Signature Page for KIADIS_CR_AIR_009_ASAP
Study CR-AIR-009 v2.0

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Study CR-AIR-009 v2.0

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Abbreviated Statistical Analysis Plan

SPONSOR:	Kiadis Pharma
PROTOCOL TITLE:	A Phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical HSCT and adjunctive treatment with ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells, versus a haploidentical HSCT with post-transplant cyclophosphamide in patients with a hematologic malignancy (HATCY study)
STUDY CODE:	CR-AIR-009

Summary:

The undersigned certify that they have read, reviewed and approved the updates to this document to include the addition to the plan for Long-term Follow-up data: addition of Section 8.13 Additional Analyses with of LTFU Data (p15); tables 14.02.02.03, 14.02.03.03, 14.02.04.03, 14.02.05.03, 14.03.04.04, 14.03.04.05; figures 14.02.01.03, 14.02.02.03, 14.02.03.03, 14.02.04.03 and listings 16.2.7.1, 16.2.7.2, 16.2.7.3, 16.2.7.4.

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	adverse event
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ALL	acute lymphoblastic leukemia
AP	alkaline phosphatase
ASAP	Abbreviated statistical analysis plan
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
Ca	calcium
CD	cluster of differentiation
Cl	chloride
CMV	cytomegalovirus
CT	computed tomography
CTC	Common Terminology Criteria
DLP	Data lock point
DRI	Disease Risk Index
EBV	Epstein-Barr virus
EBMT	European Society for Blood and Marrow Transplantation
ECG	electrocardiogram
ENT	ears, nose, throat
FACT-BMT	Foundation for the Accreditation of Cellular Therapy – Bone Marrow Transplantation questionnaire
GCP	Good Clinical Practice
GRFS	GVHD-free, relapse-free survival
GVHD	graft-versus-host-disease
HBV	hepatitis B virus
HCT-CI	hematopoietic cell transplantation-specific comorbidity index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonization
Ig	immunoglobulin
ITT	intention-to-treat
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LTFU	Long-term follow-up
MCV	mean corpuscular volume
MDASI	MD Anderson Symptom Inventory

MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MITT	modified intention-to-treat
MRD	minimal residual disease
MUGA	multiple gated acquisition
NCI	National Cancer Institute
NK	natural killer (cells)
OS	overall survival
P	phosphorus
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
PP	per protocol
PT	preferred term
PTCy	post-transplant cyclophosphamide
PTLD	post-transplant lymphoproliferative disease
QoL	quality of life
RBC	red blood cell
RRM	relapse-related mortality
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical analysis system
SF-36	Short Form 36-item health survey
SOC	system organ class
TEAE	Treatment emergent adverse event
TRM	transplant-related mortality
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus

2. Introduction

This document is an Abbreviated Statistical Analysis Plan (ASAP) designed to outline the planned analysis required to satisfy the abbreviated Clinical Study Report (CSR) of the HATCHY study (A Phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical HSCT and adjunctive treatment with ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells, versus a haploidentical HSCT with post-transplant cyclophosphamide in patients with a hematologic malignancy). Study CR-AIR-009 was terminated early for futility since it was unlikely that the study would meet the primary endpoint. Therefore, only an abbreviated Clinical Study Report will be written.

The International Conference on Harmonization (ICH) guideline E3 "Structure and Content of Clinical Study Reports", and the FDA guideline for abbreviated reports "Guidance for Industry. Submission of abbreviated reports and synopses in support of marketing applications" were used as a guide to the writing of this ASAP.

This ASAP outlines the analyses specified in the Protocol (Version 3.0, dated 23th August 2018) that are required to be reported in the abbreviated CSR.

An addendum to the ASAP has been added in section 8.13 to describe the additional analyses of the additional data collected during the long-term-follow-up (LTFU) period.

3. Study Design and Changes from the Protocol

This is a randomized (1:1), multicenter, open-label, controlled, Phase III clinical trial evaluating the efficacy and safety of a haploidentical HSCT and adjunctive treatment with ATIR101, a T-lymphocyte enriched leukocyte preparation depleted ex vivo of host alloreactive T-cells, versus a haploidentical HSCT with post-transplant cyclophosphamide (PTCy) in approximately 250 patients with a hematologic malignancy (Acute lymphoblastic leukemia [ALL] in remission, acute myeloblastic leukemia [AML] in remission, and myelodysplastic syndrome [MDS]).

Randomization will use minimization to balance treatment groups with respect to underlying disease (AML, ALL, or MDS), DRI (intermediate risk, high risk, or very high risk) and center. A stochastic treatment allocation procedure will be used so that the treatment assignment is random for all patients entered in the study.

Patients randomized in the ATIR101 group will receive a single ATIR101 dose of 2.0×10^6 viable T-cells/kg between 28 and 32 days after the HSCT. Patients randomized in the PTCy group will receive cyclophosphamide 50 mg/kg/day at 3 and 4 or 5 days after the HSCT.

Due to early termination of the study, patients will be followed for safety and efficacy for at least four (4) months post-HSCT. Patients who were not yet past the 4-month visit post-HSCT, will have the following schedule:

- For ATIR101 treated patients:
    - 1-week, 1-month, 3-month post-ATIR101 infusion (i.e. 4-month visit post-HSCT)
- For PTCy treated patients:
    - 1-week, 1-month post-PTCy infusion and 4-month visit post-HSCT

Completion of the Month-4 Visit will be the End of Active Study Follow-up.

For patients who have already completed the Month-4 visit, follow-up visits will be performed until last patient last 4 month visit, also defined as data lock point (DLP).

All patients will be followed for at least 4 months post-HSCT for the following safety and efficacy endpoints:

- incidence and severity of adverse events (AEs) (safety)
- incidence and severity of acute (a) and chronic (c) graft-versus-host-disease (GVHD) (safety)
- incidence and severity of viral, fungal and bacterial infections (safety and efficacy)
- transplant-related mortality (TRM) (safety and efficacy)
- GVHD-free, relapse-free survival (GRFS) (efficacy)
- overall survival (OS) (safety and efficacy)
- progression-free survival (PFS) (efficacy)
- relapse-related mortality (RRM) (efficacy)
- Quality of life (QoL)

In addition, data on immune reconstitution, laboratory tests, vital signs and physical examination will be available for all patients up to the time of study termination.

Due to the early termination of the trial, the classification of primary and secondary endpoints will not be applied, and a number of pre-specified analyses will not be performed. However, by-patient listings will be generated for all data collected for this study.

4. General Analysis Conventions and Definitions

Data will be analyzed using SAS (Version 9.3 or later). Figures will be created in R.

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them most likely be attributed to chance. No tests of significance will be carried out on efficacy data due to early study termination.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum and maximum values.

Time-to-event endpoints will be estimated using Kaplan-Meier (KM) techniques. When appropriate, the median along with associated 95% confidence interval (CI) will be estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the CI). Rates at fixed time points will be derived from the KM estimate along with their corresponding log-log transformed CI. KM curves will also be presented. No formal test (log-rank test) will be performed to compare the treatment groups for time-to-event distributions.

For time-to-event endpoints subject to competing risks, i.e. relapse-related mortality (RRM) and transplant-related mortality (TRM), cumulative incidence curves will be produced. No formal test (Gray's test) will be performed to compare the treatment groups.

The output tables will include two columns (ATIR101, PTCy) and will be created by time point. The 'All' column will be presented only if particularly specified. All data will be presented in the form of listings sorted by treatment group and patient ID.

4.1 Definition of Populations

All enrolled patients who were randomized will be included in the analyses. The following analysis populations will be discerned:

4.1.1 Intention-To-Treat (ITT) Population

The Intention-To-Treat (ITT) population consists of all randomized patients. This population will be used for all the data listings and efficacy evaluation.

4.1.2 Safety Population

The safety population will include all patients who received an HSCT. The safety population is the primary population for safety and efficacy evaluation.

Note: For abbreviated CSR, the safety population will not be analyzed.

4.1.3 Modified Safety Population

The Modified Safety population consists of all randomized patients who received an HSCT and ATIR101 (ATIR101 group) or at least one dose of post-transplant cyclophosphamide (PTCy group). The modified safety population defined in this ASAP has the identical definition as the Modified Intention-To-Treat (MITT) population defined in the protocol. Hence the MITT population will not be used for any pre-specified analyses covered by this statistical analysis plan. The Modified Safety population is the primary population for safety and efficacy evaluation.

4.1.4 Per Protocol (PP) Population

The Per Protocol (PP) population is a subset of the safety population, i.e. patients without major protocol deviations, defined by the sponsor prior to locking the database. The definition of "major" protocol deviations will be agreed upon, and all cases of such major deviations adjudicated prior to database lock, by a team blinded to treatment allocation.

Note: For abbreviated CSR, PP population will not be derived.

4.2 Definition of Endpoints

- GVHD-free, relapse-free survival (GRFS): defined as time from randomization until grade III/IV acute graft-versus-host disease (GVHD), chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, or death, whichever occurs first.
- Overall survival (OS): defined as the time from randomization until death from any cause
- Progression-free survival (PFS): defined as the time from randomization until relapse, disease progression, or death, whichever occurs first
- Relapse-related mortality (RRM): defined as the time from randomization to death due to disease relapse or disease progression
- Transplant-related mortality (TRM): defined as the time from randomization to death due to causes other than disease relapse or disease progression

4.3 Calculated Variables

- Day 0: defined as the day of HSCT procedure according to protocol conventions.
- Baseline: The baseline for each variable is defined as the last available assessment before HSCT.
- For time-to-event data, event time is calculated as follows:
  Event time = [Event date – date of randomization]
- Event durations (e.g. AE duration) are calculated as follows:

  Duration = [end date – start date +1]
- Time intervals (e.g. days from HSCT to ATIR101) are calculated as follows:

  Time interval = [end date – start date]

4.4 Partial Dates

If part of the starting or ending dates of an adverse event (AE) is missing, the following convention will be used:

- For a missing day in an AE 'start date', the missing day is replaced by the first day of the month (e.g. UKMAY2003 -> 01MAY2003)
- For a missing day in an AE 'end date', the missing day is replaced by the last day of the month (e.g. UKMAR2003 -> 31MAR2003)

4.5 Missing Data

Any missing baseline values will not be imputed. If a subject has a missing baseline value that is required for a particular analysis, then the subject will be excluded from the statistical analysis.

Missing values will not be imputed for any time related endpoints. For patients who have not experienced the specific endpoints/events, the last known date of visit will be used as censoring time.

Missing AE severity will not be imputed. Such AEs will be included in summaries by including a category of "missing" in the tables. If the assessment of the relationship of the AE to study medication is missing, we will assume that the AE is possibly related to study medication.

There will be no imputation of missing laboratory, vital sign, or electrocardiogram (ECG) data.

5. Study Patients

5.1 Disposition of Patients

The number of screened patients (who provide informed consent to the trial), the number of randomized patients, the number of patients fulfilling inclusion and exclusion criteria, the number of screen failures (including reason for screen failure), the number of patients who received an HSCT, the number of patients who received ATIR101/ PTCy, the number of patients that discontinued before HSCT, between HSCT and ATIR101/ PTCy, and after ATIR101/ PTCy (including reason for discontinuation) will be summarized.

Individual patient disposition information will be listed additionally including details of 'other reason' if applicable, time from randomization to PBMC apheresis (in case of ATIR101), time from PBMC apheresis to HSCT (in case of ATIR101), time from

randomization to HSCT (in case of PTCy), time from diagnosis (of first occurrence of hematologic malignancy) to HSCT, time from HSCT to ANC and Platelet engraftment, time from HSCT to ATIR101 infusion or PTCy treatment, and time from PBMC apheresis to ATIR101 infusion.

5.2 Protocol Deviations

All protocol deviations will be assessed and identified prior to the database lock. The details will be provided in a data listing by the Sponsor.

5.3 Inclusion and Exclusion Criteria

All inclusion criteria that were not met and all exclusion criteria that were met will be provided in a data listing by patient.

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to patient and donor characteristics at baseline will be displayed for the Modified Safety population and the ITT population.

The variables to be summarized for patients are:

- Demographics: age, gender, race and ethnicity
- Hematologic malignancy and disease status: indications (AML, ALL, MDS), AML/ALL/MDS WHO classification level 1 and 2, FAB classification, disease status, number of previous remissions, EBMT risk score, Karnofsky score and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) ("Sorror score")

Patient cytogenetic abnormalities, molecular abnormalities, previous therapies as well as relevant medical history will be listed only.

The variables to be summarized for donors are:

- Demographics: age, gender, race and ethnicity; family relation between donor and patient
- Human leukocyte antigen (HLA) compatibility: matches at the HLA-A, -B, C and -DRB1 loci (and if available at the DQB1 locus) of the unshared haplotype will be assessed.
- A table with percentage of x/8 and x/10 matches based on HLA A, B, DRB1, C and if available DQB1 types will be made. HLA-typing will be performed by high resolution. All four digits must be identical in order to be a match. When one allele of an HLA type matches, it is called a haploid match. When two alleles match, it is called diploid match. The calculated x/8 and x/10 scores will be added to the listing with patient and donor demographic information (i.e. age, gender, patient-donor relationship, HLA typing outcome and 2 scores).

A by patient-listing with the following information will be provided: results of computed tomography (CT) scan of the thorax/chest X-ray (if applicable), echocardiogram or multiple-gated acquisition (MUGA) scan results (if applicable), results of pulmonary function test (if applicable), creatinine clearance results (if applicable), pregnancy test results (if applicable) and human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B virus (HBV), hepatitis C virus (HCV), Treponema pallidum, human T-lymphotropic virus (HTLV)-I (if tested), HTLV-II (if tested), West Nile virus (WNV) (if tested).

In an additional listing the following donor data will be depicted: pregnancy test results (if applicable), HIV-1, HIV-2, HBV, HCV, Treponema pallidum, HTLV-I (if tested), HTLV-II (if tested), WNV (if tested) results.

7. Concomitant Treatment

All concomitant treatments related to AEs will be summarized for the modified safety population by WHO Drug Dictionary code 2018, version 1 (using ATC classification) and listed.

8. Safety and Efficacy Evaluation

Safety and efficacy evaluation will be performed on the Modified Safety population. Efficacy evaluation will be also performed on the ITT population.

8.1 Incidence and severity of acute and chronic GVHD

The following datapoints will be analysed using descriptive statistics:

- Cumulative incidence of grade II-IV and grade III-IV acute GVHD
- Cumulative incidence of moderate and severe chronic GVHD
- Cumulative incidence of chronic GVHD requiring systemic immunosuppressive treatment
- Duration of acute and chronic GVHD episodes

Incidence and severity of acute or chronic GVHD will be summarized for the whole active study follow-up period, and by time period. Time periods are defined as follows:

- HSCT to 1 month post HSCT
- 1 month to 4 months post HSCT
- Follow-up beyond 4 months post HSCT

In order to allocate a GVHD event to the correct time period, the start date of the event will be used. When two GVHD episodes occurred one after the other (i.e. start date of the second GVHD is the stop date of the first GVHD or the day after the stop date of the first GVHD), they will be considered a single GVHD event. This event will have the start date of the first record and will be counted with the highest grade throughout the whole event. This rule will be applied separately for acute and chronic GVHD events.

8.2 Incidence and severity of viral, fungal, and bacterial infections

Cumulative incidence of NCI CTCAE grade 2-5 and grade 3-5 infections will be summarized separately, for the whole active study follow-up period, and by time period. Time periods are defined as follows:

- Randomization to HSCT
- HSCT to 1 month post HSCT
- 1 month post HSCT to 4 months post HSCT
- Follow-up beyond 4 months post HSCT

In order to allocate an infection to the correct time period, the start date of the event is taken. When two infections are directly one after the other (i.e. start date of the second infection is the stop date of the first infection or the day next to the stop date of the first infection) it should be considered one infection. This case will have the start date of the first record and will be counted with highest grade throughout the whole event. This rule will be applied separately for grade 2-5 and grade 3-5 infections.

8.3 Adverse Events

Adverse events (AE) will be coded using MedDRA (Version 21.0), and evaluated for severity using NCI-CTCAE.

The safety analyses on AEs will be based on the treatment-emergent adverse events (TEAEs). A TEAE is defined as any untoward medical occurrence in a clinical investigation patient administered an investigational product or procedure and which does not necessarily have to have a causal relationship with study participation. In this study, an adverse event is treatment emergent if it is first observed or worsens on or after the date of HSCT. In case of missing start date, the adverse event will be considered as treatment emergent.

Adverse events will be summarized by MedDRA system organ class (SOC) and preferred term (PT). SOCs will be ordered by frequency (highest frequency first). PTs will be ordered alphabetically per SOC. Patients will only be counted once for each PT. In case that a patient experienced the same event more than once, the worst severity will be presented.

Tabulations of the number of patients who experienced AEs will be presented by treatment. The frequency of AEs will also be tabulated by grade.

Separate summaries will be generated for the following:

- All TEAEs
- TEAEs by severity
- ATIR101/PTCy related TEAEs
- Severe TEAEs (NCI CTCAE grade 3 or higher)
- Severe TEAEs (NCI CTCAE grade 3 or higher) related to ATIR101/PTCy
- GVHD TEAEs
- Infection TEAEs

In addition, a summary table presenting an overview of all AEs by AE type (i.e. Infection, Relapses/disease progression, GVHD, Other) will be provided.

All AEs, including non-treatment-emergent AEs will be included in individual patient data listings. The following specific AE listings will also be provided:

- GVHD AEs
- Infection AEs (including type of infection, severity, seriousness, causality, details organism, start since HSCT/ATIR101/PTCy, outcome, duration).

The GVHD AE listing will contain the following detailed information: type, severity, organ involved (and score), number of days between start of GVHD and HSCT, number of days between start of GVHD and ATIR101, duration of GVHD in days, relation to ATIR101, action taken and outcome.

For donors, all AEs will be summarized by SOC and PT and Severity. The details of AEs will be provided in a data listing.

8.4 Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized by system organ class and preferred term for:

- All SAEs
- SAEs related to ATIR101/PTCy

Separate listings will detail all serious adverse events, graft failures / graft rejections and deaths, including number of days since HSCT, date and cause of death together with investigator classification and adjudicator classification of cause of death, during the study.

The number of deaths will be tabulated together with the primary cause of death.

8.5 Events of Special Interest

In this study, the following AEs are regarded events of special interest:

- Post-transplant lymphoproliferative disease (PTLD)
- Infusion reactions
- Autoimmune hemolytic anemia (AIHA)
- Secondary malignancies
- Hemorrhagic cystitis
- Veno-occlusive disease

Incidence of AEs of special interest will be summarized by MedDRA SOC and PT.

8.6 Clinical Laboratory Determination

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for hematology, blood chemistry, and urinalysis parameters.

Hematology, blood chemistry and urinalysis parameters will be listed as follows: by patient, parameters per category in columns and visits in rows. Unscheduled visit results will be inserted based on the unscheduled visit's date. Results will be presented as, e.g. 300 unit*(L) or 850 unit**(H).

*: abnormal not clinically significant;

**: abnormal clinically significant;

L: if value below or equal to lower limit;

H: if value above or equal to higher limit.

For urinalysis only *abnormal* results are presented (result is abnormal based on the question (abnormal clinically (non-)significant?) or if outcome is not negative i.e. positive, traces, +, ++, etc.).

An overview of hematology, serum chemistry and urinalysis is presented in Table 1 below:

Table 1: List of safety laboratory tests

Hematology:	Blood Chemistry:
• Hematocrit • Hemoglobin • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count • Lymphocytes • Monocytes • Basophils • Eosinophils • Absolute neutrophil count (ANC)	• Albumin • Alkaline phosphatase (AP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • (Corrected) Calcium (Ca) • Chloride (Cl) • Creatinine • Glucose • Lactate dehydrogenase (LDH) • Magnesium (Mg) • Phosphorus (P) • Potassium (K) • Sodium (Na) • Total bilirubin • Total protein • Urea
Urinalysis:	
• Bilirubin • Glucose • Ketones • Nitrite • Blood • pH • Protein • Specific gravity • Leukocytes	

An additional listing presenting per patient and per parameter (hematology, blood chemistry, urinalysis) abnormal clinically significant values will also be made.

8.7 CMV/EBV

CMV and EBV results will be summarized in format of cross table (separate table for CMV and EBV). Overall (i.e. for all timepoints combined including unscheduled visits), for the donor/patient combinations with positive/positive, positive/negative, negative/positive and negative/negative baseline result, the percentage of patients with CMV/EBV outcome above the CMV/EBV detection limit at a minimum of one timepoint and below the CMV/EBV detection limit for all visits is presented.

In a listing, both for patient and donor, baseline CMV/EBV results are presented. In an additional patient listing both for CMV and EBV and at each timepoint, the CMV/EBV result is presented. In the listing it is also presented how many times a patient has an outcome above the detection limit (over all timepoints combined). The CMV/EBV detection limit is also presented in the listing.

8.8 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital signs (respiration rate or oxygen saturation, temperature, weight, pulse rate, and supine blood pressure after 5 minutes of rest) and physical examination data (skin, ears/nose/throat (ENT), respiratory, cardiovascular, abdomen (including liver and spleen), and lymph nodes) will be listed.

8.9 Extent of Exposure / Details of Different Study Procedures

Summary statistics will be provided for the patient conditioning regimen, HSCT procedure and adjunctive treatment.

Data listings will be provided presenting for each patient: details on patient conditioning regimen, HSCT, ATIR101 infusion/PTCy treatment.

For ATIR101 group: total amount of viable CD3+ cells/kg($x10^4$) and total amount of viable CD34+ cells/kg($x10^6$) given to the patient, amount of ATIR101 infused.

For PTCy group: source of stem cells ('G-CSF mobilized blood' or 'bone marrow') and Total mononuclear cells given to the patient ($x10^8$)

An additional table summarizing time from enrolment to apheresis, time from diagnosis to HSCT, time from apheresis to HSCT, time from HSCT to ANC and platelet engraftment, time from HSCT to ATIR101 infusion / PTCy will be made.

8.10 Bone Marrow Biopsy / Aspirate

A table will summarize at the relevant timepoints (baseline, week 4, 3 months, 4 months, and unscheduled visits) the amount and percentage of patients with myeloblasts <5% (Y/N) and the actual value of myeloblasts (in %). The presence of minimal residual disease (MRD) if available will also be summarized at the relevant timepoints.

A listing providing all details (including both blasts abd myeloblast) on bone marrow aspirate / biopsy will also be made.

8.11 Engraftment and Chimerism

Engraftment is defined as neutrophil count ≥ $0.5x10^9$/L for 3 consecutive days and platelets ≥ $20x10^9$/L for 3 consecutive days, without transfusion. The first days of occurrence of both criteria will be recorded. Time to absolute neutrophil count (ANC) engraftment and platelet engraftment (from HSCT) will be summarized according to the schedule of activities (see Section 9.1).

Chimerism results (i.e., total number of cells analyzed, percentage (%) of donor cells, assessment done prior to ATIR101Y/N) will be listed (including unscheduled visits).

8.12 Efficacy Endpoints

Due to the early study termination, the efficacy evaluation has been limited to the following endpoints as defined in this abbreviated SAP (section 4.2):

- GRFS, OS, PFS, RRM, and TRM

These endpoints will be analyzed as time-to-event variables when feasible, i.e., if there are sufficient number of events. For GRFS, OS and PFS, the corresponding KM curves will be presented along with median and 95% CI. For RRM and TRM, cumulative incidence curves will be produced.

- Quality of life (QoL)

The raw QoL data from the Foundation for the Accreditation of Cellular Therapy – Bone Marrow Transplantation questionnaire (FACT-BMT), the Short Form 36-item health survey (SF-36), the MD Anderson Symptom Inventory (MDASI) will be transferred into the following scores (if applicable) following the relevant scoring guidelines:

➢ FACT-BMT (McQuellon et al., 1997):

- Physical well-being (PWB) subscale score

- Social/family well-being (SWB) subscale score
- Emotional well-being (EWB) subscale score
- Functional well-being (FWB) subscale score
- Bone marrow transplant subscale (BMT) subscale score
- FACT-G total score
- FACT-BMT total score

➢ SF-36 (Maruish ME (Ed.), 2011) :

- PF health domain T score
- RP health domain T score
- BP health domain T score
- GH health domain T score
- VT health domain T score
- SF health domain T score
- RE health domain T score
- MH health domain T score
- HT health domain T score
- Physical component summary (PCS) T score
- Mental component summary (MCS) T score

➢ MDASI (Charles S. Cleeland, 2009):

- Mean core symptom severity subscale score
- Mean interference subscale score

QoL endpoints will be analyzed descriptively. The quantitative QoL scores and changes from Baseline will be summarized by visit.

Other efficacy data, e.g. immune reconstitution, will be provided in data listings.

8.13 Additional Analyses of LTFU Data

Enrollment into the study was terminated early for futility, visit schedules were modified and database was locked on 22Apr2020, after all patients had reached the Month 4 Visit. Data were collected after the data lock point for long term safety and efficacy information through 2 years following HSCT. Additional analyses for the long-term safety and efficacy evaluations are to be performed on the Modified Safety population. All data (not limited to the LTFU period) will be included. The endpoints to be analyzed are as follows:

- Cumulative Incidence of TRM
- Kaplan Meier Estimates of GRFS
- Kaplan Meier Estimates of OS
- Kaplan Meier Estimates of PFS

The same analysis method as described in Section 8.12 will be used.

- Incidence of Treatment Emergent SAEs

- Incidence of Treatment Emergent SAEs related to ATIR101/PTCy

Serious adverse events (SAEs) will be summarized by system organ class and preferred term.

All relevant data for individual patients will be provided in data listings.

9. Appendices

9.1 Schedule of Activities (original)

	Screening (between informed consent & confirmation eligibility)	Pre-HSCT	HSCT (Day 0)	Week 1, 2, 3	Week 4	Week 5, 6, 7, 8, 9, 10	Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24	Follow-up beyond Month 24 every 6 months
Informed consent patient/donor	X							
Patient eligibility	X							
Randomization	X							
Apheresis patient and donor PBMCs [1]		X [2]						
Collection donor PBSCs/bone marrow		X						
Conditioning regimen		X						
HSCT			X					
ATIR101 infusion [3]					X			
Cyclophosphamide infusion [4]				X [5]				
Demographics patient/donor	X							
Hematologic malignancy	X							
Medical history	X							
KPS	X							
Physical examination	X		X	X	X	X [6]	X [6]	

1 For preparation of ATIR101; ATIR101 group only
2 Including measurement of patient weight
3 ATIR101 group only
4 PTCy group only
5 On Day +3 and Day +4/+5
6 Only at Week 6, Week 8, Week 10, Month 3, and Month 4

IDDI
ADDING VALUE TO CLINICAL DATA

	Screening (between informed consent & confir-mation eligibility)	Pre-HSCT	HSCT (Day 0)	Week 1, 2, 3	Week 4	Week 5, 6, 7, 8, 9, 10	Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24	Follow-up beyond Month 24 every 6 months
CT scan thorax/chest X-ray	X [7]							
Echocardiogram/MUGA scan	X [7]							
Pulmonary function test	X [7]							
Creatinine clearance	X [8]							
Vital signs	X [9]		X	X	X [10]	X	X [11]	
Quality of life	X						X [12]	X [12]
Disease assessment [13]	X		X	X	X	X	X	X
Infection assessment	X	X	X	X	X	X	X	
CMV/EBV/adenovirus (PCR)	X		X	X	X	X	X	
Engraftment				X	X [16]	X [14]		
Chimerism				X [15]	X [16]	X [17]	X [17]	
GVHD assessment				X	X	X	X	X

[7] If not already done within 6 weeks before signing informed consent
[8] Calculated or measured, if not already done within 2 weeks before signing informed consent
[9] Including measurement of patient height at screening only
[10] For all patients (in ATIR101 group before infusion of ATIR101); Additionally, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1 hour, and 2 hours and continuous oxygen monitoring will be done if the patient has respiratory problems.
[11] Only at Month 3 and Month 4
[12] Only at Month 3, Month 6, Month 12, Month 24, Month 36, and Month 48
[13] Includes bone marrow biopsy/aspirate at Screening, Month 3, Month 6, Month 12, and Month 24 unless relapse has already been confirmed, and in case of suspected relapse
[14] In case of no neutrophil or platelet engraftment at Week 4, measurements are to be continued at weekly visits until engraftment.
[15] Only in case of suspected relapse
[16] For all patients (in ATIR101 group before infusion of ATIR101)
[17] Only at Week 10, Month 3, Month 6, Month 12, Month 24, and in case of suspected relapse post HSCT

	Screening (between informed consent & confir-mation eligibility)	Pre-HSCT	HSCT (Day 0)	Week 1, 2, 3	Week 4	Week 5, 6, 7, 8, 9, 10	Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24	Follow-up beyond Month 24 every 6 months
Mortality assessment	Continuous recording							
Hematology/biochemistry	X		X	X	X	X	X	X
Urinalysis	X				X	X [18]	X [18]	
Pregnancy test patient/donor (if applicable)	X							
Viral testing patient/donor	X [19]							
HLA compatibility	X							
ABO/Rhesus blood group	X							
Immunophenotyping	X			X [20]	X [21]	X	X	X
Peripheral blood sampling [22]	X					X [23]	X [23]	
Patient AEs (other)	X	X	X	X	X	X	X [24]	X [24]
Donor AEs	X	X [25]						
SAEs	Continuous recording							
Concomitant medications	X	X	X	X	X	X	X	X [26]

[18] Only at Week 8, Month 3, and Month 4
[19] Viral testing to be done within one month before collection of PBMCs (for ATIR101 manufacturing) and within one month of collection of stem cells
[20] Only at Week 3
[21] For all patients (in ATIR101 group before infusion of ATIR101)
[22] For research purposes. At selected sites and patients.
[23] Only at Week 8, Month 4, Month 6, Month 8, Month 10, and Month 12; Additional sampling when a pre-specified GVHD event occurs in ATIR101-treated patients within the first year after HSCT (see Section 8.1.8).
[24] Only at Month 3, Month 4, Month 5, and Month 6. However, SAEs and AEs of special interest (Section 8.3.8) are to be recorded as AEs throughout study.
[25] Up to and including the collection of stem cells
[26] Excluding medications for the treatment of non-serious infections

9.2 Schedule of Activities After Stopping Study (ATIR101 patients)

	Time after HSCT			
	Week 4	**Week 5**	**Week 8**	**Month 4**
ATIR101 infusion	X			
Physical examination	X	X	X	X
Vital signs	X [1]	X	X	
Disease assessment [2]	X	X	X	X
Infection assessment	X	X	X	X
CMV/EBV/adenovirus (PCR)	X	X	X	
Engraftment	X [3]	X	X	
Chimerism	X [3]	X		
GVHD assessment	X	X	X	X
Mortality assessment	Continuous recording			
Hematology/biochemistry	X	X	X	X
Urinalysis	X		X	X
Patient AEs (other)	X	X	X	X
SAEs	Continuous recording			
Concomitant medications[4]	X	X	X	X

1 Before infusion of ATIR101; Additionally, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1 hour, and 2 hours and continuous oxygen monitoring will be done if the patient has respiratory problems.

2 Bone marrow biopsy/aspirate only in case of suspected relapse

3 Before infusion of ATIR101

4 For AE/SAE related medication only

Schedule of Activities after stopping study (PTCy patients)

	Time after HSCT			
	Week 1	**Week 2**	**Week 5**	**Month 4**
Cyclophosphamide infusion	X [5]			
Physical examination	X	X	X	X
Vital signs	X	X	X	
Disease assessment [6]	X	X	X	X
Infection assessment	X	X	X	X
CMV/EBV/adenovirus (PCR)	X	X	X	
Engraftment	X	X	X	
Chimerism	X [7]	X [7]		
GVHD assessment	X	X	X	X
Mortality assessment	Continuous recording			
Hematology/biochemistry	X	X	X	X
Urinalysis				X
Patient AEs (other)	X	X	X	X
SAEs	Continuous recording			
Concomitant medications[8]	X	X	X	X

5 On Day +3 and Day +4/+5

6 Bone marrow biopsy/aspirate only in case of suspected relapse

7 Only in case of suspected relapse

8 For AE/SAE related medication only

9.3 List of Tables/Graphs/Listings

9.3.1 List of Statistical Tables

Number	Description	Population
Table 14.01.01.01-02	Patient disposition	All patients
Table 14.01.02.01-02	Patient demographics	Modified Safety, ITT
Table 14.01.03.01-02	Patient baseline disease characteristics	Modified Safety, ITT
Table 14.01.04.01-02	Donor demographics	Modified Safety, ITT
Table 14.01.05.01-02	Matching score based on HLA typing patient - donor	Modified Safety, ITT
Table 14.01.06.01-02	Concomitant medications	Modified Safety, ITT
Table 14.01.07.01-02	Summary of durations	Modified Safety, ITT
Table 14.02.01.01-02	Summary of Relapse/Disease Progression, Graft failure, TRM, GVHD	Modified Safety, ITT
Table 14.02.02.01-02	KM estimates of GRFS	Modified Safety, ITT
Table 14.02.02.03	KM estimates of GRFS - LTFU	Modified Safety
Table 14.02.03.01-02	KM estimates of OS	Modified Safety, ITT
Table 14.02.03.03	KM estimates of OS - LTFU	Modified Safety
Table 14.02.04.01-02	KM estimates of PFS	Modified Safety, ITT
Table 14.02.04.03	KM estimates of PFS - LTFU	Modified Safety
Table 14.02.05.01-02	Cumulative incidence of TRM (cumulative incidence function)	Modified Safety, ITT
Table 14.02.05.03	Cumulative incidence of TRM (cumulative incidence function) - LTFU	Modified Safety
Table 14.02.06.01-02	Cumulative incidence of RRM (cumulative incidence function)	Modified Safety, ITT
Table 14.02.07.01-02	Incidence and severity of viral, fungal, and bacterial infections by time period	Modified Safety, ITT
Table 14.02.08.01-02	Cumulative incidence of NCI CTCAE grade 2-5 and grade 3-5 for viral, fungal, and bacterial infections	Modified Safety, ITT
Table 14.02.09.01-02	Incidence and severity of acute or chronic GVHD by time period	Modified Safety, ITT
Table 14.02.10.01-02	Cumulative incidence of grade II-IV and grade III-IV acute GVHD	Modified Safety, ITT
Table 14.02.11.01-02	Cumulative incidence of moderate and severe chronic GVHD	Modified Safety, ITT
Table 14.02.12.01-02	Cumulative incidence of chronic GVHD requiring systemic immunosuppressive treatment	Modified Safety, ITT
Table 14.02.13.01-02	Duration of acute and chronic GVHD episodes	Modified Safety, ITT
Table 14.02.14.01-02	FACT-BMT: summary of scores and changes from Baseline	Modified Safety, ITT
Table 14.02.15.01-02	SF-36: summary of scores and changes from Baseline	Modified Safety, ITT

Table 14.02.16.01-02	MDASI: summary of scores and changes from Baseline	Modified Safety, ITT
Table 14.03.01.01	Study procedures	Modified Safety
Table 14.03.01.02	Bone marrow biopsy/aspirate	Modified Safety
Table 14.03.02	Summary of MRD	Modified Safety
Table 14.03.03.01	Summary of treatment-emergent adverse events	Modified Safety
Table 14.03.03.02	Incidence of treatment-emergent adverse events by SOC and PT	Modified Safety
Table 14.03.03.03	Incidence of treatment-emergent adverse events related to ATIR101/PTCy by SOC and PT	Modified Safety
Table 14.03.03.04	Incidence of treatment-emergent adverse events by SOC, PT and severity	Modified Safety
Table 14.03.03.05	Incidence of treatment-emergent severe adverse events (grade 3-5) by SOC and PT	Modified Safety
Table 14.03.03.06	Incidence of treatment-emergent severe adverse events (grade 3-5) related to ATIR101/PTCy by SOC and PT	Modified Safety
Table 14.03.03.07	Incidence of GVHD treatment-emergent adverse events by SOC and PT	Modified Safety
Table 14.03.03.08	Incidence of treatment-emergent Infection adverse events by SOC and PT	Modified Safety
Table 14.03.04.01	Summary of treatment-emergent serious adverse events	Modified Safety
Table 14.03.04.02	Incidence of treatment-emergent serious adverse events by SOC and PT	Modified Safety
Table 14.03.04.03	Incidence of treatment-emergent serious adverse events related to ATIR101/PTCy by SOC and PT	Modified Safety
Table 14.03.04.04	Incidence of treatment-emergent serious adverse events by SOC and PT - LTFU	Modified Safety
Table 14.03.04.05	Incidence of treatment-emergent serious adverse events related to ATIR101/PTCy by SOC and PT - LTFU	Modified Safety
Table 14.03.05	Summary of deaths	Modified Safety
Table 14.03.06.01	Summary of adverse events of special interest	Modified Safety
Table 14.03.06.02	Incidence of adverse events of special interest by SOC and PT	Modified Safety
Table 14.03.07.01	Donor adverse events by SOC and PT	Modified Safety
Table 14.03.07.02	Donor adverse events by SOC, PT and severity	Modified Safety
Table 14.03.08	CMV/EBV summary	Modified Safety

Note: If a table needs to be made on several populations e.g. ITT, the table numbering is as follows: Table 14.xx.xx.01 and Table 14.xx.xx.02.

9.3.2 List of Graphs

Number	Description	Population
Figure 14.02.01.01-02	Kaplan-Meier curve of GRFS	Modified Safety, ITT
Figure 14.02.01.03	Kaplan-Meier curve of GRFS - LTFU	Modified Safety
Figure 14.02.02.01-02	Kaplan-Meier curve of OS	Modified Safety, ITT
Figure 14.02.02.03	Kaplan-Meier curve of OS - LTFU	Modified Safety
Figure 14.02.03.01-02	Kaplan-Meier curve of PFS	Modified Safety, ITT
Figure 14.02.03.03	Kaplan-Meier curve of PFS - LTFU	Modified Safety
Figure 14.02.04.01-02	Cumulative incidence curve of TRM	Modified Safety, ITT
Figure 14.02.04.03	Cumulative incidence curve of TRM - LTFU	Modified Safety
Figure 14.02.05.01-02	Cumulative incidence curve of RRM	Modified Safety, ITT

9.3.3 List of Derived Data Listings

Number	Description	Population
Listing 16.2.1.1	Patient disposition	All enrolled patients
Listing 16.2.1.2	In- and exclusion criteria not met	ITT
Listing 16.2.1.3	Patient and donor demographics	ITT
Listing 16.2.1.4	Patient and donor baseline CMV/EBV	ITT
Listing 16.2.1.5	Patient baseline disease characteristics	ITT
Listing 16.2.1.6	Additional patients baseline disease characteristics (CT, ECG, pulmonary, creatinine, pregnancy, virology)	ITT
Listing 16.2.2.1	Durations (including time to engraftment)	ITT
Listing 16.2.2.2	Patient cytogenetic abnormalities	ITT
Listing 16.2.2.3	Patient molecular abnormalities	ITT
Listing 16.2.2.4	Patient previous therapies	ITT
Listing 16.2.2.5	Patient medical history	ITT
Listing 16.2.2.6	Concomitant medications	ITT
Listing 16.2.3.1	Time to event data: GRFS, OS, PFS, RRM, TRM, T-cell reconstitution	ITT
Listing 16.2.3.2	FACT-BMT scores	ITT
Listing 16.2.3.3	SF-36 scores	ITT
Listing 16.2.3.4	MDASI scores	ITT
Listing 16.2.4.1	Details of patient conditioning regimen	ITT
Listing 16.2.4.2	Details of HSCT procedure	ITT
Listing 16.2.4.3	Details of ATIR101/PTCy	ITT
Listing 16.2.4.4	Bone marrow aspirate	ITT
Listing 16.2.4.5	Chimerism	ITT
Listing 16.2.5.1	GVHD adverse events (patients)	ITT
Listing 16.2.5.2	All adverse events (patients)	ITT
Listing 16.2.5.3	Serious adverse events (patients)	ITT
Listing 16.2.5.4	All adverse events (donors)	ITT
Listing 16.2.5.5	Deaths	ITT
Listing 16.2.6.1	Graft failures / graft rejections	ITT
Listing 16.2.6.2	Immune reconstitution (immunophenotyping and immunoglobulins)	ITT
Listing 16.2.6.3	Laboratory data for hematology	ITT

Listing 16.2.6.4	Laboratory data for serum chemistry	ITT
Listing 16.2.6.5	Urinalysis data	ITT
Listing 16.2.6.6	Per patient listing with clinically significant abnormal lab values (hematology, blood chemistry, urinalysis)	ITT
Listing 16.2.6.7	Patient CMV/EBV	ITT
Listing 16.2.6.8	Vital signs	ITT
Listing 16.2.6.9	Physical examinations	ITT
Listing 16.2.7.1	Time to event data: GRFS, OS, PFS, TRM	Modified Safety
Listing 16.2.7.2	Serious adverse events (patients)	Modified Safety
Listing 16.2.7.3	Deaths	Modified Safety
Listing 16.2.7.4	Patient disposition	Modified Safety