Abbreviated Clinical Study Report Synopsis	
Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-CL-110
Edition Number	1
Date	08 December 2021
EudraCT Number	2016-003737-15
NCT Number	NCT03328273

A Phase 1/2 Proof-of-Concept Study Investigating AZD6738 Monotherapy and Acalabrutinib in Combination with AZD6738 (ATR Inhibitor) in Subjects with Relapsed or Refractory High-Risk Chronic Lymphocytic Leukemia (CLL)

Study Dates: First subject enrolled: 31 January 2018
Last subject enrolled: 19 October 2020
The analyses presented in this report are based on a data cutoff date of 07 September 2021

Phase of Development: 1/2

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centers

This study was conducted at 5 study sites, including 1 site in Poland and 4 sites in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and endpoints

Objectives	Endpoint/Variable
Primary	
Part 1 • To evaluate the safety and PK of ceralasertib – Arm A: When given as monotherapy in subjects with R/R, high risk CLL who have exhausted other therapeutic options according to local/regional standard of care. – Arm B: Ceralasertib given in combination with acalabrutinib in subjects with R/R, high-risk CLL who are suitable for treatment with a BTK inhibitor and ceralasertib, per investigator's clinical opinion.	• Safety assessed by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study treatment. • Plasma concentrations of ceralasertib, acalabrutinib, and the acalabrutinib metabolite ACP-5862 following ceralasertib monotherapy and ceralasertib + acalabrutinib combination treatment across collection time points and study visits.

Objectives	Endpoint/Variable
Secondary	
Part 1 • To evaluate the preliminary activity of ceralasertib when given as monotherapy and in combination with acalabrutinib, as measured by ORR (CR+PR), CR rate, DOR, PFS and OS in subjects with R/R, high-risk CLL.	Tumor response according to response criteria for CLL (Hallek et al, 2008) as assessed by investigators, at or before receiving any other anticancer therapy: • ORR: the rate of subjects who achieve a best response of CR, CRi, or PR • CR rate: the proportion of subjects who achieve CR or CRi. • DOR: the time from the first objective response (CR, CRi, or PR) to the time of documented disease progression or death due to any cause, whichever occurs first. • PFS: the time from first dose date to documented disease progression, or death from any cause, whichever occurs first. • OS: the time from first dose until the date of death from any cause

Note: Part 2 of this study was never opened and the objectives and endpoints of Part 2 are not included in this synopsis, but are described in the clinical study report.
Abbreviations: AE = adverse event; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete remission with incomplete bone marrow recovery; DLT = dose-limiting toxicity; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; R/R = relapsed/refractory; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Study design

ACE-CL-110 was a Phase 1/2, open-label, nonrandomized proof-of-concept study. The study was divided into 2 parts. Part 1 of the study was conducted to determine the dose, schedule, and safety, as well as preliminary efficacy, of ceralasertib given as monotherapy (Arm A) and in combination with acalabrutinib (Arm B) in subjects with relapsed/refractory (R/R), high-risk chronic lymphocytic leukemia (CLL). Part 2 was planned to allow for expansion of the cohorts to further test the doses and schedules of ceralasertib as monotherapy and in combination with acalabrutinib determined in Part 1. Only Part 1 of the study was conducted and is described in this clinical study report.

Arm A enrolled subjects with R/R, high-risk CLL who had exhausted other therapeutic options according to local/regional standard of care. Subjects were enrolled in Arm A in cohorts comprising 3 to 6 subjects to confirm the dose, schedule, and safety profile of ceralasertib. The starting dose (dose level 1) was 160 mg twice daily (BID) continuous. The protocol specified that if there were ≤ 1 dose-limiting toxicities (DLTs) in the first 3 subjects dosed at dose level 1, the dose cohort was to be expanded to 6 subjects to confirm the dose

and schedule. In the event of 2 or more DLTs in a cohort of 3 or 6 subjects at dose level 1, then a reduced dose (dose level -1 [160 mg BID 2 weeks on/2 weeks off]) was to be explored. If there were ≤ 1 DLTs in the first 3 subjects dosed at dose level -1, the dose cohort was to be expanded to 6 subjects to confirm the dose and schedule.

A review of the available safety and preliminary efficacy data from the first 2 ceralasertib monotherapy cohorts showed that 2 subjects had 3 DLTs (1 subject had 2 DLTs) of Grade 4 thrombocytopenia with ceralasertib monotherapy at dose level 1, and 1 subject had a DLT of Grade 4 thrombocytopenia at dose level –1. The dose level -1 cohort was therefore not expanded. It was agreed between the investigators and the sponsor that subjects are not likely to derive clinical benefit with ceralasertib monotherapy. However, there was justification for exploring the hypothesis of synthetic lethality of combining a Bruton tyrosine kinase (BTK) inhibitor with an ataxia telangiectasia and Rad-3-related protein (ATR) inhibitor in a population of subjects who are eligible for BTK therapy. Given that there are currently no substantially effective treatment options available for CLL patients after ibrutinib and venetoclax failure, and because such patients often have very advanced disease, exploring the combination of acalabrutinib with ceralasertib was considered a rational approach given the proven activity of acalabrutinib in R/R CLL and the possibility to deepen a subject's response to acalabrutinib with the addition of ceralasertib, especially in the 11q deletion population where synthetic lethality may be observed. Thus, testing of the combination was initiated in Arm B.

Arm B enrolled subjects with R/R, high-risk CLL who were suitable to receive a BTK inhibitor and ceralasertib per investigator's clinical opinion. Subjects were enrolled in Arm B in a cohort of 3 subjects to confirm the dose, schedule, and safety profile of ceralasertib + acalabrutinib combination therapy. Subjects enrolled in Arm B first received acalabrutinib monotherapy for 1 cycle (28 days) prior to the combination with ceralasertib. The aim was to build up an initial response to acalabrutinib monotherapy to potentially improve/restore abnormal hematological parameters before adding ceralasertib.

After the 28-day acalabrutinib monotherapy run-in period, subjects in Arm B received ceralasertib at 160 mg BID on a schedule of 1 week on/3 weeks off in combination with acalabrutinib (100 mg BID, continuous daily dosing). In the solid tumor program, the ceralasertib dose and schedule of 160 mg BID given on a 2 weeks on/2 weeks off schedule was found to be tolerated, either as monotherapy or in combination with other agents. Therefore, in Arm B, a starting dose of 160 mg BID ceralasertib on a schedule of 1 week on/3 weeks off was considered reasonable to combine with acalabrutinib. Furthermore, in Arm B, DLT criteria were also applied to ensure the safety of the combination being tested, followed by a review of the data by the safety review committee; therefore, safety oversight was present at all times.

For the purposes of DLT observation, the run-in period with acalabrutinib monotherapy (Cycle 1) was not considered part of the DLT observation period; the DLT period started at Cycle 2 Day 1 with the addition of ceralasertib to acalabrutinib and continued for 1 cycle (28 days) of the combination treatment.

In the event of 1 or fewer DLTs in Arm B in the first 3 subjects dosed at 160 mg BID ceralasertib 1 week on/3 weeks off in combination with 100 mg BID acalabrutinib (i.e., the third subject completed the DLT observation window), a further 3 subjects were to be dosed at this dose level to confirm the dose and schedule. In the event of 2 or more DLTs in a cohort of 3 or 6 subjects at dose level 1, then dose level -1 was to be explored. In the event of 1 or fewer DLTs in the first 3 subjects dosed at dose level -1, then 6 subjects would be tested at dose level -1 to confirm the dose and schedule.

Treatment with acalabrutinib and ceralasertib could be continued for up to 12 months until disease progression or an unacceptable drug-related toxicity occurred as defined in the protocol. Thereafter, subjects who were still considered to be deriving clinical benefit from the combination of acalabrutinib and ceralasertib could be eligible to continue with treatment based on investigator judgement and discussion with the sponsor, until disease progression or unacceptable toxicity. Under Protocol Amendment 3, all active subjects were switched to acalabrutinib monotherapy, and enrollment was closed.

The final data cutoff in support of final database lock was planned to occur approximately 6 cycles after the last subject was administered the first dose of investigational product. The end of study was defined as Last Subject Last Visit, which was the date of the last subject's 30-day (+7 days) safety follow-up (SFU) 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) SFU visit. The continued access 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 access 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 population and sample size

Diagnosis and main criteria for inclusion

This study enrolled adults with R/R, high-risk CLL.

Number of subjects (planned and analyzed)

Approximately 50 subjects were planned to be enrolled. The study enrolled and analyzed 11 subjects.

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

Acalabrutinib: hard gelatin capsules containing 100 mg of acalabrutinib, administered orally at a dose of 100 mg BID (200 mg per day) in continuous 28-day cycles.

Ceralasertib: film-coated tablets containing 20 mg to 100 mg of ceralasertib, administered orally at a dose of 160 mg BID continuous or 160 mg BID 2 weeks on/2 weeks off (in Arm A), or 160 mg BID 1 week on/3 weeks off (in Arm B).

Duration of treatment

Subjects received ceralasertib as monotherapy or in combination with acalabrutinib until disease progression or unacceptable toxicity.

Statistical methods

See Protocol Amendment 3 in Appendix 16.1.1 and Statistical Analysis Plan in Appendix 16.1.9.

Study population

Eleven subjects were enrolled and treated in this study. At the time of the data cutoff date (07 September 2021), 3 (27.3%) subjects remained on study and 8 (72.7%) subjects had discontinued from the study. All subjects discontinued ceralasertib, and 3 subjects were still on acalabrutinib treatment at the time of the data cutoff date. The median time on study for all subjects was 15.9 months (range: 4.7 to 36.3 months).

Summary of efficacy results

The overall response rate (ORR) in Arm A was 0, with 2 subjects having a best response of stable disease (SD) and 6 subjects having a best response of progressive disease (PD). In Arm B, all 3 subjects had a partial response (PR), for an ORR in Arm B of 100.0% (80%

confidence interval [CI]: 46.4%, 100.0%). Median duration of response (DOR) in Arm B was not reached. In Arm A, median progression-free survival (PFS) was 3.8 months (95% CI: 0.7, 4.6). Median PFS was not reached in Arm B. Median overall survival (OS) was 16.9% months (95% CI: 6.6, not estimable [NE]) in Arm A and was not reached in Arm B.

Summary of pharmacokinetic results

Overall, the mean predose and postdose concentrations of acalabrutinib/ACP-5862 (at 100 mg BID) and ceralasertib (at 160 mg BID) were comparable to those observed in other studies following monotherapy (e.g., Studies ACE-CL-001 and ACE-LY-004 for acalabrutinib, and D5330C00007 for ceralasertib), suggesting no interaction between the 2 drugs in the combination.

Summary of pharmacodynamic results

Pharmacodynamic results are presented in a separate report, located in Appendix 16.1.14.

Summary of safety results

The median duration of acalabrutinib treatment for subjects in Arm B was 15.9 months (range: 9.7 to 18.4 months), with 2 subjects having > 12 months of treatment. The median duration of ceralasertib treatment for subjects in both treatment arms was 3.7 months (range: 0.5 to 9.5 months).

The most common treatment-emergent adverse events (TEAEs) (≥ 2 subjects) in Arm A were anaemia (7 [87.5%]), thrombocytopenia (6 [75.0%]), upper respiratory tract infection (3 [37.5%]), and cough, diarrhoea, fatigue, nausea, dyspnoea, neutropenia, and oropharyngeal pain (2 [25.0%] each). In Arm B, no TEAE was reported in > 1 subject.

All 8 subjects in Arm A had Grade ≥ 3 TEAEs. The most common Grade ≥ 3 TEAEs in Arm A (≥ 2 subjects) were anaemia (6 [75.0%]), thrombocytopenia (5 [62.5%]), and neutropenia (2 [25.0%]). There were no Grade ≥ 3 TEAEs reported in subjects treated with acalabrutinib (Arm B).

In Arm A, all 8 subjects had TEAEs considered related to ceralasertib. The most common ceralasertib-related TEAEs in Arm A were anaemia (6 [75.0%]), thrombocytopenia (5 [62.5%]), and dyspnoea, fatigue, nausea, and neutropenia (2 [25.0%] each). In Arm B, both subjects who received ceralasertib had ceralasertib-related TEAEs (1 of the 3 subjects in Arm B did not receive any ceralasertib). No ceralasertib-related event was reported in > 1 subject in Arm B. Two subjects (66.7%) in Arm B had a TEAE considered related to acalabrutinib, with no event reported in > 1 subject in Arm B.

Five subjects died during this study, all of whom were in Arm A. Four of these subjects died due to disease progression and 1 subject died due to an unknown cause. No Grade 5 (fatal) TEAEs were reported.

Seven subjects had an SAE. In Arm A, 6 (75.0%) subjects had an SAE, including anaemia (5 [62.5%]) and thrombocytopenia (3 [37.5%]). All other SAEs in Arm A were reported in 1 subject each. In Arm B, 1 subject had an SAE of Grade 2 COVID-19 considered not related to either study drug.

There were no TEAEs that led to discontinuation of study treatment in either treatment arm.

All 3 acalabrutinib-treated subjects in Arm B had events of clinical interest (ECIs), which are events that have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitors. Hemorrhage events were reported in 2 subjects (multiple events of Grade 1 epistaxis in 1 subject, and Grade 1 contusion in 1 subject), a hypertension event was reported in 1 subject (Grade 2 hypertension), and an infection event was reported in 1 subject (SAE of Grade 2 COVID-19).

There were no clinically significant mean changes in hematology or clinical laboratory values or vital sign values over time. There was a trend toward worsening of some hematologic parameters from baseline, including decreased absolute neutrophil count, decreased hemoglobin, decreased platelets, and increased lymphocytes.

There were no acalabrutinib-treated subjects with elevations $\geq 3 \times$ upper limit of normal (ULN) in alanine aminotransferase or aspartate aminotransferase concurrent with total bilirubin $\geq 2 \times$ ULN.

Conclusions

Acalabrutinib combined with ceralasertib (N = 2) showed a safety and tolerability profile that is consistent with acalabrutinib monotherapy clinical studies. The sponsor decided not to pursue the development of ceralasertib as monotherapy or in combination with acalabrutinib for the indication of R/R CLL, and therefore there is no detailed presentation of efficacy in this abbreviated clinical study report.