A Phase 1 and 2a open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity of LAVA-051 in patients with relapsed or refractory chronic lymphocytic leukemia, multiple myeloma or acute myeloid leukemia

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Primary Objective:Part 1 Dose Escalation• To investigate the safety and tolerability of LAVA-051 in patients with relapsed/refractory CLL, MM, or AML. • To determine the RP2D of LAVA-051 in patients with relapsed/refractory CLL, MM or AML.Part 2…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON51940

Source
ToetsingOnline

Brief title
LAVA-051

Condition

- Leukaemias
- Leukaemias

Synonym
leukemia, myeloma

Research involving
Human

Sponsors and support

Primary sponsor: LAVA Therapeutics BV
Source(s) of monetary or material Support: LAVA Therapeutics BV

Intervention

Keyword: CD1d, chronic lymphocytic/acute myeloid leukemia, multiple myeloma, Phase I/IIa

Outcome measures

Primary outcome

Part 1 Dose Escalation

• Frequency and severity of AEs using the CTCAE version 5.0 and ASTCT grading

for CRS.

• Frequency and type of DLT.

Part 2 Dose Expansion

• Frequency and severity applying CTCAE and ASTCT grading of AEs at the

respective RP2D.

Secondary outcome

Part 1 Dose Escalation and Part 2 Dose Expansion

• Antitumor Response :

o For CLL patients: Response according to the most recent International

Workshop on Chronic Lymphocytic Leukemia (iwCLL) guideline.

o For MM patients: Response according to the most recent International Myeloma

Working Group (IMWG) criteria.

o For AML patients: Response according to the most recent European LeukemiaNet

(ELN) criteria.

• Pharmacokinetic parameters.

• Presence or development of anti-LAVA-051 antibodies.

Study description

Background summary

LAVA-051 is a Vγ9Vδ2-T cell engaging bispecific antibody of approximately 28 kDa that engages Vγ9Vδ2-T cells in the killing of tumor cells in a tumor target-dependent manner. Vγ9Vδ2-T cells are a population of T cells that have a critical role in immune surveillance with an ability to detect and target tumor cells. The Vγ9Vδ2-T cell receptors (TCRs) on these cells sense conformational changes in butyrophilin (BTN) 3A1/2A1 that are induced by phospho-antigens, which are generally expressed at higher levels in tumor cells. Presence of Vγ9Vδ2-T cells in blood and solid tumors strongly correlates with patient survival supporting their importance. Approaches that improve targeting and activation of Vγ9Vδ2-T cells to tumors are thought to have outstanding potential for the development of novel, efficacious and safe treatments for cancer.
LAVA-051 consists of two VHH (single variable domain of the heavy chain of heavy-chain only antibodies) domain antibodies linked via a 5 amino acid glycine-serine linker. One arm recognizes the Vδ2 chain of the γδ-TCR and thereby targets Vγ9Vδ2-T cells, the other arm is specific for the tumor antigen cluster of differentiation (CD)1d; thus LAVA-051 cross-links Vγ9Vδ2-T cells to tumor cells resulting in the activation of the Vγ9Vδ2-T cells. This will lead to degranulation of the Vγ9Vδ2-T cells, the secretion of cytolytic molecules and the subsequent death of the cancer cells.
In addition, LAVA-051 is able to induce iNKT cell activation via binding to CD1d and stabilization of the interaction between CD1d and the invariant TCR of iNKT cells. Activated iNKT cells can exert direct cytotoxicity against CD1d expressing tumor cells and, in addition, produce various cytokines that promote the activity and cytotoxic potential of other immune cells, including Vγ9Vδ2-T cells, to induce subsequent tumor cell lysis. Further, as it is known that Vγ9Vδ2-T cells can also act as antigen presenting cells, they can prime naive CD4 and CD8 T cell responses upon their activation. This unique feature may contribute to the initiation and propagation of *conventional* T cell responses, resulting in a further enhancement of the antitumor immune response.
In normal physiology, CD1d and its family members are structurally related to major histocompatibility complex (MHC) class I glycoproteins and they are

involved in the presentation of lipid antigens to CD1d-restricted T cells, including iNKT cells. Based on the sponsor*s analyses of patient samples, patient-derived CLL, MM and AML cells revealed that CD1d is expressed at varying mean fluorescence (MF) index levels per indication (CLL MF index 1.0 - 114.4, MM 0.9 to 159.2, AML 0.7 and 32.7). Vγ9Vδ2-T cell mediated tumor cell lysis was consistently observed in the majority of patient samples displaying a broad range of CD1d MF indices from ~1 to ~94. The unique features of LAVA-051 and the capabilities of the unique effector cells that it targets are believed to have the potential of making a substantial beneficial impact on the treatment of patients with relapsed/refractory CLL, MM or AML. Despite current treatment options, there is still an unmet need for patients diagnosed with these diseases as the vast majority of patients will experience relapse of disease, are refractory to or develop resistance to therapies and will eventually succumb to the consequences of the disease.

Study objective

Primary Objective:
Part 1 Dose Escalation
• To investigate the safety and tolerability of LAVA-051 in patients with relapsed/refractory CLL, MM, or AML.
• To determine the RP2D of LAVA-051 in patients with relapsed/refractory CLL, MM or AML.

Part 2 Dose Expansion
• To confirm the safety and tolerability of LAVA-051 in disease specific dose expansion cohorts.

Secondary Objectives:
Part 1 Dose Escalation and Part 2 Dose Expansion
• To explore the preliminary antitumor activity of LAVA-051.
• To evaluate the pharmacokinetics of LAVA-051.
• To evaluate the immunogenicity of LAVA-051.

Study design

This is an open-label, multi-center, Phase 1 dose escalation and Phase 2a dose expansion trial to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity of LAVA-051 in relapsed or refractory CLL, MM or AML patients.
The trial consists of two parts. The first is a Phase 1 open-label, dose escalation part to determine the safety and recommended dose of LAVA-051 for Phase 2a (RP2D). The second is a Phase 2a open-label dose expansion part, in which the number of patients will be expanded in disease specific cohorts (CLL, MM or AML) to confirm safety and assess preliminary antitumor activity (per disease cohort) of the respective recommended dose and regiment established in

the first part of the trial. In the dose expansion part, more than one dose and regimen may be evaluated in order to appropriately determine a recommended dose and regimen for further evaluation.

Intervention

The patients will receive LAVA-051 via an intravenous infusion for 120 minutes per treatment. They will receive 7 treatments in cycle 1 (Part 1) and 8 treatments for other cycles. Only patients in cohort 5 will receive their second LAVA-051 dose (Cycle 1 Day 8) by SC administration. The first and all other doses in cohort 5 will be administered IV (up to 6 cycles). After cohort 5, there will be separate cohorts of patients that receive LAVA-051 either IV or SC.

Study burden and risks

This is the first time LAVA-051 will be administered to humans and it is not yet known which side effects LAVA-051 will have in humans. The following potential side effects might occur during or after receiving LAVA-051:
• Infusion-related reactions such as flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea and all types of rashes. These infusion-related reactions appear most frequently from 10 mins to 4 hrs. after start of the administration; infusion related reactions are predominantly reported following a first administration.
• Tumor Lysis Syndrome for CLL and AML subjects. Tumor Lysis Syndrome can occur if many cancer cells die fast and release their contents into your blood. This is a very serious complication and can cause injury to your kidneys. It could also cause low blood pressure, muscle twitching, seizures and potentially deadly heart problems. If during screening your doctor has determined that you are at high risk of developing Tumor Lysis Syndrome you will receive preventive treatment during cycle 1.
• Cytokine Release Syndrome which can manifest itself by symptoms such as fever, fast heart rate, shortness of breath, headache, dizziness, nausea, and/or bluish color in skin, fingernails, and lips.
• Toxicity due to CD1d expression on non-tumor issues such as: liver, skin, kidney, intestine, uterus, pancreas, conjunctiva, epididymis, thymus and tonsils; no specific toxicities have been observed in monkeys who received a monkey-compatible CD1d antibody.
• Neurological toxicity has been observed with T cell directed therapies including adoptive T cell therapies, bispecific T cell engaging molecules (e.g. blinatumomab). While the risk of neurotoxicity with LAVA-051 is not known, subjects on study should be monitored for clinical signs and symptoms of neurotoxicity. Recommendations for the management of neurotoxicity are described in Section 8.6.4 of the protocol V6.0.

Blood collection

Taking blood may be painful or cause some bruises.
In total volume, a blood amount of 575 ml will be collected from you during a time period of 24 weeks. This amount does not cause any problems in adults. To compare: a blood donation involves 500 ml of blood being taken each time. If you have low blood count, taking blood samples regularly may contribute to you developing anemia for which you could require a blood transfusion.
When many blood samples are taken on a single day, this will be done by way of a needle used for infusions, called a canula. This is only inserted once instead of multiple times. The risks of inserting the canula are: infections, bleeding and mild discomfort and hematomas at the puncture site.

Bone marrow biopsy/Bone marrow aspiration
Depending on the type of cancer that you have, you will undergo a total of 3-4 bone marrow samplings throughout the study. In addition, extra bone marrow sampling may be performed in case of suspected disease relapse, if the study doctor thinks it is necessary.
Anesthetic to numb the area and reduce the pain will be given. This procedure may nevertheless be very painful. However, the pain only lasts for about 15 to 30 seconds. The bone area may be sore for a day or two. It is possible, but not likely that you could get an infection or have a large amount of bleeding. In very rare cases, people might have an allergic reaction to the anesthetic. The allergic reaction could include rash/hive, flushing of the face, itching, wheezing and tightness in the throat.

ECG
When an ECG is taken, it is possible that your skin reacts to the electrodes (a set of sticky patches) which are placed on your chest. This irritation usually disappears directly after the electrodes have been removed.

CT scan/Skeletal survey (x-rays)
You will be exposed to radiation when undergoing a CT-scan/ Skeletal survey (x-rays). The extra radiation falls within the limits set in your country for this type of extra radiation exposure.
Depending on the type of cancer that you have, you will undergo a MRI scan. An MRI does not emit radiation, but applies a magnetic field. It is therefore not possible to undergo an MRI scan when you have an implanted electronic device (for example a pacemaker, cochlear implant (CI), neurostimulator etc) or implanted metal or magnetic devices (for example tissue expanders, intracranial clips, and stents).
Finally, it is possible to feel claustrophobic (fear of confined or enclosed spaces) in an MRI, as you will have to lie still in a narrow space for approximately 20 minutes.
For some CT/MRI scans it is necessary that you are injected with a contrast agent. There is a small risk of developing an allergic reaction to the contrast agent. This reaction can be mild (itching, rash, nausea) or severe (difficulty breathing or state of shock). Most allergic reactions can be controlled with medication. Please inform the study doctor about possible allergies you have

such as hay fever, iodine allergy and eczema, or allergies for e.g. bees or food.
The contrast agent can also cause dehydration or damage the kidneys, which at worst results in kidney failure. If you are dehydrated or have poor kidney function, the study doctor can decide to take a blood sample to check whether your kidneys are functioning well enough, prior to making a CT scan.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient must be 18 years of age inclusive or above, at the time of signing the informed consent.
2. Patients with documented diagnosis of CLL, MM, or AML who have failed to

respond to or who have relapsed after prior therapy and are not amenable to standard treatments or for whom no standard treatments are available. Patients may have undergone prior cell therapy.
2.1. CLL/ Small Lymphocytic Lymphoma (SLL) patients:
2.1.1. Proven disease by the presence of CD5+CD19+CD23+ clonal B cells in blood, bone marrow and/or lymph nodes.
2.1.2. Patients should meet criteria for requiring therapy (the most recent iwCLL guidelines (39)) and must have measurable disease (measurable lesion > 1.5 cm diameter in at least one dimension) and/or lymphocytosis.
2.1.3. Patients must have received at least 2 prior lines of therapy and must have failed at least one line of targeted therapy (ibrutinib or venetoclax or similar) and not be amenable to- or for whom no further standard treatment is available.
2.2. MM patients:
2.2.1. Documented diagnosis of MM and measurable disease (see Appendix 6, Section 13.6.2; measurable disease is defined as serum monoclonal paraprotein (M-protein) >= 5 g/L or urine M-protein >= 200 mg/24 hours or abnormal free light chain (FLC) ratio with involved FLC > 100 mg/L or proven plasmacytoma by biopsy*).
2.2.2. Documented progression or refractory multiple myeloma as per the IMWG uniform response criteria (see Appendix 6, Section 13.6.3) following >=3 prior regimens that include at least one immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody in any order.
* If plasmacytoma is the only measurable parameter, the patient is not allowed to be included in the trial, because of difficult response evaluation.
2.3. AML patients:
2.3.1. Patients with relapsed/refractory AML (defined using World Health Organization [WHO] 2016 criteria, WHO classification definition of >= 20% blasts) of any type with the exception of acute promyelocytic leukemia (APL; AML M3). [Patients with a myelomonocytic or monocytic lineage (M4, M5) are most likely to be positive for the CD1d expression].
2.3.2. Patients with relapsed/refractory AML (defined as hematologic relaps,molecular relaps, or primary refractory disease as per ELN 2017 quidelines)
3. Males or non-pregnant, non-breastfeeding females who are:
a. Surgically sterile (hysterectomy, bilateral oophorectomy or bilateral salpingectomy, vasectomy).
b. Female of childbearing potential with a negative pregnancy test prior to first dosing and compliant with a highly effective contraceptive regimen (i.e., pregnancy rate of <1% per year: oral contraceptives, intrauterine device (IUD), intrauterine hormone-releasing systems; refer to Appendix 4. Section 13.4 for more details) from signing of the informed consent form (ICF) through 90 days after the last IMP administration. Abstinence is not considered an adequate contraceptive regimen.
c. Female, postmenopausal defined as continuous amenorrhea for at least 12 consecutive months without an alternative medical cause and a serum follicle-stimulating hormone (FSH) measurement of > 40 IU/L).

d. Male, compliant with an effective contraceptive regimen (i.e., use of male condom with female partner and assuring use of an additional highly effective contraceptive method with a failure rate of <1% per year when having sexual intercourse with a woman of childbearing potential who is not currently pregnant following from signing of the ICF through 90 days after the last IMP administration; refer to Appendix 4, Section 13.4 for more details) from signing of the ICF through 90 days after the last IMP administration). Abstinence is not considered an adequate contraceptive regimen.
e. Male, refraining from donating sperm following from signing of the ICF through 90 days after the last IMP administration.
4. Predicted life-expectancy of >= 3 months.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Adequate renal function (estimated glomerular filtration rate [eGFR] per local laboratory > 40 mL/min/1.73m2), hepatic function [(total bilirubin <= 2 times upper limit of normal (ULN), unless in patients with known Gilbert*s syndrome who must have total bilirubin <= 3 times ULN; AST and ALT <= 3.0 times ULN] and hematological function (neutrophils >= 1 x109/L; unless this is considered due to bone marrow tumor infiltration; platelet count >= 75x109/L, unless due to bone marrow tumor infiltration, in which case it must be >= 50x109/L).
7. Capable of giving signed and dated informed consent prior to initiation of any trial-related procedure that is not considered Standard of Care which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.

Exclusion criteria

1. Prior allogeneic bone marrow transplant if the patient still has active acute or chronic graft versus host disease requiring >10 mg prednisone or equivalent corticosteroids.
2. Concomitant malignancies except carcinoma in situ, basal or squamous cell skin carcinoma. Patients who had no evidence of disease from another primary cancer for 2 or more years are allowed to participate in the trial. Localized non-metastatic prostate cancer, not requiring systemic treatment, and for which no local treatment is planned, is allowed.
3. Uncontrolled or severe intercurrent medical condition.
4. Known uncontrolled central nervous system involvement.
5. Patient has any active-, uncontrolled-, or suspected infection.
6. A significant history of renal, neurologic, psychiatric, pulmonary, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect patients' participating in this trial.
7. Unstable cardiovascular function defined as: (a) symptomatic ischemia, or (b) uncontrolled clinically significant conduction abnormalities (i.e., ventricular tachycardia on antiarrhythmic agents are excluded; 1st degree

atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or (c) congestive heart failure New York Heart Association Class >= 3, or (d) myocardial infarction within 3 months or (e) QTc>480 msec using Fredericia's QT formula.
8. Previous treatment with radiotherapy, immunotherapy, investigational product or chemotherapy in the 2 weeks prior to initial IMP administration.
9. Previous treatment with an aminobisphosphonate IV (e.g., ibandronate, pamidronate, zoledronate etc) within 4 weeks prior to initial IMP.
10. Previous treatment of any systemic immunosuppressant within 2 weeks prior to initial IMP administration, with the exception of systemic corticosteroid use up to oral dose of 10 mg prednisolone daily (or equivalent for other steroids).
11. Previous treatment with live or live attenuated vaccines within 2 weeks prior to initial IMP administration. Other (new) types of vaccines need to be evaluated as to their mode of action.
12.Previous autologous haematopoietic stem cell transplantation (HSCT) or treatment with Chimeric Antigen Receptor (CAR) T-cell therapy within 6 months prior to initial IMP administration.
13. Known non-CLL/MM/AML related pre-existing clinically relevant immunodeficiency disorders.
14. Patients with Richter*s transformation are excluded.
15. Positive serological testing for Human Immunodeficiency Virus (HIV) antibody, hepatitis B surface antigen [HBsAg] and hepatitis B core antibody (anti-HBc) negative, and hepatitis C virus antibody. Patients who are positive for anti-HBc or hepatitis C antibody may be included if they have a negative PCR within 6 weeks prior to initial IMP administration. Those who are PCR positive will be excluded.
16. Known allergies, hypersensitivity, or intolerance to the excipients of the IMP.
17. Major surgery within 4 weeks of initial IMP administration or planned surgery during the time the patient is expected to participate in the trial.
18. Known ongoing drug and alcohol abuse in the opinion of the investigator.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-06-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LAVA-051

Ethics review

Approved WMO Date:	15-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2020-004583-26-NL
CCMO	NL75796.029.20