Interim Clinical Study Report	
Drug Substance	Acalabrutinib
Study Code	D8220C00007
Edition Number	1.0
Date	31 Oct 2022
NCT Number	NCT03932331

A Phase I/II Open Label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Acalabrutinib in Chinese Adult Subjects with Relapsed or Refractory Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia or Other B-cell Malignancies

Study dates: First subject enrolled for Phase II portion Cohort B: 18 Aug 2020
The analyses presented in this report are based on the clinical data cutoff being 28 Jun 2022

Phase of development: I/II

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

2. SYNOPSIS

Study center(s)

As of the data cutoff (DCO) date of this report (28 Jun 2022), this study had been conducted at 20 study centers in China, with Phase I portion being conducted at 2 centers and Phase II portion being conducted at 20 centers.

Publications

There were no publications based on this study at the time when this report was finalized.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary Objectives of Phase II Portion Cohort B	
• To assess the efficacy of acalabrutinib in Chinese patients with R/R CLL	• ORR as assessed by BICR per iwCLL 2018 criteria
Secondary Objectives of Phase II Portion Cohort B	
• To further assess the efficacy of acalabrutinib in Chinese patients with R/R CLL • To assess the safety profile of acalabrutinib in Chinese patients with R/R CLL • To assess pharmacokinetics of acalabrutinib in Chinese patients with R/R CLL	• DoR, PFS and TTR as assessed by BICR per iwCLL 2018 criteria • ORR, DoR, PFS, and TTR as assessed by investigators per iwCLL 2018 criteria • TTNT • Minimal residual disease negative rate (defined as the proportion of patients with MRD-negativity) measured in the peripheral blood by flow cytometry • OS • AEs, laboratory parameters, vital signs, and ECGs • Plasma concentration of acalabrutinib (sparse sampling)

Abbreviations: AE = adverse event; BICR = blinded independent central review; CLL = chronic lymphocytic leukemia; DoR = duration of response; ECG = electrocardiogram; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R/R = relapsed/refractory; TTNT = time to next treatment; TTR = time to response.

Cohort B included patients with R/R CLL who had failed from ≥ 1 prior systemic therapy.

This interim Clinical Study Report (CSR) reports the efficacy, safety and PK data for Cohort B of Phase II portion. Study objectives and endpoints of Phase I portion and Phase II portion Cohort A are not detailed in this report.

Minimal residual disease negative rate was defined as the proportion of patients with MRD-negativity (<1 CLL cell per 10,000 leukocytes) measured in the peripheral blood by flow cytometry.

Study design

Study D8220C00007 was a Phase I/II open label, multi-center study to assess the safety, tolerability, pharmacokinetics (PK) and clinical efficacy of acalabrutinib in Chinese adult patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) or other B-cell malignancies. The study was divided into 2 parts: Phase I portion and Phase II portion. Study design of Phase I portion and Phase II portion Cohort A are not detailed in this report.

Phase I portion

Phase I portion was the first study designed to evaluate the preliminary safety, tolerability, and pharmacokinetics of acalabrutinib in Chinese adult patients with R/R B cell malignancies.

Phase II portion

Phase II portion was to further evaluate clinical efficacy, safety, and tolerability of acalabrutinib in patients with R/R MCL and R/R CLL. The enrollment of Phase II portion was initiated per Safety Review Committee (SRC) recommendation based on preliminary safety data from Phase I portion. Phase II portion was comprised of 2 cohorts (Cohort A and Cohort B). Evaluation of efficacy and safety was performed independently for each cohort. Cohort B was to evaluate clinical efficacy, safety, and tolerability of acalabrutinib in patients with CLL who had failed from ≥ 1 prior systemic therapy. Approximately 60 R/R CLL patients were planned to be enrolled to receive 100 mg of acalabrutinib twice daily (BID) in repeated 28-day cycles.

Treatment with acalabrutinib continued until progression of disease (PD) or any other treatment discontinuation criterion was met. An early termination visit was required for any patients who discontinued study treatment for any reason, including PD (except for death, lost to follow-up or withdrawal of consent). In addition to the early termination visit, all patients who discontinued study treatment had a safety follow-up visit 30 (+7) days after his or her last dose of study treatment.

All patients had hematology, clinical chemistry, and urinalysis safety panels done at screening. Once dosing commences (Cycle 1 Day 1), all patients were evaluated for safety, including hematology and clinical chemistry at regular basis.

Tumor assessments for R/R CLL patients were performed at 12- to 24-week intervals throughout the study. The end of study will occur approximately 24 months after the last R/R CLL patient receiving first dose of study medication in Phase II portion.

The primary efficacy analysis for R/R CLL patients was based on Blinded Independent Central Review (BICR) assessment.

As specified in the study protocol, the DCO for the 1st analysis of Cohort B took place approximately 6 months after the last R/R CLL patient receiving first dose of study medication in Phase II portion. Results of the 1st analysis for R/R CLL patients are summarized in this report, with the DCO being 28 Jun 2022.

Target population and sample size

Chinese patients at least 18 years of age were enrolled in the study. The study population of Phase II portion Cohort B included patients with R/R CLL who had failed from ≥ 1 prior systemic therapy for CLL.

Planned enrollment: For Phase II portion Cohort B, approximately 60 Chinese R/R CLL patients were planned to be enrolled to receive study treatment. With 60 patients from Cohort B, an exact binomial test with a nominal one- sided 2.5% significance level would have 90% power to detect the difference between a null hypothesis ORR of 70% and an alternative ORR of 88%.

Actual enrollment: As of the DCO of this report (28 Jun 2022), a total of 84 Chinese R/R CLL patients were enrolled, out of which 60 patients received study treatment for Phase II portion Cohort B.

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

Investigational product: Acalabrutinib was manufactured by CCI and was supplied as opaque size 1 yellow and blue hard gelatinous capsules with a strength of 100 mg. Acalabrutinib was administered orally at a dose of 100 mg twice daily (BID) with approximately 240 mL of water. Acalabrutinib could be taken with or without food. For the oral administration of acalabrutinib BID, doses should be administrated approximately 12 hours apart.

Acalabrutinib batch numbers: CCI

Duration of treatment

All eligible patients were treated with acalabrutinib 100 mg BID until PD or any other treatment discontinuation criterion was met.

Statistical methods

As specified in the study protocol, there were 5 planned analyses for this study, including 3 planned analyses for cohort B R/R CLL patients in Phase II portion. Results of the 1st analysis of R/R CLL patients are summarized in this report with the DCO being 28 Jun 2022 approximately 6 months after the last R/R CLL patients being enrolled in Phase II portion. The 2nd and 3rd analysis will take place approximately 12 and 24 months after last R/R CLL patients

enrolled in Phase II portion, respectively. The study procedures, planned analyses, and analytical methods for patients in Phase I portion and Phase II portion Cohort A are not detailed in this report.

Populations for analyses/analysis sets:
Safety analysis set: All patients who received at least 1 dose of acalabrutinib.

Pharmacokinetics (PK) analysis set: All patients who received at least 1 dose of acalabrutinib with reportable acalabrutinib plasma concentration and PK parameter data, and no important protocol deviations that might impact PK.

Tumor response analysis set: All patients who received at least 1 dose of acalabrutinib with an available baseline tumor assessment.

Efficacy analyses:
Efficacy analyses were conducted based on tumor response analysis set.

The R/R CLL efficacy analysis of tumor response only applied for R/R CLL patients in Phase II portion.

The primary efficacy endpoint was BICR-assessed ORR, which was defined as the proportion of patients who achieved a complete response (CR), CR with incomplete marrow recovery (CRi), nodular partial response (nPR), and partial response (PR), as best overall response (BOR) in the tumor response analysis set per iwCLL 2018 criteria (Hallek 2018). ORR plus the proportion of patients with a BOR of partial response with lymphocytosis (PRL) were also assessed, denoted as ORR + PRL. ORR and the corresponding 95% two-sided confidential interval (CI) of ORR were presented based on Clopper-Pearson exact method. BICR-assessed ORR+PRL and the corresponding 95% two-sided Clopper-Peason CI were also presented.

The investigator-assessed ORR, as a secondary efficacy endpoint, was analyzed using a method consistent with the primary analysis. Subgroup analysis of ORR was also conducted. Descriptive statistics were provided for BOR. The analysis of BICR-assessed DoR, PFS, OS, and time to next treatment (TTNT) was estimated using the Kaplan-Meier (K-M) methods. K- M estimates were calculated for event time, such as quartiles (including median), and event- free rates were calculated at selected time points. In addition, the reason for censoring was summarized for DoR, PFS, OS, and TTNT. Regarding the time to response (TTR), the time to initial response and time to best response were summarized separately. The same analysis methods for BICR-assessed secondary endpoints (DoR, PFS, and TTR) also applied to investigator-assessed secondary endpoints. The concordance between the investigator- and BICR-assessed ORR and BOR was also provided in this study. The minimal residual disease (MRD) negativity rate was summarized.

Pharmacokinetics analyses:

All PK analyses were conducted based on the PK analysis set. For the Cohort B R/R CLL patients in Phase II portion, plasma concentrations of acalabrutinib were summarized and listed.

Safety analyses:

Safety analyses were conducted based on safety analysis set. Safety endpoints mainly included AEs, laboratory data, vital signs, Eastern Cooperative Oncology Group (ECOG), and ECGs. The safety endpoints were assessed using descriptive statistics. For lymphocytosis, the number of patients with at least one occurrence of lymphocytosis were summarized.

Study population

- There were 60 eligible patients who received study treatment in R/R CLL cohort in total. As of the DCO date (28 Jun 2022), the study treatment was ongoing for 53 (88.3%) patients and was discontinued for 7 (11.7%) patients with the main reasons for treatment discontinuation being PD (3 [5.0%] patients) and AE (2 [3.3%] patients). A total of 58 (96.7%) patients continued the study, 2 (3.3%) discontinued the study due to death.
- All the 60 patients who received study treatment in R/R CLL cohort were included in the safety analysis set, tumor response analysis set and PK analysis set.
- All the 60 patients in R/R CLL cohort were Chinese. The median age was 62.0 years (range: PPD and approximately 38.3% patients were aged ≥ 65 years. Forty- one (68.3%) patients were male.
- Most patients in CLL cohort had an ECOG score of 0 (33 [55.0%] patients) or 1 (25 [41.7%]). Twenty-three (38.3%) patients had a bulky disease of a longest diameter of ≥ 5 cm at baseline. Twenty-nine (48.3%) patients had Rai staging of high risk (stage III or IV). The median β2-microglobulin for CLL patients were 4.15 mg/L with 66.7% patient's β2-microglobulin level > 3.5 mg/L. Del (17p), del (11q), immunoglobulin heavy-chain variable (IGHV) unmutation and TP53 mutation were observed in 11.7%, 28.3%, 51.7%, and 11.7% of patients, respectively, and 38 (63.3%) patients had at least one of these chromosomal features. At baseline, 46 (76.7%) patients were diagnosed as refractory disease. Forty- four (73.3%) patients experienced cytopenia of ANC ≤ 1.5 × 10^9/L or hemoglobin ≤ 11 g/dL or platelets ≤ 100×10^9/L. Nineteen (31.7%) patients experience at least one constitutional B symptoms of weight loss, fever, night sweats, or fatigue.
- All the 60 (100.0%) patients in R/R CLL cohort had prior anticancer therapies. Forty- three (71.7%) patients had 1 prior line of anticancer therapy, 14 (23.3%) patients had 2 prior lines of anticancer therapy, and 3 (5.0%) patients had ≥ 3 lines of prior anticancer therapies. The median number of prior therapy regimens was 1.0 (range: PPD) in R/R CLL cohort, and 4 (6.7%) patients had ≥3 prior therapy regimens. The most frequently used regimens were chlorambucil (37 [61.7%] patients), rituximab as single agent or part of a regimen (21 [35%] patients), and FC or cladribine (9 [15.0%] patients). No patients reported prior radiotherapies. In R/R CLL cohort, the majority of patients (55 [91.7%] patients) received concomitant medications after being enrolled in the study.

Summary of efficacy results

- Primary endpoint - ORR assessed by BICR: The ORR per iwCLL 2018 criteria was 83.3% (95% CI: 71.5%, 91.7%). The ORR+PRL was 86.7% (95% CI: 75.4%, 94.1%). The subgroup analysis of the primary endpoint showed that there was no remarkable difference in ORR among most of the pre-defined subgroups, similar to the analysis results of the primary efficacy.
- Investigator-assessed ORR: The investigator-assessed ORR per iwCLL 2018 criteria was 76.7% (95% CI: 64.0%, 86.6%). The overall concordance rates between BICR- and investigator-assessed response was 86.7%. The subgroup analysis results of ORR assessed by the investigator also supported the BICR-assessed ORR, and there was no remarkable difference in ORR among the subgroups.
- BICR- and investigator-assessed DoR: The 12-month DoR rate (K-M point estimate) was 90.2% (95% CI: 64.1%, 97.6%), and median DoR was not reached. As assessed by the investigator, the 12-month DoR rate (K-M point estimate) was 100.0% (95% CI: 100.0%, 100.0%), and median DoR was not reached. The DoR result assessed by the investigator was basically consistent with that assessed by BICR.
- BICR- and investigator-assessed PFS: The PFS result assessed by BICR showed that as of the DCO date (28 Jun 2022), the 12-month PFS rate (K-M point estimate) was 90.7% (95% CI: 78.9%, 96.0%), and median PFS was not reached. As assessed by the investigator, the 12-month PFS rate (K-M point estimate) was 94.9% (95% CI: 84.9%, 98.3%), and median PFS was not reached. The PFS result assessed by the investigator was consistent with that assessed by BICR.
- BICR- and investigator-assessed TTR: The median time to initial response based on BICR assessment was 5.49 months (range: 2.7 to 13.8 months). The median time to initial response based on investigator assessment was 3.75 months (range: 2.7 to 13.7 months). The TTR result assessed by the investigator was generally identical with that assessed by BICR.
- Time to next treatment: A total of 3 (5.0%) patients had TTNT-related events. The 12- month TTNT rate (K-M point estimate) was 94.8% (95% CI: 84.6%, 98.3%), and median TTNT was not reached.
- Minimal residual disease: A total of 25 (41.7%) patients had MRD evaluated post- baseline. Among those who had post-baseline MRD evaluated results, no patient was assessed as MRD- negative.
- Overall survival: As of the DCO date (28 Jun 2022), 2 (3.3%) patients died. The 12- month OS rate (K-M point estimate) was 96.7% (95% CI: 87.3%, 99.2%), and median OS was not reached.

Summary of pharmacokinetic results

The PK results of R/R CLL Cohort will be presented in a separate population PK report.

Summary of safety results

- The total median treatment duration of patients was 13.85 months (range: 0.6 to 22.4 months), and the median relative dose intensity was 99.9%.

- Fifty-eight patients (96.7%) reported at least 1 treatment emergent adverse event (TEAE), of which 25 (41.7%) patients reported Grade 3 or above TEAEs by Common Terminology Criteria for Adverse Events (CTCAE) grade. Fifty-three (88.3%) patients reported treatment related TEAEs, of which 23 (38.3%) patients reported Grade 3 or above treatment related TEAEs.
- The most frequently reported TEAEs (≥ 10% of patients) by preferred term (PT) were neutrophil count decreased (20 [33.3%] patients), platelet count decreased (18 [30.0%] patients), hemoglobin decreased (14 [23.3%] patients), anemia (13 [21.7%] patients), upper respiratory tract infection (11 [18.3%] patients), headache (10 [16.7%] patients), hematocrit decreased, pneumonia (9 [15.0%] patients each), petechiae, red blood cell count decreased (8 [13.3%] patients each), rash (7 [11.7%] patients), and diarrhea (6 [10.0%] patients). The most frequently reported treatment related TEAEs (≥ 10% of patients) by PT were neutrophil count decreased (19 [31.7%] patients), platelet count decreased (18 [30.0%] patients), hemoglobin decreased (12 [20.0%] patients), anemia (11 [18.3%] patients), upper respiratory tract infection (10 [16.7%] patients), hematocrit decreased, headache, red blood cell count decreased (8 [13.3%] patients each), pneumonia, and rash (7 [11.7%] patients each). The most frequently reported Grade ≥ 3 TEAEs (reported by ≥ 5% patients) by PT were neutrophil count decreased (8 [13.3%] patients), upper respiratory tract infection (4 [6.7%] patients), anemia, hematocrit decreased, hemoglobin decreased, lymphocyte count increased, platelet count decreased, and pneumonia (3 [5.0%] patients each).
- Two (3.3%) patients died, of which PPD (1.7%) patient was due to TEAE cardiac arrest 2 days after permanently discontinuing acalabrutinib. Another PPD (1.7%) patient died of shock hemorrhagic 50 days after receiving last dose of acalabrutinib.
- Nine (15.0%) patients reported 12 serious TEAEs, of which 8 (13.3%) patients reported 9 treatment related serious TEAEs. Grade ≥ 3 SAEs were reported in 8 (13.3%) patients, including Grade 4 and Grade 5 SAEs in PPD patient each. Pneumonia was the only SAE reported in ≥ 2 patients.
- A total of 2 (3.3%) patients reported TEAEs leading to dose discontinuation, both of which were serious TEAEs. Eleven (18.3%) patients reported TEAEs leading to dose interruption. PPD (1.7%) patient reported 1 case of TEAE that led to dose modification (reduction).
- Four patients (6.7%) reported AESIs, and the PTs included ventricular arrhythmia and ventricular extrasystoles, all of which were of Grade 1 to 2 and non-serious TEAEs.
- Most ECI events were of Grade 1 or 2 in severity. No patient reported atrial fibrillation, major hemorrhage, interstitial lung disease/pneumonitis, second primary malignancies, or tumor lysis syndrome.
- No unexpected changes in hematology values from baseline to the last post-baseline results and no clinical important meaningful changes in clinical chemistry values from baseline to the last post-baseline values were observed.
- No potential Hy's law event was reported.

Conclusions

- The R/R CLL cohort of study D8220C00007 met the primary endpoint. Acalabrutinib 100 mg BID was effective in Chinese patients with R/R CLL, manifested as high ORR with responses that were durable and clinically meaningful.
- The observed TEAEs in Chinese CLL patients were consistent with the known safety profile of acalabrutinib. There were no unexpected safety observations in Chinese CLL patients.
- Treatment with acalabrutinib demonstrates a favorable benefit-risk profile and represents a promising treatment option for Chinese patients with R/R CLL.