Statistical Analysis Plan

Phase 3 Study of Ibrutinib in Combination with Venetoclax in Subjects with Mantle Cell Lymphoma

PCYC-1143-CA

June 22, 2023

Version 2.0 (Final)

Statistical Analysis Plan Approval

Protocol Number:	PCYC-1143-CA
Protocol Title:	Phase 3 Study of Ibrutinib in Combination with Venetoclax in Subjects with Mantle Cell Lymphoma (Amendment 4)
SAP Version:	2.0 (Final)
Date:	June 22, 2023

By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

[redacted]
Biostatistics
23-Jun-2023
Date (ddMMMyyyy)

[redacted]
Biostatistics
26-Jun-2023
Date (ddMMMyyyy)

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Clinical Science
23-Jun-2023
Date (ddMMMyyy)

[redacted]
Clinical Science
26-Jun-2023
Date (ddMMMyyyy)

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23-Jun-2023
Date (ddMMMyyyy)

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PST Lead-Oncology
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Date (ddMMMyyyy)

[redacted]
Statistical Programming
23-Jun-2023
Date (ddMMMyyyy)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMA	Bone Marrow Aspirate
BOR	Best Overall Response
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRR	Complete Response Rate
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
FACT-Lym	Functional Assessment of Chronic Illness Therapy – General (FACT-G) and a lymphoma-specific additional concerns subscale (Lym)
FWER	Family Wise Error Rate
IA	Interim Analysis
IDMC	Independent Data Monitoring Committee
ILD	Interstitial Lung Disease
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITT	Intent-To-Treat
HR	Hazard Ratio
KM	Kaplan-Meier
MCL	Mantel Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	MCL International Prognostic Index
MRD	Minimal Residual Disease
mOS	Median Overall Survival
mPFS	Median Progression-free Survival
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NCI ODWG	NCI Organ Dysfunction Working Group Liver Function Classification

NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
PA	Primary Analysis
PB	Peripheral Blood
PCYC	Pharmacyclics
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status
PT	Preferred Term
QoL	Quality of life
RDI	Relative Dose Intensity
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SD	Stable Disease
SMQ	Standardized MedDRA query
SOC	System Organ Class
SRC	Safety Review Committee
SRI	Safety Run-in
TEAE	Treatment-Emergent Adverse Event
TLS	Tumor Lysis Syndrome
TN	Treatment Naive
TTNT	Time to Next Treatment

1 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol Amendment 4 dated September 25, 2022 and defines key elements including variable definitions and statistical methods for analysis of data in evaluation of efficacy and safety for subjects with the Relapsed/Refractory (R/R) mantle cell lymphoma (MCL) who are enrolled in the study PCYC-1143-CA.

Study PCYC-1143-CA also contains a separate arm treatment-naïve (TN) MCL cohort which has completed enrollment; an SAP addendum will be provided for the treatment-naïve (TN) MCL cohort at the appropriate time prior to the primary analysis. Subject demographics and disease characteristics and relevant safety data will be summarized for subjects with TN MCL who are enrolled at the time of the primary analysis for the subjects with R/R MCL.

The analyses of exploratory biomarkers and pharmacokinetics (PK) data are not in the scope of this document. Throughout this SAP, "study treatment" and "study drug" are used interchangeably, and both are referring to ibrutinib and venetoclax or placebo.

Analysis methods specified in this document take precedence over those described in the protocol, should there be any differences. Any changes in the protocol will be documented in Section 7, Changes in the Protocol Planned Analysis. This SAP will be finalized before unblinding of the study results.

1.1 Study Design

This Phase 3, multinational, randomized, double-blind study is designed to compare the efficacy and safety of the combination of ibrutinib and venetoclax vs. ibrutinib and placebo in R/R subjects with MCL.

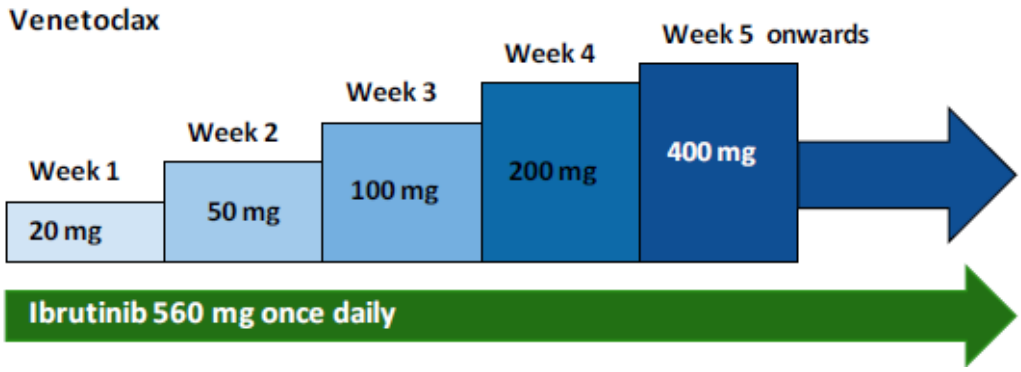
Approximately 287 subjects with R/R MCL (up to 27 SRI [Safety Run-in] subjects and 260 randomized subjects) will be enrolled.

A separate open-label cohort is designed to explore the efficacy and safety of the combination of ibrutinib and venetoclax in approximately 75 subjects with TN MCL (approximately 50 subjects ≥65 years of age and approximately 25 subjects with a TP53 mutation). There will be no Safety Run-in period for this cohort.

1.1.1 Safety Run-in Period

The study will start with an open-label SRI period for subjects with R/R MCL to evaluate the occurrence of Tumor Lysis Syndrome (TLS) and dose-limiting toxicities (DLTs) with the concurrent administration of ibrutinib and venetoclax. The TLS and DLT occurrence will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks (Figure 1). Up to 27 subjects may be enrolled during the SRI period.

Figure 1. Standard Ramp-up Schedule



1.1.2 Randomization Phase

The Randomization Phase of the study will follow a randomized, double-blind design. Ibrutinib and venetoclax/placebo will be administered using the Standard Ramp-up Schedule (without ibrutinib lead-in) that was determined to be appropriate for each TLS risk category in the Safety Run-in Phase. The Independent Data Monitoring Committee (IDMC) will review the safety recommendations made by the Safety Review Committee (SRC) and will be responsible for giving recommendations on continuing, modifying, or stopping the Randomization Phase of the study.

Subject eligibility will be determined up to 28 days prior to randomization. Approximately 260 eligible subjects will be randomized at a 1:1 ratio to ibrutinib and venetoclax or ibrutinib and placebo. Randomization will be stratified by number of prior lines of therapy, ECOG performance status (PS), and by TLS risk category through the Interactive Response Technology (IRT).

Initially, subjects at increased risk of TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg venetoclax ramp-up dose, and again at the start of the 50 mg venetoclax ramp-up dose for monitoring and prophylaxis of TLS. The IDMC will review unblinded safety data during the course of the study to determine whether continued hospitalization of these subjects during ramp-up remains warranted.

The IDMC will review unblinded safety data including all deaths and any progression associated with safety 6-9 months after the initiation of the Randomization Phase to evaluate the safety of the combination of ibrutinib and venetoclax/placebo and to confirm that continued dosing with the combination is warranted. In addition, the IDMC will review TLS data during the course of

the study to ascertain whether the continued hospitalization of subjects with high tumor burden and/or creatinine clearance <60 mL/min during ramp-up is needed. The composition of the IDMC, responsibilities, authorities, and procedures are detailed in a separate IDMC charter.

1.1.3 Treatment Time and Follow-up Time

Safety Run-in subjects and TN subjects will be treated with ibrutinib and venetoclax, and randomized subjects will be treated with ibrutinib and venetoclax or ibrutinib and placebo for approximately 104 weeks followed by ibrutinib monotherapy on both treatment arms until progressive disease (PD), unacceptable toxicity or withdrawal of consent. Venetoclax and placebo will be discontinued after 104 weeks of treatment regardless of response assessment.

All enrolled subjects who discontinue study treatment for any reason will be followed for progression (if they have not progressed before treatment discontinuation), subsequent anti-cancer therapy and survival status until study closure.

1.2 Endpoints

<table>
<tr><th>Randomized Subjects</th><th>Safety Run-in Subjects</th></tr>
<tr><td>Primary Efficacy Endpoint
Progression-free survival (PFS) per investigator assessment</td><td rowspan="3">Efficacy Assessments
• Overall response rate (ORR) and Duration of Response (DOR) per investigator assessment
• Progression-free survival per investigator assessment
• Overall Survival (OS)</td></tr>
<tr><td>Secondary Efficacy Endpoints
• Complete response rate (CRR) per investigator assessment
• Overall Response Rate (ORR) per investigator assessment
• Minimal residual disease (MRD)-negative remission rate in subjects who achieve CR per investigator assessment and are MRD-positive at baseline
• Overall Survival (OS)
• Time to next treatment (TTNT)
• Time to worsening in FACT-Lym subscale of the health-related quality-of-life questionnaire (FACT-Lym)</td></tr>
<tr><td>Exploratory Endpoint
• PFS based on investigator assessment after initiation of subsequent anti-cancer therapy (PFS2)</td></tr>
<tr><td>Safety Assessments
• Frequency, severity, and relatedness of AEs
• Frequency, severity and management of TLS</td><td>Safety Assessments
• Frequency of TLS and DLTs</td></tr>
</table>

Randomized Subjects	Safety Run-in Subjects
• Frequency of AEs requiring discontinuation of study drug or dose reductions, or leading to death	• Frequency, severity, and relatedness of AEs • Frequency of AEs causing study drug discontinuation, or dose reductions or leading to death
Overall disease assessment is according to Revised Response Criteria for Malignant Lymphoma (Cheson 2014, Lugano Classification Criteria)	

1.3 Statistical Hypotheses

The statistical hypotheses for the primary endpoint (PFS) can be written as follows:

H_0: $S_E(t) = S_C(t)$, for all t > 0, where $S_E(t)$, and $S_C(t)$ are survival functions for the experimental and control arms, respectively at all time points *t*:

vs.

H_1: The PFS distribution of the experimental treatment group, $S_E(t)$, is stochastically larger than the control group, $S_C(t)$, with strict inequality for some time point t:

$S_E(t) \geq S_C(t)$ for all $t \geq 0$, and $S_E(t) > S_C(t)$ for some $t > 0$

These hypotheses will be tested for the primary endpoint using a two-sided stratified log-rank test at an alpha level specified in Section 1.6. The source of the stratification factors will be based on IRT data.

1.4 Sample Size Determination

1.4.1 PFS

The Randomization Phase sample size is powered based on the primary endpoint of PFS. Approximately 260 subjects will be randomized at a 1:1 ratio to the ibrutinib + venetoclax arm and the ibrutinib + placebo arm. The calculations are based on the following assumptions using EAST software Version 6.4.1:

- Target hazard ratio is 0.61, which corresponds to an improvement of 9 months in median PFS (mPFS) from 14 months to 23 months for the ibrutinib + venetoclax arm compared to the ibrutinib + placebo arm.
- A total of 134 PFS events will provide approximately 80% power at a one-sided significance level of 0.025 for the study. No interim analysis (IA) is planned for PFS.

- Assuming an enrollment rate of approximately 10-11 subjects per month, the accrual is projected to complete approximately 21 months from the first subject in. The actual length of the study and the time to the primary analysis will depend on the actual enrollment rate and the number of events that occur.

1.4.2 OS

- Target hazard ratio is 0.65, which corresponds to an improvement of ~16 months in median OS (mOS) from 30 months to 46.2 months for the ibrutinib + venetoclax arm compared to the ibrutinib + placebo arm.
- A total of 155 OS events would provide ~76% power at a one-sided significance level of 0.025 adjusting for one interim analysis based on group sequential design with Lan-DeMets spending function with O'Brien-Fleming[1] boundary.
- It is anticipated that 112 and 155 OS events will be observed at the interim analysis (at ~40 months corresponding to the timing of the primary PFS analysis) and at the final analysis (at ~57 months), respectively. The level of significance for each analysis is described in Section 1.6.2.
- The calculation for OS is based on a log-rank test using EAST software version 6.5.

1.5 Planned Analysis

The effect size (HR) assumptions of PFS and OS did not consider potential impact of COVID-19 deaths when the study was initiated. In alignment with the FDA guidance[2] (Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, June 2020), in order to mitigate the potential impact on the key efficacy endpoints due to COVID-19, the follow-up will be extended to accrue more events as described in Section 1.5.1 and Section 1.5.2 below than the originally planned event numbers (134 events for PFS and 155 events for OS).

1.5.1 Primary PFS Analysis and Interim OS Analysis

The primary PFS analysis will be conducted after approximately 150 PFS events have been observed. No interim analysis is planned for PFS.

An interim analysis (IA) is planned for OS at the time of the primary PFS analysis.

1.5.2 Final OS Analysis

The final OS analysis will be conducted after the last subject was followed for at least 5 years or approximately 170 OS events are observed, whichever occurs first.

At the time of the final OS analysis, a CSR addendum will be provided.

1.6 Testing Procedure and Level of Significance

1.6.1 Adjustment of Multiplicity for Multiple Endpoints:

The one-sided Type I Family Wise Error Rate (FWER) will be controlled at 0.025 by a closed testing procedure for testing the primary endpoint (PFS) and key secondary endpoints. The following key secondary endpoints will be tested only if the primary endpoint (PFS) reaches statistical significance (1-sided 0.025) and will be ranked and tested at 1-sided statistical significance of 0.025 sequentially in the hierarchical order below:

1) CR rate per investigator assessment
2) Time to next treatment*
3) OS
4) ORR per investigator assessment

A secondary endpoint with a lower rank cannot be tested until the preceding endpoint achieves statistical significance.

*For US regulatory purposes, time to next treatment will be tested after OS as the third endpoint in the hierarchical order.

At the time of the primary PFS analysis, an interim analysis is planned for OS. Statistical significance level for each OS analysis is described in Section 1.6.2. ORR will be tested at 1-sided 0.025 using the primary PFS analysis data cut when OS significance is achieved.

1.6.2 Adjustment of Multiplicity for Multiple OS Analyses

To maintain a 1-sided overall significance level of 0.025 for OS, assuming the final OS analysis is based on 170 events, the significance level of the OS final analysis will be adjusted for the OS interim analysis as follows based on Haybittle-Peto boundary instead of O'Brien Fleming boundary as specified in the protocol (Protocol Section 10.3). The actual boundary for the OS final analysis will be based on actual number of OS events at the time of the OS final analysis.

Analysis	**# of OS Events**	**Significance level (1-sided p-value)**	**Observed Hazard Ratio/Superiority Boundary**
IA	Agnostic to number of events	0.0005	< 0.550
FA	170 (assumed)	0.024983	< 0.740

1.7 Blinding and Randomization Methods

1.7.1 Blinding Method

Subjects, investigators, and the Sponsor's study team members will remain blinded to the treatment assignment in the randomization phase. The investigator will not be provided with randomization codes nor the treatment assigned and received. The codes will be maintained within the IRT System, which has the functionality to allow the investigator to break the blind for an individual subject if necessary, to appropriately manage or treat the subject. Data that may potentially unblind the treatment assignment (e.g., study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

1.7.2 Randomization Method

The randomization of the treatment assignment will be stratified by the following factors and implemented using the IRT System:

- Number of prior lines of therapy (1-2 vs. ≥ 3)
- ECOG performance status (0-1 vs. 2)
- TLS category (low risk vs. increased risk)

Within each of the eight randomization strata, subjects will be randomly assigned at a 1:1 ratio to the two treatment arms based on permuted block size.

2 GENERAL ANALYSIS CONSIDERATION

The statistical analysis sections in this SAP are mainly for the double-blind Randomization Phase. All data collected for the subjects in the SRI portion will only be summarized with descriptive statistics or listed separately from Phase 3 data. In addition to standard summaries for TEAEs, the safety summary included for SRI subjects will be limited in scope to DLTs and TLS.

Subjects in the randomization phase will be analyzed and summarized by treatment as randomized for efficacy endpoints and as treated for safety.

Subgroup analyses are mainly to evaluate trend and assess the internal consistency of any treatment benefit and/or safety signal. Forest plots of hazard ratios and associated confidence intervals will be provided for each category of the subgroup variable to show the trend. Statistical tests will not be performed for the subgroup analysis.

General Definitions:

The date of the first dose of study treatment is defined as the date the subject received the first dose of ibrutinib or venetoclax/placebo (whichever occurs first), and the date of the last dose of study treatment is defined as the date the subject received the last dose of ibrutinib or venetoclax/placebo (whichever occurs later).

Unless otherwise specified, the baseline value is defined as the last non-missing valid value collected prior to the first administration of study treatment. For subjects who have been randomized but not treated, the randomization date will be used as the reference date for the baseline.

For the Safety Run-in Period, the TLS/DLT assessment period is defined as the standard Ramp-up Period with a minimum of 5 weeks. The DLT period ends on the 7th day of 400 mg venetoclax.

2.1 Analysis Sets

Intent-to-Treat Population in Randomization Phase

The intent-to-treat (ITT) population includes all subjects randomized into the study.

Safety Population

The safety population (SP) includes all subjects who received at least one dose of study treatment (ibrutinib or venetoclax/placebo).

Safety Run-in Period Evaluable Population

Subjects who did not complete the TLS and DLT assessment period for any reason other than TLS or a DLT or subjects who missed ≥20% of the planned doses of ibrutinib or venetoclax for reasons other than toxicity (e.g., non-compliance, withdrawal of consent, or disease progression) during the TLS/DLT assessment period will be considered non-evaluable. All other enrolled subjects in the Safety Run-in Period will be considered evaluable for the TLS/DLT assessment.

2.2 Definition of Subgroups

Analyses for the baseline subgroups will be performed for selected variables. The baseline subgroup variables (Table 1) and the cutoff values are subject to change (if warranted) to better represent the data,

Table 1 Baseline Subgroups

Baseline Subgroup	Definition of Baseline Subgroup	Analysis Type
Age	< 65, ≥ 65	E, S
Gender	Male, Female	E, S
Race	White, Non-White	E, S
Geographic region	North America, Europe, Asia Pacific	B, E, S
Number of prior lines of therapy (1-2 vs. ≥3) per CRF	1-2, ≥ 3	E
ECOG performance status per CRF	0, 1-2	E
TLS risk category per CRF	Low Risk, Increased Risk	E
Simplified MIPI score	Low Risk, Intermediate Risk, High Risk	E
Bulky tumor (largest long diameter) per investigator	< 5 cm, ≥ 5 cm	E
Enlargement of spleen per investigator	Yes, No	E
Extranodal disease per investigator	Presence, Absence	E

Baseline Subgroup	Definition of Baseline Subgroup	Analysis Type
Blastoid variant and/or pleomorphic variant of MCL	Yes, No	E
Blastoid variant of MCL	Yes, No	E
TP53 Mutation	Mutated, Not Mutated, Not Performed/Missing	E
Prior stem cell transplant (SCT)	Yes, No	E
Renal function (creatinine clearance)	< 60 mL/min, ≥ 60 mL/min	S
Hepatic function (NCI ODWG definition)	normal, mild, moderate, severe (or normal vs. abnormal as appropriate)	S

Analysis type: B=Subject Demographics, Baseline Characteristics, Baseline Disease Characteristics; E = Efficacy (PFS); MIPI: MCL International Prognostic Index; MRD: Minimal Residual Disease; NCI ODWG: NCI Organ Dysfunction Working Group Liver Function Classification (Ramanathan et al, 2008); S = Safety (Overview TEAE, TEAE by SOC/PT, Grade 3 or higher TEAE by SOC/PT).

3 SUBJECT INFORMATION

3.1 Subject Disposition

Subject enrollment will be summarized by geographic region, country and site. Subject disposition for each study drug and for study participation will be tabulated. Overall treatment duration and time on study will be summarized by treatment arm.

The disposition tables will include the following summaries by treatment arm and overall:

- Analysis populations (all subjects)
- Enrollment by geographic region, country and investigator (ITT population)
- Summary of randomization stratification per IRT (ITT population)
- Study Treatment Disposition and Discontinuation (ITT population)
- Study Status, Duration of Treatment and Study Exit (ITT population).

Time on study is calculated based on reverse Kaplan-Meier estimates of the overall survival follow-up time (i.e., subjects who died will be censored at the death date for the time on study).

3.2 Demographics, Baseline Characteristics, and Baseline Disease Characteristics

Subject demographics, baseline characteristics, and baseline disease characteristics including but not limited to age, gender, race, etc., will be summarized with descriptive statistics for the ITT population by treatment arm.

3.3 Prior and Concomitant Medications

Medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class according to the World Health Organization drug dictionary (WHODRUG B3 Mar 2021).

Prior medications are defined as medications that started prior to the date of the first dose of study treatment. Concomitant medications are defined as medications that were taken on treatment (i.e., from the date of the first dose of study treatment through the date of the last dose of study treatment).

Concomitant medications will be summarized by ATC class and preferred term (PT) by treatment arm based on the Safety Population. Each subject will be counted only once overall, for each PT, and for each ATC class.

The following concomitant medications will be summarized separately:

- CYP3A inhibitors and inducers

- Anticoagulants and antiplatelet agents
- Blood supportive products and intravenous immunoglobulin (IVIG)
- Growth factors

3.4 Extent of Exposure to Study Treatment

Exposure to study treatment will be summarized by treatment arm for the Safety Population. Descriptive statistics will be provided for the following data for each study drug (ibrutinib and venetoclax/placebo): treatment duration, total cumulative dose administered, dose intensity (average daily dose), and relative dose intensity (%) based on the entire treatment period (including both the ramp-up period and fixed dose period), and number (%) of subjects with a dose reduction or dose hold due to adverse events (AEs). In addition, dose modification of venetoclax due to CYP inhibitor will be summarized based on the check box on the Study Drug Administration page.

Planned dose intensity (PDI) for each study drug is calculated as below:

Ibrutinib:

Planned dose intensity (PDI) for ibrutinib is 560 mg per day.

Venetoclax/placebo:

Regardless of response assessment, Venetoclax/placebo will be discontinued after 104 weeks of treatment including 5 weeks of the standard dose ramp-up period (20 mg, 50 mg, 100 mg, 200 mg, and 400 mg weekly, respectively) and approximately 99 weeks of the fixed dose (400 mg) period.

The planned dose intensity (mg/day) for venetoclax/placebo is calculated as the total amount of the planned dose (mg) during the maximum treatment period allowed (104 weeks) divided by the duration of the maximum treatment period allowed (104 weeks):

$$388.2\ mg/day = \frac{(20+50+100+200+400)\ mg\ \times\ 7\ days + \ 400mg\ \times (104\times 7-35)\ days}{104\ \times 7\ days}$$

For each study drug, the actual dose intensity (ADI) (mg/day) is calculated as the total amount of dose (mg) received during the entire treatment period divided by the entire treatment duration (day), and the relative dose intensity (RDI) (%) is calculated as the (actual dose intensity/planned dose intensity)*100%.

3.5 Prior and Subsequent Anti-Cancer Treatments

Anti-cancer treatment includes anti-cancer drug therapies, anti-cancer radiation, and anti-cancer transplant/immunotherapy.

Prior anti-cancer treatments are anti-cancer treatments received prior to study treatment and will be summarized using the ITT population. Subsequent anti-cancer treatments are anti-cancer treatments received after the date of the last dose of study treatment and will be summarized using the Safety Population.

3.6 Visit Impact of Logistical Restriction Due to COVID-19

Visit impact of logistical restriction due to the COVID-19 pandemic will be summarized by the type of impact (missed visit, in person/partial assessment done, and virtual visit/phone call) recorded on the Visit Impact CRF page for each treatment arm.

Information for treatment discontinuation and study exit during the COVID-19 pandemic will be listed.

Analyses or summaries for efficacy and safety data related to COVID-19 are described in Section 4.1 and Section 5.1, respectively.

4 ANALYSIS FOR EFFICACY ENDPOINTS

Analyses of efficacy endpoints will be conducted using the ITT population, unless otherwise specified. For subgroup, sensitivity, and exploratory analyses, only the analyses that provide meaningful information will be presented in the CSR.

There are three randomization stratification factors as recorded in IRT: prior lines of therapy (1-2 vs ≥ 3), ECOG performance status (0-1 vs 2), and TLS risk category (low risk vs. increased risk). Since only 9 subjects in total were randomized to the stratum of ECOG performance status of 2, stratification by those three factors will result in empty or very small strata. Therefore, all stratified tests/analyses will only be based on two randomization stratification factors per IRT: prior lines of therapy (1-2 vs ≥ 3) and TLS risk category (low risk vs. increased risk).

The investigators will perform the overall disease assessment based on the Revised Response Criteria for Malignant Lymphoma (Cheson 2014, Lugano Classification[3]); referred to as Cheson 2014 or Lugano Classification Criteria. An Independent Review Committee (IRC) will be implemented to conduct the overall disease assessments based on the same criteria.

The overall disease assessment per the investigators will be used to conduct the primary efficacy analyses, and the overall disease assessment per IRC will be used to conduct sensitivity analyses.

Due to differences in the preferred censoring approach for PFS across jurisdictions, the estimand and analyses for PFS will be described separately for the US and other regions (see Section 4.1 and Section 4.2).

4.1 Estimand of the Primary Efficacy Endpoint

Estimand[4] is the clinical quantity of interest to be estimated in this study, which is defined by the following five attributes: Population, Study Treatment, Variable/Endpoint, Intercurrent Events and Handling Strategies, and Statistical Summary.

The estimand corresponding to the primary efficacy endpoint (PFS per investigator assessment) is the treatment effect in PFS (ibrutinib + venetoclax versus ibrutinib + placebo) in subjects with relapsed/refractory MCL in the ITT population, as measured by the earlier occurrence of progressive disease per investigator assessment or death, whichever occurs first.

The attributes of the estimand for the primary analysis of the primary endpoint (PFS per investigator assessment) are described below:

Estimand Label	Attributes of the Estimand				
	Treatment	**Population**	**Endpoint**	**Intercurrent Events***	**Statistical Summary**
PFS	• ibrutinib+ venetoclax • ibrutinib+ placebo	ITT	PFS per investigator assessment	• Discontinuation of study treatment • Use of subsequent anti-cancer therapy • Death due to COVID-19	Hazard ratio of PFS between two treatment arms. Kaplan-Meier estimates of the distribution of PFS for each treatment arm, median PFS and their 95% CIs.

*: Handling strategies for intercurrent events are described in the table below.

Intercurrent Events	**Handling Strategy for Addressing Intercurrent Events**
Discontinuation of study treatment	**Treatment policy strategy:** Use time to PD or death, whichever occurs first regardless of discontinuation of study treatment.
Use of subsequent anticancer therapy	**Treatment policy strategy:** Use time to PD or death, whichever occurs first regardless of use of subsequent anti-cancer therapy. **Hypothetical strategy:** Subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy.
Death due to COVID-19	**Composite variable strategy:** Ignore COVID-19 and consider a (pre-PD) COVID-19-related death a PFS event. **Hypothetical strategy:** Subjects are censored at the last adequate disease assessment before (pre-PD) death due to COVID-19

The strategies to handle the three intercurrent events are described as follows:

Intercurrent Events	**US**	**Other Regions**
Discontinuation of study treatment	Treatment policy strategy	
Use of subsequent anticancer therapy	Primary analysis: hypothetical strategy Supplementary analysis: treatment policy strategy	Primary analysis: treatment policy strategy Supplementary analysis: hypothetical strategy
Death due to COVID-19	Primary analysis: composite variable strategy Supplementary analysis: hypothetical strategy	

4.2 Definitions and Analyses for Efficacy Endpoints

Table 2 below describes the definitions and analyses for the efficacy endpoints.

Table 2 Definitions and Analyses for Efficacy Endpoints

Efficacy Endpoint	Definition	Analysis Method
	Primary Endpoint	
PFS assessed by investigator (INV)	Time from the date of randomization to the date of the first documentation of progressive disease (PD) or the date of death due to any causes, whichever occurs first, regardless of study drug discontinuation or use of subsequent anti-cancer treatment. Post-treatment stem cell transplantation, CAR T-cell therapy, and other cellular therapies are not considered subsequent anti-cancer treatment for subjects responding to treatment (CR or PR) For the evaluation of disease progression, an adequate post-baseline assessment is defined as an assessment where there is enough evidence to indicate the subject had or had not progressed based on Cheson 2014 (Lugano Classification Criteria). In the situation where subjects did not have a baseline disease assessment or any adequate post-baseline disease assessment, they will be censored at the date of randomization.	Primary Analysis: Treatment policy strategy and composite variable strategy as listed in Section 4.1 will be implemented to address intercurrent events. Subjects without a PFS event will be censored at the date of the last adequate post-baseline disease assessment showing no evidence of disease progression. For US, additional censoring conventions will be implemented [see Sensitivity/Supplementary Analyses item 3) below]. Stratified log-rank test will be used to test the treatment effect between the two treatment arms. Stratified Cox regression model with Efron's tie handling method will be used to calculate the hazard ratio (HR) and its 2-sided 95% confidence interval (CI). In addition, Kaplan-Meier (KM) curves will be provided for both treatment arms. For each treatment arm, the 2-sided 95% Brookmeyer-Crowley confidence interval based on the log-log-transformed Greenwood variance estimate will be calculated for median PFS (mPFS); KM estimates at selected landmark points will also be provided.

		Sensitivity/Supplementary Analyses: 1) To address the intercurrent events of use of subsequent anticancer therapy, hypothetical strategy (subjects who received subsequent anti-cancer treatment will be censored at the last adequate post-baseline disease assessment showing no evidence of PD prior to the initiation of subsequent anti-cancer treatment) is implemented. 2) Subjects who missed two or more consecutive overall disease assessments (algorithm is described in Appendix 1) prior to the PFS event will be censored at the last adequate post-baseline disease assessment showing no evidence of PD prior to the first missed disease assessment. 3) Implement the two censoring conventions from items 1) and 2) above. This will be the primary analysis only for the US regulatory consideration. 4) Analyses listed under Primary Analysis and Sensitivity/Supplementary Analyses items 1) - 3) will be repeated for the IRC assessment. 5) To address the intercurrent events of COVID-19 deaths, hypothetical strategy (Pre-PD deaths due to COVID-19 are censored) is implemented. 6) Unstratified log-rank test and unstratified Cox regression model to calculate HR and its 2-sided 95% CI; same censoring convention as the primary analysis. Subgroup Analysis: Hazard ratio and its 95% CI from unstratified Cox regression model for each subgroup. Same censoring convention as for the primary analysis. For the US, additional censoring conventions as specified for the US primary PFS analysis in item 3) above will be implemented.

Efficacy Endpoint	Definition	Analysis Method
	Secondary Endpoints	
CR Rate per INV	Proportion of subjects achieving a complete response (CR) based on the best overall response (BOR) per Cheson 2014 (Lugano Classification Criteria) recorded since the date of randomization until the initiation of subsequent anti-cancer treatment or the first documentation of progressive disease, whichever occurs first. Subjects who did not have any post-baseline disease assessments will be considered non-responders when summarizing CR rate. For responding subjects who received post-treatment stem cell transplantation (SCT), CAR T-cell therapy, or other cellular therapies, BOR will be based on disease assessments conducted prior to these treatments. To support CR rate, duration of CR is defined as time from the date of first documentation of CR to the date of first documentation of PD or death, whichever occurs first, regardless of the use of subsequent anti-cancer treatment. Censoring convention is the same as for the PFS primary analysis. For the US, additional censoring conventions as specified for the US primary PFS analysis in item 3) under Analysis Method will be implemented for duration of CR.	Primary Analysis: Rate ratio between the two treatment arms will be calculated and tested using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by the two randomization stratification factors. Supportive Analysis For duration of CR, the KM estimate of median and the KM estimates at selected landmark points will be provided for each treatment arm.
ORR per INV	Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the best overall response (BOR) per Cheson 2014 (Lugano Classification Criteria) recorded since the date of randomization until the initiation of subsequent anti-cancer treatment or the first documentation of progressive disease, whichever occurs first. Subjects who	Primary Analysis: Method is the same as for the CR rate. Supportive Analysis: Same KM estimates described above for duration of CR will be provided for DOR.

Efficacy Endpoint	Definition	Analysis Method
	did not have any post-baseline disease assessments will be considered non-responders when summarizing ORR. To support ORR, duration of response (DOR) is defined for the responders (PR or CR) as time from the date of initial response (PR or CR, whichever occurs first) to the date of first documentation of PD or death, whichever occurs first, regardless of the use of subsequent anticancer therapy. Censoring convention is the same as for the PFS primary analysis. For the US, additional censoring conventions as specified for the US primary PFS analysis in item 3) under Analysis Method will be implemented for duration of response.	
Minimal Residual Disease (MRD)-Negative Remission Rate	<u>For CR subjects per investigator only:</u> Proportion of subjects achieving an MRD-negative remission, which is defined as undetectable MRD (i.e. less than the lower limit of detection for the assay) at documented CR in MRD-evaluable subjects (i.e. subjects with positive MRD at baseline) as assessed by flow cytometry of bone marrow aspirate (BMA) and/or peripheral blood (PB)), with requirement of a confirmation of MRD-negativity in subsequent peripheral blood samples at least 12 weeks later. Only subjects with samples collected at both baseline and post-baseline are included in the denominator when calculating the MRD remission rate. MRD samples collected after the initiation of subsequent anticancer therapy will not be used for this analysis.	For CR subjects who were MRD-evaluable, the MRD-negative remission rate will be calculated and tested by Fisher's Exact test for BMA and PB separately.

Efficacy Endpoint	Definition	Analysis Method
Overall Survival (OS)	Time from the date of randomization to the date of death due to any cause.	Primary Analysis: Similar to the primary PFS analysis, composite variable strategy (COVID-19 deaths are considered OS events) is implemented to address the intercurrent events of COVID-19 deaths. Subjects without an OS event will be censored at the date last known alive. Analysis methods are the same as the primary PFS analysis. Sensitivity/ Supplemental Analyses: 1) Unstratified log-rank test and unstratified Cox regression model to calculate HR and its 2-sided 95% CI. 2) Hypothetical strategy (Subjects who died due to COVID-19 are censored at one day prior to the death date) is implemented to address the intercurrent events of COVID-19 deaths
Time to next treatment (TTNT)	Time from the date of randomization to the date of the initiation of subsequent anti-cancer treatment. Post-treatment stem cell transplantation, CAR T-cell therapy, or other cellular therapies are not considered subsequent anti-cancer treatments for subjects responding to the treatment (CR or PR). Subjects without the use of subsequent anti-cancer treatment will be censored at the last follow-up date for subsequent anti-cancer therapy.	Method is the same as for the PFS analysis
Time to worsening in FACT-Lym subscale[5,6]	Time from the date of randomization to the start date of worsening (defined by a ≥5 points reduction from baseline) in the Lym Subscale or death due to any cause, whichever occurs first. Subjects who have not met the definition of worsening will be censored at the last non-missing post-baseline PRO assessment. Subjects without baseline or post-baseline assessment will be censored at the date of randomization.	Method is the same as for the PFS analysis

Efficacy Endpoint	Definition	Analysis Method
	Exploratory Endpoints	
Progression-free Survival Based on Investigator Assessment after Initiation of Subsequent Anti-cancer Therapy (PFS2)	Time from the date of randomization to the date of the earliest of the following three types of events: • PD per investigator response assessment after administration of the first subsequent anticancer therapy • Death at any time on study • Initiation of the second subsequent anti-cancer therapy Subjects who did not experience a PFS2 event will be censored at the last adequate response assessment or the last follow-up for subsequent anti-cancer therapy (if they no longer have response assessments).	No inferential test will be conducted. For each treatment arm, the KM estimate of the median PFS2 (mPFS2) and the KM estimates at selected landmark points will be calculated using the same methods as for the primary PFS analysis.
CMH: Cochran-Mantel-Haenszel; CI: confidence interval; CR: complete response; HR: estimate hazard ratio; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response.		

5 SAFETY ASSESSMENTS

Safety data will be summarized by treatment arm based on the Safety Population.

Adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA 24.1). Severity of AEs will be graded by the investigator according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

The treatment-emergent period is defined as the period of time from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent anti-cancer treatment, whichever comes first.

Treatment-emergent adverse events (TEAEs) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment.

Adverse Events of Special interest (AESI)as listed below will be summarized by treatment arm:

- Protocol-defined events of clinical interest including hemorrhagic events and major hemorrhage.
- Other safety observations including other malignancies (including NMSC, NSC, and MSC), hypertension ("Hypertension" SMQ narrow), interstitial lung disease ("Interstitial lung disease" SMQ narrow), atrial fibrillation (PT = "atrial fibrillation"), cardiac arrhythmia ("Cardiac arrhythmias SMQ, excluding PT of "atrial fibrillation"), Cardiac failure, ventricular tachyarrhythmia ("Ventricular Tachyarrhythmia" SMQ narrow), tumor lysis syndrome ("Tumour lysis syndrome" SMQ narrow), ischemic stroke ("Ischaemic central nervous system vascular conditions" SMQ narrow), sepsis (PTs = "Sepsis", "Bacteraemia", "Fungaemia" or "Septic" (excluding "Septic screen")), cytopenias (PTs="Anemia", "Neutropenia", "Febrile Neutropenia", and "Thrombocytopenia"), infections including viral reactivation (SOC = "Infection and Infestations"), hepatic disorders (SOC = "Hepatobiliary disorders"), embryo-fetal toxicity (SOC = "Pregnancy, puerperium and perinatal conditions"), Diarrhea (PT = "Diarrhoea")

All laboratory values will be converted to and reported as international standard (SI) units. Data for hematology and biochemistry were collected at the respective local laboratories and will be summarized and analyzed by treatment arm. Laboratory parameters will be graded using the NCI CTCAE, Version 4.03. Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis.

The following safety analyses will be conducted to evaluate the use of venetoclax:

- Infectious pneumonia.
- TLS evaluated by adverse events of special interest and laboratory TLS per Howard criteria.
- Liver function abnormalities evaluated by laboratory data per Hy's law.
- GI Toxicities: No pooling will be done for diarrhea, nausea, and vomiting.
    - ♦ For each of the three preferred terms, events leading to treatment discontinuation and dose modification (dose reduction and/or dose hold) will be summarized.

Table 3 Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
AE	TEAEs, SAEs, Grade 3 or higher TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction or dose hold, TEAEs leading to death, protocol-defined events of special interest defined by SMQ terms and other safety observations	Descriptive summary statistics and/or listings
Laboratory Parameters	Worst post-baseline toxicity grade for CTCAE-gradable hematology and chemistry results. Abnormalities in creatinine clearance, uric acid levels, and liver function tests. Laboratory TLS per Howard Criteria	Descriptive summary statistics and/or listings
Vital Signs and other Observations Related to Safety	Blood pressure, heart rate, temperature, and body weight, new or worsened eye-related symptoms	Descriptive summary statistics and/or listings
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event; SMQ: standardized MedDRA (Medical Dictionary for Regulatory Activities) query.		

5.1 Data Summaries for COVID-19

TEAEs related to a COVID-19 infection will be summarized using the check box on the CRF page by treatment arm separately from other TEAEs. Deaths related to COVID-19 will be summarized or listed by treatment arm separately from deaths unrelated to COVID-19. COVID-19 laboratory tests will be listed by treatment arm.

5.2 Safety Run-in

Safety data for Safety Run-in subjects treated with study treatment will be summarized and/or listed by the TLS risk category at baseline (Low versus Increased) separately from the randomized subjects.

In addition to standard safety summaries for TEAEs, SAEs, Grade 3 or higher TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death, the summary of safety data included will be limited in scope to DLTs and TLS.

6 TREATMENT-NAÏVE COHORT

The following data will be summarized for treatment-naïve subjects who were enrolled into the study at the time of the primary PFS analysis for subjects with R/R MCL. Data summaries will be limited to the followings:

- Demographics and baseline characteristics
- Study drug exposure
- Treatment disposition and subject disposition
- Treatment-emergent adverse events

A comprehensive and complete data summary and analysis for treatment-naïve subjects will be described in an SAP addendum at the appropriate time prior to primary analysis.

7 CHANGES IN THE PROTOCOL-PLANNED ANALYSES

1. In alignment with the FDA guidance (Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, June 2020), in order to mitigate the potential impact on key efficacy endpoints due to COVID-19, the follow-up will be extended to accrue more events as described in Section 1.5.1 and Section 1.5.2 over the originally planned event numbers (134 events for PFS and 155 events for OS).

2. Change superiority boundary for the interim OS analysis from O'Brien Fleming boundary to Haybittle-Peto boundary.

3. Specify secondary and exploratory endpoints to be included in the CSR.

4. IRC will be implemented to do the overall disease assessment based on Cheson 2014 (Lugano Classification Criteria). A sensitivity analysis will be conducted for PFS using the IRC assessment.

5. Since only 9 subjects in total were randomized to the stratum of ECOG performance status of 2, stratification by the three randomization stratification factors will lead to empty or very small strata. Therefore, all stratified tests/analyses will only be based on two randomization stratification factors per IRT: prior lines of therapy (1-2 vs $\geq$ 3) and TLS risk category (low risk vs. increased risk).

6. The CR rate and ORR will be compared by rate ratio between the two treatment arms using CMH chi-square test stratified by the two randomization stratification factors instead of by the difference in proportion between the two treatment arms.

7. The MRD-negative remission rate for CR subjects evaluable for MRD will be compared by Fisher's Exact test due to the small sample size.

8 APPENDICES

8.1 Algorithm for Defining 2 or more Consecutive Assessments Prior to the PFS Event

This study has 3 planned imaging schedules: every 12 weeks in the first year, every 16 weeks in the second and third years, and every 24 weeks afterwards. The exact imaging schedules are defined in weeks (see Table 2). Based on the change between the schedules, two transitions of the imaging schedule are described as follows:

1. When the last non-PD assessment occurs at Week 37, the next assessment is planned at Week 49 (12 weeks from Week 37) and then at Week 65 (16 weeks from Week 49).
2. When the last non-PD assessment occurs at Week 129, the next assessment is planned at Week 145 (16 weeks from Week 129) and then at Week 169 (24 weeks from Week 145).

This algorithm has two steps in series:

1. Step 1 (Columns 2-4 of Table 1): To map the last adequate non-PD assessment to a closest scheduled visit based on the study day of the last adequate non-PD assessment using the midpoint window (see footnote of Table 1 for details). Once the assessment is mapped to a scheduled visit, the imaging interval for the next two subsequent consecutive visits can be decided based on the planned imaging schedule.
2. Step 2 (column 5 of Table 1): Calculate maximum days allowed for those two subsequent visits based on the planned imaging interval plus 7 days based on the protocol-specified window (+/- 7 days) for each visit.

There are five time periods in Table 1 based on three planned imaging schedules and two transitions in the imaging schedule.

Table 1: Algorithm for defining missing two or more consecutive assessments prior to the PFS events

Time Period	Last Adequate Non-PD Assessment		Imaging Schedule for the Two Subsequent Consecutive Assessments after the Last Adequate Non-PD Assessment	Maximum Gap& in Days Allowed between PFS Event and Last Adequate Non-PD Assessment
	Scheduled Visit	Study Day*		
1	Week 13-Week 25	Day 2- Day 211	12 weeks (84 days)	182=(84+7)*2
2	Week 37	Day 212 - Day 295	12 weeks (84 days) &16 weeks (112 days)	210=(84+7) + (112+7)
3	Week 49-Week 113	Day 296 – Day 841	16 weeks (112 days)	238=(112+7)*2
4	Week 129	Day 842 - Day 953	16 weeks (112 days) & 24 weeks (168 days)	294=(112+7) + (168+7)
5	Week 145 and higher	Day 954 and higher	24 weeks (168 days)	350=(168+7)*2

*: The visit window for each visit is based on the midpoint between two scheduled visits (i.e. target day +/- half of the planned interval between two scheduled visits). However, start day of Week 13 is one day after randomization (Day 2). If the last adequate non-PD assessment is the same as or earlier than the midpoint, it will be assigned to the earlier visit, and if the assessment is later than the midpoint, it will be assigned to the later visit. Study day is calculated in reference to the randomization date.
&: A 7-day window is allowed per the protocol for each subsequent visit.
Visits sharing the same imaging schedules are combined in Time Periods 1, 3, and 5, respectively; details are displayed in Table 2.

Detailed imaging schedules (by weeks) and the target day, start day, and end day of each scheduled visit along with the maximum gap in days allowed between the PFS event and the last adequate non-PD assessment are displayed in Table 2 below. Each of the five time periods is highlighted in a different color in Table 2.

Table 2: Protocol Imaging Schedule

Interval from the Previous Scheduled Visit	Scheduled Visit	Target Study Day (Start Day – End Day)* of Each Visit	Start Day - End Day (of the Time Period)	Maximum Gap& in Days Allowed between PFS Event and Last Adequate Non-PD Assessment
12 weeks=84 days	WEEK 13	D85 (D2-D127)	D2-D211 (Week 13-Week 25)	(84+7)*2=182
	WEEK 25	D169 (D128-D211)		
	WEEK 37	D253 (D212-D295)	D212-D295 (Week 37)	(84+7)+(112+7)=210 Note: Two consecutive assessments after Week 37 are at the interval of 12 and 16 weeks (at Weeks 49 & 65, respectively)
	WEEK 49	D337 (D296-D393)	D296-D841(Week 49-Week 113)	(112+7)*2=238
16 weeks=112 days	WEEK 65	D449 (D394-D505)		
	WEEK 81	D561 (D506-D617)		
	WEEK 97	D673 (D618-D729)		
	WEEK 113	D785 (D730-D841)		
	WEEK 129	D897 (D842-D953)	D842-D953 (Week 129)	(112+7)+(168+7)=294 Note: Two consecutive assessments after Week 129 are at the interval of 16 and 24 weeks (at Weeks 145 & 169, respectively)
	WEEK 145	D1009 (D954-D1093)	All visits (Week 145 and Higher) after D953 are in this time period	(168+7)*2=350
24 weeks=168 days	WEEK 169	D1177 (D1094-D1261)		
	WEEK 193	D1345 (D1262-D1429)		
	WEEK 217	D1513 (D1430–D1597)		
	WEEK 241	D1681 (D1598-D1765)		

*: End day and start day of each scheduled visit are based on the midpoint window (i.e. target day +/- half of the interval between two scheduled visits). However, start day of Week 13 is one day after randomization (Day 2). If the last adequate non-PD assessment is the same as or earlier than the midpoint, it will be assigned to the earlier visit, and if the assessment is later than the midpoint, it will be assigned to the later visit. Study day is calculated in reference to the randomization date.
&: A 7-day window is allowed per the protocol for each subsequent visit.

9 REFERENCES

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