Clinical Study Report	
Drug Substance	Acalabrutinib
Study Code	ACE-LY-001
Edition Number	1
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A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies

Study dates: First subject enrolled: 13 January 2015
Last subject last visit: 01 June 2020
The analyses presented in this report are based on a database lock date of 30 Jun 2020.

Phase of development: 1/2

Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

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.

SYNOPSIS

Study centres

This study was conducted at 7 study centers in the United States.

Publications

Barr PM, Smith SD, Roschewski M, et al. Acalabrutinib combined with PI3Kδ inhibitor ACP319 in patients with relapsed or refractory B-cell malignancies. J Clin Oncol 2018;36(15 Suppl):7518.

Objectives and criteria for evaluation

Objective	Endpoint/Variable
Primary Objective	
To characterize the safety profile of acalabrutinib and ACP-319 in subjects with relapsed or refractory B-cell malignancies.	The safety of acalabrutinib and ACP-319 will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation or dose reduction of study treatment.
Secondary Objectives	
To document the extent of study drug exposure as determined by coadministration of acalabrutinib and ACP-319	Exposure to study drug was described by summarizing the number of subjects who received at least one dose, duration of exposure, actual cumulative dose, average daily dose, and relative dose intensity.
To evaluate the PD effects of acalabrutinib and ACP-319 administration	PD analyses were performed and reported in a separate report.
To evaluate the activity of acalabrutinib and ACP-319	• Response rate • Duration of response • Progression-free survival • Time-to-next treatment

Abbreviations: AE=adverse event; PD=pharmacodynamic; PK=pharmacokinetic; SAE=serious adverse event.

Study design

This study was a multicenter, open-label, nonrandomized, sequential group, dose-escalation study planned to be conducted at approximately 30 sites. The study was divided into 2 parts: Part 1 of the study was the dose-escalation portion and Part 2 allowed for possible expansion groups (Figure S1).

A cycle was defined as a period of 28 days.

Part 1

In each dose-escalation cohort, subjects took acalabrutinib and ACP-319 twice daily (BID) at approximately 12-hour intervals. The acalabrutinib dose was fixed at 100 mg BID. The ACP-319 dose was escalated as follows:

- Cohort 1: Acalabrutinib 100 mg BID + ACP-319 25 mg BID continuously
- Cohort 2: Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously
- Cohort 3: Acalabrutinib 100 mg BID + ACP-319 100 mg BID continuously

Each dosing cohort was enrolled sequentially with 6 subjects per cohort. If ≤1 dose-limiting toxicity (DLT) was observed in the cohort during Cycle 1, escalation to the next cohort would proceed. If ≥2 DLTs were observed during Cycle 1, dosing at that dose and higher was suspended and the maximum tolerated dose (MTD) was established as the previous cohort. The MTD was defined as the highest daily dose for which fewer than 33% of the subjects experienced a DLT during Cycle 1. Escalation ended with Cohort 3 or sooner if the MTD was reached in an earlier cohort.

Part 1 of the study included adult subjects with the following disease types:

- Non-germinal center B-cell subtype (non-GCB) diffuse large B-cell lymphoma (DLBCL), characterized as de novo
- Mantle cell lymphoma (MCL), characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1
- Indolent non-Hodgkin's lymphoma (iNHL)
    - Follicular lymphoma (FL) Grade 1, 2 or 3a
    - Waldenstrom macroglobulinemia (WM)
    - Chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL)

Part 2

Part 2 consisted of expansion groups of up to 12 subjects per histology provided the safety and efficacy results from Part 1 of the study indicated that further evaluation of the combination was warranted. The possible expansion groups for Part 2 could have include adult subjects with the following disease types:

- Non-GCB DLBCL, characterized as de novo
- Germinal center B-cell subtype (GCB) DLBCL
- Richter's syndrome

- MCL, characterized by documentation of monoclonal B cells that had a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1
- iNHL
    - FL, Grade 1, 2, or 3a
    - WM
    - CLL/SLL
- Multiple myeloma (MM)
- B-cell acute lymphoblastic leukemia (B-ALL)

Treatment with acalabrutinib and ACP-319, in Part 1 and Part 2, may have been continued until disease progression or an unacceptable drug-related toxicity occurred. Dose modification provisions are provided in the study protocol. Note: Temporary withholding of study drug for as little as 7 days could cause a transient worsening of disease and/or of constitutional symptoms. All subjects who discontinued study treatment had a safety follow-up (SFU) visit 30 (+7) days after the last dose of study drug and were followed every 3 months thereafter until disease progression or the start of alternative anticancer treatment. As of Protocol Amendment 4, Part 2 enrollment was open only to subjects with non-GCB DLBCL.

All subjects had hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commenced (Day 1), all subjects receiving acalabrutinib and ACP-319 combination therapy were evaluated for safety, including serum chemistry and hematology, on Cycle 1 Days 1, 8, 15, 22, and 28, Cycle 2 Days 15 and 28, then monthly through Cycle 24, and every 3 months thereafter. Electrocardiograms (ECGs) were obtained at screening, repeatedly during Cycle 1, at each study visit through Cycle 6, and at each study visit in Cycles 9 and 12. Pharmacokinetic testing was done in Cycles 1 to 4. Pharmacodynamic testing was done in Cycles 1 and 2, and at the treatment termination (TT) visit. Radiologic tumor assessments were done at screening and at the end of Cycle 2, Cycle 4, and Cycle 6; every 3 cycles (12 weeks) through Cycle 18, and then every 6 cycles thereafter, or more frequently at the investigator's discretion.

Subjects showing clinical benefit and who were tolerating study treatment may have remained on study until the end of study, defined as 36 months after the last subject was enrolled. Subjects who were still on treatment at the end of the study and deriving clinical benefit from acalabrutinib monotherapy may have been eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy.

Subjects who were still on treatment at the final study analysis and deriving clinical benefit from acalabrutinib treatment may have continued treatment. At the time of the final data cutoff and database closure, subjects who remained in this study remained within this study protocol for continued access to study drug. All active subjects were eligible to continue to receive acalabrutinib after database closure. There was no further data collection other than reporting of serious adverse events (SAEs). Access to study treatment within this study protocol enabled

continued treatment with visit assessments per standard of care. Some subjects who met criteria of progressive disease and were continuing to gain clinical benefit from therapy may have been able to temporarily remain on acalabrutinib after discussion with the medical monitor.

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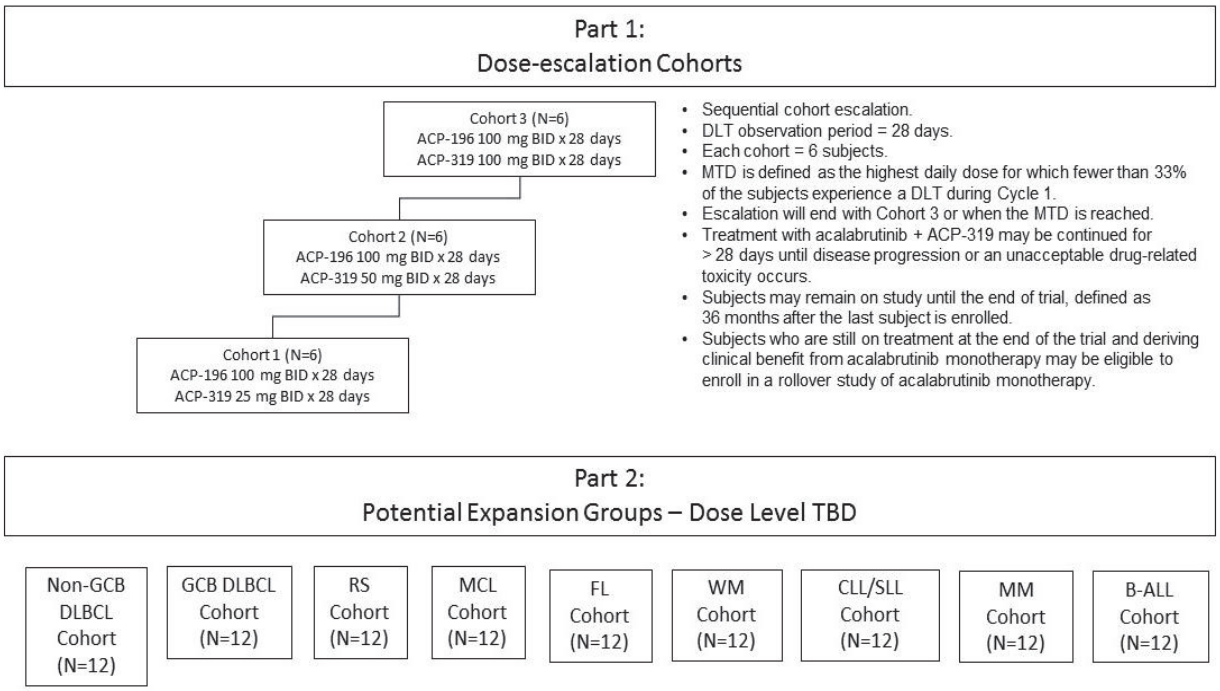
subjects on combination therapy (acalabrutinib+ACP-319) discontinued ACP-319 and continued on monotherapy (acalabrutinib) at the subject's current dose at the investigator's discretion.

Figure S1 Flow Chart of Study Design



Abbreviations: B-ALL=B-cell acute lymphoblastic leukemia; BID=twice daily; CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma; DLT=dose-limiting toxicity; FL= follicular lymphoma; GCB DLBCL=germinal center B-cell subtype diffuse large B-cell lymphoma; MM=multiple myeloma; MTD=maximum tolerated dose; non-GCB DLBCL=non-germinal center B-cell diffuse large B-cell lymphoma; RS=Richter's syndrome; TBD=to be determined; WM=Waldenström macroglobulinemia.

Note: Under Amendment 2 of this protocol, all subjects were to receive ACP-319 50 mg BID and acalabrutinib 100 mg BID in Part 2.

Note: Under Amendment 3 of this protocol, subjects with CLL/SLL in Parts 1 and 2 will receive acalabrutinib monotherapy (100 mg BID).

Note: Under Amendment 4 of this protocol, enrollment in Part 2 is closed for all cohorts except the non-GCB DLBCL cohort.

Note: Under Amendment 5 of this protocol, subjects still deriving clinical benefit from monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy.

Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID).

Target subject population and sample size

In Part 1 (dose-escalation portion), each dosing cohort was enrolled sequentially with 6 subjects per cohort. The study employed the standard National Cancer Institute definition of MTD (starting dose associated with Cycle 1 DLT in <33.3% of subjects). The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next stage of the study if the true underlying proportion of DLT was low. Escalation was to end with Cohort 3 or sooner if the MTD was reached in an earlier cohort. There was up to 18 subjects enrolled in Part 1.

In Part 2 (expansion groups), enrollment of up to 12 subjects per histology offered the opportunity to determine if there was sufficient antitumor activity to warrant further development in the selected tumor types.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Acalabrutinib 100 mg capsules, administered orally.

ACP-319, 25 mg capsules and 100 mg capsules, administered orally.

Duration of treatment

Treatment with acalabrutinib and ACP-319, in Part 1 and Part 2, may have been continued until disease progression or an unacceptable drug-related toxicity occurred.

Statistical methods

General Principals

Descriptive statistics were used to summarize baseline demographic and disease characteristics, study drug administration, efficacy, and safety outcomes. Descriptive summaries of discrete data presented the sample size and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data presented the sample size, group mean, standard deviation (SD), median, and range. Confidence intervals (CIs) may have been included as appropriate.

Baseline data, subject accountabilities, treatment, medications and safety analysis were summarized by cohorts for Part 1, by DLBCL histologies (GCB DLBCL and non-GCB DLBCL from both Part 1 and Part 2) as well as by disease histology subtype (CLL/SLL, MCL, WM, and FL) within the All-treated population. Primary efficacy analysis overall response rate (ORR) was summarized by histologies for Part 1 and by DLBCL histologies (GCB DLBCL and non-GCB DLBCL from both Part 1 and Part 2) within All-treated population, while the rest of efficacy analysis including duration of response (DOR), progression-free survival (PFS), and time to next treatment (TTNT) were summarized by DLBCL histologies (GCB DLBCL and non-GCB DLBCL from both Part 1 and Part 2) within All-treated population only.

Analysis of Efficacy Endpoints

Response Rate: ORR was defined as the proportion of subjects who achieved a response of partial response (PR) or complete response (CR) per investigator's assessment to treatment.

The primary analysis of ORR was conducted on the All-treated population. ORR and the corresponding 95% two-sided CI calculated using exact binomial distribution were presented. The order of overall response category was CR > PR > stable disease (SD) > progressive disease (PD). For best overall response, each subject was classified to only one response category based on subject's the best response during the study. Descriptive statistics were provided for best overall response. The number and proportion of subjects within each category of response as well as the associated 95% (CIs were presented. The proportion was estimated by dividing the number of subjects within each category of response by the total number of subjects in the analysis population.

Duration of Response: The duration of overall response was defined as the interval from the first documentation of response (CR or PR) to the earlier of the first documentation of definitive disease progression or death from any cause. Data from surviving, non-progressing subjects were censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. The DOR was estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs were calculated for event time quartiles, and event-free rates were calculated at selected time points. In addition, the reason for censoring was summarized.

Progression-free Survival: Progression-free survival was defined as the interval from the start of acalabrutinib and ACP-319 therapy to the earlier of the first documentation of objective disease progression or death from any cause. Data from surviving, non-progressing subjects were censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. PFS was analyzed using the same method as that for DOR.

Time to Next Treatment: Time-to-next treatment was defined as the time from start of acalabrutinib and ACP-319 therapy in this protocol to the start of subsequent anticancer therapy. Data from subjects who had not received subsequent therapy were censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented. Time-to-next treatment was analyzed using the same method as that for DOR.

Analysis of Safety Endpoints

Adverse Events (AEs): Safety analyses were performed on the All-treated population. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code all AEs to a system organ class and preferred term. The severity of the AE was assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Drug-related AEs were those assessed by investigator as related. Through Amendment 4, hematologic AEs for CLL/SLL subjects were graded according to Hallek et al. 2008. Beginning with Amendment 5, all AEs were graded according to CTCAE.

Treatment-emergent adverse events (TEAEs) were defined as those events that occurred (actual or imputed start date) on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.

TEAEs were summarized by system organ class and preferred terms in descending order of frequency, by NCI toxicity grade, and by relationship to study drug. The same summary was provided for serious TEAEs and drug-related serious TEAEs, TEAEs leading to treatment discontinuation, dose reductions, and dose withholdings.

Death information was reported in the study exit eCRF for all deaths. Incidences of deaths were to be reported, along with the primary cause of death.

Adverse Events of Clinical Interest: In addition to general analyses of AEs, events of clinical interest (ECIs) were summarized by frequency and by CTCAE toxicity grade.

Laboratory Test Results: Laboratory data of hematology and serum chemistry up to 30 days after last dose or the safety follow-up visit date, whichever was later, were reported in SI units. Applicable laboratory results were graded according to CTCAE Version 4.03 or higher. Generic normal ranges were applied whenever reference ranges were not available.

Vital Signs: Summary statistics (mean, standard deviation, median, and range) were provided for vital signs at baseline, maximum, change from baseline to maximum, last value, and change from baseline to last value.

In order to be included in the table, a subject must have had both a baseline value and a value for the given post-baseline time point.

ECOG Performance Status: Changes in Eastern Cooperative Oncology Group (ECOG) from baseline to the worst score during the treatment were provided as shift tables.

Physical Examinations: Physical examination data collected at screening and post-treatment were summarized. Descriptive statistics were calculated for each parameter.

Description of Analysis Sets

All-treated population: The safety analyses and primary efficacy analyses were performed on the All-treated population, defined as all enrolled subjects who received ≥1 dose of any study drug.

Efficacy-evaluable population: All subjects in the All-treated population who had ≥1 evaluable response assessment after the first dose of study drug. Sensitivity analyses for efficacy were carried out on the Efficacy-evaluable population.

Subject population

A total of 18 subjects were enrolled to Part 1 (dose escalation) and 22 subjects were enrolled Part 2 (expansion). All subjects discontinued acalabrutinib, ACP-319, and exited the study.

For Part 1 (CLL/SLL [8 subjects], MCL [3 subjects], WM [1 subject], FL [3 subjects], and non-GCB DLBCL [3 subjects]), the median age was 65.0 years (range: 48-77) and most subjects were male, white, and were not Hispanic or Latino. The median prior number of regimens was 2 (range: 1-6).

There were 9 GCB DLBCL subjects and 16 non-GCB DLBCL subjects; the median age was 70.0 years (range: 55-90) and most subjects were male, white, and were not Hispanic or Latino. The median prior number of regimens was 3 (range: 1-5).

There were 8 CLL/SLL, 3 MCL, 1 WM, and 3 FL subjects; the median age was 63.0 years (range: 48-70) and most subjects were male, white, and were not Hispanic or Latino. The median prior number of regimens was 2 (range: 1-6).

Summary of efficacy results

Efficacy conclusions from a total of 18 subjects with B cell malignancies for Part 1 (dose escalation), can be summarized as follows:

- Investigator-assessed ORR (CR+very good PR [VGPR]+PR) was 66.7% (95% CI: 41.0, 86.7) overall. CR was achieved in 3 subjects (16.7%), VGPR was achieved in 1 subject (5.6%), and PR was achieved in 8 subjects (44.4%).

Efficacy conclusions from a total of 25 subjects with GCB DLBCL and non-GCB DLBCL, can be summarized as follows:

- Investigator-assessed ORR (CR+VGPR+PR) was 40.0% (95% CI: 21.1, 61.3) overall. CR was achieved in 4 subjects (16.0%) and PR was achieved in 6 subjects (24.0%).

- Investigator-assessed ORR (CR+VGPR+PR) was 62.5% (95% CI: 35.4, 84.8) for non-GCB DLBCL. CR was achieved in 4 subjects (25.0%) and PR was achieved in 6 subjects (37.5%).

- The median DOR was 8.2 months (95% CI: 1.8, not estimable [NE]) overall. The median DOR was 8.2 months (95% CI: 1.8, NE) for the 10 subjects with non-GCB DLBCL.

- The median PFS was 5.4 months (95% CI: 1.6, 10.1) overall. The median PFS was 1.7 months (95% CI: 0.9, 9.3) for the 9 subjects with GCB DLBCL and was 5.5 months (95% CI: 1.6, 25.1) for the 16 subjects with non-GCB DLBCL.

- The median TTNT was 6.7 months (95% CI: 1.9, 18.1) overall. The mean TTNT was not reached for the 9 subjects with GCB DLBCL and was 7.2 months (95% CI: 1.9, 18.1) for the 16 subjects with non-GCB DLBCL.

Efficacy conclusions from a total of 15 subjects with CLL/SLL, MCL, WM, and FL, can be summarized as follows:

- Investigator-assessed ORR (CR+VGPR+PR) was 73.3% (95% CI, 44.9, 92.2). CR was achieved in 3 subjects (20.0%), VGPR was achieved in 1 subject (6.7%), and PR was achieved in 7 subjects (46.7%). Responders included 8/8 (100.0%) CLL/SLL subjects, 2/3 (66.7%) MCL subjects, 1/1 (100.0%) WM subjects, and 0/3 FL subjects.

Summary of safety results

Note that protocol amendment 3.0 discontinued ACP-319 in subjects with CLL/SLL and protocol amendment 6.0 discontinued ACP-319 in all subjects.

In Part 1 (dose escalation), 3 cohorts were enrolled (acalabrutinib 100 mg BID with ACP-319 25 mg BID [n=6], ACP-319 50 mg BID [n=6], and ACP-319 100 mg BID [n=6]). No DLTs were observed in Cohort 1, 1/6 subjects had a DLT in Cohort 2, and 2/6 subjects had a DLT in Cohort 3. The MTD for ACP-319 was defined to be 50 mg BID. Expansion proceeded with ACP-319 50 mg BID in combination with acalabrutinib 100 mg BID.

For GCB DLBCL and non-GCB DLBCL, the key exposure, safety, and tolerability findings from this study were:

- The median duration of acalabrutinib exposure was 1.7 months (range: 0.5, 58.0) with 4% of subjects receiving ≥12 months of therapy.

- The median duration of ACP-319 exposure was 1.4 months (range: 0.3, 38.7) with 80.0% patients receiving ≤3 months of ACP-319 treatment.

- Common TEAEs that occurred in ≥30% of subjects were diarrhea (56.0%), alanine aminotransferase (ALT) increased (52.0%), aspartate aminotransferase (AST) increased (48.0%), rash (40.0%), and fatigue (36.0%).

- The most common Grade ≥3 TEAEs (≥20%) were ALT increased (28.0%) and AST increased (20.0%).

- No Grade 5 TEAEs occurred.
- The most common TEAEs (≥20%) related to acalabrutinib were diarrhea (40.0%) and rash (24.0%).
- The most common TEAEs (≥20%) related to ACP-319 were ALT increased (48.0%) and AST increased (44.0% and diarrhea and rash (28.0% each).
- SAEs occurred in 52.0% subjects; the most common was immune-mediated hepatitis (8.0%).
- TEAEs that led to acalabrutinib discontinuation occurred in 4 subjects (16.0%).
- TEAEs that led to ACP-319 discontinuation occurred in 6 subjects (24.0%).
- The most frequently reported ECI category was hepatotoxicity (56.0% any grade and 28.0% Grade ≥3).
- Two subjects were reported to have elevations ≥3 x upper limit of normal (ULN) in ALT or AST concurrent with total bilirubin ≥2 x ULN.

For CLL/SLL, MCL, WM, and FL, the key exposure, safety, and tolerability findings from this study were:

- The median duration of acalabrutinib exposure was 13.8 months (range: 0.9, 63.4) with 53.3% of subjects receiving >12 months of therapy.
- The median duration of ACP-319 exposure was 1.2 months (range: 0.3, 32.3) with 13.3% of subjects receiving 12 months of therapy.
- Common TEAEs that occurred in ≥30% of subjects were diarrhea (73.3%), nausea and upper respiratory tract infection (53.3% each), headache (46.7%), ALT increased, AST increased, contusion, cough, and dizziness (40.0% each), and abdominal pain (33.3%).
- The most common Grade ≥3 TEAEs (≥20%) were ALT increased (40.0%), AST increased (33.3%), diarrhea (26.7%), and neutropenia (20.0%).
- No Grade 5 TEAEs occurred.
- The most common TEAEs (≥20%) related to acalabrutinib were diarrhea (66.7%), nausea (53.3%), contusion and headache (26.7%), and abdominal pain, anemia, dizziness, neutropenia, and vomiting (20.0% each).

- The most common TEAEs (≥20%) related to ACP-319 were diarrhea and nausea (46.7% each), ALT increased and AST increased (33.3% each), and abdominal pain, anemia, contusion, dizziness, and neutropenia (20.0% each).

- SAEs occurred in 60.0% subjects, the most common were ALT increased and AST increased (13.3% each).

- TEAEs that led to acalabrutinib discontinuation occurred in 3 subjects (20.0%).

- TEAEs that led to ACP-319 discontinuation occurred in 6 subjects (40.0%).

- The most frequently reported ECI category was infections (66.7% any grade and 20.0% Grade ≥3).

- There were no subjects with elevations ≥3 x ULN in ALT or AST concurrent with total bilirubin ≥2 x ULN.

Conclusion(s)

In Part 1 (dose escalation), the MTD of the combination of acalabrutinib and ACP-319 was defined as acalabrutinib 100 mg BID and ACP-319 50 mg BID in subjects with B cell malignancies.

Overall, subjects with B cell malignancies were combined from Part 1 (dose expansion) and Part 2 (dose escalation) to analyze subjects by histology subtype. Investigator-assessed ORR was high in subjects with non-GCB DLBCL (62.5% with median DOR of 8.2 months).

Overall, the combination therapy showed an acceptable safety and tolerability profile which was consistent with acalabrutinib monotherapy clinical trials. During the study, the combination of ACP-319 and acalabrutinib was discontinued; CCI .

For GCB DLBCL and non-GCB DLBCL subjects, the most common TEAEs (≥30%) were diarrhea (56.0%), ALT increased (52.0%), AST increased (48.0%), rash (40.0%), and fatigue (36.0%); the most common Grade ≥3 TEAEs (≥20%) were ALT increased (28.0%) and AST increased (20.0%); the most common TEAEs (≥20%) related to acalabrutinib were diarrhea (40.0%) and rash (24.0%); the most common TEAEs (≥20%) related to ACP-319 were ALT increased (48.0% and AST increased (44.0%) and diarrhea and rash (28.0% each); the most common SAE was immune-mediated hepatitis (8.0%); the most frequently reported ECI category was hepatotoxicity (56.0% any grade and 28.0% Grade ≥3); and 2 subjects with elevations ≥3 x ULN in ALT or AST concurrent with total bilirubin ≥2 x ULN.

For CLL/SLL, MCL, WM, and FL, the most common TEAEs (≥30%) were diarrhea (73.3%), nausea and upper respiratory tract infection (53.3% each), headache (46.7%), ALT increased,

AST increased, contusion, cough, and dizziness (40.0% each), and abdominal pain (33.3%); the most common Grade ≥3 TEAEs (≥30%) were ALT increased (40.0%) and AST increased (33.3%); the most common TEAEs (≥30%) related to acalabrutinib were diarrhea (66.7%) and nausea (53.3%); the most common TEAEs (≥30%) related to ACP-319 were diarrhea and nausea (46.7% each), and ALT increased and AST increased (33.3% each); the most common SAEs were ALT increased and ALT increased (13.3% each); the most frequently reported ECI category was infections (66.7% any grade and 20.0% Grade ≥3); and there were no subjects with elevations ≥3 x ULN in ALT or AST concurrent with total bilirubin ≥2 x ULN.