2. SYNOPSIS

Study centre(s)

The study was performed at 15 study sites located in different regions of India.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety of Acalabrutinib among patients with CLL/ SLL and relapsed & refractory MCL in Indian patients.	• Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs of Special Interest (AESI) including Arrhythmias (Atrial Fibrillation), Anaemia, Hypertension, Bleeding, Infections, • Reasons for discontinuation and second primary malignancies
Secondary	
• To assess the efficacy of Acalabrutinib in patients of CLL/SLL and relapsed & refractory MCL in Indian patients. • Patient-reported outcome (PRO)	• Objective response to treatment • Health related quality of life (EORTC QLQC30 Questionnaire)

Study design

The study was a phase IV, open-label, single-arm, multi-centre, prospective study conducted in India. The study evaluated the safety and efficacy of Acalabrutinib in Indian adult patients with CLL/SLL, and patients with MCL who had received at least one prior therapy. Patients with CLL/SLL and MCL who were eligible to receive Acalabrutinib treatment as per locally approved prescribing information were evaluated for inclusion into this Phase IV trial. The study was initiated after approval by the Ethics Committee.

Two cohorts of patients were included in the study (a) patients with CLL/SLL who were treatment naïve or had received at least one prior therapy (N= 89) and (b) patients with MCL who had received at least one prior therapy (N= 11). Potential patients underwent screening phase within 07 days prior to the first Acalabrutinib dose. Patients who met the protocol-defined inclusion/exclusion criteria were enrolled into the study. The participating patients underwent

following phases during the course of the study: Screening/Enrolment Phase, Treatment Phase, and Follow-up Phase.

Acalabrutinib capsules 100 mg were administered orally twice daily (BID) for 06 cycles, starting from Cycle 1 Day 1, and continuing up to Cycle 6 Day 28; or until study drug discontinuation due to either disease progression or, unacceptable toxicity, or other reasons, whichever occurred earlier.

Target population and sample size

The primary endpoint of the trial was to demonstrate the safety profile of Acalabrutinib in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious) observed during the trial. As per the Health Authority requirement, the total sample size of the study was 100.

Eligible patients who met the following inclusion criteria and none of the exclusion criteria were included in the study:

Inclusion Criteria:

Inclusion criteria for all patients including CLL/SLL and MCL.

1. Men and Women aged 18 years or more.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0,1, or 2
3. Able to receive all outpatient treatments, all laboratory monitoring, and all radiologic evaluations.
4. The following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥750 cells/µL or ≥500 cells/µL in patients with documented bone marrow involvement, and independent of growth factor support 07 days before the assessment.
    b. Platelet count ≥50,000 cells/µL or ≥30,000 cells/µL in patients with documented bone marrow involvement, and without transfusion support 07 days before the assessment
    c. Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤2.0 x ULN
    d. Total bilirubin ≤1.5 x ULN
    e. Estimated creatinine clearance of ≥30 mL/min
5. Refractory disease defined as achieving less than partial response with the most recent treatment within 6 months before study entry
7. The patients of either CLL or MCL:

a. CLL patients:

i. Treatment naïve or ≥1 prior systemic therapy for CLL
ii. Diagnosis of CD20+ CLL that meets published diagnostic criteria (Hallek

et al. 2018)

iii. An active disease that meets ≥1 of the following iwCLL 2018 criteria for requiring treatment:

1) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. Cut-off levels of Hb <10 g/dL or platelet counts $<100 \times 10^9$/L are generally regarded as an indication for treatment. However, in some patients, platelet counts $<100 \times 10^9$/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
2) Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3) Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4) Progressive lymphocytosis with an increase of ≥50% over a 2-month period or Lymphocyte Doubling Time (LDT) in <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts $<30 \times 10^9$/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
5) Autoimmune complications, including anaemia or thrombocytopenia poorly responsive to corticosteroids.
6) Symptomatic or functional extra-nodal involvement (e.g., skin, kidney, lung, spine).
7) Disease-related symptoms as defined by any of the following:
    a) Unintentional weight loss of ≥10% within the previous 06 months.
    b) Significant fatigue (i.e., ECOG performance scale 02 or worse; cannot work or unable to perform usual activities).
    c) Fever ≥100.5°F or 38.0°C for 02 or more weeks without evidence of infection.
    d) Night sweats for ≥1 month without evidence of infection.

b. MCL Patients:

i. Confirmed MCL with translocation t(11;14) (q13; q32) and/or overexpressed cyclin D1

ii. Measurable nodal disease (one or more lesions measuring ≥2 cm in the longest diameter)

iii. Relapsed after, or were refractory to, 1-5 previous treatments.

Exclusion criteria:

Exclusion criteria for all patients including CLL/SLL and MCL.

1. Known prolymphocytic leukaemia, Central Nervous System (CNS) lymphoma or leukaemia; or known history of (or currently suspected) Richter's syndrome.
2. Treatment with chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days of the first dose of study drug.
3. Prior radio-conjugated or toxin-conjugated antibody therapy.
4. Anticoagulation therapy (e.g., warfarin or equivalent vitamin K antagonists) within 07 days of the first dose of study drug.
5. Major surgery ≤30 days before the first dose of study drug.
6. History of stroke or intracranial haemorrhage ≤6 months before the first dose of study drug.
7. History of bleeding diathesis.
8. Prior exposure to a B-cell lymphoma-2 (Bcl-2) inhibitor or B-cell receptor inhibitor like BTKIs.
9. Active Cytomegalovirus (CMV) infection or serologic status reflecting active Hepatitis B or C infection, known history of infection with Human immunodeficiency virus (HIV), or any uncontrolled active systemic infection.
10. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, Congestive Heart Failure, or Myocardial Infarction within 6 months of screening, or any Class 3 or 4 cardiac diseases as defined by the New York Heart Association, Functional Classification, or QTcB >480 msec at screening.
11. Requiring treatment with proton-pump inhibitors (e.g., Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Rabeprazole, or Pantoprazole).
12. Breastfeeding or pregnant.
13. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could have compromised the subject's safety or put the study at risk.
14. Concurrent participation in another therapeutic clinical trial.

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

Acalabrutinib capsules 100 mg were administered orally twice daily (BID) for 06 cycles, starting from Cycle 1 Day 1, and continuing up to Cycle 6 Day 28; or until study drug discontinuation due to either disease progression or, unacceptable toxicity, or other reasons, whichever occurred earlier. Dose escalation or reduction was not recommended. CCI [redacted]

Duration of treatment

Treatment Phase for the study was from the start of Cycle 1 Day 1 to Cycle 6 Day 28, or until study drug discontinuation due to either disease progression or unacceptable toxicity, or other reasons whichever occurred earlier.

Statistical methods

Sample Size Justification
The primary endpoint of the trial was to demonstrate the safety profile of Acalabrutinib in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during the trial. As per the Health Authority requirement, the total sample size of the study was 100.

Hypothesis
No formal hypothesis testing was conducted.

Statistical Analysis
Categorical data was summarized using frequencies and percentages. Continuous data were summarized with descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals were supplied for key proportions (including objective response rate) using the Clopper-Pearson method.

Study population

A total of 119 patients were screened from 15 different study centres in India. 103 patients passed the screening after meeting all the inclusion and none of the exclusion criteria. They were selected and enrolled in the study. These 103 patients were divided into two groups, patients with CLL/SLL (N=90) and patients with MCL (N=13). Out of these, 100 patients (89 patients in the CLL/SLL and 11 in the MCL group) were considered in the FAS, 3 enrolled patients were discontinued due to withdrawal of the consent form. The study cohort comprises of Asian patients; majority of patients were males (80%) with mean age of 61.6 years. Among patients in the CLL/SLL and MCL group, 74 (83.15%) patients were treatment naïve.

Summary of efficacy results

Efficacy of Acalabrutinib in patients with CLL/SLL and relapsed & refractory MCL in Indian patients were analysed by measuring objective response to treatment and from patient related outcomes.

- In Group 1 i.e., patients with CLL/SLL, 1/89 (1.12%) patient achieved Complete Response/Remission (CR), 53/89 (59.55%) patients achieved Partial Response/Remission (PR) and 1/89 (1.12%) patient achieved Partial Response with Lymphocytosis (PR-L) to the treatment at Visit 5. Overall, a total of 55/89 (61.80%; 95% CI: 50.89 – 71.90) patients achieved objective response at visit 5. In the last treatment cycle (i.e., Cycle 6 at Visit 8), 4/89 (4.49%) and 50/89 (56.18%) patients achieved complete and partial response to the treatment respectively, while 1/89 (1.12%) patient showed partial response with lymphocytosis. Overall, a total of 55/89 (61.80%; 95% CI: 50.89 – 71.90) patients achieved objective response.
- In Group 2, i.e., patients with MCL, 2/11 (18.18%) patients achieved Complete Response/Remission (CR) and 3/11 (27.27%) patients achieved Partial

Response/Remission (PR) to the treatment during Visit 5. Overall, a total of 5/11 (45.45%; 95% CI: 16.75 – 76.62) patients achieved objective response following treatment. In the last treatment cycle (i.e., Cycle 6 at Visit 8), a total of 4/11 (36.36%; 95% CI: 10.93 – 69.21) patients achieved objective response; all these 4/11 patients demonstrated Partial Response/Remission (PR) to the treatment.

- Overall Analysis of objective response to the treatment demonstrated that, 3/100 (3%) patients achieved Complete response/Remission (CR), 56/100 (56%) patients achieved Partial Response/Remission (PR) and 1/100 (1%) patient achieved Partial Response with Lymphocytosis (PR-L) following the treatment. Overall, a total of 60/100 (i.e., 60%, 95% CI: 49.72 – 69.67) patients achieved objective response during Visit 5. In the last treatment cycle (i.e., Cycle 6, Visit 8), 4/100 (4%) and 54/100 (54%) patients achieved complete and partial response to the treatment respectively while 1/100 (1%) patient showed partial response with lymphocytosis. Overall, 59/100 (59%, 95% CI: 48.71 – 68.74) patients achieved objective response.
- No change was seen in the overall quality of life scores evaluated using QLQ-30 questionnaire from Visit 1 (i.e., screening phase) to Visit 8 (last treatment cycle).

Summary of safety results

Acalabrutinib treatment to CLL/SLL and relapsed & refractory MCL Indian patient for 168 days showed that there were no new safety signals.

CLL/SLL Group:

- In the CLL/SLL group, 48 (53.93%) patients experienced 178 adverse events. In majority of the patients, AEs were not related to the study drug as assessed by the investigator (35/89, [39.33%]) while in 13/89 [14.61%] patients AEs were related to the study drug.
- 22 (24.72%) patients experienced mild, 16 (17.98%) patients experienced moderate, and 8 (8.99%) patients experienced severe adverse events. Further, 1 (1.12%) patient experienced life threatening and disabling adverse event and 1 (1.12%) patient died due to adverse event.
- During the treatment period, 4 (4.49%) patients were hospitalized due to AEs, and 7 (7.87%) patients required diagnostic or clinical tests. 5 (5.62%) patients recovered without any drug treatment while study drug was discontinued in 4 (4.49%) patients. 27 (30.34%) patients recovered without sequelae, 4 (4.49%) patients recovered with sequelae, 12 (13.48%) patients did not recover during the study period, 4 (4.49%) patients were still recovering and outcome for 1 (1.12%) patient was unknown.
- In 4 (4.49%) patients, drug was withdrawn due to AEs. Among patients experiencing AEs, 10 (11.24%) patients required no treatment, while 38 (42.70%) patients underwent treatment to manage the AEs.

MCL group

- In the MCL group, 9 (81.82%) patients experienced 29 adverse events. In majority of the patients, AEs were not related to the study drug as assessed by the investigator (7/11, [63.64%]). A total of 5 (45.45%) patients experienced mild, 1 (9.09%) patient experienced moderate, and 1 (9.09%) patient experienced severe adverse event. 2 (18.18%) patients died due to adverse events.
- During the treatment period, 3 (27.27%) patients were hospitalized due to AEs. 7 (63.64%) patients recovered without sequelae while the outcome for 2 (18.18%) patients was unknown. In 1 (9.09%) patient, drug was withdrawn due to AEs. Among patients experiencing AEs, 1 (9.09%) patient required no treatment, while 8 (72.73%) patients underwent treatment to manage the AEs.

Overall

- Overall, 57 (57%) patients reported a total of 207 AEs.
- 42 patients (42%), reported AEs that were assessed by the investigator as not related to the study drug while15 [15%] patients experienced AEs that were assessed as related to the study drug.
- 27 (27%) patients experienced mild, 17 (17%) patients experienced moderate, and 9 (9%) patients experienced severe adverse events. Further, 1 (1%) patient experienced life-threatening and disabling adverse events, and 3 (3%) patients died due to adverse events. Among the patients experiencing AEs, 33 (33%) patients required no treatment, 5(%) underwent non-drug intervention, 7 (7%) patients each were hospitalized, and patients required diagnostic or clinical tests. Additionally, in 5 (5%) patients drug was withdrawn. 34 (34%) patients recovered without sequelae, 4 (4%) patients recovered with sequelae, 12 (12%) patients did not recover during the study period, 4 (4%) patients were still recovering, and outcome for 3 (3%) patient was unknown. Among patients experiencing AEs, 11 (11%) patients required no treatment, while 46 (46%) underwent treatment to manage the AEs.
- Overall, 45 (45%) patients experienced at least one TEAEs – 38 (42.70%) patients in the CLL/SLL group and 7 (63.64%) patients in the MCL group. Diarrhoea (9%), pyrexia (9%), cough (6%), anaemia (5%), constipation (4%), peripheral oedema (3%), and headache (3%) were the most frequent TEAEs experienced by patients. 11 (11%) patients experienced at least one serious TEAE – 8 (8.99%) in CLL/SLL group and 3 (27.27%) patients in the MCL group.

- 11 (11%) patients experienced at least one serious TEAE – 8 (8.99%) in CLL/SLL group and 3 (27.27%) patients in the MCL group.

Conclusion(s)

- In conclusion, the use of Acalabrutinib in the treatment of patients with CLL/SLL and MCL demonstrated that there were no new safety signals observed in this study. Most adverse events (related or not related to study drug) reported during the study were mild to moderate in nature with a very few patients experiencing severe, life-threatening, or disabling adverse events. The findings were consistent when patients with CLL/SLL and MCL were analysed separately. While majority of the patients had AEs that were considered as not related to the study drug, it is important to carefully monitor and manage adverse events in patients undergoing Acalabrutinib treatment.
- In terms of efficacy, the study showed a promising efficacy of Acalabrutinib treatment in patients with CLL/SLL and MCL. More than half of the patients achieved objective responses to Acalabrutinib at both visits including complete response, partial response and partial response with lymphocytosis demonstrating its potential effectiveness. Notably, patient compliance remained excellent, with majority of the patients (87%) being 100% compliant with the treatment medication till the end of the study.
- The evaluation of health-related quality of life was evaluated using the QLQ-30 questionnaire. No change in the overall quality of life throughout the study was observed indicating that QoL did not deteriorate from Visit 1 to Visit 8.