AUTO4 (obecabtagene autoleucel, AUTO4)

A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO4, A CAR T Cell Treatment Targeting TRBC1, in Patients with Relapsed or Refractory TRBC1 Positive Selected T Cell Non-Hodgkin Lymphoma

Statistical Analysis Plan (SAP)

Phase I – Dose Escalation

Analysis Plan Version: Version 1.0

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TABLE OF CONTENTS

SUMMARY OF CHANGES

Version	Date	Changes
1.0	04-Mar-2024	Version 1

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
aTRBC	Anti-T cell receptor beta constant
aTRBC -CAR	Anti-T cell receptor beta constant 1 chimeric antigen receptor
BCMA	B cell maturation antigen
B-NHL	B cell non-Hodgkin lymphoma
CAR	Chimeric antigen receptor
CD3, 19, 20, 28, 68, 134	Cluster of differentiation 3, 19, 20, 28, 68 134
CMR	Complete Metabolic Response
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
Cru	Complete response unconfirmed
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T lymphocyte-associated protein
CY	Cyclophosphamide
DFS	Disease-free survival
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EFS	Event free survival

Abbreviation	Definition
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLU	Fludarabine
FLU-CY	Fludarabine and cyclophosphamide
GCP	Good Clinical Practice
HLH	Haemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
i.v.	Intravenous(ly)
MAD	Maximum administered dose
MAS	Macrophage activation syndrome
MTD	Maximum tolerated dose
NHL	Non-Hodgkin lymphoma
NGS	Next-Generation Sequencing
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PPD	Perpendicular diameter (cross product of the LDi and perpendicular diameter)
PR	Partial response
PTCL	Peripheral T cell lymphoma
PTT	Partial thromboplastin time
RCR	Replication competent retrovirus
RP2D	Recommended Phase II dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant/transplantation

Abbreviation	Definition
SEC	Safety Evaluation Committee
TCR	T cell Receptor
TFLs	Tables, figures, and listings
TLS	Tumour lysis syndrome
TRBC	T cell receptor beta constant
T-NHL	T cell non-Hodgkin Lymphoma
ULN	Upper limit of normal

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Phase I part of Study AUTO4-TL1. This SAP is based on the study protocol amendment 6.0 dated 30 June 2022 and the electronic case report form (eCRF). The SAP will be finalized before Phase I database finalization. Any changes made after the finalization of the SAP will be documented in the CSR. A separate SAP will be documented later to cover the statistical analysis methods and data presentations for Phase II part of Study AUTO4-TL1.

1.1. Study Design

1.1.1. Study Overview

This is a single-arm, open-label, multi-centre, Phase I/II dose escalation and expansion study to determine the safety and clinical activity of RQR8/aTRBC1-CAR positive T cells administered intravenously (i.v.) in patients with TRBC1 positive selected T-NHL. The study will consist of two parts, a Phase I/dose escalation phase and a Phase II/dose expansion phase:

- Phase I: **Dose escalation**, using a rolling six design to identify the RP2D (optimal) dose of AUTO4. The following doses are intended to be evaluated but are subject to emerging safety data: 25 x 10^6, 75 x 10^6, 225 x 10^6, 450 x 10^6 and 900 x 10^6 RQR8/aTRBC1-CAR positive T cells, administered as a single dose.

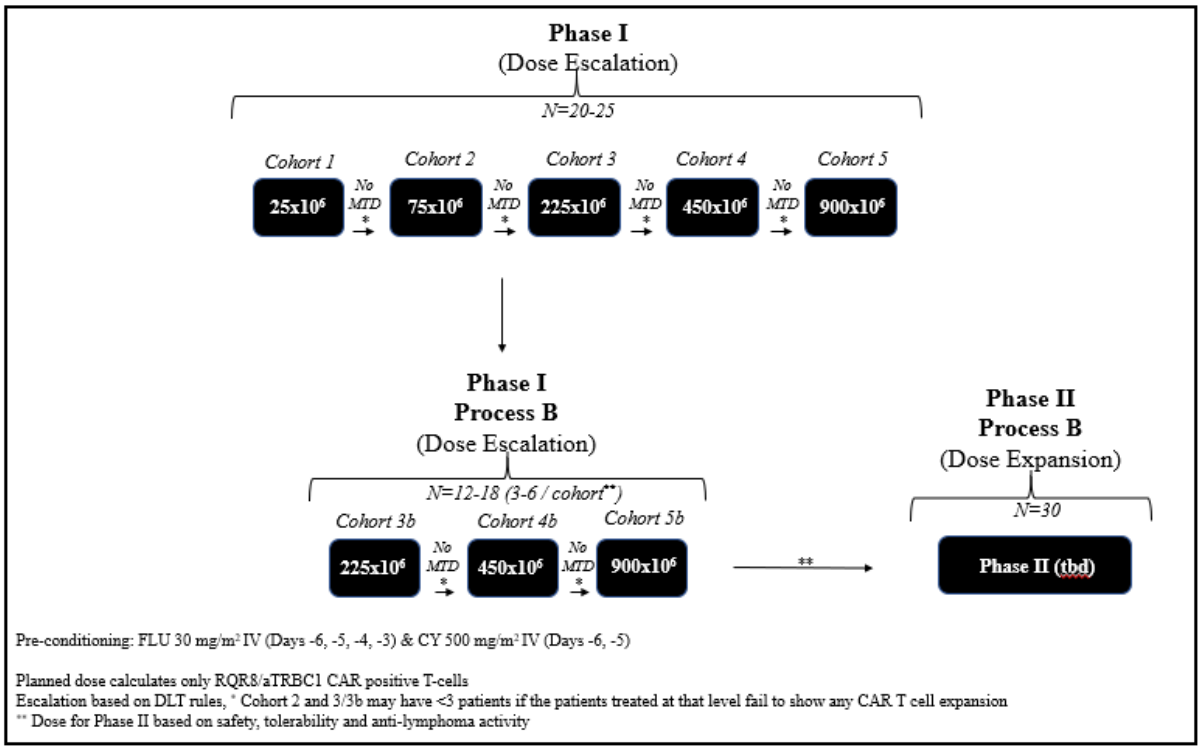
- Phase I: **Dose escalation with Process B,** using a rolling six design to identify the RP2D (optimal) dose of AUTO4. The following doses are intended to be evaluated, but are subject to emerging safety data: 225 x 10^{6*}, 450 x 10^6 and 900 x 10^6 RQR8/aTRBC1-CAR positive T cells, administered as a single dose. Drug product manufactured using an optimized process that can consistently meet the required dose (Process B) will be used to support these cohorts.

  *Cohort 2 (75 x 10^6) and 3/3b (225 x 10^6) should have at least 1 patient for the dose escalation decision. In this case, any potential single patient cohort would be expanded to n=3-6 (per rolling six study design), if at least 1 patient experiences any level of CAR T-cell expansion (above the limit of detection) or Grade ≥ 1 CRS/Neurotoxicity or ≥ Grade 2 AUTO4-related AE in the first 28 days after AUTO4 infusion. The inter-patient interval between patients in 2 different dose level cohorts can not be less than 28 days from AUTO4 infusion of the previous patients to the start of the lymphodepletion of the next patient (the Safety Evaluation Committee (SEC) will meet after the first patient in every cohort completes 28 days).

- Phase II: **Dose expansion** to assess anti-lymphoma activity and safety at the RP2D using AUTO4 Process B product.

An overview of the study design is presented in Figure 1 below. This SAP will only focus on Phase I part of the study.

Figure 1: Proposed Dose Escalation and Dose Expansion Phases



**At least 3 patients must be treated per cohort from Cohort 4 onwards (per rolling six study design), subsequent dose increase/dose level (Cohort 5) to be determined based on the available safety-, pharmacokinetic-, pharmacodynamic-data and manufacturing feasibility.

CAR = chimeric antigen receptor; CY = cyclophosphamide; DLT = dose-limiting toxicity; FLU = fludarabine; MTD = Maximum Tolerated Dose; RQR8/aTRBC1 = Ritux QBEnd/10-Ritux-cluster of differentiation 8 sort-suicide gene/anti-T cell receptor beta 1; tbd = to be determined.

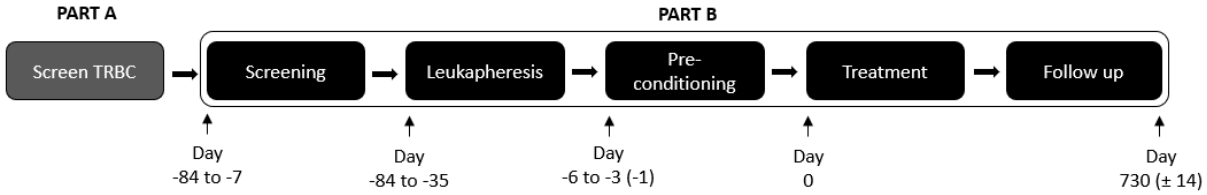
The study consists of two phases – Phase I (dose escalation and RP2D), followed by Phase II (dose expansion, efficacy and safety). Each patient (irrespective of phase) will go through the following five stages.

- **Screening stage**: There are two separate Informed Consent Forms (ICFs) during the screening stage – ICF Part A and ICF Part B. After providing written informed consent (ICF Part A) to enter the screening process to determine the TRBC1 status, patients will be screened for preliminary study eligibility, demographic details, and the provision of an archival tumour tissue sample or a newly acquired tumour tissue sample.
- Once a patient is confirmed as TRBC1 positive, the patient will be asked to consent to the main study (ICF Part B). All the remaining screening activities, including the baseline disease assessment, will occur at Screen 1 and Screen 2 – see the Schedule of Assessments for details. Only patients who are identified as TRBC1 positive, and otherwise eligible, will proceed to leukapheresis.
- **Leukapheresis**: Eligible patients that are TRBC1 positive will undergo leukapheresis to facilitate manufacture of the ATIMP, AUTO4.

- **Pre-conditioning**: If sufficient AUTO4 is successfully manufactured and released, and the patient continues to meet eligibility requirements for the study, the patient will proceed to receive a lymphodepleting pre-conditioning treatment with FLU for 4 days and CY for 2 days, to end 3 days (-1 day) before AUTO4 infusion.
- **Treatment stage**: AUTO4 will be administered i.v. as a single infusion on Day 0.
- **Follow-up stage**: The follow-up stage will begin after AUTO4 administration and end 24 months (104 weeks) after the infusion of the last patient with AUTO4 or at their disease progression or withdrawal of consent, which ever happens first. For patients who experienced disease progression post AUTO4 infusion before the End of Study and those still in CR 24-months post infusion please see the Schedule of Assessments for their follow-up schedule. An End of Study visit will be conducted for all patients.

An overview of the five study stages is presented in Figure 2.

Figure 2: Overview of the Stages of the Study



From signing of informed consent (ICF Part A) until the End of Study visit, information relating to adverse events (AEs), laboratory abnormalities, disease response and biomarker changes will be collected according to the Schedule of Assessments.

After AUTO4 infusion, all patients will be followed up for **efficacy and safety**. Patients will have periodic monitoring of response based as described in the Schedule of Assessments. Patients who proceed to hematopoietic stem cell transplantation or any other anti-T-cell lymphoma therapies while in remission will also be monitored for efficacy and safety until the EoS.

Patients who fail to respond (within 2 months post AUTO4 treatment) to treatment or who respond but subsequently relapse or progress will continue to be monitored for **safety and survival** through to EoS as per the safety and survival Schedule of Assessments.

All AUTO4-treated patients will be eligible for enrolment into a long-term follow-up protocol (AUTO-LT1) at the end of the study. The patients will be followed for safety evaluation and survival for 15 years from the AUTO4 infusion or until death or withdrawal of consent, whichever happens first.

1.1.2. Phase I Dose Escalation Rules and Rolling Six Design

Phase I is designed to determine the RP2D of AUTO4 in patients with selected T-NHL. Each dose level may treat up to six patients and is based on total RQR8/aTRBC1-CAR positive T cells. Escalation to the next dose level requires the evaluation of a dose level with at least three patients treated at the planned dose level and completing the 28-day DLT evaluation period. The dose escalation decision rules are outlined in Table 1.

Patient entry at a given dose level will follow a rolling six design which will enable patients to continue to be enrolled at a given dose level up to a maximum of six patients.

The trial is intended to consist of five dose levels (Figure 1); however, the dose levels may be adjusted depending on emerging safety data. Eligible patients will be assigned to dose groups sequentially. The inter-patient dosing interval for AUTO4 in Phase I will be **4 weeks** between the first and second patient and **2 weeks** between subsequent patients (measured from infusion of AUTO4 in one patient to start of pre-conditioning in the next patient), to allow for assessment of possible toxicity, until a dose level is declared safe.

Patients will be admitted to hospital for at least 14 days (or longer) for monitoring after receiving AUTO4 or until all AUTO4-related non-haematological toxicities have returned to ≤Grade 1 or baseline, or longer as clinically necessary. The DLT evaluation period will be **28 days** after the dose of AUTO4.

The Safety Evaluation Committee (SEC) will meet after the first patient in every cohort completes 28 days, to confirm continuation of enrolment to that cohort and thereafter meet again after the third and or sixth patient in a cohort has completed the DLT assessment period.

For Cohorts 2 (75 x 10^6 cells) and 3/3b (225 x 10^6 cells) if there is no CAR-T expansion (eg no expansion is observed above the assay limit of detection threshold) in any of the patients treated (with at least one patient treated at that dose), together with no Grade ≥ 1 CRS/Neurotoxicity or ≥ Grade 2 AUTO4-related adverse events in the DLT period (first 28 days after AUTO4 infusion) SEC may then meet to determine if that dose level can be declared safe and to escalate to the next level. If any CAR-T expansion level is seen in the potential single patient cohorts (Cohort 2 and 3) the cohort must be expanded and have a minimum of 3 patients treated to be considered complete (per rolling six study design). From cohort 4 (450 x 10^6 cells) onwards, the standard rolling six design will apply with a minimum of 3 patients treated per cohort.

Only after a cohort is declared safe by the SEC can the next higher dose level be opened.

Enrolment to a cohort (maximum n=6 evaluable patients/cohort) that has already been declared safe may be undertaken in parallel to the ongoing enrolment of a higher dose level, to enable the treatment of a patient who would not otherwise be treated (for example, a patient with manufactured product who is unable to wait until a slot is available in the higher dose cohort due to rapid disease progression). In this situation, a minimum dosing interval of 7 days will be maintained between patients - even if they are enrolled to a cohort that is declared safe in the Phase I part of the study.

The starting dose level will be 25 x 10^6 RQR8/aTRBC1-CAR positive T cells (Table 1) and if this dose is declared safe then the second cohort will receive 75 x 10^6 RQR8/aTRBC1-CAR positive T cells. Dose escalation may continue until the planned maximum administered dose (MAD) of 900 x 10^6 RQR8/aTRBC1-CAR positive T cells is reached. A dose lower than planned MAD (or next higher dose) may be evaluated if emerging safety data suggest that it may be more appropriate.

Additionally, based on emerging data, more than one RP2D may be determined. For example, if the 75 x 10^6 RQR8/aTRBC1-CAR positive T cell dose is declared as RP2D then Phase II can be opened and in parallel further evaluation of Phase I dose escalation may be continued to determine a second (higher) RP2D dose and or schedule. Should there be a need to assess more than one RP2D in Phase II then this will be undertaken only after a protocol amendment.

If patients are treated below the planned dose due to AUTO4 manufacturing limitations (outside the ± 20% window) or other reasons, then those patients will not be considered evaluable for making dose escalation decisions (additional patients will be treated to meet the minimum number needed to make the dose escalation decision). However, dose escalation decisions will consider all available data, including biomarker data and the safety profile of all patients treated. No patient will be treated below 15 x 10^6 RQR8/aTRBC1-CAR positive T cells. All patients will be evaluated for efficacy.

Table 1: Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
Zero out of three (where all three patients have been followed for the 28-day DLT period) For Cohorts with less than 3 patients (specifically Cohort 2 and 3): • zero treated have a DLT • zero Grade ≥ 1 CRS/Neurotoxicity or ≥ Grade 2 AUTO4-related adverse events in the first 28 days after AUTO4 infusion	Escalate to the next dose level. Or per sponsor decision enrol three additional patients at the current dose level for a total of six patients to further explore safety and efficacy. For Cohorts with less than 3 patients (specifically Cohort 2 and 3): Escalate to the next dose level. Or per sponsor decision, enrol two additional patients (to have a total of 3) at the current dose level or a total of six patients to further explore safety and efficacy.
One out of three (irrespective of whether all three patients have completed the 28-day DLT period)	Continue to enrol three additional patients at the current dose level for a total of six patients.
One out of six (where all six patients have completed the 28-day DLT period)	Escalate to the next dose level or an intermediate dose level.
Two or more patients in a dosing cohort (up to six patients)	The MTD has been exceeded. Either: • Evaluate a dose lower than the current dose (following a substantial protocol amendment). • Expand a prior cohort up to six patients.

DLT = dose limiting toxicity; MTD = maximum tolerated dose.
Note: The Investigators may override these guidelines if there are particular safety issues, for which moving to a higher dose is not considered appropriate.

1.1.3. Planned Dose Levels

The planned dose levels are presented in Table 2 and Table 3. These dose levels were selected as they provide an optimum range for assessing safety, CAR T cell persistence and anti-tumour activity. This range is within the dose levels assessed in other CAR T studies. Based on emerging data, intermediate or additional dose levels may also be explored as described above.

The Phase I dose escalation phase was intended to consist of five dose levels (Table 2) before the change in the manufacturing process. After the change to Process B, considering the preliminary safety results of tested lower doses with the initial manufacturing process, the two lowest dose levels (Level 1 and 2) are skipped and three dose levels are planned in this amended Phase I study with Process B: Level 3b (225 x 10^6 cells), Level 4b (450 x 10^6 cells) and Level 5b (900 x10^6 cells) (Table 3).

Table 2: Phase I Planned Dose Levels and Treatment Cohorts

Dose Levels	Treatment Cohorts	Pre-conditioning (Flu & CY; Days -6, -5, -4, -3 [-1 day])	Total RQR8/aTRBC1-CAR Positive T Cells (Day 0)	Number of Patients
Dose Level 1	Cohort 1	Yes	25×10^6	3 treated
Dose Level 2	Cohort 2	Yes	75×10^6	1-6*
Dose Level 3	Cohort 3	Yes	225×10^6	1-6*
Dose Level 4	Cohort 4	Yes	450×10^6	3-6 **
Dose Level 5	Cohort 5	Yes	900×10^6	3-6**

CAR = chimeric antigen receptor; FLU-CY = fludarabine and cyclophosphamide; RQR8/aTRBC1 = Ritux QBEnd/10-Ritux-cluster of differentiation 8 sort-suicide gene/anti-T cell receptor beta 1.
* For Cohorts 2 (75×10^6 cells) and 3 (225×10^6 cells) if there is no CAR-T expansion in any of the patients treated (with at least one patient treated at that dose) together with no Grade ≥ 1 CRS/Neurotoxicity or ≥ Grade 2 AUTO4-related adverse events in the first 28 days after AUTO4 infusion, SEC may approve escalation to next level. If any CAR-T expansion (above the assay limit of detection) is seen the cohort must have a minimum of 3 patients treated to be considered complete (per rolling six study design)
** From Cohort 4 (450×10^6 cells) onwards, standard rolling six design will apply with a minimum of 3 patients treated per cohort. Cohort is expanded from 3 to 6 patients when 1 patient has a DLT.

Table 3: Phase I (with Process B) Planned Dose Levels and Treatment Cohorts

Dose Levels	Treatment Cohorts	Pre-conditioning (Flu & CY; Days -6, -5, -4, -3 [-1 day])	Total RQR8/aTRBC1-CAR Positive T Cells (Day 0)	Number of Patients
Dose Level 3	Cohort 3b	Yes	225×10^6	1-6*
Dose Level 4	Cohort 4b	Yes	450×10^6	3-6 **
Dose Level 5	Cohort 5b	Yes	900×10^6	3-6 **

* For Cohort 3b (225×10^6 cells) if there is no CAR-T expansion in any of the patients treated (with at least one patient treated at that dose) together with no Grade ≥ 1 CRS/Neurotoxicity or ≥ Grade 2 AUTO4-related adverse events in the first 28 days after AUTO4 infusion, the SEC may approve escalation to the next level. If any CAR-T expansion (above the assay limit of detection) is seen, the cohort must have a minimum of 3 patients treated to be considered complete (per rolling six study design)
** For Cohort 4b (450×10^6 cells), the standard rolling six design will apply with a minimum of 3 patients treated per cohort. The cohort is expanded from 3 to 6 patients when 1 patient has a DLT.

Note: The dose determination is based solely upon the genetically modified cells (i.e. RQR8/aTRBC1-CAR positive T cells). A patient may be evaluable for a planned dose level if the dose is within ±20% of the prescribed RQR8/aTRBC1-CAR positive T cells dose.

- On occasion, AUTO4 production may fail to generate sufficient cells for the current dose level. In this case, the patient can be treated on study, but at a lower dose; however, if production fails to generate $\geq 15 \times 10^6$ (approximately 0.2×10^6/kg RQR8/aTRBC1-CAR positive T cells), then the patient will not be treated on the study. Only patients treated at the planned dose level will be evaluable for dose escalation decision making and primary efficacy analysis. Additional patients will be treated to meet the minimum number of patients needed to make the dose escalation decision.

- If emerging data suggest that escalation to an intermediate dose which is a lower than the planned dose is appropriate, then such an intermediate dose escalation can be undertaken. The total number of patients in Phase I may also be increased if necessary.
- If emerging safety and efficacy data suggest further dose escalation is warranted, any doses higher than 900 x 10^6 RQR8/aTRBC1-CAR T cells will not be undertaken without a protocol amendment.

1.2. Treatment

1.2.1. Leukapheresis

Following completion of all the procedures and assessments required in 'Screen 1' (including the confirmation that the patient is TRBC1 positive), patients will undergo an unstimulated leukapheresis for the generation of AUTO4.

1.2.2. Bridging Therapy

Patients may receive bridging therapy, between leukapheresis and admission for pre-conditioning therapy, prior to AUTO4 infusion. The dates of bridging therapy, the chemotherapy agents and the doses given must be recorded in the eCRF. Additionally, the intent of bridging therapy, such as prevention of disease progression or induction of response in a rapidly progressing disease, should be documented in the eCRF.

Cytotoxic chemotherapies should be stopped 2 weeks prior to AUTO4 infusion. Other therapies should also have an adequate washout as indicated in exclusion criteria. Patients should have a baseline PET/CT after the bridging chemotherapy is given and prior to starting pre-conditioning.

1.2.3. Pre-Conditioning Therapy

Patients that still meet eligibility requirements for the study and for whom the AUTO4 product has been release to specification, will proceed to receive a lymphodepleting pre-conditioning treatment with Fludarabine (FLU) and Cyclophosphamide (CY) before AUTO4 infusion. The pre-conditioning phase will begin with administration of pre-conditioning chemotherapy and will end with the beginning of treatment with AUTO4 infusion. During this phase, AEs associated with pre-conditioning chemotherapy as well as use of concomitant medications will be collected.

Prior to administration of pre-conditioning chemotherapy, patients will undergo clinical and laboratory assessments as per the Schedule of Assessments and the site Investigator or designee will determine if the patient is fit to receive pre-conditioning chemotherapy. If considered to be fit, patients will proceed to receive a lymphodepleting pre-conditioning treatment with FLU and CY for 4 days (starting Day -6 [-1 day]) and timed to end 3 days (-1 day) before AUTO4 infusion as follows:

- Day -6: FLU 30 mg/m^2 followed by CY 500 mg/m^2
- Day -5: FLU 30 mg/m^2 followed by CY 500 mg/m^2
- Day -4: FLU 30 mg/m^2
- Day -3: FLU 30 mg/m^2

The pre-conditioning chemotherapy should be completed a minimum of 3 days (-1 day) prior to AUTO4 infusion.

1.2.4. AUTO4 Administration

AUTO4 will be administered as a single rapid infusion on Day 0 in an in-patient setting. Details about the dosing level have been described in previous sections.

In most patients, it is expected that AUTO4 will be given once. However, if a patient has sufficient AUTO4 remaining from the original manufacture and meets the re-treatment criteria, a second treatment may be given (see Section 1.2.6).

1.2.5. Dose Delay of Pre-conditioning and AUTO4 Treatment

If the pre-conditioning regimen is interrupted for intercurrent illness or other reasons, the patient may complete or recommence the preparative regimen after recovery, or proceed with partial pre-conditioning according to the Investigator's judgment after consultation with the Sponsor. Patients will be closely monitored during and after the pre-conditioning regimen.

If a patient is unable to be dosed with AUTO4 on the planned day, they may undergo delayed dosing after having received the pre-conditioning chemotherapies again (if appropriate – and if they continue to meet the study enrolment criteria). Imaging studies may not need to be repeated if the patient has not received any other anti-lymphoma therapy in the interim (excluding steroids and pre-conditioning chemotherapy). Patients undergoing delayed dosing may be evaluable for dose escalation decision making if the SEC so concludes.

If the patient is deemed unsuitable to receive AUTO4, they will be discontinued from the clinical trial and replaced. Each case will be discussed with the Sponsor.

1.2.6. Re-treatment of Patients

It is expected that most patients will receive a single dose of AUTO4, as part of their treatment. However, some patients may qualify for a re-treatment upon treating physician request. This re-treatment may be for patients in whom there has been no CAR T- cell engraftment (e.g., absence or low levels of CAR T-cell expansion), and could use either remaining CAR T-cells from the initial manufacturing process (if there is AUTO4 product leftover), or by a new AUTO4 manufacturing (e.g., repeating the leukapheresis procedure and manufacturing process), if the patient clinical status allows (per treating physician decision). Specific criteria for re-treatment are described below and individual risk-benefit considerations should be taken into account upon Sponsor and treating physician discussion.

Patients undergoing a second AUTO4 infusion should receive the same pre-conditioning chemotherapy. The dose of AUTO4 can be at (or up to) the highest dose that has been declared safe with at least three patients completing the DLT period (or at least 1 patient in case there is any single patient dose cohort) and is considered to be more likely to be more active than the patient's first dose of AUTO4. Depending on the number of cells available, an intermediate dose may also be administered if considered appropriate. The decision to re-treat a patient will be made by the treating Investigator and Sponsor in consultation with the SEC. Patients re-treated will be monitored in a similar way to patients being treated for the first time, in that they would start evaluation and management as defined in the protocol, starting from the pre-conditioning stage.

1.2.7. Allowed Concomitant Medications/Therapies

Palliative radiotherapy: Palliative radiotherapy may be given concomitantly as clinically appropriate.

Other permitted therapies: The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Anti-microbials including antivirals and supportive therapy as required to prevent infections.
- Colony stimulating factors (use granulocyte-macrophage colony-stimulating factors [GM CSF] with caution up to 3 weeks after AUTO4 infusion, due to the potential to worsen CRS symptoms. Granulocyte-colony stimulating factor (G-CSF) would be the preferred myeloid growth factor over GM CSF, if medically indicated. The effects of G CSF are unknown and can be used at the physician's discretion).
- Erythropoietin, and transfusion of platelets and red cells.

Pre-and post AUTO4 infusion supportive therapies (Please refer to Protocol Section 10.2).

1.2.8. Prohibited and Cautionary Therapies

Herbal, homeopathic agents or very high dose vitamins and mineral supplements:

No herbal, homeopathic agents or very high dose vitamin and mineral supplements will be allowed between Day -10 and Day 60 following AUTO4 infusion, unless recommended by the Principal Investigator.

Corticosteroids and other immunosuppressants (except for managing treatment-related toxicity):

Patients should not be receiving corticosteroids at doses of >5 mg prednisolone or equivalent within 72 hours of leukapheresis and pre-conditioning chemotherapy administration and, at the time of AUTO4 infusion. The use of immunosuppressants such as high dose corticosteroids, should be avoided where possible, as these are likely to influence the efficacy and possibly safety of AUTO4. Corticosteroids may be used in the context of severe CRS, neurotoxicity, other inflammatory pathologies or infusion reactions. Physicians may use any medication as clinically appropriate and necessary to manage emerging AEs. The use of other immunosuppressants should be discussed with the Sponsor's Medical Monitor.

Anti-cancer therapies:

In general, patients should not receive other anti-cancer therapy or any other investigational drugs after administration of AUTO4. Administration of other systemic anti-cancer therapy at any time will be considered an indicator of treatment failure (progressive disease). However, palliative radiotherapy for symptom control can be administered without necessarily indicating progressive disease. Patients who have been administered AUTO4 and subsequently require alternative anti-cancer therapy will complete the End of Study visit and roll on to a follow-up protocol.

Live vaccinations:

Administration of live vaccinations is generally not recommended. On a case-by-case basis where specific live vaccines may be appropriate without other options, the Investigator or delegate is to

follow institution guidelines and discuss with the patient. Generally, live vaccinations should not be administered unless the T cell lymphocyte count has recovered and for at least 24 months post AUTO4 infusion.

Investigators can use any medication based on their clinical judgement and local institutional practice to optimise patient's safety. All medications should be recorded in the eCRF.

1.3. Blinding

This is an open-label single arm study, and all enrolled patients are planned to receive AUTO4 infusions. No unblinding will be applied to the study.

2. STUDY OBJECTIVES, ENDPOINTS, AND SAMPLE SIZE

2.1. Study Objectives and Endpoints

2.1.1. Primary Objectives and Endpoints

Primary objectives and endpoints for Phase I part of the study are presented in Table 4 and Table 5, respectively.

Table 4: Primary Objectives and Endpoints for Phase I

Objectives	Endpoints
To assess the safety and tolerability of AUTO4 administration.	Incidence of Grade 3 to 5 toxicity occurring within 60 days of AUTO4 infusion.
To identify the RP2D and MTD, if an MTD exists, of AUTO4.	Frequency of DLT of AUTO4 within 28 days of AUTO4 infusion.

DLT = dose limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended Phase II dose

2.1.2. Secondary Objectives and Endpoints

Secondary objectives and endpoints are presented in Table 5.

Table 5: Secondary Objectives and Endpoints for Phase I

Objectives	Endpoints
To assess the overall safety and tolerability of AUTO4.	Frequency and severity of all AEs and SAEs
	Incidence and severity of opportunistic infections following AUTO4 infusion.
To evaluate the feasibility of generating the ATIMP, AUTO4.	Proportion of patients (who are TRBC1 positive and undergo leukapheresis), for whom an AUTO4 product can be generated (feasibility).
To evaluate the overall clinical efficacy of AUTO4.	Determine the CR rate following treatment with AUTO4. Evaluate clinical outcomes including DOR, DFS, PFS, OS, time to response (CR or PR) and time to CR.
To determine the expansion and persistence of AUTO4 following infusion. Duration of TRBC1 positive T cell aplasia.	RQR8/aTRBC1-CAR positive T cells as determined by PCR and/or flow cytometry at a range of time points in the peripheral blood. Enumeration of circulating TRBC1 positive T cells assessed by flow cytometry at a range of time points in the peripheral blood.

AE = adverse event; ATIMP = advanced therapy investigational medicinal product; CR = complete response; DFS = disease free survival; DOR = duration of response; PCR = polymerase chain reaction: OS = overall survival; PFS = progression free survival; PR = partial response; SAE = serious adverse event; TRBC = T cell receptor beta constant.

2.2. Type of Planned Analyses for Phase I

2.2.1. End of Phase I

The End of Phase I analysis will be performed after all patients in Phase I part of the study have completed the study, which includes all patients in the (a) Phase I (Dose Escalation) and (b) Phase I (Dose Escalation) with Process B.

2.3. Sample Size and Power Estimation

It is anticipated that approximately 200 patients are expected to be screened for eligibility for entry to this study (this includes both Phase I and II). This assumes that approximately 35% of patients will be identified as TRBC1 positive (a small number of patients will not provide sufficient evaluable tissue) Of those that are identified as TRBC1 positive, it is assumed that approximately 20% will fail the AUTO4 manufacture and/or will not continue to meet the inclusion and exclusion criteria. Up to 73 patients in total are anticipated to be treated with AUTO4 therapy.

- **Phase I (Dose Escalation):** Up to 25 patients in total (3 to 6 patients per dose cohort), following a rolling six design (Skolnik et al. 2008)
- **Phase I (Dose Escalation) with Process B:** Up to a total of 18 patients following a modified rolling six design.
- **Phase II (Dose Expansion):** Up to 30 evaluable patients in total treated with AUTO4 Process B product, using a Simon's two-stage optimal design.

Phase I is designed to determine the RP2D of AUTO4 in patients with selected T-NHL. Each dose level may treat up to six patients and is based on total RQR8/aTRBC1-CAR positive T cells. Escalation to the next dose level requires the evaluation of a dose level with at least three patients treated at the planned dose level and completing the 28-day DLT evaluation period. Details has been previously described in Section 1.1.2.

Using Simon's 2-stage design (Simon 1989) in the Phase II part of the study, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 10 evaluable patients will be accrued (12 weeks post treatment of tenth evaluable patient). If there is only one or no responses in these 10 evaluable patients, the study will be stopped. Otherwise, if two responses or more are confirmed before the end of the first stage, the recruitment will continue, and 19 additional evaluable patients will be accrued for a total of 29. The null hypothesis will be rejected if six or more responses are observed in 29 evaluable patients. This design yields a type I error rate of 5% and power of 80% when the true response rate is 30%.

3. STATISTICAL METHODS

3.1. General Considerations for Data Analyses

3.1.1. General Information for Data Analyses

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of subjects enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, q1, q3, minimum, and maximum). In addition, for plasma concentrations and continuous PK parameters, the coefficient of variation and the geometric mean will also be calculated. Kaplan-Meier survival curves will be displayed for time-to-event variables and median survival time will be estimated with 2-sided 95% confidence interval (CI).

3.1.2. General Definitions

3.1.2.1. Screening, Enrollment, and AUTO4 Infusion

As described previously, there are two separate Informed Consent Forms (ICFs) during the **screening** stage – ICF Part A and ICF Part B. The date of signing of informed consent (ICF Part A) is considered as the **date of screening**.

From signing of informed consent (ICF Part A) until the End of Study visit, information relating to adverse events (AEs), laboratory abnormalities, disease response and biomarker changes will be collected according to the Schedule of Assessments.

Patients are considered **enrolled** for treatment once all inclusion/exclusion criteria have been fulfilled and leukapheresate has been accepted by the manufacturing facility.

The **date of enrolment** as defined above will be recorded on the screening disposition case report form (CRF) for analysis.

Patients are considered in **screening** prior to the date of enrollment.

Patients are considered to be **treated with AUTO4 therapy** once they receive any dose of AUTO4 infusion.

3.1.2.2. Baselines for Demographic and Medical History

The following will be collected at Screen 1 and Screen 2 to determine eligibility and baseline status of the patient.

TRBC1 eligibility

- Tumour Tissue Sample (TRBC1 status)

Demographic data and baseline variables

- Demographic data will include self-reported race/ethnicity, age, gender, and height at screening visit.

Medical/lymphoma history

- Medical history includes all current and past clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements). Histological confirmation of disease diagnosis will be obtained (pathology report).

3.1.2.3. Baseline for Disease Evaluation

Both positron emission tomography (PET) and a diagnostic quality computed tomography (CT) are required at screening. Both images should be taken at a similar time (< 2 weeks apart). Measurable disease on CT needs to be FDG-avid and at least 1 lesion to be >= 20mm in its shortest axis. For patients who receive bridging therapy, baseline disease assessment with PET/CT should be done after completion of bridging therapy and before preconditioning and AUTO4 infusion.

Patients will undergo baseline scan(s) – CT imaging of the neck, chest, abdomen and pelvis. MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where magnetic resonance imaging [MRI] is desirable, the MRI must be obtained at baseline). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI is only required if clinically indicated. A PET scan will additionally be conducted.

The most current disease assessments as per Lugano Classification on or prior to the date of initiation of the pre-conditioning will be used as baseline values for disease evaluation. Response evaluations will be assessed by PET scans, CT scans, MRI, physical examination, and bone marrow biopsy (if needed).

3.1.2.4. Baseline for Safety Evaluation

For **safety evaluations** (i.e. laboratory and vital signs), the last available assessment before AUTO4 infusion is taken as baseline by default, including the follows.

- Physical examination
- Weight, vital signs
- Electrocardiogram (ECG), ECHO or MUGA
- ECOG
- Laboratory (haematology, coagulation and biochemistry)

3.1.2.5. Baseline for Pharmacokinetics, Pharmacodynamics, and Biomarker Evaluations

For Pharmacokinetics (PK), Pharmacodynamics (PD), and Biomarker Evaluations, the last available assessment before AUTO4 infusion is taken as baseline by default.

3.1.2.6. Study Day

Unless otherwise noted, the study day refers to the study day from 1st AUTO4 infusion, which describes the day of the event or assessment date relative to the date of first AUTO4 infusion (reference start date). The study day is defined as:

- (date of the event/assessment − date of first AUTO4 infusion + 1), if event is on or after the date of first AUTO4 infusion;
- (date of the event/assessment − date of first AUTO4 infusion), if event precedes the date of first AUTO4 infusion. In this case, the study day will be negative.

3.1.2.7. Last Contact Date

For patients not known to have died as of the analysis cut-off date, the **last contact date** should be derived as the latest date on or before the data cut-off date from the dates listed below. No additional dates are used for last contact date derivation.

- Date of enrolment
- Start/end dates from drug administration records
- Start/end dates from post-AUTO4 new anticancer therapy for NHL
- Date of any non-missing efficacy assessment
- Date of lab / pharmacokinetics (PK) collection with non-missing values
- Date of vital sign assessment with non-missing values
- Start/end dates of adverse events (AE)
- Last date patient was known to be alive from survival follow-up

3.1.3. Dose Limiting Toxicity

Toxicities will be graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, with the exception of neurotoxicity, which will be assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT)/American Society for Blood and Marrow Transplantation (ASBMT) Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) grading criteria. The DLT criteria take into consideration the single dose nature of AUTO4 treatment (unlike repeat dose treatments of usual anti-cancer agents), the potential for differential expansion of CARs post infusion in different patients and the inclusion of consolidation therapy. As well as features inherent to CAR therapy, transient fever due to low grade CRS, and in the setting of pre-conditioning, induced cytopenias/neutropenia are seen in most patients. These are not necessarily classical neutropenic fevers resulting from infection.

The DLT evaluation period will be **28 days** after the infusion of AUTO4.

3.1.3.1. Dose Limiting Toxicity

Dose limiting toxicity will be defined as:

- Any new non-haematological AE of Grade 3 or higher toxicity using the NCI CTCAE (version 5.0), which is probably or definitely related to AUTO4 therapy, which occurs within the DLT evaluation period, and which fails to resolve to Grade 2 or better within 14 days, despite appropriate supportive measures.
- A Grade 4 CRS.
- Any other fatal adverse reaction (Grade 5) or life-threatening event (Grade 4) that cannot be managed with conventional supportive measures or which in the opinion of the SEC necessitates dose reduction or other modification to trial treatment to avoid a similar hazard in future patients. Efforts should be made to perform an autopsy in case of a fatal event where the aetiology is unclear.
- Any reason for activation of the safety switch after receiving AUTO4.
- Any event that in the opinion of treating investigators and/or Medical Monitor puts the patient at undue risk may also be considered a DLT

3.1.3.2. Maximum Tolerated Dose

Maximum Tolerated Dose (MTD): The MTD is defined as the highest dose level of AUTO4 at which ≤ one patient out of six patients experiences a DLT during the DLT evaluation period. If two or more out of six patients at a dose level experience a DLT during the DLT evaluation period, the MTD has been exceeded. If the MTD is exceeded due to a specific toxicity that can be managed with supportive care, an additional three patients may be treated at the dose level that exceeded the MTD with establishment of supportive care measures. A summary of available safety data and a description of the plans for supportive care measures with further enrolment at that dose level will be provided to Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) prior to dosing.

3.1.3.3. Maximum Administered Dose

Maximum Administered Dose (MAD): The planned MAD for this study is 900×10^6 RQR8/aTRBC1-CAR positive T cells in the event the MTD is not defined. The MAD may be lower based on emerging data.

3.1.3.4. Recommended Phase II Dose

Recommended Phase II Dose (RP2D): The RP2D is the optimal dose and will be either identical to the MTD or MAD (or a lower dose), selected on the basis of a cumulative review of safety, persistence of the CAR T cells and clinical activity. The RP2D dose level may be expanded to up to six patients to further characterise safety.

3.1.4. Efficacy Criteria

3.1.4.1. Assessment of Disease Response and Progressive Disease

Efficacy assessments for the purpose of the study result analyses will be performed by the Investigators according to the Lugano Classification (Cheson et al. 2014) (Appendix 1).

For suspected baseline disease that may not be detected by PET, e.g. skin, eye, GI wall change, appropriate screening assessments, e.g. skin biopsy, eye imaging assessment, endoscopy, are required. In the efficacy follow up, these disease locations should be re-examined and a CR can only be called if disease from all anatomical locations are resolved, evidenced by relevant assessments.

3.1.4.2. Definition of Measurable and Assessable Disease

Eligible patients must have PET-positive disease at baseline (FDG-avid disease corresponding with a 5-point scale score of 4 or 5). Patients who receive bridging therapy after study enrolment must have a PET/CT scan performed after completion of bridging therapy. Patients who do not have PET-positive disease (5-point scale score of 4 or 5) after bridging treatment will be excluded from the primary efficacy analysis. Patients with PET-positive disease at baseline but without measurable disease per CT scan will be included in the primary efficacy analysis.

For radiological assessments based on CT scan (or MRI), measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement, or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in two perpendicular dimensions. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable. Up to six measurable sites of disease, clearly measurable in two perpendicular dimensions, will be followed for each patient. Measurable sites of disease should be chosen such that they are representative of the patient's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in two perpendicular dimensions, at least one lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the GI tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than six sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

3.1.5. Safety Criteria

3.1.5.1. Adverse Event

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The severity of AEs will be graded according to the NCI CTCAE (version 5.0).

Adverse events that are not defined by the NCI CTCAE should be evaluated for severity according to the following scale:

Table 6: Severity Grading of AEs Not Listed on the NCI CTCAE Grading System

Grade	Severity	
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible.
4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable.
5	Fatal	Death because of this AE.

AE = adverse event.

Treatment-emergent AEs is defined as any AE that occurs during or after administration of AUTO4 up to 60 days after the infusion.

3.1.5.2. Serious Adverse Event

A **Serious Adverse Event** (SAE) is defined as an AE that meets any of the following criteria:

- **Results in death** (death due to disease progression will not be considered as an SAE).
- **Life-threatening** (the term 'life-threatening' refers to an event in which the patient was at risk of death at the time of the event. It does not include any AE that, had it occurred in a more severe form, might have caused death).
- **Requires in-patient hospitalisation or prolonged existing hospitalisation.**
- **Results in persistent or significant disability/incapacity.**
- **Congenital anomaly/birth defect.**
- **Medically significant** (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above).

If the event was initially non-serious, the onset of the SAE should be considered the time when the AE met the above seriousness criteria. Resolution of the SAE should also be considered when the event no longer is serious and is either a non-serious event or has resolved.

3.1.5.3. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study include the follows:

- Grade 2-5 CRS.
- Grade 2-5 neurotoxicity (including depressed level of consciousness, dysphagia, ataxia, seizures and cerebral oedema).
- Grade 3-4 Infusion Related Reaction to AUTO4.

3.2. Analysis Sets

3.2.1. Enrolled Set

The Enrolled set will consist of all patients registered and enrolled into the study. The number of patients who fail screening, together with the reason for screen failure will be summarised.

3.2.2. Infused Set

The Infused Set comprises all patients who have received at least one infusion of AUTO4 treatment.

3.2.3. Efficacy Analysis Set

All patients in the Infused Set with PET-positive disease prior to start of pre-conditioning therapy will be included in the Efficacy Analysis Set (EAS). Patients with PET-negative disease after bridging chemotherapy will not be included in the primary efficacy analysis set. Patients who did not receive bridging therapy and did not repeat disease assessment prior to pre-conditioning will be included if there is PET positive disease prior to enrollment.

3.2.4. DLT-Evaluable Set

The DLT-Evaluable Set (DES) comprises those patients enrolled in Phase I who fulfill requirements to determine if they experience a dose-limiting toxicity (DLT) or not. The DLT evaluation period will be 28 days after the dose of AUTO4.

The requirements for determining a DLT are as follows:

- Patient must have received at least one infusion of AUTO4 treatment
- Patient must be assessed for safety and complete the 28-day DLT evaluation period
- If patients are treated below the planned dose due to AUTO4 manufacturing limitations (outside the ± 20% window) or other reasons, then those patients will not be considered evaluable for making dose escalation decisions (additional patients will be treated to meet the minimum number needed to make the dose escalation decision).

However, dose escalation decisions will consider all available data, including biomarker data and the safety profile of all patients treated. No patient will be treated below 15 x 10^6 RQR8/aTRBC1-CAR positive T cells. All patients will be evaluated for efficacy.

3.2.5. Safety Set

The Safety Set comprises all patients who receive at least one dose (complete or partial dose) of AUTO4 treatment.

3.3. Protocol Deviation

Patients who did not meet at least one eligibility criterion for study but enrolled in the study will be summarized, based on the Enrolled Set. The summary will present the number and percentage of patients who did not meet specific criteria.

Protocol deviations occurring after patients entered the study are documented during routine monitoring. The number and percentage of patients with important protocol deviations will be tabulated by deviations category for the Infused Set.

All protocol deviations will be listed.

3.4. Patient Information

3.4.1. Patient Disposition

The patient disposition for each phase and cohort will be summarized for the Enrolled Set. The number and percentage of patients in each of the disposition categories will be tabulated and listed.

As a summary of study follow-up, duration from first AUTO4 infusion until analysis data cutoff or database finalization will be summarized numerically as well as by categories: <28 days, 28 days to <60 days, 60 days to <6 months, 6 months to <12 months, 12 months to <24 months, >=24 months.

3.4.2. Demographic and Baseline Characteristics

Demographic and other baseline patient characteristics data will be summarized for the Enrolled Set.

Medical history and ongoing conditions, including cancer-related conditions and symptoms at the time of informed consent will be summarized and listed. Medical histories are coded using the medical dictionary for regulatory activities (MedDRA) terminology.

3.5. Study Treatment and Other Prior or Post Treatments

3.5.1. Bridging Therapy

Bridging therapy will be summarized by the type of bridging therapy received in the Enrolled Set. Number and percentage of patients receiving bridging therapy will be summarized.

3.5.2. Pre-Conditioning Therapy

The number and percentage of patients who received pre-conditioning therapies will be summarized by medication received in the Enrolled Set. Duration of exposure, actual dose and reason for therapy discontinuation will also be summarized.

3.5.3. AUTO4 infusions

The total of CD19 CAR-positive T cell (10^6 cells) administered will be listed and summarized using descriptive statistics in the Infused Set. Number and percentage of patients who did not receive the target dose of AUTO4 infusions will be summarized by the reasons (e.g., adverse event, etc.). Time from screening and enrollment to first AUTO4 infusion will be summarized using descriptive statistics.

Number and percentage of patients who were re-treated with AUTO4 infusion, and the time from screening and enrollment to the AUTO4 treatment will be provided in a data listing.

3.5.4. Anticancer Therapies for NHL Prior to Enrolment

The number and percentage of patients who received any prior anticancer medications or radiotherapy for NHL will be summarized in the Enrolled Set.

3.5.5. New Anticancer Therapies for NHL Post AUTO4 infusion

Additional anticancer therapies for NHL post enrollment other than those specified as study treatment (Section 1.2) will be listed and summarized by ATC class and preferred term in the Enrolled Set by whether patient received AUTO4 infusion or not.

3.5.6. Other Prior, Concomitant and Post Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by System Organ Class (SOC) and preferred term (PT).

3.6. Efficacy Analysis

3.6.1. Efficacy Endpoints

Efficacy assessments for the purpose of the study result analyses will be performed by the Investigators according to the Lugano Classification (Cheson et al. 2014) (Appendix 1), which provide the definition for complete response (CR), partial response (PR), No response or stable disease (SD) and progressive disease (PD).

The efficacy endpoints are ORR, DOR, PFS, and OS:

Overall response rate (ORR): CR or PR by the Criteria for Response Assessment of NHL (i.e. Lugano Classification). The proportion of patients achieving PR and CR at 1 and 3, and 6 months post-AUTO4 infusion will also be determined.

The **time to response** (PR+CR) and the **time to CR** will be calculated. These are defined as the time from the first treatment of AUTO4 to the response (either PR or CR as appropriate).

Duration of response: DOR is defined as the time from the first observed CR or PR to documented disease progression or death due to any cause, for patients who are considered as responders.

- If a patient does not have relapse or death due to any reason prior to data cut-off, DOR will be censored at the date of the last adequate assessment by default.
- Patients who receive protocol specified anti-cancer treatment post AUTO4 infusion (Section 1.2.7) will be ignored in the main analysis.
- Patients who proceed to SCT after AUTO4 infusion will be censored at the time of SCT (including the conditioning regimen for SCT).
- Patients who receive new non-protocol anticancer therapies for NHL other than SCT will be censored as the date of last adequate assessment prior to the new therapy.
- Patients who experience event after missing two or more scheduled disease assessments will be censored at the date of last adequate assessment prior to the event.

Progression-free survival: PFS is defined as the time from the first treatment of AUTO4 to documented disease progression/relapse or death due to any cause.

- If a patient does not have relapse or death due to any reason prior to data cut-off, PFS will be censored at the date of the last adequate assessment by default.
- Patients who receive protocol specified anti-cancer treatment post AUTO4 infusion (Section 1.2.7) will be ignored in the main analysis.
- Patients who proceed to SCT after AUTO4 infusion will be censored at the time of SCT (including the conditioning regimen for SCT).
- Patients who receive new non-protocol anticancer therapies for NHL other than SCT will be censored as the date of last adequate assessment prior to the new therapy.
- Patients who experience event after missing two or more scheduled disease assessments will be censored at the date of last adequate assessment prior to the event.

Overall survival: OS is defined as the time from the first treatment of AUTO4 to death due to any cause. Date of death will be recorded.

- Patients who have not died prior to data cutoff or database finalization will be censored at the last contact date (Section 3.1.2.7).
- Patients who received SCT after AUTO4 infusion will be ignored in the main analysis.

3.6.2. Analysis Methods for Response Variables

ORR will be summarized by cohort/dose level. The number and percentage of patients in each category will be presented together with two-sided exact 95% CIs based on binomial distribution.

The number and percentage of patients with CR, PR, SD and PD will be summarized by cohort/dose level along with two-sided exact 95% CI based on binomial distribution.

The example SAS code to estimate 95% CI is shown below:

```
ods output OneWayFreqs=mFreq Binomial=mBinomial;
proc freq data=adeff;
        table response (event = '1') / nocum norow binomial (CL=exact)  alpha=0.05;
        exact binomial ;
run;
```

To explore the relationship between dose level and response (CR+PR), a dose-response logistic regression model will be fitted to the binary response, the first and second order of logarithm transformed dose as independent covariates for all patients. The response rate for each dose level will be estimated with two-sided 95% CI from this model.

The example SAS code the logistic regression and estimating model fitted CR rate and 95% CI is shown below:

```
Proc logistic data=adeff;
        model response (event = '1') = lndose lndose2 / lackfit covb;
        Output out=pred_response p=phat_response lower=lcl_response upper=ucl_response /
alpha=0.05;
Run;
```

Where *adeff* is the input dataset; *cr_response, lndose, lndose2* are variables for response, logarithm of dose level and logarithm of dose square respectively; *pred_response* is the output dataset, *phat_response, lcl_response, ucl_response* are variables for predicted response rate, lower limit of confidence interval and upper limit of confidence interval, respectively.

3.6.3. Analysis Methods for Time-to-Event Variables

PFS, DOR, PFS, and OS will be summarized using descriptive statistics. The survival curve and the median will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CIs.

The example SAS code used to produce median from Kaplan-Meier estimates and corresponding 95% CI is shown below:

```
Proc lifetest data=adtte plots=(s) outsurv=surv;
        time survtime * censor (0);
        strata cohort;
Run;
```

Where *adtte* is the input dataset, *surv* is the output dataset, *survtime*, *censor*, *cohort* are variables for survival time, censoring, and cohort/dose level, respectively.

3.6.4. Handling of Missing Data

Patients in the study who are of unknown clinical response will be treated the same as non-responders in the ORR analysis.

In case of missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" will be assigned unless at least one observation was made which qualifies for relapse. Relapse can be determined by the relapsed component alone.

Every effort will be made to resolve incomplete dates for death and disease progression (PD). If a partial date cannot be resolved, the most conservative imputation methods will be used to complete the missing information.

3.7. Safety Analysis

Safety and tolerability (determine maximum tolerated dose [MTD]) are the primary endpoints of the study, including:

- Incidence of Grade 3 to 5 toxicity occurring anytime post the initiation of AUTO4 infusion (and prior to the second AUTO4 infusion for re-treated patients, if applicable)
- Frequency of dose limiting toxicity (DLT) of AUTO4 within 28 days of the initiation of AUTO4 infusion

3.7.1. General Safety Analysis Conventions

Table 7 summarizes the mutually exclusive safety reporting periods as well as the subjects to be included in each of the segments.

All safety analyses will be based on the Safety Set unless otherwise specified.

Table 7: Safety Reporting Periods

Period	Definition	Patients Included for Analysis
Screening Period	From the date of informed consent to the date prior to enrollment.	Screened Set
Bridging Period	From day of enrollment to the day before start of pre-conditioning therapy or the day before AUTO4 infusion in case pre-conditioning therapy is not given	Enrolled Set
Pre-Conditioning Period	From the start day of pre-conditioning therapy to the day before first AUTO4 infusion, or to 30 days after last dose of pre-conditioning therapy for patients who didn't receive AUTO4 infusion.	All patients in Enrolled Set who started pre-conditioning therapy
Post-Infusion Period	From the day of first AUTO4 infusion to EOS.	Safety Set

3.7.2. Dose Limiting Toxicity

The Dose limiting toxicity (DLT) evaluation period will be 28 days after the infusion of AUTO4. A DLT is defined in Section 3.1.3.1.

The number and percentage of patients with DTL, as classified by SOC and PT will be summarized for the DLT-Evaluable Set (DES).

If patients are treated below the planned dose due to AUTO4 manufacturing limitations (outside the ± 20% window) or other reasons, then those patients will not be considered evaluable for making dose escalation decisions (additional patients will be treated to meet the minimum number needed to make the dose escalation decision). However, dose escalation decisions will consider all available data, including biomarker data and the safety profile of all patients treated. No patient will be treated below 15 x 10^6 RQR8/aTRBC1-CAR positive T cells.

3.7.3. Adverse Events

Summary statistics and analyses will be provided by dose level and overall. The safety analysis set for the study and study treatment will be used for the analysis of safety data.
Safety evaluations will be based on the incidence, severity and type of AEs, and changes in the patient's vital signs and clinical laboratory results.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities AE coding system for the purpose of summarisation. All AEs occurring in the study will be listed in by patient data listings. The following AEs will be tabulated:

- Treatment-emergent AEs, where "treatment-emergent" is defined as any AE that occurs during or after administration of AUTO4.
- Adverse events that are considered drug-related regardless of the start date of the event, or any event that is present at baseline and continues after the first dose of study treatment but worsens in intensity.
- Adverse events that are considered related to treatment (possibly, probably, or definitely related).
- Adverse events of special interest, together with grade.

Laboratory toxicity grades will be calculated for the appropriate laboratory parameters according to NCI CTCAE version 5.0.

Adverse events of special interest will be analysed in greater depth, including the time to onset and time to resolution where appropriate.

Reporting of AEs will be based on the latest MedDRA version at the time of database lock and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The reporting of cytokine release syndrome (CRS) and Immune Effector Cell Therapy-Associated Neurotoxicity Syndrome (ICANS) will be based on the ASTCT consensus grading (Lee et al. 2019). Other adverse events that are not defined by the CTCAE should be evaluated for severity according to the following scale:

An overview table will include the following details by cohort/dose level:

- Number and percentage of patients with TEAEs
- Number and percentage of patients with drug related TEAEs
- Number and percentage of patients with serious TEAEs
- Number and percentage of patients with serious drug related TEAEs

- Number and percentage of patients with TEAEs leading to permanent discontinuation of study
- Number and percentage of patients with drug related TEAEs leading to permanent discontinuation of study
- Number and percentage of patients with grade 3 or higher TEAEs
- Number of deaths

The number and percentage of patients with TEAEs, as classified by SOC and PT, will be summarized by cohort/dose level. Summaries will be provided for:

- TEAEs
- Drug related TEAEs
- Serious TEAEs
- Drug related serious TEAEs
- TEAEs leading to permanent discontinuation of study
- Drug related TEAEs leading to permanent discontinuation of study

The number and percentage of patients with TEAEs, as classified by PT only, will be summarized by cohort/dose level.

A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple toxicity grades for the same preferred term will be summarised under the maximum toxicity grade recorded for the event. AE with missing toxicity grade will be included in the all grades column of the summary tables.

AE of special interests post AUTO4 infusion (and prior to the second AUTO4 infusion for re-treated patients) will be summarized by cohort/dose level using the Safety Set. All AE of special interests will be listed, including those AEs occurred after the second AUTO4 infusion for re-treated patients.

Fatal AEs and SAEs will be listed by patient and summarised by system organ class and preferred term.

In addition, AEs occurred prior to AUTO4 infusion will be summarized by SOC and PT in the Enrolled Set.

3.7.4. Clinical Laboratory Evaluation

Blood samples for haematology, coagulation and biochemistry will be collected at each visit as specified in the Schedule of Assessments. Where appropriate, tests must be performed prior to receiving pre-conditioning chemotherapy or AUTO4 infusion. More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the patient or by abnormalities that warrant more frequent monitoring.

In general, quantitative clinical laboratory variables, i.e., hematology, biochemistry, coagulation, ferritin and C-reactive protein will be summarized using mean, standard deviation, minimum, maximum and median by cohort/dose level at each visit. Additionally, a within-patient change

will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

Laboratory tests covered by the NCI-CTCAE will be graded according to the lab results and the normal ranges provided by the local labs. For laboratory tests covered by NCI-CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same patient can be counted for both values if the patient has different laboratory values meeting each criterion. NCI-CTCAE grades of laboratory evaluations will be summarized by number and percentage of patients for each visit. Shift tables on NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented. The number and percentage of patients with grade 3 or 4 laboratory test results will be summarized by cohort/dose level and laboratory parameter (the name of the adverse event associated with the abnormal laboratory test result will be presented).

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

3.7.5. Other Safety Data

3.7.5.1. Vital Signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate and body temperature) will be summarized using mean, standard deviation, minimum, maximum and median by cohort/dose level and visit. Additionally, a within-patient change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by cohort/dose level and visit.

3.7.5.2. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and corrected QT intervals. At each time point, a single 12-lead ECG will be performed by qualified site personnel. The clinical Investigator or designee will review the printout, including ECG morphology. The ECG should be repeated in triplicate if motion artefacts or clinically relevant abnormalities are noted. The three values of each ECG parameter within a time point form the clinical Investigator or designee will be averaged to determine time-specific parameter for a patient, and used in summaries.

A by-patient data listing will provided for ECG variables, including patients with normal and abnormal results as assessed by the clinical Investigator or designee for overall interpretation.

3.7.5.3. Eastern Cooperative Oncology Group (ECOG) Performance Scores

Patients for each category of the ECOG performance status at each assessment time will be provided in a by-patient listing. Negative change scores indicate an improvement and positive scores indicate a decline in performance.

3.7.6. Special Safety Topics

Special safety topics of the study include:

- Grade 2-5 Cytokine Release Syndrome (CRS)
- Grade 2-5 Neurotoxicity (including depressed level of consciousness, dysphagia, ataxia, seizures and cerebral oedema)

Other special safety topics will be further analyzed during Phase II part of the study.

3.7.6.1. Cytokine Release and Cytokine Release Syndrome

Timing and magnitude of cytokine release, evaluated in serum using a cytokine assay:

- Data on timing (kinetic of change) will be summarised as the mean (or median) number of days post-infusion.
- Magnitude – kinetic and peak of cytokine levels, e.g., TNFα, IL-6 and IFN-γ (pg/mL), will be plotted for each patient and summarised.

CRS will be reported according to the ASTCT consensus grading (Lee et al. 2019). Detailed information regarding the first episode of CRS, including maximum CRS grade, time to onset of CRS, time of resolution of CRS, details of fever, hypotension and hypoxia, timing and duration of ICU stay, and use of anti-cytokine therapies, etc, will be summarized.

Time to resolution of the first CRS will be summarized using KM method for subjects with CRS. In case the end date of a CRS is missing, it will be censored as the minimum of the data cut-off date, last contact date and death date (if applicable).

3.7.6.2. Neurotoxicity

Immune Effector Cell Therapy-Associated Neurotoxicity Syndrome (ICANS) will be summarized according to the ASTCT consensus grading (Lee et al. 2019).

Adverse events associated with ICANS will be summarized according to MedDRA by PT and maximum CTCAE grades.

3.8. Pharmacokinetic and Pharmacodynamic Analysis

Individual cellular kinetics concentration-time profiles will be plotted based on AUTO4 transgene levels in peripheral blood. All cellular kinetics concentrations will be listed.

3.9. Biomarker Analysis

Individual concentration-time profiles will be plotted to display the depletion of TRBC1 positive T cell compartment as determined by flow cytometry on peripheral blood, including:

- CD3+
    - CD3 TRBC1+
    - CD3 TRBC1-
    - CD3 TRBC1+/- ratio
- CD4+
- CD3+ CD8+

All depletion of TRBC1 positive T cell compartment as determined by flow cytometry on peripheral blood will be listed.

4. DETAILED ANALYSIS CONVENTIONS

4.1. Missing Data Imputation

The following subsections provide details for handling missing data for AEs, concomitant medications, prior therapies, post therapies, tumor assessments, and death (or last known alive). In general, missing data for efficacy, patient report outcomes (i.e., EQ-5D-5L and EORTC QLQ-C30), pharmacokinetic, and biomarkers will not be imputed unless methods for handling missing data are specified.

4.1.1. Adverse Event Date

In case the AE start date is collected as missing or partial date, it is imputed using following rule:

- No imputation on missing date or the date with year missing
- If AE start date indicates that it is clearly after Start date of study treatment, and year is after the 1st AUTO4 infusion, then
  - If the month is missing, then impute month to JAN
  - If the day is missing, then impute to the first day of the month
- If AE start date indicates that it is clearly before Start date of study treatment, then
  - If the month is missing, then impute month to JAN
  - If the day is missing, then impute to the first day of the month
- If AE start date indicates that it is not clear whether it is before or after Start date of study treatment, then
  - If the month is missing, then impute month to the month of 1st AUTO4 infusion
  - If the day is missing, then impute day to the day of 1st AUTO4 infusion.

Table 8 provides some examples of imputation if AE start dates are missing.

Table 8: Example of Imputation for Missing Adverse Event Start Date

Partial AE start date	Start date of study treatment	Scenario	Imputed Date
yyyy-mm-dd	2020-07-20	Uncertain	<blank>
yyyy-mm-12	2020-07-20	Uncertain	<blank>
yyyy-07-12	2020-07-20	Uncertain	<blank>
2019-mm-dd	2020-07-20	Before Start date of study treatment	2019-01-01
2020-mm-dd	2020-07-20	Uncertain	2020-07-20
2021-mm-dd	2020-07-20	After Start date of study treatment	2021-01-01
2020-06-dd	2020-07-20	Before Start date of study treatment	2020-06-01
2020-07-dd	2020-07-20	Uncertain	2020-07-20

2020-08-dd	2020-07-20	After Start date of study treatment	2020-08-01

Partial AE end date will be imputed as follows:

- if day is missing: Imputed date = min (date of death if applicable, last day of the month)
- if month and day are missing: Imputed date = min (date of death if applicable, 31DEC)

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

4.1.2. Concomitant Medication date

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial concomitant medication end dates will not be imputed.

4.1.3. Prior Therapy Date

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that if year and month of therapy are same as year and month of start date of study treatment, but day is missing, the start date of therapy will be imputed as 'start date of study treatment -1'.

End date:

- if day is missing: Imputed date = min (start date of study treatment, last day of the month)
- if month and day are missing: Imputed date = min (start date of study treatment, 31DEC)

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

4.1.4. Post Therapy Date

Start date:

- if day is missing: Imputed date = max (last date of study treatment + 1, first day of the month)
- if day and month are missing: Imputed date = max (last date of study treatment + 1, 01JAN)

End date: No imputation is applied.

4.1.5. Tumor Assessment Date

Partial dates are not expected for response assessment data. However, should partial dates be present on disease assessments, if one or more investigation dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the

assessment date and assessment date is calculated as the latest of all investigation dates (e.g. whole blood, bone marrow) if the overall disease response at that assessment is CR/CRi/UNK. Otherwise, if overall response is relapsed disease or no response, the assessment date is calculated as the earliest date of all investigation dates at that evaluation number that reveals a relapse/no response. If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to occur at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

4.1.6. Date for Death or Last Known Alive

If the day or month of death is missing from the death CRF, death will be imputed to the maximum of the full (non-imputed) last contact date (the latest date on or before the data cut-off date) and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day or month of last known date subject alive is missing in the survival status CRF, it will be imputed with the following:

- Missing day: minimum of the date of assessment in the survival status CRF and 15th day of the month and year of last known date subject alive
- Missing day and month: minimum of the date of assessment in the survival status CRF and July 1st of the year of last known date subject alive

4.1.7. Date of Initial Diagnosis and Most recent Relapse

If the day or month of initial diagnosis or most recent relapse is missing, the date of initial diagnosis will be imputed to the minimum of the 1st informed consent date - 1 and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

4.2. Data Handling Conventions and Transformations

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation (ULOQ) will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the limit of quantitation). For example, if the values are reported as <50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as <1 or <0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.

- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

Natural logarithmic transformations will be used for analyzing concentrations in the PK samples. Concentration values (including trough and single post-infusion PK concentration) that are below the lower limit of quantitation (BLQ) will be presented as "BLQ" in the concentration listing, and will be treated as one-half the value of the lower limit of quantitation at post-infusion time points for summary purposes.

4.3. Analysis Windows

4.3.1. Analysis Windows

Patient visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The study day is relative to the start of AUTO4 infusion.

Table 9 to Table 11 provide the analysis windows for laboratory data, ECOG, and Vital Signs.

Table 9: Analysis Windows for Laboratory Data - Hematology and Biochemistry

Visit	Target Day	Lower Limit	Upper Limit
Prior to Enrollment	Day of enrollment		Day of enrollment
Prior to Pre-conditioning	Start Day of pre-conditioning	Day after enrollment	<= Start day of pre-conditioning
Prior to first AUTO4 infusion	1	Day after start of pre-conditioning	Day 1 before AUTO4 infusion
Baseline	0		Day 1 before AUTO4 infusion
D1	1	Day 1 after AUTO4 infusion	4
D7	7	5	10
D14	14	11	21
D28	28	22	≤ ROUND (1.5 M)
M2	M2	> ROUND (1.5 M)	≤ ROUND (2.5 M)
M3	M3	> ROUND (2.5 M)	≤ ROUND (3.5 M)
M4	M4	> ROUND (3.5 M)	≤ ROUND (4.5M)
M5	M5	> ROUND (4.5 M)	≤ ROUND (5.5M)
M6	M6	> ROUND (5 M)	≤ ROUND (7.5 M)
M9	M9	> ROUND (7.5 M)	≤ ROUND (10.5 M)
M12	M12	> ROUND (10.5 M)	≤ ROUND (13.5 M)
M15	M15	> ROUND (13.5 M)	≤ ROUND (16.5 M)
M18	M18	> ROUND (16.5 M)	≤ ROUND (19.5 M)
M21	M21	> ROUND (19.5 M)	≤ ROUND (22.5 M)
M24	M24	> ROUND (22.5 M)	≤ ROUND (27 M)
q6M until EoS**	M (K * 6 + 24)	> ROUND ((K * 6 – 3) M)	≤ ROUND ((K * 6 + 3) M)

Note: D = Day; M = Month. 1 month = 30.4375 days.
** The End of Study visit is to be performed upon completion of all study visits or in case of early withdrawal. K = 1, 2, … till the EoS visit.

Table 10: Analysis Windows for ECOG

Visit	Target Day	Lower Limit	Upper Limit
Screening	-84 or Screening day		Before Leukapheresis
Pre-conditioning	-6 or pre-conditioning day	After 1st Leukapheresis	Before 1st AUTO4 infusion
Baseline	-6		Before 1st AUTO4 infusion
D28	28	After 1st AUTO4 infusion	44
M2	M2	45	≤ ROUND (2.5M)
M3	M3	61	≤ ROUND (3.5M)
M4	M4	> ROUND (3.5M)	≤ ROUND (4.5M)
M5	M5	> ROUND (4.5M)	≤ ROUND (5.5M)
M6	M6	> ROUND (5.5M)	≤ ROUND (7.5M)
M9	M9	> ROUND (7.5M)	≤ ROUND (10.5M)
M12	M12	> ROUND (10.5M)	≤ ROUND (13.5M)
M15	M15	> ROUND (13.5M)	≤ ROUND (16.5)
M18	M18	> ROUND (16.5M)	≤ ROUND (21M)
M24	M24	> ROUND (21M)	≤ ROUND (27M)
q6M until EoS**	M (K * 6 + 24)	> ROUND ((K * 6 – 3) M)	≤ ROUND ((K * 6 + 3) M)

Note: D = Day; M = Month. 1 month = 30.4375 days.
** The End of Study visit is to be performed upon completion of all study visits or in case of early withdrawal. K = 1, 2, … till the EoS visit

Table 11: Analysis Windows for Vital Signs and O_2 Saturation

Visit	Target Day	Lower Limit	Upper Limit
Prior to Enrollment	Day of enrollment		Day of enrollment
Prior to Pre-conditioning	Start Day of pre-conditioning	Day after enrollment	<= Start day of pre-conditioning
Prior to first AUTO4 infusion	1	Day after start of pre-conditioning	Day 1 before AUTO4 infusion
Baseline	1		Day 1 before AUTO4 infusion
D7	7	2	10
D14	14	11	20
D28	28	21	≤ ROUND (1.5 M)
M2	M2	> ROUND (1.5 M)	≤ ROUND (2.5 M)
M3	M3	> ROUND (2.5 M)	≤ ROUND (3.5 M)
M4	M4	> ROUND (3.5 M)	≤ ROUND (4.5M)
M5	M5	> ROUND (4.5 M)	≤ ROUND (5.5M)
M6	M6	> ROUND (5 M)	≤ ROUND (7.5 M)
M9	M9	> ROUND (7.5 M)	≤ ROUND (10.5 M)
M12	M12	> ROUND (10.5 M)	≤ ROUND (13.5 M)
M15	M15	> ROUND (13.5 M)	≤ ROUND (16.5 M)
M18	M18	> ROUND (16.5 M)	≤ ROUND (19.5 M)
M24	M24	> ROUND (22.5 M)	≤ ROUND (27 M)
q6M until EoS**	M (K * 6 + 24)	> ROUND ((K * 6 – 3) M)	≤ ROUND ((K * 6 + 3) M)

Note: D = Day; M = Month. 1 month = 30.4375 days.
** The End of Study visit is to be performed upon completion of all study visits or in case of early withdrawal. K = 1, 2, … till the EoS visit.

4.3.2. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, while a time to event analysis would not require one value per analysis window. When a single value is required, the following rule(s) will be applied to the analysis.

If multiple non-missing numeric observations exist in a window, then records will be chosen as follows:

- For analysis prior to enrollment/pre-conditioning/infusion, the latest available record on or prior to the corresponding timing will be selected. If there are multiple records for the analysis window, the latest non-missing value will be chosen for the baseline value.
- For post AUTO4 infusion laboratory and PK test results:
    - If windows spanning multiple days, the records(s) collected on the day closest to the nominal day will be selected. If there are 2 records equidistance from the nominal day, the later day will be selected.
    - If there is more than 1 record on the selected day, the average value will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

5. CHANGES TO PROTOCOL SPECIFIED ANALYSES

Table 12 below summarizes all the changes to the analysis plan compared to the Protocol Amendment v6.0.

Table 12: Changes to the protocol specified analyses

Changes	Relevant SAP Section	Substantiality
Treatment-emergent AEs, where "treatment-emergent" is defined as any AE that occurs during or after administration of AUTO4, instead of any AE that occurs during or after administration of AUTO4 and up to 60 days after the infusion as defined by the Protocol.	3.7.3	Minor

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SCHEDULE OF ASSESSMENTS 1 (Safety and Efficacy Follow-up)

	SCREEN TRBC	SCREEN 1[$]	LEUKA-PHERESIS[@]	SCREEN 2[#]	PRE-CONDITIONING CHEMO-THERAPY		TREATMENT STAGE†				FOLLOW-UP STAGE		END OF STUDY **
		Day -84 to Day -35	Before Day -35	Day -35 to -7	Day -7 (-1d)	Day -6, -5, -4, -3 (-1 d)	Day 0	Day 1, then q.a.d. Hospitalisation ≥14 d	Weekly after discharge (±2 d)	End of DLT period* Day 28 (±3 d)	Month 2, 3, 4, 5, 6, 9, 12, 15, 18 & 24 (±7 d)	Every 6 months until EoS** (±4 wk)	
Informed Consent	Part A	Part B											
Demographic Data[1]	X												
Eligibility Criteria[2]	X	X			X		X						
Medical/ Lymphoma History[3]	X				X								
Examinations/Investigations													
ECOG Performance Status	X	X			X					X	X		X
Physical Examination[4]		X			X		X	$X^{D7, D14}$	X	X	X		X
Weight		X	X		X					X	X		X
Vital Signs[5]		X			X		X[5]	$X^{D7, D14}$	X	X	X		X
12-lead ECG[6]		X			X[6]								
ECHO or MUGA[7]		X											
Tumour Tissues Assessment													
Tumour Tissue Sample (TRBC1 status) [8]	X												

	SCREEN TRBC	SCREEN 1[$]	LEUKA-PHERESIS[@]	SCREEN 2[#]	PRE-CONDITIONING CHEMO-THERAPY		TREATMENT STAGE†				FOLLOW-UP STAGE		END OF STUDY **
		Day -84 to Day -35	Before Day -35	Day -35 to -7	Day -7 (-1d)	Day -6, -5, -4, -3 (-1 d)	Day 0	Day 1, then q.a.d. Hospitalisation ≥14 d	Weekly after discharge (±2 d)	End of DLT period* Day 28 (±3 d)	Month 2, 3, 4, 5, 6, 9, 12, 15, 18 & 24 (±7 d)	Every 6 months until EoS** (±4 wk)	
Tumour Tissue Sample (CAR T-cell persistence/TRBC1 expression)[9]								X between D7-D21 [9]			X[prog]		
Bone Marrow Biopsy (if applicable) [10]				X						X[10]			
Disease Evaluations													
CT Imaging (neck, chest, abdomen and pelvis)[11]				X						X	X[M3, M6, M9, M12, M15, M18, M24]	X	[11]
18-FDG-PET Scan (skull base to the proximal femur)[11]				X						X	X[M3, M6, M9, M12, M15, M18, M24]	X	[11]
Tissue biopsy											[11]	[11]	
Safety Labs													
Haematology[12]		X	X		X		X	X[D1, D7, D14]	X	X	X		
Biochemistry [13]		X	X		X		X	X[D1, D7, D14]	X	X	X		
Ferritin, C reactive protein[14]					X		X	X	X	X			
Coagulation[15]		X	X		X		X	X[D7, D14]					

	SCREEN TRBC	**SCREEN 1[$]**	**LEUKA-PHERESIS[@]**	**SCREEN 2[#]**	**PRE-CONDITIONING CHEMO-THERAPY**		**TREATMENT STAGE†**				**FOLLOW-UP STAGE**		**END OF STUDY ****
		Day -84 to Day -35	**Before Day -35**	**Day -35 to -7**	**Day -7 (-1d)**	**Day -6, -5, -4, -3 (-1 d)**	**Day 0**	**Day 1, then q.a.d. Hospitalisation ≥14 d**	**Weekly after discharge (±2 d)**	**End of DLT period* Day 28 (±3 d)**	**Month 2, 3, 4, 5, 6, 9, 12, 15, 18 & 24 (±7 d)**	**Every 6 months until EoS** (±4 wk)**	
Infectious Disease Screen[16]		X	X[16]										
Monitoring for infections[17]				X						X	X		
Pregnancy Test[18]		X			X		X			X	X[M3, M6, M12]		

	SCREEN TRBC	SCREEN 1[S]	LEUKA-PHERESIS[@]	SCREEN 2[#]	PRE-CONDITIONING CHEMO-THERAPY		TREATMENT STAGE†				FOLLOW-UP STAGE		END OF STUDY **
		Day -84 to Day -35	Before Day -35	Day -35 to -7	Day -7 (-1d)	Day -6, -5, -4, -3 (-1 d)	Day 0	Day 1, then q.a.d. Hospitalisation ≥14 d	Weekly after discharge (±2 d)	End of DLT period* Day 28 (±3 d)	Month 2, 3, 4, 5, 6, 9, 12, 15, 18 & 24 (±7 d)	Every 6 months until EoS** (±4 wk)	
Pharmacokinetics, Pharmacodynamic and Biomarker Assays													
Serum for cytokines[19]				X	X	X[D-6]	X[P]	X	X	X	X[M2, M3]		
Central Assessment-Blood for Tcell Subset (TRBC1+, TRBC1-, CD3+CD4+, CD3+ CD8+) Analysis [20]		X			X		X	X[D14 only]		X	X[M2, M3, M4, M5, M6, M9, M12, M15, M18, M24]		
Local Assessment-Blood for Tcell Subset (CD3+CD4+, CD3+CD8+) Analysis [20]		X			X		X	X[D14 only]		X	X[M2, M3, M4, M5, M6, M9, M12, M15, M18, M24]	X	
Blood for CAR T Cells persistance, PCR [21]					X		X[P][21]	X [21]	X	X	X[M2, M3, M4, M5, M6, M9, M12, M15, M18, M24]	X	
Blood for CAR T Cells, Flow [21]					X		X[P]	X	X	X	X[M2, M3, M4, M5, M6, M9, M12, M15, M18, M24]	X	

	SCREEN TRBC	SCREEN 1[$]	LEUKA-PHERESIS[@]	SCREEN 2[#]	PRE-CONDITIONING CHEMO-THERAPY		TREATMENT STAGE†				FOLLOW-UP STAGE		END OF STUDY **
		Day -84 to Day -35	Before Day -35	Day -35 to -7	Day -7 (-1d)	Day -6, -5, -4, -3 (-1 d)	Day 0	Day 1, then q.a.d. Hospitalisation ≥14 d	Weekly after discharge (±2 d)	End of DLT period* Day 28 (±3 d)	Month 2, 3, 4, 5, 6, 9, 12, 15, 18 & 24 (±7 d)	Every 6 months until EoS** (±4 wk)	
Blood for RCR Testing & Insertional Mutagenesis					X					X	X[M3, M6, M12, M18, M24]	X	
Immunological / genomic profiling[22]					X		X[p]	X[D7, D14]	X	X	X[M3, M6, M9, M12, M15, M18, M24]		
Treatments													
CY and FLU						X							
AUTO4 Infusion							X						
Adverse events													
Adverse Events[23]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication[24]					X	X	X			X	X[M2]	X	

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR = chimeric antigen receptor; CMV= Cytomegalovirus; CPK = creatine phosphokinase; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; CY = cyclophosphamide; D,d = day; DLT = dose limiting toxicity; EBV = Epstein Barr Virus; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EDTA = ethylenediaminetetraacetic acid; FDG = fluorodeoxyglucose; FFPE = formalin fixed paraffin embedded; FLU = fludarabine; JCV=John Cunningham Virus; HHV6= Human herpesvirus 6; M = month (where each month is approximately 4.2 weeks, with 12 months per year); MRI = magnetic resonance imaging; MUGA = multigated acquisition (cardiac scan); PET = positron emission tomography; q.a.d. = quaque altera die (every other day); RCR = replication competent retrovirus; SAE = serious adverse event; TRBC = T cell receptor beta constant.

*: End of DLT period set as **28 days** after the dose of AUTO4.

: End of Study visit is to be performed upon completion of all other study visits or in case of premature withdrawal. **The end of the study (EoS) is defined as the LPLV expected to be 24 months after the last treated patient with AUTO4 or earlier in the event of patient death or consent withdrawal. Of Note: The patients who experienced disease progression post AUTO4 infusion will continue to be followed under this study protocol until death, study closure or consent withdrawal, whichever occurs earlier (see Schedule of Assessments).

Note: Additionally, blood samples for CAR T persistence and RCR may also be collected.

$: All tests must be undertaken (and results known) before leukapheresis.
@: Leukapheresis occurs after a patient is confirmed as TRBC1 positive.
X^{Dx}: Test to be performed on a particular day or month of the schedule rather than systematically at every visit. Please refer to the number to determine the day or month of assessment.
X^{p}: Sample to be taken prior to infusion.
X^{prog}: Test to be performed at disease progression.
Enrolment confirmed once all inclusion and exclusion criteria have been fulfilled and leukapheresate has been accepted for manufacturing.

Schedule of Assessment Footnotes:

1. Demographic data: race and ethnicity, height, age (month and year) and gender.
2. Eligibility criteria: Performance, disease characteristics and organ and bone marrow function to be assessed before a new node biopsy (if patient will undergo a node biopsy). ECHO may be done after node biopsy. Eligibility criteria to be re-assessed on Day -7 (-1 day) prior to pre-conditioning when the patient should continue to meet renal, hepatic, pulmonary function and performance status requirements. On Day 0, before infusion, it will be assessed whether the patient meets the AUTO4 infusion criteria.
3. Medical/lymphoma history: to include all current and prior clinically significant diseases, surgeries, cancer history (including prior T-cell lymphoma therapies or any other cancer therapies and procedures) and prior relevant medications). Obtain histological confirmation of disease diagnosis (pathology report) and the presence of T-cell lymphoma in the archived node tissue (if archived tissue is used for the TRBC1 status assessment). Record disease status at Screen 2 after leukapheresis has been completed.
4. Physical examination: a complete physical examination and complete neurological examination to be performed at Screen 1, Day -7 (-1 day) and Day 0; then focused and/or symptom related examination as appropriate at following visits.
5. Vital signs: temperature, systolic and diastolic blood pressure, pulse/heart rate, oxygen saturation and respiratory rate will be performed while the patient is in a seated position or supine. On Day 0 of any treatment stage, record vital signs immediately prior to AUTO4 infusion and every 30 minutes (± 10 min) for the next 4 hours post AUTO4 infusion, and thereafter monitored as per hospital policy but no less than 3 times a day whilst the patient is in hospital. Record weight as per Schedule of Assessments above.
6. 12-lead ECG: Repeat as clinically necessary and when patient experiences CRS.
7. ECHO or MUGA cardiac scan: to be performed at Screen 1 and to be repeated if clinically indicated. Same method should be used throughout the study.
8. Newly acquired tumour tissue sample may be required to determine TRBC1 status unless sufficient archival tumour biopsy material can be obtained – either by core needle biopsy or excisional biopsy (archived tissue must not be >5 years old and subtype of T-NHL unchanged from time of archived tissue to current status). If a core needle is used, **an absolute minimum of two cores** are required for the evaluation of TRBC1 expression on T cells using the LymphoTrack Dx TRB Assay. However, additional two cores are requested (if medically feasible) for the further development of a TRBC companion diagnostic assay and/or biomarker assessment on FFPE tissue.
9. Lymph node Tumour Tissue Sample for CAR T-cell persistence/TRBC1 expression. If there is a suitable lesion in an accessible location which would not put the patient at any safety risk per treating physician judgment. Biopsy samples should be taken once within the first 10 days since CAR T cell infusion and at the time of progression. The tumour samples will be analysed by flow cytometry or immunohistochemistry.
10. Bone Marrow Biopsy. If the Investigator suspects there is lymphoma infiltration in the bone marrow, a bone marrow biopsy should be performed at screening (if patient receives bridging therapy it should be done after any bridging therapy). If a bone marrow biopsy is performed and shows lymphoma infiltration, a bone marrow biopsy should be repeated at the time of first complete response.
11. Imaging and scans: For those patients receiving a bridging chemotherapy regimen, the baseline PET/CT (CT portion needs to have diagnostic quality, otherwise a separate CT is needed to be taken in the same week of PET) scans must be done after completion of bridging therapy and before start of the preconditioning and AUTO4 infusion. ^{18}-FDG-PET Scan: If at 6 months the patient has a CMR on PET scan, CT scans alone may be used for future assessment timepoints, if clinically appropriate. If relapse occurs after CMR or disease progression is suspected (e.g. new or enlarging lesion(s) detected on CT scan), a PET scan is to be repeated to confirm relapse/progression together with tissue biopsy (if needed).MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI is only required if clinically indicated. If progression is suspected from scan(s), but the patient is otherwise not showing clinical progression/deterioration, the disease progression must be confirmed not less than 28 days after initial finding to rule out a pseudo-progression. In cases of starting new treatment during response, an efficacy assessment is required prior to new treatment.
12. Haematology: haemoglobin, red blood cell count, platelet count, white blood cell count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils). Test to be performed prior to chemotherapy on pre-conditioning days and prior to AUTO4 infusion on Day 0 of any treatment stage.

13. Biochemistry: Whole panel: sodium, phosphate, potassium, magnesium, chloride, bicarbonate, ALT, AST, urea or blood urea nitrogen, creatinine, serum CPK, lactate dehydrogenase, glucose, total bilirubin, calcium (albumin adjusted), total protein, albumin. Serum uric acid to be measured only on Day 0, 1, and 7 of any AUTO4 treatment stage. All tests must be performed prior to AUTO4 infusion on Day 0 of any AUTO4 treatment stage. Glomerular filtration rate should be calculated at screening as per institutional preferred method.
14. Ferritin, C reactive protein: May be done more frequently as clinically necessary and during CRS if necessary.
15. Coagulation: prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen. Day 7, after AUTO4 infusion.
16. Infectious disease screen: must be performed at screening for the eligibility criteria and within 30 days prior to leukapheresis and must be negative. It must be repeated on the day of leukapheresis (or within 7 days after). HIV-1 and 2, Hep B virus, Hep C virus, HTLV-1, HTLV-2, Syphilis.
17. Monitoring for infections: CMV, HHV6, EBV & adenovirus monitoring as per schedule in table. Additonal monitoring for opportunistic infections, such as JCV, toxoplasmosis and fungal infections as per institutional guidelines (e.g institutional guidelines used for bone marrow transplant patients) or as clinically indicated. Monitoring beyond 3 months should be done if there is low levels of CD4+ T-cells or if clinically indicated.
18. Pregnancy test: serum (β-human chorionic gonadotropin) or urine pregnancy testing for women of childbearing potential.
19. Serum for cytokines and biomarkers: During hospital stay, sample collection to be performed every other day (± 1 day). If patient experiences ≥Grade 2 CRS then additional samples should be collected daily until CRS resolves or clinically indicated
20. Blood for analysis of T cell Subsets will be done both locally and via a Central Lab. Samples are to be collected at the following timepoints: Screening, Day -7, Day 0 (predose), Day 14, Day 28, Month 2, 3, 4, 5, 6, 9, 12, 15, 18, 24, and as clinically indicated e.g. in case of opportunistic infections
21. Blood for CAR T cells persistance: one sample to be taken on Day-7, Day 0 prior to AUTO4 infusion. During hospital stay, sample collection to be performed 10 min and 1h after completion of CAR T cell infusion, on Day 1 and every other day (± 1 day) and ideally on a Monday to Friday. Following hospital discharge (Day 14), blood samples for CAR- T cells (by flow and PCR) are to be collected at the following timepoints: Day 21, Day 28, Month 2, 3, 4, 5, 6, 9, 12, 15, 18 and 24. Additional samples should be collected if clinically indicated; an additional sample should be collected at the time of disease progression.
22. Blood for Immunological / genomic profiling: During hospital stay, sample collection to be performed on Day 7 and Day 14 (± 1 day) and ideally on a Monday to Friday
23. Adverse Events: Only AEs/SAEs related to study procedures should be collected until admission for lymphodepletion chemotherapy (Day -6 [-1 day]). AEs related to intervening/bridging non-study related anti-cancer therapy administered prior to pre-conditioning or AEs associated with disease progression during the same period will not be reported as AEs. These events will be recorded as an update to the patient's medical history. After Day 60, only collect: All SAES and AUTO4 treatment-related non-serious AEs; All AEs of special interest and AEs related to a study procedure.
24. Concomitant medications: Collect as described in the Schedule of Assessments. Before Day -7 (-1 day) and after 2 months, collect only concomitant medications relevant to AUTO4 treatment-related Grade 3 to 4 AEs and treatment-related SAEs; AEs of special interest or AEs related to a study procedure.

Note: The total estimated volume of blood collected for safety, biomarkers and immunological assessments (with the exception of the leukapheresis procedure) across any one year will not normally exceed 850 mL (this is expected volume for females with serum pregnancy test). The maximum volume of blood collected on any day will unlikely exceed 80mL. No more than 470mL of blood will be collected in any 28-day period.

SCHEDULE OF ASSESSMENTS 2 (Safety and Survival Follow-up)

Applies to all patients who fail to respond to treatment or who respond but subsequently experienced disease progression. Please refer to the relevant abbreviations and footnotes in SCHEDULE OF ASSESSMENTS 1 (Safety and Efficacy Follow-up) table above for further details.

Visits / Assessments	SAFETY AND SURVIVAL FOLLOW-UP							END OF STUDY
	M2 ±7d	M3 ±7d	M6 ±7d	M9 ±7d	M12 ±7d	M24 ±7d	Every 6 months until EoS** # ±4wk	EoS**/Early Withdrawal
PATIENT INFORMATION								
Subsequent anti-T-cell lymphoma therapy and disease response	X							
Survival Status	X							
Selected Concomitant Medication [23]	X							
EXAMINATIONS, INVESTIGATIONS AND SAFETY EVALUATIONS								
Pregnancy test [17]		X	X			X		
Adverse events [22]	X							
Physical Exam	X yearly							
BIOMARKERS								
PERIPHERAL BLOOD								

Visits / Assessments	SAFETY AND SURVIVAL FOLLOW-UP							END OF STUDY
	M2 ±7d	**M3 ±7d**	**M6 ±7d**	**M9 ±7d**	**M12 ±7d**	**M24 ±7d**	**Every 6 months until EoS** [#] **±4wk**	**EoS**/Early Withdrawal**
Local Assessment- Blood for T cell Subset (CD3+CD4+, CD3+CD8+) Analysis [20]	X every 6 months							
Blood for CAR T Cells persistence, PCR [21]	X as clinically indicated							
RCR		X	X		X	X	X yearly	X
Insertional Mutagenesis		X	X		X	X	X	X

d = days; EoS = end of study; M = month; RCR = replication competent retrovirus; wk = weeks.

Appendix 1: Patients with T-NHL will be Evaluated Using Response Criteria for Non-Hodgkin Lymphoma for Documenting Disease Response

Lugano Classification (Cheson et al. 2014)

Response	Site	PET-CT-Based Response	CT-Based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in the longest transverse diameter of the lesion (LDi). No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extra-lymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in sum of the product of the perpendicular diameters for multiple lesions (SPD) of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None

Response	Site	PET-CT-Based Response	CT-Based Response
	Bone Marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease		**No metabolic response**	**Stable disease**
	Lymph nodes and extralymphatic sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following:**
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	Cross product of the LDi and perpendicular diameter (PPD) progression:
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm, and increase by ≥50% from PPD nadir, and an increase in LDi or SDi from nadir: 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Response	Site	PET-CT-Based Response	CT-Based Response
	New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (e.g., infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability, but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), fluorodeoxyglucose uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

Appendix 2: Eastern Cooperative Oncology Group Performance Status Score

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken et al. 1982).

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