.2.4	X	X					X		X					X	X (Q3M after C9)		X		
Height	D	7.2.2.3	X	X																	
Weight	D	7.2.2.3	X	X					X		X					X	X (through C6 or through C8 if continuing VAY736 therapy)				
Vital signs	D	7.2.2.2	X	X					X		X					X	X				
[redacted]																					
Laboratory assessments																					
Hematology	D	7.2.2.5.1	X	X	X	X			X		X					X	X (Q3M after C9)	X (C6)	X		
Chemistry	D	7.2.2.5.2	X	X	X	X			X		X					X	X (Q3M after C9)	X (C6)	X		
Direct and Indirect Coomb's test	D	7.2.2.5	X																		
B2-microglobulin	D	7.2.2.5	X																		
Quantitative immunoglobulins	D	7.2.2.5	X								X						X (C6& C9)				
Thyroid Panel	D	7.2.2.5	X																		
Coagulation	D	7.2.2.5	X	X															X		

[redacted]

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4	Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**1**	**15**			
Urinalysis	D	7.2.2.5.3	X																		
[redacted]																					
Efficacy assessment																					
Radiologic[1] evaluation	D	7.2.1	X													X	X (C9)	X(C6)			X
[redacted]																					
[redacted]	D	[redacted]																			
Ibrutinib resistance mutation	D	7.2.2.7	X													X	X (C7 & C9)				X
ECG	D	7.2.2.6.1	X																X		
Safety																					
Adverse events	D	8	X	Continuous																	
[redacted]																					

[redacted]

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4	Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**1**	**15**			
[redacted]																					
VAY736 administration	D	6.1.1		X					X		X					X	X (through C6 if the patient has no evidence of disease at the radiological assessment and normal blood counts at C6D15 or through C8 if there is evidence of disease at the radiological assessment or abnormal blood counts at C6D15)				
Ibrutinib administration	D	6.1.1 & 7.1.2		Continuous daily dosing through C9D1																	
PK sampling (VAY736)	D	7.2.3.1		X	X	X	X	X	X		X	X	X	X	X	X	X (C5, C6)		X		

[redacted]

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4		Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**		**1**	**15**			
																		(Additionally C7, C8 if continuing VAY736 treatment)				
PK sampling (ibrutinib)	D	7.2.3.1		X	X		X		X		X					X		X (through C6 or through C8 if continuing VAY736 treatment)		X		
VAY736 Ig	D	7.2.3.1		X				X	X		X					X		X (through C6 or through C8 if continuing VAY736 treatment)		X		
[redacted]																						
End of study	D	7.1.5																			X	X

[redacted]

	Category	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3					Cycle 4	Subsequent cycles		End of study treatment (EoT)	30-day Follow up	TTP
Day of cycle				**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**1**	**15**			
	Note: [1] During TTP efficacy follow up (every 3 months), radiological evaluations will be performed every 6 months [2] [redacted]																				

[redacted]

7.1.1 Screening

Screening starts after a patient has provided written informed consent to participate in the study and ends on the day of the first dose of VAY736 and ibrutinib. Screening assessments have to be done within 21 days prior to the first dose with the exception of baseline tumor assessments and informed consent. Screening tumor assessments collection can be conducted within 28 days of first dose and informed consent can be obtained within 3 months of the first dose. Assessments conducted prior to obtaining informed consent as a part of routine disease care can be used to satisfy eligibly criteria as long as the procedures were performed within the allowed windows.

7.1.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on VAY736 for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

7.1.1.2 Patient demographics and other baseline characteristics

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, the diversity of the study population needs to be assessed as required by Health Authorities.

7.1.2 Treatment period

The study treatment period for each patient begins when the patient receives the first dose of VAY736 in combination with ibrutinib and ends at C9D1. Patients will receive the combination of VAY736 and ibrutinib for six cycles. Patients will continue VAY736 for 2 additional cycles in combination with ibrutinib if there is evidence of disease at the radiological assessment or abnormal blood counts defined by IWCLL response criteria at C6D15. For the purpose of scheduling and evaluations, a treatment cycle is 28 days. VAY736 will be discontinued at C7D1 if the patient shows a complete radiological response or normal blood counts at C6D15 and ibrutinib will continue for an additional 2 cycles. All patients will have final response assessment [redacted] Further treatment or follow-up will depend on status of response at C9D1. One of the following actions will be taken for patients:

- Patients who experience disease progression at C9D1 (or any time prior to C9D1) will discontinue treatment and will have required end of treatment assessments conducted.
- Patients whose disease is assessed as stable disease, partial response, at C9D1 may continue ibrutinib and will be followed every 3 months for two years for TTP assessments,

[redacted]

with the exception of CT scans which will be performed every 6 months unless the patient experiences disease progression or the administration of a new therapy. If the patient continues to receive ibrutinib past C9D1, the details of administration will be recorded on the Antineoplastic therapies since discontinuation eCRF.

- For patients whose disease is assessed as CR at C9D1, investigators may consider discontinuing ibrutinib, and be followed every 3 months for two years for TTP assessments, with the exception of CT scans which will be performed every 6 months unless the patient experiences disease progression or the administration of a new therapy. Although investigators may consider discontinuing ibrutinib if patients have a CR at C9D1, if the patient continues to receive ibrutinib past C9D1, the details of administration will be recorded on the Antineoplastic therapies since discontinuation eCRF.

Patients who discontinue one of the combination drugs (ibrutinib or VAY736) prior to six cycles of treatment for reasons other than disease progression may continue the other drug until the end of treatment period (VAY736 until C6D28 or ibrutinib until C8D28). All patients regardless of study treatment duration, who have not progressed, will have a final disease assessment at C9D1 (end of treatment period).

7.1.3 Discontinuation of study treatment

Patients who discontinue study treatment (as defined in Section 7.1.2) on or before C9D1 for any reason will have an EOT visit and assessments conducted within 14 days of the last dose of study treatment or within 14 days of the decision to discontinue study treatment, see Table 7-1 or Table 7-2 for assessments to be conducted.

During the study treatment period (defined in Section 7.1.2), patients will be monitored to assess safety and any anti-tumor activity of the treatment.

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

Study treatment must be discontinued under the following circumstances:

- Adverse events, that results in a significant risk to the patient's safety.
- The following deviation from the prescribed dose regimen for study treatment: dose interruption of > 28 days from the intended day of the next scheduled dose, unless otherwise specified in Section 6.1.5.
- Pregnancy
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study terminated by Novartis
- Patient/guardian decision

Patients who have achieved a CR may discontinue treatment at investigator discretion.

[redacted]

7.1.3.1 Replacement policy

Escalation part:

Patients will not be replaced on study. However, if a subject is considered as non-evaluable for the DDS, enrollment of a new subject to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable subjects is achieved within the cohort. Minimum and maximum numbers of evaluable subjects per cohort are defined in Section 6.2.3.

Expansion part:

During the dose expansion part no replacements will be needed.

7.1.4 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

7.1.5 Follow up for safety evaluations

All patients will be followed for a 30 day safety follow-up period subsequent to completion of VAY736 therapy. Patients who continue on ibrutinib after the discontinuation of VAY736 regardless of when this occurred will be followed for safety according to the ibrutinib package insert. No new AEs or SAEs will be collected beyond the 30 day safety follow-up or during the two-year efficacy follow up period. Any data that is collected should be added to the Adverse Events CRF and the Concomitant Medications CRF. The end of study eCRF should be

[redacted]

completed after the patient has discontinued from the study, either after the 30 day safety follow-up period or at progression that occurs during the two-year efficacy follow-up.

7.1.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy will be evaluated as per the IWCLL Guidelines (Appendix 1).

Tumor assessments will be performed at screening and according to the schedule of -assessments (Table 7-1 or Table 7-2, as applicable based on the dosing regimen of VAY736). All screening tumor assessments should be performed as closely as possible to the start of treatment (preferably within 7 days) and never more than 28 days before the start of treatment. On-treatment radiological examinations and MRD assessments have a +/- 7 day window.

Clinical suspicion of disease progression at any time will require a disease evaluation promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed disease evaluation for any reason, subsequent tumor assessments should be performed according to the originally planned schedule unless a scan has been performed within 28 days.

All patients discontinuing from the study for progressive disease must have their disease progression documented.

Chest, abdomen and pelvis CT scans are required for all subjects at screening. If clinically indicated, neck CT scans should also be acquired at screening. Post baseline scans should only be performed in these anatomical regions that demonstrated disease at baseline. In case of clinical complete response, confirmation scans of chest, abdomen and pelvis are required and neck if appropriate.

CT scans should be acquired with intravenous (i.v.) contrast. If a patient is known to have a medical contraindication to CT i.v. contrast agent or develops a contraindication during the study, a CT scan without contrast should be acquired. If inguinal and/or femoral nodes are present, every effort should be made to ensure that pelvis CT scans cover both inguinal areas in their entirety.

Magnetic resonance imaging (MRI) will be allowed only in those cases when CT scans cannot be performed. Each lesion that is measured at baseline/screening must be measured by the same method throughout the study so that the comparison is consistent. For complete details, refer to Appendix 1.

[redacted]

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed as outlined in Table 7-1 or Table 7-2, as appropriate for the dosing regimen of VAY736, until documented disease progression, death, lost to follow-up, or withdrawal of consent.

[redacted] as indicated in Table 7-1 and Table 7-2. [redacted] (Hallek et al 2018). As such, patients will be defined as having [redacted] if they have blood or marrow with <1 CLL cell per 10, 000 leukocytes.

Table 7-3 Disease assessment collection plan

Procedure	Screening/baseline	During treatment/follow-up
CT or MRI *with contrast enhancement* (Chest, Abdomen, Pelvis)	Mandated	Refer to Table 7-1 or Table 7-2, as appropriate for VAY736 dose regimen.
[redacted]	[redacted]	[redacted]

7.2.2 Safety and tolerability assessments

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory measures and vital signs. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will be conducted at screening and during Cycle 1 (Table 7-1 or Table 7-2, as appropriate for VAY736 dose regimen) and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (blood pressure [BP] and pulse). A short physical exam will be at all visits starting from Cycle 2, Day 1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

[redacted]

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 or Table 7-2, as appropriate for the dosing regimen of VAY736.

7.2.2.4 Performance status

ECOG performance status scale will be used as specified in Table 7-1 or Table 7-2, as appropriate for the dosing regimen of VAY736.

Table 7-4 ECOG Performance Status

Score	Performance Status
0	Fully active, able to carry on all pre-disease activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Death

7.2.2.5 Laboratory evaluations

Table 7-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose
Immunology	B2-Microglobulin, quantitative immunoglobulins (IgA, IgG, IgM), Direct and Indirect Coomb's test
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) – only to be done if needed based on Macroscopic Panel findings
Coagulation	Prothrombin time (PT) , International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Thyroid	T4 [free], TSH

[redacted]

7.2.2.5.1 Hematology assessments

Hematology assessments in Table 7-5 will be conducted at the time points listed below on the days outlined in Table 7-1 or Table 7-2, as appropriate for the VAY736 dosing regimen, within the windows outlined in Section 7.1.3.

- C1D1: Pre-dose and 6 hours post-dose
- Remaining time points are collected as per the table. If the collection is on a treatment day, the sample is collected pre-dose.

7.2.2.5.2 Chemistry assessments

Chemistry assessments will be conducted at the time points listed below on the days listed in Table 7-5 on the days outlined in Table 7-1 or Table 7-2, as appropriate for the VAY736 dosing regimen, within the windows outlined in Section 7.1.3.

- C1D1: Pre-dose and 6 hours post-dose
- Remaining time points are collected as per the table. If the collection is on a treatment day, the sample is collected pre-dose.

7.2.2.5.3 Urinalysis

Assessments will be conducted as directed in Table 7-5 on the days outlined in Table 7-1 or Table 7-2 as appropriate for the VAY736 dosing regimen, within the windows outlined in Section 7.1.3.

[redacted]

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed in accordance with institutional practice for patients at screening, end of treatment, and as clinically indicated.

7.2.2.7 Ibrutinib resistance mutation

Blood or bone marrow samples collected on the days outlined in Table 7-1 or Table 7-2 will be analyzed in accordance with the CVAY736Y2102 laboratory manual.

[redacted]

7.2.3 Pharmacokinetics and immunogenicity:

PK samples will be collected from all enrolled patients to assess PK properties of VAY736 and ibrutinib. Immunogenicity (IG) samples will also be collected to monitor appearance of anti-drug antibodies (ADAs) directed against VAY736. Refer to Table 7-6, Table 7-7 and Table 7-8 for details on PK and IG sample collections.

[redacted]

7.2.3.1 Pharmacokinetics and immunogenicity blood sample collection and handling

If the dosing of Cycle 3 Day 1 for VAY736 or Cycle 1 Day 8 for ibrutinib is delayed, the PK sampling for the full PK profile should be delayed until the dose of VAY736 or ibrutinib is administered. On the date of administration, the PK samples should be collected to match the scheduled time points for Cycle 3 as outlined in Table 7-6 or Table 7-7 for VAY736 or Cycle 1 in Table 7-8 for ibrutinib.

Exact dates and actual PK blood draw times will be recorded on the appropriate eCRF. Any sampling problems (e.g. patient administrated with study drug before the PK blood draw took place) must be noted in the comments section of the eCRF and on appropriate source documentation.

If any of the scheduled sampling times are missed or a sample is not drawn according to this schedule, the actual collection date and time will be recorded and the remaining samples will be collected on schedule whenever possible.

If vomiting occurs within 8 hours following ibrutinib administration on the day of PK sampling, where post-dose time-points are collected, no additional study medication should be taken in an effort to replace the material that has been vomited. The time (using the 24-hour clock) of vomiting should be recorded in the Adverse Events eCRF.

Unscheduled PK samples should be collected if any of the following events occur:

- If a patient treated with investigational drugs experiences an AE that results in an unscheduled visit or fits the criteria of a SAE or DLT, as determined by the investigator.
- Whenever an ECG with a QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501 ms result is known. The exact time of sample collection should be noted in the unscheduled eCRF.
- In the event of other clinically significant AEs (such as infusion reaction/anaphylaxis) or if immunogenicity is suspected.
- During safety follow-up period either at or prior to end of safety follow-up period

Residual PK and IG serum or plasma samples used for PK and IG analysis may also be used for [redacted] metabolites and/or PD analyses related to VAY736 or ibrutinib therapy and cancer. If conducted, these results will be reported separately.

Refer to the [VAY736Y2102 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK and immunogenicity samples.

[redacted]

Table 7-6 Pharmacokinetic blood collection log for VAY736 Q2W dosing (VAY736, IG, [redacted])

Cycle	Day	Scheduled Time Point (hr)[a,b]	Analytes[c,d]
1	1	Pre-dose [b]	VAY736, IG, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736, [redacted]
		Post-dose 6 hr (±15 min)	VAY736
1	2	Post-dose 24 hr (±1 hr)	VAY736, [redacted]
1	4	Post-dose 72 hr (±2 hr)	VAY736
1	8	Post-dose 168 hr (±2 hr)	VAY736, [redacted]
1	15	Pre-dose	VAY736, IG, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
2	1	Pre-dose	VAY736, IG, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
2	15	Pre-dose	VAY736
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
3	1	Pre-dose	VAY736, IG, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736, [redacted]
3	2	Post-dose 24 hr (±1 hr)	VAY736, [redacted]
3	4	Post-dose 72 hr (±2 hr)	VAY736
3	8	Post-dose 168 hr (±2 hr)	VAY736, [redacted]
3	15	Pre-dose	VAY736, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
4	1	Pre-dose	VAY736, IG, [redacted]
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
4	15	Pre-dose	VAY736
		Post-dose 2 hr or End of infusion (±5 min)	VAY736
5	1	Pre-dose	VAY736, IG, [redacted]
5	15	Pre-dose	VAY736
6	1	Pre-dose	VAY736, IG, [redacted]
6	15	Pre-dose	VAY736
7 (if applicable)	1	Pre-dose	VAY736, IG, [redacted]
7 (if applicable)	15	Pre-dose	VAY736
8 (if applicable)	1	Pre-dose	VAY736, IG, [redacted]

[redacted]

Cycle	Day	Scheduled Time Point (hr)[a,b]	Analytes[c,d]
8 (if applicable)	15	Pre-dose	VAY736
EOT		---	VAY736, IG, [redacted]
Unscheduled		---	VAY736, IG, [redacted]

[a] Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline prior to blood sample collection.

[b] Sampling time is relative to the start of the latest VAY736 infusion; Pre-dose blood samples should be collected prior to the start of the latest VAY736 infusion

[c] VAY736 PK, IG, and [redacted] samples in serum, and [redacted] samples in whole blood

[d] IG blood samples to be collected for anti-drug antibody together with PK samples

[redacted]

Table 7-7 Pharmacokinetic blood collection log for VAY736 Q4W dosing (VAY736, IG, [redacted])

Cycle	Day	Scheduled Time Point (hr)[a,b]	Analytes[c, d]
1	1	Pre-dose [b] Post-dose 2 hr or End of infusion (±5 min) Post-dose 6 hr (±15 min)	VAY736, IG, [redacted] VAY736, [redacted] VAY736
1	2	Post-dose 24 hr (±1 hr)	VAY736, [redacted]
1	4	Post-dose 72 hr (±2 hr)	VAY736
1	8	Post-dose 168 hr (±2 hr)	VAY736, [redacted]
1	15	Post-dose 336 hr (±2 hr)	VAY736, IG, [redacted]
2	1	Pre-dose Post-dose 2 hr or End of infusion (±5 min)	VAY736, IG, [redacted] VAY736
3	1	Pre-dose Post-dose 2 hr or End of infusion (±5 min)	VAY736, IG, [redacted] VAY736, [redacted]
3	2	Post-dose 24 hr (±1 hr)	VAY736, [redacted]
3	4	Post-dose 72 hr (±2 hr)	VAY736
3	8	Post-dose 168 hr (±2 hr)	VAY736, [redacted]
3	15	Post-dose 336 hr (±2 hr)	VAY736, [redacted]
4	1	Pre-dose Post-dose 2 hr or End of infusion (±5 min)	VAY736, IG, [redacted] VAY736
5	1	Pre-dose	VAY736, IG, [redacted]
6	1	Pre-dose	VAY736, IG, [redacted]

[redacted]

Cycle	Day	Scheduled Time Point (hr)[a,b]	Analytes[c, d]
7 (if applicable)	1	Pre-dose	VAY736, IG, [redacted]
8 (if applicable)	1	Pre-dose	VAY736, IG, [redacted]
EOT		---	VAY736, IG, [redacted]
Unscheduled		---	VAY736, IG, [redacted]

[a] Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline prior to blood sample collection.

[b] Sampling time is relative to the start of the latest VAY736 infusion; Pre-dose blood samples should be collected prior to the start of the latest VAY736 infusion

[c] VAY736 PK, IG, and [redacted] samples in serum, and [redacted] samples in whole blood

[d] IG blood samples to be collected for anti-drug antibody together with PK samples

[redacted]

Table 7-8 Pharmacokinetic blood collection log for ibrutinib

Cycle	Day	Scheduled Time Point (hr)	Analytes[b]
1	1	Pre-dose	Ibrutinib
		Post-dose 0.5 hr (±5 min) [a]	Ibrutinib
		Post-dose 2 hr (±5 min) [a]	Ibrutinib
		Post-dose 6 hr (±15 min)[a]	Ibrutinib
1	2	Pre-dose	Ibrutinib
1	8	Pre-dose	Ibrutinib
		Post-dose 0.5 hr (±5 min)[a]	Ibrutinib
		Post-dose 2 hr (±5 min) [a]	Ibrutinib
		Post-dose 6 hr (±15 min)[a]	Ibrutinib
2	1	Pre-dose	Ibrutinib
3	1	Pre-dose	Ibrutinib
4	1	Pre-dose	Ibrutinib
5	1	Pre-dose	Ibrutinib
6	1	Pre-dose	Ibrutinib
7 (if applicable)	1	Pre-dose	Ibrutinib
8 (if applicable)	1	Pre-dose	Ibrutinib
EOT		---	Ibrutinib
Unscheduled		---	Ibrutinib

[a] The need for these time points in expansion phase will be assessed based on emerging PK data analyzed during the dose escalation part of the study

[b]Ibrutinib samples are collected in plasma

7.2.3.2 Analytical method

The assay to quantify ibrutinib in plasma will be a validated liquid chromatography mass spectrometry (LC-MS) assay. The details of the assay will be documented in the [VAY736Y2102 laboratory manual].

The assay to quantify VAY736 in serum will be a validated sandwich ELISA assay. The details of the assay will be documented in the [VAY736Y2102 laboratory manual].

[redacted]

The assay to quantify and assess the ADA against VAY736 in serum will be a validated ECL (Electrochemiluminescence) assay. The details of the assay will be documented in the [VAY736Y2102 laboratory manual].

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring will be conducted as outlined in Section 7.1.5. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

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.

[redacted]

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown).

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate disease assessment method (IWCLL), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an

[redacted]

already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

[redacted]

8.2.2 Reporting

For patients who sign the main study ICF, SAE collection starts at the time of main study informed consent, whether the patient is screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and as outlined in Section 7.1.5 must be reported to Novartis within 24 hours of learning of its occurrence. If a patient starts a post-treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

[redacted]

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

A formal data monitoring board will not be used for this study. Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, during the phase I part of the study Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first cycle of treatment, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level (Section 10.4.2).

8.6 Steering Committee

Not applicable

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Age will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

[redacted]

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

In addition to data entered into the eCRFs, requisition forms may also need to be completed for [redacted] PK sample collection.

9.4 Database management and quality control

Novartis personnel, or designee, will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

[redacted]

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements and all relevant pharmacokinetic and pharmacodynamics measurements.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Patients treated with the same dose level and schedule of VAY736 will be pooled into a single treatment group (includes patients from dose escalation and dose expansion parts) for all safety analysis.

For efficacy all analysis will be provided by dose level in dose escalation and by two arms in dose expansion.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses, but will be reported in the CSR as separate listings.

Continuing events (e.g., AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with a flag to indicate within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

The primary clinical study report (CSR) will be written based on all patient data from the dose escalation and dose expansion parts at the time when all patients have completed the study treatment period, or discontinued the study, or the study is terminated early. The additional data for any patients remaining in safety or disease follow-up beyond the cut-off point will be summarized in a final CSR that will be prepared at the end of study (Section 4.3).

Details of the statistical analysis and data reporting will be provided in the Novartis report and analysis preparation documents finalized prior to database lock.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) and Safety set 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.

[redacted]

10.1.2 Safety set

See definition of FAS

10.1.3 Per-Protocol set

Not applicable

10.1.4 Dose-determining analysis set

The Dose-Determining Set (DDS) includes all patients from the FAS (escalation and expansion parts) 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 the 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 (Section 7.1.3.1).

10.1.5 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all subjects who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subject provides at least one primary PK parameter
- Subject did not vomit within 8 hours after the dosing of ibrutinib

10.1.6 Other analysis sets

Not applicable

10.1.6.1 Efficacy/evaluable set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term for the FAS.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

The duration of exposure in days to VAY736 and ibrutinib as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The duration of exposure will also be presented for the combined study treatment by dose cohort in the dose escalation or by two arms in the dose expansion.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by dose cohort in the dose escalation or by two arms in the dose expansion and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

10.4 Primary objective

The primary objective is to characterize the safety and tolerability of the combination of VAY736 with ibrutinib and to determine the MTD/RD for expansion.

10.4.1 Variable

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Changes in laboratory parameters, vital signs, and electrocardiograms (ECGs)
- Incidence of DLTs during the first treatment cycle (escalation only)
- Dose interruptions, reductions and dose intensity

Estimation of the MTD in the dose-escalation part of the study will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the dose-determining set. This probability is estimated by the statistical models in Section 10.4.2.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤ 28 days following the first administration of study treatment as defined in Section 6.2.4, Table 6-3.

10.4.2 Statistical hypothesis, model, and method of analysis

Safety and tolerability

For the analysis of safety and tolerability endpoints see Section 10.5.3 in addition to DLT as below.

[redacted]

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 (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

Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier). Details of the model are given in (Appendix 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 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%.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent VAY736, and single-agent ibrutinib model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (see Spiegelhalter 2004, Neuenschwander 2010, Neuenschwander 2014). MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the single agent VAY736, and single-agent ibrutinib model parameters is given in Appendix 2 (Section 14.2).

[redacted]

The prior distribution for the interaction parameter was based upon prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in Appendix 2 (Section 14.2).

Starting dose

The starting dose is 0.3 mg/kg Q2W of VAY736 and 420 mg daily ibrutinib (Section 6.2.1). For this dose combination the prior risk of excessive toxicity is 8.9% approximately, which satisfies the EWOC criterion. A full assessment of the prior risk to patients is given in Appendix 2 (Section 14.2).

Change in dose schedule

In the case that additional dosing schedules for VAY736 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 Appendix 2 (Section 14.2).

In addition in case VAY736 Q2W dosing schedule continues and new dosing schedule is explored during dose-escalation, a BLRM of the same functional form described in Appendix 2 (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.

Listing of DLTs

DLTs will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 4.03). Listings and summaries will be based on the DDS.

[redacted]

10.5 Secondary objectives

Refer to Table 3-1 for secondary objectives. The following subsections describe the analysis of related secondary objectives.

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

All efficacy analyses are based on FAS.

Rate of CR at C9 for expansion arm A and arm B: The proportion of patients with CR, assessed by investigators per IWCLL criteria (see Appendix 1 for details) at C9 will be provided. The rate of CR 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* response rate of 20%.

Posterior summaries for CR rate (posterior mean, including 90% credible intervals and the posterior probability that the true CR 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.

Clearance of ibrutinib resistance mutation for expansion arm B is defined as less than 1% mutation bearing alleles (BTKC481 and/or PLCγ2) during treatment. The proportion of patients with negative mutation will be provided along with corresponding 90% exact confidence interval (CI).

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.

Time to progression (TTP) is the time from start of treatment to the date of event which is defined as the first documented progression 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.

TTP will be described using Kaplan-Meier methods and appropriate summary statistics. .

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events and non-serious adverse events will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE

Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE,

[redacted]

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

- Listing of ECG evaluations for all patients with at least one abnormality

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

- Shift table baseline to worst on-treatment result
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

10.5.3.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the SAP prior to database lock (DBL).

10.5.3.6 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose delays and dose reductions. Reasons for dose delays and dose reductions will be listed by patient and summarized.

10.5.4 Pharmacokinetics

PK parameters will be determined using non-compartmental method(s) for VAY736 and ibrutinib. PK parameters such as those listed in Table 10-1 will be estimated and reported, when applicable. PAS will be used in all pharmacokinetic data analysis and summary statistics.

Table 10-1 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)

Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will

[redacted]

not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Summary statistics will be presented for VAY736 and ibrutinib concentrations at each scheduled time point. Descriptive graphical plots of individual concentration versus time profiles and mean concentration versus time profiles will be generated.

Dose Proportionality

The analysis of dose proportionality may be conducted for AUC and Cmax of VAY736 using a power model on log-transformed scale, if data allows. 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.

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.

[redacted]

10.5.4.1 Data handling principles

Concentration values 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.

[redacted]

[redacted]

10.5.6 Resource utilization

Not applicable

10.5.7 Patient-reported

Not applicable

[redacted]

[redacted]

[redacted]

10.7 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 Section 6.2.3.

[redacted]

pharmacokinetic parameters as required. Minimum of fifteen patients are expected to be treated

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis, or designee, will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

[redacted] there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4

[redacted]

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility,

[redacted]

and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

11.10 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the

[redacted]

investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

Albitar A, Ma W, De Dios I, et al. (2015) High Sensitivity Testing Shows Multiclonal Mutations in Patients with CLL Treated with BTK Inhibitor and Lack of Mutations in Ibrutinib-Naive Patients. Blood, 126, 716-716.

Albitar A, Ma W, DeDios I, et al. (2017) Using high-sensitivity sequencing for the detection of mutations in BTK and PLCgamma2 genes in cellular and cell-free DNA and correlation with progression in patients treated with BTK inhibitors. Oncotarget.

Badoux X, Tam C, Lerner S, et al. (2009) Outcome of First Salvage Therapy in Patients With Chronic Lymphocytic Leukemia Relapsing After First-line Fludarabine, Cyclophosphamide, and Rituximab. Clinical Lymphoma & Myeloma, 9, E39-E40.

Barr PTR, Owen CJ, Tedeschi A, et al. (2016) Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. American Society of Hematology Annual Meeting. Blood.

[redacted]

Burger JA, Keating MJ, Wierda WG, et al. (2014) Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. Lancet Oncol, 15, 1090-1099.

Byrd JC, Brown JR, O'Brien S, et al. (2014) Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med; 371(3):213-223.

Byrd JC, Furman RR, Coutre S E, et al. (2015) Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood, 125, 2497-2506.

Byrd JC, Furman RR, Coutre SE, et al. (2013) Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med, 369, 32-42.

Chanan-Khan A, Cramer P, Demirkan F, et al. (2016) Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol, 17, 200-211.

[redacted]

Chen SS, Raval A, Johnson A J et al. (2009a) Epigenetic changes during disease progression in a murine model of human chronic lymphocytic leukemia. Proc Natl Acad Sci U S A, 106, 13433-13438.

Chen SS, Sherman MH, Hertlein E, et al. (2009b) Epigenetic alterations in a murine model for chronic lymphocytic leukemia. Cell Cycle, 8, 3663-3667.

[redacted]

Damle RN, Wasil T, Fais F, et al. (1999) Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood, 94, 1840-1847.

[redacted]

DeClaro RA, McGinn KM, Verdun N, et al (2015) FDA Approval: Ibrutinib for Patients with Previuosly Treated Mantle Cell Lymphoma and Previously Treated Chronic Lymphocytic Leukemia. Clin Cancer Res, 21, 3586-3590.

Defoiche J, Debacq C, Asquith B, et al. (2008) Reduction of B Cell Turnover in Chronic Lymphocytic Leukaemia. Brit J Haematology , 143, 240-247.

Dohner H, Stilgenbauer S, Benner A, et al. (2000) Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med, 343, 1910-1916.

[redacted]

Enzler T, Kater AP, Zhang W et al. (2009) Chronic lymphocytic leukemia of Emu-TCL1 transgenic mice undergoes rapid cell turnover that can be offset by extrinsic CD257 to accelerate disease progression. Blood, 114, 4469-4476.

Furer V, Rondaan C, Heijstek MW, et al. (2020) 2019 Update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases Annals of the Rheumatic Diseases, 79, 39-52.

[redacted]

Gorgun, G, Ramsay AG, Holderried, TA, et al. (2009) E(mu)-TCL1 mice represent a model for immunotherapeutic reversal of chronic lymphocytic leukemia-induced T-cell dysfunction. Proc Natl Acad Sci U S A, 106, 6250-6255.

Hallek, M, Cheson, BD, Catovsky, D, et al. (2018 iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood,131, 2745-2760.

He B, Chadburn A, Jou E et al. (2004) Lymphoma B cells evade apoptosis through the TNF family members BAFF/BLyS and APRIL. J Immunol, 172, 3268-3279.

Jaglowski, SM, Jones, JA, Nagar, V, et al. (2015) Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. Blood, 126, 842-850.

Janssen Research & Development, L. 2016. Investigator's Brochure IMBRUVICATM (ibrutinib) JNJ-54179060. 10.1 ed.

Johnson AJ, Lucas DM, Muthusamy N, et al. (2006) Characterization of the TCL-1 transgenic mouse as a preclinical drug development tool for human chronic lymphocytic leukemia. Blood, 108, 1334-1338.

[redacted]

Kohrt HE, Sagiv-Barfi I, Rafiq S, et al. (2014) Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. Blood, 123, 1957-1960.

Liu TM, Woyach, JA, Zhong Y, et al. (2015) Hypermorphic mutation of phospholipase C, gamma2 acquired in ibrutinib-resistant CLL confers BTK independency upon B-cell receptor activation. Blood, 126, 61-68.

Maddocks KJ, Ruppert AS, Lozanski G, et al. (2015) Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol, 1, 80-87.

[redacted]

Moore P A, Belvedere O, Orr A, et al. (1999) BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science, 285, 260-263.

Nabhan C and Rosen, ST (2014) Chronic lymphocytic leukemia: a clinical review. JAMA, 312, 2265-2276.

[redacted]

Neuenschwander B, Capkun-Niggli G, Branson M, et al. (2010) Summarizing Historical Information on Controls in Clinical Trials. Clin Trials, 7, 5-18.

Neuenschwander B, Matano A, Tang Z, et al. (2014) A Bayesian Industry Approach to Phase I Combination Trials in Oncology. Statistical Methods in Drug Combination Studies: Chapman & Hall.

O'Brien SFR, Coutre S, Flinn I, et al (2016) Five-Year Experience With Single-Agent Ibrutinib in Patients With Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Blood (sup), 128, 233.

O'Brien S, Furman RR, Coutre SE, et al (2014) Ibrutinib as Initial Therapy for Elderly Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lyphoma: an Open-Label, Multicentre, Phase 1b/2 trial. Lancet Oncol, 15, 48-58.

O'Brien S, Furman RR, Coutre S, et al (2018) Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood; 131(17):1910-1919.

Rai KR, Sawitsky A, Cronkite EP, et al. (1975). Clinical staging of chronic lymphocytic leukemia. Blood, 46(2), 219–234.

[redacted]

[redacted]

Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol, 25, 4982-4986.

[redacted]

Shanafelt TD, Borah BJ, Finnes HD, et al (2015) Impact of ibrutinib and idelalisib on the pharmaceutical cost of treating chronic lymphocytic leukemia at the individual and societal levels. J Oncol Pract; 11(3):252-258.

Shanafelt TD, Wang V, Kay NE, et al (2018) A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood; 132(Suppl 1):LBA-4-LBA-4.

[redacted]

Spiegelhalter DJ, Abrams KR, Myles JP (2004) Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Chichester: John Wiley and Sons.

Tam CS, O'Brien S, Plunkett W, et al. (2014) Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). Blood, 124, 3059-3064.

[redacted]

van Gent R, Kater AP, Otto SA, et al. (2008) In Vivo Dynamics of Stable Chronic Lymphocytic Leukemia Inversely Correlate with Somatic Hypermutation Levels and Suggest No Major Leukemic Turnover in Bone Marrow. Cancer Res, 68, 10137-10144.

Wiczer TE, Levine LB, Brumbaugh J, et al (2017) Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv; 1(20):1739-1748.

[redacted]

Woyach JA, Furman RR LiuT-M, Ozer HG, et al. (2014b) Resistance Mechanisms for the Bruton's Tyrosine Kinase Inhibitor Ibrutinib. New England Journal of Medicine, 370, 2286-2294.

Woyach JA, Ruppert AS, Guinn D, et al. (2016) BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. Journal of Clinical Oncology, 0, JCO.2016.70.2282.

[redacted]

Woyach JA, Ruppert AS, Heerema NA, et al (2018) Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med; 379(26):2517-2528.

[redacted]

[redacted]

14 Appendices

14.1 Appendix 1 – Guidelines for NCI CLL Working Group 2018 (IWCLL)

This appendix refers to Hallek et al 2018.

Table 14-1 Response definition after treatment for patients with CLL

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A *and* 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

[redacted]

Table 14-2 Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5. † Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20×10^9/L (20000/µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20000/µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
‡ Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.
§ If the absolute neutrophil count (ANC) reaches < 1×10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1×10^9/L (1000/µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

References

Hallek, M, Cheson, BD, Catovsky, D, et al (2018). iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood, 131, 2745-2760.

[redacted]

14.2 Appendix 2 – BLRM, prior, hypothetical dose escalation scenarios and operating characteristics

This appendix provides details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model.

14.2.1 Statistical model

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part. DLT of the first cycle (28 days) data is used in the model. Due to the different administrations and frequency from historical data for the VAY736 treatment group (as prior data below), the total cycle 1 dose (mg/kg) is used for the VAY736 treatment group in the model. The daily dose (mg) is used for the Ibrutinib treatment group in the model.

14.2.1.1 Single agent parts

The study is planned to administer VAY736 Q2W and Ibrutinib daily with 28-day dosing schedule and DLTs are assessed for the first cycle (28 days).

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:

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

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

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 are the increase in the log-odds of a DLT by a unit increase in log-dose.

14.2.1.2 Interaction

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:

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

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.

[redacted]

14.2.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for VAY736, $\log(\alpha_2)$, $\log(\beta_2)$ for Ibrutinib, and the interaction parameter η. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters for VAY736. A weakly-informative prior is derived for the single-agent model parameters for ibrutinib.

14.2.2.1 Prior distribution for the logistic parameters

14.2.2.1.1 Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies.

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical study VAY736Y2101 and each of the four autoimmunity clinical program historical studies, i.e., s=1,2,3,4,5 represent data from VAY736Y2101, and autoimmunity historical studies VAY736X2101, VAY736X2201, VAY736X2202, and VAY736X2203, respectively. The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi_{g(s)} \sim \text{BVN}\left(\mu, \psi_{g(s)}\right), \qquad \text{s} = 1, \ldots, 5$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi_1 \sim \text{BVN}(\mu, \psi_1)$$

The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1,2$. Covariance matrix ψ_g is defined by the standard deviations τ_{g1}, τ_{g2}, and correlation ρ (a common value for ρ is used across all groups). The parameters τ_{g1} and τ_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets $\left(\tau_{g1}, \tau_{g2}\right)$ it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_{g1} and τ_{g2}, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, 5)$$

[redacted]

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 4-6. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

14.2.2.1.2 Single agent VAY736

For the MAP model for VAY736, total cycle 1 reference dose $d^* = 3.0$ mg/kg is used; data from $S = 5$ historical studies is available; and $G = 2$ exchangeability groups are assumed.

Weakly informative priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT at the reference dose of 9.3% (i.e., based on the assumed 3.6% DLT at the starting dose from the model (1) above) , and a tripling in dose leading to a doubling in the odds of the risk of a DLT. For the 2 exchangeability groups the priors for (τ_{g1}, τ_{g2}) are assigned such that (1) their medians correspond to small and moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014). The prior distributions for the model used for deriving the MAP priors are specified in Table 14-3.

Table 14-3 Prior distributions for the parameters of the MAP model used to derive the prior for single-agent VAY736 model parameters

Exchangeable group	Parameter	Prior distribution
	μ_1	N(mean = logit(0.093), sd = 2)
	μ_2	N(mean = log(log(2)/log(3)), sd = 1)
	ρ	uniform(-1,1)
1 small heterogeneity	τ_{11}	lognormal(mean = 0.125, sd = log(2)/1.96)
	τ_{12}	lognormal(mean = 0.0625, sd = log(2)/1.96)
2 moderate heterogeneity	τ_{21}	lognormal(mean = 0.25, sd = log(4)/1.96)
	τ_{22}	lognormal(mean = 0.125, sd = log(4)/1.96)

Historical data

Autoimmunity clinical studies VAY736X2101, VAY736X2201, VAY736X2202, VAY736X2203 (Assigned to exchangeability group 2) and study VAY736Y2101 (Assigned to exchangeability group 1) subject exposures to VAY736 and DLTs are presented in the Table 14-4 below.

A review of AE records of the patients in autoimmunity clinical studies did not indicate any significant toxicity in the historical studies presented in Table 14-4 below. VAY736 was well tolerated, only few SAEs were observed and none of the SAEs were drug related. In addition those few SAEs that occurred in autoimmunity studies are irrelevant to current CLL patients.

For VAY736Y2101 there was one patient reported as dose limiting toxicity and SAE (grade 3 hemolytic autoimmune anemia), however this patient had baseline autoimmune anemia.

[redacted]

Substantial heterogeneity is assumed due to the difference in population, indication and dosing schedule from autoimmune studies to current study; Small heterogeneity is expected between VAY736Y2101 and current study. Therefore two exchangeability groups are assigned as below. The new trial is assigned to exchangeability group 1.

Table 14-4 Historical DLT data from Studies VAY736X2101, VAY736X2201, VAY736X2202, VAY736X2203 and VAY736Y2101

Historical studies/ Exchangeability groups (G)	Total cycle 1 dose (<mg/Kg>)	#of DLTs/# of evaluable pts
VAY736X2101/2	.0003	0/3
	.001	0/3
	.003	0/3
	.01	0/4
	.03	0/3
	.1	0/3
	.3	0/9
	.86	0/12
	1	0/9
	3	0/3
	10	0/3
VAY736X2201/2	3	0/6
	10	0/17
VAY736X2202/2	10	0/8
VAY736X2203/2	3	0/7
	10	0/5
VAY736Y2101/1	.008	1/3

Notes:

1. The data is based on Investigators Brochure released on 29-Aug-2016 and safety cut-off date on 30-Jun-2016.
2. .The total cycle 1 dose (mg/kg) for VAY736 treatment is used to incorporated data from different administrations.
3. DLT presented in the VAY736Y2101 is within cycle 1(28 days window); DLT presented in the autoimmunity studies are within study duration which may occurs beyond cycle 1, which can be deemed as conservative estimate for counting AEs to occur within the first cycle of VAY736 treatment.

To make the prior more robust, an additional mixture component corresponding to a high toxicity scenario is added to the MAP prior. For this component, the median probability of DLT at the total cycle 1 reference dose 3.0 mg/kg is 12%; the median for the prior distribution of log(β) is set to log(log(2)/log(3)) at the reference dose which assumes a tripling dose leads to a doubling of the odds of DLT. The median DLT rates of total cycle 1 doses 0.6 mg/kg, and 4.0 mg/kg are approximately 3.3%, and 15.4%, respectively. Standard deviations for log(α) and log(β) are set to 2 and 1 respectively, with correlation $\rho = 0$.

The weight assigned to the 3 components of the MAP prior is 0.80 in total, and the weight assigned to the high toxicity prior component is 0.20. The mixture components are weighted based upon *a priori* assessment of their relevance to the toxicity of combination of VAY736 and Ibrutinib in humans. The prior distribution is described in full in Table 14-3.

[redacted]

14.2.2.1.3 Single agent Ibrutinib

Based on clinical toxicology data (Section 1.2.4.1) a weakly informative prior is derived for which the median probability of DLT at dose 420 mg daily is assumed to be 8%. The review of historical safety data were summarized in the Table 14-5 below. The observed historical rate of discontinued from study due to adverse events is approximately 4% at 420 mg ibrutinib daily. Due to the lack of precise DLT data from historical studies, the current 8% DLT for cycle 1 is assumed to be conservative.

The median for the prior distribution of $\log(\beta)$ was set to 0, to correspond to a doubling of dose leading to a doubling of the odds of DLT. The standard deviation for $\log(\alpha)$ is derived assuming that there is 90% probability that the DLT rate is lower than 33% at 420 mg daily reference dose. The standard deviation for $\log(\beta)$ is 1. The correlation between the $\log(\alpha)$ and $\log(\beta)$ is $\rho = 0$. The prior distribution is described in full in Table 14-6.

Table 14-5 Historical data for ibrutinib

Study #	Dose of ibrutinib (daily)	# of discon. due to AEs / # of evaluable patients (%)
(Byrd et al 2013)	420mg	2/51(4%)
	840mg	4/33(12%)
(Byrd JC et al 2015)	420mg	8/195(4%)

14.2.2.2 Prior distribution for the interaction parameters

Although no interaction is expected for the two agents, uncertainty remains. Therefore, a normal prior for the log-odds multiplier η centered at 0 is used that allows for both synergistic and antagonistic toxicity.

- η is normally distributed, with mean 0, and standard deviation 0.858
- At the total cycle 1 starting dose of 0.6 mg/kg (0.3 mg/kg *2) the corresponding distribution for the odds ratio has mean 1.000 and a 97.5th percentile of 1.4, i.e. 1.4-fold increase in odds of DLT due to interaction compared to no interaction.

[redacted]

14.2.2.3 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-6. Prior summaries for DLT rates for are summarized in Table 14-7.

Table 14-6 Prior distribution for the model parameters

Parameter		Mean	Standard Deviations (SD)	Correlation	Weight
Single agent VAY736 MAP prior, total cycle 1 reference dose 3.0 mg/kg					
BVN mixture $(\log(\alpha_1), \log(\beta_1))$					
Three-component MAP prior	Component 1	(-4.795, -1.876)	(0.908, 0.665)	-0.137	0.355
	Component 2	(-4.035 -1.443)	(0.645, 0.490)	-0.017	0.347
	Component 3	(-3.770, -2.310)	(0.540, 0.668)	0.299	0.098
High-tox component	Component 4	(-1.992, -0.461)	(2, 1)	0	0.200
Single agent Ibrutinib weakly-informative prior, reference dose 420 mg					
BVN $(\log(\alpha_2), \log(\beta_2))$					
		(-2.442, 0)	(1.353, 1)	0	N/A
Interaction parameter η					
Normal					
	η	0	0.858	N/A	N/A

Table 14-7 Summary of prior distribution of DLT rates

VAY736 dose (mg/kg) Q2W	Prior probabilities that P(DLT) is in the interval:			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
	In combination with Ibrutinib 420mg daily							
0.1	0.665	0.206	0.129	0.156	0.156	0.013	0.101	0.600
0.3	**0.650**	**0.212**	**0.139**	**0.164**	**0.163**	**0.014**	**0.106**	**0.628**
1.0	0.606	0.218	0.176	0.186	0.188	0.013	0.117	0.725
2.0 (intermediate)	0.561	0.195	0.245	0.223	0.236	0.007	0.129	0.861
3.0	0.534	0.163	0.303	0.260	0.282	0.003	0.137	0.945

- The grey shaded rows indicate dose combinations not meeting the EWOC criterion, that there is ≥25% chance of excessive toxicity, i.e. DLT rate in [0.33, 1].
- The starting dose level is highlighted in bold. Total cycle 1 VAY736 dose is used in the BLRM. i.e., 2 * mg/Kg Q2W.

Change in dose schedule

In the case that additional dosing schedules for VAY736 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.

[redacted]

14.2.3 Hypothetical on-study data scenarios

To illustrate the performance of the Bayesian model used to guide dose escalation, hypothetical dose escalations scenarios following the provisional dose levels specified in Table 14-8 are displayed. In each case, the maximum dose that can be used in the next cohort of patients is shown. This maximum dose is determined using the model based assessment of the risk of DLT in future patients and the dose escalation rules as described in Section 6.2.3. In practice a dose below the maximum might be chosen based on additional safety, PK or PD information (Section 6.2.1.1).

Table 14-8 Hypothetical dose escalation scenarios

Scenario	Dose	Number of		Next dose combination		
	Ibrutinib 420 mg daily + VAY736 (mg/kg) Q2W	Patients	DLTs	Ibrutinib 420 mg daily + VAY736 (mg/kg) Q2W	Median P(DLT)	P(excessive toxicity)
1	0.3	3	0	1.0	0.076	0.065
2	0.3	3	1	0.3	0.173	0.192
3	0.3	3	2	stop		
4	0.3	4	1	1.0	0.163	0.191
5	0.3 1.0	3 4	0 0	3.0	0.052	0.111
6	0.3 1.0	3 4	0 1	1.0	0.124	0.072
7	0.3 1.0	3 6	0 1	3.0	0.131	0.233
8	0.3 1.0	3 6	0 2	1.0	0.185	0.147
9	0.3 1.0	4 5	0 1	1.0	0.105	0.044
10	0.3 1.0	4 6	0 1	3.0	0.122	0.218
11	0.3 1.0	4 5	1 0	3.0	0.082	0.145

14.2.4 Operating characteristics

A simulation study is used to illustrate the long run performance of the Bayesian dose escalation model. Several example scenarios were investigated (Section 14.2.4.1), and in each case 1000 trials were simulated, with results summarized in Section 14.2.4.1.1.

[redacted]

14.2.4.1 Scenarios

Table 14-9 shows three dose-DLT scenarios as follow:

- Scenario 1 represents the situation in which the true probability of DLT is in line with the prior, i.e. P(DLT) = prior median.
- Scenario 2: the odds of DLTs are1.5-fold larger than the ones of scenario 1.
- Scenario 3: the odds of DLTs increases steeper and rapidly early as dose goes higher, where the DLT rate at 1.0 mg/kg bi-weekly is approximately 55%.

Table 14-9 True probability of DLT for simulation scenarios

Test scenarios	Dose of VAY736(bi-weekly) in combination with Ibrutinib 420 (mg daily)				Note
	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	
1	0.101	0.106	0.117	0.137	True dose-DLT relationship based on prior median rates
2	0.152	0.159	0.176	0.206	1.5-fold odds increased from scenario 1
3	0.101	0.180	0.550	0.700	More toxic and steeper than scenario 1

14.2.4.1.1 Simulation details

Data for 1000 trials are simulated for each scenario and the total minimum number of DLT to control the declaration of MTD is fixed to one. The starting dose combination is set to 420 mg daily Ibrutinib and 0.3mg/kg Q2W VAY736 and follows the protocol specifications (Section 6.2.3). At each dose escalation, the highest VAY736 dose in combination with ibrutinib 420 mg daily satisfying the EWOC criterion is chosen for the next cohort.

The number of patients to enroll in each cohort and stopping rules used to declare MTD are defined as:

- Cohort size: 3-6
- Minimum number of patients enrolled: 15
- Maximum number of patients enrolled: 40
- Minimum number of patients enrolled at a given dose combination in order to declare MTD: 6

Simulation results

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

- Metric I: Average proportion of patients in target dose region (>=16% - 33%).
- Metric II: Average proportion of patients in over dose region (>= 33%).
- Metric III: Average proportion of patients in under dose region (< 16%).
- Metric IV: Proportion of trials with MTD in target dose region (>= 16% - 33%).

[redacted]

- Metric VI: Proportion of trials with MTD in under dose region (< 16%).
- Stopped: Proportion of trials stopped with no MTD identified.
- Ave N: Average number of patients dosed.
- Ave DLT: Average number of DLTs observed.

Table 14-10 Summary of simulation results

Scenario	Metrics (%)								
	I	II	III	IV (Target MTD)	V (Overdose MTD)	VI (Under-dose MTD)	Stopped	Ave N	Ave DLT
1	0	0	100	0	0	91.4	8.6	18.8	2.3
2	62.2	0	37.8	66.3	0	15.6	18.1	17.3	3.0
3	54.8	39.0	6.2	39.9	7.7	0.2	52.2	14.4	4.7

The operating characteristics show that the BLRM with the derived informative prior perform reasonable under the three hypothetical scenarios investigated. In scenario 1 all patients are treated in under dose region due to the low assumed true DLT rate in all dose levels (less than 13%). The proportion of patients treated in the target dose region is about 62% (Metric I) in scenario 2.

The probabilities to identify a MTD in the target dose region (Metric IV) are approximately 66% for scenario 2 and 40% for scenario 3, respectively. The chance of identifying a MTD that is in fact excessively toxic is controlled at 8% for scenario 3.

Approximately 9-19% of the trials stopped in Scenario 1 and 2. Even the lowest dose has a considerable DLT rate of above 10-15% at the starting dose even though the whole dose cure are both relatively flat. In the scenario 3, the chance of stopping without identifying a MTD is 52% due to the relative high toxicity at the starting dose, resulting in a high probability of seeing DLTs early in the dose escalation.

The average number of patients needed are between 14 to 19, and approximately 2-5 DLT's are expected.

[redacted]

References

Akaike H. (1974) A new look at the statistical model identification. IEEE Transactions on Automatic Control, AC-19. 716–723

Byrd JC, Furman RR, Coutre S E, et al. (2015) Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood, 125, 2497-2506.

Byrd JC, Furman RR, Coutre SE, et al. (2013) Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med, 369, 32-42.

Dempster AP, Laird M, Rubin DB (1977) Journal of the Royal Statistical Society. Series B (Methodological), Vol 39, 1-38.

Neuenschwander B, Matano A, Tang Z, et al. (2014) A Bayesian Industry Approach to Phase I Combination Trials in Oncology. Statistical Methods in Drug Combination Studies: Chapman & Hall.

[redacted]

14.3 Appendix 3 – Drugs which are prohibited or to be used with caution

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ibrutinib.

The following lists are based on the Novartis PK Sciences DDI List (v01 released in January 2018). The FDA's Guidance for Industry Drug Interaction Studies – Study Design, Data Analysis and Implications for Dosing and Labeling (2017) is the basis of the Novartis PK Sciences DDI List, and it was supplemented with Indiana University (IU) Flockhart Table™. and University of Washington (UW) Drug Interaction Database.

The list of medications in Table 14-11 is meant to provide guidance only and it is not a comprehensive list. If a patient is required to take a medication that is not in the list, but there may be a risk of DDI, please contact the Novartis clinical study team for further advice.

Please contact the Novartis Medical monitor with any questions.

Table 14-11 Drugs prohibited while on study

Category	Drug Names
Strong inhibitors of CYP3A	VIEKIRA PAK[1], indinavir/ritonavir[1], tipranavir/ritonavir[1], ritonavir, cobicistat ,indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[1], elvitegravir/ritonavir[1], saquinavir/ritonavir[1], lopinavir/ritonavir[1], itraconazole, voriconazole, mibefradil, , clarithromycin, posaconazole, telithromycin, grapefruit juice[2], conivaptan, nefazodone, nelfinavir, , idelalisib, boceprevir, atazanavir/ritonavir[1], darunavir/ritonavir[1]
Moderate inhibitors of CYP3A4/5	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[2], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi)[3], asafoetida resin (Ferula asafoetida)[3], verapamil Seville oranges or products containing Seville oranges (e.g. Marmalades)[2].
Strong inducers of CYP3A4/5	carbamazepine, enzalutamide, lumcaftor, phenobarbital, phenytoin, rifabutin, rifampin, mitotane, St. John's wort (*Hypericum perforatum*)[3]
Combination therapy. (in some cases combinations with ritonavir have been listed as moderate inhibitors of CYP3A in the UW database, the have all been listed as strong in the DDI guide to avoid any potential confusion) Food product. Herbal product. FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (2017) (/fdagov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), Indiana University (IU) Flockhart Table™ (/drug-interactions.medicine.iu.edu/), University of Washington (UW) Drug Interaction Database (/druginteractioninfo org/), Novartis PK Sciences DDI List (Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials, Novartis PK Sciences Internal Memorandum, v01 released in 2018 January).	