Acerta Pharma

A member of the AstraZeneca Group

Statistical Analysis Plan

Protocol Title: A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL

Protocol Number: ACE-CL-003

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A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL

Approval Page

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SAP Revision History:

Version/Date	Summary of Major Changes and Rationale
Final: 07 February 2019	New Document
Amendment 1: 27 April 2021	1. Added Protocol Amendment 7 to Introduction and Overall Study Design sections; updated study schema in accordance with schema updates made in Protocol Amendment 7. 2. Updated study treatment exposure definitions to cover rituximab and venetoclax. Added definitions for number of cycles administered, dose withholding, and dose reduction. – Section 6.2 3. Specified throughout that partial response with lymphocytosis (PRL) is only applicable for Cohorts 1 and 2. 4. Moved ECOG performance status from Demographics and Baseline Characteristics to Baseline Disease Characteristics. Added "significant fatigue" to the list of B symptoms – Section 10.0 5.Added sections 6.1 Prior Anticancer Therapies, 13.2 Adverse Events of Clinical Interest and 13.3 Deaths 6. Added region and Binet state as demographics and baseline characteristics variables -Section 10.0 7.Added infusion interruption and time to the first interruption - Section 6.3 8. Moved the ORR at cycle 16 (cohort 3 and 4) from the section of the primary efficacy endpoint to the section of secondary endpoint section -Section 12.1 and 12.2 9. Added "nPR(nodular partial remission)" to the definition of DOR(Duration of response) -Section 12.2.4 10.Added "time to complete response" and "time to response of PRL or better" – Section 12.2.5

TABLE OF CONTENTS

TABLE OF CONTENTS **4**
LIST OF ABBREVIATIONS AND DEFINITIONS **6**
1.0 Introduction 8
2.0 Study Objectives 8
3.0 OVERALL STUDY design 9
4.0 Sample size consideration 13
5.0 Analysis POPULATIONS 15
5.1 All Treated Population 15
5.2 Efficacy Evaluable Population 15
6.0 TREATMENTS AND MEDICATIONS 15
6.1 Prior Anticancer Therapies 15
6.2 Prior and Concomitant Medications 15
6.3 Study Treatment Exposure 16
7.0 Statistical Methods 17
7.1 Data Presentation 17
7.2 General Conventions 17
7.3 Analysis Windows 17
7.4 Missing Data Handling 17
8.0 Subject Disposition 18
9.0 Important Protocol deviations 18
10.0 demographics and baseline disease characteristics 18
11.0 Medical history 20
12.0 Efficacy analyses 20
12.1 Primary Efficacy Endpoint and Analysis 20
12.1.1 Overall Response Rate (ORR) 20
12.2 Secondary Efficacy Endpoints and Analyses 20
12.2.1 Overall Response Rate(ORR) 21
12.2.2 Complete Response Rate and MRD-Negative Complete Response Rate 21
12.2.3 Progression-Free Survival 21
12.2.4 Duration of Response 22
12.2.5 Time to Response 22
12.2.6 Time to Next Treatment (TTNT) 23
12.2.7 Overall Survival (OS) 23
12.2.8 Patient reported outcomes (PRO) 23
13.0 Safety Analyses 25
13.1 Adverse Events 26
13.2 Adverse Events of Clinical Interest. 26
13.3 Deaths 26
13.4 Laboratory Assessments 26
13.4.1 Data Summary Methods 26
13.4.2 T/B/NK Cell Counts 27

13.4.3 Serum Immunoglobulin 27
13.4.4 Analysis of Lymphocytosis 27
13.5 Vital Signs and Physical Examinations 28
13.6 ECOG Performance Status 28
14.0 REFERENCE 28
15.0 APPENDICES 29
Appendix A: Analysis Windows 29
Appendix B: Rai Stage Derivation Criteria 32
Appendix C: Grading Scale for Hematologic Toxicity in CLL (Hallek 2008) 33
Appendix D: Defining Prior and Concomitant Medication Flags 34
Appendix E: Patient Reported Outcomes (PRO) 35
Appendix F: Adverse Events of Clinical Interest 43

LIST OF ABBREVIATIONS AND DEFINITIONS

AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
ATC	anatomical therapeutic chemical
BID	twice per day
BTK	Bruton tyrosine kinase
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete remission (response)
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
DOR	Duration of Response
ECI	event of clinical interest
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capturing
EORTC	European Organisation for Research and Treatment of Cancer
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
IGHV	immunoglobulin heavy-chain variable
IPD	important protocol deviation
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	microRNA
MRD	Minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PD	progression disease
PFS	progression-free survival
PLCG2	phospholipase C gamma 2
PLL	prolymphocytic leukemia
PK	pharmacokinetic
PR	partial remission (response)
PRL	partial remission (response) with lymphocytosis

QD	once per day
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the product of the greatest diameters
TEAE	treatment-emergent adverse event
TNTT	time-to-next treatment
WHO	World Health Organization

1.0 Introduction

This Statistical Analysis Plan (SAP) provides details of the statistical analyses that have been outlined within the protocol for study ACE-CL-003 Protocol Amendment 7 (dated 03 April 2020), which is entitled "A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL."

The original SAP was based on protocol amendment 6 (dated 27 June 2018). The amendment 7 was made to clarify the discontinuation of acalabrutinib might be based on minimal residual disease and clinical response. Also, the protocol was updated to remove the restart of treatment for subjects in treatment-free follow-up to clarify criteria regarding discontinuation and restart of acalabrutinib. The SAP is updated to include changes made in protocol amendment 7.

The scope of the SAP will cover safety and efficacy analyses in ACE-CL-003. Minimal residual disease (MRD), pharmacokinetic (PK), and CCI analyses will be provided in the respective reports.

2.0 Study Objectives

The primary objectives are:

Cohort 1 and 2:

- To determine the overall response rate (ORR) at 12 months with the combination of acalabrutinib plus obinutuzumab in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL)
- To determine the ORR at 12 months with the combination of acalabrutinib plus obinutuzumab in subjects with treatment-naïve CLL
- To establish the safety and feasibility of the combination of acalabrutinib plus obinutuzumab

Cohort 3 and 4:

- To establish the safety of the combination of acalabrutinib plus rituximab plus venetoclax in subjects with relapsed or refractory CLL (Cohort 3)
- To establish the safety of the combination of acalabrutinib plus obinutuzumab plus venetoclax in subjects with treatment-naïve CLL (Cohort 4)

The secondary objectives are:

- To determine the complete response (CR) rate and minimal residual disease (MRD)-negative CR rate in subjects with previously untreated and relapsed and refractory CLL with these regimens (all cohorts)

- To evaluate the ORR of the combination therapy of acalabrutinib plus venetoclax plus an anti-CD20 antibody(rituximab or obinutuzumab) at Cycle 16 (Cohorts 3 and 4)
- To determine the time to response, duration of response (DOR), progression-free survival (PFS), time to complete response (CR), time-to-next treatment (TTNT), and overall survival (OS) with these regimens (all cohorts)
- To assess for serial development of resistance by baseline and longitudinal assessment of mutations of Bruton tyrosine kinase (BTK) and phospholipase C gamma 2 (PLCG2) at regular follow-up intervals and by examining diagnosis to relapse samples by whole-exome sequencing (all cohorts)
- To determine trajectory of psychological and behavioral responses to acalabrutinib and covariation with response to therapy (all cohorts)
- To determine the pharmacokinetics of orally administered acalabrutinib (all cohorts) and venetoclax (Cohorts 3 and 4)

The exploratory objectives are:

3.0 OVERALL STUDY design

This is a Phase 1b study with expansion to evaluate the safety and preliminary efficacy of acalabrutinib in combination with obinutuzumab or with venetoclax and an anti-CD20 antibody (rituximab or obinutuzumab) in 4 separate cohorts of subjects: those with relapsed/refractory CLL (Cohorts 1 and 3) and those with treatment-naïve CLL (Cohorts 2 and 4).

A standard 3+3 Phase 1 trial design began in Cohort 1 where the recommended dose was determined. Cohorts 1 and 2 were expanded to better evaluate the toxicity profile of these combination regimens and to detect moderate to large increases in ORR at 12 months relative to historical control. Cohorts 3 and 4 were enrolled to establish the safety profile of the combination of acalabrutinib plus venetoclax plus an anti-CD20 antibody.

For more details on study design, please refer to protocol. Protocol amendments and revision dates are as follows:

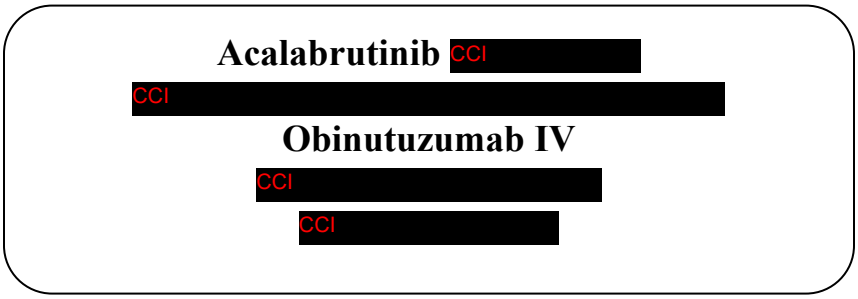
- Original protocol: 20 May 2014
- Amendment 1: 28 July 2014

- Amendment 2: 24 March 2015
- Amendment 3: 22 July 2015
- Amendment 4: 27 April 2016
- Amendment 5: 03 August 2017
- Amendment 5.1: 06 November 2017
- Amendment 6: 27 June 2018
- Amendment 7: 03 April 2020

STUDY SCHEMA

PHASE 1B DOSE-ESCALATION PORTION: OBINUTUZUMAB

- At least 6 subjects with relapsed/refractory chronic lymphocytic leukemia (CLL), then at least 6 subjects with treatment-naïve CLL

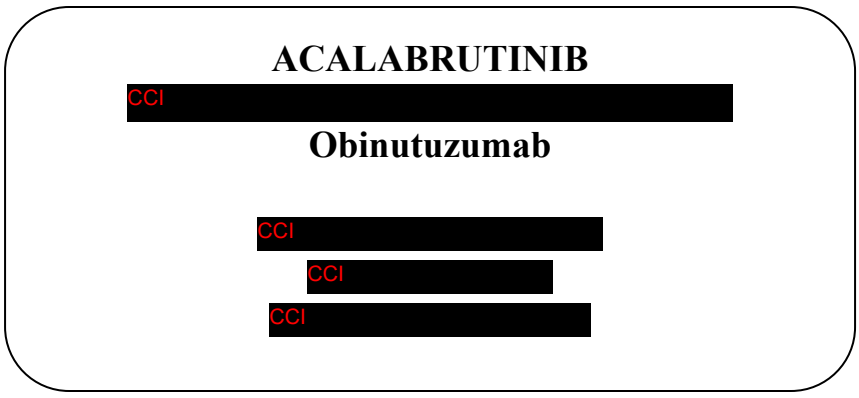


PHASE 1B EXPANSION PORTION

TWO PARALLEL COHORTS ARE TREATED IDENTICALLY

COHORT 1:
- Relapsed or refractory disease*

COHORT 2:
- No previous treatment
- 65 years or older OR refuse or are ineligible for approved chemotherapy and/or immunotherapy options



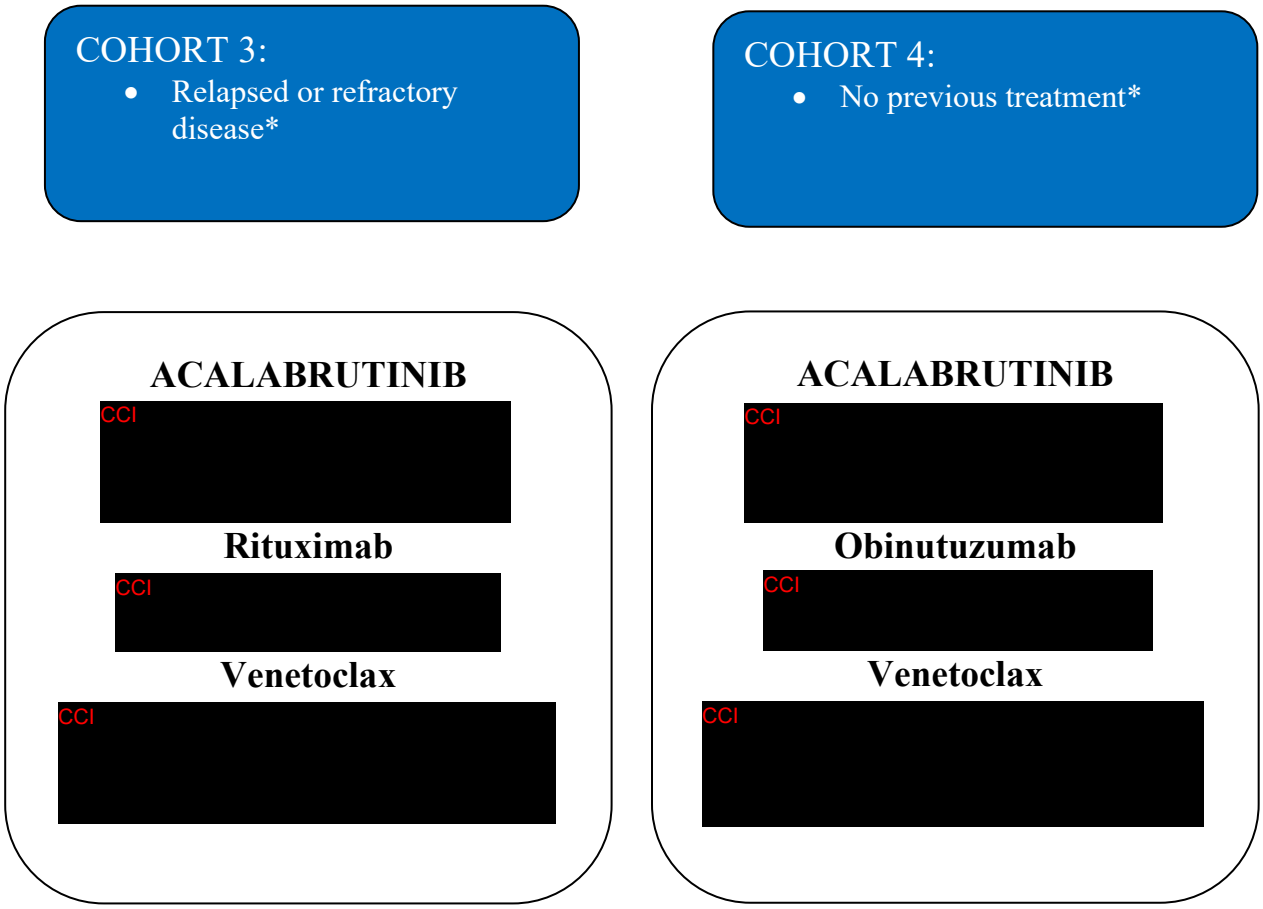
*Samples for pharmacokinetics are obtained from the first 8 subjects enrolled in the Phase 1b expansion of Cohort 1.
Subjects who achieve bone marrow minimal residual disease (MRD)-negative complete response (CR) have the option to discontinue acalabrutinib.

STUDY SCHEMA (CONTINUTED)

PHASE 1B: COHORTS 3 and 4

Twelve subjects with relapsed/refractory CLL and12 subjects with treatment-naïve CLL

TWO PARALLEL COHORTS ARE TREATED



*Samples for pharmacokinetics are obtained from the first 8 subjects enrolled in each of Cohorts 3 and 4.

[#] Discontinuation of acalabrutinib after CCI is possible by investigator decision based on minimal residual disease (MRD) and clinical response (refer to the Schedule of Assessments in Table 12 and 13 of the protocol).

4.0 Sample size consideration

The sample size for Cohorts 1 and 2 is based on: 1) dose de-escalation rules and 2) the number of subjects required to detect moderate to large increases in ORR relative to historical control with sufficient power while constraining Type I error to 0.10. This study is expected to require 45 subjects, 6 subjects evaluated for safety in each cohort and an additional 20 and 13 subjects enrolled in Cohorts 1 and 2, respectively. More subjects may be enrolled if de-escalation of dose levels is indicated in the safety evaluation.

The sample size of 12 subjects each for Cohorts 3 and 4 is chosen to provide evaluation for safety and tolerability.

Cohorts 1 and 2

Each of Cohorts 1 and 2 are expanded at the recommended dose level to include, respectively, 26 and 19 total relapsed/refractory and treatment-naïve CLL subjects. These sample sizes were chosen to obtain sufficient preliminary safety and efficacy information in these populations. With respect to toxicity and ability to detect common adverse events (AEs), there is an approximately 60% chance of observing at least 1 subject with an AE occurring at a 5% rate with 19 treatment-naïve subjects in Cohort 2 and an approximately 75% chance in the group of 26 relapsed/refractory CLL subjects in Cohort 1.

If toxicity profiles are similar and it is appropriate to summarize AEs across all subjects, there is at least a 90% chance of detecting a common AE. With respect to clinical efficacy, a 50% ORR (partial response with lymphocytosis or better) (null) at the 12-month evaluation would be considered uninteresting because this can be achieved with either acalabrutinib or obinutuzumab as single agents in both populations. However, an ORR of at least 75% in the relapsed/refractory setting for Cohort 2 and an ORR of at least 80% in the treatment-naïve setting for Cohort 1 would be of considerable interest and would warrant further investigation of the combination regimen (alternative).

If 16 or fewer responses are observed in 26 evaluable subjects with relapsed/refractory CLL in Cohort 1, the combination of acalabrutinib with obinutuzumab would not be considered promising; likewise, if 12 or fewer responses in 19 evaluable subjects who were previously untreated for CLL in Cohort 2 were observed, the combination would not be considered promising as upfront therapy. Each of these designs has at least 90% power with a one-sided alpha level of 0.10.

Cohorts 3 and 4

The sample sizes for Cohorts 3 and 4 are chosen to obtain preliminary safety information in the relapsed/refractory and treatment-naïve CLL populations. With respect to toxicity and ability to detect common AEs, there is a 46% chance of observing at least 1 subject with an AE occurring at a 5% rate with 12 subjects in each of Cohorts 3 and 4.

Below is a list of various AE rates with the chance of observing in at least 1 subject.

Sample Size	Adverse Event Rate	Chance of Observing at Least 1 Adverse Event
12	1%	11%
12	2%	22%
12	5%	46%
12	10%	72%

5.0 Analysis POPULATIONS

Analysis populations will be defined in the following sections. The efficacy and safety analyses will be performed on the All Treated Population. The primary efficacy analysis will be based on the Efficacy Evaluable Population.

5.1 All Treated Population

The All Treated Population will include all enrolled subjects who received ≥1 dose of study drug.

All enrolled subjects were treated with at least one dose of study drug in this study, thus all-treated population is the same as the enrolled population.

5.2 Efficacy Evaluable Population

The Efficacy Evaluable Population will include all subjects in the All Treated Population who had ≥1 response assessment after the first dose of study drug.

6.0 TREATMENTS AND MEDICATIONS

6.1 Prior Anticancer Therapies

A prior anticancer therapy is defined as a systemic therapy subjects received, either as a single or combination therapy, for the treatment of active CLL/SLL with an end date occurring before the date of first dose of study treatment. Therapies given as a consolidation or maintenance of a response or remission will not be considered as a separate regimen. The number of prior therapies, type of prior therapy, and time (months) from the end of last therapy to the first dose of study drug will be summarized.

6.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary. Medications started or ended prior to first dose will be considered as prior medications. Concomitant medication is defined as all medications used on or after the first dose, through the treatment phase, and for 30 days following the last dose of study drug. With use of this definition, a medication can be classified as both prior and concomitant. Medications with completely missing start and stop dates will be considered as both prior and concomitant medications.

Appendix D shows the prior and concomitant medication flags for various scenarios. The number and percentage of subjects will be presented by anatomical therapeutic chemical (ATC) classification system Level 2 and preferred term.

Prior and concomitant medications will be summarized by the WHO drug dictionary Anatomical Therapeutic Chemical (**ATC**) level 2 and preferred term (PT).

6.3 Study Treatment Exposure

Study treatment exposure will be summarized for all subjects in the Safety population. The following will be provided for each treatment component when applicable:

- Duration of exposure
  - Acalabrutinib and venetoclax (months): (last dose date – first dose date + 1) / 30.4375
  - Obinutuzumab and rituximab (days): (last dose date – first dose date + 28)
- Cumulative dose received on study (acalabrutinib, venetoclax, rituximab, and obinutuzumab)
- Average daily dose (acalabrutinib and venetoclax only)
  - Calculated as (total dose received [mg] / duration of exposure [days])
- Relative dose intensity
  - Acalabrutinib:
  - Calculated as (total cumulative dose received [mg] / (duration of exposure [days] *
  - 100 [mg] * 2) *100)
  - Obinutuzumab:
  - Calculated as (total volume infused (mg) / 8000 mg * 100)
  - Rituximab:
  - Calculated as (total dose infused [mg] / total cumulative planned dose based on
  - body surface area [375 mg/m^2] * 100)
  - Venetoclax:
  - Calculated as (total cumulative dose received [mg] / 136,990 mg * 100)
- Dose withholding
  - Acalabrutinib: missing dose for ≥ 7 consecutive days
  - Venetoclax, Obinutuzumab, Rituximab : missing dose for at least 1 day
- Dose reduction
  - Acalabrutinib: taking lower dose level for ≥ 3 consecutive days
  - Venetoclax, Obinutuzumab, Rituximab: taking lower dose level for at least 1 day
- Infusion interruption (Obinutuzumab and Rituximab only)

- Time to first interruption (days) (Obinutuzumab and Rituximab only)

7.0 Statistical Methods

7.1 Data Presentation

Tables and figures will be summarized by cohort unless otherwise specified.

No formal tests of hypotheses will be performed. P-values, if presented, will be provided for descriptive purpose. Descriptive statistics (number of subjects, mean, and standard deviation, median, minimum, and maximum) will be presented for continuous variables, including baseline demographic, disease characteristics, study drug administration, efficacy and safety outcomes. Categorical variables will be summarized as the number and percentage of subjects per category. Confidence intervals [CIs] may be included as appropriate.

7.2 General Conventions

Baseline is defined as the last measurement taken prior to the first dose of study drug administration. *Post-baseline* is defined as a measurement taken after the first dose of study drug administration.

Study Day 1 is defined as the date of first dose. For visits (or events) that occur on or after first dose date, study day is calculated as (date of visit [event] – date of first dose + 1). For visits (or events) that occur prior to first dose date, study day is calculated as (date of visit [event] – date of first dose). There is no Study Day 0.

Laboratory data summary will be based on central laboratory results. Local laboratory results will be used if central laboratory results are not available. Central laboratory results will use reference ranges provided by the central laboratory, and local laboratory results will use the reference ranges provided by local laboratories.

7.3 Analysis Windows

For parameters summarized by visit, an analysis window will be assigned to each nominal visit. Each assessment will be assigned to an analysis visit based on the analysis window in which the assessment date falls. Details are defined in Appendix A.

7.4 Missing Data Handling

No imputation for missing values of efficacy endpoints. Imputation for missing dates such as AE start or end dates and prior and concomitant medication start dates or end dates will be documented in the programming specifications.

8.0 Subject Disposition

Subject disposition will present the number and percentage of subjects in All Treated Population and Efficacy Evaluable Population, who discontinue treatment and reasons, and who do not complete the Safety follow-up as well as the reasons, time on treatment, and time on study.

9.0 Important Protocol deviations

Important protocol deviation (IPD) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. The final IPD list is used to produce the summary table and by-subject listing for IPDs.

10.0 demographics and baseline disease characteristics

The following variables collected at baseline will be presented:

- Demographics and baseline characteristics
  - Age (years)
    - Descriptive statistics
    - <65 vs. ≥65 years
    - <70 vs. ≥70 years
  - Sex (male, female)
  - Race
    - American Indian/Alaskan Native, African American/Black, Asian, Caucasian/White, Native Hawaiian/Other Pacific Islander or Other
  - Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
  - Height
  - Weight
  - Region (single site, United States)
  - ECOG performance status
- Baseline disease characteristics
  - Histology
    - For RR, TN
      - CLL
      - SLL

  - PLL
- Time since initial CLL diagnosis to first dose (years)
- Rai stage – Rai stage collected on the electronic case report form (eCRF) and derived Rai stage based on variables collected at screening visit using the criteria described in Appendix B
- Bulky disease (not applicable for RS/PLL) – defined as if at least one dimension of the lymph node measurement is
  - ≥5 cm
  - ≥10 cm
- B symptoms – weight loss, fever, night sweats, significant fatigue
- Chromosomal abnormalities
  - del(17)(p13.1) (TP53)
  - del(11)(q22.3) (ATM)
- β2-microglobulin
  - >3.5 vs. ≤3.5 mg/L
  - >3 vs. ≤3 mg/L
- Number of prior systemic therapy
  - Descriptive statistics
  - <3 vs. ≥3
- Type of prior systemic therapy
- Time since most recent therapy (months)
- Cytopenia
  - Absolute neutrophil count (ANC) ≤1.5x10^9/L
  - Hemoglobin ≤11g/dL
  - Platelet ≤100x10^9/L
  - Hemoglobin ≤11g/dL or platelet ≤100x10^9/L
  - Any of the above
- ANC (10^9/L)
- Absolute lymphocyte count (ALC) (10^9/L)
- Hemoglobin (g/dL)

- Platelets (10^9/L)
- IGHV mutation status (Unmutated IgHV, Mutated IgHV)
- ZAP-70 Methylation Status (Positive, Negative, Not Done/NA)
- Complex Karyotype
  - Subjects with complex karyotype
  - Subjects without complex karyotype

11.0 Medical history

Medical history data will be coded per the Medical Dictionary for Regulatory Activities (MedDRA), summarized by system organ class and preferred term, and presented as a data listing

12.0 Efficacy analyses

Response will be assessed by investigators based on International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Response Assessment Criteria (modified from Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis per Cheson 2012 for CLL/SLL.

The efficacy analysis will be performed using All Treated Population. The Efficacy Evaluable Population will be used for primary efficacy analysis.

12.1 Primary Efficacy Endpoint and Analysis

12.1.1 Overall Response Rate (ORR)

ORR is the proportion of subjects who achieve complete remission (CR), CR with incomplete bone marrow recovery (CRi), nodular partial remission(nPR), or partial remission (PR) while on treatment before the initiation of new anticancer therapy or stem cell transplant.
For Cohorts 1 and 2, the ORR(PR or better) at the all available response assessments up to the 12-months will be calculated and 95% exact binomial CIs will be provided.

ORR will be summarized using All Treated Population and Efficacy Evaluable Population.

For CLL disease subgroups, ORR, including PRL as a response, (only for Cohorts 1 and 2), will also be summarized in the same fashion.

12.2 Secondary Efficacy Endpoints and Analyses

The secondary efficacy analyses will be performed using All Treated Population.

12.2.1 Overall Response Rate(ORR)

The ORR of the combination therapy of acalabrutinib plus venetoclax plus an anti-CD20 antibody at Cycle 16 (Cohorts 3 and 4) will be calculated and 95% exact binomial CIs will be provided

12.2.2 Complete Response Rate and MRD-Negative Complete Response Rate

The CR rate will be calculated and corresponding 95% confidence intervals through use of exact binomial distribution will be provided. The MRD-Negative CR rate will be summarized with MRD data in separate report..

12.2.3 Progression-Free Survival

PFS is defined as the time from the date of first dose to the date of first disease progression or death due to any cause, whichever comes first. If no disease progression or death is reported for a subject, the subject will be censored at the date of last adequate assessment (censoring date). If a subject receives an autologous or allogeneic stem cell transplant, the subject will be censored at the date of transplant. If a subject starts new anticancer therapy before disease progression or death, the subject will be censored at the date of last adequate assessment prior to receiving the new anticancer therapy. Adequate assessment is defined as physical examination (PE) and complete blood count (CBC) or computed tomography (CT) for CLL disease subgroups (or PET-CT for RS/PLL disease subgroup) and CBC. If a subject does not have any adequate assessment after first dose, the subject will be censored at Day 1.

PFS is calculated as date of disease progression or death (or censoring date for censored subjects) - first dose date + 1.

Events and censoring rules for PFS are summarized as follows:

Situation	**Outcome**	**Date**	**Event Description/ Censoring Reason**
Documented Progression of Disease (PD)	Event	Earliest date of disease assessment documenting PD	PD
Death	Event	Date of Death	Death
Start of new anticancer therapy before documented PD or death	Censored	Date of last adequate assessment prior to receiving the new anticancer therapy	New anticancer therapy

Start of transplant	Censored	Date of transplant	Transplant
Withdrawal of consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrawal of consent
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No documented PD or death and the reason for not completing Safety Follow-up visit is "Other"	Censored	Date of last adequate disease assessment	Other: *specify*
No documented PD or death at the time of data cutoff	Censored	Date of last adequate disease assessment	Data cutoff
No post-baseline adequate disease assessments	Censored	Date of first dose	No post-baseline adequate disease assessments

Kaplan-Meier (KM) curve will be used to estimate the distribution of PFS. Median PFS and the 95% confidence limits and PFS rates for selected landmarks with 95% CIs will be reported. Number of progressions, deaths, and censored events by reason will be summarized.

12.2.4 Duration of Response

Duration of response (DOR) is defined as the time from the date of achieving the first CR, CRi, nPR, or PR to the date of disease progression or death due to any cause, whichever comes first. Subjects who do not experience a disease progression or death will be censored using the same rule for PFS as described in Section 12.2.3.

DOR is calculated as date of disease progression or death (or censoring date for censored subjects) – date of achieving the first CR, CRi, nPR or PR + 1.

DOR will be analyzed similarly to PFS including a KM plot, as described in section 12.2.3.

12.2.5 Time to Response

The following time to response will be calculated and summarized using descriptive statistics.

- Time to CR= (date of CR – date of first dose +1)/30.4376
- Time to CR/CRi = (date of first CR or CRi – date of first dose +1)/30.4376
- Time to response of PR or better = (date of first PR or better – date of first dose + 1) / 30.4376
-

- Time to response of PRL or better = (date of first PRL or better – date of first dose + 1) / 30.4376

12.2.6 Time to Next Treatment (TTNT)

TTNT is defined as the time from the date of first dose to the date of institution of subsequent anticancer therapy for CLL or death due to any cause, whichever comes first. Subjects who do not have the above-specified events prior to the data cutoff date will be censored at the date of last visit. TTNT will be calculated as: (Earlier date of institution of subsequent anticancer therapy for CLL or death due to any cause) – date of first treatment + 1. For censored subjects, date of last visit will replace earlier date of use of subsequent anticancer therapy for CLL or death due to any cause in the calculation.

TTNT will be analyzed similarly to PFS including a KM plot, as described in section 12.2.3.

12.2.7 Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of first doseto death due to any cause. Subjects who were not known to have died prior to the analysis data cutoff date will be censored as follows:

Situation	**Outcome**	**Date**	**Event Description/ Censoring Reason**
Death on or before data cutoff	Event	Date of death	Death
Exit study prior to data cutoff	Censored	Date of discontinuation from study participation as reported on study exit CRF	Withdrew consent/ study terminated by sponsor/study exit
Lost to follow-up prior to data cutoff	Censored	Date subject last known to be alive	Lost to follow-up
No death reported on or before data cutoff	Censored	Date subject last known to be alive	Still on study

OS will be calculated as death date (or censoring date) – the date of first dose + 1.

OS will be analyzed similarly to PFS including a KM plot, as described in section 12.2.3.

12.2.8 Patient reported outcomes (PRO)

The patient reported outcomes include:

- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) is a 30-item questionnaire designed to assess health-

related quality of life in cancer patients. There are 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact).

- Medical outcomes Study Short Form 36 (SF-36) is used to assess health -related quality of life. It consists of eight scales (physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health) yielding two summary measures: physical and mental health

EORTC QLQ-C30 and SF36 will be collected at screening, Cycle 5, Cycle 9, Cycle 13, Cycle 18, Cycle 24 and end of study.

Cohorts 1 and 2:

Cohorts 1 and 2 collected EORTC QLQ-C30 and SF-36 and they are used to assess patient-reported quality of life.

Mean in mental/physical component scale for SF36, and each item of symptoms/functioning /global health status for EORTC QLQ-C30 is calculated at baseline and cycle 24. A repeated measures ANOVA is used to assess quality of life across the study period, using baseline and 24-month outcomes. Cohort (treatment-naïve and relapsed/refractory) is the factor used among patients to assess time-related outcomes and to determine any cohort, time, and interaction effects for individual patients.

The analyses were performed by Ohio State University Comprehensive Cancer Center and the results were published in the journal Cancer Discovery [5].

Cohorts 3 and 4:

Cohorts 3 and 4 collected EORTC QLQ-C30 only and is used to measure quality of life in cancer patients. The Sponsor will perform analysis to summarize EORTC QLQ-C30 for Cohorts 3 and 4.

The EORTC QLQ-C30 scale scores will be calculated using the EORTC QLQ-C30 Scoring Manual (Fayers & et al, 2001). The instrument yields the following scales:

- Global health status / Quality of Life (QoL) (2 items)
- Functional scales
    - Physical functioning (5 items)

  - Role functioning (2 items)
  - Emotional functioning (4 items)
  - Cognitive functioning (2 items)
  - Social functioning (2 items)

- Symptom scales / items
  - Fatigue (3 items)
  - Nausea and vomiting (2 items)
  - Pain (2 items)
  - Dyspnea, insomnia, appetite loss, constipation, diarrhea, Financial impact (1 item each)

The principle for scoring is the same for all scales. In brief, outcome scores are computed by standardizing the average of the items (i.e., a raw score) making up the scale. Outcome scores are computed using a linear transformation of the raw score such that scores range from 0 to 100. Details are provided in Appendix E: Patient Reported Outcomes (PRO). A higher score represents a higher ("better") level of functioning or a higher ("worse") level of symptoms; that is, a high score for a functional scale represents a high/healthy level of functioning, a high score for the GHS represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. Note that the global health status scale is based on only the 2 specific HRQoL items and not the entire questionnaire.

If at least half the items of a scale are present for a time point, then the score will be calculated using the average of all items answered; otherwise, the score will be set to missing. For single measures, if the item is missing the scale score is set to missing.

Baseline is defined as the last available record on or prior to the start date of study treatment.

At each analysis visit and for cohort, the summary statistics (number of subjects, mean, standard deviation, median, and range) of scaled scores and changes from baseline scale scores will be calculated for global health status/QoL, each functional scale and each symptom scale by cohort at each analysis visit.

A listing of scale scores will be generated. A mean overtime plot will be generated for the global health status/quality of life. Also, the compliance to the schedule of administration will be summarized by cohort for baseline and post-baseline timepoints.

13.0 Safety Analyses

Safety analyses will be performed using the All Treated Population unless specified otherwise.

Safety will be assessed by evaluation of treatment-emergent adverse events (TEAEs), laboratory values, vital signs measurements, electrocardiogram (ECG) results, physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status.

13.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 24.0) reporting system. The investigator will grade AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 for AEs. Hematologic toxicity is assessed by the investigator according to IWCLL 2008 guidelinesfor Cohorts 1 and 2, and NCI CTCAE v4.03 for Cohorts 3 and 4. TEAEs are defined as those events that occur on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.

All TEAEs will be summarized by cohort as treated. For each cohort, AE incidence rates will be summarized with frequency and percentage by system organ class and preferred term, and the denominator for the AE incidence rate will be based on the number of subjects treated in that cohort unless otherwise specified. In addition, AE incidence rates will also be summarized by severity. and relationship to study drug. Relationship to study drug, per the investigator's judgment, is recorded on the CRF.

Subjects with multiple occurrences of events for a given preferred term, system organ class, or overall will be counted only once at the maximum severity. and strongest relationship to study drug for each preferred term, system organ class, and overall, respectively.

Summaries will be presented for:

- treatment-emergent AEs
- treatment-emergent serious adverse events (TESAEs)
- treatment-related TEAEs
- treatment-related TESAEs
- AEs leading to study drug discontinuation or dose modifications or dose delay
- treatment-emergent fatal (Grade 5) AEs

13.2 Adverse Events of Clinical Interest.

Adverse events of clinical interest(ECIs) are specified in Appendix F. Subject incidence rates of AEs of clinical interest will be summarized similarly to TEAEs by cohort.

13.3 Deaths

All reported deaths will be summarized by cohort and cause of death. A by-subject listing that includes date of death and cause of death will be provided.

13.4 Laboratory Assessments

13.4.1 Data Summary Methods

All laboratory values will be converted to and reported as SI units and classified as normal, low, or high based on the normal ranges provided by the local laboratory.

Hematologic parameters, including platelet counts, hemoglobin, and neutrophils, will be summarized by IWCLL 2008 (Appendix C) and NCI CTCAE v4.03 respectively. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03.

Per the grading scale in the IWCLL guidelines, ANC: Both baseline grade and post-baseline grade are defined based on absolute values and 2) Hemoglobin and platelet: baseline grade is not applicable (no criterion is provided to define baseline grade) and post-baseline grade is based on percentage decrease from baseline value.

Gradable parameters that have criteria available for both low and high values (e.g., hypercalcaemia for a high value of calcium and hypocalcaemia for a low value of calcium) based on the NCI CTCAE v4.03 will be summarized for both criteria (low and high). Subjects will be counted only once for each criterion/direction. The same subject can be counted for both criteria if the subject has laboratory values meeting each criterion. Subjects meeting the criteria for Grade 1 or higher for the high direction will be summarized under Grade 0 when summarizing the low direction and vice versus.

For each laboratory parameter, the baseline laboratory value/grade is defined as the last laboratory value/grade collected on or prior to the date of the first dose of study drug. The change from baseline to post-baseline value will be calculated for each parameter.

13.4.2 T/B/NK Cell Counts

Descriptive statistics will be presented at baseline, last post-baseline, minimum post-baseline, and maximum post-baselinefor the flow cytometry testing parameters ($CD3^+$, $CD4^+$, $CD8^+$, , $CD19^+$, and NK cells).

Changes from baseline at each of the last, minimum, and maximum post-baseline time points will be summarized. Figures will be presented for the mean of selected parameters over time as appropriate.

13.4.3 Serum Immunoglobulin

For IgG, IgM, and IgA levels, descriptive statistics will be presented at baseline, last post-baseline, minimum post-baseline, and maximum post-baseline. Changes from baseline at each of the last, minimum, and maximum post-baseline time points will be summarized. Figures will be presented for the mean of selected parameters over time as appropriate.

13.4.4 Analysis of Lymphocytosis

Lymphocytosis is defined as an elevation in ALC of ≥50% compared with baseline and a post-baseline assessment >5,000/μL.

The number, percentage (and 95% exact binomial CI) of subjects with at least once occurrence of lymphocytosis will be summarized.

Time to Lymphocytosis will be calculated from the date of the first dose of study drug to the first post-baseline ALC which met the lymphocytosis criteria and summarized using descriptive statistics.

Duration of lymphocytosis (DOL) is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria. Resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower or 2) an achievement of ALC value that is below 5,000/μL, whichever occurs first.

DOL = Earliest date of meeting resolution criteria - Earliest date of meeting lymphocytosis criteria + 1.

Confirmation is not required for resolution of lymphocytosis. Subjects who developed lymphocytosis but whose lymphocytosis was not resolved prior to the analysis cutoff date will be censored at the last sample date with non-missing ALC value at or prior to the analysis cutoff date. KM curves will be used to estimate the distribution of DOL. The 50th percentile of KM estimates along with its two-sided 95% CI will be used to estimate the median DOL.

13.5 Vital Signs and Physical Examinations

For each vital sign measurement, descriptive statistics will be presented at baseline, last post-baseline, minimum post-baseline, and maximum post-baseline. Change from baseline at each of the last, minimum, and maximum post-baseline time points will be summarized.

Findings of abnormal physical examinations at baseline and post-baselinewill be tabulated by body system at each visit.

Shift of blood pressure from baseline to the worst score during the treatment will be provided as shift tables.

13.6 ECOG Performance Status

Shift of ECOG from baseline to the worst score during the treatment will be summarized in a shift table.

14.0 **REFERENCE**

[1] Byrd JC, Furman RR, Coutre SE, et al. Targeting Btk with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42. Erratum in: N Engl J Med 2014b;370:786.

[2] Cheson BD, Byrd JC, Rai KR, et al. R novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2.

[3] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 2014;32:3059-68.

[4] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.

[5] Jennifer A. Woyach, James S. Blachly, Kerry A. Rogers, et al. Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia. *Cancer Discovery* 2020;10:394-405.

15.0 APPENDICES

Appendix A: Analysis Windows

Tumor assessment/CT/SPD For Cohort 1 and 2				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C4D1	85	0		127
C7D1	169	1	128	211
C10D1	253	1	212	281
C12D1	309	1	282	351
C15D1	393	13	352	435
C18D1	477	15	436	519
C21D1	561	18	520	603
C24D1	645	21	604	687
C30D1	813	27	688	855
C36D1	981	32	856	

Tumor assessment/CT/SPD For Cohort 3 and 4				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C4D1	85	0		127
C7D1	169	1	128	211
C10D1	253	1	212	295
C13D1	337	1	296	379
C16D1	421	13	380	463
C19D1	505	15	464	547
C22D1	589	18	548	617
C24D1	645	21	618	687
C30D1	813	27	688	855
C36D1	981	32	856	

Hematology / Chemistry				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C1D1	1	0		1
C1D8	8	1	2	12
C1D15	15	1	13	21
C2D1	29	1	22	43
C3D1	57	2	44	71
C4D1	85	2	72	99
C5D1	113	3	100	127
C6D1	141	4	128	155
C7D1	169	5	156	183
C8D1	197	6	184	211
C9D1	225	7	212	239
C10D1	253	8	240	267
C11D1	281	9	268	295
C12D1	309	10	296	351
C15D1	393	13	352	435

C18D1	477	15	436	519
C21D1	561	18	520	603
C24D1	645	21	604	687
C30D1	813	27	688	855
C36D1	981	32	856	

Physical Examination/ECOG				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
C1D1	1	0		1
C1D8	8	1	2	12
C1D15	15	1	13	21
C2D1	29	1	22	43
C3D1	57	2	44	71
C4D1	85	2	72	99
C5D1	113	3	100	127
C6D1	141	4	128	155
C7D1	169	5	156	183
C8D1	197	6	184	211
C9D1	225	7	212	239
C10D1	253	8	240	267
C11D1	281	9	268	295
C12D1	309	10	296	351
C15D1	393	13	352	435
C18D1	477	15	436	519
C21D1	561	18	520	603
C24D1	645	21	604	687
C30D1	813	27	688	855
C36D1	981	32	856	

Appendix B: Rai Stage Derivation Criteria

Stage	Lymphocytosis	Lymphadenopathy	Hepatomegaly or splenomegaly	Anemia	Thrombocytopenia
0	1	0	0	0	0
I	1	1	0	0	0
II	1	any	1	0	0
III	1	any	any	1	0
IV	1	any	any	any	1

1 = yes, 0 = no, any = yes or no

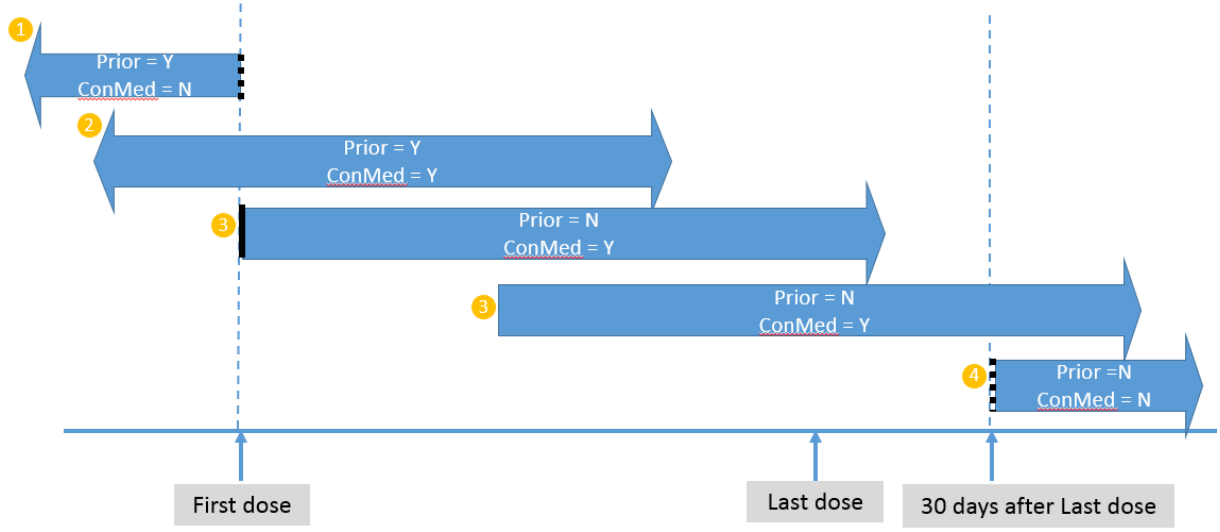
Appendix C: Grading Scale for Hematologic Toxicity in CLL (Hallek 2008)

Grade[1]	Decrease in platelets[2] or Hb[3] (nadir) from pretreatment value	Absolute neutrophil count/μL[4] (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

1. 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 reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is <20 x 10^9/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., <20 x 10^9/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (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.
4. If the ANC reaches <1 x 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 x 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 granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity but should be documented.

Appendix D: Defining Prior and Concomitant Medication Flags

The figure below depicts various scenarios of prior and concomitant medications. The prior and concomitant medication flags are specified respectively for each scenario.



1 = start < first dose and stop < first doe
2 = start < first dose and stop >= first dose
3 =start >= first dose
4 = start > last dose + 30 days

Appendix E: Patient Reported Outcomes (PRO)

1. EORTC QLQ-C30

The United States English version is provided as an example only.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Table 1 EORTC QLQ-C30 Scoring Guide

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

Scoring Algorithm

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The technical details are provided below.

If items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Calculate the raw score (RS) as follows: $RS=(I_1+I_2+ ... +I_n)/n$

Apply the linear transformation as follows:

- Functional scales: Scale score = $(1 – ((RS -1)/range)\times100$
- Symptom scales / items: Scale score = $(RS -1)/range\times100$
- Global health status/QoL: Scale score = $(RS -1)/range\times100$

where Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values (see Table 1).

If at least half the components of a scale are present, then the scale score will be calculated using the average of all items answered as the raw score; otherwise the score will be set to missing. For single measures, if the item is missing, the scale score is set to missing.

2. The Medical Outcomes Study-Short Form-36 (SF-36)

Subject ID

Quality of Life
CLL III Study
SF-36 (page 1 of 3)

Assessment

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to conduct your daily activities.

Answer every questions by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. Fill in the circle that best describes your answer.

1. In general, would you say your health is: ○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

2. Compared to one year ago, how would you rate your health, in general, now? ○ Much better now ○ Somewhat better now ○ About the same ○ Somewhat worse now ○ Much worse now

Does your health limit you in the activities listed below? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?	○	○	○
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	○	○	○
5. Lifting or carrying groceries?	○	○	○
6. Climbing several flights of stairs?	○	○	○
7. Climbing one flight of stairs?	○	○	○
8. Bending, kneeling, or stooping?	○	○	○
9. Walking more than a mile?	○	○	○
10. Walking several blocks?	○	○	○
11. Walking one block?	○	○	○
12. Bathing or dressing yourself?	○	○	○

46547

Subject ID

Quality of Life
CLL III Study
SF-36 (page 2 of 3)

Assessment

During the PAST 4 WEEKS, have you had any of the following problems with your work or other regular activities as a result of your PHYSICAL HEALTH?

13. Cut down on the amount of time you spent on work or other activities? ○ Yes ○ No

14. Were limited in the kind of work or other activities? ○ Yes ○ No

15. Accomplished less than you would like? ○ Yes ○ No

16. Had difficulty performing the work or other activities (e.g., it took extra effort)? ○ Yes ○ No

During the PAST 4 WEEKS, have you had any of the following problems with your work or other regular activities as a result of EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

17. Cut down on the amount of time you spent on work or other activities? ○ Yes ○ No

18. Accomplished less than you would like? ○ Yes ○ No

19. I did not do work or other activities as carefully as usual. ○ True ○ False

20. During the PAST 4 WEEKS, to what extent have your PHYSICAL HEALTH or EMOTIONS interfered with your normal social activities with family, friends, neighbors, or groups?

○ Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely

21. How much bodily pain did you have during the PAST 4 WEEKS?

○ None ○ Very mild ○ Mild ○ Moderate ○ Severe ○ Very severe

22. During the PAST 4 WEEKS, how much did pain interfere with your normal work (including work outside the home and housework)?

○ Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely

Subject ID

Quality of Life
CLL III Study
SF-36 (page 3 of 3)

Assessment

For each question, please indicate the one answer that comes closest to the way you have been feeling in the PAST 4 WEEKS...

During the PAST 4 WEEKS, how much of the time....

	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
23. Did you feel full of pep?	○	○	○	○	○	○
24. Have you been a very nervous person?	○	○	○	○	○	○
25. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○	○
26. Have you felt calm and peaceful?	○	○	○	○	○	○
27. Did you have a lot of energy?	○	○	○	○	○	○
28. Have you felt downhearted and blue?	○	○	○	○	○	○
29. Did you feel worn out?	○	○	○	○	○	○
30. Have you been a happy person?	○	○	○	○	○	○
31. Did you feel tired?	○	○	○	○	○	○
32. Has your HEALTH limited your social activities (like visiting friends or close relatives, etc.)?	○	○	○	○	○	○

Please choose how TRUE or FALSE these statements are for you.

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
33. I seem to get sick a little easier than other people.	○	○	○	○	○
34. I am as healthy as anyone I know.	○	○	○	○	○
35. I expect my health to get worse.	○	○	○	○	○
36. My health is excellent.	○	○	○	○	○

Table 2. The SF36 quality of life scoring system and its scales and dimensions

ITEMS	SCALES	Dimensions
3. Vigorous activities	Scale 1: Physical Functioning (PF)	Dimension A: PHYSICAL HELTH
4. Moderate activities		
5. Lift, carry groceries		
6. Climb several flights		
7. Climb one flight		
8. Bend, kneel		
9. Walk mile		
10. Walk several blocks		
11. Walk one block		
12. Bathe, dress		
13. Cut down time	Scale 2: Role-Physical (RP)	
14. Accomplished less		
15. Limited in kind		
16. Had difficulty		
21. Pain-magnitude	Scale 3: Bodily Pain (BP)	
22. Pain-interfere		
1. General health rating	Scale 4: General Health (GH)	
36. Excellent		
34. As healthy as anyone		
33. Sick easier		
35. Health worse		
23. Pep/life	Scale 5: Vitality (VT)	
27. Energy		
29. Worn out		
31. Tired		
32 Social-extent	Scale 6: Social Functioning (SF)	
20. Social-time		
17. Cut down time	Scale 7: Role-Emotional (RE)	Dimension B: MENTAL HEALTH
18. Accomplished less		
19. Not careful		
24. Nervous	Scale 8: Mental Health (MH)	
25. Down in dumps		
26. Peaceful		
28. Blue/sad		
30. Happy		
2. Change in reported health		

Appendix F: Adverse Events of Clinical Interest

Below please see the definition and searching criteria for adverse events of clinical interest.

Definition of Adverse Event of Special Interest and Events of Clinical Interest (MedDRA version 24.0)

1. Adverse Event of Special Interest (AESI)

The following preferred terms (PT) for the ventricular arrhythmias AESI include:

- Torsade de pointes
- Ventricular arrhythmia
- Ventricular extrasystoles
- Ventricular fibrillation
- Ventricular flutter
- Ventricular tachyarrhythmia
- Ventricular tachycardia

2. Events of Clinical Interest

The Events of Clinical Interest (ECIs) have been identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved Bruton's tyrosine kinase (BTK) inhibitors. The adverse events (AEs) selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by System Organ Classes (SOCs), or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category	Subcategory	Definition
Cardiac events		• SOC Cardiac disorders
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter

	Ventricular tachyarrhythmias	• PT Torsade de pointes • PT Ventricular fibrillation • PT Ventricular flutter • PT Ventricular tachyarrhythmia • PT Ventricular tachycardia
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Band Neutrophil count decreased • PT Band neutrophil percentage decreased • PT Cyclic neutropenia • PT Febrile Neutropenia • PT Idiopathic neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Cytopenias - Thrombocytopenia		• SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		• SMQ Haemorrhage terms (excl laboratory terms)
	Major hemorrhage	• As per definition (see Section 3 below)

Hepatotoxicity		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions • SMQ [narrow] Hepatitis, non-infectious • SMQ [narrow] Liver related investigations signs
Hypertension		• SMQ Hypertension [narrow]
Infections		• SOC Infections and infestations
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease
Second primary malignancies		• SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haemoatological malignant tumours SMQ) • SMQ Malignant lymphomas [narrow] SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding non melanoma skin)	• The above excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma)
Tumor lysis syndrome		• PT Tumour lysis syndrome

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HLT=high-level term; ISS=integrated safety summary; PT=preferred term; SAE=serious adverse event; SMQ=Standardised MedDRA Query; ULN=upper limit of normal. MedDRA version 24.0