SYNOPSIS

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

Status: Final
Date: 10 April 2020
Prepared by: Pharmacyclics LLC

Protocol No..: PCYC-1127-CA

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenstrom's Macroglobulinemia

IND Number: 102,688

Study Name: iNNOVATE

EudraCT Number: 2013-005478-22

Clinical Registry No.: NCT02165397

Principal Investigator and Study Centers: [redacted]

This study was conducted at 48 centers in the US, Europe, Canada, and Australia.

Final Publication (Reference): Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's macroglobulimemia. *N Engl J Med*. 2018;378;25:2399-2410.

Study Period: 07 July 2014 (first subject consented) to 18 December 2019 (final database lock date). The primary analysis clinical study report (CSR) date was 22 February 2018. This is the final CSR of this study.

Phase of Development: 3

Objectives:

Primary Objective

To evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) assessed by an independent review committee (IRC) in subjects with Waldenstrom's macroglobulinemia (WM). Efficacy evaluations will be based on the modified Consensus Response Criteria from the VIth International Workshop for Waldenstrom's Macroglobulinemia (IWWM), 2014.

Secondary Objectives

Efficacy

To compare the treatment arms in terms of the following:

- Overall response rate assessed by IRC (≥ partial response [PR]; according to the modified VIth IWWM criteria). For the purpose of this clinical study report (CSR), overall response rate is referred to as response rate.
- Hematological improvement measured by hemoglobin (Hgb).
- Time to next treatment (TTnT).
- Improvement in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) subscale score
- Overall survival (OS).

Safety

- To evaluate the safety and tolerability of ibrutinib when combined with rituximab therapy compared to rituximab in combination with placebo.

The open-label substudy objectives were to evaluate the efficacy and safety of open-label ibrutinib monotherapy in WM subjects who were considered refractory to the last prior rituximab-containing therapy. Progression-free survival, response rate, hematological improvement measured by serum Hgb, TTnT, FACIT-Fatigue, OS, and other efficacy parameters as well as safety analyses were summarized descriptively for the open-label substudy.

Methodology:

Phase 3 Study PCYC-1127-CA included a randomized, double-blind, placebo-controlled design to evaluate whether treatment with ibrutinib in combination with rituximab (Ibr+R) would result in an improvement in PFS compared to placebo in combination with rituximab (Pbo+R) in subjects with WM. In addition, an open-label substudy was included to further investigate the safety and efficacy of ibrutinib monotherapy in subjects with WM who were considered refractory to the last prior rituximab-containing therapy.

Subjects meeting eligibility criteria and randomized to Ibr+R and Pbo+R arms received intravenous rituximab weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (Weeks 1 to 4), followed by a second course of weekly rituximab for 4 consecutive weeks (Weeks 17 to 20). In addition, all subjects in Ibr+R and Pbo+R arms, according to randomization, received oral study drug (ibrutinib or matching placebo), administered daily and continuously until criteria for permanent discontinuation of study drug were met, such as IRC-confirmed disease progression, study drug was no longer tolerable by subject, or study end. All subjects in the open-label monotherapy substudy received oral ibrutinib daily and continuously until the same criteria for permanent discontinuation of study drug were met. Subjects with IRC-confirmed progressive disease were to discontinue all study treatment (ibrutinib, placebo, rituximab); access to next-line ibrutinib for subjects in the Pbo+R arm could be provided after IRC-confirmed disease 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 PCYC-1145-LT to continue ibrutinib treatment.

Approximately 150 subjects were to be randomized in a 1:1 ratio to receive ibrutinib and rituximab (Ibr+R) or placebo and rituximab (Pbo+R). The randomization of treatment assignment was stratified using the following factors: WM International Prognostic Scoring System (IPSS) assessed at screening (low vs. intermediate vs. high), number of prior systemic treatment regimens (0 vs. 1-2 vs. ≥ 3), and Eastern Cooperative Oncology Group performance status (ECOG PS) (0-1 vs. 2). Up to 30 subjects were to be enrolled in the open-label ibrutinib monotherapy substudy.

Study PCYC-1127-CA was initiated on 07 July 2014. An interim analysis was conducted with a clinical cut-off date of 17 October 2017 with 56 PFS events representing 79% of the planned total PFS events. Significance level of two-sided alpha 0.023 for the interim analysis was determined based on the actual number of IRC-confirmed PFS events using O'Brien-Fleming boundary. This interim analysis crossed the superiority boundary and therefore, was considered as the primary PFS analysis for the study, triggered by data monitoring committee recommendation after the review of interim efficacy analysis results. The primary analysis CSR was completed on 22 February 2018 with a clinical data cutoff date of 17 October 2017.

The final analysis was based on the final database lock date of 18 December 2019. This final CSR describes approximately 2 years of additional follow up data since the primary analysis.

Number of Subjects (planned and analyzed):

Randomized study

Approximately 150 subjects were planned to be randomized in this study. A total of 150 subjects were randomized, 75 subjects to Ibr+R and 75 subjects to Pbo+R, and composed the Intent-to-Treat Population which was used for efficacy analyses. All randomized subjects received at least 1 dose of study treatment, and composed the Safety Population used for safety analyses.

Open-label substudy

Up to 30 subjects were planned to be enrolled in the open-label substudy. Thirty-one subjects were enrolled in the open-label substudy, all of whom received at least 1 dose of ibrutinib and composed the all treated subjects/safety population used for efficacy and safety analyses.

Diagnosis and Main Criteria for Inclusion:

Randomized study

Eligible subjects were ≥ 18 years of age with untreated WM or previously treated WM (previously treated subjects must have had either documented disease progression or had no response [stable disease] to the most recent treatment regimen), centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second IWWM, measurable disease defined as serum monoclonal immunoglobulin M (IgM) > 0.5 g/dL, symptomatic disease meeting at least 1 of the recommendations from the Second IWWM for requiring treatment, adequate hematologic, hepatic, and renal function, prothrombin time/international normalized ratio levels as defined in the protocol, and ECOG PS ≤ 2. Subjects treated with rituximab within the last 12 months were excluded, as were subjects who had relapsed after the last rituximab-containing therapy (defined as relapse < 12 months since last dose or failure to achieve at least a minor response [MR] [≥ 25% reduction but < 50% reduction of serum IgM

from baseline]). Other key exclusion criteria included known involvement of the central nervous system by WM.

Open-label substudy

Eligible subjects must have met the inclusion criteria for the randomized study, and in addition, had disease that was refractory to the last prior rituximab-containing therapy (defined as either relapse after the last rituximab-containing therapy < 12 months since last dose of rituximab, or failure to achieve at least a MR after the last rituximab-containing therapy).

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib was supplied as 140 mg hard gelatin capsules for oral administration. Subjects assigned to the Ibr+R arm in the randomized study received 420 mg ibrutinib (3 capsules) daily in combination with rituximab. Subjects enrolled in the open-label substudy received 420 mg ibrutinib daily. The ibrutinib lot numbers used in the study were 2850071.R011, 2850071.R012, 2850071.R013, L0404313, L0404313G, L0404955, L0406976A, L0500397A, L0502215B, L0503302C, L0506525A, L0507576A, L0602632A, L0602632A7, and L0605099C1.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo was supplied as hard gelatin capsules that looked identical to ibrutinib capsules. Subjects assigned to the Pbo+R arm received placebo (3 capsules) daily in addition to rituximab.

Duration of Treatment: Subjects in the randomized study were to receive study drug (ibrutinib or placebo) daily in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was to be administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (Weeks 1 to 4), followed by a second course of weekly rituximab for 4 consecutive weeks (Weeks 17 to 20). Subjects in the open-label substudy were to receive ibrutinib daily until disease progression or unacceptable toxicity.

Endpoints: The primary endpoint was PFS as assessed by the IRC. Secondary endpoints were response rate (≥ PR) as assessed by the IRC, TTnT, rate of sustained Hgb improvement, proportion of subjects with ≥ 3 points increase from baseline by Week 25 in the FACIT-Fatigue subscale score, and OS. Safety endpoints included treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and eye-related symptoms.

For the final analysis, additional analyses included in the final CSR were 1) PFS after subsequent antineoplastic therapy (PFS2), defined as duration of time from date of randomization to the date of the earliest of the following events: a) progressive disease per investigator response assessment after administration of the first subsequent antineoplastic therapy, b) death at any time on study due to any cause, or c) initiation of a second subsequent antineoplastic therapy, and 2) OS for subjects initially randomized to Pbo+R receiving ibrutinib post-progression.

Statistical Methods:

All efficacy and safety analyses and statistical methods that were performed previously for the primary CSR were repeated for the randomized study and for the open-label substudy for the final analysis.

The additional analyses to support this final CSR were: 1) PFS2, 2) OS for subjects initially randomized to Pbo+R receiving ibrutinib post-progression, and 3) prevalence of TEAEs. Overall survival for subjects initially randomized to Pbo+R receiving ibrutinib post-progression and PFS2 were estimated by Kaplan-Meier (KM) method. The Ibr+R arm from the randomized study and the ibrutinib monotherapy arm from

the open-label substudy were pooled for safety analyses (based on prevalence) in this CSR. The summaries of exposure, TEAEs, and laboratory data were presented by ibrutinib exposure intervals of 0-1 year, 1-2 years, 2-3 years, 3-4 years, 4-5 years, and overall (0-5 years). Of the pooled subjects for safety, only 3 subjects received more than 5 years of ibrutinib treatment with a short duration (5.05, 5.06, and 5.09 years). Treatment-emergent adverse events after the first 5 years in these 3 subjects were not included in the 0-5 year prevalence analysis and were presented in a separate listing. The original safety analyses approach from the primary analysis CSR (based on incidence) were also repeated for the final analysis.

RESULTS:

The results are presented in the synopsis as follows: 1) randomized study (Ibr+R arm vs. Pbo+R arm) - subject disposition and efficacy; 2) open-label substudy (ibrutinib monotherapy arm) - subject disposition and efficacy; 3) safety analysis of pooled data from Ibr+R arm and ibrutinib monotherapy arm - subject disposition and long-term safety results.

RANDOMIZED STUDY (Ibr+R ARM vs. Pbo+R ARM) – SUBJECT DISPOSITION AND EFFICACY RESULTS

Subject Disposition: Seventy-five subjects were randomized to each treatment arm. As of the final analysis, all subjects had discontinued the study. The most common primary reasons for discontinuing the study in the Ibr+R arm were study closure by Sponsor (81.3%), death (9.3%), and withdrawal of consent (8.0%); and in the Pbo+R arm were study closure by Sponsor (74.7%), death (13.3%), and withdrawal of consent (8.0%). Of those who discontinued due to study closure by Sponsor at the time of the final analysis, 32 subjects (25 subjects in Ibr+R arm and 7 subjects in Pbo+R arm) who were still receiving ibrutinib as initial or subsequent study treatment were given an option to enroll in an extension study (PCYC-1145-LT) to continue ibrutinib treatment (data on file). With the final analysis, the median (range) time on study increased from 26.5 months (0.5+ to 38.9 months) for the primary analysis to 49.7 months (0.5+ to 62.9 months).

Efficacy Results: Based on an overall follow-up of up to 62.9 months (median 49.7 months), continued treatment in the Ibr+R arm has demonstrated ongoing clinical benefit as supported by the evidence of long-term PFS benefit and durable response rates. Importantly, treatment benefit was observed for both treatment-naive and previously treated subjects with WM. The PFS benefit (hazard ratio [HR]) was consistent for the primary and final analysis. The response rates were also consistent, with an increase of the VGPR rates at time of final analysis.

Primary efficacy analysis

- Treatment with Ibr+R reduced the risk of progression or death by 75.0% compared to Pbo+R (HR = 0.250, 95% CI: 0.148, 0.420; $p < 0.0001$).
    - The median PFS per IRC assessment was not reached for the Ibr+R arm and was 20.3 months for the Pbo+R arm. The KM point estimates of PFS per IRC assessment at 54 months were 68.0% for the Ibr+R arm and 25.3% for the Pbo+R arm. The PFS benefit (HR) was consistent for the primary and final analyses.
    - Sensitivity analysis of PFS using investigator assessment (HR = 0.208, $p < 0.0001$) was consistent with the final analysis of primary endpoint.

- The treatment effect was robust across pre-specified subgroups; importantly, the treatment effect was observed in both treatment-naive and previously treated subjects. The PFS HRs were 0.315 (95% CI: 0.142, 0.695) and 0.222 (95% CI: 0.114, 0.433) for treatment-naive and previously treated subjects, respectively. The PFS HRs were 0.235 (95% CI: 0.132, 0.419) and 0.290 (95% CI: 0.071, 1.189) for subjects with and without the MYD88 L265P mutation, respectively.

Secondary efficacy analyses

- The response rate (≥ PR) per IRC assessment was higher for the Ibr+R arm (76.0%) than the Pbo+R arm (30.7%) ($p < 0.0001$), which is in alignment with the investigator-assessed response rate. The best responses per IRC assessment in the Ibr+R arm were complete response (CR) (1.3%), very good partial response (VGPR) (29.3%), and PR (45.3%). The response rate was higher compared to the primary analysis (76.0% vs. 72.0%) due to an increase in VGPR (29.3% vs. 22.7%).
  - The response rates in the Ibr+R arm were 76.5% and 75.6% for treatment-naive and previously treated subjects, respectively. The response rates in the Pbo+R arm were 41.2% and 22.0% for treatment-naive and previously treated subjects, respectively.
  - The response rates in the Ibr+R arm were 79.3% and 72.7% for subjects with and without the MYD88 L265P mutation, respectively. The response rates in the Pbo+R arm were 32.8% and 22.2% for subjects with and without the MYD88 L265P mutation, respectively.
- TTnT demonstrated an HR of 0.102 (95% CI: 0.049, 0.212, $p < 0.0001$) for the Ibr+R arm vs. the Pbo+R arm and was similar to the results of the primary analysis. The median TTnT was not reached for the Ibr+R arm and was 18.1 months (95% CI: 11.1, 33.1) for the Pbo+R arm. At the 54-month landmark timepoint, an estimated 87.4% of subjects in the Ibr+R arm and 29.4% of subjects in the Pbo+R arm had not received subsequent treatment.
- The proportion of subjects with a sustained Hgb improvement was higher in the Ibr+R arm: 77.3% Ibr+R vs. 42.7% Pbo+R, rate ratio = 1.813 (95% CI: 1.357, 2.421), $p < 0.0001$, which was similar to the primary analysis.
- The proportion of subjects with a ≥ 3-point increase from baseline by Week 25 in the FACIT-Fatigue subscale score was 68.0% in Ibr+R arm and 54.7% in Pbo+R arm ($p = 0.1059$), and remains unchanged from the primary analysis.
- The median OS was not reached for both the Ibr+R and Pbo+R arms and a positive trend in favor of the Ibr+R arm was observed (HR = 0.808, 95% CI: 0.328, 1.990, $p = 0.6430$). The 54-month KM OS rates were 86.4% in Ibr+R arm and 84.2% in Pbo+R arm.

OPEN-LABEL SUBSTUDY (IBRUTINIB MONOTHERAPY ARM) – SUBJECT DISPOSITION AND EFFICACY RESULTS

Subject Disposition: Thirty-one subjects refractory to prior rituximab-based therapy were enrolled and treated with ibrutinib monotherapy. As of the final analysis, all subjects (100%) had discontinued ibrutinib. The primary reasons for ibrutinib discontinuation were study closure by Sponsor (45.2%), progressive disease (41.9%), adverse event [AE] (6.5%), and withdrawal by subject (6.5%). As of the final analysis, 67.7% of subjects had discontinued the open-label substudy due to study closure by Sponsor, and 25.8% of subjects due to death. Of those who discontinued due to study closure by Sponsor at the time of the final analysis, 8 subjects who were still receiving ibrutinib were given an option to enroll in an extension study (PCYC-1145-LT) to continue ibrutinib treatment (data on file). With the

final analysis, the median (range) time on study increased from 34.4 months (8.6+ to 37.7 months) for the primary analysis to 57.9 months (8.6+ to 61.1 months).

Efficacy Results: Based on an overall follow-up of up to 61.1 months (median 57.9 months), treatment with ibrutinib monotherapy resulted in durable response rates. The response rate was higher compared to that of the primary analysis due to an increase in PR.

Primary efficacy analysis – Open-label substudy

- Median PFS per IRC assessment was 38.7 months (95% CI: 25.0, NE); the 36-month and 60-month landmark estimates were 50.6% (95% CI: 31.8, 66.7) and 39.7% (95% CI: 22.3, 56.7), respectively.

Secondary efficacy analyses – Open-label substudy

- Response rates per IRC assessment were 77.4% (95% CI: 58.9, 90.4); best overall responses included CR (0%), VGPR (29.0%), and PR (48.4%). The response rate was higher compared to the primary analysis (77.4% vs. 71.0%) due to an increase in PR (48.4% vs. 41.9%).
    - The response rate per investigator assessment was also 77.4% (95% CI: 58.9, 90.4); best overall responses included CR (0%), VGPR (25.8%), and PR (51.6%).
- Ten of the 31 subjects (32.3%) received subsequent treatment. The median TTnT was not reached; at the 60-month landmark estimate, 64.6% had not received subsequent treatment.
- The proportion of subjects with sustained Hgb improvement was 71.0%. For subjects with baseline Hgb ≤110 g/L (n = 21), the proportion of subjects with sustained Hgb improvement was 81.0%. This remains unchanged from the primary analysis.
- Overall, 87.1% of subjects had a ≥ 3 points increase from baseline in the FACIT-Fatigue subscale score, and this remains unchanged from the primary analysis.
- Median OS was not reached; the KM point estimate of the OS rate at 60 months was 73.4%.

SAFETY ANALYSIS OF POOLED DATA FROM IBR+R ARM AND IBRUTINIB MONOTHERAPY ARM – SUBJECT DISPOSITION AND LONG-TERM SAFETY RESULTS

Subject Disposition: A total of 106 subjects were included in the safety population composed of the Ibr+R arm (n = 75) and ibrutinib monotherapy arm (n = 31) pooled. All subjects (100%) discontinued study treatment, and 31.1% (n = 33) of subjects rolled over to study PCYC-1145-LT. The most common primary reasons for discontinuing ibrutinib were study closure by Sponsor (57.5%), progressive disease (18.9%), withdrawal by subject (11.3%), and AEs (9.4%). The median (range) time on study was 51.7 months (4.6 to 62.9 months).

Safety Results: The results from this analysis indicated that, during the first 5 years of treatment, ibrutinib in combination with rituximab or as single agent in subjects with WM is associated with an acceptable safety and tolerability profile. The overall known safety profile of ibrutinib-treated subjects remained consistent over the 5-year period, with no new safety concerns identified.

- The prevalence of TEAEs (any grade) was 97.2% in the first period, 95.8% in the second period, 90.4% in the third period, 90.1% in the fourth period, and 75.9% in the fifth period. The most

common TEAEs of any grade (≥ 25% overall) were diarrhea, infusion related reaction, arthralgia, and hypertension.

- The prevalence of TEAEs Grade 3 or higher was 56.6% in the first period, 32.3% in the second period, 36.1% in the third period, 39.4% in the fourth period, and 22.2% in the fifth period. The most common TEAEs Grade 3 or higher (≥ 10% overall) were neutropenia, hypertension, anemia, and atrial fibrillation.

- The prevalence of serious TEAEs was 36.8% in the first period, 16.7% in the second period, 16.9% in the third period, 18.3% in the fourth period, and 9.3% in the fifth period. The most common serious adverse events (SAEs) (≥ 5% overall) were pneumonia and atrial fibrillation.

- One TEAE resulted in death overall: pneumonia (0.9% overall).

- The percentage of subjects with TEAEs leading to treatment discontinuation (ie, primary reason for discontinuation) was 2.8% in the first period, 2.1% in the second period, 2.4% in the third period, 2.8% in the fourth period, and 1.9% in the fifth period. The most common TEAEs as the primary reason for ibrutinib discontinuation (≥ 1% overall) was atrial fibrillation.

- The overall incidence of hemorrhage was 50.9%. The overall incidence of major hemorrhage was 4.7%.

- The overall incidence of atrial fibrillation was 13.2%. The prevalence of atrial fibrillation was stable or decreasing over time.

- The overall incidence of hypertension was 28.3%. Hypertension (as a grouped term) was slightly increased from the first period (16.0%) to the second period (19.8%) and then remained stable.

Conclusions:

Based on an overall follow-up of up to 62.9 months for randomized subjects, continued treatment in the Ibr+R arm has demonstrated ongoing benefit in patients with WM, as supported by the evidence of long-term PFS and durable response rates. Importantly, treatment benefit was uniformly observed for treatment-naive and previously treated subjects with WM. The PFS benefit (HR) was consistent for the primary and final analysis. The response rates were also consistent, with an increase of the VGPR rates at time of final analysis. In the final analysis of OS, a positive survival trend was observed.

Favorable long-term efficacy for rituximab-refractory subjects was demonstrated with ibrutinib monotherapy.

Based on the totality of the data, ibrutinib as single agent or in combination with rituximab is associated with an acceptable safety and tolerability profile in subjects with WM. No new safety concerns were identified over the long-term.

Ibrutinib continues to demonstrate a favorable overall benefit-risk profile with long-term treatment.