2 SYNOPSIS

Sponsor: **Individual Study Table**

Kiadis Pharma Netherlands B.V.

Name of Finished Product:

ATIR

Name of Active Ingredient:

Donor T-lymphocytes depleted of host alloreactive T-cells

Study Title:
An open-label, uncontrolled, multicenter, multinational study on the efficacy and safety of administration of donor lymphocytes depleted of alloreactive T-cells (ATIR), through the use of TH9402 and light treatment in an *ex vivo* process, in patients receiving a CD34-selected peripheral blood stem cell graft from a related, haploidentical donor

Investigators and Study Centers:
10 Investigators from study centers in Belgium (3 centers), Canada (2 centers), Germany (2 centers), the United Kingdom (1 center), the Netherlands (1 center), and the United States (1 center)

Publication (reference):
Not applicable

Studied Period:
27 October 2009 (first patient in study) to
8 February 2012 (study prematurely terminated)

Objectives:

Primary objective:

- To study the effects of the administration of a donor lymphocyte preparation selectively depleted of host alloreactive T-cells (ATIR) to patients with hematologic malignancies on 6 months and 12 months transplant-related mortality (TRM).

Secondary objectives:

- To study the effects of ATIR on overall survival (OS).
- To study the effects of ATIR on the incidence and severity of acute graft-versus-host disease (GVHD).
- To study the effects of ATIR on the incidence and severity of chronic GVHD.
- To study the effects of ATIR on progression-free survival (PFS).
- To study the effects of ATIR on the incidence and severity of bacterial, viral or fungal infections.
- To study the effects of ATIR on immune reconstitution.
- To study the effects of ATIR on the health status of patients (including quality of life).

Methodology:
CR-AIR-004 was an open-label, uncontrolled, multicenter, multinational study. Patients underwent a hematopoietic stem cell transplant (HSCT; CD34-selected graft) from a related haploidentical donor, preceded by a conditioning regimen consisting of (1) fractionated total body irradiation (TBI), fludarabine and thiotepa or, (2) non-fractionated TBI, fludarabine and thiotepa or, (3) fludarabine, thiotepa and melphalan. Infusion with ATIR was scheduled

between 28 and 42 days after the HSCT (as soon as possible but not earlier than 28 days post HSCT).
The primary analyses were planned to be conducted using 6 and 12-month follow-up data post HSCT. Patients were assessed weekly for the first 100 days after the transplantation, every month up to 6 months after the transplantation, every 2 months up to 12 months after the transplantation, and subsequently every 3 months up to 24 months after the transplantation.

Number of Patients (Planned and Analyzed):
A minimum of 60 patients were planned to be treated with the ATIR. The study was early terminated after 40 patients had been treated. Data of these 40 patients have been analyzed.

Diagnosis and Main Criteria for Inclusion:
Patients aged between 18 and 65 years who were eligible for an allogeneic transplant but without the availability of a suitable matched related or unrelated donor following a donor search (as judged by the treating physician), were eligible to participate in this trial. Patients with the following hematologic malignancies could be enrolled: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), multiple myeloma (MM), myeloproliferative syndrome (MPS), and non-Hodkin's lymphoma (NHL). Eligible patients were classified as having a primary indication (Group 1) or a secondary indication (Group 2) depending on their malignancy type and disease status. In general, patients with a primary indication are expected to have a better prognosis compared to patients with a secondary indication.
Donors were haploidentical (i.e. 2 to 3 mismatches at the HLA-A, -B and/or -DR loci of the unshared haplotype) family members aged between 16 and 75 years who were eligible to donate hematopoietic cells.

Investigational Medicinal Product (IMP), Dose and Mode of Administration:
For manufacturing of the IMP, donor and recipient lymphocytes collected by apheresis were co-cultured in a mixed lymphocyte reaction (MLR) to stimulate proliferation of alloreactive T-cells (the recipient cells are gamma irradiated prior to the MLR). Subsequently the cells were exposed to *ex vivo* photodynamic treatment (PDT), using the photosensitizing compound TH9402, for the depletion of host alloreactive T-cells. The IMP was cryopreserved until infusion to the patient between Day 28 and Day 42 (as soon as possible, but not earlier than 28 days post HSCT). The IMP was administered intravenously (IV) at a dose of $2x10^6$ viable T-cells/kg at formulation.

Duration of Treatment:
The IMP was administered as a single IV infusion.

Criteria for Evaluation:
Primary endpoints of the study were the (cumulative) incidences of TRM at 6 and 12 months after the HSCT. TRM was defined as death due to causes other than disease relapse/progression, or other causes which were unrelated to the transplant procedure (e.g. accident, suicide).
The primary aim of the trial was to show that the incidence of TRM with ATIR was low compared with historical data from the literature.

Statistical Methods:
Efficacy: TRM and OS were analyzed using descriptive statistics and the Kaplan-Meier method.
Safety: descriptive statistics.

Termination of the Study:

After 40 patients had been treated, Kiadis Pharma decided to temporarily halt patient enrollment due to an increased rate of batches that were out of specification without a clearly defined root cause. During the failure investigation it became clear that Kiadis Pharma also had to investigate the quality of the IMP as well as interim efficacy data.

- Characterization of the IMP (and intermediates) manufactured for this study showed a large proportion of dead or dying cells after thawing the samples (data on file). Further investigations revealed that the storage of the apheresis materials (mostly 48-72 hours at 2-8 °C) prior to the manufacturing of the IMP is likely to have contributed to the low viability of cells in the final product compared to the IMP in Study CR-GVH-001 (first-in-man study of ATIR), which was manufactured from freshly collected cells.
- Interim mortality data of all patients treated with the IMP (N=40) did not show an improvement of TRM or OS after administration of the IMP in Study CR-AIR-004 compared with patients who received a haploidentical HSCT without addition of donor-T-cells (interim results of observational cohort Study CR-AIR-006). Thus, the IMP manufactured for Study CR-AIR-004 was not efficacious.

In conclusion, the IMP manufactured for Study CR-AIR-004 was in general not comparable to the IMP manufactured for Study CR-GVH-001 and mainly contained dead or dying cells. As a result Kiadis Pharma has decided to prematurely terminate Study CR-AIR-004 on 8 February 2012.

Summary of Results

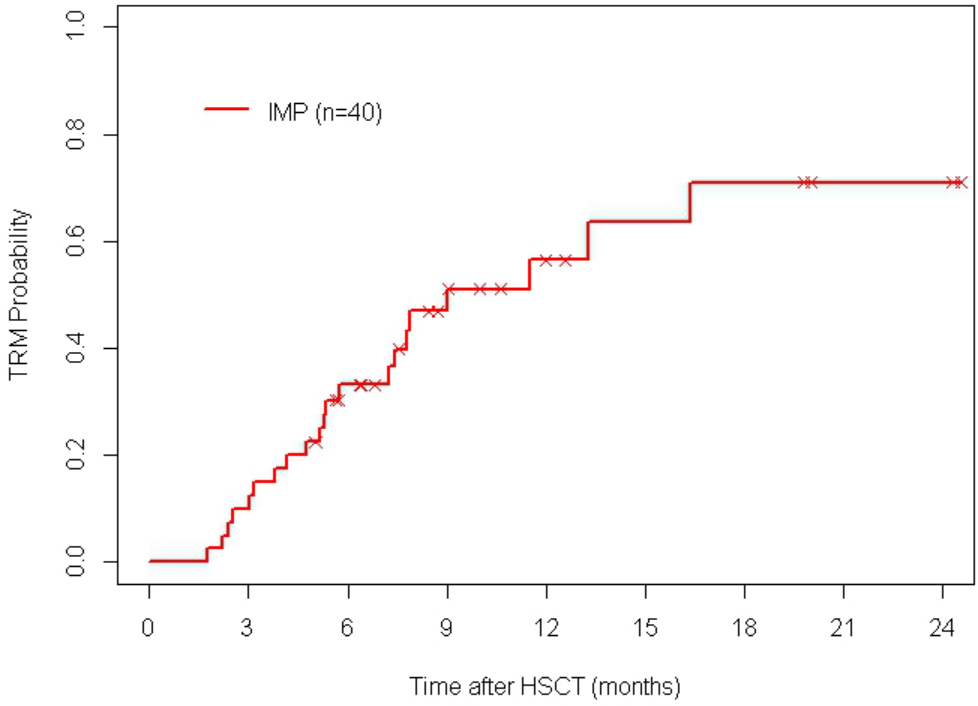
Of the 68 screened patients, 64 were enrolled, and 40 were treated with IMP. Two patients completed the follow-up period of 2 years. At the termination of the study (on 8 February 2012), 12 patients who had received IMP were still in the follow-up phase of the study with a median follow-up of 7.2 months post HSCT (range 5.7-20.0 months).
The 40 patients infused with IMP (24 males, 16 females) had a median age of 45 years (range 19-65). The majority of them (90%) were white. In total, 26 patients (65%) were diagnosed with a primary indication (Group 1) and 14 patients (35%) were diagnosed with a secondary indication (Group 2). Within the 40 patients treated with the IMP (N=40), the most frequently observed hematologic malignancies were AML (52.5%) and ALL (15%). Donors of the patients who received the IMP had either 2 incompatibilities (32.5% of the donors) or 3 incompatibilities (67.5% of the donors) at the HLA-A, -B, and –DR loci compared to the patient.

Efficacy:

Of the 40 patients treated with IMP, 25 patients died during the study at a median of 5.8 months post haploidentical HSCT (mean 7.0 months, range 1.7-16.4 months). Of these 25 patients, 21 patients died as a result of transplant-related mortality (TRM) and 4 died due to disease relapse/progression.

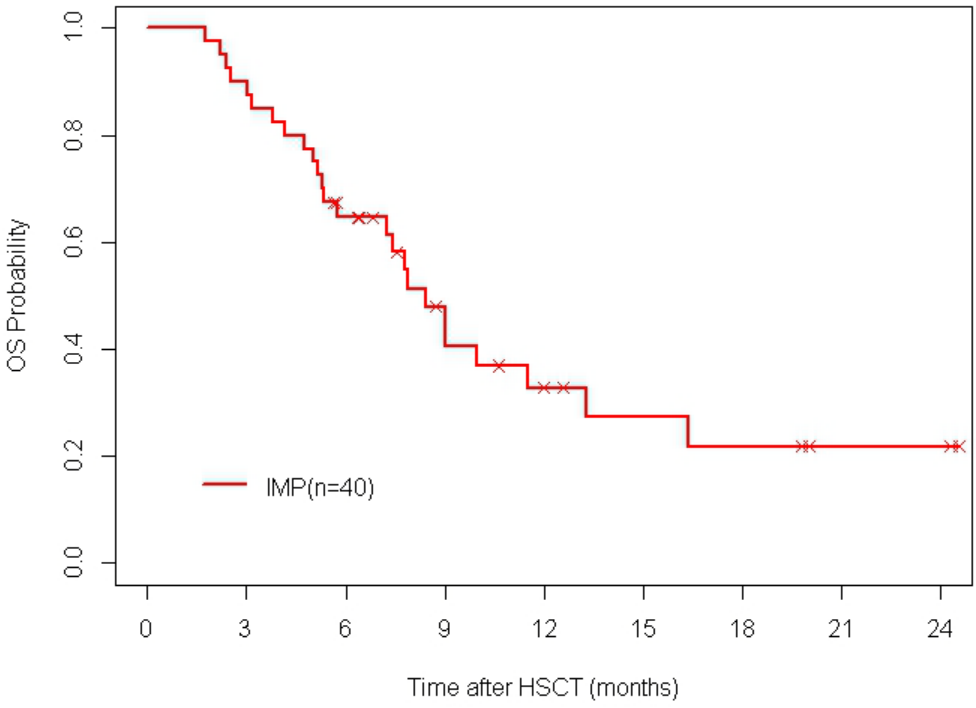
The figure below presents TRM probability by time for patients treated with IMP. Censoring has been applied for patients who died within 2 years post HSCT due to disease relapse/progression and patients with less than 2 years follow-up. At 12 months post HSCT, TRM probability is estimated to be 56%.

TRM probability by time for patients treated with IMP



The figure below presents OS probability by time for patients treated with IMP. Censoring has been applied for patients with less than 2 years follow-up. At 12 months post HSCT, OS probability is estimated to be 33%.

OS probability by time for patients treated with IMP



Kaplan-Meier estimates at 6, 12, and 24 months post HSCT overall and by group are displayed in the table below.

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

	6 months after the HSCT	12 months after the HSCT	24 months after the HSCT
Transplant-related mortality (TRM)			
Overall (N=40)	33%	56%	71%
Indication Group 1 (n=26)	36%	74%	83%
Indication Group 2 (n=14)	29%	29%	53%
Overall survival (OS)			
Overall (N=40)	65%	33%	22%
Indication Group 1 (n=26)	61%	20%	13%
Indication Group 2 (n=14)	71%	54%	36%

Safety:

Overview of adverse events

		Patients treated with IMP (N=40)
Treatment-emergent AEs	No of patients (%) No of events	40 (100%) 1105
IMP-related AEs	No of patients (%) No of events	15 (37.5%) 173
Treatment-emergent SAEs	No of patients (%) No of events	39 (97.5%) 187
IMP-related SAEs	No of patients (%) No of events	9 (22.5) 20
Deaths	No of patients (%)	27 (67.5%) #

Treatment-emergent defined as starting after HSCT;
IMP-related defined as either possibly, probably, or certainly related to the IMP as judged by the investigator
Including 2 deaths which occurred after termination of the study

In total, 40 patients (100%) reported 1105 treatment-emergent adverse events during the study. The most frequently observed treatment-emergent adverse events were pyrexia (n=19; 47.5%), diarrhea (n=16; 40%), CMV infection (n=13; 32.5%), hypokalaemia (n=12; 30%), and epistaxis (n=12; 30%). In total, 15 patients (37.5%) reported 173 IMP-related adverse events during the study. The most frequently observed IMP-related adverse events were diarrhea (n=4; 10%), acute GVHD (n=4; 10%), and rash (n=4; 10%).

The most frequent treatment-emergent SAEs by PT or SOC are summarized in the table below. The SOC with the highest incidence was "Infections and infestations" (32 patients, 80%).

Incidence of treatment-emergent serious adverse events

System Organ Class (SOC) if incidence ≥ 20% Preferred Term (PT) if incidence ≥ 10%	**Patients treated with IMP * (N=40)**
Infections and infestations	**32 (80%)**
Bronchopulmonary aspergillosis	4 (10%)
Cytomegalovirus infection	7 (17.5%)
Oral herpes	4 (10%)
Pneumonia	5 (12.5%)
Sinusitis	5 (12.5%)
General disorders and administration site conditions	**13 (32.5%)**
Pyrexia	6 (15%)
Respiratory, thoracic and mediastinal disorders	**11 (27.5%)**
Gastrointestinal disorders	**10 (25%)**

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (25%)**
Leukaemia recurrent	4 (10%)
Post transplant lymphoproliferative disorder	4 (10%)
Blood and lymphatic system disorders	**8 (20%)**

* Numbers and percentages represent the patients for whom a treatment-emergent with a specific PT or SOC has been reported.

The most frequently reported IMP-related SAE was acute graft versus host disease (GVHD; 3 patients, 7.5%). The SOCs with the highest incidence were “Immune system disorders” and "Infections and infestations" (both 4 patients, 10%).

Of the patients who had received IMP, 25 died during the study and two died within 1 month after termination of the study. Of the 27 patients who died, 23 died primarily due to TRM (infections and other causes) and 4 died due to disease relapse/progression.

GVHD has been reported for 12 patients, of whom 11 patients (27.5%) developed GVHD after infusion of IMP. For 5 patients (12.5%) grade III or IV acute GVHD has been reported (onset range 19-102 days after IMP infusion), while another 3 patients (7.5%) developed grade II acute GVHD. Severe chronic GVHD has been reported for 2 patients (5%; 190 and 220 days after IMP infusion). All GVHD cases required treatment. For 4 patients (10%) GVHD (3 acute, 1 chronic) has been reported as an IMP-related SAE. In 4 patients (10%) the Central Independent Safety Assessment Committee (CISAC) indicated that GVHD had been one of the causes of death.

During the study, for 4 patients (10%) graft failure/rejection or slow engraftment was reported and in 6 patients (15%) the hematologic malignancy relapsed or progressed.

CONCLUSIONS

Efficacy Conclusion:

Study CR-AIR-004 has been prematurely terminated. The infusion of IMP after the HSCT did not seem to have a beneficial effect on TRM or OS compared to published historical data of T-cell depleted haploidentical HSCTs. This lack of efficacy can be explained by the finding that the IMP manufactured for Study CR-AIR-004 mainly contained dead or dying cells and as a result, was not comparable to the IMP (ATIR) manufactured for Study CR-GVH-001.

Safety Conclusion:

The IMP manufactured for Study CR-AIR-004 did not raise safety concerns.

Final Report Date:

Revision 22 February 2017

Prepared in:

Microsoft Word 2007