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DESCRIPTION OF THE INTENDED ACTIVITIES (version 2)

This document should not contain confidential information.

1. GENERAL DETAILS

- 1.1. Number of the licence: *IM-MV 17-002*.
- 1.2. This description of the intended activities applies to the calendar year: *2018*.
- 1.3. The date on which the first patient or subject will be treated (only applicable if the description of the intended activities applies to the year of start of the study): *The first subject is expected to be recruited in May with an anticipated treatment in July 2018.*

2. DESCRIPTION OF THE ACTIVITIES

- 2.1. Describe the purpose of the study/studies:

To determine the safety and clinical efficacy of CAR-T cells when administered to patients with relapsed or refractory Multiple Myeloma (MM) with AUTO2, relapsed or refractory diffuse large B cell lymphoma (DLBCL) or acute lymphoblastic leukaemia (ALL) with AUTO3 and relapsed or refractory T cell non-Hodgkin lymphoma with AUTO4. All studies consist of two phases each with their own objectives:

- *The primary objectives of phase I, dose escalation are: 1) To establish the safety and tolerability of the therapeutic agent and 2) To establish the recommended dose for phase II and the maximum tolerated dose (MTD), where an MTD exists.*
- *The primary objective of phase II, dose expansion is to evaluate the clinical activity of the therapeutic agent at the recommended phase II dose established in phase I. The secondary objectives in this phase are to evaluate the feasibility of producing the therapeutic agent, the overall clinical efficacy, and the safety and tolerability.*

- 2.2. Give a short description of the study:

These studies include the evaluation of CAR-T cell products as a therapy for the treatment of MM, DLBCL and ALL. The product in the AUTO2 study have a CAR-T cell with A Proliferation Inducing Ligand (APRIL) expression, which targets two MM cell antigens: BCMA and TACI. AUTO3 has two CARs on a T-cell targeting CD19 and CD22. AUTO4 has a CAR-T cell that targets T cell receptor beta constant region-1 (TRBC1). Patients in both phases of the AUTO2, AUTO3 and AUTO4 studies will successively undergo the following steps: screening, leukapheresis, preconditioning, treatment and follow-up.

- *Phase I (dose escalation): To establish the optimal dose for the Phase II study based on safety, tolerability and clinical activity. The AUTO2 study will evaluate doses from 15×10^6 to 450×10^6 . The AUTO3 study will evaluate doses from 10×10^6 to approximately 375×10^6 CAR-positive T-cells.*

The AUTO2 study will include up to 4 cohorts (up to 6 patients per cohort) and up to approximately 24 patients. The AUTO3 studies may include up to 6 cohorts and up to approximately 30 patients. In 2018, we expect to be able to include up to 10 patients in the AUTO2 study, up to 10 patients in the AUTO3 studies and up to 3 patients in the AUTO4 study.

- *Preparation location: NA, the Sponsor supplies the product ready for use*
- *Location of preparation and administration including thawing: clinic consulting room, room number 3B 68*
- *Product administration location: a patient room in the clinic will be reserved for each administration. This will be one of the following rooms: unit 3B, room numbers 14, 18, 24, 28, 30, 34, 36, 42, 44, 46, 50, 52, 58 and 66.*

- the log can be accessed:

The logs will be stored in the SCT lab, room CCA 4.43.

2.7 Provide the location details, including physical address, where patients will be treated and hospitalised:

Department of Haematology, Clinic 3B, VUMC, De Boelelaan 1117, 1081 HV Amsterdam

2.8 Describe how the special requirements stated in the relevant article in the licence will be met:

Article 3 of the decision includes several special requirements. Information on how these will be met is given below:

- 1) *Tests on production cells and virus batch for the presence of RCR: test by the Sponsor (manufacturer) using a validated cell-culture based test. Batches are released when no RCR is detected.*
- 2) *The elimination of free vector particles in the product has been determined as sufficient (5 times greater than required according to COGEM guidance). These two criteria are tested by the manufacturer. The manufacturer releases the product and provides a QP certificate which is enclosed with the product. This document is stored in the patient's log.*
- 3) *Patients are free from HIV, HTLV, HBV and HCV. These tests are performed at the VUMC using standard methods. The results are recorded in EPIC and are also stored in the patient's log.*
- 4) *Patients are excluded from donation of blood, organs, tissue and cells. This requirement is included in the Informed Consent Form which all patients must sign for participation in the study. The Informed Consent Form is stored as part of the log data.*

2.9 Describe all aspects to be monitored from a human and environmental health perspective:

Given the negligible risks for humans and the environment, monitoring other than the usual monitoring performed as part of the patient's medical care and evaluation of the course of the study is not needed.

3. WASTE MANAGEMENT

3.1. Describe the composition of the expected waste:

All waste materials that may contain the product or (may) have been in contact with the product will be disposed of as specific hospital waste (SZA). This mainly concerns the following attributes: infusion bag containing product, parts of the infusion system (tubes, needles, adhesive materials), protective clothing (coats, hairnets) and gloves. Reusable material, such as instruments that may have been in contact with the product will be cleaned and sterilised by the Central Sterilisation Department according to the hospital's standard operating procedure.

3.2. Give the location where waste will be stored before it is transported or disposed of:

All SZA collected will be stored in closed waste containers in waste station Clinic 3B 96, from where the Logistics Unit will transport it to the central waste depot on the VUMC campus.

3.3. Describe how waste will be processed:

Waste will be collected as specific hospital waste (SZA) in UN-certified waste containers. It will be processed according to the requirements in the VUMC Waste Manual. Waste containers are collected from the waste stations together with other SZA from the VUMC by the Logistics Unit of the Facilities Management Department and taken to the central hazardous waste station on a daily basis where all the waste is placed in transport containers that meet the ADR requirements for substance category 6.2 transport. Full containers are transported to the ZAVIN incineration plant on a weekly basis.

- *Phase II (dose expansion): To further characterise the safety of AUTO2, AUTO3 and AUTO4 to determine the efficacy at the recommended dose established in phase I. We do not expect to be able to start the phase II part of these studies in 2018.*

2.3. Give a description of the batch of GMO(s) to be used, including at least the following:

- A description of the GMO(s): the name, nature of the vector, description of the modifications:

The AUTO2 product consists of autologous enriched T-cells (i.e. harvested from the patient) that are transduced using a retroviral vector (RV22668) to include an APRIL CAR construct consisting of the receptor-binding domain of APRIL (without the proteoglycan-binding domain) linked to the hinge region of IgG1. This part is further connected to the transmembrane domain consisting of endodomains of CD28, OX40 and CD3 zeta.

The construct also codes for RQR8. This is a compact safety-switch protein, consisting of two copies of a rituximab-binding peptide, a flanking fragment of CD34 linked to a CD8 stalk, a transmembrane domain and an anchor.

The AUTO3 product consists of autologous enriched T-cells (i.e. harvested from the patient) that are transduced using a retroviral vector (RV28463) to include 2 CAR constructs targeting CD19 and CD22. These CARs are linked to intracellular endodomains containing OX40 (CD19CAR), 41BB (CD22 CAR) and TCRz (both CARs) via a transmembrane anchor (CD8aSTK for CD19CAR and COMP for CD22 CAR).

The AUTO4 product consists of autologous enriched T-cells (i.e. harvested from the patient) that are transduced using a retroviral vector (RV29328) to include a CAR construct targeting TRBC1 linked to the hinge region of IgG1. This part is further connected to the tyrosinase-related protein-1 (Tyrp-1) transmembrane domain linked to intracellular endodomains containing 41BB and CD3 zeta. The AUTO4 construct also codes for the RQR8 safety-switch protein, as described for AUTO2 above.

- The concentrations of the GMO(s):

Depending on the phase of the study, the AUTO2 product contains 15 to 450 x 10⁶ RQR8-APRIL positive CAR T-cells.

Depending on the phase of the study, the AUTO3 product contains approximately up to 375 x 10⁶ CD19/CD22 CAR positive T-cells.

Depending on the phase of the study, the AUTO4 product contains 25 to approximately 225 x 10⁶ RQR8/aTRBC1-CAR positive T-cells.

- The nature of any organisms or biologically active substances present in addition to the GMO(s):

No other GMO, organisms or biologically active substances are present in addition to the GMO.

- Any environmental safety rejection criteria the batch complies with:

A3.3 of the risk assessment (page 30) describes the biosafety release parameters. In summary, these are:

- *Contamination: Mycoplasma, endotoxin and sterility are measured using validated tests. Acceptance criteria for these assays are 'None detected', < 5 EU/kg patient and*

'No growth' respectively.

As the environmental risks of the product are negligible, further monitoring of batches other than monitoring of these biosafety parameters is not required.

2.4 What is the maximum dose per administration to a patient or subject, and what is the maximum cumulative dose administered to the patient or subject in the study:

In 2018, we expect to reach the maximum dose in cohort 4 in the AUTO2 study. In this cohort 450×10^6 RQR8/APRIL CAR positive T-cells will be administered in total.

In 2018, we expect to reach cohort 2-3 in the phase 1 part of the AUTO3 studies. In these cohorts the maximum dose could be approximately 375×10^6 CD19/CD22 CAR positive T-cells administered in total (and dependent on the patient's body weight).

In 2018, we expect the maximum dose in cohort 2 in the AUTO4 study. In this cohort 75×10^6 RQR8/aTRBC1-CAR positive T-cells will be administered in total.

Patients may be eligible for retreatment upon relapse, should they still meet the treatment criteria but may be an exceptionally rare possibility at the VUmc in 2018.

Describe the route(s) of administration that will be used to administer the GMO to the patient or subject: *Intravenous*

2.5 Number of patients or subjects already included in the study and number of patients or subjects still to be included in the study:

No patients have as yet been included at the VUmc with these products (AUTO2, AUTO3, AUTO4).

Four patients have been treated with AUTO2 as of 22nd March 2018 in the United Kingdom. In 2018 we expect to include and treat up to 10 patients at the VUmc.

Seven patients have been treated with AUTO3 as of 22nd March 2018 in the United Kingdom. In 2018, we expect to include up to 10 patients in the AUTO3 studies at the VUmc.

No patients have as yet been included in the AUTO4 study. We expect to include up to 3 patients in 2018 at the VUmc, subject to clinical trial submission/approval being received in 2018.

2.6 Provide the location details, including physical addresses and numbers of the rooms where:

- the batch will be stored:

*Physical address: VU Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam
Product storage room number: building CCA, room 4.47*

- the biological material, other than waste, from this study will be stored:

Some biological samples from patients, like serum cytokines, will be stored at -80 degrees Celsius awaiting shipment to the sponsor. No biological material will be stored at VUmc permanently.

- the batch will be prepared and where procedures will be performed using biological material (from patients or subjects) for this study: