SYNOPSIS

Name of Sponsor/Company	Pharmacyclics LLC
Name of Finished Product	Ibrutinib
Name of Active Ingredient	Ibrutinib (PCI-32765)

Status: Approved
Date: 30 March 2020
Prepared by: Pharmacyclics LLC

Protocol No.: PCYC-1130-CA

Title of Study: A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

IND Number: 102,688

EudraCT Identifier: 2014-002069-31

Principal Investigator and Study Centers:

[redacted]

This study was conducted at a total of 9 sites in the United States and 80 sites in rest-of-world.

Final Publication: Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019 Jan;20(1):43-56. doi: 10.1016/S1470-2045(18)30788-5. Epub 2018 Dec 3. (published correction: doi: 10.1016/S1470-2045(18)30923-9; e10).

Study Period: 06 October 2014 (first informed consent signed) to 17 October 2019 (with last subject last visit: 03 September 2019)

Phase of Development: 3

Objectives:

Primary Objective: To evaluate the efficacy of ibrutinib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab based on the Independent Review Committee (IRC) assessment of progression-free survival (PFS). Efficacy was evaluated according to 2008 International Workshop for Chronic Lymphocytic Leukemia (iwCLL) criteria with the modification for treatment-related lymphocytosis, in subjects with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Secondary Objectives:

To compare between the treatment groups in terms of the following:

Efficacy

- Overall response rate (ORR) according to iwCLL 2008 criteria as assessed by the IRC.
- Rate of minimal residual disease (MRD)-negative responses.
- Overall survival (OS).
- Hematological improvement measured by platelet and hemoglobin counts.
- Patient-reported outcomes as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EuroQoL Five-Dimension (EQ-5D-5L).

Safety

- To evaluate the safety and tolerability of ibrutinib in combination with obinutuzumab compared with chlorambucil in combination with obinutuzumab.
- To evaluate obinutuzumab-related infusion reactions by treatment arm.

Methodology: This was a randomized, multicenter, open-label, Phase 3 study designed to evaluate the safety and efficacy profile of ibrutinib in combination with obinutuzumab compared to chlorambucil plus obinutuzumab in subjects with CLL/SLL who were treatment-naive and required active therapy. Subjects were randomized to 1 of 2 treatment arms and received the respective regimens:

- Arm A: Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity *plus* intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1, and 1000 mg on Day 1 of each cycle up to 6 cycles; in this report; this treatment combination is referred to as Ibr+Ob (ibrutinib+obinutuzumab).
- Arm B: Chlorambucil given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle *plus* intravenous obinutuzumab per instructions shown for Arm A; in this report; this treatment combination is referred to as Clb+Ob (chlorambucil+obinutuzumab).

Single-agent ibrutinib treatment continued for subjects who were randomized to Ibr+Ob as well as those who were randomized to Clb+Ob and subsequently crossed over to ibrutinib after confirmed progression. At study closure, sites with active subjects without progressive disease who were still receiving ibrutinib treatment were given an option to enroll in an extension study to continue ibrutinib treatment.

Study 1130 was initiated on 06 October 2014. The primary analysis of this study was conducted with a clinical data cut-off date of 26 March 2018, and the clinical study report (CSR) was completed on 20 July 2018. In the current CSR addendum, data are summarized for subjects through the clinical data cut-off date for the final analysis (17 October 2019, with last subject last visit on 03 September 2019), covering approximately 19 months of additional follow-up.

Number of Subjects (Planned and Analyzed): A total of 229 subjects were randomized; all of these were included in the intent-to-treat (ITT) population, which was used for the efficacy analysis. The

high-risk population was used for the analysis of randomized subjects with deletion of the short arm of chromosome 17 (del 17p)/tumor suppressor protein P53 (TP53) mutation, deletion of the long arm of chromosome 11 (del 11q), or unmutated immunoglobulin heavy chain variable region (IGHV) at baseline per central laboratory results (n = 148). The safety population was used for the analyses of all safety assessments and included all subjects who received at least 1 dose of study treatment (n = 228 subjects).

Main Eligibility Criteria: Eligible subjects were required to have had a diagnosis of active CLL/SLL conformant to iwCLL 2008 diagnostic criteria. All subjects were required to have measurable nodal disease (defined as at least 1 lymph node with > 1.5 cm in the longest diameter in a site not previously irradiated) per computed tomography scan. Key exclusion criteria included any previous CLL/SLL treatment; known lymphoma or leukemia of the central nervous system; and history or current evidence of Richter's transformation.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib was administered orally once daily at a starting dose of 420 mg. Lot numbers for ibrutinib used in the study were L0406368A3, L0500397A3, L0503008C1, L0506693A2, L0507576A3, L0406368A1, L0409672C1, and L0607371A4, and L0607371A5.

Reference and Combination Therapies, Doses, Modes of Administration, Batch No.: Chlorambucil was administered orally on Days 1 and 15 of each cycle at a dose of 0.5 mg/kg body weight. Obinutuzumab was administered as an infusion at a dose of 1000 mg, with the exception of the infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg).

Duration of Treatment: Subjects were to receive ibrutinib until disease progression or unacceptable toxicity. Treatments with chlorambucil and obinutuzumab, which were administered for up to 6 cycles, were completed by the time of the primary analysis.

Endpoints: For the primary analysis, the primary endpoint of this study was PFS per IRC assessment. The secondary endpoints were PFS per IRC assessment in the high-risk subpopulation (subjects with del 17p/TP53 mutation or del 11q at baseline per central laboratory results); rate of sustained hemoglobin improvement; rate of MRD-negative response; ORR per IRC assessment; OS; rate of infusion-related reactions (IRRs); rate of sustained platelet improvement; rate of clinically meaningful improvement in EQ-5D-5L; and safety and tolerability of Ibr+Ob compared with Clb+Ob.

Final analysis for PFS and ORR was based on investigator assessment because after the primary analysis the IRC did not perform further assessments for response and only reviewed cases of suspected progressive disease. Additionally, PFS analyses in the Ibr+Ob arm were performed for subgroups according to the presence or absence of specific mutations (del 17p/TP53 mutation or del 17p alone). Investigator-assessed PFS of the high-risk population (del 17p/TP53 mutation/del 11q/unmutated IGHV) was analyzed as a secondary endpoint due to its inclusion in the current prescribing information. All other secondary endpoints evaluated during the primary analysis were assessed with the exception of the rates of IRRs and clinically meaningful improvement in EQ-5D-5L.

Statistical Methods: For the final analysis, the primary endpoint of PFS per investigator assessment was summarized for each treatment arm using Kaplan-Meier estimates and compared by log-rank test. Investigator-assessed PFS in the high-risk population and OS in the ITT population were analyzed using the same method as for the primary endpoint. The rate of sustained hemoglobin improvement, rate of MRD-negative response, and ORR by investigator assessment were compared between treatment arms using a chi-square test. Additional analyses performed for the final analysis were investigator-assessed PFS after the initiation of subsequent anti-neoplastic therapy (PFS2); PFS and OS after next-line ibrutinib treatment; and time to next treatment for subjects who were randomized to Ibr+Ob and discontinued

ibrutinib treatment. Descriptive summaries and/or listings were provided for treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and other safety parameters including laboratory data. Certain safety evaluations (ie, 9-month analyses, elevated uric acid) were not performed after the primary analysis. All statistical methodologies were consistent with those used in the primary analysis.

RESULTS:

Subject Disposition: A total of 229 subjects were randomized in the ITT population, with 113 subjects randomized to the Ibr+Ob arm and 116 subjects randomized to the Clb+Ob arm. As of the final analysis, the median time on study for all subjects was 44.6 months (45.5 months for the Ibr+Ob arm and 43.0 months for the Clb+Ob arm). All subjects in the Ibr+Ob arm had either completed or discontinued study treatment at the time of the present analysis. Study termination by the Sponsor was reported as the most common primary reason for ibrutinib discontinuation in 57.5% of subjects in the Ibr+Ob arm.

In the Clb+Ob arm, all subjects had either completed or discontinued treatment already by the data cut-off date of the primary analysis. One subject in this arm did not receive any study treatment due to use of high-dose steroids after randomization but prior to the start of study treatment (which made the subject ineligible). At the time of the final analysis, 43.1% of subjects initially treated in the Clb+Ob arm received next-line ibrutinib therapy following cross-over or commercial ibrutinib.

As of the final analysis, all subjects had discontinued the study. Overall, the most common primary reasons for exiting the study in both treatment arms were termination of the study by the Sponsor (74.2%) and death (18.3%).

Efficacy Results: Based on a median follow-up of 44.6 months, treatment with Ibr+Ob continued to result in a clinically meaningful improvement of investigator-assessed PFS compared to Clb+Ob in subjects with treatment-naive CLL/SLL.

Primary Efficacy endpoint

- Treatment with Ibr+Ob resulted in an improvement in investigator-assessed PFS vs. Clb+Ob (hazard ratio [HR] = 0.251, 95% confidence interval [CI]: 0.162, 0.389, $p < 0.0001$). The median PFS was not reached for Ibr+Ob and was 21.9 months for the Clb+Ob arm. Results for PFS remained consistent across predefined subgroups.

Secondary Efficacy endpoints

- For the high-risk population (del 17p/TP53 mutation/del 11q/unmutated IGHV), the PFS HR was 0.169 (95% CI: 0.102, 0.282, $p < 0.0001$). The median PFS was 49.0 months for the Ibr+Ob arm and was 18.0 months for the Clb+Ob arm.

- Treatment with Ibr+Ob resulted in sustained hemoglobin improvement for 44.2% of subjects compared to 44.0% in subjects randomized to Clb+Ob ($p = 0.9657$). In subjects with baseline anemia (hemoglobin ≤ 110 g/L), treatment with Ibr+Ob resulted in sustained hemoglobin improvement for 70.6% of subjects compared to 62.0% in subjects randomized to Clb+Ob ($p = 0.3611$).

- Treatment with Ibr+Ob resulted in a MRD negativity rate in the bone marrow of 24.8% vs. 17.2% in the Clb+Ob arm ($p = 0.1612$) and a MRD negativity rate in the peripheral blood or bone marrow of 38.1% vs. 25.0% in the Ibr+Ob and Clb+Ob arms, respectively ($p = 0.0334$).

- Treatment with Ibr+Ob resulted in an ORR per investigator assessment of 91.2% vs. 81.0% with Clb+Ob (p = 0.0273) and a CR rate of 41.6% vs. 17.2% in the Ibr+Ob and Clb+Ob arms, respectively (p < 0.0001).
    - The median duration of response per investigator assessment was not reached for the Ibr+Ob arm and was 19.4 months for the Clb+Ob arm.
- The median OS was not reached in either treatment arm (HR = 1.083, 95% CI: 0.595, 1.973; p = 0.7934).
- Treatment with Ibr+Ob resulted in sustained platelet improvement for 30.1% of subjects compared to 14.7% of subjects randomized to Clb+Ob (p = 0.0050). In subjects with baseline thrombocytopenia (platelets ≤ 100 x 10^9/L), treatment with Ibr+Ob resulted in 57.1% of subjects with sustained improvement in platelet count compared to 45.5% in subjects randomized to Clb+Ob (p = 0.4115).

Safety Results:

As of the final analysis, the median treatment duration for ibrutinib was 42.3 months in the Ibr+Ob arm, which was 13.0 months longer than the primary analysis (29.3 months). For the final analysis, there was no change in the exposure data for chlorambucil in the Clb+Ob arm (median treatment duration: 5.1 months) or obinutuzumab in either the Ibr+Ob or Clb+Ob arm (median treatment duration for both treatment arms: 4.6 months).

As of the final analysis, extended treatment with ibrutinib in the Ibr+Ob arm continued to be associated with an acceptable safety profile, and no new safety signals were identified during extended follow-up. The safety results for the Clb+Ob arm are largely unchanged compared to the results from the primary analysis; as a consequence, results shown here are those from the Ibr+Ob arm:

- The most common TEAEs (≥ 20% of subjects) were neutropenia (44.2%), thrombocytopenia (35.4%), diarrhea (34.5%), cough (29.2%), IRR (24.8%), and arthralgia (23.9%).
- Grade 3 or higher TEAEs occurred in 79.6% of subjects; the most common (≥ 5% of subjects) were neutropenia (36.3%), thrombocytopenia (19.5%), pneumonia (8.8%), atrial fibrillation (6.2%), and febrile neutropenia (5.3%).
- Treatment-emergent SAEs occurred in 61.1% of subjects; the most common events (≥ 2% of subjects) were pneumonia (7.1%), atrial fibrillation (5.3%), febrile neutropenia (4.4%), pyrexia (3.5%), gastroenteritis, thrombocytopenia, urinary tract infection, acute coronary syndrome, and adenocarcinoma of colon (2.7% each).
- Fatal TEAEs occurred in 14 subjects (12.4%). Four fatal events occurred after the primary analysis: death (cause unknown), septic shock, pneumonia, and respiratory tract infection (1 subject each)
- Adverse events (AEs) were listed as the primary reason for ibrutinib discontinuation for 25 subjects (22.1%); the only AE listed as the primary reason for ibrutinib discontinuation in more than 1 subject was thrombocytopenia (2 subjects, 1.8%).
- Treatment-emergent AEs leading to dose reduction of ibrutinib occurred in 17 subjects (15.0%).
- Major hemorrhage occurred in 5 subjects (4.4%).

- Non-melanoma skin cancer was reported for 7 subjects (6.2%) during the entire study period.
- Atrial fibrillation was observed in 17 subjects (15.0%).
- Interstitial lung disease was observed in 6 subjects (5.3%).

Conclusions: In this final analysis, with an overall follow-up of 52.3 months, a continued, clinically meaningful, and durable response to ibrutinib in the Ibr+Ob arm, was observed for both the overall population with treatment-naive CLL/SLL as well as for those with high-risk genomic features (del 17p/TP53 mutation, del 11q, or unmutated IGHV). Ibrutinib treatment eliminates the negative prognostic effects of del 17p/TP53 mutations on PFS. Subsequent treatment with ibrutinib after cross-over demonstrated a beneficial effect for subjects with disease progression who were initially randomized to treatment with Clb+Ob. Treatment with ibritinib in the Ibr+Ob arm continued to demonstrate an acceptable safety and tolerability profile with no new safety signals observed.