# CLINICAL STUDY SUBPROTOCOL

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|---|---|
| **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) – *Substudy D – Relapsed/Refractory Hairy Cell Leukemia* |
| **Note:** | This subprotocol should be used in conjunction with the KT-US-568-0138 master protocol |
| **Protocol Number:** | KT-US-568-0138-D (ZUMA-25D) |
| **Indication:** | Relapsed/refractory hairy cell leukemia |
| **Kite Investigational Product** | Brexucabtagene Autoleucel |
| **Kite IND Number:** | 028542 |
| **EU CT Number:** | 2022-501262-21-00 |
| **Clinical Trials.gov Identifier:** | NCT05537766 |
| **Sponsor:** | Kite Pharma, Inc.<br>2400 Broadway<br>Santa Monica, CA 90404<br>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:** | Original: 23 May 2022<br>Amendment 1.0: 20 July 2022<br>Amendment 1.1: 12 January 2023<br>Amendment 2.0: 01 March 2023 |

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, the United Kingdom, 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.

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# 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)

***Substudy D – Relapsed/Refractory Hairy Cell Leukemia***

**Indication:** Adult subjects with relapsed/refractory (r/r) hairy cell leukemia (HCL)

**Kite IND Number:** 028542

**EU CT Number:** 2022-501262-21-00

**Clinical Trials.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 50

**Objectives and Endpoints:** Objectives and endpoints that are common to all indications are detailed in the KT-US-568-0138 master protocol.

Additional objectives and endpoints that are specific to this substudy are detailed below.

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| • To evaluate the efficacy of brexucabtagene autoleucel in subjects with HCL by determining the objective response rate (ORR) by central assessment | • ORR by central assessment defined as the proportion of subjects who achieve either complete response (CR) or partial response (PR) |
| **Secondary Objective** | **Secondary Endpoint** |
| • To evaluate the efficacy of brexucabtagene autoleucel in subjects with HCL by ORR by investigator assessment | • ORR by investigator assessment defined as the proportion of subjects who achieve either CR or PR |
| **Exploratory Objective** | **Exploratory Endpoint** |
| • To evaluate the measurable residual disease (MRD) negative response rate in subjects with HCL who have achieved a CR by central assessment | • Rate of MRD negative response among subjects who have achieved a CR by central assessment |

**Study Design:** This substudy protocol contains details regarding all elements of the study that are unique to subjects with r/r HCL. In contrast, the KT-US-568-0138 master protocol contains additional information that is common for all indications in this basket study. Both the KT-US-568-0138 master protocol and this substudy protocol should be referenced in parallel.

This is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of brexucabtagene autoleucel in subjects with r/r HCL. Subjects with r/r HCL must have received at least 2 lines of prior systemic therapy including a purine nucleoside analog (PNA) and moxetumomab pasudotox if eligible and commercially available.

Initially, 1 subject will be enrolled and infused. No additional subjects will be enrolled until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects can be enrolled in parallel. After these initial 3 subjects have been evaluated for at least 28 days, the safety review team (SRT) will make recommendations on further conduct of this substudy.

Following enrollment, eligible subjects will be treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy, followed by an initial dose of $2 \times 10^6$ anti-CD19 chimeric antigen receptor (CAR) T cells/kg body weight. Following review by the SRT, the dose may be lowered to $1 \times 10^6$ anti-CD19 CAR T cells/kg body weight.

Disease response will be assessed at Day 28, Month 3 and then every 3 months up to Month 12, followed by every 6 months up to Month 36, and then annually out to Month 60.

Additional study details are provided in the KT-US-568-0138 master protocol.

The study schema is detailed in Figure 1 of the KT-US-568-0138 master protocol.

**Number of Subjects Anticipated to be Enrolled and Treated:** Approximately 20 subjects with r/r HCL will be enrolled and treated in this substudy. Three to 6 additional subjects may be enrolled if the SRT recommends proceeding at the lower dose level.

**Target Population:** Male or female adults ≥ 18 years of age diagnosed with r/r HCL

**Duration of Treatment and Study Participation:** The treatment period will be 1 week following infusion, and the duration of the study is 60 months.

**Eligibility Criteria Unique to the HCL Substudy:**

In addition to the common eligibility criteria specified in the KT-US-568-0138 master protocol, all the following additional substudy-specific eligibility criteria must also be met.

**HCL Substudy-specific Inclusion Criteria:**

1) Subjects will be eligible regardless of the duration of remission prior to relapse and must have confirmed HCL (r/r classic HCL or r/r HCL variant) by immunophenotyping and histology with a need for therapy based on at least 1 of the following criteria:
   - neutrophils $< 1.0 \times 10^9$/L
   - platelets $< 100 \times 10^9$/L

- hemoglobin < 11 g/dL
- symptomatic splenomegaly
- symptomatic lymphadenopathy

2) Subjects must have received:

- At least 2 prior therapies, including at least a PNA and moxetumomab pasudotox if eligible and available

**HCL Substudy-specific Exclusion Criteria:**

1) Prior history of allogeneic stem cell transplant

**Study Procedures:** Subjects will undergo procedures and assessments as detailed in the schedule of assessments (see Section 12.2).

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

Treatment consists of a lymphodepleting chemotherapy regimen, followed by a single infusion brexucabtagene autoleucel. Additional details are provided in the KT-US-568-0138 master protocol.

**Safety Review Team and Data Safety Monitoring Board:** 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 after 3 or 6 subjects in this substudy have been treated with the initial dose ($2 \times 10^6$ anti-CD19 CAR T cells/kg of body weight) and followed for 28 days, as detailed in the KT-US-568-0138 master protocol.

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review serious adverse event (SAE) information (listings or narratives) and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout subject treatment in the study and per the DSMB charter or DSMB discretion. The DSMB may request additional safety or efficacy data or recommend modifying the study conduct. The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may or may not be source data verified to facilitate timely DSMB review.

SUSARs and SAE listings or narratives may be submitted to the DSMB chair as described in the DSMB charter.

Additional details regarding the SRT, DSMB, and dose-limiting toxicities are provided in the KT-US-568-0138 master protocol.

**Statistical Methods:**

Hypothesis: An alternative hypothesis is proposed with a target 60% ORR per central assessment against a null hypothesis that the ORR is ≤ 26%. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than 26%.

Sample Size Calculation: This single-arm, open-label substudy will enroll and treat 20 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve a statistical power of 90% if there is at least a 34% improvement in ORR (brexucabtagene autoleucel: 60% versus historical control: 26%) with a type 1 error rate of 0.025 (1-sided).

Analyses: An interim analysis will be conducted after 10 subjects (50%) have had the opportunity to be evaluated for response 3 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary of an ORR of 29.4% is based on the beta spending function of rho family (parameter = 2), with a crossing probability of 60% under the null hypothesis (ORR ≤ 26%). A decision will be made by the sponsor based on DSMB recommendation, with the complete benefit/risk profile of brexucabtagene autoleucel being taken into account. If a decision is made to discontinue this substudy, then this analysis will be considered the primary analysis of this substudy.

If the decision based on the interim analysis is to continue the substudy, the primary analysis will be conducted after 20 subjects have been enrolled and treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be assessed for response at least 12 months after the brexucabtagene autoleucel infusion.

Hypothesis testing will be based on the number of objective responders observed among the 20 subjects, as described above. The point estimate of the ORR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on an exact test. If more than 20 subjects are treated with the SRT-recommended dose in the substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 30 months after the after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

Additional descriptive analyses may occur after the primary analysis and follow-up analysis described above have been completed.

The final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

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.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| CAR | chimeric antigen receptor |
| CNS | central nervous system |
| CR | complete response/remission |
| CRS | cytokine release syndrome |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| DSMB | Data Safety Monitoring Board |
| eCRF | electronic case report form |
| HCL | hairy cell leukemia |
| ICANS | immune effector cell-associated neurotoxicity syndrome |
| IV | intravenous(ly) |
| MRD | measurable residual disease |
| MRI | magnetic resonance imaging |
| ORR | objective response rate |
| PET | positron emission tomography |
| PNA | purine nucleoside analog |
| PR | partial response/remission |
| r/r | relapsed/refractory |
| 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 |

# 1. INTRODUCTION

Refer to the KT-US-568-0138 master protocol for information related to brexucabtagene autoleucel (KT-US-568-0138 master protocol - Section 1.1), previous clinical studies (KT-US-568-0138 master protocol – Section 1.2.2), and the study rationale (KT-US-568-0138 master protocol - Section 1.4).

## 1.1. Disease Background

### 1.1.1. Epidemiology

Hairy cell leukemia (HCL) is an indolent and rare B-cell leukemia comprising 2% of all leukemias, corresponding to an estimated 1,200 cases annually in the US .

### 1.1.2. Diagnosis

The normal B cell counterpart of HCL remains debated; however, expression signatures suggest that HCL is derived from the post-germinal center memory B cell . The World Health Organization classifies 2 separate forms of HCL: i) classic HCL in which the specific mutation, *BRAF (V600E)*, is present in the majority of patients; and ii) HCL variant in which the *BRAF (V600E)* mutation is absent (Grever et al, 2017). By flow cytometry, both forms of HCL are characterized by the B-cell antigens FMC7, CD11c, CD19, CD20, CD22 and have strongly positive surface immunoglobulin expression; however, whereas classic HCL is positive for CD25 and CD123, HCL variant is most often negative .

Clinically, HCL is characterized by symptoms of fatigue, weakness and infections and some patients will present with splenomegaly . In addition, often patients present because of incidental findings of pancytopenia. In the initial work-up, leukemic cells are typically found infiltrating the bone marrow and spleen, and may also be found in the liver, lymph nodes, and rarely in the skin. Small numbers of circulating hairy cells may also be present .

### 1.1.3. Frontline Treatment

The median survival of patients with HCL without effective treatment is about 4 years . However, HCL treatment was revolutionized with the advent of purine nucleoside analog (PNA) therapy in the late 1980s and the PNAs cladribine and pentostatin have shown durable CR rates of 72 to 89% in the frontline setting , with most patients remaining in CR after several years of follow-up. While the majority of patients with HCL will require treatment, a minority (about 10%) may not require immediate therapy and may be closely observed until therapy is needed.

### 1.1.4. Second-line Treatment

Despite the efficacy of PNA therapy, up to 40 to 50% of HCL patients relapse and for these patients second-line PNA therapy induces less durable remissions and is associated with a significant risk of side-effects, including bone marrow aplasia, persistent CD4 lymphopenia,

infections, and neurotoxicity . Accordingly, the current clinical guidelines recommend alternative therapies in the relapsed/refractory (r/r) setting, depending on the duration of CR or relapse. For patients with a duration of response of less than 2 years, a clinical trial or alternative therapies or purines may be explored, including rituximab ± vemurafenib or peg-interferon-α.

In a study in subjects with r/r HCL, Nieva et al found an objective response rate (ORR) of only 25% in subjects who relapsed after PNA treatment and received rituximab as second-line therapy. These findings underscore that novel therapies, beyond PNAs and rituximab, are needed to induce durable remissions for patients in need of third or more lines of therapy for HCL. While moxetumomab pasudotox (anti-CD22 immunotoxin) has been approved for the third line treatment of HCL, its use has been limited since the drug is only approved and available in the US. Also, the oral BRAF inhibitor vemurafenib in combination with rituximab has shown promising response rates, but whether this will lead to regulatory approval remains uncertain . As such, a significant unmet medical need remains for patients with treatment resistant HCL.

# 2. OBJECTIVES AND ENDPOINTS

Refer to the Section 2 of the KT-US-568-0138 master protocol for a summary of common objectives and endpoints for this study.

Additional objectives and endpoints that are specific for this substudy are detailed in Table 1.

**Table 1. Substudy-specific Objectives and Endpoints**

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| • To evaluate the efficacy of brexucabtagene autoleucel in subjects with HCL by determining the ORR by central assessment | • ORR by central assessment defined as the proportion of subjects who achieve either CR or PR |
| **Secondary Objective** | **Secondary Endpoint** |
| • To evaluate the efficacy of brexucabtagene autoleucel in subjects with HCL by ORR by investigator assessment | • ORR by investigator assessment defined as the proportion of subjects who achieve either CR or PR |
| **Exploratory Objective** | **Exploratory Endpoint** |
| • To evaluate the MRD negative response rate in subjects with HCL who have achieved a CR by central assessment | • Rate of MRD negative response among subjects who have achieved a CR by central assessment |

Abbreviations: CR, complete response; HCL, hairy cell leukemia; MRD, measurable residual disease; ORR, objective response rate; PR, partial response.

# 3. STUDY DESIGN

## 3.1. Study Design

This substudy protocol contains details regarding all elements of the study that are unique to subjects with HCL. In contrast, the KT-US-568-0138 master protocol contains additional information that is common for all indications in this basket study. Both the KT-US-568-0138 master protocol and this substudy protocol should be referenced in parallel.

This is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of brexucabtagene autoleucel in subjects with r/r HCL. Subjects with r/r HCL must have received at least 2 lines of prior systemic therapy including a purine nucleoside analog (PNA) and moxetumomab pasudotox if eligible and commercially available.

Initially, 1 subject will be enrolled and infused. No additional subjects will be enrolled until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects can be enrolled in parallel. After these initial 3 subjects have been evaluated for at least 28 days, the safety review team (SRT) will make recommendations on further conduct of this substudy.

Following enrollment, eligible subjects will be treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy, followed by an initial dose of $2 \times 10^6$ anti-CD19 chimeric antigen receptor (CAR) T cells/kg body weight. Following review by the SRT, the dose may be lowered to $1 \times 10^6$ anti-CD19 CAR T cells/kg body weight.

Disease response will be assessed at Day 28, Month 3 and then every 3 months up to Month 12, followed by every 6 months up to Month 36, and then annually out to Month 60.

Additional details of the study design are provided in Section 3 of the KT-US-568-0138 master protocol.

The study schema is detailed in Figure 1 of the KT-US-568-0138 master protocol.

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. Additional details of the SRT are provided in Section 8.1.

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review investigator-reported safety and efficacy data against the futility rules after 10 subjects (50%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 3 months after the brexucabtagene autoleucel infusion. Additional details of the DSMB are provided in Section 8.1.

The end-of-study is defined in the Master protocol (refer to Section 3.4 of the Master protocol).

# 4. SUBJECT POPULATION

## 4.1. Number of Subjects and Subject Selection

Approximately 20 subjects with r/r HCL who have received at least 2 lines of prior therapy will be enrolled and treated. Three to 6 additional subjects may be enrolled if the SRT recommends proceeding at the lower dose level (refer to Section 8.10.1 of the KT-US-568-0138 master protocol for additional details).

## 4.2. Eligibility Criteria

To be enrolled in the study, subjects must meet the common eligibility criteria detailed in Section 4.2 of the KT-US-568-0138 master protocol. In addition, subjects must also meet all of the additional, substudy-specific eligibility criteria detailed in Section 4.2.1 and Section 4.2.2.

### 4.2.1. HCL Substudy-specific Inclusion Criteria

1) Subjects will be eligible regardless of the duration of remission prior to relapse and must have confirmed HCL (r/r classic HCL or r/r HCL variant) by immunophenotyping and histology with a need for therapy based on at least one of the following criteria:

   - neutrophils $< 1.0 \times 10^9$/L
   - platelets $< 100 \times 10^9$/L
   - hemoglobin < 11 g/dL
   - symptomatic splenomegaly
   - symptomatic lymphadenopathy

2) Subjects must have received:

   - At least 2 prior therapies, including at least a PNA and moxetumomab pasudotox if eligible and available

### 4.2.2. HCL Substudy-specific Exclusion Criteria

1) Prior history of allogeneic stem cell transplant

# 5. STUDY TREATMENT

Study treatment consists of lymphodepleting chemotherapy and a single infusion of brexucabtagene autoleucel, as described in Section 3.2 of the KT-US-568-0138 master protocol.

Bridging therapy is not applicable for subjects participating in this substudy.

Refer to Section 5 of the KT-US-568-0138 master protocol for additional details regarding brexucabtagene autoleucel treatment, prior and concomitant medications, and excluded medications.

# 6. STUDY ASSESSMENTS UNIQUE TO HAIRY CELL LEUKEMIA

The study assessments that are either unique to HCL or that are managed differently for subjects with HCL are described here. Please refer to the KT-US-568-0138 master protocol Section 6 for details of all other study assessments. Study assessments described in the KT-US-568-0138 master protocol and herein are to be performed according to the schedule of assessments (SOA) presented in Section 12.2 (Table 5 and Table 6) of this substudy protocol.

## 6.1. Clinical Laboratory Tests

Clinical laboratory tests for disease-specific assessments are presented in Table 2. The hematology assessments are performed at the local laboratory only, the bone marrow trephine biopsy will be assessed at both local and central laboratory assessment, and the bone marrow aspirate will be assessed at the central laboratory only.

**Table 2. Clinical Laboratory Tests for Disease-specific Assessments**

| Serum Chemistries (Serum) | Hematology (Blood) | Other |
|---|---|---|
| No additional HCL-specific serum chemistry tests are required for this substudy | Peripheral blood assessment of circulating leukemic cells (see Section 6.4.1)<br>Hematologic disease response parameters (see Section 6.5):<br>• Lymphocyte count<br>• Absolute neutrophil count<br>• Platelet count<br>• Hemoglobin<br>Peripheral blood assessment of MRD, only in the case of a fibrotic bone marrow (see Section 6.6.1) | Bone marrow aspirate and trephine biopsy to assess bone marrow involvement and MRD (see Section 6.4.3) |

Abbreviations: HCL, hairy cell leukemia; MRD, measurable residual disease; SOA, schedule of assessments.
Note: Refer to the SOA in Section 12.2 for timing of assessments.

## 6.2. Brain Magnetic Resonance Imaging

If required, brain magnetic resonance imaging (MRI) will be performed with contrast whenever possible or without contrast in case of contraindication.

Screening:

- At screening, subjects with current symptoms or clinical signs of central nervous system (CNS) malignancy, such as severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurological findings on physical examination must undergo a brain MRI to rule out current CNS metastasis, in which case such subjects are not eligible for the study.

- If required, the MRI should be performed as close to enrollment/leukapheresis as possible and within 28 days before leukapheresis for eligibility. An MRI collected as standard of care (SOC) within this timeframe is acceptable.

- After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat MRI is required to reassess eligibility prior to the start of lymphodepleting chemotherapy.

- CNS involvement will be assessed by local review, and images will not be sent for central review.

Post-infusion:

- Subjects with new-onset symptoms or clinical signs of CNS disease, as described above, are recommended to have a brain MRI.

- In addition, in the case of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), refer to the American Society of Clinical Oncology (ASCO) management guidelines for guidance of requirements for brain imaging . In summary: i) a brain MRI can be considered for all grades of CRS; ii) a brain MRI or other neuroimaging can be considered for ICANS Grade 2 or higher, as supported by the ASCO management guidelines.

- A brain MRI only needs to be submitted to the independent central reviewer when there is evidence of disease progression.

### 6.3. Lumbar Puncture

Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.

Screening:

- Subjects with symptoms or clinical signs of CNS malignancy (eg, new-onset severe headaches, neck stiffness, or focal neurologic findings), or leptomeningeal carcinomatosis, will have a lumbar puncture performed at screening for examination of cerebrospinal fluid (CSF) to determine presence of CNS malignancy. There must be no evidence of CNS involvement to be eligible for this study.

- After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat lumbar puncture is required to reassess eligibility prior to the start of lymphodepleting chemotherapy.

Post-infusion:

- Subjects with symptoms or clinical signs of CNS malignancy, such as new-onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical examination, will have a lumbar puncture for examination of CSF (and brain MRI as described in Section 6.2).

- In the case of CRS and ICANS refer to the ASCO management guidelines for guidance for requirements for lumbar puncture examination . In summary: i) lumbar puncture is recommended for consideration in cases of CRS; ii) For ICANS, lumbar puncture is recommended for Grade 3 or higher neurotoxicity and may be considered for Grade 2.

CSF samples will be analyzed at the local laboratory. An aliquot will be sent to the central laboratory for assessment of analytes (including cytokines) and immune cell subsets.

## 6.4. Disease Assessments

Disease response will be assessed in accordance with recommendations from the Consensus Guidelines for the Diagnosis and Management of Patients with Classic Hairy Cell Leukemia ; see Section 12.3.1.

Disease assessments will be performed according to the schedule presented in the SOA (see Section 12.2) and as described below. Assessment of hemoglobin, platelets, or absolute neutrophil count (ANC) must be performed at least 4 weeks after the subject has received any transfusions or growth factors. If the need for transfusions or growth factors means that the disease response assessment cannot fall within the scheduled study visit window, an unscheduled disease response assessment should be performed as soon as possible thereafter (all other assessments should be performed at the visit per the SOA). Assessment of disease response will be considered non-evaluable if a blood transfusion was administered in the 4 weeks preceding the assessment.

In addition, subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

### 6.4.1. Assessment of Leukemic Cells by Peripheral Blood Smear or Flow Cytometry

The assessment of leukemic cells in peripheral blood will be performed locally at the timepoints specified in the SOA (see Section 12.2). The assessment can be via routine smear (hematoxylin/eosin staining) or by other methodologies (eg, flow cytometry). The assessment is required to confirm a CR in accordance with the consensus guidelines and may also be done at the investigator’s discretion at any time and, in cases of disease progression, if clinically indicated.

The local laboratory assessment will be reported in the electronic case report form (eCRF). Data extracted from the eCRF will be provided to the vendor performing the independent central primary endpoint assessment.

### 6.4.2. Imaging Requirements

Computed tomography (CT) of diagnostic quality or MRI is required in all subjects to assess hepatomegaly, splenomegaly and lymphadenopathy in accordance with the consensus guidelines.

For all imaging, the following requirements should be met:

- If CT is used it must be of diagnostic quality with intravenous (IV)-iodinated contrast, performed by either of the following modalities, depending on the site's capability:
  - as part of a combined positron emission tomography-diagnostic CT (if performed as SOC; or
  - as a separate diagnostic quality CT (with IV-iodinated contrast)
- The CT scan must include the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease.
- If IV-iodinated contrast is contraindicated per the investigator, then the diagnostic CT scan can use non-iodinated contrast. If non-iodinated contrast is not available or not recommended by the investigator, then the diagnostic CT can be nonenhanced.
- In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest without contrast.
- All screening and disease assessment CT or MRI scans will be submitted to and reviewed by an independent central reviewer.
- Technical and shipping requirements for the CT or MRI scans will be outlined in the study imaging manual.
- On-study images will be performed with the same imaging modality and anatomical location as imaged at baseline.
- A central radiological review will be made in accordance with the response criteria outlined in Section 12.3 . Moreover, the median spleen diameter will be recorded. A local investigator assessment will also be made and reported in the eCRF.

Screening/Baseline:

- Diagnostic CT or MRI scans are required at screening for all subjects, which should be performed within 28 days of enrollment/leukapheresis and as close as possible to enrollment/leukapheresis.
  - A CT or MRI scan performed at the trial site, after the subject's last line of therapy and before signing of the informed consent form (ICF) may be used (if relevant requirements described above are fulfilled) and if within 28 days before enrollment/leukapheresis and no other anticancer treatment has been administered. A screening image is required for referred subjects.

Disease Assessment:

- Follow-up CT or MRI imaging is required at the timepoints specified in the SOA and at any time disease progression is suspected.

### 6.4.3. Bone Marrow Biopsy/Aspirate

Bone marrow aspirate and biopsies will be analyzed by the investigator at the local laboratory. All bone marrow samples should be sent to the central laboratory for confirmation of diagnosis (screening bone marrow only) and measurable residual disease (MRD) assessment (refer to the central laboratory manual for details).

The following requirements for the bone marrow assessment must be met:

- SOC testing should be performed. The assessment methods, immunohistochemistry, flow cytometry or other will be reported in the eCRF.
- The morphological status of the bone marrow will be reported in the eCRF (ie, presence or absence of morphological evidence of HCL, percentage improvement in bone marrow biopsy infiltration of HCL).
- Bone marrow data extracted from the eCRF will be provided to the vendor performing the independent central primary endpoint assessment.

Screening/Baseline:

- A bone marrow aspirate and biopsy will be required in all subjects at screening and within 28 days prior to enrollment. These samples are required to be sent to the central laboratory for post-enrolment central confirmation of eligibility.

Disease Response Assessment:

- At the time of the disease response assessments specified in the SOAs (see Section 12.2), bone marrow aspiration and trephine biopsy are required to confirm a CR or PR if there is normalization of peripheral blood counts, and must be performed if disease progression is suspected.
- Bone marrow assessments may also be performed at the investigator's discretion and if clinically indicated at disease progression.
- Aspirate samples should be provided for central analysis of MRD (refer to Section 6.6.1), whenever possible at the time of CR.

Progression:

If a bone marrow biopsy is clinically indicated to confirm disease progression, a portion of this is required to be sent to the central laboratory for additional exploratory analysis.

## 6.5. Hematology Assessments

Local laboratory measurement of lymphocyte count, ANC, platelet count, and hemoglobin are required at screening and at all time points indicated in the SOA for disease assessments, per the consensus guidelines. As described in Section 6.4, assessment of ANC, platelets, or growth factors for disease response should be done at least 4 weeks after receiving any transfusion or growth factors.

## 6.6. Disease-specific Exploratory Assessments

Screening bone marrow aspirate and biopsies will be collected for central laboratory assessment of somatic mutations of *BRAF (V600E)* and B-cell lymphoma characterization by an immunohistochemistry B-cell lymphoma panel to confirm the HCL diagnosis and for use as prognostic markers in exploratory analyses.

### 6.6.1. Measurable Residual Disease Analysis

MRD assessments by evaluation of bone marrow aspirate samples or peripheral blood (if the bone marrow aspirate is fibrotic) will be performed by central analysis using allele-specific DNA polymerase chain reaction testing for *BRAF (V600E)* (sensitivity, ≥0.01% mutant copies). *BRAF* mutation MRD analysis will be performed by a centralized specialty laboratory (see the central laboratory manual) using bone marrow aspirate samples, when obtained in accordance with Section 6.4.3.

Further details are provided in the central laboratory manual.

# 7. STUDY PROCEDURES UNIQUE TO HAIRY CELL LEUKEMIA

Refer to Section 7 of the KT-US-568-0138 master protocol for the list of procedures for this study.

# 8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

Refer to Section 8 of the KT-US-568-0138 master protocol for adverse events and toxicity management. The SRT and independent DSMB for this subprotocol are described below.

## 8.1. Safety Review Team and Data Safety Monitoring Board

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 after 3 to 6 subjects in this substudy have been treated with the initial dose ($2 \times 10^6$ anti-CD19 CAR T cells/kg of body weight) and followed for 28 days, as detailed in the KT-US-568-0138 master protocol.

An independent DSMB will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review investigator-reported safety and efficacy data against the futility rules after 10 subjects (50%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 3 months after the brexucabtagene autoleucel infusion. The DSMB will also review serious adverse event (SAE) information (listings or narratives) and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout subject treatment in the study and per the DSMB charter or DSMB discretion. The DSMB may request additional safety or efficacy data or recommend modifying the study conduct. The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

SUSARs and SAE listings or narratives may be submitted to the DSMB chair as described in the DSMB charter.

Additional details regarding the SRT, DSMB, and dose-limiting toxicities are provided in Section 8.10.1, Section 8.10.2, and Section 8.1.2 of the KT-US-568-0138 master protocol, respectively.

# 9. STATISTICAL CONSIDERATIONS

An overview of the statistical considerations that are specific to this subprotocol are provided below. Refer to Section 9 of the KT-US-568-0138 master protocol for an overview of the statistical considerations that are common across indications.

Details will be provided in the statistical analysis plan (SAP) at finalization.

## 9.1. Hypothesis

An alternative hypothesis will be tested with a target 60% ORR per central assessment against a null hypothesis that the ORR is ≤ 26%. The reference rate of 26% was based on Nieva et al . The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than 26%.

The hypothesis testing will be conducted at a significance level of 0.025 (1-sided). The responses from subjects in the study population are assumed to be independent and follow a binomial distribution.

## 9.2. Definition of Substudy Endpoints

In addition to the secondary and exploratory endpoints outlined in the KT-US-568-0138 master protocol, the endpoints outlined below also apply to this substudy.

### 9.2.1. Definition of Substudy Primary Endpoint

The primary endpoint for this substudy is the ORR by central assessment defined as the proportion of subjects who achieve either CR or PR, per the response criteria described by Grever and colleagues (; see Section 12.3.1).

### 9.2.2. Definition of Substudy Secondary Endpoint

The secondary endpoint for this substudy is defined in Table 3.

**Table 3. Definition of Substudy Secondary Endpoint**

| Secondary Endpoint | Definition |
|---|---|
| ORR by investigator assessment | The proportion of subjects who achieve either CR or PR by investigator assessment |

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response

### 9.2.3. Definition of Other Substudy Endpoint of Interest

The exploratory endpoint for this substudy is defined in Table 4.

**Table 4. Definition of Substudy Exploratory Endpoint**

| Exploratory Endpoint | Definition |
|---|---|
| Rate of MRD negative response among subjects who have achieved a CR by central assessment | Rate of MRD negative response in bone marrow among subjects who have achieved a CR by central assessment, where MRD negative is defined as MRD < $10^{-4}$ per the standard assessment |

Abbreviations: CR, complete response; MRD, measurable residual disease.

## 9.3. Determination of Sample Size

This single-arm, open-label substudy will enroll and treat 20 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve a statistical power of 90% if there is at least a 34% improvement in ORR (brexucabtagene autoleucel: 60% versus historical control: 26%) with a type 1 error rate of 0.025 (1-sided) under the 2-look design based on normal approximation, with variance of standardized test statistic under null hypothesis ($H_0$) using EAST (Version 6.5). The empirical power is 87% per simulation based on binomial distribution without normal approximation. Statistically significant treatment effect can be claimed in this substudy if ≥ 10 responders (≥ 50.0%) are observed among the 20 subjects at the primary analysis.

## 9.4. Planned Analyses

### 9.4.1. Interim Analysis and Early Stopping Guidelines

An interim analysis will be conducted after 10 subjects (50%) have had the opportunity to be evaluated for response 3 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary of an ORR of 29.4% is based on the beta spending function of rho family (parameter = 2), with a crossing probability of 60% under the null hypothesis (ORR ≤ 26%). The futility boundary is crossed if ≤ 2 responders are observed among the 10 subjects. A decision will be made by the sponsor based on DSMB recommendation, with the complete benefit/risk profile of brexucabtagene autoleucel being taken into account. If the decision is made to discontinue this substudy, then this analysis will be considered the primary analysis of this substudy.

### 9.4.2. Primary Analysis

If the decision based on the interim analysis is to continue the substudy, a primary analysis will be conducted after 20 subjects have been enrolled and treated with the SRT-recommended dose of brexucabtagene autoleucel (modified intent-to-treat [mITT] analysis set) and the last subject has had the opportunity to be assessed for response at least 12 months after the brexucabtagene autoleucel infusion.

Hypothesis testing will be based on the number of objective responders observed among the 20 subjects, as described above. The point estimate of the ORR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on an exact test. In the event that more than 20 subjects are treated with the SRT-recommended dose in the substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

### 9.4.3. Follow-Up Analysis

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 30 months after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

Additional descriptive analyses may occur after the primary analysis and follow-up analysis described above have been completed.

### 9.4.4. Final Analysis

The duration of the study is 60 months. The final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

# 10. RESPONSIBILITIES

Please refer to Section 10 of the KT-US-568-0138 master protocol for details regarding investigator and sponsor responsibilities.

# 11. REFERENCES

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# 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 (ZUMA-25) – *Substudy D – Relapsed/Refractory Hairy Cell Leukemia*

Amendment 2.0, 01 MARCH 2023

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

| | |
|---|---|
| See appended signature page | See appended signature page |
| Kite Medical Monitor Name (Printed) | Signature |
| See appended signature page | |
| 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. Schedule of Assessments

**Table 5. Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods**

| Timeframe: | Screening | Pretreatment Period | | | | Treatment Period | | Post-treatment Follow-up Period | | | | Suspected Disease Progression[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrollment/ Leukapheresis | Lymphodepleting Chemotherapy | | | Infusion of Brexucabtagene Autoleucel and Monitoring | | (Each visit calculated from D0) | | | | |
| Procedure | Within 28 days before enrollment | Within approx. 5 days after eligibility confirmation | D−5 | D−4 | D−3 | D0 | D1 to D7[a] | D14 (±2 d) | D28 (±3 d) | W8 (±1 w) | M3 (±2 w) | |
| Informed Consent | X | | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Previous cancer treatment history | X | | | | | | | | | | | |
| Physical examination[c] | X | X | X | X | X | X | Daily | X | X | X | X | X |
| Weight (height at screening only) | X | X | | | | | | | | | | |
| Vital signs[d] | X | X | X | X | X | X | Daily | X | X | X | X | X |
| Neurologic examination[e] | X | | | | | X | QOD | X | X | X | X | |
| ECOG performance status | X | | X | | | | | | | | | |
| LVEF (ECHO or MUGA) | X | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | |
| Brain MRI (if applicable)[f] | X[f] | | | | | | | | | | | |
| Lumbar puncture (if applicable)[g] | X[g] | | | | | | | | | | | |
| PROs: EORTC-QLQ-C30 and EQ-5D-5[h] | X | | X | | | X | | | X | | X | |

| Timeframe: | Screening | Pretreatment Period | | | | Treatment Period | | Post-treatment Follow-up Period | | | | Suspected Disease Progression[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrollment/ Leukapheresis | Lymphodepleting Chemotherapy | | | Infusion of Brexucabtagene Autoleucel and Monitoring | | (Each visit calculated from D0) | | | | |
| Procedure | Within 28 days before enrollment | Within approx. 5 days after eligibility confirmation | D−5 | D−4 | D−3 | D0 | D1 to D7[a] | D14 (±2 d) | D28 (±3 d) | W8 (±1 w) | M3 (±2 w) | |
| ***Disease response assessments (hematology components captured within CBC under local labs, please also refer to the imaging manual and central laboratory manual for guidance)*** | | | | | | | | | | | | |
| Imaging CT/MRI[i] | X | | | | | | | | X | | X | X |
| Bone marrow aspirate and biopsy[j] | X | | | | | | | | X | | X | X |
| Assessment of leukemic cells in peripheral blood[k] | X | | | | | | | | X | | X | X |
| Overall response assessment | | | | | | | | | X | | X | X |
| ***Local laboratory assessment*** | | | | | | | | | | | | |
| Chemistry panel (CrCl at screening) (serum) | X | X | X | X | X | X[l] | Daily | X | X | X | X | X |
| CBC with differential (blood) | X | X | X | X | X | X[l] | Daily | X | X | X | X | X |
| LDH[m], CRP, ferritin (serum) | | X | X | | | X[l] | Daily | X | X | | | |
| β-hCG pregnancy test ([WOCBP] serum or urine) | X | X[n] | X[n] | | | | | | X | | X | X |
| Serology for EU/CH/UK sites (serum)[o] | X[o] | X[o] | | | | | | | | | | |
| HIV positive subjects only: HIV viral load and CD4 count | X[p] | | | | | X | | | X | | X | |

| Timeframe: | Screening | Pretreatment Period | | | | Treatment Period | | Post-treatment Follow-up Period | | | | Suspected Disease Progression[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrollment/ Leukapheresis | Lymphodepleting Chemotherapy | | | Infusion of Brexucabtagene Autoleucel and Monitoring | | (Each visit calculated from D0) | | | | |
| Procedure | Within 28 days before enrollment | Within approx. 5 days after eligibility confirmation | D−5 | D−4 | D−3 | D0 | D1 to D7[a] | D14 (±2 d) | D28 (±3 d) | W8 (±1 w) | M3 (±2 w) | |
| ***Central laboratory assessments (please refer to the central laboratory manual for guidance)*** | | | | | | | | | | | | |
| CBC with differential (blood) | | X | | | | X[l] | D3, D7 | X | X | X | X | X |
| Anti-brexucabtagene autoleucel antibodies (serum) | | X[q] | | | | | | | X | | X | X |
| Analytes, including cytokines (serum/plasma)[r] | | X[q] | | | | X[l] | D1, D2, D3, D5, D7 | X | X | X | X | X |
| Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs)[r] | | X[q] | | | | X[l] | D3, D7 | X | X | X | X | X |
| RCR (PBMCs)[s] | | | | | | X[l] | | | | | X | |
| MRD assessment via peripheral blood (only in case of fibrotic bone marrow aspirate) | X | | | | | | | | (X[j,k]) | | (X[j,k]) | (X[j,k]) |
| Leukapheresis | | X | | | | | | | | | | |
| Fludarabine/ cyclophosphamide[t] | | | X | X | X | | | | | | | |
| Brexucabtagene autoleucel infusion (IV) and premedications | | | | | | X | | | | | | |
| Concomitant medications | X | X | X | X | X | X | Daily | X | X | X | X | X |
| Adverse events and serious adverse events[u] | | | X | X | X | X | Daily | X | X | X | X | X |

Abbreviations: approx., approximately; ASCO, American Society of Clinical Oncology; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CR, complete response;CrCl, creatinine clearance; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebospinal fluid; CT, computed tomography; D/d, day; ECG, electrocardiogram;ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTCQLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level scale; EU, European Union; hCG, human chorionic gonadotropin; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICF, informed consent form; IV, intravenous; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction, M, month; MRD, measurable residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PBMCs, peripheral blood mononuclear cells; PR, partial response; PRO, patient-reported outcome; QOD, every other day; RCR, replication-competent retrovirus; SOA, schedule of assessments; SOC, standard of care; UK, United Kingdom; W/w, week, WOCBP, women of child bearing potential.

**Note: Please refer to the footnotes listed below in parallel with Section 6 of this protocol and the KT-US-568-0138 master protocol.**

a For EU, CH and UK, post-infusion monitoring extended by monitoring on Days 8, 9, and 10 (vital signs, blood draw for chemistry panel with CRP and CBC and neurological examination). For EU and UK, the subject may remain hospitalized or return to the clinic daily for this extended monitoring, at the discretion of the investigator. For CH, patients must remain hospitalized.

b Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

c Physical examination will include assessment of splenomegaly, hepatomegaly, and lymphadenopathy. Subjects with symptoms or clinical signs related to CRS should undergo physical examination at least daily until symptoms resolve to baseline.

d Vital signs will include blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. It is recommended that vital signs are monitored during and after study treatment and then routinely per institutional guidelines. Vital signs may be monitored more frequently as clinically indicated.

e Neurologic examination: A neurologic examination, including an ICE cognition assessment (may also include the mini-mental status exam), should be performed on Day 0 before the brexucabtagene autoleucel infusion and can be performed every other day during the hospitalization period. If a subject hospitalization is extended beyond Day 7, a neurologic examination including a cognition assessment will continue to be performed as clinically indicated.

f Brain MRI:

- Screening through start of lymphodepletion: At screening, subjects with current symptoms or clinical signs of CNS malignancy, such as severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurological findings on physical examination must undergo brain MRI to rule out current CNS metastasis, in which case such subjects are not eligible for the study. After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat MRI is required to reassess eligibility prior to the start of lymphodepleting chemotherapy (See Section 6.2).
- Post-infusion: Subjects with new-onset symptoms of CNS malignancy/disease, as described above, are recommended to have a brain MRI. In addition, in the case of CRS and ICANS refer to the ASCO management guidelines for guidance of requirements for brain imaging . In summary: i) brain MRI can be considered for all grades of CRS; ii) brain MRI or other neuroimaging and can be considered for ICANS Grade 2 or higher, as supported by the ASCO management guidelines.

g Lumbar puncture: Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.

- Screening: Subjects with a history of CNS malignancy, or leptomeningeal carcinomatosis, or symptoms/clinical findings associated with CNS malignancy (eg, new-onset severe headaches, neck stiffness, or focal neurologic findings) will have a lumbar puncture performed at screening for examination of CSF to determine the presence of CNS malignancy.
- Post-infusion: Subjects with symptoms or clinical signs of CNS malignancy, such as new-onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical examination, will have a lumbar puncture for examination of CSF including sending a sample to the central laboratory. In the case of CRS and ICANS refer to the (ASCO management guidelines for guidance for requirements for lumbar puncture examination . In summary: i) a lumbar puncture is recommended for consideration in cases of CRS; ii) For ICANS, a lumbar puncture is recommended for Grade 3 or higher neurotoxicity and may be considered for Grade 2 (see Section 6.3).

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

i Imaging CT/MRI:

- Screening/baseline: CT or MRI (for assessment of liver, spleen and lymph nodes) should be performed as close to enrollment as possible and within 28 days before enrollment/leukapheresis for eligibility (unless imaging is available from SOC assessment within 28 days before enrollment).
- Disease assessment: Follow-up imaging is required at the timepoints specified in the SOA and at any time disease progression is suspected.

j Bone marrow aspirate and biopsy:
- Screening/baseline: A bone marrow aspirate and biopsy are required at screening and within 28 days prior to enrollment. These samples are required to be sent to the central laboratory for post-enrolment central confirmation of eligibility (refer to the central laboratory manual for details).
- Disease assessment: Bone marrow aspiration and biopsy are required at Day 28 and Month 3, thereafter may also be done at the investigator's discretion and at any time to confirm a CR or PR and must be performed if disease progression is suspected. Submission of bone marrow aspirate to the central lab is required at the time of CR for MRD assessment by *BRAF* mutation. If the bone marrow aspirate is fibrotic, a peripheral blood sample is required for central laboratory MRD assessment by *BRAF* mutation.

k Assessment of circulating leukemic cells: The assessment of circulating leukemic cells in peripheral blood can be via routine smear Wright's stain) or by other methodologies (eg, flow cytometry). The assessment may be done at the investigator's discretion and at any time to confirm a CR. If the bone marrow aspirate is fibrotic, submission of circulating blood to the central lab is also required for MRD assessment by BRAF mutation.

l Assessments may be performed on the day before administration of brexucabtagene autoleucel (ie, on Day −1). For tests performed at the central laboratory, this decision will be driven by the availability of the central laboratory to process samples on the day they are collected from the subject (refer to the laboratory manual for holidays). For samples collected on Day 0, collection will occur before the start of the brexucabtagene autoleucel infusion.

m LDH should continue to be monitored after the baseline assessment as clinically indicated.

n Pregnancy test (serum or urine): For EU/CH/UK study sites, the test will be completed within 7 days before both leukapheresis and lymphodepleting chemotherapy for women of childbearing potential.

o Serology tests for EU/CH/UK study sites (serum): Serology tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and EU/CH/UK regulations. Testing may be done within the 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.

p Hepatitis B and C testing is also required at screening.

q Baseline for assessments of brexucabtagene autoleucel CAR T cells, analytes, and anti-brexucabtagene autoleucel antibodies: A sample will be collected at enrollment/before the leukapheresis procedure.

r Analytes (including cytokines) (serum) and brexucabtagene autoleucel CAR T cells (PBMCs):
- Samples on Day 3 may be collected ± 1 day.
- If a subject is re-admitted to the hospital after the initial hospitalization observation period with any brexucabtagene autoleucel-related adverse events, blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- If the subject experiences a Grade 3 or higher brexucabtagene autoleucel-related toxicity, such as Grade 3 CRS or neurologic event, 1 additional blood draw for brexucabtagene autoleucel CAR T cells (PBMCs) and serum analytes will be collected at the time of the Grade 3 or higher brexucabtagene autoleucel-related toxicity and upon resolution of the event, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- Blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes should be collected at the time of disease progression prior to starting subsequent anticancer therapy.
- Exploratory T-cell immunogenicity will be performed with PBMCs at leukapheresis and Month 3. Extra blood collection is required for such testing.
- Exploratory analyses will include lymphocyte subsets.

s RCR (PBMCs):
- Samples will be collected at baseline (before CAR T-cell infusion) and at Month 3.
- If a subject develops a secondary malignancy during the study, every effort should be made to obtain a blood sample to assay for RCR and vector elements. In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, RCR, presence of common cancer-drivers/mutations and insertional mutagenesis.

t Mesna will be administered around the time of the cyclophosphamide dose according to institutional standards (refer to Section 5.1.2.3 and Section 7.5.3 of the KT-US-598-0138 master protocol).

u Collection of serious adverse events starts from signing of the screening ICF, and collection of adverse events starts from commencement of the leukapheresis procedure.

## Table 6. Schedule of Assessments: Post-treatment Follow-up Period

| **Timeframe:** | **Long-term Follow-up Period (Each visit calculated from Day 0)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **M6 (± 2 w)** | **M9 (± 2 w)** | **M12 (± 2 w)** | **M18 (± 1 M)** | **M24 (± 1 M)** | **M30 (± 1 M)** | **M36 (± 1 M)** | **M48 (± 3 M)** | **M60 (± 3 M)** | **Suspected Disease Progression[a]** |
| Physical examination[b] | X | X | X | X | X | X | X | X | X | X |
| Vital signs | | | | | | | | | | X |
| PROs: EORTC-QLQ-C30 and EQ-5D-5L[c] | X | X | X | X | X | | | | | |
| ***Disease response assessment (hematology components captured within CBC under local labs, please also refer to the imaging manual and central laboratory manual for guidance)*** | | | | | | | | | | |
| Imaging CT/MRI[d] | X | X | X | X | X | X | X | X | X | X |
| Bone marrow aspirate and biopsy[e] | | | | | X | | | | | X |
| Assessment of leukemic cells in peripheral blood[f] | | | | | X | | | | | X |
| Overall response assessment[] | X | X | X | X | X | X | X | X | X | X |
| ***Local laboratory assessments*** | | | | | | | | | | |
| CBC with differential (blood)[g] | X | X | X | X | X | X | X | X | X | X |
| Chemistry panel (serum) | | | | | | | | | | X |
| LDH[h] | | | | | X | | | | | X |
| B-hCG pregnancy test ([WOCBP] serum or urine) | | | | | | | | | | X |
| HIV positive subjects only: HIV viral load and CD4 count | X | X | X | X | X | X | X | X | X | |

| Timeframe: | Long-term Follow-up Period (Each visit calculated from Day 0) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **M6 (± 2 w)** | **M9 (± 2 w)** | **M12 (± 2 w)** | **M18 (± 1 M)** | **M24 (± 1 M)** | **M30 (± 1 M)** | **M36 (± 1 M)** | **M48 (± 3 M)** | **M60 (± 3 M)** | **Suspected Disease Progression[a]** |
| ***Central laboratory assessments (please refer to the central laboratory manual for guidance)*** | | | | | | | | | | |
| CBC with differential (blood)[g] | X | X | X | X | X | | | | | X |
| Analytes, including cytokines (serum/plasma)[i] | | | | | | | | | | X |
| Anti-brexucabtagene autoleucel antibodies (serum) | X | X | X | | | | | | | X |
| Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs)[i] | X | X | X | X | X | | | | | X |
| RCR (PBMCs)[j] | X | | X | | | | | | | |
| MRD assessment via peripheral blood (only in case of fibrotic bone marrow aspirate)[e] | (X)[e] | | | | | | | | | (X)[e] |
| All brexucabtagene autoleucel-related SAEs and any deaths regardless of causality | X | X | X | X | X | X | X | X | X | X |
| Targeted AE/SAEs[k] | X | X | X | X | X[k] | X | X[k] | X | X | X |
| Targeted concomitant medications[l] | X | X | X | X | X | X | X[l] | X | X | X |
| Subsequent therapy for HCL[m] | X | X | X | X | X | X | X | X | X | X |
| Survival status[n] | X | X | X | X | X | X | X | X | X | X |

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; CT, computed tomography; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level scale; GP, general practitioner; HCL, hairy cell leukemia; HCP, healthcare provider; LDH, lactate dehydrogenase; LTFU, long-term follow-up; M, month; MRD, measurable residual disease; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PR, partial response; PROs, patient-reported outcomes; RCR, replication-competent retrovirus; SAE, serious adverse event; SOA, schedule of assessments; w, weeks.

**Note: Please refer to the footnotes listed below in parallel with Section 6 of this protocol and the KT-US-568-0138 master protocol.**

a Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

b Physical examination will include assessment of splenomegaly, hepatomegaly, and lymphadenopathy.

c PROs are to be completed before any assessments or procedures are performed (excluding blood draws) and before the subject receives any disease status information.

d Follow-up imaging diagnostic CT or MRI is required at the timepoints specified. Additional assessments may be performed, if clinically indicated, during the course of the study at any time disease progression is suspected.

e Bone marrow aspiration and biopsy may be done at the investigator's discretion and at any time to confirm a CR or PR, and must be performed if disease progression is suspected. Submission of bone marrow aspirate to the central lab is required at the time of CR for MRD assessment by *BRAF* mutation. If the bone marrow aspirate is fibrotic, a peripheral blood sample is required for central laboratory MRD assessment by *BRAF* mutation.

f Assessment of circulating leukemic cells in peripheral blood can be via routine smear (hematoxylin/eosin staining) or by other methodologies (eg, flow cytometry). The assessment may be done at the investigator's discretion and at any time to confirm a CR and at disease progression, if clinically indicated.

g CBC with differential (blood):

- Local laboratory assessments: Blood will be collected at the timepoints specified through Month 60 or until disease progression, whichever occurs first, and sent to the local laboratory for clinical/safety evaluation.
- Central laboratory assessments: Blood will be collected at the timepoints specified through Month 24 and sent to the central laboratory for assessment of CBC with differential (these samples are in addition to samples collected at the specified timepoints that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).

h LDH should continue to be monitored after the baseline assessment as clinically indicated.

i Analytes (including cytokines) (serum) and brexucabtagene autoleucel CAR T cells (PBMCs):

- If a subject is re-admitted to the hospital after the initial hospitalization observation period with any brexucabtagene autoleucel-related AEs, blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- If the subject experiences a Grade 3 or higher brexucabtagene autoleucel-related toxicity, such as Grade 3 CRS or neurologic event, 1 additional blood draw for brexucabtagene autoleucel CAR T cells (PBMCs) and serum analytes will be collected at the time of the Grade 3 or higher brexucabtagene autoleucel-related toxicity and upon resolution of the event, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- Blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes should be collected at the time of disease progression prior to starting subsequent anticancer therapy.
- Exploratory analyses will include lymphocyte subsets.

j RCR (PBMCs):

- Samples will be collected at Months 6 and 12 and analyzed. Additional samples will be collected and analyzed only if an RCR event is clinically suspected and/or a subject's PBMC sample tests positive for RCR within the first 12 months following brexucabtagene autoleucel infusion.
- If a subject develops a secondary malignancy during the study or follow-up and RCR is suspected, every effort should be made to obtain a blood sample to assay for RCR and vector elements. In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, RCR, presence of common cancer-drivers/mutations and insertional mutagenesis (see Section 6.3.15.3 of the KT-US-598-0138 master protocol).

k Targeted AEs/SAEs include neurologic events, hematologic events, serious infections, autoimmune disorders, and secondary malignancies. From 3 months after the brexucabtagene autoleucel infusion, targeted AEs/SAEs will be reported through Month 60 after the initial brexucabtagene autoleucel infusion or until disease progression and/or the start of subsequent anticancer therapy, whichever occurs first. After Month 60, the subject will transition to the LTFU study where targeted AEs/SAEs will be reported through 15 years. All new malignancies (defined as the development of any new malignancies occurring after the administration of brexucabtagene autoleucel) are to be reported; however, only secondary malignancies (defined as the development of any new malignancy suspected to be possibly related to brexucabtagene autoleucel) are considered to be targeted AEs/SAEs.

l Targeted concomitant medications will be collected up to 60 months after the brexucabtagene autoleucel infusion or until disease progression or the start of subsequent anticancer therapy, whichever occurs first.

m Subsequent anticancer therapy administered after brexucabtagene autoleucel infusion for a subject's disease will be collected until 1 of the following occurs: subject completes the post-treatment follow-up period, is considered lost to follow-up, withdraws consent, or dies. The subject and/or the referring HCP and/or GP may be contacted directly by telephone or email to collect information about subsequent therapy.

n Subject and/or referring HCP and/or GP may be contacted directly by telephone or email to assess survival status.

## 12.3. Disease Response Criteria

Response criteria in hairy cell leukemia based on Grever et al 2017 .

### 12.3.1. Response Criteria in HCL

| | |
|---|---|
| **Complete Response (CR)** | • No evidence of leukemic cells in the peripheral blood and/or by routine H/E staining of bone marrow.<br>• Resolution of any splenomegaly. by computed tomography (CT) or magnetic resonance imaging (MRI).<br>• Normalization CDC as exhibited by:<br>— absolute neutrophil count > 1.5 x $10^9$/L,<br>— platelets >100 x 109/L, and<br>— hemoglobin > 11.0 g/dL without blood transfusions for at least 4 weeks. |
| **Partial Response (PR)** | The subject must have the following (if abnormal prior to treatment):<br>• ≥50% reduction in organomegaly by CT or MRI, or resolution to size consistent with CR,<br>• minimum of 50% improvement in bone marrow biopsy infiltration with hairy cell leukemia<br>• Normalization CBC as exhibited by:<br>— ANC > 1.5 x 109/L<br>— Platelets ≥ 100 x 109/L<br>— Hemoglobin ≥ 11.0 g/dL without blood transfusions for at least 4 weeks. |
| **Stable Disease (SD)** | Stable disease will be characterized by not meeting the criteria for CR, partial response, or progressive disease (PD) as outlined below. |
| **Progressive Disease (PD)** | PD is defined by at least one of the following compared to pretreatment:<br>• increase in symptoms related to disease<br>• ≥ 25% increase in organomegaly<br>• ≥ 25% decline in hematologic parameters (ANC, Hgb, and/or platelets |

Abbreviations: ANC; absolute neutrophil count; CR, complete response; CBC, complete blood count; CT, computed tomography; magnetic resonance imaging; PD, progressive disease; PR, partial response; SD, stable disease.

## 12.4. Protocol Amendment History

### 12.4.1. 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 study sites planned | Number of study sites increased from approximately 40 to 50 | Increased the number of study sites to optimize enrolment |
| Section 12.2 Schedule of assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods | Removal of EORTC-QLQ-C30 and EQ-5D PRO collection at enrollment/leukapheresis timepoint | Correction of typo. The PRO assessment will be at Day -5 in all subjects |
| Section 6.4.3 Bone marrow biopsy/aspirate | Disease Response Assessment:<br>• Added clarification that aspirate samples should be provided for central analysis of MRD (refer to Section 6.6.1), whenever possible**, at the time of CR** | Addition for clarification, since central analysis of MRD is applicable only at the time of CR |
| Section 12.2 Schedule of assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods | Footnote j: Bone marrow aspirate and biopsy:<br>Added clarification that disease assessment:<br>Bone marrow aspiration and biopsy are required at Day 28 and Month 3, thereafter may also be done at the investigator's discretion and at any time to confirm a CR or PR and must be performed if disease progression is suspected. Submission of bone marrow aspirate to the central lab is required **at the time of CR for MRD assessment** by BRAF mutation | Addition for clarification, since central analysis of MRD is applicable only at the time of CR |
| Section 12.2 Schedule of assessments, Table 6 Schedule of Assessments: Post-treatment Follow-up Period | Added clarifying text in Footnote e: Bone marrow aspiration and biopsy may be done at the investigator's discretion and at any time to confirm a CR or PR and must be performed if disease progression is suspected. Submission of bone marrow aspirate to the central lab is **required at the time of CR** for MRD assessment by BRAF mutation. | Addition for clarification, since central analysis of MRD is applicable only at the time of CR |

### 12.4.2. Amendment 1.1 EU-specific Amendment (dated 12 January 2023)

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

For changes from Amendment 1 to Amendment 2, please refer to Sections 12.4.2 and Section 12.4.3. Amendment 2 incorporates all changes in Amendment 1.1 together with the changes outlined in Section 12.4.3.

Protocol changes that are common across all substudies are detailed in the Master protocol (Appendix 12.10).

| 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 Statistical Methods and Sections 9.1 Hypothesis and 9.4.2 Primary Analysis | • "significantly" removed from statement that "The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than 26%."<br>• Text edited to now state that the p-value 'will be' calculated based on an exact test, rather than 'may be' tested. | For clarity |
| Section 3.1 Study Design | Added text to detail that the end of study is defined in the Master protocol (Section 3.4). (Defined as the LPLV within each specific substudy) | For clarity |
| Synopsis Eligibility Criteria Unique to the HCL Substudy and Section 4.2.1 HCL Substudy-specific Inclusion Criteria | Inclusion criterion 1 updated to state that "Subjects will be eligible regardless of the duration of remission prior to relapse and must have confirmed HCL by immunophenotyping and histology with a need for therapy based on at least one of the following criteria" | For clarity and to align with updated diagnostic methodology for HCL immunophenotyping |
| Section 12.2 Schedule of Assessments Table 5 | Pregnancy test added at Day 28 | Alignment with CTFG guidelines for pregnancy testing following administration of fludarabine and cyclophosphamide |

### 12.4.3. 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 |
|---|---|---|
| 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) – *Substudy D – Relapsed/Refractory Hairy Cell Leukemia"*. The evaluation of safety (secondary endpoint) 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 4.2.1 Inclusion Criteria | Inclusion criteria #1 edited to include subjects diagnosed with either r/r classic or r/r HCL variant | For clarification |
| Section 6.2 Brain Magnetic Resonance Imaging | Added clarification that<br>• at screening CNS involvement will be assessed by local review, and images will not be sent for central review<br>• A brain MRI only needs to be submitted to the independent central reviewer when there is evidence of disease progression | For clarification |
| Section 12.2 Schedule of Assessments Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods | Serology for EU, **CH** and EU<br><br>MRD assessment added at screening | Request by Swiss Regulatory Authority and correction for baseline MRD assessment |
| Section 12.2 Schedule of assessments Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods | Footnote 'a': ForEU and UK, the subject may remain hospitalized or return to the clinic daily for this extended monitoring, at the discretion of the investigator. For CH, patients must remain hospitalized for 10 days post brexucabtagene autoleucel infusion | Request by Swiss Regulatory Authority |
| Section 12.2 Schedule of assessments Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods | Footnote 'j' amended to include "if the bone marrow aspirate is fibrotic, a peripheral blood sample is required for central laboratory MRD assessment by *BRAF* mutation". | For clarification and alignment with subprotocol Section 6.6.1 |
| Section 12.2 Schedule of assessments Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods | Footnotes 'n' pregnancy testing and 'o' serology testing updated to include Switzerland | Request by Swiss Regulatory Authority and alignment with Master protocol Section 6 |

| Section Number and Name | High-level Description of Change | Brief Rationale |
|---|---|---|
| Section 12.2 Schedule of assessments Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods | Footnote 'r': Clarification added that samples on Day 3 may be collected ± 1 day | Provides flexibility regarding central laboratory sample collection when the Day 3 visit falls over a weekend |
| Section 12.2 Schedule of assessments, Table 6 Schedule of Assessments: Post-treatment Follow-up Period | Visit M18 window changed from ±1 week to ±1 month | Provides added flexibility |
| Section 12.3.1 Response Criteria in HCL | Progressive disease definition updated to include "increase in symptoms related to disease"; and "≥ 25% increase in organomegaly" | Correction of missing criteria |