

ORIGINAL ARTICLE

## Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia

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### ABSTRACT

#### BACKGROUND

Irreversible inhibition of Bruton's tyrosine kinase (BTK) by ibrutinib represents an important therapeutic advance for the treatment of chronic lymphocytic leukemia (CLL). However, ibrutinib also irreversibly inhibits alternative kinase targets, which potentially compromises its therapeutic index. Acalabrutinib (ACP-196) is a more selective, irreversible BTK inhibitor that is specifically designed to improve on the safety and efficacy of first-generation BTK inhibitors.

#### METHODS

In this uncontrolled, phase 1–2, multicenter study, we administered oral acalabrutinib to 61 patients who had relapsed CLL to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib. Patients were treated with acalabrutinib at a dose of 100 to 400 mg once daily in the dose-escalation (phase 1) portion of the study and 100 mg twice daily in the expansion (phase 2) portion.

#### RESULTS

The median age of the patients was 62 years, and patients had received a median of three previous therapies for CLL; 31% had chromosome 17p13.1 deletion, and 75% had unmutated immunoglobulin heavy-chain variable genes. No dose-limiting toxic effects occurred during the dose-escalation portion of the study. The most common adverse events observed were headache (in 43% of the patients), diarrhea (in 39%), and increased weight (in 26%). Most adverse events were of grade 1 or 2. At a median follow-up of 14.3 months, the overall response rate was 95%, including 85% with a partial response and 10% with a partial response with lymphocytosis; the remaining 5% of patients had stable disease. Among patients with chromosome 17p13.1 deletion, the overall response rate was 100%. No cases of Richter's transformation (CLL that has evolved into large-cell lymphoma) and only one case of CLL progression have occurred.

#### CONCLUSIONS

In this study, the selective BTK inhibitor acalabrutinib had promising safety and efficacy profiles in patients with relapsed CLL, including those with chromosome 17p13.1 deletion. (Funded by the Acerta Pharma and others; ClinicalTrials.gov number, NCT02029443.)

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**C**HRONIC LYMPHOCYTIC LEUKEMIA (CLL) is the most prevalent leukemia among adults. Although chemoimmunotherapy prolongs the duration of remission and overall survival among most patients with CLL,<sup>1,2</sup> relapse virtually always occurs. This has prompted aggressive discovery efforts for new therapies in CLL. Because B-cell receptor signaling is a driving factor for CLL tumor-cell survival,<sup>3,4</sup> proximal kinases involved in this pathway have been therapeutic targets. Bruton's tyrosine kinase (BTK) is immediately downstream of the B-cell receptor and is essential for the activation of several tumor-cell survival pathways relevant to CLL.<sup>5</sup> In addition, BTK is involved in chemokine-mediated homing and adhesion of CLL cells to the microenvironment, which contribute to their maintenance and proliferation.<sup>6,7</sup>

In mice and humans, loss of BTK function results in a B-cell-dysfunction phenotype with decreased serum immunoglobulin levels and an increased predisposition to infections. Few other adverse effects have been reported.<sup>8-10</sup> The unique structure of BTK, which is characterized by a cysteine (C481) within the ATP-binding pocket, makes it an attractive therapeutic target. Ibrutinib is a first-in-class, irreversible small-molecule inhibitor of BTK that has the ability to covalently bind to C481.<sup>11</sup> Ibrutinib has shown substantial single-agent activity in patients with relapsed CLL and in previously untreated patients.<sup>12-14</sup> Progressive disease during ibrutinib treatment is uncommon in patients with previously untreated CLL and also in patients with low-risk genomic abnormalities.<sup>12-14</sup>

Among those with high-risk genomic features, progression occurs more frequently, either shortly after the start of ibrutinib therapy, owing to Richter's transformation (CLL that has evolved into large-cell lymphoma), or later with progressive CLL.<sup>15</sup> Ibrutinib also irreversibly binds to other kinases (e.g., epidermal growth factor receptor [EGFR], tyrosine kinase expressed in hepatocellular carcinoma [TEC], interleukin-2-inducible T-cell kinase [ITK], and T-cell X chromosome kinase [TXK]).<sup>11</sup> These pharmacodynamic features may be responsible for ibrutinib-related adverse events that are not typically observed in BTK-deficient patients, such as rash, diarrhea, arthralgias or myalgias, atrial fibrillation, ecchymosis, and major hemorrhage.<sup>12-14</sup>

Acalabrutinib (ACP-196) is a second-generation, selective, irreversible inhibitor of BTK that has improved pharmacologic features, including favorable plasma exposure, rapid oral absorption, a short half-life, and the absence of irreversible targeting to alternative kinases, such as EGFR, TEC, and ITK. Given the success of ibrutinib in the treatment of relapsed CLL,<sup>12-14</sup> we sought to determine whether selective targeting of BTK by acalabrutinib would be effective, as measured by response and safety profile; side effects represent the most common reason that patients discontinue ibrutinib treatment.<sup>15,16</sup>

Furthermore, we hypothesized that it might be possible to administer acalabrutinib twice daily, thus achieving a complete and continuous level of drug binding to BTK (>95% over a period of 24 hours), without increased toxic effects from inhibition of alternative kinases. Full target coverage may reduce drug resistance caused by mutations in the BTK enzyme and may also lower the rate of Richter's transformation.

## METHODS

### STUDY DESIGN

Preclinical studies with CLL cells and normal immune cells were performed according to methods outlined in the Supplementary Appendix (available with the full text of this article at NEJM.org) after written informed consent was obtained as part of an institutional review board–approved protocol at Ohio State University. The phase 1–2 multicenter study was designed to determine the recommended dose, safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib in patients with relapsed CLL. All patients provided written informed consent. The institutional review board at each participating site approved the study protocol (available at NEJM.org). The study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

### PATIENTS

Eligibility criteria included the following: a diagnosis of relapsed CLL or small lymphocytic lymphoma, as defined by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)<sup>17</sup>; a need for treatment, according to the

IWCLL guidelines; receipt of at least one previous therapy for CLL; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (on a scale from 0 to 5, with higher numbers indicating greater disability); adequate organ function, defined by creatinine and bilirubin levels of no more than 1.5 times the upper limit of the normal range and an alanine aminotransferase level of no more than 2.5 times the upper limit of the normal range; and an absence of active infection. An absolute neutrophil count of at least 750 cells per cubic millimeter and a platelet count of at least 50,000 per cubic millimeter were required if no bone marrow involvement was present, but no restrictions for cytopenia were applied if bone marrow involvement was present. Exclusion criteria were any cancer that limited expected survival to less than 2 years, the need for warfarin therapy (other anticoagulation therapy was allowed), active gastrointestinal inflammation or malabsorption, and the use of medications associated with torsades des pointes, high-grade atrioventricular block, or a corrected QT interval of 480 msec or greater.

#### EVALUATION AND TREATMENT

All patients had a baseline assessment that included interphase cytogenetic analysis, mutational analysis of immunoglobulin heavy-chain variable (*IGHV*) genes, measurement of serum  $\beta_2$ -microglobulin, and inquiry about B symptoms (i.e., weight loss, night sweats, and fever). Patients were successively enrolled in cohorts that were to receive oral acalabrutinib at a dose of 100 mg, 175 mg, 250 mg, or 400 mg once daily as part of the dose-escalation (phase 1) portion of the study or 100 mg twice daily as part of the expansion (phase 2) portion. The definition of dose-limiting toxic effects included grade 3 or greater nonhematologic toxic effects (except for alopecia or nausea, vomiting, or diarrhea that resolved with an intervention); grade 4 neutropenia lasting more than 5 days; grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding; grade 3 or greater febrile neutropenia; or a dosing delay due to toxic effects for more than 7 consecutive days. Escalation to the next cohort was allowed if fewer than two dose-limiting toxic effects were noted in six patients.

#### DISEASE EVALUATION

Patients were evaluated at screening, weekly for the first month, every 2 weeks for the second month, monthly for 4 months, and every 3 months thereafter. Assessments included history taking, physical examination, and laboratory studies for signs of toxic effects. Numbers of T cells, natural killer cells, and monocytes were measured at baseline and before cycles 3, 10, and 16 (each cycle lasted 28 days). Serum immunoglobulin levels were measured on the same schedule. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.03. Hematologic toxic effects were graded according to IWCLL criteria.<sup>17</sup>

Study end points for phase 1 included safety (maximum tolerated dose), pharmacodynamics, and pharmacokinetics; end points for phase 2 included the overall response rate, progression-free survival, and long-term side-effect profile. Response assessments, including radiologic examination, were performed at the end of cycles 2, 4, 6, 9, 12, 15, 18, and 21 for most patients. Bone marrow biopsy was performed in all patients at 12 months or when all other criteria for a complete response were met. Response was evaluated on the basis of the IWCLL criteria,<sup>17</sup> but isolated lymphocytosis was not considered to indicate a relapse (a summary of the response criteria is available in Table S6 in the Supplementary Appendix). A partial response in the context of lymphocytosis was considered to be a partial response with lymphocytosis. Patients could be evaluated for efficacy if they had received at least one dose of acalabrutinib and had undergone at least one tumor-response assessment during treatment.

#### PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Detailed pharmacokinetic analyses were performed with the use of a validated assay during cycle 1 of therapy. BTK occupancy (the level of drug binding to BTK) by acalabrutinib was measured in peripheral-blood mononuclear cells with the aid of a biotin-tagged analogue probe at baseline, 4 hours after administration of acalabrutinib on days 1, 8, and 28, and before administration of acalabrutinib on days 2, 8, and 28. Phosphorylation of BTK was measured by means of intracellular flow cytometry. Immunoblot

analysis was performed with the use of methods described previously.<sup>18</sup> The murine thrombosis model has been described previously.<sup>19</sup> Additional details for laboratory studies are provided in the Supplementary Appendix.

#### STUDY OVERSIGHT

This study was designed by the first, third, and last authors together with the sponsor (Acerta Pharma). The clinical investigators and their research teams collected and evaluated all the data and assessed all the patients. The sponsor was responsible for analyzing the data. Investigators had open access to all data and analyses under standard confidentiality agreements. The first author wrote the initial draft of the manuscript. No professional medical-writing services were used. All the authors reviewed the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses reported and the fidelity of the study to the protocol.

#### STATISTICAL ANALYSIS

Results are presented through October 1, 2015. All the safety and efficacy analyses included patients who received acalabrutinib. One patient who discontinued treatment after 8 days was excluded from the analysis of the overall response rate, according to the protocol, because computed tomography had not been performed during treatment. However, laboratory assessments and physical examination showed that the patient had had a response and that the disease was not progressing when treatment was discontinued. Descriptive statistics were used to summarize the findings. The Wilcoxon signed-rank test was used to assess the change from baseline in immune-cell counts, cytokine levels, and immunoglobulin levels. Only patients with data at baseline and for each subsequent follow-up visit were included, and no adjustment for multiplicity was made. Because many exploratory tests were performed, P values of less than 0.05 should not be regarded as definitive, but rather as hypothesis-generating. Progression-free survival was defined as the time from the first dose of acalabrutinib to documented disease progression or death and was estimated with the use of the Kaplan–Meier method.<sup>20</sup> Data on progression-free survival for patients who discontinued treatment without documented disease progres-

sion were censored at the time of the last clinical assessment. Noncompartmental pharmacokinetic analyses were performed with the use of validated WinNonlin software (Certara USA).

## RESULTS

#### MECHANISM OF ACTION

The chemical structures of acalabrutinib and ibrutinib are shown in Figure S1 in the Supplementary Appendix. Acalabrutinib showed dose-dependent inhibition of B-cell receptor signaling in primary CLL cells (Fig. S2A in the Supplementary Appendix). In kinase-inhibition assays, acalabrutinib was a more selective BTK inhibitor than ibrutinib (Table S1 in the Supplementary Appendix). These biochemical findings are physiologically relevant, because acalabrutinib did not inhibit EGFR, TEC, or ITK signaling (Fig. S2B through S2D in the Supplementary Appendix). The findings provide structural, biochemical, and in vitro differentiation of acalabrutinib from ibrutinib. These data, combined with objective clinical responses in a study of naturally occurring canine B-cell lymphomas, provided justification for the clinical development of acalabrutinib for the treatment of CLL.<sup>21</sup>

#### PATIENT DEMOGRAPHICS

A total of 61 patients were sequentially enrolled at six sites in the United States and the United Kingdom and received at least one dose of acalabrutinib. The baseline characteristics of the patients are listed in Table 1. At a median follow-up of 14.3 months (range, 0.5 to 20), 53 patients are still receiving treatment. The primary reasons for treatment discontinuation in 8 patients were the investigator's or patient's decision in the case of 2 patients; active autoimmune hemolytic anemia that required additional therapy in 1 patient; fatal pneumonia in 1 patient; adverse events of diarrhea, gastritis, and dyspnea in 1 patient each; and CLL progression in 1 patient.

#### PHARMACOKINETIC MEASUREMENTS

Acalabrutinib was rapidly absorbed and eliminated after oral administration (Fig. 1A). Pharmacokinetic results showed that exposure to acalabrutinib increased in a dose-proportional manner, with no drug accumulation. Mean peak plasma values occurred between 0.6 and 1.1 hours. The mean half-life was approximately 1 hour across

all cohorts. Additional pharmacokinetic measurements are summarized in Table S2 in the Supplementary Appendix.

#### PHARMACODYNAMIC MEASUREMENTS

The binding of acalabrutinib to the C481 residue was assessed in all treatment cohorts, with data summarized in Figure 1B. Starting with the dose of 100 mg once daily, BTK occupancy was complete (99 to 100%) 4 hours after dosing and ranged from 87 to 95% before dose administration with once-daily dosing. Because acalabrutinib has no plasma accumulation, we explored the feasibility and safety of a dosing regimen of 100 mg twice daily. Figure 1C shows improved BTK occupancy of 99% 4 hours after dose administration and 97% before dose administration on days 8 and 28. The interruption of B-cell receptor signaling was also assessed by measurement of phosphorylated BTK, as shown in Figure 1D. After treatment with acalabrutinib, complete loss of phosphorylated BTK was observed at the respective time points across all cohorts. Assessment of the *in vivo* function of platelets isolated from the blood of patients receiving acalabrutinib or ibrutinib (as a positive control) revealed a reduction in platelet–vessel wall interactions in the latter but not the former in a humanized mouse model of thrombosis (Fig. S4 in the Supplementary Appendix). Direct natural-killer-cell–mediated cytotoxicity was evaluated with the use of peripheral blood from the patients. Non–antibody-dependent cytotoxicity was not impaired with acalabrutinib treatment as compared with the pretreatment control (Fig. S3 in the Supplementary Appendix). Proinflammatory cytokines decreased significantly from baseline to day 28 of treatment (Fig. S5 in the Supplementary Appendix).

#### SAFETY

Long-term therapy with acalabrutinib has not been associated with any high-grade cumulative toxic effects. Most of the events that were observed were grade 1 or 2 and resolved over time (Table 2). The most common adverse events were headache (with overall events occurring in 43% of the patients and grade 3 or 4 events in 0%), diarrhea (overall in 39% and grade 3 or 4 in 2%), increased weight (overall in 26% and grade 3 or 4 in 2%), pyrexia (overall in 23% and grade 3 or 4 in 3%), and upper respiratory tract infection

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.**

Characteristic	Value (N=61)
<b>Age</b>	
Median — yr	62
Range — yr	44–84
≥65 yr — no. (%)	27 (44)
≥70 yr — no. (%)	15 (25)
Diagnosis of chronic lymphocytic leukemia — no. (%)	61 (100)
<b>ECOG performance status — no. (%)*</b>	
0	22 (36)
1	36 (59)
2	3 (5)
<b>Bulky lymph nodes — no. (%)</b>	
≥5 cm in diameter	28 (46)
≥10 cm in diameter	3 (5)
<b>Rai risk classification — no. (%)†</b>	
Low	1 (2)
Intermediate	19 (31)
High	41 (67)
<b>No. of previous therapies</b>	
Median	3
Range	1–13
<b>Cytopenia at baseline — no. (%)</b>	
Absolute neutrophil count ≤1500/μl	15 (25)
Hemoglobin ≤11.0 g/dl	21 (34)
Platelet count ≤100,000/μl	32 (52)
<b>Prognostic factors — no./total no. (%)</b>	
Unmutated immunoglobulin variable-region heavy-chain gene	38/51 (75)
Chromosome 17p13.1 deletion‡	18/59 (31)
Chromosome 11q22.3 deletion‡	17/59 (29)
β <sub>2</sub> -microglobulin >3.5 mg/liter	47/58 (81)

\* Values for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher numbers indicating greater disability.

† The Rai stage (which ranges from 0 [low risk] to I or II [intermediate risk] to III or IV [high risk]) was derived at the time of screening for this trial.

‡ Deletion of chromosome 17p13.1 or chromosome 11q22.3 was determined at a local laboratory or by a review of the patient's medical history.

(overall in 23% and grade 3 or 4 in 0%). Severe diarrhea, rash, arthralgia or myalgia, bruising, and bleeding events each occurred in no more than 2% of patients. No major hemorrhage or atrial fibrillation was noted. Serious adverse events are listed in Table S3 in the Supplementary Appendix. Only one death (due to pneumo-

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