PPD -15-H-0016 Study Statistical Analysis Plan

A Phase II Study Using ACP-196 (Acalabrutinib) in Patients with Relapsed/Refractory and Treatment Naïve Deletion 17p CLL/SLL: Pharmacodynamic Assessment of BTK Inhibition and Anti-Tumor Response

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SAP Revision History:

Version/Date	Summary of Major Changes and Rationale
1/ March 15, 2017	Initial version
2/January 4, 2019	Added Efficacy section to follow the current protocol
3/September 23, 2020	Finalized for the final CSR by taking out interim analysis from the introduction section, adding reference to the current protocol amendment

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this document is to provide a statistical analysis plan(SAP), based on the Protocol 15-H-0016 Amendment K, "A Phase II Study Using ACP-196 (Acalabrutinib) in Patients with Relapsed/Refractory and Treatment Naïve Deletion 17p CLL/SLL: Pharmacodynamic Assessment of BTK Inhibition and Anti-Tumor Response", dated 27 April 2018.

This study was initiated by PPD, and the principal investigator at PPD developed the protocol. Statistical methods in this SAP will supersede those described in the protocol. Major differences will be noted in the SAP.

The protocol was last amended to amendment M, dated 16Mar2020, but the statistical analysis scope and method remain unchanged.

Any changes to the methods described in the final SAP will be documented in the clinical study report (CSR). A separate pharmacodynamics report will be provided for the CSR.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is

- To determine the response to acalabrutinib in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

2.2 Secondary Objectives

The secondary objectives of this study are

- Safety and tolerability of acalabrutinib
- Duration of response (DoR) to acalabrutinib
- Time to progression on acalabrutinib
- Progression-free survival (PFS)
- Overall survival (OS) on acalabrutinib
- Explore the biologic effects of once-daily dosing as compared with twice-daily dosing of acalabrutinib on CLL tumor cells
- To measure BTK inhibition and on-target effects of single-agent acalabrutinib in CLL cells in lymph node, bone marrow, and blood of subjects with CLL or SLL

3 OVERALL STUDY DESIGN

3.1 Study Design

This is a Phase II single-center trial. It is an open-label study of acalabrutinib in patients with CLL or SLL with a lead-in period for pharmacodynamic (PD) assessment. Subsequently, patients received acalabrutinib continuously until disease progression or development of drug related toxicity.

For pharmacodynamics assessment during the lead-in period, patients will receive acalabrutinib for 3 days followed by study drug hold for a portion of the research sampling at different intervals from last dose. Study drug will be restarted after completion of research sampling.

Up to 60 patients will be screened and up to 48 patients may start treatment with the expectation that 44 evaluable patients will remain in the study.

Patients will be enrolled into 2 different study arms based on the presence or absence of superficial lymphadenopathy:

- Arm A will enroll up to 32 patients with superficial lymphadenopathy, who will undergo lymph node biopsy to assess PD endpoints
- Arm B will enroll up to 16 patients (with or without lymphadenopathy) who will undergo bone marrow biopsy to assess PD endpoints.

In each arm, patients will be randomized to receive one of two dosing regimens:

- acalabrutinib, 200 mg once daily (acalabrutinib 200 mg QD) or
- acalabrutinib, 100 mg twice daily (acalabrutinib 100 mg BID).

Thus, up to 24 patients will receive acalabrutinib 200 mg QD and up to 24 patients will receive acalabrutinib 100 mg BID. Randomization will be provided by the CCI .

If Arm A completes accrual before Arm B, then all remaining patients will be enrolled into Arm B.

For all patients, peripheral blood samples will be collected at the time that biopsies are done; that is, on Day 3 at 4 hours after dosing (peak level), on Day 4 (trough level), on Day 5 (trough level plus 24 hours off drug).

On Day 6, after all sampling is complete, patients resume continuous treatment until disease progression or limiting side effects.

Subjects in once-daily cohorts will be permitted, at the Investigator's discretion, to transition to twice-daily dosing after 6 cycles of acalabrutinib.

3.2 Study Endpoints

Response assessments will be determined by investigators based on International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria incorporating the 2012 and 2013 clarifications for patients treated with kinase inhibitors. Response includes complete response (CR), partial response (PR), and partial response with lymphocytosis (PRL).

3.2.1 Efficacy Endpoints

Primary endpoint:

- ORR (overall response rate)

Secondary endpoints:

- PFS (progression-free survival)

- TTP (time to progression)
- DOR (duration of response)
- OS (overall survival)
- Time to Initial Response
- Safety and Tolerability of once daily and twice daily dosing of acalabrutinib

3.2.2 Safety

Safety and tolerability of once-daily and twice-daily dosing of acalabrutinib will be assessed using the following safety evaluations during the study:

- Treatment-emergent adverse event (TEAE)
- Physical examinations
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory evaluations, including:
  - Hematology
  - Chemistry
  - Immunology

3.2.3 Exploratory Endpoint

- CCI

3.3 Sample Size

The study will enroll 44 subjects evaluable for response to complete the primary endpoint. The subjects in two different dosing regimens are pooled to evaluate the primary endpoint of response. Each dosing regimen will include approximately 22 subjects. To account for subjects discontinuing participation before having completed 6 months on treatment, the sponsor will enroll up to 4 additional subjects. Thus up to 48 subjects may be started on study drug. To account for screening failures, up to 12 additional subjects may be screened for protocol. Up to 60 subjects will sign the screening consent and up to 48 will sign the standard consent to start treatment, with the intention of accruing 44 evaluable subjects.

For pharmacodynamics studies, we aim to have at least 6 subjects donating paired tumor samples pretreatment and on-treatment in each cohort for a total of 36 subjects.

CCI

4 ANALYSIS SETS

4.1 Enrolled Population

The enrolled population will include all subjects who completed the enrollment procedures.

4.2 All Treated Population

The All Treated population is defined as all enrolled subjects who receive ≥ 1 dose of study drug.

4.3 Efficacy Evaluable Population 6m (EEP6)

The Efficacy Evaluable Population 6m (EEP6) will include all subjects receiving at least 6 months of treatment.

4.3.1 Efficacy Evaluable Population (EEP)

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

5 GENERAL STATISTICAL METHODS

5.1 Data Presentation

For categorical variables, summary tabulations of the number and percentage of subjects within each category will be presented. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented.

Subject level data will be presented in listings. All listings that contain an evaluation date will contain a relative study day. Definition of study day is given in Section 5.3.2.

5.2 Coding and Grading

Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity of non-hematologic AEs. Hematologic Toxicity will be graded by Hallek (2008) as specified in Appendix C of this document.

Prior and Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version September 2018.

5.3 General Definitions

5.3.1 Definition of Baseline and Post Baseline

For safety endpoints and efficacy analysis, such as laboratory measurements, the last observation before first dose of study treatment will be considered the baseline measurement unless otherwise specified.

For demographics and baseline characteristics, the baseline will be defined as the most recent measurement prior to the first administration of study drug.

Post baseline will be defined as measurements taken after the first dose of study drug.

5.3.2 Definition of Study Day

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

For listings (such as for adverse events) that include the derivation of "days since last dose," it is defined as (event date – date of last dose). Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

5.3.3 Analysis Window Calculation

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the visit.

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 that includes the assessment date. Details are provided in Appendix A.

In data listings, the relative day of all dates will be presented. Analyses will be according to actual visit dates and times. Listings do not require calculation of visit windows.

5.4 Missing Data Handling

No imputation of values for missing data will be performed, except for missing or partial start and end dates for adverse events, prior/concomitant medications, prior anti-cancer therapies, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, the date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, then the first dose date will be used; if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used; if the imputed AE end date is before the AE start date, the AE start date will be used.

Subjects who are lost to-follow up (or who drop out) will be included in statistical analyses to the point of their last evaluation.

5.5 Deviations from protocol and other issues

Time to initial response is not specified as an efficacy endpoint in the protocol. Since it provides information about the onset of response, it is added to the SAP as an efficacy endpoint.

Any changes to the analyses described in the protocol or in approved versions of this analysis plan will be fully documented in the CSR.

6 SUBJECT DISPOSITION

The number and percentage of subjects in Enrolled Population, All Treated Population, and Efficacy Evaluable Population who discontinued treatment and the reasons for treatment discontinuation and who did not complete the safety follow-up and the reasons for study exit, and time on study will be presented.

7 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be described and summarized and by-subject listing will be provided.

8 BASELINE DATA

Screening/baseline variables will be summarized and presented for the All Treated population. No inferential statistical comparisons will be performed between the two dosing regimens with respect to screening/baseline variables.

8.1 Demographic and Baseline Characteristics

- Sex (male vs. female)
- Age
- Age category
  - <65 vs. ≥65 years
  - <70 vs. ≥70 years
- Ethnicity (Hispanic or Latino, Non-Hispanic or Non-Latino)
- Race
  - American Indian/Alaskan Native
  - African American/Black,
  - Asian
  - Caucasian/White
  - Native Hawaiian/Other Pacific Islander
  - Other

8.2 Baseline Disease Characteristics

- Weight (kg)
- Histology (CLL/SLL)
- Time from initial diagnosis to first dose (years)

- ECOG performance status
- Rai stage – derived based on variables collected at screening visit using the criteria described in Appendix B.
- B Symptoms – weight loss, fever, night sweats, fatigue
- Bulky disease: defined as if at least one dimension of the lymph node measurement is
  - ≥5 cm
  - ≥10 cm
- Chromosomal abnormalities:
  - 17p del (with or without 11q del)
  - 11q del (with or without 17p del)
  - 17p del or 11q del
  - Neither 17p del nor 11q del
  - Unmutated IgHV vs mutated IgHV
  - Positive NOTCH 1 vs negative NOTCH 1
  - Positive TP53 vs negative TP53
- Beta-2 Microglobulin
  - >3 vs. ≤3 mg/L
  - >3.5 vs. ≤3.5 mg/L
- 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
- Absolute lymphocyte counts (ALC; 10^9/L)
- Hemoglobin (g/dL)
- Platelet counts (10^9/L)
- Prior RBC transfusion within 28 days before randomization (yes, no)
- Sum of product diameter (SPD) for lymph nodes (cm^2)
- Palpable liver by physical exam
- Palpable spleen by physical exam

9 TREATMENT AND MEDICATIONS

9.1 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 a start/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 a separate regimen. The number of lines and type of prior therapy will be summarized.

9.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary. The number and percentage of subjects will be presented for each preferred term. 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 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.

9.3 Exposure to Study Drug

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize:

- Duration of exposure (the interval between first dose date and last dose date)
- Cumulative dose (total amount of drug received during treatment)
- Average daily dose (the ratio of cumulative dose to treatment duration)
- Relative dose intensities (the ratio of average daily dose to expected daily dose)

The reasons for acalabrutinib dose withhold and reduction will be summarized and presented as the number and percentage of subjects with non-missing data per category.

Dose withhold of acalabrutinib is defined as missing dose for ≥ 7 consecutive days.

Dose reduction defined as taking lower dose level (<200 mg per day) for acalabrutinib for ≥ 3 consecutive days.

10 EFFICACY ANALYSIS

10.1 Overall Response Rate (ORR)

ORR is the proportion of subjects who achieve CR, CR with incomplete marrow recovery (CRi), or PR while on treatment before the initiation of new anti-cancer therapy or stem cell transplant. The corresponding 95% CIs using exact binomial distribution will be provided.

ORR will be summarized using Efficacy Evaluable Population and All Treated Population. Efficacy Evaluable Population is the primary analysis population.

For CLL/SLL disease subgroups, ORR including PRL as a response will also be summarized in the same fashion.

10.2 Progression-Free Survival (PFS)

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. If a subject does not experience any disease progression or death, 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/SLL disease subgroups 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 (censoring date for censored subjects) - first dose date + 1.

Events and censoring rules for PFS are summarized as follows:

Situation	**Date of Progression or Censoring**	**Outcome**
PFS events include death or first disease progression that occurred at or prior to the data analysis cutoff date.		
Death before first disease assessment	Date of death	Event
Disease progression or death between scheduled visit	Earliest date of disease progression or death	Event
All other cases will be censored as follows:		
No baseline tumor assessments	First treatment date	Censored
No adequate post-baseline	First treatment date	Censored
No disease progression or death at the time of data cutoff (including	Date of last adequate assessment before data cutoff	Censored
No disease progression or death before withdrew consent or lost to follow-up	Date of last adequate assessment before data cutoff	Censored
No disease progression or death before or after start of subsequent anticancer therapy	Date of last adequate assessment before start of subsequent anticancer therapy	Censored

Situation	Date of Progression or Censoring	Outcome
Disease progression or death after 2 or more consecutively missed visits	Date of last adequate assessment before the consecutively missed visits	Censored

Kaplan-Meier (KM) curve will be used to estimate the distribution of PFS. PFS rate based on KM point estimate and its corresponding 95% CI will be calculated at 25th percentile, median (50th percentile), 75th percentile, and selected landmark points for each treatment arm. The difference in PFS between Arms A and B at the above time points will also be calculated. Number of progressions, deaths, and censored events by reason will be summarized.

10.3 Time to Progression (TTP)

TTP is defined as the time from the date of first dose to the date of first disease progression. Subjects who do not have disease progression by the time of data cutoff or die will be censored at the last adequate disease assessment prior to data cutoff or prior to death date.

TTP is calculated as date of disease progression - first dose date + 1.

Kaplan-Meier (KM) curve will be used to estimate the distribution of TTP. The same summary statistics for PFS will be presented for TTP.

10.4 Duration of Response (DOR)

DOR is defined as the time from the date of achieving the first CR, CRi, or PR to the date of disease progression or death due to any cause, whichever comes first. Subjects who do not have a disease progression or death will be censored using the same rule for PFS as described in Section 10.2.

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

Kaplan-Meier (KM) curve will be used to estimate the distribution of DOR. The same summary statistics for PFS will be presented for DOR.

For CLL/SLL disease subgroups, DOR including PRL as one of the responses will also be summarized in the same fashion.

10.5 Overall Survival (OS)

OS is defined as the time from date of first acalabrutinib treatment until date of death or last follow-up.

Subjects who were not known to have died prior to the analysis data cutoff date will be right-censored as follows:

Situation	Censoring Date
Loss to follow-up immediately after first treatment date	First treatment date
Not known to have died at or prior to analysis data cutoff date	Date subject last known to be alive before analysis data cutoff date

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

10.6 Time to Initial Response

Time to initial response of PR or better will be calculated as (date of first PR or better – date of first dose + 1) / 30.4376 and summarized using descriptive statistics. Time to initial response of PRL or better for CLL/SLL disease subgroups will also be summarized in the same fashion.

11 SAFETY ANALYSIS

Safety will be assessed by evaluation of treatment-emergent adverse events (TEAEs), laboratory values, vital signs measurements, and physical examinations.

11.1 Adverse Events

Adverse events (AEs) will be coded by system organ class (SOC) and preferred terms (PTs) through the use of the Medical Dictionary for Regulatory Activities (MedDRA) reporting system.

TEAEs are defined as those events that occur (actual or imputed start date) 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 AEs with partial onset or stop dates will be identified and the partial dates will be imputed as rules in Section 5.4 Missing Data Handling.

The occurrence of AEs will be presented by SOC and PT. If a subject experiences the same event more than once, the event will be counted only once under the maximum severity in tabulation. Adverse events will be presented by relationship and by severity. The investigator will judge each event to be “not related” or “related” to study treatment.

Summaries will be presented for:

- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Treatment-related adverse event
- Treatment-related serious adverse events
- Grade 3 or higher TEAEs
- Grade 3 or higher treatment-related TEAEs
- Fatal (Grade 5) TEAEs
- AEs that led to study drug discontinuation, dose modifications, or dose delay

- Events of Clinical Interest, defined in Integrated Summary of Safety (ISS), Appendix B.

Listings of TEAEs, serious AEs, and death will be provided.

11.2 Laboratory Test Results

Laboratory data of hematology, serum chemistry, serum immunoglobulin, and T/B/NK cell count will be summarized. Shift tables will be presented to summarize grade change from baseline to worse post-baseline grade. Listing of hepatitis B test result will be provided. Local laboratory reference ranges were those specified in AMA Manual of Style 10th Edition (2017).

11.3 Vital Signs and Body Weight

Summary statistics (mean, standard deviation, median, and range) will be produced for vital signs and body weight at baseline, maximum, change to maximum, minimum, change to minimum, last value, and change to last value.

11.4 B Symptoms

Descriptive statistics will be presented for B-symptoms. For subjects who were symptomatic at baseline, sample size and percent of subjects with resolution at post-baseline assessment will be summarized by visit. For those who were as asymptomatic at baseline, sample size and percentage of subjects with onset of symptoms at post baseline assessment will also be summarized by visit.

11.5 ECOG Performance Status

Change of ECOG score from baseline to the worst post baseline score will be provided as shift tables.

11.6 Electrocardiogram

ECG data including corrected QT (QTc) interval will be collected at screening and will be summarized for baseline. Descriptive statistics will be calculated for the QTc parameters.

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13 REFERENCES

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; 111:5446-5456.

AMA Manual of Style 10th Edition. SI Conversion Calculator. Table 2. Selected Laboratory Tests, With Reference Ranges and Conversion Factors. website http://www.amamanualofstyle.com/page/si-conversion-calculator;jsessionid=D18DF5F7CEF17B8E4231B9721627449C. Accessed 16 February 2017

14 APPENDICES

Appendix A: Analysis Windows

ECOG				
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
Screening	-30	0		
C1D1	1	1	1	2
C1D3	3	1	3	4
C1D4	4	1	5	5
C1D5	5	1	6	17
C1D28	28	1	18	42
C2D28	56	2	43	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	42	1219	1302
C48D28	1344	45	1303	1386
C51D28	1428	48	1387	1470
C54D28	1512	51	1471	1554
C57D28	1596	54	1555	

CBC				
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
Screening	-30	0		
C1D1	1	1	1	3
C1D4	4	1	4	5
C1D5	5	1	6	17
C1D14	14	1	18	21
C1D28	28	1	22	
C2D28	56	2	57	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1470
C48D28	1344	45	1471	1386
C51D28	1428	48	1387	1470
C54D28	1512	51	1471	1554
C57D28	1596	54	1555	

Beta-2 microglobulin				
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
Screening	-30			
C1D1	1	1	1	2
C1D3	3	1	3	4
C1D4	4	1	5	5
C1D5	5	1	6	17
C1D28	28	1	18	42
C2D28	56	2	43	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1470
C48D28	1344	45	1471	1386
C51D28	1428	48	1387	1470
C54D28	1512	51	1471	1554
C57D28	1596	54	1555	

Acute care panel/mineral panel/hepatic panel/Total protein				
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
Screening	-30	0		
C1D1	1	1	1	3
C1D4	4	1	4	5
C1D5	5	1	6	17
C1D14	14	1	18	21
C1D28	28	1	22	56
C2D28	56	2	57	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1470
C48D28	1344	45	1471	1386
C51D28	1428	48	1387	1470
C54D28	1512	51	1471	1554
C57D28	1596	54	1555	

Serum Immunoglobulin				
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
Screening	-30	0		
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1302
C48D28	1344	45	1303	1386
C51D28	1428	48	1387	1470
C54D28	1512	51	1471	1554
C57D28	1596	54	1555	

Serum protein electrophoresis with immunofixation				
nominal visit	study day	nominal month	lower (inclusive)	upper (inclusive)
C1D1	1	1	-3	1
C6D28	168	6	153	

Serum protein electrophoresis with immunofixation is required to be taken within 15-day window at end of Cycle 6. This strict rule is applied to the upper and lower limit of this analysis window.

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/SLL (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 $<20 \times 10^9$/L (20,000/µL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $<20 \times 10^9$/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 $<1 \times 10^9$/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 $<1 \times 10^9$/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.