Clinical Study Report	
Drug Substance	Acalabrutinib
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A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy

Study dates:
First subject enrolled: 08 March 2016
Last subject last visit: 16 October 2020
The analyses in this report are based on a database lock date of 16 December 2020.

Phase of development:
2

International Co-ordinating Investigator:
PPD
The Ohio State University
PPD
Columbus, OH 43210
USA

Sponsor's Responsible Medical Officer:
PPD
PPD
AstraZeneca Pharmaceuticals LP
PPD
South San Francisco, CA 94080
USA

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study centers

This study was conducted at 25 study centers in the United States, Belgium, Spain, France, the United Kingdom, and Israel.

Publications

Rogers KA, Thompson PA, Allan JN, et al. Phase 2 study of acalabrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. J Clin Oncol 2019;37(Suppl):Abstr 7530.

Rogers KA, Thompson PA, Allan JN et al. Phase 2 study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica 2021 [Epub ahead of print]. doi:10.3324/haematol.2020.272500.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoint/Variable
Primary Objective	
Evaluate the efficacy of acalabrutinib in subjects with relapsed/refractory CLL who were intolerant of ibrutinib therapy	Efficacy was evaluated based on the modified IWCLL 2008 criteria. The primary efficacy endpoint was: • Investigator-assessed ORR Secondary efficacy endpoints included: • Investigator-assessed DOR • Investigator-assessed PFS • Investigator-assessed TTNT • Investigator-assessed OS
Secondary Objective	
Evaluate the safety and tolerability of acalabrutinib in subjects with relapsed/refractory CLL who were intolerant of ibrutinib therapy	• Frequency, type, relationship, and severity of AEs based on the CTCAE v4.03 for both hematologic and nonhematologic AEs • Frequency of AEs leading to discontinuation of study drug • Laboratory assessments
Exploratory Objectives	
CCI [redacted]	

AE = adverse event; CCI [redacted] CLL = chronic lymphocytic leukemia; CTCAE v4.03 = Common Terminology Criteria for Adverse Events, Version 4.03; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; CCI [redacted] ORR = overall response rate; OS = overall survival; CCI [redacted] PFS = progression-free survival; CCI [redacted] TEAE = treatment-emergent adverse event; TTNT = time-to-next treatment.

Study design

This was a multicenter, open-label, nonrandomized, Phase 2 study evaluating the efficacy and safety of acalabrutinib in subjects with relapsed/refractory chronic lymphocytic leukemia (CLL; N = 60) who were intolerant of ibrutinib therapy. For this study, ibrutinib intolerant was defined as patients who could not tolerate, or no longer could tolerate, ibrutinib therapy due to adverse reactions associated with treatment. Such patients may have benefited from treatment with an

alternative Bruton tyrosine kinase (BTK) inhibitor with a more favorable safety profile than ibrutinib.

Subjects were considered ibrutinib intolerant (at any dose/or duration) if they had discontinued ibrutinib therapy due to Grade 3 or 4 adverse events (AEs) that persisted in spite of optimal supportive care measures (e.g., atrial fibrillation/flutter, cardiac arrhythmia, diarrhea, rash, ecchymosis, myalgia, or arthralgia), or if subjects had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures, that persisted for ≥2 weeks or that recurred ≥2 times, whether dose was reduced or discontinued. Subjects were treated with acalabrutinib 100 mg twice daily (BID). Treatment may have continued until disease progression or an unacceptable drug-related toxicity occurred.

Each treatment cycle consisted of 28 days (4 weeks). Radiologic tumor assessments were done at screening, at the end of Cycles 3, 6, 9, 12, 18, 24, and then every year thereafter, while receiving acalabrutinib treatment. Confirmation of complete response (CR) required bone marrow analysis and radiologic tumor assessment. Safety evaluations were done at every visit and consisted of assessment of AEs, physical examinations, and safety laboratory panels. Visits were every 2 weeks for the first 2 cycles, then monthly through the end of Cycle 6, then every 3 cycles thereafter. Subjects who discontinued study drug for any reason other than disease progression were followed for disease progression, regardless of whether the subject received new anticancer treatment. A treatment termination (TT) visit was required for safety assessments for any subject who permanently discontinued study drug for any reason (except for death, loss to follow-up, or withdrawal of consent), including disease progression, and was scheduled within 7 days of the last dose of study drug, if possible. In addition to the TT visit, all subjects who discontinued study drug had a safety follow-up (SFU) visit 30 (+7) days after the last dose of study drug.

All endpoints in this study were investigator assessed. Clinical sites were used to collect and store computed tomography (CT) scan images.

Target study population and sample size

The target study population was adult subjects with a diagnosis of CLL, which had relapsed after or was refractory to ≥1 previous treatment for CLL, who were intolerant of ibrutinib, and had documented disease progression after stopping ibrutinib.

The planned sample size was approximately 60 subjects. A total of 60 subjects were enrolled and treated.

Investigational product: dosage, mode of administration and batch numbers

Acalabrutinib 100-mg capsules, administered orally at a dose of 100 mg BID (200 mg per day). Individual batch numbers are listed in Appendix 16.1.6.

Duration of treatment

Subjects received acalabrutinib in 28-day continuous cycles. Treatment may have been continued until disease progression or an unacceptable drug-related toxicity occurred.

Statistical methods

Determination of sample size

CCI

[redacted]

Analysis methods

No formal tests of hypothesis were performed. Descriptive statistics were used to summarize data.

The All Treated Population included all enrolled subjects who received ≥1 dose of study drug and the efficacy and safety analyses were performed on the All Treated Population.

Efficacy analyses:

Response was assessed by investigators based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Response Assessment Criteria (2008).

The primary endpoint was investigator-assessed ORR. ORR was defined as the proportion of subjects achieving a best overall response of either CR, complete remission with incomplete bone marrow recovery (CRi), partial response (PR), or partial response with lymphocytosis (PRL) at or before initiation of subsequent anticancer therapy. ORR and the associated 95% exact (Clopper-Pearson) CI were provided.

Secondary endpoints:

- Progression-free survival (PFS) was defined as the time from the date of first dose to the date of first disease progression or death due to any cause, whichever came first. If a subject did not have disease progression or death, the data were censored at the date of last adequate assessment (censoring date). If a subject started new anticancer therapy before disease progression or death, the subject was censored at the date of last adequate assessment prior to receiving the new anticancer therapy. Adequate assessment was defined as physical examination and complete blood count (CBC) or CT and CBC. If a subject did not have any adequate assessment after first dose, the subject was censored at Day 1.

- Duration of response (DOR) was defined as the time from the date of achieving the first CR, CRi, PR, or PRL to the date of disease progression or death due to any cause, whichever came first. Subjects who did not have a disease progression or death were censored using the same rules as PFS.

- Time-to-next treatment (TTNT) was defined as the time from date of first acalabrutinib treatment to date of institution of subsequent anticancer therapy for CLL or death due to any cause, whichever came first. Subjects who did not have the above-specified events prior to the data cutoff date were censored at the date of last visit.

- Overall survival (OS) was defined as the time from date of first dose date to date of death due to any cause. Subjects who did not have a confirmed death at or prior to the analysis data cutoff date were censored.

Safety Analyses:

- AEs were coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) reporting system at the time of the database lock. The investigator graded AEs according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for AEs. Hematologic toxicity was assessed by the grading scale in the IWCLL 2008 and NCI CTCAE v4.03. Treatment-emergent adverse events (TEAEs) were defined as those events that occurred on or after the first dose of study drug through the treatment phase and within 30 days following the last dose of study drug. The occurrence of AEs was presented by System Organ Class and Preferred Term. If a subject experienced the same event more than once, the event was counted only once under the maximum severity (in tabulation). AEs were presented by relationship and by severity. The investigator judged each event to be "not related" or "related" to study treatment.

- Descriptive statistics summarized laboratory data (hematology and serum chemistry) and vital signs. CCI and serum immunoglobulin were displayed over time. For all subjects with baseline and any postbaseline absolute lymphocyte count (ALC) measurements, ALC at peak summary was provided. Median percent change in ALC from baseline along with its 95% confidence interval (CI) also were displayed graphically overall time.

Study population

A total of 60 subjects were enrolled in the study in the All Treated Population. All 60 subjects exited the study; the primary reasons for study exit were study terminated by sponsor (66.7%), death (21.7%), and withdrawal by subjects (10.0%). The median time on study was 41.1 months (range: 1.1-54.8 months).

The median age of subjects was 69.5 years (range: 43.0-88.0). Most of the subjects enrolled were white (93.3%), male (63.3%), and not Hispanic or Latino (90.0%). The median time from initial CLL diagnosis to first dose of study treatment was 9.0 years (range: 0.86-25.66). Poor prognostic characteristics at baseline included presence of 17p deletion (del) or 11q del (43.3%), unmutated immunoglobulin heavy-chain variable (IgHV; 76.7%), and Rai Stage III-IV (46.7%). Approximately half of the subjects (51.7%) had cytopenia at baseline, including low platelets (35.0%), low hemoglobin (30.0%), and/or low ANC (11.7%).

Summary of efficacy results

Efficacy conclusions from 60 subjects with CLL, with a median time on study of 41.1 months are summarized as follows:

- Investigator-Assessed ORR:
    - The ORR (CR+CRi+PR) was 70.0% (95% CI: 56.8, 81.2) with 2 subjects achieving CR and 40 subjects achieving PR.
    - The ORR including PRL was 78.3% (95% CI: 65.8, 87.9) with 5 subjects achieving PRL.
- Investigator-Assessed PFS:
    - The median estimated PFS was not estimable (NE; 95% CI: 33.7, NE). The Kaplan-Meier (KM) estimate of the proportion of subjects without a PFS event was 70.6% (95% CI: 56.5, 80.8) at 24 months, 57.7% (95% CI: 42.9, 69.9) at 36 months, and 53.3% (37.2, 66.9) at 48 months.
- Investigator-Assessed DOR:
    - The median DOR based on investigator assessment was NE (95% CI: 29.9, NE). The KM estimate of the proportion of responders without a PD or death event was 85.6% (95% CI: 70.8, 93.3) at 12 months, 83.2% (95% CI: 68.0, 91.6) at 24 months, and 64.9% (95% CI: 45.6, 78.8) at 36 months.
- Investigator-Assessed TTNT
    - The median TTNT based on investigator assessment was 44.0 months (95% CI: 27.4, NE). The KM estimate of the proportion of subjects without a next treatment was 82.7% (95% CI: 70.3, 90.3) at 12 months, 68.5 (95% CI: 54.7,

78.9) at 24 months, 59.3% (95% CI: 45.2, 70.8) at 36 months, and 36.5% (95% CI: 17.3, 56.0) at 48 months.

- Overall Survival

    - The median OS was NE (95% CI: NE, NE). The KM estimate of OS was 81.1% (95% CI: 68.4, 89.0) at 24 months, 77.5% (95% CI: 64.4, 86.3) at 36 months, and 72.7% (95% CI: 58.5, 82.7) at 48 months and 54 months.

Summary of safety results

The key exposure, safety, and tolerability findings from this study were:

- The median acalabrutinib treatment duration was 36.0 months (range: 0.3-54.8 months).

- The safety and tolerability profile of acalabrutinib as monotherapy was consistent with acalabrutinib monotherapy clinical studies. There were no unexpected safety findings identified in this study.

- The most common TEAEs were diarrhea (53.3%), contusion and headache (43.3% each), upper respiratory tract infection (33.3%), and cough and dizziness (31.7% each).

- The most common TEAEs considered related to acalabrutinib were headache (31.7%), contusion (30.0%), diarrhea (21.7%), dizziness (11.7%), and arthralgia (10.0%).

- Grade 5 (fatal) TEAEs included pneumonia (2 subjects) and bronchopulmonary aspergillosis and ventricular fibrillation (1 subject each); none were considered related to acalabrutinib.

- SAEs were reported in 32 (53.3%) subjects. The most frequent SAEs were pneumonia (11.7%), and sepsis and syncope (5.0% each). SAEs considered related to acalabrutinib occurred in 10 (6.7%) subjects; the most frequent were cardiac failure congestive, non-cardiac chest pain, and pneumonia (2 subjects each).

- Ten (16.7%) subjects had TEAEs that led to study drug discontinuation. Pneumonia led to study drug discontinuation in 2 (3.3%) subjects. All other TEAEs that led to study drug discontinuation were reported in 1 subject each.

- Analysis of ECIs showed that:

    - Cardiac events were reported in 15 (25.0%) subjects. Serious cardiac events occurred in 4 subjects (cardiac failure congestive in 2 subjects and atrial fibrillation and ventricular fibrillation in 1 subject each; 3 of the 4 subjects had a

history of atrial fibrillation). There was 1 Grade 5 serious cardiac event (ventricular fibrillation) considered not related to study treatment.

- Cytopenias events of anemia (11 [18.3%]), leukopenia (16 [26.7%], and thrombocytopenia (10 [16.7%]) occurred. No subject discontinued acalabrutinib due to a cytopenia event and 1 subject had an SAE of cytopenia (anemia).

- Hemorrhage events occurred in 40 (66.7%) subjects and major hemorrhage events occurred in 3 (5.0%) subjects. Two subjects had serious major hemorrhage events (Grade 3 hematuria and injection site hemorrhage). One subject discontinued acalabrutinib due to a major hemorrhage event of subdural hematoma.

- Eight (13.3%) subjects had hepatotoxicity events and 1 subject discontinued acalabrutinib due to an SAE of transaminases increased. No other subject had a serious hepatotoxicity event.

- Hypertension events occurred in 9 (15.0%) subjects; of these 9 subjects, 7 subjects had pre-existing hypertension. Grade 3 hypertension events occurred in 3 (5.0%) subjects; 1 subject had a serious Grade 3 hypertension event (hypertension); and no subject discontinued acalabrutinib due to a hypertension event.

- Infection events occurred in 46 (76.7%) subjects. Grade ≥3 infection events occurred in 18 (30.0%) subjects. Serious infection events occurred in 17 (28.3%) subjects. Two subjects discontinued acalabrutinib due to an infection event (Grade 3 pneumonia and Grade 5 pneumonia). There were 6 subjects with a Grade 4 or Grade 5 infection event (Grade 4 sepsis [3 subjects], Grade 5 pneumonia [1 subject], Grade 5 bronchopulmonary aspergillosis [1 subject], and Grade 5 pneumonia and Grade 4 bronchopulmonary aspergillosis [1 subject]).

- One subject had interstitial lung disease/pneumonitis (Grade 2 bronchiolitis), which was not considered related to study drug, not considered serious, and did not lead to acalabrutinib discontinuation.

- Treatment-emergent second primary malignancies occurred in 14 (23.3%) of subjects. Treatment-emergent second primary malignancies, excluding non-melanoma skin, occurred in 5 (8.3%) subjects. Grade 3 second primary malignancies, excluding non-melanoma skin, occurred in 3 (5.0%) subjects. Three subjects (5.0%) had serious second primary malignancies, excluding non-melanoma skin (chronic myelomonocytic leukemia and malignant melanoma in situ in 1 subject and gastrointestinal adenocarcinoma and squamous cell carcinoma in 1 subject each). One subject discontinued study treatment due to an

AE of second primary malignancy, excluding non-melanoma skin (endometrial cancer).

- There were no events of tumor lysis syndrome.

- Analysis of laboratory and other safety data showed that:
  - There were no clinically significant mean changes in clinical laboratory values or vital sign values over time.
  - There was a trend towards mean ALC decreases, hemoglobin increases, and platelet increases over time, which generally indicate improvement in CLL.

Conclusions

Acalabrutinib monotherapy was shown to be well tolerated with an acceptable safety and tolerability profile that is consistent with previous acalabrutinib monotherapy clinical studies. Acalabrutinib demonstrated efficacy in this population of subjects with relapsed/refractory CLL who were intolerant of ibrutinib therapy. As assessed by the investigator and based on IWCLL 2008, ORR was 70.0%, with 2 subjects achieving CR and 40 subjects achieving PR. The ORR including PRL was 78.3% with 5 subjects achieving PRL.