A dose-escalation, open label phase I study to assess the safety, feasibility and preliminary efficacy of HA-1H TCR modified T cells, MDG1021, in patients with relapsed or persistent hematologic malignancies after allogeneic hematological stem cell transplantation with or without unmanipulated donor lymphocyte infusion.

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Primary objectives for the dose-escalation part of the study: • To assess the safety and tolerability of HA-1H TCR transduced T cells (MDG1021) in patients with relapsed or persistent hematologic malignancies after allo-HSCT with or without…

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55022

Source
ToetsingOnline

Brief title
CD-TCR-003

Condition

- Other condition
- Leukaemias

Synonym
blood disease, haematologic malignancies

Health condition

AML, CML, MM, ALL, MDS, MPN, MF and malignant B- or T-cell lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Miltenyi Biomedicine
Source(s) of monetary or material Support: Industry;Miltenyi Biomedicine

Intervention

Keyword: ATMP, HA-1H TCR T cell, Hematological malignancies, immunotherapy

Outcome measures

Primary outcome

DOSE-ESCALATION PART OF THE STUDY

Primary endpoints:

• Incidence and severity of adverse events (AE) at 28 days according to the

CTCAE v5.0

• MTD and/or RP2D of MDG1021 as determined by DLTs up to 28 days post

transfusion.

EXPANSION PART OF THE STUDY

Primary endpoint:

• Incidence and severity of adverse events (AE) of MDG1021 at the RP2D at 28

days according to the CTCAE v5.0

Secondary outcome

ENDPOINTS FOR BOTH PARTS OF THE STUDY

Secondary endpoints: all assessed at day 28, and months 3, 6, and 12, unless specified otherwise.

• Incidence and severity of adverse events (AEs) >= grade 3 only at day 28 according to the NCI CTCAE v5.0

• ORR

• OS

• PFS

• DoR

• Quality of life assessed by using the EQ-5D-5L (EuroQol) also before IMP administration, but not at day 28

Study description

Background summary

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the treatment of choice for a number of otherwise incurable hematologic malignancies. The elimination of malignant cells after allo-HSCT or donor lymphocyte infusion (DLI) results in part from a *graft versus leukemia or graft versus lymphoma* (GVL) effect that is mediated by donor T cells recognizing polymorphic minor histocompatibility antigens (MiHAs) on recipient cells. MiHAs are encoded by polymorphic genes, presented as peptides bound to MHC molecules on recipient cells, i.e. malignant cells, that may elicit immune responses when they are recognized by effector T cells. The MiHA HA-1H that is highly expressed in leukemia and normal hematopoietic cells, but not on cells outside of the hematopoietic system, is a compelling target for immunotherapy after allo-HSCT with or without DLI in a constellation of a donor not carrying the immunogenic HA-1H variant and the recipient having the immunogenic HA-1H variant. The MiHA HA-1H is presented on HLA-A*02:01

Hence, an adoptive immunotherapy using HLA-A*02:01 restricted HA-1H TCR T cells targeting the immunogenic form of HA-1H harbors the potential to cause a the therapeutic antileukemic effect and minimize other toxicities, while potentially ensuring durable remission.
In the general population, approximately 25% of people present both HA-1 and the HLA-A*02:01-restricting allele. About 15% to 20% of patients who undergo allo-HSCT or DLI for their hematological malignancy would be suitable for HA-1H TCR T cell immunotherapy when the donor has an HA-1H or HLA-A02 mismatch. This constitutes the rationale to conduct a phase I study to assess the safety, feasibility as well as to evaluate preliminary efficacy of the administration of HA-1H TCR transduced patients own T cells (MDG1021) and establish its maximum tolerated dose (MTD) or recommended dose for development (RP2D).

Study objective

Primary objectives for the dose-escalation part of the study:
• To assess the safety and tolerability of HA-1H TCR transduced T cells (MDG1021) in patients with relapsed or persistent hematologic malignancies after allo-HSCT with or without unmanipulated DLI.
• To establish the MTD and/or RP2D of MDG1021.
Primary objective for the expansion part of the study:
To assess the safety and tolerability, as assessed by NCI CTCAE v5.0, of HA-1H TCR transduced T cells (MDG1021) at the selected RP2D in relapsed or persistent hematologic malignancies after allo-HSCT with or without unmanipulated DLI.

Secondary objective for both parts of the study:
• To evaluate clinical response to MDG1021, including overall response (ORR), overall survival (OS), progression free survival (PFS) and duration of response (DoR)
To assess the quality of life

Feasibility objective for both parts of the study:
To assess the feasibility of manufacturing and administering of MDG1021

Exploratory objectives for both parts of the study:
• To evaluate HA-1H TCR transduced T cells with respect to in vivo expansion and persistence.
• To evaluate HA-1H TCR transduced T cells function and phenotype in vivo and in vitro
• To investigate biomarkers and molecular signatures, potentially related to safety, anti-tumor activity, the mode-of-action of MDG1021 and / or the pathophysiology of the disease
• To evaluate disappearance of recipient hematopoiesis (chimerism analysis)

Study design

A dose-escalation, open label phase I study to assess the safety, feasibility and preliminary efficacy of HA-1H TCR modified T cells, MDG1021, in patients with relapsed or persistent hematologic malignancies following allogenic hematological stem cell transplantation (allo-HSCT) with or without unmanipulated DLI.
After having provided signed informed consent, subjects will undergo testing for eligibility to participate in the phase I study. Eligible subjects must have a positive genotype for HLA-A*02:01 and HA-1H (i.e. the immunogenic form of HA-1), while the donor must either be HLA-A*02:01 positive but negative for HA-1H or have a single HLA mismatch being HLA-A*02:01 negative. Furthermore, at least 10x10^6 donor CD8+ T cells should be harvested by leukapheresis from the patient to initiate MDG1021 production.
The aim of the study is to determine the RP2D of MDG1021 that will be determined on the basis of safety and ability to manufacture a cohort specific MDG1021 dose. The dose-escalation part of the study is designed to assess the safety and the MTD of MDG1021, using a standard 3+3 cohort design, with up to 3 additional subjects to be enrolled in case of dose limiting toxicity (DLT).
Subjects will receive the investigational medical product (IMP) on study day 1 by a single IV transfusion and will remain in the study for 1 year. Thereafter, the patient will be offered to participate in a long-term follow-up study as mandated by the regulatory requirements for gene modified advanced therapy medicinal products (ATMP).
The MTD is defined as the highest dose level of MDG1021 at which not more than 1 patient experiences a DLT in a specific dose cohort, assessed by National Cancer Institute common terminology criteria for adverse events (NCI CTCAE v5.0) and further defined below.
The data monitoring safety board (DSMB) will be involved in the decision to escalate to the next dose level of MDG1021.
The first MDG1021 cohort will include 3 eligible subjects to receive Dose 1 (D1). If no DLT occurs the D2 dose cohort of MDG1021 will be initiated. If for 1 out of 3 subjects DLT occurs, up to 3 additional subjects will receive D1. If 1 out of 6 subjects have a DLT, the RP2D for MDG1021 is defined to be D1, unless the DSMB recommends to escalate to D2. If > 1 subject have a DLT, the study may be discontinued, pending recommendation of the DSMB.
The second MDG1021 cohort will include 3 eligible subjects to receive Dose 2 (D2). If no DLT occurs the D3 dose cohort of MDG1021 will be initiated. If 1 out of 3 subjects DLT occurs, of up to 3 additional subjects will receive D2. If 1 out of 6 subjects have a DLT, the RP2D for MDG1021 is defined to be D2, unless the DSMB recommends to escalate to D3. If > 1 subjects have a DLT, the RP2D for MDG1021 is defined to be D1.
The third MDG1021 cohort will include 3 eligible subjects to receive Dose 3 (D3). If for 1 out of 3 subjects DLT occurs, up to 3 additional subjects will receive D3. If 1 out of 6 subjects have a DLT, the RP2D for MDG1021 is defined to be D3. If > 1 subject have a DLT, the RP2D for MDG1021 is defined to be D2.
Manufacturing could potentially result in an out of specification (OOS) IMP, however, since this is a patient derived, patient specific, last treatment option material, every effort will be made to make it available for treatment

due to ethical reasons. Patients, who are treated with OOS IMP, will be analyzed in the full analysis data set (FAS), but not in the per protocol data set (PP).
A DLT event is defined as any of the following events occurring at any dose level of the dose escalation part of the study, excluding toxicity that is clearly and directly related to disease progression or intercurrent illness:
• Graft versus host disease (GVHD): Onset of acute GVHD overall grade >= III within 4 weeks after IMP administration
• Hematological DLT: Prolonged cytopenia CTCAE grade >= 4 not resolved at day 28, newly developed and not attributable to underlying disease, bridging or lymphodepleting regimen
• Non-hematological DLT: Any CTCAE Grade >= 3 toxicity will be considered as DLT except from:
• Cytokine release syndrome (CRS; CRS graded according Lee et al. 2018) CTCAE grade 3
• CRS CTCAE grade 4 responding to treatment within 48 h (Lee et al., 2018)
• aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increase CTCAE grade 3 that does resolve to <= Grade 1 within 14 days
• Nervous system disorders CTCAE grade 3 in the absence of CRS
• Nervous system disorders CTCAE grade 4 in the absence of CRS that do respond to treatment within 48 hours
• Transfusion-related toxicities that can be treated or controlled to grade <= 2 by medical management
• Tumor lysis syndrome (TLS) CTCAE grade 3
• TLS CTCAE grade 4 that does resolve within 7 days
• Electrolyte abnormalities CTCAE grade 3
• Electrolyte abnormalities of CTCAE grade 4 that do resolve to <= grade 2 within 72 hours with or without treatment
• Isolated asymptomatic elevations of biochemical laboratory values which respond to medical intervention
• Fatigue
Any other unacceptable toxicity at least possibly related to the transfusion of MDG1021 in the view of the investigator and the DSMB.
Upon completion of the dose-escalation part of the study, 20 eligible patients will be treated in the expansion part of the study with MDG1021 at the RP2D to further evaluate safety, feasibility and preliminary efficacy.

Intervention

MDG1021, the IMP, is a gene modified ATMP which contains autologous T cells, expressing the HLA-A*02:01 restricted TCR targeting HA-1H, in a 0.9% saline solution with human serum albumin in a total volume of 100 mL in a standard infusion bag.
Three dose levels of MDG1021 will be investigated to determine the RP2D. The following dose levels will be administered by a single intravenous (IV) transfusion up to 30 minutes:
• D1: target dose of 0.3x10^6 HA-1H transduced T cells/kg BW ±20% in 100 mL

• D2: target dose of 1x10^6 HA-1H transduced T cells/kg BW ±20% in 100 mL
• D3: target dose of up to 3x10^6 HA-1H transduced T cells/kg BW ±20% in 100 mL, whereas the lower range for D3 is >D2 (i.e. >1.2x10^6)
The following rules apply to IMP administration:
• Dose calculation will not be increased above 120 kg body weight.
• In case of BW decrease of >20% between screening and IMP administration the dose will be adjusted by limiting the infused volume of the IMP accordingly to the maximum dose allowed
• In case of a serious intolerability event it should be evaluated, according to the patient situation and the administered dose, whether the IMP administration should continue, interrupted or discontinued. A rescue therapy correlating to the seriousness of symptoms should be initiated when appropriate.
• Manufacturing could potentially result in an out of specification (OOS) product, however, since this is a patient derived, patient specific, last treatment option material, every effort will be made to make it available for treatment due to ethical reasons:
o If all safety release criteria are met (free of microbial contamination etc.), but not all parameters regarding identity, potency or purity (i.e. transduction rate), then the IMP can be administered after a decision by the investigator that is supported by the sponsor, although a certification by the qualified person (QP) might be missing.
o If the dose of the IMP per kg body weight could not be reached during manufacturing, the IMP can be administered, after a decision of the investigator that is supported by the sponsor, even without certification by the QP, if a minimal dose of at least 0.3x10^6 ±20% cells/kg BW can be achieved.

Study burden and risks

The infusion of HA-1H TCR transduced T cells can suppress and cure blood or bone marrow disease, but there is no certainty. Disadvantages of taking part in the study can include the possible side effects and detrimental effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

1. Relapsed or persistent disease is defined according to disease specific guidelines (AML, CML, MM, ALL, MDS, MPN, MF and malignant B- or T-cell lymphoma) and includes MRD positivity.
2. Patients positive for HLA-A*02:01 according to genotyping results
3. Patients positive for HA-1H
4. Patients who received the allo-HSCT at least 100 days preceding the leukapheresis
5. Patients (i.e. recipient) transplanted with a sibling or unrelated HSCT donor
a. donor being HLA-A*02:01 positive and HA-1H negative, or
b. a donor with a single mismatch at HLA-A*02:01, being HA-1H positive or negative
Patients from whom at least 10x10^6 donor CD8+ T cells can be harvested by leukapheresis
6. Age >= 18 years, of either sex
7. (Eastern Cooperative Oncology Group) ECOG performance status 0-2.
8. Life expectancy of at least 3 months
9. Patients must be able to understand and be willing to give signed informed consent

Exclusion criteria

1. Evidence of acute or chronic graft versus host disease (GVHD) >= grade II
2. Serologic evidence of acute or chronic hepatitis B virus infection (i.e. positive for HBsAg or IgM anti-HBc). Positive HIV and HCV serology or active bacterial infection

3. Medical or psychological conditions that would make the patient unsuitable candidate for cell therapy at the discretion of the investigator. Special risks to be considered:
a. Creatinine > 2.5 times the upper limit of normal (ULN) serum level
b. Total bilirubin, ALAT, ASAT > 3.0 x ULN serum level
c. Cardiac left ventricular ejection fraction < 35% at rest
d. Severe restrictive or obstructive lung disease
4. Clinically significant and ongoing immune suppression including, but not limited to immunosuppressive agents (e.g. cyclosporine or corticosteroids (at an equivalent dose of >= 10 mg prednisone per day)). Inhaled steroid and physiological replacement for adrenal insufficiency is allowed
5. Patients with a history of primary immunodeficiency
6. Patients with a currently active second malignancy other than nonmelanoma skin cancers or subjects with history of prior malignancy and previously treated with a curative intent therapy less than 1 year ago
7. Patients both with urinary outflow obstructions and on dialysis or patients for whom cyclophosphamide is contraindicated for other reasons
8. Known or suspected hypersensitivity or intolerance to IMP, cyclophosphamide, fludarabine and/or tocilizumab or to any of the excipients
9. Participation in any clinical study < 60 days prior to first IMP administration in case of antibodies and < 14 days for all other IMPs
10. Vulnerable patients and/or patients unwilling or unable to comply with procedures required in this clinical study protocol
11. Pregnant or lactating women
12. Women of child-bearing potential not using highly effective method(s) of birth control (i.e., with low failure rate < 1% per year) throughout the study and/or unwilling to be tested for pregnancy. A negative serum β-hCG test is required at baseline
13. Fertile men not agreeing to use effective contraceptive methods during the clinical study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-11-2020
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	10-12-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	01-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002346-20-NL
CCMO	NL72062.000.19