Clinical Study Report Synopsis	
Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-CL-001
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A Phase 1/2, Multicenter, Open-Label, and Dose-Escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia

Study dates: First subject enrolled: 30 January 2014
Last subject enrolled: 29 April 2016
The analyses presented in this report are based on a data cutoff date of 15 July 2021.

Phase of development: 1/2

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study Centers

The study was conducted at 12 centers in 3 countries: United States (8 centers), United Kingdom (3 centers), and Italy (1 center).

Publications

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Covey T, Gulrajani M, Cheung J, et al. Pharmacodynamic evaluation of acalabrutinib in relapsed/refractory and treatment-naive patients with chronic lymphocytic leukemia (CLL) in the phase 1/2 ACE-CL-001 study. Blood. 2017;130(Suppl 1):1741.

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Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objectives	Endpoint/variable
Primary Objectives	
To establish the safety and the MTD of orally administered acalabrutinib in subjects with CLL/SLL	Safety was assessed by evaluation of AEs, ECIs, and SAEs; hematology, clinical chemistry, urinalysis, and other laboratory variables; and vital signs. MTD was defined as the largest daily dose for which < 33% of the subjects experienced a DLT during Cycle 1.
To determine the pharmacokinetics of orally administered acalabrutinib and identification of its major metabolite	Noncompartmental pharmacokinetics parameters were calculated for acalabrutinib and its major metabolite based on plasma concentrations.
Secondary Objective	
To evaluate tumor response by ORR, DOR, and PFS[a]	ORR, DOR, and PFS as assessed by the investigator.
Exploratory Objective	
CCI [redacted]	

a This clinical study report presents efficacy results for subjects in the R/R subgroup (from Cohorts 1, 2a, 2b, 2c, 3, 4a, and 4b) and the treatment-naive subgroup (from Cohorts 7 and 11).

Abbreviations: AE=adverse event; BTK=Bruton tyrosine kinase; CLL=chronic lymphocytic leukemia; DLT=dose-limiting toxicity; DOR=duration of response; ECI=event of clinical interest; MTD=maximum tolerated dose; ORR=overall response rate; PFS=progression-free survival; SAE=serious adverse event; SLL=small lymphocytic lymphoma.

Study Design

Study ACE-CL-001 was a multicenter, open-label, nonrandomized, sequential-group, dose-escalation study, conducted at 12 study centers globally. This study was designed to determine the recommended dose and to evaluate the safety, pharmacokinetics, and pharmacodynamics of acalabrutinib in subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including those who underwent Richter's syndrome (RS) and prolymphocytic leukemia (PLL). Assessment of tumor response, including overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS), was a secondary endpoint.

Subjects, men and women ≥ 18 years of age with measurable CLL/SLL, received acalabrutinib CCI [redacted] at doses defined at the time of enrollment into the cohorts described below. Subjects with stable

disease or tumor response continued therapy until disease progression (radiologic or clinical) or until the investigator considered the study treatment to be intolerable or no longer in the subject's best interest (duration of treatment was increased from CCI with Protocol Amendment 5; additional cycles allowed per Protocol Amendment 6). Subjects who met criteria of disease progression and who were continuing to gain clinical benefit from therapy could temporarily remain on acalabrutinib after discussion with the medical monitor (modified via Protocol Amendment 11).

Phase 1 (Dose Escalation)

The study was initially a Phase 1 study in relapsed/refractory (R/R) subjects to evaluate 6 different dosing regimens of acalabrutinib to determine the maximum tolerated dose (MTD). The MTD was defined as the highest daily dose for which < 33% of subjects experienced a dose-limiting toxicity (DLT) during Cycle 1. The following dose cohorts were evaluated as part of the dose-escalation portion of the study.

CCI Cohorts

- Cohort 1: CCI
- Cohort 2a: CCI
- Cohort 3: CCI
- Cohort 4a: CCI

CCI Cohorts

- Cohort 2b: CCI
- Cohort 4b: CCI

Phase 2 (Expansion)

No DLTs were observed in the Phase 1 dose-escalation portion of the study, and the MTD was not reached at doses up to CCI

The study was expanded, per Protocol Amendment 3, to include additional disease subgroups (Cohorts 7 to 10). Per Protocol Amendment 4, Cohort 2c and Cohort 11 were added. Per Protocol Amendment 5, the dose regimens for escalation Cohorts 1, 2a, and 4a were switched to CCI and Cohort 2b was expanded. Per Protocol Amendment 6, all subjects were switched to CCI except for subjects in Cohorts 9 and 10.

The Phase 2 component of the study included the following disease subgroups:

- R/R subgroup:
  - Cohort 2b: Subjects from the dose-escalation phase continued to receive CCI
  - Cohort 2c: Originally CCI subjects were switched to CCI per Protocol Amendment 6
- Treatment-naive subgroup: This group consisted of subjects with confirmed diagnosis of CLL/SLL who required treatment and a) did not want to receive chemoimmunotherapy or b) had comorbidities that would preclude chemoimmunotherapy.
  - Cohort 7: Originally CCI subjects were switched to CCI per Protocol Amendment 6
  - Cohort 11: CCI
- Ibrutinib-intolerant subgroup: This group consisted of subjects with confirmed diagnosis of CLL/SLL who were not tolerating ibrutinib due to ibrutinib-related adverse events (AEs).
  - Cohort 8a: Originally CCI subjects were switched to CCI per Protocol Amendment 4
  - Cohort 8b: CCI

  Note: In the summary tables, Cohort 8 comprises subjects in Cohort 8a who started with CCI then switched to CCI and subjects in Cohort 8b who received CCI
- RS/PLL transformation subgroup: This group consisted of subjects with biopsy-proven diffuse large B-cell lymphoma (DLBCL) Richter's transformation or PLL transformation. A transformation from CLL to DLBCL occurs in 5% to 10% of CLL patients. This group initially enrolled subjects with RS and was expanded to include subjects with PLL in Protocol Amendment 4.
  - Cohort 9: CCI
- Ibrutinib R/R subgroup: This group consisted of subjects with confirmed diagnosis of CLL/SLL whose best response after 2 cycles of ibrutinib therapy was stable disease or nonresponse or relapsed subjects who initially responded to ibrutinib and had signs of clinical progression.
  - Cohort 10: CCI

Study assessments were conducted on the same schedule for all cohorts. All subjects had hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commenced (Day 1), all subjects were evaluated for safety (including serum chemistry and hematology) once weekly for the first 4 weeks, every 2 weeks in Cycle 2, and monthly thereafter. Study assessments also included pancreatic function (serum amylase and serum lipase), cardiac troponin, and electrocardiograms (ECGs).

Subjects underwent disease evaluation, which was tested differently in subjects with Richter's transformation. For all cohorts except Cohort 9 (RS/PLL transformation subgroup),

radiologic tumor assessment was done at screening and at the end of Cycles 2, 4, and 6; then every 6 cycles until Cycle 36; and then every 12 cycles thereafter. For subjects in Cohort 9, radiologic tumor assessment was done at screening and at the end of Cycles 2, 4, 6, 9, 12, 15, 18, 21, and 24 and every 6 cycles thereafter. Otherwise, radiologic tumor assessments were done at investigator discretion. Confirmation of complete response (CR) required bone marrow analysis and radiologic tumor assessment.

Pharmacokinetic (PK) and CCI testing was conducted in Cycle 1 and Cycle 6 CCI

Subjects who discontinued study treatment had a safety follow-up visit at 30 (+7) days after the last dose of acalabrutinib.

The final data cutoff in support of final database lock was planned to occur approximately 63 cycles after the last subject was administered the first dose of investigational product (modified via Protocol Amendment 12). This clinical study report (CSR) presents the results of the final data analysis based on the final database lock. The end of study was defined as Last Subject Last Visit, which was defined as the date of the last subject's 30-day (+7 days) safety follow-up visit.

Subjects who were still on treatment at the time of this final data cutoff could continue to receive investigational product within the current study through a continued treatment period (managed by the sponsor's Post Analysis and Reporting Team [PART] program) as long as, in the investigator's opinion, the subject was deriving clinical benefit and had not fulfilled any discontinuation criteria. During this continued treatment period, assessments reverted to the standard of care for each individual site. Data were not entered into the clinical study database after the final data cutoff date. Investigational product dispensation and reconciliation were handled by the study site at each subject's visit. The investigational product accountability information was to still be collected until all subjects had completed treatment. Individual study sites were to be closed after database lock had occurred and once their last subjects completed the 30-day (+7 days) safety follow-up visit. The continued treatment period was to remain available to subjects until the Last Subject Last Visit as defined above. Subjects who continued on acalabrutinib were to receive care per the investigator's clinical judgement and were to be monitored until disease progression and/or until they discontinued acalabrutinib. Specifically, during this continued treatment period, all serious adverse events (SAEs), overdoses, and pregnancies were to be reported until 30 days (+7 days) after the last dose of investigational product. SAEs, overdoses, and pregnancies were to be recorded in the subject's medical records.

Target Subject Population

Diagnosis and Main Criteria for Inclusion

The study population consisted of men and women ≥ 18 years of age. Key inclusion criteria for all disease subgroups were measurable CLL/SLL defined as at least 1 lymph node ≥ 2 cm as measured in the longest diameter; active disease meeting at least 1 of the International Workshop on CLL 2008 criteria for requiring treatment; and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Additionally, subjects in the R/R disease subgroup had CLL/SLL which had relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL. Subjects in the treatment-naive disease subgroup had CLL/SLL requiring treatment per National Cancer Institute (NCI) or International Working Group guidelines and either did not want to receive chemoimmunotherapy or had comorbidities that precluded chemoimmunotherapy. Subjects in the ibrutinib-intolerant disease subgroup were unable to tolerate ibrutinib due to ibrutinib-related AEs. Subjects in the RS/PLL disease subgroup had biopsy-proven DLBCL Richter's transformation or PLL transformation. For all disease subgroups except the ibrutinib R/R and RS/PLL subgroups, subjects were excluded if they had relapsed after, or were refractory to, prior Bruton tyrosine kinase (BTK) inhibitor therapy.

Number of Subjects (Planned and Analyzed)

A total of approximately 286 subjects were planned to be enrolled in this study, and 306 subjects were enrolled.

Investigational Product: Dosage, Mode of Administration and Batch Numbers

Acalabrutinib was provided as 25 mg and 100 mg opaque hard gelatin capsules. Acalabrutinib was self-administered CCI [redacted] as defined by the subjects' assignments into the cohorts detailed in the study design. Dose-modification provisions were permitted as defined in the protocol. Intrasubject dose escalation from CCI [redacted] was allowed with discussion and approval from the medical monitor. Lot numbers of study treatment provided to each subject are provided in Appendix 16.1.6. No comparator was used in this study.

Duration of Treatment

Subjects with stable disease or tumor response continued therapy until progressive disease (radiologic or clinical) or until the investigator considered the study treatment to be intolerable or no longer in the subject's best interest. Per Protocol Amendment 11, subjects who had progressive disease but were continuing to gain clinical benefit from therapy could temporarily remain on acalabrutinib after discussion with the medical monitor.

Statistical Methods

Determination of Sample Size

Phase 1, Dose Escalation

The sample size of the Phase 1 dose-escalation portion of the study was not determined based on power considerations. The MTD was defined as the largest daily dose for which < 33% of the subjects experience a DLT during Cycle 1. No DLT was observed during the dose-escalation phase of the study, and the MTD was not reached.

Phase 2, Expansion

Each cohort of the Phase 2 expansion portion tested the null hypothesis that the ORR was ≤ 10% against the alternative hypothesis that it was ≥ 35%. Using Simon's optimal 2-stage design (Simon 1989), a total sample size of 30 subjects per cohort had power = 0.90 to achieve a 1-sided significance level of ≤ 0.025. In Stage 1, 11 subjects were planned to be enrolled per cohort; if ≥ 2 subjects (18%) achieved an objective response of a partial response (PR)/PR with lymphocytosis (PRL) or better within the first 4 cycles of treatment, then that cohort continued to full enrollment. Under the Simon 2-stage design, an ORR of ≥ 23% (i.e., ≥ 7 subjects responding of 30 subjects evaluated) would achieve a significance level of ≤ 0.025. Using an exact binomial confidence interval (CI), an ORR of 23% (i.e., 7 subjects responding of 30 subjects evaluated) would achieve a 2-sided 90% lower bound of 11.5%. See the Statistical analysis plan (SAP) Table 1 for the 2-sided exact 90% binomial CIs on the true response rate for the range of possible values for the observed response rate.

Original protocol through Protocol Amendment 2: There was no expansion cohort in these protocol versions. The original protocol included dose-escalation Cohorts 1, 2a, 2b, and 3. Protocol Amendment 2 added dose-escalation Cohorts 4a and 4b. All cohorts comprised subjects with R/R disease.

Protocol Amendment 3: This amendment added expansion Cohort 7 (treatment-naive), Cohort 8a (ibrutinib-intolerant), Cohort 9 (RS/PLL) with 8 to 12 subjects each, and Cohort 10 (ibrutinib R/R) with 12 to 16 subjects.

Protocol Amendment 4: Existing subjects in Cohort 8a (ibrutinib-intolerant) were switched from CCI [redacted] and new subjects enrolled in this cohort received CCI [redacted] (Cohort 8b) starting from Cycle 1 Day1. Expansion Cohorts 2b, 2c (R/R), 8b (ibrutinib-intolerant), and 11 (treatment-naive) were added. The sample size for each expansion cohort was changed to 30 subjects based on Simon's 2-stage design (Simon 1989).

Protocol Amendment 5: The sample size was increased from 30 subjects to 200 subjects for Cohort 2b (R/R) and to 60 subjects for Cohort 11 (treatment-naive) to provide safety and efficacy data in support of the Phase 3 program of acalabrutinib in CLL.

Protocol Amendment 6: No change in sample size was required.

Protocol Amendment 7: The sample size was decreased from 200 subjects to 65 subjects for Cohort 2b (R/R), which was considered sufficient to meet the primary objective of the study. The sample size for Cohort 8b (ibrutinib-intolerant) was increased from 30 subjects to 35 subjects to obtain additional safety and efficacy data in this population.

Protocol Amendments 8, 9, 10, 11, and 12: No change in sample size was required.

A total of approximately 286 eligible subjects were planned to be enrolled in this study.

Analysis Methods

No formal tests of hypotheses were performed. Descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) were presented for continuous variables including baseline demographics, disease characteristics, study treatment administration, and efficacy and safety outcomes. Categorical variables were summarized as the number and percentage of subjects per category.

Investigator assessed tumor response for CLL/SLL was based on International Workshop on Chronic Lymphocytic Leukemia 2008 criteria per Hallek et al. 2008 with incorporation of the clarification for treatment-related lymphocytosis per Cheson et al. 2012 and for RS per Cheson et al. 2014.

ORR was defined as the proportion of subjects achieving CR, CR with incomplete marrow recovery (CRi) or PR while on treatment before the initiation of new anticancer therapy or stem cell transplant. The corresponding 95% CIs using exact binomial distribution were provided. For RS/PLL subgroup, ORR was defined as the proportion of subjects achieving CR or PR. ORR was summarized using Efficacy Evaluable Population as the primary analysis population and the All-Treated Population. For CLL subgroups (with the exception of RS/PLL), ORR including PRL as a response was summarized in the same fashion. The corresponding 95% CIs using exact binomial distribution were provided.

DOR was defined as the time from the date of achieving the first CR, CRi, or PR to the date of disease progression or death due to any cause, whichever occurred first. Subjects who did not have disease progression or death were censored using the same rule for PFS. For RS/PLL, DOR was defined as achieving first CR or PR. The Kaplan-Meier (KM) method was used to estimate the distribution of DOR. The same summary statistics for PFS are presented for

DOR. For CLL subgroups (except RS/PLL), DOR including PRL as one of the responses was also summarized in the same fashion.

Time to initial response of PR or better was calculated as ([date of first PR or better – date of first dose + 1] / 30.4376) and was summarized using descriptive statistics. Time to initial response of PRL or better for CLL disease subgroups (i.e., except RS/PLL disease subgroup) was also summarized in the same fashion.

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 subject was censored at the date of last adequate assessment (censoring date). If a subject received an autologous or allogeneic stem cell transplant, the subject was censored at the date of transplant. 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 or computed tomography (CT) for CLL subgroups (or positron-emission tomography [PET]-CT for RS/PLL subgroup) and complete blood count. If a subject did not have any adequate assessment after the first dose, the subject was censored at Day 1. The KM method was used to estimate the distribution of PFS. Median PFS and the 95% CIs and PFS rates for selected landmarks with 95% CIs were reported. The number of progressions, deaths, and censored events by reason were summarized.

CCI [redacted] In addition, DOR (including PR or better) was performed on the Efficacy Evaluable Population and the All-Treated Population for chromosomal abnormalities subgroups as specified above.

Safety was assessed by evaluation of AEs, laboratory values, vital signs measurements, ECG results, physical examinations, and ECOG performance status. Safety analyses were performed on the All-Treated Population, unless otherwise specified.

Subject Population

As of the data cutoff date (15 July 2021), 306 subjects were enrolled at 12 centers in 3 countries: United States (8 centers), United Kingdom (3 centers), and Italy (1 center).

A total of 301 subjects received at least 1 dose of study treatment and all 301 subjects discontinued treatment, including 120 (39.9%) subjects who were still receiving acalabrutinib at the time of transition to PART. The median time on study for all subjects was 58.5 months (range: 0.03 to 88.80 months); however, there was a wide variation among disease subgroups. While the median time on study in the RS/PLL subgroup was much lower in comparison to

the overall population, this subgroup comprised subjects with a more aggressive/late-stage form of the underlying disease. At the time of transition to PART, 120 (39.9%) subjects were still receiving acalabrutinib and thus the reason for acalabrutinib discontinuation is 'study terminated by sponsor.' The next most common reason for discontinuation of treatment was disease progression (29.9%) followed by AEs (12.0%).

Most subjects were male (67.4%) and white (90.0%). The median age was 65.0 years PPD 51.8% of all subjects were ≥65 years of age and 29.9% were ≥ 70 years of age.

A total of 269 (89.4%) subjects had CLL and 3 (1.0%) subjects had SLL at baseline. The median time from initial diagnosis of CLL to first dose of study treatment was 6.4 years (range: 0.06 to 25.51 years); however, the time varied across the disease subgroups, particularly in the treatment-naive subgroup where the median time was 3.4 years. Most subjects had an ECOG performance status of 0 (30.9%) or 1 (64.8%) and a baseline Rai stage (derived) of I to II (intermediate risk; 30.2%) or III to IV (high risk; 41.2%). High-risk features including deletion of either 17p or 11q were present in 42.6% of subjects who underwent genetic testing (270 of the 301 subjects underwent genetic testing for 17p and 11q deletion). Of these, 23.7% of subjects had del 17p with or without del 11q and 18.9% had del 11q without or missing del 17p. Nearly all subjects (99.0%) had measurable lymph nodes at baseline; 42.3% of subjects had lymph nodes ≥ 5 cm. Any B symptoms were reported for 18.3% of subjects, primarily drenching night sweats (15.9%). The majority (63.1%) of subjects had cytopenia (neutropenia, anemia, and/or thrombocytopenia) at study entry.

Summary of Efficacy Results

Efficacy results are discussed for subjects in the R/R and treatment-naive subgroups.

The ORR by investigator assessment for the Efficacy Evaluable Population of the R/R disease subgroup (N = 130; including subjects from Phase 1 and Phase 2 of the study) was 93.1% (95% CI: 87.3%, 96.8%), including 5 (3.8%) CRs and 116 (89.2%) PRs. The ORR was consistently high across all dose cohorts (≥ 75%). For subjects with del 17p, the ORR was 90.0% (95% CI: 73.5%, 97.9%). The ORR by investigator assessment for the Efficacy Evaluable Population of the treatment-naive subgroup (N = 97) was 99.0% (95% CI: 94.4%, 100%), including 9 (9.3%) CRs and 87 (89.7%) PRs For subjects with del 17p, the ORR was 100% (95% CI: 66.4%, 100%).

For both the R/R and treatment-naive disease subgroups, high ORR was observed in all subgroup analysis sets defined by age, sex, race, number of prior systemic therapies (< 3 or ≥ 3; in R/R subgroup only), or chromosomal abnormalities. In the R/R disease subgroup, numerical differences in ORR were observed between subjects by age (< 65 and ≥ 65 years), prior systemic therapies (< 3 and ≥ 3), and immunoglobulin heavy chain variable (IgHV)

status (mutated and unmutated). In addition, the ORR decreased with increasing baseline Rai stage (derived) and increasing baseline ECOG performance status. Among treatment-naive subjects, no notable numerical differences in ORR were observed between subgroup analysis sets

In the R/R disease subgroup, with a maximum follow-up time of 81 months, median DOR for the Efficacy Evaluable Population was 60.1 months. In the treatment-naive disease subgroup, with a maximum follow-up time of 76 months, median DOR was not reached. Using KM point estimates, 50.4% of R/R subjects and 90.6% of treatment-naïve subjects were event-free at 60 months.

In the R/R disease subgroup, with a maximum follow-up time of 88 months, median PFS for the Efficacy Evaluable Population was 66.1 months. In the treatment-naive disease subgroup, with a maximum follow-up time of 78 months, median PFS was not reached. Using KM point estimates, 52.5% of R/R subjects and 92.4% of treatment-naive subjects were progression-free at 60 months.

The median time to initial response for the responders in the R/R disease subgroup was 5.4 months (range: 1.7 to 66.2 months) and in the treatment-naive disease subgroup was 3.7 months (range: 1.7 to 22.1 months).

Summary of Pharmacokinetic Results

A separate PK report was generated and is provided in Appendix 16.1.13.

CCI

[redacted]

Summary of Safety Results

Safety results are discussed for the subjects in the 5 disease subgroups (R/R [including subjects enrolled in Phase 1 and Phase 2 of the study], treatment-naive, ibrutinib-intolerant, RS/PLL, and ibrutinib R/R).

The median duration of exposure for the 301 total subjects was 56.7 months (range: 0.03 to 88.80 months). The median actual cumulative dose was 326.1 g, and the median average daily dose was 191.5 mg/day.

Almost all (99.7%) subjects experienced ≥ 1 AE during the study, and the most common AEs were diarrhea (53.2%) and headache (47.5%). Most (71.1%) subjects had Grade ≥ 3 AEs, and

the most common Grade ≥ 3 AEs were neutropenia (13.6%), pneumonia (11.6%), and hypertension (10.0%). The most common treatment-related AEs were headache (31.6%), contusion (19.3%), and diarrhea (17.6%). The AEs across the disease subgroups were generally similar, with the exception of the RS/PLL subgroup, which had a higher frequency of AEs associated with anemia (31.0%) and neutropenia (24.1%). SAEs were reported in 58.8% of subjects, and AEs that led to discontinuation of study treatment were reported in 12.6% of subjects. No DLTs were observed in the Phase 1 portion of this study, and the MTD was not reached at acalabrutinib doses up to CCI

A total of 40 (13.3%) subjects died. The most common reason for death was an AE (7.0%), with pneumonia being the most common (2.0%), followed by disease progression (6.3%). None of the fatal AEs was considered by the investigator to be treatment-related. Frequencies and causes of death across the disease subgroups were generally comparable with the exception of the RS/PLL subgroup, which experienced a higher death rate (48.3%) as compared with all treated subjects (13.3%); most of these deaths in the RS/PLL subgroup were due to disease progression (37.9%).

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/or pharmacological effects of approved BTK inhibitors. The most common ECI categories were infections, hemorrhage, cardiac events, second primary malignancies, hypertension, leukopenia, and anemia. The most commonly reported ECIs (≥ 10% of subjects) by PT were upper respiratory tract infection (40.9%), contusion (35.9%), hypertension (21.6%), pneumonia (20.6%), sinusitis (20.3%), petechiae (16.9%), anaemia (14.6%), neutropenia (13.6%), ecchymosis (13.0%), urinary tract infection (12.6%), bronchitis (12.0%), and epistaxis (1.6%). Grade ≥3 ECI categories reported for ≥ 10% of subjects included infections (27.9%), leukopenia (17.6%; specifically, PT neutropenia [13.6%]), and hypertension (11.0%).

There were no clinically significant mean changes in clinical laboratory values, serum immunoglobulin values, T/B/natural killer (NK) cell counts, or vital sign values over time. There was a trend toward worsening of baseline toxicity grade for some hematology parameters (including decreased absolute lymphocyte count [ALC], absolute neutrophil count [ANC], leukocytes, and platelets) and for some clinical chemistry parameters (including decreased phosphate, decreased sodium, and increased urate). Thirty-three (11.0%) subjects with an ECOG performance score of 0 or 1 at baseline had a worst postbaseline score of 2 or 3; 1 subject shifted from a score of 1 to 4, and 2 subjects shifted from 2 to 3.

One pregnancy occurred during the study which resulted in a live birth; there were no reported complications.

In general, the safety of acalabrutinib was consistent across the dose cohorts within the R/R subgroup during the dose-escalation phase.

Conclusions

- Acalabrutinib was well tolerated with an acceptable benefit-risk profile when administered to subjects with CLL/SLL and the various disease subtypes included in this study. No new safety signals were identified in this safety analysis for acalabrutinib in the treatment of subjects with CLL/SLL.
- Acalabrutinib induced high ORRs with rapid and durable responses in subjects with CLL who were R/R or treatment-naive.