5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subject or their legally authorized representative, if permitted, must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, ≥ 18 and < 80 years old, with a life expectancy of ≥ 12 months
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Absolute neutrophil count (ANC) ≥ 0.5 × 10^9/L. (antibacterial prophylaxis [fluoroquinolone preferred unless contraindicated] would be required for ANC < 1.0 ×10^9/L)
  - Hemoglobin ≥ 8.0 g/dL
  - Platelet count ≥ 75 × 10^9/L, or ≥ 25 × 10^9/L in the presence of bone marrow involvement or splenomegaly
  - Serum aspartate aminotransferase and serum alanine aminotransferase ≤ 3.0 × upper limit of normal (ULN) unless due to hepatic involvement of disease or non-hepatic origin.
  - Total bilirubin level ≤ 1.5 × ULN, or ≤ 5 × ULN for subjects with hepatic involvement of disease or non-hepatic origin. Subjects with Gilbert's syndrome may have total bilirubin levels > 1.5 × ULN, but direct bilirubin must be < 2 × ULN.
  - Estimated creatinine clearance ≥ 40 mL/min (as calculated by the Cockcroft-Gault formula, modified as needed for factors such as body weight, see Appendix M).
  - Prothrombin time/international normalized ratio/activated partial thromboplastin time ≤ 1.5 × ULN, unless receiving anticoagulation.
- 4. Subject is willing and able to comply with procedures required in this protocol.
- 5. Subject must be able to tolerate SC injections.
- 6. Subject must have available adequate fresh or paraffin-embedded tissue at Screening.

  Note: Archival paraffin-embedded tissue must be obtained within 8 weeks prior to Cycle 1 Day 1.

Disease/Condition Activity

- 7. Subject must have newly diagnosed, histologically confirmed CD20+ DLBCL (de novo or histologically transformed from a diagnosis of follicular lymphoma) at most recent representative tumor biopsy based on the pathology report, with a World Health Organization (WHO) 2016 classification and including:
  - DLBCL, Not Otherwise Specified (NOS).
  - High grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangement with DLBCL morphology.
  - T-cell/histiocyte-rich large B-cell lymphoma.
  - Epstein Barr virus positive DLBCL, NOS.
  - Follicular lymphoma Grade 3b.

  Note: The local pathology report must be available at Screening to support CD20+ and eligible histology.

  Composite/intermediate histology with any of the following components is not allowed: high grade B-cell lymphoma, NOS; Hodgkin's lymphoma; primary mediastinal (thymic) large B-cell lymphoma; Burkitt; plasmablastic lymphoma or any CD20- lymphoma, such as, anaplastic lymphoma kinase-positive large B-cell lymphoma, human herpesvirus type 8-positive DLBCL, or primary effusion lymphoma.
- 8. Subject must have an IPI score of 2-5 (Appendix G). The number of subjects with IPI 2 will be capped at 35% of the overall sample size.
- 9. Subject has at least one target lesion defined as:
  - ≥ 1 measurable nodal lesion (long axis > 1.5 cm) or ≥ 1 measurable extra-nodal lesion (long axis > 1 cm) on CT scan or MRI.

    AND
  - PET-positive on PET-CT scan.
- 10. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2 prior to initiating R-CHOP treatment. Note that subject with an initial ECOG performance status ≥ 3 may be screened if pre-phase treatment is planned. Subject may be eligible if ECOG performance status were to improve to 0-2 during pre-phase treatment.
- 11. Subject is planned to receive 6 cycles of standard R-CHOP per investigator determination.

Subject History

- 12. Subject has no history of prior systemic anti-lymphoma therapy for DLBCL (including any definitive radiotherapy with curative intent) other than corticosteroids with or without vincristine during pre-phase treatment or non-curative intent palliative radiotherapy with the stipulation that radiated lesions cannot be selected as target lesion for response assessment.

- 13. Subject with histology transformed from follicular lymphoma (tFL) must not have previously been treated with > 1 lines of therapy for FL and must not have had an anthracycline-containing regimen or a CD3-CD20 bispecific antibody.
- 14. Subject has no history of primary mediastinal lymphoma, or mediastinal or pericardial radiation.
- 15. Subject does not have a primary CNS tumor or known CNS involvement at Screening.
- 16. Subject has no history of severe allergic or anaphylactic reactions to anti-CD20 mAb therapy or known allergy or intolerance to any component or excipient of epcoritamab (e.g., Sorbitol) or the CHOP regimen.
- 17. Subject has not had major surgery within 4 weeks prior to randomization.
- 18. Subject has no clinically significant cardiovascular disease, including:
  - Myocardial infarction or stroke within 6 months prior to enrollment.

    OR
  - The following conditions within 3 months prior to enrollment: unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV), uncontrolled cardiac arrhythmia

    OR
  - Screening 12-lead electrocardiogram (ECG) showing a baseline QT interval as corrected by Fridericia's formula (QTcF) > 470 msec (male) or > 480 sec (female)

    OR
  - Other clinically significant electrocardiogram (ECG) abnormalities within 6 months prior to enrollment unless deemed stable and appropriately treated.
- 19. Left ventricular ejection fraction must be ≥ 50% by multi-gated acquisition or transthoracic echocardiography at Screening.
- 20. Subject has no clinically significant liver disease, including hepatitis, current alcohol abuse, or cirrhosis.
- 21. Subject has no known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds). No new IV therapy or intravenous antibiotics may be initiated within 2 weeks prior to first dose of study drug.
- 22. Subject does not have an active hepatitis B virus or Hepatitis C virus infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
- 23. Subject has no known history of Human Immunodeficiency Virus (HIV) infection. Note: HIV testing does not need to be conducted at screening unless it is required per local guidelines or institutional standards.
- 24. Subject must not have active tuberculosis (TB) or history of completed treatment for active TB within the past 12 months.

Note: Interferon gamma release assay (IGRA) testing must be performed if active or latent TB is suspected (e.g., clinical signs and symptoms of TB, contact history, or if the subject lives in or has traveled to or lived in the WHO high TB burden countries).[18] For subjects with positive IGRA, active pulmonary tuberculosis must be excluded with clinical evaluation and radiologic imaging, and once subjects may be enrolled treatment for latent TB infection (recommend isoniazid monotherapy for a total of 6 months) has been initiated.

- 25. Subject must not have an active cytomegalovirus (CMV) disease. If preemptive or prophylactic antiviral treatment is initiated, lab eligibility criteria #3 would have to be met on C1D1. Note: Foscarnet use within 7 days prior to C1D1 or during C1-C2 is prohibited.
- 26. Subject has no known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test or 2 negative antigen test results at least 24 hours apart. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen-failed and may only rescreen if the following have been met:
  - At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 27. Subject has no history of other prior malignancies, except:
  - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.
  - Localized prostate cancer, post-radical prostatectomy with non-rising prostate-specific antigen levels < 0.1 ng/mL.
- 28. Subject has no neuropathy Grade > 1 or demyelinating form of Charcot-Marie-Tooth Disease.
- 29. Subject has no current autoimmune disease requiring immunosuppressive therapy except for up to 20 mg prednisone daily or equivalent.
- 30. Subject has no life-threatening illness, medical condition, or organ system dysfunction that, in the Investigator's opinion, could compromise the subject's safety, compliance with the protocol, interpretation of the study results, or put the study outcomes at undue risk.
- 31. Subject has no current seizure disorder requiring therapy within the past 12 months. Patients with history of seizure disorder must have complete CNS workup.

Concomitant Medications

- 32. Subject has no medication known to decrease T-cell numbers or activity or other concurrent immunosuppressive medication except for up to 20 mg prednisone daily or equivalent, unless for disease control during screening (refer to Section 5.4).
- 33. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another therapeutic clinical study or was previously enrolled in this study.
- 34. Subject has not received vaccination with live vaccines within 28 days prior to randomization or is expected to need any live vaccination during study participation including at least 3 months following the last dose of study treatment.

Contraception

- 35. All females of child-bearing potential must have a **negative serum pregnancy test** (beta human chorionic gonadotropin) at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 36. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from 30 days prior to randomization through at least 12 months after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 37. Female must be not **pregnant, breastfeeding, donating eggs (ova, oocytes), or considering becoming pregnant** during the study or for 12 months after the last dose of study drug.
- 38. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from 30 days prior to randomization through 12 months after the last dose of study drug, to practice the protocol-specified contraception.
- 39. Male must be not considering **fathering a child or donating sperm** during the study or for 12 months after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

Females of Non-Childbearing Potential

- Females do not need to use birth control during or following study drug treatment if considered to be of non-childbearing potential due to meeting any of the following criteria:
  - Postmenopausal: A postmenopausal state is defined as no menses in subjects > 45 years of age for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the post-menopausal range (≥ 30 IU/L) may be used to confirm a postmenopausal state in subjects not using hormonal contraception or hormonal replacement therapy.

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
- Females who have not experienced menarche (at least 1 menstrual period).

Note: If the reproductive potential changes after the start of the trial (e.g., female subject who is not heterosexually active becomes active, premenarchal female subject experiences menarche), a female subject must begin adequate contraception (i.e., highly effective methods of contraception).

Females of Childbearing Potential

- A female subject must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 12 months after receiving the last dose of study treatment.
- A female subject of childbearing potential must have a negative serum (beta human chorionic gonadotropin) pregnancy test at screening and a negative serum or urine pregnancy test before study treatment administration at randomization.
- A female subject must commit to one of the following methods of birth control. Adequate contraception is defined as a highly effective method of contraception (see list below). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.
  - Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation initiated at least 30 days prior to randomization.
    Note: Hormonal contraception may be susceptible to interaction with study treatment, which may reduce the efficacy of the contraception method.
    - Oral, intravaginal, or transdermal
  - Progestogen-only hormonal birth control associated with inhibition of ovulation initiated at least 30 days prior to randomization. Note: Hormonal contraception may be susceptible to interaction with study treatment, which may reduce the efficacy of the contraception method.
    - Oral, injectable, or implantable
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system
  - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject)
  - Sexual abstinence – Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic

abstinence [e.g., calendar, ovulation, symptothermal method, post-ovulation methods] and withdrawal are not acceptable)

Notes: Hormonal contraception may be susceptible to interaction with study treatment, which may reduce the efficacy of the contraception method.

Implantable, IUDs, intrauterine hormone-releasing system, bilateral tubal occlusion, and vasectomized partner are all contraception methods that, in the context of this guidance, are considered to have low user dependency.

Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label and should be maintained for 12 months after the last dose of study drug.

Contraception Requirements for Males

A male subject who is sexually active with a female of reproductive potential and has not had a vasectomy must agree to use a barrier method of birth control and must agree not to donate sperm during the entire trial and for 12 months after receiving the last dose of study treatment.

His female partner(s) must also use at least 1 of the above listed highly effective contraception methods of birth control.

Male subjects should be provided information to seek advice about cryopreservation of sperm prior to treatment with study drugs.

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, the following medications are prohibited during the trial from the first dose of study drugs:

- Any systemic anti-lymphoma therapy, e.g., chemotherapy, immunotherapy, or experimental therapy, or unplanned radiation therapy on target lesion, other than assigned study treatment, until:
  - Confirmed residual disease after completion of study treatment or upon decision to permanently discontinue study treatment
  - PD at any time during treatment

  Note: Any subsequent anti-lymphoma therapy and associated information should be documented in the eCRF.

- Intrathecal CNS prior to Cycle 5 Day 1 or high-dose methotrexate CNS prophylaxis prior to Cycle 7 Day 1 (see Section 5.4 for more details)
- Corticosteroids that ***exceed*** a total daily dose of 20 mg of prednisolone or equivalent administered for more than 10 days unless for the management of AEs (excluding corticosteroids given for disease control during screening or as premedication or as CRS prophylaxis/therapy)
- Herbal preparations or related over-the-counter (OTC) preparations containing herbal ingredients, including rooibos tea, are not permitted during participation in the trial.
- Live attenuated vaccines beginning 28 days prior to randomization and for 3 months following the last dose of study treatment or per local label. Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted, however, intranasal influenza vaccines are live attenuated and are not allowed.

Refer to Section 5.4 for radiotherapy guidelines.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to any study drug administration through Safety Follow-up (120 days after discontinuation of rituximab or epcoritamab, whichever is later).

Any questions regarding concomitant or prior therapy should be raised to the Sponsor emergency contact. Information regarding potential drug interactions with epcoritamab can be located in the Investigator's Brochure.

Allowed Concomitant Medications/Therapy	**Comments/Notes**
Preplanned radiotherapy (i.e., radiation that was planned before randomization to be given at the end of study treatment disease assessment)	May be administered to initial sites of bulky or extranodal disease according to institutional practice. If indicated, preplanned radiotherapy should be initiated within 8 weeks after the last study drug treatment and should start after all "EOT assessments," including PET-CT scans for disease response assessment, are completed. Any radiotherapy should be preplanned by the center and documented prior to randomization and then entered in the eCRF once the patient is randomized. All unplanned radiotherapy administered to patients will be considered as a new anti-lymphoma treatment.
Local palliative, low-dose radiotherapy on non-target lesions outside of mediastinum/pericardium region	Permitted as per institutional guidelines. Local palliative, low-dose radiotherapy on non-target lesions is allowed for relief of compressive signs or symptoms provided it's been scheduled prior to initiation of study therapies and must be initiated no later than 2 weeks after C1D1.

Allowed Concomitant Medications/Therapy	Comments/Notes
Pre-phase treatment for lymphoma/disease control	For subjects in urgent need for lymphoma symptom control prior to the start of study treatment: • Prednisone up to 100 mg/day or equivalent for ≤ 7 days prior to planned C1D1 (i.e., Day -7 to Day -1) administered per institutional guidelines with or without • 1 mg vincristine × 1 dose administered 7 days prior to planned C1D1 (i.e., Day -7) administered per institutional guidelines It is strongly recommended that baseline tumor assessments be completed prior to initiation of pre-phase treatment. The ECOG performance status and LDH test prior to initiation of pre-phase treatment will be used to calculate IPI scores. ECOG performance status during pre-phase treatment may be used for eligibility qualification.
CNS prophylaxis	For subjects deemed to be at high-risk for CNS relapse, i.e., with a CNS IPI score of 4-6 (Appendix N), renal/adrenal involvement, HGBCL with MYC and BLC2 and/or BLC6 translocations, or other disease sites such as testis or marrow which are known to be associated with high risk of CNS relapse by the investigator, CNS prophylaxis according to institutional practice and its use documented on the eCRF is permitted but with the following requirement: high-dose methotrexate (MTX) may be given after R-CHOP treatment is completed. Intrathecal MTX may be given at least 3 weeks prior to randomization and on or after Cycle 5 Day 1 of R-CHOP treatment. For subjects deemed to be at significantly higher risk for CNS relapse, i.e., a CNS IPI score of 6, intrathecal MTX outside of this window may be given with sponsor approval. Note: Intrathecal MTX may not be given during Cycles 1-2 or during any ongoing CRS or ICANS event (event must be completely resolved).
Rituximab infusion-related prophylaxis	Details in the Operations Manual, Section 3.5 in Appendix P.
G-CSF and other hematopoietic growth factors	Treatment with colony stimulating factors (CSFs, including G-CSF/GM-CSF) is permitted when clinically indicated or at the Investigator's discretion according to standard institutional practice and international guidelines such as that recommended by ASCO.[19] General primary and secondary prophylactic use of colony stimulating factors (CSFs, including G-CSF/GM-CSF) is recommended. Primary CSFs prophylaxis is required for subjects with risk factors for febrile neutropenia, such as ≥ 65 years old or bone marrow lymphoma involvement. G-CSF given as primary prophylaxis will be administered in each cycle of therapy during Cycle 1–6, e.g., starting no later than Day 7 after administration of myelotoxic chemotherapy (doxorubicin, cyclophosphamide). Dosing of G-CSF should follow each site's institutional standards or may be at the investigator's discretion. An example of appropriate G-CSF dosing for prophylaxis is found in the ASCO-recommended guidelines.

Allowed Concomitant Medications/Therapy	Comments/Notes
	In case of febrile neutropenia or recurring Grade ≥ 3 neutropenia, use of growth factors is required.
Antibacterial, antiviral, and Antifungal prophylaxis	Pneumocystis jirovecii (PCP) prophylaxis (e.g., trimethoprim/sulfamethoxazole [TMP-SMX], dapsone, atovaquone, or equivalent) is mandatory when 4 or more consecutive days of > 20 mg prednisone or equivalent are given (e.g., during CRS prophylaxis or AE management) and for patients who are at an increased risk for pneumonia from PCP (e.g., patients with low CD4+ cell counts (< 350 cells/µL). For further antimicrobial recommendations, refer to Summary of Recommendations for Antimicrobial Prophylaxis based on ASCO and IDSA clinical practice guidelines[20] (Appendix H). Additional information is available at www.asco.org/supportive-care-guidelines.
Red blood cell and platelet transfusions, if clinically indicated	Permitted as clinically indicated according to institutional guidelines.
CRS management for epcoritamab	Details in the Operations Manual, Section 3.5 in Appendix P.
Multivitamins, vitamin D, calcium, and supplements	Permitted as per institutional guidelines for prevention of weight loss.
Prescribed medicinal cannabinoids	Permitted as palliative therapy.
Omeprazole or equivalent therapy	Permitted as peptic ulcer prevention.
5HT3 antagonists or equivalent therapy	Permitted as anti-emetics.
Loperamide	Permitted as the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose regimen should be according to standard practice.
Bowel care	Recommended to prevent constipation and should be administered per standard practice.
Tocilizumab	Treatment for CRS. Refer to Appendix I. Alternative therapeutics may be used based on Local/Institutional guidelines in addition to availability (e.g., siltuximab and anakinra).
Corticosteroids	Refer to Appendix I and Appendix J for grading and management of CRS and ICANS/neurotoxicity or other AEs, respectively. As part of pre-phase treatment, prednisone up to 100 mg/day or equivalent for ≤ 7 days prior to planned C1D1 (i.e., Day -7 to Day -1) is permitted. Prednisone premedication for study treatment. Details in the Operations Manual, Section 3.4 (Appendix P).

Allowed Concomitant Medications/Therapy	Comments/Notes
Rasburicase and/or standard of care uric acid lowering agents	Prevention and/or treatment (i.e., hydration and anti-gout agents) of clinical tumor lysis syndrome is permitted, as per institutional guidelines. Refer to Appendix K and Appendix L.
Diphenhydramine or equivalent antihistamines	Premedication for study treatment. Details in the Operations Manual, Section 3.4 in Appendix P.
Acetaminophen or equivalent antipyretics	Premedication for study treatment. Details in the Operations Manual, Section 3.4 in Appendix P.

AE = adverse event; ASCO = American Society of Clinical Oncology; CNS = central nervous system; CRS = cytokine release syndrome; CSFs = colony stimulating factors; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end-of-treatment; G-CSF = granulocyte colony-stimulating factor.; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICANS = Immune effector cell-associated neurotoxicity syndrome; IPI = International Prognostic Index; LDH = Lactate dehydrogenase; MTX = methotrexate; PET-CT = Positron emission tomography-computed tomography

Epcoritamab can cause transient release of cytokines that may potentially suppress cytochrome P450 (CYP) enzymes. Cytokine levels were transiently elevated and mostly peaked 24 hours after the first full dose in Cycle 1 with levels returning to baseline. Additionally, only minimal elevations in peripheral cytokines relative to baseline were observed at subsequent doses.

The potential for epcoritamab to cause cytokine-mediated alteration of CYP metabolizing enzymes is unknown; therefore, patients should be closely monitored for potential toxicities primarily in Cycle 1 (owing to potential increase in exposures) following concomitant therapy with CYP3A4 substrates that have narrow therapeutic index such as fentanyl, cyclosporine, tacrolimus, and sirolimus (not an exhaustive list) (Appendix O). If necessary, doses for CYP3A4 substrates should be adjusted per label recommendations.

Based on local label recommendations for the each of the drugs in R-CHOP combination, strong CYP3A inhibitors/inducers, and strong P-glycoprotein (P-gp) inhibitors may need to be avoided and/or used with caution and patients may need to be closely monitored. Examples of strong clinical inhibitors/inducers of CYP3A or strong clinical inhibitors of P-gp transporters are provided on the Food and Drug Administration (FDA)'s website for Drug Development and Drug Interactions (Appendix O).

CYP450 enzymes in the liver are down regulated by infection and inflammatory stimuli, including cytokines such as IL-6. Inhibition of IL-6 signaling in patients with rheumatoid arthritis who are treated with tocilizumab may restore CYP450 activities to higher levels than those patients not treated with tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CY2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The effects of tocilizumab on CYP2C8 or transporters are unknown. In vivo studies with omeprazole (metabolized by CYP2C19 and CYP3A4) and simvastatin (metabolized by CYP3A4) showed up to a 28% and 57% decrease in exposure 1 week following a single dose of tocilizumab, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index (see Appendix O), where the dose is individually adjusted. Upon initiation or discontinuation of tocilizumab in patients being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug

concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of epcoritamab and/or R-CHOP on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drugs, when possible, is ***preferred*** to be given at least 14 days prior to SARS-CoV-2 vaccine administration.
- A minimum period of 3 days must occur between the administration of an appropriate COVID-19 vaccine and the administration of any study drug (to avoid overlapping AEs).

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with DLBCL and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual (Appendix P) for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects, Discontinuation, and Follow-Up After Subject Discontinuation of Study Drug or Study

Study treatment will be discontinued in the event of any of the following:

- Disease progression as determined by Lugano criteria, except when meeting LYRIC criteria for indeterminate response.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator or the Sponsor Medical Monitor.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug or begins or intends to breastfeed.