EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2019
EMA/CHMP/CAT/343753/2019
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Luxceptar

International non-proprietary name: Viable T-Cells

Procedure No. EMEA/H/C/002397/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

During the procedure, the name of the medicinal product was changed from ATIR101 to Luxceptar. Both names are used interchangeably in the assessment report.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

7AAD	7-Amino-Actinomycin-D
ADME	Absorption, distribution, metabolism and excretion
AIHA	Autoimmune hemolytic anemia
ALKP	Alkaline phosphatase
ALL	Acute lymphoblastic leukemia
ALT	Alanine transaminase
AML	Acute myeloid leukemia
APC	Antigen presenting cell
AST	Aspartate transaminase
ATG	Anti-thymocyte globulin
ATMP	Advanced therapy medicinal product
BCL	B-cell lymphoma
BMT	bone marrow transplantation
BSA	Bovine Serum Albumin
CD	Cluster of Differentiation
CFSE	Carboxyfluorescein diacetate succinimidyl ester
CHMP	Committee for Medicinal Products for Human Use
CM	Central memory (T-cells)
CML	Chronic myeloid leukemia
CMV	Cytomegalievirus
CMO	Contract Manufacturing Organisation
CoA	Certificate of Analysis
CRA	Controlled Rate Freezer
CQA	Critical Quality Attributes
CYP	Cytochrome P450
DC	Donor Cells
DLI	donor lymphocyte infusion
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DP	Drug Product
DRK-BSD	Deutsches Rotes Kreuz-Blutspendedienst
DS	Drug Substance
EBV	Epstein-Barr virus
EBMT	European Society of Blood and Marrow transplantation
EEA	European Economic Area
EMA	European Medicines Agency
EU	Endotoxin units
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Food and Drug Administration
FMEA	Failure-Mode-and -Effect-Analysis
FSC	Forward scatter
G-CSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVHD	graft versus host disease
GVL	graft versus leukemia
HAPLO	Haploidentical
HBV	Hepatitis B-Virus
HCV	Hepatitis C-Virus
HI	Heat-inactivated
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
HVG	Host versus graft
IPC	In-Process Control
IMP	Investigational medicinal product
IND	Investigational New Drug
IL	Interleukin

iR	Irradiated Recipient Cells
ITT	Intent-to-treat population
i.v.	Intravenous
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MITT	Modified intent-to-treat population
MLA	Mouse lymphoma assay
MLR	Mixed lymphocyte reaction
MNCs	Mononuclear Cells
MTD	Maximum tolerated dose
MMUD	Mismatched unrelated donor
MUD	Matched unrelated donor
NaCl	Sodium chloride
NAT	Nucleic acid testing
Ne	Not estimable
NK cells	Natural Killer cells
OR	Odds ratio
OS	Overall survival
PF	Pre-cursor frequency
PI	Proliferation index
PIP	Pediatric Investigation Plan
Ph. Eur.	European Pharmacopoeia
P-gp	P-glycoprotein
PBMC	Peripheral blood mononuclear cell
PBP	Photobleached product
PDT	Photodynamic treatment
PFS	Progression-free survival
Pha	Phytohemagglutinin
PK	Pharmacokinetics
QC	Quality control
QTPP	Quality Target Product Profile
RBC	Red blood cells
R&D	Research & Development
RH	Relative humidity
RRM	Relapse-related mortality
RT	Room temperature
SAE	Serious adverse event
SD	Standard Deviation
SME	Small or medium-sized enterprise
SmPC	Summary of Product Characteristics
SOC	System organ class
SSC	Side scatter
TBI	total body irradiation
TCR	T-cell Receptor
TFT	trifluorothymidine
TH9402	4,5-dibromorhodamine methyl ester
TK	Thymidine kinase
TRM	Transplant-related mortality
TSE	Transmissible spongiform Encephalopathy
TTC	Threshold of toxicological concern
UCB	Umbilical cord blood
VZV	Varicella zoster virus
WBC	white Blood Cells

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CAT considers that the application for Luxceptar, in the indication: "Luxceptar is indicated as an adjunctive treatment to a haploidentical, T-cell depleted haematopoietic stem cell transplantation (HSCT) in adult patients with high-risk haematological malignancies in complete remission" is currently not approvable since a major objection has been identified**.**

Additionally, the CAT recommends convening an *ad hoc* expert group consisting of experts in haematopoietic stem cell transplantation to address the below mentioned issues.

Questions to be posed to additional experts

The CAT acknowledges that there are several shortcomings of the analysis (balance of baseline factors, only analysis of major subgroups) and still uncertainties (relation to infections and GvHD, concomitant treatment) regarding the treatment effect of ATIR101 rendering the benefit/risk ratio negative. Furthermore, the representativeness of the control population with regard to emerging treatment options is questionable. Thus, an *ad hoc* expert group should discuss the following question:

1. **What is the view of the experts on the observed effect considering the uncertainties caused by the limited number of patients, heterogeneity of the target population, the pooling of data across studies, and the single arm study nature of the data?**
2. **What is the view of the experts on the relevance of external control groups chosen by the applicant?**
3. **Does this product address the unmet medical need in this therapeutic area?**

Inspection issues

GMP inspection(s)

Requests for a GMP-inspection at the contract manufacturing organisation (CMO) including quality control sites, quality control laboratory at Kiadis Pharma Netherlands B.V. (quantity, identity, purity, impurities, potency) and the back-up contract analytical laboratory for microbiological control are considered not necessary.

GCP inspection(s)

A request for a routine GCP inspection has been adopted for the clinical study CR-AIR-007. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure. The inspection was performed at the sponsor site in The Netherlands and at two investigator sites: one in Belgium and one in Canada. The integrated inspection report was issued on 31/10/2017.

New active substance status

Based on the review of the data the CHMP/CAT considers that the active substance "viable T-cells" contained in the medicinal product "Luxceptar/ATIR101" is to be qualified as a new active substance in comparison to the known active substance "Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)" previously authorised in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in the manufacturing process.

2. Executive summary

2.1. Problem statement

Allogeneic HSCT is an established treatment option for many hematological malignancies. Due to their immediate availability, the use of haploidentical family donors has emerged in the last decade as an alternative in situations where an HLA-identical sibling or matched unrelated donor is not available. The incomplete HLA-match between donor and recipient of haploidentical HSCT offers a potent graft-versus-leukemia (GVL) effect that may lead to the complete eradication of malignant cells but also causes graft rejection and GVHD. Methods to reduce or control GVHD in the haploidentical setting are the use of immunosuppressive drugs and the depletion of T-cells in the graft. Limitations of T-cell depleted grafts are a higher risk of graft rejection, severe immune deficiency for up to 1 year after HSCT, leading to a high risk of life-threatening infectious complications and, consequently, high transplant-related mortality (TRM) and low overall survival (OS). Additionally, the GVL effect could be compromised, leading to an increase in relapse. Reintroducing mature T-cells early after a T-cell depleted HSCT could be a solution, but the risk of inducing GVHD through unmanipulated donor lymphocyte infusions (DLIs) is significant. Therefore, manipulated T-cells are employed. ATIR101 is such a preparation where e*x vivo* photodepletion should eliminate alloreactive T-cells causing GVHD from donor lymphocyte preparations.

2.1.1. Disease or condition

ATIR101 should be indicated as an adjunctive treatment to a haploidentical, T-cell depleted haematopoietic stem cell transplantation (HSCT) in adult patients with high-risk haematological malignancies in complete remission.

ATIR101 as adjunctive treatment in HSCT should allow early immune reconstitution, potential protection against infections and disease relapse, while not causing severe GVHD (grade III/IV).

2.1.2. Epidemiology

From the latest EBMT (European Society of Blood and Marrow transplantation) survey (Passweg *et al.* 2016) it can be calculated/estimated that the number of HSCTs in the EEA (European Economic Area) was approximately 35,000 in the year 2014. Considering the continuous increase of HSCTs in the last years, it can be extrapolated that in 2016 40,000 HSCTs will be performed in the EEA. This correlates to a prevalence of 0.8/10,000 in the EEA, based on a population of 513 million. It needs to be noted that the number given above relates to all HSCT procedures done, so both autologous and allogeneic. Of the 40,829 HSCTs identified by the EBMT survey in 2014, 15,765 (43%) were allogeneic, correlating to a prevalence of 0.3/10,000, again based on a population of 513 million.

The main indications for allogeneic HSCT in Europe in 2014 were hematopoietic malignancies with the majority being patients with acute myeloid leukemia (AML) (36%), acute lymphoblastic leukemia (ALL) (16%), and myelodysplastic syndrome/ myeloproliferative neoplasm (MDS/MPN) (15%), together comprising 67% of allogeneic transplantations in Europe in 2014 (Passweg *et al.* 2016).

2.1.3. Aetiology and pathogenesis

Allogeneic HSCT is associated with major, potentially life-threatening complications, i.e. graft-versus-host disease (GVHD), graft rejection/failure, and infections. Also, patients receiving HSCT for the treatment of a hematological malignancy might relapse. Different HSCT approaches in conjunction with

pharmacological treatments are currently used to minimize post-transplantation complications and to improve the outcome of HSCT.

Due to their immediate availability, the use of haploidentical family donors has emerged in the last decade as an alternative in situations where an HLA-identical sibling or matched unrelated donor are not available (Passweg 2015). A haploidentical family donor is usually a 50% match to the recipient and may be the recipient's parent, sibling, or child, but also a second degree relative (such as an uncle/aunt or half-sibling). The incomplete HLA-match between donor and recipient offers a potent graft-versus-leukemia (GVL) effect that may lead to the complete eradication of malignant cells but also causes graft rejection and GVHD (Zahid 2016). Established approaches of GVHD prophylaxis are based on the use of immunosuppressive drugs, including post-transplantation cyclophosphamide as a newly evolving treatment standard. Another method to reduce or control GVHD in the haploidentical setting is the depletion of T-cells in the graft.

2.1.4. Clinical presentation

The use of *ex vivo* T-cell depleted grafts has significantly reduced the risk of GVHD without the need for post-transplant immunosuppression (Devine 2011). Approaches for the removal of T-cells from the graft are the positive selection of CD34 (stem) cells or selective T-cell depletion, such as CD3/CD19 or α/β T-cell depletion.

A potential limitation of T-cell depleted grafts is a higher risk of graft rejection, as preclinical data indicate that donor-derived T-cells facilitate engraftment. In the haploidentical HSCT setting, this dilemma has been solved by administering a very high dose of CD34 cells, with a small fraction of T-cells, and additionally the use of anti-thymocyte globulin (ATG) in the conditioning scheme. However, T-cell depletion has a marked effect on immune recovery, with patients remaining severely immunocompromised for up to 1 year after HSCT, leading to a high risk of life-threatening infectious complications and, consequently, high transplant-related mortality (TRM) and low overall survival (OS). Additionally, depleting T-cells from the graft could also compromise the GVL effect, leading to an increase in relapse.

2.1.5. Management

The treatment options after T-cell depleted haploidentical HSCT are the reintroduction of unmanipulated donor lymphocyte infusions (DLIs) or the concept of reintroducing manipulated T-cells. Unmanipulated DLIs have a high risk of inducing GVHD. There is an approved manipulated T-cell preparation, in which donor T-cells are genetically modified to express the herpes simplex virus thymidine kinase suicide gene. This medicinal product is intended to engraft and stimulate immune-reconstitution after HSCT. If GVHD occurs, ganciclovir is administered and is metabolized to its toxic form ganciclovir triphosphate by the activated, transduced T-cells causing GVHD, which will subsequently undergo apoptosis. ATIR101 would be another manipulated donor lymphocyte preparation. It does not require genetic modification of the donor T-cells and only functionally eliminates the potentially GVHD-causing cells.

2.2. About the product

ATIR101 is a donor T-lymphocyte preparation, depleted *ex vivo* of host alloreactive T-cells using photodynamic treatment (PDT). The active substance is "viable T-cells". ATIR101 is an Advanced Therapy Medicinal Product consisting primarily of allogeneic donor-derived T-cells that have not been genetically modified. It is an individualized medicinal product given to the patient in adjunction of HLA haploidentical hematopoietic stem cell transplantation (HSCT).

The cell suspension contains 2.5-13x 10^6 viable T-cells/mL, dimethyl sulfoxide, and plasma in sodium chloride in a total volume of 20 mL. The concentration and number of viable T-cells per infusion bag will vary per batch as a result of patients reported body weight. The applicant refers to the total number of viable T-cells at the time of formulation. ATIR101 may contain up to 45% non-viable white blood cells (WBC) at formulation and up to 68% non-viable (WBC) after thawing.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Clinical Development Program

Based on the findings of a phase I/II dose-escalation study (CR-GVH-001) in patients with advanced hematological malignancies, an ATIR101 dose of 2.0 x 10^6 viable T-cells/kg body weight was selected for continued clinical testing. Subsequent to the dose-escalation study, a phase II study (CR-AIR-007) was conducted in patients with hematological malignancies (acute myeloid leukemia [AML] or acute lymphoblastic leukemia [ALL] in complete remission or myelodysplastic syndrome [MDS]). This phase II study is the pivotal study for the present Marketing Authorization Application (MAA), providing the principal efficacy and safety information for ATIR101 as adjunctive treatment in HSCT for high-risk haematological malignancies in complete remission.

A total of 42 patients received ATIR101 in these 2 studies, i.e. 19 patients in study CR-GVH-001 and 23 patients in study CR-AIR-007. Study CR-GVH-001, including its 5-year follow-up period, is completed. In study CR-AIR-007, the primary endpoint was reached (6-month TRM), and 12and 24 months TRM data are available as well.

A phase II interventional study (CR-AIR-004) was prematurely terminated because of quality issues of the investigational medicinal product (IMP).

The observational cohort study CR-AIR-006 was performed to assess efficacy and safety parameters in patients with hematological malignancies who received different types of transplants (i.e. HSCT from a T-cell depleted haploidentical donor, a matched unrelated donor, a one locus mismatched unrelated donor; or a double umbilical cord blood transplantation) but no ATIR101 treatment. These patients, in particular patients receiving HSCT from a T-cell depleted (CD34-cell selected) haploidentical donor, represent the principal control group for patients treated with ATIR101.

Scientific Advice

National scientific advice meetings were held by four European National Competent Authorities (PEI Germany, MHRA United Kingdom, MPA Sweden, and SMCA Lithuania). Six written scientific advices/protocol assistances were provided by CHMP (EMA). There were also meetings with the FDA. Overall, the clinical development of ATIR101 generally complies with the provided scientific advices.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

General GMP compliance was shown for all sites: CMO and release test laboratories. For the applicant Kiadis Pharma Netherlands B.V. Paasheuvelweg 25 A, AMSTERDAM, 1105BP, Netherlands" (who also operates as a laboratory for release testing) an updated version of the Manufacturer`s Authorisation (date 2018-04-05) was provided. Valid GMP certificates are provided for the testing site at Kiadis Pharma Netherlands (Science Park 406, 1098 XH Amsterdam, The Netherlands) and the backup site contract laboratory for sterility and endotoxin testing.

For the CMO an updated version of the Manufacturer`s Authorisation for commercial ATIR101 (issued 18 February 2019) is provided in conjunction with a valid GMP certificate (issued in 2016).

GLP

Pivotal toxicology study was not GLP-compliant but was performed GLP-like. Tests for genotoxicity were all GLP compliant except the Ames test to test impact of photodynamic treatment (PDT).

GCP

The applicant confirms that all trials in the ATIR101 clinical development program have been conducted according to ICH Good Clinical Practice guidelines. Clinical trials conducted outside of the European Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Following the routine inspection performed for the clinical trial CR-AIR-007, the inspection team concluded the following: Although major findings were reported that could have affected the integrity of the collected and reported data, the inspectors consider the data of the CR-AIR-007 trial, as reported in the interim CSR, to be acceptable. The responses to the inspection report including the timely implementations of the actions for future clinical studies, as set out in the CAPA plan, will further enhance the quality of clinical trials performed by Kiadis. It is the recommendation of the inspectors that the data of the CR-AIR-007 trial can be used for evaluation and assessment of the application.

2.5. Type of application and other comments on the submitted dossier

Legal basis

This application follows a centralized procedure according to Regulation (EC) No 726/2004 based upon Article 3(1) –Annex 1a– Advanced Therapy Medicinal Product. The application is also submitted in accordance to Article 8(3), new active substance, of Directive 2001/83/EC.

Accelerated procedure

N/A

Conditional approval

With the responses to the 2nd D180 LoOI the applicant asked the CAT/CHMP to potentially consider a conditional marketing authorisation.

The submission (eCTD 005) includes the following justification from the applicant:

Given the unmet medical need of this population of patients and the commitment of the applicant to provide additional comprehensive data from ongoing and new clinical studies, the applicant would like the CAT/CHMP to potentially consider a conditional marketing authorisation enabling early access to ATIR101 in patients in need of an haploidentical HSCT.

Unmet medical needs continue to exist in haploidentical HSCT.

At the time of assessment, there was is only a single approved medicinal product in the EU in adults as adjunctive treatment with haploidentical HSCT, i.e. for the same indication as ATIR101. In 2016, a conditional marketing authorization was granted to Zalmoxis (EMEA/H/C/002801). Zalmoxis (nalotimagene carmaleucel) is constituted of donor's T-lymphocytes genetically modified to express the HSVTK suicide gene. This allows the selective killing of dividing cells upon administration of the pro-drug ganciclovir (GCV), thereby controlling GVHD in these patients. However, the suicide gene also limits the use of Zalmoxis as CMV infection and reactivation are frequently observed and a major concern in patients undergoing HSCT. Active CMV infections are generally treated with GCV or

valganciclovir (VCV) and as a consequence, Zalmoxis cannot be administrated to patients with infections requiring administration of these drugs at the time of infusion. In these cases, Zalmoxis treatment must be postponed until 24 hours after the last GCV or VCV intake. A longer interval might apply in case of renal failure (Zalmoxis EPAR 2016). ATIR101 does not have these limitations and can also be infused to patients with CMV infections treated with GCV or VCV. It should also be noted that only 53% of eligible patients (30 out of 57) enrolled in clinical study TK007, received Zalmoxis infusion due to various reasons (Zalmoxis EPAR 2016), indicating that Zalmoxis cannot be provided to all eligible patients.

Moreover, ATIR101 consists of a single infusion for each patient while in case of Zalmoxis, possibly multiple infusions (up to maximum 4) with a one-month interval have to be administered which is potentially burdensome for the patient and treatment center. ATIR101 does not contain a genetically modified component and therefore, no modification in the DNA or RNA of the cells. As such ATIR101 will not have any unknown effect related to genetic manipulation. ATIR101 therefore may be easier to accept as treatment without concerns of longterm risks. To date the availability and commercial use of Zalmoxis has been limited despite it being approved in 2016. No information other than the information listed in the EPAR is available in literature or from other public sources and no recommendations are included in European guidelines on the use of Zalmoxis in HSCT (EBMT 2019).

Although not a registered treatment, cyclophosphamide is currently being used after HSCT by many clinical centers across Europe. Cyclophosphamide, an alkylating agent, is approved as a cytotoxic anticancer treatment for various solid tumor indications and hematological malignancies. Cyclophosphamide is a potent immunomodulator that has been successfully used in off-label setting to prevent GVHD after HLA-matched and HLA-mismatched HSCT in case the full donor graft was administered. Studies have shown that administration of cyclophosphamide early after HSCT preferentially killed activated, circulating alloreactive T-cells while sparing resting, non-alloreactive T-cells. Haploidentical transplantation with PTCy is currently widely used in clinical practice in patients for whom no matched donor is available. This treatment regimen however is associated with a high rate of relapse, which can be as high as 45%, in patients receiving haploidentical HSCT and about a quarter of patients continue to suffer from chronic GVHD (Brunstein et al. 2011; Ciurea et al. 2015; McCurdy et al. 2017; Piemontese et al. 2017; Sugita et al. 2015). In addition, the need for continued immunosuppression for a prolonged time after transplantation limits the use of post-transplant cyclophosphamide particularly in patients with underlying renal dysfunction. Furthermore, these patients may experience many toxicities from these immunosuppressive agents, when used post HSCT, including neurotoxicity, nephrotoxicity, gastrointestinal disturbances and may have an increased risk for infections.

Therefore, although there is an approved product in the same indication and a non-registered treatment option currently used in many European transplant centers there is still an unmet medical need for medicinal products targeting this patient group. ATIR101 is developed to addresses this unmet medical need.

Rapporteur's assessment of applicant's justification on conditional approval

Without precluding on an opinion on benefit-risk ratio, and as the available clinical data package is not considered to be fully comprehensive at this stage, the applicant is requested to submit their justification on whether all the requirements for a conditional marketing authorization as laid down in Article 4 of Commission Regulation (EC) No 507/2006 could in their view be considered as fulfilled i.e.

- the risk-benefit balance of the medicinal product, is positive

- it is likely that the applicant will be in a position to provide the comprehensive clinical data within a reasonable time frame including an feasibility analysis with adequate mile stones

- unmet medical needs will be fulfilled

- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The applicant should provide a comprehensive justification that ATIR101 addresses the unmet medical need to a similar or greater extent as the already under conditional approval authorized product Zalmoxis. (Please refer to the CHMP guideline EMA/CHMP/509951/2006, Rev.1).

Exceptional circumstances

N/A

Biosimilar application

N/A

1 year data exclusivity

See Assessment Report for ATIR101 on similarity with authorised orphan products.

Significance of paediatric studies

An agreed PIP for ATIR101 (EMEA-001980-PIP01-16) is in place (EMA decision P/0078/2017, dated 17 Mar 2017). The PIP includes a clinical phase II study to evaluate the safety and efficacy of ATIR101 in pediatric patients up to 18 years of age. Initiation of the study is deferred until the manufacturing process has been adapted to smaller cell numbers which should be shortly after submission for marketing authorisation. Therefore, a PIP compliance check is not required yet.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

ATIR101 are donor T-lymphocytes, which have been depleted of recipient-reactive T-cells using photodynamic treatment (PDT) with the Rhodamin123 derivate TH9402 and visual light. ATIR101 is manufactured to not cause severe Graft versus Host Disease (GVHD) in the recipient but claimed to comprise sufficient numbers of donor T-cells capable of eliciting an effective immune response. The active substance "viable T-cells" is defined as $CD45^+CD3^+7AAD^-$-cells. The allogeneic, family-related, HLA-haploidentical donor is the same individual who donates the stem cell graft which is given to patients approximately one month prior to ATIR101.

ATIR101 is frozen in a cryoconservation solution containing dimethylsulfoxide (DMSO) and plasma, intended for storage over a period of 6 months below minus 135°C. Therefore ATIR101 must be thawed before application.

ATIR101 is provided in a fixed total volume of 20 mL in the one strength of 50 - 260 x 10^6 cells as dispersion for infusion (corresponding to 2.0x10^6 viable T-cells/kg of the patient's body weight).

3.1.2. Active Substance

General Information

Post-PDT cells are considered as the active substance (also referred to as DS). Since ATIR101 Drug Product is manufactured as a continuous process without storage or release of intermediates, the distinction between DS and finished product (also referred to as DP) is artificial. The DS is not formally released or stored as there is no hold step at this point in manufacturing. Post-PDT-cells are a mixture of:

- Viable lymphocytes with a normal morphology characterised by a rounded shape with a little spherical nucleus and a small cell size.
- Non-viable, trypan blue positive or 7AAD positive cells with a slightly irregular, ragged outer membrane and a larger nucleus; cell size is similar or slightly larger than viable lymphocytes.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Manufacturer

Manufacturing of DS takes place at a Contract Manufacturing Organization (CMO). GMP compliance is confirmed by a valid GMP certificate issued in connection to the updated Manufacturer's Authorisation for commercial ATIR101.

Description of manufacturing process and process controls

The description of the DS manufacturing process is considered sufficient and includes a flow chart, a narrative description of the process and the identification of in-process controls (IPCs), which are further defined by ranges. Further details about certain manufacturing steps are provided. For control of materials the applicant provided additional information on materials utilised for ATIR101 manufacturing processes.

Each batch of ATIR101 DS is manufactured separately on an individual patient basis. For each batch a unique donor/recipient combination is used, i.e. one donor per recipient, the donor being the same individual who donates the stem cell graft.

Donor and recipient lymphocytes are collected by leukopheresis and co-cultured in a mixed lymphocyte reaction (MLR) to stimulate proliferation of alloreactive T-cells. Subsequent light exposure eliminates the alloreactive T-cells.

Control of critical steps and intermediates

Identification and Controls of Critical Steps

ATIR101 is manufactured in a continuous process until freezing of the DP. No declared intermediates with corresponding hold-times, release tests and specifications are identified in the DS manufacturing process.

The donated cells (and plasma) are designated as Starting Materials, including mandatory serological test results and certification (control of CoAs and accompanying papers). Further acceptance criteria have been identified which are controlled upon receipt as per CoAs. Critical steps throughout the DS process and all IPCs are included in the flow chart and process description in the dossier. Control of cell count and viability are of importance in controlling the process. Also, diligent control of rapid processing and timing (duration) of individual steps, especially throughout PDT (the latter reflecting control of operating parameters) is applied to ensure consistent processing. Applicable IPCs are performed at the end of each step (e.g. after final resuspension) with the exception of the first manufacturing step where they are performed before processing.

Description of In-Process Controls

The IPC tests for the manufacturing process and respective criteria are provided and, in general, found to be adequate. The process is adapted to allow for the inherent variability of the starting material and as caused by the apheresis procedure at the clinical sites used.

Acceptance criteria for IPCs were initially based on literature and historical data, as well as developmental batches and have been confirmed by data obtained from the 32 batches used for the clinical trial CR-AIR-007. The methods applied for IPCs (cell counts, viabilities and T-cell viability, as well as sterility performed for starting materials) are identical to methods used for product release and are described in the dossier (Section 2.3.P.5.2). One control of the plasma is implemented.

Control of materials

Apheresis collection sites

Starting materials are prepared and shipped to the CMO by apheresis collection sites. Apheresis collection sites have to be certified according to EU Directive 2004/23/EC (Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; March 2004) and Commission Directive 2006/17/EC (certain technical requirements for the donation, procurement and testing of human tissues and cells; February 2006). Kiadis Pharma provided a detailed description of the apheresis collection and the shipment procedure to each tissue establishment involved in starting material procurement. Manufacture of the starting material (collection of autologous /allogenic lymphocyte apheresis and plasma and laboratories for biological testing) can only be implemented in apheresis centres that are approved, licenced or authorised by competent authorities of the member states for the respective activities. This is stated in the dossier. If centres also hold a JACIE accreditation, such documentation will be reviewed as well, but qualification of apheresis centres/tissue establishments will be based on respective approval of competent authorities. The general qualification process is performed by the applicant on individual responsibility. The former incomplete list of "Qualified Apheresis Units, Tissue Establishments and Viral test laboratories" was deleted from the dossier. Therefore, details on the individual apheresis centres are only known by the applicant. The future MA holder needs to keep solid documentation of the apheresis centres and laboratories updated.

Starting Materials Donor and Recipient: Mononuclear Cells

Donors are selected by the transplant-team of the recipient inter alia based on their HLA-type. A unique identifying code is allocated to the cell donation to ensure proper identification of the donor and the traceability of all donated material throughout the production process. Certificates of Analyses are issued for procurement of cells summarizing the important specifications for the apheresis donation. Donor/Recipient biological testing is performed on the donors/recipients serum according to the Directive 2004/23/EC and Commission Directive 2006/17/EC. Samples for biological testing are taken within 30 days prior to cell and plasma donation. Tests are carried out by authorised laboratories, qualified by Kiadis Pharma, using CE-marked testing kits when possible. The parameters for biological testing are summarised in the dossier. Nucleic acid amplification-testing (NAT) for HIV, HBV and HCV genomes will be performed mandatory and in response to special requirements of competent authorities of certain member states.

Starting Materials Donor: Plasma

A Certificate of Analysis is issued for every plasma donation accompanying the shipment to the CMO.

The applicant must assure that standardised apheresis procedures are in place for all intended procurement centres incl. CE marked devices, tubing sets as well as an appropriate skin disinfection procedure. A summary of "Targets and specifications for plasma and PBMCs in apheresis materials collected for manufacture of ATIR101" is provided. The intended apheresis sites for procurement of starting material for manufacture of ATIR101 are qualified by the applicant according to authorisations /licences or equivalent documents from competent authorities (see above: apheresis collection sites).

The applicant provided information about the intended time frame for the apheresis of MNCs to manufacture ATIR101 prior to the stem cell apheresis for the donor and prior to the stem cell transplantation for the recipient. The applicant describes that for biological testing samples from the allogenic donor as well as from the recipient are taken within 30 days prior to cell and plasma donation. Minimal criteria according to EU Directive 2006/17/EC are declared to be ensured in any case.

As long as the applicant keeps the storage time below 6 months below minus 135°C of the final DP ATIR101 (process 3.1) a repeat sampling and testing of donor blood is not required.

Shipping of Starting Materials

Shipping is performed at 2-8 °C in a shipping box which is provided to the apheresis collection site by Kiadis Pharma. During shipment a temperature logger records the temperature of the content. The shipment box has been validated.

Incoming control of Starting Materials

Upon arrival at the CMO the cells and plasma are immediately processed. Actions are performed to control the shipping of the two apheresis bags and the plasma bag. A review of the accompanying documents is performed and samples from the apheresis bags are taken for sterility testing, cell number and viability.

Raw materials

The applicant has provided information on the quality control tests and specifications of raw materials as provided by the suppliers.

Details of the cell culture media preparation and composition are provided in the dossier. Overall descriptions of the manufacturing steps are given. Further clarification and details to fully document the processes, e.g. timeframes (incl. tolerance) of the different steps are provided. Further details about transitions of cell suspensions and solutions and repositories (incl. CE-certificates) are described.

Process validation

Since the majority of tests are performed at the DP level, data showing process robustness are discussed in Section 2.3.P.3.5, including a failure modes and effect analysis (FMEA) of the manufacturing process.

Manufacturing process development

The development of ATIR101 production process is described in section 3.2.S.2.6.

The development of ATIR101 production process started with the design of a quality target product profile (QTPP) prospectively and dynamically describing the summary of the quality characteristics of the DP that is intended to be manufactured. Next, this QTPP was translated into a list of critical quality attributes (CQAs) which define ATIR101. A CQA is used as a critical requirement: if a product does not meet a CQA, the product is not considered to be conforming to ATIR101 quality requirements and consequently any development that would lead to such parameters will be disqualified. Based on the

general requirements the CQAs were identified with definition of corresponding controls and limits as listed in the dossier.

Process versions and implemented changes

The ATIR101 process has been in clinical development for a long time, the applicant introduced certain changes to ascertain quality during the manufacturing process. An overview of the process versions used for production of ATIR101 and IMP used in different clinical trials was provided by the applicant.

The introduction of changes from ATIR101 initial manufacturing process used in CR-GVH-001 (dose escalation study) and the process used in CR-AIR-007 was sufficiently declared and results of "head-to-head" comparability runs were provided.

After FMEA of ATIR101 manufacturing process used in CR-AIR-0007, a number of risks associated with transport issues of the starting cells were identified. Therefore, the need to implement a hold time for transportation of the donor and recipient cells from the apheresis centers to the manufacturing site resulted in a change for the intended commercial ATIR101 compared to the previous manufacturing process.

The proposed commercial ATIR101 was not employed in clinical applications.

To verify influences of the intended maximum hold time on the manufacturing steps (especially starting materials) and on the entire manufacturing process "head-to-head" comparability of ATIR101 manufacturing process used in CR-AIR-007 versus the proposed commercial process was provided.

The applicant has now shown sufficient data summaries for comparability runs of ATIR101 process used in CR-AIR-007 versus ATIR101 proposed commercial process where the final release specifications according to section 3.2.P.5.1 including identity are met.

It should be noted that no data is presented to show the remaining presence of virus-specific T-cells in future commercial ATIR101 despite the hold time of apheresis products.

Characterisation

Due to the continuous manufacturing process no explicit characterisation is performed on the DS. Therefore, it is acceptable that most parts of the analysis are done on the level of DP (see DP release). To describe composition and function of ATIR101 a summary of analyses (which is not indented for DP release testing) was presented from cell preparations derived from clinical study CR-AIR-007 from donor cells in comparison to ATIR101.
Descriptions of the research-based assays are provided (CTD section 3.2.S.3.1).
Taken together the additional data to demonstrate the presence of virus specific T-cells in clinical batches of CR-AIR-007 are very much acknowledged. For clarity the product information was updated as follows: *"Preservation of virus specific T-cells, if present in the collected donor cells has been demonstrated in vitro for the clinically relevant viruses EBV, CMV and Influenza virus by flow cytometric analysis and pMHC - dextramers / tetramers. Data are generated on a limited number of ATIR101 batches of the clinical study CR-AIR-007 within research-based characterization assays."*

Specification

Since the production of ATIR101 is a continuous process and there is no hold step at the DS level, no release tests are performed on the DS. All release tests are performed on the DP (Section 3.2.P.5).

Stability

Stability studies are performed on DP. Given the continuous manufacturing process, this is acceptable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

ATIR101 is provided as dispersion for infusion of 50 - 260×10^6 viable T-cells in 20 mL (corresponding to 2.0 x 10^6 viable T-cells /kg of the patient's body weight). The cell suspension (dispersion for infusion) is stored deep-frozen in cryobags.

The active ingredient of ATIR101 consists of viable donor T-lymphocyte depleted *ex vivo* of host alloreactive T-cells. Each batch of ATIR101 is manufactured for an individual patient.

Composition

ATIR101 contains cells suspended in cryopreservation medium consisting of DMSO and heat inactivated (HI) plasma in saline. The number of cells in each cryobag depends on the patient's bodyweight and is calculated and adjusted during the first step of DP manufacturing.

Regarding the number of viable T-cells (the active ingredient of ATIR101) the applicant clarified discrepant details with respect to tolerance of the final dosage of ATIR101. Due to individual differences of batches of ATIR101 (viability and recovery) and potential changes of the patient's body weight some degree of variability seemed inevitable.

Container Closure System

ATIR101 is deep-frozen in 50 mL Cryostore Freezing Bags. Protective metal cassettes are used as secondary packaging material. Details of the primary container are provided in the dossier. ATIR101 is shipped in a liquid nitrogen containing dry-shipper in a shipping box at a temperature < minus 135°C. The information given on Description and Composition of the DP is sufficient.

Pharmaceutical Development

Information on excipients, formulation development, physiochemical and biological properties, manufacturing process development, and container closure are provided in the dossier on DS level.

Manufacture of the product and process controls

Manufacturing and release testing of DP including sterility, endotoxin and Mycoplasma testing takes place at the same CMO responsible for manufacturing of DS.

Batch Formula is described as 2 cryobags à 20mL according to the composition. Only one bag is intended for application. In case sufficient cells are available, a second cryobag containing the same number of cells is manufactured and frozen as salvage unit (to be used in case of damage or loss of the first ATIR101 cryobag).

Manufacturing of Finished Product

The manufacturing process of DP is described in segmented steps. In summary it is the formulation of the DS (post-PDT-cells) by resuspending the cells in freeze medium and filling into cryobags. In general, the information given by applicant is acceptable. The cryobags and sample vials are frozen immediately in a controlled rate freezer. The applicant provided information about the controlled rate freezer device. The frozen bags and samples are stored in the vapour phase of liquid nitrogen until prepared for shipping.

Packaging and shipping

After an ATIR101 batch has been released the cryobag is packaged into the transport container. ATIR101 cryobags are shipped in a liquid nitrogen containing dry-shipper at a temperature below minus 135°C.

Preparation of infusion at the hospital

At the hospital, the label on the cryobag is matched to the identity of the patient and then ATIR101 is thawed and infused via an infusion system (central line). Detailed instructions are provided to the clinical site on the thawing and infusion of ATIR101. After thawing, no storage of ATIR101 DP before application is recommended. Thus SmPC / PIL / labelling documents were amended accordingly.

Controls of critical steps and intermediates

After sealing, the cryobags are inspected for tightness of the seal by applying slight manual pressure to the bag and visual inspection for leaks.

Process validation and/or evaluation

Information on the validation of historical processes ATIR101 is given in the dossier. During the development of the DP the applicant used elements of the Quality-by-Design-approach.

Additionally diverse FMEAs were performed. Relevant results were provided and the conclusions drawn are, in general, agreed upon. Additional details regarding the material used in the experiments should be provided.After successful establishment of the manufacturing process, validation of the ATIR101 proposed commercial process was performed by production of at least 4 batches within pre-defined acceptance ranges by the CMO.

Microbiological Safety

A comprehensive overview of the DP manufacturing process, subdivided in several substages, together with respective flow charts is provided. IPCs are indicated in the flow diagrams, but microbiological release controls are outlined in next CTD modules.

As terminal sterilisation is inapplicable for ATIR101, the DP is manufactured in an aseptic process with all processing steps conducted in continuously monitored Class A in B environments. Validation of the aseptic manufacturing process has been successfully completed with three process simulation runs and confirmed requalification on a six months interval.

In general, two ATIR101 cryobags each containing 2.0×10e6 viable T-cells/kg body weight are manufactured per batch, in addition to samples used for microbiological release testing (endotoxin and microbiological control) and for retention purposes, which are filled into cryovials.

The final DP is filled into sterile cryobags and tubing of the bags is sealed off with a radio-frequency heat-sealer. Seams are both, visually and manually inspected for integrity which appears an adequate safety measure from microbiological perspective.

Product specification

Release testing is performed on samples taken from the same cell suspension used to fill the cryobags. Testing samples are aliquoted and then subjected to the same controlled freezing program as the ATIR101 cryobags. In order to assess the quality of the frozen product, samples are tested immediately after thawing.

All analytical data are available at the time of batch release and prior to shipment and administration of the product to the patient.

Summary of Release specification of Drug Product

An overview of QC methods at QC testing facilities clarified which QC sample of the DP are to be analyzed at the manufacturer site.
In summary, identity, quantity are addressed by flow cytometric analysis in combination with automated measurement of nucleated cells (WBC). The important parameters "viable T-cells post

thaw" and "recovery viable T-cells post thaw" are calculated accordingly. As a parameter for purity, "T-cells in viable WBCs" are analyzed by flow cytometry. The potency assay is based on CFSE-proliferation determination of proliferation indices (PI) upon stimulation by third party cells versus PI upon stimulation with recipient. Additional PI upon recipient cells and upon donor cells was calculated as impurities.

Microbiological Safety

DP release specifications have been justified and comprised all relevant microbiological parameter covered by tests for Endotoxin (Ph. Eur. 2.6.14), Mycoplasma (Ph. Eur. 2.6.7) and microbiological control (Ph. Eur. 2.6.27). All microbiological test results are available at the time of batch release and were always in compliance with the specifications for batches produced to date.

Batch results

Data of statistical analysis of the 28 successful batch results of ATIR101 manufactured for the clinical trial CR-AIR 007 is included in the dossier.

Stability of the product

The applicant provided data sets of stability exercises from validation or engineering runs of ATIR101 manufactured according to the proposed commercial process. Data of the 5 validation runs were provided. For all 3 Engineering runs data for proposed-storage period is included in dossier.
Results of the already completed stability runs met the specifications and therefore could justify the proposed storage period of the intended storage of ATIR101.

However, some details attracted attention. It is noticed, that the exemplary data to prove stability of the proposed commercial ATIR101 contain several data sets which in retrospective fall short of the specification for recovery of viable T-cells post-thaw tightened at a later stage of the marketing authorization procedure.
Nevertheless, all future commercial ATIR101 batches are expected to meet the new specifications for release.

In-use stability

Updated data tables for in-use stability on ATIR101 manufactured according to the proposed commercial process over the time after thawing were provided. The applicant explained the in-use stability study was performed in a laboratory whose temperature is actively controlled to be kept between 16.5 – 26.0°C, and therefore the study conditions are considered to be representative to room temperature.
The proceedings of the in-use stability exercise were given in more detail.
References to in-use storage have been deleted within SmPC / Product Information.

Comparability exercise for Finished Medicinal Drug Product

The introduction of changes from ATIR101 initial manufacturing process used in CR-GVH-001 (dose escalation study) and the process used in CR-AIR-007 was sufficiently declared and results of three "head-to-head" comparability runs were provided. Comparability exercises from 4 "head-to-head runs" of ATIR101 manufacturing process used in CR-AIR-007 versus the proposed commercial process were performed by the applicant. Descriptions of the proceedings of the comparability runs were given. The applicant has shown sufficient data summaries for comparability runs where the final release specifications according to section 3.2.P.5.1 including identity are met.

It should be noted that no data were presented to show the remaining presence of virus-specific T cells in the future commercial ATIR101

Additional comparability exercise in relation to the implemented data of the clinical study CR-AR-008

The applicant pooled additional clinical data obtained on 9 patients in study CR-AIR-008, with the data obtained in the pivotal study CR-AIR-007. To legitimate quality differences of the ATIR101 drug products utilised within clinical studies CR-AIR-007 and CR-AIR-008 additional documents were provided.

- **Overview of the main characteristics of the different ATIR101 manufacturing processes**
  After performing the first dose-escalation trial CR-GVH-001, the applicant continued development of its ATIR101 manufacturing process during the conduct of clinical studies with the intention of identifying risk mitigation strategies as well as process optimization. An overview of the key characteristics of the different manufacturing processes was provided. Differences between the manufacturing processes used in CR-AIR-007 and CR-AIR-008 were highlighted.
  From the development studies, data is available on 11 separate ATIR101 manufacturing runs from healthy donor material in which the cells were split into two and further processed in parallel with both manufacturing processes. The results of the side-by-side execution of the two processes were provided.
- **Comparison of Quality Control data of CR-AIR-007 and CR-AIR-008**
  A summary of the obtained data during Quality Control release testing of ATIR101 batches serves to support the potential pooling of the clinical data of the 23 subjects treated with a single dose of ATIR101 in study CR-AIR-007 and the 9 subjects treated with a single dose of ATIR101 in study CR-AIR-008, the QC data for these 23 + 9 subjects. Although some differences expected due to the personalised nature of ATIR101, the same ranges are seen for the successfully produced batches given to patients who received a single dose of ATIR101 in both studies.
- **Stability of ATIR101 from process used in CR-AIR-008**

A total of 4 technology transfer batches of ATIR101 were subjected to determine stability of ATIR101 manufactured according to the process used in CR-AIR-008. The results up to 6-month storage period were provided.

The applicant provided additional data to support the pooling of the clinical data obtained on 9 patients in study CR-AIR-008, with the data obtained in the pivotal study CR-AIR-007. This was expected due to the fact that the applicant originally excluded information of the drug product ATIR101 utilised in the clinical study CR-AIR-008 from the dossier.

Taken together some differences of the ATIR101 products from both clinical studies could be detected in the various data sets. However a general comparability of certain quality parameter could be presented. This was of special importance to support the values of the recently added clinical data from study CR-AIR-008.

Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The DS is produced from no TSE risk material and no TSE risk reagents or excipients have been identified.

Virus safety

The ATIR101 manufacturing process has no capacity to remove and/or inactivate viruses. Since ATIR101 consists of viable cells, no sterilisation or viral inactivation steps are part of the production process. As a consequence, other safety measures, in particular careful selection and testing of starting and raw materials are very important. This minimises a possible contamination with adventitious viruses. Therefore, all materials used in transport of cells and plasma, and during ATIR101 manufacturing are either free of animal-derived components or, if they are not free of animal derived material have been extensively screened for viral contamination. These tests failed to demonstrate the presence of viral contaminants. In view of the testing performed on the donor and the recipient, the final product testing, the quality of the raw materials, and the small scale of the process (single dose manufactured from a unique donor/recipient combination) it is deemed highly unlikely that ATIR101 poses a risk for contamination with adventitious agents.

In summary, the virus/TSE safety of ATIR101 has been sufficiently demonstrated.

Summary of Microbiological Safety

DP manufacture including microbiological in-process and release testing is conducted at the CMO with an additional back-up CMO facility responsible for release relevant sterility/microbiological control and endotoxin testing

As terminal sterilisation is inapplicable for ATIR101 the DP is manufactured in an aseptic process with all processing steps conducted in continuously monitored Class A in B environments. Validation of the aseptic manufacturing process has been successfully completed with three process simulation runs and confirmed requalification on a six months interval.

Donor and recipient MNCs, as well as plasma are defined as starting materials for DS manufacture. Donor selection and preparation of starting materials is confirmed to be in line with Dir. 2004/23/EC and 2006/17/EC to assure microbial safety at pre-manufacturing stage. At receipt, starting materials are controlled for microbiological quality via BacT/ALERT and mainly processed in sterile transfer bags as well as culture flasks. The autologous plasma is filtered to remove large protein aggregates and its microbiological safety sufficiently ensured via microbiological control (Ph. Eur. 2.6.27) with the acceptance criterion "sterile (no growth"). None of the batches were found to be unsterile. Raw materials, containers and disposables appear of adequate quality and media and solutions are either provided sterile or 0.22 µm sterile filtered prior use. All media and solutions are prepared freshly on the day of use (ATIR101 manufacturing) and only used at the same day

DP release specifications have been sufficiently justified comprising relevant microbiological parameter covered by tests for Endotoxin (Ph. Eur. 2.6.14), Mycoplasma (NAT, Ph. Eur. 2.6.7) and microbiological control (Ph. Eur. 2.6.27).

Requested information and confirmatory data has been provided for the microbiological control methods demonstrating compliance with Ph. Eur. requirements. In general, two ATIR101 cryobags each containing 2.0×10e6 viable T-cells/kg body weight (at formulation) are manufactured per batch, in addition two samples used for microbiological release testing (endotoxin and microbiological control) and for retention purposes, which are filled into cryovials. The final DP is filled into CE-marked sterile CryoStore freezing bags and tubing of the bags is sealed off with a radio-frequency heat-sealer. Visual and manual inspections for integrity are conducted. All microbiological test results are available at the time of batch release and were always in compliance for all batches produced to date. Endotoxin values presented for 23 DP batches were in compliance with established specifications, sufficiently demonstrating batch consistency along with an adequate safety margin to the maximum allowed endotoxin level.

Conclusion
The presented microbiological safety concept appears acceptable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

In general, the dossier submitted for ATIR101 is of acceptable quality and provides a description of the characterisation, manufacture and control of the finished product.

The manufacturing process proposed for the commercial manufacture of ATIR101 was not yet applied in clinical studies. The proposed changes were intended for improvement and risk mitigations.

The applicant pooled clinical data obtained on 9 patients in study CR-AIR-008 with the data obtained in the pivotal study CR-AIR-007. The applicant provided additional data to support the pooling of the clinical data obtained on 9 patients in study CR-AIR-008, with the data obtained in the pivotal study CR-AIR-007. This was expected due to the fact that the applicant originally excluded information of the drug product ATIR101 utilised in the clinical study CR-AIR-008 from the dossier.

Some differences of the ATIR101 products from both clinical studies could be detected in the provided various data sets. However a general comparability of certain quality parameter could be presented. This was of special importance to support the values of the recently added clinical data from study CR-AIR-008.

Former major objections about batch release assay for potency and stability studies and other concerns about the proposed commercial ATIR101 were solved.

At present there is only a recommendation left. From a quality point of view no concerns preclude a positive opinion for marketing authorisation.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for ATIR101 **could be approvable** from the quality point of view.

3.2. Non clinical aspects

3.2.1. Pharmacology

The nonclinical pharmacology data package of ATIR101 includes one in vivo proof-of concept study in mice with a murine cell-based product comparable to ATIR101. This in vivo proof-of-concept study investigated the effect of PDT / TH9402-mediated elimination of alloreactive T-cells from C57BL/6 mice (stimulated by irradiated spleen cells from BALB/c mice) on subsequent cytotoxic activity versus spleen cells from BALB/c mice (host) or BCL1 B-cell lymphoma cells (graft versus leukemia (GVL)). Furthermore, the effect on occurrence of GVHD in lethally irradiated BALB/c mice and in C3H/HeJ mice (third-party) and on GVL function in lethally irradiated BCL1-inoculated BALB/c mice was studied. It was shown that ex vivo PDT successfully eliminated activated T-cells primed with host histocompatibility antigens but not the resting antitumor and anti–third-party T-lymphocytes.

3.2.2. Pharmacokinetics

According to the CHMP "Guideline on human cell-based medicinal products (EMEA/ CHMP/ 410869/ 2006)", classical pharmacokinetic studies on absorption, distribution, metabolism and excretion are not applicable for cell-based medicinal products, and thus no such studies were performed with ATIR101.

Two in vitro metabolism studies were performed with TH9402 as part of the impurity qualification. Briefly, in these studies it was shown that CYP3A4/5 is the major enzyme involved in the metabolism of TH9402. CYP2B6, CYP1A2 and also CYP2C9 appeared to have a minor contribution. Further it was shown that TH9402 is a strong inhibitor of CYP3A4/5 (IC50 4 µM (2.33 µg/ml)), CYP2C19 (IC50 7 µM (4.08 µg/ml)), CYP2C9 (IC50 10 µM (5.83 µg/ml)) and CYP2D6 (IC50 12 µM (7 µg/ml)), and a weak inhibitor of CYP1A2 (IC50 > 100 µM (58.3 µg/ml)). Considering the very low doses and anticipated exposure to TH9402 in humans, these findings are not considered to have clinical relevance.

3.2.3. Toxicology

The nonclinical safety and toxicity program for ATIR101 was designed in accordance with recommendations as outlined in the CHMP "Guideline on human cell-based medicinal products (EMEA/ CHMP/ 410869/ 2006)", taking into account the nature of the product and its intended use.

No single dose toxicity studies were performed. However, a repeated dose toxicity study was conducted in mice with the purpose of evaluating the effect of repetitive inoculations of spleen cells exposed to PDT using TH9402 ex vivo (referred to as "ATIR101-like cell-based product").

No genotoxicity or carcinogenicity / tumorigenicity studies were performed with ATIR101; also, no reproductive/ developmental toxicity or stand-alone local tolerance studies were performed.

As the photosensitizing reagent TH9402 is only used during the manufacturing process, its presence in ATIR101 represents a process-related impurity. Toxicity studies performed with the aim of impurity qualification comprise a GLP single dose toxicity study in rats, three GLP Ames tests and one GLP mouse lymphoma assay. For reasons of completeness, two pharmacokinetic cytochrome P450 (CYP) inhibition studies conducted with TH9402 are presented as part of the impurity qualification as well. In addition, the impact of PDT (effects of TH9402 with and without PDT) was investigated in one non-GLP Ames test, a GLP chromosome aberration test, and a GLP mouse lymphoma assay.

Repeat dose toxicity

A non-GLP safety study in a syngeneic transplant model in C57BL/6J mice was conducted with the purpose of evaluating the effect of repetitive inoculations of in vivo primed spleen cells exposed to PDT using TH9402 ex vivo (ATIR101-like cell-based product). The effects of injection of 4×10^5 T-cells treated ex vivo with the photosensitizing reagent TH9402 and light versus the injection of 4×10^5 non-treated T-cells were compared (in total 4 weekly injections of 4×10^5 cells each, 1.6×10^6 cells in total). Total body irradiated B10BR H-2 mice received bone marrow and spleen cells from C57BL/6J H-2 mice. After 2-3 weeks, spleen cells were isolated from B10BR H-2 mice (donor cells). C57BL/6J H-2 mice (5 males / group) were irradiated and received a T-cell depleted bone marrow transplantation (BMT) as well as 4×10^5 in vivo primed T-cells, once per week for 4 weeks, starting 2 weeks after BMT. In one group the T-cells were exposed to TH9402 and subjected to PDT (ATIR101-like cell-based product), while the T-cells administered to the other group were not exposed to TH9402 / PDT.

The mice all lost weight after the irradiation, with a maximal loss of about 15% after 6 days, which is normal after BMT. Subsequently, all mice recuperated their initial weight between 20 and 30 days. Except for the weight loss, the mice were healthy and alive for the entire duration of the observation period of 54 days post BMT, after which the mice were euthanised and their organs submitted for analysis. The live cell population in the donor cells was greater in the untreated group than in the PDT / TH9402 treated group. The opposite was true for the proportion of dead cells, which ranged from 4.69% to 17.26% in the untreated group and increased to 18.17% to 65.24% in the PDT / TH9402-treated group. The proportion of apoptotic cells was similar for both conditions. The quantity of residual intracellular TH9402 was evaluated by fluorometry following PDT treatment of the spleen cells and it was determined that the treated mice received an average of 1.67 ng of residual TH9402 per

injection. Finally, there were no organ weight changes, macroscopic or microscopic changes, or bone marrow changes that were considered treatment-related.

Impurity qualification

The acute toxicity of TH9402 and TH9402 PBP was assessed in a GLP single dose toxicity study in rats. TH9402 or TH9402 PBP injected i.v. at a dose of 2000 µg/kg (3.43 µmol/kg) did not cause any sign or symptom of toxicity in the rats.

A statistically significant difference in some hematology and biochemistry parameters between the test and control rats were deemed irrelevant as these parameters were well within their normal physiological limits as reported in the literature and based on the test laboratory's historical data.

Taking the proposed specification for TH9402 into account, the theoretical safety factor for the dose tested (2000 µg/kg rat) taking into account allometric considerations (human equivalent dose of 320 µg/kg based on a factor of 6.2 for conversion between rat and human3), is approximately 80,000 to 400,000.

The potential genotoxicity of TH9402 and TH9402 PBP was tested in three in vitro Ames bacterial mutation tests. TH9402 and TH9402 PBP were negative in the Ames test suggesting no potential for mutagenicity. In a mouse lymphoma assay TH9402 and TH9402 PBP were shown to be non-mutagenic at concentrations of up to 5 µg/ml (8.6 µM) and 6 µg/ml (10.3 µM), respectively.

Standard PK investigations in relation to the process-related impurity TH9402 have not been performed as TH9402 is not administered directly to the patient but is administered ex vivo to cells, which are washed following the PDT prior to administration to the patient resulting in residual TH9402 levels of lower than 0.1 µg/dose. However, in vitro metabolism studies (Cytochrome P450 (CYP) inhibition in human liver microsomes) were performed with TH9402 as part of impurity qualification. Briefly, in these studies it was shown that CYP3A4/5 is the major enzyme involved in the metabolism of TH9402. CYP2B6, CYP1A2 and also CYP2C9 appeared to have a minor contribution. Further it was shown that TH9402 is a strong inhibitor of CYP3A4/5 (IC50 4 µM (2.33 µg/ml)), CYP2C19 (IC50 7 µM (4.08 µg/ml)), CYP2C9 (IC50 10 µM (5.83 µg/ml)) and CYP2D6 (IC50 12 µM (7 µg/ml)), and a weak inhibitor of CYP1A2 (IC50 > 100 µM (58.3 µg/ml)).

Considering the very low doses and anticipated exposure to TH9402 in humans (theoretical worst case exposure of 0.02 ng/ml, based on specified residual levels of TH9402), these findings are unlikely to have clinical relevance.

Impact of PDT

The impact of the PDT procedure using TH9402 on bacteria and mammalian cells was investigated in three in vitro genotoxicity studies.

Phytohemagglutinin (PHA)-activated human peripheral blood lymphocytes were exposed to different concentrations of the reagent TH9402 (uptake phase) followed by a period of efflux (extrusion) and subsequent exposure of the cells to light of visible wavelength (photodynamic treatment); these experiments were performed in the presence or absence of metabolic activation. The results from the chromosomal aberration study showed a dose response effect on chromosome aberrations that are found after PDT with TH9402 at concentrations of 26 µM and higher, regardless of metabolic activation. Importantly, no aberrations were seen after PDT using the lowest TH9402 concentrations which allows for the concentration used in the manufacturing of ATIR101. Therefore, it can be concluded that PDT using TH9402 at a concentration of as used in the manufacturing of ATIR101 has no clastogenic potential.

The mutagenic potential of illuminated TH9402 was further tested in L5178Y/TK+/- mouse lymphoma cells in the presence and absence of metabolic activation. These cells express one locus of the thymidine kinase (TK) and are thereby sensitive to trifluorothymidine (TFT) that interferes with DNA synthesis and prevents cellular replication. Mutagenic compounds may alter the single TK locus, leading to L5178Y/TK-/- cells that are capable of proliferation in the presence of TFT. An important caveat of this study is that TH9402 preferentially accumulates in cancer cells such as these murine lymphoma cells compared to normal cells, causing higher residual intracellular concentrations of TH9402 after illumination. Therefore, the results obtained in this test system will overestimate the effect on human peripheral lymphocytes. In the presence of metabolic activation, mutagenicity of TH9402 was equivocal as no substantial increase in mutant frequency was seen at TH9402 concentrations below 40 µM. In the absence of metabolic activation, mutagenicity was seen at a TH9402 concentration of 7 µM. Yet, given the selective accumulation of TH9402 in cancer cells, this is likely to be an overestimation of the mutagenic effect as in ATIR101 normal cells, accumulating less TH9402, are subjected to PDT / TH9402 treatment.

3.2.4. Ecotoxicity/environmental risk assessment

In agreement with the European guideline on environmental risk assessment (EMEA/ CHMP/ SWP/4447/00 corr 2), no ERA studies are submitted for ATIR101 or any of its components.

3.2.5. Discussion on non-clinical aspects

Pharmacology

In terms of pharmacodynamics the applicant presented results from one pivotal proof-of-concept study showing that PDT using TH9402 ex vivo successfully eliminated antigen-specific cytotoxic T-cells that were generated in mixed-lymphocyte culture but did not eliminate resting anti-leukemia and anti-third-party T-lymphocytes. The concept of performing one pivotal non-clinical proof-of-concept study had been acknowledged within EMA Scientific Advice. Likewise, data were considered sufficient to support the proof-of concept in the CAT certification report.
The omission of studies on secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction is justified.

Pharmacokinetics

No studies on pharmacokinetics have been performed with ATIR. It is agreed that according to the CHMP "Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)", classical pharmacokinetic (PK) studies on absorption, distribution, metabolism and excretion (ADME) are not applicable for cell-based medicinal products.
Cell-specific aspects, i.e. biodistribution, migration of cells within the host, persistence, viability, growth and proliferation of cells and their phenotype and any alteration of phenotype have been sufficiently addressed. It is agreed that the intravenously infused donor cells are not expected to behave differently compared to the patient's own circulating lymphocytes. This assumption is supported by clinical experience as HSCT is being routinely used for the treatment of a number of haematological malignant and non-malignant diseases for many years, with no reported adverse effects that have been attributed to disturbances of biodistribution, migration or persistence, viability and growth of the cells. Also, a number of T-cell products are currently under clinical investigation for a range of disorders without so far any signs for unwanted biodistribution or persistence of infused T-cells (e.g. Cruz et al., 2010).
As part of the impurity qualification two in vitro metabolism studies (i.e. cytochrome P450 (CYP) inhibition in human liver microsomes) were performed with TH9402. Here effects were seen at concentrations of 0.5 or 2.5 µM (0.29 or 1.46 µg/ml) and 1-100 µM (0.58 or 58.30 µg/ml), respectively, which are magnitudes above the maximal anticipated concentration in patients

(theoretical worst case exposure of 0.02 ng/ml based on specified residual levels of TH9402). Thus, the findings in the CYP inhibition studies are considered unlikely to have any clinical relevance.

Toxicology

In terms of toxicology the applicant presented results from a repeat dose toxicity study which is considered to be pivotal for the nonclinical safety assessment of ATIR. In this study the effects of the injection of in vivo primed 4 x 10^5 T-cells treated ex vivo with the photosensitizing reagent TH9402 and light, versus the injection of 4 x 10^5 non-treated T-cells were compared. In brief, no unexpected results from repeated inoculations of ATIR-like cell-based product were observed: doses of up to 1.6 x 10^7 cells/kg per dose (single cell dose of 4 x 10^5 cells/mouse, and a mean body weight of 0.025 kg) and up to 4 infusions did not result in any unwanted effects. Thus, the proposed clinical dose (i.e. 2 x 10^6 cells/kg) is covered manifold by this study.

No further toxicity studies have been performed with "complete" ATIR. But studies were conducted to investigate the potential toxicity of the photosensitizing compound TH9402 and the photodynamic treatment (PDT).

Toxicity of TH9402 and TH9402 PBP was investigated in a single dose toxicity study and in studies addressing the potential genotoxic risk. In the single dose toxicity study in rats TH9402 or TH9402 PBP was injected i.v. at a dose of 2000 µg/kg (3.43 µmol/kg). The injections did not cause any sign or symptom of toxicity. Taking the proposed specification for TH9402 into account, the theoretical safety factor for the dose tested (2000 µg/kg rat) taking into account allometric considerations (human equivalent dose of 320 µg/kg based on a factor of 6.2 for conversion between rat and human), is approximately 80,000 to 400,000.

The potential genotoxic risk of residual TH9402 or TH9402 photobleached product was addressed via three Ames test and one mouse lymphoma assay. Data from Ames bacterial mutation tests showed no mutagenic effect of TH9402 or its photobleached form with or without metabolic activation. It might also be argued that residual TH9402 levels and levels of TH9402 PBP are well below the TTC of 1.5 µg/day for genotoxic impurities with unknown mechanism of action as indicated by the CHMP "Guideline on the limits of genotoxic impurities (CHMP/SWP/5199102)". Hence, the process-related impurity TH9402 and its photobleached product are not considered to pose a genotoxic risk to the patient upon treatment with ATIR.

As there is a potential concern for oncogenic transformation induced by the PDT procedure, the potential mutagenic effect of PDT was examined in respective studies.
In the Ames test the PDT procedure was found to be mutagenic in two strains at certain concentrations. However, due to cytotoxicity, no mutagenicity was determinable in the remaining tester strains or at higher concentrations. In the gene mutation test using mouse lymphoma cell TH9402 was mutagenic without S9 activation and equivocal with S9 activation. No substantial increase in mutant above that in the negative control was observed at ≤5 µM without S9 activation and at ≤40 µM with S9 activation. However, extrapolation of results obtained from AMES test and mouse lymphoma cells to the clinical application of ATIR101 is limited, since effects due to the presence of TH9402 in Salmonella strains and mouse lymphoma cells subjected to the PDT procedure might not be identical to effects of PDT procedure applied on primary human lymphocytes incorporating TH9402.

In activated human peripheral blood lymphocytes a dose response effect on chromosome aberrations was found after PDT with TH9402 at concentrations of 26 µM and higher, regardless of metabolic activation. No aberrations were seen after PDT using the lowest TH9402 concentrations of 18 µM, which allows for a 3-4 fold safety margin to the concentration used in the manufacturing of ATIR. However, all but one of the tested concentrations of TH9402 subjected to PDT with or without metabolic activation was to be regarded as cytotoxic considering the defined threshold of cytotoxicity of 50% as given in the OECD guideline. The only exception being 10.5 µg/ml (18 µM) TH9402

subjected to PDT with metabolic activation with a cytotoxicity of 49% on the limit of acceptance according to the OECD guideline. Thus, the validity of this study has to be questioned based on study design and technical limitations that may introduce false positive results leading to an overestimation of the clastogenic potential of the PDT procedure using TH9402. Overall, the efforts of the applicant to determine the genotoxic risk of the PDT procedure are acknowledged and do comprise state-of the art testing. Unfortunately, results do not provide a clear picture due to methodological weaknesses of the assays. However, further in-vitro investigations are not appraised to further elucidate on this aspect. However, based on the TTC concept the genotoxic risk is considered to be low. Finally, this aspect was addressed within clinical data (including karyotyping of clinical batches) and further clinical use. Accordingly, in the RMP the applicant has defined to provide data on the incidence of secondary malignancies.

3.2.6. Conclusion on non-clinical aspects

Overall, the non-clinical program is considered sufficient to support marketing authorisation of ATIR101. In terms of pharmacodynamics results from the pivotal study support the proof-of-concept. The omission of studies on pharmacokinetics of ATIR101 is justified. The residual TH9402 impurity in ATIR101 is not considered to pose any clinical relevant risk in terms of liver enzyme inhibition. In terms of toxicology the presented data do not raise safety concerns. The potential risk of genotoxicity/tumourigenicity is considered low and was further addressed by karyotyping of clinical batches and respective pharmacovigilance monitoring of patients treated with ATIR101.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Table 1 Tabular overview of clinical studies

Study No. Phase (Countries)	**Objective**	**Study design, type of control Main inclusion criteria**	**Patients**	**Study status**
ATIR101 studies				
CR-GVH-001 Phase I/II (CA)	Dose escalation	Open-label, single-arm, single rising-doses of 1.0 x10^4 to 5.0 x 10^6 viable T-cells/kg Patients with severe hematological malignancies undergoing haploidentical T-cell depleted HSCT	N=19	Completed 18 Jan 2005 - 26 Mar 2013
CR-AIR-007 Phase II (BE, CA, DE, UK)	Efficacy, safety	Open-label, single-arm, uncontrolled using a single dose of 2 x 10^6 viable T-cells/kg Patients with AML or ALL in complete remission or MDS and undergoing a haploidentical T-cell depleted HSCT	N=23	Completed 19 Mar 2013 - 19 Sep 2017
CR-AIR-008 Phase II Europe, North America	Efficacy, safety	Open-label, single-arm, two-dose regimen of 2 x 10^6 viable T-cells/kg Patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor	N=15	, Reporting phase 9 Oct 2015 – 17 Dec 2018
Non-ATIR101				

CR-AIR-004 Phase II (BE, CA, DE, NL, UK, US)	Efficacy, safety	Open-label, single-arm, uncontrolled, single dose of 10^6 T-cells/kg Patients with hematological malignancy (ALL, AML, CLL, CML, MDS, multiple myeloma, myeloproliferative syndrome, or NHL) undergoing a haploidentical T-cell depleted HSCT	N=40	Terminated Early 27 Oct 2009 - 8 Feb 2012
Non-interventional study				
CR-AIR-006 (BE, CA, GE, NL, UK, US)[2]	Control	Observational cohort study Patients with hematological malignancies (AML, ALL, both in complete remission, or MDS) who received either haploidentical T-cell depleted HSCT, matched or 1-locus mismatched HSCT, or double cord HSCT	N=158	Completed 17 Feb 2006 - 8 May 2013

3.3.1. Pharmacokinetics

Conventional absorption, distribution, metabolism, and elimination studies are usually not relevant for human cell-based medicinal products (see the 'Guideline on human cell-based medicinal products' EMEA/CHMP/410869/2006). Accordingly, pharmacokinetic studies of ATIR101 in human subjects or patients have not been performed.

3.3.2. Pharmacodynamics

Mechanism of action

ATIR101 is given to patients approximately one month after a haploidentical hematopoietic stem cell transplantation. ATIR101 is expected to provide patients with T-cell based immunity to bridge the period of temporal immune deficiency following myeloablative conditioning and hematopoietic stem cell transplantation (HSCT), until the engrafted stem cells will have generated a fully functional immune system. By selectively eradicating GVHD-causing cells (host-alloreactive T cells) from the T-cell enriched lymphocyte preparation, ATIR101 is expected to not elicit grade III/IV acute GVHD. Therefore, there might not be a need for the use of prophylactic immunosuppressant drugs after transplantation and ATIR101 infusion, allowing a functional immune system to develop faster and more efficiently in the patient. In addition, this may allow donor lymphocytes retained in ATIR101 to exert a GVL effect, thereby limiting relapse.

Immune reconstitution after administration of ATIR101

In the clinical studies of ATIR101, cell counts of T-cell subsets (immunophenotyping, CD3, CD4, CD8, CD19, and CD56) and immunoglobulin concentrations (IgA, IgG, IgM) were evaluated in order to characterise immune reconstitution in patients having received ATIR101.

No binding thresholds are defined for immune reconstitution, but immune reconstitution is usually assumed to have happened if CD3 T-cell counts exceed 100 to 200 cells/μL (equivalent to 0.1 to 0.2 x 10^9 cells/L). Alternatively, immune reconstitution may be assumed if total CD3 cell counts exceed 200 cells/μL (0.2 x 10^9 cells/L) and counts of the T-cell subsets, i.e. CD4 helper cells and CD8 cytotoxic T-cells, exceed 100 cells/μL (0.1 x 10^9 cells/L).

In patients treated with ATIR101, reconstitution of cellular immunity was observed from about 5 to 6 months after HSCT onwards. In study CR-AIR-007, the median CD3 cell count exceeded the threshold of 100 cells/μL from Month 6 onwards and the threshold of 200 cells/μL from Month 10 onwards (Figure 2). Eighteen of 23 patients (78.3%) reached CD3 counts above 0.1 x 10^9/L at least once during the study period, while 13 patients (56.5%) reached CD3 counts above 0.2 x 10^9/L [CR-AIR-007, Listing 16.2.31b]. CD4 cells (helper T-cells) and CD8 cells (cytotoxic T-cells) are subsets of CD3 cells. The trajectories of CD3 CD4 and CD3 CD8 T-cells were similar to that of all CD3 T-cells in general: there were virtually no cell counts for up to 4 months after HSCT, after which cell counts started to increase gradually.

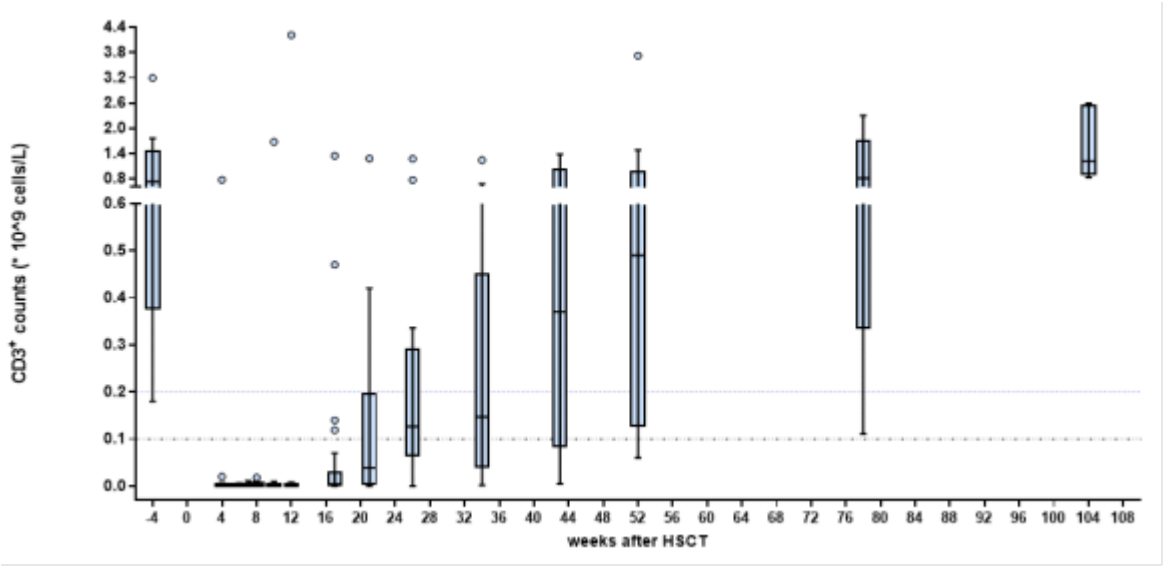


Figure 1 Number of CD3 T-cells over time - study CR-AIR-007, MITT

Box-and-whisker plots: box indicates the 25th and 75th percentiles; whiskers drawn using the Tukey method; median indicated by horizontal line in the box.
Source data: [CR-AIR-007, Figures 25 to 27]

Immune reconstitution data from studies CR-AIR-007 and CR-AIR-004 (as comparator with prospective data) are summarized in the figure below (Figure 2).

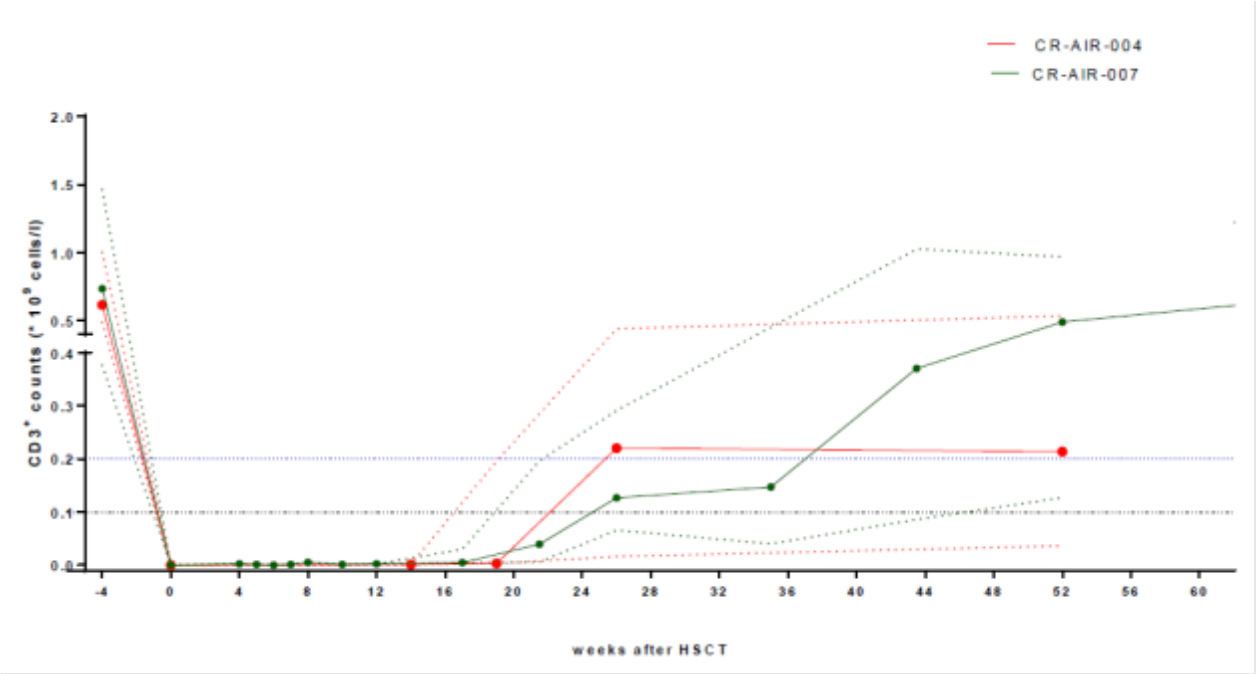


Figure 2 T-cell Immune reconstitution CR-AIR-004 and CR-AIR-007
Symbols indicate medians, dotted lines the IQR

As can be seen in Figure 2, reconstitution of T-cells (CD3+) in CR-AIR-004 is comparable to that observed in study CR-AIR-007.

Next to immune reconstitution the infections were compared between the two studies. The early infections (within 60 days post HSCT) and late infections (61-182 days post HSCT) are summarized in Table 2.

Table 2 Type and incidence of infections in the CR-AIR-007 and in the CR-AIR-004 study in the early and in the late post-transplantation phase after HSCT

	CR-AIR-007 n=23		**CR-AIR-004 n=29**		**CR-AIR-007[1] n=23**		**CR-AIR-004[2] n=28[3]**	
Any infection, n (%)	20 (87.0%)		26 (89.7%)		19 (82.6%)		22 (78.6%)	
Adverse Events, n	54		122		82		82	
Viral infection	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Patients, n (%)	15	65.2%	16	69.6%	16	69.6%	22	78.6%
Grade 3	2	8.7%	4	17.4%	4	17.4%	12	42.9%
Grade 4	0	0.0%	1	4.3%	1	4.3%	1	3.6%
Grade 5	0	0.0%	2	8.7%	2	8.7%	5	17.9%
Fungal infection								
Patients, n (%)	9	39.1%	10	34.5%	10	43.5%	6	21.4%
Grade 3	2	8.7%	5	17.2%	1	4.3%	3	10.7%
Grade 4	0	0.0%	0	0.0%	0	0.0%	1	3.6%
Grade 5	0	0.0%	0	0.0%	1	4.3%	0	0.0%
Bacterial infection								
Patients, n (%)	11	47.8%	19	65.5%	7	30.4%	14	50.0%
Grade 3	5	21.7%	10	34.5%	1	4.3%	6	21.4%
Grade 4	2	8.7%	2	6.9%	1	4.3%	2	7.1%
Grade 5	0	0.0%	1	3.4%	0	0.0%	0	0.0%

For each patient, the worst severity of infections by category (i.e. separately for viral, fungal, and bacterial infections) is shown. Severity was graded according to CTCAE vs. 4.0.
Allocation of events to assessment periods is based on the onset date of the respective AE. Infections with unknown causative agent are not included in this table.
[1] Of the 23 CR-AIR-007 patients, 5 died in this time-frame (at days 103, 110, 122, 150 and 171).
[2] Of the 28 CR-AIR-004 patients, 9 patients died or follow-up was stopped in this time frame (at days 67, 73, 77, 92, 115, 145, 153, 172 and 172).
[3] 1 patient of the CR-AIR-004 study died before day 61 (at day 53), therefore total n=28 and not 29.

Source data: [CR-AIR-007, CR-AIR-004]

Comparison of data on infections from the two studies show that there are less severe infections (grade 3-5) in patients treated with ATIR101 in study CR-AIR-007 when compared to the control group in study CR-AIR-004, both in the early and in late post-transplantation phase.

Compared with cell counts before HSCT, mean CD56 NK cell counts had increased by about 4 weeks after HSCT and remained at that level for the remainder of the study (Figure 3).

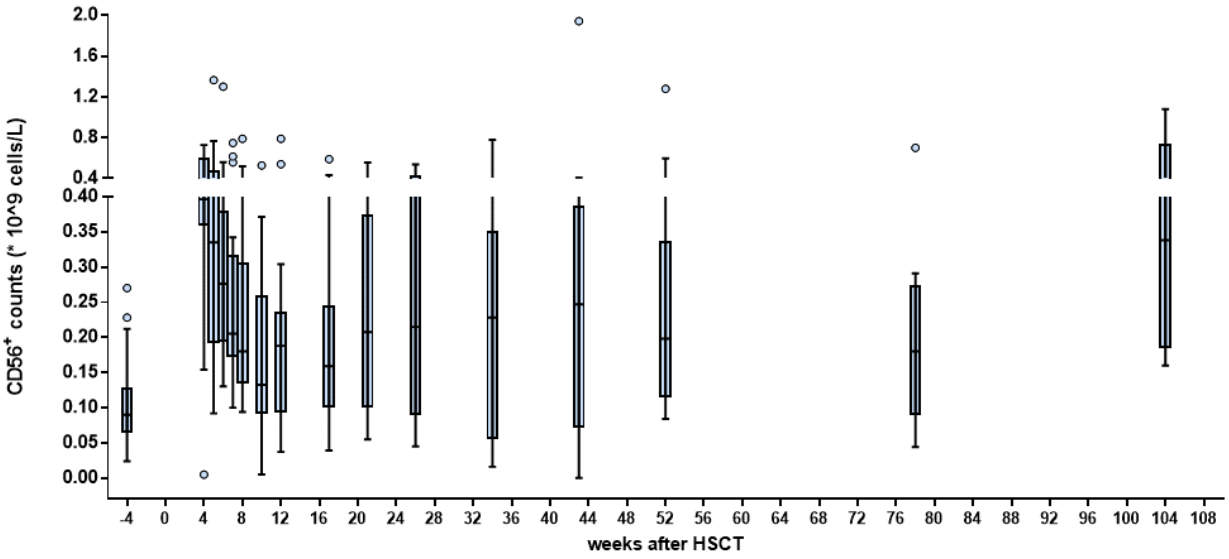


Figure 3 Number of CD56 NK cells over time - study CR-AIR-007, MITT

Box-and-whisker plots: box indicates the 25th and 75th percentiles; whiskers drawn using the Tukey method; median indicated by horizontal line in the box.
Source data: [CR-AIR-007, Figure 12]

There was no major change in humoral immunity, as B-cell counts as well as immunoglobulin concentrations reached close to normal levels soon after HSCT [Module 2.7.2, Figures 2-8; 2-10 to 2-12].

Findings for reconstitution of cellular and humoral immunity in study CR-GVH-001 were consistent with the results for the pivotal study CR-AIR-007 [Module 2.7.2, Section 2.2.2.2].

Recovery of cellular immunity in response to EBV reactivation

For 4 patients treated with ATIR101 in the dose escalation study CR-GVH-001 and experiencing EBV reactivation, the course of EBV viral load and of the CD3, CD4, and CD8 cells over time is shown in Figure 5. In 2 patients, receiving ATIR101 at doses of 3 x 10^5 or 2 x 10^6 viable T- cells/kg resulted in a complete disappearance of EBV, without additional rituximab treatment (shown in the upper part of the figure).

The other 2 patients with rising EBV titers received rituximab. A single dose of rituximab was sufficient to control the infection, and in one of these patients, the elevated EBV PCR titer had already subsided at the time of the rituximab administration.

In all 4 patients, CD3, CD4, and CD8 cell counts increased in response to the EBV reactivation, indicating a role for T-cell expansion in the clearance of the EBV infection.

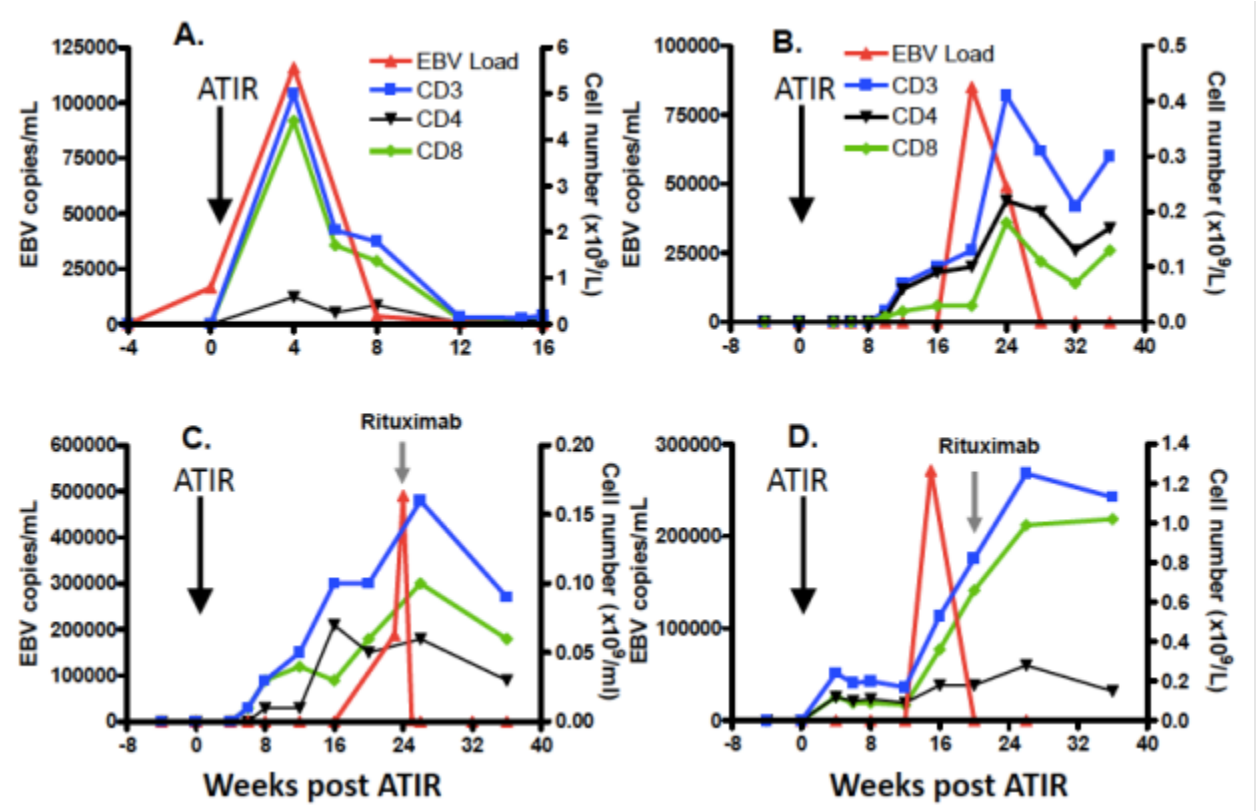


Figure 4 Cellular immunity in 4 patients with EBV reactivation - CR-GVH-001

Source data: [CR-GVH-001, Figure 10]

3.3.3. Discussion on clinical pharmacology

The reconstitution of T-cells (CD3+CD4+ and CD3+CD8+) after administration of ATIR101 was shown to happen from about 5 to 6 months after HSCT onwards, which is comparable to the experience of T-cell reconstitution after HSCT without lymphocyte donation. According to additional presented data, ATIR101 infusion has no obvious influence on the reconstitution of the T-cell numbers after HSCT. There was no relevant difference to study CR-AIR-004, which was applied as control with prospective data. Nevertheless, evaluation of a limited dataset of studies CR-AIR-007 and CR-AIR-004 let assume that there is still an effect on infections even in the early phase after HSCT. Patients treated with ATIR101 in study CR-AIR-007 tend to have less severe infections when compared to the control study CR-AIR-004. Specific Tcells might expand and might exert immunological reaction regardless of the circulating peripheral cell numbers. But, this effect of ATIR101 on immune reconstitution and control of infections needs further evaluation.

A temporal increase in T-cells (CD3+ cells) was seen after ATIR101 administration in four cases. The T-cell response seemed related to EBV reactivation in peripheral blood. However, there is no direct proof that the T-cells derived from the ATIR101 product. The transplanted stem cell graft could also have been served as T-cell source. The applicant argues that the amount of CD3+ cells given through the graft is low and at that time a high dose of ATG is circulating in the recipients' body eliminating residual T-cells. Therefore, T-cell expansion might be more likely due to ATIR101 administration. This position is acknowledged. Furthermore, in two of the patients, rituximab were administered, putting in to question validity of the claim that ATIR101 would eliminate need for immunosuppressant drugs following HSCT. However, the applicant states that Rituximab was not administered as

immunosuppressant but to prevent progression of infected B-cells into PTLD in patients with EBV reactivation. None of the usual immunosuppressant drugs were used during or after ATIR101 administration to avoid GVHD.

Remaining non-T-cells are considered product-related impurities and comprise of NK-cells, B-cells and monocytes. NK cells, which belong to the innate immune system, reconstituted more rapidly after HSCT and were even increased compared to values before HSCT. At the time of ATIR101 infusion (between 28 and 32 days post HSCT), B-cells begin to reconstitute.

3.3.4. Conclusions on clinical pharmacology

In conclusion, these data suggest that:

Administration of ATIR101 showed reconstitution of T-cells from about month 5 to 6 after HSCT. Even though ATIR101 infusion does not lead to earlier immune reconstitution (measured as number of T-cells (CD3+ cells) in the peripheral blood), cells in ATIR101 might be able to prevent and/or fight infections resulting in an observed effect of less severe infections both in early and late phase after HSCT.

T-cell response to EBV reactivation was documented in four patients. This can be regarded as a hint of the functional activity of the provided T-cells of the ATIR101 product. Control of infection due to the expansion of EBV specific T-cells already present in the HSCT seems to be unlikely. NK cells, which belong to the innate immune system, reconstituted rapidly after HSCT. No obvious impact on humoral immunity was seen.

Overall, there are still uncertainties regarding ATIR101's proposed mechanism of action i.e. to provide patients with T-cell based immunity. The effect of ATIR101 on immune reconstitution and control of infections is planned to be studied in the ongoing study CR-AIR-009.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

Summary of main efficacy results

Dose response study

First-in-man study CR-GVH-001

This was a single-center, open-label study, including adult patients with advanced hematological diseases or malignancies without any alternative treatment and eligible for haploidentical HSCT as per investigator judgement.

Approximately 28 to 42 days after HSCT, patients received a single infusion of ATIR101 at one of 7 different dose levels of viable T-cells/kg body weight (see table 3). Dose escalation was performed according to the modified Continual Reassessment Method.

After HSCT and ATIR101 administration, patients were to be followed for a total of 5 years. The primary objective was the determination of the maximum tolerated dose (MTD). Safety was also assessed in terms of: occurrence of infections; AEs; safety laboratory assessments, and physical examinations. Efficacy was assessed in terms of PFS; TRM; RRM; OS; GVHD; immune reconstitution; and occurrence of infections (during 18 months following ATIR101 administration).

Overall, 19 patients were treated according to the predefined dose escalation rules and up to the planned highest dose level L7 (Table 3). The MTD for ATIR101, defined as the dose level where 33% of the patients developed acute GVHD Grade III/IV within 30 days after ATIR101 administration (DLT),

was not reached as no patient experienced DLTs. Therefore, selection of the dose for further testing in phase II trials was based on the assessment of a dose-response relationship of ATIR101.

Table 3 Planned dose levels investigated in study CR-GVH-001

Dose level	ATIR101-dose[1] (T-cells/kg body weight)	Number of patients treated (planned)
L1	1.0×10^4	1
L2	5.0×10^4	3
L3	1.3×10^5	3
L4	3.2×10^5	3
L5	7.9×10^5	3
L6	2.0×10^6	3
L7	5.0×10^6	3

Protocol-defined dose levels, given as the approximate number of viable T-cells following photodynamic treatment (PDT)
[1]One patient at dose level L7 received a lower than planned dose (i.e. 2.6×10^6 T-cells/kg) because the number of cells obtained during IMP preparation was not sufficient to prepare and administer the full dose [CR-GVH-001, Listings 16.2.2.1 and 16.2.6.3].

Study CR-GVH-001 provided data on the relationship between ATIR101 dose and clinical activity and between dose and safety, which were used to determine a dose for subsequent clinical studies. Dose levels were grouped as low dose (L1 to L3), intermediate dose (L4 to L6), and high dose (L7).

Higher ATIR101 dose groups were shown to be associated with a higher OS and PFS probability and lower RRM and TRM probability. In particular, the OS probability was highest and the TRM probability was lowest in the intermediate dose group (L4-L6), compared to the low dose group (L1 to L3) or to the high dose (L7) (see Table 4 and Table 5).

Table 4 Kaplan-Meier estimates for OS (overall and by dose level) at landmark time points relative to HSCT - study CR-GVH-001, FAS

Time after HSCT	OS probability [%]			
	All patients	Low dose level (L1-L3)	Intermediate dose level (L4-L6)	High dose level (L7)
1 year	63	43	78	67
2 years	47	29	67	33
5 years	37	14	67	0

Sample size: 7 patients were treated at the low dose level; 9 patients were treated at the intermediate dose level; 3 patients were treated at the high dose level (total: 19 patients).

Table 5 Kaplan-Meier estimates for TRM (overall and by dose level) at landmark time points relative to HSCT - study CR-GVH-001, FAS

Time after HSCT	TRM probability [%]			
	All patients	Low dose level (L1-L3)	Intermediate dose level (L4-L6)	High dose level (L7)
1 year	24	49	0	33
2 years	36	66	0	67
5 years	44	66	0	100

Sample size: 7 patients were treated at the low dose level; 9 patients were treated at the intermediate dose level; 3 patients were treated at the high dose level (total: 19 patients).
Source data: [CR-GVH-001, Table 16]

A similar trend, although less pronounced, was seen for PFS: it tended to be higher in the higher dose groups in Year 1; while it was highest for the intermediate dose group after 2 and 5 years. RRM was lowest in the L7 group.

Patients receiving higher ATIR101 doses (i.e. L6 and L7) appeared to have a higher risk to develop GVHD (Table 6). However, acute GVHD was generally of low grade (not higher than grade II), and GVHD generally responded to immunosuppressive treatment. No GVHD occurrences were reported that led directly to the patient's death. In the highest dose cohort, however, immunosuppressive treatment required for patients with GVHD grade II led to subsequent infections and patients dying as a result of these infections (considered as being TRM).

Table 6 Patients with GVHD - study CR-GVH-001, FAS

	Dose level	Grade / intensity	Biopsy confirmed	Outcome
Acute				
	L1	Grade I[1]	Yes	Resolved
	L2	Grade II	Yes	Not resolved[2]
	L6	Grade II	Yes	Resolved
	L7	Grade II	Yes	Resolved
	L7	Grade II	Yes	Not resolved[2]
Chronic				
	L2	Severe	Yes	Not resolved[2]
	L4	Severe	No	Resolved
	L5	Severe	Yes	Not resolved[2]
	L6	Severe	Yes	Resolved
	L7	Severe	Unknown	Not resolved[2]

[1]GVHD onset was prior to ATIR101 administration.
[2]No end date reported, ongoing at time of death
Source data: [CR-GVH-001, Listings 16.2.1.3 and 16.2.6.8]

No relationship was seen between ATIR101 dose level and the occurrence of clinical infections within 30 days after IMP administration. Between Week 5 and Month 18, the infection rate tended to decrease with increasing dose level, and this was observed up to dose level L6 (2.0 x 10^6 T-cells/kg). However, a high number of infections occurred at the highest dose level (5.0 x 10^6 T-cells/kg), attributed to the use of immunosuppressive drugs for the treatment of GVHD (Table 7).

Table 7 Clinically significant infections with onset between Week 5 and 18 months after administration of ATIR101 - study CR-GVH-001, FAS

Dose level	Any infection		Type of infection		
	Patients with infections (n)	Infections (n)	Bacterial/parasitic (n)	Viral (n)	Fungal (n)
L1 (1.0 x 10^4 T-cells/kg)	0	0	0	0	0
L2 (5.0 x 10^4 T-cells/kg)	3	13	8	3	2
L3 (1.3 x 10^5 T-cells/kg)	3	6	2	3	1
L4 (3.2 x 10^5 T-cells/kg)	2	4	1	1	2
L5 (7.9 x 10^5 T-cells/kg)	1	7	4	1	2
L6 (2.0 x 10^6 T-cells/kg)	1	1	0	0	1
L7 (5.0 x 10^6 T-cells/kg)	3	8	3	3	2

Only infections confirmed by a positive culture are shown.
Infections caused by the same infectious agent were counted only once.
Source data: [CR-GVH-001, Table 12]

Main study(ies)

Pivotal Study CR-AIR-007

This was an open-label, single-arm, multicenter study. Patients with hematological malignancies (AML or ALL in complete remission or MDS) and eligible for HSCT but without matched related or unrelated donor following donor search could participate.

Adult patients received HSCT from a related, haploidentical donor, followed by a single infusion of ATIR101 at a dose of 2.0 x 10^6 viable T-cells/kg approximately 28 to 32 days after HSCT. Patients were to be followed for a total of 2 years after the HSCT.

The primary efficacy endpoint of the study was TRM at 6 months after HSCT. Secondary endpoints, assessed from HSCT up to 24 months after HSCT, included incidence and severity of acute and chronic GVHD; immune reconstitution; incidence and severity of infections; TRM; relapse-related mortality (RRM); OS; and progression-free survival (PFS). Safety was assessed in terms of AEs, safety laboratory assessments, vital signs, and CMV/EBV monitoring.

The primary endpoint (6-month TRM) was reached in March 2016. The study was completed in September 2017 including 24-month follow-up of the last patient.

Table 8 Summary of efficacy for trial 007

<table>
<tr><td colspan="4"><u>Title:</u> <u>An exploratory, open-label, multicenter study to evaluate the safety and efficacy of ATIR, donor T-lymphocytes depleted ex vivo of host alloreactive T-cells, in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor</u></td></tr>
<tr><td>Study identifier</td><td colspan="3">CR-AIR-007</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">After myeloablative conditioning patients received T-cell depleted (CD34 cell selected) HSCT from a related, haploidentical donor. A single infusion of ATIR101 at a dose of 2 x 10^6 viable T-cells/kg followed ~28 and 32 days after HSCT. Post-transplantation immunosuppressive therapy in the absence of GVHD was to be avoided unless medically indicated. Patients who were CMV or EBV positive or had a CMV or EBV positive donor were to receive prophylactic or preemptive treatment.
Patients were to be followed for 2 years after the HSCT.</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:

Duration of Extension phase:</td><td>3 years
median time ~109 days:
• from informed consent to apheresis: 22 days (range: 7- 64 days)
• from apheresis to HSCT: 29 days (range 13-64)
• from apheresis to ATIR101 infusion: 58 days (range 41-102).
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Exploratory: safety and efficacy of ATIR101</td></tr>
<tr><td>Treatments groups</td><td colspan="2">ATIR101</td><td>Single infusion of 2.0 x 10^6 viable T-cells/kg ~28 to 32 days after HSCT with 2 years post HSCT follow up; n=23</td></tr>
<tr><td rowspan="4">Endpoints and definitions</td><td>Primary endpoint</td><td>Efficacy</td><td>TRM at 6 months post HSCT</td></tr>
<tr><td rowspan="3">Secondary endpoints</td><td colspan="2">All secondary endpoints were assessed from HSCT up to 24 months after HSCT</td></tr>
<tr><td>Efficacy and safety</td><td>GVHD</td></tr>
<tr><td>PD and efficacy</td><td>immune reconstitution</td></tr>
</table>

		Efficacy and safety	infections
		Efficacy	TRM
		Efficacy	RRM
		Efficacy	OS
		Efficacy	PFS
Database lock	Date not provided		
Results and Analysis			
Analysis description	**Primary* and Secondary Analysis**		
Analysis population and time point description	ATIR101 group, Modified intent to treat population (n=23) Kaplan-Meier probabilities		

Descriptive statistics and estimate variability	Time points post HSCT	TRM	RRM	OS	PFS
	6 months, %	13*	5	83	78
	95% CI	(5, 36)	(1, 28)	(60, 93)	(55, 90)
	12 months, %	32	10	61	61
	95% CI	(17, 56)	(3, 35)	(38, 77)	(38, 77)
	24 months, %	50	23	39	36
	95% CI	(32, 71)	(9, 52)	(20, 58)	(18,54)

	ATIR101 group, ITT (n=26) Frequencies, within 2 years post HSCT		
		GVHD	Infections
	n (%)	3 (11.5)	21 (80.8)
Effect estimate per comparison	N/A		
Notes			

Non-interventional Study CR-AIR-006

This was a multi-center, non-interventional, observational cohort study. The study population was aligned as much as feasible with that of the pivotal study CR-AIR-007, using similar inclusion and exclusion criteria. In particular, the study was designed to collect data on transplantation outcome in patients receiving haploidentical, T-cell depleted HSCT without adjunctive treatment with ATIR101, matching the patients receiving haploidentical, T-cell depleted HSCT with ATIR101 in the pivotal study, for which the data serve as control group.

Collected data included: pre-transplantation data (baseline disease status, use of bone marrow biopsy or aspirate, and conditioning regimen); data on the transplantation; and 12-month follow- up data on GVHD, infections (analyzed as safety parameter), disease relapse/progression, and mortality. The same efficacy endpoints were analyzed as in the interventional studies ofATIR101.

Table 9 Summary of efficacy for trial 006

Title: An observational cohort study on transplant-related mortality in patients receiving either a hematopoietic stem cell transplantation without ATIR101 or an umbilical cord blood transplantation						
Study identifier	CR-AIR-006					
Design	In this non-interventional, observational cohort study patients receiving either a HSCT without ATIR101 or an umbilical cord blood transplantation were observed for 1 year. Patients are grouped by treatment in 3 groups (haploidentical donors, unrelated donors and umbilical cord donors). Haploidentical donors (HAPLO) group without ATIR101 serves as external control for comparison with patients treated with ATIR101 in study 007. Patients were not treated with ATIR101 in this study					
	Duration of main phase:	1 year of observation post HSCT (completed)				
	Duration of Run-in phase:	no clear timelines provided.				
	Duration of Extension phase:	not applicable				
Hypothesis	Exploratory: efficacy and safety of HSCT without ATIR101 or an UCB transplantation.					
Treatments groups	HAPLO	HSCT from a haploidentical donor without ATIR101, n=35				
	MUD	HSCT from a fully matched unrelated donor, n=64				
	MMUD	HSCT from a 1-locus mismatched unrelated donor, n=37				
	UCB	double umbilical cord blood transplantation, n=22				
Endpoints and definitions	Co-primary endpoint	Efficacy	TRM, RRM, OS, and PFS.			
		Safety	incidence and severity of acute and chronic GVHD			
Database lock	Date not provided					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	All subjects, 12 months post transplantation Kaplan-Meier probabilities, CIs are not provided					
Descriptive statistics and estimate variability	Treatment group	HAPLO	MUD	MMUD	UCB	
	Patient no	35	64	37	22	
	TRM at 6 months*, %	37	6	22	32	
	TRM at 12 months, %	70	10	25	37	
	RRM, %	20	5	11	9	
	OS, %	20.0	85.9	64.2	54.5	
	PFS, %	20	77	59	55	
	GVHD frequencies at 12 months post HSCT					
	n (%)	17 (49)	41 (64)	21 (57)	15 (68)	
	*primary endpoint in pivotal study 007					
Effect estimate per comparison	N/A					

Clinical studies in special populations

N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

Pooled analysis of study CR-AIR-007 (MITT population) and study CR-AIR-006.

Comparability of Patient Populations

Patients in the HAPLO groups of the 2 studies were generally comparable with regard to median age (CR-AIR-007: 41.0 years; CR-AIR-006: 43.0 years) and sex distribution (female patients, CR-AIR-007: 47.8%, CR-AIR-006: 42.9%).

The majority of patients in both studies had AML (CR-AIR-007: 69.6%, CR-AIR-006: 71.4%), although the studies differed with regard to the less frequent malignancies i.e. ALL (30.4% vs. 11.4%) and MDS (0% vs. 17.1%). All patients in study CR-AIR-007 were in complete remission, vs. 82.9% of patients in CR-AIR-006, where 8.6% of patients had partial remission and 5.7% had refractory disease (these were mainly patients with MDS). Data were in line with the pre-specified study populations of AML or ALL in remission or MDS, which were defined by both protocols CR-AIR-007 and CR-AIR-006. The median time from diagnosis of the hematological malignancy to HSCT was somewhat longer in study CR-AIR-007 (265 days) than study CR-AIR-006 (213 days). The use of a TBI or non-TBI conditioning regimen was balanced in study CR-AIR-007 (TBI: 47.8%, non-TBI: 52.2%), while the majority of patients in study CR-AIR-006 had received a TBI regimen (71.4%).

In study CR-AIR-007 the median dose of CD34 cells administered at HSCT was 11 x 10^6 cells/kg (range 4.7-24.4 x 10^6 cells/kg); the median CD3 cell count was 0.29 x 10^4 cells/kg (range 0.01-1.8 x 10^4 cells/kg). In study CR-AIR-006 the median number of cells received during the transplantation was 7.0 x 10^6 cells/kg for CD34 cells (range: 2.2 to 15.1 x 10^6 cells/kg) and 4.0 x 10^4 cells/kg for CD3 cells (range 0.2 to 40 x 10^4 cells/kg).

Efficacy Analyses

The pooled analysis of efficacy data from studies CR-AIR-007 and CR-AIR-006 included events that happened in the first 12 months after HSCT, i.e. during the time span for which events were recorded in the observational cohort study CR-AIR-006.

The percentage of patients who died was much lower in the pivotal study than in untreated control patients (i.e. the HAPLO group) in study CR-AIR-006. This difference was primarily due to a lower proportion of patients who experienced TRM in the pivotal study.

In both groups, the primary source of TRM was infection. However, the overall incidence of TRM due to infectious causes in the pivotal study was about half of that of the HAPLO group in study CR-AIR-006. TRM due to GVHD occurred in the control study but not in the pivotal study.

For patients who died, there was no notable difference in the median time to death (based on descriptive statistics) (Table 10).

Table 10 Cause of death and cause of TRM - study CR-AIR-007 vs. CR-AIR-006

	CR-AIR-007 HSCT plus ATIR101	CR-AIR-006 HSCT
Patients, n (%)	23 (100.0)	35 (100.0)
Patients who died, n (%)	9 (39.1)	28 (80.0)
Cause of death		
Disease relapse	2 (8.7)	3 (8.6)
Disease progression	0	2 (5.7)
TRM	7 (30.4)	23 (65.7)
Other	0	0
TRM		
GVHD	0	4 (11.4)
Infection	5 (21.7)	14 (40.0)
Graft failure/rejection	0	0
Other	2 (8.7)	5 (14.3)
Time to death[1]		
Median (range)	188.8 (110-258)	191.3 (2-350)

Analysis based on the MITT for study CR-AIR-007 and all patients in study CR-AIR-006
[1]From HSCT
Source data: [Pooled analysis report, Table 14.03.03.02]

The number of patients with TRM event at 6 months was 3 (13.0%) in the pivotal study and 13 (37.1%) in the HAPLO group of study CR-AIR-006. The odds ratio (OR) for TRM at 6 months (defined as the primary endpoint) for patients in the pivotal study vs. the HAPLO group of study CR-AIR-006 was 0.21 (95% CI 0.05, 0.92); the comparison was statistically significant (p=0.0309). This indicates that patients administered ATIR101 after a T-cell depleted HSCT had a significantly lower TRM than patients who did not receive adjunctive treatment with ATIR101. The treatment difference was maintained at 12 months, when 7 patients (30.4%) and 23 (65.7%) patients, respectively, had experienced TRM, and the OR was 0.23 (95% CI 0.07, 0.75; p=0.0147).

Median time to TRM was not estimable (ne) in the pivotal study; it was 7.6 months in the control group i.e. the HAPLO group of study CR-AIR-006. The hazard ratio (HR) for TRM was 0.30 (95% CI 0.12, 0.75) with a p value of 0.0066, indicating a statistically significantly lower TRM in study CR-AIR-007 as compared to the HAPLO group in study CR-AIR-006. The 12-month TRM probability was 32.2% in the pivotal study, compared with a more than 2-fold higher TRM probability of 70.3% in the control group (Table 11).

Table 11 Transplant-related mortality - study CR-AIR-007 vs. CR-AIR-006

	CR-AIR-007 HSCT plus ATIR101	CR-AIR-006 HSCT
Patients, n	23 (100.0)	35 (100.0)
Patients with TRM event, n (%)		
At 6 months	3 (13.0)	13 (37.1)
At 12 months	7 (30.4)	23 (65.7)
Time to TRM [months], median (95% CI)	ne (8.5; ne)	7.6 (5.8; 8.4)
Hazard ratio (95% CI)[1]	0.30 (0.12; 0.75)	
p-value[1]	0.0066	
TRM probability (%) at landmark time points[2]		
6 months	13.5	37.1
9 months	32.2	66.6
12 months	32.2	70.3

Analysis based on the MITT for study CR-AIR-007 and all patients in study CR-AIR-006
[1]Hazard ratio of HSCT plus ATIR101 (CR-AIR-007) vs. HSCT (CR-AIR-006); log-rank test; adjusted for type of hematological malignancy
[2]Kaplan-Meier estimates
Source data: [Pooled analysis report, Tables 14.02.01.01, 14.02.01.02, 14.02.01.03]

Patients in the HAPLO group of study CR-AIR-006 had the highest TRM probability. The Kaplan-Meier curve for patients in the pivotal study separated from the HAPLO curve early after HSCT/ATIR101 administration and remained distinctly below the curve for the HAPLO group for the remainder of the study period. The ATIR101 curve was roughly comparable to the Kaplan-Meier curves for the MMUD groups and patients receiving umbilical cord blood in study CR-AIR-006 (Figure 5).

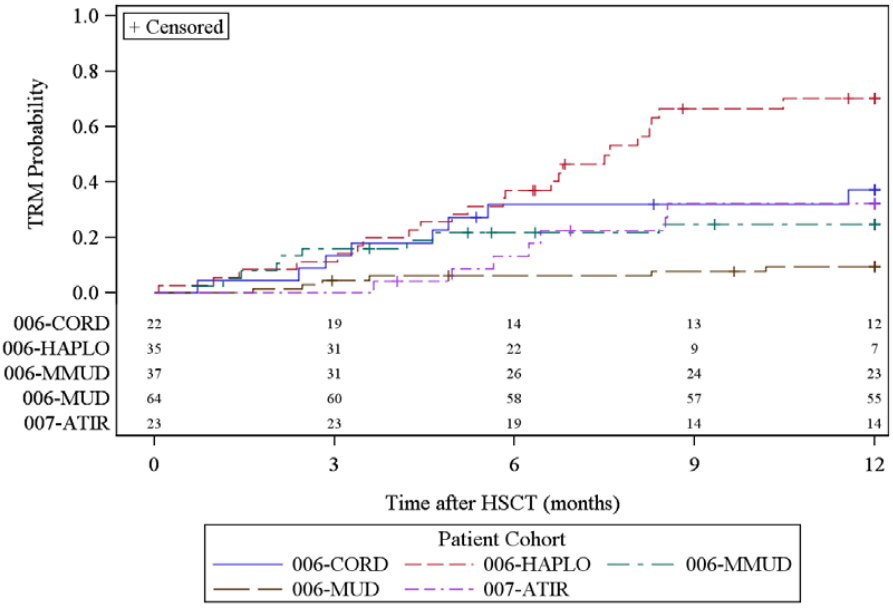


Figure 5 Probability of TRM - study CR-AIR-007 vs. CR-AIR-006

007-ATIR: patients receiving ATIR101; study CR-AIR-007.
006-CORD: patients receiving a double umbilical cord blood transplantation without ATIR101; study CR-AIR-006.
006-HAPLO: patients receiving T-cell depleted HSCT without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a fully matched donor without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a 1-locus mismatched unrelated donor without ATIR101; study CR-AIR-006
Source data: [Pooled analysis report, Figure 14.02.01]

Nine patients (39.1%) died in the pivotal study within the first 12 months, vs. 28 patients (80.0%) in the HAPLO group of study CR-AIR-006. Median time to death was estimable only in the HAPLO group (6.8 months). The HR for OS was 0.32 (95% CI 0.15, 0.71) with a p-value of 0.0035, indicating a statistically significant improvement of OS in ATIR101-treated patients, as compared to the control group (Table 12).

At all landmark time points, the OS probability was higher in the pivotal study than in the control group. This was also reflected in the 12-month OS probability which was 60.9% in the pivotal study and 20.0% in the HAPLO group of study CR-AIR-006.

Table 12 Overall survival - study CR-AIR-007 vs. CR-AIR-006

	CR-AIR-007 HSCT plus ATIR101	CR-AIR-006 HSCT
Patients, n	23 (100.0)	35 (100.0)
Patients with event	9 (39.1)	28 (80.0)
OS [months], median (95% CI)	ne (6.9; ne)	6.8 (5.8; 8.2)
Hazard ratio (95% CI)[1]	0.32 (0.15, 0.71)	
p-value[1]	0.0035	
OS probability at landmark time points[2]		
6 months	82.6	62.9
9 months	60.9	25.7
12 months	60.9	20.0

Analysis based on the MITT for study CR-AIR-007 and all patients in study CR-AIR-006
[1]Hazard ratio of HSCT plus ATIR101 (CR-AIR-007) vs. HSCT (CR-AIR-006); log-rank test; adjusted for type of hematological malignancy
[2]Kaplan-Meier estimates
Source data: [Pooled analysis report, Table 14.02.02]

The HAPLO group of study CR-AIR-006 had the lowest survival probability of all groups analyzed (Figure 6). ATIR101-treated patients had a higher OS probability that the HAPLO group of study CR-AIR-006 that was maintained throughout the study, as indicated by clearly separated Kaplan-Meier curves. The OS probability of ATIR101-treated patients was comparable to that of patients receiving grafts from a mismatched unrelated donor or an umbilical cord blood graft. The OS probability was highest in patients receiving a graft from a matched unrelated donor.

The outcome of the MUD group was surprisingly high, based on assumed transplant outcomes for this type of HSCT. This was taken as an indicator of the overall performance of the selected transplantation centers in this type of procedure.

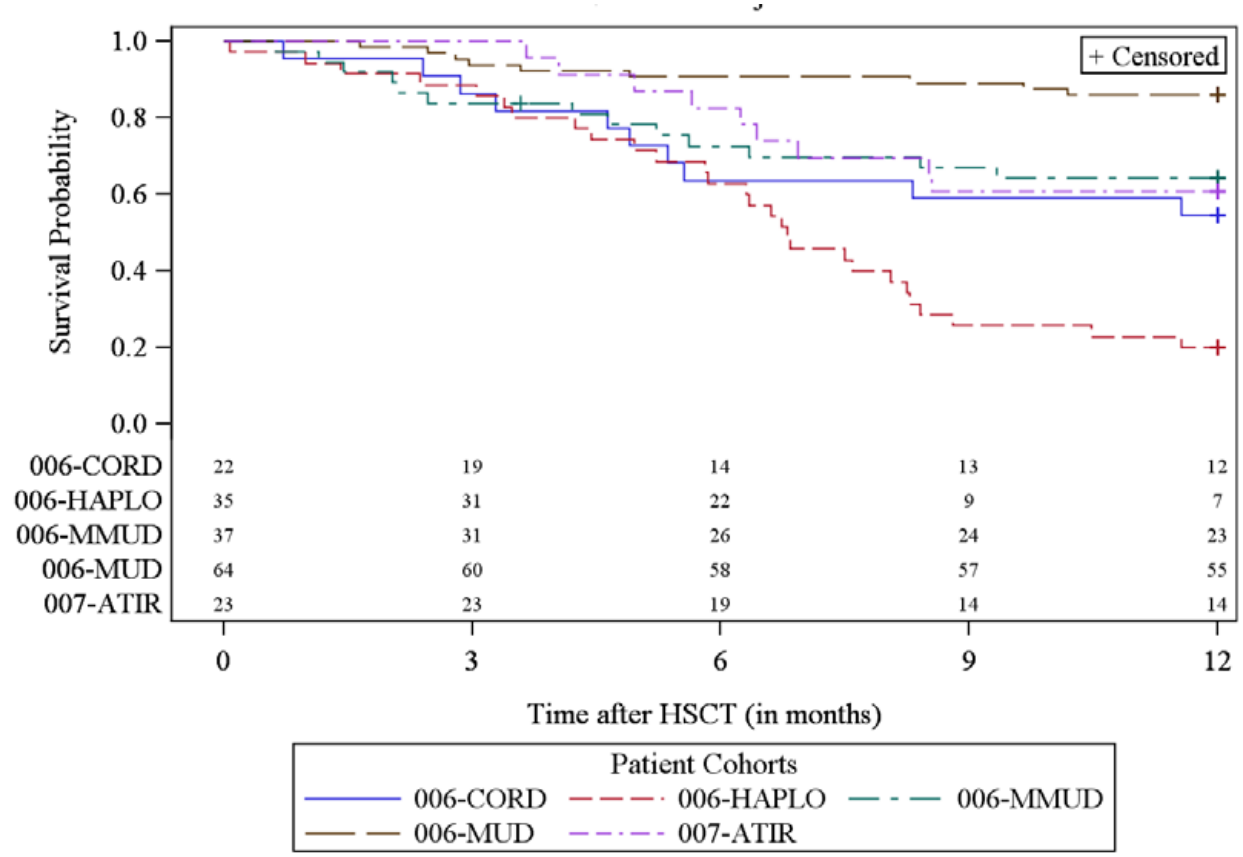


Figure 6 Probability of OS - study CR-AIR-007 vs. CR-AIR-006

007-ATIR: patients receiving ATIR101; study CR-AIR-007.
006-CORD: patients receiving a double umbilical cord blood transplantation without ATIR101; study CR-AIR-006.
006-HAPLO: patients receiving T-cell depleted HSCT without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a fully matched donor without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a 1-locus mismatched unrelated donor without ATIR101; study CR-AIR-006
Source data: [Pooled analysis report, Figure 14.02.02]

In contrast to the analyses of TRM and OS, the analysis of GVHD in study CR-AIR-007 was performed based on the ITT. In study CR-AIR-007, 7 patients (26.9%) experienced any GVHD within 12 months, compared with 15 patients (42.9%) in the HAPLO group of study CR-AIR-006. The majority of GVHD events occurred in the first 6 months after HSCT. In fact, no GVHD was reported later than 6 months after HSCT in study CR-AIR-006, while 2 of 7 patients with GVHD in the pivotal study experienced events later than 6 months after HSCT. The majority of patients had acute GVHD only while a single patients with acute GVHD in the pivotal study also developed chronic GVHD, and 3 patients in study CR-AIR-006 had chronic GVHD only (Table 13).

In the pivotal study, acute GVHD within the first 12 months was of grade I or II only. In the HAPLO group, acute GVHD was mostly of grade I or II, but 2 patients experienced acute GVHD grade IV events.

Chronic GVHD of moderate intensity was reported in a single patient (3.8%) in the pivotal study; in the HAPLO group, chronic GVHD was severe in 2 patients (5.7%) and of unknown intensity in one further patient.

Table 13 GVHD overall and by severity- study CR-AIR-007 vs. CR-AIR-006

	CR-AIR-007 HSCT plus ATIR101 (n=26)			CR-AIR-006 HSCT (n=35)		
	At 100 days	At 6 months	At 12 months	At 100 days	At 6 months	At 12 months
Any GVHD						
Patients, n (%)	2 (7.7)	5 (19.2)	7 (26.9)	9 (25.7)	15 (42.9)	15 (42.9)
Events, n	3	7	11	9	15	15
Only acute GVHD	2 (7.7)	5 (19.2)	6 (23.1)	9 (25.7)	12 (34.3)	12 (34.3)
Only chronic GVHD	0	0	0	0	3 (8.6)	3 (8.6)
Acute and chronic GVHD	0	0	1 (3.8)	0	0	0
Acute GVHD						
Patients with events, n (%)						
Grade I	1 (3.8)	3 (11.5)	3 (11.5)	4 (11.4)	5 (14.3)	5 (14.3)
Grade II	1 (3.8)	2 (7.7)	4 (15.4)	4 (11.4)	5 (14.3)	5 (14.3)
Grade III	0	0	0	0	0	0
Grade IV	0	0	0	1 (2.9)	2 (5.7)	2 (5.7)
Unknown	0	0	0	0	0	0
Chronic GVHD						
Patients with events, n (%)						
Mild	0	0	0	0	0	0
Moderate	0	0	1 (3.8)	0	0	0
Severe	0	0	0	0	2 (5.7)	2 (5.7)
Unknown	0	0	0	0	1 (2.9)	1 (2.9)

Analysis based on the ITT for study CR-AIR-007 and all patients in study CR-AIR-006
Every patient is counted by the worst severity of GVHD experienced.
Source data: [Pooled analysis report, Table 14.03.01]

The 12-month cumulative incidences for acute GVHD grade II-IV, acute GVHD grade III-IV, and chronic GVHD were all lower in the pivotal study than in the control group. However, numerical differences between the groups did not reach statistical significance (Table 14).

Table 14 12-month cumulative incidence of GVHD - study CR-AIR-007 vs. CR-AIR-006

	CR-AIR-007 HSCT plus ATIR101	CR-AIR-006 HSCT	p-value[1]
Patients, n	26 (100.0)	35 (100.0)	
Acute GVHD grade II-IV (95% CI)	15.4 (4.7, 31.8)	20.0 (8.7, 34.7)	0.5689
Acute GVHD grade III-IV	0.0 (ne, ne)	5.7 (1.0, 16.9)	0.2191
Chronic GVHD	3.8 (0.3, 16.8)	8.6 (2.1, 20.8)	0.4492

Analysis based on the MITT for study CR-AIR-007 and all patients in study CR-AIR-006
[1]Gray's test for equality of cumulative incidence functions
Source data: [Pooled analysis report, Table 14.03.02]

The cumulative incidence rate for acute GVHD grade II-IV was lowest in ATIR101-treated patients, while it was highest in patients receiving an umbilical cord blood draft (Figure 7).

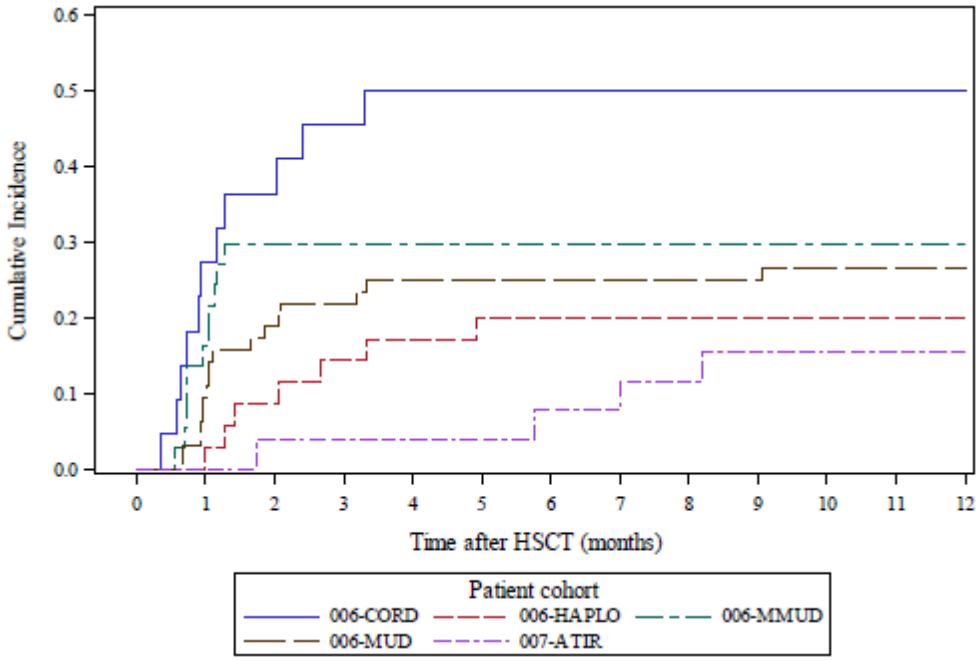


Figure 7 Cumulative incidence functions of grade II-IV acute GVHD - study

CR-AIR-007 vs. CR-AIR-006
007-ATIR: patients receiving ATIR101; study CR-AIR-007.
006-CORD: patients receiving a double umbilical cord blood transplantation without ATIR101; study CR-AIR-006.
006-HAPLO: patients receiving T-cell depleted HSCT without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a fully matched donor without ATIR101; study CR-AIR-006.
006-MMUD: patients receiving HSCT from a 1-locus mismatched unrelated donor without ATIR101; study CR-AIR-006
Source data: [Pooled analysis report, Figure 14.03.01]

The cumulative incidence of chronic GVHD was lowest in ATIR101-treated patients and highest in recipients of umbilical cord blood grafts and MUD grafts. (Figure 7).

Analysis of study CR-AIR-007 and pooled control group from CR-AIR-006 and CR-AIR-004

Comparability of CR-AIR-004 and CR-AIR-006

For this analysis, only those patients, who matched the inclusion criteria to study CR-AIR-007 were added from the study CR-AIR-004. Patients in both control studies 006 and 004 were in general comparable, those in study 006 were somewhat older (median age 43 vs 39), more patients in 004 group had ALL (11.4% vs 17.2%), and more patients in study 006 had MDS (17.1% vs 10.3%).

Cellular composition of grafts

Higher median CD34 cell count was applied [$11x10^6$ cells/kg vs $7x10^6$ cells/kg for HAPLO/ATIR101 vs HAPLO arms] and higher CD3 cell count was used in HAPLO groups [$0.29x10^4$ cells/kg vs $4x10^4$ cells/kg for HAPLO/ATIR101 vs HAPLO arms] (Figure 8).

The data points for both CR-AIR-007 (ATIR101) and CR-AIR-004 + CR-AIR-006 (pooled control).

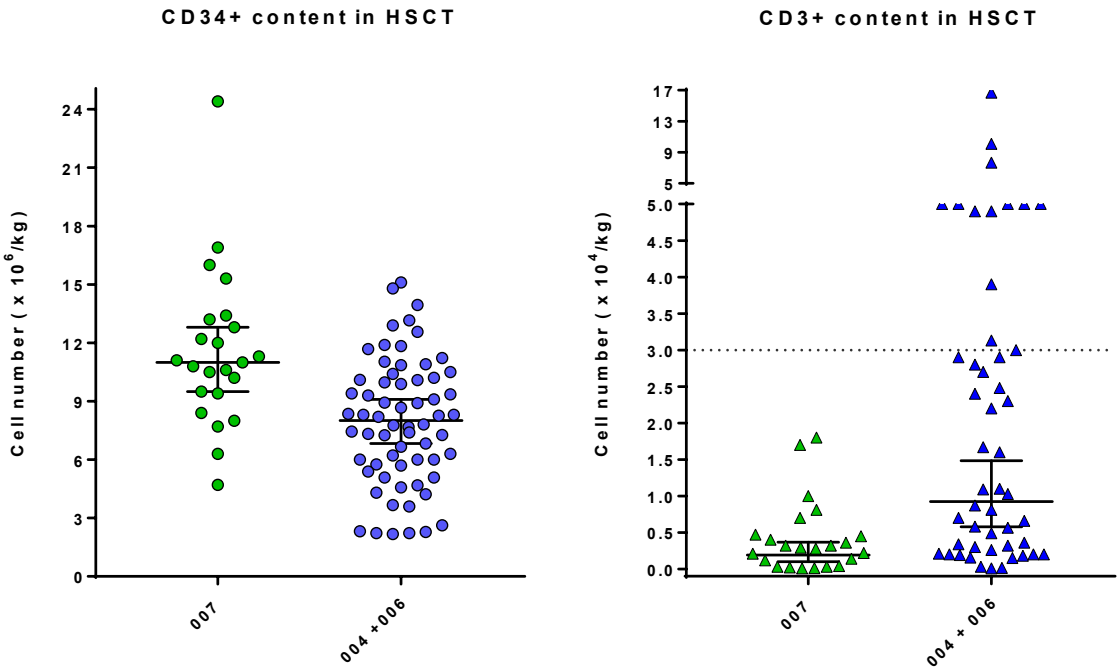


Figure 8 Analysis of study CR-AIR-007 and pooled control group from CR-AIR-006 and CR-AIR-004

CD3+ cell content graft

The median CD3 cell dose in the donor graft was 0.29 x 10^4 cells/kg (range; 0.01 – 1.80 x 10^4) in CR-AIR-007 and 1.09 x 10^4 cells/kg (range; 0.01 – 16.7 x 10^4) in the pooled control group (CR-AIR-004 + CR-AIR-006). Although the median cell dose is a bit higher than the reported value in CR-AIR-007 and the range of values reported overlap, there is a much greater variation in the control population, specifically with a wider range of values at the upper end. This is mainly due to the data from the retrospective study CR-AIR-006, where a wide range of CD3 cell doses was reported. In both prospectively conducted studies CR- AIR-007 and CR-AIR-004, the level of CD3 cells in the donor graft was advised per protocol to be kept below 3 x 10^4 cells/kg.

Performing a subgroup analysis on the data by removing patients with higher levels of CD3+ cells in the donor graft from the control population, did not impact the efficacy analysis. For both TRM and OS the difference between CR-AIR-007 and the pooled control remains similar and significant. At the primary endpoint for CR-AIR-007, 6-month TRM, the difference remains statistically significant with an Odds Ratio of 0.24 (95%CI; 0.06 – 0.95) and a p-value of 0.0348.

CD34+ cell content donor graft

With the CR-AIR-004 study as an additional control study, the differences in the CD34 cell dose in the donor graft of the HAPLO/ATIR101 group versus the HAPLO only group still remain. The median CD34 content in the pivotal study was 11.0 x 10^6 cells/kg (range; 4.7 - 24.4 x 10^6 cells/kg) which is higher than the median dose in the pooled control studies, 8.0 x 10^6 cells/kg (range; 2.2 – 15.1 x 10^6 cells/kg).

Concomitant medications

Detailed information on the use of concomitant medication, specifically related to management of infections was not available from study CR-AIR-006. However, from the prospectively conducted study CR-AIR-004, concomitant medication data were provided, as this was recorded in all patients.

Table 15 Concomitant medications used to manage infections in more than 30% of the patients (either in the CR-AIR-007 and/or the CR-AIR-004 control study) in the first year after HSCT.

ATC 1st level group ATC 3rd level group	ATC code	CR-AIR-007	CR-AIR-004
Patients, n (%)		23	29
Antiinfectives for systemic use	**J**	**23 (100)**	**29 (100)**
Direct acting antivirals	JO5A	22 (95.7)	29 (100)
Other antibacterials	JO1X	22 (95.7)	24 (82.8)
Antimycotics for systemic use	JO2A	22 (95.7)	28 (96.6)
Sulfonamides and trimethoprim	JO1E	22 (95.7)	23 (79.3)
Other beta-lactam antibacterials	JO1D	18 (78.3)	25 (86.2)
Quinolone antibacterials	JO1M	16 (69.6)	18 (62.1)
Beta-lactam antibacterials, penicillins	JO1C	15 (65.2)	18 (62.1)
Immunoglobulins	JO6B	9 (39.1)	11 (37.9)
Macrolides, lincosamides, and streptogramins	JO1F	5 (21.7)	11 (37.9)
Aminoglycoside antibacterials	JO1G	2 (8.7)	11 (37.9)
Alimentary tract and metabolism	**A**	**15 (65.2)**	**18 (62.1)**
Stomatological preparations	AO1A	11 (47.8)	12 (41.4)
Systemic hormonal preparations, excl. sex hormones and insulin*	**H**	**14 (60.9)**	**23 (79.3)**
Corticosteroids for systemic use, plain	HO2A	13 (56.5)	23 (79.3)
Dermatologicals	**D**	**11 (47.8)**	**12 (41.4)**
Corticosteroids, plain	D07A	7 (30.4)	3 (10.3)
Antiparasitic products, insecticides and repellents	**P**	**7 (30.4)**	**9 (31.0)**
Sensory organs	**S**	**1 (4.3)**	**9 (31.0)**

* Prescribed to treat various indications including AIHA, EBV+ PTLD, pulmonary and respiratory infections, as infection prophylaxis etc.

Efficacy analysis

In the analysis using the pooled control population, the Odds Ratio (95% CI) of TRM at 6 and 12 months were 0.25 (0.06 – 0.94) and 0.28 (0.10 – 0.81), with a p-value of 0.034 and 0.017 respectively, favouring the patients treated with ATIR101. At the primary endpoint of 6-months, the difference in TRM between CR-AIR-007 and the pooled control group remains statistically significant. The analysis based on CR-AIR-006 alone as control showed an OR of 0.21 (0.05 – 0.92; p=0.031) and 0.23 (0.07 – 0.75; p=0.015) respectively. TRM in the CR-AIR-007 (HSCT + ATIR101) group is significantly lower at 6 and 12 months post-HSCT than in the HSCT only group. The HR of TRM based on the KM analysis confirm this observation, with a p-value of 0.0066 and 0.0075 respectively.

In the analysis using the pooled control population the Odds Ratio (95% CI) of OS at 6 and 12 months was 0.33 (0.10 – 1.11) and 0.22 (0.08 – 0.63), with p-value of 0.069 and 0.004 respectively. The analysis based on CR-AIR-006 alone as a control showed an OR of 0.32 (0.09 – 1.20; p=0.085) and 0.14 (0.04 – 0.53; p=0.003) at 6 and 12 months respectively. The HR of OS based on the KM analysis confirms favour towards ATIR101 treatment, with a p-value of 0.0035 and 0.0033 respectively.

Extended efficacy analysis

The applicant made efforts to broaden the data base since the very small number of patients was an important concern. Nine patients of study CR-AIR-008, who were also treated with a single dose of ATIR101 (MITT population), were added to the 23 patients of the pivotal phase II study CR-AIR-007 enlarging the MITT population from 23 to 32 patients. Comparison of the baseline characteristics and

clinical outcomes of both studies show that these two patient populations are sufficiently similar. Pooling of these data sets appear acceptable. Moreover, the applicant also selected a matched control group from the EBMT Registry database. Comparable outcomes between the 22 patents form the EBMT Registry and the control groups from studies 006 and 004 were observed. Contemporary registry data of the same timeframe in which ATIR101 was given (January 2012 to December 2017) were available in 11 patients and did also not reveal differences in outcome in comparison to the originally used controls.

An overall analysis for efficacy endpoints was performed for the largest patient set available, that is the pooled ATIR101 dataset (007+008) versus the extended pooled control dataset (006+004)+EBMT cohort.

Table 16 Comparison of efficacy and safety parameters for pooled ATIR101 dataset and extended pooled control dataset (MITT)

	ATIR101 studies CR-AIR-007 + CR-AIR-008 (n=32)	Control group CR-AIR-004 + CR-AIR-006 +EBMT (n=84)
TRM		
Cumulative incidence estimates		
6 months	12.5%	29.3%
12 months	28.1%	56.1%
HR (95% CI)	0.38 (0.18-0.77)	
p-value[1]	0.008	
OS		
Kaplan-Meier estimates		
6 months	81.2%	65.8%
12 months	62.5%	26.8%
HR (95% CI)	0.38 (0.20-0.71)	
p-value[1]	0.002	
PFS		
Kaplan-Meier estimates		
6 months	78.1%	60.4%
12 months	59.4%	26.4%
HR (95% CI)	0.40 (0.22-0.74)	
p-value[1]	0.003	
RRM		
Kaplan-Meier estimates		
6 months	6.2%	4.9%
12 months	9.4%	17.1%
HR (95% CI)	0.39 (0.11-1.38)	
p-value[2]	0.144	
Acute GVHD	20.5%	21.9%
Chronic GVHD		
6 months	3.2%	12.3%
12 months	12.9%	17.1%
HR (95% CI)	0.63 (0.20 – 1.98)	
p-value[1]	0.428	

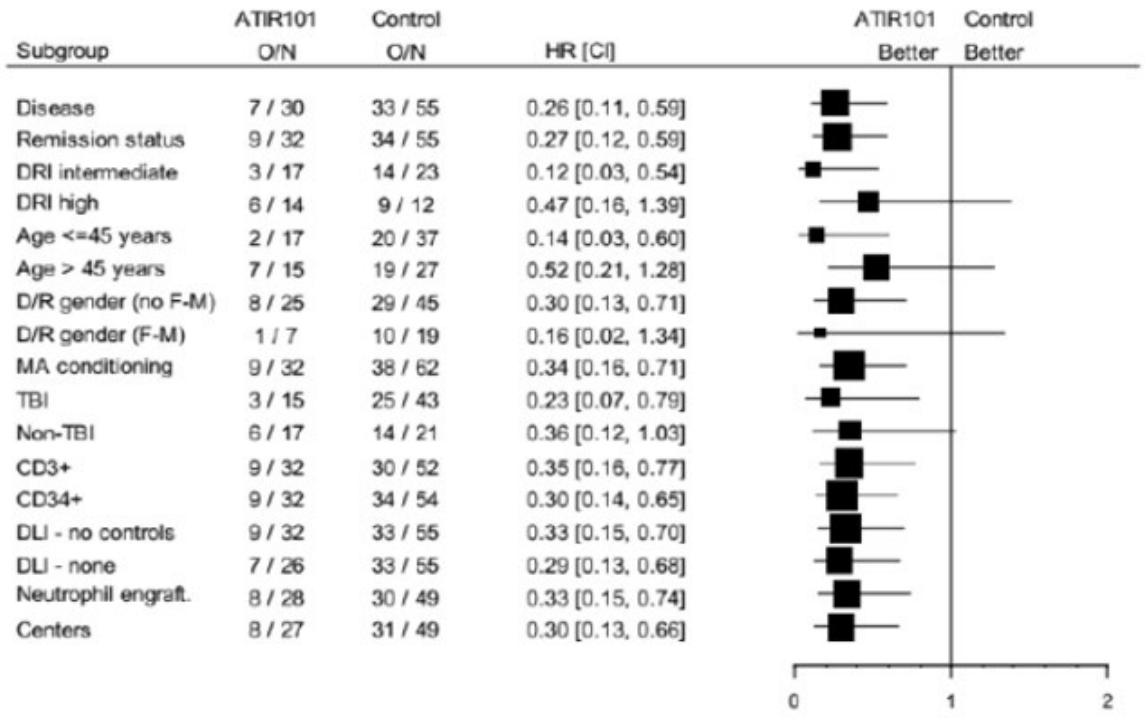
[1] Gray test
[2] log-rank test
Source data: Attachment 3

Subgroup analyses

The evaluation of the potential prognostic factors was performed with the pooled ATIR101 dataset and pooled control dataset to confirm the results obtained earlier.

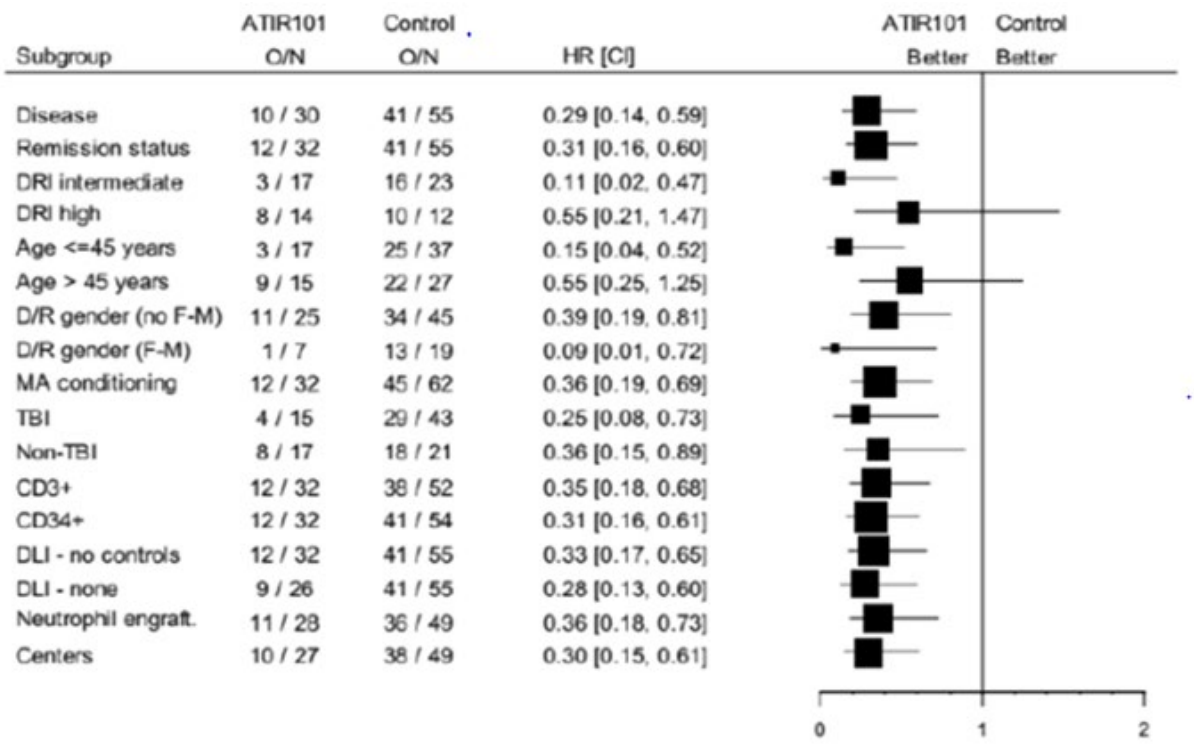
Table 17 Method description: subgroup analyses

Factor	Abbreviation	Patient population
Disease factors		
Disease at diagnosis	**Disease**	Patients with MDS were excluded
Remission status	**Remission status**	Only patients in CR
Disease Risk Indexes	**DRI intermediate** **DRI high**	All intermediate risk patients were compared. All high risk patients were compared.
Patient-related factors		
Age at HSCT	**Age <=45 years** **Age >45 years**	Outcomes patients ≤ 45 years of age were compared. Outcomes patients > 45 years of age were compared.
Donor-related factors		
Donor recipient gender combination	**D/R gender (No F-M)** **D/R gender (F-M)**	Male patients with a female donor were excluded. Male patients with a female donor were compared.
Peri-transplant factors		
Conditioning regimen: Myeloablative	**MA conditioning**	Patients with reduced intensity conditioning were excluded.
Conditioning regimen: TBI vs non-TBI	**TBI: Conditioning regimen**	All TBI patients were compared. All non-TBI patients were compared.
Graft composition: $CD3^+$	**$CD3^+$**	Patients receiving grafts with $CD3^+ > 3x10^4$ cells/kg were excluded.
Graft composition: $CD34^+$	**$CD34^+$**	Patients receiving grafts with $CD34^+$ counts $< 4.5 \times 10^6$ cells/kg were excluded.
Patients receiving DLI in control studies	**DLI – no controls**	Patients in CR-AIR-004 and CR-AIR-006 given an additional DLI were excluded.
Patients receiving DLI in all studies	**DLI – none**	Only patients with no DLI given. All patients given an additional DLI from all studies were excluded.
Time to neutrophil engraftment	**Neutrophil engraft.**	Patients with time to neutrophil engraftment > 19 days were excluded.
Comparability of transplant center	**Centers**	Only patients from sites that provided patients in both ATIR101 and Control pooled data sets were included. ¶



O/N: Observation/Number;
For explanation of subgroup description see Table 14.
Source data: Attachment 2, Part 10

Figure 9 Forest plot of transplant-related mortality (Kaplan-Meier) in the different analysis subgroups



O/N: Observation/Number;
For explanation of subgroup description see Table 14.
Source data: Attachment 2, Part 10

Figure 10 Forest plot of Overall Survival (Kaplan-Meier) in the different analysis subgroups

COVARIATE ANALYSES

The applicant has performed a covariate analysis with the pooled ATIR101 dataset and the pooled control dataset. In addition, a covariate analysis was performed with the pooled ATIR101 dataset and the extended pooled control dataset in collaboration with the EBMT. As the endpoint is TRM at 12 months post-HSCT, i.e. a binary outcome, a multivariable logistic regression model was deemed to be appropriate to assess the potential confounding of prognostic factors not included earlier. EBMT used the definition of TRM from the Kiadis studies, that is the probability of dying due to causes other than disease relapse or progression, which are competing events. Therefore, EBMT applied methods for competing risks for the TRM analysis.

Pooled ATIR101 dataset and pooled control dataset (007+008 and 006+004)

Method and Justification

In order to ensure that the results on the TRM at 12 months are robust and to address the impact of, and potential bias from, some confounding factors potentially favoring the ATIR101 arm, a logistic regression model adjusting for covariates was conducted on the MITT population (from ATIR101 studies CR-AIR-007, CR-AIR-008 and control studies CR-AIR-004, CR-AIR-006) as a sensitivity analysis.

Variables recognized as clinically important were forced into the model regardless of whether they were statistically significant. Based on the recommendations of experts in the field and accounting for data availability, the following risk factors were included in the model:

- Disease at diagnosis (AML, ALL, and MDS)
- Conditioning regimen (TBI, non-TBI)
- Remission status (First remission, second remission or higher including refractory disease)
- EBMT risk score (0-7) (Gratwohl 2012)
- Age of patient
- Time from diagnosis to transplant
- Donor type
- Donor/recipient gender combination
- Total number of viable CD34+ (x 10^6 cells/kg) given to patient

Results

The results of the univariable logistic regression model on the larger cohort showed a statistically significant reduced risk of TRM at 12 months for subjects treated with ATIR101 compared to subjects in the control group (Odds Ratio (OR): 0.25; 95% CI: 0.10; 0.63; p-value: 0.003). After adjusting for other prognostic factors, treatment with ATIR101 still showed a statistically significant reduced risk of TRM compared to the control group (OR: 0.19; 95% CI: 0.07; 0.57; p-value: 0.003) (Table 18). The same analysis has been performed on the ITT population and confirmed the beneficial effect of ATIR101 on TRM (OR:0.23; 95% CI: 0.08; 0.65; p-value: 0.006)

Table 18 Univariable and multivariable logistic regression for TRM at 12 months comparing pooled ATIR101 dataset versus pooled control dataset

	TRM at 12 months		Unadjusted odds ratios			Adjusted odds ratios		
Variable	Total	Event-N	OR (95% CI)	P-value	Global p-value	OR (95% CI)	P-value	Global p-value
Treatment group					0.003			0.003
Control	64	39	ref					
ATIR101	32	9	0.25 (0.10-0.63)	0.003		0.19 (0.07-0.57)	0.003	
Disease at diagnosis					0.303			0.418
MDS	11	8	ref					
AML	66	31	0.33 (0.08-1.36)	0.126		0.32 (0.05-2.15)	0.239	
ALL	19	9	0.34 (0.07-1.68)	0.184		0.50 (0.06-4.05)	0.517	
Conditioning regimen					0.680			0.196
Non-TBI	38	20	ref					
TBI	58	28	0.84 (0.37-1.91)	0.677		0.51 (0.19-1.41)	0.196	
Remission status					0.830			0.849
CR1	63	31	ref					
>=CR2	33	17	1.10 (0.47-2.55)	0.830		1.17 (0.23-6.00)	0.849	
EBMT Risk Index					0.900			0.979
6	7	4	ref					
2	22	10	0.63 (0.11-3.48)	0.591		0.89 (0.08-9.80)	0.926	
3	35	16	0.63 (0.12-3.25)	0.582		0.79 (0.09-7.39)	0.839	
4	18	10	0.94 (0.16-5.46)	0.943		0.72 (0.12-4.91)	0.739	
5	14	8	1.00 (0.16-6.26)	1.000		1.19 (0.16-8.69)	0.867	
Total Viable CD34+ [1]	96	48	0.94 (0.84-1.05)	0.275	0.275	1.02 (0.90-1.17)	0.721	0.721

[1] (x 10^6 cells/kg) given to patient

Pooled ATIR101 dataset and extended pooled control dataset (007+008 and 006+004+EBMT)

Method and Justification

The larger sample, resulting from combining the patients from the control studies CR-AIR-004, CR-AIR-006 and the patients identified in the EBMT Registry in the period 2006-2017, allowed to increase the power of the analysis, in addition to analyzing TRM using a competing risk model (Fine and Gray 1999).

Variables included in the model were:

- Disease at diagnosis (AML, ALL, and MDS)
- Remission status (First remission, second remission or higher including refractory disease)
- Age of patient
- Year of transplant

Results

The cumulative incidence curves presented in Figure 11 indicate that control subjects were at higher risk of TRM compared to ATIR101 subjects. The 12-months cumulative incidence of TRM was 56.1% (45.0%-67.2%) for control subjects, and 28.1% (12.5%-43.7%) for ATIR101 treated subjects (Table 19).

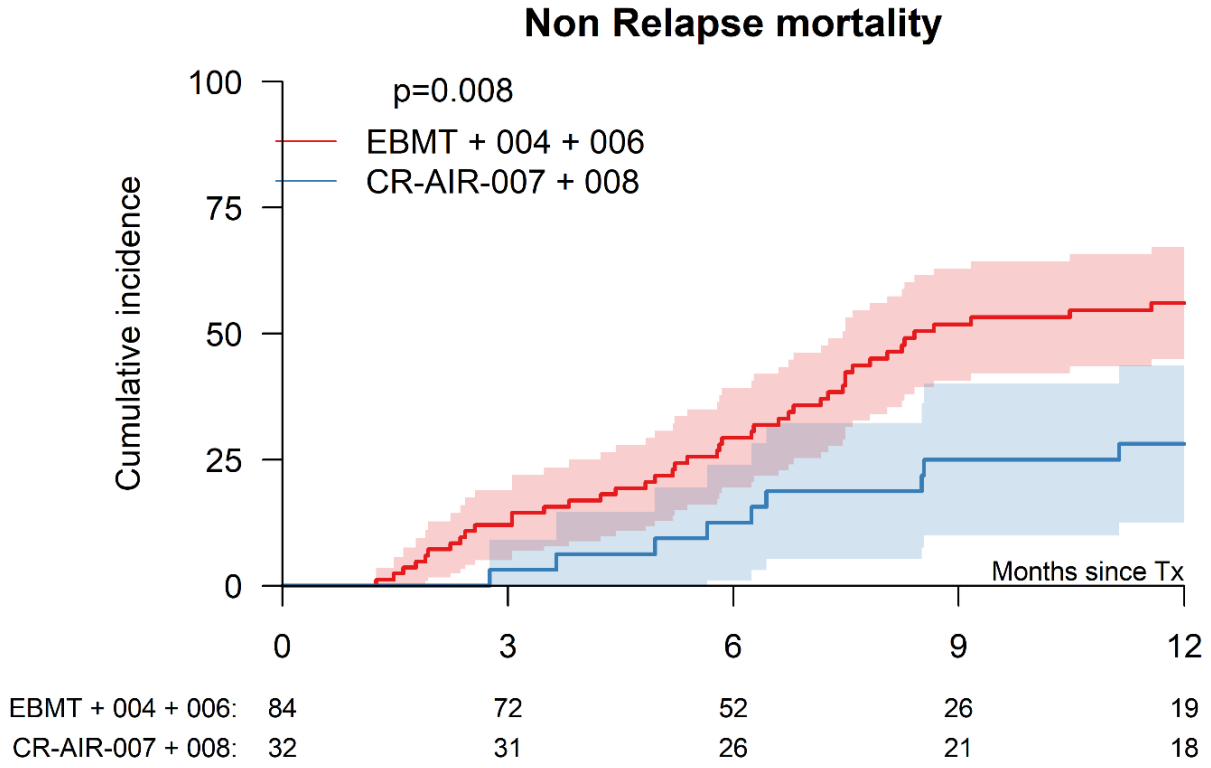


Figure 11 Cumulative incidence of TRM stratified by treatment

Table 19 Cumulative incidence of TRM at 6 and 12 months post-transplant by treatment group

	TRM		
	6 month	12 month	p-value
Control	29.3% (19.4%-39.2%)	56.1% (45.0%-67.2%)	0.008
ATIR101	12.5% (1.0%-24.0%)	28.1% (12.5%-43.7%)	

Source data: Attachment 3

In order to control for confounders, a regression model was performed adjusting for disease (AML, ALL versus MDS), remission status (second or higher remission versus first remission), age of the patient and year of transplant. The results of this analysis confirmed that ATIR101 patients had a statistically significant reduced risk of TRM compared to the control group (HR: 0.28; 95% CI: 0.10 – 0.80; p-value: 0.017) (Table 19).

Table 18. Multivariable analysis of TRM at 12 months post-transplant

Variable	Total	Event-N	HR (95% CI)	p-value
Treatment group				
Control	84	44	ref	
ATIR101	32	9	0.28 (0.10 - 0.80)	0.017
Disease at diagnosis				
MDS	13	9	ref	
AML	77	35	0.96 (0.42 - 2.22)	0.932
ALL	26	9	1.14 (0.36 - 3.62)	0.818
Remission status				
CR1	66	28	ref	
>=CR2	50	25	1.08 (0.60 - 1.95)	0.799
Age of patient	116	51	1.03 (1.01 - 1.05)	0.015
Year of transplant	116	51	1.04 (0.91 - 1.19)	0.557

Source data: Attachment 3

Supportive study(ies)

N/A

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy of ATIR101 was assessed in the open-label, single-arm, multicenter Phase II study CR-AIR-007, including adult patients with hematological malignancies (AML or ALL in complete remission or MDS) and eligible for HSCT but without matched related or unrelated donor (following donor search) could participate in the study. In this study, patients received T-cell depleted (CD34 cell selected) HSCT from a related, haploidentical donor, followed by a single infusion of ATIR101 at a dose of 2 x 10^6 viable T-cells/ kg approximately 28 and 32 days after HSCT. Post-transplantation immunosuppressive therapy (e.g. corticosteroids) in the absence of GVHD was to be avoided unless medically indicated. Patients who were CMV or EBV positive or had a CMV or EBV positive donor were to receive prophylactic or preemptive treatment. A total of 26 patients underwent HSCT, of these, 23 patients were treated with ATIR101. The primary efficacy endpoint of study CR-AIR-007 was TRM at 6 months after HSCT. Secondary endpoints, assessed from HSCT up to 24 months after HSCT, included incidence and severity of acute and chronic GVHD; immune reconstitution; incidence and severity of infections; TRM; relapse-related mortality (RRM); OS; and progression-free survival (PFS).This study was amended to exclude the use of unmanipulated DLI for indications other than impending relapse or graft failure. A subgroup analysis shows that administration of unmanipulated DLI before the amendment has impacted the outcome of CR-AIR-007 negatively on both TRM and OS. The primary endpoint (6-month TRM) was reached in March 2016. The study was completed in September 2017, when the last patient had 24-month follow-up.

Supportive information is derived from the open-label, dose escalation, single center Phase I study CR-GVH-001. Adult patients with severe hematological diseases or malignancies without alternative treatment and eligible for haploidentical HSCT as per investigator judgement could participate. Patients were assigned to ascending dose levels. Seven dose levels were tested i.e. 1.0 x 10^4, 5.0 x 10^4, 1.3 x 10^5, 3.2 x 10^5, 7.9 x 10^5, 2.0 x 10^6, and 5.0 x 10^6 viable T-cells per kg/body weight (referred to as L1 to L7). Assignment to dose levels followed the modified continual reassessment method. Following myeloablative conditioning, patients underwent T-cell depleted (CD34 cell selected) HSCT. At 28 to 42 days after HSCT, patients received a single infusion of ATIR101 at the assigned dose level. Patients could receive all supportive therapy including anti-infective therapy and immunosuppression as

medically indicated, according to the treatment standards of the clinical site, and at the discretion of the investigator. In total 19 patients underwent HSCT with subsequent ATIR101 infusion. After HSCT and the administration of ATIR101, patients were to be followed for a total of 5 years. The primary objective was to determine the MTD and the safety of ATIR101. Efficacy was assessed in terms of PFS; TRM; RRM; OS; immune reconstitution; and occurrence of infections (from Week 5 through to 18 months after ATIR101 administration).

Another interventional study (CR-AIR-004) was prematurely terminated because of IMP quality issues. Results from study CR-AIR-004 do not add to efficacy data base of ATIR101 due to around 90% non-viable cells in the IMP. This study served as an additional control for evaluation of efficacy of ATIR101.

An external, historical control group was set up, i.e. patients undergoing haploidentical, T-cell depleted (CD34 cell selected) HSCT in the non-interventional, multicenter, observational cohort study CR-AIR-006, including adult patients (18 to 65 years) with hematological malignancies (AML or ALL in complete remission, or MDS) who had received allogeneic T-cell depleted (CD34 cell selected) HSCT from a haploidentical donor (HAPLO group) or from a fully matched or 1-locus mismatched unrelated donor (MUD/MMUD groups), or a double umbilical cord blood transplantation with no more than 2 HLA-mismatches between each of the units and the recipient (UCB group). It was planned to include a total of approximately 270 patients, i.e. 75 patients in the HAPLO group, 65 patients in the MUD group, 65 patients in the MMUD group, and 65 patients in the UCB group. Due to the large size of the MUD group, a random selection procedure was performed. Of the 247 MUD patients, 64 were selected for further data collection. In total 341 patients were entered into the study database. Patient data collected included: baseline disease status, conditioning regimen; transplantation details; and data on GVHD, infections, relapse/progression, and mortality, for 12 months after HSCT. The same efficacy endpoints were analyzed as in the interventional studies of ATIR101, i.e. TRM, RRM, OS, and PFS within 12 months after HSCT.

Efficacy data and additional analyses

The analysed number of patients treated with ATIR101 is very low. But it is compensated by a follow-up period of 24 months in the pivotal study. Primary analyses were performed with ITT and mITT. The ITT population includes three additional patients not having received ATIR101 and shows comparable results to the mITT population. The patient populations of studies CR-GVH-001, CR-AIR-007 and CR-AIR-006 are comparable with regard to age and gender. But, their baseline disease characteristics show differences. In all studies the majority of patients had AML. But, in study CR-AIR-007 the other part of the patients suffered from ALL only, whereas in study CR-GVH-001 various other entities like NHL, MDS, CLL and CML were included, but no ALL. In study CR-AIR-006, ALL and MDS cases were collected in addition to AML. Furthermore, patients could participate in study CR-GVH-001 whether they were in remission or not. Thus, 14 patients (74%) had active disease at the time of HSCT. In study CR-AIR-007, all patients were in complete remission. In study CR-AIR-006 also cases with partial remission and refractory disease were included. Thus, it is unclear whether the target population of study CR-AIR-007 can be regarded representative for the efficacy analysis of ATIR101 in HSCT. In addition, there were differences with regard to conditioning regimen. In study CR-AIR-007 all patients received a myeloablative conditioning regimen, while 25.7% of patients had a reduced intensity regimen in the HAPLO group of study CR-AIR-006. In the other groups (MUD, MMUD, UCB) even more than 40% of patients received reduced intensity regimen. Higher median CD34 cell count was applied [$11x10^6$ cells/kg vs $7x10^6$ cells/kg for HAPLO/ATIR101 vs HAPLO arms] and higher CD3 cell count was used in HAPLO groups [$0.29x10^4$ cells/kg vs $4x10^4$ cells/kg for HAPLO/ATIR101 vs HAPLO arms. There were also temporal imbalances due to the need for pooled analysis considering not only total period of historical control but also separately periods of 2006-2012 and 2012-2013 that is concurrent to ATIR101 treatment time. Further, exclusion criteria between studies CR-AIR-006 and CR-AIR-007

differed with regard to disease severity since expected survival of less than 3 months was excluded in study CR-AIR-007). The applicant addressed the impact of various imbalances. The analysis on concomitant medication between CR-AIR-007 and the control group from CR-AIR-004, shows that there is no relevant difference in use of medication to manage infections. All patients were treated intensively in the post-transplant period with medication to manage infections, as to be expected from clinical practice. But there are still open issues with regard to selection bias due to applied CD34+ cell doses between studies and missing information on balanced concomitant therapies. These confounding factors might have influenced the comparability of the efficacy data of these studies and could favour the ATIR101 arm.

In study CR-GVH-001 no patient developed a Grade III/IV acute GVHD, thus a dose selection based on the MTD was not possible. A dose of 2.0 x 10^6 T-cells/kg of ATIR101 (L6) was selected according to the relationship between ATIR101 dose and data on clinical efficacy and safety since the MTD for ATIR101 was not reached as no patient experienced DLTs. In general, the selected dose appears reasonable regarding the highest OS probability and lowest TRM probability (0%) in the intermediate dose group. The L6 dose also showed the lowest infection rate. Of note, the highest dose group had no case of relapse-related mortality, but most cases of GVHD and a quite high infection rate.

In study CR-AIR-007 10 out of 23 patients (43.5%) experienced TRM mainly due to infection in 8 patients (34.8%). The other 2 patients had 'multiple organ failure'. In particular, the TRM rate at 6 months, defined as the primary endpoint of the study, was 13% (16%), 32% (36%) at 12 months and 43.5% (50%) at 24 months for the MITT population (ITT population). The RRM rate at 12 months was 10% and the PFS rate at 12 months was 61% for the MITT population. The respective OS rate at 12 months was 61% and at 24 months 39%. Since ATIR101 is a preparation of donor T-lymphocytes, development of GVHD is an important parameter for efficacy analysis. A total of 19 GVHD events were reported in 9 patients (39.1%), including 8 patients with acute GVHD only (maximum grade II: 13.0%; grade III: 8.7%, grade IV: 4.3%) and one patient (4.3%) with acute GVHD grade I and severe chronic GVHD. No patients experienced GVHD within 100 days after the ATIR101 infusion. All cases of acute GVHD with an onset within the first year after HSCT, a time period in which acute GVHD may be expected after any HSCT, were of grade I or II. Three patients experienced acute GVHD of grade III or IV and of very late onset, i.e. 380 to 530 days after ATIR101. However, these 3 patients developed acute GVHD shortly after the administration of unmanipulated DLI. Overall, nine patients had acute or chronic GVHD after ATIR101. This is a quite low number in comparison to unmanipulated donor lymphocytes. In addition, the acute cases of GVHD related to ATIR101 were of low severity (Grade I and II). These results indicate that the depletion of host-alloreactive T-cells is successful. But, there was one case of severe chronic GVHD after ATIR101 administration. No conclusions can be made regarding incidences of GVHD per time interval due to the low numbers. The incidence of infections irrespective of causative agent was 82.6% from ATIR101 infusion up to 6 months after HSCT, 56.5% between 6 and 12 months after HSCT, and 52.2% between Year 1 and 2 after HSCT. Infections were mostly of grade 1 or 2. Infections of grade 3 occurred with a lower incidence, while infections of grade 4 or 5 were infrequently reported. Between HSCT and ATIR101 infusion, viral, fungal, and bacterial infections had approximately the same incidence (35-39%). In all time intervals after ATIR101 infusion, viral infections were noticeably more frequent than fungal or bacterial infections. An influence on the frequency or kind of infections cannot be seen over the assessment periods. In general, the data of the pivotal study appear favourable for haploidential HSCT including a low relapse rate, but assessment in connection with an appropriate control is required (see below).

The results of the observational cohort study correlate with the clinical experience and published data on T-cell depleted haploidentical, MUD, MMUD and Cord blood HSCT demonstrating a generally bad outcome of T-cell depleted haploidentical HSCT. In comparison to matched unrelated donor transplantations, the main problem of T-cell depleted haploidentical HSCT is a high incidence of

transplant-related mortality due to the severe depletion of T-cells from the transplanted graft, which is needed to avoid rejection and GVHD. In fact, GVHD is reported to be lower after T-cell depleted haploidentical HSCTs compared to the matched transplantation modalities although the degree of HLA disparity is the highest. The collected data of the MUD group show a high 12-month OS probability.

The patients receiving haploidentical, T-cell depleted HSCT plus ATIR101 in study CR-AIR-007 were directly compared with patients receiving haploidentical, T-cell depleted HSCT without ATIR101 in study CR-AIR-006. Overall, lower number of patients died in the pivotal study (CR-AIR-007) than in the untreated control patients (i.e. the HAPLO group) of study CR-AIR-006. The 12-month OS probability was 60.9% in the pivotal study in comparison to 20.0% in the HAPLO group of study CR-AIR-006.This difference was primarily due to a lower proportion of patients who experienced TRM in the pivotal study. The number of patients with TRM event at 12 months was 7 (30.4%) in the pivotal study and 23 (65.7%) in the HAPLO group of study CR-AIR-006, which is statistically significant. In both groups, the primary source of TRM was infection. The overall incidence of TRM due to infectious causes was 5 cases (21.7%) in the pivotal study in comparison to 14 cases (40.0%) in the HAPLO group of study CR-AIR-006 at 12 months. The rate and kind of infections were not compared and discussed across the pivotal study and the non-interventional study. Following request the applicant provided a comparison of study CR-AIR-007 with study CR-AIR-004 as control regarding the incidence, type of infections that occurred during the early and the late post-transplantation phase. Overall, the total number of viral and bacterial infections was a bit reduced in patients treated with ATIR101. In both post-transplantation phases infections were less severe in study CR-AIR-007 when compared to study CR-AIR-004 in which more higher-grade (grade 3, 4 and 5) infections were observed. But, there was a higher number of fungal infections of low grade in the late post HSCT phase of the ATIR101 study (10 out of 23) compared to 6 out of 29 in the control study. Evaluation of more patients is needed.

TRM due to GVHD occurred in the retrospective control study but not in the pivotal study. In study CR-AIR-007, 7 patients (26.9%) experienced any GVHD within 12 months, compared with 15 patients (42.9%) in the HAPLO group of study CR-AIR-006. Furthermore, the 12-month cumulative incidences for acute GVHD grade II-IV, acute GVHD grade III-IV, and chronic GVHD were all lower in the pivotal study than in the control group. But no statistical significance was reached. In the HAPLO group, three patients died because of a relapse and two patients due to disease progression (5/35; 14.3%). In the pivotal study, death was caused by relapse in two patients (2/23; 8.7%). Thus, there is no important difference between these studies. Corresponding data of the dose escalation study CR-GVH-001 show even higher RRM i.e. 17% in all patients and 22% in dose groups L4-L6. At present the GVL effect is not statistically significant in the clinical studies provided. But there might be a trend towards less relapse in patients given a T-cell depleted HSCT followed by adjunctive treatment with ATIR101. Of note, ATIR101 studies were not designed to investigate a GVL effect. More pronounced results on potential GVL effect are expected in the currently ongoing randomized phase III study with much greater patient number.

No data in paediatric patients are available since the initiation of a study in paediatric patients is deferred according to the agreed PIP. In the main efficacy trials (CR-GVH-001, CR-AIR-007, CR-AIR-006) only patients up to the age of 65 years have been included. This age limit is based on the high rate of toxicity and TRM of myeloablative conditioning regimen. However, recipient age is continuously rising since reduced-intensity conditioning HSCT combined with progress in the supportive care allows today for safer transplantation. Since ATIR101 could especially be beneficial for the elderly the applicant intends to include patients older than 65 years in the ongoing phase III study (CR-AIR-009). In patients with impaired renal or hepatic function a significant impact on efficacy is not expected.

The Applicant provided an extensive re-analysis of the available data to further substantiate the evidence for a treatment benefit in TRM and OS. These analyses were based on an enriched population

both, in the active arm where studies 007 and 008 were pooled and in the historic control where studies 006 and 004 were pooled and an additional analysis with 006, 004 and EBMT data was provided by EBMT.

Subgroup analyses based on the Kiadis data support the statement that a treatment benefit is present in all major subgroups. Small(er) subgroups were termed outliers and were not presented. This is considered to add some uncertainty to the assessment but is not considered too seriously impact the overall conclusion. Covariate adjusted analyses were presented in addition. Different prognostic factors were used for the Kiadis only data (Disease at diagnosis, Conditioning regimen, Remission status, EBMT risk score, Total number of viable CD34+ cells) and the Kiadis + EBMT data (Disease at diagnosis, Remission status, Age of patient, Year of transplant). All analyses show a positive treatment effect in TRM. The results are robust and do not seem to depend on the applied methods. Of note, the multivariate models do not take predictive effects (i.e., different treatment effects in different subgroups) into account but only prognostic effects.

3.3.7. Conclusions on clinical efficacy

A dose of 2.0 x 10^6 T-cells/kg of ATIR101 was selected according to the relationship between ATIR101 dose and data on clinical efficacy and safety.

Efficacy results of ATIR101 indicate improved transplant-related mortality, overall survival, occurrence and grade of GVHD by the data of the pivotal study in comparison to a control group of an observational cohort study. The results on RRM across studies do not support a GVL effect of ATIR101. In addition, the influence on the infection rate and the kind of infections after HSCT is not as pronounced as anticipated, since ATIR101 is supposed to improve the recovery of the immune responses. Efficacy data of the elderly need to be collected in the ongoing studies.

However, the benefit of adjunctive ATIR101 therapy is not proven mainly due to the uncertainty caused by the small sample size and doubts on the appropriateness of the historical control. The impact of known confounders (e.g. CD34+ dose, management of infections) have not been sufficiently addressed and secular trends may play an important role.

Providing an extensive re-analysis, sufficient evidence seems to be given that the treatment effect is stable over a wider range of subgroups (and in the multivariate models adjusted for prognostic confounders) despite some shortcomings and uncertainties.

During the Oral explanation at the CAT, the applicant proposed to restrict the originally claimed indication only to patients that were in complete remission, in order to minimise the heterogeneity of the target patient populations. This was deemed acceptable to the Committee.

3.3.8. Clinical safety

Patient exposure

ATIR101 is not currently approved or marketed in any country worldwide.

To date, 46 patients have been exposed to ATIR101. In study 007 safety analyses were performed on the ITT population (n = 26, patients who underwent HSCT), and selected analyses were performed on MITT (n = 23, patients who received ATIR). In study 001, all patients who had received ATIR101 (n = 19), were included to safety evaluation (FAS population). In addition, 4 patients received ATIR101 in terms of compassionate use. There were also several patients exposed to ATIR101 in study 004, but one of the advices given to the MAA was not to include data from this study to safety (or efficacy) analysis. The study 004 was prematurely terminated because of quality issues of IMP and thus the information of this study cannot be directly applicable to ATIR101 safety profiling.

Forty patients received a single ATIR101 infusion and two patients had a second infusion. Twenty-six patients received a dose of 2.0 x 10^6 cells/kg.

Table 20 Patient exposure

	Patients with HSCT	Patients exposed to ATIR	Patients exposed to the proposed dose	Patients with 2 years safety data	Patients with 5 years safety data
Study 007	26	23	23	8	N/A*
Study 001	19	19	3	9	5
Study 006 HAPLO	35	0	0	N/A**	N/A**
Compassionate use	4	4	No information	No information	No information
TOTAL	84	**46**	26	32	5

* only 2 years of follow up post HSCT was anticipated in study 007
** only 1 year follow up post HSCT was anticipated in study 006

The pivotal study is planned for 2 years and was completed on 17th September 2017. Long term data are limited. I.e., in both studies 001 and 007, data regarding long term safety are very scarce (only 5 resp. 8 patients from each trial had reached the long-term safety data assessment point). Majority of the patients did not survive till the end of follow-up. This might be due to the degree of illness that most patients were diagnosed with.

Adverse events

In study CR-AIR-007, infections, relapse/disease progression, GVHD, and SAEs were reported throughout the study, while all other, non-serious AEs were reported for 4 weeks after the ATIR101 infusion. The analysis of AEs in this study was based on the intent-to-treat (ITT) population. Treatment-emergent AEs were those with an onset on or after the day of ATIR101 infusion. The analyses presented in this Clinical Overview are based on treatment-emergent AEs if not indicated otherwise.

In study CR-GVH-001, AEs were recorded for the first 30 days after ATIR101 infusion. However, SAEs were reported throughout the study. The analysis of AEs was based on all treated patients. Treatment-emergent AEs were those with onset on or after the day of ATIR101 infusion.

Therefore, only treatment-emergent AEs are discussed following the above definitions, if not specified otherwise.

In both studies, the vast majority of patients experienced at least one AE. Drug-related AEs occurred in 38.5% of patients in study CR-AIR-007 and 5.3% of patients in study CR-GVH-001. The incidence of SAEs was lower in study CR-AIR-007 (76.9%) than in study CR-GVH-001 (89.5%), [Table 21].

Table 21 Overall summary of treatment-emergent adverse events in interventional ATIR101 studies

	CR-AIR-007	CR-GVH-001
Patients[1], n	26 (100.0)	19 (100.0)
Patients with…		
Any AE, n (%)	23 (88.5)	17 (89.5)
Any drug related AE	10 (38.5)	1 (5.3)
SAEs[2]	20 (76.9)	17 (89.5)
AEs with fatal outcome	14 (53.8)	12 (63.2)
AEs by severity[3]		
Grade 1 / mild	0	12 (63.2)
Grade 2 / moderate	2 (7.7)	14 (73.7)
Grade 3 / severe	6 (23.1)	3 (15.8)
Grade 4	2 (7.7)	0
Grade 5[4]	13 (50.0)	Not assessed

[1] Study CR-AIR-007: ITT (patients undergoing HSCT) cut-off 27 September 2016; study CR-GVH-001: treated set
[2] Patient 3 in study CR-GVH-001 had 17 AEs with outcome death reported (because all AEs ongoing at the time of death were set to having a fatal outcome). Of these AEs, only 2 were reported as SAEs, and only one SAE was reported as SAE with fatal outcome (multi-organ failure).
[3] For study CR-AIR-007, the worst intensity by patient is reported; for study CR-GVH-001, all severities per patient were analyzed.
4 In study CR-AIR-007, the CTCAE grade of GVHD was not recorded and therefore not considered in the analysis. In particular, one patient with acute GVHD grade IV with fatal outcome but missing CTCAE grade is not included in the count of patients with CTCAE grade 5 events. See Section 2.1.2.1 for more details.

Study CR-AIR-007

Of 26 patients receiving HSCT (and forming the ITT), 23 patients were treated with ATIR101.

Table 22 Overview of adverse events - ITT population

	HSCT (N=26)		ATIR (N=23)	
	No of patients (%)	No of events	No of patients (%)	No of events
Adverse events (AEs)	26 (100%)	626	23 (100%)	612
Infections	26 (100%)	356	23 (100%)	347
Relapse/disease progression	4 (15.4%)	5	4 (17.4%)	5
GVHD	10 (38.5%)	21	9 (39.1%)	19
Other	25 (96.2%)	244	23 (100%)	241
Treatment-emergent AEs			23 (100%)	
ATIR-related AEs			8 (34.8%)	

Treatment-emergent defined as starting after ATIR101infusion; ATIR-related defined as either possibly, probably, or certainly related to ATIR101(or missing relationship) as judged by the investigator
Source Table 84, Table 88, Table 90

Severity of AEs was documented according to CTCAE version 4.0. For GVHD events, only the grading according to standard criteria (i.e. from grade I to grade IV for acute GVHD and from mild to severe for chronic GVHD) was recorded, but not the CTCAE grade. Therefore, GVHD is not included in the analysis of AEs by severity.

Common Adverse Events

The most frequent treatment-emergent AEs by SOC were infections and infestations (95.7%), followed by investigations (82.6%). The most frequent PTs were CMV test positive (43.5%), EBV antigen positive (34.8%), oral candidiasis (34.8%), pneumonia (30.4%), and acute GVHD (30.4%) (Table 23). The most frequent AEs are not unexpected in this population of patients with severe hematological malignancies undergoing HSCT (Table 30).

Of note, all AEs in the SOC of neoplasms were either events indicative of relapse of the underlying disease, post-transplant lymphoproliferative disease (PTLD), or fever associated with AML. There was no indication of a secondary malignancy.

Table 23 Treatment-emergent adverse events that occurred in more than 20% patients at the SOC or PT level, sorted by SOC frequency

System organ class Preferred term	ATIR (N=23)
Patients, n (%)	
Patients with any AE	23 (100)
Infections and infestations	22 (95.7)
Oral candidiasis	8 (34.8)
Oral herpes	5 (21.7)
Pneumonia	7 (30.4)
Staphylococcal infection	6 (26.1)
Upper respiratory tract infection	6 (26.1)
Investigations	19 (82.6)
CMV test positive	10 (43.5)
EBV antigen positive	8 (34.8)
Blood and lymphatic system disorders	13 (56.5)
Autoimmune haemolytic anaemia	5 (21.7)
Neutropenia	5 (21.7)
Gastrointestinal disorders	11 (47.8)
General disorders and administration site conditions	8 (34.8)
Pyrexia	6 (26.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (34.8)
Respiratory, thoracic and mediastinal disorders	8 (34.8)
Immune system disorders	7 (30.4)
Acute GVHD	7 (30.4)
Skin and subcutaneous tissue disorders	7 (30.4)

Treatment-emergent defined as starting on or after day of ATIR101 infusion
Source data: [CR-AIR-007, Table 88]

Related Adverse Events

Drug-related AEs were reported in 34.8% of the patients (Table 24). The only preferred term reported in more than a single patient was acute GVHD (17.4%). This analysis does not include one AE that started before the administration of AIR101: One patient developed acute GVHD grade I (considered not ATIR101-related) 25 days after HSCT. The event worsened to grade II and was judged as being probably ATIR101-related 52 days after HSCT (and 21 days before ATIR101 - the event of GVHD was the reason to postpone ATIR101 administration in this patient.

Table 24 ATIR-related adverse events, sorted by SOC frequency- study CR-AIR-007, MITT

SOC Preferred term	ATIR (N=23)
Patients, n (%)	
Patients with at least one related AE	8 (34.8)
Immune system disorders	4 (17.4)
Acute GVHD	4 (17.4)
Chronic GVHD	1 (4.3)
Blood and lymphatic system disorders	1 (4.3)
Autoimmune haemolytic anaemia	1 (4.3)
Gastrointestinal disorders	1 (4.3)
Oesophagitis	1 (4.3)
Infections and infestations	1 (4.3)
Parvovirus infection	1 (4.3)
Viral uveitis	1 (4.3)
Investigations	1 (4.3)
EBV antigen positive	1 (4.3)
Skin and subcutaneous tissue disorders	1 (4.3)
Rash	1 (4.3)

ATIR-related defined as either possibly, probably, or certainly related to ATIR101 (or missing relationship) as judged by the investigator
Source data: [CR-AIR-007, Table 90]

Study CR-GVH-001

Common Adverse Events

The most frequently reported treatment-emergent AEs by preferred term were constipation (31.6%) and pancytopenia and pyrexia (both: 21.1%) (Table 25). A single patient (5.3%) had an AE in the SOC of neoplasms: PTLD.

Table 25 Adverse events that occurred in more than 20% patients at the SOC or preferred term level, sorted by frequency - study CR-GVH-001

SOC Preferred term	All patients
Patients, n (%)	19 (100.0)
Patients with any AE	17 (89.5)
Gastrointestinal disorders	11 (57.9)
Constipation	6 (31.6)
Infections and infestations	8 (42.1)
Blood and lymphatic system disorders	6 (31.6)
Pancytopenia	4 (21.1)
General disorders and administration site	5 (26.3)
Pyrexia	4 (21.1)
Nervous system disorders	5 (26.3)
Respiratory, thoracic and mediastinal disorders	4 (21.1)
Skin and subcutaneous tissue disorders	4 (21.1)

Source data: [CR-GVH-001, Table 38]

Related Adverse Events

A single patient experienced an AE that was considered as related to ATIR101, i.e. a patient with acute GVHD.

Serious adverse events and deaths

Study CR-AIR-007

Deaths

Fourteen patients (53.8%) experienced treatment-emergent AEs with fatal outcome and/or of grade 5 (including 1 patient with acute GVHD with fatal outcome but missing CTCAE grade). One additional patient with a fatal AE of septic shock does not count towards the treatment emergent AEs with fatal outcome as he was never treated with ATIR101.

In the majority of patients (8/26, 30.8%), the fatal AE belonged to the SOC of infections and infestations. None of the AEs leading to death was judged as being ATIR101-related. It is important to highlight that 6 patients had received DLI shortly before the onset of the fatal event [see section 3.3, baseline data, study-CR-AIR-007].

Additionally, one patient discontinued from the study 57 days after HSCT due to graft failure but consented with limited follow-up, which resulted in report of death (without reporting an SAE) 211 days post HSCT due to respiratory exacerbation by ARDS and cardiovascular failure, both secondary to hemophagocytic syndrome and infection.

Serious Adverse Events

The most frequent SAEs by SOC were infections and infestations (73.1%), followed by blood and lymphatic system disorders (30.8%), and neoplasms (26.9%). All other SAEs by SOC were reported in less than 20% of all patients. The most frequent SAEs by preferred term were AIHA (19.2%), followed by acute GVHD and febrile neutropenia (each: 15.4%).

ATIR-related SAEs were reported in three patients: acute GVHD (3.8%), chronic GVHD (3.8%), and AIHA (3.8%), respectively.

Table 26 Serious adverse events occurring in more than a single patient, sorted by SOC frequency - ITT population

SOC Preferred term	All SAEs	Treatment-emergent SAEs
Patients, n (%)	26 (100.0)	23 (100.0)
Patients with any SAE	24 (92.3)	20 (87.0)
Infections and infestations	19 (73.1)	15 (65.2)
Bacterial sepsis	3 (11.5)	1 (4.3)
Pneumonia	3 (11.5)	2 (8.7)
Septic shock	3 (11.5)	2 (8.7)
Staphylococcal sepsis	2 (7.7)	1 (4.3)
Blood and lymphatic system disorders	8 (30.8)	8 (34.8)
AIHA	5 (19.2)	5 (21.7)
Febrile neutropenia	4 (15.4)	4 (17.4)
Neoplasms benign, malignant and unspecified	7 (26.9)	7 (30.4)
Leukaemia recurrent	3 (11.5)	3 (13.0)
Post-transplant lymphoproliferative disorder	3 (11.5)	3 (13.0)
Immune system disorders	5 (19.2)	5 (21.7)
Acute GVHD	4 (15.4)	4 (17.4)
General disorders and administration site conditions	4 (15.4)	4 (17.4)
Pyrexia	3 (11.5)	3 (13.0)
Respiratory, thoracic and mediastinal disorders	4 (15.4)	4 (17.4)
Pulmonary embolism	2 (7.7)	2 (8.7)
Investigations	3 (11.5)	3 (13.0)
Cytomegalovirus test positive	2 (7.7)	2 (8.7)
Nervous system disorders	3 (11.5)	3 (13.0)
Gastrointestinal disorders	2 (7.7)	2 (8.7)
Injury, poisoning and procedural complications	2 (7.7)	1 (4.3)

Source data: [CR-AIR-007, Table 96, Table 99]

Study CR-GVH-001

Deaths

Twelve patients (63.2%) had AEs with fatal outcome. The most frequent AEs or groups of AEs with fatal outcome were multi-organ failure (5 patients, 26.3%), infection events (4 patients, 21.1%), and events of disease progression or recurrence (4 patients, 21.1%). None of the AEs were related to ATIR101.

Of note, 3 out of 5 patients receiving unmanipulated DLIs died within 1 to 4 months of receiving the DLI, all of them dying of disease progression.

Table 27 Adverse events with fatal outcome - study CR-GVH-001

Dose level	Reported SAE with fatal outcome (SOC, *preferred term*)
L1	General disorders and administration site conditions *Multi-organ failure#* [1]
L2	General disorders and administration site conditions *Disease progression*
L2	General disorders and administration site conditions *Disease progression#'* Neoplasms benign, malignant and unspecified *Leukemia recurrent*
L3	Infections and infestations *Lobar pneumonia#* General disorders and administration site conditions *Multi-organ failure#*
L2	Infections and infestations *Encephalitis herpes* Infections and infestations *Encephalitis cytomegalovirus* Infections and infestations *Pneumonia cytomegaloviral* Infections and infestations *Bronchopneumonia#* General disorders and administration site conditions *Pyrexia*
L3	Infections and infestations *Varicella#* Gastrointestinal disorders *Gastrointestinal hemorrhage* Gastrointestinal disorders *Diarrhea* Gastrointestinal disorders *Vomiting* Gastrointestinal disorders *Nausea* Gastrointestinal disorders *Abdominal pain*
L5	General disorders and administration site conditions *Disease progression#*
L5	Neoplasms benign, malignant and unspecified *Leukemia recurrent#*
L6	-[2]
L7	General disorders and administration site conditions *Multi-organ failure#*
L7	General disorders and administration site conditions *Multi-organ failure#* Metabolism and nutrition disorders *Hyperglycemia#*
L7	General disorders and administration site conditions *Multi-organ failure#* Infections and infestations *Pneumonia#* Infections and infestations *Sepsis#*

Dose levels (number of viable T-cells): L1 (1.0×10^4); L2 (5.0×10^4); L3 (1.3×10^5); L4 (3.2×10^5); L5 (7.9×10^5); L6 (2.0×10^6); L7 (5.0×10^6)

[1] This patient had a total of 17 AEs with outcome death reported i.e. febrile neutropenia, pancytopenia, hepatic candidiasis, hepatic enzyme increased, staphylococcal sepsis, PTLD, jaundice, oxygen saturation decreased, pleural effusion, lymphadenopathy, renal failure acute, neurological symptom, lung infiltration, anuria, multi-organ failure, hepatomegaly, ascites. Of these, pyrexia and multi-organ failure were treatment-emergent SAEs; multi-organ failure was reported as SAE with fatal outcome.

[2] For this patient, death was reported in the database as efficacy event, but no SAE was reported. The reason of death was determined as disease progression.

Cause of death as determined by the investigator

Serious Adverse Events

SAEs were reported in 17 patients (89.5%). None of the SAEs was judged as being related to ATIR101. The most frequent SAEs by SOC were general disorders and administration site conditions (68.4%), followed by infections and infestations (63.2%), and blood and lymphatic system disorders (47.4%). The most frequent SAEs preferred term were pyrexia (47.4%), followed by multi-organ failure (26.3%), and pancytopenia, pneumonia, and leukemia recurrent (each: 21.1%).

One patient had a total of 17 AEs with outcome death reported, of which only pyrexia and multi-organ failure were reported as SAE and were treatment-emergent, and only multiorgan- failure was reported as an SAE with a fatal outcome.

SAEs in the SOC of neoplasms included events associated with relapse (leukemia recurrent in 4 patients and myelodysplastic syndrome [reported term: myelodysplastic syndrome relapse] in 1 patient); lymphoma in 1 patient (reported term: suspected EBV lymphoma), and squamous cell carcinoma (reported term: pulmonary epidermoid carcinoma). The AE of squamous cell carcinoma was reported at 2 years and 10 months after the administration of ATIR101. The investigator judged the AE as not being ATIR101-related but as due to the patient's smoking and possibly related to conditioning.

Table 28 Serious adverse events that occurred in more than a single patient at the preferred term level, sorted by frequency - study CR-GVH-001

SOC Preferred term	All patients
Patients, n (%)	19 (100.0)
Patients with any SAE	17 (89.5)
General disorders and administration site conditions	13 (68.4)
Pyrexia	9 (47.4)
Multi-organ failure	5 (26.3)
Disease progression	3 (15.8)
Asthenia	2 (10.5)
Infections and infestations	12 (63.2)
Pneumonia	4 (21.1)
Sinusitis	3 (15.8)
Lung infection	2 (10.5)
Respiratory syncytial virus infection	2 (10.5)
Blood and lymphatic system disorders	9 (47.4)
Pancytopenia	4 (21.1)
Febrile neutropenia	2 (10.5)
Neoplasms benign, malignant and unspecified	7 (36.8)
Leukemia recurrent	4 (21.1)
Respiratory, thoracic and mediastinal disorders	7 (36.8)
Dyspnea	2 (10.5)
Organizing pneumonia	2 (10.5)
Gastrointestinal disorder	5 (26.3)
Diarrhea	3 (15.8)
Nausea	2 (10.5)
Vomiting	2 (10.5)
Renal and urinary disorder	3 (15.8)
Renal failure acute	2 (10.5)
Investigations	5 (26.3)
Hepatic enzyme increased	2 (10.5)

Source data: [CR-GVH-001, Table 42]

Laboratory findings

Study CR-AIR-007

Hematology

Small proportions of patients had clinically significant low hematology values.

Biochemistry

Clinically significant abnormal biochemistry values were identified in a low numbers of patients. The only parameter for which clinically significant changes were observed in more than single patients were increased alanine transaminase (ALT; 2 patients, 7.7%), and decreased potassium (7.7%).

CMV/EBV status

Of the patients who were CMV negative at baseline, no patient experienced CMV reactivation, regardless of the CMV status of the donor. Among CMV positive patients, 2 of 3 patients with a CMV negative donor experienced reactivation, and 8 out of 11 patients with a CMV positive donor experienced viral reactivation.

A total of 10 patients (38.5%) had AEs reported that were indicative of a CMV infection/reactivation i.e. 10 patients (38.5%) with a preferred term of CMV test positive, of which 1 patient (3.8%) had also a preferred term of CMV infection reported. Most patients experienced more than 1 occurrence of a positive CMV test reported as AE, but in most cases, it was also documented that the event presented CMV reactivation solely based on laboratory testing, without symptoms or sites of infection. The number of patients with SAEs was 1 (3.8%) for CMV infection and 2 (7.7%) for CMV test positive [CR-AIR-007]. None of the AEs was of grade 5, i.e. had a fatal outcome.

Likewise, none of the EBV negative patients experienced viral reaction, regardless of the EBV status of the donor. Of the 23 patients who were EBV positive at baseline and had an EBV positive donor, 5 patients experienced viral reactivation according to laboratory testing.

Based on the AEs reported, 9 patients (34.6%) had AEs reported that were indicative of an EBV reactivation. Since PTLD is known to typically occur alongside an EBV infection, the EBV status was also checked for patients with PTLD i.e. four patients [15.4%], of whom three patients also had an AE of EBV antigen positive. In an initially EBV-negative patient, EBV reactivation *de novo* was seen, which most likely originated from the donor who was EBV positive. Before the onset of the EBV reactivation, this patient had received a DLI from the same donor (3×10^5 CD3 cells/kg; unmanipulated) and had subsequently developed GVHD, which was treated with immunosuppressive medication (treatment still ongoing at onset of EBV reactivation).

Study CR-GVH-001

Hematology

High proportions of patients had low blood cell counts (white blood cells [WBC], RBC, platelets, lymphocytes), low hemoglobin, and low hematocrit values at baseline, and this proportion increased further after myeloablative conditioning. For WBC, platelets, and neutrophils, a reversal of the trend was seen after about 6 months, when the proportion of patients with low values decreased to about 40 to 50% for WBC and platelets and to 10 to 24% for neutrophils. Findings reflect immune reconstitution.

The proportion of patients with low RBC and lymphocyte count and low hematocrit generally remained at 100% or close to 100% through to Month 12, and the proportion of patients with low hemoglobin decreased moderately to 70% at Month 12.

Biochemistry

A high percentage of patients had liver enzyme values above the reference from baseline through to Week 8 (AST: 21 to 56%; ALT: 32 to 63%; ALKP: 16 to 39%). The percentage of high AST values appeared to increase over time through to Week 8 (after which a reversal of the trend was seen), while the proportion of patients with high ALT values remained invariably high for the first year after ATIR101 administration. No time trend was apparent for ALKP. For all 3 parameters, clinically significant values were noted for about 2 to 3 patients at each of the visits from Week 2 through to Week 6, and thereafter at most visits for 1 to 2 patients through to Month 6 (Month 9 for ALKP). Bilirubin values outside of the reference range were also noted for 1 or 2 patients at each of the time points from baseline trough Month 12, with individual patients having clinically significant values from Week 3 to Week 6 and from Week 10 to Month 12. A trend over time was not noticeable.

Blood urea nitrogen (BUN) values above and below the reference range were observed in 1 to 5 patients from Day 0 (ATIR101 administration) through to Week 8, although the proportion appeared to be highest at Week 1 and to decrease thereafter. However at Month 6, 9, and 12, total numbers of 7, 7 and 4 patients, respectively, had high BUN values. Clinically significant BUN values were reported at Week 4 (1 patient), Month 6 (1 patient), and Month 9 (3 patients).

One patient each had high creatinine values at Week 4 and 8, respectively. From Month 3 onwards, the number of patients with high creatinine values started to increase: 1 patient at Month 3, 3 patients at Month 6, 5 patients at Month 9, and 4 patients at Month 12, and a continuously high number following Month 12. One patient had a clinically significant creatinine value at Week 4 and Month 6, while 3 patients had clinically significant values at Month 9.

CMV/EBV status

CMV positive patients and patients with CMV positive donors were to be monitored for 1 year after ATIR101 administration. The EBV status was not routinely monitored.

Six patients were CMV positive at baseline, of which 2 had a CMV positive donor. The remaining 13 patients in the study were CMV negative at baseline; 2 of them had a CMV positive donor. During the 1-year monitoring period, CMV reactivation was observed in 3 patients, all of them CMV positive at baseline, and one of them also having a CMV positive donor.

There were no patients with non-serious CMV AEs reported. Two patients (10.5%) experienced a total of 4 relevant SAEs i.e. CMV chorioretinitis (5.3%), encephalitis CMV (5.3%), pneumonia cytomegaloviral (5.3%), and CMV test positive (5.3%).

Three patients experienced (S)AEs associated with EBV infection/reactivation.

Safety in special populations

Due to the small number of patients exposed to ATIR101, analyses of safety parameters in patient subgroups based on intrinsic or extrinsic factors were not performed. Special studies e.g. in children or in the elderly were not conducted.

Immunological events

Autoimmune Hemolytic Anemia

AIHA is the increased destruction of red blood cells (RBCs) in the presence of anti-RBC autoantibodies with or without complement activation (Barcellini 2015). AIHA is a recognized complication after allogeneic HSCT that contributes to the morbidity, and possibly mortality, of patients (Sanz 2007). Several risk factors are being discussed for AIHA, among the most important ones being unrelated donors and T-cell depletion (Sanz 2007; Wang 2015). For all patients in the ATIR101 studies

documented to have AIHA, an in-depth medical review was performed. It was concluded that the observed cases of AIHA were most likely related to the T-cell depleted HSCT while there was no indication of a direct relationship with ATIR101.

Study CR-AIR-007

Five patients (19.2%) had AIHA reported, all events being serious. AIHA was drug-related in a single patient, in whom AIHA was ongoing at the time of death. In all the other patients, AIHA resolved.

Study CR-GVH-001

Neither non-serious nor serious AEs of AIHA were reported. However, 2 patients (10.5%) had AIHA documented during physical examinations or as part of investigator comments.

Post-transplant Lymphoproliferative Disease

Study CR-AIR-007

In 4 patients, a total of 6 AEs of PTLD were reported, including 3 SAEs. In two patients, PTLD was ongoing at the time of death. In one patient, PLTD resolved and in one patient, 2 PTLD events resolved and one event is continuing.

Study CR-GVH-001

Overall, 2 patients had relevant SAEs indicative of PTLD or lymphoproliferative disease in association with an EBV infection. The fatal event of multi-organ failure in one of the two patients was considered as secondary to PTLD. The other patient had an lymphoma, which was not drug-related; the outcome is unknown.

Infusion Reactions

Study CR-AIR-007

In a single patient, the AE was identified as potential infusion reaction with rash of grade 1 (reported term: rash - arms bilaterally) that started 2 days after the ATIR101 infusion and resolved within 11 days. The event was considered as possibly related to ATIR101. One patient (3.8%) had preferred terms of anaphylactic reaction and hypersensitivity reported. The event was not judged as being ATIR101-related.

The AEs were reported 285 and 337 days, respectively, after the ATIR101 infusion.

Study CR-GVH-001

Medical review identified one AE that, based on the reported term and the timely relationship, might possibly be attributed to an infusion reaction. This was patient no. 20 with rash (reported term: skin rash superior limbs). The AE started on the day of the ATIR101 infusion and lasted for 26 days. The AE was mild and not drug-related; no action was taken.

Safety related to drug-drug interactions and other interactions

ATIR101 is a patient-specific somatic cell therapy that is administered as a solution (cell suspension) via the intravenous route. Interactions of ATIR101 with other drugs, in particular interactions mediated via the P450 system or via drug transporter proteins such as P-gp, are not expected. Therefore, no dedicated studies have been performed to investigate potential drug interactions of ATIR101.

Discontinuation due to AES

ATIR101 is administered as a single dose for the reconstitution of T-cell based immunity, in order to bridge the period of temporal immune deficiency following myeloablative conditioning and HSCT. In

this context, concepts of withdrawal effects or rebound after treatment discontinuation are not considered to be applicable.

3.3.9. Discussion on clinical safety

Forty-two patients have been exposed to ATIR101 in clinical trials. Forty patients received a single ATIR101 infusion and two patients had a second infusion. Twenty-six patients received a dose of 2.0 x 10^6 cells/kg. Four additional patients received ATIR101 in terms of compassionate use. Thus, the number of exposed patients is quite low. The main submitted study was planned for 2 years and was completed in September 2017. Of note, the majority of the patients did not survive till the end of follow-up. Thus, long term data are also limited. This might be due to the degree of illness that most patients were diagnosed with.

Overall, the picture of common AEs complies with the underlying hematological malignancy in conjunction with HSCT and the preceding myeloablative conditioning showing frequently infections and gastrointestinal disorders. The differences in the safety profile between the pivotal study CR-AIR-007 and the dose-escalation study CR-GVH-001 is mainly due to the different recording of AEs. Especially the percentage of ATIR101-related AEs is higher in study CR-AIR-007 than in study CR-GVH-001 with only a single patient of acute GVHD as related AE. In study CR-AIR-007 GVHD was considered as ATIR101-related in 4 patients with acute GVHD and 1 patient with acute GVHD and subsequent chronic GVHD. Acute GVHD cases were of low severity grade I /grade II and developed within 102 to 182 days after HSCT and ATIR101 administration, which is the usual time period for acute GVHD. All three patients with acute GVHD of higher severity, grade III (8.7%) or grade IV (4.3%) developed much later i.e. 351 to 497 days after HSCT and had received unmanipulated DLI. There were also single ATIR related cases of gastrointestinal disorders, infections, AIHA, EBV antigen positive and rash. But, the only preferred term reported in more than a single patient was acute GVHD (19.2%), which is in compliance with the mechanism of a donor lymphocyte preparation. In study CR-AIR-007 more AEs with higher grade of severity were recorded than in study CR-GVH-001 where only mild and moderate AEs were reported. There was only one AE (rush) indicative of infusion reaction or allergic/hypersensitivity reaction. In both studies none of the AEs leading to death was judged as being ATIR101-related.

The laboratory findings such as decreased hemoglobin values and blood cell counts, increased liver values, elevation of BUN and creatinine are not unexpected given the underlying disease and earlier anticancer treatments. Laboratory data show that CMV/EBV reactivations occurred in a relatively high number of CMV/EBV positive ATIR101-treated patients, but did not fully match with clinical events reported as AE, which were infrequent, rarely serious, and usually not fatal. In study CR-GVH-001 there were also common events of clinical CMV infections i.e. CMV chorioretinitis, encephalitis CMV and pneumonia cytomegaloviral, which have not been related to ATIR. PTLD, which is typically observed in connection with EBV infection, was in the range of PTLD incidences reported in the literature. PLTD was reported in 4 patients in study CR-AIR-007 and in 2 patients in study CR-GVH-001. None were related to ATIR. Unusual or unexpected pathogens that would raise special have not been detected. The development of specific antibodies is not expected and has not been investigated in the immunocompromised patients. AIHA is an usual complication after allogeneic HSCT due to the presence of anti-RBC autoantibodies with or without complement activation. In study CR-AIR-007 one ATIR101 related case was reported. Although MAA concludes, that this AIHA is most likely to be related to T-cell depleted HSCT, rather than have a direct relationship with ATIR101. No relevant interactions with ATIR101 are to be expected. There are no safety data for patients < 18 years of age and > 65 years of age available. In addition, safety in patients and patients with renal or hepatic impairment is not analysed since these patients were excluded from the pivotal study.

3.3.10. Conclusions on clinical safety

Clinical safety has been analysed from the data of two clinical trials. No unexpected patterns in the reported adverse events and serious adverse events were observed. The main ATIR101 related AE was acute GVHD of low grade. Results of study CR-AIR-008, which shows development of high-grade aGVHD after two doses of ATIR, were addressed. None of the AEs leading to death was judged as being ATIR101-related. There are no safety data for children and the elderly as well as patients with renal or hepatic available. However, the applicant was not able to provide a complete comparative safety analysis, including safety of the adjuvant setting due to limitations of the study protocol. More extensive analysis is required from the ongoing phase 3 study CR-AIR-009.

However, even if no unexpected events have been observed there is considerable uncertainty on the safety profile of this product because of the low patient exposure which ultimately has to be taken into account when evaluating benefit-risk balance.

3.4. Risk management plan

The Applicant submitted an updated RMP version 0.4 within their response.

3.4.1. Safety Specification

The applicant updated the list of safety concerns as follow:

Table 29 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Graft-versus-host disease
Important potential risks	• Autoimmune haemolytic anaemia • Cytomegalovirus and Epstein-Bar reactivation • Post-transplant lymphoproliferative disorder • Hypersensitivity to any of the excipients (including dimethyl sulfoxide)
Missing information	• Long-term safety and efficacy • Use in elderly patients

3.4.2. Pharmacovigilance Plan

Summary of planned additional PhV activities from RMP

Table 30 On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
CR-AIR-008 Last subject completed study, analyses ongoing	Safety and efficacy of a repeat dose administration	• GVHD • CMV and EBV reactivations • PTLD • Infections • Mortality • Other (serious) adverse events including AIHA and hypersen-sitivity reactions	Original protocol Amendment 1 Study start (FPFV) Study completion (LPLV) Final report	9 Jul 2015 20 Nov 2015 Oct 2015 17 Dec 2018 Dec 2018 Q2/3 2019
CR-AIR-009 Ongoing	Safety and efficacy compared to PTCy	• GVHD • CMV and EBV reactivations • PTLD • Infections • Mortality • Infusion reactions • AIHA • Secondary malignancies • Haemorrhagic cystitis • Veno-occlusive disease • Other (serious) adverse events including hyper-sensitivity reactions • Use in elderly patients	Protocol: version 1.0 version 2.0 version 3.0 FPFV LPLV Final report	 23 Nov 2016 26 Sep 2017 23 Aug 2018 29 Nov 2017 Q1 2023 Q3/4 2023

Category 3 - Required additional pharmacovigilance activities				
PASS-AIR-001 Planned	• Safety of ATIR101 as adjunctive treatment in adult patients undergoing a T-cell depleted haploidentical HSCT for hematologic malignancies in complete remission in routine clinical practice; • Safety of ATIR101 as adjunctive treatment to a T-cell depleted haploidentical HSCT in routine clinical practice with respect to important identified and potential risks	Incidence and severity of: • acute (Grade II-IV) and chronic GVHD events; • AIHA; • CMV/EBV reactivation; • PTLD; • Hypersensitivity reactions; • OS; • Non-relapse mortality (NRM), defined as death without previous occurrence of a relapse.	Protocol Start data collection Interim report End of data collection Final report Progress reports in PSUR	Q3 2019 Q4 2019 Q2 2025 Q2 2029 Q1 2030 According to PSUR schedule
CR-AIR-011 Planned	Long-term outcome in patients who have completed studies CR-AIR-007/008 or have received ATIR101 on a named patient basis	• Incidence and severity of acute and chronic GVHD • TRM • RRM • OS • PFS • GRFS • Incidence of infections leading to hospitalization.	Protocol End of study Final report Progress reports in PSUR	Q1 2019 Q3 2024 Q1/2 2025 According to PSUR schedule

AIHA: autoimmune haemolytic anaemia; CMV: cytomegalovirus; EBV: Epstein-Barr virus; FPFV: first patient first visit; GVHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; LPLV: last patient last visit; PTLD: post-transplant lymphoproliferative disease.

The objectives of the Studies CR-AIR-008 and CR-AIR-009 are comparing efficacy and safety of ATIR101 in patients with a hematologic malignancy. In addition, both studies address all the safety concerns related to ATIR101. In light of the topics addressed and the need for further data these studies have been categorised as imposed studies in the RMP as **category 2** studies as requested.

The applicant confirms that the previously submitted protocol of the single-arm registry study CR-REG-001 was intended to be a long-term follow-up study of patients who have received ATIR101 in clinical studies. The originally submitted protocol has been revised (see **CR-AIR-011** below) and in addition, the applicant proposes to revise the pharmacovigilance plan and to include another study which enables the use of a control arm (**PASS-AIR-001**). An overview of both studies is presented below.

1. **PASS-AIR-001: Post-authorization safety study (Category 3 PASS)** of ATIR101 prescribed in patients undergoing a T-cell depleted haploidentical hematopoietic stem cell transplantation (HSCT) for hematologic malignancies in complete remission based on secondary use of data from the EBMT Registry.

The applicant proposes the PASS to follow-up patients receiving ATIR101 in a commercial setting. The PASS has been developed and will be conducted in collaboration with the EBMT. Use of the EBMT registry will allow the inclusion of a control group. This control group will comprise of patients receiving a haploidentical T-cell depleted transplantation without adjunctive cell infusion. The objective of the PASS is to investigate the safety of ATIR101 as adjunctive treatment to a T-cell depleted haploidentical HSCT in routine clinical practice with respect to the important identified and potential risks listed in the RMP *i.e.*, (acute and chronic) GVHD, AIHA, CMV/EBV reactivation, PTLD, and hypersensitivity to any of the excipients. In addition, data on overall survival and non-relapse mortality will be collected. Data until 3 years after the HSCT will be extracted from the EBMT Registry for all included patients. Based on the currently known safety profile, the 3-year period for follow-up of identified and potential risks of ATIR101 is considered sufficient. No prolonged biological activity is expected, considering ATIR101's mechanism of action. Furthermore, ATIR101 is not a genetically modified product.

Data will be extracted by the EBMT from the Registry at regular intervals and transferred to Kiadis Pharma. Data sets will include all patients in European EBMT centers who have received ATIR101, and all patients who have had a T-cell depleted haploidentical HSCT without any adjunctive cell therapy treatment. The EBMT registry will collect data from HSCT patients using ATIR101 via the standard EBMT data collection forms.

The final data extraction will be done when **185 eligible patients** in the ATIR101 group have been included and followed up until three years after HSCT.

2. **CR-AIR-011: Observational long-term follow-up study (Category 3 PASS)** of patients who have received ATIR101 following a hematopoietic stem cell transplantation in Phase II studies or on a named patient basis.

The proposed observational study (previously indicated as patient registry CR-REG-001) will be a follow-up study to assess long-term outcome in patients who have received ATIR101 following a haplo-identical HSCT. Patients treated with ATIR101 in one of the two completed clinical trials CR-AIR-007 and CR-AIR-008 with completed active follow-up and patients treated on a named patient basis up until 01 July 2019 for which no follow-up had previously been arranged will be enrolled in this study. The study will collect information on survival, cause of death, incidence of GVHD, incidence of infections leading to hospitalization, and relapse up to five-year post-HSCT.

As studies CR-AIR-007 and CR-AIR-008 were not controlled, no comparison with other treatments is possible within the scope of a long-term follow study. Nevertheless, the collection of the efficacy parameters like OS and PFS beyond the follow-up duration as per individual protocols will provide relevant information about the condition and status of patients after having received ATIR101. The applicant should ensure that safety outcomes have been aligned with the RMP.

The applicant estimated that approximately **20 patients** will be enrolled in the study

The applicant's proposal for a two-arm registry study **PASS-AIR-001** (as Category 3) using EBMT data in addition to Long-term follow-up **CR-AIR-011** (which is a single-arm extension of completed Phase II trials CR-AIR-007 and CR-AIR-008) **could be acceptable**, provided the applicant adequately addresses the topics in the List of Outstanding Issues.

3.4.3. Risk minimisation measures

Summary of risk minimisation measures from the RMP

Table 31 Proposal from applicant for risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Graft-versus-host disease	Routine risk communications: • *SmPC sections 4.3 and 4.8* • *SmPC section 4.4, where recommendation to avoid unmanipulated donor lymphocyte infusions is provided* • *PL sections 2 and 4* • *Restricted prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-008 (Cat. 2) • CR-AIR-009 (Cat. 2) • PASS-AIR-001 (Cat. 3) • CR-AIR-011 (Cat. 3)
Autoimmune haemolytic anaemia	Routine risk communications: • *SmPC section 4.8.* • *PL section 4* • *Restricted prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-008 (Cat. 2) • CR-AIR-009 (Cat. 2) • PASS-AIR-001 (Cat. 3)
CMV and EBV reactivation	Routine risk communications: • *SmPC sections 4.4 and 4.8* • *SmPC section 4.4, preference to match donor and patient baseline statuses and recommendation for regular EBV/CMV monitoring* • *PL sections 2 and 4* • *Restricted prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-008 (Cat. 2) • CR-AIR-009 (Cat. 2) • PASS-AIR-001 (Cat. 3) • CR-AIR-011 (Cat. 3)
Post-transplant lymphoproliferative disorder	Routine risk communications: • *SmPC section 4.4, warning for EBV monitoring* • *PL section 2* • *Restricted prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-008 (Cat. 2) • CR-AIR-009 (Cat. 2) • PASS-AIR-001 (Cat. 3) • CR-AIR-011 (Cat. 3)
Hypersensitivity to any of the excipients (including DMSO)	Routine risk communications: • *SmPC section 4.3* • *PL section 2* • *Restricted prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-008 (Cat. 2) • CR-AIR-009 (Cat. 2) • PASS-AIR-001 (Cat. 3)
Long-term safety and efficacy	Routine risk communication: • *None* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: • PASS-AIR-001 (Cat. 3) • CR-AIR-011 (Cat. 3)
Use in elderly patients	Routine risk communication: • *None* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • CR-AIR-009 (Cat. 2)

The Applicant did not propose additional risk minimisation measures for any of the safety concerns.

The Applicant stated that no regulatory educational material is considered necessary as SmPC and PIL are sufficient in order to inform the HCP and patients about ATIR. On the other hand, the Applicant proposed that all HCP prescribing ATIR101will receive detailed instructions on the requirements for collection of apheresis materials from donor and patients including instructions for shipment to the manufacturing site. These instructions are referenced in the RMP and in the product information, but have not been included as (additional) risk minimisation measures or educational materials in the RMP as these instructions are not related to clinical safety concerns. Rather these instructions ensure product quality/integrity, which should fall within the remit of good practices regarding treatment/administration/distribution/logistics (*e.g.* assurance of the cold-chain) of the centers using ATIR. In the PRAC Rapporteur's view currently no additional risk minimisation measures are warranted.

Conclusion

The CHMP/PRAC considered that the risk management plan version 0.4 is **could be acceptable**, provided the applicant adequately addresses the 3rd List of Outstanding Issues.

Public summary of the RMP

Section VI (summary of the RMP) of the RMP requires revision in line with the recommendations made on the RMP section safety specification, PhV plan and risk minimization measures for ATIR. Updated RMP should be submitted.

PRAC Outcome

N/A

3.5. Pharmacovigilance system

The Committee considers that the pharmacovigilance system summary (Version 2.0 signed on 08/May/2017) submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.6. New active substance status

Based on the review of the data the CHMP/CAT considers that the active substance "viable T-cells" contained in the medicinal product "ATIR101" is to be qualified as a new active substance in comparison to the known active substance "Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)" previously authorised in the European

Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in the manufacturing process.

4. Orphan medicinal products

Orphan designation

Orphan Designations have been granted on 2016-06-27 (ODD EU/3/16/1678) for the **Treatment in haematopoietic stem cell transplantation**, on 2014-11-19 (ODD EU/3/14/1356) for the **Treatment of acute myeloid leukaemia** and on 2008-09-05 (ODD EU/3/08/561) for the **Prevention of Graft-versus-Host disease.**

According to the conclusion of the COMP (Opinion dated 27/06/16) the prevalence of hematopoietic stem cell transplants per year is 1 per 10,000 individuals in the EU.

The therapeutic indication claimed by the applicant falls within the scope of the orphan designated condition.

Similarity

The application contains a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. The assessment of similarity was appended to Day 80 report.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

ATIR101 is intended for adjunctive treatment in hematopoietic stem cell transplantation (HSCT) for a malignant disease. ATIR101 should be administered to patients who have received a haploidentical HSCT from the same donor as the donor of the cells used in ATIR101.

The incomplete HLA-match between donor and recipient of haploidentical HSCT offers a potent graft-versus-leukemia (GVL) effect that may lead to the complete eradication of malignant cells but also causes graft rejection and GVHD. Methods to reduce or control GVHD in the haploidentical setting are the use of immunosuppressive drugs and the depletion of T-cells in the graft. Limitations of T-cell depleted grafts are a higher risk of graft rejection, severe immune deficiency for up to 1 year after HSCT, leading to a high risk of life-threatening infectious complications and, consequently, high transplant-related mortality (TRM) and low overall survival (OS). Additionally, the GVL effect could be compromised, leading to an increase in relapse. Reintroducing mature T-cells early after a T-cell depleted HSCT could be a solution, but the risk of inducing GVHD through unmanipulated donor lymphocyte infusions (DLIs) is significant. Therefore, manipulated T-cells are employed. ATIR101 is such a preparation where e*x vivo* photodepletion should eliminate alloreactive T-cells causing GVHD from donor lymphocyte preparations. ATIR101 as adjunctive treatment in HSCT should allow early immune reconstitution, potential protection against infections and disease relapse, while not causing severe GVHD (grade III/IV). In the pivotal study CR-AIR-007, transplant-related mortality (TRM) at 6 months post HSCT was chosen as the primary endpoint, which is mostly driven by infections. In addition, following key secondary endpoints were investigated up to 24 months post HSCT: TRM, RRM,

OS, and PFS, incidence and severity of acute and chronic GVHD, incidence and severity of viral, fungal, and bacterial infections and immune reconstitution.

5.1.2. Available therapies and unmet medical need

The treatment options after T-cell depleted haploidentical HSCT are the reintroduction of unmanipulated donor lymphocyte infusions (DLIs) or the concept of reintroducing manipulated T-cells. Unmanipulated DLIs have a high risk of inducing GVHD. At the time of assessment, there was is an approved manipulated T-cell preparation (Zalmoxis), in which donor T-cells are genetically modified to express the herpes simplex virus thymidine kinase suicide gene. This medicinal product is intended to engraft and stimulate immune-reconstitution after HSCT. If GVHD occurs, ganciclovir is administered and is metabolized to its toxic form ganciclovir triphosphate by the activated, transduced T-cells causing GVHD, which will subsequently undergo apoptosis. Zalmoxis is authorized under Conditional Approval. ATIR101 would be another manipulated donor lympocyte preparation. It does not require genetic modification of the donor T-cells and only functionally eliminates the potentially GVHD-causing cells. According to the guideline (EMA/CHMP/509951/2006, Rev.1) ATIR101 would be a second product for considering Conditional Marketing Authorisation in this field. Since the Specific Obligation has not been fulfilled by Zalmoxis yet, ATIR101 needs to address the unmet medical need to a similar or greater extent according to the guideline section 4.1.2 (c).

5.1.3. Main clinical studies

To date, 42 patients with severe hematological malignancies have been treated with ATIR101 in clinical studies, including 23 patients in the pivotal study CR-AIR-007 receiving a single ATIR101 dose of 2.0 x 10^6 T-cells/kg, and 19 patients in dose-escalation study CR-GVH-001 receiving single doses ranging from 1.0 x 10^4 to 5.0 x 10^6 T-cells/kg (including 3 patients receiving a dose of 2.0 x 10^6 T-cells/kg).

Studies CR-AIR-007 and CR-GVH-001, which were open-label and uncontrolled, included a population of adult patients up to 65 years of age mostly with AML or ALL. The patients underwent haploidentical HSCT with mainly myeloablative conditioning. Such a treatment is often not an option for patients with low performance status or elderly patients because of the toxicity of the procedure. Therefore, adjunctive treatment to reduce TRM is required in this heavily pre-treated patient population.

5.2. Favourable effects

In the pivotal study (CR-AIR-007), the TRM probability at 6 months, defined as the primary endpoint, was estimated as 13.5%. A control group of patients receiving haploidentical, T-cell depleted HSCT alone (CR-AIR-006) had a TRM probability at 6 months of 37.1%. Comparison between these groups indicates that ATIR101 led to a statistically significant reduction in TRM, with a HR vs control of 0.30 (p=0.0066). The beneficial effect of ATIR101 is also supported by the fact that infection was the main cause of TRM (pivotal study: 5/7 TRM cases; control group: 14/23 TRM cases). At 12 months there is still a marked difference of TRM probability between HSCT plus ATIR101 and HSCT alone of 32.2% versus 70.3%. Data of the first-in-man study (CR-GVH-001) support this effect showing a 12-month TRM probability of 24% in all patients. In addition, OS was significantly prolonged in HSCT plus ATIR101 namely the 12-month OS probability was 61% in the pivotal study in comparison to 20% in the control group (p=0.0035). The OS data are also supported by study CR-GVH-001 with a 12-month OS probability of 63% in all patients. The groups (plus ATIR101 and without ATIR101) did not significantly differ with regard to the relapse rate (8.7% versus 14.3%). Furthermore, patients treated with ATIR101 had lower 12-month cumulative incidences for acute GVHD and chronic GVHD than untreated control patients.

5.3. Uncertainties and limitations about favourable effects

Only 23 patients have been treated in the pivotal study, which was an uncontrolled trial. The data of the ATIR101 untreated control group have separately been collected in an observational study.

There were differences between these studies (CR-AIR-007 and CR-AIR-006) with regard to CD3 and CD34 cell count, observed periods, underlying haematological malignancies (ALL, MDS), remission status, and myeloablative conditioning regimen and managing infectious complications post HSCT. Reduction in TRM indirectly shows an influence of ATIR101 on infections. Impact of biases due to confounding factors favouring ATIR101 arm have not sufficiently been addressed.

The rate and kind of infections in comparison to the retrospective control has not been evaluated. A comparison of study CR-AIR-007 with study CR-AIR-004 as control analysed the incidence, type of infections that occurred during the early and the late post-transplantation phase. Overall, the total number of viral and bacterial infections was reduced by a small amount in patients treated with ATIR101. In both post-transplantation phases infections were less severe in study CR-AIR-007 when compared to study CR-AIR-004 in which more higher-grade (grade 3, 4 and 5) infections were observed. But, there was a higher number of fungal infections of low grade in the late post HSCT phase of the ATIR101 study (10 out of 23) compared to 6 out of 29 in the control study.

It is important to note that of the 10 patients with TRM (12 months), 4 patients had received unmanipulated DLI shortly before the onset of the TRM event, which has influenced TRM negatively for ATIR101. Statistical significance was not reached for 12-month cumulative incidences of acute GVHD and chronic GVHD between ATIR101 treated and ATIR101 untreated patients.

5.4. Unfavourable effects

Drug related AEs were identified in 9 patients (n=8 in CR-AIR-007, n=1 in CR-GVH-001). The main ATIR101 related AE was acute GVHD. There were also single ATIR101 related cases of gastrointestinal disorders, infections, AIHA (autoimmune haemolytic anaemia), EBV antigen positivity and rash.

The nature and frequency of all AEs reported are usually associated with HSCT and, do not give rise to concern per se. None of the AEs leading to death was judged as being ATIR101-related.

5.5. Uncertainties and limitations about unfavourable effects

The available safety database of 42 unique subjects is quite small. Only 26 patients received the proposed dosage of 2.0 x 10^6 T-cells/kg. There is a follow-up period of 2 years in the pivotal trial.

The time frame between HSCT and ATIR101 administration is small (30 days). Since the cells are of the same donor, the relationship of AE caused by HSCT or ATIR101 is difficult to disentangle. This limits the approach of the MAA to analyse risks of ATIR101-administration as stand-alone but not as an adjuvant to HSCT.

There are no safety data in elderly patients available.

The low patient exposure causes uncertainty around the safety profile and true incidence of AE. Additional uncertainty is introduced because of the unknown representativeness of the current patient sample compared to the future target population.

5.6. Effects Table

Table 32 Effects Table for ATIR101 for adjunctive treatment in HSCT for malignant disease; data cut-off: 27 September 2016.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
TRM	Event at 12 months	n (%)	7 (30.4)	23 (65.7)	**(+)**: big effect size for both PEP at 12 months (+/-): low number of treated patients (n=23), control group of a separate observational study, differences in baseline characteristics, various concomitant treatments, analysis of MITT population	S.007, S.006, and T.14.02. 01.01 of Pooled analysis
	Hazard ratio	95% CI	0.30 (0.12,0.75)			
	p-value (log-rank test)		0.0066			
	TRM probability at 6 months	%	13.5	37.1		
	TRM probability at 12 months	%	32.2	70.3		
OS	OS probability at 6 months	%	82.6	62.9	See above	See above
	OS probability at 12 months	%	60.9	20.0		
GVHD (TRM)	Incidence of fatal aGvHD and cGvHD at 12 months	Pts (%)	0	4 (11.4%)	**(+):** lower GVHD rates in pts receiving HSCT/ATIR **(+/-):** no statistical evaluation; questionable non-attribution of event to ATIR101	T.3-26 in M.2.7.3, S.007, S.006
Infections (TRM)	Incidence of fatal infections at 12 months		5 (21.7)	14 (40%)	**(+):** lower infection rates in pts receiving HSCT/ATIR **(+/-):** no statistical evaluation; questionable managements of infections	
Relapse /disease progression	Incidence of fatal relapse and disease progression at 12 months	Pts (%)	DR: 2 (8.7%) DP:0%	DR: 3 (8.6%) DP: 2 (5.7%)	**(+):** lower DP rates in HSCT/ATIR101 group **(+/-):** questionable methodology for residual disease; inclusion of non-remitted patients in control; no effect on relapse	
Unfavourable Effects						
Total ADR/ SADR	Incidence at 12 months	Pts (%)	10/26 (38%)/ 100%	0	**(-):** high proportion of total ADR, all of those are SADR **(+/-):** no analysis for control setting	S.007, S.006

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
GVHD	12-month cumulative-incidence of acute GVHD grade II-IV	95% CI	15.4 (4.7,31.8)	20.0 (8.7,34.7)	Additional administration of DLI, relation to HSCT	S.007, S.006
	12-month cumulative-incidence of acute GVHD grade III-IV	95% CI	0.0	5.7 (1.0,16.9)		T.14.03.02 of Pooled analysis
	12-month cumulative-incidence of chronic GVHD	95% CI	3.8 (0.3,16.8)	8.6 (2.1,20.8)		
Infections	Incidence of all infections at 12 months as AE	Pts (%)	26/26 (100%)	No information provided	**(-):** very high infection rate **(+/-):** no comparative data	S.007, S.006
AIHA	Reported as serious ADR	Pts (%)	1/26 (3.8%)	No information	(-): SADR related to ATIR	AIHA

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

ATIR101 is intended to bridge the immune deficiency after HSCT and is intended to prevent infections. Since TRM is mainly driven by infections this may reflect the proposed effect of ATIR101. A possible benefit of ATIR101 could be inferred by a lowered TRM and a improved OS when comparing treated l patients and historical controls. Since TRM is the main risk after haploidentical HSCT a favourable effect of ATIR101 may be assumed. Patients treated with ATIR101 had lower 12-month cumulative incidences for acute GVHD and chronic GVHD compared to untreated control patients. Statistical significance on GVHD was not reached, but the data indicate that ATIR101 has a favourable effect on TRM and OS without increasing the risk for GVHD. In addition, acute GVHD was of low grade (1 or 2) except after administration of unmanipulated DLI. Since there was no obvious difference in relapse related mortality, no conclusion can be made with regard to graft versus leukemia effect.

However, there are important uncertainties when interpreting the observed estimates for TRM and OS. These uncertainties are mainly caused by the low number of patients treated and the used historical controls. The risk of confounding appears particularly high in this complex therapeutic area. For example biases regarding CD34+ cell dose and adequacy in managing infectious complications post HSCT (magnitude of immunization and prophylaxis and treatment of viral/fungal infections) have been identified.

According to subgroup analyses an covariate adjusted analyses sufficient evidence seems to be given that the treatment effect is stable over a wider range of subgroups (and in the multivariate models adjusted for prognostic confounders), despite some shortcomings and uncertainties,

5.7.2. Balance of benefits and risks

Based on the provided data and analyses an effect of treatment on primary endpoint (TRM) seems evident. Treatment with ATIR101 did not show any major unexpected safety issues. However, several uncertainties regarding the observed effect remain, which cannot be addressed by the available data.

Also recent changes in the treatment landscape have not been considered. Overall, the benefit/risk balance is negative at this point.

Therefore, the CAT recommends convening an ad hoc expert group consisting of experts in haematopoietic stem cell transplantation to address the following issues:

- **What is the view of the experts on the observed effect considering the uncertainties caused by the limited number of patients, heterogeneity of the target population, the pooling of data across studies, and the single arm study nature of the data?**
- **What is the view of the experts on the relevance of external control groups chosen by the applicant?**
- **Does this product address the unmet medical need in this therapeutic area?**

Since there is no comprehensive data set available which would be sufficient to support a full marketing authorisation, conditional approval could only be considered in the context of an unmet medical need. Thus, the consideration of a Conditional Marketing Authorisation needs to be further justified by the applicant.

5.8. Conclusions

The overall B/R of Luxceptar/ATIR101 is currently negative.