1.0 Title Page

Statistical Analysis Plan

Study M16-788

A Phase 3b Study in Previously Untreated Chronic Lymphocytic Leukemia (CLL) Subjects, Excluding Those with the 17p Deletion, to Evaluate Debulking Regimens Prior to Initiating Venetoclax Combination Therapy

Date: 26 June 2023

Version 3.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the full statistical analyses for venetoclax (ABT-199) Protocol M16-788 Version 4 or later. It will provide details of statistical methods and describe analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS® version 9.3 or newer (SAS Institute Inc, Cary, North Carolina, USA).

SAP will not be updated in case of future administrative or minor amendments to the protocol unless the changes have any impact on the analysis of the study data.

4.0 Study Background

4.1 Objective

Primary Objectives:

- To evaluate the anti-tumor effects of both induction therapies of obinutuzumab (Group A) or obinutuzumab in combination with bendamustine (Group B) prior to initiation of venetoclax and obinutuzumab therapy with the goal of initiating venetoclax in all subjects with low-tumor burden as defined by peripheral lymphocyte counts of $< 25 \times 10^9$/Land all lymph nodes < 5 cm per computed tomography (CT) scans.
- To evaluate the efficacy of this regimen as defined by the complete remission (CR) or complete remission with incomplete marrow recovery (CRi) rate following the debulking regimens and subsequent venetoclax and obinutuzumab therapy per 2008 Modified International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-sponsored Working Group [IWCLL NCI-WG] criteria.

Secondary Objectives:

- To evaluate Overall Response Rate (ORR), Duration of Overall Response (DoR), Progression-Free Survival (PFS), Time to Progression (TTP), Overall

Survival (OS), and the level of Minimal Residual Disease (MRD) defined as the rate of MRD negativity in the peripheral blood.

- To evaluate safety and tolerability of the debulking regimens, venetoclax ramp-up, and the venetoclax and obinutuzumab combination.

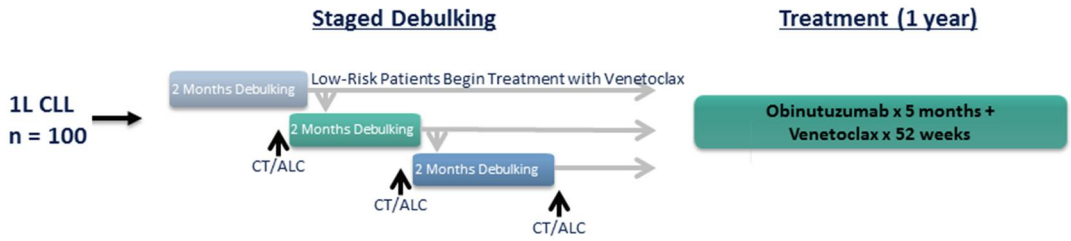
4.2 Study Design

This is a multi-cohort, open-label study in previously untreated CLL/SLL, excluding those with the 17p deletion, to evaluate a debulking strategy that would enable all subjects to receive subsequent venetoclax as outpatients with lower risk of tumor lysis.

4.2.1 Study Design and Design Diagram

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



Debulking

Subjects with median tumor burden (any lymph node 5 to < 10 cm or absolute lymphocyte count ≥ 25×10^9 /*L*) or, with high tumor burden (any lymph node ≥ 10 cm or absolute lymphocyte count ≥ 25×10^9 /*L* and any lymph node ≥ 5 cm)will receive induction therapy with either obinutuzumab (Group A) or obinutuzumab in combination with bendamustine (Group B) upon initiating the debulking period. Group assignment will not change if bendamustine is subsequently added or removed from a subject's debulking regimen during the debulking period. Subjects with > 10 cm nodes or nodal mass or the presence of del(11q) and > 5 cm nodes should receive obinutuzumab-bendamustine to

ensure optimal cytoreduction prior to venetoclax initiation. This regimen may also be selected for cytoreduction in other subjects at the discretion of the investigator.

For subjects receiving obinutuzumab-bendamustine during the debulking period, use of growth factor support in treating or preventing neutropenia is allowed and encouraged. For those patients categorized as having high risk of tumor lysis syndrome (TLS), use of prophylactic rasburicase as well as laboratory monitoring on Cycle 1 Day 2 are recommended.

Subjects will receive induction therapy with restaging evaluation, including CT scans, at 2 months. If subjects are not determined to meet low tumor burden criteria, reassessment will occur at 4 months, and 6 months, if needed. If tumor burden does not decrease after at least two cycles of obinutuzumab, and there are no signs of disease progression, subjects in Group A may have bendamustine added, at the start of Cycle 3 or Cycle 5, for the remaining cycles of debulking. If a subject's disease progresses, does not respond to, or the patient is otherwise intolerant of debulking with bendamustine-obinutuzumab, the subject will discontinue the study after discussion with the AbbVie TA MD. Following a maximum of six cycles of debulking, if a subject has not met low tumor burden criteria, it will be up to PI discretion (after consultation with the AbbVie TA MD) whether to initiate venetoclax or discontinue the subject from the study. Any subjects receiving obinutuzumab in combination with bendamustine should discontinue bendamustine upon achieving low tumor burden status and initiating venetoclax.

Venetoclax Plus Obinutuzumab Regimen

Venetoclax will be initiated when lymphocyte count $< 25 \times 10^9 /L$ and all lymph nodes < 5 cm at restaging evaluation with CT scan. If the subject has not achieved low tumor burden status (absolute lymphocyte count $< 25 \times 10^9 /L$ and all lymph nodes < 5 cm) after six cycles of debulking, the subject may proceed to venetoclax after discussion with the study physician.

For both debulking groups, subjects will receive obinutuzumab in combination with venetoclax for 5 months to maximize synergy. Venetoclax therapy will continue for a total treatment period of 52 weeks.

Based upon pre-dose laboratory assessments (prior to venetoclax Day 1), venetoclax administration will begin with therapy initiated in the home early enough to enable clinic monitoring of laboratory values at 6 – 8 hours post dosing to assess for emergence of tumor lysis. At the first dose of 20 mg and 50 mg venetoclax, laboratory analytes will be assessed pre-dose on Day 0 (prior to venetoclax Day 1), 6 – 8 hours post-dose on Day 1, and the following morning prior to dosing to assess emergence of tumor lysis. At all subsequent dose levels laboratory analytes will only be assessed prior to the first dose of venetoclax at the new dose level. Venetoclax (400 mg) will be continued for a total duration of 53 weeks, including a 5-week dose-ramp-up schedule.

A Disease Assessment for response will be performed at screening, 5 months after the last dose of obinutuzumab, and at 3 months from the end of treatment, or any period of the study per protocol specified.

In the case of a CR or CRi, a confirmatory bone marrow aspirate will be required. A portion of the aspirate will be split from this sample and stored for possible future analysis which may include MRD assessment.

Disease response will be assessed by the investigator, based on laboratory results, physical examinations, using the 2008 modified IWCLL Guidelines for Tumor Response with the addition of CT imaging (or MRI) when available. All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI if CT is medically contraindicated).

4.2.2 Variables Used for Stratification at Randomization

This is an open-label study where subjects are enrolled based on tumor burden. No randomization or stratification procedures will be performed.

4.3 Endpoint

4.3.1 Primary Endpoints

- Rate of Low Tumor Burden: Defined as the proportion of subjects who achieved low tumor burden (per the conditions: absolute lymphocyte counts $< 25 \times 10^9$/L AND all lymph nodes < 5 cm) at the end of the debulking period (before the start of venetoclax).
- Complete Response Rate: Defined as the proportion of subjects who achieved a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) (per the 2008 Modified IWCLL NCI-WG criteria) up through the completion of the 65-week disease response assessment after the start of venetoclax.

4.3.2 Secondary Efficacy Endpoint

- Overall Response Rate (ORR): Defined as the proportion of subjects who achieved a best response of complete remission [CR], complete remission with incomplete marrow recovery [CRi], nodular partial remission [nPR], and partial remission [PR] (per the 2008 Modified IWCLL NCI-WG criteria) up through the completion of the 65-week disease response assessment after the start of venetoclax.
- Duration of Response (DoR): Defined as the number of days from the date of first response (CR, CRi, nPR, or PR) (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression or death. All disease progression will be included regardless whether the event occurred while the subject was taking any study drug or had previously discontinued any study drug.
- Progression-Free Survival (PFS): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug.

- Time to Progression (TTP): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug.
- Overall Survival (OS): Defined as number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of death.
- Minimal Residual Disease (MRD) Negativity Rate: Minimal Residual Disease negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). Rate of MRD negativity status will be defined as the proportion of subjects who have MRD negativity status.

4.3.3 Safety Endpoint

Safety evaluations include adverse event (AE) monitoring, serious adverse event (SAE) monitoring, physical examinations, vital sign measurements, and clinical laboratory assessments (hematology, and chemistry), and incidence and reasons for any premature discontinuation, dose reductions, or interruptions of study drug as a measure of safety and tolerability for the entire study duration.

4.4 Sample Size Justification

Given that this is a hypothesis generating study, no formal statistical comparisons will be performed. The planned study will enroll total sample size of 120 subjects.

4.5 Interim Analysis

After 20 subjects have completed the ramp-up regimen with venetoclax, an exploratory analysis will be performed to assess the overall safety profile among all subjects who have been enrolled and received study drug, with an emphasis on the risk of TLS. As it is expected that all 20 subjects will be in the low risk group for tumor lysis, further subgroup analyses will be performed to better understand risk stratification in these subjects. These results may identify new subsets of risk based on 1) disease related factors such as

lymphadenopathy and absolute lymphocyte count and 2) individual subject related factors such as renal function, performance status and co-morbidities. In addition, safety and efficacy data for the debulking regimens will be reviewed by an internal data monitoring committee (DMC) in treating CLL/SLL and the use of venetoclax. Based on that feedback the study team may choose to modify the safety monitoring plan and treatment regimens by amendment to the protocol.

An additional interim analysis for efficacy and similar safety measures will be performed once 50 subjects have completed at least one disease response assessment after the start of venetoclax.

4.6 Multiplicity Testing Procedures for Type-I Error Control

This is a hypothesis generating study where subjects are enrolled based on tumor burden and not randomization. Therefore multiplicity testing procedures will not be applied for the statistical analysis.

4.7 Missing Data Imputation

The missing data imputation will not be performed in statistical analysis.

5.0 Analysis Populations and Important Subgroups

5.1 Analysis Population

For all analyses, study drug is defined as any dose of venetoclax, obinutuzumab, or bendamustine. All enrolled subjects who received at least one dose of any study drug (All Treated Subjects) will be used for all safety, efficacy, and baseline analyses. Details will be explained in a SAP supplement.

5.2 Subgroup

Subgroups will be based on demographic and baseline characteristics (age, gender, race, ethnicity, and high risk CLL/SLL factors such as 11q Del, 13q Del, and so forth). Full details about subgroups and analysis windows will be provided in the SAP supplement.

6.0 Efficacy Analyses

6.1 General Considerations

The efficacy analysis will be performed on All Treated Subjects defined in Section 5.1, unless otherwise specified. The efficacy analyses will be performed for the debulking treatments (obinutuzumab or combination therapy of obinutuzumab + bendamustine), and for all treated subjects.

No statistical test will be performed on any efficacy endpoints. Descriptive statistics and the 95% confidence interval (CI) will be presented, where applicable. The efficacy analysis specified below will be performed either for protocol specified interim analysis, or when the last subject has completed the Week 65 disease assessment after the start of venetoclax (including early termination from study).

6.2 Primary Efficacy Analysis

Rate of Low Tumor Burden

The rate of low tumor burden will be defined as the proportion of subjects who achieved the low tumor burden category (absolute lymphocyte counts < 25×10^9/L AND all lymph nodes < 5 cm) at the end of the debulking period (before the start of venetoclax). For the rate calculation, the numerator will be the number of subjects who achieved the low tumor burden and the denominator will be all treated subjects. In addition, 95% CI for the rate based on the binomial distribution (Clopper-Pearson exact method) will be constructed.

Complete Response Rate

Complete response rate will be defined as the proportion of subjects who achieved a best response of CR or CRi per the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator up through the completion of the 65-week disease response assessment after the start of venetoclax. All treated subjects will be used as denominator in the calculation

of complete response rate. In addition, the 95% confidence interval for complete response rate based on the binomial distribution (Clopper-Pearson exact method) will be provided.

6.3 Secondary Efficacy Analyses

Overall Response Rate (ORR)

ORR will be defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, or PR based on the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator up through the completion of the 65-week disease response assessment after the start of venetoclax. PR response will be confirmed by not less than 49 days from the first PR was observed. The corresponding exact 95% confidence interval for the proportion (Clopper-Pearson exact method) will be constructed. Subjects who do not respond will be considered non-responders.

Duration of Response (DoR)

DoR will be defined as the number of days from the day the criteria are met for CR, CRi, nPR, or PR (whichever is recorded first per the 2008 Modified IWCLL NCI-WG criteria) to the earliest date that progressive disease (PD) is objectively documented (radiographic or clinical) or death (i.e., DoR = PD/death/censoring date – earliest CR/CRi/nPR/PR date + 1 day). For subjects who have a PR before CR, CRi, or nPR in subsequent visits, the DoR is computed from the earliest PR. If a subject is still responding then the subject's data will be censored at the date of the last available disease assessment. Only subjects with an objective response will be included in the analysis of DoR. The distribution of the duration of overall response will be estimated using Kaplan-Meier methodology. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Progression-Free Survival (PFS)

PFS will be defined as the number of days from the date of first dose of any study drug to the date of earliest disease progression (PD) (radiographic or clinical) or death

(i.e., PFS = PD/death/censoring date – first dose date + 1 day). If the subject does not experience disease progression or death then the subject's data will be censored at the date of the last available disease assessment. If a subject does not have any post baseline tumor assessment or clinical assessment for progression, the data will be censored at the date of first dose of any study drug plus 1 day. Progression-free survival will be analyzed by Kaplan-Meier methodology. Median duration of PFS will be calculated and 95% confidence interval for median duration of PFS will be presented.

Time to Progression (TTP)

TTP will be defined as the number of days from the date the subject started any study drug to the date of earliest disease progression (radiographic or clinical) (i.e., TTP = PD/censoring date – first dose date + 1 day). If the subject does not experience disease progression then the subject's data will be censored at the date of the last available disease assessment. If a subject does not have any post baseline disease assessments, the data will be censored at the first dose date of any study drug plus 1 day. The distribution of the time to progression will be estimated using Kaplan-Meier methodology. Median time to progression and the corresponding 95% confidence interval will be estimated.

Overall Survival (OS)

OS will be defined as the number of days from the first dose date of any study drug to the date of the subject's death (i.e., OS = death/censoring date – first dose date + 1 day). All events of death will be included, regardless of whether the event occurred while the subject was still taking any study drug, or after the subject discontinued any study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive prior to the cutoff date for any interim analysis. The date of the last known to be alive will be determined by selecting the last available date of the following study procedures for a subject: study visit/contact date, tumor assessment/disease assessment, clinical disease progression, physical examination, vital signs assessment, clinical laboratory collection, study drug, adverse event assessment, concomitant

medication assessment, drug or study completion, survival visit, and post treatment therapy assessment. The distribution of OS will be estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% confidence interval will be estimated.

Minimal Residual Disease (MRD) Response Rate

The rate of MRD response will be defined as the proportion of subjects who achieved MRD negative status with less than one CLL cell per 10,000 leukocytes (or below 10^{-4}) in the peripheral blood after the start of venetoclax. All treated subjects will be included in the denominator for the calculation of MRD response rate. Minimal residual disease response will be summarized by categories: MRD negative, MRD positive, or MRD unknown/missing. The 95% confidence intervals based on the binomial distribution (Clopper-Pearson exact method) will be provided. Additionally, MRD response rate will be summarized by overall response category (CR and/or PR).

Additional exploration will be performed for the baseline tumor burden status (high or medium) by each debulking treatment to evaluate the rate of low tumor burden at the debulking period (before the start of venetoclax). All treated subjects in the denominator for the calculation of the low tumor burden rate. The rate will be provided with the corresponding 95% confidence interval (Clopper-Pearson exact method).

6.4 Efficacy Subgroup Analyses

To evaluate the impact of initiation of venetoclax on efficacy, the subgroup analyses will be performed for complete response rate, and ORR rate for the analysis population defined in Section 5.1. Subgroups specified in Section 5.2 will be assessed and visualized in a forest plot. Additional subgroups will be deemed as needed and will be mentioned in a SAP supplement.

7.0 Safety Analyses

7.1 General Considerations

Safety assessments will only include subjects who have received at least one dose of any study drug. The safety of study drug will be assessed by evaluation of adverse events, serious adverse events, deaths, and changes in laboratory determinations, vital sign parameters, any study drug and study discontinuation, dose reductions, or interruptions. Safety data will also be assessed by the debulking regimen as well as by the post debulking regimen. Post debulking period is considered from the first dose date of venetoclax. Detail analysis procedures will be provided in SAP supplement.

7.2 Analysis of Adverse Events

All summaries/analyses involving AEs will include treatment-emergent adverse events (TEAE) only, unless otherwise specified. Treatment-emergent AEs are defined as any event with onset after the first dose of any study drug (venetoclax, obinutuzumab, or bendamustine) and no more than 30 days after the last dose of any study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of any study drug).

For summaries of AEs related (reasonable possibility) to study drug, at each level of summation (overall, MedDRA system organ classes [SOCs], and preferred terms [PTs]) each subject is counted only once. If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship of "no reasonable possibility" present. The only exception is if the subject has another occurrence of the same AE with the relationship of "reasonable possibility." In this case, the subject will be counted under the reasonable possibility category.

Adverse event data will be summarized and presented using the MedDRA coding dictionary version 20.1 or higher.

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event summaries:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event by debulking and post debulking periods (detail explanation in a SAP supplement)
    - Period is define as: debulking regimen period (obinutuzumab or combination of obinutuzumab + bendamustine), and post debulking period (combination of obinutuzumab + venetoclax, and mono therapy venetoclax). Mono therapy venetoclax will be considered 30 days after the last dose of obinutuzumab.
- Any treatment-emergent serious adverse event
- Any treatment-emergent serious adverse event by debulking and post debulking periods
- Adverse events broken down by NCI toxicity (CTCAE V4.03) grade
- Any treatment-emergent NCI toxicity (CTCAE V4.03) grade 3, 4, or 5 adverse events
- Any treatment-emergent NCI toxicity (CTCAE V4.03) grade 3 or 4 adverse event
- Any treatment-emergent adverse event leading to death
- Venetoclax:
    a. Any treatment-emergent adverse event leading to discontinuation of venetoclax
    b. Any treatment-emergent adverse event leading to venetoclax interruption
    c. Any treatment-emergent adverse event leading to venetoclax reduction
    d. Any treatment-emergent adverse event that is rated at least possibly related to venetoclax by the investigator (Reasonable Possibility Related)

- Obinutuzumab:
  a. Any treatment-emergent adverse event leading to discontinuation of obinutuzumab
  b. Any treatment-emergent adverse event leading to obinutuzumab interruption
  c. Any treatment-emergent adverse event leading to obinutuzumab reduction
  d. Any treatment-emergent adverse event that is rated at least possibly related to obinutuzumab by the investigator (Reasonable Possibility Related)
- Bendamustine:
  a. Any treatment-emergent adverse event leading to discontinuation of bendamustine
  b. Any treatment-emergent adverse event leading to bendamustine interruption
  c. Any treatment-emergent adverse event leading to bendamustine reduction
  d. Any treatment-emergent adverse event that is rated at least possibly related to bendamustine by the investigator (Reasonable Possibility Related)

In addition, the list of selected adverse events that shown in Table 1, based on the PSSAP version 4 will be summarized.

Table 1. Selected Adverse Events

Risk	Search Criteria
Tumor Lysis Syndrome -AESI	SMQ 20000219 – "Tumour lysis syndrome" (Narrow-scope)
Neutropenia – expanded search	Neutropenia CMQ 10000101
Neutropenia	PT terms – "Neutropenia," and "Neutrophil count decreased"
Serious Infection	SAEs in the SOC of "Infections and Infestations"
Second Primary Malignancy	SMQ 20000194 – "Malignant tumours" (Narrow) and SMQ 20000217 - "Myelodysplastic syndromes" (Narrow)
Lymphopenia	PT terms – "Lymphopenia" and "Lymphocyte count decreased"
Anemia	PT terms – "Anaemia" and "Haemoglobin decreased"
Thrombocytopenia	PT terms – "Thrombocytopenia" and "Platelet count decreased"

7.3 Deaths

The number of deaths will be summarized (1) for death occurring during the first day of any study drug and within 30 days after the last dose of any study drug, (2) for death occurring > 30 days after the last dose of any study drug, (3) for all deaths in this study, i.e., 1) and 2).

7.4 Analysis of Laboratory Data

7.4.1 Definition of Baseline

The baseline value for laboratory variables will be defined as:

- For a subject without IV hydration, the baseline value will be defined as the last non-missing measurement prior to receiving the first dose of any study drug.
- The baseline lab value for a subject with IV hydration will be defined as the last non-missing lab measurement prior to receiving IV hydration before the first of dose any study drug.

7.4.2 Analysis of Shift from Baseline in Clinical Laboratory Data

For shifts relative to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), baseline and post-baseline laboratory observations (maximum and final) will be categorized as grade 0, grade 1, grade 2, grade 3, or grade 4 according to NCI CTCAE grade version 4.03 (publication date: 14 June 2010).

For laboratory tests for which a normal range limit is one end of the grade 1 range then values that are either within the normal range or outside it in direction opposite the test will be classified as grade 0 values. For other tests, values outside the grade 1 range in the direction opposite that of the test will be classified as grade 0.

The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of any study drug unless specified differently, and as the last post-baseline measurement collected no more than 30 days after the last dose of any study drug.

The maximum NCI toxicity grade value is the value with highest NCI toxicity grade collected after the first dose of study drug and within 30 days following the last dose of study drug. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day.

For each variable, shift tables will be generated that cross tabulate the number of subjects with baseline values of grade 0, grade 1, grade 2, grade 3, or grade 4 versus maximum or final observations of grade 0, grade 1, grade 2, grade 3, or grade 4. For a laboratory parameter for which grading is performed separately for low and high values, a separate summary will be presented for each grading scale.

7.5 Laboratory Search Strategy for TLS

To determine if subjects' laboratory values qualify for TLS, the Howard criteria[1] will be used. The Howard criteria for lab TLS comprise of ≥ 2 of the following electrolyte abnormalities within 24 hours of each other and are specified in Table 2.

Table 2. Howard Criteria for TLS

Element	Value
Uric Acid	> 475.8 µmol/L or 8 mg/dL
Potassium	> 6.0 mmol/L
Phosphorus	> 1.5 mmol/L or 4.5 mg/dL
Calcium	< 1.75 mmol/L or 7.0 mg/dL

The following summaries of laboratory TLS as assessed by Howard criteria will be provided:

- Number and percentage of subjects meeting the Howard criteria for laboratory TLS (at least two values meeting the criteria in Table 2, occurring within 24 hours of each other).
- Listing of all the lab test values for each subject meeting the Howard criteria for laboratory TLS.

7.6 Analysis of Vital Signs

For selected vital signs variables, a listing of all observations collected will be generated for subjects that had at least one post-baseline observation meeting pre-defined criteria for potentially clinically significant values. The number and percentage of subjects who have at least one post-baseline observation meeting the pre-defined criteria for potentially clinically significant values will be provided for each variable.

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 3 below.

Table 3. Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart rate	Low	Value < 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value < 36°C
	High	Value ≥ 38.5°C

8.0 Summary of Changes

- Updated the efficacy analysis
- Included exploratory analysis
- Updated the censoring rules for time to the events analysis
- Updated the definition of baseline lab data
- Updated the safety data analysis

9.0 Reference

1. Howard SC, Jones DP, Pui CH, et al. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.