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Interim Clinical Study Report

Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-CL-007
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A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia

Study dates: First subject randomized: 14 September 2015
Last subject randomized: 08 February 2017
The analyses presented in this report are based on a data cutoff date of 08 February 2019 with data extract on 09 April 2019.

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

Study enrollment was completed on 08 February 2017. This study was conducted at 142 study centers in 18 countries.

Publications

None as of the data cutoff date of 08 February 2019.

2.1 Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B) based on IRC assessment of progression-free survival (PFS) per International Workshop on Chronic Lymphocytic Leukemia criteria (IWCLL; 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 previously untreated 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 comes first. KM curve was used to estimate the distribution of PFS.
Key Secondary	Efficacy	To evaluate obinutuzumab+chlorambucil (Arm A) compared with acalabrutinib monotherapy (Arm C) in terms of:	
		• IRC-assessed PFS per IWCLL 2008 in subjects with untreated 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 comes first. KM curve was used to estimate the distribution of PFS.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Other Secondary	Efficacy	To evaluate the comparison of acalabrutinib+obinutuzumab (Arm B) versus obinutuzumab+chlorambucil (Arm A) and acalabrutinib monotherapy (Arm C) versus obinutuzumab+chlorambucil (Arm A) in terms of:	
		• IRC-assessed ORR per IWCLL 2008 criteria	ORR was defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, or PR at or before initiation of subsequent anticancer therapy. ORR including PRL was defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, PR or PRL at or before initiation of subsequent anticancer therapy
		• TTNT	TTNT was defined as the time from randomization to start date of non-protocol specified subsequent anticancer therapy for CLL or death due to any cause, whichever came first. TTNT was analyzed in the same fashion as that for the primary efficacy analysis
		• OS	OS was defined as the time from date of randomization to death due to any cause.
Exploratory	Efficacy	CCI [redacted]	

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		CCI [redacted]	
Safety		• Incidence and severity of AEs, SAEs, and changes in laboratory measurements.	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 score.

AE=adverse event; CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with incomplete bone marrow recovery; CSR=clinical study report; del=deletion; ECOG=Eastern Cooperative Oncology Group; CCI [redacted] 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; PRL=partial response except for lymphocytes; CCI [redacted] PR=partial response; SAE=serious adverse event; TEAE=treatment-emergent 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 not received any prior systemic treatment for CLL. The study was designed to determine the efficacy of acalabrutinib in combination with obinutuzumab versus obinutuzumab in combination with chlorambucil (primary endpoint) and acalabrutinib monotherapy versus obinutuzumab in combination with chlorambucil (key secondary endpoint) in subjects with previously untreated CLL, as measured primarily by Independent Review Committee (IRC)-assessed progression-free survival (PFS). Overall response rate (ORR), time to next treatment (TTNT), overall survival (OS), and patient-reported outcomes (PROs) were also assessed.

Subjects were randomized in a 1:1:1 ratio into 3 arms. Subjects randomized to Arm A received obinutuzumab+chlorambucil, subjects randomized to Arm B received acalabrutinib+ obinutuzumab, and subjects randomized to Arm C received acalabrutinib monotherapy.

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 geographic region (North America and Western Europe versus Other).

Each treatment cycle was 28 days (4 weeks). Subjects in Arms A and C received acalabrutinib 100 mg BID orally starting Cycle 1 Day 1 until unacceptable drug-related toxicity or disease progression. Subjects in Arms A and B received 100-1000 mg as an intravenous (IV) infusion starting on Cycle 1 Day 1 for a total of 6 cycles. Subjects in Arm A received chlorambucil 0.5 mg/kg orally on Days 1 and 15 of Cycles 1 through 6.

At the investigator's discretion, subjects randomized to the obinutuzumab+chlorambucil arm who had an Independent Review Committee (IRC)-confirmed disease progression and who met crossover eligibility criteria could receive crossover treatment with single-agent acalabrutinib100 mg BID orally 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 (Cheson et al. 2012). The investigator evaluated sites of disease by radiological imaging (primary), physical examination or other procedures as necessary, review of hematology results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline were used throughout the study. A central laboratory performed all hematology testing for the primary endpoint analysis. Confirmation of complete response (CR) required bone marrow analysis and radiologic tumor assessment. 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 score.

All subjects who permanently discontinued study drug for any reason (except for death, loss to follow-up or withdrawal of consent), including disease progression, had an early termination (ET) visit for safety assessments within 7 days of the last dose of all study drugs. The ET visit was not required for subjects who discontinued from the study treatment within 10 days of a scheduled study visit or if the ET visit would be performed within 14 days of the safety follow-up (SFU) visit. If the SFU visit was within ±7 days of a regularly scheduled visit during the Post-treatment Phase, the visits could be combined into a single visit.

After progression, subjects were followed for subsequent anticancer therapy (with start date of therapy and IWCLL indication for treatment initiation), additional malignancy occurrence, and survival status. Subjects were followed until death, loss to follow-up, consent withdrawal, or study closure, whichever occurred first.

The primary efficacy analysis was based on assessment from an IRC. As part of the IRC review, radiographic evaluations assessed by independent central radiologists and hematology results from a central laboratory were provided when available, when not available, hematology results from local laboratories were provided. Detailed procedures are described in the IRC charter (Appendix 16.1.16). An independent Data Monitoring Committee (DMC) was formed and constituted according to regulatory agency guidelines. The DMC reviewed the safety data periodically and provided recommendations according to the DMC charter (Appendix 16.1.16).

One interim analysis was planned for the study. Details and results of this planned interim analysis are provided in Section 9.8.4.

The end of study is defined as the point when the last subject on the study has documented disease progression or death, or has been lost to follow-up, whichever occurs first. The anticipated study duration is 4.5 years including enrollment time.

This interim clinical study report presents the results of the planned interim analysis and presents data collected through the cutoff date of 08 February 2019.

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 not received any prior systemic therapy for CLL.

Number of Subjects (Planned and Analyzed)

The study was planned to enroll approximately 510 subjects. A total of 535 subjects were randomized and all 535 subjects were analyzed in the intent-to-treat (ITT) population.

Investigational Product and Comparators: 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 provided in Appendix 16.1.6.

Obinutuzumab: 100-1000 mg diluted from 25 mg/mL liquid concentrate, administered as IV infusion for a total of 6 treatment cycles. On Cycle 1 Day 1, subjects received obinutuzumab 100 mg. On Cycle 1 Day 2, subjects received 900 mg. On Cycle 1 Days 8 and 15, subjects received 1000 mg. On Day 1 of Cycles 2 to 6, subjects received 1000 mg.

Chlorambucil: 2 mg film-coated tablet: administered orally at doses of 0.5 mg/kg on Days 1 and 15 of Cycles 1 through 6 for a total of 6 treatment cycles.

Duration of Treatment

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

Daily administration of acalabrutinib continued until disease progression or unacceptable toxicity. Obinutuzumab and chlorambucil were administered for a maximum of 6 cycles.

Statistical Methods

Determination of Sample Size

The study was expected to enroll approximately 510 subjects with a 1:1:1 randomization ratio between the 3 treatment arms (approximately 170 subjects per arm). The sample size calculation was driven by hypothesis test between acalabrutinib+obinutuzumab and obinutuzumab+chlorambucil.

The study was sized to achieve approximately 90% power to detect a hazard ratio (HR) (acalabrutinib+obinutuzumab/obinutuzumab+chlorambucil) of 0.60 for PFS which, under the model assumptions, CCI [redacted]

CCI [redacted] Given the study assumptions, the minimum detectable treatment difference at the final analysis of PFS corresponds to a CCI [redacted]

Analysis Methods

Analyses of all efficacy endpoints were conducted on the ITT Population, which was defined as all randomized subjects to be analyzed according to the arm to which they were randomly assigned (N=179 for acalabrutinib+obinutuzumab, N=179 for acalabrutinib monotherapy, and N=177 for obinutuzumab+chlorambucil). These endpoints (except OS) included data prior to crossover for obinutuzumab+chlorambucil subjects who crossed over to acalabrutinib monotherapy. Overall survival was analyzed based on the ITT population during the entire study including the crossover period.

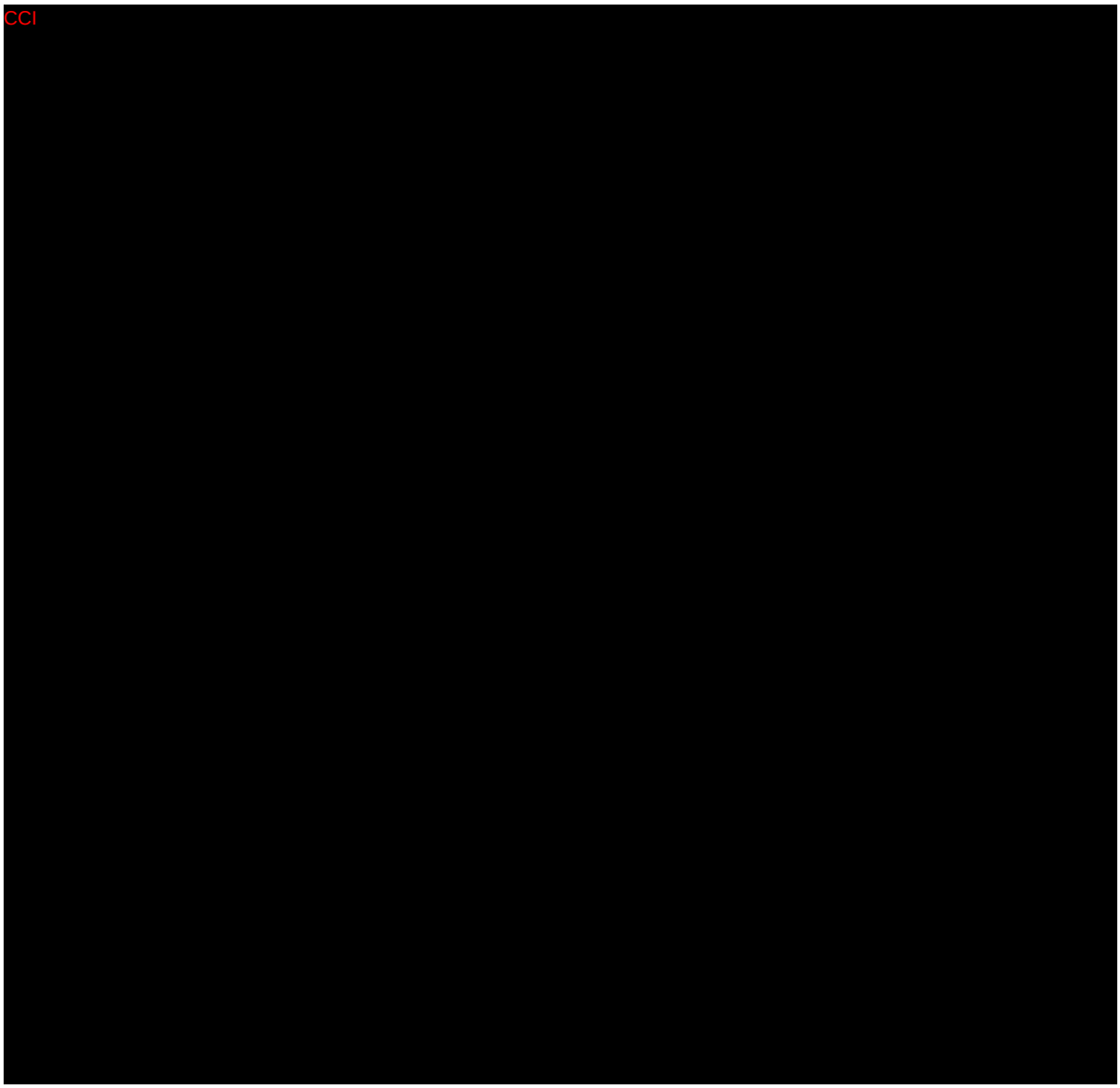
The primary efficacy analysis was to compare PFS as assessed by IRC between obinutuzumab+chlorambucil and acalabrutinib+obinutuzumab in the ITT population using a stratified log rank test adjusting for randomization stratification factors. The estimate of the HR (acalabrutinib+obinutuzumab/obinutuzumab+chlorambucil) and the corresponding 95% CI was computed using a Cox proportional hazards model stratified by randomization stratification factors. Randomization stratification factors were based on interactive web response system (IWRS) assignment. Kaplan-Meier (KM) curve was used to estimate the distribution of PFS. The proportion of subjects who are progression free were estimated based on KM method and its corresponding 95% CI were calculated at selected timepoints for each treatment arm. A summary of PFS events was provided by 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.

The key secondary efficacy endpoint was IRC-assessed PFS between obinutuzumab+ chlorambucil and acalabrutinib monotherapy in the ITT population. The analysis method was the same method used for the primary efficacy analysis; subgroup and sensitivity analyses were also performed in the same manner (see above).

Additional efficacy endpoints comparing acalabrutinib+obinutuzumab versus obinutuzumab+chlorambucil and acalabrutinib monotherapy versus obinutuzumab+ chlorambucil included IRC-assessed ORR, ORR with partial response with lymphocytosis (PRL), TTNT, and OS. 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. ORR including PRL was analyzed using the same methods. TTNT and OS were analyzed using in the same fashion as the primary analysis.

CCI



Safety analyses were performed using the Safety Population, defined as all subjects who received any amount of study drug. For the obinutuzumab+chlorambucil subjects who crossed over to acalabrutinib monotherapy, all safety analyses, except for death, included data only prior to the crossover period. Refer to Section 9.8.1.3 for details on the safety statistical methods.

Subject Population

Study enrollment is completed. The study randomized a total of 535 subjects in 142 study sites in 18 countries between 14 September 2015 through 08 February 2017. Subjects were randomized (1:1:1) as follows: 179 subjects in the acalabrutinib+obinutuzumab arm, 179 subjects in the acalabrutinib monotherapy arm, and 177 subjects in the obinutuzumab+ chlorambucil arm. A total of 9 randomized subjects (1 subject in the acalabrutinib monotherapy arm and 8 subjects in the obinutuzumab+chlorambucil arm) did not receive at least 1 dose of a study drug.

As of the data cutoff date of 08 February 2019, 163 subjects (91.1%) in the acalabrutinib+ obinutuzumab arm and 152 subjects (85.9%) in the obinutuzumab+chlorambucil arm have completed 6 cycles of obinutuzumab and 137 subjects (77.4%) in the obinutuzumab+ chlorambucil arm completed 6 cycles of chlorambucil. A total of 289 subjects were still receiving acalabrutinib treatment (146 subjects [81.6%] in the acalabrutinib+ obinutuzumab arm and 142 subjects [79.3%] in the acalabrutinib monotherapy arm). No subjects were still receiving obinutuzumab or chlorambucil.

The median age for all subjects was 70.0 years. The majority of all subjects (83.7%) were ≥65 years old, and over half (61.3%) were male. Almost all subjects (93.3%) were white, and not Hispanic or Latino (89.9%). There were no noteworthy differences in demographics between the 3 treatment arms.

A total of 87 subjects were <65 years of age, 13/87 subjects (14.9%) had a creatinine clearance of 30-69 mL/min, 66/87 subjects (75.9%) had a Cumulative Illness Rating Scale–Geriatric (CIRS-G) score >6. Among those subjects <65 years of age, 75/87 subjects (86.2%) met either creatinine clearance or CIRS-G eligibility score criteria.

Summary of Efficacy Results

The acalabrutinib+obinutuzumab arm demonstrated a statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab+chlorambucil arm, with a 90% reduction in risk of disease progression or death (HR=0.10 [95% CI: 0.06–0.17]; p<0.0001). With a median follow-up of 28.5 months in the acalabrutinib+obinutuzumab arm and 28.0 months in the obinutuzumab+chlorambucil arm, the median estimated PFS for acalabrutinib+ obinutuzumab was not reached; the median estimated PFS for obinutuzumab+chlorambucil was 22.6 months (95% CI: 20.2–27.6). The KM estimate of the proportion of subjects without a PFS event at 12 months was 95.9% (95% CI: 91.7–98.0) for acalabrutinib+obinutuzumab and 84.6% (95% CI: 78.0–89.3) for obinutuzumab+chlorambucil. The KM estimate of the proportion of subjects without a PFS event at 36 months was 89.6% (95% CI: 82.0–94.1) for acalabrutinib+obinutuzumab and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+ chlorambucil.

The PFS benefit of acalabrutinib+obinutuzumab compared with obinutuzumab+chlorambucil was consistent across all prespecified subgroups, including 17p deletion, 11q deletion, TP53 mutation, unmutated immunoglobulin heavy-chain variable (IgHV), Rai stage III-IV, B2–microglobin >3.5 mg/L at baseline, and bulky disease ≥5 cm, with HR ranging from 0.04–0.18. 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+obinutuzumab compared with obinutuzumab+chlorambucil (HR=0.08 [95% CI: 0.04–0.15]).

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+obinutuzumab compared with obinutuzumab+chlorambucil (HR=0.11 [95% CI: 0.06–0.18]; p<0.0001). All other sensitivity analyses were also consistent with the primary analysis, with HR ranging from 0.08–0.11, which was statistically significant for all analyses (p<0.0001).

The acalabrutinib monotherapy arm demonstrated a statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab+chlorambucil arm, with an 80% reduction in risk of disease progression or death (HR=0.20 [95% CI: 0.13–0.30]; p<0.0001). With a median follow-up of 28.4 months in the acalabrutinib monotherapy and 28.0 months in the obinutuzumab+chlorambucil arm, the median estimated PFS for acalabrutinib monotherapy was not reached; the median estimated PFS for obinutuzumab+chlorambucil was 22.6 months (95% CI: 20.2–27.6). The KM estimate of the proportion of subjects without a PFS event was 92.9% (95% CI: 87.8–95.9) for acalabrutinib monotherapy and 84.6% (95% CI: 78.0–89.3) for obinutuzumab+chlorambucil at 12 months and 63.9% (95% CI: 29.4–84.9) for acalabrutinib monotherapy and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+chlorambucil at 36 months.

The PFS benefits of acalabrutinib monotherapy compared with obinutuzumab+chlorambucil was consistent across all prespecified subgroups, including 17p deletion, 11q deletion, TP53 mutation, unmutated IgHV, Rai stage III-IV, B2-microglobin >3.5 mg/L at baseline, and bulky disease ≥5 cm, with HR ranging from 0.07–0.76. 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 monotherapy compared with obinutuzumab+chlorambucil (HR=0.13 [95% CI: 0.08–0.21]).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the key secondary endpoint analysis and showed similar improvement in PFS for acalabrutinib monotherapy compared with obinutuzumab+chlorambucil (HR=0.20 [95% CI: 0.13–0.31]; p<0.0001). All other sensitivity analyses were also consistent with the key

secondary endpoint analysis, with HR ranging from 0.15–0.21, which was statistically significant (without multiplicity adjustment) for all analyses (p<0.0001).

IRC-assessed ORR (CR+CRi+nPR+PR) for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 93.9%, 85.5%, and 78.5%, respectively. IRC-assessed ORR difference between acalabrutinib+obinutuzumab and obinutuzumab+ chlorambucil was 15.3% (p<0.0001). Per IRC assessment, CR was achieved in 23 subjects in the acalabrutinib+ obinutuzumab arm, 1 subject in acalabrutinib monotherapy arm, and 8 subjects in the obinutuzumab+chlorambucil. PR was achieved in 143 (79.9%) subjects in the acalabrutinib+ obinutuzumab arm, 150 (83.8%) subjects in the acalabrutinib monotherapy arm, and 128 (72.3%) subjects in the obinutuzumab+chlorambucil arm.

CCI [redacted]

TTNT was significantly prolonged for both the acalabrutinib+obinutuzumab arm (HR=0.14 [95% CI: 0.08–0.26]; p<0.0001) and the acalabrutinib monotherapy arm (HR=0.24 [95% CI: 0.15–0.40]; p<0.0001) compared with obinutuzumab+chlorambucil arm. The KM estimate of the proportion of subjects without starting next anticancer treatment for acalabrutinib+ obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 93.2%, 92.6%, and 78.5%, respectively, at 18 months and 90.0%, 86.3%, and 50.2%, respectively, at 36 months.

The estimated median OS was not reached in any of the treatment arms, with an HR of 0.47 (95% CI: 0.21–1.06; p=0.0577) for the acalabrutinib+obinutuzumab and an HR of 0.60 (95% CI: 0.28–1.27; p=0.1556) for acalabrutinib monotherapy arm compared with obinutuzumab+chlorambucil arm.

Summary of CCI [redacted]

CCI [redacted]

Summary of Safety Results

The median duration of exposure to acalabrutinib in the acalabrutinib+obinutuzumab arm was 27.7 months (range: 0.7–40.3 months) and was 27.7 months (range 0.3–40.2 months) in the acalabrutinib monotherapy arm.

Common TEAEs that occurred in ≥20% of acalabrutinib+obinutuzumab arm subjects were headache (39.9%), diarrhea (38.8%), neutropenia (31.5%), fatigue (28.1%), contusion (23.6%), arthralgia (21.9%), cough (21.9%), upper respiratory tract infection (21.3%), and nausea (20.2%). Most of these common TEAEs were Grade 1 or 2, with the exception of neutropenia (most TEAEs were Grade 3-4). Common TEAEs that occurred in ≥20% of acalabrutinib monotherapy arm subjects were headache (36.9%), diarrhea (34.6%), and nausea (22.3%). Of these frequent TEAEs, all were Grade 1 or 2 in severity, with the exception of 2 subjects (1.1%) with Grade 3 TEAEs of headache, and 1 subject (0.6%) with a Grade 3 TEAE of diarrhea. None of these frequent TEAEs were Grade 4. Common TEAEs that occurred in ≥20% of obinutuzumab+ chlorambucil subjects were neutropenia (45.0%), infusion-related reaction (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%). Most of these frequent TEAEs were Grade 1 or 2, with the exception of neutropenia (most TEAEs were Grade 3-4).

Subjects in the acalabrutinib monotherapy treatment arm had notably lower rates of most Grade ≥3 TEAEs compared to the other 2 treatment arms: 70.2%, 49.7%, and 69.8% for subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil arms, respectively. The most frequently occurring Grade ≥3 TEAEs were neutropenia (29.8%, 9.5%, and 41.4% for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively), thrombocytopenia (8.4%, 2.8%, and 11.8%, respectively), and anemia (5.6%, 6.7%, and 7.1%, respectively).

Treatment-related TEAEs were reported less frequently in the acalabrutinib monotherapy treatment arm than in either of the acalabrutinib+obinutuzumab (65.7% versus 80.9%, respectively) or obinutuzumab+chlorambucil (65.7% versus 91.1%, respectively) treatment arms.

Overall, 8 subjects (4.5%) in the acalabrutinib+obinutuzumab arm, 12 subjects (6.7%) in the acalabrutinib monotherapy arm, and 13 subjects (7.7%) in the obinutuzumab+chlorambucil arm died as of the data cutoff date of 08 February 2019. Deaths within 30 days of the last dose of study drug occurred in 3 subjects (1.7%) in both the acalabrutinib+obinutuzumab and acalabrutinib monotherapy arms and in 2 subjects (1.2%) in the obinutuzumab+chlorambucil arm. Two additional subjects died during the crossover period (1 of these deaths was within the last 30 days of acalabrutinib dose).

SAEs occurred in 38.8%, 31.8%, and 21.9% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. The most common SAE in the acalabrutinib+obinutuzumab arm was pneumonia (6.7%), which was also the most common Grade ≥3 SAE (at 4.5%). No SAEs (any grade or Grade ≥3) occurred in the acalabrutinib monotherapy arm with a frequency of over 3%. The most common SAEs (>3% of subjects) in the obinutuzumab+chlorambucil arm were tumor lysis syndrome (TLS) (4.7%) and febrile neutropenia (4.1%), both of which were also the most common Grade ≥3 SAEs (4.7% and 4.1%, respectively).

A total 10.7% of subjects in the acalabrutinib+obinutuzumab arm and 9.5% of subjects in the acalabrutinib monotherapy arm discontinued acalabrutinib treatment due to TEAEs. The most common TEAEs leading to acalabrutinib discontinuation were hepatitis B reactivation and sepsis (2 subjects each), all in the acalabrutinib+obinutuzumab arm. A total of 6.2% of subjects in the acalabrutinib+obinutuzumab arm and 5.9% of subjects in the obinutuzumab+ chlorambucil arm discontinued obinutuzumab treatment due to TEAEs. The most common TEAEs leading to obinutuzumab discontinuation were infusion-related reaction (1.1% of subjects in the acalabrutinib+obinutuzumab arm and 1.2% in the obinutuzumab+ chlorambucil arm) and neutropenia (1.1% and 1.8% in the acalabrutinib+ obinutuzumab and obinutuzumab+chlorambucil arms, respectively). In the obinutuzumab+chlorambucil arm, 14.2% of subjects discontinued chlorambucil treatment due to TEAEs. The most frequent TEAEs leading to chlorambucil discontinuation were neutropenia (6.5%), thrombocytopenia and upper respiratory tract infection (1.2% each).

Most subjects had events of clinical interest (ECIs), which are events based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of an approved BTK inhibitor. Atrial fibrillation occurred in 3.4%, 3.9%, and 0.6% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil arms, respectively. Neutropenia events (including the preferred terms of neutropenia, neutrophil count decreased and febrile neutropenia) occurred with less frequency in the acalabrutinib monotherapy arm than the other 2 treatment arms: 33.1%, 11.7%, and 49.1% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. Hemorrhage events occurred with less frequency in the obinutuzumab+chlorambucil arm than the other 2 treatment arms: 42.7%, 39.1%, and 11.8% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. Hepatotoxicity occurred more frequently in the acalabrutinib+obinutuzumab arm than the other 2 arms: 9.0%, 2.2%, and 4.7% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+ chlorambucil arms, respectively. Infections occurred at the highest rate of all ECI categories: 69.1%, 65.4%, and 43.8% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. Second primary malignancies occurred in 10.7%, 8.4%, and 3.6% of subjects in the acalabrutinib+

obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. TLS events occurred most commonly in the obinutuzumab+chlorambucil arm: 1.7%, 0%, and 8.9% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively. Interstitial lung disease/pneumonitis events were infrequent (0.6%, 1.1%, and 0.6% of subjects in the acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil arms, respectively).

There were no clinically meaningful trends in hematology or clinical laboratory values, serum immunoglobulin values, T/B/NK cell counts, or vital sign values among acalabrutinib-treated subjects. In the obinutuzumab-containing treatment arms, there was a common trend toward worsening of baseline toxicity grade for the hematology parameters of decreased absolute lymphocyte count (ALC), absolute neutrophil count (ANC), hemoglobin, platelets, and leukocytes. In the acalabrutinib-containing treatment arms, there were trends toward worsening of baseline toxicity grade for decreased ANC and platelets, and increased leukocytes. By Hallek 2008 criteria, the frequency of hematologic abnormalities (Grade 3-4) of decreased ANC and decreased platelets was notably lower in the acalabrutinib monotherapy arm compared to the other 2 treatment arms: decreased ANC (11.7% acalabrutinib monotherapy versus 34.3% acalabrutinib+ obinutuzumab and 46.7% obinutuzumab+chlorambucil) and decreased platelets (7.3% acalabrutinib monotherapy versus 15.2% acalabrutinib+obinutuzumab and 29.0% obinutuzumab+chlorambucil). Lymphocytosis occurred in slightly more subjects in the acalabrutinib monotherapy arm than in either of the other 2 treatment arms: 63.1% acalabrutinib monotherapy versus 57.9% acalabrutinib+obinutuzumab, and 0% for obinutuzumab+chlorambucil. A total of 6 subjects (2 subjects in each treatment arm) fulfilled the biochemical criteria for Hy's law (elevations $\geq$3×ULN in ALT or AST, concurrent with total bilirubin $\geq$2×ULN).

Conclusion

The primary endpoint was met in this study in subjects with treatment-naïve CLL; acalabrutinib+obinutuzumab demonstrated a clinically meaningful and statistically significant improvement in PFS compared with obinutuzumab+chlorambucil, with a 90% reduction in risk of IRC-assessed disease progression or death (HR=0.10; $p<0.0001$). The key secondary endpoint was met in this study; acalabrutinib monotherapy demonstrated a clinically meaningful and statistically significant improvement in PFS compared with obinutuzumab+ chlorambucil, with an 80% reduction in risk of IRC-assessed disease progression or death (HR=0.20; $p<0.0001$). The PFS benefit of acalabrutinib+obinutuzumab and acalabrutinib monotherapy compared with obinutuzumab+chlorambucil 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 (either in combination with obinutuzumab or as monotherapy) showed an acceptable safety profile and was well tolerated.