Clinical Study Protocol: CR-AIR-008

Study Title:	An exploratory, open-label, multicenter study to evaluate the safety and efficacy of a two-dose regimen of ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment), in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor
Study Number:	CR-AIR-008
Study Phase:	Phase II
Product Name:	ATIR101 (previously referred to as ATIR)
EudraCT Number:	2015-002821-20
Indication:	Prevention of complications, such as infections and GvHD, and/or relapse after a haploidentical allogeneic hematopoietic stem cell transplantation
Coordinating Investigators:	Prof. Denis Claude Roy, MD Research Center and Cellular Therapy Laboratory Maisonneuve-Rosemont Hospital (Montreal, Canada) Prof. Dr. med. Stephan Mielke Allogeneic Stem Cell Transplant Center Julius Maximilian University of Würzburg (Würzburg, Germany)
Sponsor:	Kiadis Pharma
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	Date
Original Protocol:	9 July 2015
Amendment 1:	20 November 2015

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SYNOPSIS

Sponsor:
Kiadis Pharma

Name of Finished Product:
ATIR101 (previously referred to as ATIR)

Name of Active Ingredient:
ATIR101 is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment)

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

Study Number:
CR-AIR-008

Study Phase:
Phase II

Study Objective:
To study the safety and efficacy of a repeat dose administration of ATIR101 in patients with a hematologic malignancy who received a T-cell depleted haploidentical hematopoietic stem cell transplantation (HSCT).

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

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

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

Assessments will be performed at weekly visits from the day of the first ATIR101 infusion (Week 4) until 6 weeks after the second ATIR101 infusion (Week 16), at monthly visits from 4 until 6 months after the HSCT, and every 3 months from 6 until 12 months after the HSCT.

Study Population:

In total, 15 patients with a hematologic malignancy who are eligible for a haploidentical HSCT will be treated with two doses of ATIR101 (unless the second dose is halted for safety reasons).

Patient inclusion criteria

- Any of the following hematologic malignancies:
  - Acute myeloid leukemia (AML) in first remission with high-risk features or in second or higher remission
  - Acute lymphoblastic leukemia (ALL) in first remission with high-risk features or in second or higher remission
  - Myelodysplastic syndrome (MDS): transfusion-dependent, or intermediate or higher IPSS-R risk group
- Karnofsky performance status ≥ 70%
- Eligible for haploidentical stem cell transplantation according to the investigator
- Male or female, age ≥ 18 years and ≤ 65 years

Patient exclusion criteria

- Availability of a fully matched related or unrelated donor following a donor search
- Diffusing capacity for carbon monoxide (DLCO) < 50% predicted
- Left ventricular ejection fraction < 50% (evaluated by echocardiogram or MUGA)
- AST > 2.5 x ULN (CTCAE grade 2)
- Bilirubin > 1.5 x ULN (CTCAE grade 2)
- Creatinine clearance < 50 mL/min (calculated or measured)
- Positive HIV test
- Positive pregnancy test (women of childbearing age only)
- Prior allogeneic HSCT
- Estimated probability of surviving less than 3 months
- Known allergy to any of the components of ATIR101 (e.g., dimethyl sulfoxide)
- Known presence of HLA antibodies against the non-shared donor haplotype
- Any other condition which, in the opinion of the investigator, makes the patient ineligible for the study

Donor inclusion criterion

- Haploidentical family donor with 2 to 3 mismatches at the HLA-A, -B and/or -DR loci of the unshared haplotype
- Male or female, age ≥ 16 and ≤ 75 years (If applicable, local legal requirements for donors under the age of 18 will be followed)
- Eligible for donations of human blood and blood components according to local requirements and regulations
- Eligible for donation according to the transplantation center

Donor exclusion criteria

- Positive pregnancy test or nursing (women of childbearing age only)
- Positive viral test for HIV-1, HIV-2, HBV, HCV, Treponema pallidum, HTLV-1 (if tested), HTLV-2 (if tested), or WNV (if tested)

Hematopoietic Stem Cell Transplantation (HSCT):

In order to prepare the patient for the HSCT one of the following conditioning regimens is recommended.

TBI regimen

- Fractionated total body irradiation (TBI); 200 cGy twice daily for 3 days on Day -10 to -8 (1200 cGy in 6 fractions)
- Fludarabine; 30 mg/m^2 intravenously (IV) once daily for 5 days on Day -7 to -3
- Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7
- Anti-thymocyte globulin (ATG; Thymoglobulin®); 2.5 mg/kg once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 8 hours. During the course of ATG, patients will receive methylprednisolone 2 mg/kg/day IV.

Non-TBI regimen

- Fludarabine; 30 mg/m^2 IV once daily for 5 days on Day -8 to -4
- Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7
- Melphalan; 60 mg/m^2 IV once daily for 2 days on Day -2 and -1
- ATG (Thymoglobulin®); 2.5 mg/kg once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 8 hours. During the course of ATG, patients will receive methylprednisolone 2 mg/kg/day IV.

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 8-11×10^6 CD34+ cells/kg with a maximum of 3×10^4 CD3+ cells/kg as assessed by flow cytometry. To ensure a consistently highly purified stem cell graft, clinical sites will use the CliniMACS® CD34 isolation system (from Miltenyi Biotec) as part of their institutional procedures for preparing the stem cell graft.
Post-transplantation immunosuppressive therapy (e.g. corticosteroids) in the absence of GvHD should be avoided unless medically indicated. To prevent infections with cytomegalovirus (CMV), patients who are CMV positive or have a CMV positive donor will receive prophylactic treatment, and all patients will be subject to regular quantitative PCR monitoring followed by adequate (pre-emptive) treatment if indicated.
To prevent infections with Epstein-Barr virus (EBV), patients who are EBV positive or have an EBV positive donor will be subject to regular quantitative PCR monitoring followed by adequate (pre-emptive) treatment if indicated.

Investigational Medicinal Product, Dose, and Mode of Administration:

ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment), will be cryopreserved until infusion to the patient. ATIR101 will be infused intravenously at a dose of 2×10^6 viable T-cells/kg body weight between 28 and 32 days after the HSCT (or later if required by the patient's medical condition). If not halted for safety reasons, patients will receive a second ATIR101 infusion between 70 and 74 days after the HSCT but at least 42 days after the first ATIR101 infusion (or later if required by the patient's medical condition). The second ATIR101 infusion will consist of a dose of 2×10^6 viable T-cells/kg (or an adjusted dose of 1×10^6 viable T-cells/kg when required).

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.

Duration of Treatment and Study:

ATIR101 will be administered as two intravenous infusions at 28-32 days and 70-74 days after the HSCT, respectively. Patients treated with ATIR101 will be followed up until 12 months after the HSCT.
The study is anticipated to be conducted between October 2015 and June 2017.

Assessments:

- GvHD assessment:
  - Occurrence and severity of acute and chronic GvHD
- Mortality:
  - Occurrence of death, cause of death
- Disease assessment:
  - Occurrence of relapse or disease progression
- Infection assessment:
  - Occurrence and severity of viral, fungal, and bacterial infections, including viral reactivations
- Immune reconstitution:
  - Total lymphocytes and immunophenotyping on peripheral blood as measured by flow cytometry: CD3+ (T-cells), CD3+ CD8+ (cytotoxic T-cells), CD3+ CD4+ (helper T-cells), CD3- CD56+ (NK-cells), and CD19+ (B-cells)
  - Immunoglobulins in peripheral blood: IgG, IgA, IgM

Statistical Methods:

<u>Primary endpoint (safety)</u>

- Incidence of acute graft versus host disease (GvHD) grade III/IV up to 180 days post HSCT. Thus, the primary analysis will be based on the data at 180 days after the HSCT.

<u>Secondary endpoints (safety and efficacy)</u>

- Incidence and severity of acute and chronic graft versus host disease (GvHD)
- Time to T-cell reconstitution, defined as the time to CD3+ in peripheral blood higher than

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

All endpoints will be analyzed using descriptive statistics. Immune reconstitution will be graphically displayed in time. The Kaplan-Meier method will be used to display and estimate probability of time-related survival data (OS, PFS, GRFS). In addition, cumulative incidence curves taking into account competing risks will be used to display and estimate cumulative incidences of TRM, RRM, and GvHD.

Date of Original Approved Protocol:
9 July 2015

Date of Most Recent Protocol Amendment:
20 November 2015 (Amendment 1)

Prepared in:
Microsoft Word 2007

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LIST OF ABBREVIATIONS

AE	adverse event
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
BID	twice daily
cGy	centigray
CMP	clinical monitoring plan
CMV	cytomegalovirus
CNS	central nervous system
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
DMP	data management plan
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
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

FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
GRFS	GvHD-free, relapse-free survival
GvHD	graft versus host disease
GvL	graft versus leukemia
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
IMP	investigational medicinal product
IPSS-R	Revised International Prognostic Scoring System
ITT	intention-to-treat
IV	intravenous(ly)
KPS	Karnofsky Performance Scale
LDH	lactate dehydrogenase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MITT	modified intention-to-treat

MLR	mixed lymphocyte reaction
MUGA	multiple gated acquisition
NAT	nucleic acid test
NCI	National Cancer Institute
NK	natural killer (cells)
OS	overall survival
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction
PDT	photodynamic treatment
PFS	progression-free survival
PFT	pulmonary function test
PO	orally
PP	per protocol
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
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
TRM	transplant-related mortality
ULN	upper limit of normal
VZV	Varicella zoster virus
WBC	white blood cell

WHO	World Health Organization
WHO-UMC	World Health Organization Uppsala Monitoring Centre
WNV	West Nile virus

1 INTRODUCTION

For many end stage patients with hematologic malignancies such as acute leukemias and myelodysplastic syndrome (MDS), a hematopoietic stem cell transplantation (HSCT) remains the only curative option. However, even though an allogeneic stem cell transplantation can provide a cure in contrast to most other treatments, it is not a first line treatment, because of complications related to the procedure.

One of the major complications of allogeneic HSCT (both with matched sibling donors and unrelated matched donors) is the occurrence of acute graft versus host disease (GvHD), in which the T-cells from the donor react against the tissue of the patient. Without prophylactic use of immunosuppressants post transplantation the incidence of acute GvHD can approach 100% (Goker *et al.* 2001) and even with prophylactic use of immunosuppressants 30-60% of patients will develop some level of acute GvHD (Abo-Zena and Horwitz 2002; Jagasia *et al.* 2012; Ruggeri *et al.* 2006).

GvHD is subdivided into acute GvHD and chronic GvHD (Glucksberg *et al.* 1974; Horwitz and Sullivan 2006; Jagasia *et al.* 2015; Przepiorka *et al.* 1995; Vogelsang 2001). Acute GvHD is responsible for significant morbidity and up to 20% of mortality in allogeneic stem cell recipients (from HLA-matched sibling and unrelated matched donors) (Martino *et al.* 1999; Pasquini and Zhu 2015).

In order to manage the risk of acute GvHD it is currently essential that a matched donor can be found. For patients who are eligible for an allogeneic HSCT and who do not have a human leukocyte antigen (HLA)-matched sibling, an allogeneic HSCT from an HLA-matched unrelated donor is an alternative option (Gratwohl *et al.* 2007; Ljungman *et al.* 2006). The use of a matched (related or unrelated) donor is considered standard of care for patients who are eligible for an HSCT. However, a major limitation of using matched donors is that for a significant number of patients a matched unrelated donor cannot be found in a timely manner and consequently many patients do not receive this treatment. If family members who are only partially HLA-matched to the recipient (haploidentical donors) could be used as stem cell donor, up to 95% of patients in urgent need for an HSCT could find a donor and receive this potentially life-saving treatment. Almost all patients have at least one partially HLA-matched parent, sibling, or child, who is eligible as a donor. The immediate availability of this mismatched family member can have important treatment implications as a patient's condition can deteriorate during a search period to look for a fully HLA-matched donor in the donor bank.

The haploidentical transplant procedure has become feasible through use of methods to remove T-cells from the graft (T-cell depletion), in order to reduce the risk of (acute) GvHD, and subsequent administration of a megadose of CD34+ cells (Champlin *et al.* 2002; Tabilio *et al.* 2004). However, the downside of this approach is that patients remain severely immune compromised for a prolonged period of time, with a high risk of life-threatening infections resulting in a high treatment-related mortality (TRM) rate (Koh *et al.* 2007). Larger series have shown the outcome of these transplants to remain disappointing with 2-year leukemia survival ranging between 20-40% (Ciceri *et al.* 2007). One way to potentially reduce this

high TRM rate is to provide functional T-cells to the patient early after the stem cell transplantation through a donor lymphocyte infusion (DLI), which can lead to faster immune reconstitution and provide early protection against opportunistic infections. However, giving unmanipulated, mature T-cells early after the stem cell transplantation, especially if more than 1×10^4 cells/kg are infused, may lead to life-threatening acute GvHD (Aversa *et al.* 1998; Lewalle *et al.* 2003), making this approach impractical.

Removal of alloreactive T-cells, which would cause acute GvHD, could make it possible to infuse a high dose of T-cells after the transplantation, without increasing the risk of GvHD. Kiadis Pharma Netherlands B.V. (hereafter Kiadis Pharma) is developing ATIR101 (previously referred to as ATIR), a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells using photodynamic treatment (PDT). ATIR101 is manufactured through the *ex vivo* use of TH9402 and PDT (Theralux platform). Kiadis Pharma has demonstrated that TH9402 *in vitro* accumulates in human T-cells activated with allogeneic major histocompatibility complex (MHC)-mismatched cells and upon light activation selectively depletes these cells while anti-third party immune responses is preserved (Guimond et al. 2000). In addition, in a lethally irradiated murine model of mismatched allogeneic transplantation, *ex vivo* treatment of activated T-cells before their *in vivo* administration allowed 90% of the mice to survive more than 100 days. Moreover, the cells treated *ex vivo* with TH9402 and PDT, retained the ability to induce GvHD in third-party mice and graft versus leukemia (GvL) function (Boumedine et al. 2004; Guimond et al. 2002). Several investigators have confirmed the selective depletion of alloreactive cells by *ex vivo* treatment with TH9402 and PDT in HLA-mismatched stimulator-responder pairs (Mielke *et al.* 2008).

A different approach for haploidentical donor transplants has been developed by investigators from Baltimore (Luznik *et al.* 2010). They use unmanipulated bone marrow grafts and administer a high dose of cyclophosphamide (50 mg/kg) on Day 3 and 4 after the HSCT, in order to eliminate reactive T-cells in the body. Additionally, these patients are given immunosuppressants for a prolonged period. Although this approach has shown to limit TRM and to make these transplants feasible, a high rate of relapse is observed, potentially due to the use of immunosuppressants (Brunstein *et al.* 2011). In addition, a relatively high rate of GvHD is still observed (Kanakry *et al.* 2014).

Clinical Experience with ATIR101

In a phase I/II study (CR-GVH-001), conducted at the Maisonneuve-Rosemont Hospital in Montreal, patients with high risk hematologic malignancies eligible for an allogeneic HSCT, but for whom a matched donor was not available, were treated with a haploidentical HSCT followed by a single infusion of ATIR101. ATIR101 was administrated 28-40 days following the transplantation of a CD34-selected stem cell graft, without adding immunosuppressive therapy after the HSCT, unless clinically indicated. After infusing a dose of 1×10^4 cells/kg to the first patient (L1), cohorts of 3 patients were exposed to increasing doses of ATIR101, starting at 5×10^4 cells/kg (L2) and escalating upwards to 5×10^6 cells/kg (L7). A total of 19 patients have been infused with ATIR101 at different cell dose levels. No patient experienced grade III-IV acute GvHD, and no ATIR101-related serious adverse events were

reported. Based on this study the maximum tolerated dose of ATIR101 could not be determined, but there was a clear clinical difference between the lower and higher dose ranges. Within 2 years after the HSCT, TRM was observed in 6 patients, 4 in the lower dose cohorts (L1-L3; up to 1.3×10^5 cells/kg), 2 in the highest dose cohort (L7; 5×10^6 cells/kg) and none in the dose cohorts L4-L6 (3.2×10^5 - 2.0×10^6 cells/kg). Long-term follow-up (5 years) in the effective dose range between 3.2×10^5 and 2.0×10^6 cells/kg (L4-L6) showed that none of the 9 patients died due to TRM (3 out of 9 patients died to RRM) and 6 out of 9 patients survived for more than 5 years, which was an unexpectedly high survival rate, as only a few patients were in complete remission at the time of transplantation. This study shows that ATIR101 at an effective dose is safe and well-tolerated as an addition to a T-cell depleted haploidentical HSCT and reduces TRM. Based on the results of study CR-GVH-001, the optimal dose of ATIR101 for further development was considered to be 2×10^6 T-cells/kg.

In an ongoing phase II multicenter study (CR-AIR-007), conducted in Europe and North America, 23 patients with high-risk acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) are planned to be treated with a single infusion of 2×10^6 cells/kg ATIR101 following a haploidentical HSCT. At the interim analysis (conducted in September 2014), 10 patients had been treated with ATIR101 (2×10^6 cells/kg) and had completed at least 6 months of follow-up after the HSCT. Three of the first 10 patients had died at the cut-off, all due to TRM caused by an infection, with 2 patients dying within the first 6 months post HSCT, resulting in a TRM rate at 6 months post HSCT (primary endpoint) of 20% (2/10). All death cases were judged to be unrelated to ATIR101 infusion. A delay in the occurrence of TRM and severe infections was seen compared to a similar set of 35 patients undergoing a T-cell depleted haploidentical HSCT without the addition of T-cells post HSCT (preliminary data from observational cohort study CR-AIR-006). No ATIR101-related cases of acute GvHD grade III/IV were reported, showing the effective elimination of alloreactivity. In the patients who showed (mild) acute GvHD the onset of the disease was quite delayed (not before 131 days post HSCT). Among the first 10 patients, six patients (60%) were free of severe infections (i.e. NCI grade 3-5) between ATIR101 infusion and 6 months post HSCT. No cases of relapse or disease progression were observed. T-cell reconstitution (i.e. $\geq 0.2\times10^9$/L) was observed about 6 months after the HSCT. These interim results support continuation of patient enrolment.

Study Rationale

The objective of the current study is to study the safety and efficacy of a repeat dose administration of ATIR101 (two doses of 2×10^6 viable T-cells/kg body weight) in patients with a hematologic malignancy who received a T-cell depleted haploidentical HSCT. In the previous clinical studies with ATIR101, a single dose of 2×10^6 cells/kg was found to be safe (no acute GvHD grade III/IV). In study CR-AIR-007 we observed that no patients died within the first 100 days post HSCT and that T-cell reconstitution was seen around 6 months after the HSCT. Before T-cell reconstitution was reached, two patients had died due to systemic viral infections. The infusion of a second dose of ATIR101 at 70-74 days after the HSCT might further reduce the time to T-cell reconstitution and thereby decrease the occurrence of severe infections and TRM, while it is not expected to jeopardize patient safety by causing acute GvHD grade III/IV.

Risk-benefit Assessment

For many end stage patients with a hematologic malignancy, an 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 potentially life-saving treatment, because a suitable 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 recipient, as stem cell donor (haploidentical donors), followed by the administration of donor lymphocytes, which have been selectively depleted of host alloreactive T-cells (ATIR101). It is expected that patients will benefit from ATIR101 by protecting them from life-threatening infections without increasing the risk of life-threatening GvHD. Moreover, the possibility that the anti-malignancy effects of the T-cells have been preserved could provide another benefit to the patients. This potential graft versus leukemia effect could reduce the risk of relapse and thereby further increase the probability of long-term survival.

In conclusion, the current study offers patients with a hematologic malignancy in (urgent) need of an HSCT, a reasonable chance to improve their survival probability. Therefore, participation in this study provides patients the prospect of direct benefit.

The following potential adverse reactions of ATIR101 are listed in the Investigator's Brochure:

- Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) related reactions.
  Because ATIR101 consists of donor T-lymphocytes, the causal relationship between CMV/EBV related adverse events and ATIR101 administration cannot be ruled out if the donor is positive for CMV/EBV at screening. In this study a mandatory regimen to prevent and treat CMV and EBV disease will be implemented (see Section 5.6.4).
- Post Transplant Lymphoproliferative Disease (PTLD)
  Because ATIR101 contains donor T-lymphocytes, the causal relationship between PTLD and ATIR101 administration cannot be ruled out if the donor is positive for EBV at screening.
- Infusion reactions.
  Potential adverse reactions after the infusion could include allergic reactions to the ingredients of ATIR101: immediate fever or chills, skin rash, bronchospasm, or anaphylactic shock, and delayed serum-sickness-like reactions.
- Graft versus host disease.
  Due to the ATIR101 manufacturing process and 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 completely.

2 STUDY OBJECTIVE

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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

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

All patients treated with ATIR101 will be followed up until 12 months after the HSCT. Assessments will be performed at weekly visits from the day of the first ATIR101 infusion (Week 4) until 6 weeks after the second ATIR101 infusion (Week 16), at monthly visits from 4 until 6 months after the HSCT, and every 3 months from 6 until 12 months after the HSCT.

See Appendix 1 for a detailed schedule of assessments.

3.2 Rationale for Study Design

In the phase I/II study CR-GVH-001 and the phase II study CR-AIR-007 single doses of ATIR101 up to 5×10^6 viable T-cells/kg have been infused without causing any acute GvHD grade III/IV. Therefore, two doses of 2×10^6 viable T-cells/kg are expected to be safe and well tolerated as well, not exceeding the maximum dose exposure in prior studies. However, to ensure patient safety, a safety evaluation will be conducted on the first six patients at 120 days post HSCT (see Sections 3.1 and 5.3).

3.3 Study Duration

ATIR101 will be administered as two intravenous infusions at 28-32 and 70-74 days after the HSCT, respectively. Patients treated with ATIR101 will be followed up until 12 months after the HSCT. The end of the study is defined as the date at which the last data point from the last patient is received.

The study is anticipated to be conducted between October 2015 and June 2017.

4 STUDY POPULATION SELECTION

4.1 Study Population

In total, 15 patients with a hematologic malignancy who are eligible for a haploidentical HSCT will be treated with two doses of ATIR101 (unless the second dose is halted for safety reasons).

4.2 Patient Inclusion Criteria

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

- Any of the following hematologic malignancies:
  - Acute myeloid leukemia (AML) in first remission with high-risk features or in second or higher remission
  - Acute lymphoblastic leukemia (ALL) in first remission with high-risk features or in second or higher remission
  - Myelodysplastic syndrome (MDS): transfusion-dependent, or intermediate or higher IPSS-R risk group
- Karnofsky performance status ≥ 70%
- Eligible for haploidentical stem cell transplantation according to the investigator
- Male or female, age ≥ 18 years and ≤ 65 years

4.3 Patient Exclusion Criteria

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

- Availability of a fully matched related or unrelated donor following a donor search
- Diffusing capacity for carbon monoxide (DLCO) < 50% predicted
- Left ventricular ejection fraction < 50% (evaluated by echocardiogram or MUGA)
- AST > 2.5 x ULN (CTCAE grade 2)
- Bilirubin > 1.5 x ULN (CTCAE grade 2)
- Creatinine clearance < 50 mL/min (calculated or measured)
- Positive HIV test
- Positive pregnancy test (women of childbearing age only)
- Prior allogeneic HSCT
- Estimated probability of surviving less than 3 months
- Known allergy to any of the components of ATIR101 (e.g., dimethyl sulfoxide)
- Known presence of HLA antibodies against the non-shared donor haplotype
- Any other condition which, in the opinion of the investigator, makes the patient ineligible for the study

4.4 Donor Inclusion Criteria

Each donor must meet the following criteria to be enrolled in this study.

- Haploidentical family donor with 2 to 3 mismatches at the HLA-A, -B and/or -DR loci of the unshared haplotype
- Male or female, age ≥ 16 and ≤ 75 years (If applicable, local legal requirements for donors under the age of 18 will be followed)
- Eligible for donations of human blood and blood components according to local requirements and regulations
- Eligible for donation according to the transplantation center

4.5 Donor Exclusion Criteria

Donors who meet any of the following criteria will be excluded from the study.

- Positive pregnancy test or nursing (women of childbearing age only)
- Positive viral test for HIV-1, HIV-2, HBV, HCV, Treponema pallidum, HTLV-1 (if tested), HTLV-2 (if tested), or WNV (if tested)

5 STUDY TREATMENT

5.1 Description of Treatment

5.1.1 Hematopoietic Stem Cell Transplantation

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) 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; Tabilio *et al.* 2004). To ensure a consistently highly purified stem cell graft, clinical sites will use the CliniMACS® CD34 isolation system (from Miltenyi Biotec) as part of their institutional procedures for preparing the stem cell graft.

In order to prepare the patient for the HSCT one of the following myeloablative conditioning regimens is recommended. Deviations from these recommended conditioning regimens are to be discussed between the coordinating investigator, Kiadis Pharma, and the investigator of the respective site.

<u>TBI regimen</u>

- Fractionated total body irradiation (TBI); 200 cGy twice daily for 3 days on Day -10 to -8 (1200 cGy in 6 fractions)
- Fludarabine; 30 mg/m^2 intravenously (IV) once daily for 5 days on Day -7 to -3
- Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7
- Anti-thymocyte globulin (ATG; Thymoglobulin®); 2.5 mg/kg once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 8 hours. During the course of ATG, patients will receive methylprednisolone 2 mg/kg/day IV.

<u>Non-TBI regimen</u>

- Fludarabine; 30 mg/m^2 IV once daily for 5 days on Day -8 to -4
- Thiotepa; 5 mg/kg IV twice daily for 1 day on Day -7
- Melphalan; 60 mg/m^2 IV once daily for 2 days on Day -2 and -1
- ATG (Thymoglobulin®); 2.5 mg/kg once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 8 hours. During the course of ATG, patients will receive methylprednisolone 2 mg/kg/day IV.

5.1.2 Investigational Medicinal Product (ATIR101)

For manufacturing of ATIR101, donor and patient peripheral blood mononuclear cells (PBMCs) as well as donor plasma are collected by apheresis 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 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. 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 at two manufacturing facilities, under supervision of Kiadis Pharma: the Centre d'Excellence en Thérapie Cellulaire, Hôpital Maisonneuve-Rosemont (Montréal, Canada) and the Deutsches Rotes Kreuz-Blutspendedienst Baden-Württemberg-Hessen (Frankfurt am Main, Germany). Cell processing at the manufacturing facility will start as soon as possible but within 24 hours after the end of the apheresis.

The selective depletion of host alloreactive T-cells in ATIR101 is shown schematically below (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 MHC antigens of the irradiated patient's cells. Subsequent *ex vivo* PDT, using the photosensitizing compound TH9402, depletes the host alloreactive T-cells resulting in the cellular product ATIR101. Those cells that are activated accumulate more light-sensitive TH9402 than non-activated cells and are consequently more susceptible to the effect of PDT treatment. The T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (ATIR101) is cryopreserved until infusion into the patient following the HSCT. The whole manufacturing process takes 5 days and additional quality control tests for product release take 14 days.

For each patient batch, two 20-mL units (bags) of ATIR101 will be prepared, containing 2×10^6 viable T-cells/kg. A third unit (bag) will contain the remaining ATIR101 cells (10-20 mL equivalent with a dose of $1\text{-}2\times10^6$ viable T-cells/kg) and can be used as a rescue dose when required. The units are frozen and stored until release to the sites.

Each batch of ATIR101, manufactured for the individual patient, will be tested on key quality attributes, of which depletion of alloreactivity is crucial. After formal release, each frozen ATIR101 unit will be shipped separately to the clinical site just before ATIR101 infusion is required.

Retain- and research samples of ATIR101, the starting materials, and any intermediates are taken and stored. The research samples can be used for performing tests to further optimize the ATIR101 manufacturing process and better understand the mechanism of action of ATIR101. None of the samples will be used for genetic research purposes.

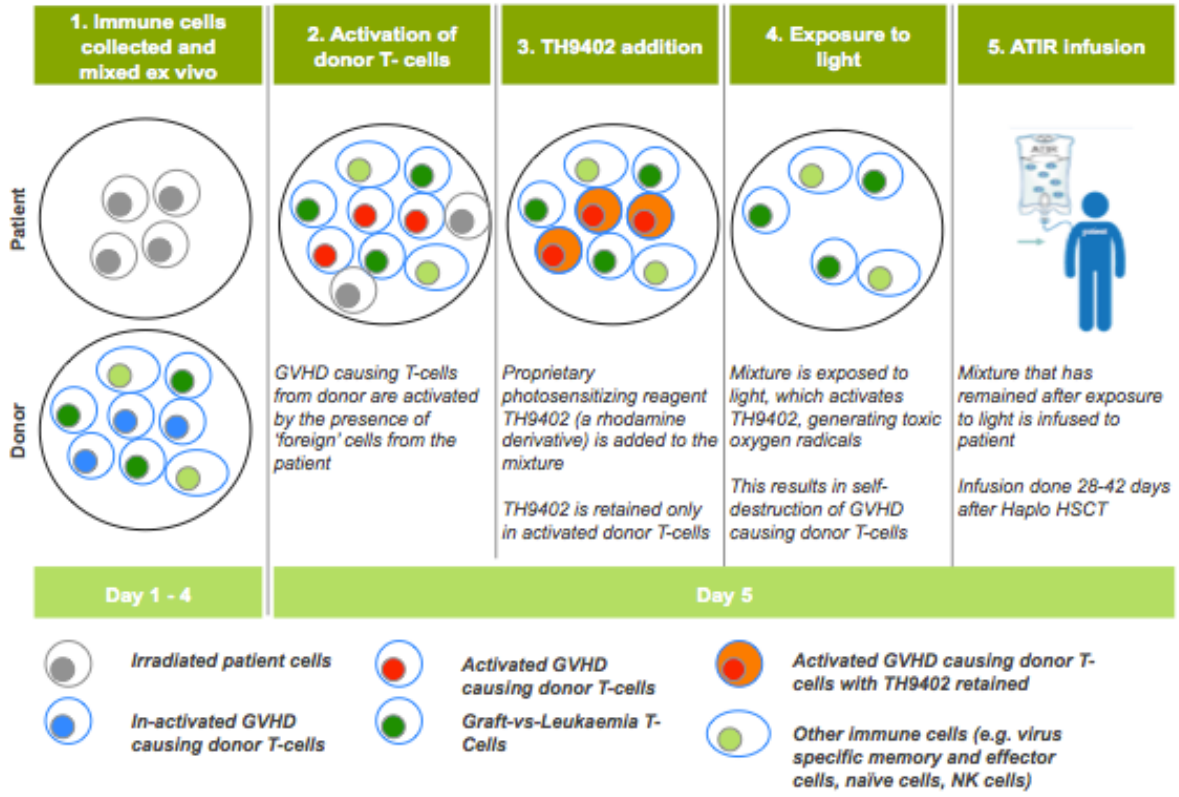

Figure 1 Schematic overview of the ATIR101 procedure

5.2 Treatments Administered

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 "solution 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% DMSO, and 30% donor plasma in saline 0.9%. The total volume of a unit is 20 mL (dose 2×10^6 viable T-cells/kg).

ATIR101 will be infused intravenously at a dose of 2×10^6 viable T-cells/kg body weight between 28 and 32 days after the HSCT (or later if required by the patient's medical condition). If not halted for safety reasons, patients will receive a second ATIR101 infusion between 70 and 74 days after the HSCT but at least 42 days after the first ATIR101 infusion (or later if required by the patient's medical condition). The second ATIR101 infusion will consist of a dose of 2×10^6 viable T-cells/kg (or an adjusted dose of 1×10^6 viable T-cells/kg when required).

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

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

In the event the patient fails to demonstrate hematologic engraftment (neutrophil count $\geq 0.5\times10^9$/L for 2 consecutive days and platelets $\geq 20\times10^9$/L for 3 consecutive days, without transfusion) bone marrow aspirate and biopsy will be performed and infusion of ATIR101 will be decided on a case by case basis after discussion between the coordinating investigator, Kiadis Pharma, and the investigator of the respective site.

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. The frozen product should be thawed in approx. 2 minutes at the bedside 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 without any ice crystals) until infusion of the entire unit (including rinsing the infusion bag with saline) should not take more than 10 minutes. Detailed instructions on the thawing and infusion process are provided in the Product Handling & Shipping Manual. Patients will be carefully monitored up to 4 hours after the infusion for any infusion reactions.

5.3 Selection and Timing of Dose for Each Patient

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

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.

Intravenous infusion of the first ATIR101 dose will be scheduled between 28 and 32 days after the HSCT (or later if required by the patient's medical condition). The second ATIR101 dose will be scheduled between 70-74 days after the HSCT but at least 42 days after the first ATIR101 infusion (or later if required by the patient's medical condition).

If beyond 120 days after the HSCT, according to the treating physician, a donor lymphocyte infusion is indicated (e.g., due to impending relapse or graft failure), a rescue dose of ATIR101 might be considered, 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.

5.4 Method of Assigning Patients to Treatment Groups

In this study all eligible patients will receive two units of 2×10^6 viable T-cells/kg ATIR101, unless the occurrence of DLT requires a decrease or halt of the second dose (see Section 5.3).

5.5 Blinding

In this open-label study no blinding will be applied.

5.6 Concomitant Therapy

All medications used during the study, except for ATIR101, 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, including prophylactic or preemptive use of anti-infective medication
- Medication for the treatment of disease relapse
- Medication for the treatment of other reported adverse events
- Additional hematopoietic stem cell grafts
- Additional lymphocyte infusions
- Hematopoietic growth factors
- Vaccinations

5.6.1 Immunosuppressives

Detailed recommendations on the treatment of graft versus host disease are provided in a separate guidance document.

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

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 1 mg/kg prednisolone).

5.6.2 Hematopoietic Growth Factors

Usually engraftment is rapid without G-CSF treatment. G-CSF has shown to reduce T-cell reactivity (Franzke *et al.* 2003). Therefore, post-transplantation G-CSF treatment should be

avoided unless medically indicated. The use of G-CSF will be at the discretion of the investigator.

5.6.3 Donor Lymphocyte Infusions (DLIs)

It is not allowed to treat patients with an unmanipulated DLI. If a DLI is indicated beyond 120 days post HSCT (e.g., due to impending relapse or graft failure) a rescue dose of ATIR101 might be considered, if available (see also Section 5.3). 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.

5.6.4 Anti-viral Drugs

Detailed recommendations on the prophylactic and preemptive treatment of viral infections are provided in a separate guidance document.

5.6.4.1 Cytomegalovirus (CMV)

In case of CMV positive recipient *and/or* donor:

- Mandatory CMV prophylaxis including ganciclovir and foscarnet. The following dosing schedule is recommended (Day 0 is the day of the 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.

All patients

- Weekly CMV monitoring by quantitative PCR from HSCT until Week 16 after the HSCT, monthly until Month 6 after the HSCT, and every 3 months until Month 12 after the HSCT. More frequent CMV monitoring is recommended depending on the patient's risk and the investigator's judgment.
- If quantified viral DNA levels exceed the institutional threshold for treatment of CMV (as established for each study center before participation in the study), patients should be treated with ganciclovir (recommended dose 5 mg/kg IV q12h) or valganciclovir (recommended dose 900 mg PO BID).

5.6.4.2 Epstein-Barr Virus (EBV)

In case of EBV positive recipient *and/or* donor:

- If donor or patient is EBV positive before transplantation or as indicated, EBV will be monitored weekly until Week 16 after the HSCT, monthly until Month 6 after the HSCT,

and every 3 months until Month 12 after the HSCT. More frequent EBV monitoring is recommended depending on the patient's risk and the investigator's judgment.

- If quantified viral DNA levels exceed the institutional threshold for treatment of EBV (as established for each study center before participation in the study), patients should be treated with rituximab.
  The following schedule is recommended:
  1. 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.
  2. 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 biopsy 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.
- 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.

5.6.4.3 Herpes Simplex Virus (HSV)

If during the study the investigator assesses the patient to be HSV positive but CMV negative, prophylactic treatment is recommended for at least 1 year and continued subsequently until the CD4+ lymphocyte count is above 0.2×10^9/L.

5.6.4.4 Varicella Zoster Virus (VZV)

If during the study the investigator assesses the patient to be VZV positive, prophylactic treatment is recommended for at least 1 year and continued subsequently until the CD4+ lymphocyte count is above 0.2×10^9/L. If the patient is VZV positive and CMV positive, prophylactic treatment is recommended for at least 1 year and until the CD4+ lymphocyte count is above 0.2×10^9/L (even if the patient receives ganciclovir or valganciclovir for CMV treatment).

5.6.5 Anti-bacterial, Anti-parasitic, and Anti-fungal Drugs

Detailed recommendations on the prophylactic treatment of bacterial, parasitic, and fungal infections are provided in a separate guidance document.

Prophylactic treatment against bacterial, parasitic and fungal infections prior to or post-transplantation according to institutional practices is recommended.

5.7 Treatment Compliance

Drug accountability of ATIR101 will be documented at the study centers.

5.8 Packaging and Labeling

ATIR101 will be packed in infusion bags as units of 20 mL (dose 2×10^6 viable T-cells/kg). Labeling will be done in accordance with applicable international guidelines.

5.9 Storage and Accountability

ATIR101 must be stored in liquid nitrogen (vapor phase). Storage of ATIR101 at the site is described in detail in the Product Handling & Shipping Manual.

In accordance with international guidelines, both Kiadis Pharma and the manufacturing facility will maintain records of all investigational products dispensed worldwide. After the completion of the study, the manufacturing facility 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.

Traceability

In this study traceability 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.

In accordance with international guidelines, Kiadis Pharma will maintain records of the origin of all cellular materials (donor lymphocytes) for a period of 30 years.

6 STUDY PROCEDURES

6.1 Informed Consent

Prior to participation in the study, each patient and his/her donor will sign the informed consent form. More details on the informed consent are given in Section 10.3.

6.2 Patient Characteristics and Eligibility

Demographics

Date of birth and gender of the patient will be recorded.

Hematologic malignancy

WHO classification of hematologic malignancy (Vardiman *et al.* 2009), cytogenetic and molecular abnormalities, date of first diagnosis, and presence of minimal residual disease will be recorded.

The EBMT risk score will be assessed according to Gratwohl (Gratwohl 2012; Michallet *et al.* 2010). See Appendix 2 for details.

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

Medical history

All existing medical conditions at the time of screening and other relevant medical history including information on previous 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 3).

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 4).

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.

High resolution CT scan of the thorax

A high resolution CT scan of the thorax 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.

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.

Pulmonary function test

A pulmonary function test will be used to assess the functional status of the lungs. This assessment may have been done within 6 weeks before signing informed consent.

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

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

Pregnancy test

A pregnancy test will be performed in females unless the patient is diagnosed as postmenopausal or if surgically sterilized.

Viral testing

At screening, the patient's blood 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, HLTV-I (not in Europe), HLTV-II (not in Europe), and WNV (North America only; in Canada depending on area at risk and season).

6.3 Donor Characteristics and Eligibility

Demographics

Date of birth and gender of the donor will be recorded as well as the family relation between donor and patient.

HLA compatibility

Mismatches at the HLA-A, -B and/or -DR loci (and if available at the HLA-C and –DQ loci) of the unshared haplotype will be assessed.

Viral testing

At screening, the donor's blood will be tested for the presence of the following viruses (and other micro-organisms) in accordance with local regulatory requirements and regulations for donations of human blood and blood components: EBV, CMV, HIV-1, HIV-2, HBV, HCV, Treponema pallidum, HLTV-I (not in Europe), HLTV-II (not in Europe), and WNV (North America only; in Canada depending on area at risk and season).

Pregnancy test

A pregnancy test will be performed in females unless the donor is diagnosed as postmenopausal or if surgically sterilized.

6.4 Vital Signs

The following vital sign parameters will be measured: respiration rate or oxygen saturation, pulse rate, temperature, weight, 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, 2, 3, and 4 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems.

6.5 Safety Laboratory Tests

Subjects will be in a seated or supine position during blood collection. Safety laboratory tests will include the following:

Table 1 List of safety laboratory tests

Hematology:	Blood Chemistry:
- Hematocrit	- Albumin
- Hemoglobin	- Alkaline phosphatase (AP)
- Mean corpuscular volume (MCV)	- Alanine aminotransferase (ALT)
- Platelet count	- Aspartate aminotransferase (AST)
- Red blood cell (RBC) count	- 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)
	- Sodium (Na)
	- Total bilirubin
Urinalysis:	- Total protein
- Bilirubin	- Urea

- Glucose
- Ketones
- Nitrite
- Blood
- pH
- Protein
- Specific gravity
- Leukocytes

CMV/EBV monitoring (PCR)

Patients will be monitored for CMV and EBV using local quantitative polymerase chain reaction (PCR) assays (see also Section 5.6.4).

Weekly CMV monitoring by quantitative PCR until Week 16 after the HSCT, monthly until Month 6, and every 3 months until Month 12. More frequent monitoring for CMV is recommended depending on the patient's CMV status at baseline and the investigator's judgment.

If donor or patient is EBV positive before transplantation or as indicated, EBV will be monitored weekly until Week 16 after the HSCT, monthly until Month 6, and every 3 months until Month 12. More frequent monitoring for EBV is recommended depending on the patient's EBV status at baseline and the investigator's judgment.

Engraftment

Engraftment is defined as neutrophil count $\geq 0.5\times10^9$/L for 2 consecutive days and platelets $\geq 20\times10^9$/L for 3 consecutive days, without transfusion. The first days of occurrence of these two 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.

Chimerism

A blood sample for assessment of chimerism will be collected on the days of the ATIR101 infusions, prior to the infusion of ATIR101. Chimerism will be assessed in peripheral blood lymphocytes and polynuclear cells (neutrophils) by PCR amplification.

6.6 Efficacy and Safety Assessments

6.6.1 Immune Reconstitution

Immunophenotyping

Immunophenotyping on peripheral blood samples by means of flow cytometry assessment of immune subsets should be done if the absolute lymphocyte count is higher than 0.1×10^9/L.

Immunophenotyping assessments are planned at screening, just before the ATIR101 infusions (Week 4 and Week 10), and at 5, 7, 9, 11, 12, 13, 14, 15, and 16 weeks after the HSCT, as well as at 5, 6, 9, and 12 months after the HSCT.

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

All measurements must be reported in absolute numbers of circulating lymphocytes ($\times10^9$/L) instead of percentages.

Immunoglobulins

The production of antibodies will be assessed by measuring the immunoglobulin levels of IgG, IgA, and IgM in peripheral blood.

Immunoglobulin assessments are planned at screening, just before the ATIR101 infusions (Week 4 and Week 9), at 11, 13, and 16 weeks after the HSCT, as well as at 5, 6, 9, and 12 months after the HSCT.

Additional assessments

Serum and peripheral blood will be collected for additional assessments of T-cell, B-cell and NK-cell reconstitution:

- Serum samples for measuring cytokine levels and/or immunoglobulins against specific antigens (e.g. vaccine response), prepared from 8-10 mL whole blood, will be collected at screening, at HSCT, just before the ATIR101 infusions (Week 4 and Week 10), at 5, 7, 9, 11, 12, 13, 14, 15, and 16 weeks after the HSCT, as well as at 5, 6, 9, and 12 months after the HSCT.

- Peripheral blood samples for measuring pathogen-specific T-cells will be collected at 6 and 12 weeks after the HSCT, as well as 6 and 12 months after the HSCT and when a clinically relevant viral reactivation or infection is diagnosed. The required volume of peripheral blood depends on the absolute CD3 count:

CD3 count ($\times 10^9$/L):	**Required volume (mL):**
≤ 0.2	50
> 0.2 and ≤ 0.4	35
> 0.4	20

6.6.2 Infection Assessment

In this study an infection is defined as a clinically apparent infectious disease with symptoms or detectable viral reactivation. Details of all infections will be recorded on the Infection AE page of the eCRF, including start date, stop date, NCI CTCAE severity grade (see Section 6.7), outcome, 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.

6.6.3 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 (see Section 6.7). In case of suspected relapse chimerism will be assessed to support the diagnosis. In addition, a bone marrow aspirate and/or biopsy must be performed at fixed visits unless relapse has already been confirmed (Screening, Month 6 after HSCT, Month 12 after HSCT) and in case of suspected relapse. If a bone marrow aspirate and/or biopsy was already performed within 6 weeks prior to a scheduled visit, the assessment does not need to be repeated.

6.6.4 Graft versus Host Disease Assessment

In this study GvHD must be classified into acute and chronic GvHD according to its clinical manifestations (Filipovich *et al.* 2005). Acute GvHD will be graded according to standard criteria (Przepiorka *et al.* 1995), which is also done for the severity of chronic GvHD (Filipovich *et al.* 2005) (see details in Appendix 5). Whenever deemed feasible, tissue biopsies will be obtained to confirm the GvHD diagnosis and to assess its severity. If not available yet, unscheduled hematology and blood chemistry laboratory tests (see Table 1) must be done to support the diagnosis of GvHD. Details of all GvHD events will be recorded on the GvHD AE page of the eCRF.

All GvHD cases will be subject to independent adjudication. If present, histological data are to be put at the adjudicator's disposal.

6.6.5 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
  - Disease progression
  - Transplant-related mortality (TRM) defined as death due to causes other than disease relapse or progression, or other known causes which are unrelated to the transplantation procedure (e.g. accident, suicide)
  - Other known cause unrelated to the transplantation procedure or underlying disease (e.g. accident, suicide)

All death cases will be subject to independent adjudication (see Section 10.8).

6.7 Adverse Events

Definition

A pre-treatment adverse event (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; it does not necessarily have to have a causal relationship with study participation.

A treatment-emergent adverse event (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.

Reporting of adverse events in patients

Within this study, infections including all detectable viral reactivations (see Section 6.6.2), relapse/disease progression (see Section 6.6.3), and GvHD (see Section 6.6.4) will be recorded separately, apart from the other AEs. While infections (including viral activations), relapse/disease progression and GvHD will be reported throughout the study, other AEs will only be reported until 16 weeks after the HSCT. AEs occurring before the first ATIR101 infusion that are related to the conditioning regimen or the HSCT and are listed in Appendix 6 do not need to be reported in the eCRF. However, all serious AEs during the study (see Section 6.8) must be reported in the eCRF.

Each event should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values and 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.

Pre-existing conditions (present at the time of signing the informed consent) are considered concurrent medical conditions and should not be recorded as AEs but as medical history. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded. Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").

AEs will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (June 2010). 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 AE page of the eCRF.

Each AE is to be evaluated for duration (start and end dates), severity grade and causal relationship with the study medication (certain, probable, possible, unlikely/unrelated). In addition, the actions taken for the AE will also be documented on the eCRF.

Reporting adverse events in donors

All AEs that occur from signing the informed consent of the donor until collection of the stem cells must be recorded on the AE page of the donor eCRF, except for the AEs that are caused by the administration of G-CSF, which should not be reported.

Severity

The severity grade of an AE provides a qualitative assessment of the extent or intensity of an adverse event, 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 grade for AEs will be based on the NCI CTCAE, version 4.0 (June 2010).[*]

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.

[*] Available on: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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

5 = Grade 5: Death related to adverse event

Causal relationship

All AEs will be examined to determine any relationship to ATIR101 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.

Actions taken

The actions taken in response to an adverse event are described on a numerical scale, from 0 to 3 that cover the various possibilities. The actions taken, as presented in the eCRF, are provided below. One or more of these is to be selected.

0 = No action taken
1 = Concomitant medication taken
2 = Non-drug therapy given
3 = Hospitalization / prolonged hospitalization

6.8 Serious Adverse Events

Definition

A serious adverse event (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;
- 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.

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

Reporting serious adverse events

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 in the eCRF, on the applicable AE page.

The SAE report form should be sent by fax to Drug Safety Solutions, Inc (Raleigh, USA).

SAE fax number:	**+1 919-844-6948**
Backup fax number:	+1 919-882-8337

Both the original and the duplicate NCR copy of the SAE report form, together with the fax confirmation sheet, must be kept at the study site. If the initial report is made verbally or by telephone, a written confirmation via 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 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 Kiadis Pharma 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.

6.9 Concomitant Medication Assessments

The following concomitant medications must be recorded in the eCRF:

- Medication for the treatment of GvHD
- Medication for the treatment of infections, including prophylactic or preemptive use of anti-infective medication
- Medication for the treatment of disease relapse
- Medication for the treatment of other reported adverse events
- Additional hematopoietic stem cell grafts
- Additional lymphocyte infusions
- Hematopoietic growth factors
- Vaccinations

6.10 Discontinuation of Patients from the Study

Patients who are planned to receive two doses of ATIR101 and who receive only one dose, will not be discontinued from the study, but will require the enrolment of an additional patient.

Patients who do not receive ATIR101 will be discontinued from the study and replaced by a new patient. In addition, the investigator may discontinue a patient from the study for any of the following reasons:

- The patient relapsed before collection of PBMCs for the manufacturing of ATIR101 and did not achieve remission upon additional chemotherapy,
- The stem cell graft is not suitable for patient administration,
- The patient requests to be withdrawn, or 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 eCRF as end-of-study information.

When a patient is discontinued from the study after having received a stem cell transplantation (with or without ATIR101 infusion), and if the patient agreed on the ICF, limited information on disease status, GvHD, and mortality at 6 and 12 months after the HSCT will be collected. If a patient is discontinued from the study after ATIR101 infusion, efforts will be made to report SAEs until at least 3 months after the infusion of ATIR101.

If a patient for whom ATIR101 has been manufactured 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 if treatment with an HSCT followed by ATIR101 may be beneficial at a later stage. After re-assessment of patient eligibility the study schedule may be resumed if ATIR101 can still be administered within its shelf-life.

In case it will be decided that the study will be prematurely terminated, all patients who are still in the study should at least complete the visit at Week 16 after the HSCT. After premature termination of the study, patients will be followed up for the occurrence of serious adverse events (SAEs) until 6 months after ATIR101 administration.

7 STUDY ASSESSMENTS BY VISIT

Unless otherwise specified, study assessments in this section apply to the patient. See Appendix 1 for a tabulated schedule of study assessments.

7.1 Screening: Between Informed Consent and Apheresis

- Informed consent patient and donor
- Apheresis patient and donor
- Patient characteristics and eligibility
  - Demographics
  - Hematologic malignancy
  - Medical history
  - Performance status
  - Physical examination
  - High resolution CT scan of the thorax (if not already done within 6 weeks before signing informed consent, unless the patient experienced a significant event between the date of the original assessment and the date of screening)
  - Echocardiogram/MUGA scan (if not already done within 6 weeks before signing informed consent, unless the patient experienced a significant event between the date of the original assessment and the date of screening)
  - Pulmonary function test (if not already done within 6 weeks before signing informed consent, unless the patient experienced a significant event between the date of the original assessment and the date of screening)
  - Creatinine clearance (calculated or measured, if not already done within 2 weeks before signing informed consent)
  - Pregnancy test; only for females who are not diagnosed as postmenopausal or who are surgically sterilized
  - Viral testing
- Donor characteristics and eligibility
  - Demographics
  - HLA compatibility
  - Viral testing
  - Pregnancy test; only for female donors who are not diagnosed as postmenopausal or who are surgically sterilized
- Donor adverse events
- Vital signs
- Safety laboratory tests
  - Hematology
  - Blood chemistry
  - Urinalysis
- Efficacy and safety assessments
  - Immunophenotyping
  - Immunoglobulins
  - Serum sampling for additional assessments of immune reconstitution

  - Infection assessment
  - Disease assessment
    A bone marrow aspirate and/or biopsy are performed if not already done within 6 weeks before signing informed consent.
  - Other adverse events
- Concomitant medications

7.2 HSCT (Day 0)

- HSCT
- Physical examination
- Donor adverse events (until collection of stem cells)
- Vital signs
- Safety laboratory tests
  - Hematology
  - Blood chemistry
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
- Efficacy and safety assessments
  - Serum sampling for additional assessments of immune reconstitution
  - Infection assessment
  - Disease assessment
  - Other adverse events
- Concomitant medications

7.3 Week 1, Week 2, and Week 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

Study assessments:

- Weekly safety laboratory tests
  - Hematology
  - Blood chemistry
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
- Efficacy and safety assessments
  - Infection assessment

  - Disease assessment
  - GvHD assessment
  - Other adverse events
- Concomitant medications
- Engraftment

7.4 First ATIR101 Infusion (Week 4)

The visit must be performed within 28-32 days after the HSCT unless the patient's medical requires that ATIR101 is infused later, e.g. because the patient is suffering from acute GvHD. If the first ATIR101 infusion is postponed, the subsequent weekly visits will be moved accordingly and extra visits before the first ATIR101 infusion will be scheduled.

Study assessments:

- ATIR101 infusion
- Physical examination
- Vital signs before ATIR101 infusion
  In addition, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1, 2, 3, and 4 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems.
- Safety laboratory tests
  - Hematology
  - Blood chemistry
  - Urinalysis
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
  - Chimerism before ATIR101 infusion
- Efficacy and safety assessments
  - Immunophenotyping before ATIR101 infusion
  - Immunoglobulins before ATIR101 infusion
  - Serum sampling for additional assessments of immune reconstitution; before ATIR101 infusion
  - Infection assessment
  - Disease assessment
  - GvHD assessment
  - Other adverse events
- Concomitant medications

7.5 Week 5, Week 6, Week 7, Week 8, and Week 9

Visits must be performed within the following windows:

- Week 5: 5 weeks ± 2 days after the HSCT

- Week 6: 6 weeks ± 2 days after the HSCT
- Week 7: 7 weeks ± 2 days after the HSCT
- Week 8: 8 weeks ± 2 days after the HSCT
- Week 9: 9 weeks ± 2 days after the HSCT

Study assessments:

- Physical examination, only at Week 6 and Week 8
- Vital signs
- Safety laboratory tests
  - Hematology
  - Blood chemistry
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
- Efficacy and safety assessments
  - Immunophenotyping, only at Week 5, Week 7, and Week 9
  - Serum sampling for measuring cytokine levels and/or immunoglobulins against specific antigens, only at Week 5, Week 7, and Week 9
  - Peripheral blood sampling for measuring pathogen-specific T-cells, only at Week 6
  - Infection assessment
  - Disease assessment
  - GvHD assessment
  - Other adverse events
- Concomitant medications

7.6 Second ATIR101 Infusion (Week 10)

The visit must be performed 70-74 days after the HSCT but at least 42 days after the first ATIR101 infusion, unless the patient's medical condition requires that ATIR101 is infused later, e.g. because the patient is suffering from acute GvHD. If the second ATIR101 infusion is postponed, the subsequent weekly visits will be moved accordingly and one or more unscheduled visits may be added before the second ATIR101 infusion.

Study assessments:

- ATIR101 infusion
- Physical examination
- Vital signs before ATIR101 infusion
  In addition, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1, 2, 3, and 4 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems.
- Safety laboratory tests
  - Hematology

  - Blood chemistry
  - Urinalysis
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
  - Chimerism before ATIR101 infusion
- Efficacy and safety assessments
  - Immunophenotyping before ATIR101 infusion
  - Immunoglobulins before ATIR101 infusion
  - Serum sampling for measuring cytokine levels and/or immunoglobulins against specific antigens; before ATIR101 infusion
  - Infection assessment
  - Disease assessment
  - GvHD assessment
  - Other adverse events
- Concomitant medications

7.7 Week 11, Week 12, Week 13, Week 14, Week 15, and Week 16

Visits must be performed within the following windows:

- Week 11: 11 weeks ± 2 days after the HSCT
- Week 12: 12 weeks ± 2 days after the HSCT
- Week 13: 13 weeks ± 2 days after the HSCT
- Week 14: 14 weeks ± 2 days after the HSCT
- Week 15: 15 weeks ± 2 days after the HSCT
- Week 16: 16 weeks ± 2 days after the HSCT

Study assessments:

- Physical examination, only at Week 12, Week 14, and Week 16
- Vital signs
- Safety laboratory tests
  - Hematology
  - Blood chemistry
  - Urinalysis, only at Week 16
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
- Efficacy and safety assessments
  - Immunophenotyping
  - Immunoglobulins, only at Week 11, Week 13, and Week 16
  - Serum sampling for measuring cytokine levels and/or immunoglobulins against specific antigens

- Peripheral blood sampling for measuring pathogen-specific T-cells, only at Week 12
- Infection assessment
- Disease assessment
- GvHD assessment
- Other adverse events

- Concomitant medications

7.8 Month 5, Month 6, Month 9, and Month 12

Visits must be performed within the following windows:

- Month 5 after HSCT: 5 months ± 1 week after the HSCT
- Month 6 after HSCT: 6 months ± 1 week after the HSCT
- Month 9 after HSCT: 9 months ± 2 weeks after the HSCT
- Month 12 after HSCT: 12 months ± 2 weeks after the HSCT

Study assessments:

- Safety laboratory tests
  - CMV monitoring (PCR)
  - EBV monitoring (PCR), if donor or patient is EBV positive before HSCT or as indicated
- Efficacy and safety assessments
  - Immunophenotyping
  - Immunoglobulins
  - Serum sampling for measuring cytokine levels and/or immunoglobulins against specific antigens
  - Peripheral blood sampling for measuring pathogen-specific T-cells, only at Month 6 and Month 12
  - Infection assessment
  - Disease assessment
    At Month 6 and Month 12 a bone marrow aspirate and/or biopsy are performed (unless relapse has already been confirmed and if not already done within 6 weeks before the visit).
  - GvHD assessment
- Concomitant medications

7.9 End of Study

When a patient discontinues from the study the primary reason for study withdrawal is recorded along with the date of study discontinuation (see also Section 6.10).

When a patient is discontinued from the study after having received a stem cell transplantation (with or without ATIR101 infusion), and if the patient agreed on the ICF, limited information on disease status, GvHD, and mortality at 6 and 12 months after the HSCT will be collected.

8 QUALITY CONTROL AND ASSURANCE

8.1 ATIR101 Manufacturing

ATIR101 will be manufactured as individualized patient batches at a manufacturing facility, under supervision of Kiadis Pharma. Before start of the study, Kiadis Pharma Quality Assurance (QA) will qualify the 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 used in study CR-AIR-008. 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.

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 project manual. The purpose of the project manual 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 project manual 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 requirements. For deviations from the approved protocol see also Section 10.9.

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.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Details of the planned analyses will be described in a statistical analysis plan (SAP). Any deviations from the SAP will be justified in the clinical study report.

9.2 Determination of Sample Size

In this exploratory study, 15 patients with a hematologic malignancy who are eligible for a haploidentical HSCT will be treated with two doses of ATIR101. This sample size has been calculated with the following formula based on the primary endpoint (incidence of acute GvHD grade III/IV up to 180 days post HSCT):

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

where n = sample size

z^* = z-value related to confidence interval, i.e. **1.645** for a one-sided 95% confidence interval

m = desired margin of error, i.e. **13%**

p^* = estimated population proportion, i.e. **10%** acute GvHD grade III/IV 180 days post HSCT

9.3 Analysis Populations

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

Intention-to-treat (ITT) population

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

Modified intention-to-treat (MITT) population

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

Per protocol (PP) population

The PP population consists of all patients who:

- Received the first ATIR101 between 28 and 42 days after the HSCT,
- Received the second ATIR101 infusion between 70 and 84 days after the HSCT (if they received a second ATIR101 infusion),

- Showed hematologic engraftment (neutrophil count $\geq 0.5\times10^9$/L for 2 consecutive days and platelets $\geq 20\times10^9$/L for 3 consecutive days, without transfusion) at the time of the first ATIR101 infusion (see Section 5.2), and
- Did not present any major protocol deviations (see Section 10.9).

Safety population

The safety population will include all patients who received an HSCT and provided informed consent.

9.4 Demographics and Baseline Characteristics

Descriptive statistics will be provided for demographics and other baseline characteristics.

9.5 Primary Endpoint (Safety)

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

From the assumptions in Section 9.2 it can be derived that the study fails if the incidence of acute GvHD grade III/IV up to 180 days post HSCT in the MITT population exceeds 23% (desired margin of error + estimated population proportion).

9.6 Secondary Endpoints

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

- Incidence and severity of acute and chronic graft versus host disease (GvHD)
- Time to T-cell reconstitution, defined as the time to CD3+ in peripheral blood higher than 0.2×10^9/L (at two consecutive measurements; time to first measurement)
- Incidence and severity of viral, fungal, and bacterial infections
- Transplant-related mortality (TRM), defined as death due to causes other than disease relapse or progression, or other causes which are unrelated to the transplantation procedure (e.g. accident, suicide)
- Relapse-related mortality (RRM), defined as death due to disease relapse or disease progression
- Overall survival (OS), defined as the time from HSCT until death from any cause
- Progression-free survival (PFS), defined as the time from HSCT until relapse, disease progression, or death, whichever occurs first
- GvHD-free, relapse-free survival (GRFS), defined as the time until acute GvHD grade III/IV, chronic GvHD requiring systemic treatment, relapse, or death, whichever occurs first (Holtan *et al.* 2015)

All endpoints will be analyzed using descriptive statistics. Immune reconstitution will be graphically displayed in time. The Kaplan-Meier method will be used to display and estimate probability of time-related survival data (OS, PFS, GRFS). In addition, cumulative incidence curves taking into account competing risks will be used to display and estimate cumulative incidences of TRM, RRM, and GvHD.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Independent Ethics Committee (IEC) Approval

The study protocol and any amendments must be reviewed by an appropriate independent ethics committee (IEC) that is constituted and operating in accordance with Good Clinical Practice (GCP) and applicable national/local laws and regulations. The study may only start after receipt of written IEC approval by the sponsor.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (and all amendments thereof) and that are consistent with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (Topic E6 [R1]) as well as the applicable regulatory requirements.

10.3 Patient and Donor Information and Consent

- The informed consent forms and any other written study materials provided to the patients and donors have to be approved by an IEC 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.
- 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.
- 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.

10.4 Patient Confidentiality

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.

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 (if appropriate), and Kiadis Pharma.

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.

10.5 Study 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, 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 monitor(s). The sponsor will provide the monitor(s) with adequate training on the study protocol. The study will be monitored in accordance with the clinical monitoring plan.

10.6 Electronic Case Report Forms and Study Records

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 but were not eligible for study participation, the minimum demographic data (date 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 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.

10.7 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to monitor the safety of the patients in study CR-AIR-008. The IDMC will consist of three members, who are not affiliated to the sponsor. The members of the IDMC are responsible for safeguarding the interests of the patients by reviewing the safety and mortality data during the study. 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.

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.

10.8 Adjudication Committees

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

- To ensure a more 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 together with the treating investigator. If this final GvHD assessment is different from the assessment made earlier by the treating investigator, the eCRF will be adjusted according to the final assessment agreed upon. 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.

10.9 Major Protocol Deviations

In this study the following deviations from the protocol will be considered major protocol deviations and will be reported as such in the clinical study report:

- Non-adherence to inclusion/exclusion criteria
- Patient suffering from active GvHD (any grade) at the time of ATIR101 infusion (see Section 5.2)

- Patient having received steroid-based immunosuppressive therapy (excluding topical steroids) at the time of ATIR101 infusion (see Section 5.2).
- Patient received an unmanipulated DLI (see Section 5.6.3)

10.10 Access to Source Documentation

The investigator and the study site must accept monitoring and auditing by Kiadis Pharma or their representatives as well as inspections from the IEC 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, 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.

10.11 Data Generation and Analysis

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 (DMP). Coding of medical terms will be performed using MedDRA.

10.12 Retention of Data

All essential documents as defined by ICH-GCP must be retained by the investigator for as long as necessary to comply with national and international regulations but at least 2 years after the last marketing approval or after discontinuation of clinical development. Kiadis Pharma will notify the investigators when the investigator study file is no longer needed.

10.13 Financial Disclosure

The investigators have no disclosable financial interests in or arrangements with the sponsor of this clinical study, i.e. Kiadis Pharma Netherlands B.V.

10.14 Publication and Disclosure Policy

Publication policy

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.

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Appendix 1 Schedule of Study Assessments

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

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

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

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

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

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

Appendix 2 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 transplant (months)	< 12	> 12	-
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

Appendix 3 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 4 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 5 Classification of Graft versus Host Disease (GvHD)

ACUTE GRAFT VERSUS HOST DISEASE (Przepiorka *et al.* 1995)

Severity of Individual Organ Involvement

Skin

Stage 1 maculopapular rash involving less than 25% of the body surface
Stage 2 maculopapular rash involving 25-50% of the body surface
Stage 3 generalized erythroderma
Stage 4 generalized erythroderma with bullous formation and often with desquamation

Liver

Stage 1 bilirubin 2-3 mg/dL
Stage 2 bilirubin 3-6 mg/dL
Stage 3 bilirubin 6-15 mg/dL
Stage 4 bilirubin > 15 mg/dL

Gut

Diarrhea is graded Stage 1 to 4 in severity. Nausea and vomiting and/or anorexia caused by GvHD is assigned as Stage 1 severity.

The severity of gut involvement is assigned to the most severe involvement noted. Patients with visibly bloody diarrhea are at least a Stage 2 gut and grade III overall.

Stage 1 diarrhea > 500 mL/day in the absence of infectious/medical cause.
Stage 2 diarrhea > 1000 mL/day
Stage 3 diarrhea > 1500 mL/day
Stage 4 severe abdominal pain with or without ileus

Grading of acute GvHD

Grade	Skin	Liver	Gut
I	Stage 1-2	0	0
II	Stage 3 **or**	Stage 1 **or**	Stage 1
III	-	Stage 2-3 **or**	Stage 2-4
IV	Stage 4 **or**	Stage 4	

CHRONIC GRAFT-VERSUS-HOST DISEASE

The global scoring system for chronic GvHD (Filipovich *et al.* 2005) reflects the clinical effect of chronic GvHD on the patient's functional status. Elements included in this global scoring system include both the number of organs or sites involved and the severity within each affected organ (note that 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 involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites).
- Moderate chronic GvHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GvHD.
- Severe chronic GvHD indicates major disability caused by chronic GvHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GvHD.

Table 2 shows the scoring system for individual organs.

Table 2 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 *Clinical features:* Maculopapular rash Lichen planus-like features Papulosquamous lesions or ichthyosis Hyperpigmentation Hypopigmentation Keratosis pilaris	No symptoms	<18% BSA with disease signs but NO sclerotic features	19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	>50% BSA OR deep sclerotic features "hidebound" (unable to pinch) OR impaired mobility, ulceration or severe pruritus

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Erythema Erythroderma Poikiloderma Sclerotic features Pruritus Hair involvement Nail involvement **% BSA involved**				
MOUTH	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 *Mean tear test (mm):* >10 6-10 ≤5 Not done	No symptoms	Mild dry eye symptoms not affecting ADL (requiring eye drops <3 x per day) OR asymptomatic signs of keratoconjunctivitis sicca	Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	No symptoms	Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	Symptoms associated with mild to moderate weight loss (5-15%)	Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	Normal LFT	Elevated Bilirubin, AP, AST or ALT <2 x ULN	Bilirubin >3 mg/dL or Bilirubin, enzymes 2-5 x ULN	Bilirubin or enzymes > 5 x ULN
LUNGS† FEV1 DLCO	No symptoms FEV1 >80% OR LFS=2	Mild symptoms (shortness of breath after climbing one flight of steps) FEV1 60-79% OR LFS 3-5	Moderate symptoms (shortness of breath after walking on flat ground) FEV1 40-59% OR LFS 6-9	Severe symptoms (shortness of breath at rest; requiring O_2) FEV1 <39% OR LFS 10-12
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM)	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis,	Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
		AND not affecting ADL	moderate decrease ROM **AND** mild to moderate limitation of ADL	(unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	No symptoms	Symptomatic with mild signs on exam AND no effect on coitus and minimal discomfort with gynecologic exam	Symptomatic with moderate signs on exam AND with mild dyspareunia or discomfort with gynecologic exam	Symptomatic WITH advanced signs (stricture, labial agglutination or severe ulceration) AND severe pain with coitus or inability to insert vaginal speculum

OTHER INDICATORS, CLINICAL MANIFESTATIONS OR COMPLICATIONS RELATED TO CHRONIC GvHD

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

Esophageal stricture or web___
Pericardial effusion___
Pleural Effusion(s)___
Ascites (serositis)___
Nephrotic syndrome___
Peripheral neuropathy___
Myasthenia gravis___
Cardiomyopathy___
Eosinophilia > 500µL___
Polymyositis___
Cardiac conduction defects___
Coronary artery involvement___
Platelets <100,000/µL ___
Progressive onset___
Others: specify:___

†Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. GvHD indicates graft versus host disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Appendix 6 Adverse Events Not to Be Reported in the Electronic Case Report Form When Occurring Before ATIR101 Infusion

1. ANTICIPATED AEs DUE TO THE USE OF HEMATOPOIETIC GROWTH FACTORS:
   - Fever and muscle or bone pain due to G-CSF

2. ANTICIPATED AEs DUE TO THE CONDITIONING REGIMEN (expected to occur in the period between the start of the conditioning regimen and ATIR101 infusion):
   - Neutropenia, leukopenia, and thrombocytopenia
   - Marrow aplasia
   - Fever, chills, allergic reaction, dermatological reactions, increased liver enzymes, alopecia, hematuria, gastrointestinal toxicity, and sterility
   - Anaemia
   - Additional acute toxicities including nausea and vomiting, mucositis, diarrhea, parotitis, and skin erythema
   - Fatigue and lethargy
   - Hypoproteinaemia, hypoglycaemia, hyperglycaemia
   - Blood electrolytes abnormal
   - Renal impairment

Appendix 7 Sponsor Signature

Study Title:	An exploratory, open-label, multicenter study to evaluate the safety and efficacy of a two-dose regimen of ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment), in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor
Study Number:	CR-AIR-008
Original Protocol Date:	9 July 2015
Amendment 1 Date:	20 November 2015

This clinical study protocol has been approved by the sponsor.

Signed:_____ Date: 20 November 2015

Jeroen Rovers, MD PhD
Chief Medical Officer
Kiadis Pharma Netherlands B.V.

Appendix 8 Investigator's Signature

Study Title:	An exploratory, open-label, multicenter study to evaluate the safety and efficacy of a two-dose regimen of ATIR101, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment), in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor
Study Number:	CR-AIR-008
Original Protocol Date:	9 July 2015
Amendment 1 Date:	20 November 2015

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 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: …….

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