CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Master Protocol*
Protocol Number:	KT-US-568-0138 (ZUMA-25) – master protocol
Note:	This master protocol should be used in conjunction with the substudy protocols KT-US-568-0138-A, KT-US-568-0138-B, KT-US-568-0138-C and KT-US-568-0138-D. **Note: Substudies KT-US-586-0138-A and KT-US-568-0138-D were terminated early by the Sponsor (effective 21 June 2023).**
Indication:	Adult subjects with rare B-cell malignancies, defined in separate disease specific substudies: • Substudy A – relapsed/refractory Waldenstrom macroglobulinemia: terminated early by Sponsor (effective 21 June 2023) • Substudy B – relapsed/refractory Richter transformation • Substudy C – relapsed/refractory Burkitt lymphoma • Substudy D – relapsed/refractory hairy cell leukemia: terminated early by Sponsor (effective 21 June 2023)
Kite Investigational Product:	Brexucabtagene autoleucel
Kite IND Number: **EU CT Number:**	028542 Substudy A- 2022-501259-10-00: terminated early by Sponsor (effective 21 June 2023) Substudy B- 2022-501260-18-00 Substudy C- 2022-501261-46-00 Substudy D- 2022-501262-21-00: terminated early by Sponsor (effective 21 June 2023)
Clinical Trials.gov Identifier:	NCT05537766
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America

Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Protocol Version/Date: **Amendment History:**	Original: 23 May 2022 Amendment 1.0: 20 July 2022 Amendment 1.1: 12 January 2023 Amendment 2.0: 01 March 2023 Amendment 3.0: 17 August 2023
Country-specific Requirements:	Country-specific requirements are listed in Appendix 12.4

This study will be conducted under United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, and Switzerland are not included under the IND application and are not considered to be IND application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory and local requirements.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

Kite Pharma, Inc.
2400 Broadway
Santa Monica, CA 90404

Protocol Title: A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Master Protocol*

Indication: Adult subjects with rare B-cell malignancies, defined in separate, disease-specific substudies:

- Substudy A – relapsed/refractory (r/r) Waldenstrom macroglobulinemia (WM): terminated early by Sponsor, effective 21 June 2023
- Substudy B – r/r Richter transformation (RT)
- Substudy C – r/r Burkitt lymphoma (BL)
- Substudy D – r/r hairy cell leukemia (HCL): terminated early by Sponsor, effective 21 June 2023

Kite IND Number: 028542

EU CT Numbers: Substudy A- 2022-501259-10-00: terminated early by Sponsor, effective 21 June 2023)
Substudy B- 2022-501260-18-00
Substudy C- 2022-501261-46-00
Substudy D- 2022-501262-21-00: terminated early by Sponsor, effective 21 June 2023)

ClinicalTrials.gov Identifier: NCT05537766

Kite Investigational Product: Brexucabtagene Autoleucel

Other Investigational Product/IND Number: Not applicable

IDE Number: Not applicable

Number of Study Sites Planned: Approximately 25

Objectives and Endpoints: The objectives and endpoints that are common to all indications are detailed in the table below. Additional objectives and endpoints that are specific to the indications being studied are detailed in the respective protocol of each substudy.

Primary Objective	Primary Endpoint
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with rare B-cell malignancies, by determining the Response Rates as defined within the substudies by central assessment.	• Response rates by central assessment as defined in each substudy
Secondary Objectives	**Secondary Endpoints**
• To evaluate the Complete Response (CR) by central assessment as defined within each substudy.	• CR rate by central assessment as defined in each substudy
• Determine response durability	• Duration of Response
• Determine survival status	• Overall Survival
• Determine survival status without progression	• Progression-free survival
• Determine the time to next treatment (TTNT) after administration of brexucabtagene autoleucel	• TTNT defined as the time from enrollment (for Full Analysis Set [FAS]) or brexucabtagene autoleucel infusion (for modified intention to treat [mITT]) to the initiation of subsequent anticancer therapy/treatment
• Determine the time to first response	• Time to first response from brexucabtagene autoleucel infusion to the first response as defined in the substudy
• Determine the time to best response	• Time to best response from brexucabtagene autoleucel infusion to the best response as defined in the substudy
• Evaluate the safety of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Incidence of adverse events (AEs) and common terminology criteria for adverse events (CTCAE) grade changes in safety laboratory values • Incidence of AEs defined as dose-limiting toxicities (DLTs) • Incidence of antibodies to brexucabtagene autoleucel (immunogenicity) • Incidence of replication-competent retrovirus (RCR) in peripheral blood mononuclear cells (PBMCs) at baseline and after brexucabtagene autoleucel infusion
• To evaluate the effect of brexucabtagene autoleucel on patient reported outcomes (PROs) and quality of life assessments	• Changes over time in the PRO assessment domains, EORTC-QLQ-C30 and EQ-5D-5L

Exploratory Objectives	Exploratory Endpoints
• To evaluate the pharmacokinetic profile of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Levels of chimeric antigen receptor (CAR) T cells in blood and association with clinical outcomes (efficacy and toxicity) • Levels of blood B cells and relationship with pharmacokinetic profile and clinical outcome
• To evaluate the pharmacodynamic profile of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Levels of serum analytes (including cytokines and chemokines) in blood and relationship with events of interest (eg, cytokine release syndrome (CRS) and neurotoxicity).
• To explore the phenotypic and functional characteristics of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Product characteristics, including T-cell phenotypes and relationship with clinical outcome
• To explore immunogenicity against brexucabtagene autoleucel	• Incidence of anti-brexucabtagene autoleucel CAR reactivity

Study Design:

This is a Phase 2, open-label, multicenter study evaluating the efficacy of brexucabtagene autoleucel in adult subjects with rare B-cell malignancies.

This study will use a basket study design with separate, indication-specific substudies. The study was originally designed to include r/r WM, r/r RT, r/r BL, and r/r HCL. However, the study is designed to have the flexibility to independently open and close individual substudies.

Following the early termination of the r/r WM (Substudy A) and r/r HCL (Substudy D) substudies (effective 21 June 2023), subjects are only to be recruited to the r/r RT and r/r BL substudies.

This master protocol contains details regarding all elements of the study that are common across each of the indications. In contrast, each of the separate substudy protocols contain additional information that is unique to an individual indication (ie, WM, RT, BL or HCL). A substudy-specific schedule of assessments (SOA) is located in each of the respective substudy protocols. The KT-US-568-0138 master protocol and relevant substudy protocol should be referenced in parallel.

Initially, 1 subject will be enrolled and infused in each substudy. No additional subjects will be enrolled within a substudy until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects in each substudy can be enrolled in parallel. After these initial 3 subjects in an individual substudy have been evaluated for at least 28 days, the Safety Review Team will make recommendations on further substudy conduct.

The screening period will have a duration of up to 28 days and will begin on the date a subject signs the Institutional Review Board/Independent Ethics Committee approved informed consent form and continues through to either confirmation of enrollment (ie, commencement of leukapheresis), until a subject withdraws consent before enrollment, or it is determined that a subject is a screen failure (ie, does not meet the study eligibility criteria, as defined in the KT-US-568-0138 master protocol and respective substudy protocol).

To reduce the risk of Bruton's tyrosine kinase (BTK) inhibitor withdrawal symptoms and IgM flare, subjects in the WM substudy will be allowed ibrutinib through screening and for up to 30 hours (5 half-lives) prior to starting lymphodepleting chemotherapy. Subjects in the RT substudy, if already receiving a BTK inhibitor, may also receive ibrutinib through screening and leukapheresis, at the discretion of the investigator.

Informed consent must be obtained before completion of any non-standard of care, study-specific procedures. Procedures that are part of the standard of care are not considered study-specific procedures and may be performed before obtaining consent and used to confirm eligibility.

A subject is considered as enrolled in the study at the commencement of leukapheresis. Subjects must have undergone screening procedures and their results must have been confirmed by the investigator to meet the study eligibility criteria at screening. For laboratory tests performed after screening and before initiation of leukapheresis, allowance will be made for an expected normal variation of ±5% of laboratory test value cutoffs noted in the inclusion criteria. If there is a need to repeat leukapheresis for a subject, they must continue to meet the study eligibility criteria (or be within ±5% of the laboratory test value cutoffs noted in the inclusion criteria) before the leukapheresis procedure is performed. (The ±5% cutoffs do not apply to the hematological parameters listed in the common inclusion criteria #4 if lower values are attributable to underlying disease).

After enrollment/leukapheresis, subjects in the RT and BL substudies may receive optional, protocol-defined bridging therapy at the discretion of the investigator. If bridging therapy has been administered, a new baseline disease assessment is required, as outlined in the SOA in the respective substudies.

Subjects will undergo lymphodepleting chemotherapy with fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) for 3 consecutive days from Day -5 to Day -3 (see Section 3.2.3 for details) followed by 2 rest days (Day -2 and Day -1).

On Day 0, subjects will receive a single infusion of brexucabtagene autoleucel administered intravenously (IV) at a target dose of either 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg, depending on the safety review team recommended dose (or a flat dose of 2×10^8 or 1×10^8, respectively, anti-CD19 CAR T cells in subjects > 100 kg), with an initial hospitalization period of at least 7 days; this is considered as the treatment period. From Day 7 to Day 28, subjects will be required to stay within close vicinity to the clinic, with immediate access to urgent care by the investigator.

After completing the treatment period, all subjects will be followed during the post-treatment follow-up period. Counting from Day 0 (the day of brexucabtagene autoleucel infusion), subjects will return to the clinic for evaluation at Day 14, Day 28, Week 8, Month 3, then every 3 months up to Month 12. Additional substudy-specific visits will occur as outlined below:

- RT and BL: Month 18 and Month 24
- WM and HCL: every 6 months up to 36 months and then annually up to 60 months

Disease response will be assessed as appropriate for each indication and as described in each substudy protocol.

An SOA for each indication is provided in each of the respective substudy protocols.

The study schema is provided in Figure 1.

Number of Subjects Anticipated to be Enrolled and Treated:

A total of approximately 90 subjects will be enrolled and treated across 2 separate substudies as detailed below.

- r/r WM: 60 subjects: Study terminated early by Sponsor, effective 21 June 2023
- r/r RT: 60 subjects
- r/r BL: 30 subjects
- r/r HCL: 20 subjects: Study terminated early by Sponsor, effective 21 June 2023

Target Population:

Male or female adults ≥ 18 years of age and with rare B-cell malignancies defined in the respective substudy protocols:

- Substudy A – r/r WM: Study terminated early by Sponsor, effective 21 June 2023
- Substudy B – r/r RT
- Substudy C – r/r BL
- Substudy D – r/r HCL: Study terminated early by Sponsor, effective 21 June 2023

Duration of Treatment and of Study Participation:

Subjects will receive a single infusion of brexucabtagene autoleucel.

The duration of treatment for individual subjects will vary depending on a subject's screening requirements, response to treatment, their survival and their indication. Subjects with RT and BL will be followed for approximately 24 months after the brexucabtagene autoleucel infusion, and subjects with WM and HCL will be followed for approximately 60 months after the brexucabtagene autoleucel infusion. Thereafter, subjects who received brexucabtagene autoleucel will transition to a separate long-term follow-up (LTFU) study (KT-US-982-5968) to continue follow-up out to 15 years from the time of the initial infusion.

Subjects who were enrolled but who did not receive brexucabtagene autoleucel will also be followed for the duration described above but will not be required to transition to the LTFU study. Of note, such subjects will have reduced follow-up requirements excluding disease response assessments but including survival status and subsequent anticancer therapy, as outlined in Section 7.7.3 and Section 7.11, respectively.

Eligibility Criteria Common to all Substudies:

To be enrolled in the study, subjects must meet all the following inclusion criteria that are common to each of the substudies. Subjects must also meet additional disease-specific inclusion criteria, as specified in Section 4.2.1 of the respective substudy protocols.

Inclusion Criteria Common to all Substudies:

1) Male or female 18 years of age or older and who have provided written informed consent
2) Presence of toxicities due to prior therapy must be stable and recovered to Grade 1 or lower (except for clinically nonsignificant toxicities such as alopecia)
3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4) Adequate hematological function (unless lower values are attributable to underlying disease) as indicated by:
   - Absolute neutrophil count ≥ 500/μL
   - Platelet count ≥ 50,000/μL
   - Hemoglobin level ≥ 8 g/dL
   - Absolute lymphocyte count ≥ 100/μL
5) Adequate renal, hepatic, pulmonary, and cardiac function defined as:
   - Creatinine clearance (as estimated by Cockcroft-Gault formula) ≥ 60 mL/min
   - Serum alanine aminotransferase and aspartate aminotransferase levels ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 × ULN if documented liver involvement
   - Total bilirubin levels ≤ 1.5 × ULN, except in subjects with Gilbert's syndrome

- Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an echocardiogram or multigated acquisition scan and no clinically significant electrocardiogram findings
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

6) The following washout periods must be satisfied prior to leukapheresis/enrollment:
   - Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) must be avoided for 7 days before leukapheresis
   - BTK inhibitors (eg, ibrutinib or acalabrutinib), must be avoided at least 1 week or 5 half-lives, whichever is shorter, before leukapheresis unless otherwise specified in the subprotocols
   - Anti-neoplastic drugs used in previous therapy must be avoided within 1 week or 5 half-lives (whichever is shorter) prior to leukapheresis
   - Systemic inhibitory/stimulatory immune checkpoint molecule therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists) must be avoided at least 3 half-lives prior to leukapheresis
   - Alemtuzumab must be avoided at least 6 months prior to enrollment
   - PEG-asparaginase must be avoided at least 3 weeks prior to enrollment
   - Cladribine and pentostatin must be avoided 3 months prior to enrollment
   - Donor lymphocyte infusion within 28 days prior to enrollment
   - Any treatment with immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor, anti-interleukin [IL] 6 or anti-IL6 receptor) unless this treatment is included in prior or bridging regimens, in which case a washout period of 7 days is required prior to leukapheresis
7) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

Exclusion Criteria Common to all Substudies:

To be enrolled in the study, subjects must not meet any of the following exclusion criteria that are common to each of the substudies. Subjects must also not meet any of the additional disease-specific exclusion criteria, as specified in Section 4.2.2 of the respective substudy protocols.

1) Prior CAR therapy or other genetically modified T-cell therapy
2) Prior treatment with any anti-CD19 therapy
3) History of severe immediate hypersensitivity reaction attributed to aminoglycosides

4) History of severe immediate hypersensitivity reaction to cyclophosphamide or fludarabine
5) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment. Patients with a simple urinary tract infection and uncomplicated bacterial pharyngitis and responding to active treatment are eligible only if the patient satisfies the criteria of being afebrile (ie, temperature lower than 38^{o}C) for at least 24 hours prior to the investigator confirming a patient's eligibility
6) HIV-positive patients, unless taking appropriate anti-HIV medications, having an undetectable viral load by quantitative polymerase chain reaction (qPCR) and a CD4 count >200 cells/uL
7) Acute or chronic active hepatitis B or hepatitis C infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America guidelines or applicable country guidelines
8) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted
9) History or presence of detectable cerebrospinal fluid malignant cells or brain metastases, unless otherwise specified in the substudy eligibility criteria
10) History or presence of central nervous system (CNS) disorder, such as cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral edema with confirmed structural defects by appropriate imaging. History of stroke or transient ischemic attack within 12 months before enrollment. Subjects with seizure disorders requiring active anticonvulsive medication
11) Presence of cardiac atrial or cardiac ventricular lymphoma involvement
12) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months before enrollment
13) Requirement for urgent therapy due to tumor mass effects (eg, blood vessel compression, bowel obstruction, or transmural gastric involvement)
14) Presence of primary immunodeficiency
15) History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years
16) History of deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months before enrollment
17) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

18) History of severe immediate hypersensitivity reaction to any of the agents/excipients used in this study

19) Live vaccine ≤6 weeks before the planned start of the lymphodepleting chemotherapy regimen and anticipation of need for such a vaccine during the first 12 months after brexucabtagene autoleucel infusion

20) Females who are pregnant or breastfeeding (because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant). Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

21) Not willing to practice birth control from the time of consent through 12 months after completion of the brexucabtagene autoleucel infusion

22) In the investigator's judgment, the subject is unlikely to complete all study-specific visits or procedures, including follow-up visits, or comply with the study requirements for participation

Study Procedures/Frequency:

Study procedures common to all of the indications are described in the KT-US-568-0138 master protocol, and any procedures unique to the specific indication are described in the respective substudy protocols.

All procedures and their frequencies are outlined in the SOAs within the substudy protocols (substudy protocol Section 12.2).

Subjects will undergo procedures including, but not limited to, the collection of informed consent, medical history, physical exam, neurological examination, ECOG performance status, disease staging, and blood draws. Subjects will also undergo cardiac function assessment.

Females of childbearing potential will undergo either urine or serum pregnancy testing.

All subjects will be asked to report concomitant therapies, AEs, and subsequent anticancer therapy routinely throughout the conduct of the study.

Subjects will undergo leukapheresis for the collection of PBMCs necessary for brexucabtagene autoleucel manufacturing. Lymphodepletion chemotherapy will be followed by 2 rest days and then an infusion of brexucabtagene autoleucel.

Additional blood draws for the assessment of cytokines, anti-brexucabtagene autoleucel antibodies, and RCR are to be performed as clinically indicated and are detailed in the respective substudy SOAs.

The post-treatment follow-up period will include physical examinations, disease response assessments, and survival status.

Study Assessments:

The study assessments that are common to all indications and that are managed the same way across all substudies are described here in the KT-US-568-0138 master protocol. Assessments that are unique to a specific indication or that are managed differently depending on the indication (eg, lumbar puncture and disease response assessments) are described in the study assessment section of the respective substudy protocols.

Study assessments described in this section are to be performed according to the schedule presented in the respective SOA for each substudy.

Safety:

Safety assessments will include collection of AEs, clinical laboratory tests, physical examinations, weight, vital signs, neurologic examinations, ECOG performance status, cardiac function, brain magnetic resonance imaging (if applicable), lumbar puncture (if applicable), collection of concomitant medications, and assessment of the presence of anti-brexucabtagene autoleucel antibodies and RCR, as described in the following sections.

Safety assessments will be conducted according to the schedule presented in the SOA of each respective substudy.

Efficacy:

Disease assessments will be performed as specified in Section 6 of the respective substudy protocols and at the time points specified in the substudy protocol SOAs.

Pharmacokinetics/Pharmacodynamics:

PBMC samples for pharmacokinetic assessments will be drawn according to the schedule presented in the substudy protocol SOAs.

Pharmacokinetic assessments include the monitoring of levels of brexucabtagene autoleucel CAR T cells in blood over time.

Serum (and plasma) samples for pharmacodynamic assessments will be drawn according to the schedule presented in the substudy protocol SOAs.

Pharmacodynamic assessments will include monitoring levels of analytes in serum over time. Analytes can include, but are not limited to, homeostatic/proliferative cytokines (eg, IL-2, IL-7, IL-5), inflammatory/immune-modulating cytokines, correlates of acute phase response (eg, C-reactive protein, ferritin, sIL-2Rα), chemokines, and immune-effector molecules (eg, perforin, granzyme A and granzyme B).

Investigational Product and Study Treatments, Dose, and Mode of Administration:

Substudy A – r/r WM: terminated early by Sponsor (effective 21 June 2023)

- Optional Ibrutinib treatment is allowed through screening and leukapheresis if required (investigator discretion) to reduce the risk of BTK inhibitor withdrawal symptoms and IgM flare. Refer to Section 3.1.1.1 of the WM substudy protocol for details.

Substudy B – r/r RT

- Optional bridging therapy is allowed between leukapheresis and lymphodepletion if required (investigator discretion) to limit rapid disease progression. In addition, ibrutinib treatment is allowed to continue through screening and leukapheresis if required (investigator discretion). Refer to Section 7.2 of the RT substudy protocol for details.

Substudy C – r/r BL

- Optional bridging therapy is allowed between leukapheresis and lymphodepletion if required (investigator discretion) to limit rapid disease progression. Refer to Section 7.2 of the BL substudy protocol for details.

Substudy D – r/r HCL: terminated early by Sponsor (effective 21 June 2023)

- No additional treatment between enrollment and lymphodepletion is allowed.

Lymphodepletion Therapy:

All subjects will receive a 3-day lymphodepleting chemotherapy regimen consisting of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) on Day -5, Day -4, and Day -3, followed by 2 rest days (Day -2 and Day -1).

Brexucabtagene Autoleucel Infusion:

All subjects will receive a single infusion of brexucabtagene autoleucel administered IV at a target dose of either 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg (depending on required dose reduction as assessed by the safety review team) on Day 0. For subjects weighing > 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells (or 1×10^8 anti-CD19 CAR T cells if dose reduction is required) will be administered.

Safety Review Team and Data Safety Monitoring Board:

A Safety Review Team (SRT) that is internal to the study sponsor and in collaboration with at least 1 study investigator will review safety and efficacy data and make recommendations regarding further study conduct, progression and/or dose modification in each substudy after 3 or 6 subjects have been treated with the initial dose (2×10^6 anti-CD19 CAR T cells/kg of body weight or a maximum flat dose of 2×10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg) and followed for 28 days (Section 8.10.1). In case of DLTs, the SRT can recommend i) to proceed with the starting dose; ii) to include an additional 3 subjects for evaluation prior to recommending dose; or iii) that the remaining patients to be dosed with 1 x 10^6 anti-CD19 CAR T cells/kg or a maximum flat dose of 1×10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg (with a subsequent SRT to be held after at least 3 subjects have been treated and followed for 28 days). Only subjects treated with the selected target dose will be included in the evaluable subject population for the primary analysis.

DLTs are defined as the following brexucabtagene autoleucel-related events with onset within the first 28 days after the infusion of brexucabtagene autoleucel.

Table 1. Dose Limiting Toxicities

Dose-limiting Toxicities	Exceptions
Any brexucabtagene autoleucel related Grade 5 event	• Grade 5 disease progression
Hematologic toxicity Grade 4 does not recover to Grade ≤ 2 by Day 28	• Any hematologic toxicity Grade 4 attributable to underlying disease • Lymphopenia
Grade 3 or 4 thrombocytopenia lasting of any duration if accompanied by Grade 2 or higher bleeding	• None
All brexucabtagene autoleucel related Grade 4 nonhematologic toxicities including opportunistic infections and complications associated with HIV[a]	• None
Any brexucabtagene autoleucel related Grade 3 neurotoxicity including ICANS, regardless of duration	• None
All brexucabtagene autoleucel related Grade 3 nonhematological toxicities lasting ≥ 7 days including opportunistic infections and complications associated with HIV[a]	• Grade 3 fever • Grade 3 aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to Grade 2 or lower within 14 days • Grade 3 nausea and/or anorexia • Grade 3 febrile neutropenia returning to baseline within 2 weeks • Grade 3 insomnia, fatigue, and malaise • Grade 3 infection that improves to Grade 2 or lower within 2 weeks • Grade 3 TLS including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, or hyperuricemia)
All brexucabtagene autoleucel related Grade 3 cardiac and/or pulmonary events of any duration	• Grade 3 cardiac and/or pulmonary events if related to CRS and improves to Grade 2 or lower within 72 hours

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TLS, tumor lysis syndrome
Notes: Adverse events are graded using the NCI CTCAE v5.0. CRS and neurotoxicity is graded according to the ASTCT consensus grading for CRS and ICANS {Lee 2019}. The severity of individual signs/symptoms of CRS and neurological events will be graded according to NCI CTCAE v5.0 for those signs/symptoms that are not part of the grading scale.

a Infections associated with HIV and AIDS such as (but not exclusive to): Candidiasis of bronchi, trachea, or lungs, extrapulmonary Cryptococcosis, Cytomegalovirus disease (other than liver, spleen or nodes), Histoplasmosis, disseminated or extrapulmonary, Mycobacterium avium complex, kansasii or other species (disseminated or extrapulmonary), Pneumocystis jirovecii pneumonia or complications such as HIV-associated Encephalopathy

Table 2. Recommendations Based on DLTs

Number of Subjects With a Dose Limiting Toxicity in a Cohort	Potential Recommendation
0 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and no DLT occurs in the subsequent 3 subjects	If the dose is determined tolerable, then this will be the recommended dose.
1 of 3 subjects	Enrol 3 more subjects at the same dose level.
≥ 2 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and ≥1 DLT occurs in the subsequent 3 subjects	The lower dose level will be established as the recommended dose (if assessed to be tolerable and recommended by the SRT).

An independent Data Safety Monitoring Board (DSMB) will review safety data throughout the study duration to make study conduct recommendations based on an overall assessment of risk versus benefit after the target dose for each substudy is confirmed by the SRT. There will be a single interim analysis in each substudy. The DSMB will review safety and efficacy data against the non-binding futility rules as described in each substudy.

Statistical Methods:

Hypothesis: Brexucabtagene autoleucel will improve the disease response rates compared with pre-specified historical control data, as described within each substudy.

Sample Size Calculation: The sample size and power considerations are based on a systemic literature review of historical control response rates for each indication, and each substudy is designed to be independent of each other without data borrowing across the substudies.

The type-1 and type-2 errors are controlled for each substudy. No multiplicity adjustment is made on global type-1 error across the substudies, as the primary goal of this basket study is to determine the treatment effect of brexucabtagene autoleucel separately in each substudy rather than generalizing the treatment effect evaluation between all the studied indications. Nevertheless, a low type-1 error (0.025, 1-sided) and high statistical power (≥ 80%) has been planned for each substudy.

Of the indications under investigation, HCL and BL have the lowest incidence and, as such, slower accrual for these substudies is likely to be encountered. A sample size of 20 and 30 was selected for HCL and BL, respectively, based on the anticipated slower rate of enrollment and a goal of acquiring clinically meaningful results for the HCL and BL substudies within a reasonable timeframe.

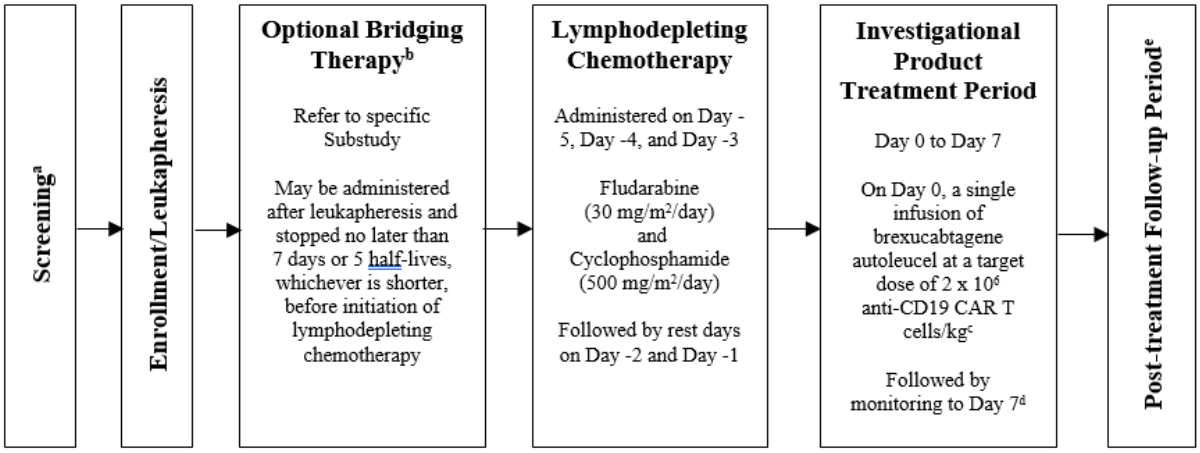
The statistical considerations for each of the indications are described in detail in each respective substudy.

This study will be conducted in compliance with this protocol; the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines of Good Clinical Practice, including archiving of essential documents; and all applicable regulatory and local requirements.

This study will be conducted under United States Code of Federal Regulations Title 21 Part 312 or equivalent.

STUDY SCHEMA

Figure 1. Study and Treatment Schema



Abbreviations: BL, Burkitt lymphoma; CAR, chimeric antigen receptor; HCL, hairy cell leukemia; LTFU, long-term follow-up; SOC, standard of care; RT, Richter transformation; WM, Waldenstrom macroglobulinemia

a Refer to the substudy protocols for details of the use of ibrutinib through screening and leukapheresis (WM and RT subjects only).

b Bridging therapy (RT and BL subjects only) will be administered at the discretion of the investigator. If prescribed, bridging therapy will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, before initiation of lymphodepleting chemotherapy. Refer to specific substudies for details.

c A single infusion of brexucabtagene autoleucel administered intravenously at a target dose of 2 x 10^6 or 1 x 10^6 anti-CD19 CAR T cells/kg, in case of required dose reduction, depending on the safety review team recommended dose. For subjects weighing > 100 kg a maximum flat dose of 2 x 10^8 or 1 x 10^8 anti-CD19 CAR T cells will be administered in case of required dose reduction.

d Refer to Section 12.4 for requirements by country regulatory agencies.

e Subjects with RT and BL will be followed for approximately 24 months after the brexucabtagene autoleucel infusion and subjects with WM and HCL will be followed for approximately 60 months after the brexucabtagene autoleucel infusion. Thereafter, subjects who received brexucabtagene autoleucel will transition to a separate LTFU study, KT-US-982-5968, to continue follow-up out to 15 years (refer to Section 3.5).

LIST OF ABBREVIATIONS

AE	adverse event
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ASTCT	American Society for Transplantation and Cellular Therapy
BL	Burkitt lymphoma
BMI	body mass index
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CPF	cell processing facility
CR	Complete response/remission
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Patients Questionnaire
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Scale
eSAE	electronic serious adverse event
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	general practitioner

GVHD	graft-versus-host disease
HCL	hairy cell leukemia
HCLc	classic hairy cell leukemia
HCLv	variant hairy cell leukemia
HCP	healthcare provider
HLH	hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
IP	investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
IV	intravenous(ly)
KM	Kaplan Meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
MCL	mantle cell lymphoma
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PO	orally
PR	partial response/remission
PRO	patient-reported outcome
qPCR	quantitative polymerase chain reaction
QTc	corrected QT

r/r	relapsed/refractory
RCR	replication-competent retrovirus
RT	Richter transformation
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of assessments
SOC	standard of care
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TTNT	time to next treatment
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WM	Waldenstrom macroglobulinemia

1. INTRODUCTION

1.1. Brexucabtagene Autoleucel

The brexucabtagene autoleucel chimeric antigen receptor (CAR) T-cell product consists of a single-chain antibody fragment against CD19 linked to the CD28 costimulatory and CD3ζ T-cell activation domains {Jackson 2016}. Following CAR engagement with CD19+ target cells, CD3ζ activation induces the downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions {Roberts 2018}. The intracellular CD28 domain provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin (IL)-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells {Restifo 2012}.

Refer to the current Investigator's Brochure (IB) for additional information on brexucabtagene autoleucel.

1.2. Summary of Relevant Nonclinical and Clinical Studies With Brexucabtagene Autoleucel

1.2.1. Nonclinical Studies With Brexucabtagene Autoleucel

Human T cells transduced with the vector carrying an anti-CD19 CAR construct identical to that used in the production of brexucabtagene autoleucel were previously evaluated for CAR expression, phenotypic markers, and cytokine production after co-culture with CD19+ target cells {Kochenderfer 2009}. In this previous study, transduced cells produced cytokines upon stimulation with CD19+ targets, but not with CD19– targets, and results of cytotoxicity assays demonstrated that anti-CD19 CAR T cells killed primary chronic lymphocytic leukemia (CLL) cells in a dose-dependent and CD19-specific manner.

Anti-murine CD19 CAR T cells were assessed using a mouse lymphoma model comprising immunocompetent C3H mice and syngeneic 38c13 B-cell lymphoma cells expressing murine CD19. Results showed that treatment with anti-murine CD19 CAR T cells eradicated established lymphoma masses and increased survival (up to 50 days) compared to control groups.

Refer to the current IB for additional information.

1.2.2. Clinical Studies With Brexucabtagene Autoleucel

Brexucabtagene autoleucel is being evaluated for the treatment of B-cell leukemias and lymphomas. In 2020, results from the KTE-C19-102 (ZUMA-2) study led to the accelerated approval of brexucabtagene autoleucel by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with relapsed/refractory (r/r) mantle cell lymphoma (MCL). The European Medicines Agency (EMA) also granted conditional approval of brexucabtagene autoleucel for the treatment of adult patients with r/r MCL after 2 or more lines

of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor. In 2021, based on the results from the KTE-C19-103 (ZUMA-3) study, brexucabtagene autoleucel received FDA approval for the treatment of adult patients with r/r B-cell precursor acute lymphoblastic leukemia (ALL).

ZUMA-2 (NCT0260313) was a single-arm, open-label, multicenter study in 82 adult subjects with r/r MCL. Among the 60 efficacy-evaluable subjects, the objective response rate was 87% (52/60 subjects), including 37 subjects (62%) achieving a complete remission (CR). The median duration of response for subjects who achieved CR ranged from 1.9+ to 29.2+ months. The most common (≥ 10%) Grade 3 or higher adverse events (AEs) were anemia, neutropenia, thrombocytopenia, hypotension, hypophosphatemia, encephalopathy, leukopenia, hypoxia, fever, hyponatremia, hypertension, infection with pathogen unspecified, pneumonia, hypocalcemia, and lymphopenia. Serious adverse reactions occurred in 66% of subjects.

ZUMA-3 (NCT02614066) was a single-arm, open-label, multicenter study in 78 adult subjects with r/r B-cell precursor ALL. Efficacy was established on the basis of CR within 3 months after brexucabtagene autoleucel infusion and the duration of CR. Twenty-eight (51.9%) of the 54 efficacy-evaluable subjects achieved CR, and with a median follow-up for responders of 7.1 months, the median duration of CR was not reached. The most common (≥ 10%) Grade 3 or 4 AEs were fever, febrile neutropenia, hypotension, encephalopathy, cytokine release syndrome, hypoxia, and infection with pathogen unspecified.

Refer to the current IB for additional information on other ongoing clinical studies being conducted with brexucabtagene autoleucel.

1.3. Disease Background

This Phase 2, multicenter, open-label, basket study aims to evaluate the efficacy of anti-CD19 CAR T-cell therapy in adults with rare B-cell malignancies with a high unmet medical need, including r/r Waldenstrom macroglobulinemia (WM) {Grunenberg 2019}, r/r Richter transformation (RT) {Rossi 2018}, r/r Burkitt lymphoma (BL) {Short 2017, Tiacci 2015}, and r/r hairy cell leukemia (HCL) {Tiacci 2015}.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023.

Despite advances in therapeutic options, outcomes for subjects with these rare B-cell malignancies remain poor. Commonly, these indications arise from the B-cell lineage expressing the transmembrane protein CD19, thus providing a potential therapeutic target which has been explored in other malignancies such as multiple subtypes of non-Hodgkin lymphoma (NHL), CLL or ALL {Davila 2016}. CD19 expression begins at the pro-B-cell stage and continues throughout B-cell differentiation {Anderson 1984, Nadler 1983, Uckun 1990, Uckun 1988}.

Two CD19-targeted CAR T-cell therapies have been developed by Kite – axicabtagene ciloleucel (YESCARTA®) and brexucabtagene autoleucel (TECARTUS®). These therapies consist of autologous patient T cells that have been engineered ex vivo to express a CAR targeting CD19 on the cell surface of normal and malignant B cells. Both therapies differ in that

during the brexucabtagene autoleucel manufacturing process the harvested T cells in the leukapheresis product are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. This enrichment step is needed for use in certain B-cell malignancies in which circulating lymphoblasts are a common feature. Separating T cells from the CD19-expressing tumor cells ensures no circulating tumor cells are transduced, and prevents tumor cells from potentially driving expansion and exhaustion of the CAR T cells or causing relapse due to epitope masking {Ruella 2016, Ruella 2018}. Since circulating lymphoma/leukemia cells may be present in subjects diagnosed with the diseases being evaluated under study protocol KT-US-568-0138, brexucabtagene autoleucel was selected as the investigational therapy.

The background information and rationale for the investigation of brexucabtagene autoleucel in each indication is described in the respective substudy protocol.

1.3.1. Disease Indication-specific Information

Refer to the respective sections of each substudy protocol for background information regarding the epidemiology (Section 1.1.1), diagnosis (Section 1.1.2), frontline treatment (Section 1.1.3) and second-line treatment (Section 1.1.4) of WM (substudy KT-US-568-0138-A), Section 1.1.3 of RT (substudy KT-US-568-0138-B), BL (substudy KT-US-568-0138-C) and HCL (substudy KT-US-568-0138-D).

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023.

1.4. Study Rationale

Treatment options for patients with r/r WM, r/r RT, r/r BL, and r/r HCL are limited and historical outcomes are poor.

For third line and beyond WM subjects, prior therapy must have included a BTK inhibitor. Also, chemotherapy and/or use of a proteasome inhibitor must have been attempted. For third line and beyond HCL, subjects must have received at least 2 prior lines of therapy, including at least a PNA and moxetumomab pasudotox (if eligible and available). For r/r RT and r/r BL subjects, no established standard of care exists, and mean survival is less than 12 months. For all study indications, no established standard of care exists, and only subjects who have exhausted the available approved treatment options will be included in this study. Accordingly, the unmet medical need for these subjects is significant.

Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treat many cancer types. T cells play an important role in killing diseased cells throughout the body, but need to possess the appropriate tumor specificity, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. CAR T cells may address these issues and are a promising approach for cancer therapy.

Brexucabtagene autoleucel is an engineered autologous T-cell immunotherapy by which a patient's own T cells are collected and subsequently genetically altered to recognize CD19 that is expressed on the cell surface of B-cell malignancies. In ZUMA-2 and ZUMA-3, which investigated the safety and efficacy of brexucabtagene autoleucel in adult patients with r/r MCL and r/r ALL, respectively, brexucabtagene autoleucel provided significant and clinically meaningful outcomes with a positive benefit/risk profile. Similar outcomes were attained with axicabtagene ciloleucel in adult NHL patients.

Accordingly, having shown significant clinical benefit of brexucabtagene autoleucel in subjects with more frequent B-cell malignancies, the goal of the KT-US-568-0138 study is to assess the safety and efficacy of brexucabtagene autoleucel in subjects diagnosed with relatively rare B-cell malignancies with high unmet medical need. As such, this study will assess the safety and efficacy of brexucabtagene autoleucel in subjects with r/r WM, r/r RT, r/r BL, and r/r HCL (with comparisons to historical controls).

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023.

1.5. Benefit/Risk Assessment for the Study

The positive benefit/risk profile of CD19-directed CAR T-cell therapies such as brexucabtagene autoleucel and axicabtagene ciloleucel has been established in various aggressive and indolent r/r NHLs, r/r MCL and r/r adult ALL, while currently under investigation in r/r pediatric ALL. The proposed indications are in alignment with the described expression of the CD19 antigen, and the well-established mechanism of action of brexucabtagene autoleucel.

The safety profile of brexucabtagene autoleucel and its administration as a single dose following lymphodepletion chemotherapy is well established, with most AEs occurring within 30 days of infusion. AEs, which can be severe (even fatal), are typically well defined, reversible (severe AEs), and manageable with no apparent long-term consequences other than B-cell aplasia in most individuals. The most common events reported with brexucabtagene autoleucel to date {Kite Pharma Inc 2021} include, but are not limited to, cytopenias, infections, CRS, and neurologic events. Strategies have been developed to monitor for early detection and manage the risks associated with these AEs.

Refer to the current version of the IB for a summary of the findings from nonclinical studies and the known and potential benefits and risks associated with brexucabtagene autoleucel T-cell therapy.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory and local legal requirements.

2. OBJECTIVES AND ENDPOINTS

The primary and secondary objectives of the study and associated endpoints that are common to all the substudies are detailed in Table 3.

Additional substudy-specific objectives and endpoints are provided in Section 2 of each respective substudy protocol.

Table 3. Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with rare B-cell malignancies, by determining the Response Rates as defined within the substudies by central assessment	• Response rates by central assessment as defined in each substudy
Secondary Objectives	**Secondary Endpoints**
• To evaluate the CR by central assessment as defined within each substudy.	• CR rate by central assessment as defined in each substudy
• Determine response durability	• DOR
• Determine survival status	• OS
• Determine survival status without progression	• PFS
• Determine the TTNT after administration of brexucabtagene autoleucel	• TTNT defined as the time from enrollment (for Full Analysis Set [FAS]) or brexucabtagene autoleucel infusion (for modified intention to treat [mITT]) to the initiation of subsequent anticancer therapy/treatment
• Determine the time to first response	• Time to first response from brexucabtagene autoleucel infusion to the first response as defined in the substudy
• Determine the time to best response	• Time to best response from brexucabtagene autoleucel infusion to the best response as defined in the substudy
• To evaluate the safety of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Incidence of AEs and CTCAE grade changes in safety laboratory values • Incidence of AEs defined as DLTs • Incidence of antibodies to brexucabtagene autoleucel (immunogenicity) • Incidence of RCR in PBMCs at baseline and after brexucabtagene autoleucel infusion
• To evaluate the effect of brexucabtagene autoleucel on patient reported outcomes (PROs) and quality of life assessments	• Changes over time in the PRO assessment domains, EORTC-QLQ-C30 and EQ5D-5L

Exploratory Objectives	Exploratory Endpoints
• To evaluate the pharmacokinetic profile of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Levels of CAR T cells in blood and association with clinical outcomes (efficacy and toxicity) • Levels of blood B cells and relationship with pharmacokinetic profile
• To evaluate the pharmacodynamic profile of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Levels of serum analytes (including cytokines and chemokines) in blood and relationship with toxicity (eg, CRS and neurotoxicity)
• To explore the phenotypic and functional characteristics of brexucabtagene autoleucel in subjects with rare B-cell malignancies	• Product characteristics, including T-cell phenotypes and relationship with clinical outcome
• To explore immunogenicity against brexucabtagene autoleucel	• Incidence of anti-brexucabtagene autoleucel CAR reactivity

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose limiting toxicity; DOR, duration of response; FAS, full analysis set; mITT, modified intent-to-treat; OS, overall survival; PFS, progression-free survival; PBMC, peripheral blood mononuclear cell; RCR, replication-competent retrovirus; TTNT, time to next treatment.

3. STUDY DESIGN

3.1. Study Design

This Phase 2, open-label, multi-center study will use a basket study design with individual indication-specific substudies for r/r WM, r/r RT, r/r BL and r/r HCL.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023.

This master protocol contains details regarding all elements of the study that are common across each of the indications. In contrast, each of the separate substudy protocols contain additional information that is unique to an individual indication (ie, WM, RT, BL or HCL). A substudy-specific schedule of assessments (SOA) is provided in each of the respective substudy protocols. Both the KT-US-568-0138 master protocol and relevant substudy protocol should be referenced in parallel. The study is designed to have the flexibility to independently open and close individual substudies.

Initially, 1 subject will be enrolled and infused per substudy. After the first subject is enrolled and infused, no additional subjects will be enrolled in an individual substudy until the first subject has been monitored for at least 28 days after the brexucabtagene autoleucel infusion. Subsequently, an additional 2 subjects in each substudy can be enrolled in parallel. After these 3 initial subjects in a substudy have undergone evaluation for at least 28 days after the brexucabtagene autoleucel infusion, a Safety Review team (Section 8.10.2) will review the safety data and make recommendations on further study conduct, progression, and/or dose modification in each substudy.

The screening period will have a duration of up to 28 days and will begin on the date a subject signs the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) and continues through confirmation of enrollment (ie, commencement of leukapheresis), or until a subject withdraws consent before enrollment, or it is determined that a subject is a screen failure (ie, does not meet the study eligibility criteria; see Section 4.2).

If required to reduce risk of BTK inhibitor withdrawal symptoms and IgM flare, subjects in the WM substudy already receiving a BTK inhibitor will be allowed to receive ibrutinib through screening and up to 5 half-lives (30 hours) prior to starting lymphodepleting chemotherapy. Subjects in the RT substudy, if already receiving a BTK inhibitor, may also receive ibrutinib through screening and leukapheresis at the discretion of the investigator.

After enrollment/leukapheresis, subjects in the RT and BL substudies may receive optional protocol-defined bridging therapy, at the investigator's discretion. If bridging therapy has been administered, a new baseline disease assessment is required, as outlined in the SOA of the respective substudies.

Subjects will undergo lymphodepleting chemotherapy with fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) for 3 consecutive days from Day -5 to Day -3 (see Section 5 for details) followed by 2 rest days (Day -2 and Day -1).

On Day 0, subjects will receive a single infusion of brexucabtagene autoleucel administered intravenously (IV) at a target dose of either 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg, depending on the safety review team recommended dose (or a flat dose of 2×10^8 or 1×10^8, respectively, anti-CD19 CAR T cells in subjects > 100 kg). In combination with an initial mandatory hospitalization period of at least 7 days; this is considered as the treatment period (refer to Section 12.4 for country-specific post-infusion monitoring requirements). Subjects will be required to stay within close vicinity to the clinic, with immediate access to urgent care by the investigator until after Day 28.

After completing the treatment period, all subjects will be followed in the post-treatment follow-up period. Counting from Day 0 (the day of brexucabtagene autoleucel infusion), subjects will return to the clinic for evaluation at Day 14 and Day 28, Week 8, Month 3, and then every 3 months up to Month 12. Additional substudy-specific visits will occur as outlined below:

- RT and BL: Month 18 and Month 24
- WM and HCL: every 6 months up to 36 months, and then annually up to 60 months

Thereafter, subjects will transition to a separate long-term follow-up (LTFU) study (KT-US-982-5968) to continue follow-up out to 15 years (refer to Section 3.5).

Disease response will be assessed as appropriate to each indication and as described in each substudy protocol.

The study schema is provided in Figure 1.

An SOA for each indication is provided in the respective substudy protocol.

3.1.1. Rationale for Study Design Elements

The rationale for the study design elements that apply universally across each of the specified disease indications are detailed below. For study design elements that are unique to a specific substudy (eg, use of ibrutinib in WM and RT), a detailed rationale is provided within the respective substudy protocol.

3.1.1.1. Rationale for Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy regimens have been shown to have multiple mechanisms benefiting CAR T-cell therapy, including eliminating sinks for homeostatic cytokines, such as IL-2, IL-7, and IL-15, eradicating immunosuppressive elements, such as regulatory T cells and myeloid-derived suppressor cells, inducing costimulatory molecules and downregulating indoleamine 2,3-dioxygenase in tumor cells, and promoting expansion, function, and persistence of adoptively transferred T cells {Becnel 2019}. Furthermore, studies have indicated that CAR T-cell expansion over the first month may be associated with response and/or durability of the CAR T-cell treatment{Neelapu 2017a}.

The combination of cyclophosphamide and fludarabine is a potent lymphodepleting regimen {Gattinoni 2005}. A combination of cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) administered on Day -5, Day -4 and Day -3 prior to CAR T-cell infusion has been shown to be efficacious and safe in in previous studies {Neelapu 2017b}.

3.1.1.2. Rationale for use of Brexucabtagene Autoleucel

Two CD19-targeted CAR T-cell therapies (Axicabtagene ciloleucel [YESCARTA®] and brexucabtagene autoleucel [TECARTUS®]) have been developed by Kite. These therapies consist of autologous patient T cells that have been engineered ex vivo to express a CAR targeting CD19 on the cell surface of normal and malignant B cells. The 2 therapies differ in that during the brexucabtagene autoleucel manufacturing process the harvested T cells in the leukapheresis product are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. This enrichment step is needed for use in certain B-cell malignancies in which circulating lymphoblasts are a common feature. Separating T cells from the CD19-expressing tumor cells ensures no circulating tumor cells are transduced and prevents tumor cells from potentially driving expansion and exhaustion of the CAR T cells or causing relapse due to epitope masking {Ruella 2018}. Since circulating lymphoma/leukemia cells may be present in subjects diagnosed with the diseases being evaluated under study protocol KT-US-568-0138, brexucabtagene autoleucel was selected as the investigational therapy.

3.1.1.3. Rationale for the Starting Dose of Brexucabtagene Autoleucel

Three dose levels for brexucabtagene autoleucel (0.5×10^6, 1×10^6, and 2×10^6 anti-CD19 CAR T cells/kg) have been explored in several indications including r/r MCL (ZUMA-2), adult (ZUMA-3) and pediatric r/r ALL/NHL (ZUMA-4). In this study, the starting dose of 2×10^6 anti-CD19 CAR T cells/kg has been selected as a dose with a known efficacy profile for adults with r/r MCL and an established safety profile{TECARTUS 2021}.

While the 0.5×10^6 anti-CD19 CAR T cells/kg dose explored in the ZUMA-3 study demonstrated diminished efficacy compared to the higher dose levels, efficacy has been shown with both higher doses. The safety profile of brexucabtagene autoleucel has been well established for dose levels of 1×10^6 and 2×10^6 anti-CD19 CAR T cells/kg dose through the acquisition of extensive clinical study data (as of 23 January 2022, a total of 295 subjects had received brexucabtagene autoleucel in clinical studies), as well as in the clinical post-approval setting (as of 23 January 2022, the estimated exposure in the commercial setting was 661 patients and an additional 168 patients in the compassionate use setting). Moreover, clinical data on axicabtagene ciloleucel in refractory diffuse large B-cell lymphoma (DLBCL) from ZUMA-1 (NCT02348216) and second line DLBCL in ZUMA-7 (NCT03391466) suggest that the dose of 2×10^6 anti-CD19 CAR T cells/kg is both safe and efficacious in aggressive NHL subtypes similar to RT and BL {Chen 2019}. WM and HCL are indolent NHL subtypes with WM, having biological similarities to marginal zone lymphoma (MZL) {Rinaldi 2011} with partially overlapping genomic profiles {Sun 2016}. MZL was studied in ZUMA-5 using the 2×10^6 anti-CD19 CAR T cells/kg dose and showed a positive benefit/risk profile. HCL is considered biologically distinct, but shows similar indolent characteristics as follicular lymphoma, MZL, and MCL for which the dose of 2×10^6 anti-CD19 CAR T cells/kg is well established{Berger 2005, Jacobson 2021a, Jacobson 2021b, YESCARTA 2021}.

To further evaluate the safety of brexucabtagene autoleucel in these rare indications, a Safety Review Team (SRT) will assess the safety data of the first 3 to 6 patients included in each substudy as an additional safety measure. Each of the indications (ie, WM, RT, BL, and HCL) are considered as distinct diseases and, as such, each substudy will be evaluated independently in regard to SRT and subsequent Data Safety Monitoring Board (DSMB) assessments. However, should a new safety signal be observed in any of the first 3 patients within each substudy during the dose limiting toxicity (DLT) period, the SRT may recommend dose de-escalation. Further details including DLT definitions are provided in Section 8.1.2.

3.2. Study Treatments

Study treatments that apply to all of the disease indications are described here. For treatments that are unique to a specific substudy, details are provided within the respective substudy protocol. This includes optional bridging therapy (RT and BL subjects only), and ibrutinib as an optional treatment option through screening and leukapheresis (WM and RT subjects only).

3.2.1. Leukapheresis

Subjects will undergo leukapheresis to obtain PBMCs for the manufacture of brexucabtagene autoleucel. Approximately 12 to 15-liters of apheresis material will be processed with a goal to target approximately 5×10^9 to 10×10^9 mononuclear cells. Leukapheresed cells obtained from subjects at participating study sites will be packaged for expedited shipment to the cell processing facility (CPF) for the manufacture of brexucabtagene autoleucel, as described in the Investigational Product Manual (IPM). Refer to Section 7.5.1 for more information regarding the leukapheresis procedure.

3.2.2. Bridging Therapy (Optional; for RT and BL Subjects Only)

Bridging therapy is applicable to RT and BL subjects only. Please refer to Section 7.2 of the RT substudy protocol, and Section 7.1 of the BL substudy protocol for details.

3.2.3. Lymphodepleting Chemotherapy

All subjects will receive lymphodepleting chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) administered on Day −5, Day −4, and Day −3, followed by 2 rest days (Day -2 and Day -1).

If, after the start of the lymphodepletion regimen, the creatinine clearance falls below 70 mL/min, subsequent doses of fludarabine will be adjusted according to institutional guidelines.

Refer to Section 7.5.4 for details about the lymphodepleting chemotherapy procedures.

3.2.4. Brexucabtagene Autoleucel

On Day 0, a single infusion of brexucabtagene autoleucel will be administered IV at a target dose of 2×10^6 anti-CD19 CAR T cells/kg or a maximum flat dose of 2×10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg. In case of DLTs, the SRT may recommend the dose administered to be reduced to 1×10^6 anti-CD19 CAR T cells/kg or a flat dose of 1×10^8 anti-CD19 CAR T cells in subjects > 100 kg.

Refer to Section 8.10.1 for details of the SRT and Section 8.1.2 for details of DLTs.

Instructions associated with administration of brexucabtagene autoleucel are provided in Section 7.6.

Brexucabtagene autoleucel is the Investigational Medicinal Product (IMP) being assessed in this study (Appendix 12.9). Brexucabtagene autoleucel has been granted marketing authorization in numerous regions, including the US, EU, Canada, Great Britain, and Switzerland, and will be used in this study for new indications.

3.2.5. Auxiliary Medicinal Products

All other medications described throughout the Master Protocol and subprotocols are considered auxiliary medicinal products. Auxiliary products are used in accordance with their authorized product information in any given country (eg, Package Insert, SmPC) and institutional guidelines. The identified and potential risks, and risk minimization, should be managed as described within either the authorized product information and/or in accordance with institutional guidelines. A list of all auxiliary medicinal products is provided in Appendix 12.9.

3.3. Duration of Subject Participation

The duration of treatment for individual subjects will vary depending on their indication, screening requirements, response to treatment, and survival status. Subjects with RT and BL will be followed for approximately 24 months and subjects with WM and HCL will be followed for approximately 60 months. Thereafter, subjects who received brexucabtagene autoleucel will transition to the separate Kite LTFU study (KT-US-982-5968) to continue follow-up out to 15 years (refer to Section 3.5).

Subjects who were enrolled but who did not receive brexucabtagene autoleucel will also be followed for the durations described above but will not be required to transition to the LTFU study. Of note, such subjects will have reduced follow-up requirements excluding disease response assessments but including survival status and subsequent anticancer therapy, as outlined in Section 7.7.3 and Section 7.11.

3.4. End-of-Study Definition

The end-of-study is defined for each substudy as the time when the last remaining subject within the specific substudy has completed their last visit (last patient last visit; LPLV) and either transitions to a separate LTFU study (Section 3.5), or when the last remaining subject, while still

a participant in the specific substudy, is considered lost to follow-up, withdraws full consent, or dies, whichever occurs earlier. In addition, the sponsor may decide to terminate an individual substudy or the whole study at any time.

3.5. Long-term Follow-up

Subjects who have received an infusion of brexucabtagene autoleucel and who have completed the Post Treatment Follow Up Period either at Month 24 (RT and BL) or Month 60 (WM and HCL), or if a substudy is terminated early by Kite (eg, due to lack of efficacy), will transition to a separate Kite LTFU study (KT-US-982-5968).

Subjects will continue to be monitored for occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to brexucabtagene autoleucel and presence of replication-competent retrovirus (RCR) and vector elements, as appropriate, for up to 15 years from the time of the initial brexucabtagene autoleucel infusion (refer also to Section 7.7). In the LTFU study, subjects will continue assessments at time points contiguous with their time point in this study. The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects and a need to understand and mitigate the potential risks of late onset AEs that could be the potential consequence of this emerging technology.

3.6. Study Discontinuation Criteria

The SRT and/or DSMB can make a recommendation to the sponsor to discontinue the study early based on the guidelines in the SRT and DSMB charters, respectively. The DSMB will review the data accrued from each substudy and provide ongoing recommendations on study conduct to the Kite Head of Cell Therapy Clinical Development (or designee). The recommendations may include continuing a substudy without modification, continuing a substudy with modification, stopping a substudy, or communicating that additional data are required for review.

Refer to Section 8.10.1 (SRT) and/or Section 8.10.2 (DSMB) for more information. The sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons.

3.7. Number of Participating Study Sites

Approximately 25 study sites located in the US and Europe will participate in this study. During the conduct of the study, additional regions, countries, or study sites may be added, as necessary.

3.8. Source Data

The source data for this study will be obtained from original documents/records and central laboratory, local laboratory, specialty laboratory (for pharmacokinetics and/or pharmacodynamics data), and/or medical record data.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 90 subjects will be enrolled and treated across the separate substudies.

Approximately 60 subjects with r/r WM who have received at least 2 lines of prior therapy will be enrolled and treated. Additional WM-specific eligibility criteria are detailed in the WM substudy protocol.

Approximately 60 subjects with r/r RT who have received 1 line of prior therapy will be enrolled and treated. Additional RT-specific eligibility criteria are detailed in the RT substudy protocol.

Approximately 30 subjects with r/r BL who have received at least 1 line of prior therapy will be enrolled and treated. Additional BL-specific eligibility criteria are detailed in the BL substudy protocol.

Approximately 20 subjects with r/r HCL who have received at least 2 lines of prior therapy will be enrolled and treated. Additional HCL-specific eligibility criteria are detailed in the HCL substudy protocol.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria Common to all Indications

To be enrolled in the study, subjects must meet all the following inclusion criteria that are common to each of the substudies. Subjects must also meet additional disease specific- inclusion criteria, as specified in Section 4.2.1 of the respective substudy protocols.

1) Male or female 18 years of age or older and who have provided written informed consent

2) Presence of toxicities due to prior therapy must be stable and recovered to Grade 1 or lower (except for clinically nonsignificant toxicities such as alopecia)

3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

4) Adequate hematological function (unless lower values are attributable to underlying disease) as indicated by:

   — Absolute neutrophil count (ANC) ≥ 500/μL

   — Platelet count ≥ 50,000/μL

   — Hemoglobin level ≥ 8 g/dL

5) Absolute lymphocyte count ≥ 100/μL

6) Adequate renal, hepatic, pulmonary, and cardiac function defined as:

- Creatinine clearance (as estimated by Cockcroft-Gault formula) ≥ 60 mL/min
- Serum alanine aminotransferase and aspartate aminotransferase levels ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 × ULN if documented liver involvement
- Total bilirubin levels ≤ 1.5 × ULN, except in subjects with Gilbert's syndrome
- Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an echocardiogram (ECHO) or multigated acquisition scan (MUGA) and no clinically significant electrocardiogram (ECG) findings
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

7) The following washout periods must be satisfied prior to leukapheresis/enrollment:

- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) must be avoided for 7 days before leukapheresis
- BTK inhibitors (eg, ibrutinib or acalabrutinib), must be avoided at least 1 week or 5 half-lives, whichever is shorter, before leukapheresis unless otherwise specified in the subprotocols
- Anti-neoplastic drugs used in previous therapy must be avoided within 1 week or 5 half-lives (whichever is shorter) prior to leukapheresis
- Systemic inhibitory/stimulatory immune checkpoint molecule therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists) must be avoided at least 3 half-lives prior to leukapheresis
- Alemtuzumab must be avoided at least 6 months prior to enrollment
- PEG-asparaginase must be avoided at least 3 weeks prior to enrollment
- Cladribine and pentostatin must be avoided 3 months prior to enrollment
- Donor lymphocyte infusion within 28 days prior to enrollment
- Any treatment with immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor [TNF], anti-interleukin [IL] 6 or anti-IL6 receptor) unless this treatment is included in prior or bridging regimens, in which case a washout period of 7 days is required prior to leukapheresis

8) Female subjects of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

4.2.2. Exclusion Criteria Common to all Indications

Subjects enrolled in the study must not meet any of the following exclusion criteria that are common to all indications. In addition, subjects must also not meet any of the disease -specific exclusion criteria, detailed in the respective substudy protocols:

1) Prior CAR therapy or other genetically modified T-cell therapy

2) Prior treatment with any anti-CD19 therapy

3) History of severe immediate hypersensitivity reaction attributed to aminoglycosides

4) History of severe immediate hypersensitivity reaction to cyclophosphamide or fludarabine

5) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment. Patients with a simple urinary tract infection and uncomplicated bacterial pharyngitis and responding to active treatment are eligible only if the patient satisfies the criteria of being afebrile (ie, temperature lower than 38^{o}C) for at least 24 hours prior to the investigator confirming a patient's eligibility

6) HIV-positive patients, unless taking appropriate anti-HIV medications, having an undetectable viral load by quantitative polymerase chain reaction (qPCR) and a CD4 count > 200 cells/uL

7) Acute or chronic active hepatitis B or hepatitis C infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America guidelines or applicable country guidelines

8) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted

9) History or presence of detectable cerebrospinal fluid (CSF) malignant cells or brain metastases, unless otherwise specified in the substudy eligibility criteria

10) History or presence of central nervous system (CNS) disorder, such as cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral edema with confirmed structural defects by appropriate imaging. History of stroke or transient ischemic attack within 12 months before enrollment. Subjects with seizure disorders requiring active anticonvulsive medication

11) Presence of cardiac atrial or cardiac ventricular lymphoma involvement

12) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months before enrollment

13) Requirement for urgent therapy due to tumor mass effects (eg, blood vessel compression, bowel obstruction, or transmural gastric involvement)

14) Presence of primary immunodeficiency

15) History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

16) History of deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months before enrollment

17) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

18) History of severe immediate hypersensitivity reaction to any of the agents/excipients used in this study

19) Live vaccine ≤ 6 weeks before the planned start of the lymphodepleting chemotherapy regimen and anticipation of need for such a vaccine during the first 12 months after brexucabtagene autoleucel infusion

20) Females who are pregnant or breastfeeding (because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant). Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

21) Not willing to practice birth control from the time of consent through 12 months after completion of the brexucabtagene autoleucel infusion

22) In the investigator's judgment, the subject is unlikely to complete all study-specific visits or procedures, including follow-up visits, or comply with the study requirements for participation

4.3. Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at their institution.

Subjects can decline to continue receiving protocol-required treatment and/or other study-specific procedures at any time during the study but continue to participate in certain follow-up elements of the study (Section 7.12). This is referred to as partial withdrawal of consent. Refer to Section 7.12 for instructions on follow-up and data to be collected.

Withdrawal of full consent from the study means that the subject does not wish to receive further protocol-required treatment or undergo study-specific procedures, and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study and, where permitted by local regulations, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available and per local guidance and regulations, to obtain survival data for any subject for whom the survival status is not known. Moreover, per local guidance and regulations, sites may be also asked to retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product (IP) and/or other protocol-required therapies, study-specific procedures, or the study as a whole at any time before study completion.

4.3.1. Reasons for Removal From Treatment

Reasons for removal of a subject from the protocol-required treatment or study-specific procedures include any of the following:

- AE (eg. an AE occurring prior to dosing, such as uncontrolled infections, stroke, bleeding etc., resulting in the subject no longer being eligible to proceed to dosing with brexucabtagene autoleucel or an AE occurring post-dosing precluding further study-specific procedures per Investigator discretion)
- Withdrawal by subject
- Investigational medicinal product (IMP) not available (eg, including, but not limited to, manufacturing failure or IMP with reduced cell viability (out of specification))
- Lost to follow-up
- Death
- Termination of the substudy/study by the sponsor
- Other (eg, noncompliance)

4.3.2. Reasons for Removal From Study

Reasons for removal of a subject from the study are as follows:

- Withdrawal by subject
- Lost to follow-up

- Death
- Termination of the substudy/study by the sponsor
- Other (eg, investigator decision or noncompliance. Investigator decision for removal of patient from the study can be justified in cases where the potential risks of continuing the study treatment(s) and protocol-required assessments outweigh the potential benefit for an individual patient posing unacceptable safety risks and/or affect assessments of the clinical status to a significant degree)

4.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects receiving the SRT recommended dose is attained in the DLT-evaluable or the modified intent-to-treat (mITT) set (subjects who discontinued before the DLT assessment will be replaced). Subjects who have a DLT assessment and later discontinue before the end of study will not be replaced. Refer to Section 9.6.5 for the definition of the DLT-evaluable or mITT set.

5. STUDY TREATMENT

5.1. Description of Study Treatment

5.1.1. Bridging Chemotherapy

Bridging therapy is only applicable to RT and BL subjects. Please refer to Section 7.2 of the respective substudy protocols for details.

5.1.2. Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy will be used to induce lymphocyte depletion and create an optimal environment for the in vivo expansion of brexucabtagene autoleucel. The lymphodepleting regimen used for this study will be fludarabine and cyclophosphamide.

Lymphodepleting chemotherapy will be supplied by the study site. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of the chemotherapy agents described below. Any consideration for changes to the lymphodepleting chemotherapy dose should be discussed with the Kite medical monitor.

5.1.2.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

If, after the start of the lymphodepletion regimen, the creatinine clearance falls below 70 mL/min, subsequent doses of fludarabine will be adjusted according to institutional guidelines.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

5.1.2.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

5.1.2.3. Mesna

Mesna (sodium-2-mercaptoethanesulfonate; $C_2H_5NaO_3S_2$) is a detoxifying agent used to reduce the risk of hemorrhagic cystitis induced by chemotherapy.

Mesna will be administered around the time of the cyclophosphamide dose according to institutional standards.

Refer to the most recent version of the brexucabtagene autoleucel package insert for specific details surrounding the administration of mesna.

5.1.3. Brexucabtagene Autoleucel

CCI

5.2. Packaging, Labeling, Storage, and Handling of Study Treatment

5.2.1. Brexucabtagene Autoleucel Packaging, Labeling, Storage, and Handling

Refer to the IPM for details about brexucabtagene autoleucel formulation, packaging and labeling, instructions for storage and handling of brexucabtagene autoleucel, and ordering of clinical supplies.

5.3. Dosage and Administration

Refer to Section 3.2.4 for brexucabtagene autoleucel planned dose levels. Refer to Section 7.6.2 for assessments and procedures to be performed on the day of brexucabtagene autoleucel administration.

Refer to the IPM for details and instructions on administration of brexucabtagene autoleucel.

Administration or dosing errors (eg, whether the complete volume in the bag was administered to the subject) should be documented in the subject's source documentation and respective electronic case report form (eCRF).

5.4. Prior and Concomitant Medications

During the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, granulocyte colony-stimulating factor), routine anti-emetic prophylaxis, and anti-HIV medication, except those medications listed in Section 5.5.

5.5. Excluded Medications

5.5.1. Washout Periods Prior to Leukapheresis/Enrollment

The following washout periods must be satisfied prior to leukapheresis/enrollment:

- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) must be avoided for 7 days before leukapheresis.
- Systemic corticosteroids must be avoided as premedication in subjects for whom CT scans with contrast are contraindicated (eg, subjects with contrast allergy or impaired renal clearance) if the administration is within 7 days before leukapheresis or 5 days before brexucabtagene autoleucel administration (washout period).
- BTK inhibitors (eg, ibrutinib or acalabrutinib) must be avoided at least 1 week or 5 half-lives, whichever is shorter, before leukapheresis unless otherwise specified in the subprotocols
- Anti-neoplastic drugs used for prior therapy must be avoided within 1 week or 5 half-lives (whichever is shorter) prior to leukapheresis

- Systemic inhibitory/stimulatory immune checkpoint molecule therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists) must be avoided at least 3 half-lives prior to leukapheresis
- Alemtuzumab must be avoided at least 6 months prior to enrollment
- PEG-asparaginase must be avoided at least 3 weeks prior to enrollment
- Cladribine and pentostatin must be avoided 3 months prior to enrollment
- Donor lymphocyte infusion within 28 days prior to enrollment
- Any treatment with immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-TNF, anti-IL 6 or anti-IL6 receptor) unless this treatment is included in prior or bridging regimens, in which case a washout period of 7 days is required prior to leukapheresis

5.5.2. Excluded Medications or Medications to be Used With Caution After Leukapheresis/Enrollment

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) should be avoided for 5 days before infusion of brexucabtagene autoleucel.

Moreover, corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after brexucabtagene autoleucel administration unless used to manage brexucabtagene autoleucel-related toxicities or discussed with the Kite medical monitor.

Vaccination with live viral vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during brexucabtagene autoleucel treatment, and for 12 months after treatment with brexucabtagene autoleucel. Please refer to the current IB for additional information about vaccination, including COVID-19 vaccines.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided whenever possible for subjects who are at risk of bleeding due to thrombocytopenia.

Treatments for underlying disease, such as chemotherapy, immunotherapy, targeted agents, radiation, high-dose corticosteroids (other than those defined/allowed in this master protocol and substudy protocols), and other investigational agents are prohibited, except as needed for treatment of disease progression after brexucabtagene autoleucel administration.

If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor. Please refer to the IB for additional information about excluded medications.

5.6. Accountability and Return of Study Treatment

5.6.1. Accountability of Study Treatment

Refer to the IPM for details about accountability of brexucabtagene autoleucel.

5.6.2. Return or Disposal of Study Treatment

Unused study drug should remain in storage (at ≤ –150° C) until further instruction from Kite to either return the study drug or dispose of the study drug on site. Kite must approve the disposal of unused study drug bags on site. Refer to the IPM for details.

The study monitor will review the study treatment records at periodic intervals.

6. STUDY ASSESSMENTS COMMON TO ALL SUBSTUDIES

The study assessments that are common to all indications and that are managed the same way across all substudies are described here. Assessments that are unique to a specific indication or that are managed differently depending on the indication (eg, lumbar puncture and disease response assessments) are described in the study assessment section of the substudy protocols.

Study assessments described in this section are to be performed according to the schedule presented in the respective SOA for each substudy.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023

6.1. Demographic Data

Demographic data will be collected at screening for each subject as per country and local regulations and guidelines. Where applicable, demographic data may include sex, year of birth, race, ethnicity, and country of enrollment with the intent to assess the possible association of demographics with subject safety and treatment effectiveness.

6.2. Medical and Treatment History

Relevant medical history before the start of AE reporting (ie, from before enrollment [leukapheresis]) will be collected at screening. Relevant medical history is defined as data about the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the eCRFs.

In addition to the medical history, all history related to a subject's disease, treatment, and response to treatment will be collected and must date back to the original diagnosis. Any prior treatment received, as outlined in the substudy protocol, must be documented. Additionally, for the RT substudy, prior treatment received for CLL must also be collected. For subjects who are being referred from another clinic or institution to the participating study site, copies of the subject's chart should be obtained.

Please also refer to Section 6 of the respective substudy protocols for substudy-specific requirements.

6.3. Safety Assessments

Safety assessments will include collection of AEs, clinical laboratory tests, physical examinations, weight, vital signs, neurologic examinations, ECOG performance status, cardiac function, brain magnetic resonance imaging (MRI) (if applicable), lumbar puncture (if applicable), collection of concomitant medications, and assessment of the presence of anti-brexucabtagene autoleucel antibodies and RCR, as described in the following sections.

Safety assessments will be conducted according to the SOA for each respective substudy.

6.3.1. Adverse Events

All AEs, SAEs, and DLTs will be collected at each study visit, as indicated in the SOA for each substudy. Subjects will be asked about any AEs that might have occurred since the last study visit.

6.3.2. Clinical Laboratory Tests

6.3.2.1. Laboratory Tests for Safety and Pharmacokinetic/Pharmacodynamic Assessments

Clinical laboratory tests using blood, serum, urine or CSF (if applicable) samples will be performed to assess safety. Additional samples may be collected as needed for further safety testing.

All clinical laboratory test assessments listed in Table 4 will be performed across all substudies at the local laboratory except for assays for anti-brexucabtagene autoleucel antibodies and RCR which will be performed at the central laboratory.

(Note: In addition to collection of blood samples for assessment at the local laboratory of complete blood count [CBC] with differential, blood samples will also be sent to the central laboratory at various timepoints identified in the substudy SOAs. This will occur in parallel with sampling for pharmacokinetic, pharmacodynamic and exploratory assessments Refer to the central laboratory manual for details.

Table 4. Clinical Laboratory Tests for Safety Assessments Common Across All Substudies

Serum Chemistries (Serum)	Hematology (Blood)	Other
Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bicarbonate (CO_2) total (as clinically indicated) Bilirubin total and direct Blood urea nitrogen or urea Calcium total Chloride Creatinine Creatinine clearance (as estimated by Cockcroft Gault formula) (screening only) Glucose Inorganic phosphorus	Absolute lymphocyte count CBC with differential CD4 cell count (HIV positive patients only) **PBMCs:** RCR (central laboratory) qPCR for HIV viral load (HIV positive patients only)	**Serum:** Anti-brexucabtagene autoleucel CAR antibodies (central laboratory) C-reactive protein Ferritin Pregnancy test Serology anti-HIV1+2 test (at screening only) HIV positive patients serologic testing for hepatitis B and hepatitis C (at screening only) **CSF:** Presence of malignant cells (if applicable)

Serum Chemistries (Serum)	Hematology (Blood)	Other
Lactate (as clinically indicated) Lactate dehydrogenase Magnesium total Potassium Sodium Uric acid		

Abbreviations: CAR, chimeric antigen receptor; CBC, complete blood count; CSF, cerebrospinal fluid; PBMC, peripheral blood mononuclear cell; qPCR, quantitative polymerase chain reaction; RCR, replication-competent retrovirus.
Notes: All laboratory tests listed above, except for anti-brexucabtagene autoleucel antibodies, and RCR, are performed at the local laboratory.

- Per institutional guidelines, CBC with differential must include WBC count, neutrophils or ANC (including bands according to standard of care), lymphocytes or absolute lymphocyte count, hemoglobin, and platelets.
- Lactate dehydrogenase (LDH) should continue to be monitored after the baseline assessment, as clinically indicated.
- C-reactive protein (CRP) and ferritin will also be tested at the central laboratory as part of the pharmacodynamics evaluation (ie, analytes including cytokines; refer to Section 6.7) at the time points listed in the respective substudy SOAs (for subprotocol A and subprotocol C, refer to Table 4 and Table 5. For subprotocol B and subprotocol D, refer to Table 5 and Table 6 in the respective substudy protocols).
- Refer to Section 6.3.16.2 for information on RCR testing.
- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test (β-human chorionic gonadotropin) is positive, the subject should not be enrolled. If a standard-of-care pregnancy test is collected during the course of the study and the result is positive, the investigator should report the pregnancy to Kite per instructions specified in Section 8.9.2.1. If a female partner of a male subject becomes pregnant during the conduct of the study, the pregnancy must be reported to Kite per instructions specified in Section 8.9.2.1. Refer to Section 12.4.3 for details regarding pregnancy testing of European Union (EU) and Swiss subjects before both leukapheresis and lymphodepleting chemotherapy.
- If the blood urea nitrogen test cannot be performed by the local laboratory, urea should be analyzed.
- At European study sites, serologic tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and EU/CH regulations. Testing may be done within 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.
- HIV positive patients must undergo tests for viral load by qPCR and CD4 count.

Refer to Section 6.3.14 for information regarding serology testing.

If a subject is re-admitted to the hospital after the initial 7-day hospitalization period with any brexucabtagene autoleucel-related AEs, blood samples for assessment of brexucabtagene autoleucel CAR T cells and cytokines will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge, unless the collection overlaps with a scheduled one, as per the respective substudy SOA. Blood samples for assessment of brexucabtagene autoleucel CAR T cells and cytokines must also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.

6.3.2.2. Laboratory Tests associated with Evaluating Disease Response

Refer to the respective substudy protocol (Section 6) and substudy SOA for specific laboratory testing associated with evaluating disease response.

6.3.3. Physical Examination

Physical examinations will be performed at screening and at the time points noted in the respective substudy SOA.

Physical examination will include assessments of splenomegaly, hepatomegaly, lymphadenopathy, including (if applicable) Waldeyers ring (throat area, tonsils, adenoids and other lymphoid tissue).

Subjects with symptoms related to CRS should undergo physical examination at least daily until symptoms resolve to baseline.

Clinically significant adverse changes (as determined by the investigator) when compared with the baseline examination will be reported as AEs.

6.3.4. Weight

Weight (plus height at screening) will be collected at screening and at the time points noted in the respective substudy SOA.

6.3.5. Vital Signs

Vital signs including blood pressure, heart rate, respiration rate, oxygen saturation, and temperature will be collected. Vital signs will be monitored as indicated in the SOA for each substudy.

In addition to the time points indicated in the SOA for each substudy, it is recommended that vital signs are monitored during and after the brexucabtagene autoleucel infusion and then routinely per institutional guidelines. Vital signs may be monitored more frequently as clinically indicated.

6.3.6. Neurologic Examinations

To establish a baseline the subject's neurological status will be evaluated at screening.

Neurological examinations, including an immune effector cell-associated encephalopathy cognition assessment as outlined by the American Society for Transplantation and Cellular Therapy (ASTCT) immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading {Lee 2019} will be performed according to the time points specified in the substudy SOAs.

A neurological assessment (which may include the Mini-Mental Status Exam) should be performed prior to brexucabtagene autoleucel infusion on treatment Day 0, then continue every other day during the minimum 7-day hospitalization period (refer to Section 12.4 for specific requirements of country regulatory agencies regarding duration of observation period). If a subject has extended hospitalization after Day 7, a neurologic assessment will continue to be performed as clinically indicated. Neurologic examinations performed on Day 0 to Day 7 can be done by a licensed physician or equivalent who is not necessarily an investigator in the study.

Any abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition, and emotion).

Refer to Section 8.4.1.1 and Section 8.8 for information on the grading and management of neurotoxicity events. Grading should be continued daily during any period of Grade 2 or higher neurologic events until symptoms return to baseline.

During the hospitalization period for subjects treated with brexucabtagene autoleucel, the frequency of evaluations of neurological status may need to be increased. Changes in neurological status should be reported as an AE if considered clinically significant at the discretion of the investigator.

6.3.7. Performance Status (Eastern Cooperative Oncology Group Score)

Performance status as measured by the ECOG scale will be performed at the time points specified in the respective substudy SOA to quantify the subject's general well-being and ability to perform activities of daily life.

6.3.8. Cardiac Function

6.3.8.1. Echocardiogram/Multigated Acquisition Scan

Cardiac function (defined as the left ventricular ejection fraction), as measured by ECHO or MUGA, will be assessed during the screening period to confirm study eligibility. No evidence of clinically significant pericardial effusion, as required by eligibility, will also be confirmed.

If the last chemotherapy regimen the subject received is not considered cardiotoxic, an ECHO or MUGA performed within 28 days before signing the ICF may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO or MUGA performed after the subject received their last chemotherapy treatment and within 28 days before signing the ICF may be used for confirmation of eligibility.

6.3.8.2. Electrocardiogram

To establish a baseline, an ECG will be performed at screening. ECG assessments will include partial response (PR) duration, QRS duration, QT duration, and RR duration, and corrected QT (QTc) interval. The QTc interval will be calculated using Fridericia's formula {Fridericia 2003}.

6.3.9. Brain MRI

Brain MRIs will be performed as specified in Section 6.2 of the substudy protocols and the substudy SOAs.

6.3.10. Lumbar Puncture

Lumbar puncture will be performed as specified in Section 6.3 of the respective substudy protocols and the substudy SOAs.

6.3.11. Patient-reported Outcomes

The patient-reported outcomes (PROs) to be used in this study include the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire (EORTC QLQ-C30) and European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L). A description of each PRO is provided in Section 12.6.

The time points at which the PROs should be administered are provided in the SOAs for each respective substudy. These PROs are expected to be completed by all subjects who remain on-study at the scheduled assessments, up to and until disease progression.

All PRO measures will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual.

The PROs are to be completed by the subject before any study-specific assessments or procedures are performed (excluding blood draws), before a subject receives any disease status information, and on Day 0 prior to the brexucabtagene infusion.

The sponsor will provide training for relevant site personnel for the administration of the questionnaires, so that subjects fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection {Fallowfield 1987}. The measures are self-reported, and the subject must complete the questionnaires in private and should not be given help from relatives or study staff; help in interpreting the questions is not allowed. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in 1 of the country languages available.

6.3.12. Concomitant Therapies and Procedures

Information about concomitant therapies and procedures will be collected at the timepoints specified in the respective substudy SOAs. Reporting requirements for concomitant medications are provided in Table 5. Specific concomitant medication collection requirements and instructions are included in the eCRF completion guidelines. Refer to Section 5.4 and Section 5.5 for information about allowed/excluded medications.

Table 5. Reporting Requirements for Concomitant Medications and Procedures

Subjects Who Are:		
Not Enrolled (ie, Screen Failures, or Not Leukapheresed)	**Enrolled, but Do Not Receive Brexucabtagene Autoleucel**	**Enrolled and Received Brexucabtagene Autoleucel**
Concomitant medications related to serious adverse event(s) will be recorded from the date of the signing of the screening ICF through 30 days after the last study-specific screening procedure.	Concomitant medications will be recorded from the date of signing of the ICF until 30 days after the last study-specific procedure has occurred (eg, leukapheresis or lymphodepleting chemotherapy) or until the initiation of a new anticancer therapy, whichever occurs first.	• Concomitant medications and procedures, including oxygen, blood products, intubation, and dialysis, will be recorded from the date of signing of the ICF until 3 months after completing treatment with brexucabtagene autoleucel. • After the 3-month follow-up period, targeted concomitant medications and other medicinal products will be recorded for 60 months after the brexucabtagene autoleucel infusion, or until disease progression or subsequent therapy, whichever occurs first (for the RT and BL subjects reporting after 24 months will continue within the LTFU protocol). • Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and anticancer therapies (eg, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant/BMT, high-dose corticosteroids, radiation, surgery, and investigational products). • All concomitant medications used to treat targeted AEs should be recorded throughout the study.

Abbreviations: AE, adverse event; BL, Burkitt lymphoma; BMT, bone marrow transplant; ICF, informed consent form; LTFU, long-term follow-up; RT, Richter transformation.

6.3.13. Pregnancy Testing

Pregnancy testing in females of childbearing potential (Refer to Section 12.3.1 for the definition of childbearing potential) will occur at the time points indicated in the respective substudy SOAs. Refer to Section 3 for details regarding pregnancy testing of EU/CH subjects.

6.3.14. Serology Testing

For all subjects, serology anti-HIV1+2 test at screening, unless available HIV test results within 3 months prior to enrolment, or if the subject has been confirmed to be HIV positive prior to screening.

For HIV positive subjects, testing for hepatitis B and hepatitis C at screening (refer to Section 4.2.2 for exclusion criteria related to hepatitis B or hepatitis C infection).

At EU/CH study sites, serologic tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and EU/CH regulations. Serology testing may be done within 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/ enrolment.

6.3.15. HIV Viral Load and CD4 Count

Subjects who are HIV positive who are taking appropriate anti-HIV medications with an undetectable viral load by qPCR and with a CD4 count > 200 cells/µL at screening will be eligible to participate in the study. For subjects who are HIV positive, screening for active Hepatitis B and Hepatitis C virus is required. Moreover, regular assessments of viral load and CD4 counts will be performed according to the respective substudy SOAs.

6.3.16. Other Safety Assessments

6.3.16.1. Antibodies to Brexucabtagene Autoleucel

The presence of antibodies against the brexucabtagene autoleucel CAR will be assessed in serum samples, prior to leukapheresis (baseline), on Day 28 post-infusion, and then at Month 3, Month 6, Month 9 and Month 12, as per the respective substudy SOAs. The evaluation will be performed by a central laboratory. Refer to the central laboratory manual for further details.

6.3.16.2. Replication-Competent Retrovirus

As brexucabtagene autoleucel comprises retroviral vector-transduced T cells, the presence of RCR in the blood of treated subjects will be monitored as per the substudy SOAs. The evaluation of RCR will be performed by a central laboratory. Refer to the central laboratory manual for further details.

Peripheral blood mononuclear cells (PBMCs) for RCR testing will be collected at baseline (before the start of brexucabtagene autoleucel infusion) and at Month 3, Month 6, and Month 12. Thereafter, samples will only be collected and tested if an RCR event is clinically suspected and/or a subject tests positive for RCR at any time point within the first year. If the latter, samples/testing for RCR will continue per physician/investigator discretion.

If a subject dies of a suspected retrovirus-associated disease or develops a new malignancy suspected to be associated with brexucabtagene autoleucel during the study or long-term follow-up, a blood sample and tumor biopsy may be obtained and sent to the central laboratory to assay for brexucabtagene autoleucel CAR T cells and/or RCR.

6.3.16.3. Assessments in the Event of a Secondary Malignancy

In the case of a secondary malignancy, every effort will be made to obtain a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a diagnostic workflow, including tests such as transgene elements, RCR, presence of common cancer-drivers/mutations and insertional mutagenesis. Samples will be submitted to the central laboratory for evaluation. Refer to the central laboratory manual for further details.

6.4. Disease Assessments

Subjects will be evaluated for disease response by the site investigator as specified in Section 6 of the substudy protocols and at the time points specified in the respective substudy protocol SOAs.

6.5. Bone Marrow Aspirate / Biopsy requirements for Subjects With Unexplained Cytopenias or Suspicion of Hemophagocytic Lymphohistiocytosis

A bone marrow aspirate and biopsy should be considered for any subject with unexplained cytopenias or where there is suspicion of hemophagocytic lymphohistiocytosis (HLH). The samples should be reviewed at the local laboratory, and a portion of the sample should be sent to the central laboratory for exploratory analyses.

6.6. Pharmacokinetic Assessments

PBMC samples for pharmacokinetic assessments will be drawn according to the schedule presented in the respective substudy protocol SOAs. Samples on Day 3 may be collected ± 1 day.

Pharmacokinetic assessments include monitoring of levels of brexucabtagene autoleucel CAR T cells in blood over time.

6.7. Pharmacodynamic Assessments

Serum (and plasma) samples for pharmacodynamic assessments will be drawn according to the schedule presented in the substudy protocol SOAs.

Pharmacodynamic assessments will include monitoring levels of analytes in serum over time.

CCI

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.8. Other Assessments

Samples for the assessments described in the following sections will be drawn according to the schedule presented in the substudy SOAs.

6.8.1. Central Confirmation of Diagnosis

Local assessments for diagnosis and determination of study eligibility will be made by the primary investigator at each site. Diagnosis will be confirmed retrospectively by a centralized specialty laboratory (see central laboratory manual) using peripheral blood, bone marrow aspirate, bone marrow core biopsy, and/or tumor tissue in the form of formalin-fixed, paraffin-embedded block, unstained pre-cut slides along with a pathology report, as appropriate for each indication and described in the subprotocols.

6.8.2. Exploratory Assessments

Indication-specific exploratory assessments are described in Section 6 of the respective substudy protocols.

6.8.2.1. Other Exploratory Assessments

CSF may be harvested from subjects who develop ICANS or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte and myeloid populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of brexucabtagene autoleucel.

Additional exploratory analyses are described in each indication-specific substudy protocols.

6.8.3. Survival Data

At the time points identified in the substudy SOAs, as well as additional time points outside of the SOA at the sponsor's discretion, subjects and/or the subject's referring healthcare provider (HCP) and/or general practitioner (GP) may be contacted directly by telephone or email or a search of public records per local regulations to assess survival status.

7. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the respective substudies at each study period/visit, and that are common to all indications, are described in the following sections and will be performed at the time points presented in the respective SOA for each substudy. Study procedures that are unique to a specific indication are described in the respective substudy protocol.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023

The investigator must document any deviation from the protocol procedures and notify Kite or the contract research organization (CRO).

7.1. Subject Informed Consent

Before a prospective subject can participate in the clinical study, the investigator must obtain written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and potential risks. Subjects should sign the most current IRB/IEC-approved ICF before any study-specific activity or procedure is performed. Refer to Section 10.1.3 for more information about the informed consent process.

All subjects who are enrolled in the study should be reconsented with any updated version of the IRB/IEC-approved ICF if relevant to their participation in the study. Subjects who partially withdraw consent should be reconsented with the revised ICF.

7.1.1. Informed Consent for Optional Research

In addition to the study-specific informed consent form (ICF) to be signed by each subject participating in the study, additional, optional consent will be sought from subjects for permission to use the remainder of study biospecimens for optional future research and/or genetic research in accordance with applicable regulations.

7.2. Subject ID Assignment

Each subject who enters the screening period will receive a unique subject ID number before any study-specific procedure or activity is initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject ID number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened or enrolled in the KT-US-982-5968 LTFU study.

7.3. Screening

The up to 28-day screening period begins on the date the subject signs the IRB/IEC-approved ICF and continues through confirmation of enrollment (ie, commencement of leukapheresis [Section 7.5.1]), or until the subject withdraws consent before enrollment, or it is determined that the subject is a screen failure (ie, does not meet the eligibility criteria per Section 4.2). Study sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled, or the reason why the subject failed screening. These data will be entered in the eCRF.

Informed consent must be obtained before completion of any nonstandard of care, study-specific procedures. Procedures that are part of the standard of care such as blood samples or disease stabilizing prior therapy, are not considered study-specific procedures and may be performed before obtaining consent and if relevant used to confirm eligibility. Confirmation of these data must occur within the time allowance as outlined below and in the SOA for each substudy.

The procedures to be completed during the screening period are detailed in the SOA for each substudy.

7.3.1. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the up to 28-day screening period will be permitted to rescreen once. The investigator should consult with the medical monitor about rescreening cases. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days after signing of the original ICF, the assessment or procedure that initially resulted in the subject failing screening will be performed, including any other procedures that fell outside of the designated screening window (eg, laboratory assessments); all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs or leukapheresis is delayed more than 28 days after the signing of the original ICF, the subject must be reconsented and all screening procedures/assessments must be repeated.

7.4. Enrollment

A subject is considered enrolled in the study at commencement of leukapheresis. Subjects must have undergone screening procedures and their results must have been confirmed by the investigator to meet the study eligibility criteria (Section 4.2) at screening. For laboratory tests performed after screening and before initiation of leukapheresis, allowance will be made for expected normal variation of within 5% of laboratory test value cutoffs noted in the inclusion criteria. A subject may not proceed to enrollment if they do not meet the eligibility criteria as indicated during screening and by laboratory tests performed after screening and before the initiation of leukapheresis. If there is a need for a subject to have leukapheresis repeated, they must continue to meet the study eligibility criteria (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria) before the leukapheresis procedure is performed. (The ±5% cutoffs do not apply to the hematological parameters listed in the common inclusion criteria #4 if lower values are attributable to underlying disease).

7.5. Pretreatment Period

7.5.1. Leukapheresis

Leukapheresis is to be performed within approximately 5 days after eligibility confirmation. Refer to Section 3.2.1 for a description and definition of leukapheresis. Before leukapheresis commences, the following criteria must be met:

- In general, all criteria that were confirmed during screening for eligibility must not be known to be violated before leukapheresis, except that allowance will be made for expected normal variation of within 5% of laboratory test value cutoffs noted in the inclusion criteria. Additionally, the investigator must review and confirm that the last CBC with differential and chemistry panel results from the blood draw before the start of leukapheresis meet the criteria detailed in inclusion criterion ±5%. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and the results are outside the criteria listed in Section 4.2 (or outside ±5% of the laboratory test value cutoffs noted in the inclusion criteria), the subject should not be leukapheresed, and the Kite medical monitor must be consulted (The ±5% cutoffs do not apply to the hematological parameters listed in the common inclusion criteria #4 if lower values are attributable to underlying disease).

- Subjects must have no evidence of clinically significant infection before leukapheresis. Should a subject have clinically significant infection immediately before leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed > 5 days after eligibility confirmation, a CBC with differential and chemistry panel must be repeated.

- If the WBC count from a sample collected at the time of leukapheresis is ≥ 20,000 cells/µL, the Kite medical monitor must be consulted before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days before leukapheresis (refer to Section 5.5).

Refer to Section 5.5.1 for medications that are not allowed before leukapheresis occurs.

The procedures/requirements that will occur on the leukapheresis collection day are detailed in the substudy SOAs.

In the event of a manufacturing failure of the CAR T-cell product (eg, the planned number of CAR T cells is not reached or there are observations affecting product safety), the leukapheresis procedure may be repeated.

7.5.2. Bridging Therapy (Optional; for RT and BL Subjects Only)

Bridging therapy (if deemed necessary for disease control) is applicable at the discretion of the investigator to RT and BL subjects only. Please refer to Section 7.2 of the respective substudy protocols for details.

7.5.3. Baseline Disease Assessment Post Bridging (Optional; for RT and BL Subjects Only) and Post-Ibrutinib (Optional; for WM Subjects Only)

For subjects requiring bridging therapy (optional for RT and BL subjects only) or ibrutinib to reduce the risk of BTK inhibitor withdrawal symptoms (optional for WM subjects only), a disease assessment must be performed prior to initiating lymphodepleting chemotherapy to establish a new baseline. This disease assessment will not affect whether to initiate lymphodepleting chemotherapy and infusion of brexucabtagene autoleucel.

7.5.4. Lymphodepleting Chemotherapy

On Day −5 through Day −3 before the administration of brexucabtagene autoleucel, subjects will receive a nonmyeloablative lymphodepleting regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of brexucabtagene autoleucel CAR T cells in vivo.

Subjects will receive the following 3-day chemotherapy regimen per the schedule detailed below:

1) IV hydration with 1 L of 0.9% NaCl given before cyclophosphamide or fludarabine on all 3 days of infusion

2) Cyclophosphamide (500 mg/m^2/day; IV) over approximately 60 minutes on Day −5, Day −4, and Day −3

3) Fludarabine (30 mg/m^2/day; IV) over approximately 30 minutes on Day −5, Day −4, and Day −3

4) An additional 1 L of 0.9% NaCl at completion of the cyclophosphamide or fludarabine infusion on all 3 days of infusion

5) Mesna together with cyclophosphamide (sodium 2-mercaptoethanesulfonate; a detoxifying agent used to inhibit cyclophosphamide induced hemorrhagic cystitis) per institutional guidelines

If, after the start of the lymphodepletion regimen, the creatinine clearance falls below 70 mL/min, subsequent doses of fludarabine will be adjusted according to institutional guidelines.

Lymphodepleting chemotherapy will be supplied by the study site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of described chemotherapy agents.

Subjects should be instructed to drink plenty of liquids both during and for 24 hours following the chemotherapy. In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

Brexucabtagene autoleucel product must be available before initiation of lymphodepleting chemotherapy.

7.5.4.1. Requirements for Initiating Lymphodepleting Chemotherapy and the Brexucabtagene Autoleucel Infusion

Administration of brexucabtagene autoleucel to subjects with ongoing infection or inflammation, even if subjects are asymptomatic, may increase the risk of high-grade and fatal toxicity. All efforts should be made to rule out such conditions before both lymphodepleting chemotherapy and brexucabtagene autoleucel infusion. If any of the following criteria are met before initiation of lymphodepleting chemotherapy or the brexucabtagene autoleucel infusion, the workup listed in Section 7.6.4 must be performed to determine the potential cause if there is no identified source of infection:

- Temperature > 38 ºC within 72 hours before lymphodepleting chemotherapy or the brexucabtagene autoleucel infusion
- CRP ≥ 100 mg/L any time between enrollment to the start of lymphodepleting chemotherapy or the start of the brexucabtagene autoleucel infusion
- WBC count or differential concerning for infectious process between enrollment to the start of lymphodepleting chemotherapy or start of the brexucabtagene autoleucel infusion (eg, WBC ≥ 20,000, rapidly increasing WBC, or differential with a high percentage of segments/bands)

Additionally:

- All eligibility criteria listed in Section 4.2 of the master protocol and substudy protocols must continue to be met before the start of both the lymphodepleting chemotherapy and the start of the brexucabtagene autoleucel infusion. If any screening assessments or procedures are repeated after enrollment (initial confirmation of eligibility) and the results are outside the eligibility criteria listed in Section 4.2 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), then the condition must resolve before proceeding with lymphodepleting chemotherapy or the brexucabtagene autoleucel infusion (the ±5% cutoffs do not apply to the hematological parameters listed in the common inclusion criteria #4, if lower values are attributable to underlying disease or have been impacted by the lymphodepleting chemotherapy)

- Complete history and physical examination, including head, eyes, ears, nose, and throat and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation

- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before lymphodepleting chemotherapy or the brexucabtagene autoleucel infusion (prophylactic use of antimicrobials is allowed)

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per an infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with the infectious disease service (if applicable)

- The most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, polymerase chain reaction [PCR], stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive

- Once the above criteria are met the subject can proceed with lymphodepleting chemotherapy, following the procedures described in Section 7.5.4, and the brexucabtagene autoleucel infusion, following the procedures described in Section 7.6.2 and Section 7.6.3.

7.5.4.2. Lymphodepleting Chemotherapy

The procedures to be completed during Day −5, Day −4 and Day −3 are detailed in the respective substudy SOAs.

7.6. Treatment Period (Day 0 to Day 7)

Assessments and procedures to be performed during the treatment period will be according to the schedule presented in the respective substudy SOAs.

All subjects will be hospitalized during the treatment period from before the brexucabtagene autoleucel infusion (Day 0) until a minimum of 7 days after treatment (Day 7) unless otherwise required by country regulatory agencies (refer to Section 12.4).

All subjects will receive the brexucabtagene autoleucel infusion at a healthcare facility and be monitored daily for a minimum of 7 days after treatment unless otherwise required by country regulatory agencies (refer to Section 12.4).

Central venous access, such as a port or peripherally inserted central catheter, is required for administration of brexucabtagene autoleucel infusion. Catheter care, per institutional guidelines, should be followed.

Brexucabtagene autoleucel infusion is a subject-specific product, and the product must not be infused if the information on the subject-specific label does not match the intended subject's information (eg, subject ID number). The volume of brexucabtagene autoleucel infusion infused, thaw start/stop time, and brexucabtagene autoleucel infusion administration start/stop time must all be noted in the subject's medical record. The product must not be thawed until the subject is ready for the infusion.

Materials and instructions for the thawing, timing, and administering of brexucabtagene autoleucel infusion are outlined in the IPM. The IPM must be reviewed before administration of brexucabtagene autoleucel infusion. Study sites should follow institutional guidelines for the infusion of cell products.

Requirements that need to be met before the initiation of the brexucabtagene autoleucel infusion are described in Section 7.5.4.1.

If the brexucabtagene autoleucel infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy (refer to Section 7.5.4).

7.6.1. Brexucabtagene Autoleucel Premedications (Day 0)

The following pre-brexucabtagene autoleucel infusion medications should be administered approximately 1 hour before infusion of brexucabtagene autoleucel.

- Acetaminophen/paracetamol 500 to 1,000 mg orally (PO) or equivalent
- Diphenhydramine 12.5 to 25 mg IV or 25 mg PO or equivalent

7.6.2. Infusion of Brexucabtagene Autoleucel (Day 0) and Assessments/Procedures to be Performed Before (Days −1 or 0) and After (Days 1 to 7) Infusion

The assessments and procedures performed on the day of administration of brexucabtagene autoleucel, and on additional days during the treatment period, are detailed in the respective substudy SOAs.

7.6.3. Monitoring After Brexucabtagene Autoleucel Infusion

Subjects will remain hospitalized for at least 7 days after the brexucabtagene autoleucel infusion, unless otherwise required by country regulatory agencies (refer to Section 12.4) and will be closely monitored for signs and symptoms of CRS and neurologic events. In addition, the assessments described in the respective substudy SOAs will be performed during this period.

Subjects should not be discharged from the hospital until all brexucabtagene autoleucel-related nonhematologic toxicities resolve to Grade 1 or return to baseline. Subjects may be discharged with noncritical and clinically stable or improving toxicities (eg, renal insufficiency) even if higher than Grade 1, if deemed appropriate by the investigator.

Subjects should remain hospitalized for ongoing brexucabtagene autoleucel-related fever, hypotension, hypoxia, or ongoing neurologic events higher than Grade 1 or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the study site for at least 4 weeks after the brexucabtagene autoleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

Refer to Section 5.4 and Section 5.5 for descriptions of medications that should not be taken before and after the brexucabtagene autoleucel infusion.

7.6.4. Requirements for Workup for Potential Infectious and/or Inflammatory States

For subjects with symptoms and/or clinical findings indicating a potential infectious or inflammatory state, and in the absence of an identified source of infection (eg, line infection or pneumonia on chest x-ray), the minimum workup to be performed before administration of lymphodepleting chemotherapy and/or brexucabtagene autoleucel consists of the following:

- Consult the Kite medical monitor
- Infectious disease service consult (if available)
- Perform computed tomography (CT) imaging of the chest with IV contrast. CT imaging of the abdomen and pelvis with IV contrast should also be considered as clinically indicated. If there is a medical contraindication to contrast, then a non-contrast CT is allowed
- The following must be performed (before initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic × 2 bottles each), urinalysis, and urine culture. Deep/induced sputum culture if clinically indicated
  - All indwelling lines, such as central venous catheters, should be examined for any signs of infection, and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, or metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan or Fungitell®)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus)

- If a CNS process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed

- Any additional sign- or symptom-directed investigation should be performed as clinically indicated

Before proceeding with lymphodepleting chemotherapy and/or the brexucabtagene autoleucel infusion, the above workup must not suggest the presence of an active infection, and all requirements for lymphodepleting chemotherapy and/or the brexucabtagene autoleucel infusion must be satisfied. If the brexucabtagene autoleucel infusion is delayed > 2 weeks following lymphodepleting chemotherapy, the protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy (refer to Section 7.5.4).

If the above workup was triggered due to CRP ≥ 100 mg/L, CRP should be repeated. If CRP continues to increase significantly, an evaluation should be performed for any other potential infectious or inflammatory condition that was not previously evaluated.

7.7. Post-treatment Follow-Up Period

7.7.1. Post-treatment Assessment Visits

Assessments and procedures to be performed during the post-treatment assessment period will be according to the schedule presented in the respective substudy SOAs.

After completing the brexucabtagene autoleucel infusion and being discharged from the hospital, all subjects will be followed during the post-treatment assessment period. Counting from Day 0 (the day of brexucabtagene autoleucel infusion), subjects will return to the clinic for evaluation at the following intervals:

- Day 14 (± 2 days)

- Day 28 (± 3 days)

- Week 8 (± 1 week)

- Month 3 / 6 / 9 / 12 (± 2 weeks)

- Month 18 / 24 (± 1 month)

- Month 30 / 36 / 48 / 60 (± 1 month); WM and HCL substudies only

The procedures to be completed are outlined in the respective substudy SOA.

If the subject is readmitted to the hospital with any brexucabtagene autoleucel-related AE after the initial hospitalization for the brexucabtagene autoleucel infusion, the following samples will be collected on the day of admission, then weekly, and on the day of discharge; samples will be sent to the central laboratory:

- Analytes including cytokines (serum/plasma)
- brexucabtagene autoleucel T cells (PBMCs)

Should the subject fail to return to the clinic for a scheduled protocol-specific visit, study sites will need to make at least 2 attempts by a combination of telephone and (e)mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, the subject will be considered lost to follow-up and no additional contact will be required.

7.7.2. Evaluation Visit After Disease Progression

If a subject's disease progresses, the assessments/procedures listed in the respective substudy SOAs should be followed.

If disease progression is identified at a scheduled visit, the assessments scheduled for that visit will be performed in addition to any additional assessments or procedures listed in the SOA as required for disease progression. If necessary, some of these procedures can be performed at an additional unscheduled visit. If disease progression is identified between scheduled visits, the subject will be asked to attend an unscheduled visit for disease assessment and the procedures listed in the SOA.

Refer to Section 7.7.3 for information on follow-up for subjects whose disease progresses after receiving brexucabtagene autoleucel.

7.7.3. Follow-up Assessments and Procedures for Enrolled Subjects Who Did Not Receive Brexucabtagene Autoleucel or Whose Disease Progressed After Brexucabtagene Autoleucel Treatment

For subjects who are enrolled, but who did not receive brexucabtagene autoleucel or those where progressive disease (PD) has been identified after brexucabtagene autoleucel treatment, the following assessments/procedures will be completed at the time points outlined in the respective substudy SOAs.

- Survival status: Subjects and/or the subject's referring HCP and/or GP may be contacted directly by telephone or email to assess survival status
- Subsequent anticancer therapy (refer to Section 7.11)
- AE/SAE reporting until 30 days after the last study-related procedure (refer to Section 8.6 for safety reporting guidelines)
- Concomitant medication documentation until 30 days after the last study-specific procedure has occurred or until the initiation of new anticancer therapy, whichever occurs first (refer to Section 6.3.12)

- For subjects whose disease progressed after brexucabtagene autoleucel treatment, the following additional procedures are to be completed:
  - SAE reporting for all new malignancies (refer to Section 8.6.1.2)
  - RCR testing (refer to Section 6.3.16.2)
  - If applicable, anti-brexucabtagene antibody testing
- Subjects who were enrolled but did not receive brexucabtagene autoleucel will be followed only until the end of this study (defined in Section 3.4).

7.8. Assessments and Procedures for Subjects with Disease Progression

Subjects with disease progression will undergo the following assessments/procedures, as described in the 'suspected disease progression' section of the respective substudy SOAs.

- Physical examination
- Vital signs
- Disease response assessments
- Local and central laboratory assessments
- Concomitant medications
- AEs and SAEs

7.9. Follow-up Assessments and Procedures for Subjects who Undergo an Allogeneic Stem Cell Transplant after Brexucabtagene Autoleucel Treatment

Subjects who undergo an allogeneic stem cell transplantation will continue in the study and will undergo the following assessments/procedures at the time points outlined in the respective substudy SOAs.

- Disease assessment
- Survival status
- Subsequent anticancer therapy (refer to Section 7.11)
- AE/SAE reporting (refer to Section 8.6 for safety reporting guidelines)
- Concomitant medication documentation (refer to Section 6.3.12)
- RCR testing (refer to Section 6.3.16.2 for details)
- Anti-brexucabtagene antibodies testing, if applicable

7.10. Care After Completion of Participation in the Study

After completion of this study subjects who are infused with brexucabtagene autoleucel will continue in the LTFU study for continued monitoring as described in Section 3.5. Kite will not provide additional care for study subjects after their participation in the study has ended.

7.11. Subsequent Anticancer Therapy

Subsequent anticancer therapy should not be administered unless a subject's disease progression has been documented and confirmed. Subsequent anticancer therapy refers to treatment administered after the brexucabtagene autoleucel infusion that is necessary to treat a subject's disease, such as non-study-specified chemotherapy, immunotherapy, targeted agents, stem cell transplant, radiation therapy, high-dose corticosteroids (other than those defined/allowed in this protocol), and other investigational agents.

Allogeneic transplant therapy (and associated conditioning treatment) will not be counted as a subsequent anticancer therapy.

All anticancer therapy administered to subjects who are enrolled in the study will be recorded in the study eCRF until the end of study (defined in Section 3.4) or, while still a participant in this study, the subject is considered lost to follow up, withdraws consent, or dies.

Any anticancer therapy administered for a new or secondary malignancy should be documented as a concomitant medication and not a subsequent therapy.

After confirmed disease progression and start of subsequent anticancer therapy, no further on-study disease response assessments are required.

7.12. Instructions for Follow-up and Data to be Collected for Subjects Withdrawn From Treatment/Study

If partial withdrawal of consent occurs (defined in Section 4.3), the investigator must discuss with the subject the appropriate process for discontinuation from study treatment or other study-specific procedures and must discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the respective substudy SOA, including the following:

- Survival status, including the cause of death
- Safety reporting, including new malignancies; SAEs related to brexucabtagene autoleucel including, but not limited to, neurologic events, infections, blood or immune disorders, and pregnancies
- Targeted concomitant medications (refer to Table 5, Section 6.3.12)
- Subsequent therapies
- Central laboratory samples (per the respective substudy SOA)

The level of follow-up and method of communication should also be discussed between the research staff and subject and documented in the source documents.

If withdrawal of full consent occurs (defined in Section 4.3), the investigator is to discuss with the subject appropriate procedures for withdrawal from the study. In such cases, the subject data collected up to withdrawal of consent will be retained and included in the analysis of the study and, where permitted by local regulations, publicly available data (eg, death records) can be included after withdrawal of consent.

Please refer to Section 4.3 for additional details.

7.13. Sample Storage

Subject biospecimens, as well as any derivatives from these samples, will be stored for 15 years from the date that the last subject was treated with brexucabtagene autoleucel, in case any protocol-required analyses need repeating. In addition, Kite may conduct analyses on remaining samples to address exploratory research questions related to the mechanism of action of the treatment or disease-related features, for which subjects will be asked to provide consent. Each subject will have the right to have their sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor. The investigator should provide the sponsor the study and subject ID number so that the sample can be located and destroyed. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

8.1. Definitions of AEs and SAEs

8.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or increased blood pressure in a subject with pre-existing hypertension) must be provided.

An AE does not include the following:

- A pre-existing condition that has not worsened during the study or involves an intervention (such as elective cosmetic surgery or a medical procedure) while on study is not considered an AE. Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs.
- Hospitalization for study treatment infusions or study-mandated procedures, or as a precautionary measure per institutional policy are not considered AEs (refer also to Section 8.5).
- The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods is not considered to be an AE. Worsening of signs and symptoms of the malignancy under study are considered AEs.

Refer to Section 8.6.1 for information and instructions for recording and reporting AEs. Refer to Section 8.6.3 for information and instructions for recording and reporting AEs due to disease progression.

8.1.2. Dose Limiting Toxicities

Dose limiting toxicities are defined as shown in Table 6 and Table 7 with onset within the first 28 days after the brexucabtagene autoleucel infusion. Dose limiting toxicities requiring a pause in enrollment are described in Section 8.10.3

Table 6. Dose-limiting Toxicities

Dose-limiting Toxicities	Exceptions
Any brexucabtagene autoleucel related Grade 5 event	• Grade 5 disease progression
Hematologic toxicity Grade 4 does not recover to Grade ≤ 2 by Day 28	• Any hematologic toxicity Grade 4 attributable to underlying disease • Lymphopenia
Grade 3 or 4 thrombocytopenia lasting of any duration if accompanied by Grade 2 or higher bleeding	• None
All brexucabtagene autoleucel related Grade 4 nonhematologic toxicities including opportunistic infections and complications associated with HIV[a]	• None
Any brexucabtagene autoleucel related Grade 3 neurotoxicity including ICANS, regardless of duration	• None
All brexucabtagene autoleucel related Grade 3 nonhematological toxicities lasting ≥ 7 days including opportunistic infections and complications associated with HIV[a]	• Grade 3 fever • Grade 3 aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to Grade 2 or lower within 14 days • Grade 3 nausea and/or anorexia • Grade 3 febrile neutropenia returning to baseline within 2 weeks • Grade 3 insomnia, fatigue, and malaise • Grade 3 infection that improves to Grade 2 or lower within 2 weeks • Grade 3 TLS including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, or hyperuricemia)
All brexucabtagene autoleucel related Grade 3 cardiac and/or pulmonary events of any duration	• Grade 3 cardiac and/or pulmonary events if related to CRS and improves to Grade 2 or lower within 72 hours

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy, CRS, cytokine release syndrome; DLT, dose limiting toxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TLS, tumor lysis syndrome

Notes: Adverse events are graded using the NCI CTCAE v5.0. CRS and ICANS is graded according to the ASTCT consensus grading {Lee 2019}. The severity of individual signs/symptoms of CRS and neurological events will be graded according to NCI CTCAE v5.0 for those signs/symptoms that are not part of the grading scale.

a Infections associated with HIV and AIDS such as (but not exclusive to): Candidiasis of bronchi, trachea, or lungs, extrapulmonary Cryptococcosis, Cytomegalovirus disease (other than liver, spleen or nodes), Histoplasmosis, disseminated or extrapulmonary, Mycobacterium avium complex, kansasii or other species (disseminated or extrapulmonary), Pneumocystis jirovecii pneumonia or complications such as HIV-associated Encephalopathy

Table 7. Recommendations Based on Dose Limiting Toxicities

Number of Subjects With a Dose Limiting Toxicity in a Cohort	Potential Recommendation
0 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and no DLT occurs in the subsequent 3 subjects	If the dose is determined tolerable, then this will be the recommended dose
1 of 3 subjects	Enroll 3 more subjects at the same dose level.
≥ 2 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and ≥ 1 DLT occurs in the subsequent 3 subjects	The lower dose level will be established as the recommended dose (if assessed to be tolerable and recommended by the SRT)

Abbreviations: DLT, dose limiting toxicity; SRT, safety review team

8.1.3. SAEs

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Is fatal
- Is life-threatening (ie, an event that places the subject at immediate risk of death; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of planned hospitalization (refer to Section 8.5 for definition of prolongation of planned hospitalization for this study)
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated admission to a healthcare facility
  - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the planned hospitalization
  - Refer to Section 8.5 for hospitalizations that are not considered to be SAEs.
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another medically important serious event. If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to the NCI CTCAE v5.0; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded in the eCRF.

Progression of the malignancy during the study is not considered to be an SAE; signs and symptoms of disease progression can be considered as SAEs (and documented as being due to disease progression).

Refer to Section 8.6.1.2 for information and instructions for recording and reporting SAEs. Refer to Section 8.6.3 for information and instructions for recording and reporting SAEs due to disease progression.

8.1.4. Targeted Adverse Events and Serious Adverse Events

Targeted AEs/SAEs include neurologic events, hematologic events, infections, graft versus host disease (GVHD) or aggravation of GVHD, autoimmune disorders, and secondary malignancies. Concomitant medications used to treat targeted AEs should be recorded throughout the study.

Although only secondary malignancies are considered as targeted AEs/SAEs, all new malignancies will be reported. New malignancies are defined as the development of any new malignancies occurring after the brexucabtagene autoleucel infusion. A secondary malignancy is defined as a new malignancy suspected to be possibly related to brexucabtagene autoleucel (ie, temporally associated with brexucabtagene autoleucel and without compelling alternate etiologies).

Refer to Sections 8.6.1.1 and 8.6.1.2 for information and instructions for recording and reporting targeted AEs and targeted SAEs, respectively.

8.2. Pregnancies

There is currently no relevant clinical experience with brexucabtagene autoleucel in pregnant or lactating females, and reproductive studies in animals have not been performed. Accordingly, brexucabtagene autoleucel must not be administered to either pregnant females or females who are breastfeeding. Females of childbearing potential must have a negative pregnancy test before enrollment due to the potential for dangerous effects of bridging and/or lymphodepleting chemotherapy on the fetus. Females of childbearing potential should be monitored according to local and country-specific regulations.

Female subjects are recommended to use highly effective contraception (ie, a method with an annual failure rate of < 1%) for at least 12 months after completing lymphodepleting chemotherapy dosing or brexucabtagene autoleucel administration, whichever is longer. Male subjects should not father a child for at least 12 months after completing lymphodepletion chemotherapy dosing or brexucabtagene autoleucel, whichever is longer. Male subjects are recommended to use a condom or practice sexual abstinence during this time, in addition to their female partner using a highly effective method of contraception.

Refer to Section 12.3.2 for a complete list of highly effective contraception methods. Refer to Section 8.9.2.1 for reporting instructions for any pregnancy or lactation cases.

8.3. Clinical Laboratory and Vital Sign Abnormalities

8.3.1. Abnormal Clinical Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or an adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Is associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

8.3.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded in the eCRF.

8.4. Assessments of AE and SAE Severity and Causality

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

8.4.1. Assessment of AE/SAE Severity

The severity of AEs will be graded according to the NCI CTCAE version v5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov). For events that are not listed in the CTCAE (eg, hypogammaglobulinemia), the investigator may grade the severity according to the guidance in Table 8.

Table 8. Severity Grading of AEs

Grade	Clinical Description of Severity
1	Mild, or Asymptomatic or mild symptoms, or Clinical or diagnostic observations only, or Intervention not indicated
2	Moderate, or Minimal, local, or noninvasive intervention indicated, or Limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life-threatening, or Hospitalization or prolongation of hospitalization indicated, or Disabling, or Limiting self-care ADL[b]
4	Life-threatening consequences, or Urgent intervention indicated
5	Death related to AE

Abbreviations: ADL, activities of daily living; AE, adverse event.
a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

8.4.1.1. Grading of CRS and Neurologic Events

Severity of CRS and ICANS events will be graded according to the ASTCT consensus grading {Lee 2019}.

The severity of individual signs/symptoms of CRS and neurologic events will be graded according to the NCI CTCAE v5.0 for those signs/symptoms that are not part of the ASTCT grading scale.

Refer to Section 8.8 for details regarding the management of these toxicities.

8.4.2. Assessment of AE/SAE Relationship to Brexucabtagene Autoleucel and Study Procedures

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) brexucabtagene autoleucel, 2) leukapheresis, 3) bridging therapy, 4) lymphodepleting chemotherapy, or 5) any study-specific procedure. The relationship is indicated by a "related" or "not related" response and entered in the eCRF. In assessing causality, the investigator or qualified subinvestigator will use clinical judgment and the following considerations:

- Not related: Evidence exists that the AE has an etiology other than the IP or study procedure. For SAEs, an alternative causality must be provided (eg, disease progression, concurrent disease[s], concomitant medications, or other)
- Related: There is reasonable possibility that the event may have been caused by the IP or as a result of a study procedure

8.5. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 8.6.1.2. Hospitalization is considered as prolonged when a subject continues in the hospital beyond the study-specific hospitalization period after infusion of brexucabtagene autoleucel.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing medical condition (diagnosed prior to study entry) which was scheduled prior to informed consent / study start
- Hospitalization due to progression of the underlying malignancy (Refer to Section 8.6.3 for instructions on reporting underlying signs/symptoms of the underlying malignancy/disease progression as AEs/SAEs.)

8.6. Investigator Requirements and Instructions for Reporting AEs, SAEs, and Deaths to the Sponsor

8.6.1. Reporting Adverse Events and Serious Adverse Events

The investigator or a delegated and qualified subinvestigator must address the below for AEs/SAEs:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution

- Severity (Section 8.4.1)
- Assessment of relatedness to brexucabtagene autoleucel, lymphodepleting chemotherapy, or study procedures (Section 8.4.2)
- Action taken

Additional relevant data with respect to describing the AE/SAE will be collected in the eCRFs. For AEs/SAEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the eCRF AE form. The exception is for CRS where both the diagnosis and significant signs and symptoms will be captured on the eCRF AE form.

The investigator is expected to follow reported AEs/SAEs until stabilization or resolution. If a subject begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

Refer to Section 8.6.3 for instructions on reporting AEs/SAEs associated with disease progression.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE/SAE. In the event a subject requests to withdraw from protocol-required therapies, study-specific procedures, or the study due to an AE/SAE, the subject should undergo the procedures outlined in the Month 3 visit of the respective substudy SOA.

Refer to Section 8.6.1.1 and Section 8.6.1.2 for additional information on reporting AEs and SAEs, respectively.

8.6.1.1. Reporting AEs

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject during the AE-reporting period described in Table 9. Refer to Section 8.6.3 for instructions on reporting AEs associated with disease progression.

Table 9. Reporting Requirements for AEs

Subjects Who Are Enrolled:	
But Did Not Receive the Brexucabtagene Autoleucel Infusion	**And Received the Brexucabtagene Autoleucel Infusion**
AEs that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study-specific procedure (eg, leukapheresis, bridging chemotherapy, or lymphodepleting chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be reported	AEs that occur from enrollment (ie, commencement of leukapheresis) through 3 months after the brexucabtagene autoleucel infusion or until initiation of another anticancer therapy, whichever occurs first, are to be monitored and reported
	After 3 months, only targeted AEs will be reported through 15 years after the initial brexucabtagene autoleucel infusion, until disease progression, and/or the start of subsequent anticancer therapy, whichever occurs first, and will be recorded in the eCRF • Targeted AEs include neurological events, hematological events, infections, GVHD or aggravation of GVHD, autoimmune disorders, and secondary malignancies[a] — (Note[a]: All new malignancies are to be reported; however, only secondary malignancies are considered as targeted AEs)
	All AEs deemed related to the brexucabtagene autoleucel infusion should be recorded in the eCRF and reported regardless of the study period

Abbreviations: AE, adverse event; eCRF, electronic case report form; GVHD, graft-versus-host disease.
a A new malignancy is defined as the development of any new malignancy, occurring after the brexucabtagene autoleucel infusion. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to brexucabtagene autoleucel (ie, temporally associated with brexucabtagene autoleucel and without compelling alternate etiologies).

8.6.1.2. Reporting SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject during the SAE reporting periods described in Table 10. Refer to Section 8.6.2for instructions on reporting deaths, and Section 8.6.3 for reporting SAEs associated with disease progression.

Table 10. Reporting Requirements for SAEs

Subjects Who Are:	
• Screen Failures • Enrolled but Did Not Receive the Brexucabtagene Autoleucel Infusion	• Enrolled and Received the Brexucabtagene Autoleucel Infusion
For subjects who are screen failures or enrolled but did not receive brexucabtagene autoleucel infusion: All SAEs that occur from signing of the screening ICF through 30 days after the last study-specific procedure (eg, screening procedure, leukapheresis, bridging therapy, or lymphodepleting chemotherapy) or until initiation of subsequent anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported.	All SAEs that occur from signing of the screening ICF through 3 months after the brexucabtagene autoleucel infusion or until initiation of subsequent anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported.
	After 3 months, only targeted SAEs will be reported through 15 years after the initial brexucabtagene autoleucel infusion (reporting will continue after the end of this study within the LTFU/ KT-US-982-5968 trial), until disease progression, or the start of subsequent anticancer therapy, whichever occurs first, and will be recorded in the eCRF. • Targeted SAEs include neurologic events, hematological events, infections, GVHD or aggravation of GVHD, autoimmune disorders, and secondary malignancies[a] — Note[a]: All new malignancies are to be reported; however, only secondary malignancies are considered as targeted SAEs
	All SAEs deemed related to the brexucabtagene autoleucel infusion should be recorded in the eCRF and reported regardless of study period.
	All deaths that occur from signing of the screening ICF. Refer to Section 8.6.2 and Section 8.6.3 for instructions on reporting deaths.

Abbreviations: eCRF, electronic case report form; GVHD, graft-versus-host-disease; ICF, informed consent form; LTFU, long-term follow-up; SAE, serious adverse event.

a A new malignancy is defined as the development of any new malignancy after the brexucabtagene autoleucel infusion; the investigator must assess causality against brexucabtagene autoleucel, lymphodepleting chemotherapy, bridging therapy, or study procedures. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to brexucabtagene autoleucel (ie, plausibly associated with the brexucabtagene autoleucel infusion and without compelling alternate etiologies).

Unless otherwise indicated in Table 10:

- The following must be submitted to Kite via the electronic SAE (eSAE) system within 24 hours after the investigator's knowledge of the event:
  - — All SAEs

- The following events must be submitted as SAEs via the eSAE system within 24 hours after the investigator's knowledge of the event:
  - CRS events Grade 3 or higher
  - Neurologic events Grade 3 or higher
  - All events of cerebral edema
  - All events of HLH/macrophage activation syndrome

If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the paper SAE Report Form and sent via email to the SAE reporting mailbox: PPD. Subsequently, SAEs will be entered into the eSAE system once it becomes available.

After completion of this study and database closure, any relevant information on ongoing SAEs must be submitted to Kite within 24 hours after the investigator's knowledge of the event using the portable document format (PDF) version of the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: PPD.

All SAEs will be reported to the health authorities per local reporting guidelines.

8.6.2. Reporting Deaths

Death must be recorded on the death eCRF if it occurs at any point during the entire duration of the study. Refer to Section 8.6.3 for instructions on reporting deaths associated with the underlying malignancy/disease progression.

All deaths must be recorded on the Death eCRF, but only deaths caused by an AE should be reported as an SAE. For example, in an event of fatal pneumonia, the event should be reported as an SAE of pneumonia and the outcome as fatal. The event or condition that caused or contributed to the fatal outcome should be recorded on the SAE eCRF with entries including the start date of the event and death date as the stop date of the event. Every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Although death is an outcome and not a distinct AE, death may be reported as an SAE (ie, PT = death) when the cause of death is unknown (eg, sudden or unwitnessed death with unknown cause).

Any death occurring after signing of the main study ICF and within 3 months after brexucabtagene autoleucel infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours after the investigator's knowledge of the event. Any death occurring after the 3-month SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment, the brexucabtagene autoleucel infusion, and/or study-required treatments (eg, lymphodepleting chemotherapy).

8.6.3. Reporting Adverse Events, Serious Adverse Events, and Deaths Associated With Disease Progression

Progression of the malignancy ("disease progression") as assessed by the measurement of malignant lesions on radiographs or other methods during the study should not be reported as an AE or SAE.

For situations when an AE or SAE is due to the malignancy under investigation, the sign(s) and symptom(s), including worsening of sign(s) and symptom(s), of the malignancy under study should be reported as an AE/SAE in the appropriate section of the eCRF and the investigator should check the appropriate data field to indicate these signs and symptoms are due to the underlying disease/disease progression.

If the malignancy has a fatal outcome within 3 months after the brexucabtagene autoleucel infusion, the event leading to death must be recorded as an SAE with CTCAE severity of Grade 5 and outcome of "fatal." Within this 3-month period, the death that is due to the underlying disease/disease progression must be reported immediately to Kite as an SAE, as follows:

- If there are no signs and symptoms of alternate underlying disease associated with the death (although the death has been determined to be due to disease progression), the death should be reported immediately to Kite as an SAE with the primary tumor type (eg, "hairy cell leukemia") as the event term.

- If the death is due to a sign or symptom of the underlying disease/disease progression and the sign or symptom is a targeted SAE, then the SAE will be reported as the event term. The investigator should check the appropriate eCRF data field to indicate that these signs and symptoms are due to the underlying disease/disease progression.

8.7. Sponsor Reporting Requirements (Includes Reporting of SAEs and Deaths)

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), EU Regulation (536/2014) and relevant updates, and other country-specific legislation or regulations, Kite may be required to expedite to worldwide regulatory agencies reports of serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Regulation (536/2014), Kite or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs, as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Kite using reference safety information specified in the current IB or relevant local label as applicable.

All investigators will receive a safety notification of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical where this is required by local regulatory agencies and in accordance with the local institutional policy.

8.8. Toxicity Management

8.8.1. Toxicities Associated With Brexucabtagene Autoleucel Treatment

To date, the following important identified risks have been associated with brexucabtagene autoleucel treatment: CRS, neurologic events, cytopenias, infections, and hypogammaglobulinemia. For grading of these toxicities, please refer to Section 8.4.1.1. A guide to the ICE score is presented in Section 12.5.

Management of these toxicities will be performed according to the American Society of Clinical Oncology 2021 guidelines for management {Santomasso 2021} or per the authorized brexucabtagene autoleucel product information in any given country. In accordance with these guidelines, tocilizumab is required to be available for the treatment of CRS.

In addition, the following are considered important potential risks associated with brexucabtagene autoleucel: secondary malignancy, immunogenicity, replication competent retrovirus, tumor lysis syndrome, and aggravation of GVHD. For grading of these toxicities, please refer to Section 8.4.1. Management recommendations of these toxicities can be found in the IB. Tumor lysis syndrome should be managed in accordance with the authorized Tecartus product information and/or institutional guidelines.

As the safety experience with brexucabtagene autoleucel increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the protocol for guidance regarding managing brexucabtagene autoleucel related toxicities.

8.9. Special Situations Reports

8.9.1. Definitions of Special Situations

Special situation reports include all reports of medication error (eg, actual or potential, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy reports [Maternal Pregnancy and Partner Pregnancy]) regardless of an associated AE.

Medication error (actual or potential) is any unintentional error in the prescribing, dispensing, or preparation for administration or administration of an IP while the medication is in the control of a healthcare professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Misuse is defined as any intentional and inappropriate use of an IP that is not in accordance with the protocol instructions or local prescribing information.

An overdose is defined as accidental or intentional administration of a quantity of an IP (eg, lymphodepleting chemotherapy or other study-specified IP) given per administration or cumulatively that is above the maximum recommended dose as per the protocol or product

labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an IP as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Kite IP.

Counterfeit or falsified medicine is defined as any IP with a false representation of 1) its identity, 2) its source, or 3) its history.

8.9.2. Instructions for Reporting Special Situations

8.9.2.1. Instructions for Reporting Pregnancies

Any pregnancy in a female subject enrolled in the study must be reported, regardless of the time after the brexucabtagene autoleucel infusion. If pregnancy occurs in a female partner of a male subject within 12 months after completing lymphodepleting chemotherapy or the brexucabtagene autoleucel infusion, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by Kite. Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance via email: PPD or fax:PPD .

The pregnancy itself or an induced elective abortion to terminate a pregnancy without medical reasons are not considered AEs. Any premature termination of a pregnancy (eg, spontaneous abortion, induced therapeutic abortion due to complications, or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

The pregnant subject or subject partner should receive appropriate monitoring and care until conclusion of the pregnancy. The outcome should be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the LTFU period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance via email: PPD or fax: PPD.

8.9.2.2. Reporting Other Special Situations

All other special situations must be reported on the Special Situations Reporting Form and forwarded to the Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator becomes aware of the situation. These reports must consist of situations that involve study drug and/or Kite concomitant medications but do not apply to non-Kite concomitant medications.

Special situations involving non-Kite concomitant medications do not need to be reported on the Special Situations Reporting Form; however, special situations that result in AEs due to a non-Kite concomitant medication must be reported as an AE.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse" but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE Report Form. Details of the symptoms and signs, clinical management, and outcome of the AEs or SAEs will be reported, when available. Refer to Section 8.6 and the eCRF completion guidelines for instructions on special situation reporting.

8.10. Safety Review Team, Data Safety Monitoring Board, and Criteria to Pause Enrollment

8.10.1. Safety Review Team

An SRT, comprising the study sponsor and at least 1 study investigator, will be specifically chartered to review the safety data and make recommendations on further study conduct, progression, and/or dose modification in each substudy after 3 to 6 subjects have been treated with the initial dose (2×10^6 anti-CD19 CAR T cells/kg of body weight or a maximum flat dose of 2×10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg) and followed for 28 days. In accordance with the rules defined in Table 7, the SRT can recommend to i) proceed with the starting dose; ii) include an additional 3 subjects for evaluation prior to recommending dose; or iii) recommend the remaining patients to be dosed with 1×10^6 anti-CD19 CAR T cells/kg or a maximum flat dose of 1×10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg (with a subsequent SRT to be held after at least 3 subjects have been treated and followed for 28 days). Enrollment will be paused to allow the SRT to review safety data that have been acquired for 28 days post infusion in all treated subjects in a DLT cohort, prior to providing a recommendation on the continued dose selection. Enrollment will re-start once the dose recommendation is available. Only subjects treated with the selected target dose will be included in the evaluable subject population for the primary analysis.

Initially, 1 subject will be enrolled and infused in each substudy. No additional subjects will be enrolled until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects in each substudy can be enrolled in parallel. After these initial 3 subjects in an individual substudy have been evaluated for at least 28 days, the Safety Review Team will make recommendations on further substudy conduct.

The SRT recommendations will be formally communicated to the participating study sites.

8.10.2. Data Safety Monitoring Board

An independent DSMB will be chartered to review safety and futility data throughout the study duration to make study conduct recommendations based on an analysis of risk versus benefit after the target dose of 2 x 10^6 or 1 x 10^6 anti-CD19 CAR T cells/kg (or for subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells or 1 x 10^8 anti-CD19 CAR T cells if dose reduction is required) for each substudy is confirmed by the SRT. The DSMB will review safety and efficacy data against the non-binding futility rules as described in each substudy protocol. The DSMB will review data accruing from each substudy and provide ongoing recommendations on study conduct to the Kite Head of Cell Therapy Clinical Development (or designee). Moreover, the DSMB will be provided with all available data on the serious adverse events (SAEs; listings or narratives) and suspected unexpected serious adverse reactions (SUSAR) from the global safety database for review prior to implementing the SRTs dose recommendations.

8.10.3. Criteria to Pause Enrollment

As part of its oversight of the study, the DSMB will continuously assess whether to continue, pause or stop the study. Considering the biological heterogeneity of the indications under investigation, pausing enrollment to each substudy will occur independently.

In the SRT phase (that includes the treatment of the initial 3 or 6 subjects), any Grade 5 adverse event that is related to brexucabtagene autoleucel treatment will trigger a pause in enrollment.

Moreover, enrollment will be paused following the treatment of the 3 subjects constituting a DLT cohort, to assess the frequency of DLTs and to allow the SRT to review 28 days of data post infusion in all treated subjects prior to providing a recommendation on the target dose.

After the pivotal dose has been confirmed, enrollment within a substudy will be paused if:

A Grade 5 brexucabtagene autoleucel-related AE occurs

or

Subject incidence of the following Grade 4 brexucabtagene autoleucel-related AEs is ≥ 33%:

- ICANS (graded according to the ASTCT consensus grading {Lee 2019})
- CRS (graded according to the ASTCT consensus grading {Lee 2019})
- Other non-hematological Grade 4 SAEs
- Infection (treatment-related)

Additionally, study enrollment will be paused when the required number of subjects have been enrolled in the planned interim analyses for each substudy, until the data from this interim analysis have been assessed.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis Plan

An overview of the statistical considerations is provided below, with additional details for each indication described in the corresponding substudy protocols.

Details of the statistical analysis plan (SAP) are provided in the SAP document.

Note: Substudies in WM and HCL were terminated early by the Sponsor, effective 21 June 2023. No analyses will be conducted on these 2 substudies.

9.2. Hypothesis

Brexucabtagene autoleucel will improve the disease response rates compared with pre-specified historical control data as described within each substudy.

9.3. Definition of Study Endpoints

9.3.1. Definitions of Primary Endpoints

Primary endpoints are substudy specific and are described in the respective substudy protocols.

9.3.2. Definition of Secondary Endpoints

Definitions of secondary endpoints shared across the substudies are detailed in Table 11, additional substudy specific secondary endpoints are described in the respective substudy protocols.

Table 11. Definitions of Secondary Endpoints

Secondary Endpoint	Definition
DOR	DOR is derived only among subjects who experience an objective response. It is defined as time from first objective response to disease progression per indication specific response criteria or death from any cause. Subjects who do not meet the criteria for disease progression and who have not died will be censored at the last evaluable disease assessment.
PFS	Time from enrollment (for FAS) or brexucabtagene autoleucel infusion (for mITT) to disease progression per indication specific response criteria or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. FAS and mITT are defined in Section 9.6.5.1 (Table 13)

Secondary Endpoint	Definition
OS	Time from enrollment (for FAS) or brexucabtagene autoleucel infusion (for mITT) to death from any cause.
TTNT	Time from enrollment (for FAS) or brexucabtagene autoleucel infusion (for mITT) to initiation of next anticancer treatment
Time to first response	Time from enrollment (for FAS) or brexucabtagene autoleucel infusion (for mITT) to first objective response
Complete Response (CR)	CR rate by central assessment as defined in each substudy
Time to best response	Time from enrollment (for FAS) or brexucabtagene autoleucel infusion (for mITT) to best objective response
Changes over time in the PRO assessment domains, EORTC-QLQ-C30 and ED-5D-5L	Changes in EORTC QLQ-C30 and EQ-5D-5L domains from baseline to post baseline
Incidence of AEs and CTCAE grade changes in safety laboratory values	
Incidence of dose limiting toxicities	Incidence of AEs defined as dose limiting toxicities (Table 6)
Incidence of antibodies against brexucabtagene autoleucel (immunogenicity)	The presence of anti-FMC63 antibodies, where FMC63 is the parent antibody for the single-chain variable fragment that is used for production of brexucabtagene autoleucel. The presence of antibodies against a properly folded-FMC63 CAR protein will be assessed before and after infusion of brexucabtagene autoleucel. These antibodies are referred to as anti-brexucabtagene autoleucel antibodies.

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CTCAE, common terminology criteria for adverse events; DOR, duration of response; EORTC-QLQ-C30, European organization for research and treatment of cancer quality of life questionnaire C30 version 3.0; EQ-5D-5L, European quality of life 5-dimension 5-level scale; =FAS, full analysis set; mITT, modified intent to treat; OS, overall survival; PFS, progression free survival; PRO, patient-reported outcome; TTNT, time to next treatment

9.3.3. Definition of Other Endpoints of Interest

Definitions of other endpoints of interest are detailed in Table 12.

Table 12. Definitions of Other Endpoints of Interest

Other Endpoints of Interest	Definition
Incidence of RCR	Incidence of RCR will be assessed before and after infusion of brexucabtagene autoleucel. Frequency and percentage will be presented.
Levels of anti-CD19 CAR T cells in blood and relationship with clinical outcomes (efficacy and toxicity)	Presence, expansion and persistence of CAR T cells in blood will be monitored following infusion with brexucabtagene autoleucel at time points detailed in the substudy SOAs.
Serum analytes (including cytokines and chemokines)	Concentration of serum analytes (including those listed in Section 6.7) before and after infusion of brexucabtagene autoleucel. Possible associations with clinical outcome will be investigated and summarized.
Circulating B-cell levels	Circulating levels of B cells before and after infusion of brexucabtagene autoleucel and the association with pharmacokinetics will be investigated and summarized.
T-cell product characteristics	T-cell phenotypes and relationship with clinical outcome. Possible association with efficacy and toxicity readouts of interest (eg, response rates, CRS and Neurotoxicity) will be investigated and summarized.
Incidence of T-cell reactivity against brexucabtagene autoleucel CAR (T-cell Immunogenicity)	Presence of endogenous T-cell reactivity against the FMC63 CAR will be assessed before and after infusion of brexucabtagene autoleucel as detailed in the substudy SOAs; results will be tabulated.

Abbreviations: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; RCR, replication competent retrovirus; SOA, schedule of assessments

9.4. Determination of Sample Size

Sample size determinations are substudy specific and are described in the respective substudy protocols.

The power estimation and statistical inference are based on the mITT population as defined in Section 9.6.5.1 (ie, the subjects who are enrolled and treated with brexucabtagene autoleucel, with measurable disease at baseline (or post-bridging therapy, if applicable)).

9.5. Access to Individual Subject Treatment Assignments and Minimization of Bias

This is an open-label study, and subjects and investigators will be aware of the treatment received. Data handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the SAP, SRT charter, DSMB charter, and Trial Integrity Document.

9.6. Planned Analyses

9.6.1. Interim Analysis and Early Stopping Guidelines

An interim analysis and futility assessment will be conducted in each substudy and is described in the substudy protocols. The interim analysis data will be reviewed by the DSMB taking into account the complete benefit/risk profile of brexucabtagene autoleucel. The sponsor will decide if the substudies should be stopped early based on DSMB recommendation and the overall assessment of risk and benefit. Study enrollment will be paused to allow time for the interim analyses.

Details regarding the planned interim analysis and the non-binding futility rule for each of the substudies are provided in the respective substudy protocols.

9.6.2. Primary Analysis

Details regarding the primary analyses for the substudies are provided in the respective substudy protocols.

9.6.3. Final Analysis

The final analysis will occur when all subjects have completed the study. Details regarding the final analyses for the substudies are provided in the respective substudy protocols.

9.6.4. Long-term Data Analysis

All subjects receiving the brexucabtagene autoleucel infusion will be followed for survival for up to approximately 15 years after the brexucabtagene autoleucel infusion (refer to Section 3.4 and Section 3.5).

After the primary analysis, additional follow-up analyses of efficacy and safety may be performed as needed to satisfy regulatory requirements.

9.6.5. Analysis Conventions

9.6.5.1. Analysis Sets

The analysis sets that will be used to analyze study data within each substudy are detailed in Table 13.

Table 13. Analysis Sets

Analysis Set	Definition
ITT (Full analysis) set	• Consists of all enrolled subjects (ie, the subjects who had leukapheresis). The full analysis set will be used for summaries of subject disposition, as well as analyses on the key efficacy endpoints (disease response rate, DOR, PFS, and OS).
mITT analysis set	• Consists of all subjects enrolled and treated with the pivotal dose of brexucabtagene autoleucel, with measurable disease at baseline (or post-bridging therapy, if applicable). The mITT analysis set will be used for all efficacy analyses unless otherwise specified.
DLT-evaluable set	• Consists of first 3 subjects treated. If 1 of these subjects experience a DLT within 28 day of brexucabtagene autoleucel infusion, an additional 3 subjects will be included in the DLT-evaluable set.
Safety analysis set	• Consists of all subjects treated with any dose of brexucabtagene autoleucel. This analysis set will be used for all analyses of safety.

Abbreviations: DLT, dose-limiting toxicity; DOR, duration of response; mITT, modified intent-to-treat; OS, overall survival; PFS, progression-free survival.

9.6.5.2. Data Handling Convention

Every effort will be made to obtain complete data for all important endpoints. In the case of missing data, missing values will be imputed or censored using appropriate statistical approaches with sensitivity analysis. More detail will be provided in the SAP.

9.7. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age.

9.8. Efficacy Analysis

The efficacy analysis using disease assessment data (eg, disease response rates, DOR and progression-free survival [PFS]) will be conducted based on central assessment; the disease response rate and key secondary endpoints such as DOR, PFS, and overall survival (OS) analysis will also be conducted based on investigator assessment.

9.8.1. Disease Response Rate

The primary endpoint on incidence of disease response and exact 2-sided 95% confidence intervals (CIs) will be generated for mITT and full analysis set (FAS) subjects. An exact binomial test will be used to compare the observed response rates per central assessment to the historical response rate as described in each substudy. The statistical inference on the efficacy evaluation of brexucabtagene autoleucel will be based on the mITT set. The disease response rate analysis will also be conducted using investigator assessment.

9.8.2. Best Objective Response

The incidence of subjects with CR, very good PR (for WM only), PR, table disease, PD, and not evaluable as the best response to treatment and exact 2-sided 95% CIs about the incidence will be generated for mITT and FAS subjects.

9.8.3. Duration of Response

Kaplan-Meier (KM) estimates and 2-sided 95% CIs will be generated for the DOR for the subjects who responded to brexucabtagene autoleucel. The DOR will be derived using disease assessments obtained on study before initiation of a new anticancer therapy (including stem cell transplant). Subjects who do not meet the criteria for disease progression and who have not died will be censored at the last evaluable disease assessment. Disease assessments obtained after new anticancer therapies (including stem cell transplant) will not contribute to the derivation of DOR. Such subjects will have DOR censored at the last evaluable disease assessment prior to the commencement of the anticancer therapy or stem cell transplant. For subjects who undergo stem cell transplant while in remission, a supplementary analysis will be conducted in which disease assessments obtained after stem cell transplant are included in the derivation of DOR.

9.8.4. Progression-free Survival

KM estimates and 2-sided 95% CIs will be generated for PFS time for both mITT and FAS subjects. Estimates of the proportion of subjects alive and progression free at 3-month intervals will be provided. PFS will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (including stem cell transplant). Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. For subjects who undergo stem cell transplant while in remission, a supplementary analysis will be conducted in which disease assessments obtained after stem cell transplant are included in the derivation of PFS.

9.8.5. Overall Survival

KM estimates and 2-sided 95% CIs will be generated for OS for both mITT and FAS subjects. Estimates of the proportion of subjects alive at 3-month intervals will be provided. Subjects who have not died by the analysis data cutoff date will be censored at their last known alive date.

9.9. Safety Analysis

Subject incidence rates of treatment-emergent AEs (TEAEs), defined as AEs with an onset on or after the brexucabtagene autoleucel infusion, will be summarized. TEAEs including all, serious, fatal, Grade 3 or higher (per CTCAE v5.0) will be tabulated by preferred term and/or system organ class. CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized descriptively. Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities.

Tables and/or narratives of deaths through the post-treatment follow-up and treatment-related SAEs will be provided.

9.10. Multiplicity Adjustment

No multiplicity adjustments will be made.

9.11. Pharmacokinetics Analysis

Results and summary statistics (eg, peak and area under the curve from Day 0 to Day 28) will be tabulated. Possible association with efficacy and toxicity readout of interest (eg, ORR, CRS and Neurotoxicity) will be investigated and summarized. The relationship with levels of CAR T cells (pharmacokinetics) and efficacy readouts (eg, disease response rate, CR rate and Ongoing Response Rate) will be summarized and tabulated.

9.12. Pharmacodynamics Analysis

Results and summary statistics will be tabulated. Possible association with toxicity readouts of interest (eg, CRS and neurotoxicity) will be investigated and summarized.

9.13. Patient-reported Outcome Analysis

Changes in EORTC QLQ-C30 domains, EQ-5D-5L index, and visual analog scale (VAS) scores from screening will be summarized with descriptive statistics. In addition, the mean/median changes in EORTC QLQ-C30 domains, EQ-5D-5L index, and VAS scores from screening over time will be presented with plots.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the IP during the course of a clinical study. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Kite of any change in reportable interests during the study and for 1 year after completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

10.1.2. IRB/IEC Approvals

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each study site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the study, investigators are to submit site-specific and study SAEs (provided to the study site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

10.1.3. Informed Consent

Before a subject can participate in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and potential risks. The consent process and subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the most current IRB/IEC-approved ICF is to be signed and personally dated by the subject and person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with the institution's policy and IRB/IEC requirements, and a copy of the ICF will be provided to the subject.

All subjects who are enrolled into the study should be reconsented with any updated version of the IRB/IEC-approved ICF if relevant to their participation in the study.

The ICF will inform subjects about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or allow the use of the remainder of their already collected specimens for optional future genomic research, in accordance with applicable regulations. The results of the tests done on the samples will not be given to the subject or investigator, given that the results do not inform clinical decision making.

10.1.4. Confidentiality

The investigator must assure that the subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an ID code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Kite or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded for the proper subject (refer to specific laboratory instructions for further information). Subject data will be processed in accordance with all applicable regulations.

Kite has established processes in place to ensure the security and confidentiality of data records and personal information. This includes: restricting access, via secure login information for individual authorized users, to electronic personal data and study data systems; pseudonymization of trial subject data; encryption of all personal data in transit and at rest; and a robust data privacy and security due diligence process with third party vendors, which includes a written contract with each vendor to abide by privacy and security obligations. Processes are also in place to avoid loss of information. Should a data security breach occur, Kite will follow their relevant SOPs to mitigate the impact. Kite will abide by all available National and International data protection legislation. Further details on what personal data are collected, where they are stored, how they are processed and who will have access is described in the study country specific patient information sheets.

The investigator agrees that all information received from Kite, including but not limited to the IB, this protocol, eCRFs, the study drug, and any other study information, remain the sole and exclusive property of Kite during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Kite. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Per federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/GCP guidelines, investigators and institutions are required to permit direct access to the sponsor, CRO, IRB/IEC, and regulatory agencies to a subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which include personal information.

Subject confidentiality must be maintained on all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique ID number.
- Year of birth/age at time of enrollment will be reported according to local laws and regulations.

For the reporting of SAEs, subjects will be identified by their respective subject ID number and year of birth (as per their local reporting requirements).

10.1.5. Study Files and Retention of Records

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfill these responsibilities should be outlined and included in the delegation of authority form.

Source documents are original documents, data, and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence, and death registries.

The investigator and study staff are responsible for maintaining a comprehensive filing system of all subject records that are readily retrieved to be monitored and/or audited at any time by the key sponsor contact (or delegate), regulatory authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject ID lists
- Essential documents for the conduct of this clinical study
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence.

Original source documents supporting entries into eCRFs must be maintained at the study site and readily available upon request. No study documents should be discarded without prior written agreement between Kite and the investigator. Should storage no longer be available to archive source documents or need to be moved to an alternative location, the research staff should notify the key sponsor contact before shipping the documents.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject ID
- Documentation that the subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in the study (including study number/name)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of the IP, including the start and stop times of the brexucabtagene autoleucel infusion
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medications (including the start and end dates, dose [if relevant], and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

Traceability records for the product, from procurement through manufacture to administration of the product, should be kept by each relevant party (eg, the sponsor and investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with Kite. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and subject information at the study site to the product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject transfers to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

10.1.6. Electronic Case Report Forms

All data will be collected in an eCRF system. All entries must be completed in English and concomitant medications should be identified by trade names. For further details surrounding the completion of eCRFs, refer to the eCRF completion guidelines.

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the respective substudy SOA and procedures. The eligibility criteria and enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF completion guidelines provided by the sponsor.

Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Kite staff who routinely review the data for completeness, correctness, and consistency. The study site investigator or coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry and providing the reason for the update (eg, data entry error). Original entries, as well as any changes to data fields, will be stored in the audit trail of the system. At a minimum, before any interim time points or database lock (as instructed by Kite), the investigator will use his/her log-in credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents.

At the conclusion of the study, Kite will provide the study site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 10.1.5.

10.1.7. Access to Study Information

The investigator will make available all source documents and other records for this study to Kite's appointed study monitors, IRBs/IECs, or regulatory or health authority inspectors. By signing the investigator statement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits, audits, and regulatory authority inspections.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Kite. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented approval before modifications can be implemented. Documentation acknowledging agreement with the protocol amendment from the investigator and approval from the IRB/IEC are to be submitted to the key sponsor contact.

10.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Kite will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following EU Regulation No. 536/2014, a CSR will be submitted within 1 year after the global end of study (defined in Section 3.4).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Kite clinical trial agreement.

10.2.3. Financing and Insurance

Kite has insurance that provides compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Kite will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Good Clinical Practice

The investigator, sponsor, and sponsor delegates will ensure that this study is conducted in accordance with ICH GCP guidelines, including the E6(R2) addendum for GCP, and applicable laws and regulations.

10.3.2. Quality Control and Quality Assurance

The key sponsor contact, monitors, auditors, or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records to assure that subject confidentiality is respected.

The monitor is responsible for source document verification of eCRF data at regular intervals during the study. Protocol adherence and accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed.

In accordance with ICH GCP and the audit plan, a study site may be chosen for a Kite Quality Assurance site audit. A Kite Quality Assurance site audit would include, but is not limited to, an inspection of the facility(ies), review of subject and study-related records, and compliance with protocol requirements, as well as ICH GCP and applicable regulatory policies. Investigators will provide Kite Quality Assurance auditors access to subject records.

Representatives of regulatory authorities may conduct inspections of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Ethics

Study KT-US-568-0138 will be conducted under a US Investigational New Drug application or equivalent and in accordance with recognized international scientific and ethical standards, including but not limited to the ICH guideline for GCP and original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US CFR Title 21, Part 312, and EU Regulation (2001/2014), as well as other local legislation.

10.3.4. Study Discontinuation

Both Kite and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination.

11. REFERENCES

Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984;63 (6):1424-33.

Becnel MR, Nastoupil LJ, Samaniego F, Davis RE, You MJ, Green M, et al. Lenalidomide Plus Rituximab (R(2)) in Previously Untreated Marginal Zone Lymphoma: Subgroup Analysis and Long-Term Follow-up of an Open-Label Phase 2 Trial. Br J Haematol 2019;185:874-82.

Berger F, Traverse-Glehen A, Felman P, Callet-Bauchu E, Baseggio L, Gazzo S, et al. Clinicopathologic features of Waldenstrom's macroglobulinemia and marginal zone lymphoma: are they distinct or the same entity? Clin Lymphoma 2005;5 (4):220-4.

Chen B, Fend F, Campo E, Quintanilla-Martinez L. Aggressive B-cell lymphomas—from morphology to molecular pathogenesis. Annals of Lymphoma 2019;3 (1).

Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 21, 2020.

Davila ML, Sadelain M. Biology and clinical application of CAR T cells for B cell malignancies. International Journal of Hematology 2016.

Fallowfield LJ, Baum M, Maguire GP. Do psychological studies upset patients? Journal of the Royal Society of Medicine 1987;80 (1):59.

Finney HM, Lawson AD, Bebbington CR, Weir AN. Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product. J Immunol 1998;161 (6):2791-7.

Fridericia LS. The Duration of Systole in an Electrocardiogram in Normal Humans and in Patients with Heart Disease. Ann Noninvasive Electrocardiol 2003;8 (4):343-51.

Gattinoni L, Klebanoff CA, Palmer DC, Wrzesinski C, Kerstann K, Yu Z, et al. Acquisition of full effector function in vitro paradoxically impairs the in vivo antitumor efficacy of adoptively transferred CD8+ T cells. J Clin Invest 2005;115 (6):1616-26.

Grunenberg A, Buske C. Treatment options for relapsed Waldenström's Macroglobulinemia. HemaSphere 2019;3 (S2):65-7.

Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. Nat Rev Clin Oncol 2016;13 (6):370-83.

Jacobson C, Locke FL, Ghobadi A, Miklos DB, J. LL, Oluwole OO, et al. Long-Term (4-and 5-Year) Overall Survival in ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel in Patients with Refractory Large B-Cell Lymphoma [Presentation]. 63rd American Society of Hematology (ASH) Annual Meeting and Exposition; 2021a December 11; Atlanta, GA & Online.

Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2021b.

Kochenderfer JN, Feldman SA, Zhao Y, Xu H, Black MA, Morgan RA, et al. Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor. J Immunother 2009;32 (7):689-702.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-38.

Nadler LM, Anderson KC, Marti G, Bates M, Park E, Daley JF, et al. B4, a human B lymphocyte-associated antigen expressed on normal, mitogen-activated, and malignant B lymphocytes. J Immunol 1983;131 (1):244-50.

Neelapu S, Locke F, Bartlett N, Lekakis L, Miklos D, Jacobson C, et al. Axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL): primary results of the pivotal trial ZUMA-1. International Conference on Malignant Lymphoma (ICML) 2017a.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017b;377 (26):2531-44.

Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol 2012;12 (4):269-81.

Rinaldi A, Mian M, Chigrinova E, Arcaini L, Bhagat G, Novak U, et al. Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome. Blood 2011;117 (5):1595-604.

Roberts KG. Genetics and Prognosis of ALL in Children vs Adults. Am Soc Hematol 2018;2018 (1):137-45.

Rossi D, Spina V, Gaidano G. Biology and treatment of Richter syndrome. Blood 2018;131 (25):2761-72.

Ruella M, Maus MV. Catch Me If You Can: Leukemia Escape after CD19-Directed T Cell Immunotherapies. Comput Struct Biotechnol J 2016;14:357-62.

Ruella M, Xu J, Barrett DM, Fraietta JA, Reich TJ, Ambrose DE, et al. Induction of Resistance to Chimeric Antigen Receptor T Cell Therapy by Transduction of a Single Leukemic B Cell. Nat Med 2018;24:1499-503.

Santomasso BD, Nastoupil LJ, Adkins S, Lacchetti C, Schneider BJ, Anadkat M, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol 2021;39 (35):3978-92.

Short NJ, Kantarjian HM, Ko H, Khoury JD, Ravandi F, Thomas DA, et al. Outcomes of adults with relapsed or refractory Burkitt and high-grade B-cell leukemia/lymphoma. Am J Hematol 2017;92 (6):E114-E7.

Sun R, Medeiros LJ, Young KH. Diagnostic and predictive biomarkers for lymphoma diagnosis and treatment in the era of precision medicine. Mod Pathol 2016;29 (10):1118-42.

TECARTUS, Kite Pharma Inc. TECARTUS® (brexucabtagene autoleucel) suspension for intravenous infusion. U.S Prescribing Information. Santa Monica, CA. Revised October. 2021:

Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med 2015;373 (18):1733-47.

Uckun FM. Regulation of Human B-Cell Ontogeny. Blood 1990;76 (10):1908-23.

Uckun FM, Jaszcz W, Ambrus JL, Fauci AS, Gajl-Peczalska K, Song CW, et al. Detailed Studies on Expression and Function of CD19 Surface Determinant by Using B43 Monoclonal Antibody and the Clinical Potential of Anti-CD19 Immunotoxins. Blood 1988;71 (1):13-29.

YESCARTA, Kite Pharma Inc. YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion. U.S. Prescribing Information. Santa Monica, CA. Revised April. 2021:

12. APPENDICES

12.1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies

Amendment 3.0, 17 AUGUST 2023

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

See appended electronic signature	See appended electronic signature
Kite Medical Monitor Name (Printed)	Signature
See appended electronic signature	
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner, and dependent children)
- Subinvestigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed)	Signature
Date	Study Site Number

12.2. Schedules of Assessment

The assessments and procedures to be performed during the treatment and post-treatment follow-up periods are presented in the schedule of assessments in Section 12 of each substudy protocol.

12.3. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trial Facilitation Group (CTFG) {Clinical Trials Facilitation and Coordination Group (CTFG) 2020} together with requirements from Kite, as described in the following sections.

12.3.1. Definition of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

12.3.2. Birth Control Methods That May Be Considered as Highly Effective

Methods that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[a] when used together with barrier contraceptives (condoms or diaphragm with spermicide):
  - —Oral
  - —Intravaginal
  - —Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a] when used together with barrier contraceptives (condoms or diaphragm with spermicide):
  - —Oral
  - —Injectable

[a] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method. Hormonal contraceptives are only assessed as an appropriate contraceptive measure if used simultaneously with barrier contraceptives (condoms or diaphragm with spermicide).

  - Implantable[b]

- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b,c]
- Sexual abstinence[d]

12.3.3. Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.
[c] A vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
[d] 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 study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and preferred and usual lifestyle of the subject.

12.4. Country-specific Regulatory Agency Requirements

12.4.1. Requirement for a Multidisciplinary Consultation Meeting Before Subject Inclusion in France

In accordance with Agence nationale de sécurité du médicament et des produits de santé (ANSM) requirements, a multidisciplinary team is required to consult prior to inclusion of a subject in the trial.

12.4.2. Post-infusion Monitoring

12.4.2.1. For All European Union Countries

The post-infusion monitoring of subjects, described in Section 7.6.3 of this protocol, will be extended by monitoring on Days 8, 9, and 10, according to the procedures outlined in the substudy schedule of assessments, “treatment period” column. The subject may remain hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator. Daily monitoring will include vital signs (refer to Section 6.3.5), blood draw for chemistry panel with C-reactive protein, blood draw for complete blood count with differential, and neurological examination (refer to Section 6.3.6). Any observed toxicity will be managed according to instructions detailed in Section 8 of this protocol.

12.4.2.2. For Switzerland

All subjects in Switzerland will be hospitalized during the treatment period from before the brexucabtagene autoleucel infusion (Day 0) until a minimum of 10 days after treatment (Day 10). Subjects will be monitored post-infusion as described in Section 7.6.3.

12.4.3. Pregnancy testing

Females of childbearing potential should be monitored according to local and country-specific regulations.

For EU/CH study sites, a pregnancy test will be completed within 7 days before both leukapheresis and lymphodepleting chemotherapy for women of childbearing potential.

12.5. Immune Effector Cell-associated Encephalopathy Score

A guide to the immune effector cell-associated encephalopathy score is presented in Table 14.

Table 14. Immune Effector Cell-associated Encephalopathy Score[a]

Task		Score
Orientation:	Orientation to year, month, city, and hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, or button)	3 points
Following commands:	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing:	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

a Immune effector cell-associated encephalopathy score as developed by the American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells {Lee 2019}.

12.6. Patient-reported Outcomes

All patient-reported outcomes described are expected to be completed by the subject before any procedures are performed, excluding blood draws, and at the time points noted in the respective substudy.

12.6.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 Version 3.0

This measure is a 30-item questionnaire designed to provide a multidimensional assessment of health-related quality of life (HRQoL), with a recall period of 1 week. The European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire (EORTC QLQ-C30) version (v)3.0 includes the following scales:

- 5 multi-item functional scales (assessing physical, role, emotional, cognitive, and social functioning) and 3 symptom scales (fatigue, nausea and vomiting, and pain)
- 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)
- 2 global scales (Global Health Status and HRQoL)

No items are shared between the scales. The first 28 of 30 items have 4-level ordinal responses from 1 (“not at all”) to 4 (“very much”). The final 2 items, comprising the global health status and HRQoL scale, have 7-level ordinal responses from 1 (“very poor”) to 7 (“excellent”). Each scale is measured from 0 to 100 after a linear transformation. Higher scores for functional scales and the Global Health Status or Global HRQoL scales indicate a higher level of functioning and a better HRQoL, respectively, whereas higher scores in symptom scales represent a higher level of symptoms.

This instrument does not sum together all items, which can potentially group differences and allows an assessment of change across the 15 different domains. In its current version (v3.0), the questionnaire takes approximately 11 minutes to complete.

12.6.2. European Quality of Life 5-dimension 5-level Questionnaire

The European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) is a generic measure of health status captured on the day of assessment. Two components comprise the EQ-5D-5L: the EQ-5D descriptive system and the EQ visual analog scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is divided into 5 levels of severity: “no problems”, “slight problems”, “moderate problems”, “severe problems”, and “extreme problems”.

The EQ-5D-5L VAS is a vertical VAS for recording self-rated current HRQoL state reported from 0, described as “the worst health you can imagine”, to 100, described as “the best health you can imagine”.

The EQ-5D-5L takes approximately 5 minutes to complete.

12.7. Practical Body Weight Calculation for Subjects Whose Body Mass Index (BMI) is > 35 kg/m^2

Dose calculation based on actual or practical body weight is as follows:

- Actual body weight at leukapheresis is to be used for brexucabtagene autoleucel. For subjects weighing > 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells will be administered.
- Actual body weight is to be used for lymphodepleting chemotherapy and mesna when the subject's body mass index (BMI) is ≤ 35 kg/m^2.
- Practical body weight is to be used for lymphodepleting chemotherapy and mesna when the subject's BMI is > 35 kg/m^2. See formula below.

BMI determination:

- BMI = weight (kg)/[height (m)]^2 or
- BMI = 703 × weight (lb)/[height (in)]^2

Calculation of ideal body weight:

- Male = 50 kg + 2.3 (number of inches over 60 inches)
  - Example: ideal body weight of 5'10" male
  - 50 + 2.3 (10) = 73 kg
- Female = 45.5 kg + 2.3 (number of inches over 60 inches)
  - Example: ideal body weight of a 5'3" female
  - 45.5 + 2.3 (3) = 52.4 kg
- Calculation of "practical weight": Calculate the average of the actual and the ideal body weights.

12.8. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Subject safety monitoring and follow-up:

   a) Subjects may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

      Mitigation plan: For subjects who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the subjects within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

      i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

      ii) Review the current list of concomitant medications and document any new concomitant medications.

      iii) If applicable, confirm electronic/paper diary questionnaires and patient reported outcomes have been completed and transmitted.

   b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, blood draws, imaging, physical exams).

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Central lab kits may be sent to subject's local hospital lab for sample collection. Relevant imaging (e.g. PET-CT, CT) can be done at the subject's local hospital and images transferred or sent to the investigative site. Physical exams can be completed by a local physician with results sent to investigative site.

   c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

      Mitigation plan: The site staff will follow their approved informed consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by

the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the investigative site at the earliest opportunity.

2) Protocol and monitoring compliance:

   a) Protocol deviations may occur in situations where scheduled visits or procedures cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure at a protocol-specified time point, an unscheduled visit should be conducted as soon as possible when conditions allow so that the required procedure can be performed. The situation should be recorded and explained as a protocol deviation. Any missed subject visits must be reported in the eCRF, if possible, and recorded as deviations to the protocol because of the pandemic, so that they can be appropriately documented and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure ongoing data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on-site, must be tracked centrally and updated on a regular basis.

3) Missing data and data integrity:

   There may be an increased amount of missing data because of subject's missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of brexucabtagene autoleucel in study subjects remains unchanged.

12.9. Tabulated List of Investigational Medicinal Products and Auxiliary Medicinal Products

A list of all investigational and auxiliary medicinal products which can be used in Protocol KT-US-568-0138 (Master and all Subprotocols) is provided in Table 15 and Table 16 in compliance with EU Reg. 536/2014 Annex I Section D No. 17 lit. f.

Table 15 List of Investigational Medicinal Products

Investigational Medicinal Products	Further information on dosage, dose regimen, route of administration and treatment period
Brexucabtagene autoleucel	Please refer to Section 3.2.4 of the Master protocol.

Table 16. List of Auxiliary Medicinal Products

Auxiliary Medicinal Products (AxMPs) [a]	Further information on dosage, dose regimen, route of administration and treatment period
Master Protocol (applicable to all substudies)	
Acetaminophen (paracetamol) or equivalent	Please refer to Section 7.6.1. of the Master protocol
Diphenhydramine or equivalent	
Cyclophosphamide (as lymphodepleting chemotherapy)	Please refer to Section 5.1.2 and Section 7.5.4 of the Master protocol.
Fludarabine	
Mesna	
Tocilizumab	AxMPs are not all specified in the protocol, however, are suggested within the standard of care toxicity management guidelines referred to in Section 8.8
Dexamethasone (as toxicity management)	
Methylprednisolone	
Substudy A – Additional AxMPs	
Ibrutinib	Please refer to Section 5.2. of the Substudy A protocol.
Substudy B – Additional AxMPs	
Ibrutinib	For use as treatment prior to lymphodepleting chemotherapy, please refer to Section 5.2. of the Substudy B protocol.
	For use as bridging therapy, please refer to Section 7.2 (Table 2) of the Substudy B protocol
Cyclophosphamide (as bridging therapy)	Please refer to Section 7.2 (Table 2) of the Substudy B protocol
Rituximab	
Doxorubicin	
Vincristine	

Auxiliary Medicinal Products (AxMPs) [a]	Further information on dosage, dose regimen, route of administration and treatment period
Prednisolone	
Ifosfamide	
Carboplatin	
Etoposide	
Gemcitabine	
Oxaliplatin	
Venetoclax	
Prednisone	
Dexamethasone	
Substudy C – Additional AxMPs	
Cyclophosphamide (as bridging therapy)	Please refer to section 7.1 Optional Bridging Therapy (Table 2) of the Substudy C protocol
Dexamethasone	
Rituximab	
Doxorubicin	
Vincristine	
Prednisolone	
Ifosfamide	
Carboplatin	
Etoposide	
Gemcitabine	
Oxaliplatin	
Substudy D – no additional AxMPs	

a All auxiliary medicinal products listed have marketing authorisation in all countries participating in ZUMA-25 Substudy. No AxMP is classified as a narcotic, psychotropic, radiopharmaceutical, or orphan medicine.

12.10. Protocol Amendment History

A high-level summary of amendment changes are provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

12.10.1. Amendment 1.0 (dated 20 July 2022)

Changes from the original protocol (dated 23 May 2022) to Amendment 1.0 (dated 20 July 2022) are detailed below.

Section Number and Name	High-level Description of Change	Brief Rationale
Synopsis Number of subjects anticipated to be enrolled and treated	BL sample size increased from 20 to 30 subjects	BL sample size increased in consideration of EMA Scientific Advice recommendations
Synopsis Statistical methods	Updated sample size of Burkitt Lymphoma to 30 subjects.	BL sample size increased in consideration of EMA Scientific Advice recommendations
Synopsis Number of study sites planned	Number of study sites increased from approximately 40 to 50	Increased the number of study sites to optimize enrollment
Section 3.2.1 Leukapheresis	Correction that 12 to 15 liters of apheresis material will be processed	Correction. Detailed volume is processed but not obtained from the subject
Section 3.7 Number of participating sites	Number of study sites increased from approximately 40 to 50	Increased the number of study sites to optimize enrolment
Section 4.1 Number of subjects and subject selection	BL sample size increased from 20 to 30 subjects and thus total subjects enrolled increased to 170.	BL sample size increased in consideration of EMA Scientific Advice recommendations
Section 7.7.3 Follow-up assessments and procedures for enrolled subjects who did not receive brexucabtagene autoleucel or whose disease progressed after brexucabtagene autoleucel treatment	Removal of text “For RT and BL subjects who sign the optional portion of the ICF, fresh tumor samples will need to be collected (refer to respective substudy protocols for details).”	Correction. Removed text as no longer applicable

12.10.2. Amendment 1.1- EU-specific Protocol Amendment (dated 12 January 2023)

Changes from Amendment 1 (dated 20 July 2022) to Amendment 1.1 (dated 12 January 2023) are detailed below. For changes from Amendment 1 to Amendment 2, please refer to Section 12.10.2 and Section 12.10.3. Amendment 2 incorporates all changes in Amendment 1.1 together with the changes outlined in Section 12.10.3.

Section Number and Name	High-level Description of Change	Brief Rationale
Title page and synopsis	Added EU CT and NCT numbers	EU CT and NCT numbers not previously available
Synopsis and Section 4.2.1 Inclusion Criteria Common to all Indications	Inclusion criteria 1 language updated adding that subjects must have provided written informed consent	Requirement for informed consent described in body of protocol, for clarity also added to inclusion criteria
Table 1 (Synopsis) and Table 6 (Section 8.1.2) – Dose limiting toxicities	• Exception removed regarding brexucabtagene autoleucel related Grade 4 non hematological toxicities • Confirmed and updated text to clarify that any brexucabtagene autoleucel related Grade 3 neurotoxicity, including ICANS, regardless of duration, will constitute a DLT • Changed "Exception of any grade TLS including manifestations attributable to TLS" to "Exception of Grade 3 TLS including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, or hyperuricemia)" regarding brexucabtagene autoleucel related Grade 3 nonhematological toxicities	All Grade 4 non-hematological events to be considered as DLTs and TLS reconsidered so that Grade 4 and 5 events would be considered a DLT. Language about ICANS added for clarity.
Table 2 (Synopsis) and Table 7 (Section 8.1.2) – Recommendations Based on Dose Limiting Toxicities	Criteria for numbers of subjects with a DLT in a cohort clarified	For clarification
Section 1.4 Study Rationale	Added additional language describing that all study indications no established standard of care exist	To clarify that only subjects who have exhausted all the available approved treatment options will be included in this study
Section 3.2.4 Brexucabtagene autoleucel	Added text to state that "brexucabtagene autoleucel is the Investigational Medicinal Product (IMP) being assessed in this study (Appendix 12.9). Brexucabtagene autoleucel has been granted marketing authorization in numerous regions, including the US, EU, Canada, Great Britain, and Switzerland, and will be used in this study for new indications"	For clarity

Section Number and Name	High-level Description of Change	Brief Rationale
Section 3.2.5 Auxiliary Medicinal Products	New section added to define that all other medications described in the Master protocol and subprotocols are considered auxiliary medicinal products. These medications are used in accordance with their authorized product information. The identified and potential risks and the risk minimization should be managed as described within the authorized product information and/or in accordance with institutional guidelines	Regulatory update to define the medications considered as auxiliary medications and to detail the use of these medications /
Section 3.4 End-of-Study Definition	The end-of-study is defined for each substudy as the time when the last enrolled subject within the specific substudy has completed their last visit (last patient last visit; LPLV)	For clarity
Section 3.6 Study Discontinuation Criteria	Added details regarding the role of the DSMB in reviewing substudy data and providing recommendations on study conduct, including that the recommendations may include that a substudy should be stopped	For clarity
Section 4.3.1 Reasons for Removal From Treatment	Added further information regarding why AEs may lead to removal of a subject from treatment and why the IMP may not be available	For clarity
Section 8.2 Pregnancies	Revised the language to state that male subjects should not (previously recommended not to) father a child for at least 6 months after completing lymphodepletion chemotherapy dosing or brexucabtagene autoleucel, whichever is longer	Strengthened the language regarding male subjects and fathering a child
Section 8.5 Hospitalization and Prolonged Hospitalization	For hospitalization scenarios, not considered to be SAEs, added further definition for planned hospitalization ie, a planned hospitalization for a pre-existing medical condition (diagnosed prior to study entry) which was scheduled prior to informed consent/study start	For clarity
Section 8.6.1.1. Reporting AEs Table 9	Table 9 updated to add missing information concerning reporting requirements for subjects who have received brexucabtagene autoleucel. AE reporting is required from enrollment through 3 months after the brexucabtagene autoleucel infusion or *until initiation of another anticancer therapy*, whichever occurs first.	Correction of missing information
Section 8.7 Sponsor Reporting Requirements (Includes Reporting of SAEs and Deaths)	References to EU Clinical Trials Directive 2001/20/EC changed to EU Regulation 536/2014	Regulatory update

Section Number and Name	High-level Description of Change	Brief Rationale
Section 8.8.1 Toxicities Associated with Brexucabtagene Autoelucel Treatment	Added text to detail that toxicities associated with brexucabtagene autoleucel will be managed according to ASCO guidelines or per the authorized Tecartus product information and that tocilizumab is required to be available for the treatment of CRS. In addition, text was added clarifying that tumor lysis syndrome should be managed in accordance with the authorized brexucabtagene autoleucel product information and/or institutional guidelines	Added brexucabtagene autoleucel toxicities may also be managed according to authorized Tecartus product information
8.10.1 Safety Review Team	Enrollment will be paused to allow the SRT 28 days of data post infusion in all treated subjects in a DLT cohort prior to providing a recommendation on the continued dose selection, and re-starting enrollment.	Self-explanatory
8.10.2 Data Safety Monitoring Board	Added further language to clarify the data received by the DSMB. The DSMB will review data accruing from each substudy and provide ongoing recommendations on study conduct to the Kite Head of Cell Therapy Clinical Development (or designee). Moreover, the DSMB will be provided with all data on the serious adverse events (SAEs; listings or narratives) and suspected unexpected serious adverse reactions (SUSAR) from the global safety database for review prior to implementing the SRTs dose recommendations.	For clarity
Section 8.10.3 Criteria to Pause Enrollment	Pausing rules updated. Specifically: <u>During the SRT phase</u> Enrollment will be paused following the treatment of 3 subjects in a DLT cohort, to assess the frequency of DLTs and to allow the SRT 28 days of data post infusion in all treated subjects prior to providing a recommendation on the target dose. <u>After the pivotal dose has been established</u> The study will be paused in response to any Grade 5 brexucabtagene autoleucel related AE, no matter when this occurs. The study will also be paused if the incidence of the following Grade 4 related brexucabtagene autoleucel related AEs is ≥ 33%: ICANS, CRS, other non-hematological Grade 4 SAEs and infections (treatment related). The previously described requirement of these AEs having a duration lasting more than 7 days has been removed.	Criteria strengthened for subject safety

Section Number and Name	High-level Description of Change	Brief Rationale
Section 10.1.4 Confidentiality	Updated confidentiality information to include language regarding the processes Kite have in place to ensure the security and confidentiality of data records and personal information	Language previously missing
Section 10.3.3 Ethics	Changed "European Community Directive 2001/20/EC" to "EU Regulation (2001/2014)"	Regulatory requirement
Section 12.3.2 Birth Control Methods That May Be Considered as Highly Effective	Added requirement for a barrier contraceptive method (condoms or diaphragm with spermicide) to be used together with hormonal contraceptive measures	Strengthen the pregnancy prevention methods
Appendix 12.9 Tabulated List of Investigational Medicinal Products and Auxiliary Medicinal Products	Added Appendix 12.9 to define and provide information on the Investigational Medicinal Product IMP used in this study and the medications considered auxiliary medicinal products	Regulatory requirement

12.10.3. Amendment 2.0 (dated 01 March 2023)

Changes from Amendment 1.1 (dated 12 January 2023) to Amendment 2 (dated 01 March 2023) are detailed below

Section Number and Name	High-level Description of Change	Brief Rationale
Entire document	Minor spelling corrections	Self-explanatory
Title Page	Study title updated to read "A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Master Protocol"* The evaluation of safety removed from the study title.	Request during Part 1 EU-CTR application to update the trial title to focus on the primary endpoint only.
Title Page	Amendment history added	Self-explanatory
Synopsis and Section 4.2.2 Exclusion Criteria	Exclusion criterion #18 updated to include hypersensitivity to excipients	Request by Swiss Regulatory Authority
Section 3.2.2 Bridging Therapy	Clarification provided regarding reference to RT and BL study protocols regarding bridging therapy	Self-explanatory
Section 3.2.3 Lymphodepleting Chemotherapy, Section 5.1.2.1 Fludarabine and Section 7.5.4 Lymphodepleting Chemotherapy	Added clarifying text that if, after the start of the lymphodepletion regimen, the creatinine clearance falls below 60 mL/min, subsequent doses of fludarabine will be adjusted according to institutional guidelines	For clarification

Section Number and Name	High-level Description of Change	Brief Rationale
Section 3.4 End-of-study Definition	End of study definition clarified to also include if a subject transitions to a separate LTFU study	For clarification
Section 5.5.1 Washout Periods Prior to Leukapheresis /Enrollment	Added additional text regarding systemic corticosteroids "Systemic corticosteroids must be avoided as premedication in subjects for whom CT scans with contrast are contraindicated (eg, subjects with contrast allergy or impaired renal clearance) if the administration is within 7 days before leukapheresis or 5 days before brexucabtagene autoleucel administration (washout period)"	Additional requirement for the avoidance of steroids described.
Section 5.5.2 Excluded Medications or Medications to be used with Caution After Leukapheresis/Enrollment	Section title updated to also refer to medications to be used with caution. Text surrounding use of live vaccines aligned with exclusion criteria 19 "Vaccination with live viral vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during brexucabtagene autoleucel treatment, and **for 12 months after** treatment with brexucabtagene autoleucel". Added text referring investigators to the current IB for additional information about vaccination, including COVID-19 vaccines**.**	Alignment of protocol text as described and added reference to current IB added for further information on vaccination, for clarity
Section 6.3.2.1 Laboratory Tests for Safety and Pharmacokinetics /Pharmacodynamics Assessments, Table 4 Clinical Laboratory Tests for Safety Assessments Common Across all Substudies	Added requirement for serology anti HIV+2 test at screening only for all patients	Testing for HIV status required in all subjects at screening
Section 6.3.2.1 Laboratory Tests for Safety and Pharmacokinetic/Pharmacodynamic Assessments	Added additional information that if the blood urea nitrogen test cannot be performed by the local laboratory, urea should be analyzed Switzerland added to the requirements for serology testing at European study sites	Self-explanatory Request by Swiss Regulatory Authority
Section 6.3.11 Patient-reported Outcomes	Additional detail added that PROs are expected to be completed by all subjects who remain on-study at the scheduled assessments, **up to and until disease progression** Added that "the sponsor will provide training for relevant site personnel for the administration of the questionnaires, so that subjects fill in the questionnaires as completely and accurately as possible".	For clarification

Section Number and Name	High-level Description of Change	Brief Rationale
Section 6.3.14 Serology Testing	New section added to provide guidance on serology testing	For clarification
Section 6.3.16.2 Replication-Competent Retrovirus	Clarifying language added that after month 12, samples will only be collected and tested if an RCR event is clinically suspected and/or a subject tests positive for RCR at any time point within the first year. If the latter, samples/testing for RCR will continue per clinical discretion. If a subject dies of a suspected retrovirus-associated disease or develops a new malignancy suspected to be associated with brexucabtagene autoleucel during the study or long-term follow-up, a blood sample and tumor biopsy may be obtained and sent to the central laboratory to assay for brexucabtagene autoleucel CAR T cells and/or RCR	Self-explanatory
Section 6.6 Pharmacokinetic Assessments	Clarification that samples on Day 3 may be collected ± 1 day	Provides flexibility regarding central laboratory sample collection when the Day 3 visit fall over a weekend
Section 7.1.1 Informed Consent for Optional Research	New section added describing the seeking of the subject's permission to use the remainder of study biospecimens for optional future research and/or genetic research in accordance with applicable regulations.	For clarification
Section 7.4 Enrollment	Added clarifying text that "a subject may not proceed to enrollment if they do not meet the eligibility criteria as indicated during screening and by laboratory tests performed after screening and before the initiation of leukapheresis".	For clarification
Section 7.6.4 Requirements for Workup for Potential and/or Inflammatory States	Added clarifying text that "for subjects with symptoms and/or clinical findings indicating a potential infectious or inflammatory state, and in the absence of an identified source of infection (eg, line infection or pneumonia on chest X-ray), the minimum workup to be performed before administration of lymphodepleting chemotherapy and/or brexucabtagene autoleucel consists of the following:"	For clarification
Section 7.13 Sample Storage	Text updated to indicate that subject biospecimens '**will**' rather than '**may**', be stored for 15 years after brexucabtagene autoleucel infusion**, in case any protocol-required analyses need repeating**.	For clarification added that subject specimens will be stored for 15 years in case any protocol-required analyses need repeating and described

Section Number and Name	High-level Description of Change	Brief Rationale
	In addition, Kite may conduct analyses on remaining samples to address exploratory research questions related to the mechanism of action of the treatment or disease related features, **for which subjects will be asked to provide consent**.	use of remaining samples with the subjects consent
Section 8.2 Pregnancies	Updated time for recommended use of contraception in female subjects and time period that male subjects should not father a child from 6 to 12 months.	Updated following requests from regulatory authorities
Section 8.6.1.2 Reporting SAEs, Table 10 Reporting Requirements for SAEs	Footnote for Table 10 regarding new malignancies updated to describe that the investigator must assess causality against brexucabtagene autoleucel, lymphodepleting chemotherapy, bridging therapy, or study procedures. In addition, for secondary malignancies, language updated to indicate rather than a temporal association, there should be a plausible association with the brexucabtagene autoleucel infusion and without compelling alternate etiologies.	For clarification regarding the Investigator assessment of etiology for new malignancies
Section 8.6.1.2 Reporting SAEs	Added text that reads "After completion of this study and database closure, any relevant information on ongoing SAEs must be submitted to Kite within 24 hours after the investigator's knowledge of the event using the portable document format (PDF) version of the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: PPD "	Language added regarding continued SAE reporting requirements and methods after study closure
Section 8.6.2 Reporting Deaths	Added text that reads" All deaths must be recorded on the Death eCRF, but only deaths caused by an AE should be reported as an SAE. For example, in an event of fatal pneumonia, the event should be reported as an SAE of pneumonia and the outcome as fatal. The event or condition that caused or contributed to the fatal outcome should be recorded on the SAE eCRF with entries including the start date of the event and death date as the stop date of the event. Every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Although death is an outcome and not a distinct AE, death may be reported as an SAE (ie, PT = death) when the cause of death is unknown (eg, sudden or unwitnessed death with unknown cause).	For clarification

Section Number and Name	High-level Description of Change	Brief Rationale
Section 8.8.1 Toxicities Associated with Brexucabtagene Autoelucel Treatment	Added clarification that a guide to the ICE score is presented in Section 12.5	For clarification
Section 8.9.2.1 Instructions for Reporting Pregnancies	Added language on the timeframe for reporting requirements for pregnancies in female partners of male subjects i.e required within 12 months after completing lymphodepleting chemotherapy or the brexucabtagene infusion	Timeframe for reporting pregnancy in a female partner of a male subject added
Section 10.1.3 Informed Consent	Added language to provide a reason why optional future genomic research test results will not be shared i.e. the results do not inform clinical decision making	For clarification
Section 10.2.2 Study Report and Publications	Minor edits to guidance regarding study report and publications and updated language surrounding Investigators and publication rules which should be in accordance with the Kite clinical trial agreement.	Self-explanatory
Section 12.4 Country-specific Regulatory Agency Requirements, 12.4 Post-Infusion Monitoring, 12.4.2.2 For Switzerland	New section added regarding post-infusion monitoring in Switzerland i.e. subjects should remain in hospital for 10 days after brexucabtagene autoleucel for monitoring	Request from Swiss Regulatory Authority and Ethics Committee
Section 12.4 Country-specific Regulatory Agency Requirements, 12.4.3 Pregnancy Testing	Switzerland added to the list of European countries requiring pregnancy testing 7 days prior to leukapheresis and lymphodepleting chemotherapy	Request from Swiss Regulatory Authority and Ethics Committee
Section 12.7 Practical Body Weight Calculation for Subjects Whose Body Mass Index (BMI) is > 35 kg/m^2	Clarified that for dose calculations, body weight **at time of leukapheresis** is to be used for brexucabtagene autoleucel	For clarification
Section 12.7 Practical Body Weight Calculation for Subjects Whose Body Mass Index (BMI) is > 35 kg/m^2	Removed text related to IL-2 dose	Text was originally added in error

12.10.4. Amendment 3.0 (dated 17 August 2023)

Changes from Amendment 2.0 (dated 01 March 2023) to Amendment 3.0 are tabulated below.

Section Number and Name	High-level Description of Change	Brief Rationale
General	Correction of typographical errors	Self-explanatory
Title page and throughout the document	Added text to detail that substudies A and D were terminated early by the Sponsor, effective 21 June 2023 Removed references to sites in the United Kingdom	Sponsor decision to terminate substudies A and D No sites in the United Kingdom will be participating in the study
Synopsis	Added statements that substudies A and D were terminated early by the Sponsor, effective 21 June 2023	Sponsor decision to terminate substudies A and D
Synopsis – Number of Study Sites Planned	Number of study sites reduced from approximately 50 to approximately 25	Number of sites reduced due to early termination of substudies A and D
Synopsis – Study Design	Clarifying language added to indicate that, following the early termination of substudies A and D, subjects are only to be enrolled in substudies B and C (effective 21 June 2023)	Sponsor decision to terminate substudies A and D
Section 1.3 Study Design	Edit text to indicate that studies focus on efficacy and not safety	To reflect that focus of study is on efficacy
Section 3.2.3 – Lymphodepleting Chemotherapy	Creatinine clearance threshold change from 60 to 70 mL/min	To align with fludarabine product information
Section 3.7 Number of Participating Study Sites	Number of sites reduced from approximately 50 to approximately 25. Reference to sites in Canada removed	Number of sites reduced due to early termination of substudies A and D. No sites in Canada recruiting subjects
Section 4.1 Subjects and Subject Selection	Edited to indicate that approximately 90 subjects will be enrolled in the 2 active substudies (RT and BL)	Numbers adjusted to reflect early termination of substudies A and D
Section 5.1.2.1 Fludarabine	Creatinine clearance threshold change from 60 to 70 mL/min	To align with fludarabine product information
Section 6.3.16.2 Replication-Competent Retrovirus	Edited to indicate that samples/testing for RCR will be per physician/investigator discretion	To specify that the testing must be undertaken by physician/investigator
Section 7.5.4 Lymphodepleting Chemotherapy	Creatinine clearance threshold change from 60 to 70 mL/min	To align with fludarabine product information

Section Number and Name	High-level Description of Change	Brief Rationale
Section 8.10.3 Criteria to Pause Enrollment	Added text to indicate that study enrollment will be paused when the required number of subjects have been enrolled in the planned interim analyses for each substudy, until the data from this interim analysis have been assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment
Section 9.6.1 Interim Analysis and Early Stopping Guidelines	Added text to indicate that study enrollment will be paused while allowing time for the interim analyses to be assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment

ZUMA-25 Master protocol Amendment 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	21-Aug-2023 12:54:09