5 TRIAL POPULATIONS

5.1 Inclusion Criteria (All Subjects)

Each potential subject must fulfil all of the following criteria to be enrolled in the trial.

1. Subject must sign an ICF, prior to any screening procedures, indicating that he or she understands the purpose of and procedures required for the trial and are willing to participate in the trial prior to any other trial related assessments or procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA). If a subject refuses to consent to DNA research in these specific regions, the subject is still eligible to participate in the trial.
2. Must be at least 18 years of age
3. Criterion moved to Section 5.1.1 as per Amendment 1
4. Criterion moved to Section 5.1.1 as per Amendment 1
5. Criterion moved to Section 5.1.1 as per Amendment 1
6. ECOG performance status score of 0, 1, or 2 (Appendix 5)
7. Criterion modified as per Amendment 1

   7.1 Evidence of CD20 positivity at screening
8. Criterion modified as per Amendment 1

8.1 Has acceptable laboratory parameters as follows:

Parameter		**Result**
a.	Creatinine clearance or serum creatinine	> 45 mL/min (Cockcroft-Gault; see Appendix 2) or serum creatinine ≤1.5 times the upper limit of normal (x ULN)
b.	Serum alanine transaminase (ALT)	≤3 × ULN
c.	Serum aspartate transaminase (AST)	≤3 × ULN
d.	Bilirubin	≤1.5 × ULN unless due to Gilbert's syndrome *Note: Subjects with Gilbert's syndrome may be included if total bilirubin is ≤ 3 x ULN and direct bilirubin is ≤ 1.5 x ULN*
e.	Hemoglobin	≥9.0 g/dL unless anemia is due to marrow involvement of CLL *Note: Blood transfusion may be administered during screening to meet this requirement*
f.	Absolute neutrophil count	≥1.0 × 10^9/L (1000/µL) unless neutropenia is due to bone marrow involvement of CLL. *Note: Growth factor support is allowed in case of bone marrow involvement.*
g.	Platelet count	≥30 × 10^9/L (30,000/µL) *Note: Transfusion may be administered during screening to meet this requirement.*
h.	Coagulation status	PT/INR/aPTT ≤1.5 × ULN

9. Received a cumulative dose of corticosteroids less than the equivalent of 250 mg of prednisone within the 2-week period before the first dose of epcoritamab
10. Subject must have availability of fresh bone marrow material at screening.
11. Criterion moved to Section 5.1.1 as per Amendment 1

12. A woman with reproductive potential (Appendix 11) must agree to use adequate contraception during the trial, and for 12 months after the last administration of epcoritamab. Adequate contraception is defined as highly effective methods of contraception (defined Appendix 12).
13. A woman of childbearing potential must have a negative serum (beta-hCG) pregnancy test at screening and a negative serum or urine pregnancy test before treatment administration on Day 1 of every cycle.
14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 12 months after last treatment.
15. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg either condom with spermicidal foam/gel/film/cream/suppository and partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and 12 months after receiving the last dose of epcoritamab.
16. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.1.1 Inclusion Criteria Specific to the R/R CLL Cohort

17. Must have active CLL disease that needs treatment with at least 1 of the following criteria being met (Hallek et al., 2018b):
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
    b. Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
    c. Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
    d. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months
    e. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids
    f. Symptomatic or functional extra nodal involvement (eg, skin, kidney, lung, spine)
    g. Disease-related symptoms as defined by any of the following:
       - Unintentional weight loss ≥ 10% within the previous 6 months
       - Significant fatigue
       - Fevers ≥ 38.0°C (100.5°F) for 2 or more weeks without evidence of infection.
       - Night sweats for ≥ 1 month without evidence of infection
18. R/R CLL after receiving at least 2 prior lines of systemic antineoplastic therapy, including treatment with (or intolerance of) a BTK inhibitor (eg, ibrutinib). Relapse is defined as evidence of disease progression in a subject who has previously achieved a CR or PR for ≥6 months. Refractory disease is defined as treatment failure (not achieving a CR or PR) or as progression within 6 months from the last dose of therapy.
19. Has measurable disease with at least one of the following criteria:
    a. $\geq 5 \times 10^9$/L (5,000/μL) B lymphocytes in peripheral blood
    b. Presence of measurable lymphadenopathy and/or organomegaly
20. Must take prophylaxis for TLS

5.1.2 Inclusion Criteria Specific to the Richter's Syndrome Cohort

21. Must have a clinical history of CLL/SLL with biopsy-proven transformation toward aggressive lymphoma (ie, DLBCL subtype).
22. Deemed as ineligible for chemoimmunotherapy at investigator's discretion or refuse to receive intensive chemotherapy.
23. Must have measurable disease as determined by both
    a. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT scan demonstrating positive lesion compatible with CT (or MRI)-defined anatomical tumor sites; and
    b. A CT scan (or MRI) with involvement of ≥2 clearly demarcated lesions/nodes with long axis >1.5 cm and short axis >1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and a short axis ≥1.0 cm.

5.2 Exclusion Criteria (All Subjects)

Any potential subject who meets any of the following criteria will be excluded from participating in the trial.

1. Criterion moved to Section 5.2.1 and modified as per Amendment 1
2. Subject received prior treatment with a CD3 × CD20 bispecific antibody.
3. Subject received any prior allogeneic HSCT or solid organ transplantation.
4. Criterion modified as per Amendment 1

   4.1. Subject received treatment with an anti-cancer agent, eg:
   a. Small molecules such as BTK inhibitor, BCL2 inhibitor, or PI3K inhibitor within 5 half-lives prior to the first dose of epcoritamab; or
   b. Anti-CD20 mAb or chemotherapy within 2 weeks prior to the first dose of epcoritamab; or
   c. Radio-conjugated or toxin conjugated antibody or CAR-T cell therapy within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of epcoritamab
   d. Subject received treatment with an investigational drug, within 4 weeks or 5 half-lives, whichever is shorter prior to the first dose of epcoritamab.
5. Criterion deleted as per Amendment 1
6. Criterion modified and moved to criterion #4d as per Amendment 1
7. Subject has autoimmune disease or other diseases that require permanent or high-dose immunosuppressive therapy.
8. Criterion modified as per Amendment 1

   8.1 Subject has clinically significant cardiac disease including but not limited to:
   a. Criterion modified and moved to criterion #23
   b. Criterion modified as per Amendment 1

   b.1 Unstable or uncontrolled disease/condition related to or affecting cardiac function, eg, unstable angina, congestive heart failure grade III or IV as classified by the New York Heart Association (see Appendix 3), cardiac arrhythmia (CTCAE v5.0 grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities
   c. Myocardial infarction, intracranial bleed, or stroke within the past 6 months

d. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec

9. Criterion modified and moved to criterion #8d as per Amendment 1
10. Subject received vaccination with live vaccines within 28 days prior to the first dose of epcoritamab.
11. Subject has toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
12. Subject has known CNS involvement at screening.
13. Subject has known past or current malignancy other than inclusion diagnosis, except for:
    a. Cervical carcinoma of Stage 1B or less
    b. Non-invasive basal cell or squamous cell skin carcinoma
    c. Non-invasive, superficial bladder cancer
    d. Prostate cancer with a current PSA level < 0.1 ng/mL
    e. Any curable cancer with a CR of >2 years duration
14. Subject has suspected allergies, hypersensitivity, or intolerance to epcoritamab or its excipients (refer to the IB for more information).
15. Criterion moved to Section 5.2.1 as per Amendment 1
16. Criterion modified as per Amendment 1

    16.1 Has had major surgery within 4 weeks prior to enrollment.

17. Has known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    a. Positive test for antibodies to the hepatitis B core antigen (anti-HBc) AND
    b. Negative test for antibodies to the hepatitis B surface antigen (anti-HBs).
18. Known medical history or ongoing hepatitis C infection that has not been cured.
19. Criterion modified as per Amendment 1.

    19.1. Known history of seropositivity for HIV infection. Note: HIV testing is required at screening only if required per local health authorities or institutional standards.

20. Subject is a woman who is pregnant or breast-feeding, or who is planning to become pregnant while enrolled in this trial or within 12 months after the last dose of epcoritamab.
21. Subject is a man who plans to father a child while enrolled in this trial or within 12 months after the last dose of epcoritamab.
22. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
23. Subject has uncontrolled intercurrent illness, such as ongoing or active infection requiring intravenous antibiotics treatment at the time of enrollment or within the previous 2 weeks prior to the first dose of epcoritamab.

5.2.1 Exclusion Criteria Specific to the R/R CLL Cohort

24. Any history of RS or evidence indicating a potential Richter's transformation.
25. Subject is unable to tolerate uric acid reducing medications.

5.2.2 Exclusion Criteria Specific to the Richter's Syndrome Cohort

26. Diagnosis of Richter's syndrome not of the DLBCL subtype such as Hodgkin's lymphoma, prolymphocytic leukemia.
27. Subject received autologous HSCT within 3 months prior to the first dose of epcoritamab.
28. Subject received more than 1 prior line of therapy for RS.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (see Section 5.1 and Section 5.2). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons), and any SAEs or AE related to a trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be re-assessed at the rescreening visit.

Screen failures may be rescreened only once. Subjects are required to sign a new ICF if updates have been made since signing the most recent ICF.