Protocol Number: ACE-WM-001

Protocol Title: An Open-label, Phase 2 Study of ACP196 in Subjects with Waldenström Macroglobulinemia

Version: 2.0

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The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas

DocuSigned by:
PPD

02 February 2018
Date

02/Feb/2018
Date

2 Feb 2018
Date

Statistical Analysis Plan

An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia

Protocol Number: ACE-WM-001

Version:	**Version 2.0**
Date:	**31 January 2018**
Study Statistician:	PPD

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ACP-196	acalabrutinib
AE(s)	adverse event(s)
AMA	American medical association
ANC	absolute neutrophil count
BID	twice per day
CI	confidence interval
CR	complete response (remission)
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DOR	duration of response
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
EORTC	european organization for research and treatment of cancer
HGB	hemoglobin
IRC	independent review committee
IPD	important protocol deviation
MCL	mantle cell lymphoma
MedDRA	medical dictionary for regulatory activities
MR	minor response
NCI	national cancer institute
NDA	new drug application
ORR	overall response rate
OS	overall survival
PD	progressive disease
CCI	[redacted]
PFS	progression-free survival
PK	pharmacokinetics
PLT	platelet
PR	partial response
PRO	patient reported outcome
PT	preferred term
QD	once per day
QLQ-C30	core quality of life questionnaire

QTc	corrected QT interval
R/R	relapsed/refractory
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SI	the international system of units
SOC	system organ class
TEAE(s)	treatment-emergent adverse events
VGPR	very good partial response
WHO	world health organization
WM	waldenström macroglobulinemia

1. INTRODUCTION

This statistical analysis plan (SAP) provides details of efficacy and safety analyses that have been outlined within ACE-WM-001 protocol amendment 7.0, which is entitled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia" dated 26December2017. The original SAP was based on protocol amendment 5.0 dated 23June2016. It was for interim safety clinical study report (CSR) to support the new drug application (NDA). This SAP is updated to include efficacy analysis. Protocol amendment 6.0 dated 21December2016 added a co-primary endpoint of overall response rate (ORR), as defined by the modified 3rd IWWM workshop criteria (Kimby 2006), and as assessed by investigators. The secondary endpoint of ORR as assessed by the IRC was revised to indicate that the response criteria for this endpoint will be according to the modified 3rd IWWM workshop criteria. In addition, the secondary endpoints for duration of response (DOR) and progression-free survival (PFS) were updated to clarify that DOR and PFS by the investigator would be assessed according to both response assessment criteria for Waldenström Macroglobulinemia (WM) (Owen (2013) and modified 3rd IWWM workshop criteria), and DOR and PFS by the independent review committee (IRC) would be assessed using the modified 3rd IWWM workshop criteria only. The additional objective and endpoints were added to align with response criteria used in standard practice and prior clinical trials. Owen's response criteria add additional rigor and thus is kept as a co-primary endpoint.

Hereafter, acalabrutinib (a generic name for ACP-196) will be used in place of ACP-196 in this document.

Separate reports will be generated for pharmacokinetic (PK) and CCI [redacted] data.

The analysis will be executed by the biometrics department of Acerta Pharma unless otherwise specified.

2. OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to:

- To determine the ORR of acalabrutinib in subjects with WM as assessed by investigator.

2.2 Secondary Objectives

The secondary objectives are as follows:

- To determine the ORR of acalabrutinib by IRC
- To determine the DOR of acalabrutinib by investigator and by IRC, respectively
- To determine the PFS of acalabrutinib by investigator and by IRC, respectively
- To determine the overall survival (OS) of acalabrutinib
- To characterize the PK profile of acalabrutinib
- To characterize the safety of acalabrutinib
- To evaluate the effect of acalabrutinib in health-related quality of life

2.3 CCI

CCI

3. STUDY OVERVIEW

3.1 Study Design

This study is a multicenter open-label clinical trial evaluating the safety and efficacy of acalabrutinib CCI in subjects with previously treated WM using a Simon's optimal two-stage design. In addition, a small cohort of subjects with previously untreated WM will be enrolled as an exploratory cohort to determine the preliminary safety and efficacy of acalabrutinib in this patient population.

Treatment with acalabrutinib may be continued until disease progression (PD) or an unacceptable drug-related toxicity occurs. All subjects who discontinue acalabrutinib will have a safety follow-up visit 30 (+ 7) days after the last dose of study drug to monitor for resolution or progression of adverse event(s) (AEs) and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates PD within this timeframe.

All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, monthly thereafter until Cycle 12, and every 3 months after Cycle 12.

PK testing will be done in Cycle 1 only, and [redacted] testing will be done in Cycle 1 and Cycle 2. PK [redacted] will be done on all subjects in the previously untreated cohort and on up to 12 subjects in the previously treated cohort.

Assessments for efficacy will be done at the end of every cycle. For subjects with baseline (screening) extramedullary disease, follow-up radiologic assessments are required at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), Cycle 6 (± 7 days), and then every 3 cycles (12 weeks, ± 7 days) thereafter or more frequently at the investigator's discretion.

A single, independent interim analysis of ORR will be performed when subjects from Stage 1 (28 subjects) are evaluable for response.

The primary analysis defined as all subjects have completed Cycle 27 or have discontinued before Cycle 27. Based on enrollment of the last subject on 23December2015, the data cut-off for primary analysis is anticipated to be in February 2018. The end of study is defined as 48 cycles after the last subject is enrolled on study and is anticipated to be in August 2019. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study of acalabrutinib monotherapy.

This study will use an IRC to confirm ORR, DOR and PFS for the final analysis. IRC assessments will not be available for primary analysis.

3.2 Sample Size

Multiple protocol amendments have been made since the first subject was enrolled. Major changes on study design that impacted sample size and treatment cohort are listed below:

Protocol Version	Date (M/D/YYYY)	Treatment Cohort and Dose Regimen	Planned Sample Size
Original A1	5/12/2014 9/19/2014	Subjects with previously treated WM are randomized 1:1 to [redacted]	Previously treated WM: N= 32 16 in [redacted] 16 in [redacted]

A2 (v 2.0) (v 2.1)	11/17/2014 11/20/2014	• Added a Simon two-stage design to evaluate the efficacy of CCI in subjects with previously treated WM. • Added a small cohort of 8 to 12 subjects with previously untreated WM. • Removed the CCI dosing regimen for enrollment.	Previously treated WM: N= 76 Previously untreated WM: N=8 to 12
A3 and later amendments	1/5/2015	• Changed from CCI to CCI for enrollment. • All subjects previously on CCI CCI were switched to CCI CCI	Previously treated WM: N= 76 Previously untreated WM: N=8 to 12

In total, 106 subjects were enrolled over a 15-month period. The treatment cohorts are as follows:

Cohort	Population	Dose Regimen	Patient Enrolled	Enrollment Status
1	Previously treated	CCI	86	Closed
	Previously treated		5	Closed
2	Previously untreated		14	Closed
	Previously untreated		1	Closed

During development of WM-001, this study was designed to test the null hypothesis that the ORR is ≤ 35% against the alternative hypothesis that it is ≥ 55%. For previously treated WM patients, using Simon's optimal two-stage design, a total sample size of 76 subjects has 90% power to achieve a one-sided significance level of 0.025. In Stage 1, 28 subjects will be evaluated for efficacy. If ≥ 12 out of 28 subjects (43%) achieve a response, then the study will continue to full enrollment. In Stage 2, a further 48 subjects will be enrolled. With original Simon's optimal two-stage design, an ORR of ≥ 46% (i.e., ≥ 35 subjects responding out of 76 subjects evaluated) will achieve a one-sided significance level of ≤ 0.025.

4. STUDY ENDPOINTS

4.1 Co-primary Endpoints

The co-primary endpoints are:

- ORR, defined as a subject achieving a minor response (MR) or better according to the response assessment criteria for WM (Owen 2013), as assessed by investigators
- ORR, defined as a subject achieving a MR or better according to the response assessment criteria defined by modified 3rd IWWM workshop criteria (Kimby 2006), as assessed by investigators

4.2 Secondary Endpoints

Efficacy:

- ORR, defined by modified 3rd IWWM workshop criteria (Kimby 2006), as assessed by IRC
- DOR by investigator, assessed using response assessment criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006)
- DOR by IRC, assessed using the modified 3rd IWWM workshop criteria (Kimby 2006)
- PFS by investigator, assessed using Response Assessment Criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006)
- PFS by IRC, assessed using the modified 3rd IWWM workshop criteria
- Overall survival (OS)
- Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts
- Effect of acalabrutinib on serum immunoglobulin levels

Safety:

- Frequency, severity, and relatedness of AEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions

Pharmacokinetics:

- Plasma pharmacokinetics of acalabrutinib

Patient reported outcomes (PRO):

- Health-related quality of life

4.3 CCI

CCI

5. ANALYSIS POPULATION

The analysis population is defined as follows:

All-treated population: All enrolled subjects who receive ≥ 1 dose of study drug. The demographics, baseline and disease characteristics, safety analyses and efficacy analyses will be performed on the all-treated population.

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.

Efficacy-evaluable population: All subjects in the all-treated population who have ≥ 1 evaluable response assessment after the first dose of study drug. Co-primary endpoints and ORR based on IRC assessments will also be performed using efficacy-evaluable population.

6. SUBGROUP ANALYSIS

Subgroup analysis for primary efficacy endpoints and ORR based on IRC assessment using both criteria will be planned for demographics and baseline characteristics as follows:

- Age (< 65 years versus ≥ 65 years)
- ECOG performance status at baseline (0 versus >= 1)
- Number of prior systemic therapies (1 ~ 3 versus > 3)
- Hemoglobin (HGB <= 110 g/L versus HGB > 110 g/L)
- Serum IgM (< 4000 mg/dl versus >= 4000 mg/dl)
- Bone marrow disease involvement (positive/negative/indeterminant)

CCI

7. INTERIM ANALYSIS

An interim analysis for futility based on response rate was performed in September 2015 per protocol amendment 3.0 dated 13March2015. As of the data cut-off on 31August2015, 14 responders were observed among 27 subjects. The required response rate for continuation (≥ 12/28 responders) was exceeded and enrollment continued based on this result.

A safety interim analysis was performed based on data cut-off on 02January2017. An interim safety CSR based on this data was submitted to FDA to support the sponsor's new drug application (NDA) for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

8. PRIMARY AND FINAL ANALYSIS AND CLINICAL STUDY REPORT

The primary analysis will occur when all subjects have completed Cycle 27 or have discontinued before Cycle 27 as per protocol amendment 7.0. A final analysis will be performed at end of study. End of study is defined as 48 cycles after enrollment of last subjects.

Onset of response is expected to be around 2 months. The primary analysis time point corresponds to a minimum of more than 2 years of follow-up for all subjects and it allows time to demonstrate durability of response. Base on the literature, PFS is expected to mature around 4 years and the final analysis time point allows a robust estimate of overall PFS.

The final CSR will be written based on the primary analysis. The CSR addendum will be based on final analysis with updates.

9. MISSING VALUES

- Safety Data

No imputation of values for missing data will be performed except for missing or partial dates according to prespecified, conservative imputation rules. The algorithm for handling missing or partial dates is provided in Appendix 13.2.

- Efficacy Data

The method for handling missing data is described in the definition for each of the efficacy endpoints. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date, the algorithm in Appendix 13.2 will be used.

10. STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Descriptive statistics will be used to summarize disposition, demographic, baseline characteristics, disease characteristics, prior anticancer therapy, concomitant medication, study drug administration, efficacy and safety outcomes. Descriptive summary of discrete data will present the sample size and the incidence as frequency and percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range.

Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, the exact method for CIs will be employed unless otherwise specified.

Calculation of time to event or duration of event (e.g., DOR) will be based on actual study day of the event rather than nominal visit date.

10.2 Subject Accountability

The number of subjects enrolled by site, country and region (US and ex-US) will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Subject status on study drug
- Count and reason for study drug discontinuation
- Subject status for the study
- Count and reason for study termination
- Time on study

10.3 Important Protocol Deviations

The important protocol deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These

definitions of IPD categories, sub-category codes and descriptions will be used during the study. The final IPD list is used to produce the summary of IPDs table and the list of subjects with IPDs.

10.4 Baseline Data

10.4.1 Demographics

- Age (continuous)
- Age category (< 65 years versus ≥ 65 years)
- Sex (Male, Female)
- Ethnicity
- Race
- Region

10.4.2 Baseline Characteristics

- Height (cm)
- Weight (kg)
- ECOG performance status

10.4.3 Baseline Disease Characteristics

- Number of prior systemic therapies (continuous and grouped as 1 ~ 3 versus > 3)
- Time (years) from initial diagnosis to first acalabrutinib dose
- Serum IgM (mg/dl) (continuous and grouped as > 4000 mg/dl))
- Extramedullary disease (yes/no)
- Advanced disease (extrameduallary disease and/or bone marrow involvement) (yes/no)
- Bone marrow involvement (positive/negative/indeterminant)
- Refractory disease at baseline (yes/no)
- Hematology: hemoglobin (HGB), absolute neutrophil counts (ANC), platelet counts (PLT) and absolute lymphocyte counts.

- Clinically meaningful cytopenia (ANC <= 1.5 x 10^9 /L; HGB<=100 g/L; HGB <= 110 g/L; PLT <= 100 x 10^9 /L; HGB <= 110 g/L or PLT <= 100 x 10^9 /L; Any of above)

10.5 Treatment and Medications

10.5.1 Prior Anticancer Therapies

A prior anticancer therapy is defined as plasmapheresis or a systemic therapy subjects received, either as a single or combination therapy, for the treatment of WM 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 lines and type of prior therapy for WM will be summarized.

10.5.2 Concomitant Medications

Concomitant medications are defined as medications (any prescription or over-the-counter preparations, including vitamins and supplements) that were taken between 21 days before the date of the first dose of study drug and 30 days after the last dose of study drug. Concomitant medications after enrollment will be summarized by the World Health Organization (WHO) drug dictionary preferred term (PT).

10.5.3 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)
- Actual cumulative dose administered (the total dose administered during the drug exposure period)
- Average daily dose (the ratio of actual cumulative dose administered and duration of exposure)
- Relative dose intensities (the ratio of actual cumulative dose to the planned cumulative dose)

A summary table that included number of subjects (and reasons) who had any dose withheld (any missed dose >= 7 days), and number of subjects (and reasons) who had

any dose reduction (any dose CCI [redacted] will be generated.

10.6 Analyses of Efficacy Endpoints

10.6.1 Definition of Primary Endpoints

ORR is defined as the proportion of subjects achieving a best overall response of either complete remission (CR), very good partial response (VGPR), partial response (PR), or MR before initiation of new anticancer therapy.

10.6.2 Analysis Method for Primary Endpoints

ORR will be estimated as the proportion of responders based on the best overall response. The 2-sided 95% CI will be calculated for ORR based on exact method. No formal statistical tests are performed for ORR.

Descriptive statistics will be provided for best overall response. The major response rate defined as the proportion of subjects who achieve PR or better (CR, VGPR, PR) will also be presented similarly as ORR. The ORR summaries will be generated separately for Owen 2013 criteria and modified 3rd IWWM workshop criteria.

10.6.3 Definition of Secondary Endpoints

- Duration of Response

DOR is defined as the interval from the first documentation of CR, VGPR, PR or MR to the earlier of the first documentation of definitive PD or death from any cause. DOR will be evaluated by IRC and investigator. Data from surviving, non-progressing subjects will be censored according to rules as documented in table 13.3.1 in appendix.

- Progression-free Survival

Progression-free survival (PFS) is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of definitive PD or death from any cause. Data from surviving, non-progressing subjects will be censored according to rules as documented in table 13.3.1 in appendix.

- Overall Survival

The duration of overall survival (OS) will be measured from the start of acalabrutinib therapy until the date of death from any cause. Subjects who are known to be alive as

their last known status will be censored at their last date known to be alive. The censoring rule are documented in table 13.3.2 in appendix.

- Patient Reported Outcome (PRO) --- EORTC QLQ-30

The EORTC QLQ-30 v3.0 will be used to assess the health-related quality of life. The EORTC QLQ-C30 v3.0 includes 30 separate items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scoring details are documented as:

Domain	Scale	Number of Items	Item Range*	Component/Question Item Numbers
Global health status/QoL				
Global health status/QoL	QL2	2	6	29,30
Functional scales				
Physical functioning	PF2	5	3	1 to 5
Role functioning	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9,19
Dyspnea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhea	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;

From item 1 to 28 are scored as follows with the lower score indicates better quality of life: 1=not at all; 2=a little bit; 3=quite a bit; 4=very much. Item 29 and 30 are scored from 1 to 7, with 1 indicates very poor and 7 indicates excellent.

10.6.4 Analysis Method for Secondary Endpoints

- ORR by IRC

Secondary analysis including the ORR evaluated by IRC based on modified 3rd IWWM workshop criteria. Summary table will be provided in the similar ways as specified in section 10.6.2.

- DOR

Kaplan-Meier method will be used for DOR analysis. KM estimates with 95% CIs will be calculated for event time quartiles, and event-free rates will be calculated at selected timepoints. The analysis will be generated separately for Owen 2013 criteria and modified 3rd IWWM workshop criteria. In addition, a listing for DOR will be generated including the reason for censoring. Only a subset of subjects will be included in DOR analysis.

- PFS

The analysis of PFS is similar as DOR. A listing of PFS will be generated including the reason for censoring.

- Overall Survival

The analysis of OS is similar as DOR. A listing of OS will be generated including the reason for censoring.

- PRO --- EORTC QLQ-30

For all scales, the raw score (RS) is the mean of the component items:

$$\text{raw score} = \text{RS} = (\text{I}_1 + \text{I}_2 + \cdots + \text{I}_\text{n})/\text{n}$$

For functional scales:

$$\text{score} = \left(1 - \frac{\text{RS} - 1}{\text{range}}\right) \times 100$$

For symptom scales/ items and global health status/QoL:

$$\text{score} = \left(\frac{\text{RS} - 1}{\text{range}}\right) \times 100$$

If at least half of the items from the scale been answered, use all the items that were completed and apply the standard equations above for calculating the scale scores. Ignore any items with missing values when making the calculation. If more than half of

the items from the scale is missing, the scale score is set as missing. For single-item measures, set score to missing if item is missing. The analysis windows for PRO scores are defined in table 10.4 at appendix.

At each assessment point, summary statistics of absolute and changes from baseline scale scores will be calculated. Summary tables of these statistics will be generated for all-treated population and a subset of subjects who achieve MR or better.

A listing of scale scores will be generated. A mean overtime plot will be generated for the global health status/quality of life.

10.7 Analyses Safety Endpoints

10.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 will be used to code all AEs to a system organ class (SOC) and a PT. Subject incidence of the following events will be tabulated by SOC and PT in descending order of frequency through the AE reporting period. Summaries will also be presented by the severity of the AE (per common terminology criteria for adverse events [CTCAE], Version 4.03 or higher) and by relationship to study drug. Treatment emergent adverse event data will be summarized unless specified otherwise.

- 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

Death summary table and a listing will be provided.

10.7.2 Adverse Events of Clinical Interest

AEs of clinical interest are defined in section 8.5.1 of the SAP for acalabrutinib integrated summary of safety dated 21March2017.

Subject incidence rates of AEs of clinical interest will be tabulated using the CTCAE Version 4.03 or higher.

10.7.3 Laboratory Test Results

Laboratory data of hematology, serum chemistry, serum immunoglobulin, and T/B/NK cell count up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in SI units. Applicable laboratory results will be graded according to CTCAE Version 4.03 or higher. Generic normal ranges specified in American Medical Association (AMA) Manual of Style 10th Edition (2017) will be applied whenever reference ranges are not available.

Shift from baseline to worst grade during the treatment will be provided as shift tables for selected parameters. Figures of selected parameter will be plotted overtime as appropriate.

Figures of absolute values from baseline will be generated to assess effect of acalabrutinib on peripheral T/B/NK cell counts and on serum immunoglobulin levels.

10.7.4 Vital Signs

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

To be included in the table, a subject must have both a baseline value and a post-baseline value for the given post-baseline time point.

10.7.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

Change of ECOG from baseline to the maximum score up to 30 days after last dose or the safety follow-up visit date, whichever is later will be provided as shift tables.

10.7.6 Electrocardiogram (ECG)

ECG data is collected at screening. The investigator assessment of clinical significance categorized as normal, abnormal but not clinically significant, and abnormal clinically significant will be summarized. The number of subjects with corrected QT interval (QTc) greater than 480 msec will also be provided. A listing of subject with abnormal and clinically significant baseline ECG results or QTc> 480 msec will be produced.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There is no major change from protocol-specified analyses.

12. LITERATURE CITATIONS / REFERENCES

Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. BJH 2013;160:171-176.

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Steven P. Treon, Christina K. Tripsas, et al. Ibrutinib in Previously Treated Waldenström's Macroglobulinemia. N Engl J Med 2015 Oct 29;372(15):1430-1440.

EORTC QLQ-C30 Scoring Manual, 3rd Edition 2001, EORTC, Brussels. ISBN 2-9300 64-22-6.

13. APPENDICES

13.1 Definitions

13.1.1 Study Day

The study day will be calculated refer to the date of first dose date. Study Day 1 is defined as the date of first dose of study drug. For assessments that occur on or after first dose date, study day is defined as (date of assessment – date of first dose + 1). For assessments that occur prior to first dose date, study day is defined as (date of assessment – date of first dose).

13.1.2 Baseline Value and Post-baseline Value

Unless otherwise specified, the baseline value is defined as the last measurement taken on or prior to the first dose of study drug.

$$\text{Change from baseline} = \text{Postbaseline value} - \text{Baseline value}$$

$$\text{Percentage change from baseline} = \left(\frac{\text{change from baseline}}{\text{baseline}}\right) \times 100\%$$

13.1.3 Duration of Treatment and Time on Study

Duration of treatment will be calculated from the date of the first dose of study drug to the date of the last dose of study drug:

$$\text{Duration of treatment} = (\text{last study drug date} - \text{first study drug date}) + 1$$

Time on study will be calculated from the date of the first dose of study drug to the date of study exit or analysis data cut-off date, whichever is the earliest.

$$\text{Time on study} = (\text{study exit date/data cut date} - \text{first study medication date}) + 1$$

13.1.4 Average Daily Dose and Relative Dose Intensity

$$\text{Average Daily Dose (mg/day)} = \text{Total cumulative dose taken (mg)/Duration of treatment}$$

$$\text{Relative Dose Intensity} = \left(\frac{\text{Total cumulative dose taken}}{\text{Total expected dose}}\right) \times 100\%$$

where:

$$\text{Total cumulative dose taken} = \text{sum of actual daily dose taken through the duration of treatment;}$$

$$\text{Total expected dose} = \text{Duration of treatment} \times \text{Protocol assigned daily dose}$$

13.1.5 Age

Age in years will be calculated at the date of enrollment.

13.1.6 Year and Month

One year equals to 365.25 days and 1 month equals to 30.4375 days.

13.1.7 Treatment-emergent Adverse Events

Treatment-emergent AEs 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.

13.1.8 Refractory Disease

Refractory disease will be categorized as “yes”, “no” based on eCRF.

13.1.9 Extrameduallary Disease, Bone Marrow Involvement and Advanced Disease at Baseline

Data reported on ‘bone marrow biopsy and aspirate’ CRF will be used to derive bone marrow involvement. Subjects with bone marrow involved “positive” box checked at baseline will be considered to have bone marrow involved at baseline.

Data reported on ‘tumor assessment prompt’ CRF will be used to drive extrameduallary disease. Subjects with extrameduallary disease “yes” checked at baseline will be considered to have extrameduallary disease.

Subjects with either bone marrow involvement and/or extrameduallary disease at baseline will be considered to have advanced disease.

13.2 Imputation Rules for Partial or Missing Dates

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, 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, the first dose date will be used, or if the imputed AE start date is after the AE end date, 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, 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 death date will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

For the missing death dates, if death year and month are available but day is missing:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

If both month and day are missing for death date or a death date is entirely missing, do not impute and censor the subject survival time.

13.3 Censoring Rules

The censoring rules for the DOR and PFS are documented in table 13.3.1.

Table 13.3.1 Censoring Rules for DOR and PFS

Situation	Outcome	Event Description/ Censoring Reason	Last Analysis Date for DOR/PFS
Documented PD+ before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first	Event	PD	Earliest date of documented PD
Death without documented PD and not receiving new anticancer therapy on or before data cutoff	Event	Death	Date of Death
Documented PD or death after new anticancer therapy and the new anti-cancer started before data cutoff date	Censored	New anticancer therapy	Date of last lack of PD* assessment on or prior to initiation of new anticancer therapy
No documented PD or death at the time of data cutoff and new anticancer therapy started before the data cutoff	Censored	New anticancer therapy	Date of last lack of PD assessment on or prior to initiation of new anticancer therapy
Documented PD or death after new anticancer therapy and the new anticancer therapy started after data cutoff date	Censored	Data cutoff	Date of last lack of PD* assessment on or before data cutoff date
No documented PD or death and subject not received new anti-cancer therapy or new anti-cancer therapy started after the data cutoff	Censored	Data cutoff	Date of last lack of PD assessment on or before data cutoff
Withdrew consent without documented PD or death	Censored	Withdrew consent	Date of last lack of PD assessment before withdrew or on/before data cutoff date, whichever occurred first

* If multiple PD appears, the last lack of PD assessment refers to the last lack of earliest PD assessment.

+All the PDs mentioned in SAP refer to confirmed PD as specified per protocol.

The censoring rules for the OS are documented in table 13.3.2.

Table 13.3.2 Censoring Rules for OS

Situation	Outcome	Event Description or Censoring Reason	Last Analysis Date for OS
Death on/before analysis data cutoff date	Event	Death	Death date
Patient alive on/before analysis data cutoff date	Censored	On-going	Date of last known alive
Not known to have died on/before analysis data cutoff date	Censored	Lost follow up	Date last known alive before analysis data cutoff date
Death after analysis data cutoff date	Censored	Death	Date of analysis data cutoff

13.4 Analysis Windows for EORTC QLQ-30

The analysis windows for EORTC QLQ-30 is documented in table 13.4. In the case that more than 1 score is found with a time window, the score closest to the window center will be used in the analysis. In the case that there are 2 values that are equidistant from the center, the value prior to the center will be used.

Table 13.4 Analysis Windows for EORTC QLQ-30

Cycle	Study Day	Windows
Baseline	study day 1	Day ≤ 1
Cycle 2 Day 28	study day 56	21 < Day ≤ 84
Cycle 4 Day 28	study day 112	84 < Day ≤ 140
Cycle 6 Day 28	study day 168	140 < Day ≤ 210
Cycle 9 Day 28	study day 252	210 < Day ≤ 294
Cycle 12 Day 28	study day 336	294 < Day ≤ 378
Cycle 15 Day 28	study day 420	378 < Day ≤ 462
Cycle 18 Day 28	study day 504	462 < Day ≤ 546
Cycle 21 Day 28	study day 588	546 < Day <= 630
Cycle 24 Day 28	study day 672	630 < Day <= 714
Cycle 27 Day 28	study day 756	714 < Day <= 798
Cycle 30 Day 28	study day 840	798 < Day <= 882
Cycle 33 Day 28	study day 924	882 < Day <= 966
Cycle 36 Day 28	study day 1008	966 <Day <= 1050
Cycle 39 Day 28	study day 1092	1050 < Day <= 1134
Cycle 42 Day 28	study day 1176	1134 < Day <= 1218
Cycle 45 Day 28	study day 1260	1218 < Day <= 1302
Cycle 48 Day 28	study day 1344	1302 < Day <= 1386