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Final Safety Clinical Study Report Synopsis

Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-LY-002
Edition Number	2 (supersedes interim clinical safety report)
Date	14 November 2018
EudraCT Number	2014-001341-25

An Open-label, Phase 1b Study of ACP 196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma

Study dates: First subject consented: 07 August 2014

Data cutoff for this final clinical study report: 30 October 2017

Phase of development: 1b

International Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

Edition 1 Interim clinical safety report; 02 May 2017

Edition 2 Final clinical study report; 14 November 2018

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

Study Centers

Subjects were enrolled at 7 sites in the United States (US) and United Kingdom (UK).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	Characterize the safety profile of acalabrutinib in subjects with relapsed or refractory ABC DLBCL	Safety was assessed by AEs including SAEs and AEs of clinical interest; hematology, clinical chemistry and other laboratory variables; vital signs and ECOG PS scores.
Secondary	PK	Characterize the PK profile of acalabrutinib	Noncompartmental PK parameters were calculated for acalabrutinib based on plasma concentrations.
Secondary	PD	Evaluate the PD effects of acalabrutinib	BTK occupancy and B-cell activation were assessed.
Secondary	Efficacy	Evaluate the activity of acalabrutinib as measured by response rate, DOR, time-to-next treatment, and PFS	ORR, DOR, and PFS as assessed by the investigator and based on based on Lugano criteria, and time-to-next treatment for DLBCL.

Abbreviations: ABC = activated B-cell; AE = adverse event, BTK = Bruton tyrosine kinase; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response, ECOG= Eastern Cooperative Oncology Group; ORR = overall response rate; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacodynamics; PS = performance status; SAE = serious adverse event; SAP = Statistical Analysis Plan.

Study Design

Study ACE-LY-002 was a multicenter, open-label study to evaluate the safety, PK, pharmacodynamics and activity of acalabrutinib at a dose of 100 mg twice a day (bid) (200 mg daily dose) in subjects with relapsed or refractory de novo activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL).

Subjects received acalabrutinib 100 mg twice a day (bid) in repeated 28-day cycles; treatment continued until disease progression or unacceptable drug-related toxicity occurred. Subjects showing clinical benefit and who were tolerating acalabrutinib were allowed to remain on study through the end of Cycle 12 and beyond. All subjects who discontinued study drug, including those who discontinued treatment due to disease progression, had a safety Follow-up visit 30 (±7) days after the last dose of study drug unless they started another cancer therapy within that timeframe or withdrew consent.

Safety assessments included analysis of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events (AEs) leading to study drug discontinuation or does reduction. Laboratory assessments (serum chemistry and hematology) were performed once weekly for the first 4 weeks, every 2 weeks in Cycle 2, and monthly thereafter. Pharmacokinetic/pharmacodynamic (PK/PD) testing were conducted in Cycles 1 and 2. The effect of acalabrutinib on biologic markers of B-cell function was also evaluated. Efficacy in this study was based on the Lugano Classification for non-Hodgkin's lymphoma. Radiologic tumor assessments were done at Screening and at 8- to 12-week intervals during the study.

This final clinical study report presents the safety and efficacy data collected through the cutoff date of 30 October 2017.

Target Subject Population and Sample Size

The study enrolled adult subjects with pathologically confirmed relapsed or refractory de novo ABC DLBCL who had previously received a standard anthracycline and rituximab-based first-treatment regimen. Relapsed subjects were defined as subjects who had a partial response or better to previous anticancer therapy and subsequently progressed. Refractory subjects were defined as subjects whose best response to the previous anticancer therapy was stable disease or who had an unknown response to previous therapy. Subjects were to have no prior exposure to a B-cell receptor (BCR) inhibitor.

Ten subjects with relapsed disease and 10 with refractory disease were planned to be enrolled. The study enrolled and analyzed 11 relapsed and 10 refractory subjects.

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

Acalabrutinib 100 mg capsules, administered orally at a dose of 100 mg bid (200 mg per day). Ten batches of acalabrutinib were used in this study; individual batch numbers and further information are included in the clinical study report. No comparator was used in this study.

Duration of Treatment

The end of study was defined as the point when the last subject enrolled completed the end of Cycle 12, or withdrew for any reason and completed the 30-day Follow-up visit (if applicable), whichever occurred first. Subjects experiencing clinical benefit were allowed to continue to receive treatment after Cycle 12.

Statistical Methods

No formal tests of hypotheses were performed. Descriptive statistics were used to summarize baseline demographic and disease characteristics, study drug administration, and safety and efficacy outcomes. Categorical variables were summarized for each cohort (Relapsed and Refractory) separately and for the total study population.

Efficacy analyses were performed on the Relapse and Refractory cohorts separately, and on the total subject population. The analysis of overall response rate (ORR), progression-free survival (PFS), and time-to-next treatment were conducted on the All-treated population. The analysis of duration of response (DOR) was conducted on the subset of the All-treated population who achieved complete response (CR) or partial response (PR) as the best overall response. The analyses of DOR, PFS, and time-to-next-treatment were estimated using the Kaplan-Meier (KM) method.

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 20.1. 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 or higher) and by relationship to study drug as assessed by the investigator. 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 (AEGTs). The following ECIs were summarized: cardiac events (including a subset of atrial fibrillation), cytopenias (anemia, leukopenia, neutropenia), thrombocytopenia, hemorrhage (including a subset of major hemmorhage), hepatic events, hypertension, infection, interstitial lung disease/pneumonitis, second primary malignancies (second primary malignancies excluding skin), and tumor lysis syndrome.

Laboratory data of hematology, serum chemistry, serum immunoglobulin, and T/B/NK cell counts up to 30 days after last dose or the safety follow-up visit date, whichever is later, were graded according to CTCAE version 4.03. For selected laboratory test parameters, summary statistics were produced for baseline value, post-baseline value at the last visit, minimum and maximum post-baseline values, and changes of these post-baseline values from baseline. Shift from baseline to the maximum grade during the treatment was provided as shift tables for selected parameters.

Summary statistics were produced for vital signs at baseline, post-baseline values from the last visit, minimum and maximum post-baseline values, and changes of these post-baseline values from baseline. Change of Eastern Cooperative Oncology Group (ECOG) score from baseline to the maximum score during the treatment was provided as a shift table. Electrocardiograms (ECGs) were performed at Screening and Follow-up only. Subjects with abnormal clinically significant ECG assessment or corrected QT interval (QTc) >480 msec at Screening were listed.

Subject Population

The study enrolled 11 relapsed and 10 refractory subjects with ABC DLBCL at 5 sites in the US and 2 sites in the UK. All 21 subjects were treated with acalabrutinib and all but 1 subject (in the Refractory cohort) had discontinued treatment at the time of the data cutoff (30 October 2017). The median age of all subjects was 64 years (range 32 to 84). Approximately half of subjects in the study were female (52.4%), and more than half of subjects were <65 years of age. Most subjects were white and not Hispanic or Latino. The median time from initial DLBCL diagnosis to the first dose of acalabrutinib was higher for

subjects in the Relapse cohort (69.1 months; range 17.7 to 301.9) than for subjects in the Refractory cohort (10.0 months; range 4.6 to 34.0), consistent with the protocol-defined prior treatment response of the 2 cohorts. The subjects enrolled in this study were representative of the intended target population of patients with relapsed or refractory ABC DLBCL.

Summary of Efficacy Results

The ORR in this study was 23.8%. A total of 4 subjects, including 2 in each cohort, achieved a CR, and 1 subject in the Relapse cohort had a PR as the best response. Median DOR for the 5 subjects with CR or PR was 7.8 months (95% CI: 1.8, Not Estimable [NE]), based on KM estimates. Median PFS for all subjects based on KM estimates was 1.9 months (95% CI: 1.8, 2.7).

Eleven subjects had a new anticancer therapy reported; the median time-to-next treatment for these subjects was 3.0 months (range: 0.8 – 21.9 months). Median time-to-next treatment based on KM estimates was 4.0 months (95% CI: 3.0, 7.5).

Median overall survival for all subjects was 15.5 months (95% CI: 4.0, NE).

All efficacy results were similar for the Relapse and Refractory cohorts, with the exception of overall survival, which was notably higher in the Relapse cohort (median of 15.5 months; 95% CI: 3.1, 15.5) than in the Refractory cohort (median of 6.0 months; 95% CI: 1.8, NE).

Summary of Pharmacokinetic Results

Pharmacokinetic results are presented in Appendix 12.1.13.

Summary of Pharmacodynamic Results

Pharmacodynamic results are presented in Appendix 12.1.14.

Summary of Pharmacokinetic/Pharmacodynamic Relationships

The PK/PD relationship of acalabrutinib is discussed in Appendix 12.1.14.

Summary of Safety Results

All 21 subjects received acalabrutinib. The median duration of treatment was 2.3 months (range 0.5 to 22.5) and the extent of exposure was similar in both cohorts.

The most commonly reported AEs were diarrhoea (42.9%), fatigue (42.9%), anaemia (28.6%), cough (28.6%), dizziness (28.6%), headache (23.8%), and nausea (23.8%). Approximately half of subjects had AEs that were CTCAE grade ≥3. One subject had grade 4 respiratory failure (serious and considered not treatment-related) and grade 5 septic shock (fatal, not treatment-related). One other subject had grade 4 pneumonia (serious, not treatment-related) and grade 5 respiratory failure on the same day (fatal, not treatment-related). One additional subject had grade 5 metastases to meninges (not treatment-related). There were no noteworthy differences between the 2 cohorts in the frequency of grade ≥3 events or in the frequency of treatment-related AEs.

Most AEs reported in this study did not lead to study treatment discontinuation. Three subjects (14.3%) discontinued study treatment due to an AE (metastases to meninges [fatal], respiratory failure [fatal], and pyrexia), and 3 subjects (14.3%) had a dose delay due to an AE.

Three subjects died due to AEs considered not related to study treatment (septic shock, respiratory failure, and metastases to meninges), and 5 subjects died of disease progression. Fifteen SAEs were reported for 9 (42.9%) subjects. Serious events of abdominal pain, pyrexia and respiratory failure were each reported for 2 (9.5%) subjects. All other SAEs were reported for 1 subject each. Two subjects had SAEs considered related to study treatment (pyrexia and positive influenza B virus test).

Several subjects had ECIs, which are events identified based on their association with subjects with relapsed hematological malignancies and known side effects of an approved Bruton tyrosine kinase (BTK) inhibitor. No events of atrial fibrillation, neutropenia, thrombocytopenia, major hemorrhage, hypertension, second primary malignancy, pneumonitis or tumor lysis syndrome were reported. Grade ≥3 ECIs included anemia in 5 subjects, and infection in 4 subjects, which included pneumonia, septic shock, rhinovirus, urinary tract infection, and viral infection.

There were no clinically important mean changes from baseline in selected serum chemistry, hematology, and serum immunoglobulin values from baseline to last post-baseline values. There was 1 potential biochemical Hy's law cases in this study, but no drug-induced liver injury was noted. There were no clinically meaningful trends in post-treatment vital signs. Five subjects had higher ECOG performance scores after the first dose; however, all subjects had ECOG performance scores ≤2.

Conclusions

Acalabrutinib demonstrated efficacy in this population of relapsed or refractory ABC DLBCL, with an ORR of 23.8%, including 4 subjects with CR based on the Lugano classification. Acalabrutinib also demonstrated an acceptable tolerability profile with a low incidence of SAEs (including fatal), severe AEs, and low frequency of treatment discontinuation due to AEs.