Clinical Study Report Synopsis	
Drug Substance	Acalabrutinib
Study Code	ACE-WM-001
Edition Number	1
Date	30 July 2021
EudraCT Number	2014-003212-36
NCT Number	NCT02180724

An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia[1]

Study Dates: First subject enrolled: 08 September 2014

The analyses presented in this final report are based on a data cutoff date of 31 March 2021

Phase of Development: 2

International Co-ordinating Investigator:

PPD
PPD
PPD
Leeds,
LS9 7TF United Kingdom

Sponsor's Responsible Medical Officer:

PPD
PPD
Cambridge,
CB2 1PQ United Kingdom

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.

[1] In Italy only, the original protocol title "An Open-label, Phase 1b/2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia" remains in effect.

2. SYNOPSIS

Study Centers

This multicenter study was conducted at 27 study sites in 6 countries: United Kingdom (51.9% of subjects), United States (26.4%), France (7.5%), Netherlands (6.6%), Italy (4.7%), and Greece (2.8%).

Publications

Owen R, McCarthy H, Rule S, et al. Acalabrutinib in patients with Waldenström macroglobulinemia. J Clin Onc 2018;36 (suppl; abstract 7501).

Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, Phase 2 study. Lancet Haematol 2019; published online Dec 19. http://dx.doi. org/10.1016/S2352-3026(19)30210-8.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Endpoint/Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the ORR of acalabrutinib in subjects with WM as assessed by the investigator	ORR defined as a subject achieving a MR or better according to the response assessment criteria for WM (Owen et al. 2013) and modified 3rd IWWM workshop criteria (Kimby et al. 2006)
Secondary	Efficacy	To determine the DOR of acalabrutinib as assessed by the investigator	DOR using response assessment criteria for WM (Owen et al. 2013) and modified 3rd IWWM workshop criteria (Kimby et al. 2006)
Secondary	Efficacy	To determine the PFS of acalabrutinib as assessed by the investigator	PFS using response assessment criteria for WM (Owen et al. 2013) and modified 3rd IWWM workshop criteria (Kimby et al. 2006)
Secondary	Efficacy	To determine the OS of acalabrutinib	OS measured from the start of acalabrutinib therapy until the date of death
Secondary	Pharmacokinetic	To characterize the PK profile of acalabrutinib	Plasma PK of acalabrutinib characterized using noncompartmental analysis
Secondary	Safety	To characterize the safety of acalabrutinib	Frequency, severity, and relatedness of AEs Frequency of AEs requiring discontinuation of study drug or dose reductions

Objective			Endpoint/Variable
Priority	**Type**	**Description**	**Description**
Secondary	Other	To evaluate the effect of acalabrutinib in health-related quality of life	The EORTC QLQ-C30 v3.0 was used to assess the health-related quality of life
CCI			

AE = adverse event; CCI DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-30; IWWM = International Workshops on Waldenström Macroglobulinemia; MR = minor response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; WM = Waldenström macroglobulinemia.

Study Design

This study is an ongoing multicenter, open-label clinical study evaluating the safety and efficacy of acalabrutinib CCI in subjects with Waldenström macroglobulinemia (WM) using a Simon's optimal 2-stage design (Simon 1989). In addition to the previously treated cohort, a small exploratory cohort of subjects with treatment-naive WM was enrolled to determine the preliminary safety and efficacy of acalabrutinib in this patient population. In the Netherlands and France, enrollment for the treatment-naive cohort began after efficacy had been confirmed in Stage 1 of the Simon's optimal 2-stage design; in other locations, both previously treated and treatment-naive cohorts enrolled simultaneously.

In the original protocol, 32 previously treated subjects (Stage 1 of Simon's optimal 2-stage design) were planned to be randomized 1:1 into the following 2 cohorts: Cohort 1 to receive acalabrutinib CCI and Cohort 2 to receive acalabrutinib CCI CCI After enrollment started, the dose regimen was amended twice, and ultimately, all subjects received CCI thereafter. In addition, a separate cohort of 8 to 12 subjects who were treatment-naive was added. Multiple protocol amendments have occurred since the first subject was enrolled into this study, with many changes affecting study design and sample size. After enrollment started, the CCI dose was eliminated, and the subjects who were enrolled under the original study design and received treatment with CCI of study drug administration was 1 cycle.

Efficacy parameters were based on investigator assessment according to the response assessment criteria for WM (Owen et al. 2013) and the modified 3rd International Workshops on Waldenström Macroglobulinemia (IWWM) workshop criteria (Kimby et al. 2006). The primary endpoint was evaluated by overall response rate (ORR), defined as a subject

achieving a minor response (MR) or better according to the response assessment criteria for WM (Owen et al. 2013) and by the modified 3rd IWWM workshop criteria (Kimby et al. 2006).

Assessments of overall response were done at screening, the end of every cycle from Cycle 1 to Cycle 12, every 3 cycles after Cycle 12 through Cycle 48, and every 6 cycles thereafter. New tumor assessments were made at screening, at the end of Cycles 2, 4, and 6, every 3 cycles until Cycle 27, and every 6 cycles thereafter. For subjects with baseline (screening) extramedullary disease, follow-up radiologic assessments were required at the end of Cycles 2, 4, and 6, and then every 3 cycles until Cycle 27, and every 6 cycles thereafter or more frequently at the investigator's discretion. Overall response assessments included evaluation of physical examinations, recording of symptoms, laboratory evaluations, and radiologic evaluations per the schedule of assessments. Subjects who had signs and symptoms of disease progression outside of the scheduled assessment were evaluated by the investigator with a physical examination and serum immunoglobulins and serum M protein to determine if disease progression was present. Additionally, any suspected case of disease progression was to be assessed with a computed tomography (CT) scan for subjects with baseline extramedullary disease, and was to be reported to the medical monitor. Subjects could continue study treatment until progression was confirmed by a serial examination (eg, physical examination, serum immunoglobulins and serum M protein, or CT scan) at least 2 weeks later.

Endpoints for efficacy, safety, pharmacokinetics (PK), CCI and health-related quality of life are described in Table S1.

Treatment with acalabrutinib could continue until disease progression or unacceptable drug-related toxicity. Dose modification provisions were provided in the protocol (see Protocol Amendment 9.0, Section 3.5.6). A treatment termination (TT) visit was required for safety assessments for any subjects who permanently discontinued study drug for any reason (except for death, loss to follow-up, or withdrawal of consent), including progressive disease (PD), and was to be scheduled within 7 days of the last dose of study drug, if possible. In addition to the TT visit, all subjects who discontinued acalabrutinib had a safety follow-up (SFU) visit 30 (+ 7) days after the last dose of study drug to monitor for resolution or progression of adverse events (AEs) and to document the occurrence of any new events, regardless of whether the subject received a new anticancer therapy or demonstrated PD within this timeframe.

The end of the study was defined as the date of the last subject's last visit. The final analysis was planned to occur after an approximate 5-year median follow-up period. Subjects who were still on treatment at the time of the final analysis and deriving clinical benefit from acalabrutinib treatment could continue treatment. At the time of the final data cutoff and

database closure, subjects who remained on study treatment could stay on the same treatment regimen, with only safety data (serious adverse events [SAEs]) collected by the study sites. This clinical study report with a data cutoff date of 31 March 2021 presents the final analysis for Study ACE-WM-001.

Target Subject Population

Diagnosis and Main Criteria for Inclusion

Men and women ≥ 18 years of age with a confirmed diagnosis of WM who required treatment and had no prior exposure to a B-cell receptor inhibitor (eg, Bruton tyrosine kinase, phosphoinositide-3 kinase, or spleen tyrosine kinase inhibitors) or B-cell lymphoma 2 inhibitors (eg, ABT-199):

- Previously treated: Subjects with WM that relapsed after or was refractory to ≥ 1 prior therapy for WM
- Treatment-naive: Subjects with untreated WM who did not want to receive chemoimmunotherapy or had comorbidities that precluded chemoimmunotherapy (eg, symptomatic hyperviscosity with an immunoglobulin M ≥ 5000 mg/dL or disease-related neuropathy)

Number of Subjects (Planned and Analyzed)

Multiple protocol amendments resulting in major changes on study design affected the originally planned sample size (see statistical analysis plan [SAP], Section 3.2). In total, 106 subjects were enrolled and included in the All-Treated Population.

Investigational Product: Dosage, Mode of Administration and Batch Numbers

Investigational product was supplied as capsules of acalabrutinib CCI administered orally at a dose of CCI For manufacturing batch numbers, see Appendix 16.1.6.

Duration of Treatment

Subjects received acalabrutinib until disease progression or unacceptable drug-related toxicity.

Statistical Methods

Determination of Sample Size

This study was designed to test the null hypothesis that the ORR was ≤ 35% against the alternative hypothesis that it was ≥ 55%. For previously treated WM subjects, using Simon's optimal 2-stage design, a total sample size of 76 subjects has 90% power to achieve a 1-sided

significance level of 0.025. In Stage 1, 28 subjects were evaluated for efficacy. Because ≥ 12 out of 28 subjects (43%) achieved a response, the study continued to full enrollment. In Stage 2, a further 48 subjects were enrolled. With original Simon's optimal 2-stage design, an ORR of ≥ 46% (ie, ≥ 35 subjects responding out of 76 subjects evaluated) will achieve a 1-sided significance level of ≤ 0.025.

Multiple protocol amendments have occurred since the first subject was enrolled into this study. For a list of major changes on study design that affected sample size and treatment cohort, see the SAP, Section 3.2.

Analysis Methods

No formal tests of hypotheses were performed. Descriptive statistics were used to summarize disposition, demographic, baseline characteristics, disease characteristics, prior anticancer therapy, concomitant medication, study drug administration, and efficacy and safety outcomes. Categorical variables were summarized for each cohort separately.

Efficacy Analyses: The primary efficacy endpoint was ORR, defined as the proportion of subjects achieving a best overall response of either complete response (CR), very good partial response (VGPR), partial response (PR), or MR before initiation of new anticancer therapy. Efficacy analyses were performed on the All-Treated Population, defined as all subjects who received ≥ 1 dose of study drug. The 2-sided 95% confidence interval (CI) was calculated for ORR based on exact method. The major response rate, defined as the proportion of subjects who achieve PR or better (CR, VGPR, PR), was presented similarly as for ORR. The ORR summaries were generated separately for Owen 2013 criteria and modified 3rd IWWM workshop criteria.

Duration of response (DOR) was defined as the interval from the first documentation of CR, VGPR, PR or MR to the earlier of the first documentation of definitive PD or death from any cause. If disease progression or death were not reported for a subject, the subject was censored according to the censoring rules described in the SAP Appendix 12.3. The Kaplan-Meier (KM) method was used for DOR analysis. KM estimates with 95% CIs were calculated for event time quartiles, and event-free rates were calculated at selected time points. The analyses were generated separately for Owen 2013 criteria and modified 3rd IWWM workshop criteria.

Progression-free survival (PFS) was defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of definitive PD or death from any cause. If disease progression or death were not reported for a subject, the subject was censored according to the censoring rules described in the SAP Appendix 12.3. The analysis of PFS was similar to that described for DOR above.

The duration of overall survival (OS) was measured from the start of acalabrutinib therapy until the date of death from any cause. Subjects who were known to be alive as of their last known status were censored at their last date known to be alive. The analysis of OS was similar to that described for DOR above.

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 (EORTC QLQ-C30) v3.0 was used to assess the health-related quality of life. The EORTC QLQ-C30 v3.0 includes 30 separate items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scoring details are described in the SAP. At each analysis visit and for each treatment group, the summary statistics of absolute and changes from baseline scale scores were calculated. Summary tables of these statistics were generated for the All-Treated Population and for the subset of subjects who achieved MR or better.

Pharmacokinetics CCI Details of PK CCI analyses can be found in the PK report (Appendix 16.1.13) CCI
CCI

Safety Analysis: Safety analyses were performed using the All-Treated Population. AEs and SAEs were coded by system organ class (SOC) and preferred term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA) reporting system, version 24.0. All AEs summarized were treatment-emergent. Summaries were also presented by the severity of the AE (per Common Toxicity Criteria for Adverse Events [CTCAE] version 4.03) and by relationship to study drug as assessed by the investigator. Grade ≥ 3 AEs, AEs that led to permanent study drug treatment discontinuation, AEs that led to dose reduction, SAEs, and AEs that resulted in death were also summarized. Events of clinical interest (ECIs) selected for dedicated analysis were evaluated using Standardized MedDRA Queries, where available, by SOC, or by sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Laboratory data of hematology, serum chemistry, serum immunoglobulin, and T/B/natural killer (NK) cell counts were summarized. For selected laboratory test parameters, summary statistics were produced for baseline value, postbaseline value at the last visit, minimum and maximum postbaseline values, and changes of these postbaseline values from baseline. Shift from baseline to the maximum grade during the treatment was provided as shift tables for selected parameters. For each vital sign measurement, descriptive statistics were presented and change from baseline were summarized. Shift of Eastern Cooperative Oncology Group (ECOG) performance status from baseline to the worst score during the treatment was summarized in a shift table.

Subject Population

The study enrolled 106 subjects and all subjects received study treatment. At the time of study closure, 50 (47.2%) subjects were still receiving acalabrutinib and thus the reason for acalabrutinib discontinuation was 'study terminated by sponsor.' The median age of subjects was 69.0 years (range 39.0 to 90.0 years). Most subjects were ≥ 65 years of age (71.7%), male (68.9%), White (88.7%), and were enrolled in sites outside of the United States (73.6%).

The demographics and baseline disease characteristics of the study population are representative of the intended target population of patients with WM. The median number of prior therapies was 2 (range 1 to 7). The most common prior therapies for WM were anti-CD20 therapy as a single agent or part of a regimen (87.0%), cyclophosphamide based regimen (34.8%), chlorambucil based regimen (31.5%), proteosome inhibitor based regimen (30.4%), and purine analogue +/- rituximab (22.8%). Consistent with a largely relapsed/refractory population, most subjects in this study had advanced disease (99.1%), bone marrow involvement (97.2%), and extramedullary disease (64.2%). A total of 62.3% of subjects had cytopenia at baseline, with anemia (hemoglobin < 110 g/L) being the most common (60.4%).

Summary of Efficacy Results

Efficacy conclusions from 106 subjects with WM based on results as of the data cutoff date (31 March 2021) with a median follow-up of 63.7 months (range 4.6 to 78.3 months) can be summarized as follows:

- ORR (CR+VGPR+PR+MR) per investigator assessment based on Owen criteria was 94.3% (95% CI: 88.1, 97.9), with 3.8% of subjects achieving CR, 20.8% of subjects achieving VGPR, 58.5% of subjects achieving PR, and 11.3% of subjects achieving MR. ORR per investigator assessment based on modified 3rd IWWM Workshop criteria was also 94.3% (95% CI: 88.1, 97.9), with 1.9% of subjects achieving CR, 36.8% of subjects achieving VGPR, 42.5% of subjects achieving PR, and 13.2% of subjects achieving MR.

- Median investigator-assessed DOR based on Owen criteria was 64.7 months (95% CI: 54.1, not estimable [NE]). The KM estimate of the proportion of responders without a PFS event was 87.8% (95% CI: 79.6, 92.9) at 12 months, 76.3% (95% CI: 66.4, 83.5) at 36 months, and 55.5% (95% CI: 44.2, 65.4) at 60 months. Median investigator-assessed DOR based on modified 3rd IWWM Workshop criteria was 64.7 months (95% CI: 59.9, NE). The KM estimate of the proportion of responders without a PFS event was 88.9% (95% CI: 80.8, 93.7) at 12 months, 78.3% (95% CI: 68.7, 85.3) at 36 months, and 60.0% (95% CI: 48.6, 69.6) at 60 months.

- Median investigator-assessed PFS based on Owen criteria was 67.5 months (95% CI: 55.4, NE). The KM estimate of the proportion of subjects without a PFS event was 88.4% (95% CI: 80.4, 93.2) at 12 months, 74.1% (95% CI: 64.3, 81.6) at 36 months, and 57.9% (95% CI: 47.4, 67.1) at 60 months. Median investigator-assessed PFS based on modified 3rd IWWM Workshop criteria was 67.5 months (95% CI: 57.0, NE). The KM estimate of the proportion of subjects without a PFS event was 87.4% (95% CI: 79.3, 92.5) at 12 months, 75.3% (95% CI: 65.7, 82.6) at 36 months, and 60.3% (95% CI: 49.7, 69.2) at 60 months.

- The median OS was not reached. The KM estimate of OS was 94.3% (95% CI: 87.8, 97.4) at 12 months, 84.3% (95% CI: 75.6, 90.1) at 36 months, and 74.8% (95% CI: 65.0, 82.2) at 60 months.

- For EORTC QLQ-C30 global health status and most functional scales, mean scores improved during treatment, with positive changes from baseline at most time points until Cycle 60. Mean (SD) change from baseline in global health status was 5.0 [26.56]) at Cycle 12, 7.6 (24.20) at Cycle 27, and -0.4 (26.85) at Cycle 60. A worsening from baseline was generally observed for most symptom scales, with mean (standard deviation [SD]) changes from baseline at Cycles 12, 27, and 60, respectively, for fatigue (-11.3 [27.58], -12.4 [24.78], and 0.0 [26.34]), nausea/vomiting (-1.2 [12.79], -1.8 [13.97], and -1.6 (12.50]), dypsnoea (-14.3 [30.86], -9.4 [33.84], and -3.1 [28.93]), insomnia (-5.2 [27.59], -8.3 [27.86], and -2.3 [24.55]), appetite loss (-3.8 [21.64], -5.3 [24.83], and -7.0 [15.53], constipation (-5.2 [23.15], -3.1 [20.33], and -1.6 [17.75]). Pain remained generally similar to baseline, with mean (SD) changes from baseline of 1.7 (19.69), -1.8 (21.64), and 1.9 (21.89) at Cycles 12, 27, and 60, respectively. Diarrhoea improved early in treatment but was similar to baseline beyond Cycle 27, with mean (SD) changes from baseline of 6.2 (19.90), 1.0 (19.67) and 0.0 (23.00) at Cycles 12, 27, and 60, respectively.

Summary of Pharmacokinetic Results

PK results are presented in Appendix 16.1.13.

CCI [redacted]

Summary of Safety Results

The median duration of exposure was 60.8 months (range 2.8 to 78.3 months). At the time of the data cutoff for this report, most subjects (83.0%) had > 12 months of treatment.

The most common AEs (in ≥ 20% of subjects) were headache (41.5%), diarrhoea (38.7%), arthralgia (32.1%), fatigue (30.2%), upper respiratory tract infection (29.2%), contusion (28.3%), dizziness (26.4%), constipation and cough (25.5% each), nausea (24.5%), lower respiratory tract infection (23.6%), and back pain (21.7%). Most of these AEs were Grade 1 or 2. The most common Grade ≥ 3 AEs (in ≥ 5% of subjects) were neutropenia (17.0%), pneumonia (10.4%), lower respiratory tract infection (6.6%), and anaemia (5.7%).

Study treatment-related AEs were reported in 90.6% of subjects. The most common treatment-related AEs were headache (33.0%), and contusion and diarrhea (20.8% each).

Twelve (11.3%) subjects died due to treatment-emergent adverse events (TEAEs), including 2 subjects who died due to COVID-19 events. One Grade 5 AE (intracranial hematoma) was assessed by the investigator as treatment-related.

SAEs were reported in 68 (64.2%) subjects, and 28 (26.4%) subjects had an SAE that was assessed by the investigator as treatment-related. The most common SAEs (in ≥ 3% of subjects) were pneumonia (10.4%), lower respiratory tract infection (9.4%), pyrexia (4.7%), and cellulitis, hip fracture, sepsis, and urinary tract infection (3.8% each).

Twenty (18.9%) subjects had an AE that led to discontinuation of study treatment. No AE that led to discontinuation of study treatment was reported in more than 1 subject.

Cardiac events were reported in 20.8% subjects. The most common cardiac events by Preferred term (PT) was atrial fibrillation (10.4%). Anemia events were reported in 11.3% of subjects, including 11 subjects with the PT anaemia and 1 subject with microcytic anaemia. Neutropenia events were reported in 20.8% of subjects and included PTs of neutropenia (18.9%), and febrile neutropenia and neutropenic sepsis (1.9% each). Hemorrhage events were reported in 62.3% of subjects. Major hemorrhage events were reported in 8.5% of subjects. Hepatotoxicity events were reported in in 7.5% of subjects and included alanine aminotransferase increased (6.6%) and aspartate aminotransferase increased (4.7%). Hypertension events were reported in 6.6% of subjects. Infection events were reported in 82.1% of subjects, and Grade 3/4 events were reported in 30.2% of subjects. The most common infections (≥ 10% of subjects) were upper respiratory tract infection (29.2%), lower respiratory tract infection (23.6%), pneumonia (14.2%), respiratory tract infection, sinusitis, and urinary tract infection (13.2% each), and cellulitis and nasopharyngitis (10.4% each). Previously treated subjects in this study had a higher frequency of infection AEs than treatment-naïve subjects. One subject had a non-serious Grade 2 event of interstitial lung disease/pneumonitis (PT lung opacity). Treatment-emergent second primary malignancies occurred in 17.0% of subjects, including 3 subjects with Grade 5 (fatal) events (central nervous system lymphoma, glioblastoma multiforme, and oesophageal carcinoma). Twelve

(11.3%) subjects had a second primary malignancy excluding non-melanoma skin. There were no events of tumor lysis syndrome.

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 decreased absolute neutrophil count (ANC) and decreased leukocytes from baseline. No other trends were observed in shifts (comparing baseline measurement to maximum reported measurement on study) for hematology laboratory parameters. There was a trend toward worsening of increased uric acid and decreased sodium from baseline. No other trends were observed in shifts for chemistry laboratory parameters. There were no 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.

Conclusion

Acalabrutinib demonstrated efficacy in this population of subjects with previously treated or treatment-naïve WM. As assessed by the investigator, ORR was 94.3% by both Owen criteria and modified 3rd IWWM Workshop criteria. Based on Owen criteria, 3.8% of subjects achieved CR, 20.8% of subjects achieved VGPR, 58.5% of subjects achieved PR, and 11.3% of subjects achieved MR. Based on modified 3rd IWWM Workshop criteria, 1.9% of subjects achieved CR, 36.8% of subjects achieved VGPR, 42.5% of subjects achieved PR, and 13.2% of subjects achieved MR. Acalabrutinib monotherapy was well tolerated in subjects with WM and demonstrated a safety and tolerability profile that is consistent with other acalabrutinib monotherapy clinical trials.