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A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia

Study Dates: First subject enrolled: 28 July 2015
Last subject enrolled: 31 October 2017
The analyses presented in this report are based on a CCI

Phase of Development: 3

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study Centers

This study was conducted at 124 study centers in 15 countries.

Publications

None at the time of this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective	Endpoint/Variable
Primary Objective	
To assess whether acalabrutinib is non-inferior to ibrutinib with respect to PFS, based on IRC assessment, in subjects with R/R CLL with high-risk prognostic markers.	PFS, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause. KM curve was used to estimate the distribution of PFS and a stratified Cox proportional hazards model was used to estimate the HR.
Secondary Objectives	
To evaluate the benefit:risk of acalabrutinib versus ibrutinib in terms of: • Grade ≥ 3 infections • Richter's transformation • Atrial fibrillation • OS	The incidences of treatment-emergent Grade ≥ 3 infections, Richter's transformation, and atrial fibrillation were compared between the 2 treatment arms. OS was defined as the time from date of randomization to date of death due to any cause.
Safety Objective	
The safety and tolerability including AEs of interest and laboratory assessments.	Safety and tolerability were assessed by the incidence of TEAEs, changes in laboratory parameters and vital signs from baseline, analysis of lymphocytosis, ECG, and ECOG performance status.

Objective	Endpoint/Variable
Exploratory Objectives	
CCI [redacted]	
Additional Exploratory Objectives (see Section 9.9.2)	
CCI [redacted]	

Abbreviations: AE=adverse event; CLL = chronic lymphocytic leukemia; CCI [redacted]
ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IRC = Independent Review Committee; CCI [redacted] KM = Kaplan-Meier; CCI [redacted] OS = overall survival; PFS = progression-free survival; CCI [redacted] R/R = relapsed/refractory; TEAE = treatment-emergent adverse event.

Study Design

This is an ongoing, randomized, multicenter, open-label, non-inferiority Phase 3 study designed to evaluate the efficacy and safety of acalabrutinib (100 mg twice daily [BID]) versus ibrutinib (420 mg once daily [QD]) in subjects with relapsed/refractory (R/R) chronic

lymphocytic leukemia (CLL) who had high-risk prognostic markers (eg, 17p deletion and/or 11q deletion) per National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2019). The primary endpoint is progression-free survival (PFS) based on Independent Review Committee (IRC) assessment.

Subjects were randomized in a 1:1 ratio into 2 arms to receive either acalabrutinib 100 mg BID (Arm A) or ibrutinib 420 mg QD (Arm B).

Subjects were randomized based on the following stratification factors: presence of 17p deletion (yes versus no), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), and number of prior therapies (1-3 versus ≥ 4).

Subject participation included a Screening Phase, a Treatment Phase, a Post-treatment Phase, and a Post-disease Progression Phase. During the Screening Phase (up to 28 days before first dose of study drug), the subject's eligibility and baseline characteristics were determined. During the Treatment Phase (from randomization until study drug discontinuation), subjects received study drug daily until disease progression or unacceptable toxicity. During the Post-treatment Phase, subjects were followed for disease progression or death, unless they withdrew consent or were lost to follow-up.

The Post-disease Progression Phase began once the IRC confirmed that a subject had progressive disease (PD). In this phase, subsequent anticancer therapy with start date of therapy, International Workshop on Chronic Lymphocytic Leukemia (IWCLL) indication for treatment initiation, additional malignancy occurrence, and subject survival status were recorded. The Post-disease Progression Phase continued until death, loss to follow-up, consent withdrawal, or study closure, whichever occurred first. Survival status and the date of death were documented for each subject randomized to treatment, regardless of whether or not the subject received treatment.

Assessment of response and progression were conducted in accordance with the IWCLL 2008 criteria with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression was not to be considered PD. The investigator evaluated sites of disease by radiologic imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline were to be used throughout the study. Response evaluations were done every 12 weeks from Week 1 Day 1 through Week 100, and then every 24 weeks thereafter until disease progression regardless of whether or not a subject had discontinued study drug. Hematology results were done within 7 days of computed tomography (CT) scans.

The primary efficacy analysis was based on assessment from an IRC. As part of the IRC review, radiographic evaluations assessed by independent central radiologists and hematology

results from a central laboratory were provided. An independent Data Monitoring Committee (DMC) was formed and constituted according to regulatory agency guidelines. The DMC reviewed the safety data periodically and provided recommendations according to the DMC charter.

An Early Termination visit was done for subjects who permanently discontinued study drug early for any reason. A Safety Follow-up visit was conducted 30 (+ 7) days after the last dose of study drug unless a subject received a new anticancer therapy within this timeframe.

The end of trial was defined as the point when the last subject on study had completed CCI of follow-up or had been lost to follow-up, whichever occurred first.

Target Subject Population and Sample Size

Diagnosis and Main Criteria for Inclusion

Adult subjects with CLL that met published IWCLL 2008 criteria for diagnosis and for requiring treatment, who had received ≥ 1 prior systemic therapies for CLL, and who had 17p deletion and/or 11q deletion documented by a central laboratory.

Number of Subjects (Planned and Analyzed)

The study was planned to enroll approximately 500 subjects. A total of 533 subjects were randomized and all 533 subjects were analyzed.

Investigational Product and Comparator: Dosage, Mode of Administration and Batch Numbers

Acalabrutinib: 100-mg capsules, administered orally at a dose of 100 mg BID (200 mg per day). For individual batch numbers, see Appendix 16.2.5.1.

Ibrutinib: 140-mg capsules, administered orally at a dose of 420 mg QD.

Duration of Treatment

Subjects received acalabrutinib or ibrutinib until unacceptable drug-related toxicity or disease progression.

Statistical Methods

Determination of Non-Inferiority Margin and Sample Size

The non-inferiority (NI) margin of CCI with regard to median PFS, was selected to ensure that the efficacy of acalabrutinib would not be substantially inferior to ibrutinib in the event of a positive statistical outcome for the study. Assuming the median PFS for the ibrutinib arm

was [redacted] and the time-to-event was exponentially distributed, a [redacted] in median PFS would be [redacted] for acalabrutinib.

The [redacted] for median PFS translates into a hazard ratio (HR) scale margin of 1.429, which was selected using the fixed margin method described in the United States FDA Guidance for Industry: Non-Inferiority Clinical Trials (2010). This method, which is also in line with Committee for Medicinal Products for Human Use (CHMP) Guidance on the Choice of the Non-inferiority Margin (2005), uses a 2-step procedure to select the NI margin:

1. Determine M_1 (as per FDA terminology), the entire effect of the active control (ibrutinib) assumed to be present in the NI study from historical data;

2. Determine M_2 (as per FDA terminology), the largest clinically acceptable difference (degree of inferiority) of the test drug (acalabrutinib) compared to the active control (ibrutinib).

As the FDA Guidance describes, M_2, the pre-specified NI margin the non-inferiority study should meet, must never be greater than M_1.

Ofatumumab is currently used for the treatment of patients with CLL. In the RESONATE study (Byrd et al 2014), ibrutinib demonstrated superiority over ofatumumab in PFS in an all-comers setting as well as in patients in the high-risk 17p deletion and 11q deletion populations. The results of the study provide the basis for choosing the NI margin. [redacted] is estimated to be [redacted] The [redacted] is used to account for the lack of information on study-to-study variability from a single historical study. The [redacted] translates into the [redacted]

Based on the median PFS for subjects with 17p deletion or 11q deletion treated with ibrutinib in the Phase 2 study (Byrd et al 2013), we assumed the median PFS of ibrutinib in this study would be approximately [redacted] As described above, the [redacted] on median PFS translates into a HR of 1.429 (M_2) for acalabrutinib versus ibrutinib. The selected M_2 of 1.429 [redacted]

Assuming [redacted] for PFS and an NI margin of 1.429, a sample size of 500 subjects (randomized 1:1 to each of the 2 arms) would provide 80% power at a 1-sided, 0.025 significance level to test the non-inferiority hypothesis. The accrual period was assumed to be about [redacted] with a follow-up period of approximately [redacted] after the last subject entered the study. The calculation assumed over the course of the study, [redacted] The NI test was to be performed when approximately 250 PFS

events had been observed. Based on these assumptions, the CCI [redacted]

Analysis Methods

The primary efficacy endpoint was PFS, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first. Analyses were based on the intent-to-treat (ITT) population, defined as all randomized subjects, to be analyzed according to the arm to which they were randomly assigned. The estimate of the HR (acalabrutinib/ibrutinib) and its corresponding 95% CI were computed using a Cox proportional hazards model stratified by the following randomization stratification factors: 17p deletion (yes versus no) and number of prior therapies (1 to 3 versus ≥ 4). If the upper bound of the 2-sided 95% CI for the HR was below 1.429, acalabrutinib was to be concluded to be non-inferior to ibrutinib. Kaplan-Meier (KM) curves were used to estimate the distribution of PFS. The proportion of subjects who were progression-free and the corresponding 95% CI were estimated based on the KM method at select time points. Sensitivity analyses in support of the primary analysis of PFS included unstratified analysis, analysis including PFS without censoring for subsequent anticancer therapy, analysis including PFS events after 2 or more consecutively missed visits, analysis including only subjects in the per protocol population, and an (ad hoc) evaluation of the impact of deaths caused by COVID-19 on PFS. Selected subgroup analyses (including age, race, sex, geographic region, presence of chromosomal abnormalities, number of prior therapies, and baseline disease status) were also performed.

Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. OS was analyzed using the ITT population. OS was analyzed in the same fashion as that for primary efficacy endpoint as described above. A stratified log rank test was performed, adjusting for the randomization stratification factors used for the primary analysis. Additionally, a subgroup analysis was performed for OS.

Analysis of the incidences of treatment-emergent Grade ≥ 3 infections, Richter's transformation (assessed by central pathology), and atrial fibrillation were based on the safety population, and were summarized and compared between the 2 treatment arms using 2-sided Cochran-Mantel-Haenszel tests adjusted for the same randomization strata used for the primary analysis of PFS. In addition, subgroup analyses were performed for each endpoint. For each endpoint, the risk difference (Arm A – Arm B) and its corresponding 95% CI for each subgroup were calculated based on normal approximation (with use of Wilson's score).

Subject Population

The study enrolled and randomized 533 subjects in the acalabrutinib arm (N=268) and ibrutinib arm (N=265). Four randomized subjects were not treated with study drug and thus

were excluded from the safety population (3 randomized to acalabrutinib and 1 randomized to ibrutinib). Subjects in the safety population were analyzed as treated; per the Statistical Analysis Plan (SAP), if a subject incorrectly received both acalabrutinib and ibrutinib in any amount, the subject was analyzed under the acalabrutinib arm. One subject randomized to the ibrutinib treatment arm was inadvertently administered acalabrutinib for 21 days starting on the day of randomization, then subsequently administered ibrutinib for 82 days before discontinuing treatment due to medical monitor instruction, and was analyzed in the acalabrutinib safety population. As of the CCI 141 (52.6%) subjects in the acalabrutinib arm and 155 (58.5%) subjects in the ibrutinib arm had discontinued randomized study treatment. With a median follow-up of 41.1 months in the acalabrutinib arm and 40.7 months in the ibrutinib arm, 335 (62.9%) subjects in both arms were still on study.

Demographic and baseline characteristics were generally well balanced and there were no noteworthy differences between treatment arms. The median age for all subjects was 66 years (range: 28 to 89). Almost three-quarters (71.1%) of subjects were male, 94.2% were white, and 88.6% were not Hispanic or Latino.

Summary of Efficacy Results

Acalabrutinib demonstrated non-inferior IRC-assessed PFS in this study compared with ibrutinib, with a HR of 1.00 (95% CI: 0.79, 1.27). The median PFS for acalabrutinib was 38.4 months (95% CI: 33.0, 38.6); the median PFS for ibrutinib was 38.4 months (95% CI: 33.0, 41.6). The KM estimate of the proportion of subjects without a PFS event in the acalabrutinib and ibrutinib arms, respectively, was 51.4% (95% CI: 44.7, 57.8) and 53.8% (95% CI: 47.0, 60.1) at 36 months.

Acalabrutinib demonstrated generally consistent efficacy in terms of IRC-assessed PFS compared with ibrutinib for most subgroups associated with poor prognosis with HR ranging from 0.69 to 1.25, including subjects with 17p deletion, subjects with ≥ 4 prior therapies, subjects aged ≥ 65 years, subjects ≥ 75 years, bulky disease ≥ 5 cm, Rai stage III-IV, cytopenia present at baseline, subjects with 11q deletion, subjects with TP53 mutation, subjects with unmutated immunoglobulin heavy-chain variable (IGHV), subjects with complex karyotype, and B2-microglobulin > 3.5 mg/L at baseline.

All sensitivity analyses of IRC-assessed PFS, including the key sensitivity analysis of PFS without censoring for subsequent anticancer therapy, were consistent with the primary analysis, with HR ranging from 0.99 to 1.01.

Treatment-emergent atrial fibrillation (including the Preferred term [PT] atrial flutter) was reported in 9.4% of subjects in the acalabrutinib arm and 16.0% of subjects in the ibrutinib arm, which was statistically significant (p = 0.0228).

Treatment-emergent Grade ≥ 3 infections were reported in 30.8% of subjects in the acalabrutinib arm and 30.0% of subjects in the ibrutinib arm, which was not statistically significant (p = 0.8777). Treatment-emergent Richter's transformation was reported in 10 (3.8%) subjects in the acalabrutinib arm and 13 (4.9%) subjects in the ibrutinib arm.

The median OS was not reached in either treatment arm, with a HR of 0.82 (95% CI: 0.59, 1.15). The KM estimate of OS at 36 months for acalabrutinib and ibrutinib, respectively, was 80.7% (95% CI: 75.2, 85.0) and 75.8% (95% CI: 70.0, 80.7).

Summary of CCI [redacted]

CCI [redacted]

Summary of CCI [redacted]

CCI [redacted]

Summary of Safety Results

The median duration of acalabrutinib treatment was 38.3 months (range: 0.3 to 55.9), with 86.5% of subjects receiving ≥ 1 year of therapy. The median duration of ibrutinib treatment was 35.5 months (range: 0.2 to 57.7), with 76.4% of subjects receiving ≥ 1 year of therapy.

Common treatment-emergent adverse events (TEAEs) that occurred in ≥ 10% of subjects in either the acalabrutinib or ibrutinib arm, respectively, were diarrhoea (34.6% and 46.0%), headache (34.6% and 20.2%), cough (28.9% and 21.3%), upper respiratory tract infection (26.7% and 24.7%), pyrexia (23.3% and 19.0%), anaemia (21.8% and 18.6%), neutropenia (21.1% and 24.7%), fatigue (20.3% and 16.7%), nausea (17.7% and 18.6%), pneumonia (17.7% and 16.3%), arthralgia (15.8% and 22.8%), thrombocytopenia (15.0% and 13.3%), dyspnoea (13.9% and 8.7%), bronchitis (12.8% and 8.7%), constipation (11.7% and 14.1%), contusion (11.7% and 18.3%), nasopharyngitis (10.9% and 10.3%), dizziness (10.5% and 9.9%), vomiting (10.5% and 13.7%), oedema peripheral (9.8% and 14.4%), rash (9.8% and 12.5%), myalgia (9.4% and 10.3%), atrial fibrillation (9.0% and 15.6%), hypertension (8.6% and 22.8%), urinary tract infection (8.3% and 13.7%), back pain (7.5% and 12.9%), epistaxis (7.1% and 10.6%), muscle spasms (6.0% and 13.3%), and dyspepsia (3.8% and 12.2%). Most TEAEs in both treatment groups were Grade 1 or 2.

Grade ≥ 3 TEAEs were reported in a lower proportion of subjects in the acalabrutinib arm (68.8%) compared with the ibrutinib arm (74.9%), and this trend was consistent across most prognostic subgroups. The most common Grade ≥ 3 TEAE in both treatment arms was neutropenia, reported in 19.5% and 22.8% of acalabrutinib and ibrutinib subjects, respectively, followed by anaemia (11.7% and 12.9%, respectively) and pneumonia (10.5% and 8.7%, respectively).

Grade 5 TEAEs occurred in 20 (7.5%) subjects in the acalabrutinib arm and 28 (10.6%) subjects in the ibrutinib arm. Treatment-related Grade 5 TEAEs were reported in 3 acalabrutinib-treated subjects (pneumonia in 2 subjects and haemorrhage intracranial in 1 subject) and 4 ibrutinib-treated subjects (tumour lysis syndrome, upper respiratory tract infection, pneumonia bacterial, and haemophagocytic lymphohistiocytosis).

TEAEs reported as related to study treatment were reported in 76.3% of subjects in the acalabrutinib arm and 84.8% of subjects in the ibrutinib arm. In the acalabrutinib arm, the most common (≥ 10%) treatment-related TEAE was headache (22.2%), followed by neutropenia (18.0%) and diarrhoea (15.4%). In the ibrutinib arm, the most common treatment-related TEAE was diarrhoea (26.2%), followed by neutropenia (21.7%), arthralgia (14.8%), contusion (11.8%), atrial fibrillation (11.0%), and hypertension (10.3%).

Sixty-two (23.3%) treated subjects in the acalabrutinib arm and 73 (27.8%) treated subjects in the ibrutinib arm died as of the data cutoff date, including 28 (10.5%) and 30 (11.4%) subjects in the 2 arms, respectively, who died during the treatment-emergent period, and 34 (12.8%) and 43 (16.3%) subjects in the 2 arms, respectively, who died beyond the treatment-emergent period. The most common primary cause of death in both treatment groups was an AE, reported in 10.5% and 12.5% of subjects in the acalabrutinib and ibrutinib arms, respectively, followed by disease progression in 7.9% and 8.4% of subjects in the 2 arms, respectively.

Serious adverse events (SAEs) occurred in 53.8% and 58.6% of subjects in the acalabrutinib and ibrutinib arms, respectively. The most common SAE was pneumonia in both the acalabrutinib arm (10.2%) and the ibrutinib arm (9.9%). Treatment-related SAEs occurred in 19.5% of subjects in the acalabrutinib arm and 25.5% of subjects in the ibrutinib arm. The most common treatment-related SAE in the acalabrutinib arm was pneumonia (4.1%). The most common treatment-related SAE in the ibrutinib arm was atrial fibrillation (4.6%), followed by pneumonia (3.8%).

TEAEs that led to discontinuation of study treatment occurred in a lower proportion of subjects in the acalabrutinib arm (14.7%) compared with the ibrutinib arm (21.3%). Subgroup analysis showed that this trend was consistent across most subgroups associated with poor prognosis. In the acalabrutinib arm, the most common TEAE that led to study treatment discontinuation was anaemia in 3 (1.1%) subjects. In the ibrutinib arm, the most common

TEAE that led to study treatment discontinuation was atrial fibrillation (7 [2.7%]), followed by pneumonia (5 [1.9%]).

Most subjects had events of clinical interests (ECIs), which are events that have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitors. Atrial fibrillation (including atrial flutter) occurred in 24 (9.0%) acalabrutinib subjects compared with 42 (16.0%) ibrutinib subjects. Neutropenia events (including the PTs of neutropenia, febrile neutropenia, neutropenic sepsis, and neutrophil count decreased) occurred in 62 (23.3%) acalabrutinib subjects and 68 (25.9%) ibrutinib subjects. Hemorrhage events occurred in 101 (38.0%) acalabrutinib subjects compared with 135 (51.3%) ibrutinib subjects. Major hemorrhage was reported in 12 (4.5%) acalabrutinib subjects and 14 (5.3%) ibrutinib subjects. Hepatotoxicity events occurred in 15 (5.6%) acalabrutinib subjects and 22 (8.4%) ibrutinib subjects. Hypertension events occurred in 25 (9.4%) acalabrutinib subjects and 61 (23.2%) ibrutinib subjects. Infections occurred in 208 (78.2%) acalabrutinib subjects (82 [30.8%] with Grade ≥ 3 events) and 214 (81.4%) ibrutinib subjects (79 [30.0%] with Grade ≥ 3 events). Interstitial lung disease/pneumonitis occurred in 7 (2.6%) acalabrutinib subjects and 17 (6.5%) ibrutinib subjects. Treatment-emergent second primary malignancies occurred in 50 (18.8%) acalabrutinib subjects (23 [8.6%] with Grade ≥ 3 events) and 36 (13.7%) ibrutinib subjects (15 [5.7%] with Grade ≥ 3 events). Second primary malignancies excluding non-melanoma skin were reported in 24 (9.0%) and 20 (7.6%) subjects in the acalabrutinib and ibrutinib arms, respectively, with Grade ≥ 3 events reported in 16 (6.0%) and 14 (5.3%) subjects in the 2 treatment arms, respectively. Thirteen acalabrutinib-treated subjects had SAEs of second primary malignancies, including 1 subject with a Grade 5 event. Tumor lysis syndrome occurred in 1 subject in each treatment arm, including 1 Grade 5 event in an ibrutinib subject, considered related to study treatment.

There were no clinically significant mean changes in hematology or clinical laboratory values, serum immunoglobulin values, T/B/NK cell counts, or vital sign values over time in either treatment arm. In both treatment arms, a shift from baseline to higher Common Terminology Criteria for Adverse Events (CTCAE) grades was observed for some hematology parameters, including increased absolute lymphocyte count (ALC), decreased absolute neutrophil count (ANC), decreased hemoglobin, decreased platelets, and increased leukocytes. The frequency of hematologic abnormalities in the acalabrutinib and ibrutinib arms, respectively, was similar for ANC (45.1% and 49.4%), hemoglobin (49.6% and 46.0%), and platelets (41.7% and 43.3%). Lymphocytosis occurred in similar proportions of subjects in the acalabrutinib arm (72.5%) and ibrutinib arm (74.3%). There was 1 subject who met biochemical criteria for Hy's law.

Conclusions

In this study in subjects with high-risk R/R CLL, acalabrutinib demonstrated non-inferior IRC-assessed PFS compared to ibrutinib (HR of 1.00 [95% CI: 0.79, 1.27]). Primary efficacy was consistent across most prespecified subgroups. Subjects treated with acalabrutinib had a clinically meaningful and statistically significantly lower incidence of atrial fibrillation compared to subjects treated with ibrutinib. Acalabrutinib showed an acceptable safety and tolerability profile which is consistent with other acalabrutinib monotherapy clinical trials. The comparable efficacy and improved safety of acalabrutinib in this study demonstrated a favorable benefit:risk profile compared with ibrutinib.