



CLINICAL STUDY SUBPROTOCOL

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) – <i>Substudy A – Relapsed/Refractory Waldenstrom Macroglobulinemia</i>
Note:	This subprotocol should be used in conjunction with the KT-US-568-0138 master protocol
Protocol Number:	KT-US-568-0138-A (ZUMA-25A)
Indication:	Relapsed/refractory Waldenstrom macroglobulinemia
Kite Investigational Product	Brexucabtagene Autoleucel
Kite IND Number:	028542
EU CT Number:	2022-501259-10-00
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:	Original: 23 May 2022 Amendment 1.0: 20 July 2022 Amendment 1.1: 12 January 2023 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.

CONFIDENTIALITY STATEMENT
This document contains confidential information of Kite Pharma, Inc., a wholly owned subsidiary of Gilead Sciences Inc. This document must not be disclosed to anyone other than the study site research staff, collaborators, and members of the Institutional Review Board/Independent Ethics Committee, a scientific review board, or an equivalent. The information in this document cannot be used for any purpose other than the conduct of the clinical investigation without the prior written consent of Kite Pharma, Inc.

TABLE OF CONTENTS

CLINICAL STUDY SUBPROTOCOL	1
TABLE OF CONTENTS	3
LIST OF IN-TEXT TABLES	4
PROTOCOL SYNOPSIS	5
LIST OF ABBREVIATIONS	10
1. INTRODUCTION	11
1.1. Disease Background	11
1.1.1. Epidemiology	11
1.1.2. Diagnosis	11
1.1.3. Frontline Treatment	11
1.1.4. Second-line Treatment	12
2. OBJECTIVES AND ENDPOINTS	13
3. STUDY DESIGN	14
3.1. Study Design	14
3.1.1. Rationale for Study Design Elements	15
4. SUBJECT POPULATION	16
4.1. Number of Subjects and Subject Selection	16
4.2. Eligibility Criteria	16
4.2.1. WM Substudy-specific Inclusion Criteria	16
4.2.2. WM Substudy-specific Exclusion Criteria	17
5. STUDY TREATMENT	18
5.1. Description of Study Treatment	18
5.2. Prior and Concomitant Medications and Permitted Treatments	18
6. STUDY ASSESSMENTS UNIQUE TO WALDENSTROM MACROGLOBULINEMIA	19
6.1. Clinical Laboratory Tests	19
6.2. Brain Magnetic Resonance Imaging	20
6.3. Lumbar Puncture	21
6.4. Disease Assessments	21
6.4.1. Assessment of Quantitative Monoclonal IgM, IgA, and IgG	22
6.4.2. Assessment of Serum Protein Electrophoresis	22
6.4.3. Serum Immunofixation	22
6.4.4. Imaging Requirements	23
6.4.5. Bone Marrow Biopsy/Aspirate	24
6.5. Disease-specific Exploratory Assessments	25
7. STUDY PROCEDURES UNIQUE TO WALDENSTROM MACROGLOBULINEMIA	26
7.1. Screening	26
8. ADVERSE EVENTS AND TOXICITY MANAGEMENT	27
8.1. Safety Review Team and Data Safety Monitoring Board	27
9. STATISTICAL CONSIDERATIONS	28
9.1. Hypothesis	28
9.2. Definition of Substudy Endpoints	28

9.2.1.	Definition of Substudy Primary Endpoint.....	28
9.2.2.	Definition of Substudy Secondary Endpoints	28
9.3.	Determination of Sample Size	29
9.4.	Planned Analyses.....	29
9.4.1.	Interim Analysis and Early Stopping Guidelines	29
9.4.2.	Primary Analysis	29
9.4.3.	Follow-Up Analysis.....	30
9.4.4.	Final Analysis	30
10.	RESPONSIBILITIES	31
11.	REFERENCES	32
12.	APPENDICES	34
12.1.	Sponsor and Investigator Signature Page	35
12.2.	Schedule of Assessments	36
12.3.	Disease Response Criteria	47
12.3.1.	Definitions of Response for Waldenstrom Macroglobulinemia.....	47
12.3.2.	Waldenstrom Macroglobulinemia International Workshop Diagnosis Criteria.....	47
12.4.	Protocol Amendment History	48
12.4.1.	Amendment 1.0 (dated 20 July 2022)	48
12.4.2.	Amendment 1.1 EU-specific Amendment (dated 12 January 2023).....	48
12.4.3.	Amendment 2.0 (dated 01 March 2023).....	49

LIST OF IN-TEXT TABLES

Table 1.	Substudy-specific Objectives and Endpoints	13
Table 2.	Clinical Laboratory Tests for Disease-specific Assessments	19
Table 3.	Definitions of Substudy Secondary Endpoints	29
Table 4.	Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Period.....	36
Table 5.	Schedule of Assessments: Post-treatment Follow-up Period	44

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 A – Relapsed/Refractory Waldenstrom Macroglobulinemia	
Indication: Adult subjects with relapsed/refractory (r/r) Waldenstrom macroglobulinemia (WM)	
Kite IND Number: 028542 EU CT Number: 2022-501259-10-00 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
<ul style="list-style-type: none"> To evaluate the efficacy of brexucabtagene autoleucel in WM by determining the combined rate of complete response (CR) and very good partial response (VGPR) by central assessment per the Sixth International Workshop in WM 	<ul style="list-style-type: none"> Combined rate of CR and VGPR rate by central assessment defined as the proportion of subjects who achieve either CR or VGPR
Secondary Objectives	Secondary Endpoints
<ul style="list-style-type: none"> To determine the efficacy of brexucabtagene autoleucel in subjects with WM, by determining the Objective Response Rate (ORR) by central assessment 	<ul style="list-style-type: none"> ORR, defined as the proportion of subjects who achieve a best response of CR, VGPR, or partial response (PR)
<ul style="list-style-type: none"> To determine the combined rate of CR and VGPR by investigator assessment 	<ul style="list-style-type: none"> Combined CR and VGPR rate by investigator assessment defined as the proportion of subjects who achieve either CR or VGPR
<ul style="list-style-type: none"> To determine the rates of individual responses by central assessment 	<ul style="list-style-type: none"> Rate of VGPR and PR, separately

Study Design: This substudy protocol contains details regarding all elements of the study that are unique to subjects with WM. 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 WM.

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 the further conduct of this substudy.

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

Subjects enrolled in this substudy, if already receiving a Bruton's tyrosine kinase (BTK) inhibitor, may receive ibrutinib through screening and leukapheresis at the discretion of the investigator, as described in Section 5.2 and Section 7.1.

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 60 subjects with r/r WM will be enrolled 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 WM

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 WM Substudy:

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

WM Substudy-specific Inclusion Criteria:

- 1) Confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (see Section 12.3.2)

- 2) Relapsed or refractory disease after 2 or more lines of therapy. Subjects will be eligible regardless of the duration of remission prior to relapse.
 - Prior therapy must have included a BTK inhibitor. Also, chemotherapy and/or a proteasome inhibitor must have been attempted, with either subsequent documented disease progression or no response (stable disease)
- 3) Requiring treatment as defined in the recommendations from the Second International Workshop on WM
- 4) Measurable disease, defined as presence of serum immunoglobulin (Ig) M with a minimum IgM level of > 2 times the upper limit of normal of each institution is required
- 5) The inclusion criteria concerning washout periods prior to leukapheresis in the KT-US-568-0138 master protocol must be met, with the exception that ibrutinib may be continued through leukapheresis and up to 5 half-lives (30 hours) prior to the start of lymphodepletion

WM Substudy-specific Exclusion Criteria:

- 1) History of allogeneic stem cell transplantation. A prior autologous stem cell transplantation is allowed, but at least 6 months should have elapsed
- 2) Plasmapheresis for symptomatic hyperviscosity or serum IgM > 5,000 mg/dL < 35 days prior to the screening IgM assessment
- 3) Exclusion of IgM monoclonal gammopathy of undetermined significance or IgM multiple myeloma
- 4) Presence of a central nervous system involvement (Bing-Neel syndrome). Subjects with a prior history of Bing-Neel syndrome are eligible if they show a negative cerebrospinal fluid and no involvement by imaging

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 of 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 to 6 subjects in this substudy have been treated with the initial dose (2×10^6 anti-CD19 CAR T cells/kg 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 20% combined CR and VGPR rate per central assessment against a null hypothesis that the combined CR and VGPR rate is $\leq 6\%$. The hypothesis is that the combined CR and VGPR to brexucabtagene autoleucel per central assessment is $> 6\%$.

Sample Size Calculation: This single-arm, open-label substudy will enroll and treat 60 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve a statistical power of 88% if there is at least a 14% improvement in combined CR and VGPR rate (brexucabtagene autoleucel: 20% versus historical control: 6%) at an alpha level of 0.025 (1-sided).

Analyses: An interim analysis will be conducted after 20 subjects (33%) have had the opportunity to be evaluated for response 6 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 overall response rate of 7.5% is based on the beta spending function of rho family (parameter = 0.35), with a crossing probability of 61% under the null hypothesis (overall response rate $\leq 6\%$). 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, a primary analysis will be conducted after 60 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 responders observed among the 60 subjects, as described above. The point estimate of the combined CR and VGPR rate 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 60 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 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

ASCO	American Society of Clinical Oncology
BTK	Bruton's tyrosine kinase
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
EMD	extramedullary disease
ICANS	immune effector cell-associated neurotoxicity syndrome
Ig	immunoglobulin
IP	investigational product
MRI	magnetic resonance imaging
PET	positron emission tomography
PR	partial response
r/r	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of assessments
SOC	standard of care
SPEP	serum protein electrophoresis
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
VGPR	very good partial response
WBC	white blood cell
WM	Waldenstrom macroglobulinemia

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

Waldenstrom macroglobulinemia (WM) is a B-cell disorder characterized by immunoglobulin M monoclonal gammopathy and lymphoplasmacytic cell infiltration of the bone marrow and other organs. WM is a rare disorder with approximately 1,000 to 1,500 new cases diagnosed every year in the United States, and is predominantly observed in older adults (median age at the time of diagnosis is 60 to 75 years) .

1.1.2. Diagnosis

To establish a diagnosis of WM, it is mandatory to demonstrate both an IgM monoclonal gammopathy and bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation . The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIgM+, CD19+, CD20+, and CD22+. The lymphocytes in WM are typically negative for CD5, CD10, or CD23. However, this should not exclude diagnosis as exceptions occur and about 10% to 20% of cases may express CD5, CD10, or CD23. *MYD88 (L265P)* mutations are present in > 90% of patients with WM and can help differentiate WM/lymphoplasmacytic lymphoma from IgM myeloma or marginal zone lymphoma .

1.1.3. Frontline Treatment

Similar to other indolent lymphomas, a ‘watch and wait’ approach is a standard paradigm for asymptomatic patients, and current guidelines advise that treatment should only be initiated for WM patients who have hyperviscosity or additional symptoms such as neuropathy, symptomatic adenopathy, organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, anemia, or presence of cytopenia . While treatment options have improved over recent years, no currently approved therapies have curative potential, and all patients with WM ultimately relapse . Accordingly, treatment strategies must consider patient age and comorbidities, and balance disease control with compromising quality of life, risk of long-term toxicities, and the development of secondary malignancies. In general, therapeutic agents that are potentially limiting to future treatment options should be avoided during the initial therapy (eg, continuous oral alkylating agents or nucleoside analogs, especially if an autologous stem cell transplantation is being considered). The reasons for this approach is an increased risk for disease transformation or development of myelodysplastic syndromes or secondary acute myeloid leukemia .

The recommended frontline therapies currently include combinations of bendamustine and rituximab with and without dexamethasone. In addition, targeted therapy with a Bruton's tyrosine kinase (BTK) inhibitor is currently recommended either with or without rituximab. Various other drugs and combinations exist both as preferred but also as alternative primary therapy depending on the comorbidities and frailty of the patients. These include proteasome inhibitors such as ixazomib or carfilzomib and nucleoside analogues such as cladribine or fludarabine.

1.1.4. Second-line Treatment

Upon relapse, administering the same regimen used for primary treatment is reasonable if the regimen was well tolerated and induced prolonged response. While the introduction of BTK inhibitors has substantially improved outcomes in the relapsed/refractory (r/r) setting, the efficacy of BTK inhibitors can be negatively impacted by mutations in *CXCR4* and *MYD88* that are observed in a substantial number of patients.

While another treatment option is allogeneic stem cell transplant, which has been shown to be efficacious in patients with WM, it is associated with substantial treatment-related morbidity and mortality, thereby limiting its utility.

Few studies have investigated the third-line setting for WM, and such studies often include subjects who have been exposed to various previous therapies. However, when specifically evaluating third-line subjects and applying the response rate definition of complete response and very good partial response (CR+VGPR), response rates ranging between 0% and 37% have been reported. These data underscore the fact that current therapies remain unsatisfactory and highlight the need for new therapeutic options.

2. OBJECTIVES AND ENDPOINTS

Refer to 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
<ul style="list-style-type: none">To evaluate the efficacy of brexucabtagene autoleucel in WM by determining the combined rate of CR and VGPR by central assessment per the Sixth International Workshop in WM	<ul style="list-style-type: none">Combined rate of CR and VGPR rate by central assessment defined as the proportion of subjects who achieve either CR or VGPR
Secondary Objectives	Secondary Endpoints
<ul style="list-style-type: none">To determine the efficacy of brexucabtagene autoleucel in subjects with WM by determining the Objective Response Rate (ORR) by central assessment	<ul style="list-style-type: none">ORR, defined as the proportion of subjects who achieve a best response of CR, VGPR, or PR
<ul style="list-style-type: none">To determine the combined rate of CR and VGPR by investigator assessment	<ul style="list-style-type: none">Combined CR and VGPR rate by investigator assessment defined as the proportion of subjects who achieve either CR or VGPR
<ul style="list-style-type: none">To determine the rates of individual responses by central assessment	<ul style="list-style-type: none">Rate of VGPR and PR, separately

Abbreviations: CR, complete response; PR, partial response; VGPR, very good partial response; WM, Waldenstrom macroglobulinemia.

3. STUDY DESIGN

3.1. Study Design

This substudy protocol contains details regarding all elements of the study that are unique to subjects with WM. 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 WM who have received at least 2 lines of prior therapy.

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 the further conduct of this substudy.

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

Subjects enrolled in this substudy, if already receiving a BTK inhibitor, may receive ibrutinib through screening and leukapheresis at the discretion of the investigator, as described in Section 5.2 and Section 7.1.

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 20 subjects (33%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 6 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).

3.1.1. Rationale for Study Design Elements

3.1.1.1. Rationale for Allowance of Ibrutinib

If required, and per investigator discretion, ibrutinib treatment will be a non-mandatory treatment option through screening and leukapheresis and up to 5 half-lives (30 hours) prior to the start of lymphodepletion for subjects already receiving a BTK inhibitor, as described in Section 5.2 and Section 7.1. Allowing continued ibrutinib treatment (including initiation of ibrutinib in subjects receiving another BTK inhibitor) will minimize the risk of BTK inhibitor withdrawal symptoms and IgM flares. Only ibrutinib (and not acalabrutinib or zanubrutinib) is allowed due to differences in the impact on T-cell function between these drugs.

3.1.1.2. Assessment of IgM Levels

As it is anticipated that a significant number of eligible subjects will be receiving BTK inhibitor treatment, and since such treatment is known to lower IgM levels both while receiving treatment and for several months following withdrawal, a true baseline value and subsequent IgM response assessments at Day 28 and Month 3 will be difficult to obtain. To account for this, the following will apply:

- To closely monitor and document IgM levels, serum IgM will be assessed at screening, prior to receiving lymphodepleting chemotherapy (for those subjects continuing ibrutinib therapy only), prior to dosing on Day 0, Day 7, and Day 14 and then per the schedule of assessments (SOA) (Table 4).
- The screening assessment will serve as the baseline value for subjects not receiving ibrutinib at screening, whereas the pre-lymphodepleting IgM assessment will serve as the baseline value for subjects who are receiving ibrutinib through screening to Day -7. For subjects who stop BTK inhibitor or ibrutinib therapy, a 30-hour washout period must be observed prior to collection of the screening IgM level.
- IgM levels obtained within 5 half-lives (ie, ≤ 35 days) after plasmapheresis will not be considered as nadir for the screening assessment or for response evaluation. Only IgM levels obtained more than 35 days after plasmapheresis can be used for the screening assessment and in response determination.
- Treatment failure will not be established at the Day 28 and Month 3 evaluation if only elevated IgM levels disqualify a subject from achieving a CR, VGPR, or partial response (PR). In such cases, a repeat disease response assessment should be performed to confirm the disease response (at the investigator's discretion or at the next scheduled visit).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 60 subjects with r/r WM 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 recommend 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. WM Substudy-specific Inclusion Criteria

- 1) Confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (see Section 12.3.2)
- 2) Relapsed or refractory disease after 2 or more lines of therapy. Subjects will be eligible regardless of the duration of remission prior to relapse.
 - Prior therapy must have included a BTK inhibitor. Also, chemotherapy and/or a proteasome inhibitor must have been attempted, with either subsequent documented disease progression or no response (stable disease).
- 3) Requiring treatment as defined in the recommendations from the Second International Workshop on WM
- 4) Measurable disease, defined as presence of serum IgM with a minimum IgM level of > 2 times the upper limit of normal of each institution is required
- 5) The inclusion criteria concerning washout periods prior to leukapheresis in the KT-US-568-0138 master protocol must be met, with the exception that ibrutinib may be continued through leukapheresis and up to 5 half-lives (30 hours) prior to the start of lymphodepletion

4.2.2. WM Substudy-specific Exclusion Criteria

- 1) History of allogeneic stem cell transplantation. A prior autologous stem cell transplantation is allowed, but at least 6 months should have elapsed
- 2) Plasmapheresis for symptomatic hyperviscosity or serum IgM > 5,000 mg/dL < 35 days prior to the screening IgM assessment
- 3) Exclusion of IgM monoclonal gammopathy of undetermined significance or IgM multiple myeloma
- 4) Presence of central nervous system (CNS) involvement (Bing-Neel syndrome). Subjects with a prior history of Bing-Neel syndrome are eligible if they show a negative cerebrospinal fluid (CSF) and no involvement by imaging

5. STUDY TREATMENT

5.1. Description of 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.

Prior and concomitant medications that are either unique to WM or that are managed differently for subjects with WM are described below. 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.

5.2. Prior and Concomitant Medications and Permitted Treatments

Subjects who were receiving ibrutinib prior to study entry, and for whom investigators deem it to be required, are permitted to continue this therapy through leukapheresis and up to 5 half-lives (30 hours) prior to the start of lymphodepletion, at the investigator's discretion. Subjects receiving another BTK inhibitor and who require continued BTK inhibitor treatment should switch to ibrutinib at the discretion of the investigator at the start of screening.

If subjects continue ibrutinib through the screening period and leukapheresis, a re-assessment of baseline eligibility must be performed at least 5 half-lives (30 hours) after cessation of ibrutinib treatment and before initiating lymphodepleting chemotherapy.

Plasmapheresis is not allowed between screening and infusion with brexucabtagene autoleucel in order to obtain a true baseline IgM value but may be used to prevent and/or treat IgM flares and symptomatic hyperviscosity postinfusion. Where possible, plasmapheresis should be avoided within 35 days of a scheduled disease response evaluation. Subjects who have undergone plasmapheresis within 35 days of a scheduled disease response will be considered non-evaluable.

6. STUDY ASSESSMENTS UNIQUE TO WALDENSTROM MACROGLOBULINEMIA

The study assessments that are either unique to WM or that are managed differently for subjects with WM are described here. Please refer to Section 6 of the KT-US-568-0138 master protocol 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 SOA presented in Section 12.2 (Table 4 and Table 5) of this substudy protocol.

6.1. Clinical Laboratory Tests

Clinical laboratory tests for disease-specific assessments are presented in Table 2. Quantitative serum Igs (IgA, IgG and IgM), serum protein electrophoresis (SPEP) and serum immunofixation will be assessed at both the central and local laboratory (refer to the central laboratory manual for details). Whereas coagulation (prothrombin time, in vivo recovery, and activated prothrombin time), serum free light chain assay, B₂-microglobulin and the bone marrow aspirate and biopsy are assessed at the local laboratory only.

Table 2. Clinical Laboratory Tests for Disease-specific Assessments

Serum Chemistries (Serum)	Hematology (Blood)	Other
Quantitative serum IGs (IgA, IgG, and IgM) Serum protein electrophoresis (SPEP) Serum immunofixation Coagulation (PT, INR and aPTT) Serum free light chain assay B ₂ -microglobulin	No additional WM-specific hematology tests are required for this substudy	Bone marrow aspirate and trephine biopsy to assess bone marrow involvement (see Section 6.4.5)

Abbreviations: aPTT, activated partial thromboplastin time; Ig, immunoglobulin; IgG, immunoglobulin G; INR, International Normalized Ratio; PT, prothrombin time; SOA, schedule of assessments; SPEP, serum protein electrophoresis; WM, Waldenstrom macroglobulinemia.

Notes: Refer to the SOA in Section 12.2 for timing of assessments.

- Coagulation assessments to be repeated at investigator discretion and in the case of suspicion of pathological findings or progressive disease

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:

- Subjects with a prior history of CNS involvement (Bing-Neel syndrome) must have a brain MRI at screening to confirm absence of CNS involvement in order to be eligible for the study.
- 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 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 but within 28 days before leukapheresis for eligibility. An MRI collected as 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 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 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, a 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 Sixth International Workshop on WM; 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. 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 Quantitative Monoclonal IgM, IgA, and IgG

Quantitative monoclonal IgM, IgA, and IgG assessments will be performed both locally and centrally at the timepoints specified in the SOA (see Section 12.2). The local laboratory assessment of IgM will be used to determine subject eligibility and disease response per investigator assessment. The serum samples submitted to a central laboratory will be used for evaluation of the primary endpoint (refer to the central laboratory manual for details). Local laboratory results will be recorded in the electronic case report form (eCRF). Central laboratory results will be provided to the vendor performing the central disease response assessment.

In order to characterize IgM levels reflecting BTK inhibitor truncation and infusion of brexucabtagene autoleucel, IgM will be assessed during screening, prior to receiving lymphodepleting chemotherapy (for those continuing ibrutinib therapy), prior to dosing on Day 0, Day 7, and Day 14, and then as per scheduled visits (see Section 12.2).

A CR requires reconfirmation, demonstrating normal serum IgM levels (and absence of IgM paraprotein by immunofixation) by a measurement repeated at least 2 weeks later. Both a local and central evaluation should be made. Note: In the case of CR, the disease response reported should be based on the repeated IgM levels.

Treatment failure cannot be established at the Day 28 and Month 3 evaluation if only elevated IgM levels disqualify from achieving a CR, VGPR, or PR. In this event, a repeat disease response assessment should be performed to confirm the disease response (at the investigator's discretion or at the next scheduled visit).

Where possible, plasmapheresis should be avoided within 35 days of a scheduled disease response evaluation. Subjects who have undergone plasmapheresis within 4 weeks of a scheduled disease response will be considered non-evaluable.

6.4.2. Assessment of Serum Protein Electrophoresis

Assessment of SPEP, for evaluation of serum-M protein, will be performed both locally and centrally at the timepoints specified in the SOAs (see Section 12.2). The samples submitted to the central laboratory will be used for assessment of the primary endpoint (refer to the central laboratory manual for details). Local laboratory results will be recorded in the eCRF. Central laboratory results will be provided to the vendor performing the central disease response assessment.

6.4.3. Serum Immunofixation

The assessment of serum immunofixation will be performed both locally and centrally, at the timepoints specified in the SOAs (see Section 12.2). The samples submitted to the central laboratory will be used for assessment of the primary endpoint (refer to the central laboratory manual for details). Local laboratory results will be recorded in the eCRF. Central laboratory results will be provided to the vendor performing the central disease response assessment.

Note: Repetitive serum immunofixation on study is only required to confirm a CR (required whenever the subject has no detectable monoclonal protein). A CR requires reconfirmation demonstrating normal serum IgM levels and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later. Both a local and central evaluation should be made.

6.4.4. Imaging Requirements

Computed tomography (CT) imaging of diagnostic quality is required in all subjects at screening to assess for presence of extramedullary disease (EMD). Follow-up CT scans will be required in subjects with confirmed EMD by local radiology review at screening and prior to lymphodepleting chemotherapy (only in subjects receiving ibrutinib), as described below.

For all imaging, the following requirements should be met:

- The CT must be of diagnostic quality with IV-iodinated contrast, performed by either of the following modalities, depending on the site's capability:
 - as part of a combined positron emission tomography (PET)-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.
- For subjects where the local radiology review has confirmed presence of EMD at screening, the screening and rebaseline scans, if applicable (i.e post ibrutinib if continued, see Section 5.2) and all subsequent disease assessment CT scans will be submitted to and reviewed by an independent central reviewer.
- Technical and shipping requirements for the CT 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 categorical response (ie, determination of completion resolution, reduction, no progression of EMD for subjects with confirmed presence of EMD) will be assessed by central radiological review in accordance with the Sixth International Workshop on WM disease response criteria for the primary endpoint. A local investigator assessment will also be made and reported in the eCRF.

Screening/Baseline:

- Diagnostic CT 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 scan performed at the trial site, after the subject's last line of therapy and before signing of the informed consent form may be used (if relevant requirements described above are fulfilled) if within 28 days before enrollment/leukapheresis and no other anticancer treatment has been administered. For referred subjects a screening image is required.
 - In subjects with EMD, as confirmed per local radiology review, who continue to receive ibrutinib through apheresis and up to Day -7, the CT scan must be repeated before initiating lymphodepleting chemotherapy to establish a new baseline.

Disease Assessment:

- For all subjects with confirmed EMD by local radiology review at screening/baseline, diagnostic CT scans will be performed at the time points outlined in the SOA ([Table 4](#) and [Table 5](#)) through Month 60 or until disease progression, whichever comes first.
- Additional assessments may be performed, if clinically indicated, during the course of the study at any time disease progression is suspected.
- For subjects with or without EMD, imaging should be performed per SOC any time the subject presents with symptoms suggestive of disease progression.

6.4.5. Bone Marrow Biopsy/Aspirate

Bone marrow aspirate and biopsies will be analyzed by the investigator at the local laboratory. At screening only, bone marrow samples should be sent to the central laboratory for confirmation of diagnosis (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.
- Attempts should be made to characterize residual infiltrates with respect to their B-cell and plasma cell content.
- The morphological status of the bone marrow will be reported in the eCRF (ie, morphologically normal bone marrow aspirate and trephine biopsy or morphologically abnormal bone marrow aspirate and trephine biopsy).
- 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.
- For subjects who continue to receive ibrutinib, a bone marrow aspirate and trephine biopsy will need to be repeated prior to initiating lymphodepleting chemotherapy to establish a new baseline.

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 (ie, if there is an absence of serum monoclonal IgM protein by immunofixation, normal serum IgM and complete resolution of EMD, if present at baseline).
- Bone marrow assessments may also be performed at the investigator's discretion and if clinically indicated at disease progression.

6.5. Disease-specific Exploratory Assessments

Screening bone marrow aspirate and biopsies will be collected for central laboratory assessment of somatic mutations of *MYD88* and *CXCR4* and presence of *CD138* via immunohistochemistry to confirm the WM diagnosis and for use as prognostic markers in exploratory analyses. Details for sample collection and processing are described in the central laboratory manual.

7. STUDY PROCEDURES UNIQUE TO WALDENSTROM MACROGLOBULINEMIA

Refer to Section 7 of the KT-US-568-0138 master protocol for the list of procedures for this study. Additional procedures for this WM subprotocol are listed below and presented in Section [12.2](#), [Table 4](#) and [Table 5](#) of this substudy protocol.

7.1. Screening

Due to the risk of BTK inhibitor withdrawal symptoms and IgM flares , subjects currently on a BTK inhibitor when entering the screening period may continue (if on ibrutinib) or should be switched to ibrutinib (if on other BTK inhibitor treatment), which may be used through leukapheresis and up to 5 half-lives (30 hours) prior to the start of lymphodepletion (refer to Section [5.2](#)).

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 (2×10^6 anti-CD19 CAR T cells/kg of body weight) and followed for 28 days, as detailed in the KT-US-568-1038 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 20 subjects (33%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 6 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 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 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 statistical considerations that are common across indications.

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

9.1. Hypothesis

An alternative hypothesis will be tested with a target 20% combined CR and VGPR rate per central assessment against a null hypothesis that the combined CR and VGPR rate is $\leq 6\%$. The reference rate of 6% was based on a systematic literature review and meta-analysis. The hypothesis is that the combined CR and VGPR to brexucabtagene autoleucel per central assessment is greater than 6%.

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 as outlined below also apply to this substudy.

9.2.1. Definition of Substudy Primary Endpoint

The primary endpoint for this substudy is the combined CR and VGPR response rate, defined as the proportion of subjects who achieve either CR or VGPR by central assessment per the Sixth International Workshop in WM (see Section 12.3.1).

9.2.2. Definition of Substudy Secondary Endpoints

Secondary endpoints for this substudy are defined in [Table 3](#).

Table 3. Definitions of Substudy Secondary Endpoints

Secondary Endpoints	Definition
Objective Response Rate (ORR) by central assessment	The proportion of subjects who achieve a best response of CR, VGPR, or PR by investigator assessment
Combined CR and VGPR rate by investigator assessment	The proportion of subjects who achieve either CR or VGPR by investigator assessment per the Sixth International Workshop in WM
Rates of VGPR and PR, separately	The proportion of subjects who achieve a best response of VGPR or PR by central assessment, respectively, per the Sixth International Workshop in WM

Abbreviations: CR, complete response; PR, partial response; VGPR, very good partial response; WM, Waldenstrom macroglobulinemia.

9.3. Determination of Sample Size

This single-arm, open-label substudy will enroll and treat 60 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve statistical power of 88% if there is at least a 14% improvement in combined CR and VGPR (brexucabtagene autoleucel: 20% versus historical control: 6%) at an alpha level 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 89% per simulation based on binomial distribution without normal approximation. Statistically significant treatment effect can be claimed in this substudy if ≥ 8 responders ($\geq 13.3\%$) are observed among the 60 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 20 subjects (33%) have had the opportunity to be evaluated for response 6 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 a combined CR and VGPR rate of 7.5% is based on the beta spending function of rho family (parameter = 0.35), with a crossing probability of 61% under the null hypothesis (combined CR and VGPR rate $\leq 6\%$). The futility boundary is crossed if 1 or no responder is observed among the 20 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 60 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 responders observed among the 60 subjects, as described above. The point estimate of the combined CR and VGPR rate 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 60 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

- Buske C, Leblond V, Dimopoulos M, Kimby E, Jager U, Dreyling M, et al. Waldenstrom's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi155-9.
- Castillo JJ, Allan JN, Siddiqi T, Advani RH, Meid K, Leventoff C, et al. Venetoclax in Previously Treated Waldenstrom Macroglobulinemia. *J Clin Oncol* 2022;40 (1):63-71.
- Castillo JJ, Gustine JN, Meid K, Dubeau T, Severns P, Treon SP. Ibrutinib withdrawal symptoms in patients with Waldenstrom macroglobulinemia. *Haematologica* 2018;103 (7):e307-e10.
- Davis J. E, Sharpe C, Mason K, Tam C. S, Koldej R. M, Ritchie D. S. Ibrutinib protects T cells in patients with CLL from proliferation-induced senescence. *Journal of Translational Medicine* 2021;473 (19):1-13.
- Dimopoulos MA, Kastritis E. How I treat Waldenstrom macroglobulinemia. *Blood* 2019;134 (23):2022-35.
- Dimopoulos MA, Zervas C, Zomas A, Kiamouris C, Viniou NA, Grigoraki V, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab. *J Clin Oncol* 2002;20 (9):2327-33.
- Ghobadi A, Locke F, Neelapu S, Siddiqi T, Chavez J, Hosing C, et al. Updated Phase 1 Results from ZUMA-1: A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 (Anti-CD19 CAR T Cells) in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL). American Association for Cancer Research (AACR) Annual Meeting 2016;Abstract #CT135.
- Ghobrial I M, Witzig T E, Gertz M, LaPlant B, Hayman S, Camoriano J, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia. *American Journal of Hematology* 2014;89 (3):237-42.
- Ghobrial IM, Redd R, Armand P, Banwait R, Boswell E, Chuma S, et al. Phase I/II trial of everolimus in combination with bortezomib and rituximab (RVR) in relapsed/refractory Waldenstrom macroglobulinemia. *Leukemia* 2015;29 (12):2338-46.
- Hampel P. J, Ding W, Call T. G, Rabe K. G, Kenderian S. S, Witzig T. E, et al. Rapid disease progression following discontinuation of ibrutinib in patients with chronic lymphocytic leukemia treated in routine clinical practice. *Leukemia & Lymphoma* 2019;60 (11):2712-9.

- Kyriakou C, Canals C, Sibon D, Cahn JY, Kazmi M, Arcese W, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2010;28 (13):2227-32.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Hairy Cell Leukemia. Version 1.2022 - September 8, 2021. 2021:
- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2022 — June 24, 2021:
- Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol* 2013;160 (2):170 - 6.
- Owen RG, Treon SP, Al-Katib A, Fonseca R, Greipp PR, McMaster ML, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol* 2003;30 (2):110-5.
- 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.
- Souchet L, Levy V, Ouzegdouh M, Tamburini J, Delmer A, Dupuis J, et al. Efficacy and long-term toxicity of the rituximab-fludarabine-cyclophosphamide combination therapy in Waldenstrom's macroglobulinemia. *American Journal of Hematology* 2016;91 (8):782-6.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Fourth ed. International Agency for Research on Cancer; 2008. vol 2).
- Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in Previously Treated Ibrutinib in Previously Treated. *N Engl J Med* 2015;372 (15):1430-40.
- Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med* 2012;367 (9):826-33.

12. APPENDICES

Section 12.1.	Sponsor and Investigator Signature Page
Section 12.2.	Schedule of Assessments
Section 12.3.	Disease Response Criteria
Section 12.4.	Protocol Amendment History

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 A – Relapsed/Refractory Waldenstrom Macroglobulinemia*

Amendment 2.0, 01 MARCH 2023

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

See appended electronic signature
Kite Medical Monitor Name (Printed)

See appended electronic signature
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. Schedule of Assessments

Table 4. Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Period

Timeframe:	Screening	Pretreatment Period					Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression ^b
Procedure	Within 28 days before enrollment	Enrollment/ Leukapheresis	Optional Ibrutinib Therapy Note: ibrutinib is optional and these procedures only apply if ibrutinib has been administered	Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
		Within approx. 5 days after eligibility confirmation	Post-ibrutinib disease assessment (if applicable)	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	X	Daily	X	X	X	X	X
Weight (height at screening only)	X	X											
Vital signs ^d	X	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									

Timeframe:	Screening	Pretreatment Period					Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression ^b
Procedure	Within 28 days before enrollment	Enrollment/ Leukapheresis	Optional Ibrutinib Therapy Note: ibrutinib is optional and these procedures only apply if ibrutinib has been administered	Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
		Within approx. 5 days after eligibility confirmation	Post-ibrutinib disease assessment (if applicable)	D-5	D-4	D-3	D0	D1 to D7 ^a	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
LVEF (ECHO or MUGA)	X												
ECG	X												
Brain MRI (if applicable) ^f	X ^f												
Lumbar puncture (if applicable) ^g	X ^f												
PROs: EORTC-QLQ-C30 and EQ-5D-5L ^h	X			X			X			X		X	
<i>Disease response assessments (please also refer to the imaging manual and central laboratory manual for guidance)</i>													
CT scan ⁱ	X		X							X		X	X
Bone marrow aspirate and biopsy ^j	X		X							X		X	X
Quantitative serum immunoglobulins IgA, IgG and IgM ^k	X		X				X	D7	X	X	X	X	X

Timeframe:	Screening	Pretreatment Period					Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression ^b
Procedure	Within 28 days before enrollment	Enrollment/ Leukapheresis	Optional Ibrutinib Therapy Note: ibrutinib is optional and these procedures only apply if ibrutinib has been administered	Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
		Within approx. 5 days after eligibility confirmation	Post-ibrutinib disease assessment (if applicable)	D-5	D-4	D-3	D0	D1 to D7 ^a	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
Serum protein electrophoresis (SPEP)	X		X							X		X	X
Serum immunofixation ^{l,m}	X		X							X		X	X
Overall response assessment ^l										X		X	X
Local laboratory assessments													
Chemistry panel (CrCl at screening) (serum)	X	X		X	X	X	X ⁿ	Daily	X	X	X	X	X
CBC with differential (blood) ^o	X	X		X	X	X	X ⁿ	Daily	X	X	X	X	X
LDH ^p , CRP, ferritin (serum)		X		X			X ⁿ	Daily	X	X			X
Coagulation (PT, INR and aPTT) ^q	X			X									X
Serum free light chain assay	X			X						X		X	X

Timeframe:	Screening	Pretreatment Period					Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression ^b
Procedure	Within 28 days before enrollment	Enrollment/Leukapheresis	Optional Ibrutinib Therapy Note: ibrutinib is optional and these procedures only apply if ibrutinib has been administered	Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
		Within approx. 5 days after eligibility confirmation	Post-ibrutinib disease assessment (if applicable)	D-5	D-4	D-3	D0	D1 to D7 ^a	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
β ₂ -microglobulin	X			X									
β-hCG pregnancy test ([WOCBP] serum or urine)	X	X ^r		X ^r						X		X	X
Serology for EU/CH/UK sites (serum) ^s	X ^s	X ^s											
<u>HIV positive subjects only</u> : HIV viral load and CD4 count	X ^t						X			X		X	
Central laboratory assessments (please refer to the central laboratory manual for guidance)													
CBC with differential (blood)		X					X ⁿ	D3, D7	X	X	X	X	X
Anti-brexcabtagene autoleucel antibodies (serum)		X ^u								X		X	X
Analytes, including cytokines (serum/plasma) ^v		X ^u					X ⁿ	D1, D2, D3, D5, D7	X	X	X	X	X

Timeframe:	Screening	Pretreatment Period					Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression ^b
Procedure	Within 28 days before enrollment	Enrollment/ Leukapheresis	Optional Ibrutinib Therapy Note: ibrutinib is optional and these procedures only apply if ibrutinib has been administered	Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
		Within approx. 5 days after eligibility confirmation	Post-ibrutinib disease assessment (if applicable)	D-5	D-4	D-3	D0	D1 to D7 ^a	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs) ^v		X ^u					X ⁿ	D3, D7	X	X	X	X	X
RCR (PBMCs) ^w							X ⁿ					X	
Leukapheresis		X											
Fludarabine and Cyclophosphamide ^x				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 ^y				X	X	X	X	Daily	X	X	X	X	X

Abbreviations: approx., approximately; ASCO, American Society of Clinical Oncology; BTK, Bruton's tyrosine kinase; 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, cerebrospinal fluid; CT, computed tomography; D/d, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; 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; EU, European

Union; hCG, human chorionic gonadotropin; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICF, informed consent form; Ig, immunoglobulin; IV, intravenous; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; M, month; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PBMCs, peripheral blood mononuclear cell; PD, progressive disease, PR, partial response; PRO, patient reported outcome; QOD, every other day; RCR, replication-competent retrovirus; SOA, schedule of assessments; UK, United Kingdom; VGPR, very good partial response; 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 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 autoleucl infusion and can be performed QOD 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: Subjects with a prior history of CNS involvement (Bing-Neel syndrome) must have a brain MRI at screening to confirm absence of CNS involvement in order to be eligible for the study. 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 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 cerebrospinal fluid (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 autoleucl infusion on Day 0.
- i CT scan:
 - Screening/baseline: CT scans should be obtained during screening and within 28 days before enrollment/leukapheresis to assess for presence of EMD. In subjects with confirmed EMD at screening, if the subject receives ibrutinib therapy between the last CT scan and lymphodepleting chemotherapy, the CT scan must be repeated for

- disease re-evaluation. For subjects where the local radiology review has confirmed presence of EMD at screening, the screening and post ibrutinib (baseline), if applicable, CT scans will be submitted to and reviewed by an independent central reviewer.
- Disease assessment: Follow-up CT scans will be required in subjects with confirmed EMD by local radiology review at screening. Additional assessments may be performed, if clinically indicated, 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). For subjects who continue to receive ibrutinib, a bone marrow aspirate and trephine biopsy will need to be repeated prior to initiating lymphodepleting chemotherapy to establish a new baseline.
 - Disease assessment: A bone marrow aspiration and trephine biopsy are required to confirm a CR (ie, if there is an absence of serum monoclonal IgM protein by immunofixation, normal serum IgM and complete resolution of EMD, if present at baseline). Bone marrow assessments may also be performed at the investigator's discretion and if clinically indicated at disease progression.
- k Quantitative IgM, IgA, and IgG: In order to establish a baseline IgM assessment, IgM will be assessed during screening and after cessation of ibrutinib treatment and prior to start of lymphodepletion (if the subject received ibrutinib therapy at screening), as well as prior to dosing on D0, on D7 and D14 and then as per the SOA.
- l Serum immunofixation: Required at screening and after cessation of ibrutinib treatment and prior to start of lymphodepletion (if the subject received ibrutinib therapy at screening). Repetitive serum immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable monoclonal protein) and then repeated to continue to confirm CR or until disease progression.
- m Overall disease response assessment: A CR requires reconfirmation demonstrating normal serum IgM levels and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later. For initial disease response assessments at D28 and M3, due to the possibility of BTK inhibitor withdrawal symptoms and delayed IgM flare, if the response criteria for CR/VGPR or PR are met, with the exception of IgM criteria, then this would not qualify as treatment failure and a repeat disease response assessment should be performed at the investigator's discretion or the next scheduled visit. Where possible, plasmapheresis should be avoided within 4 weeks of a scheduled disease response evaluation. Subjects who have undergone plasmapheresis within 4 weeks of a scheduled disease response will be considered non-evaluable.
- n 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.
- o CBC with differential (blood): At the timepoints at which PBMC samples are collected for analysis of brexucabtagene autoleucel T-cell levels, blood samples will also be collected and sent to the central laboratory for assessment of CBC with differential (note: these samples are in addition to those sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).
- p LDH should continue to be monitored after the baseline assessment as clinically indicated.
- q Coagulation assessments to be repeated at investigator discretion and in case of suspicion of pathological findings or progressive disease.
- r 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 WOCBP.
- s 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.
- t Hepatitis B and C testing is also required at screening.
- u 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.
- v Analytes (including cytokines) (serum/plasma) and brexucabtagene autoleucel CAR T cells (PBMCs):
- Samples on Day 3 may be collected \pm 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.
- w 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.
- x 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-568-0138 master protocol).
- y 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 5. Schedule of Assessments: Post-treatment Follow-up Period

Timeframe:	Long-term Follow-up Period (Each visit calculated from Day 0)									Suspected Disease Progression ^a
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)	
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					
<i>Disease assessments (please also refer to the imaging manual and central laboratory manual for guidance)</i>										
CT scan ^d	X									X
Bone marrow aspirate and biopsy ^e	X									X
Quantitative serum IgA, IgG, and IgM	X	X	X	X	X	X	X	X	X	X
Serum protein electrophoresis (SPEP)	X	X	X	X	X	X	X	X	X	X
Serum immunofixation ^f	X	X	X	X	X	X	X	X	X	X
Overall response assessment ^g	X	X	X	X	X	X	X	X	X	X
<i>Local laboratory assessments</i>										
CBC with differential (blood) ^h	X	X	X	X	X	X	X	X	X	X
Chemistry panel (serum)										X
LDH ⁱ	X									X
Serum free light chain assay	X	X	X	X	X	X	X	X	X	X
Coagulation (PT, INR and aPTT) ^j	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)									Suspected Disease Progression ^a
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)	
<i>Central laboratory assessments (please refer to the central laboratory manual for guidance)</i>										
CBC with differential (blood) ^h	X	X	X	X	X					X
Analytes, including cytokines (serum/plasma) ^k										X
Anti-brexucabtagene autoleucel antibodies (serum)	X	X	X							X
Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs) ^k	X	X	X	X	X					X
RCR (PBMCs) ^l	X		X							
All brexucabtagene autoleucel-related SAEs and any deaths regardless of causality	X	X	X	X	X	X	X	X	X	X
Targeted AE/SAEs ^m	X	X	X	X	X	X	X	X	X	X
Targeted concomitant medications ⁿ	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for WM ^o	X	X	X	X	X	X	X	X	X	X
Survival status ^p	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; CRS, cytokine release syndrome; CT, computed tomography; EMD, extramedullary disease; 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; hCG, human chorionic gonadotrophin; HCP, healthcare provider; IG, immunoglobulin; LDH, lactate dehydrogenase; LTFU, long-term follow-up; M, month; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PRO, patient-reported outcome; RCR, replication-competent retrovirus; SAE, serious adverse event; SOA, schedule of assessment; w, weeks; WM, Waldenstrom macroglobulinemia; 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 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 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 CT scans will be required in subjects with confirmed EMD by local radiology review at screening. Additional assessments may be performed, if clinically indicated, at any time disease progression is suspected.
- e Bone marrow aspiration and biopsy may also be done at the investigator's discretion and are required at any time to confirm a CR (ie, if absence of serum monoclonal IgM protein by immunofixation, normal serum IgM and complete resolution of EMD if present at baseline) and if clinically indicated at disease progression.

- f Repetitive serum immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable monoclonal protein) and then repeated every time until disease progression.
- g Overall disease response assessment: A CR requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.
- h CBC with differential (blood):
- Local laboratory assessments: Blood will be collected at the time points 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 time points 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 time points that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).
- i LDH should continue to be monitored after the baseline assessment as clinically indicated.
- j Coagulation assessments to be repeated at investigator discretion and in case of suspicion of pathological findings or PD
- k 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.
- l 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-568-0138 master protocol).
- m 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.
- n 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.
- o 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.
- p Subjects and/or referring HCP and/or GP may be contacted directly by telephone or email to assess survival status.

12.3. Disease Response Criteria

12.3.1. Definitions of Response for Waldenstrom Macroglobulinemia

Definitions of Response for Waldenstrom Macroglobulinemia as per the Sixth International Workshop .

- **Complete response (CR):** Absence of serum monoclonal IgM protein by immunofixation; normal serum IgM level and complete resolution of extramedullary disease (EMD), ie, lymphadenopathy and splenomegaly if present at baseline; morphologically normal bone marrow/aspirate and trephine biopsy. A CR requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.
- **Very good partial response (VGPR):** Monoclonal IgM protein is detectable; $\geq 90\%$ reduction in serum IgM level from baseline; complete resolution of EMD, ie, lymphadenopathy and splenomegaly if present at baseline; no new signs or symptoms of active disease.
- **Partial response (PR):** Monoclonal IgM protein is detectable; $\geq 50\%$ but $< 90\%$ reduction in serum IgM level from baseline; reduction of EMD (ie, lymphadenopathy and splenomegaly if present at baseline; no new signs or symptoms of active disease).
- **Minor response:** Monoclonal IgM protein is detectable; $\geq 25\%$ but $< 50\%$ reduction in serum IgM level from baseline; no progression in extramedullary disease (ie, lymphadenopathy/splenomegaly if present at baseline; no new signs or symptoms of active disease).
- **Stable disease:** Monoclonal IgM protein is detectable; $< 25\%$ reduction and $< 25\%$ increase in serum IgM level from baseline; no new signs or symptoms of active disease.
- **Progressive disease:** $\geq 25\%$ increase in serum IgM level from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease.

12.3.2. Waldenstrom Macroglobulinemia International Workshop Diagnosis Criteria

Proposed Criteria for the Diagnosis of Waldenstrom Macroglobulinemia

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
- Diffuse, interstitial, or nodular pattern of bone marrow infiltration
- CD19+, CD20+, sIgM+. Note that CD5, CD10, CD23 can be expressed in some cases of Waldenstrom macroglobulinemia but does not exclude diagnosis

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	To optimize enrollment
Section 12.2 Schedule of assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Period	Removed schedule of PROs: EORTC-QLQ-C30 and EQ-5D-5L at Post-Ibrutinib disease assessment (if applicable)	Correction. Removed PROs assessment timepoint no longer applicable
Section 12.2 Schedule of assessments Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Period	Footnote u: 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	Correction. A repeated blood sample collection for subjects who received ibrutinib therapy is no longer applicable

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 Section 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	EU CT and NCT numbers provided	EU CT and NCT numbers previously unavailable
Synopsis (Statistical Methods) and Sections 9.1 Hypothesis and 9.4.2 Primary Analysis	<ul style="list-style-type: none"> “significantly” removed from statement that “The hypothesis is that the combined CR and VGPR to brexucabtagene autoleucel per central assessment is significantly > 6%.” Text edited to now state that the p-value ‘<u>will</u> be’ calculated based on an exact test, rather than ‘may be’ tested. 	For clarity

Section Number and Name	High-level Description of Change	Brief Rationale
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 WM Substudy) and Section 4.2.1 WM Substudy-specific Inclusion Criteria	Inclusion criterion 2 amended to include that subjects will be eligible regardless of the duration of remission prior to relapse	For clarity
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Period	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) – <i>Substudy A – Relapsed/Refractory Waldenstrom Macroglobulinemia</i> ”. The evaluation of safety (secondary endpoint) was 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
Section 6.2 Brain Magnetic Resonance Imaging	At screening CNS involvement will be assessed by local review, and images will not be sent for central review Post-infusion, a brain MRI only needs to be submitted to the independent central reviewer when there is evidence of disease progression	For clarification
Section 6.4.4 Imaging Requirements	For assessment of EMD, the term ‘measurable’ has been replaced with ‘presence of’ or simply ‘EMD’ throughout this section, to align with the disease response criteria, which assesses presence or absence of EMD. Added text to clarify when scans should be submitted for central review (ie, required for subjects where the local radiology review has confirmed presence of EMD at screening)	Language regarding EMD updated to align with the disease response criteria. Correction to previous language which indicated all screening / baseline scans were to be submitted for central review

Section Number and Name	High-level Description of Change	Brief Rationale
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Period	PROs: EORTC-QLQ-C30 and EQ-5D-5L, removed from post-ibrutinib disease assessment column	Timepoint is captured in the schedule of assessments at Day -5
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Period	Footnote a: 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 for 10 days after brexucabtagene autoleucel.	Request by Swiss Regulatory Authority
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Period	Footnote i: Screening: For subjects where the local radiology review has confirmed presence of EMD at screening , the screening and post ibrutinib (baseline), if applicable, CT scans will be submitted to and reviewed by an independent central reviewer Disease assessment: Follow-up CT scans will be required in subjects with confirmed EMD by local radiology review at screening Footnote i and j: EMD language updated to remove the term ‘measurable’	Footnotes updated to align with Section 6.4.4 Imaging requirements and changes described above
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Period	Footnotes ‘r’ pregnancy testing and ‘s’ serology testing updated to include Switzerland	Request by Swiss Regulatory Authority and alignment with Master protocol Section 6
Section 12.2 Schedule of Assessments, Table 4 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Period	Footnote v: Samples on Day 3 may be collected \pm 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 5 Schedule of assessments: Post-treatment Follow-up Period	Window M18 changed from \pm 2 weeks to \pm 1 month	Provides added flexibility
Section 12.2 Schedule of Assessments, Table 5 Schedule of assessments: Post-Treatment Follow-up Period	Footnote d: Follow-up CT scans will be required in subjects with confirmed EMD by local radiology review at screening	For clarification