Clinical Study Report	
Drug Substance	Acalabrutinib (ACP-196)
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A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia

Study dates:
First subject enrolled: 01 December 2016
Last subject enrolled: 17 January 2018
The analyses presented in this report are based on a data cutoff date of 15 January 2019 for IRC efficacy-related analyses and 03 September 2021 for all other analyses.

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 102 study centers in 25 countries.

Publications

Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2020;38(25):2849–61.

Ghia P, Pluta A, Wach M, et al. Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final Result. J Clin Oncol 2020;38(Suppl):Abstr 8015.

Ghia P, Pluta A, Wach M, et al. Acalabrutinib vs rituximab plus idelalisib or bendamustine by investigator choice in relapsed/refractory chronic lymphocytic leukemia: results from a pre-planned interim analysis of the Phase 3 ASCEND Study. Abstract LBA2606 at: European Hematology Association 2019 Annual Meeting. Available online. Accessed June 2019.

Ghia P, Pluta A, Wach M, et al. Acalabrutinib vs rituximab plus idelalisib (iDR) or bendamustine (BR) by investigator choice in relapsed/refractory (RR) chronic lymphocytic leukemia: phase 3 ASCEND study. Presented at: 2019 International Conference on Malignant Lymphoma; June 18-22, 2019; Lugano, Switzerland. Abstract 048. onlinelibrary.wiley.com/doi/10.1002/hon.54_2629.

Ghia P, Pluta A, Wach M, et al. ASCEND Phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia. HemaSphere 2019;3:S1.

Jurczak W, Pluta A, Wach M, et al. Three-year follow-up of the ASCEND trial: acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia. Blood 2021;138(Suppl 1):393.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective	Endpoint/Variable
Primary Objective	
To evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with idelalisib/rituximab (IR) or bendamustine/rituximab (BR) (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al. 2012), hereafter referred to as IWCLL 2008 criteria, in subjects with R/R CLL	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 came first. KM curve was used to estimate the distribution of PFS.
Secondary Objectives	
To evaluate Arm A compared with Arm B in terms of:	
• Investigator-assessed PFS per IWCLL 2008 criteria	PFS, defined as the time from date of randomization to the date of first investigator-assessed disease progression or death due to any cause, whichever came first. KM curve was used to estimate the distribution of PFS.
• Investigator- and IRC-assessed ORR per IWCLL 2008 criteria (defined as the proportion of subjects who achieve a best response of CR, CRi, nPR, or PR)	Best overall response was defined as the best response as assessed by the investigator or IRC on or before the initiation of subsequent anticancer therapy.
• OS	OS was defined as the time from date of randomization to death due to any cause.
• PROs by FACIT-Fatigue	Change from baseline in GFS at Week 24 and Week 48, proportion of subjects with improvement/stable/deterioration in GFS, and time to first clinically meaningful improvement in GFS.
• Investigator- and IRC-assessed DOR (defined as the time from the first documentation of objective response to the earlier time of disease progression or death from any cause)	DOR determined by IRC and by investigators was analyzed in the same fashion as PFS described above.
• TTNT (defined as the time from randomization to institution of nonprotocol-specified treatment for CLL)	TTNT was analyzed in the same fashion as PFS described above.
Safety Objective	
Incidence and severity of AEs and SAEs	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
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Abbreviations: AE=adverse event; ANC=absolute neutrophil count; BR=bendamustine/rituximab; CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with incomplete bone marrow recovery; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; CCI [redacted] FACIT=Functional Assessment of Chronic Illness Therapy; GFS=global fatigue score; CCI [redacted] IR=idelalisib/rituximab; IRC=independent review committee: IWCLL=International Workshop on Chronic Lymphocytic Leukemia; KM=Kaplan-Meier; CCI [redacted] nPR=nodular partial response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; PR=partial response; PRBC=packed red blood cells; R/R=relapsed/refractory; SAE=serious adverse event; TTNT=time to next treatment.

Study Design

This is an ongoing Phase 3 open-label, randomized study in subjects with documented CD20-positive chronic lymphocytic leukemia (CLL) who had received ≥ 1 prior treatment regimen. The study was designed to compare the efficacy of acalabrutinib monotherapy versus idelalisib/rituximab (IR) or bendamustine/rituximab (BR) as measured primarily by progression-free survival (PFS). Overall response rate (ORR), overall survival (OS), duration

of response (DOR), time to next treatment (TTNT), and patient-reported outcomes (PROs) were also assessed.

Subjects were randomized in a 1:1 ratio into 2 arms: subjects randomized to Arm A received acalabrutinib monotherapy; subjects randomized to Arm B received investigator's choice of either IR or BR.

Subjects were randomized based on the following stratification factors: presence of 17p deletion, Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), and number of prior therapies (1, 2 or 3 versus ≥ 4).

Each treatment cycle was 28 days (4 weeks). Subjects in Arm A received acalabrutinib orally starting Cycle 1 Day 1 until unacceptable drug-related toxicity or disease progression. Subjects in Arm B who received the IR regimen received idelalisib orally starting Cycle 1 Day 1 until disease progression or unacceptable toxicity, and rituximab on Day 1 of the first cycle, then every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions. Subjects in Arm B who received the BR regimen received bendamustine as an intravenous (IV) infusion on Days 1 and 2 of each 28-day cycle, for a maximum of 6 cycles, and rituximab on Day 1 of Cycles 1 to 6.

At the investigator's discretion, subjects randomized to Arm B who had confirmed disease progression and who met crossover eligibility criteria could receive crossover treatment with single-agent acalabrutinib until disease progression or unacceptable toxicity.

Assessment of response and progression was conducted in accordance with the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria for CLL (Hallek et al. 2008), with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression was not considered progressive disease (PD) (Cheson et al. 2012). 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. Confirmation of complete response (CR) required bone marrow analysis and radiologic tumor assessment. A central laboratory performed all hematology testing for the primary endpoint analysis. Baseline tumor assessments were performed at screening, and response evaluations were done every 12 weeks (± 14 days) through Cycle 25, and then every 24 weeks (± 14 days) thereafter.

Safety and tolerability were assessed by the incidence of treatment-emergent adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, analysis of lymphocytosis, ECG, and ECOG performance status.

Subjects who discontinued study drug for any reason including disease progression had a treatment termination (TT) visit for safety assessments within 7 days of the last dose of all study drugs. In addition to the TT visit, all subjects who discontinued all study drugs had a safety follow-up visit (SFU) visit 30 days (+ 7 days) after the last dose of all study drugs. Posttreatment disease follow-up visits occurred approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject received a new anticancer therapy. During this period, subjects were followed for disease progression via computed tomography (CT)/magnetic resonance imaging (MRI) scans, complete blood count (CBC) with differential, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).

After progression, subjects were followed for survival status, subsequent anticancer therapy, and additional malignancy occurrence approximately every 12 weeks until death, withdrawal by subject, loss to follow-up, or study closure.

The primary efficacy analysis was based on assessment from an Independent Review Committee (IRC). As part of the IRC review, radiologic evaluations assessed by independent central radiologists and hematology results from a central laboratory were provided. An independent Data Monitoring Committee (DMC) reviewed the safety data periodically and provided recommendations according to the DMC charter.

The end of study was defined as the date of the last visit of the last subject in the study.

Subjects who were still on treatment at the time of the 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. Subjects who continued on acalabrutinib within the PART program were to receive care per the investigator's clinical judgment and were to be monitored until disease progression and/or until they discontinued acalabrutinib. Specifically, during this continued treatment period, all 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 and Sample Size

Diagnosis and Main Criteria for Inclusion

Documented CD20-positive CLL that met published criteria for diagnosis and for requiring treatment (Hallek et al. 2008) who had received ≥ 1 prior systemic therapies for CLL.

Number of Subjects (Planned and Analyzed)

The study was planned to enroll approximately 306 subjects. A total of 310 subjects were randomized and all 310 subjects were analyzed.

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

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

Idelalisib: 100-mg and 150-mg tablets, administered at a dose of 150 mg PO BID.

Bendamustine: administered at a dose of 70 mg/m^2 as an IV infusion on Days 1 and 2 of each 28-day cycle, for a maximum of 6 cycles.

Rituximab: When administered with idelalisib, rituximab was administered at a dose of 375 mg/m^2 as an IV infusion on Day 1 of the first cycle, followed by 500 mg/m^2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions. When administered with bendamustine, rituximab was administered at a dose of 375 mg/m^2 as an IV infusion on Day 1 of the first cycle and 500 mg/m^2 on Day 1 of Cycles 2 to 6.

Duration of Treatment

Subjects in all cohorts received study treatment in 28-day continuous cycles.

Subjects received acalabrutinib and idelalisib until unacceptable toxicity or disease progression. Subjects received bendamustine and rituximab for the treatment durations specified above.

Statistical Methods

Determination of Sample Size

The study was expected to enroll approximately 306 subjects with a 1:1 randomization ratio between Arm A and B. CCI

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Analysis Methods

The primary efficacy analysis was to compare PFS as assessed by IRC between Arms A and B in the intent-to-treat (ITT) population using a stratified log-rank test adjusting for randomization stratification factors. The estimate of the HR (Arm B/Arm A) and the corresponding 95% CI was computed using a Cox proportional hazards model stratified by randomization stratification factors. Kaplan-Meier (KM) curve was used to estimate the distribution of PFS. PFS rate based on KM point estimate and the corresponding 95% CI were calculated at selected timepoints for each treatment arm. 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, and the exclusion of subjects with important protocol deviations from the analysis. Selected subgroup analyses were also performed.

ORR was summarized by number and percentage of subjects, and the corresponding 95% CI was calculated based on normal approximation (using Wilson's score). ORR was analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factors. The concordance between investigator-assessed and IRC-assessed best overall response was summarized by treatment arm. OS, investigator-assessed PFS, IRC- and investigator-assessed DOR, and TTNT were analyzed in the same fashion as that for primary efficacy endpoint described above. A sensitivity analysis for OS was conducted in which Arm B subjects who crossed over to receive acalabrutinib were censored at the day prior to first dose of acalabrutinib.

Subject Population

The study enrolled 310 subjects in the acalabrutinib arm (N = 155) and IR/BR arm (N = 155). All but 3 subjects (1 randomized to acalabrutinib and 2 randomized to IR/BR) received study treatment. At the time of transition to PART, 74 (47.7%) subjects randomized to acalabrutinib were still receiving acalabrutinib and thus the reason for acalabrutinib discontinuation was 'study terminated by sponsor.' Eighty subjects in the IR/BR arm (63 subjects previously on IR and 17 subjects previously on BR) crossed over to acalabrutinib monotherapy, 48.8% of whom were still on acalabrutinib treatment at the time of the final data cutoff date (study terminated by sponsor).

The median age for all subjects was 67 years (range: PPD About two-thirds (62.9%) of subjects were ≥ 65 years old, and 21.0% of subjects were ≥ 75 years old. About two-thirds (67.1%) of subjects were male, 92.3% were white, and 89.0% were not Hispanic or Latino. Most subjects were enrolled in Central and Eastern Europe (63.9%) or Western Europe (21.0%). There were no noteworthy differences in demographics between the 2 treatment arms.

Summary of Efficacy Results

As planned and reported in the interim clinical study report (dated 17 July 2019), because the study did cross the boundary at interim analysis, the interim analysis of efficacy was considered the final analysis. IRC assessments were discontinued after the interim analysis. Therefore, all IRC-related efficacy analyses in this clinical study report were based on the interim analysis data cutoff date of 15 January 2019. All other efficacy analyses were based on the final analysis data cutoff date of 03 September 2021, unless otherwise specified.

With a median follow-up of 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm, acalabrutinib monotherapy demonstrated a statistically significant improvement in IRC-assessed PFS compared with IR/BR, with a 69% reduction in risk of disease progression or death (HR = 0.31 [95% CI: 0.20, 0.49]; $p < 0.0001$). The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.5 months (95% CI: 14.0, 17.1). The KM estimate of the proportion of subjects without a PFS event at 12 months was 87.8% (95% CI: 81.3, 92.1) for acalabrutinib and 68.0% (95% CI: 59.4, 75.1) for IR/BR. The KM estimate of the proportion of subjects without a PFS event at 18 months was 79.0% (95% CI: 69.7, 85.8) for acalabrutinib and 38.6% (95% CI: 27.3, 49.8) for IR/BR.

The PFS benefit of acalabrutinib compared with IR/BR was consistent across all prespecified subgroups, including 17p deletion, 11q deletion, *TP53* mutation, unmutated immunoglobulin heavy-chain variable (IGHV), Rai stage III-IV, B2-microglobulin > 3.5 mg/L at baseline, and bulky disease ≥ 5cm, with HRs ranging from 0.21 to 0.33. Subjects with at least 1 chromosomal characteristic associated with poor prognosis (17p deletion, *TP53* mutation, 11q deletion, or unmutated IGHV) had a greater PFS benefit with acalabrutinib versus IR/BR (HR=0.27 [95% CI: 0.17, 0.44]).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib compared with IR/BR (HR = 0.33 [95% CI: 0.22, 0.52]; $p < 0.0001$). All sensitivity analyses were consistent with the primary analysis, with HRs ranging from 0.29 to 0.31, which was statistically significant for all analyses ($p < 0.0001$).

With a median follow-up of 46.52 months in the acalabrutinib arm and 45.34 months in the IR/BR arm, investigator-assessed PFS (based on a data cutoff date of 03 September 2021) was

consistent with the primary analysis, with a statistically significant improvement in PFS for acalabrutinib compared with IR/BR (HR = 0.28 [95% CI: 0.20, 0.38]; p < 0.0001). The overall concordance rates between the IRC-assessed and investigator-assessed PD (based on a data cutoff date of 15 January 2019) for acalabrutinib and IR/BR were 93.5% and 81.3%, respectively.

IRC-assessed ORR (CR+CRi+nPR+PR) for acalabrutinib and IR/BR was 81.3% and 75.5%, respectively. The ORR including PRL for acalabrutinib and IR/BR was 88.4% and 77.4%, respectively. Investigator-assessed ORR (CR+CRi+nPR+PR) for acalabrutinib and IR/BR was 82.6% and 83.9%, respectively; ORR including PRL was 92.3% and 87.7%, respectively.

With a median follow-up of 46.52 months in the acalabrutinib arm and 45.34 months in the IR/BR arm, the median OS was not reached in either treatment arm, with an HR of 0.69 (95% CI: 0.46, 1.04; p = 0.0783).

Acalabrutinib demonstrated a clinically relevant improvement in DOR compared with IR/BR, both by IRC assessment (HR = 0.33 [95% CI: 0.19, 0.59]) and investigator assessment (HR = 0.23 [95% CI: 0.16, 0.33]). Based on IRC assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 9.5% and 35.9% of subjects, respectively, and based on investigator assessment, disease progression in the acalabrutinib and IR/BR arms occurred in 24.2% and 66.2% of subjects, respectively. Based on IRC assessment, the KM estimate of the proportion of responders without a PFS event at 12 months for acalabrutinib and IR/BR was 85.0% (95% CI: 76.1, 90.8) and 59.5% (95% CI: 48.2, 69.1), respectively. Based on investigator assessment, the KM estimate of the proportion of responders without a PFS event for acalabrutinib and IR/BR, respectively, was 91.4% (95% CI: 85.0, 95.1) and 57.8% (95% CI: 48.6, 66.0) at 12 months, 80.6% (95% CI: 72.5, 86.6) and 33.5% (95% CI: 25.1, 42.0) at 24 months, and 68.6% (95% CI: 59.3, 76.2) and 22.5% (95% CI: 15.3, 30.5) at 36 months.

Acalabrutinib significantly prolonged TTNT compared with IR/BR (HR = 0.29 [95% CI: 0.21, 0.40]); p < 0.0001). The KM estimate of the proportion of subjects without starting next anticancer treatment for acalabrutinib and IR/BR, respectively, was 88.9% (95% CI: 82.8, 93.0) and 79.8% (95% CI: 72.3, 85.4) at 12 months, 79.1% (95% CI: 71.8, 84.7) and 48.5% (95% CI: 40.2, 56.4) at 24 months, and 66.4% (95% CI: 58.3, 73.3) and 23.9% (95% CI: 17.1, 31.2) at 36 months.

Summary of Safety Results

The median duration of acalabrutinib treatment among subjects randomized to acalabrutinib monotherapy was 44.2 months (range: 1.1 to 54.2 months) during the main study period, with 72.7% of subjects receiving ≥ 2 years of therapy. Among the 80 subjects in the IR/BR arm who crossed over to acalabrutinib monotherapy; the median duration of acalabrutinib

treatment was 21.9 months (range: 0.3 to 41.9 months) with 42.5% of subjects receiving ≥ 2 years of therapy. Exposure to acalabrutinib in this study was considerably higher than exposure to idelalisib (median of 11.5 months) and bendamustine (median exposure of 5.6 months).

Common TEAEs (≥ 10% of subjects) in the acalabrutinib arm during the main study period were neutropenia (24.0%), headache (23.4%), diarrhoea (21.4%), upper respiratory tract infection (20.1%), pneumonia (19.5%), anaemia (17.5%), cough (17.5%), pyrexia (16.2%), arthralgia (13.0%), thrombocytopenia (13.0%), bronchitis (12.3%), fatigue (12.3%), and respiratory tract infection (11.7%). Most TEAEs in the acalabrutinib arm were Grade 1 or 2. Common TEAEs reported during the crossover period were anaemia and neutropenia (20.0% each), arthralgia (17.5%), headache (15.0%), thrombocytopenia (13.8%), diarrhoea and pyrexia (12.5% each), pneumonia (11.3%), and cough (10.0%). Common TEAEs in IR-treated subjects were diarrhoea (52.5%), neutropenia (46.6%), pyrexia (19.5%), upper respiratory tract infection (16.9%), thrombocytopenia (16.1%), cough (15.3%), nausea, pneumonia, and rash (14.4% each), alanine aminotransferase increased (11.9%), and anaemia and nasopharyngitis (11.0% each). Common TEAEs in BR-treated subjects were neutropenia (34.3%), fatigue and infusion-related reaction (22.9% each), nausea (20.0%), pyrexia (17.1%), constipation, diarrhoea, and thrombocytopenia (14.3% each), and anaemia and upper respiratory tract infection (11.4% each). There were few events of febrile neutropenia (1 [0.6%], 3 [2.5%], and 1 [2.9%] subjects in the acalabrutinib, IR, and BR arms, respectively).

The most common Grade ≥ 3 TEAE in all treatment groups was neutropenia, reported in 18.8%, 39.8%, and 31.4% of subjects receiving acalabrutinib, IR, and BR, respectively, in the main study period. Among subjects receiving acalabrutinib in the main study period, other common Grade ≥ 3 TEAEs (reported in ≥ 5% of subjects) were anaemia (13.0%) and pneumonia (9.7%). Other common Grade ≥3 TEAEs in the IR arm were diarrhoea (26.3%), pneumonia (10.2%), alanine aminotransferase increased and thrombocytopenia (8.5% each), neutrophil count decreased (7.6%), anaemia and pyrexia (6.8% each), transaminases increased (5.9%), and aspartate aminotransferase increased (5.1%). Other commonly reported Grade ≥ 3 TEAEs in the BR group included anaemia (8.6%).

TEAEs reported as related to study treatment in the main study period occurred in 74.0% of subjects in the acalabrutinib arm and 89.5% of subjects in the IR/BR arm. TEAEs reported as related to acalabrutinib, idelalisib, bendamustine, rituximab in IR, and rituximab in BR were reported in 74.0%, 94.1%, 62.9%, 52.5%, and 54.3% of subjects who received those study drugs, respectively. Common acalabrutinib-related TEAEs were neutropenia (18.2 %), headache (14.9%), diarrhoea (9.7%), thrombocytopenia (8.4%), contusion (7.8%), anaemia (6.5%), fatigue (5.8%), and pneumonia (5.2%). Acalabrutinib-related TEAEs during the crossover period were reported in 52.5% of subjects and included neutropenia (12.5%),

headache (11.3%), anaemia (10.0%), diarrhoea and thrombocytopenia (7.5% each), and neutrophil count decreased (5.0%).

Grade 5 (fatal) TEAEs occurred in 16 (10.4%) subjects who received acalabrutinib in the main study period, 9 (7.6%) subjects who received IR, and 2 (5.7%) subjects who received BR. One event of Grade 5 brain neoplasm malignant was considered related to acalabrutinib treatment. Nine (11.3%) of 80 subjects in the acalabrutinib crossover period had a TEAE with a fatal outcome, and 2 additional subjects had a fatal event outside the treatment-emergent period.

SAEs occurred in 45.5%, 65.3%, and 25.7% of subjects who received acalabrutinib, IR, and BR, respectively, in the main study period. Grade ≥ 3 SAEs occurred in 42.2%, 60.2%, and 25.7% of subjects in the 3 treatment arms, respectively. Treatment-related SAEs occurred in 18 (11.7%) subjects in the acalabrutinib arm and 56 (36.6%) subjects in the IR/BR arm. SAEs related to study treatment with acalabrutinib, idelalisib, bendamustine, rituximab in IR, and rituximab in BR were reported in 11.7%, 42.4%%, 8.6%, 12.7%, and 5.7% of subjects who received those study drugs, respectively. Anaemia, atrial fibrillation, and pneumonia were the only acalabrutinib-related SAEs reported in ≥ 2 subjects in the main study period. During the crossover period, SAEs were reported in 38.8% of subjects.

TEAEs that led to discontinuation of study treatment in the main study period occurred in 23.4%, 66.9%, and 17.1% of subjects in the acalabrutinib, IR, and BR treatment arms, respectively. TEAEs that led to dose reduction were reported in 6.5%, 11.9%, and 14.3% of subjects in the 3 arms, respectively, and TEAEs that led to dose withholding were reported in 46.8%, 68.6%, and 20.0% of subjects in the 3 arms, respectively. During the crossover period, 17.5% of subjects had TEAEs that led to discontinuation of acalabrutinib.

Most subjects had ECIs, which are events that are known side effects of an approved Bruton tyrosine kinase (BTK) inhibitor. Atrial fibrillation occurred in 7.8%, 3.4%, and 2.9% of subjects in the acalabrutinib, IR, and BR treatment arms, respectively, in the main study period. Two (2.5%) subjects had atrial fibrillation during the crossover period. Neutropenia events (including neutropenia, decreased neutrophil count, and febrile neutropenia) occurred in 26.0%, 52.5%, and 37.1% of subjects in the acalabrutinib, IR, and BR treatment arms, respectively, during the main study period. Neutropenia events were reported in 25.0% of subjects during the crossover period. Hemorrhage events were reported in 30.5%, 8.5%, and 5.7% of subjects in the acalabrutinib, IR, and BR arms, respectively, in the main study period, and major hemorrhage events were reported in 3.2%, 2.5%, and 2.9% of subjects in the 3 treatment arms, respectively. During the crossover period, hemorrhage events were reported in 17.5% of subjects, and 5.0% of subjects had events of major hemorrhage. Events of hepatotoxicity were reported in 5.8%, 29.7%, and 8.6% of subjects in the acalabrutinib, IR, and BR arms, respectively, in the main study period. One subject (1.3%) had a hepatotoxicity

event during the crossover period. Hypertension was reported in 7.8%, 5.9%, and no subjects treated with acalabrutinib, IR, and BR, respectively, during the main study period. During thecrossover period, 1 subject (1.3%) had hypertension. Infections occurred in 68.2%, 72.9%, and 48.6% of subjects treated with acalabrutinib, IR, or BR, respectively, during the main study period, and Grade ≥ 3 infections occurred in 29.2%, 33.9%, and 11.4% of subjects in the3 treatment arms, respectively. During the crossover period, 52.5% of subjects had infections,including 25.0% of subjects with Grade ≥ 3 infections. Interstitial lung disease/pneumonitis occurred in 1.9%, 7.6%, and no subjects in the acalabrutinib, IR, and BR treatment arms, respectively, during the main study period. During the crossover period, 5.0% of subjects hadinterstitial lung disease/pneumonitis. Treatment-emergent second primary malignancies occurred in 18.2%, 4.2%, and 5.7% of subjects in the acalabrutinib, IR, and BR treatment groups, respectively, during the main study period. Twelve acalabrutinib-treated subjects had SAEs of second primary malignancies during the main study period, including 4 subjects withGrade 5 events. Two subjects had secondary primary malignancies considered related to acalabrutinib. During the crossover period, 9 (11.3)% subjects had second primary malignancies. TLS occurred in 1 acalabrutinib-treated subject and 1 IR-treated subject during the main study period; both events resolved and did not lead to study treatment discontinuation. There were no subjects with TLS during the crossover period.

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 among acalabrutinib-treated subjects. There was a trend toward worsening of baseline toxicity grade for some hematology parameters, decreased ANC, decreased hemoglobin, decreased platelets,and increased leukocytes. Lymphocytosis occurred in 71.4%, 51.7%, and 2.9% of subjects in the acalabrutinib, IR, and BR treatment arms, respectively. There were no acalabrutinib- treated subjects with elevations ≥ 3 × ULN in ALT or AST concurrent with total bilirubin
≥ 2 × ULN.

Conclusion

In this study in subjects with R/R CLL, acalabrutinib demonstrated a clinically meaningful and statistically significant improvement in PFS compared with IR/BR, with a 69% reductionin risk of IRC-assessed disease progression or death (HR = 0.31; $p < 0.0001$). The PFS benefit of acalabrutinib was consistent across all prespecified subgroups including subjects with high-risk cytogenetic features, and was also demonstrated in subjects who progressed after starting subsequent anticancer therapy. Acalabrutinib showed an acceptable safety and tolerability profile which was consistent with the other acalabrutinib monotherapy clinical trials.