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Study CR-AIR-008 v2.0

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Statistical Analysis Plan

Sponsor:	Kiadis
Protocol Title:	An exploratory, open-label, multicenter study to evaluate the safety and efficacy of a two-dose regimen of ATIR101, a T-lymphocyte enriched leukocyte preparation depleted ex vivo of host alloreactive T-cells (using photodynamic treatment), in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor
Study Code:	CR-AIR-008

The undersigned certify that they have read, reviewed and approved this document.

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Signature and date

IDDI
ADDING VALUE TO CLINICAL DATA

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST	aspartate aminotransferase
Ca	calcium
CD	cluster of differentiation
Cl	chloride
CMV	cytomegalovirus
CT	computed tomography
CTC	Common Terminology Criteria
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
ECG	electrocardiogram
ENT	ears, nose, throat
EU	European union
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

Abbreviation	Term
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonization
ICF	informed consent form
Ig	immunoglobulin
ITT	intention-to-treat
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MITT	modified intention-to-treat
MUGA	multiple gated acquisition
NCI	National Cancer Institute
NK	natural killer (cells)
OS	overall survival
P	phosphorus
PFS	progression-free survival
PP	per protocol
RBC	red blood cell
RRM	relapse-related mortality
SAE	serious adverse event
SAP	statistical analysis plan
TRM	transplant-related mortality
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus

2. Introduction

This Statistical Analysis Plan was written for the clinical trial CR-AIR-008 conducted in EU and Canada. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Study Objective

The study objective was to study the safety and efficacy of a repeat dose administration of ATIR101 in patients with a hematologic malignancy who received a T-cell depleted haploidentical hematopoietic stem cell transplantation (HSCT).

3.1.2 Study Endpoints

Primary safety endpoint

- The primary endpoint is the incidence of acute graft versus host disease (GVHD) grade III/IV up to 180 days post HSCT. Therefore, the primary analysis will be based on the data at 180 days after the HSCT.

Secondary endpoints (up to 12 months post HSCT)

- Incidence and severity of acute and chronic graft versus host disease (GVHD)
- Time to T-cell reconstitution, defined as the time to CD3+ in peripheral blood higher than 0.2×10^9/L (at two consecutive measurements; time to first measurement)
- Incidence and severity of viral, fungal, and bacterial infections
- Transplant-related mortality (TRM), defined as death due to causes other than disease relapse or progression, or other causes which are unrelated to the transplantation procedure (e.g. accident, suicide)
- Relapse-related mortality (RRM), defined as death due to disease relapse or disease progression
- Overall survival (OS), defined as the time from HSCT until death from any cause
- Progression-free survival (PFS), defined as the time from HSCT until relapse, disease progression, or death, whichever occurs first
- GVHD-free, relapse-free survival (GRFS), defined as the time from HSCT until acute GVHD grade III/IV, chronic GVHD requiring systemic treatment, relapse, or death, whichever occurs first

3.2 Study Design

Study CR-AIR-008 is an exploratory, open-label, multicenter study. After signing informed consent, patients will receive an HSCT from a related, haploidentical donor, followed by a first ATIR101 infusion at a dose of 2×10^6 viable T-cells/kg between 28 and 32 days after the HSCT. Patients will receive a second ATIR101 infusion at a dose of 2×10^6 viable T-cells/kg between 70 and 74 days after the HSCT.

To evaluate safety of the second dose administration, the first 6 patients treated will be evaluated for the occurrence of dose-limiting toxicity (DLT), defined as acute GVHD grade III/IV within 120 days post HSCT (or within 42 days after the second ATIR101 infusion in case of prior dose delays). If within the first 6 patients no DLT is observed, treatment of the remaining 9 patients will continue with two ATIR101 doses of 2×10^6 viable T-cells/kg. If within the first 6 patients at least 2 patients show DLT, the second ATIR101 infusion will be adjusted to a dose of 1×10^6 viable T-cells/kg. If in one of the next 3 patients treated at this lower dose again DLT is observed, the second ATIR101 infusion will be halted and the remaining patients will be given only a single dose of ATIR101.

All patients treated with ATIR101 will be followed up until 12 months after the HSCT.

See **Appendix 1** for a detailed schedule of assessments.

3.3 Sample Size Justification

In total, 15 patients with a hematologic malignancy who are eligible for a haploidentical HSCT will be treated with two doses of ATIR101 (unless the second dose is halted for safety reasons). This sample size has been calculated with the following formula based on the primary endpoint (incidence of acute GVHD grade III/IV up to 180 days post HSCT):

$$n > \left(\frac{z^*}{m}\right)^2 p^*(1-p^*)$$

Where:
n = sample size
z* = z-value related to confidence interval, i.e. 1.645 for a one-sided 95% confidence interval
m = desired margin of error, i.e. 13%
p* = estimated population proportion, i.e. 10% acute GVHD grade III/IV 180 days post HSCT

The primary endpoint is the incidence of acute GVHD grade III/IV up to 180 days post HSCT. Therefore, the primary analysis will be based on the data at 180 days after the HSCT. In the protocol it is defined that the study fails if the incidence of acute GVHD grade III/IV up to 180 days post HSCT in the MITT population exceeds 23%.

However, the above sample size calculation does not take into account that the number of patients meeting the primary endpoint is expected to be small (<10). Therefore, we cannot assume a normal distribution of proportions exists and exact statistics have to be applied.

For different data scenarios the upper limit of the one-side 70% confidence interval has been calculated with the Clopper-Pearson exact method using the R-package.

The y-value represents the number of "successes" (patients meeting the primary endpoint).

conf. level (power)	y (number of successes)	upper limit conf. interval (one-sided)
70%	0	0.077
70%	1	0.155
70%	**2**	**0.228**
70%	3	0.299
70%	4	0.368

The infusion of two doses of ATIR101 will be regarded safe for further clinical development if the upper limit of the one-sided confidence interval of the primary safety endpoint is below 23%. With a power of 70% and applying the Clopper-Pearson exact method, this corresponds to a maximum of 2 out of 15 patients in which acute GVHD grade III/IV within 180 days is observed. If the upper limit of the 70% confidence interval of the primary safety endpoint is above 23% (i.e. 3 or more out of 15 patients), the result of the study will be regarded indefinite and the study fails. In the latter case clinical development of the two-dose regimen will be halted.

4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.3 or higher). Plots will be made in R.

As all patients will be treated with (one or two doses of) ATIR101, no tests of significance or no formal comparisons whatsoever will be carried out.

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.

Moreover, the tables will be created by time point, as appropriate for the protocol or at a specified time point only if particularly specified. Listings are patient listings and ordered by patient id.

4.1 Study Period and Visit Window Definitions

4.1.1 Study Periods

ATIR101 was administered as one or two intravenous infusions. Patients treated with ATIR101 will be followed up until 12 months after the HSCT.

The end of the study is defined as the date at which the last data point from the last patient is received. In case it is decided that the study will be prematurely terminated, all patients who are still in the study should at least complete the visit at week 16 after the HSCT. After premature termination of the study, patients will be followed up for the occurrence of serious adverse events (SAEs) until 6 months after ATIR101 administration.

There are five distinct study periods:

- Screening period: period between informed consent & apheresis
- First treatment period: this period is divided in the following visits:
    - HSCT
    - Period between HSCT & ATIR101 infusion: weeks 1, 2 and 3
    - First ATIR101 infusion at week 4
- First follow-up period: weeks 5, 6, 7, 8 and 9
- Second treatment period: second ATIR101 infusion at week 10
- Second follow-up period: this period is divided in the following visits:
    - Weeks 11, 12, 13, 14, 15 and 16 (after HSCT)
    - Months 5, 6, 9 and 12 (after HSCT)

4.1.2 Visit Windows

Visits must be performed within the following windows:

- Screening: between informed consent and apheresis
- HSCT (Day 0)
- Week 1: 1 week ± 2 days after the HSCT
- Week 2: 2 weeks ± 2 days after the HSCT
- Week 3: 3 weeks ± 2 days after the HSCT
- First ATIR101 infusion (Week 4): 28-32 days after the HSCT (unless postponed for medical reasons)
- Week 5: 5 weeks ± 2 days after the HSCT
- Week 6: 6 weeks ± 2 days after the HSCT
- Week 7: 7 weeks ± 2 days after the HSCT
- Week 8: 8 weeks ± 2 days after the HSCT
- Week 9: 9 weeks ± 2 days after the HSCT
- Second ATIR101 infusion (Week 10): 70-74 days after the HSCT but at least 42 days after the first ATIR101 infusion (unless postponed for medical reasons)
- Week 11: 11 weeks ± 2 days after the HSCT
- Week 12: 12 weeks ± 2 days after the HSCT
- Week 13: 13 weeks ± 2 days after the HSCT
- Week 14: 14 weeks ± 2 days after the HSCT
- Week 15: 15 weeks ± 2 days after the HSCT
- Week 16: 16 weeks ± 2 days after the HSCT
- Month 5: 5 months ± 1 week after the HSCT
- Month 6: 6 months ± 1 week after the HSCT
- Month 9: 9 months ± 2 weeks after the HSCT
- Month 12: 12 months ± 2 weeks after the HSCT

4.2 Planned analyses

The final analysis will be performed when the last patient has been followed until 12 months after the HSCT or reached end of study.

4.3 Definition of Populations

All patients who provided informed consent and received an HSCT will be included in the analyses. The following analysis populations will be discerned:

4.3.1 Intention-To-Treat (ITT) Population

The ITT population consists of all enrolled patients who received an HSCT whether or not they received ATIR101.

4.3.2 Modified Intention-To-Treat (MITT) Population

The MITT population consists of all ITT patients who received at least one dose of ATIR101. The primary analyses will be conducted using the MITT population.

4.3.3 Per Protocol (PP) Population

The PP population consists of all patients who:

- Received the first ATIR101 between 28 and 42 days after the HSCT,
- Received the second ATIR101 infusion between 70 and 84 days after the HSCT (if they received a second ATIR101 infusion),
- Showed hematologic engraftment (neutrophil count $\geq 0.5\times10^9$/L for 2 consecutive days and platelets $\geq 20\times10^9$/L for 3 consecutive days, without transfusion) at the time of the first ATIR101 infusion, and
- Did not present any major protocol deviations (see protocol Section 10.9).

All primary and secondary endpoint analyses will be remade using the PP population.

4.3.4 Safety Population

The Safety population will include all patients who received an HSCT and provided informed consent. Note that for this trial ITT and Safety populations are identical. ITT will be used for indicating population used (instead of Safety).

4.4 Subgroup Definitions

Efficacy tables and graphs that will be made on ITT/ MITT/ PP population will be made for three groups: 1) all patients in the population 2) subgroup of patients that received one dose of ATIR101, and 3) subgroup of patients that received two doses of ATIR101. Safety tables that will be made on ITT / Safety population will be made for four groups: 1) patients that underwent HSCT and received single dose of ATIR101, 2) patients that underwent HSCT regardless of ATIR101, 3) subgroup of patients that received single dose of ATIR101, 4) subgroup of patients that received at least one dose of ATIR101. The different groups will be shown in the tables as different columns. Treatment Assignment and Treatment Arms are not applicable, as all patients will be treated with ATIR101.

4.5 Calculated Variables

- Study day 0 is defined as the day of HSCT procedure.

- The baseline for each variable is defined as the last assessment done in the screening period (between ICF and apheresis). Apheresis itself is part of baseline.
- Age is defined as follows: [(date of ICF)-(date of birth)+1]/365.25
- Event durations (e.g. AE duration) are calculated as follows: [end date – start date +1]
- Time intervals (e.g. time from HSCT to ATIR101) are calculated as follows: [end date – start date]
- Day of occurrence is calculated as follows: [event date –date of HSCT +1]

4.6 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)

Missing AE intensities 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.

4.7 Methods To Be Used For Handling 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.

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

4.8 Changes to Protocol

This SAP is referring to amendment 1 of 20 November 2015 to original protocol from 9 July 2015.

5. Study Patients

5.1 Disposition of Patients

The number of screened patients (who provided informed consent to the trial), the number of patients fulfilling in- and exclusion criteria, the number of enrolled patients (included in the study), the number of screen failures (including reason for screen failure), the number of patients who received an HSCT, the number of patients that discontinued before HSCT (including reason for discontinuation), the number of patients who received one dose of ATIR101, the number of patients who received two doses of ATIR101, the number of patients who discontinued after HSCT and before first ATIR101, after first ATIR101, and after second ATIR101 (including reason

for discontinuation) as well as the number of patients completing the study after first ATIR101 and after second ATIR101 will be summarized.

Individual patient disposition information will be listed additionally including details of 'other reason' if applicable, time from enrolment to apheresis, time from apheresis to HSCT, time from diagnosis (of first occurrence of hematologic malignancy) to HSCT, time from HSCT to ANC and Platelet engraftment, time from HSCT to first ATIR101 infusion, time from apheresis to first ATIR101 infusion and time from first till second ATIR101 infusion.

5.2 Protocol Deviations

The major protocol deviations including an account of all identified major protocol deviations and other reasons for exclusion from the PP population (see 4.3.3. for definition of PP population) for the MITT population will be summarized. The details will be listed by patient. An additional listing will be made presenting all patients that are excluded from PP analysis (presenting patient ID, reason (protocol deviation or other), specification).

5.3 In- and Exclusion Criteria

Listing of all in- and exclusion criteria not met will be provided.

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to patient and donor characteristics at baseline will be displayed for both the ITT and the MITT populations.

The variables to be summarized for patients are:

- Demographics: age, gender
- 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 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
- HLA compatibility: mismatches at the HLA-A, -B and/or -DR loci (and if available at the HLA-C and –DQ loci) of the unshared haplotype will be assessed

An additional table with percentage of 3/6, 4/6, 5/6 and 6/6 matches based on HLA A, B and DR types for patients and donors and with percentage of x/8 and x/10 matches based on HLA A, B, C, DR and DQ types will be made. Assessment of matching (diploid, haploid) is made based on first two digits of both alleles per HLA type if only two digits are presented or if comparison is done between a two-digit result and a four-digit result. If the first two digits are equal, there is a match; otherwise a mismatch. If a four-digit result is compared to another four-digit result, 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. These calculated x/6 and if available x/8 or 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).

An additional listing depicting for patients the following information will be made: results of CT scan of the thorax (if applicable), echocardiogram or MUGA scan results (if applicable), results of pulmonary function test (if applicable), creatinine clearance results (if applicable), pregnancy test results (if applicable) and HIV-1, HIV-2, HBV, HCV, Treponema pallidum, HTLV-I (if tested), HTLV-II (if tested), WNV (if tested). In an additional listing the following donor data will be depicted: pregnancy test results (if applicable) and 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 will be summarized for the ITT population by WHO Drug code 2016, version 1 (using ATC classification) and listed.

8. Efficacy Evaluation

Efficacy evaluation will be performed on the MITT population. For the primary and secondary endpoints analyses (combination of efficacy and safety), sensitivity analyses will also be performed on the ITT and PP population.

8.1 Primary Endpoint

The primary endpoint is the incidence of acute graft versus host disease (GVHD) grade III/IV up to 180 days post HSCT. Therefore, the primary analysis will be based on the data at 180 days after the HSCT. From the assumptions in Section 3.3 (Sample Size Justification) it can be derived that the study fails if the incidence of acute GVHD grade III/IV up to 180 days post HSCT in the MITT population exceeds 23% (desired margin of error + estimated population proportion). The proportion acute GVHD grade III/IV 180 days post HSCT will be calculated on all patients that received one or two doses ATIR101 combined only (as this is reflecting the sample size calculation).

8.2 Secondary Endpoints

In this study the following secondary endpoints up to 12 months post HSCT have been identified:

- Incidence and severity of acute and chronic GVHD by time period. Time periods are defined as follows:
  - HSCT to first ATIR101 infusion
  - First ATIR101 infusion to 6 months post HSCT
  - 6 months to 1 year post HSCT
- Time from HSCT to T-cell reconstitution (i.e. the time to CD3+ in peripheral blood higher than $0.2x10^9$/L at two consecutive measurements; time to first measurement)
- Incidence and severity of viral, fungal, and bacterial infections by time period. Time periods are defined as follows:
  - Enrolment to HSCT
  - HSCT to first ATIR101 infusion
  - First ATIR101 infusion to 6 months post HSCT
  - 6 months to 1 year post HSCT

- Transplant-related mortality (TRM defined as death due to causes other than disease relapse or progression, or other causes which are unrelated to the transplantation procedure (e.g. suicide, accident)).
- Relapse-related mortality (RRM; defined as death due to disease relapse or disease progression).
- Overall survival (OS defined as the time from HSCT until death from any cause, or until last follow-up evaluation in the study for patients who were still alive.).
- Progression-free survival (PFS defined as the time from HSCT until relapse, disease progression, or death, whichever occurs first).
- GVHD-free, relapse free survival (GRFS), defined as the time until acute GVHD grade III/IV, chronic GVHD requiring systemic treatment, relapse, or death, whichever occurs first.

These endpoints will be analysed using descriptive statistics (tabulations for incidence and severity of viral, fungal and bacterial infections and GVHD). A separate summary for severe infections (grade 3/4/5) will also be made.

Time-related survival data (OS, PFS, GRFS) will be displayed with the Kaplan-Meier method. KM estimates at 6, and 12 months will also be provided. Time to event data will also be listed for the different survival endpoints (OS, PFS, GRFS). Times are displayed in months. Cumulative incidence curves taking into account competing risks will be used to display and estimate cumulative incidences of TRM (competing risk RRM), RRM (competing risk TRM), GVHD (competing risk death without GVHD) and time from HSCT to T-cell reconstitution (competing risk death without T-cell reconstitution).

If deemed necessary, comparison of the KM curves between the 1-dose group and the 2-dose group will be performed by using the log-rank test. The equality of cumulative incidence functions across patient groups will be tested using Gray's method (Gray 1988).

8.3 Immune reconstitution

- Total lymphocytes and immunophenotyping on peripheral blood as measured by flow cytometry: CD3+ (T-cells), CD3+ CD8+ (cytotoxic T-cells), CD3+ CD4+ (helper T-cells), CD3- CD56+ (NK-cells), and CD19+ (B-cells)
- Immunoglobulins in peripheral blood: IgG, IgA, IgM

Total lymphocytes and immunophenotyping on peripheral blood as measured by flow cytometry: CD3+ (T-cells), CD3+ CD8+ (cytotoxic T-cells), CD3+ CD4+ (helper T-cells), CD3- CD56+ (NK-cells), and CD19+ (B-cells); and immunoglobulins in peripheral blood: IgG, IgA, IgM, will be summarized and listed. All CD measurements must be reported in absolute numbers of circulating lymphocytes ($x10^9$/L). The listing is made as follows: by patient, parameters per category in columns and visits in rows. To the listing of immunoglobulins it will be added with * if result is abnormal clinically not significant or with ** if abnormal clinically significant. For CD3+, CD3+ CD8+, CD3+ CD4+, CD3- CD56+, and CD19+, and for IgG, IgA and IgM a box plot with 25th and 75th percentiles (summarizing all data per available time point) will also be made.

8.4 Extent of Exposure

Summary statistics will be made of the patient conditioning regimen (i.e. recommended TBI regimen, recommended non-TBI regimen,other) and HSCT

procedure: total amount of viable CD3+ cells/kg(x10^4) given to the patient and the total amount of viable CD34+ cells/kg(x10^6) given to the patient.

Four additional listings are made presenting for each patient: details on patient conditioning regimen, HSCT and first and second ATIR101 infusion. Variables presented but not limited to for patient conditioning regimen: conditioning regimen followed, medication name, start and stop date, dose and units and frequency. Variables presented for HSCT: date of HSCT, total amount of viable CD3+ cells/kg(x10^4) given to the patient and total amount of viable CD34+ cells/kg(x10^6) given to the patient. Variables presented for first ATIR101 infusion: date of ATIR101 infusion with reason if not within 28-32 days after HSCT, number of days from HSCT, ATIR101 thawing interrupted Yes/No together with reason, start date/time of ATIR101 infusion, amount of ATIR101 infused, ATIR101 infusion interrupted Yes/No together with reason, etc. Variables presented for second ATIR101 infusion: date of ATIR101 infusion with reason if not within 70-74 days after HSCT, number of days from HSCT, ATIR101 thawing interrupted Yes/No together with reason, start date/time of ATIR101 infusion, amount of ATIR101 infused, ATIR101 infusion interrupted Yes/No together with reason, etc.

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 first ATIR101 infusion, time from HSCT to second ATIR101 infusion, time from apheresis to first ATIR101 infusion and time from apheresis to second ATIR101 infusion will be made.

8.5 Bone Marrow Biopsy / Aspirate

A table will summarize at the relevant time points (baseline, 6 months, 12 months and unscheduled visits) the amount and percentage of patients with myeloblasts <5% (Y/N) and the actual value of myeloblasts (in %) by bone marrow aspirate and biopsy separately.
A listing providing all details on bone marrow aspirate / biopsy will also be made.

8.6 Engraftment and Chimerism

Engraftment is defined as neutrophil count ≥ 0.5x10^9/L for 2 consecutive days and platelets ≥ 20x10^9/L for 3 consecutive days. Time to ANC engraftment and platelet engraftment (from HSCT) will be summarized together with other time summaries (see 9.1). Chimerism results (i.e. total number of cells analysed, % donor cells, assessment done prior to ATIR101 infusion?) will be listed (including unscheduled visits).

9. Safety Evaluation

The safety evaluation will be performed on the ITT population.

9.1 DLT

To evaluate safety of the second dose administration, the first 6 patients treated will be evaluated for the occurrence of dose-limiting toxicity (DLT), defined as acute GVHD grade III/IV within 120 days post HSCT (or within 42 days after the second ATIR101 infusion in case of prior dose delays). If within the first 6 patients no DLT is observed, treatment of the remaining 9 patients will continue with two ATIR101 infusions of 2×10^6 viable T-cells/kg. If within the first 6 patients at least 2 patients show DLT, the second ATIR101 infusion will be adjusted to a dose of 1×10^6 viable T-cells/kg. If in one of the next 3 patients treated at this lower dose again DLT is observed, the second

ATIR101 infusion will be halted and the remaining patients will be given only a single dose of ATIR101.

Details of the DLTs are presented in a listing.

9.2 Adverse Events

Adverse events will be coded using MedDRA (Version 19.0).

For patients, adverse events (AEs) will be analyzed in terms of their type, incidence, severity and relationship to the study drug. An adverse event is treatment emergent if it is first observed or worsens on or after the date of first ATIR101 administration. In case of missing start date, the adverse event will be considered as treatment emergent. In listings it will be indicated if the AE is treatment emergent or not. If the event is ongoing at death, the event duration will be calculated using death date.

Tabulations of the number of patients who experienced AEs as well as severity of the events will be presented overall and by system organ class and preferred term. SOCs will be ordered by frequency (highest frequency first). PTs will be ordered alphabetically per SOC. Patients will only be counted once for each preferred term. In case a patient experienced the same event more than once, the worst severity will be presented. Both for AEs and SAEs, separate tables for ATIR101 related events only (defined as certainly, probably or possibly related or with missing relationship on AE form) will be made (by SOC and PT).

In addition, a summary table presenting an overview of all infection AEs from study entry (number/% of patients with at least one (S)AE, number/% of AEs with specific outcome, number/% of AEs per grade) will be provided. Number of events will also be indicated.

Tabulations of the number of donors who experienced (S)AEs as well as severity of the events will be presented overall and by system organ class and preferred term. Donors will only be counted once for each preferred term. In case a donor experienced the same event more than once, the worst severity will be presented.

A tabulation of AEs/SAEs will be made summarizing these events on the classification/category given (i.e. infection, relapse, GVHD, other etc.). Number of events will also be indicated.

For patients, the following AE listings will be made:

- GVHD AEs (including start since HSCT/ATIR101*, outcome, duration, GVHD severity grade, NCI CTCAE severity grade, seriousness, causality).

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.

- Infection AEs (including type of infection, severity, seriousness, causality, details organism, start since HSCT/ATIR101*, outcome, duration).
- Relapse AEs (including details on evaluation method, chimerism, start since HSCT/ATIR101*, outcome, duration).
- Other AEs (including further information, severity, seriousness, causality, start since HSCT/ATIR101*, outcome, duration).

* *Number of days between start of AE and first & second dose of ATIR101*

- SAEs (type, reason for seriousness, duration, outcome)

For donors, a listing of all (S)AEs will be made.

9.3 Deaths and Serious Adverse Events

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

Separate listings will detail all serious adverse events, graft failures / graft rejections and deaths, including number of days since HSCT/ATIR101*, date and cause of death together with investigator classification of cause of death, during the study.

The number of deaths will be tabulated together with the primary cause of death. The details of the 'other cause' will be included in the listing.

9.4 Clinical Laboratory Determination

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

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) Urinalysis: • Bilirubin	• Albumin • Alkaline phosphatase (AP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Calcium (Ca) • Chloride (Cl) • Creatinine • Glucose • Lactate dehydrogenase (LDH) • Magnesium (Mg) • Phosphorus (P) • Potassium (K) • Sodium (Na) • Total bilirubin

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• Glucose • Ketones • Nitrite • Blood • pH • Protein • Specific gravity • Leukocytes	• Total protein • Urea

9.5 CMV/EBV

CMV and EBV results are summarized in format of cross table (separate table for CMV and EBV). Overall (i.e. for all time points 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 limit at least one time point and below the CMV/EBV limit for all visits is presented.

In a listing, aVital 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) will be listed.

Physical examination data (skin, ears/nose/throat (ENT), respiratory, cardiovascular, abdomen (including liver and spleen), and lymph nodes) will be listed.

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10. References

Gray, R. (1988), "A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk," The Annals of Statistics, 16, 1141–1154.

SAS Statistical Analysis System. SAS Institute, Inc. Cary, NC, 1996.

Appendix 1: Schedule of Study Assessments

	Screening: between informed consent & apheresis	HSCT (Day 0)	Week 1, 2, 3	1st ATIR101 infusion Week 4	Week 5, 6, 7, 8, 9	2nd ATIR101 infusion Week 10	Week 11, 12, 13, 14,15, 16	Month 5, 6, 9, 12
Informed consent patient and donor	X							
Apheresis patient and donor	X							
HSCT		X						
ATIR101 infusion				X		X		
Patient characteristics and eligibility								
Demographics	X							
Hematologic malignancy	X							
Medical history	X							
Performance status	X							
Physical examination	X	X		X	X [1]	X	X [2]	
High resolution CT scan of the thorax	X [3]							
Echocardiogram/MUGA scan	X [3]							
Pulmonary function test	X [3]							
Creatinine clearance	X [4]							
Pregnancy test	X							
Viral testing	X							

[1] Only at Week 6 and Week 8
[2] Only at Week 12, Week 14, and Week 16
[3] If not already done within 6 weeks before signing informed consent
[4] Calculated or measured, if not already done within 2 weeks before signing informed consent

	Screening: between informed consent & apheresis	HSCT (Day 0)	Week 1, 2, 3	1st ATIR101 infusion Week 4	Week 5, 6, 7, 8, 9	2nd ATIR101 infusion Week 10	Week 11, 12, 13, 14,15, 16	Month 5, 6, 9, 12
Donor characteristics and eligibility								
Demographics	X							
HLA compatibility	X							
Pregnancy test	X							
Viral testing	X							
Donor adverse events	X	X [1]						
Vital signs	X	X		X [2]	X	X [2]	X	
Safety laboratory tests								
Hematology	X	X	X	X	X	X	X	
Blood chemistry	X	X	X	X	X	X	X	
Urinalysis	X			X		X	X [3]	
CMV monitoring (PCR)		X	X	X	X	X	X	X
EBV monitoring (PCR) [4]		X	X	X	X	X	X	X
Engraftment			X					
Chimerism				X [5]		X [5]		

1 Until collection of stem cells
2 Before ATIR101 infusion. In addition, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1, 2, 3, and 4 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems.
3 Only at Week 16
4 If donor or patient is EBV positive before HSCT or as indicated
5 Before ATIR101 infusion

	Screening: between informed consent & apheresis	HSCT (Day 0)	Week 1, 2, 3	1st ATIR101 infusion Week 4	Week 5, 6, 7, 8, 9	2nd ATIR101 infusion Week 10	Week 11, 12, 13, 14,15, 16	Month 5, 6, 9, 12
Efficacy and safety assessments								
Immunophenotyping	X			X [1]	X [2]	X [1]	X	X
Immunoglobulins	X			X [1]		X [1]	X [3]	X
Serum sampling [4]	X	X		X [1]	X [2]	X [1]	X	X
Peripheral blood sampling [5]					X [6]		X [6]	X [6]
Infection assessment	X	X	X	X	X	X	X	X
Disease assessment [7]	X	X	X	X	X	X	X	X
GvHD assessment			X	X	X	X	X	X
Mortality	Continuous recording							
Other adverse events	X	X	X	X	X	X	X	
Serious adverse events	Continuous recording							
Concomitant medications	X	X	X	X	X	X	X	X

1 Before ATIR101 infusion
2 Only at Week 5, Week 7, and Week 9
3 Only at Week 11, Week 13, and Week 16
4 For measuring cytokine levels and/or immunoglobulins against specific antigens
5 For measuring pathogen-specific T-cells
6 Only at Week 6, Week 12, Month 6, and Month 12
7 Includes bone marrow aspirate and/or biopsy at Screening, Month 6 and 12 after HSCT unless relapse has already been confirmed, and in case of suspected relapse

11. List of Tables/Graphs/Listings

11.1 List of Statistical Tables

Number	Description	Population
Table 14.01.01	Patient disposition	All patients
Table 14.01.02	Summary of major protocol deviations and other reasons for exclusion from the PP population	MITT
Table 14.01.03	Patient demographics	ITT, MITT
Table 14.01.04	Patient baseline disease characteristics	ITT, MITT
Table 14.01.05	Donor demographics	ITT, MITT
Table 14.01.06	Matching score based on HLA typing patient - donor	ITT, MITT
Table 14.01.07	Concomitant medications	ITT
Table 14.01.08	Summary of durations	ITT, MITT
Table 14.02.01	Incidence of acute graft versus host disease (GVHD) grade III/IV up to 180 days post HSCT	MITT, ITT, PP
Table 14.02.02.01	Incidence and severity of acute and chronic GVHD by time period	MITT, ITT, PP
Table 14.02.02.02	Incidence and severity of viral, fungal, and bacterial infections by time period	MITT, ITT, PP
Table 14.02.02.03	KM estimates of OS (at 6 and 12 months)	MITT, ITT, PP
Table 14.02.02.04	KM estimates of PFS (at 6 and 12 months)	MITT, ITT, PP
Table 14.02.02.05	KM estimates of GRFS (at 6 and 12 months)	MITT, ITT, PP
Table 14.02.03.01	Cumulative incidence of TRM (cumulative incidence function)	MITT, ITT, PP
Table 14.02.03.02	Cumulative incidence of RRM (cumulative incidence function)	MITT, ITT, PP
Table 14.02.03.03	Cumulative incidence of GVHD (cumulative incidence function)	MITT, ITT, PP

Table 14.02.03.04	Cumulative incidence of T-cell reconstitution (cumulative incidence function)	MITT, ITT, PP
Table 14.02.04	Immune reconstitution (immunophenotyping and immunoglobulins)	MITT,
Table 14.02.05	Extent of exposure	MITT
Table 14.02.06	Engraftment and Chimerism	MITT
Table 14.02.07	Bone marrow aspirate	MITT
Table 14.03.01.01	Patient adverse events summary	ITT
Table 14.03.01.02	Patient adverse events by SOC and PT	ITT
Table 14.03.01.03	Patient adverse events by SOC, PT and severity	ITT
Table 14.03.01.04	Patient ATIR101 related adverse events by SOC and PT	ITT
Table 14.03.01.05	Patient treatment-emergent adverse events by SOC and PT	ITT
Table 14.03.01.06	Patient treatment-emergent adverse events by SOC, PT and severity	ITT
Table 14.03.02.01	Patient serious adverse events summary	ITT
Table 14.03.02.02	Patient serious adverse events by SOC and PT	ITT
Table 14.03.02.03	Patient serious adverse events by SOC, PT and severity	ITT
Table 14.03.02.04	Patient ATIR101 related serious adverse events by SOC and PT	ITT
Table 14.03.02.05	Patient treatment-emergent serious adverse events by SOC and PT	ITT
Table 14.03.02.06	Patient treatment-emergent serious adverse events by SOC, PT and severity	ITT
Table 14.03.03	Overview of all patient infection adverse events	ITT
Table 14.03.04.01	Donor adverse events by SOC and PT	ITT
Table 14.03.04.02	Donor adverse events by SOC, PT and severity	ITT
Table 14.03.05	Deaths	ITT
Table 14.03.06	CMV/EBV summary	ITT

Note: if a table needs to be made on several populations e.g. MITT and ITT the table numbering is as follows: Table 14.x.x.1 and Table 14.x.x.2.

11.2 List of Graphs

Number	Description	Population
Figure 14.02.01	Kaplan-Meier plot PFS	MITT, ITT, PP
Figure 14.02.02	Kaplan-Meier plot OS	MITT, ITT, PP
Figure 14.02.03	Kaplan-Meier plot GRFS	MITT, ITT, PP
Figure 14.02.04	Cumulative incidence curve of TRM	MITT, ITT, PP
Figure 14.02.05	Cumulative incidence curve of RRM	MITT, ITT, PP
Figure 14.02.06	Cumulative incidence curve of GVHD	MITT, ITT, PP
Figure 14.02.07.01	Box-plot for lymphocytes	MITT
Figure 14.02.07.02	Box-plot for CD3+	MITT
Figure 14.02.07.03	Box-plot for CD3+ CD8+	MITT
Figure 14.02.07.04	Box-plot for CD3+ CD4+	MITT
Figure 14.02.07.05	Box-plot for CD3- CD56+	MITT
Figure 14.02.07.06	Box-plot for CD19+	MITT
Figure 14.02.07.07	Box-plot for IgG	MITT
Figure 14.02.07.08	Box-plot for IgM	MITT
Figure 14.02.07.09	Box-plot for IgA	MITT

Note: if a figure needs to be made on several populations e.g. MITT and ITT/PP, the figure numbering is as follows: Figure 14.x.x.1 and Figure 14.x.x.2.

11.3 List of Derived Data Listings

Notes: Listings will be produced on ALL patients, and sorted by patient ID. The patient ID will be followed by one of the letters below (i.e. a, b, c, d, or e) to indicate if patient belongs to:

(a) MITT single dose

(b) MITT double dose

(c) ITT single dose (no MITT)

(d) Screening failure

(e) No HSCT (no screening failure)

And this list will be put in a footnote.

Number	Description	Population
Listing 16.02.01	Patient disposition	All patients
Listing 16.02.02	Durations (including time to engraftment)	All patients
Listing 16.02.03	Major protocol deviations	All patients
Listing 16.02.04	Patients excluded from per-protocol population	All patients
Listing 16.02.05	In- and exclusion criteria not met	All patients
Listing 16.02.06	Patient and donor demographics	All patients
Listing 16.02.07	Patient and donor baseline CMV/EBV	All patients
Listing 16.02.08	Patient baseline disease characteristics	All patients
Listing 16.02.09	Additional patients baseline disease characteristics (CT, ECG, pulmonary, creatinine, pregnancy, virology)	All patients
Listing 16.02.10	Patient cytogenetic abnormalities	All patients
Listing 16.02.11	Patient molecular abnormalities	All patients
Listing 16.02.12	Patient previous therapies	All patients

Listing 16.02.13	Patient medical history	All patients
Listing 16.02.14	Concomitant medications	All patients
Listing 16.02.15	PFS: time to event data	All patients
Listing 16.02.16	OS: time to event data	All patients
Listing 16.02.17	GRFS: time to event data	All patients
Listing 16.02.18	Details of patient conditioning regimen	All patients
Listing 16.02.19	Details of HSCT procedure	All patients
Listing 16.02.20	Details of ATIR101 infusion	All patients
Listing 16.02.21	Bone marrow aspirate	All patients
Listing 16.02.22	Engraftment and Chimerism	All patients
Listing 16.02.23	DLTs	All patients
Listing 16.02.24	GVHD adverse events (patients)	All patients
Listing 16.02.25	Infection adverse events (patients)	All patients
Listing 16.02.26	Relapse adverse events (patients)	All patients
Listing 16.02.27	Other adverse events (patients)	All patients
Listing 16.02.28	Serious adverse events (patients)	All patients
Listing 16.02.29	All adverse events (donors)	All patients
Listing 16.02.30	Deaths (including graft failures / graft rejections)	All patients
Listing 16.02.31	Graft failures / graft rejections	All patients
Listing 16.02.32	Immune reconstitution (immunophenotyping and immunoglobulins)	All patients
Listing 16.02.33	Laboratory data for hematology	All patients
Listing 16.02.34	Laboratory data for serum chemistry	All patients

Listing 16.02.35	Urinalysis data	All patients
Listing 16.02.36	Per patient listing with clinically significant abnormal lab values (hematology, blood chemistry, urinalysis)	All patients
Listing 16.02.37	Patient CMV/EBV	All patients
Listing 16.02.38	Vital signs	All patients
Listing 16.02.39	Physical examinations	All patients