APPENDIX 9.1

STATISTICAL ANALYSIS PLAN

pharmacyclics
An AbbVie Company

Statistical Analysis Plan

TITLE: **A Multicenter Open-Label Phase 2a Study of Ibrutinib Monotherapy or in Combination with either Cytarabine or Azacitidine in Subjects with Acute Myeloid Leukemia**

PROTOCOL: **PCYC-1131-CA**

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1. INTRODUCTION

This Phase 2a open-label, non-randomized U.S. multicenter study is designed to evaluate the safety and efficacy of ibrutinib monotherapy and in combination with low dose cytosine arabinoside (LD-AraC) or azacitidine in the treatment of subjects with Acute Myeloid Leukemia (AML).

This statistical analysis plan (SAP) describes the statistical methodology of efficacy and safety for this study. This plan does not cover the pharmacokinetic (PK) or biomarker analyses. These analyses will be performed and reported by the DMPK Department and Biomarker group of Pharmacyclics, respectively.

1.1. Study Objectives

The primary objectives are to evaluate the efficacy of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in the treatment of AML using the overall remission rate (ORR, defined as the proportion of subjects achieving a complete remission (CR) or complete remission with incomplete marrow recovery (CRi)) according to the LeukemiaNet guidelines (Döhner 2010, Appendix 6 in Protocol Amendment 1.0) and to evaluate the safety and tolerability of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in subjects with AML.

The secondary objectives are to evaluate clinical efficacy by assessing relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS) and to evaluate clinical benefit defined as CR, CRi, morphologic leukemia-free state, and partial remission (PR).

The exploratory objectives are to determine the PK of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in an AML population and to evaluate prognostic and predictive biomarkers relative to treatment outcomes (ie, BTK/pBTK, secreted proteins, gene expression profiling, mutational analysis). Exploratory objectives are outside the scope of this SAP.

1.2. Study Endpoints

Response criteria from the LeukemiaNet guidelines have been used by all investigators to assess efficacy outcomes. In accordance with the study protocol, the primary efficacy endpoint is defined as the ORR per investigator assessment of ibrutinib monotherapy and in combination with LD-AraC or azacitidine, respectively. The secondary efficacy endpoints include RFS for subjects who achieve a CR or CRi; EFS; OS and Clinical Benefit Rate (CBR; defined as the proportion of subjects achieving CR, CRi, morphologic leukemia-free state, or PR). Safety endpoints include the safety and tolerability of ibrutinib monotherapy and in combination with LD-AraC or azacytidine.

1.3. Study Design

A maximum of 101 subjects will be enrolled in 3 treatment cohorts.

- Cohort 1 – ibrutinib monotherapy: ibrutinib 560 mg once daily on a continuous basis. Up to 33 response evaluable subjects
- Cohort 2 – ibrutinib + LD-AraC: ibrutinib 560 mg once daily on a continuous basis plus low dose cytarabine. Up to 34 response evaluable subjects
- Cohort 3 – ibrutinib + azacitidine: ibrutinib 560 mg once daily on a continuous basis plus IV azacitidine. Up to 34 response evaluable subjects

The study will begin with safety run-in phase in Cohort 2 only. Six subjects will receive ibrutinib at a dose level of 560 mg once daily on a continuing basis starting 2 days prior to the first cytarabine dose. Assessment for dose limiting toxicities (DLTs) will continue for the first treatment cycle. If 2 of the first 6 subjects experience DLT(s), 3 additional subjects will be assessed for DLT(s). If 3 or more of the 9 subjects experience DLT(s), enrollment will be halted at the 560 mg dose level. At sponsor's discretion, a dose of 420 mg ibrutinib or lower (plus LD-AraC) may be explored. If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled in Cohort 1 or 2 at the discretion of the investigator. Efficacy parameters will be monitored closely. In the event response assessments suggest futility in the ibrutinib + AraC cohort, further enrollment in either cohort 1 or 2 will be closed and a new cohort of ibrutinib + azacitidine will be started. For Cohort 3 the same safety run-in principle as Cohort 2 (6+3 design) will be implemented. Study treatment will continue in subjects who demonstrate a PR or better on their Cycle 2 Day 1 bone marrow assessment according to the LeukemiaNet guidelines or based on clinical benefit as determined by the treating physician. Treatment may continue thereafter until unacceptable toxicity, treatment failure (TF), or withdrawal of consent. Subjects treated in the ibrutinib monotherapy cohort who experience a documented TF or relapse will be permitted to add LD-AraC to ibrutinib per investigator discretion.

1.4. Sample Size Considerations

The sample size of 6 or 9 safety run-in subjects for safety review was based on clinical experience and conventional DLT studies. The total sample size was calculated to detect a meaningful signal of activity of each treatment regimen while minimizing risk of continuing enrollment under null conditions. The sample size was estimated for each treatment cohort without multiplicity adjustment. The study will enroll approximately 101 subjects in total, including 33 response evaluable subjects for monotherapy and 34 response evaluable subjects for each combo therapy. The sample size of 33 subjects was calculated to test the null hypothesis that the ORR of ibrutinib monotherapy is ≤5% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥20%, with a significance level of 5%, and 80% power. The sample size of 34 subjects was calculated to test the null hypothesis that the ORR of ibrutinib plus LD-AraC or ibrutinib plus azacitidine is ≤15% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥35%, with a significance level of 5%, and 80% power.

2. GENERAL ANALYSIS CONSIDERATION

2.1. Analysis Populations

All treated population includes all enrolled subjects who received at least 1 dose of study drug in each study cohort. The DLT population will include the first 6 to 9 safety run-in subjects who signed the informed consent form and were enrolled for the safety run-in period, and were evaluable for DLT. The DLT population will be used to summarize dose limiting toxicities in the first 6 to 9 subjects in the safety run-in period. No subgroup analysis will be performed.

2.2. Analysis Conventions

Descriptive statistics (mean, standard deviation or standard error, median, minimum, and maximum) will be used to summarize continuous variables. Categorical variables will be summarized by counts and percentages. Unless otherwise specified, exact 95% confidence intervals will be constructed for event rates or response rates. As appropriate, data collected on the electronic case report form (eCRF) will be presented in data listings upon request. All statistical analyses will be performed using SAS® version 9.2 or later.

3. SUBJECT INFORMATION

All analyses in this section will be based on the all treated population for each treatment cohort unless otherwise specified, including subject disposition, demographics and baseline characteristics, baseline disease characteristics, prior AML therapies, concomitant medications including CYP3A inhibitors, and exposure to ibrutinib.

3.1. Protocol Deviations

In general, protocol violations/deviations will be reviewed by the study team during the study, and important protocol deviations will be determined based on the review. The information on important protocol deviations will be generated based on the review outcome for all subjects by the clinical team.

4. EFFICACY

4.1. Change from Protocol-defined Analysis

The study was terminated early due to lack of efficacy. As such, none of the protocol-defined efficacy endpoints including primary efficacy endpoints and secondary efficacy endpoints listed in Sections 1.2 will be calculated except for OS. A subject listing with all the available response assessment data for all treated patients will be provided. Overall survival will be analyzed as described in Section 4.2.

4.2. Overall Survival (OS)

Overall survival is defined as the duration of time from the date of first study drug to the date of death from any cause. Subjects who are not known to have died at or prior to the database lock date will be censored at the date last known alive or database lock date, whichever occurs first.

OS(day) = Date of death or censoring date – date of first dose of study drug + 1

The date last known alive will be derived as the latest among dosing records, lab measurements, vital signs, assessment dates. The median OS and its 95% CI will be obtained using Kaplan-Meier method. Overall survival at landmark time points (e.g. 1,2,3 months and etc. from first ibrutinib date) will also be obtained from Kaplan-Meier method.

5. SAFETY

Adverse events, changes in clinical laboratory results from baseline, summary of vital signs and ECG values will be provided. All safety analyses will be based on all treated population (except for DLT evaluation which will be based on DLT population).

5.1. DLT Assessment

At the safety review meeting, DLTs will be assessed for the first 6 to 9 subjects in the DLT population. Listing of subjects for DLT assessment will be provided.

5.2. Adverse Events

Adverse events collected in the CRF (verbatim terms) by investigators will be coded to a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.03.

5.2.1. Treatment-emergent Adverse Events

Treatment-emergent adverse events will be summarized by system organ class and preferred terms and by NCI toxicity grade. The same summary will be provided for treatment-related AEs, AEs leading to treatment discontinuation, AEs leading to treatment discontinuation for subjects who discontinued treatment due to AE, AEs leading to dose reduction and serious TEAEs. Adverse event overview on the incidences of all the above will be presented.

5.2.2. Adverse Events of Special Interest

5.2.2.1. Hemorrhagic Events

Bleeding events: Identified by MedDRA Hemorrhage SMQ without lab SMQ.

Major hemorrhage: Defined as any bleeding event identified by Hemorrhage SMQ without lab SMQ that satisfies at least one of the following three criteria: Grade 3 or higher in severity, Serious AE or all grades of CNS hemorrhage.

5.2.3. Other Malignancies

Other malignancies are defined as new malignant tumors including categories non-melanoma skin cancer, melanoma skin cancer and other non-skin cancers. Both treatment-emergent adverse events of other malignancies and all other malignancies AEs reported during the study will be summarized.

5.2.4. Other Safety Observations in AE Reporting

Treatment-emergent adverse events including other cardiac arrhythmia (excluding atrial fibrillation), Interstitial Lung Disease events (ILD) and Severe Cutaneous Adverse Reactions (SCAR) will be summarized by preferred terms based on SMQ searches and/or medical monitor and safety scientist review.

Summary of treatment-emergent adverse events including leukostasis, infections, tumor lysis syndrome (TLS), cytopenias, hypersensitivity, hepatic disorders and atrial fibrillation can be obtained from existing AE summary tables.

5.2.5. Deaths

Treatment-emergent adverse events leading to deaths will be summarized.

5.3. Clinical Laboratory Tests

All gradable laboratory parameters will be graded using the NCI CTCAE version 4.03. A summary of worst post-baseline toxicity grade will be provided. The events with Grade 3 and 4 as the worst post-baseline toxicity grade will be also provided. Only subjects whose grades worsened are counted in the numerator of percentage calculation while the denominator is all subjects in each treatment cohort all treated population. Liver function abnormality by Hy's law will be summarized. Listing of white blood cell (WBC) count, platelet count, blood blasts (%) and abnormal cells will be presented.