Clinical Study Report Addendum Synopsis	
Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-LY-004
Edition Number	Addendum to Edition 2.0
Date	19 April 2021
EudraCT Number	2014-002117-28

An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma

Study Dates: First subject consented: 02 March 2015
Original CSR (Edition 1.0) data cutoff date: 28 February 2017
24-Month Follow-Up (Edition 2.0) data cutoff date: 12 February 2018
Addendum data cutoff date: 04 December 2020

Phase of Development: 2

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Version History

Edition 1.0	Final clinical study report; 19 May 2017
Edition 2.0	24-Month Follow-up Update; 31 July 2018
Addendum to Edition 2.0	Addendum (54-Month Close-Out Analysis); 19 April 2021

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Introduction

This clinical study report (CSR) addendum presents the efficacy and safety data for the 54-month close-out analysis, which was planned to occur approximately 54 months after enrollment of the last subject. The data cutoff date for the 54-month close-out analysis is 04 December 2020. Full study results through the cutoff date of 12 February 2018 are presented in ACE-LY-004 Clinical Study Report Edition 2.0 (24-month follow-up update). Only updated information is presented in this CSR addendum.

Publications

The following publications have been produced since the ACE-LY-004 Clinical Study Report Edition 2.0 (dated 31 July 2018):

Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib (Acala) monotherapy in hematologic malignancies: Pooled analysis from clinical trials. J Clin Oncol 2020;38(15_suppl):8064.

Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib monotherapy in mature B cell malignancies: pooled analysis from clinical trials. Abstract EP698. Presented at the European Hematology Association (EHA) Annual Meeting, June 11-21, 2020 (virtual meeting).

Wang M, Rule S, Zinzani PL, et al. Acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a Phase 2 study. Blood 2020;136 (supplement):38-9.

Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma [letter]. Leukemia 2019;33:2762–6.

Wang M, Rule S, Zinzani PL, et al. Long-term follow-up of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma. Blood 2018;132 (Supplement 1):2876.

Objectives and Criteria for Evaluation

There have been no changes to the objectives and criteria for evaluation in the 54-month close-out analysis. Please refer to ACE-LY-004 Clinical Study Report Edition 2.0 (24-month follow-up update).

Study Design

Study ACE-LY-004 is a Phase 2, multicenter, open-label study in subjects with histologically documented mantle cell lymphoma (MCL), who had relapsed after at least 1 (but not more than 5) prior treatment regimens. This study was designed to determine the activity of acalabrutinib in subjects with relapsed/refractory (R/R) MCL as measured primarily by response rate according to investigator assessment. Duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were also assessed.

Approximately 117 subjects were planned to be enrolled and to receive 100 mg of acalabrutinib twice daily (BID) continuously in repeated 28-day cycles. Treatment with acalabrutinib was continued until disease progression or an unacceptable treatment-related toxicity occurred. Dose modification provisions were provided as defined in the study protocol. An Early Termination Visit was required for any subjects who permanently discontinued study treatment for any reason including disease progression (exceptions included death, lost to follow-up, or withdrawal of consent). In addition to the Early Termination Visit, all subjects who discontinued study treatment had a Safety Follow-up Visit 30 (+7) days after his or her last dose of acalabrutinib.

During treatment, computed tomography (CT) scans with contrast (unless contraindicated) were performed for tumor assessments at the end of Cycle 2 (±7 days), Cycle 4 (±7 days), and Cycle 6; and then every 6 cycles (24 weeks) thereafter, or more frequently at the investigator's discretion. Positron emission topography (PET)/CT scans were performed at the end of Cycle 2 (±7 days) and Cycle 6 as well as any time to confirm complete response (CR) or as clinically indicated. For Cycles ≥ 6, CT and PET/CT scans may have been performed within an imaging window of up to 21 days before and up to 7 days after the scheduled study visit date. Subjects with confirmed CR were not required to undergo further PET/CT scans on study unless there was suspicion of progressive disease (PD). Endoscopy was mandatory to confirm CR for any subjects with a documented history of gastrointestinal involvement.

Subjects who discontinued acalabrutinib for reasons other than PD were followed approximately every 24 weeks from the end of study treatment until PD or the start of subsequent anticancer therapy, whichever occurred first. During this period, scans were performed approximately every 24 weeks to assess disease status.

Subjects who progressed or began subsequent anticancer therapy—for all subjects who had not withdrawn consent—were contacted approximately every 24 weeks by clinic visit or telephone, to assess survival and the use of subsequent anticancer therapy until death or loss to follow-up.

All subjects had hematology, chemistry, and urinalysis safety panels performed at Screening. Once dosing began (Day 1), all subjects were evaluated for safety weekly for the first

4 weeks, every 2 weeks in Cycle 2, every 4 weeks in Cycles 3 to 12, and every 24 weeks thereafter. Pharmacokinetic (PK)/pharmacodynamic testing were conducted in Cycles 1 and 2 in up to 48 subjects. Tumor assessments were completed at 8- to 24-week intervals during the study.

Subjects who were still on treatment at the time of the close-out analysis and who were deriving clinical benefit from acalabrutinib treatment could continue treatment. At the time of the final data cutoff and database closure, subjects who remained in this study could be transitioned to a separate rollover study or remain within this study protocol for continued access to study drug. Once all active subjects were eligible to continue to receive acalabrutinib and after database closure, there was to be no further data collection other than reporting of serious adverse events (SAEs) per protocol. The end of study was defined as the last subject last visit date.

Target Subject Population and Sample Size

There have been no changes to the target subject population and sample size. Please refer to ACE-LY-004 Clinical Study Report Edition 2.0 (24-month follow-up update).

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

There have been no changes to the investigational product description. For individual batch numbers, see Appendix 16.1.6.

Duration of Treatment

There have been no changes to the duration of treatment. Please refer to ACE-LY-004 Clinical Study Report Edition 2.0 (24-month follow-up update).

Statistical Methods

There have been no changes to the statistical methods. Please refer to ACE-LY-004 Clinical Study Report Edition 2.0 (24-month follow-up update).

Subject Population

A total of 124 subjects were enrolled into the study between 02 March 2015 and 05 January 2016 and all received study treatment. As of the 54-month close-out analysis, all 124 subjects have discontinued acalabrutinib treatment and have exited the study. The most common reason for treatment discontinuation was disease progression (62.1%). The most common reason for study exit was death (47.6%). The median time on study was 38.1 months (range: 0.3 to 68.8).

There are no changes in the demographics and baseline disease characteristics in the 54-month close-out analysis. Demographics and baseline disease characteristics were representative of the intended target population of patients with R/R MCL who had received at least 1 prior therapy.

Summary of Efficacy Results

With a median follow-up of 38.1 months, the results of the 54-month close-out analysis support the earlier results of the final CSR (Clinical Study Report Edition 1.0) and the 24-month follow-up update (Clinical Study Report Edition 2.0). Based on investigator assessment according to the Lugano classification, overall response rate (ORR) was 81.5% (95% confidence interval [CI]: 73.5%, 87.9%), and the CR rate was 47.6% (95% CI: 38.5%, 56.7%). Since the 24-month update, there were 6 subjects who went from partial response (PR) to CR, and 1 subject who went from stable disease (SD) to PR. ORR based on the 54-month close-out analysis was consistent across all the prespecified subgroups that were analyzed, including age, sex, race, number of prior lines of therapy, Ann Arbor Stage, Eastern Cooperative Oncology Group (ECOG) status, gastrointestinal involvement, tumor bulk, and type of prior therapy.

Median DOR was 28.6 months (95% CI: 17.5, 39.1). The estimated DOR rate was 72.2% (95% CI: 62.0%, 80.0%) at 12 months, 59.0% (95% CI: 48.4%, 68.2%) at 18 months, 53.4% (95% CI: 42.8%, 62.9%) at 24 months, 41.9% (95% CI: 31.7%, 51.8%) at 36 months, and 35.8% (95% CI: 25.9%, 45.7%) at 48 months.

Median PFS was 22.0 months (95% CI: 16.6, 33.3). The Kaplan-Meier (KM) estimate of the proportion of subjects without a PFS event was 67.8% (95% CI: 58.5%, 75.4%) at 12 months, 49.6% (95% CI: 40.1%, 58.4%) at 24 months, and 37.2% (95% CI: 28.2%, 46.1%) at 36 months. Results of a sensitivity analysis of PFS based on investigator assessment according to the Lugano classification, which included events after the start of subsequent therapy, were consistent with the primary analysis results for PFS.

Median OS was 59.2 months (95% CI: 36.5, not estimable [NE]). The KM estimate of OS was 86.8% (95% CI: 79.3%, 91.7%) at 12 months, 76.6% (95% CI: 68.0%, 83.2%) at 18 months, 72.4% (95% CI: 63.5%, 79.5%) at 24 months, 60.5% (95% CI: 51.1%, 68.7%) at 36 months, and 52.4% (95% CI: 42.9%, 61.0%) at 48 months.

Summary of Pharmacokinetic Results

A PK report was not generated for the 54-month close-out analysis.

Summary of Pharmacodynamic Results

A pharmacodynamic report was not generated for the 54-month close-out analysis.

Summary of Safety Results

Overall, acalabrutinib administered at 100 mg BID was generally well tolerated in subjects with R/R MCL in this study, and the results of the 54-month close-out analysis are consistent with those of the 24-month follow-up analysis. The median duration of treatment was 17.5 months (range: 0.1 to 65.3). A total of 59.7% of subjects received acalabrutinib for > 12 months, and 43.5% received acalabrutinib for > 24 months.

The most frequently reported treatment-emergent adverse events (TEAEs) (≥ 20% of subjects) were headache (38.7%), diarrhoea (37.9%), fatigue (29.8%), cough (23.4%), and myalgia and nausea (21.8% each). The most frequently reported Grade 3 or 4 TEAEs (≥ 5% of subjects) were anaemia (11.3%), neutropenia (11.3%), and pneumonia (7.3%). Four subjects had Grade 5 (fatal) TEAEs, which included events of aortic stenosis, pulmonary embolism, non-small cell lung cancer, and suicide (Preferred term [PT] suicide attempt). There were no treatment-related Grade 5 (fatal) TEAEs.

As of the data cutoff date for the 54-month close-out analysis, 59 (47.6%) subjects had died. Eight (6.5%) subjects died within 30 days of the last dose of acalabrutinib, and 51 (41.1%) subjects died more than 30 days after the last dose of acalabrutinib. The most common cause of death was disease progression (40 [32.3%]). Six (4.8%) subjects died due to an adverse event (AE).

Treatment-emergent SAEs were reported in 62 (50.0%) subjects. The most frequently reported SAE was pneumonia (8 [6.5%]), followed by anaemia (6 [4.8%]), general physical health deterioration (4 [3.2%]), and colitis, gastrointestinal haemorrhage, pyrexia, sepsis, tumour lysis syndrome, upper respiratory tract infection, and vomiting (2 [1.6%] each). All other SAEs were reported in 1 subject each. Treatment-related SAEs were reported in 22 (17.7%) subjects and included pneumonia (3 [2.4%]), and anaemia, colitis, and upper respiratory tract infection (2 [1.6%] each).

Fifteen (12.1%) subjects discontinued acalabrutinib due to AEs; no TEAEs that led to study drug discontinuation were reported in more than 1 subject. Fifty-one (41.1%) subjects had TEAEs that led to dose delay; the most frequently reported were herpes zoster (8 [6.5%]), pneumonia and vomiting (6 [4.8%] each), nausea (5 [4.0%]), anaemia and neutropenia (4 [3.2%] each), rash and urinary tract infection (3 [2.4%] each), and cataract, diarrhoea,

gastrointestinal haemorrhage, headache, intestinal obstruction, and neutrophil count decreased (2 [1.6%] each). All other events were reported in 1 subject each. Three (2.4%) subjects had dose modifications due to a TEAE.

Most subjects had events of clinical interest (ECIs), which are events that are known side effects of an approved Bruton tyrosine kinase (BTK) inhibitor. Cardiac events were reported in 16 (12.9%) subjects and included atrial fibrillation (3 [2.4%]) and mitral valve incompetence and tachycardia (2 [1.6%] each). All other cardiac events were reported in 1 subject each. Anemia events were reported in 18 (14.5%) subjects; all events were Preferred term (PT) anaemia. Thrombocytopenia events (including events of thrombocytopenia and platelet count decreased) occurred in 9 (7.3%) subjects. Neutropenia events (including PTs of neutropenia, febrile neutropenia, and neutrophil count decreased) were reported in 18 (14.5%) subjects. Hemorrhage events were reported in 46 (37.1%) subjects. Five (4.0%) subjects had major hemorrhage events. Hepatotoxicity events were reported in 7 (5.6%) subjects. Five (4.0%) subjects had hypertension events. Infections were reported in 84 (67.7%) subjects. Grade 3 and Grade 4 infections were reported in 21 (16.9%) subjects. Three (2.4%) subjects had events of interstitial lung disease. Second primary malignancies were reported in 16 (12.9%) subjects, including 6 (4.8%) subjects with Grade 3 or Grade 4 second primary malignancies. One subject had Grade 5 (fatal) non-small cell lung cancer. Three (2.4%) subjects had tumor lysis syndrome.

There were no clinically significant mean changes in hematology or chemistry laboratory values, serum immunoglobulin values, T cell/B cell/ natural killer (T/B/NK) cell counts, or vital sign values over time. A shift from baseline to higher CTCAE grades was observed in various hematological laboratory parameters, including decreased absolute lymphocyte count (ALC), increased ALC, decreased absolute neutrophil count (ANC), decreased hemoglobin, decreased leukocytes, and decreased platelets. Lymphocytosis occurred in 43 (35.0%) of 123 subjects, and resolved in 34 (79.1%) of 43 subjects. The most common laboratory abnormality was increased creatinine, reported in 114 (92.7%) subjects (all were Grade 1 or Grade 2). Grade 3 increased uric acid occurred in 23 (18.7%) subjects, and 12 (9.8%) subjects had Grade 4 increased uric acid. One subject met biochemical criteria for Hy's law; this case was not classified as a clinical Hy's law case because an alternate etiology was present (the subject had biliary obstruction and disease progression).

Conclusions

The results of the 54-month close-out analysis of this open-label Phase 2 study in subjects with R/R MCL treated with acalabrutinib monotherapy support the earlier results of the final CSR (Clinical Study Report Edition 1.0) and the 24-month follow-up update (Clinical Study Report Edition 2.0). Acalabrutinib monotherapy resulted in a high ORR and CR rate, with responses that were durable and clinically meaningful. Acalabrutinib treatment showed an

acceptable safety profile, as the majority of reported events were low grade in severity and resulted in few treatment discontinuations. Thus, treatment with acalabrutinib demonstrates a favorable benefit-risk profile and represents a promising treatment option for patients with R/R MCL.