SPONSOR:

Autolus

PROTOCOL NUMBER:

AUTO3-PA1

STATISTICAL ANALYSIS PLAN

Author:	[redacted]
Version:	**Final 1.0**
Date:	**30-Jul-2020**

1 Cover and signature pages

Sponsor:	Autolus
Protocol Number:	AUTO3-PA1
Study Title:	A Single-Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 in Paediatric And Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia
Document Version No	Final 1.0

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

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2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of special interest
ALL	Acute lymphoblastic leukaemia
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATIMP	Advanced therapy investigational medicinal product
BM	Bone marrow
BOR	Best overall response
CAR	Chimeric antigen receptor
CD3-ζ, -19, -20, -22, -28, -134, -137	Cluster of differentiation 3, 19, 20, 22, 28, 134, 137
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRi	Complete response with incomplete recovery of counts
CRF	Case Report Form
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cy/Flu	Cyclophosphamide and fludarabine
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
DLT	Dose limiting toxicity
DSUR	Development safety update report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic Case Report Form

EFS	Event-free survival
FAS	Full analysis set
GCP	Good clinical practice
HSCT	Haematopoietic stem cell transplantation
HR	High risk
HIV	Human immunodeficiency virus
i.v	Intravenous(ly)
IA	Interim analysis
ICH	International Conference on Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
LAIP	Leukaemia-associated immunophenotype
LFS	Leukaemia-free survival
LVEF	Left ventricular ejection fraction
LVSF	Left ventricular shortening fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NE	Not evaluable
OS	Overall survival
OX40	Tumour necrosis factor receptor superfamily 4 [TNFRSF4] and cluster of differentiation 134 [CD134]) endodomain
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive Disease
PDvs	Protocol deviations
PedsQL	Pediatric Quality of Life Inventory

PET-CT	Positron emission tomography-computerised tomography
PFS	Progression-free survival
PPS	Per protocol analysis set
PT	Preferred Term
qPCR	Quantitative polymerase chain reaction
QTCF	Heart rate-corrected QT interval (Fridericia's formula)
RCR	Replication competent retrovirus
RFS	Relapse-free survival
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Standard deviation
SI	International System
SOC	System Organ Class
SST	Serum separator tube
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor
TEAE	Treatment-emergent adverse event
TFL(s)	Table(s), figure(s), listing(s)
WBC	White blood cell
WHODDE	World Health Organization drug dictionary

3 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in the analysis of study AUTO3-PA1 for Autolus of AUTO3, a CAR T cell treatment targeting CD19 and CD22, in patients with paediatric and adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia.

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol AUTO3-PA1 Version 8.0 (10 May 2019).

4 Study Objectives

PRIMARY OBJECTIVES

The primary objectives of the study are defined on Phase I and Phase II as follows:

- Primary objective for Phase I (dose escalation):
    - To assess the overall safety and tolerability of AUTO3 administration;
    - To confirm and evaluate the recommended Phase II dose (RP2D) and dosing schedule, and maximum tolerated dose (MTD), if an MTD exists, of AUTO3 in both paediatric and adult patients.
- Primary objective for Phase II (expansion):
    - To evaluate the anti-leukaemic effect of AUTO3 in paediatric and young adult patients (aged 1-24 years).

SECONDARY OBJECTIVES

- To assess the safety and tolerability of AUTO3;
- To evaluate the feasibility of generating AUTO3;
- To evaluate the clinical efficacy of AUTO3;
- To determine the expansion and persistence of AUTO3 following adoptive transfer (Note: the cellular kinetics analysis related to this objective will be documented separately outside this main SAP);

- Duration of B-cell aplasia.

[redacted]

5 Study Design

5.1 STUDY DESIGN AND POPULATION

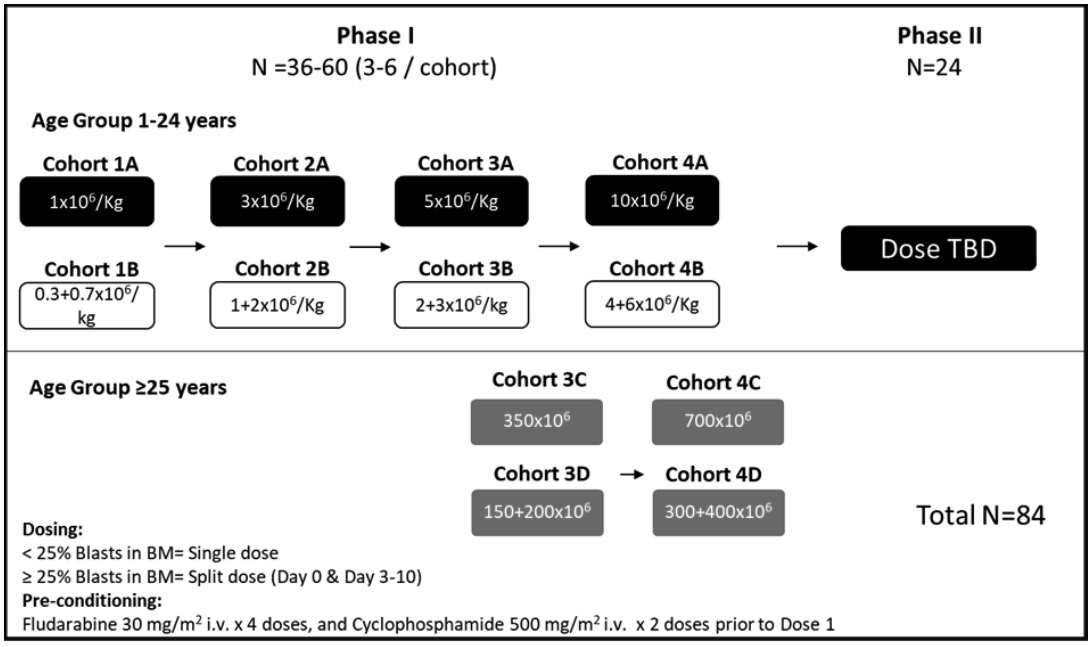
The study is a single-arm, open-label, multi-center, Phase I/II dose-escalation and expansion study, evaluating the safety and clinical activity of AUTO3, when administered to paediatric and adult patients with relapsed or refractory B cell ALL. The study will consist of 2 parts, a Phase I (dose escalation) in paediatric and young adults (1-24 years) and adults (≥25 years), followed by a Phase II (dose expansion) in only paediatric and young adults (>1-24 years).

- **Phase I (Dose Escalation):** To identify the optimal dose schedule (based on safety, tolerability, and anti-leukaemic activity) of AUTO3 based on disease burden, 36-60 patients with ALL will be treated in the dose escalation phase starting at 1.0 x 10^6/kg CD19/CD22 CAR-positive T cells administered as a single or split dose based on disease burden. Then escalating to 3 x 10^6/kg,5 x 10^6/kg and 10 x 10^6/kg CD19/CD22 CAR-positive T cells administered in a similar manner. Patients ≥ 25 years of age will be enrolled on to adult ALL dose cohorts. Adult ALL dose escalation may start at the highest paediatric/young adult dose considered safe after dosing 3 patients. Dosing will be based on a fixed dose which is equivalent to a dose in a 70 kg person.
- **Phase II (Dose Expansion):** To further characterise the safety and assess the efficacy of AUTO3 at the recommended dose schedule confirmed in Phase I; up to 24 paediatric and young adult patients will be treated in dose expansion phase.

Up to 100 patients in total are expected to be enrolled into Phase I and Phase II of the study and up to 84 patients in total are anticipated to be treated with AUTO3.

An overview of the study design is presented in Figure 1 below.

Figure 1. Dose Escalation and Dose Expansions Phases



The study will take approximately 5 years from recruitment to the last patient's last 24-month follow-up visit. The end of the trial will be 24 months after the last patient has received an AUTO3 infusion or the last patient last visit if this occurs earlier due to patient death or withdrawal.

After completion of the 24-month follow-up period, or following AUTO3 treatment and early withdrawal from this study, all patients will be followed until death or for up to 15 years from the first AUTO3 infusion under a separate long-term follow-up study protocol. The long-term follow-up study will be covered by a separate protocol (AUTO-LT1).

After completion of the end of study visit in AUTO3 PA1 study, survival status may be collected for the patients who haven't withdrawn consent (patients that haven't consented to AUTO-LT1 study and patients who have consented to AUTO-LT1 study).

5.2 STUDY TREATMENTS AND ASSESSMENTS

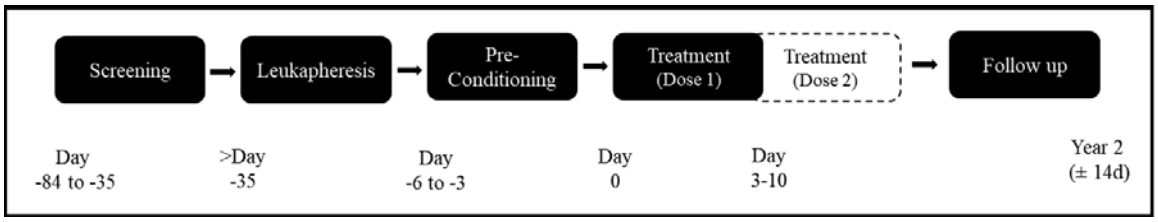
The study will consist of the following 5 stages:

- **Screening**: After providing written informed consent for study participation, all patients will be screened for study eligibility. Eligible patients will proceed to leukapheresis.
- **Leukapheresis**: Eligible patients will undergo leukapheresis to facilitate manufacture of AUTO3. If sufficient quantity of the cells (prescribed dose ± 20%) are produced, the patient will proceed to the pre-conditioning phase.
- **Pre-Conditioning**: If sufficient AUTO3 for the prescribed dose is successfully manufactured and the patients continue to meet eligibility requirements for the study, they will proceed to receive a prescribed lymphodepleting pre-conditioning treatment with cyclophosphamide (CY) and fludarabine (FLU) before AUTO3 infusion.
- **Treatment**: AUTO3 for the prescribed dose will be administered i.v. as a single infusion on Day 0 or split into two, with the second split dose given between Day 3-10 in patients with higher blast count in the BM. The treatment phase will extend from Day 0 (infusion day) until the end of the DLT observation period, 30 days (±3 days) post last AUTO3 infusion. Phase I patients are expected to be admitted for a minimum of 30 days (±3 days), or longer if necessary for monitoring and management. The duration of admission of Phase II patients will be 30 days (±3 days) but may be reduced based on emerging data with a protocol amendment.

- **Follow-up**: The follow-up phase will begin after the treatment stage and end 24 months (±14 days) after first infusion with AUTO3 or at disease progression or withdrawal of consent, which ever happens first (End of Study visit performed for early withdrawal).

An overview of the 5 study stages is presented in Figure 2.

Figure 2. Overview of the Stages of the Study



The schedule of assessments to be performed during the study is detailed in [redacted]

Eligible patients will receive a single or split dose i.v. infusion of AUTO3 following pre-conditioning treatment. The AUTO3 product contains both transduced (CD19/CD22 CAR-positive) and non-transduced cells. The dose is expressed as the number of CD19/CD22 CAR-positive T cells. Up to 4 dose levels [single dose for patients with <25% blasts or split (approx. 1/3rd, 2/3rd split) for patients with ≥25% blasts] are planned in Phase I as described below in Table 1.

The Safety Evaluation Committee (SEC) may increase the dosing interval based on emerging data. The DLT evaluation period will be 30 days (±3 days) after the last dose of AUTO3. The SEC will meet after the first patient in every cohort completes 14 days, to confirm continuation of enrolment to that cohort and thereafter meet again after the third or sixth patient in a cohort has completed the DLT assessment period.

The planned study cohorts for Phase I are presented in Table 1.

Table 1: AUTO3 Treatment Cohorts and Schedules (Phase I/dose escalation)

Dose Level	Treatment Cohorts	BM Blast %	Dosing Schedule Paediatric/Young Adults (1-24y) (Schedules A&B)		Dosing Schedule Adults (≥25y) (Schedules C&D)	
			Dose 1 Day 0	Dose 2 Day 3-10	Dose 1 Day 0	Dose 2 Day 3-10
Dose Level 1	Cohort 1A	<25% blasts	1.0 x 10^6/kg	None	N/A	N/A
	Cohort 1B	≥25% blasts	0.3 x 10^6/kg	0.7 x 10^6/kg	N/A	N/A
Dose Level 2	Cohort 2A	<25% blasts	3.0 x 10^6/kg	None	N/A	N/A
	Cohort 2B	≥25% blasts	1.0 x 10^6/kg	2.0 x 10^6/kg	N/A	N/A
Dose Level 3	Cohort 3A	<25% blasts	5.0 x 10^6/kg	None		
	Cohort 3B	≥25% blasts	2.0 x 10^6/kg	3.0 x 10^6/kg		
	Cohort 3C	<25% blasts			350 x 10^6	None
	Cohort 3D	≥25% blasts			150 x 10^6	200 x 10^6
Dose Level 4	Cohort 4A	<25% blasts	10.0 x 10^6/kg	None		
	Cohort 4B	≥25% blasts	4.0 x 10^6/kg	6.0 x 10^6/kg		
	Cohort 4C	<25% blasts			700 x 10^6	None
	Cohort 4D	≥25% blasts			300 x 10^6	400 x 10^6

Note: The adult starting dose will be lower (210 x 10^6 CD19/CD22 CAR-positive T cells) if a DLT has been observed in the paediatric group at 5 x 10^6/kg CD19/CD22 CAR-positive T cells.

Adult patients (≥25 years) will receive a fixed dose calculated based on a 70 kg adult weight.

5.3 RANDOMISATION AND BLINDING

Randomisation will not be used in this study. As this is an open-label study, blinding procedures are not applicable.

5.4 SAMPLE SIZE JUSTIFICATION

Up to 100 patients in total are expected to be enrolled into both the dose escalation and expansion parts of the study, and up to 84 patients in total are anticipated to be treated with AUTO3 therapy. The difference between the number of enrolled and treated patients accounts for manufacturing failures and inability of some patients to meet AUTO3 infusion criteria.

- Phase I (Dose escalation): up to 36-60 patients treated in total (up to 3-6 per dose cohort, following a Rolling 6 design (Skolnik et al. 2008)), which will be consist of:
    - 24-36 patients in the paediatric/young adult patient cohorts (age 1-24 years)
    - 12-24 patients in the adult patient cohorts (≥25 years)

  Additional number accounts for the possibility of patient with higher disease burden being evaluated using a single dose.
- Phase II (Dose expansion): up to 24 evaluable paediatric/young adult patients (aged 1-24 years) in total, using a Simon's 2-stage optimal design.

Simon's 2-stage design (Simon 1989) will be used for Phase II. The null hypothesis that the true response rate is 25% will be tested against a 1-sided alternative. In the first stage, nine patients will be accrued. If there are two or fewer responses in these nine patients, the study will be stopped.

Otherwise, 15 additional patients will be accrued for a total of 24. The null hypothesis will be rejected if 10 or more responses are observed in 24 patients. This design yields a 1-sided type I error rate of 5% and 80% power when the true response rate is 50%.

6 Statistical Considerations

The SAS system version 9.4 (or higher), will be used for all analysis, unless otherwise specified.

[redacted]

[redacted]

6.2 MISSING DATA HANDLING

No other imputation for missing data will be carried out other than to complete partial dates using standard imputation techniques as described below.

For the time to event variables censoring rules will apply as defined in section 8.10, so there should be no missing data.

6.3 PARTIAL DATE IMPUTATION

The following rules should be used when modifying partial or missing dates for reporting purposes such as defining on treatment flags.

A permanent new date variable should be created if there is a requirement to be used in determining flags, sort orders and other derived variables needed for a table, listing or figure. Imputed date variable names will be defined in the derived dataset specifications.

Original (raw) date variables must not be overwritten. Imputed dates will not be displayed in the listings.

Database does not allow adverse events to have any partial dates.

General rules

Prior/Concomitant Medications or Further Treatments

Prior/concomitant medications and any further treatments (chemotherapy, stem cell transplant, antibody-based therapy, further dose CD19/22 CAR T cell (off study), symptom care, other therapy) are considered to have started at the earliest possible date and end at the latest possible date.

In case of partial start dates with missing day:

- Any partial start date in the same month as the AUTO3 infusion would be imputed at the date of the AUTO3 infusion.
- Any partial start date in the month before AUTO3 infusion and in the same month as pre-conditioning treatment would be imputed at the date of earliest pre-conditioning treatment date during that month.
- Any partial CM start date would be imputed at the first day of the month, regardless of if during the same month as pre-conditioning or AUTO3 infusion.
- Any partial start date after the month of AUTO3 infusion would be imputed at the first day of the month.
- Any partial start date before the month of first AUTO3 infusion and before the month of first pre-conditioning treatment would be imputed at the last day of the month.

In case of partial start dates with missing day and missing month:

- Any partial start date during the year of AUTO3 infusion would be imputed at the date of the AUTO3 infusion.
- Any partial start date before the year of first AUTO3 infusion and during the year of pre-conditioning treatment would be imputed at the date of earliest pre-conditioning treatment date during that year.
- For any concomitant medication or further treatments starting before or during the year of AUTO3 infusion, the start date would be imputed at 01 January of that year.
- For any concomitant medication or further treatments starting after the year of first AUTO3 infusion, the start date would be imputed at 01 January of that year.
- For any concomitant medication or further treatments started before the year of first AUTO3 infusion and before the year of first pre-conditioning treatment, the start date would be imputed as the 31 December of that year.

In case of partial end dates with missing day:

- Partial end dates would be imputed at the last day of the month or at the date of study discontinuation, whichever occurs first.

In case of partial end dates with missing day and month:

- Partial end dates would be imputed at the last day of December (i.e. 31st December) or at the date of study discontinuation, whichever occurs first.

Some examples are given below (YYYY-MM-DD).

In most cases, start dates are imputed as first day of the month or first of January.

Data Type	Start Date	Imputed Start Date	First pre-condition treatment date	Last pre-condition treatment date	First AUTO3 infusion date	End Date	Imputed End Date
Prior/Concomitant Meds/ Further treats	2017-02	2017-02-01	2016-12-11	2016-12-13	2016-12-17	2017-02	2017-02-29
Prior/Concomitant Meds/ Further treats	2017-02	2017-02-03	2017-01-27	2017-01-29	2017-02-03	2017-02	2017-02-29
Prior/Concomitant Meds/ Further treats	2017-02	2017-02-11	2017-02-11	2017-02-13	2017-02-18	2017-02	2017-02-29
Prior/Concomitant Meds/ Further treats	2017-02	2017-02-03	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31
Prior/Concomitant Meds/ Further treats	2017	2017-01-27	2017-01-27	2017-01-29	2017-02-03	2017	2017-03-16 £
Prior/Concomitant Meds/ Further treats	2017-03	2017-03-01	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31
Prior/Concomitant Meds/ Further treats	2017-01	2017-01-27	2017-01-27	2017-01-29	2017-02-03		2017-03-01 *
Prior/Concomitant Meds/ Further treats	2017-01	2017-01-31	2017-02-27	2017-02-29	2017-03-03	2017-01	2017-01-31

£ Patient discontinued on 2017-03-16; * Patient discontinued on 2017-03-01.

Date of Diagnosis

Partial dates for initial diagnosis will be imputed as the 15th of the month if the month is present, or the 1st of July if only the year is present.

Response Assessment

Partial dates are not expected for response assessment data. However, should partial dates be present on treatment disease assessments:

- First of the month or the date of AUTO3 infusion (whichever is later) if the day part is missing, but month and year parts are present.
- First of January or the date of AUTO3 infusion (whichever is later) if the day and month parts are missing, but year part is present.

Death

Partial dates are not expected for deaths. However, in case of partial date for death, the date would be imputed as:

- The day after the last visit/assessment date when the patient was known alive, if the death date is completely missing, or if the month and year parts are the same as the month and year parts of the last visit/assessment date.
- First of the month if the day part is missing, but month and year parts are present.
- First of January if the day and month parts are missing, but year is present

6.4 BASELINE

Baseline is defined as the last non-missing value/result where assessment date is less than or equal to the date of first pre-conditioning treatment, unless otherwise specified for individual assessments or below. Baseline will be determined based on all assessments, including additional assessments.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value.

6.5 REPORTING GUIDELINES

The following guidelines will be followed:

- **Page Orientation:** Landscape.
- **Post-text listings**: will be generated in .lst and converted to rtf and PDF.
- **Post-text tables**: will be generated using ODS rtf and converted to PDF.
- **Post-text figures**: will be generated directly in .rtf and converted to PDF.
- No in-text outputs are planned.
- **Font**:
    - Listings will use Courier New font with minimum of 8 point font size.
    - Tables will use Arial font with a font size of 9.
    - Figures will use Times New Roman font with a font size of 10.
- **Margins**: Left: 3.8 cm, Right: 2 cm, Top: 3 cm, Bottom 2 cm on A4 paper.
- Columns header will be left aligned.
- **Treatment labels** will be the following and displayed in the following order, unless otherwise stated:
    - Screening only
    - 1x10^6 cells/kg
        - Including patients in Cohorts 1A and 1B
    - 3x10^6 cells/kg
        - Including patients in Cohorts 2A and 2B
    - 5x10^6 cells/kg
        - Including patients in Cohorts 3A and 3B
    - CAR T naive >=3x10^6 cells/kg
    - All infused patients
    - Overall
- All summaries and analyses will be presented by the planned dose, unless otherwise

stated.

- **Visit labels**: Outputs will display visit labels as per CRF.
- **Unscheduled visit / repeat assessments**: Data obtained at unscheduled or repeat assessments will be included in time to event analyses, baseline determination and anti-tumor effect. All other data from unscheduled or repeat assessment will not be included in summaries but only be presented in data listings, if not otherwise specified.
- Data collected during re-treatment will only be listed, if not otherwise specified. An exception is for adverse events, where all adverse events will be included in summaries under the **planned** dose for the treatment period.
- **N:** The number of patients in the specified population and cohort.
- **Treatment presentation:** Generally, data will be summarized for all data available by cohort, CAR T naive >=3x10^6 cells/kg and all infused patients unless otherwise specified.
- **Continuous data** will be summarized using number of patients (n), mean, standard deviation (SD), median, minimum value, maximum value and number of missing data (if there are any). For time to event summaries, median, quartiles (Q1 and Q3) and corresponding 95% confidence interval (CI) for the median and quartiles will be presented.
- **Categorical data** will be summarized using n and percentage based on number of non-missing data.
    - All categories will be presented, even if no patients are counted in a particular category.
    - In case 1 or more patients have missing data for the summary, the number of missing data will be presented as a separate category, labelled accordingly as 'Missing', if not otherwise stated.
    - Counts of zero in any category will be presented without percentage.
    - All summaries percentages will be calculated using the number of patients with an assessment, unless otherwise stated.
    - For AEs, medical history, prior and concomitant medications the counts are based on single counts of patients with multiple events/treatments under same category, while the percentages are calculated using N.
- **Precision of summary statistics:**
    - Integer – Sample size (n, N) and number of missing data (if displayed);
    - One additional decimal place than reported/collected – mean, median, other

percentile, confidence interval;

- Two additional decimal places than reported/collected – standard deviation;
- Same number of decimal places as reported/collected – minimum, maximum;
- Percentages – one decimal place.

- **Study day, as per visit schedule is** calculated with reference to first AUTO3 infusion date as Day 0 for consistency with the protocol. **This study day is not used for TFLs**.
- **Study day, for inclusion in CDISC compliant datasets and TFLs:** Will be calculated with reference to first AUTO3 infusion date as Day 1. It will be included in CDISC compliant datasets only and will be displayed in TFLs. This will be calculated as (assessment date – date of first AUTO3 infusion) +1 if it's on or after first date of AUTO3 infusion, or (assessment date – date of first AUTO3 infusion) if it is prior to AUTO3 infusion.
- **DLT period:** 30 days (±3 days) after last AUTO3 infusion (or until start of a new ALL therapy, whichever happens first).
- Data will be presented in listings by cohort. The order will be patient ID, visit, assessment date/time and assessment type/parameters (in order collected on e-CRF, unless otherwise specified). In case of clinical laboratory results, the listings will be presented in order of study phase and cohort, patient ID, parameter, assessment date/time, visit.
- Dates will be presented in format YYYY-MM-DD.
- Version 5.0 of the NCI-CTC grading criteria (CTCAE v5.0) will be used for relevant tables.
- Latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used for relevant tables. The version will be documented in the footnote of the corresponding TFLs.
- Latest version of the WHO-DD/DDE dictionary will be used for prior and concomitant medication coding. The version will be documented in the footnote of the corresponding TFLs.

7 Analysis Sets

7.1 ANALYSIS SETS

Screened set

The screened set will consist of all patients who have signed informed consent and were screened in the study.

Safety set

All patients who received at least 1 dose (complete or partial dose) of AUTO3 therapy will be included in the safety set.

Infused set

All patients who receive at least 1 dose (complete or partial dose) of AUTO3 therapy will be included in the infused set. This is the same as the safety set.

7.2 PROTOCOL DEVIATIONS

The full list of types of protocol deviations (PDs) and their relation to the analysis sets, along with the method of identification of each protocol deviation, are detailed in the protocol deviation criteria form which is separate to this SAP. This will be used as a basis for identifying patients with protocol deviations throughout the study.

Protocol deviations noted during the trial will be tracked throughout the study by Autolus. The PDs will be read into SAS® prior to reporting.

Prior to database lock, PDs will be reviewed and agreement of the final analysis populations made.

Important protocol deviations will be summarized by deviation category. A listing of all confirmed reported protocol deviations (with both Important PD = Yes or No) by patient will also be provided along with the deviation category, verbatim term and deviation date.

8 Methods of Analyses and Presentations

8.1 PATIENT DISPOSITION

The patient disposition summaries will be presented on overall group using the Screened Set.

The summary of patient disposition will be showing the number and percentages of patients

belonging to the following categories:

- Discontinued before leukapheresis (and reasons)
- Leukapheresed
  - Discontinuation prior AUTO3 infusion (and reasons)
  - AUTO3 infused

Information on analysis populations, study completion and discontinuation will also be displayed in patient listings.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarized on the Screened set:

- Age;
- Age group:
  - <10 years, ≥10 to <18 years, ≥18 years;
  - <2 years, ≥2 to <12 years, ≥12 to <18 years, ≥18 years;
- Gender;
- Race;
- Ethnicity;
- Weight at screening, before leukapheresis;
- Karnofsky score (for patients ≥10 years of age) and Lansky score (for patients <10 years of age) at study entry.

Separately the following acute lymphoblastic leukaemia disease characteristics will be summarized on the Infused set:

- Age at initial diagnosis;
- High risk first relapse;
- Second or greater relapse;
- Karyotype at screening: Normal/Abnormal;
- Cytogenetics abnormality at screening;
- History of CNS disease;
- Extramedullary disease at screening;
  - CNS

        - CNS involvement at study entry with corresponding CNS1/CNS2/CNS3 (where CNS1: <5/mcl WBC in the CSF without blasts; CNS2: <5/mcl WBC in the CSF with blasts; CNS3: >=5/mcl WBC in the CSF with blasts and/or clinical signs of CNS leukemia).
    - Testis
    - Other
- CNS status prior to pre-conditioning (No disease, CNS1, CNS2, CNS3)
- Bone marrow blast at pre-conditioning:
    - % blasts;
    - Morphological blast count category (≥ 50% blasts, ≥25-<50% blasts, ≥5-<25% blasts, <5%, Missing);
        - Patients in morphological remission (i.e. <5%) will be further categorized by MRD level (PCR) (MRD >= 10-2, MRD >=10^{-3} - < 10^{-2}, MRD >= 10^{-4} - <10^{-3}, MRD >=10^{-5} - < 10^{-4})

A summary on the risk of ALL based on the inclusion criteria will be presented on the Infused set.

In addition, listings of all demographic and baseline characteristics data will be produced.

8.3 PRIOR ACUTE LYMPHOBLASTIC LEUKAEMIA THERAPIES

Number of patients and associated percentages having specific types of prior therapies (with prior blinatumomab, inotuzumab, CAR-T therapies, stem cell transplant) will be summarized on the infused set.

Listings of all prior acute lymphoblastic leukaemia therapies and treatments will be produced (listings for first line treatments, CNS therapies and relapse protocol therapies). In addition, a listing containing prior stem cell transplant details will be also presented.

8.4 MEDICAL HISTORY

Medical histories and concomitant diseases will be coded using MedDRA. Summaries of patient medical histories and concomitant diseases will be produced on the Infused set.

Listings of medical history will be produced. Also, a separate listing presenting surgical and medical procedures will be provided.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Medications other than the study treatment (including leukapheresis related medications, pre-conditioning related medications and AUTO3 related medications) will be coded using the WHO-DD/DDE dictionary. Medications will be defined as follows:

- Prior Medication: Any medication whose medication start date is before the first AUTO3 infusion date.
- Concomitant Medication: Any medication whose medication start or end date is either the same as or after the first AUTO3 infusion date.

Any medication with a missing medication end date will be assumed to be concomitant medication. Also, ongoing medications are considered as concomitant medications. A medication can be both a prior and a concomitant medication.

Summaries of prior medications and concomitant medications will be produced by ATC class and preferred term on the infused set.

Medications defined as both prior and concomitant will appear in both tables.

In addition, listings of prior and concomitant medications will be presented.

8.6 BRIDGING THERAPIES AND NEW ANTI-CANCER THERAPIES

Bridging therapies (therapies between informed consent up to AUTO3 dosing) and new anti-cancer treatment post AUTO3 infusion will be presented in separate listings.

Bridging therapies will be summarized by preferred term on the infused set.

8.7 LEUKAPHERESIS

A listing of leukapheresis details will be presented. Leukapheresis related medications will be presented and summarized with the prior and concomitant medications.

8.8 STUDY TREATMENT

Pre-Conditioning: Fludarabine and Cyclophosphamide

The number and percentage of patients who received at least one dose of the pre-conditioning regimen will be summarized by medication received in the Infused Set. Duration of exposure (days) will also be summarized.

A listing of pre-conditioning treatment administration with Fludarabine and Cyclophosphamide will be presented.

Study treatment: AUTO3

Days from informed consent and leukapheresis to first AUTO3 infusion will be calculated as [(Date of first AUTO3 treatment – Date of informed consent / last leukapheresis) + 1] and summarized.

For AUTO3 infusion exposure summaries statistics will be presented for the following:

- Number of cells administered to the patient (as collected on the corresponding CRF, in 10^6 cells);
- Number of cells administered to the patient calculated in 10^6 cells/kg, derived as [Number of cells administered to the patient (10^6 cells)/Weight (kg) as recorded at screening];
- Number and percentage of patients who received single vs split infusions.
- Percentage of patients receiving planned dose, which is defined by an amount of 80-120% of percentages of cells administered from the planned dose. All patients that received less the 80% of cells administered from the planned dose will be considered as not having received the planned dose.

Details of AUTO3 infusion administration and treatment exposure will be listed.

8.9 FOLLOW-UP TIMES

Duration from first AUTO3 infusion until LPLV will be calculated and summarized in number of months on the Infused set.

Survival follow-up time will be calculated for each patient using the following formula:

> Survival follow-up time (months) = [(Date of last follow-up visit when patient was known alive (or date of death (if applicable)) – Date of first AUTO3 treatment) + 1]/ 30.4375 days.

Survival follow-up times will be summarized on the Infused set.

In addition, days from informed consent and leukapheresis to first AUTO3 infusion will be summarized on the Infused set.

8.10 EFFICACY DATA ENDPOINTS AND ANALYSES

Response evaluations will be based on the response criteria for ALL according to the National Comprehensive Cancer Network guidelines version 2.2014, as presented in Appendix B.

Disease evaluation will be performed to assess disease status, response and progression/relapse at Day 30, at Month 2, Month 3, Month 4, Month 6, Month 8, Month 10, Month 12, Month 15, Month 18, Month 21, Month 24 (or at end of study for early discontinuation). All post-baseline response assessments will be considered for the analyses (unless otherwise stated).

All time to event efficacy endpoints defined will be calculated in days and converted to months considering the following conversion: 1 month = 30.4375 days.

A listing will be provided detailing the disease status, response and progression/relapse for each patient at each visit. Extramedullary and CNS involvement, bone marrow aspirate as part of the disease assessments will be presented in listings. Also, all efficacy endpoints defined as below will be listed.

8.10.1 Primary Efficacy Endpoint and Analyses

8.10.1.1 Anti-leukaemic effect of AUTO3

The anti-leukaemic effect of AUTO3 is assessed through the response to the treatment. The following responses are assessed:

- Morphological response (CR/CRi);
- Molecular response by polymerase chain reaction (PCR);
- Molecular response by flow cytometry.

The table below summarises the possible responses taken into account and the type of response assessed:

Type of response	**CRF (database) response**	**Relevant derived results**
Unconfirmed morphological response CR/CRi (response at each assessment)	No blasts or <5% blasts in bone marrow AND no extramedullary disease^	Morphological CR/ Morphological CR with incomplete count recovery (CRi)
	Blasts >=5% in bone marrow AND never achieved **unconfirmed** CR/CRi at anytime	Morphological no response (NR)
Confirmed morphological response CR/CRi (response needs to be confirmed 28+ days apart)*	No blasts or <5% blasts in bone marrow AND no extramedullary disease	Morphological CR /Morphological CRi
	Blasts >=5% in bone marrow AND never achieved **unconfirmed** CR/CRi at anytime	Morphological NR
Molecular response by PCR**	MRD negative $<10^{-4}$	Negative
	MRD Positive ($>=10^{-4}$)	Positive
Molecular response by flow**	<0.01% (LAIP detected)	Negative
	>=0.01% (Persistent Disease)	Positive

^Programming note=Where extramedullary disease=No if response is 'no' or 'not applicable' or data is missing or assessment not done.

*Patients need to have two consecutive assessments of morphological CR/CRi for the confirmed morphological response. Morphological CR/CRi has to be confirmed by 2 consecutive responses spaced at least 4 weeks (28 days) apart.

**CRF/Database responses and protocol responses for molecular response by PCR and flow are not consistent (CRF wording contains a typo that classifies 10-4 as MRD negative), as CRF responses do not follow protocol. Protocol responses are being followed for data capture procedures (sites have used protocol based responses to complete data in the CRF) but CRF responses need to be taken into account for programming purposes.

Morphological and molecular relapse:

- Morphological relapse is defined as patients who achieved a CR/CRi and who have reappearance of >=5% blasts in bone marrow, or patient is otherwise indicated as

disease progression (e.g. via blood film or extramedullary disease). Patients with molecular relapse only will not be considered as morphological relapse.

- Flow molecular relapse is defined as patients who achieved MRD negative by flow and who have then MRD positive by flow.
- PCR molecular relapse is defined as patients who achieved MRD negative by PCR and who have then MRD positive by PCR.
- CD19 and CD22 status will be assessed if patients had morphological relapse or molecular relapse by flow cytometry (whichever occurs earliest).

Date of disease molecular relapse is determined as follows:

- Molecular by PCR: If subject has at least one MRD Negative post first AUTO3 infusion followed by a MRD Positive assessed by PCR: date of disease molecular relapse is the earliest date of MRD Positive after a MRD negative;
- Molecular by flow: If subject has at least one MRD Negative post first AUTO3 infusion followed by a MRD Positive assessed by flow: date of disease molecular relapse is the earliest date of MRD Positive after a MRD negative;
- Morphological: Date of disease morphological relapse is defined as the earliest date of NR (>=5% blasts) for which the previous response was a CR/CRi (no blasts or <5% blasts and no extramedullary disease) or extramedullary disease at any site after CR/CRi.

Best overall response (BOR) post-AUTO3 infusion will be presented by each type of best overall response separately, based on each of the 3 types of responses (morphological, molecular MRD by PCR, molecular MRD by flow), assessed from all assessments post-AUTO3 infusion.

In addition, a summary of number of responders/non-responders and number of patients with observed (unconfirmed) morphological CR/CRi, confirmed morphological CR/CRi, MRD negative/positive by PCR, MRD negative/positive by flow will be presented for the infused analysis set. In addition, two-sided 95% Clopper-Pearson confidence intervals (CI) of response rate will also be presented.

8.10.1.1.1 Morphological Event-Free survival

The morphological event-free survival (EFS) is defined as the time from first AUTO3 treatment until the earliest of treatment failure (defined as not achieving CR/CRi post AUTO3 infusion), morphological relapse or death due to any cause, whichever occurs first.

Patients who reach the time point of analysis without an event defined above will have the EFS censored at the date of last adequate disease assessment for response.

Patients who receive a new anti-cancer therapy post AUTO3 will be censored at the last adequate disease assessment. Patients proceed to post AUTO3 HSCT while in morphological

remission will be censored at the date of HSCT.

For patients with treatment failure, EFS will be considered as event at Day 1.

Estimates for the survival function for EFS will be summarized using KM method in the Infused set.

Morphological EFS will also be presented graphically.

8.10.1.1.2 Morphological Relapse-Free Survival

The morphological event-free survival (RFS) is defined as the time from first achievement of morphological CR/CRi post AUTO3 treatment until the earliest of treatment failure (defined as not achieving CR/CRi post AUTO3 infusion), morphological relapse or death due to any cause, whichever occurs first.

Patients who reach the time point of analysis without an event defined above will have the RFS censored at the date of last adequate disease assessment for response.

Patients who receive a new anti-cancer therapy post AUTO3 will be censored at the last adequate disease assessment. Patients proceed to post AUTO3 HSCT while in remission will be censored at the date of HSCT.

For patients with treatment failure, RFS will be considered as event at Day 1.

Estimates for the survival function for RFS will be summarized using KM method among all patients who have achieved confirmed morphological CR/CRi in the Infused set.

Morphological RFS will also be presented graphically.

8.10.1.1.3 Molecular by PCR Event-Free Survival

The molecular event-free survival (EFS) is defined as the time from first AUTO3 treatment until the earliest of treatment failure (defined as not achieving CR/CRi post AUTO3 infusion), molecular relapse, morphological relapse or death due to any cause, whichever occurs first.

Patients who reach the time point of analysis without an event defined above will have the EFS censored at the date of last adequate disease assessment for response.

Patients who receive a new anti-cancer therapy post AUTO3 will be censored at the last adequate disease assessment. Patients who proceed to post AUTO3 HSCT while in remission will be censored at the date of HSCT.

For patients with treatment failure, EFS will be considered as event at Day 1.

Estimates for the survival function for EFS will be summarized using KM method in the Infused set.

Molecular EFS will also be presented graphically.

8.10.1.1.4 Molecular by PCR Relapse-Free Survival

The molecular event-free survival (RFS) is defined as the time from achievement of molecular CR/CRi post AUTO3 treatment until the earliest of treatment failure (defined as not achieving CR/CRi post AUTO3 infusion), molecular relapse, morphological relapse or death due to any cause, whichever occurs first.

Patients who reach the time point of analysis without an event defined above will have the RFS censored at the date of last adequate disease assessment for response.

Patients who receive a new anti-cancer therapy post AUTO3 will be censored at the last adequate disease assessment. Patients proceed to post AUTO3 HSCT while in remission will be censored at the date of HSCT.

For patients with treatment failure, RFS will be considered as event at Day 1.

Estimates for the survival function for RFS will be summarized using KM method among all patients who achieved confirmed CR/CRi with molecular response in the Infused set.

Molecular RFS will also be presented graphically.

8.10.1.1.5 Overall Survival

Overall survival (OS) is defined as the period from the date of first AUTO3 treatment up to the

date of death, regardless of cause of death.

Patients alive at the time of the analysis will have the OS censored at the date of last assessment when the patient was known alive.

Date of last assessment patient is known alive will be determined based on survival log data, on vital sign, laboratory (hematology and biochemistry), disease status and response and extramedullary & CNS involvement assessments, blood samples (cytokines, RCR & insertional mutagenesis), adverse events and concomitant medications and survival follow-up.

For patients with no post-baseline assessments a censored OS at day 1 will be considered.

Estimates of the survival function for OS will be summarized via KM method.

OS will also be presented graphically.

8.10.1.2 Immunophenotyping for the status of CD19/22 expression

CD19 and/or CD22 disease status will be assessed at screening and morphological or molecular relapse by flow cytometry as outlined in the schedule of assessments in [redacted]

CD19/22 status at time of relapse will be presented in a listing.

8.10.2 Additional Efficacy and Biomarker Assessments

The following measurements are essential in establishing the clinical efficacy of AUTO3 and associated response on which the primary and secondary efficacy endpoints are based on as described in section 8.10.1.

Serum cytokine levels (e.g. tumor necrosis factor-alpha (TNF-alpha), IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, interferon gamma) will be listed and plotted over time by treatment groups.

In addition, the following assessments will be listed:

- Immunoglobulin results: IgG, IgA, IgM;
- Lumbar puncture as part of CSF examination;
- Flow cytometry for lymphocyte subsets as assessed at specific timepoints to characterize the duration of B cell aplasia;
- RCR testing and insertional mutagenesis.

8.11 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS AND ANALYSES

All pharmacokinetics and pharmacodynamic analysis will be performed by Sponsor.

8.12 QUALITY OF LIFE OR PHARMACOECONOMIC ENDPOINTS AND ANALYSES

Not applicable.

8.13 SAFETY DATA ENDPOINTS AND ANALYSES

8.13.1 Adverse Events (AEs)

Adverse events will be coded using the MedDRA coding system. The version of the dictionary will be provided in the adverse events TFLs footnotes.

AUTO3 TEAE is defined as any AE with onset during the post AUTO3 infusion period.

AEs that are considered related to Cyclophosphamide, Fludarabine and/or AUTO3 treatment (possibly, probably, or definitely related) will be collected accordingly on the eCRF.

Any AE that is present at baseline but worsens in intensity after the first dose of study treatment should be entered into the eCRF as different AE record with the differing grade recorded.

The number and percentage of patients will be summarized by System Organ Class (SOC) and Preferred Term (PT). Patients will be counted only once within each SOC and PT by dose level. SOCs will be presented by descending overall frequency, while PTs will be presented by descending overall frequency within each SOC. The following summaries will be presented for primary AUTO3 treatment:

- AUTO3-TEAEs, within 60 days (i.e. occurring on study days 1 through 60) and anytime post infusion
- AUTO3-TEAEs, related to AUTO3 treatment, within 60 days and anytime post infusion
- Serious TEAE, within 60 days and anytime post infusion
- DLT TEAEs
- Fatal TEAEs (i.e. grade 5 toxicity TEAEs), within 30 days (i.e. occurring on study days 1 through 30) and anytime post infusion
- CRS, within 60 days and anytime post infusion
- Neurotoxicity, within 60 days and anytime post infusion
- Neurotoxicity, related to AUTO3 treatment, within 60 days and anytime post infusion
- AUTO3-TEAEs, specific AEs (i.e. Neutropenia or Neutrophil count decreased, Thrombocytopenia or Platelet count decreased, Anemia or Hemoglobin count decreased, Infections (including all SOC Infections and infestations)) within 30 days,

within 60 days and anytime post infusion.
- Non-serious AUTO3-TEAEs for CT.gov reporting.

All summaries will be presented on the safety set.

All information on AEs will be listed. Separate listings of SAEs will be provided.

8.13.2 AEs of special interest (AESIs)

8.13.2.1 CRS AEs

Time to onset will be calculated only for CRS AEs that started after the primary AUTO3 infusion as follows:

Time to onset (days) = [(Date of start of AE deemed as CRS symptom – Date of first primary AUTO3 treatment) +1]

Duration of first CRS will be calculated after the primary AUTO3 infusion, as follows:

Duration of first CRS (days) = [(Date of end of CRS – Date of start of CRS)+1].

End of CRS is defined as resolution of all of the following events: pyrexia, febrile neutropenia, hypotension and hypoxia.

Note, that duration of CRS is referring to first CRS episode in case there are more than one AEs deemed as CRS symptoms. In case there is a change in CRS grade, for the same CRS episode, then the duration will be calculated as one CRS episode. For example, if we have a CRS Grade 1 from Day 3 to Day 5, and then grade changes to Grade 3 from Day 6 to Day 10, with Day 10 to be considered the resolved day, then the CRS duration is from Day 3 to Day 10, and therefore is 8 days.

8.13.2.2 Neurotoxicity AEs

Time to onset will be calculated only for neurotoxicity TEAEs (first for all neurotoxicity TEAEs and then for neurotoxicity TEAEs related to AUTO3 treatment) that started after the first AUTO3 infusion, as follows:

Time to onset (days) = [(Date of start of AE – Date of first AUTO3 treatment)] +1

Duration of first neurotoxicity TEAE will be calculated after the first AUTO3 infusion, as follows:

Duration of first neurotoxicity TEAE (days) = [(Date of end of neurotoxicity TEAE – Date of start of neurotoxicity TEAE)+1].

Note, that duration of neurotoxicity TEAE is referring to first neurotoxicity TEAE episode in case there are more than one neurotoxicity TEAE cases. In case there is a change in neurotoxicity TEAE grade, for the same neurotoxicity TEAE episode, then the duration will be calculated as one neurotoxicity TEAE episode. For example, if we have a neurotoxicity TEAE Grade 1 from Day 3 to Day 5, and then grade changes to Grade 3 from Day 6 to Day 10, with Day 10 to be considered the resolved day, then the neurotoxicity TEAE duration is from Day 3 to Day 10, and therefore is 8 days.

8.13.3 Clinical Laboratory Evaluations

Laboratory results will be listed in separate listings for all haematology, coagulation and biochemistry (including serum ferritin) parameters.

In addition, infectious disease screen results will be presented in a listing.

A listing containing the pregnancy test results will also be presented.

8.13.4 12-lead Electrocardiogram (ECG)

ECG will be performed during screening and will be repeated if clinically indicated. The heart rate, PR, RR, QT intervals, QRS duration, corrected QTCF intervals and an overall interpretation will be collected.

All ECG assessment measurements and also the derived QTCF will be listed.

8.13.5 Echocardiogram (ECHO) /MUGA

ECHO will be performed during screening and will be repeated if patient experiences CRS or if clinically indicated. The ECHO will include an evaluation for left ventricular ejection fraction (LVEF) and ventricular shortening fraction (LVSF).

All LVEF and LVSF results from ECHO assessment results will be listed.

8.13.6 Vital Signs

Temperature, systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation will be recorded. On Day 0 of any treatment phase, vital signs will be recorded immediately prior to AUTO3 infusion and every 30 mins (± 10 mins) for 4 hours post AUTO3

infusion, but no less than 3 times a day.

All vital signs measurements will be listed.

8.13.7 Physical and Neurological Examination

A complete physical examination will be conducted at screening and Day -7 including a complete neurological examination. Also, physical and neurological examination will be conducted at subsequent visits during treatment and follow-up phases. Any detected abnormalities will be recorded as medical history (abnormalities noted before AUTO3 infusion) or adverse events (abnormalities noted after AUTO3 infusion) and will be summarized and listed as described in section 8.4 or section 8.12.1, respectively. No separate listing of physical and neurological examination data will be considered.

8.13.8 Karnofsky and Lansky Performance Status

All Karnofsky and Lansky performance assessments will be listed.

8.13.9 Death information

The number and percentage of deaths and the primary reason for death, within 30 days and anytime post infusion will be presented on the safety set.

All patients who died and their reason for death will also be listed.

8.13.10 Hospitalization information

Hospitalization and ICU data will be listed.

8.13.11 Subsequent therapies

Anti-cancer medications and therapies received post AUTO3 infusion will be listed.

9 Interim Analyses

Given the premature termination of the study, the interim analyses initially planned will not be performed.

10 Changes to Planned Analyses

The following are changes to the planned analyses from that stated in the protocol (Version 8.0, 10 May 2019):

- Censoring of patients receiving a new anti-cancer treatment will be applied for the analysis of the disease-free survival, in addition to the other censoring rules.
- Molecular event-free survival (EFS) and molecular relapse-free survival (RFS) were defined instead of morphological progression-free survival (PFS) as defined in the study protocol.
- Protocol states: 'In the main analysis of RFS, patients who proceed to SCT after AUTO3 infusion will be censored at the time of SCT. In addition, a sensitivity analysis of RFS will be performed without taking time of SCT into account.'. Sensitivity analysis of RFS will not be performed.
- See section 6.1 – Termination of the study – based on this, the planned Interim analyses and Phase II analyses in the protocol will not be performed.

11 Document History

Date	Version	Modified by	Brief details of changes made to template
30JUL2020	1.0	[redacted]	Initial final version of SAP

12 References

[1] Simon R. (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10(1):1-10.

[2] Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. (2008) Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26(2):190-5.

[3] (CTCAE v5.0) https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

13.2 APPENDIX B – Response Criteria for Acute Lymphoblastic Leukaemia (National Comprehensive Cancer Network Guidelines)

Patients with acute lymphoblastic leukaemic (ALL) will be evaluated using Response Criteria for Acute Lymphoblastic Leukaemia (National Comprehensive Cancer Network Guidelines, version 2.2014) for documenting disease response as shown below.

Response Criteria for Blood and Bone Marrow	
Complete response (CR)	• No circulating blasts or extramedullary disease • No lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or central nervous system (CNS) involvement • Trilineage haematopoiesis and <5% blasts • Absolute neutrophil count >1000/µL • Platelet count >100,000/µL • No recurrence for 4 weeks
CR with incomplete recovery of Counts (CRi)	• Recovery of platelets to <100,000/µL • Recovery of absolute neutrophil count to <1000/µL
Overall response rate	Sum of CR and CR with incomplete recovery of counts.
Refractory ALL	Failure to achieve CR at the end of induction therapy.
Progressive ALL	Increase ≥25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.
Relapsed ALL	Reappearance of blasts in the blood or bone marrow (>5%) or any extramedullary site after CR.
Response Criteria for CNS Disease	
CNS remission	Achievement of no lymphoblast in cerebrospinal fluid (CSF) (cytospin or flow) regardless of white blood cell (WBC) count in patients with WBC count <5/mcL or ≥5/mcL and presence of lymphoblasts in CSF at diagnosis.
CNS relapse	New development of WBC count ≥5/mcL and presence of lymphoblasts in CSF or clinical signs of CNS leukaemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.
Response Criteria for Mediastinal Disease	
CR	Complete resolution of mediastinal enlargement by CT.
CR unconfirmed	Residual mediastinal enlargement that has regressed by >75% in sum of the products of the greatest perpendicular diameters.

Partial response	>50% decrease in the sum of the products of the greatest perpendicular diameters.
Progressive disease	>25% increase in the sum of the products of the greatest perpendicular diameters.
No response	Failure to qualify for partial response or progressive disease.
Relapse	Recurrence of mediastinal enlargement after achieving CR or CR unconfirmed.

ALL = acute lymphoblastic leukaemia; CNS = central nervous system; CR = complete response; CSF = cerebrospinal fluid; WBC = white blood cell.

13.3 APPENDIX C – Clinical Laboratory Tests Performed by Local Laboratory

Assessment	Description
Haematology	Haemoglobin, platelet count, and WBC count with differential (neutrophils, lymphocytes).
Coagulation	Prothrombin time, international normalised ratio, activated partial thromboplastin time, and fibrinogen.
Biochemistry Whole Panel	Sodium, phosphate, potassium, magnesium, chloride, bicarbonate or total CO2, alanine aminotransferase, serum uric acid/urate, blood urea nitrogen/urea, creatinine, serum creatine phosphokinase, total bilirubin, calcium, C-reactive protein, and albumin. All tests must be performed prior to AUTO3 infusion on Day 0.
Limited Panel	Ferritin 2-3 times a week until Day 21 or until resolution of CRS.
Pregnancy test	Serum (β-human chorionic gonadotropin) or urine pregnancy testing for women of childbearing potential.
Serology (at screening only)	• Human immunodeficiency virus (HIV) antibody. • Hepatitis B core antibody: if positive, further testing (deoxyribonucleic acid [DNA] by PCR) to rule out active disease or chronic carrier. Must be confirmed negative prior to screening. • Hepatitis C virus antibody: if positive for hepatitis C virus, further testing (by ribonucleic acid PCR) should be performed to rule out active infection. • Anti-HTLV-1. • Anti-HTLV-2. • Syphilis Serology.

CRS = cytokine release syndrome; DNA = deoxyribonucleic acid; HIV = human immunodeficiency virus; HTLV = human T-cell lymphocyte virus; PCR = polymerase chain reaction; WBC = white blood cell.

13.4 Tables, Figures and Listing shells

A separate document was considered to cover the tables, figures and listings shells.