Clinical Study Protocol: CR-AIR-009

Study 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 Number: CR-AIR-009

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Study Phase: III

Product Name: ATIR101

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP E6[R2]), and applicable local laws and regulations. The principal investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB) or independent ethics committee (IEC), except where necessary to eliminate an immediate hazard to the study participants. All relevant personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

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 Description:

Study CR-AIR-009 is a Phase III randomized controlled multicenter open-label study comparing two parallel groups. After signing informed consent, a total of 250 patients will be randomized in a 1:1 fashion to receive either a T-cell depleted hematopoietic stem cell transplantation (HSCT; CD34 selection) from a related, haploidentical donor, followed by ATIR101 infusion, or a T-cell replete HSCT, followed by a high dose of post-transplant cyclophosphamide (PTCy).

Randomization will use minimization to balance treatment groups with respect to underlying disease (AML, ALL, or MDS), Disease Risk Index (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 4/5 days after the HSCT. All patients will be followed up for at least 24 months post HSCT.

Objectives:

The primary objective of this study is to compare safety and efficacy of a haploidentical T-cell depleted HSCT and adjunctive treatment with ATIR101 versus a haploidentical T-cell replete HSCT with post-transplant administration of high dose cyclophosphamide (PTCy) in patients with a hematologic malignancy.

An additional objective of the study is to compare the effect of the two treatments on quality of life.

Endpoints:

The primary endpoint of the study is GVHD-free, relapse-free survival (GRFS). GRFS is 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. This endpoint captures both safety and efficacy.

Secondary endpoints:

- Overall survival (OS)
- Progression-free survival (PFS)
- Relapse-related mortality (RRM)
- Transplant-related mortality (TRM)

Other endpoints:

- Immune reconstitution
- Incidence and severity of acute and chronic GVHD
- Incidence and severity of viral, fungal, and bacterial infections
- Incidence and severity of adverse events
- Quality of life: FACT-BMT, SF-36, MDASI, and EQ-5D-5L total scores

Study Population:

The study population consists of male or female patients aged 18-70 years with a hematologic malignancy (AML in remission, ALL in remission, or MDS) who are eligible for a haploidentical HSCT. The Karnofsky Performance Status (KPS) should be ≥ 70%. Each patient must have a related haploidentical donor aged 16-75 years available, who is eligible according to local requirements and regulations. Vulnerable participants such as pregnant women and children will not be enrolled in the study.

In total, 250 patients are planned to be randomized.

Phase:

III

Description of Sites Enrolling Participants:

Approximately 50 sites globally are planned to enroll participants in the study.

Description of Study Intervention:

The advanced therapy medicinal product (ATMP) ATIR101 is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells using photodynamic treatment (PDT) with the photosensitizing reagent TH9402. ATIR101 is presented as a "dispersion for infusion". Patients in the ATIR101 group will be infused with ATIR101 intravenously (IV) at a single dose of 2.0×10^6 viable T-cells/kg body weight between 28 and 32 days after a CD34-selected HSCT (or later if required by the patient's medical condition).

The drug cyclophosphamide, which is part of the control intervention, is presented as a lyophilized powder for IV infusion, which is commercially available for human use under various brand names. Patients in the PTCy group will be infused with cyclophosphamide 50 mg/kg/day IV at 3 and 4/5 days after a non-manipulated, T-cell replete HSCT.

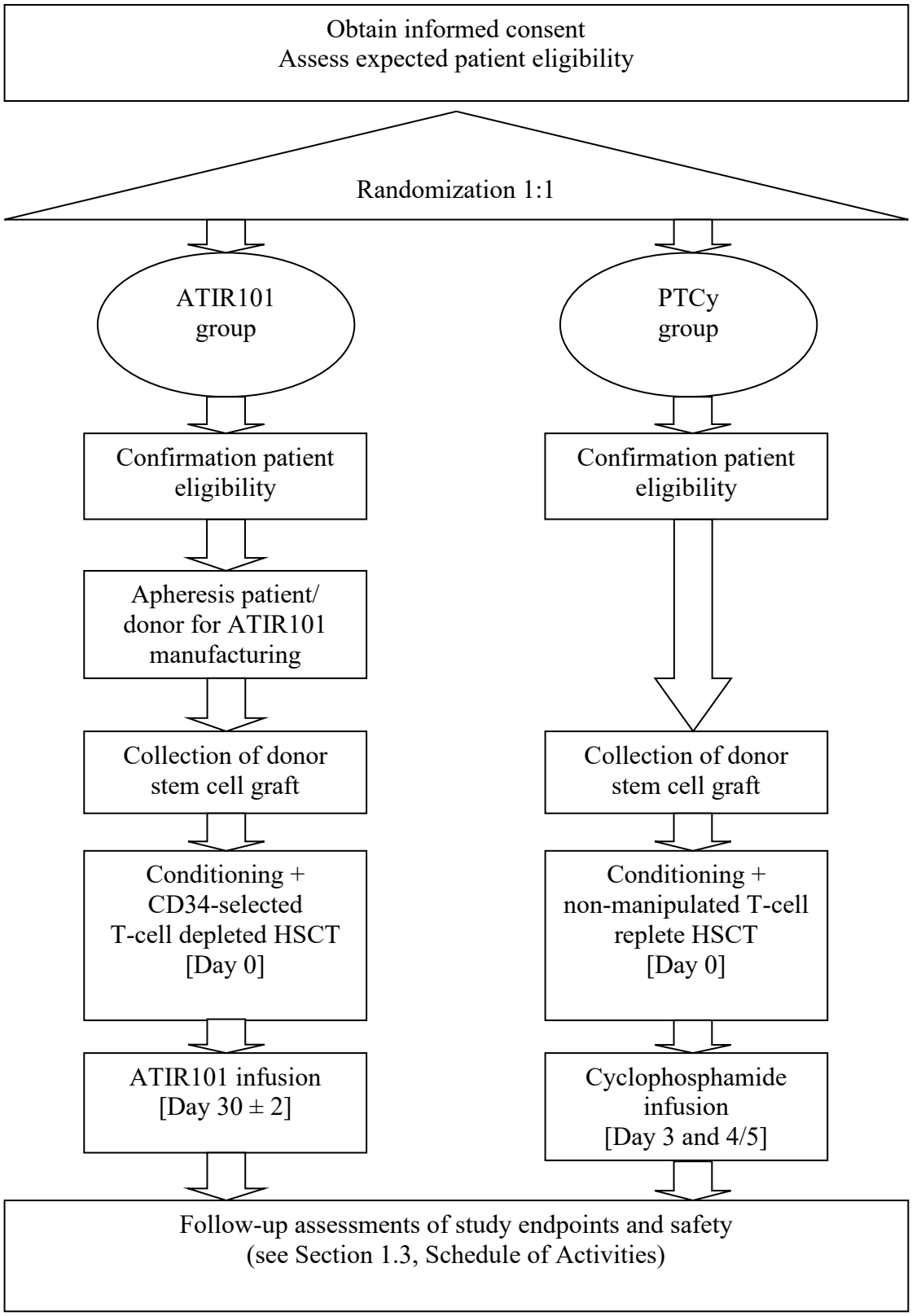
Study Duration:

The estimated time from start of enrolment until completion of the interim data analysis of the primary endpoint amounts to 29 months. The estimated time from start of enrolment until completion of the final data analyses amounts to approximately 38 months.

Participant Duration:

Each patient is planned to be in the study for at least approximately 26 months, i.e. from signing informed consent to visit at 24 months post HSCT. Patient follow-up beyond 24 months post HSCT will be discontinued when a total number of 156 GRFS events has been reached. Each donor is planned to be in the study for approximately 1-2 months.

1.2 Schema


Obtain informed consent
Assess expected patient eligibility
Randomization 1:1
ATIR101 group
PTCy group
Confirmation patient eligibility
Confirmation patient eligibility
Apheresis patient/ donor for ATIR101 manufacturing
Collection of donor stem cell graft
Collection of donor stem cell graft
Conditioning + CD34-selected T-cell depleted HSCT [Day 0]
Conditioning + non-manipulated T-cell replete HSCT [Day 0]
ATIR101 infusion [Day 30 ± 2]
Cyclophosphamide infusion [Day 3 and 4/5]
Follow-up assessments of study endpoints and safety (see Section 1.3, Schedule of Activities)

1.3 Schedule of Activities

	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
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

	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

2 INTRODUCTION

2.1 Study Rationale

In this Phase III clinical study ATIR101 will be evaluated for its clinical benefit when used as adjunctive treatment after a haploidentical HSCT in patients with a hematologic malignancy (AML, ALL, or MDS). The dosing regimen of ATIR101 (single dose of 2.0×10^6 viable T-cells/kg IV at 28-32 days post HSCT) has been well established in previous Phase I-II clinical studies. To reflect current practice of haploidentical transplants for hematologic malignancies, the patient population is limited to patient for whom no suitable HLA matched sibling or unrelated donor is available in a timely manner.

The study is designed to confirm results obtained in Phase I-II clinical studies and to compare the outcomes of patients receiving ATIR101 post HSCT in a randomized setting to a control group of patients receiving a high dose of cyclophosphamide post HSCT, an upcoming treatment modality for patients in need of a haploidentical HSCT.

2.2 Background

2.2.1 Allogeneic Transplantations Using Haploidentical Donors

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established treatment option for many malignant disorders. HSCT comprises the elimination of the patient's bone marrow, usually by means of myeloablative conditioning involving high-dose chemotherapy and possibly total body irradiation, followed by transplantation of donor stem cells. Major complications of HSCT include graft-versus-host disease (GVHD) and other life-threatening complications such as graft rejection/failure and infection. Even with the use of immunosuppressive prophylaxis, 30 to 60% of patients will develop some level of acute GVHD (Abo-Zena and Horwitz 2002; Jagasia *et al.* 2012; Ruggeri *et al.* 2006).

Use of a human leukocyte antigen (HLA) matched donor, ideally an HLA-identical sibling, will reduce the above-mentioned risks. Unfortunately, such an ideal donor will only be available for about 25% of the patients. A matched unrelated donor (MUD) from a donor registry can be an alternative. However, despite the establishment of worldwide donor registries, the probability of finding a MUD within a medically reasonable time (*i.e.* 2 to 3 months) can be low. The probability of finding such a donor in the international registries ranges from 10% in poorly represented ethnic groups to 60% to 80% in Caucasians (Reisner *et al.* 2011). Even when a donor has been identified, he/she might not be able or willing to donate stem cells. Results from donor searches are available at a minimum of 6 weeks (if a match can be identified in the national registries) but usually it takes 2 to 4 months or longer (Heemskerk *et al.* 2005; Hirv *et al.* 2009). Overall, this option might not be viable for patients who urgently need a stem cell transplantation and many patients relapse while HLA typing is in progress or while waiting for the start of the transplant procedure.

Interest in the use of haploidentical donors arises from the immediate availability of a one haplotype-matched family donor for virtually all patients, particularly those who urgently need transplantation (Aversa *et al.* 1998). In the last decade, the use of haploidentical donors

has emerged as an alternative when an HLA-identical sibling or MUD is not available (Passweg *et al.* 2015).

The haploidentical transplant procedures have become feasible using methods to reduce or control GVHD, either by T-cell replete or T-cell deplete methods. In T-cell deplete strategies *ex vivo* graft manipulation with CD34-selection or selective T-cell depletion (CD3/CD19 and αβ/CD19 depletion) is applied. Most recently, T-cell replete strategies using high doses of post-transplant cyclophosphamide (PTCy) or extensive immunosuppression without prior graft manipulation have emerged as successful approaches to reduce GVHD. With both T-cell replete and T-cell deplete strategies, deficiencies in recovery of T- and B-cells remain, which are associated with increased rates of infections and disease relapse.

2.2.1.1 T-Cell Depleted (TCD) HSCT

The recognition that GVHD is caused by donor derived T-cells led to the strategy of T-cell depletion in order to reduce the risk of GVHD (Aversa *et al.* 1998). Use of *ex vivo* T-cell depleted (TCD) grafts has significantly reduced the risk of GVHD without the need for post-transplant immunosuppression (Devine *et al.* 2011). The most used approach for removal of T-cells from the graft has been the positive selection of CD34+ hematopoietic stem cells using immunomagnetic beads. A potential limitation of TCD grafts is a higher risk of graft rejection, as preclinical data has indicated that donor-derived T-cells facilitate engraftment. In the haploidentical HSCT setting this has been solved by profound *in vivo* and *in vitro* lymphodepletion and administering a mega dose of CD34+ cells with a small fraction of T-cells, and additionally the use of ATG in the conditioning regimen. Another limitation of TCD grafts is that higher rates of viral and invasive fungal infections, and Epstein-Barr virus (EBV) associated post-transplant lymphoproliferative disease (PTLD) have been noted with TCD HSCT as a consequence of impaired T-cell reconstitution (Goker *et al.* 2001). T-cell depletion has a marked effect on immune recovery with patients remaining severely immunocompromised for extensive periods of time after HSCT (up to 1 year or more), leading to a high risk of life-threatening (infectious) complications resulting in high transplant-related mortality (TRM) and low overall survival (OS) (Aversa *et al.* 1998; Handgretinger *et al.* 2001; Koh *et al.* 2007). Additionally, depleting T-cells from the graft could compromise the graft-versus-leukemia (GVL) effect, leading to an increase in relapse (Sehn *et al.* 1999).

Re-introducing unmanipulated T-cells early after a TCD HSCT is a solution for the above given limitations, but the risk of inducing life-threatening GVHD would be significant (Lewalle *et al.* 2003). However, the adoptive transfer of selected, allo-depleted or genetically manipulated T-cells clearly is an alternative. Photodynamic treatment (PDT) is a method developed to allow elimination of alloreactive T-cells from a donor lymphocyte preparation, resulting in a DLI which can be given at higher doses, without causing severe GVHD (Bastien *et al.* 2010; Boumedine and Roy 2005).

2.2.1.2 Post-Transplant Cyclophosphamide

High-dose cyclophosphamide is a potent immunomodulatory agent that has been used successfully for the prevention of GVHD after HLA-matched and –mismatched HSCT where

the full donor graft was administered. Preclinical studies had shown that administration of cyclophosphamide early after HSCT preferentially killed activated, cycling alloreactive T-cells while sparing resting, non-alloreactive T-cells, like human regulatory T-cells (Luznik *et al.* 2001). Initial clinical results of this approach using a high dose of cyclophosphamide on Day +3 and +4 post-transplant, with additional use of immunosuppressive agents like tacrolimus and mycophenolate mofetil, showed primary graft failure in 13% of patients and complete T-cell engraftment in the remaining patients by Day +28 (Luznik *et al.* 2008). Cumulative incidences of grade II-IV and grade III-IV acute GVHD were 34% and 6%, respectively. Non-relapse mortality rate and relapse rate at 1 year were 15% and 51%, respectively. Actuarial OS at two years post HSCT was 36%.

To date, haploidentical non-myeloablative and myeloablative transplantation with post-transplant cyclophosphamide, commonly known as the Baltimore protocol, is being used widely in patients for whom no matched donor is available. Data from two BMT CTN sponsored Phase II studies (BMT CTN 0603 & 0604) were used to compare the outcome of haploidentical transplants in high-risk hematologic malignancies, using post-transplant cyclophosphamide, against transplants done using double umbilical cord blood (dUCB) grafts, without PTCy (Brunstein *et al.* 2011). This data showed that haploidentical HSCT with PTCy is at least as effective as dUCB transplants, with less non-relapse mortality after haplo-HSCT (7% versus 24%) and higher 1-year OS (62% versus 54%), but with an increase in relapse at 1 year post-transplant (45% versus 31%). Other studies have also shown comparable transplant outcomes of haploidentical HSCT, using PTCy, compared to HLA-matched related and unrelated donor transplants (Bashey *et al.* 2013; Burroughs *et al.* 2008).

A recent study evaluated the data from the CIBMTR database in patients with AML (Ciurea *et al.* 2015) who either received a haploidentical HSCT, using PTCy, or a matched unrelated HSCT. OS was comparable between the two transplant regimens, with 1-year OS of 65% in both patient groups. Patients receiving a haploidentical HSCT had less acute and chronic GVHD, with grade II-IV acute GVHD reported in 16% and chronic GVHD in 28%, compared to 33% and 45% in unrelated donor transplants. Non-relapse mortality was comparable, but relapse occurred more frequently in the first year post HSCT in patients who received a haplo-HSCT (41% versus 32%). The higher rate of relapse continues to be a challenge, in addition to the required immunosuppression that needs to be given to patients for a prolonged period of time after the transplant.

2.2.1.3 GVHD-Free, Relapse-Free Survival (GRFS) Endpoint

A new composite endpoint has been introduced by the Blood and Marrow Transplant Clinical Trial Network (BMT CTN), to better define a successful transplant outcome. This GVHD-free, relapse-free survival (GRFS) endpoint is defined as freedom from grade III-IV acute GVHD, chronic GVHD requiring systemic treatment, relapse, and death (Holtan *et al.* 2015). Data from a large, single center patient cohort was analyzed for GRFS among 531 consecutive adult recipients of allogeneic transplantation (Solh *et al.* 2016). They found for the whole cohort that although 78% of patients are alive at 1 year post HSCT only 31% of transplant recipients survived 1 year without experiencing at least 1 GRFS event. For haploidentical donor transplants (n=128), done at this institute using the post-transplant cyclophosphamide approach, the reported 1-year GRFS rate was 33% (95% CI 25-41).

2.2.2 Study Intervention

ATIR101, an individualized advanced therapy medicinal product (ATMP), is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment). ATIR101 is being developed as adjunctive treatment to haploidentical HSCT for the reduction of morbidity and mortality due to infections, GVHD, and/or relapse in patients with hematologic malignancies.

For manufacturing of ATIR101, donor and patient peripheral blood mononuclear cells (PBMCs) are collected by apheresis on the same day. For the patient this apheresis is done in advance of the conditioning regimen for the HSCT and for the donor this additional apheresis is done before the apheresis to collect the stem cell graft (PBSCs).

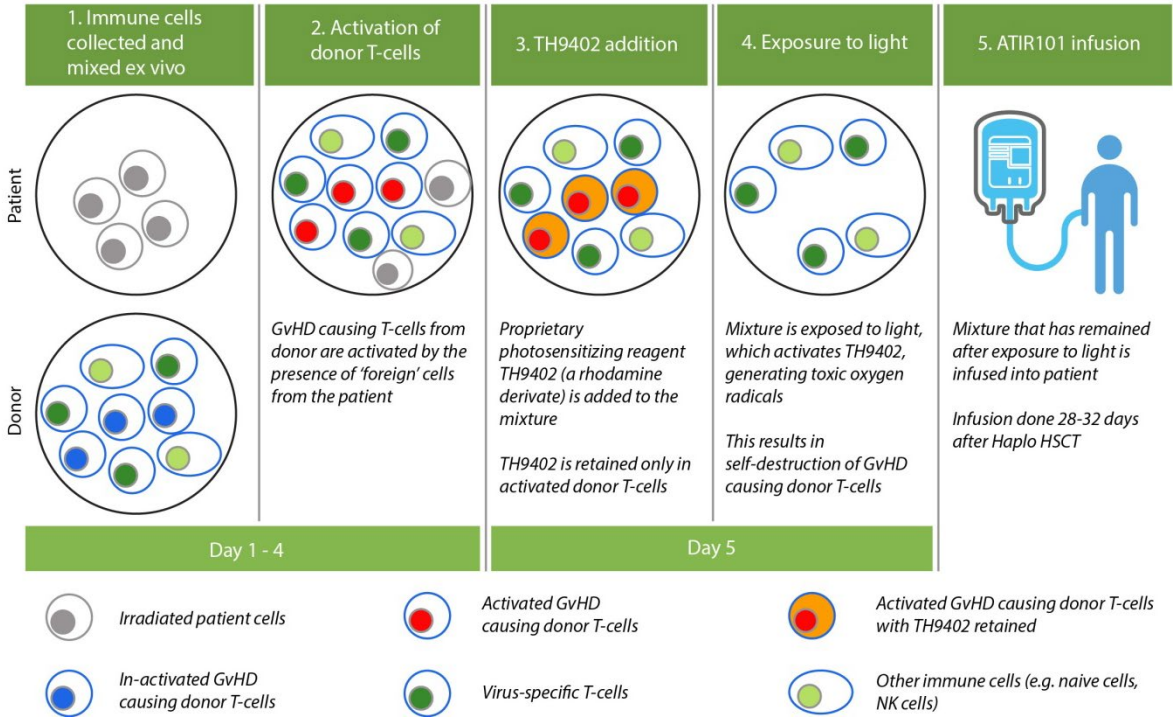


Figure 1 Schematic overview of the ATIR101 procedure

The selective depletion of host alloreactive T-cells in ATIR101 is shown schematically in Figure 1. During processing patient and donor cells are co-cultured in a mixed lymphocyte reaction (MLR) to stimulate activation of host alloreactive T-cells (the patient cells are gamma irradiated prior to the MLR). In the MLR, donor lymphocytes are activated against the major discordant major histocompatibility complex (MHC) antigens of the irradiated patient's cells. Those cells that are activated accumulate more light-sensitive TH9402 than non-activated cells and are consequently more susceptible to the effect of PDT.

2.2.2.1 Relevant Nonclinical Findings

TH9402 is a specifically designed derivative of rhodamine, a substance that is often used in cell biology to stain mitochondria in living cells because of its low toxicity and its specific attraction and retention in these organelles. Similarly, TH9402 binds to mitochondria. TH9402 absorbs light at a peak wavelength of 514 nm in the visible green spectrum and transfers the absorbed energy to oxygen, leading to the production of reactive oxygen species (mainly singlet oxygen) inside the cells. Subsequent oxidative reactions of these species with various biomolecules ultimately cause programmed cell death. TH9402 accumulates in cells with low P-glycoprotein (Pgp) pump activity such as activated lymphocytes. These target cells will accumulate significantly higher amounts of photosensitizer than resting cells and will be selectively depleted upon exposure to light.

The light exposure device used in the manufacturing of ATIR101 is custom designed to deliver light of a specific wavelength range that results in the photo activation of TH9402 molecules incorporated by cells. Special lamps with peak emission around 514 nm are positioned below the glass treatment surface of the device, delivering a tightly controlled light dose.

T-cells in ATIR101 can be characterized as being sufficiently depleted of recipient-reactive T-cells that might cause severe acute GVHD while having maintained the general ability to become activated by other stimuli, like infectious epitopes and malignant cells, and are therefore expected to be able to fight infections and disease relapse in the human body (Bastien *et al.* 2012; Guimond *et al.* 2002; Mielke *et al.* 2008).

In vitro assays have been developed to show that ATIR101 batches are indeed depleted of alloreactive cells while the remaining cells retain their reactivity to other stimuli. The various leukocyte subsets have been measured both in the original donor cells as well as in ATIR101. T-cells (CD3+), monocytes (CD14+), B-cells (CD19+), NK-cells (CD3- CD16/56+) are present in the original donor cells while ATIR101 is strongly enriched for T-cells (> 90%).

The proliferation of the cells in ATIR101 and the original donor cells after stimulation with recipient cells and third-party cells have been compared using the CFSE-dilution based proliferation assay. A selective depletion of recipient-reactive cells is observed, while reactivity to third party cells is retained. Thus, alloreactive T-cells have been largely eliminated from ATIR101 with preservation of T-cell response to other antigenic stimuli.

To better characterize the capacity of ATIR101 to fight infections, virus specific CD8+ cells against EBV and CMV were measured using a variety of HLA-multimers both in ATIR101 and in original donor cells. Anti-viral T-cells are largely preserved in ATIR101.

In a proof of concept study in a mouse stem cell transplantation model, PDT using TH9402 *ex vivo* successfully eliminated foreign HLA-specific cytotoxic T-cells but did not eliminate resting anti-leukemia and anti-third-party T-lymphocytes. In particular, without a donor lymphocyte infusion (DLI), stem cell transplanted and BCL1 leukemia inoculated mice developed leukemia with 50% mortality at 100 days. Infusion of untreated DLIs prevented relapse, but resulted in 100% mortality due to GVHD. However, upon infusion of DLIs that

were depleted of host-alloreactive T-cells (by PDT/TH9402), 90% of mice survived > 100 days without BCL1 tumors and GVHD. These data show that PDT/TH9402 treatment of donor lymphocytes prevents GVHD, while preserving third-party immune response and GVL effects (Chen *et al.* 2002).

2.2.2.2 Relevant Clinical Research

Dose Ranging Study (CR-GVH-001)

This was an open-label, single-arm, non-randomized, single-center study conducted in 19 patients with severe hematological malignancies undergoing haploidentical peripheral blood stem cell transplantation with CD34+ cell selection and subsequent infusion of T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (ATIR101). Adult patients with severe hematologic malignancies, who do not have the possibility of receiving an allogeneic transplant from a human leukocyte antigen (HLA) matched sibling donor were eligible to participate in this study.

Cohorts of patients received an increasing dose of ATIR101 with the primary objective to determine the maximum tolerated dose (MTD) using the incidence of grade III-IV acute GVHD within 30 days after infusion as dose limiting toxicity (DLT). Secondary objectives were to evaluate the immune reconstitution following ATIR101 and its effect on the incidence and severity of infections and relapse.

The haploidentical donor was mobilized with G-CSF and the peripheral blood stem cells (PBSCs) were collected and placed on a CD34 selection column to prepare the graft consisting of approximately 10×10^6 CD34+ cells/kg with a maximum of 3×10^4 CD3+ cells/kg. Patients were subject to a myeloablative conditioning regimen comprised of total body irradiation (TBI), thiotepa, rabbit ATG, fludarabine and methylprednisolone before transplantation. ATIR101 was infused IV 35 ± 7 days post transplant, once engraftment had been established. Seven dose levels of ATIR101 T-cells were tested in this study using the classic 3+3 design.

Patients have been followed up for 5 years after ATIR101 infusion. The primary safety parameter of this study was the occurrence of GVHD. No patients developed grade III/IV acute GVHD. Therefore, the MTD, which was defined as the dose of T-cells at which DLT toxicity (acute GVHD grade III/IV within 30 days) occurs in 33% of the patients following ATIR101 infusion, has not been reached in this study with doses up to 5.0×10^6 viable T-cells/kg body weight.

The data of study CR-GVH-001 indicate that with the use of ATIR101, a high dose of T-cells can be infused safely to patients with hematologic malignancies following a (mismatched) haploidentical stem cell transplantation. The use of ATIR101 allowed early immune reconstitution while preventing grade III/IV acute GVHD. To boost immune reconstitution the goal is to administer the highest possible dose without the occurrence of grade III/IV acute GVHD. Since in dose cohort L7 (5.0×10^6 T-cells/kg) all patients developed GVHD, which required (extensive) immunosuppressive treatment, and the infection rate was

markedly higher compared to dose cohort L6 (2.0×10^6 T-cells/kg), the optimal dose of ATIR101 for further development was considered to be 2.0×10^6 T-cells/kg.

Phase II Study (CR-AIR-007)

This is an open-label, single-arm, non-randomized, multicenter study conducted in patients with hematological malignancies (AML, ALL, or MDS) undergoing haploidentical peripheral blood stem cell transplantation with CD34+ cell selection and subsequent single infusion of T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (ATIR101) (Roy and Mielke 2018).

Study CR-AIR-007 is completed and has achieved its objective of treating 23 patients with ATIR101. Patient age ranged from 21 to 64 years (median: 41 years). The majority of patients had AML (16 patients, 70%), and 7 patients (30%) had ALL. At the time of transplant, 15 patients were in first remission (CR1) and 8 patients were in second or subsequent remission phase. The Disease Risk Index (DRI) (Armand *et al.* 2014) was high in 57% of patients and intermediate in 43% of patients; the cytogenetic risk profile was intermediate for 39% and adverse for 61% of the patients. Patients received the graft most frequently from a sibling (39.1%) or child (39.1%) and less frequently from a parent (17.4%). Donors were generally 3/6 HLA matched (70%) or 4/6 HLA matched (26%).

Patients underwent myeloablative conditioning, consisting of a] TBI (1200 cGy: n=11) or b] melphalan (120 mg/m^2: n=12), along with thiotepa (10 mg/kg), fludarabine (30 mg/m^2 x 5d) and ATG (2.5 mg/kg x 4d). A CD34-selected stem cell graft from a haploidentical donor was given, containing a mean of 11×10^6 CD34+ cells/kg (range 4.7-24.4$\times10^6$) and 0.29×10^4 CD3+ cells/kg (range 0-1.8$\times10^4$). In addition, donor lymphocytes from the same donor were processed using PDT technology, creating a donor lymphocyte infusion depleted of alloreactive T-cells (ATIR101). ATIR101 was infused at a median of 28 days (range 28-73) post HSCT at a fixed dose of 2.0×10^6 CD3+ cells/kg, without use of any post-transplant GVHD prophylaxis.

At the end of the study, median follow-up of ATIR101-treated patients was 20 months post HSCT (range 3.6-24.4). All patients engrafted rapidly after transplantation, with neutrophil and platelet engraftment achieved at a median of 12 (range 8-34) and 11 (range 9-35) days, respectively. Overall, 10 patients (43.5%) died due to TRM and four patients (17.4%) due to disease relapse. At 2 years post HSCT, probabilities (based on Kaplan-Meier estimates) were 48% for TRM, 25% for RRM, and 39% for OS.

Within the first 12 months post HSCT, no acute GVHD grade III/IV occurred, while four grade II cases and three grade I cases were observed. Interestingly, these cases all had late onset (> 100 days post HSCT) except for two patients showing acute GVHD grade I and II, respectively, before ATIR101 infusion, thereby delaying the infusion until resolution of GVHD. Between 1 and 2 years after HSCT, GVHD grade III-IV was reported for three patients and severe chronic GVHD for one patient. Of note, all patients who developed acute GVHD grade III or IV had received an unmanipulated donor lymphocyte infusion (DLI) shortly before GVHD onset. One patient with acute GVHD grade I following ATIR101 infusion progressed into severe chronic GVHD after > 12 months post HSCT.

In total, for four patients in the (M)ITT population disease relapse (or disease progression) was reported. Two patients relapsed early after HSCT (within 100 days) and two relapsed more than a year after HSCT. All four patients died due to RRM during the study.

Data from study CR-AIR-007 were compared with data from the observational, non-interventional cohort study CR-AIR-006. This study with 1-year follow-up included adult patients (18 to 65 years) with hematological malignancies (AML, ALL, both in complete remission, and MDS) who had received allogeneic TCD HSCT (CD34+ cell selection) from a haploidentical donor, or allogeneic HSCT from a fully matched or 1-locus mismatched unrelated donor (MUD/MMUD).

In comparison to patients receiving TCD HSCT without additional donor lymphocytes (external control group of study CR-AIR-006; no head-to-head comparison), infusion of ATIR101 led to a marked, statistically significant reduction of TRM and improvement in OS (Table 1). TRM for ATIR101 patients in study CR-AIR-007 was 13% at 6 months and 32% at 12 months, compared with 37% and 70% in patients treated with TCD HSCT only in study CR-AIR-006 (these patients had received a CD34-selected graft from a haploidentical donor following a similar preparative regimen for the same disease conditions at the same transplant centers but did not receive ATIR101 post transplant). The OS probability was 83% at 6 months and 61% at 12 months in ATIR101-treated patients, vs. 63% and 20% in the Haplo without ATIR101 group of study CR-AIR-006.

Table 1 Kaplan-Meier estimates of OS and TRM at 6 and 12 months after HSCT

	OS		**TRM**	
	6 months	**12 months**	**6 months**	**12 months**
CD34-Haplo-HSCT + ATIR101 *CR-AIR-007 (n=23)*	83%	61%	13%	32%
CD34-Haplo-HSCT (external control) *CR-AIR-006 (n=35)*	63%	20%	37%	70%
p-value of difference between survival curves	p=0.0029		p=0.0065	

The GVHD-free, relapse-free survival (GRFS) for HSCT + ATIR101 is estimated to be 57% at 1-year post HSCT, which compares favorably to the TCD HSCT only control group (20%), and also against patients undergoing a MUD transplantation (41%), derived from the same centers (Figure 2).

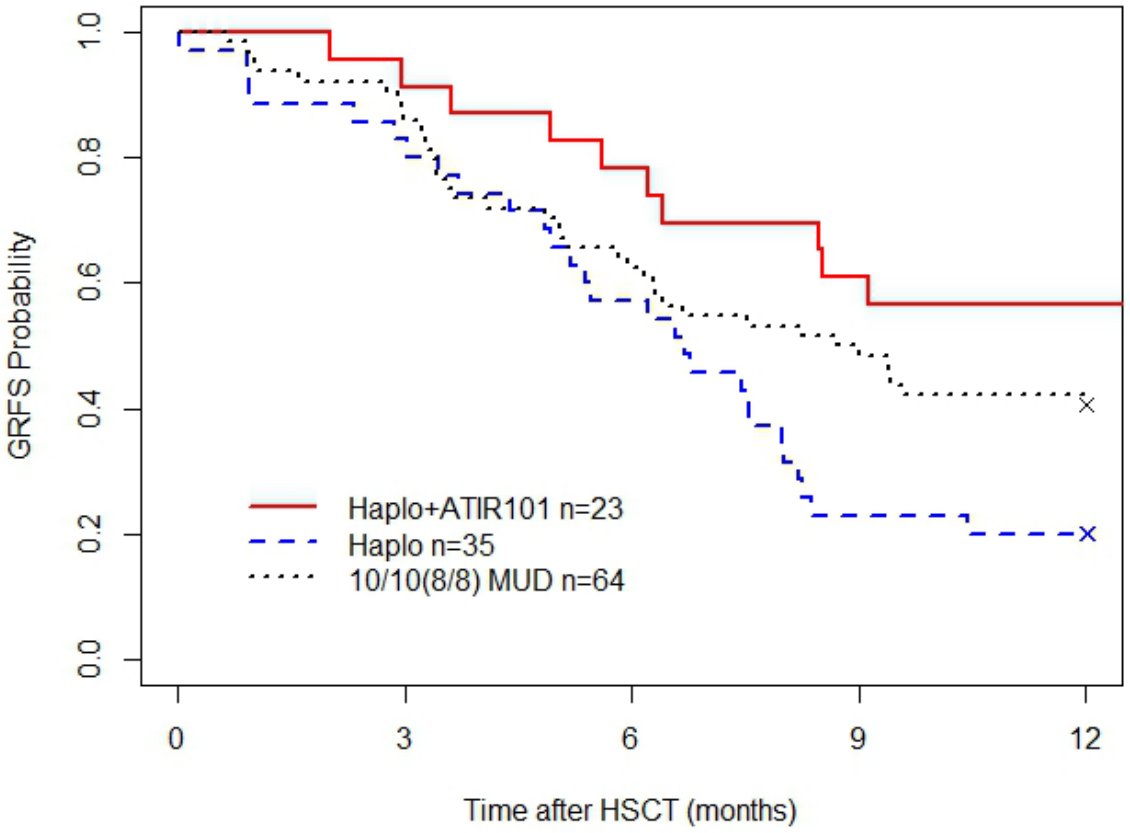


Figure 2 Survival curves of GRFS probability versus time after HSCT (data study CR-AIR-007 and external controls study CR-AIR-006)

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Potential adverse reactions of the study intervention ATIR101 are:

- Graft-versus-Host Disease
  Because ATIR101 contains mismatched donor lymphocytes and due to the possibility, that a small percentage of alloreactive T-cells could remain in ATIR101, a causal relationship between acute or chronic GVHD and ATIR101 administration cannot be ruled out. Data from previous ATIR101 studies show that GVHD serious adverse events probably, possibly, or certainly related to ATIR101 have been reported in nine patients. Therefore, acute and chronic GVHD are currently considered expected serious adverse reactions of ATIR101.
- CMV and EBV related reactions
  CMV and EBV related reactions and reactivations have been observed in previous ATIR101 studies. Due to the immune-compromised state of the patient CMV and EBV may be transmitted from donor to recipient during stem cell transplantation or can originate from a de novo infection after HSCT. A previous CMV/EBV infection resulting in latent presence of the virus in lymphocytes may lead to reactivation due to the

immune-compromised state of the patient after HSCT. Because ATIR101 contains donor lymphocytes, the causal relationship between CMV/EBV related adverse events (AEs) and ATIR101 administration cannot be ruled out if the donor is positive for CMV/EBV at screening.

- Post-transplant lymphoproliferative disease (PTLD)
  Because ATIR101 contains donor lymphocytes, the causal relationship between PTLD and ATIR101 administration cannot be ruled out if the donor is positive for EBV at screening. PTLD typically occurs with EBV infection. PTLD possibly related to ATIR101 according to the sponsor was reported in three patients in study CR-AIR-007.
- Hypersensitivity to any of the excipients (including DMSO)
  Potential adverse reactions after the infusion could include allergic or hypersensitivity reactions to some of the constituents of ATIR101 (e.g. the excipient DMSO): immediate fever or chills, skin rash, bronchospasm, or anaphylactic shock, and delayed serum-sickness-like reactions. Rash possibly related to ATIR101 has been reported in one patient in study CR-AIR-007.
- Autoimmune hemolytic anemia (AIHA)
  AIHA was reported in five patients (19.2%) in study CR-AIR-007 and one patient (5.9%) in study CR-AIR-008. Based on the available literature and data from these patients it was preliminarily concluded that the observed cases of AIHA are most likely related to the TCD HSCT that the patients underwent. In AIHA, donor lymphocytes are believed to produce autoantibodies against donor antigens, leading to hemolysis. Although a direct relationship between AIHA and ATIR101 infusion does not seem to be likely at the moment, it cannot be excluded.

The marketed drug cyclophosphamide, which is part of the control intervention, is associated with the following (very) commonly occurring adverse reactions (Baxter 2016):

System organ class	Preferred term	Frequency *
Infections and infestations	Infections	Common
Blood and lymphatic system disorders	Myelosuppression	Very common
	Haemolytic uraemic syndrome	Very common
Immune system disorders	Immunosuppression	Very common
Hepatobiliary disorders	Hepatic function abnormal	Common
Skin and subcutaneous tissue disorders	Alopecia	Very common
Renal and urinary disorders	Cystitis	Very common
	Microhematuria	Very common
	Haemorrhagic cystitis	Common
	Macrohematuria	Common
Reproductive system and breast disorders	Impairment of spermatogenesis	Common
General disorders and administration site conditions	Fever	Very common
	Asthenia	Common
	Mucosal inflammation	Common

* Very common: frequency ≥ 1/10; Common: frequency ≥ 1/100 and < 1/10

As with all cytotoxic therapy, treatment with cyclophosphamide involves the risk of secondary tumours and their precursors as late sequelae. The risk of urinary tract cancer as well as the risk of myelodysplastic alterations, partly progressing to acute leukemia, is

increased. Other malignancies reported after use of cyclophosphamide include lymphoma, thyroid cancer, and sarcomas. In some cases, the secondary malignancy developed several years after cyclophosphamide treatment had been discontinued.

Patients (in the ATIR101 group) and donors may experience adverse reactions from the apheresis procedure such as light-headedness/fainting due to temporary hypotension. tingling sensations around the mouth and fingers, and slight muscle cramps.

The most common risks for the donor are associated with G-CSF administered for stem cell collection: fatigue, nausea, flu-like muscle soreness, bone pain, thrombocytopenia, and high WBC count.

The most common risks for the patient are associated with the conditioning regimen, HSCT, and anti-viral and immunosuppressant regimen. These risks include infections, graft rejection, GVHD, disease relapse and adverse reactions to concomitant therapies (e.g., radiation therapy, chemotherapy, anti-viral drugs, and immunosuppressants in the PTCy group).

2.3.2 Known Potential Benefits

For the majority of patients with high-risk hematologic malignancy, an allogeneic HSCT remains the only curative option. The use of a matched (related or unrelated) donor from the donor registries is considered standard of care for patients who are eligible for an HSCT. However, a significant number of patients do not receive this treatment, because a suitable HLA-matched related or unrelated donor cannot be found in a timely manner or cannot be found at all. This protocol offers patients in need of an HSCT, who lack a suitable HLA-matched sibling or unrelated donor, the opportunity to receive a potentially life-saving treatment by the use of mismatched relatives, who are only partially HLA-matched to the patient, as stem cell donor (haploidentical donors).

2.3.3 Assessment of Potential Risks and Benefits

This protocol offers patients in need of an HSCT, who lack a suitable HLA-matched sibling or unrelated donor, the opportunity to receive a potentially life-saving treatment by the use of mismatched relatives, who are only partially HLA-matched to the patient, as stem cell donor (haploidentical donors). Patients will receive either a TCD HSCT followed by ATIR101 (study intervention) or a T-cell replete HSCT followed by a high dose of cyclophosphamide (control intervention).

A T-cell replete haploidentical HSCT followed by a high dose of cyclophosphamide is an upcoming widely used treatment if no HLA-matched donor is available in a timely manner. Although the conditioning regimen, the transplant, and required medications involve certain risks (see above), these are definitely outweighed by the benefit of survival rates comparable to those of matched donor transplants. However, treatment with cyclophosphamide involves the risk of occurrence of secondary tumors, specifically urinary tract tumors and acute leukemias, even several years after cyclophosphamide treatment has been discontinued.

A TCD HSCT followed by ATIR101 is an investigational treatment in patients without the availability of a matched donor in a timely manner. This treatment modality is associated with some known risks (see above). Interestingly, Phase II studies showed promising outcome rates with regard to overall survival, disease relapse and GVHD. Therefore, the clinical benefit of this treatment is expected to outweigh the risk for the patient.

Furthermore, all patients will contribute to increasing the knowledge on the efficacy and safety of a haploidentical HSCT and adjunctive ATIR101 treatment compared to the widely used T-cell replete HSCT followed by a high dose of cyclophosphamide (Baltimore protocol), which might be of benefit for future patients. In conclusion, the overall benefit/risk ratio for patients participating in the study is positive.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is to compare safety and efficacy of a haploidentical T-cell depleted HSCT and adjunctive treatment with ATIR101 versus a haploidentical T-cell replete HSCT with post-transplant administration of high dose cyclophosphamide (PTCy) in patients with a hematologic malignancy. An additional objective of the study is to compare the effect of the two treatments on quality of life.

Most of the study endpoints are times to event. Unless specified otherwise, summary statistics (cumulative incidences or proportion of patients free of the event of interest) will be presented for time to event endpoints at 3 months, 6 months, 12 months and 24 months. Some endpoints clearly capture the efficacy of ATIR101, some clearly capture the safety of ATIR101, and some provide a combined assessment of efficacy and safety.

3.2 Primary Endpoint

The primary endpoint of the study is GVHD-free, relapse-free survival (GRFS). GRFS is defined as time from randomization until grade III/IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, or death, whichever occurs first (Holtan *et al.* 2015). This endpoint captures both safety and efficacy.

Composite endpoints acknowledge that both survival and rates of other critical events are important when testing new therapies. Recently, the Blood and Marrow Transplant Clinical Trials Network recognized the potential utility of the novel composite endpoint of GRFS in trials of allogeneic HSCT. Each of the GRFS components (grade III/IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, and death) is clinically meaningful. GRFS therefore represents ideal recovery from HSCT and a measure of cure without ongoing morbidity. Using a cohort of 628 adult patients with hematological malignancies who underwent reduced intensity conditioning (RIC) and HSCT between 2006 and 2009 followed by GVHD prophylaxis with tacrolimus and methotrexate, data from the Center for International Blood and Marrow Transplant Research determined that the 1-year probability of GRFS was 23% (95% CI 20-26). Thus, only approximately one-quarter of adult patients transplanted for malignant disease survived without at least one of these major complications during the first 12 months after HSCT (Bolaños-Meade *et al.* 2015).

Data from a large, single center patient cohort was analyzed for GRFS among 531 consecutive adult recipients of allogeneic transplantation (Solh *et al.* 2016). They found that although 78% of patients are alive at 1 year post HSCT only 31% of transplant recipients survived 1 year without experiencing at least 1 GRFS event and only 24% survive it 2 years post-transplant without 1 GRFS event. These findings are in line with a recent report from the University of Minnesota that showed a 1-year survival rate of 63% and a 1-year GRFS rate of 31% (Holtan *et al.* 2015).

The Blood and Marrow Transplant Clinical Trials Network has incorporated this composite endpoint into new prospective trials of allogeneic HSCT. It is believed to better assess a successful transplant because it incorporates survival and freedom from relapse as well as the occurrence of clinically significant GVHD with its well-recognized effects on quality of life.

3.3 Secondary Endpoints

Overall survival (safety and efficacy)

Overall survival (OS) is defined as the time from randomization until death from any cause.

Progression-free survival (efficacy)

Progression-free survival (PFS) is defined as the time from randomization until relapse, disease progression, or death, whichever occurs first.

Relapse-related mortality (efficacy)

Relapse-related mortality (RRM) is defined as the time from randomization to death due to disease relapse or disease progression.

Transplant-related mortality (safety and efficacy)

Transplant-related mortality (TRM) is defined as the time from randomization to death due to causes other than disease relapse or disease progression.

3.4 Other Endpoints

Immune reconstitution (efficacy)

- Time to T-cell reconstitution, defined as the time to CD3+ > 0.2×10^9/l in peripheral blood (at two consecutive measurements; time to first measurement)

Incidence and severity of acute and chronic GVHD (safety)

Acute and chronic GVHD will be diagnosed, classified, and graded according to NIH criteria (see Section 8.1.5). The following endpoints are assessed:

- 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 viral, fungal, and bacterial infections (efficacy)

- Cumulative incidence of NCI CTCAE grade 2-5 and grade 3-5 infections

Incidence and severity of adverse events (safety)

- Cumulative incidence of NCI CTCAE grade 3-5 adverse events

Quality of life

- FACT-BMT, SF-36, MDASI, EQ-5D-5L total scores (change from screening)

4 STUDY DESIGN

4.1 Overall Design

Study CR-AIR-009 is a Phase III randomized controlled multicenter open-label study comparing two parallel groups. After signing informed consent, a total of about 250 patients will be randomized in a 1:1 fashion to receive either a TCD HSCT (CD34 selection) from a related, haploidentical donor, followed by ATIR101 infusion, or a T-cell replete HSCT, followed by a high dose of PTCy.

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 4/5 days after the HSCT. All patients will be followed up for at least 24 months post HSCT. Patient follow-up beyond 24 months post HSCT will be discontinued when a total number of 156 GRFS events has been reached.

4.2 Scientific Rationale for Study Design

The study is designed to confirm results obtained in Phase I-II clinical studies and to compare the outcomes of patients receiving ATIR101 post HSCT in a randomized setting to a control group of patients receiving a high dose of cyclophosphamide post HSCT, an upcoming treatment modality for patients in need of a haploidentical HSCT. The study aims at showing superiority in the ATIR101 group compared to the PTCy group.

4.3 Justification for Dose

In study CR-GVH-001 the optimal dose of ATIR101 for further development was considered to be 2.0×10^6 viable T-cells/kg. Data of studies CR-AIR-007 and CR-AIR-006 show significant improvement of TRM and OS after ATIR101 treatment at a dose of 2.0×10^6 viable T-cells/kg compared to patients who did not receive ATIR101.

The dose of cyclophosphamide of 50 mg/kg/day at 3 and 4/5 days after the HSCT is based on published data of the Baltimore protocol, which showed comparable outcomes of haploidentical HSCT followed by PTCy and matched (un)related donor transplants (Bashey *et al.* 2013; Burroughs *et al.* 2008),

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study and a total number of 156 GRFS events has been reached. After study completion, patients treated with ATIR101 who consented will be enrolled in the

observational patient registry CR-REG-001, involving passive follow-up until 5 years after the HSCT.

A donor is considered to be in the study up to and including collection of the stem cells for the HSCT.

The end of the study is defined as the date at which the last data point from the last patient is received globally.

5 STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Any of the following hematologic malignancies:
   - Acute myeloid leukemia (AML) in first cytomorphological remission (with < 5% blasts in the bone marrow) with Disease Risk Index (DRI) intermediate or above, or in second or higher cytomorphological remission (with < 5% blasts in the bone marrow)
   - Acute lymphoblastic leukemia (ALL) in first or higher remission (with < 5% blasts in the bone marrow)
   - Myelodysplastic syndrome (MDS): transfusion-dependent (requiring at least one transfusion per month), or intermediate or higher IPSS-R risk group)
2. Clinical justification of allogeneic stem cell transplantation where a suitable HLA matched sibling or unrelated donor is unavailable in a timely manner.
3. Availability of a related haploidentical donor with one fully shared haplotype and 2 to 4 mismatches at the HLA-A, -B, -C, and -DRB1 loci of the unshared haplotype, as determined by high resolution HLA-typing
4. Karnofsky Performance Status (KPS) ≥ 70%
5. Male or female, age ≥ 18 years and ≤ 70 years
   Patients aged ≥ 65 years must have a Sorror score ≤ 3
6. Patient weight ≥ 25 kg and ≤ 130 kg
7. Availability of a donor aged ≥ 16 years and ≤ 75 years who is eligible according to local requirements and regulations. Donors aged < 16 years are allowed if they are the only option for an HSCT, if they are permitted by local regulations, and if the IRB/IEC approves participation in the study.
8. For females of childbearing potential[27] who are sexually active and males who have sexual contact with a female of childbearing potential: willingness to use reliable methods of contraception (oral contraceptives, intrauterine device, hormone implants, contraceptive injection or abstinence) during study participation
9. Given written informed consent (patient and donor)

5.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Diagnosis of chronic myelomonocytic leukemia (CMML)
2. Availability of a suitable HLA-matched sibling or unrelated donor in a donor search
3. Prior allogeneic hematopoietic stem cell transplantation
4. Diffusing capacity for carbon monoxide (hemoglobin corrected DLCO) < 50% predicted
5. Left ventricular ejection fraction < 45% (evaluated by echocardiogram or MUGA scan)
6. AST and/or ALT > 2.5 × ULN (CTCAE grade 2)

[27] A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile.

7. Creatinine clearance < 50 ml/min (calculated or measured)
8. Positive pregnancy test or breastfeeding of patient or donor (women of childbearing age only)
9. Estimated probability of surviving less than 3 months
10. Known allergy to any of the components of ATIR101 (e.g., dimethyl sulfoxide)
11. Known hypersensitivity to cyclophosphamide or any of its metabolites
12. Any contraindication for GVHD prophylaxis with mycophenolate mofetil, cyclosporine A, or tacrolimus
13. Known presence of HLA antibodies against the non-shared donor haplotype
14. Positive viral test of the patient or donor for HIV-1, HIV-2, HBV[28], HCV[28], Treponema pallidum, HTLV-1 (if tested), HTLV-2 (if tested), WNV (if tested), or Zika virus (if tested)
15. Any other condition that, in the opinion of the investigator, makes the patient or donor ineligible for the study

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. This might include patients who have been randomized but for whom eligibility cannot be confirmed (see Section 6.3). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who do not meet the criteria for enrolment in this study (screen failure) may be rescreened. If rescreening is needed due to laboratory assessments, physical examination or other diagnostic assessments being out of protocol defined ranges, the out of protocol assessment(s) may be repeated once within four weeks of initial screening. If rescreening indicates that the participant is still not eligible, the patient cannot continue. A total rescreening needs to be done if more than four weeks have passed since the initial screening. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

Patients will be approached for participation in the study after the decision to proceed with a transplantation has been made and if no suitable matched related or unrelated donor is available in due time following a donor search and a suitable haploidentical donor has been

[28] HBV/HCV: Only patients with active infection or infection history and donors with active infection are excluded.

identified. A transplant physician will verify patient eligibility criteria for enrolment in the study and ineligible patients will proceed off study without further follow-up. Patient recruitment will not exclude women and members of minority groups in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Vulnerable participants such as pregnant women and children will not be enrolled in the study.

The required sample size is 250 patients, and 156 events are required for the final analysis of the primary endpoint considering two specific types of study withdrawal, i.e. patients not reaching HSCT and patients for whom ATIR101 could not be produced. The sample size calculation additionally assumes that 10% of patients will be lost to follow-up at 1 year post HSCT in each treatment group.

In this multinational study approximately 50 transplant centers are anticipated to participate. The screening target is four to six patients per transplant center. The accrual duration forecast is 30 months and the estimated time to get a sufficient number of events for final analysis of the primary endpoint is 38 months.

6 STUDY INTERVENTION

6.1 Study Interventions Administration

6.1.1 Study Intervention Description

Patients in the ATIR101 group will receive a single ATIR101 dose, which is an ATMP manufactured on an individual basis. For ATIR101 manufacturing donor and patient peripheral blood mononuclear cells (PBMCs) as well as donor plasma are collected by apheresis on the same day according to the procedure described in the Product Handling & Shipping Manual as well as Kiadis Pharma-defined specifications for cell content. For the patient this apheresis is done in advance of the conditioning regimen for the HSCT (see Section 8.1.1) and for the donor this additional apheresis is done in general 0.5-3 weeks before the apheresis for the stem cell graft. Donation, collection and testing of human tissues and cells will be done in compliance with relevant local regulations (e.g., Directive 2004/23/EC). The apheresis materials will be prepared for temperature-controlled shipment and shipped to the manufacturing facility according to the procedure that is described in the Product Handling & Shipping Manual. ATIR101 will be manufactured by a contract manufacturing organization under responsibility of Kiadis Pharma.

For each patient batch, one 20-ml unit (bag) of ATIR101 will be prepared containing 2.0×10^6 viable T-cells/kg, and if sufficient cells are available at the time of formulation, an additional unit (rescue dose) will be prepared containing at least 1.0×10^6 viable T-cells/kg. Each batch of ATIR101, manufactured for the individual patient, will be tested on key quality attributes, of which depletion of alloreactivity while preserving third party reactivity is crucial. The units are frozen and stored. After formal release, the frozen ATIR101 unit will be shipped to the clinical site just before ATIR101 infusion is required.

Patients in the PTCy group will be given cyclophosphamide, which is a marketed drug supplied by the hospital pharmacy.

6.1.2 Dosing and Administration

Patients in the ATIR101 group will be infused IV with ATIR101 at a single dose of 2.0×10^6 viable T-cells/kg body weight between 28 and 32 days after the HSCT (or later if required by the patient's medical condition; see below). The actual dose of ATIR101 (number of viable T-cells) will be based on the patient's body weight at screening. When the patient's body weight at the time of ATIR101 administration differs from the patient's body weight at screening, the dose should not be adjusted.

In exceptional cases a second (rescue) dose of ATIR101 might be considered in the ATIR101 group, if available. See Section 6.5.1 for details.

ATIR101 will not be infused at the time of the planned infusion if:

- The patient is suffering from active GVHD (any grade), and/or
- The patient is receiving steroid-based immunosuppressive therapy (excluding topical steroids).

Once the symptoms of GVHD have been resolved and no steroid-based immunosuppression is used any more, the investigator can decide to infuse ATIR101 at the pre-specified dose. However, if there are clear signs of T-cell reconstitution (CD3+ > 0.05×10^9 cells/l) at the time of the delayed administration, ATIR101 should not be administered without consent of the sponsor.

In the event the patient fails to demonstrate hematologic engraftment (see Section 8.2.11), bone marrow aspirate or biopsy might be performed and on a case by case basis it will be decided whether to infuse ATIR101 or not, after discussion between one of the coordinating investigators, Kiadis Pharma, and the investigator of the respective site.

If the ATIR101 infusion is delayed or a rescue dose is given, extra visits should be performed to achieve at least a weekly patient follow-up for six weeks after ATIR101 infusion. The extra visits will be recorded as unscheduled visits in the eCRF. At these visits the same assessments as after a Week 4 ATIR101 infusion will be performed.

Patients in the PTCy group will be given cyclophosphamide 50 mg/kg/day IV for 2 days on Day +3 and Day +4/+5. Prior to administration of cyclophosphamide, patients must receive appropriate hydration and mesna according to institutional standards.

6.2 Preparation/ Handling/ Storage/ Accountability

6.2.1 Acquisition and Accountability

ATIR101 will be shipped frozen to the clinical sites in a dry shipper saturated with liquid nitrogen guaranteeing a temperature < -135 °C for at least 7 days. ATIR101 will remain stored in the dry shipper until infusion. If infusion will not be done within the maximum storage time of the dry shipper (approx. 7 days), the product can either be shipped back to the manufacturing facility or stored locally (details are given in the Product Handling & Shipping Manual).

Drug accountability of ATIR101 will be documented at the study centers. In accordance with international guidelines, both Kiadis Pharma and the manufacturing facilities will maintain records of all ATIR101 products dispensed worldwide. After the completion of the study, the manufacturing facilities will take a full account of the product and provide it to Kiadis Pharma. All waste materials that have been used for the preparation and/or administration of ATIR101 at the manufacturing facility and at the study site will be destroyed according to local regulations on an ongoing basis.

Traceability of ATIR101

In this study traceability of ATIR101 is defined as the ability to locate and identify each individual unit of blood cells/plasma during any step from apheresis, through processing, testing and storage, to distribution of ATIR101 to the patient or disposal and vice versa. This also implies the ability to identify the donor, the ability to identify the patient at the study site and the ability to locate and identify all relevant data relating to products and materials coming into contact with those blood cells/plasma.

Traceability of patients and donors is ensured by documenting the identity of patients and donors including their donor/patient number at the study site. Both patient and donor identities are protected and are only identified by code numbers that can be linked at the study site to their full identity.

Traceability of blood cells/plasma from apheresis until distribution of ATIR101 is ensured by the procedures of the manufacturing facility. Traceability of ATIR101 at the study site is ensured by maintaining an accountability log.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The study intervention ATIR101 is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells using PDT with the photosensitizing reagent TH9402. ATIR101 is presented as a "dispersion for infusion". The cell suspension contains 2.5-13×10^6 viable T-cells/ml (for a patient weight range of 25-130 kg), 10% dimethylsulfoxide (DMSO), and 30% donor plasma in saline 0.9%. The total volume of a unit is 20 ml (dose 2.0×10^6 viable T-cells/kg) or in case of a rescue dose (see Section 6.5.1) 10-20 ml (dose 1.0-2.0×10^6 viable T-cells/kg). It is packed in a cryopreservation bag. Labels are designed according to local regulations.

Cyclophosphamide, which is part of the control intervention, is presented as a lyophilized powder for intravenous infusion, which is commercially available for human use under various brand names. It is supplied in vials for single dose use.

6.2.3 Product Storage and Stability

ATIR101 must be stored in liquid nitrogen (vapor phase) until infusion. The current shelf life is 18 months.

Unopened cyclophosphamide vials must be stored below 25°C (77°F). The reconstituted solution for administration must be used immediately.

6.2.4 Preparation

The frozen ATIR101 product should be thawed in approx. 2 minutes and the entire unit should be infused intravenously immediately (i.e. when last ice crystals are dissolved). In general, the time from the moment ATIR101 has been thawed (i.e. temperature 0°C/32°F without any ice crystals) until infusion of the entire unit (including rinsing the infusion bag with saline) should not take more than 20 minutes. Detailed instructions on the thawing and infusion process are provided in the ATIR101 Product Handling & Shipping Manual.

Cyclophosphamide must be reconstituted using 0.9% sodium chloride for injection or water for injection and can be further diluted according to the instructions of the manufacturer. Cyclophosphamide should be handled and disposed in a manner consistent with other cytotoxic drugs. To minimize the risk of dermal exposure, gloves must always be worn when handling vials containing cyclophosphamide.

6.3 Measures to Minimize Bias: Randomization and Blinding

Patients expected to comply with the inclusion and exclusion criteria as judged by the investigator will be randomized in a 1:1 fashion to either the ATIR101 group or the PTCy group. Before randomization each and every patient must sign informed consent and demographics, details of the hematologic malignancy, vital signs, and DRI will be recorded. Randomization will be performed by applying a stochastic minimization technique with a minimization probability parameter of 0.80 (Pocock and Simon 1975), to balance treatment groups with respect to underlying disease (AML, ALL, or MDS), DRI (intermediate risk, high risk, or very high risk) and center. Randomization will be carried out by using an interactive web response system (IWRS).

After randomization, patient eligibility will be confirmed by checking compliance with all inclusion and exclusion criteria. In case of non-compliance with one or more inclusion and exclusion criteria the patient will be regarded as a screening failure and will not be enrolled in the study. Based on experiences with previous ATIR101 studies it is anticipated that eligibility will be confirmed for almost all randomized patients.

6.4 Study Intervention Compliance

Administration of ATIR101 and cyclophosphamide will be performed and documented by study site personnel.

6.5 Concomitant Therapy

All concomitant prescription medications used during the study, in addition to the study intervention (ATIR101) or control intervention, will be considered concomitant. The following concomitant medications should be recorded in the electronic case report form (eCRF):

- Medication for the treatment of GVHD
- Medication for the treatment of infections [29]
- Prophylactic or preemptive use of anti-infective medication
- Medication for the treatment of disease relapse
- Medication for the treatment of other reported AEs
- Post-transplant prophylactic use of immunosuppressive medication
- Medication for prophylaxis against cyclophosphamide-induced hemorrhagic cystitis
- Additional hematopoietic stem cell grafts
- Additional lymphocyte infusions
- Hematopoietic growth factors
- Vaccinations
- Medication for the treatment of veno-occlusive disease

[29] Medication for the treatment of non-serious infections should only be recorded until Month 24.

Immunosuppressive Medication

Post-transplant prophylaxis against GVHD will not be permitted in the ATIR101 group unless discussed with and approved by the sponsor.

Post-transplant immunosuppressive therapy (e.g. corticosteroids) in the absence of GVHD should be avoided in the ATIR101 group unless medically indicated. The use of immunosuppressives shortly before infusion of ATIR101 or thereafter will inhibit the effects of ATIR101.

In addition to cyclophosphamide, patients in the PTCy group will receive immunosuppressive medications for GVHD prophylaxis (e.g. mycophenolate mofetil, cyclosporine A, tacrolimus) based on institutional guidelines.

G-CSF

Post-transplant G-CSF treatment should be avoided within a week prior to ATIR101 infusion, unless medically indicated. The use of post-transplant G-CSF after ATIR101 infusion will be at the discretion of the investigator after consultation of the sponsor.

Mesna and Hydration

Prior to administration of cyclophosphamide, patients must receive appropriate hydration and mesna according to institutional standards to prevent cyclophosphamide-induced hemorrhagic cystitis (see Section 6.1.2).

CMV

If the patient is cytomegalovirus (CMV) positive, it is strongly recommended to use a CMV positive donor. All patients (ATIR101 and PTCy group) will be subject to regular quantitative quantitative polymerase chain reaction (PCR) monitoring. If quantified viral DNA levels exceed the institutional threshold for treatment of CMV (as established for each study center), patients should be treated pre-emptively with ganciclovir or valganciclovir according to institutional guidelines.

ATIR101 group:

To prevent infections with CMV, patients in the ATIR101 group who are CMV positive or have a CMV positive donor must be given prophylactic treatment including ganciclovir and foscarnet. The following dosing schedule is recommended (Day 0 is the day of HSCT):

- From Day -9 through Day -2: ganciclovir 5 mg/kg IV q12h.
- From Day 4 through Day 20: foscarnet 90 mg/kg IV q24h.
- From Day 21 until Day 100: valganciclovir 900 mg PO daily 5 days a week, or ganciclovir 5 mg/kg IV q24h 5 days a week.
- Dosage is to be adjusted depending on renal function.

EBV

To prevent PTLD, all patients will be subject to regular quantitative PCR monitoring for Epstein-Barr virus (EBV) followed by adequate (pre-emptive) treatment if indicated. If quantified viral DNA levels exceed the institutional threshold for treatment of EBV (as established for each study center), patients should be treated with rituximab. It is also recommended to start rituximab if a patient who was EBV positive in the past, demonstrates enlarged lymph nodes, even if PCR for EBV is low or negative.

The following schedule is recommended:

- Immediately after the rise in EBV DNA is detected, rituximab (anti-CD20) 375 mg/m^2 IV is started once weekly, until PCR for EBV becomes negative.
- If PTLD is suspected on the basis of clinical symptoms, CT scans of thorax, abdomen and pelvis, as well as bone marrow aspiration and biopsy, and -when possible- lymph node extraction should be conducted. If results of the CT scan, bone marrow examinations, and lymph nodes demonstrate PTLD, rituximab is repeated weekly for at least 2 weeks.

Adenovirus

To prevent infections with adenovirus, patients will be subject to regular quantitative PCR monitoring followed by adequate treatment. If quantified viral DNA levels exceed the institutional threshold for treatment of adenovirus (as established for each study center), patients should be treated according to local institutional guidelines.

Toxoplasma

Patients with a positive serology test for toxoplasma gondii at screening or with a toxoplasma gondii positive donor will receive prophylaxis with trimethoprim-sulfamethoxazole (or alternatively atovaquone) per local institutional guidelines.

HSV and VZV

Patients tested positive for herpes simplex virus (HSV) or varicella zoster virus (VZV) at screening must receive prophylaxis with acyclovir or valacyclovir (in the absence of foscarnet) per local institutional guidelines for at least one year or until the CD4+ lymphocyte count has normalized.

Other viral, fungal and bacterial prophylaxis will be given according to local institutional guidelines.

Participation in Other Clinical Studies

Participation in another clinical study is to be discussed between the investigator and Kiadis Pharma.

6.5.1 Rescue Medicine

It is not recommended to treat patients with a non-manipulated DLI for any reason, as the risk of developing life-threatening GVHD is extremely high. If a DLI is indicated due to impending relapse or uncontrolled infection, a rescue dose of ATIR101 might be considered in the ATIR101 group, if available. The investigator can request Kiadis Pharma for shipment of an ATIR101 unit containing a rescue dose. This request should be supported by a clinical rationale for the infusion of a rescue dose.

GVHD is treated based on institutional standards. Limited GVHD of the skin should be treated locally only (steroid cream). Advanced stages and confirmed gut or liver GVHD require treatment according to institutional policy (e.g. IV steroids 0.5 mg/kg prednisolone, four times daily).

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

If a patient relapses before the HSCT, the patient is not necessarily discontinued from the study. The investigator may decide to keep the patient in the study without any follow-up visits until at a later stage, treatment with an HSCT followed by ATIR101 or PTCy may be beneficial. After re-assessment of patient eligibility, the study schedule may be resumed if deemed clinically relevant.

7.2 Participant Discontinuation/Withdrawal from the Study

The patient and donor are free to withdraw from participation in the study at any time upon request.

The investigator may terminate participation in the study for any of the following reasons:

- The patient relapsed before collection of PBMCs for the manufacturing of ATIR101 or before HSCT, and did not achieve remission upon additional chemotherapy,
- The ATIR101 batch is not suitable for patient administration,
- The stem cell graft is not suitable for patient administration,
- The patient is unwilling or unable to comply with study requirements,
- The patient is lost to follow-up, or
- Any other reason which, in the opinion of the investigator, justifies discontinuation of the patient from the study.

For any patient who is discontinued from the study, the reason must be recorded in the electronic case report form (eCRF) as end-of-active study follow-up information. Adverse events ongoing at study discontinuation will be followed up for outcome information until resolution or stabilization, if possible (see Section 8.3.4). Patients prematurely discontinued from the study will not be replaced.

When an eligible patient (see Section 6.3) is discontinued from active study follow-up after randomization, every effort will be made to collect data on disease status, GVHD, and mortality at 12, 24, and if applicable at 36 and 48 months after the HSCT (or in case of no HSCT, at 12, 24, and if applicable at 36 and 48 months after randomization).

If a patient is discontinued from the study after ATIR101 or PTCy infusion, every effort will be made to report SAEs until at least 3 months after ATIR101 or PTCy infusion.

7.3 Lost to Follow-Up

A patient will be considered lost to follow-up if he or she fails to return for two scheduled visits and cannot be contacted by the study site staff.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

8.1.1 Standard of Care Study Procedures

Eligible patients are randomized to either the ATIR101 group or the PTCy group. Patients in both groups will undergo a conditioning regimen followed by an HSCT as part of regular standard of clinical care. In this section the conditioning regimens and HSCT procedures are described.

For patients who weigh less than 125% of their ideal body weight (IBW), dosing of all drugs specified in this section should be based on actual body weight. For patients who weigh greater than or equal to 125% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). Calculation of IBW and AIBW is described in detail in Appendix 7.

Conditioning Regimens

All patients will undergo a conditioning regimen, either using a total body irradiation (TBI) regimen (Champlin *et al.* 2002) or a non-TBI based regimen. In order to balance the regimens between both treatment groups as much as possible, one of the following conditioning regimens must be used for both the ATIR101 group and the PTCy group (day numbers are relative to the day of HSCT). However, in the PTCy group, no thiotepa will be given in the TBI regimen. Both conditioning regimens for the PTCy group are in accordance with published data (Bacigalupo *et al.* 2015; Gaballa *et al.* 2016; Solomon *et al.* 2015). Minor scheduling deviations from these conditioning regimens are to be discussed between the investigator and Kiadis Pharma.

TBI REGIMEN

- Fractionated TBI 200 cGy twice daily for 3 days on Day -10 to -8 (1200 cGy in 6 fractions)
- Fludarabine 30 mg/m^2 IV once daily for 5 days on Day -7 to -3 (150 mg/m^2)
- **ATIR101 group only:** Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7 (10 mg/kg)

NON-TBI REGIMEN

- Fludarabine; 30 mg/m^2 IV once daily for 5 days on Day -8 to -4 (150 mg/m^2)
- Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7 (10 mg/kg)
- Melphalan; 60-70 mg/m^2 IV once daily for 2 days on Day -2 and -1 (120-140 mg/m^2) *

  * At the discretion of the investigator, melphalan can be given at 60 or 70 mg/m^2 depending on the patient's condition.

Hematopoietic Stem Cell Transplantation (HSCT)

Patients randomized to the ATIR101 group will receive a TCD graft from the donor, using the CD34+ cell selection method. Patients randomized to the PTCy group will receive a non-manipulated (full, T-cell replete) graft from the donor, either using bone marrow or peripheral blood stem cells (PBSCs)

ATIR101 Group

Patients randomized to the ATIR101 group will receive a TCD graft from the donor, using the CD34+ cell selection method. The collection and preparation of the donor stem cell graft is performed according to institutional procedures at the study center. The study centers will mobilize peripheral blood stem cells (PBSCs) from the donor with granulocyte colony-stimulating factor (G-CSF) administered subcutaneously at a dose of approx. 8 µg/kg twice daily for approx. 4 to 7 days. The PBSCs will be collected by apheresis. According to the Perugia protocol for haploidentical transplants, the CD34-selected stem cell graft is targeted to contain at least 5×10^6 CD34+ cells/kg but if possible $8\text{-}11\times10^6$ CD34+ cells/kg with a maximum of 3×10^4 CD3+ cells/kg as assessed by flow cytometry (Champlin *et al.* 2002). To ensure a consistently highly purified stem cell graft, clinical sites will use the CliniMACS® CD34 isolation system (Miltenyi Biotec) as part of their institutional procedures for preparing the stem cell graft. To achieve the target CD34+ cell dose, more than one stem cell graft may be given.

Prior to the transplant all patients in the ATIR101 group will be given rabbit anti-thymocyte globulin (ATG; Thymoglobulin®). The recommended dose of rabbit ATG is 2.5 mg/kg IV once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 4-8 hours (10 mg/kg total dose); during the course of ATG, patients will receive methylprednisolone 1-2 mg/kg/day IV. Scheduled deviations from this recommended ATG dosing schedule are to be discussed between the principal investigator and Kiadis Pharma.

PTCy Group

Patients randomized to the PTCy group will receive a non-manipulated (full) T-cell replete graft from the donor, either using bone marrow or PBSCs. The collection and preparation of the donor stem cell graft is performed according to institutional procedures at the study center. The study centers will mobilize PBSCs from the donor with granulocyte colony-stimulating factor (G-CSF) or will use bone marrow as source of stem cells, depending on the center's preference and experience. Donor bone marrow harvest will be done under anesthesia and the graft will not be manipulated, except for removal of red blood cells. The recommended target of mononuclear cells in bone marrow to be infused is 4×10^8 cells/kg body weight. The recommended target of PBSCs to be infused is 5×10^6 CD34+ cells/kg body weight. To achieve the target CD34+ cell dose, more than one stem cell graft may be given.

Viral Testing

Viral testing will be performed at the local laboratory, and if required by local regulations the tests will also be done on a separate blood sample at the manufacturing facility.

Blood of the patient and the donor will be tested for the presence of the following viruses (and other micro-organisms) in accordance with local regulatory requirements and regulations: EBV, CMV, HIV-1, HIV-2, HBV, HCV, Treponema pallidum, Toxoplasma gondii, herpes simplex virus (HSV), varicella zoster virus (VZV), HTLV-I (if applicable), HTLV-II (if applicable), WNV (if applicable), and Zika virus (if applicable). This viral testing must be done on samples obtained within one month before collection of PBMCs. If the patient is CMV positive, it is strongly recommended to use a CMV positive donor.

HLA Compatibility

Mismatches at the HLA-A, -B, -C, and -DRB1 loci (and if possible at the HLA–DQB1 locus) of the unshared haplotype will be assessed at the local laboratory by high resolution HLA-typing.

Blood Group

ABO and Rhesus blood group of patient and donor will be assessed at the local laboratory.

8.1.2 Disease Assessment

The status of the hematologic disease will be assessed regularly. Details of relapse or disease progression will be recorded on the Relapse/Disease Progression AE page of the eCRF.
A bone marrow biopsy must be performed at fixed visits unless relapse has already been confirmed (Screening, Month 3, Month 6, Month 12, and Month 24 post HSCT) and in case of suspected relapse. In case a bone marrow biopsy cannot be obtained, it may be replaced by a bone marrow aspirate. If a bone marrow aspirate and/or biopsy had already been obtained within 2 weeks prior to signing informed consent (or start of re-screening) or 6 weeks prior to a scheduled visit (from Month 3 onwards), the assessment does not need to be repeated.

In addition, in case of suspected relapse post HSCT, chimerism will be assessed to support the diagnosis.

A test for the presence of minimal residual disease (MRD) can be done locally at the study center as per institutional standards and the results will be recorded in the eCRF.

8.1.3 Infection Assessment

In this study an infection is defined as a clinically apparent infectious disease with symptoms or detectable viral reactivation, especially of CMV, EBV, or adenovirus. Details of all infections will be recorded on the Infection AE page of the eCRF, including type of infection, infection site, start date, stop date, NCI CTCAE severity grade (see Section 8.3.3), outcome, and action taken. Whenever an infectious episode is suspected, appropriate diagnostic measures need to be taken, including blood cultures to allow assessment of the specific pathogen causing the infection.

8.1.4 CMV/EBV/Adenovirus Monitoring

Patients will be monitored for CMV, EBV, and adenovirus, using PCR assays at the local laboratory.

CMV

Weekly CMV monitoring by quantitative PCR will be performed until Week 10 after the HSCT, monthly until Month 6, every 2 months until Month 12, and every 3 months until Month 24. More frequent monitoring for CMV is recommended depending on the patient's CMV status at baseline and the investigator's judgment, according to local, institutional guidelines.

Guidelines for prophylactic medications and treatments against CMV are provided in Section 6.5.

EBV

Weekly EBV monitoring by quantitative PCR will be performed until Week 10 after the HSCT, monthly until Month 6, every 2 months until Month 12, and every 3 months until Month 24. More frequent monitoring for EBV is recommended depending on the patient's EBV status at baseline and the investigator's judgment, according to local, institutional guidelines.

Guidelines for pre-emptive medications and treatments against EBV are provided in Section 6.5.

Adenovirus

Weekly adenovirus monitoring by quantitative PCR will be performed until Week 10 after the HSCT, monthly until Month 6, every 2 months until Month 12, and every 3 months until Month 24. More frequent monitoring for adenovirus is recommended depending on the patient's adenovirus status at baseline and the investigator's judgment, according to local, institutional guidelines.

8.1.5 Graft-Versus-Host Disease Assessment

GVHD events will be diagnosed and classified based on the NIH criteria (Filipovich *et al.* 2005) as summarized in Table 2.

Table 2 Categories of acute and chronic GVHD

Category	Time of symptoms after HSCT or DLI	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Acute GVHD will be graded according to the Glucksberg scale (Harris *et al.* 2016) (see Appendix 6). Chronic GVHD will be graded according to NIH criteria (Filipovich *et al.* 2005; Jagasia *et al.* 2015) (see Appendix 6). Whenever deemed possible, tissue biopsies will be obtained to confirm the GVHD diagnosis and to assess its severity. However, acute and chronic GVHD remain clinical diagnoses, which are considered present when diagnosed and treated, even in the absence of biopsy confirmation.

Details of all GVHD events will be recorded on the GVHD AE page of the eCRF, including start date, stop date, NCI CTCAE severity grade (see Section 8.3.3), GVHD grade, outcome, and action taken. For chronic GVHD events it will also be recorded whether they require systemic immunosuppressive treatment. The start date of the GVHD event is defined as the date of initiation of GVHD treatment or the date of biopsy confirmation of GVHD, whichever is earlier. Resolution of the GVHD event is defined as complete response, i.e. resolution of all signs and symptoms according to the treating investigator. Early symptoms before diagnosis not treated as GVHD and flares after resolution of the GVHD event will be reported as separate AEs.

8.1.6 Mortality

If a patient dies, the following information must be recorded in the eCRF:

- Date of death
- Cause of death (specification)
- Investigator classification of cause of death into:
  - Disease relapse/progression

- Transplant-related mortality (TRM) defined as death due to causes other than disease relapse or disease progression

All death cases will be subject to independent adjudication (see Section 8.3.3).

8.1.7 Immunophenotyping

Immunophenotyping on peripheral blood samples by means of flow cytometry assessment of immune subsets at the local laboratory according to local practice should be done if the absolute lymphocyte count is higher than 0.1×10^9/l.

Immunophenotyping assessments are planned at screening, at 3, 4, 5, 6, 7, 8, 9, and 10 weeks after the HSCT, as well as at 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, and 24 months post HSCT (and if applicable every 6 months thereafter).

The following cell markers/cell marker combinations are to be measured:

- CD3+ identifying T-cells
- CD3+ CD8+ identifying cytotoxic T-cells
- CD3+ CD4+ identifying helper T-cells
- CD3- CD56+ identifying natural killer (NK)-cells
- CD19+ identifying B-cells

8.1.8 Peripheral Blood Sampling for Research Purposes

Sampling for GVHD Research Project

Patients treated with HSCT plus ATIR101, who develop acute GVHD (grade III-IV) or chronic GVHD requiring systemic immunosuppressive treatment within the first year after stem cell transplantation, will be asked to donate a peripheral blood sample at a volume of 35 ml for further research including genetic testing, focused solely on exploring the nature of the GVHD adverse event. Samples will be obtained only from patients, who gave their permission for an additional blood collection in case of GVHD. Participants who do not wish to donate peripheral blood samples for research purposes may still participate in the study.

The peripheral blood samples should preferably be collected before steroid treatment. The samples will be handled according to the provided laboratory manual and subsequently sent to the laboratory of the sponsor.

Sampling for General Immune Reconstitution

At selected study sites, peripheral blood samples for further research of immune reconstitution will be collected from a subgroup of patients who signed a separate informed consent. These blood samples will be collected at a volume of 35 ml at screening, 8 weeks post HSCT, as well as at 4, 6, 8, 10 and 12 months post HSCT. Additional samples, also at a volume of 35 ml, will be taken when any of those patients develops a viral infection NCI grade 3/4 (sample to be taken preferably before treatment starts or in case of disease

progression despite of treatment). Participants who do not wish to donate peripheral blood samples for research purposes may still participate in the study.

The samples will be handled according to the provided laboratory manual and subsequently sent to the laboratory of the sponsor where they will be used for ancillary assays of immune reconstitution and immune cell characterization.

8.1.9 Quality of Life

The Foundation for the Accreditation of Cellular Therapy – Bone Marrow Transplantation questionnaire (FACT-BMT, version 4), the Short Form 36-item health survey (SF-36, version 2), the MD Anderson Symptom Inventory (MDASI), and the EQ-5D-5L will be scored at Screening, Month 3, Month 6, Month 12, and Month 24 (and if applicable Month 36 and Month 48), provided that validated translations in local language are available.

8.2 Safety and Other Assessments

8.2.1 Demographics

Year of birth, gender, race[30], and ethnicity[30] of patient and donor will be recorded as well as the family relation between donor and patient.

8.2.2 Hematologic Malignancy

WHO classification (Arber *et al.* 2016) and FAB classification of the hematologic malignancy, cytogenetic and molecular abnormalities, date of first diagnosis, and presence of minimal residual disease (if assessed) will be recorded.

The DRI will be assessed according to Armand (Armand et al. 2014). See Appendix 2 for details.

The EBMT risk score will be assessed according to Gratwohl (Gratwohl 2012). See Appendix 3 for details.

All prior relapses and treatments of the hematologic malignancy will be recorded, including treatments that led to previous remissions if applicable.

8.2.3 Medical History

All existing medical conditions at the time of screening and other relevant medical history including information on previous other malignancies will be recorded.

Comorbidity will be assessed according to the items of the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (Sorror *et al.* 2005) (see Appendix 4).

[30] Unless recording of race and ethnicity is not allowed by local regulations.

8.2.4 Karnofsky Performance Status

Performance status will be assessed as a percentage (0-100%) according to the Karnofsky Performance Status (KPS) scale (Schag *et al.* 1984) (see Appendix 5).

8.2.5 Physical Examination

At least the following body systems will be examined: skin, ears/nose/throat (ENT), respiratory, cardiovascular, abdomen (including liver and spleen), and lymph nodes. All abnormal findings will be recorded.

8.2.6 CT Scan Thorax or Chest X-ray

A high-resolution CT scan of the thorax or a chest X-ray will be used to assess the presence of any generalized lung disease. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening).

8.2.7 Echocardiogram or MUGA Scan

An echocardiogram or MUGA scan will be used to assess the patient's cardiac function. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening).

8.2.8 Pulmonary Function Test

A pulmonary function test measuring the DLCO will be used to assess the functional status of the lungs. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening). The hemoglobin (Hb) corrected DLCO will be calculated with one of the following formulas (Macintyre *et al.* 2005) and can be compared with the DLCO predicted value:

$$Males\colon\ DLCO_{corrected\ for\ Hb} = \frac{DLCO_{measured}}{(1.7 \times Hb\ [g/dl]\ /\ (10.22 + Hb\ [g/dl])}$$

$$Females\colon\ DLCO_{corrected\ for\ Hb} = \frac{DLCO_{measured}}{(1.7 \times Hb\ [g/dl]\ /\ (9.38 + Hb\ [g/dl])}$$

8.2.9 Creatinine Clearance

To assess renal function creatinine clearance will be either calculated or measured:

- Calculation by using the Cockcroft-Gault formula (Cockcroft and Gault 1976)

$$Creatinine\ clearance\ [ml/min] = \frac{(140 - Age) \times Weight\ [kg] \times 0.85[if\ female]}{72\ \times Serum\ creatinine\ [mg/dl]}$$

- Measurement by collecting 24-hour urine

$$Creatinine\ clearance\ [ml/min] = \frac{Urine\ creatinine\ [mg/dl]\ \times Urine\ flow\ [ml/min]}{Serum\ creatinine\ [mg/dl]}$$

Serum creatinine and urine creatinine will be assessed at the local laboratory. These assessments may have been done within 2 weeks before signing informed consent (or start of re-screening).

8.2.10 Vital Signs

The following vital sign parameters will be measured for the patient at regular intervals: respiration rate or oxygen saturation, pulse rate, temperature, weight, height (at screening only), and supine blood pressure after 5 minutes of rest. In addition, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1 hour, and 2 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems after ATIR101 infusion.

Weight and height of donors for patients in the ATIR101 group will be recorded pre HSCT.

8.2.11 Engraftment

Neutrophil engraftment is defined as neutrophil count $\geq 0.5\times10^9$/l for 3 consecutive days and platelet recovery is defined as platelets $\geq 20\times10^9$/l for 3 consecutive days, without transfusion. The first days of occurrence of both criteria will be recorded.

Primary graft failure is defined as lack of initial engraftment of donor cells. The patient never recovers from neutropenia (neutrophil count $< 0.5\times10^9$/l), resulting in pancytopenia and an urgent need for re-transplantation. Secondary graft failure is defined as loss of donor cells after initial engraftment. In this case autologous recovery is common; however, marrow aplasia and pancytopenia may also develop.

8.2.12 Chimerism

A blood sample for assessment of chimerism will be collected at Week 4 (before ATIR101 infusion, if applicable), at Week 10, Month 3, Month 6, Month 12, Month 24, and in case of suspected relapse. Chimerism will be assessed in peripheral blood lymphocytes and polynuclear cells (neutrophils) by PCR amplification at the local laboratory.

8.2.13 Safety Laboratory Tests

Patients will be in a seated or supine position during blood collection. Safety laboratory tests will include hematology, blood chemistry, and urinalysis tests (see Table 3). Safety laboratory tests will be performed at the local laboratory.

Table 3 List of safety laboratory tests

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

8.2.14 Pregnancy Test

At screening, a pregnancy test (serum or urine β-HCG test) will be performed in female patients and donors unless they are diagnosed as postmenopausal or if surgically sterilized.

8.2.15 Auxiliary Scientific Studies

Patients in selected centers may be offered participation in auxiliary scientific studies based on approval by the local ethical committee and the sponsor such as special immune reconstitution studies and human artificial skin models for the prediction of residual GVHD. These studies are regarded separate studies and require independent informed consent from the patient.

8.2.16 Health Economics Data Collection

Data will be collected on the cost of medication and/or treatments given during the entire study period for health economics assessment of both transplant regimens used in this study.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AEs)

A pre-treatment AE is defined as any untoward medical occurrence in a clinical investigation patient who has participated in the pre-treatment period of the study but prior to administration of the investigational product.

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

8.3.2 Definition of Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalization or prolongation of existing inpatients' hospitalization;
  In this study, the following hospitalizations will not lead to reporting of an SAE:
  - Elective hospitalization for a pre-existing condition that has not worsened
  - Hospitalization for logistical reasons
  - Hospitalization for study procedures
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event that satisfies any of the following:
  - May require intervention to prevent the items listed before
  - Is likely to affect the safety of the patient, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

The severity grade of an AE provides a qualitative assessment of the extent or intensity of an AE, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure).

The severity grade should be recorded in the eCRF according to the grading below. Severity grades of specific AEs will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI *et al.* 2017).

1 = Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 = Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

3 = Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

4 = Grade 4: Life-threatening consequences; urgent intervention indicated.

5 = Grade 5: Death related to adverse event

8.3.3.2 Relationship to Study Intervention

All AEs will be examined to determine any relationship to ATIR101 or post-transplant cyclophosphamide using the WHO-UMC system for standardized case causality assessment. The assessment criteria are listed below:

Certain:

- An event or laboratory test abnormality, with plausible relationship to administration of the investigational product.
- The event cannot be explained by the disease or other drugs.
- Response to withdrawal is plausible (pharmacologically, pathologically).
- Event definitive pharmacological or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon).
- Re-challenge satisfactory, if needed.

Probable:

- An event or laboratory test abnormality, with reasonable time relationship to administration of the investigational product.
- Unlikely to be attributed to the disease or other drugs.
- Response to withdrawal clinically reasonable.
- Re-challenge not required.

Possible:

- An event or laboratory test abnormality, with reasonable time relationship to administration of the investigational product.
- Could also be explained by the disease or other drugs.
- Information on drug withdrawal may be lacking or unclear.

Unrelated/Unlikely:

- Event or laboratory test abnormality, with a time to administration of the investigational product that makes a relationship improbable (but not impossible).
- Disease or other drugs provide plausible explanations.

8.3.3.3 Expectedness

The Medical Monitor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the list of expected adverse reactions included in the Reference Safety Information section of the Investigator's Brochure.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

The time period for AE reporting starts when the ICF is signed. For the donor, all AEs will be reported until and including the collection of the stem cells. For the patient, infections (including viral activations) will be reported until two years after the HSCT. Relapse/disease progression, GVHD, AEs of special interest (Section 8.3.8), and SAEs (see Section 8.3.6) will be reported throughout the study. Other AEs including local and systemic reactions not meeting SAE criteria will be reported until 6 months after the HSCT.

Events will be followed for outcome information until resolution or stabilization. If required by local regulations, evaluation of donor AEs will be done by a sub-investigator (physician) who is independent from the investigator evaluating the patient.

8.3.5 Adverse Event Reporting

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a patient presenting for medical care, or upon review by a study monitor. All AEs, whether spontaneously reported by the patient, discovered during general questioning by the investigator, or detected through physical examination, laboratory test or other means will be recorded on the appropriate eCRF.

AEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, investigator's assessment of severity, relationship to study intervention, actions taken, and time of resolution/stabilization of the event. All AEs must be documented appropriately regardless of relationship.

Each event should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values and electrocardiogram [ECG] findings) or symptoms should not be recorded as additional AEs. However, if the diagnosis is unknown or uncertain, signs and symptoms must be recorded.

Within this study, GVHD (see Section 8.1) will be recorded separately from the other AEs in the eCRF.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE but as medical history. However, if the patient's medical condition deteriorates at any time during the study, it will be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3.6 Serious Adverse Event Reporting

All SAEs at any time during the study through the last follow-up visit required by the protocol must be reported by the investigator within 24 hours of knowledge of their occurrence to the sponsor or representative, independent of the circumstances or suspected cause. The report must be completed on the SAE report form in English and must include a relationship assessment. Information about every SAE will be collected and recorded on the SAE report form as well as simultaneously in the applicable eCRF pages, including at least data on screening, HSCT, ATIR101/PTCy infusion, AEs and concomitant medications.

The SAE report form should be sent by e-mail or fax to ProPharma Group (St. Paul MN, USA).

E-mail addresses:	**saereports@drugsafety.biz and saereporting@kiadis.com**
SAE fax number:	**+1 919-844-6948**
Backup fax number:	+1 919-882-8337

The original SAE report form, together with the fax confirmation sheet (if applicable), must be kept at the study site. If the initial report is made verbally or by telephone, a written confirmation via e-mail or fax must follow within 24 hours. The investigator will be requested to supply detailed information regarding the event at the time of the initial report.

Each SAE should be recorded as a single diagnosis on the SAE report form. Accompanying signs (including abnormal laboratory values and ECG findings) or symptoms should not be recorded as additional SAEs. However, if the diagnosis is unknown, signs and symptoms should be recorded. As soon as the diagnosis causing the signs and symptoms is known, the event terms will be adjusted to the final diagnosis.

For all SAEs occurring during the study, the investigator must submit follow-up reports to the sponsor or representative regarding the patient's subsequent course until the SAE has resolved, or until the condition stabilizes (in the case of persistent impairment), or the patient dies. In the event that a patient dies, an autopsy report (if available) must be forwarded to the sponsor or its representative. The timelines and procedure for follow-up reports are the same

as those for the initial report. The form and fax confirmation sheet must be retained by the site.

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting to the regulatory authorities by the sponsor or its representative. The sponsor will also prepare expedited reports for other safety issues that might materially alter the current benefit-risk assessment of the investigational product.

8.3.7 Reporting Events to Participants

Not applicable.

8.3.8 Events of Special Interest

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

- PTLD
- Infusion reactions
- AIHA
- Secondary malignancies
- Hemorrhagic cystitis
- Veno-occlusive disease

Events of special interest (serious or non-serious) must be reported throughout the study on the eCRF.

8.3.9 Reporting of Pregnancy

Pregnancies occurring during participation in the study after randomization, including pregnancies of partners of male patients, will be reported as an AE and will be followed up. The competent authority and IEC/IRB will be informed on these pregnancies.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

Unanticipated problems (UPs) involving risks to participants are defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IEC/IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

In general, an AE observed during the conduct of a study should be considered an unanticipated problem (UP) involving risk to human subjects, and reported to the involved IECs/IRBs, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The UP report to be sent to the IEC/IRB will include the following information:

- Protocol identifying information: protocol title and number, name principal investigator, and the IEC/IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

Changes in the conduct of the study as a result of an UP, will be submitted for approval to the competent authority as a substantial amendment.

8.4.3 Reporting Unanticipated Problems to Participants

If applicable, the investigator will inform participants about UPs that may be relevant to the patient's consent or may influence the patient's willingness to continue participation in the study.

8.5 Study Visits

A schedule of activities by study visit in tabular form is displayed in Section 1.3.

8.5.1 Screening (between Informed Consent & Confirmation Eligibility)

- Informed consent patient/donor
- Patient eligibility
- Randomization
- Demographics patient/donor
- Hematologic malignancy; including WHO/FAB classification, cytogenetic and molecular abnormalities, DRI, EBMT risk score, date of first diagnosis, and prior treatments/ relapses

- Medical history; including comorbidity (HCT-CI)
- KPS
- Physical examination
- CT scan thorax or chest X-ray; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Echocardiogram or MUGA scan; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Pulmonary function test; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Creatinine clearance; calculated or measured, if not already done within 2 weeks before signing informed consent (or start of re-screening)
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, height, and supine blood pressure after 5 minutes of rest
- Quality of life; FACT-BMT, SF-36, MDASI, and EQ-5D-5L (if available in local language)
- Disease assessment; including bone marrow biopsy or aspirate if not already obtained within 2 weeks before signing informed consent (or start of re-screening)
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Hematology/biochemistry
- Urinalysis
- Pregnancy test patient/donor (if applicable)
- Viral testing patient/donor; EBV, CMV, HIV-1, HIV-2, HBV, HCV, Treponema pallidum, adenovirus, Toxoplasma gondii, HSV, VZV, HTLV-I (if applicable), HTLV-II (if applicable), WNV (if applicable), or Zika virus (if applicable). This viral testing must be done on samples obtained within one month before collection of PBMCs.
- HLA compatibility; mismatches at the HLA-A, -B, -C, and -DRB1 loci (and if possible at the HLA–DQB1 locus) of the unshared haplotype
- Immunophenotyping if the absolute lymphocyte count > 0.1×10^9/l
- At selected sites and patients: peripheral blood sampling for research purposes
- Patient AEs (other)
- Donor AEs
- Concomitant medications

8.5.2 Pre-HSCT (between Confirmation Eligibility & HSCT)

- Apheresis patient and donor PBMCs for ATIR101 manufacturing including measurement of patient weight (ATIR101 group only)
- Collection of donor stem cell graft (PBSCs or bone marrow)
- Conditioning regimen
- Infection assessment
- Patient AEs (other)
- Donor AEs; up to and including the collection of stem cells
- Concomitant medications

8.5.3 HSCT (Day 0)

- HSCT; either TCD CD34-selected (ATIR101 group) or T-cell replete (PTCy group)
- Physical examination
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Hematology/biochemistry
- Patient AEs (other)
- Concomitant medications

8.5.4 Week 1, 2, 3

Visits must be performed within the following windows:

- 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

Activities:

- Cyclophosphamide infusion; on Day +3 and Day +4/+5 (PTCy group only)
- Physical examination
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Engraftment
- Chimerism; only in case of suspected relapse
- GVHD assessment
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l; only at Week 3
- Hematology/biochemistry
- Patient AEs (other)
- Concomitant medications

8.5.5 Week 4

The visit must be performed within 28-32 days after the HSCT.

Activities:

- ATIR101 infusion (ATIR101 group only), unless the patient's medical condition requires that ATIR101 is infused later, e.g. because the patient is suffering from acute GVHD.
- Physical examination
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest (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.
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Engraftment (in ATIR101 group before infusion of ATIR101)
- Chimerism (in ATIR101 group before infusion of ATIR101)
- GVHD assessment
- Hematology/biochemistry
- Urinalysis
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l (in ATIR101 group before infusion of ATIR101)
- Patient AEs (other)
- Concomitant medications

8.5.6 Week 5, 6, 7, 8, 9, 10

Visits must be performed within the following windows:

- Week 5: 5 weeks ± 3 days after the HSCT
- Week 6: 6 weeks ± 3 days after the HSCT
- Week 7: 7 weeks ± 3 days after the HSCT
- Week 8: 8 weeks ± 3 days after the HSCT
- Week 9: 9 weeks ± 3 days after the HSCT
- Week 10: 10 weeks ± 3 days after the HSCT

Activities:

- Physical examination; only at Week 6, Week 8, and Week 10
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)

- Engraftment; in case of no neutrophil or platelet engraftment at Week 4, measurements are to be continued at weekly visits until engraftment
- Chimerism; only at Week 10 and in case of suspected relapse
- GVHD assessment
- Hematology/biochemistry
- Urinalysis; only at Week 8
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l
- At selected sites and patients: peripheral blood sampling for research purposes; only at Week 8; additional sampling when a pre-specified GVHD event occurs in ATIR101-treated patients (see Section 8.1.8).
- Patient AEs (other)
- Concomitant medications

8.5.7 Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24

Visits must be performed within the following windows:

- Month 3 after HSCT: 12 weeks ± 1 week after the HSCT
- Month 4 after HSCT: 16 weeks ± 1 week after the HSCT
- Month 5 after HSCT: 5 months ± 1 week after the HSCT
- Month 6 after HSCT: 6 months ± 1 week after the HSCT
- Month 8 after HSCT: 8 months ± 2 weeks after the HSCT
- Month 10 after HSCT: 10 months ± 2 weeks after the HSCT
- Month 12 after HSCT: 12 months ± 2 weeks after the HSCT
- Month 15 after HSCT: 15 months ± 2 weeks after the HSCT
- Month 18 after HSCT: 18 months ± 2 weeks after the HSCT
- Month 21 after HSCT: 21 months ± 2 weeks after the HSCT
- Month 24 after HSCT: 24 months ± 2 weeks after the HSCT

<u>Activities:</u>

- Physical examination; only at Month 3 and Month 4
- Vital signs; only at Month 3 and Month 4; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Quality of life; FACT-BMT, SF-36, MDASI, and EQ-5D-5L (if available in local language); only at Month 3, Month 6, Month 12, and Month 24;
- Disease assessment (at all visits);
  Including bone marrow biopsy; only at Month 3, Month 6, Month 12, and Month 24, and in case of suspected relapse
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Chimerism; only at Month 3, Month 6, Month 12, Month 24, and in case of suspected relapse
- GVHD assessment
- Hematology/biochemistry

- Urinalysis; only at Month 3 and Month 4
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l
- At selected sites and patients: peripheral blood sampling for research purposes; only at Month 4, Month 6, Month 8, Month 10, and Month 12; additional sampling when a pre-specified GVHD event occurs in ATIR101-treated patients (see Section 8.1.8).
- Patient AEs (other); 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 the study.
- Concomitant medications

8.5.8 Follow-up Beyond Month 24: Every 6 Months

Visits must be performed within the following windows until a total number of 156 GRFS events has been reached:

- Month 30 after HSCT: 30 months ± 4 weeks after the HSCT
- Month 36 after HSCT: 36 months ± 4 weeks after the HSCT
- Month 42 after HSCT: 42 months ± 4 weeks after the HSCT
- Month 48 after HSCT: 48 months ± 4 weeks after the HSCT
- Etc.

Activities:

- Quality of life; FACT-BMT, SF-36, MDASI, and EQ-5D-5L (if available in local language); only at Month 36 and Month 48
- Disease assessment;
  Including bone marrow biopsy in case of suspected relapse
- GVHD assessment
- Hematology/biochemistry
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l
- Patient SAEs and AEs of special interest (Section 8.3.8) are to be recorded as AEs throughout the study.
- Concomitant medications (excluding medications for the treatment of non-serious infections)

When a total number of 156 GRFS events has been reached, the remaining patients who are in follow-up beyond Month 24 will be contacted by telephone for the following end-of-study assessments:

- Disease assessment
- GVHD assessment
- Patient SAEs and AEs of special interest
- Concomitant medications

9 STATISTICAL CONSIDERATIONS

The planned analyses are summarized below. Any deviations from these analyses will be justified in the clinical study report. Details of the planned analyses will be described in the statistical analysis plan (SAP).

9.1 Statistical Hypotheses

For the primary endpoint GRFS, interest focuses on whether the hazard rate in the ATIR101 group significantly differs from that in the PTCy group. Hence the null and alternative hypotheses are:

H_0 Hazard ratio ATIR101/PTCy = 1

H_1 Hazard ratio ATIR101/PTCy ≠ 1

9.2 Sample Size Determination

For the primary endpoint, GRFS, data from previous trials suggest that the 12-month GRFS will be equal to 52.2% in the ATIR101 group versus 36% in the control group (a hazard ratio equal to 0.636). These 12-month GRFS rates allow for two specific types of study withdrawal, i.e. patients not reaching HSCT and patients in whom ATIR101 could not be produced. The sample size calculation additionally assumes that 10% of patients will be lost to follow-up at 1 year in each treatment group. A power of 0.8 will be required for this magnitude of treatment effect, and a two-tailed significance level equal to 0.05. An interim analysis will be performed at two-thirds information time, using a spending function close to an O'Brien-Fleming type boundary.

Based on these assumptions, the sample size required is 250 patients, and 156 events are required for the final analysis of GRFS to take place. If the 12-month GRFS rates are close to the assumed values, the interim analysis should take place towards the end of the accrual period, and the final analysis about 8 months later. The overall 12-month GRFS rate will be monitored for both treatment arms combined. If the overall 12-month GRFS rate is substantially lower than anticipated, the sponsor may decide to increase the sample size by maximum 20% (i.e. to 300 patients) so that the timing of the interim and final analysis is not unduly postponed. The percentage of the two types of study withdrawal described in the paragraph above will also be monitored. If the percentage of protocol deviations is substantially larger than anticipated, the Sponsor may decide to increase the sample size by maximum 20% (i.e. to 300 patients) so that the power of the study is protected.

9.3 Populations for Analyses

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

Intention-to-treat (ITT) population

The ITT population consists of all randomized patients. The ITT population is the primary efficacy dataset for the primary and secondary endpoints.

Modified intention-to-treat (MITT) population

The MITT 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).

Per protocol (PP) population

Prior to locking the database, the sponsor will define a PP population as a subset of the MITT population of patients without major protocol deviations. The PP population will be used to (1) shed light on potential reasons why the primary analysis of the ITT population may have failed to reach significance, or (2) investigate how major protocol deviations may have had an impact on the magnitude of the treatment benefit. 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.

Safety population

The safety population consists of all patients who received an HSCT.

9.4 Statistical Analyses

9.4.1 General Approach

For time to event endpoints, standard statistical methods will be used, including Kaplan-Meier curves, the logrank test and the Cox proportional hazards model. The assumption of proportional hazards will be tested. All analyses will be stratified by underlying disease and Disease Risk Index (DRI).

For binary endpoints, treatment groups will be compared through the Cochran-Mantel-Haenszel test, stratified by underlying disease and DRI. The impact of prognostic factors upon these endpoints will be assessed through logistic regression models.

Unless specified otherwise, descriptive statistics (cumulative incidences or proportion of patients free of the event of interest) will be presented for time to event endpoints at 3 months, 6 months, 12 months, and yearly thereafter. The 95% confidence intervals will be calculated for the treatment contrast.

The following missing data handling strategies for primary efficacy endpoint and secondary endpoints will be used:

- There will be no imputation of missing values.

- There will be no "administrative" censoring for any reason, i.e. all events will be used in the analyses. The only censored observations will be for patients who have not experienced the event of interest. For instance, patients who died due to disease relapse or disease progression will be censored in the analysis of time to TRM.

9.4.2 Analysis of the Primary Efficacy Endpoint

The primary endpoint of the study is GRFS, treated as a time to event variable. The primary approach for the primary efficacy analysis will be a randomization test to reflect the treatment allocation procedure. The randomization test will be based on a large number of simulated trials, say S, in which the treatments are re-allocated to the patients actually entered in the study (in the same order of entry) using the same minimization algorithm. Each simulated trial uses a different seed for the random number generator. The test statistic, say Δ, is calculated for the actual trial (Δ_{obs}) and for each simulated trial (Δ_i , $i = 1, \ldots, S$). The significance probability (P-value) of the randomization test is calculated directly from the empirical distribution of Δ under the null hypothesis. Let s be the number of Δ_i*'s* for which $|\Delta_i| \geq |\Delta_{obs}|$. The two-sided randomization P-value is equal to s/S. The number of simulated trials S will be chosen to ensure that the P-value is estimated correctly to the second significant digit (Buyse 2010).

Standard times to event analyses described in Section 9.4.1 will be considered supportive analyses of the primary efficacy endpoint.

9.4.3 Analysis of the Secondary Endpoints

Secondary endpoints will be tested for significance using a Hochberg procedure. The procedure works as follows: let p_1, p_2, p_3 and p_4 be the p-values of the tests for each of the four secondary endpoints, with $p_1 \geq p_2 \geq p_3 \geq p_4$. Let α be the significance level (e.g. 5%) appropriate for the analysis. If $p_1 \leq \alpha$, all four secondary endpoints show a significant treatment effect. If $p_1 > \alpha$ and $p_2 \leq \alpha/2$, the endpoints corresponding to p_2, p_3 and p_4 show a significant treatment effect. If $p_1 > \alpha$ and $p_2 > \alpha/2$ and $p_3 \leq \alpha/3$, the endpoints corresponding to p_3 and p_4 show a significant treatment effect. If $p_1 > \alpha$ and $p_2 > \alpha/2$ and $p_3 > \alpha/3$ and $p_4 \leq \alpha/4$, the endpoint corresponding to p_4 shows a significant treatment effect. If $p_1 > \alpha$ and $p_2 > \alpha/2$ and $p_3 > \alpha/3$ and $p_4 > \alpha/4$, no secondary endpoint shows a significant treatment effect.

Of note, the assumption of independence or positive correlation between the test statistics is required for the Hochberg procedure to preserve the type I error when one-sided testing is used (Dmitrienko *et al.* 2009). Two-sided testing will be used throughout and will not be at risk of an inflated type I error.

Standard times to event analyses described in Section 9.4.1 will be considered supportive analyses of the secondary endpoints.

A competing risk analysis will be performed for the following events that are considered failures for the primary endpoint and for some of the secondary endpoints: grade III/IV acute graft-versus-host disease (GVHD, including death from GVHD), chronic GVHD requiring

systemic immunosuppressive treatment, disease relapse/progression (including disease-related death), and death from all causes other than GVHD or disease relapse/progression. Gray's test will be used to compare the randomized treatment arms for the competing risks, and the Fine-Gray proportional hazards model will be used to adjust these comparisons for covariates of interest (Fine and Gray 1999; Gray 1988).

9.4.4 Safety Analyses

Safety variables include the reported AEs, SAEs, laboratory tests, vital signs and physical examination.

AEs will be coded and evaluated for severity using NCI-CTCAE and will be summarized by MedDRA system organ class and preferred term. Separate summaries will be generated for the following:

- All AEs
- Severe AEs (Grade 3 or higher)
- SAEs

Listings will be provided of:

- SAEs
- AEs leading to treatment discontinuation
- AEs resulting in death
- AEs listed according to maximum severity

The frequency of AEs will be tabulated by grade. Adverse events will be compared using χ^2 tests or, for low counts, using Fisher's exact test. In view of the anticipated large number of statistical tests, P-values will not be interpreted in the usual sense but will be used as a "flagging device" to highlight differences worth further scrutiny.

Laboratory tests: 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.

Other safety data (e.g., vital signs) will be tabulated and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

9.4.5 Baseline Descriptive Statistics

The two treatment groups will be compared on baseline characteristics, using descriptive statistics and inferential statistics.

9.4.6 Planned Interim Analyses

An interim analysis will be conducted when at least 105 GRFS events have occurred. The IDMC will review the results of the interim analysis. The sponsor will remain blinded to

these results, except if significance is reached at the time of the interim analysis ($P < 0.01246$), with a treatment effect greater than anticipated (hazard ratio of 0.61 or better). At the time of the final analysis, significance will be reached ($P < 0.04613$) with a treatment effect lower than anticipated, but still clinically worthwhile (hazard ratio of 0.73 or better).

9.4.7 Sub-Group Analyses

Subgroup analyses will be carried out by underlying disease, DRI, age, sex, and race/ ethnicity. Forest plots will be presented with a descriptive intent. Interaction tests will be carried out to investigate potential modulation of the treatment effect by baseline patient characteristics, but the trial is neither planned nor powered to detect interactions. Further sub-group analyses will be specified in the SAP.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

9.4.9 Exploratory Analyses

Exploratory analyses will be specified in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study intervention. In this study the following consent forms are available:

- Informed consent for the patient
- Informed consent for the donor
- Informed assent for the minor donor (aged 16 or 17 years; only if allowed according to local requirements and regulations)
- Informed consent for the parents/legal guardians of the minor donor (aged 16 or 17 years; only if allowed according to local requirements and regulations)
- Informed consent for the patient for peripheral blood sampling for further research of immune reconstitution, if applicable

10.1.1.2 Consent Procedures and Documentation

- The informed consent forms and any other written study materials provided to the patients and donors have to be approved by an IEC/IRB before patient enrollment.
- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to patients and donors, using the written information, and for obtaining their full understanding and written consent to participate in the study at their own free will. If required by local regulations, the informed consent procedure of the donor will be done by a sub-investigator who is independent from the investigator evaluating the patient.
- The investigator or other responsible personnel who provided explanations to the patient and the donor (including collaborators who gave supportive information, if applicable), should sign and date the written information.
- In case of a donor under age, the donor as well as his/her legal representative should be informed about the study and must sign and date the written information.
- Informed consent must be obtained prior to the first observations/examinations of the screening period are performed (use of assessments which were performed before signing informed consents is subject of informed consent).
- The investigator or other responsible personnel must give a copy of the signed consent form to the patient and the donor and store the original.
- The process and communication of the consent should be documented on medical records of the patient and donor.
- The investigator or other responsible personnel should note the following when obtaining consent from patients and donors:

- No patient/donor may be subjected to undue influence, such as compulsory enrollment into a study.
- The language and expressions used in the written information should be as plain and understandable as possible. Patients should be given the opportunity to ask questions and receive satisfactory answers to the inquiry and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the patient to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor, and auditor upon request.

Supply of new and important information influencing the patient's consent and revision of the written information

- The investigator/sub-investigator should immediately inform the patient orally whenever new information becomes available that may be relevant to the patient's consent or may influence the patient's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented on medical records, for example, and it should be confirmed whether the patient is willing to remain in the study or not.
- If the investigator or the sponsor recognizes the necessity to revise the written information in the terms and conditions applicable to the first point, the written information should be revised immediately based on the newly available information and be re-approved by the IEC/IRB.
- The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in the previous bullet even if patients are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations and the patient and donor should sign and date the informed consent form. The investigator or other responsible personnel should give a copy of the signed informed consent form to the patient and donor who had given consent with the written information and store the original appropriately as done for the first informed consent.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor to the investigators and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IEC/IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance and/or data quality are addressed and satisfy the sponsor, IEC/IRB and/or the competent authority.

In case it will be decided that the study will be prematurely terminated or suspended, all patients who are still in the study should at least complete the visit at Month 4 post HSCT. After premature termination of the study, efforts will be made to follow up patients for the occurrence of serious adverse events (SAEs) until 3 months after ATIR101 or cyclophosphamide administration.

10.1.3 Confidentiality and Privacy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her medical welfare.

Kiadis Pharma will use the information obtained during the conduct of this study for the development of ATIR101. The study investigator is obliged to provide Kiadis Pharma with complete test results and all data developed in this study, as described in this protocol. This information may be disclosed to appropriate competent authorities.

Access to stored samples will be limited. Samples and data will be stored using codes assigned by the investigators. The code key linking the participant name to the research record will be kept by the investigator and may not be released outside the study site. The coded data does not include any identifying information of the participant, such as name or address. Data will be kept in password-protected computers. Only investigators, the sponsor and affiliates or contracted parties will have access to the coded samples and data.

Even though individuals involved in the study, including the study monitors and auditors, may get to know matters related to patients' privacy due to direct access to source documents, or from other sources, they may not disclose the contents to third parties.

Data generated by this study must be available for inspection upon request by representatives of the EMA, the FDA, Health Canada, any other competent authority, IECs/IRBs (if appropriate), and Kiadis Pharma.

10.1.4 Future Use of Stored Specimens and Data

The blood and urine samples that are taken for efficacy and safety analyses will be analyzed by the local laboratory at the hospital soon after collection and destroyed after this analysis.

In a subgroup of patients at selected study sites only and after consent of the patient, peripheral blood samples will be obtained for research purposes (see Section 8.1.8).

Samples and data collected under this protocol will be used to study the efficacy and safety of ATIR101. During the manufacturing of ATIR101, mandatory samples are taken for manufacturing testing. It is possible that some of these samples will not be used for the standard tests. If the study participant consents, these remaining samples may also be used for research to increase knowledge on ATIR101 and to improve ATIR101 manufacturing and treatment with ATIR101. These samples will not be used for genetic research purposes.

All remaining samples will be destroyed after ATIR101 has become an accepted treatment or after the company has stopped development of ATIR101. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

Data collected for this study will be analyzed and stored at a delegated contract research organization (CRO) for data management. After the study is completed, the de-identified, archived data will be stored, under the supervision of the sponsor.

10.1.5 Key Roles and Study Governance

Coordinating Investigators:	Prof. Denis Claude Roy, MD Research Center and Cellular Therapy Laboratory Maisonneuve-Rosemont Hospital (Montreal, Canada)
	Prof. Stephan Mielke, MD Centre for Allogeneic Stem Cell Transplantation Karolinska University Hospital (Stockholm, Sweden)
Sponsor Contact:	Annelies Legters, MSc Senior Director Clinical Operations Kiadis Pharma (Amsterdam-Zuidoost, The Netherlands) Phone +31 20 240 5250 E-mail a.legters@kiadis.com
Medical Monitor:	Bernd-Jan Sanson, MD Head of Clinical and Medical Affairs EU Kiadis Pharma (Amsterdam-Zuidoost, The Netherlands) Phone +31 20 240 5250 E-mail b.sanson@kiadis.com
Study Monitoring	CTI Clinical Trial Services, Inc (Covington, KY, USA)
Data Management:	IDDI (Louvain-la-Neuve, Belgium)
Statistician:	Marc Buyse IDDI (Louvain-la-Neuve, Belgium)
Safety Management:	ProPharma Group (St. Paul MN, USA)

10.1.6 Safety Oversight

Safety oversight under the direction of an independent data monitoring committee (IDMC) composed of individuals with the appropriate expertise will be established to monitor the safety of the patients in study CR-AIR-009. The members of the IDMC are responsible for safeguarding the interests of the patients by reviewing the safety and mortality data during the study. They are not affiliated to the sponsor. The IDMC will serve as an independent advisory group to the sponsor and is required to provide recommendations about continuing (with or without modifications) or stopping the study. The IDMC will meet regularly to assess safety and efficacy on each arm of the study, including the results of the interim analysis.

Procedures to be used for the IDMC, including composition and roles and responsibilities of its members, will be described in detail in the IDMC charter.

In addition, a Medical Monitor of the sponsor will advise the study investigators and will monitor participant safety. The role of the Medical Monitor is to 1) review all AEs on a regular basis throughout the study; 2) be available to advise the investigators on study-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study.

10.1.7 Clinical Monitoring

Kiadis Pharma is responsible for monitoring the clinical study to ensure that patients' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol, to GCP ICH E6(R2), and to applicable regulatory requirements, and that study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor will determine the extent and nature of the monitoring and assign clinical monitors who are (sponsor independent) GCP-trained. The sponsor will provide the monitor(s) with adequate training on the study protocol. The study will be monitored in accordance with the clinical trial monitoring plan, which specifies the monitoring tasks.

10.1.8 Quality Assurance and Quality Control

10.1.8.1 ATIR101 Manufacturing

ATIR101 will be manufactured as individualized patient batches at manufacturing facilities, under supervision of Kiadis Pharma. Before start of the study, Kiadis Pharma Quality Assurance (QA) will qualify each manufacturing facility including its quality system. The qualification program includes site visit(s), verification audit(s), and the generation of a quality agreement between Kiadis Pharma and the manufacturing facility.

Kiadis Pharma will train personnel from the manufacturing facility in the optimized process to be used in study CR-AIR-009. Manufacturing will only start after the technology transfer is completed and the manufacturing process has been qualified by successful qualification runs. The manufacturing batch records will be subject of a separate training by experts from Kiadis Pharma.

Quality Control (QC) testing of ATIR101, the raw (starting) materials and intermediates will be performed at the manufacturing facility, contract laboratories, and/or the Kiadis Pharma R&D laboratory. Contract laboratories will be qualified by Kiadis Pharma QA prior to the start of ATIR101 manufacturing.

Because ATIR101 is manufactured as individualized patient batches and for every patient a different patient-donor combination is used, there is a chance that a batch fails to meet the acceptance criteria for administration within this study protocol. These cases will be discussed and trended in Quality Review Meetings, during which appropriate follow-up measures will be initiated.

10.1.8.2 Clinical Study

Procedures relevant to the clinical management of this study are either described in the applicable standard operating procedures (SOPs), or in the management and oversight plan. The purpose of the management and oversight plan is to describe all procedures which have not been covered in the SOPs. If new SOPs are generated or updated during the course of the study, the management and oversight plan will be updated and reference will be made to the new SOP.

Kiadis Pharma will not allow any waivers to the applicable protocol throughout the conduct of the study. An unplanned excursion from the protocol not implemented or intended as a systematic change, which could not be justified as necessary to protect the safety, rights, or welfare of the subjects, will be reported and followed up according to the local IEC/IRB requirements.

The investigator and the study site must accept monitoring and auditing by Kiadis Pharma or their representatives as well as inspections from the IEC/IRB and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents when they are requested by the monitors and auditors, the IEC/IRB, or regulatory authorities. The confidentiality of the patients' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access. In accordance with Kiadis Pharma procedures, this study may be subject to an independent QA GCP audit and/or a sponsor-initiated inspection at the study sites.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

The investigator or designee must enter all protocol-required data in the available electronic case report form (eCRF). An eCRF will be developed for both the patient and the donor. In the interest of collecting data in the most efficient manner, the investigator or designee should enter data (including laboratory values) into the eCRF as soon as possible after the patient's visit. The eCRFs and any supporting documents should be available for retrieval at any given time. The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them. If the monitor finds no inconsistencies, the appropriate eCRF parts are electronically signed. If any inconsistency is detected on the eCRFs, the monitor must query the investigator and the investigator should

make corrections/additions in the eCRF or provide an explanation within the eCRF system. The monitor should verify the corrected data with source documents to confirm that there are no inconsistencies between them, and also check that appropriate records on the corrections/additions of data are maintained.

For screening failures, defined as patients who signed informed consent (and may have been randomized) but were not eligible for study participation, the minimum demographic data (year of birth and gender) and reason for withdrawal will also be collected in an eCRF.

The investigator is responsible to ensure that all data in the eCRFs are accurate and complete, and that all entries are verifiable with source documents. Source data must be available at the site to document the existence of the study patients and donors, and to substantiate the integrity of study data collected. In case a patient is prematurely discontinued, the reason for discontinuation must be documented in the source documents.

In order to obtain objective clinical GVHD and mortality data two adjudication committees will be established:

- To ensure an objective approach for the classification and severity grading of GVHD events, Kiadis Pharma will request an independent GVHD adjudication committee to review each (possible) GVHD case and to come to a final assessment for GVHD classification and severity grading. This final assessment will be recorded on a separate CRF page and will be added to the clinical database. Procedures to be used for the GVHD adjudication committee will be described in detail in a separate charter.

- To ensure an objective assessment of the classification of the cause of death, Kiadis Pharma will request an independent death adjudication committee to review each death case and to provide a final assessment for the cause of death. This final assessment will be recorded on a separate CRF page and will be added to the clinical database. Procedures to be used for the death adjudication committee will be described in detail in a separate charter.

Data management will be coordinated by a delegated CRO, in accordance with their SOPs for data management. All study specific processes and definitions will be described in the data management plan. Coding of medical terms will be performed using the Medical Dictionary for Regulatory Activities (MedDRA) and medications will be coded with the WHO Drug Dictionary (WHO-DD).

10.1.9.2 Study Records Retention

ICH guidelines for Good Clinical Practice require that all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory tests, and medication inventory records, must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH

region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Kiadis Pharma. It is the responsibility of Kiadis Pharma to inform the Investigator as to when these documents no longer need to be retained.

ATIR101 traceability records must be kept for a minimum of 30 years after the expiry date of the product.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or requirements in other procedures. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IEC/IRB per their guidelines. The site principal investigator/study staff is responsible for knowing and adhering to their IEC/IRB requirements. If required by local guidelines, protocol deviations will also be reported to and assessed by the competent authorities.

10.1.11 Publication and Data Sharing Policy

<u>Publication policy</u>

The sites and the principal investigators shall have the right to publish and present results of the study following submission to Kiadis Pharma Netherlands B.V. for review of the manuscript, abstract or presentation intended for publication or presentation at least 70 days prior to the date of submission for publication or presentation. Kiadis Pharma Netherlands B.V. shall complete its review within 60 days of receipt of the submitted manuscript, abstract or presentation. Kiadis Pharma Netherlands B.V. may request that the principal investigators or the sites delete from the manuscript, abstract or presentation any confidential information. At the end of the 60-day period, the sites and the principal investigators will have the right to publish and present the material, abstract and presentation. However, single site data may not be published and/or presented prior to the publication of the multicenter data from the overall study.

Disclosure policy

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

10.2 Additional Considerations

10.2.1 Reporting of Serious Breaches

Serious breaches are defined as breaches of the conditions and principles of GCP in connection with the study, that are likely to affect, to a significant degree, the safety or physical or mental integrity of the participants in the study or the scientific value of the study. The sponsor shall notify the competent authorities concerned about a serious breach according to local laws and regulations.

10.2.2 Protocol Amendments

After the start of the clinical study, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the study participants or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the sponsor shall submit these to the competent authorities and IECs/IRBs together with a rationale for the changes. The changes will only be implemented after approval from both the competent authority and the IEC/IRB has been obtained.

10.3 Abbreviations

AE	adverse event
AIHA	autoimmune haemolytic anaemia
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
ATMP	advanced therapy medicinal product
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BUN	blood urea nitrogen
cGy	centigray
CFSE	carboxyfluorescein succinimidyl ester
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMML	chronic myelomonocytic leukemia
CMV	cytomegalovirus
CR	complete remission
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DRI	Disease Risk Index

dUCB	double umbilical cord blood
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ENT	ears, nose, throat
EQ-5D-5L	EQ-5D 5-level version
FAB	French-American-British
FACT-BMT	Foundation for the Accreditation of Cellular Therapy – Bone Marrow Transplantation questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GRFS	GVHD-free, relapse-free survival
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
Hb	hemoglobin
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
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
Ig	immunoglobulin

IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MDASI	MD Anderson Symptom Inventory
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MITT	modified intention-to-treat
MLR	mixed lymphocyte reaction
MMUD	mismatched unrelated donor
MRD	minimal residual disease
MTD	maximum tolerated dose
MUD	matched unrelated donor
MUGA	multiple gated acquisition
N/A	not applicable
NCI	National Cancer Institute
NCT	National Clinical Trial
NHI	National Institutes of Health
NK	natural killer (cells)
OS	overall survival
PBSC	peripheral blood stem cell
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDT	photodynamic treatment

PFS	progression-free survival
Pgp	P-glycoprotein
PO	orally
PP	per protocol
PTCy	post-transplant cyclophosphamide
PTLD	post-transplant lymphoproliferative disease
q12h	each 12 hours
q24h	each 24 hours
QA	Quality Assurance
QC	Quality Control
RBC	red blood cell
RRM	relapse-related mortality
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form 36-item health survey
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
TCD	T-cell depleted
TRM	transplant-related mortality
ULN	upper limit of normal
UP	unanticipated problem
VZV	varicella zoster virus
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WHO-UMC	World Health Organization Uppsala Monitoring Centre
WNV	West Nile virus

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12 APPENDICES

Appendix 1 Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes Risk

IPSS-R cytogenetic risk groups	
Cytogenetic prognostic subgroups	**Cytogenetic abnormalities**
Very good	-Y, del(11q)
Good	normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R prognostic score values							
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blast, %	≤ 2		> 2-< 5		5-10	> 10	
Hemoglobin, g/dl	≥ 10		8-< 10	< 8			
Platelets, $\times 10^9$/l	≥ 100	50-<100	< 50				
ANC, $\times 10^9$/l	≥ 0.8	< 0.8					
Risk score is obtained by adding scores of these five prognostic variables							

IPSS-R prognostic risk categories and scores	
Risk category	**Risk score**
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

Source: (Greenberg *et al.* 2012)

Appendix 2 Disease Risk Index (DRI)

DRI group	Disease (stage)
LOW	AML favorable cytogenetics CR
INTERMEDIATE	AML intermediate cytogenetics CR ALL CR1 Low-risk MDS§ adverse cytogenetics (early stage) Low-risk MDS§ intermediate cytogenetics (early or advanced stage[a]) High-risk MDS* intermediate cytogenetics (early stage)
HIGH	AML favorable cytogenetics (advanced stage[a]) AML adverse cytogenetics CR AML intermediate cytogenetics (advanced stage[a]) ALL CR2 ALL CR3 High-risk MDS* intermediate cytogenetics (advanced stage[a]) High-risk MDS* adverse cytogenetics (early or advanced stage[a]) Low-risk MDS§ adverse cytogenetics (advanced stage[a])
VERY HIGH	AML (advanced stage[a]) AML adverse cytogenetics (advanced stage[a])

CR = complete remission

§ Low-risk MDS refers to MDS with ≤ 5% blasts (refractory anemia with or without ringed sideroblasts and refractory cytopenia with multilineage dysplasia)

* High-risk MDS refers to MDS with > 5% blasts (refractory anemia with excess blasts [RAEB-1 and RAEB-2])

[a] Advanced stage refers to induction failure or active relapse

AML cytogenetics *Favorable:* Inv(16); *Intermediate:* Normal, All other abn.; *Adverse:* Complex (≥4 abn.)

MDS cytogenetics *Favorable:* Del(5q), Del(20q), Monosomy Y, Normal; *Intermediate:* Trisomy 8, All other abn.; *Adverse:* Abnormal 7, Complex (≥3 abn.)

Source: (Armand *et al.* 2010; Armand *et al.* 2014; Armand *et al.* 2012)

Appendix 3 EBMT Risk Score

EBMT risk score = sum of the scores for each of the five risk factors

Risk factor	0 points	1 point	2 points
Age (yr)	< 20	20 - 40	> 40
Disease stage *	Early	Intermediate	Late
Time interval from diagnosis to transplantation (months)	< 12 (any time interval for patients in early disease stage)	> 12 (only applies to patients in intermediate or late disease stage)	-
Donor type	HLA- identical sibling	Unrelated donor, other	-
Donor recipient sex combination	Any other combination	Female donor, male recipient	-

*** Classification of disease stage for calculation of EBMT risk score**

Disease stage	ALL, AML	MDS
Early	In first complete remission	Untreated or in first complete remission
Intermediate	In second complete remission	In second complete remission or in partial remission
Late	In all other disease stages	In all other disease stages

Source: (Gratwohl 2012)

Appendix 4 Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI)

Comorbidity	Definition of comorbidities	HCT-CI weighted score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease*, congestive heart failure, myocardial infarction, or EF ≤50%	1
Inflammatory bowel disease	Crohns disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after Day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dl, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

*One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide.

HCT-CI summary score is based on the sum of the HCT-CI weighted scores (Sorror *et al.* 2005).

Appendix 5 Karnofsky Performance Status (KPS) Scale

Performance Status (%)	Condition
100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

Appendix 6 Severity Grading of Graft-Versus-Host Disease

ACUTE GRAFT-VERSUS-HOST DISEASE (Harris *et al.* 2016)

GVHD Target Organ Staging

Skin

Stage 0 no active (erythematous) GVHD rash
Stage 1 maculopapular rash involving < 25% of the body surface
Stage 2 maculopapular rash involving 25-50% of the body surface
Stage 3 maculopapular rash involving > 50% of the body surface
Stage 4 generalized erythroderma (> 50% of the body surface) *plus* bullous formation and desquamation (> 5% of the body surface)

Liver

Stage 0 bilirubin < 2 mg/dl
Stage 1 bilirubin 2-3 mg/dl
Stage 2 bilirubin 3.1-6 mg/dl
Stage 3 bilirubin 6.1-15 mg/dl
Stage 4 bilirubin > 15 mg/dl

Upper Gastrointestinal (GI)

Stage 0 no or intermittent nausea, vomiting, or anorexia
Stage 1 persistent nausea, vomiting or anorexia

Lower GI (diarrhea stool output/day for adults)

Stage 0 < 500 ml/day or < 3 episodes/day
Stage 1 500-999 ml/day or 3-4 episodes/day
Stage 2 1000-1500 ml/day or 5-7 episodes/day
Stage 3 > 1500 ml/day or > 7 episodes/day
Stage 4 severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Overall grading of acute GVHD (based on most severe target organ involvement)

Grade	Skin	Liver	Lower GI	Upper GI
I	Stage 1-2	Stage 0	Stage 0	Stage 0
II	Stage 3 **and/or**	Stage 1 **and/or**	Stage 1 **and/or**	Stage 1
III	Stage 0-3	Stage 2-3 **and/or**	Stage 2-3	Stage 0-1
IV	Stage 4 **and/or**	Stage 4 **and/or**	Stage 4	Stage 0-1

CHRONIC GRAFT-VERSUS-HOST DISEASE

The global scoring system for chronic GVHD (Filipovich *et al.* 2005; Jagasia *et al.* 2015) reflects the clinical effect of chronic GVHD on the patient's functional status. Eight organs or sites (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joint and fascia, and genital tract) are considered for calculating global score. Elements included in the proposed global scoring include both the number of organs or sites involved and the severity score within each affected organ. Performance status scoring is not incorporated into the global scoring system. The global descriptions of mild, moderate, and severe were chosen to reflect the degree of organ impact and functional impairment due to chronic GVHD. Note that the global scoring system can be applied only after the diagnosis of chronic GVHD is confirmed by either (1) the presence of a diagnostic feature or, if a diagnostic feature is not present, (2) at least 1 distinctive manifestation of chronic GVHD with the diagnosis supported by histologic, radiologic, or laboratory evidence of GVHD from any site.

- Mild chronic GVHD:
  1 or 2 organs involved with no more than score 1 **plus** lung score 0
- Moderate chronic GVHD:
  3 or more organs involved with no more than score 1 **OR**
  at least 1 organ (not lung) with a score of 2 **OR**
  lung score 1
- Severe chronic GVHD:
  At least 1 organ with a score of 3 **OR**
  lung score of 2 or 3

Table 4 shows the scoring system for individual organs.

Table 4 Organ scoring of chronic GVHD

	SCORE 0	**SCORE 1**	**SCORE 2**	**SCORE 3**
PERFORMANCE SCORE KPS, ECOG or LPS	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN†				
Score % BSA *GVHD features to be scored by BSA:* Maculopapular rash/erythema Lichen planus-like features Papulosquamous lesions or ichthyosis Keratosis pilaris-like	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GVHD				
Skin features *Other GVHD features (not scored by BSA):* Hyperpigmentation Hypopigmentation Poikiloderma Severe or generalized pruritus Hair involvement Nail involvement	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
MOUTH Lichen planus-like features present	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms **with** disease signs with partial limitation of oral intake	Severe symptoms **with** disease signs on examination with major limitation of oral intake
EYES Keratoconjunctivitis sicca (KCS) confirmed by ophtalmologist	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops >3 x per day or punctal plugs), **WITHOUT** vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
GI TRACT Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥ 5% Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
LIVER	Normal total bilirubin and ALT or AP <3 x ULN	Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥3 x ULN	Elevated total bilirubin but ≤3 mg/dl or ALT >5 x ULN	Elevated total bilirubin >3 mg/dl

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS **				
Symptom score	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score % FEV1	FEV1 ≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
JOINTS AND FASCIA **P-ROM score** Shoulder (1-7) Elbow (1-7) Wrist/finger (1-7) Ankle (1-4)	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT Currently sexually active	No symptoms	Mild signs‡ and females with or without discomfort on exam	Moderate signs‡ and may have symptoms with discomfort on exam	Severe signs‡ with or without symptoms

OTHER INDICATORS, CLINICAL FEATURES OR COMPLICATIONS RELATED TO CHRONIC GVHD

(check all that apply and assign a score to its severity (0-3) based on functional impact where applicable (none-0, mild-1, moderate-2, severe-3)

Pericardial effusion___
Ascites (serositis)___
Peripheral neuropathy___
Eosinophilia >500/µL___
Platelets <100,000/µL ___
Others (specify):_____

Pleural effusion(s)___
Nephrotic syndrome___
Myasthenia gravis___
Polymyositis___
Weight loss* >5% without GI symptoms ___

ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, upper limit of normal; P-ROM, Photographic range of motion; FEV1, forced expiratory volume in 1 second. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of BSA score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Appendix 7 Calculation of Ideal Body Weight (IBW) and Adjusted Ideal Body Weight (AIBW)

For patients who weigh less than 125% of their ideal body weight (IBW), dosing of all drugs part of the conditioning regimen should be based on actual body weight. For patients who weigh greater than or equal to 125% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

Calculation of IBW (Peterson *et al.* 2016)

US version: height measured in inches:

Males: $IBW\ [kg] = 50.0 + 2.3\ \times\ (height\ [in] - 60)$

Females: $IBW\ [kg] = 45.5 + 2.3\ \times\ (height\ [in] - 60)$

Metric version: height measured in cm:

Males: $IBW\ [kg] = 50.0 + 0.91\ \times\ (height\ [cm] - 152)$

Females: $IBW\ [kg] = 45.5 + 0.91\ \times\ (height\ [cm] - 152)$

Calculation of AIBW (Hicks *et al.* 2012)

Males and females: $AIBW = IBW + 0.25\ \times (actual\ body\ weight - IBW)$

Appendix 8 Sponsor Signature

Study 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 Number:	CR-AIR-009
Original Protocol:	Version 1.0 (23 November 2016)
Amendment 1-3:	Version 2.0 (26 September 2017)
Amendment 4:	Version 3.0 (23 August 2018)

This clinical study protocol has been approved by the sponsor.

Signed:_____ Date:_____

Andrew Sandler, MD
Chief Medical Officer
Kiadis Pharma Netherlands B.V.

Appendix 9 Coordinating Investigator Signatures

Study 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)
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Amendment 1-3:	Version 2.0 (26 September 2017)
Amendment 4:	Version 3.0 (23 August 2018)

This clinical study protocol has been approved by the coordinating investigator.

Signed:_____ Date:_____

Prof. Denis Claude Roy, MD
Research Center and Cellular Therapy Laboratory
Maisonneuve-Rosemont Hospital (Montreal, Canada)

Study 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)
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Amendment 4:	Version 3.0 (23 August 2018)

This clinical study protocol has been approved by the coordinating investigator.

Signed:_____ Date:_____

Prof. Stephan Mielke, MD
Centre for Allogeneic Stem Cell Transplantation
Karolinska University Hospital (Stockholm, Sweden)

Appendix 10 Principal Investigator Signature

Study 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 Number:	CR-AIR-009
Original Protocol:	Version 1.0 (23 November 2016)
Amendment 1-3:	Version 2.0 (26 September 2017)
Amendment 4:	Version 3.0 (23 August 2018)

I have read all pages of this clinical study protocol for which Kiadis Pharma Netherlands B.V. is the sponsor. I agree that it contains all the information required to conduct this study. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with the ICH GCP guidelines (ICH E6[R2]) and the provisions of the Helsinki Declaration. I will also ensure that all relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents."

Signed:_____ Date:_____

Printed name: …….

Address: …….

……

……