A randomised, placebo controlled, double blind, multicentre proof of concept study to assess the safety and efficacy of two doses of VAD044 in patients with hereditary haemorrhagic telangiectasia (HHT)

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PART I:Primary:• To investigate the safety and tolerability of two doses of VAD044 administered daily for up to 12 weeks in HHT patients.Secondary:• To assess the effects of two doses of VAD044 for up to 12 weeks of treatment on:o Epistaxis:•...

Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53637

Source
ToetsingOnline

Brief title
VAD044C002

Condition

- Cardiac and vascular disorders congenital

Synonym
Rendu Osler Weber (ROW)

Research involving

Human

Sponsors and support

Primary sponsor: Vaderis Therapeutics AG
Source(s) of monetary or material Support: Vaderis Therapeutics AG

Intervention

Keyword: Phase 1b study in HHT patients

Outcome measures

Primary outcome

Primary Endpoint

PART I:

• AEs including SAEs and AEs of special interest (AESIs), physical exams, vital signs, electrocardiograms (ECGs), and safety laboratory parameters.

PART II:

Open-label part (part II)

• AEs including SAEs and AEs of special interest (AESIs), physical exams, vital signs, electrocardiograms (ECGs), and safety laboratory parameters.

Secondary outcome

Secondary Endpoints

PART I:

Key Secondary Endpoints:

• Monthly* total number of epistaxis events (Week 12);

• Monthly* total duration of epistaxis (Week 12);

• Monthly* average of flow intensity (Week 12);

• Monthly* average of the mod-ESS derived from the epistaxis digital app (Week

12);

• Monthly* standard ESS measured at the study visits (Week 12);

Other Secondary Endpoints:

• Haemoglobin value at Week 12;

• Ferritin and transferrin saturation levels at Week 12;

• Total elemental iron received from iron infusion and estimated from blood transfusion (Treatment period compared to the 12 weeks preceding the Treatment period);

• Total blood transfusion requirements (number of packed red blood cell [PRBC] units transfused during the Treatment period compared to the 12 weeks preceding the Treatment period);

• Overall health-related quality of life (QoL) measured using SF-12 standard questionnaire at Week 12;

• Monthly* NOSE HHT score (Week 12);

• VAD044 PK parameters following repeat administration.

• Phosphorylated protein kinase B (pAKT) inhibition levels in blood using PRP assay (subset of patients in selected sites) at Weeks 4, 8, 12 and 20.

*Month refers to 28-day period for above endpoint assessments

Open-label part (part II)

• total number of epistaxis events at Months 1, 3, 6, 9 and 12;

• total duration of epistaxis at Months 1, 3, 6, 9 and 12;

• average of flow intensity at Months 1, 3, 6, 9 and 12;

• mod-ESS derived from the epistaxis digital app at Months 3, 6, 9 and 12;

• standard ESS measured at Months 3, 6, 9 and 12;

• Haemoglobin value at Months 3, 6, 9 and 12;

• Ferritin and transferrin saturation levels at Months 3, 6, 9 and 12;

• Total elemental iron received from iron infusion and estimated from blood transfusion during the 12 months treatment duration period;

• Total blood transfusion requirements during the 12 months treatment duration period;

• Overall health-related quality of life (QoL) measured using SF-12 standard questionnaire at Months 6 and 12;

Study description

Background summary

Hereditary haemorrhagic telangiectasia (HHT) is an inherited genetic disorder that affects the blood vessels.
VAD044 is an allosteric protein kinase B (AKT) inhibitor which is being developed for the treatment of hereditary haemorrhagic telangiectasia (HHT). Although treatment guidelines (Faughnan et al., 2020) provide recommendations for the clinical management of key manifestations of the disease, there are no approved therapies for the treatment of HHT and there is a large unmet medical need for effective treatments.
Rationale for testing VAD044 in HHT: The hypothesis for using VAD044 is that it could lead to restoration of close to normal AKT activation. The normalisation of AKT is expected to lead to the restoration of normal function and phenotype of abnormal vessels.
Epistaxis is the principal manifestation of HHT, affecting >90% of patients and is caused by the rupture of nasal telangiectases. It is hypothesised that, with a systemic treatment targeting vascular defects such as VAD044, an improvement in epistaxis during treatment of HHT would be caused by, and indicative of, improvements in the vascular integrity or architecture of the nasal telangiectases.

Study objective

PART I:
Primary:
• To investigate the safety and tolerability of two doses of VAD044 administered daily for up to 12 weeks in HHT patients.
Secondary:
• To assess the effects of two doses of VAD044 for up to 12 weeks of treatment on:
o Epistaxis:
• Epistaxis frequency, duration, and flow intensity;
• Epistaxis severity score (ESS) including standard ESS and modified ESS (mod-ESS);
o Blood loss related parameters:
• Haemoglobin, ferritin, and transferrin saturation levels;
• Iron supplementation needs;
• Blood transfusion requirements;
o Patient reported outcomes (PROs) using Nasal Outcome Score for Epistaxis in HHT (NOSE HHT), 12-item short form survey (SF 12) standard questionnaires;
• To characterise the pharmacokinetic (PK) profile of VAD044 40 mg and 30 mg doses;
• To characterise the pharmacodynamic (PD) effects of VAD044 in blood (in subset of patients in selected sites);
• To determine the recommended Phase 2 dose (RP2D).

PART II:
Primary:
• To investigate the long-term safety and tolerability of VAD044 administered daily for up to 12 months in HHT patients.
Secondary:
• To assess the effects of VAD044 for up to 12 months of treatment on:
o Epistaxis:
* Epistaxis frequency, duration, and flow intensity.
* Epistaxis severity score (ESS) including standard ESS and modified ESS (mod-ESS);
o Blood loss related parameters:
* Haemoglobin, ferritin, and transferrin saturation levels.
* Iron supplementation needs.
* Blood transfusion requirements.
o Patient reported outcomes (PROs) using 12-item short form survey (SF-12) standard questionnaires.

Study design

PART I:
This Phase 1b proof of concept study is a randomised, placebo controlled, double blind, multicentre study and will investigate 2 doses of VAD044 in adult HHT patients.
The patients will be randomised into VAD044 30 mg or 40 mg or placebo group in

the ratio 1:1:1, according to a centralised randomisation process. The patient will be stratified according to anaemia severity before randomisation.
• The study will include Screening period, Observation period, Treatment period, and Follow-up period.
Screening period: The Screening period (approximately 8 weeks before first dose), starts once the patient has provided written informed consent and ends on the day when the patient enters the Observation period.
Observation period: The patients who fulfil the inclusion/exclusion criteria will enter the Observation period. The Observation period will last about 8 weeks and ends one day before first dose. The patients will have a telephone visit during Week 4 of the Observation period and a Baseline visit between Week 6 and Week 8 of the Observation period at hospital/site. The Observation period can be extended beyond 8 weeks but not more than 12 weeks.
The patients who meet the Epistaxis severity criteria (defined as a confirmed 4-week cumulative frequency of >=20 episodes of epistaxis and with a cumulative duration of 80 mins [i.e., approximately 20 mins per week]) will undergo the baseline assessments. The patient must be also compliant with epistaxis data entry during the 4-week period and should not have missed entry for more than 7 days; if the patient missed entry for 5 to 7 days during the 4-week period, his/her eligibility should be confirmed with the Sponsor and the Medical monitor.
Randomisation: Randomisation will occur after the end of Observation period before the start of study treatment. The patient can only be randomised if they reconfirmed the study eligibility criteria (inclusion/exclusion criteria) at Baseline visit.
Treatment period: The patients will receive the allocated treatment for up to 12 weeks. A patient diary will need to be provided to record the drug compliance.
The patients will have hospital/site visits on Weeks 2, 4, 8 and 12 (End of Treatment [EoT] visit) and telephone visits at Weeks 6 and 10. In case of non-adherence to study requirements or adverse events (AEs) reported by the patients during a call, an unscheduled visit could be planned on a case-by-case basis.
Follow-up period: All patients will be followed for up to 8 weeks after the last dose until End of Study (EoS) visit. The follow-up visits will be scheduled at a 4-week interval.
PART II:
Study design
Patients who have completed study Part I can participate in the open-label extension study (Part II). The patients can roll over immediately after last visit of the Part I or at any time at their convenience and according to their availability, but within a timeframe no longer than 8 months after the last visit (visit 12) of the part I. If there is a treatment gap, the patients are expected to be treated for HHT according to standard of care.

Intervention

Doses to be studied:
PART I:
• Group 1: 40 mg (higher dose) of VAD044
• Group 2: 30 mg (lower dose) of VAD044
• Group 3: Placebo
Dosage form and route: Oral gelatin capsules

PART II:
Dose to be studied:
• 30 mg of VAD044 once daily for the first 4 weeks afterwards the daily dose can be increased to 40 mg daily according to the judgement of the investigator. For patients who had a dose reduction in the double blind part of the study, the starting dose will be 20 mg, which can be increased to 30 mg daily after 4 weeks and subsequently to 40 mg daily (after a minimum of 4 weeks at 30 mg) based on judgement of the investigator.

Study burden and risks

Based on a study which took place with healthy volunteers that had taken VAD044 and safety information from other types of human drugs working in a similar manner, the following risks have been identified with VAD044:
• Skin rashes have been observed in 28% of subjects having received VAD044. This side effect has not been severe in any of the subjects but can be annoying. This is a well-known effect from drugs with similar properties, and this usually disappear in approximately 10 days,
• There is a risk of seeing blood sugar levels increase. Blood sugar levels have not increased above the normal levels in the subjects who have taken VAD044 at the doses tested in the current study, but this may happen, and this is why blood sugar levels will be checked regularly. If blood sugar level increases above normal values, then the dose will be adapted, and lower dose of study treatment will be given.
• VAD044 has also the potential to increase the QT interval in ECG, which may lead to cardiac arrhythmia (an irregular heartbeat). The effect has not been seen at the doses that are investigated in the current study, but higher doses can produce a slight QT prolongation. The patient will be regularly monitored by regular electrocardiograms to verify any abnormality.
In addition, animal studies showed that VAD044 may have an effect on the proliferation (multiplication) of some immune cells, this was observed only at the highest doses tested in animals. Also, it is possible that the concentration of antibodies that the patient produces after a vaccination, or an infection may be slightly lower than usual. Changes in the number of white cells (immune cells) was not observed in the study in human, but the patient will be closely monitored for white cell counts, and the patient will be asked not to receive live vaccines (i.e., vaccines that uses an attenuated form of the germ that causes a disease. Examples of such vaccines are measles, mumps, rubella vaccines. The patient will be also asked to be vaccinated for COVID-19 prior to entering the study.

Other drugs that work in a similar way can induce some digestive manifestations such as diarrhoea, but this has not been observed with VAD044.
There may be other risks or side effects that are related to the study drugs and that are unknown at this time

Risks associated with study procedures:
Blood sampling, ECG, liver echo doppler and TTCE risks are not specific to the study. Risks or discomforts associated to these procedures can happen when routinely performed for any other medical reason or for HHT.
• Blood sampling: The risks that come with taking blood samples include mild pain where the needle enters the skin and afterwards maybe bruises. In rare cases it may cause blood clot or the injection place may become infected. The total blood volume to be taken through the study is approximated at 345 ml.
• Electrocardiogram (ECG): although the ECG test itself is painless, being connected to the ECG machine involves preparation of the skin on the chest in order to place the sensors. The sensors are sticky patches that are attached to the chest. Skin irritations are rare but could occur from the electrodes or gel that is used. The skin irritation usually disappears when the patches are removed.
• TTCE (Trans Thoracic Contrast Echocardiography): It is a common procedure in patients with HHT that is used to detect potential abnormal vessel connections in the lung vasculature (also called right to left shunt). This requires the infusion of saline. The investigation is done by an experienced doctor and will look at the heart cavities.
• Liver echo doppler: It is an imaging technique that measures the blood flow into the vessels of the liver. This is done by an experienced doctor and is painless.
• Photographs: No risk is associated with the photographs to be taken of external visible telangiectasia, these will be processed at a safe distance from lesions and in a way that the patient cannot be identified, patient's privacy will be fully respected.

Skin biopsy and nasal endoscopy are optional, the patient can accept or refuse:
• Biopsy: A skin biopsy will be taken from the body (not on face). The biopsy is the removal of a small piece of body or skin tissue. The patient will be given a local anaesthetic to numb the area before the biopsy is taken. The risks and potential complications are small and can include pain or bruising where the skin was biopsied, bleeding, infection, and reaction to local anaesthetic.
• Nasal endoscopy: It consists of introducing an endoscope which is a thin flexible tube with a tiny camera and light into nose to look and take images of nasal telangiectasia. Endoscopy will be performed by ENT of the hospital who is well experienced in performing such procedure. The procedure is generally safe, however as the patient is suffering from nasal telangiectasia, a dilatation of inside nasal vessels, the endoscopy may inadvertently cause nose bleeding at endoscope passage in the nostril.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

PART I
1. Patients aged >=18 years.
2. Able to understand and comply with the requirements for the study, including the epistaxis app completion using a smartphone.
3. Patients with definite diagnosis of HHT by the Curaçao criteria defined as having at least 3 of the following criteria:
a. Spontaneous and recurrent epistaxis;
b. Multiple telangiectases at characteristic sites: lips, oral cavity, fingers, nose;
c. Visceral lesions: GI telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs;
d. A first degree relative with HHT according to these criteria.

4. Patients with typically several (>=5) epistaxis per week with some episodes of epistaxis reported to exceed 5 mins duration supported by clinical judgement, and an ESS >4 during the month prior to Screening.
5. Patients with anaemia (haemoglobin levels <11 g/L in men and <10 g/L in women) or parenteral infusion of at least 250 mg of iron in the preceding 6 months.
6. Glycosylated haemoglobin (HbA1c) <=6.0% in patients without established diagnosis of diabetes.
7. Fasting plasma glucose (FPG) or non-fasting plasma glucose <=5.6 mmol/L in patients without established diagnosis of diabetes mellitus. Note: a single value measured between signing informed consent and entering the treatment period satisfies this criterion (this criterion therefore does not need to be met to enter the observation period)..
8. Patients with COVID-19 vaccination(s) (with or without booster) or positive COVID-19 antibody test (spike or nucleocapsid antibody). The last vaccine/booster shot should have been performed at least 14 days before the first dose of the IMP.
9. A female patient is eligible to participate if she is neither pregnant nor nursing, and of non-childbearing potential or agrees to use highly effective methods of birth control throughout the Treatment period until 30 days after last IMP administration (for details on contraception refer to Appendix 6). Women are considered post-menopausal and of non-childbearing potential if they meet any of the following: (1) are above age 60; (2) have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) and with follicle stimulating hormone (FSH) >40UI/L (as measured once during or before screening);, or (3) have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before screening. In the case of bilateral oophorectomy alone, female patient is considered of non-childbearing potential only when the reproductive status of the patient has been confirmed by FSH hormone level assessment.
10. Male patients must agree to use two (2) reliable and acceptable methods of contraception with their female partner and refrain from donating sperm throughout the Treatment period until 30 days after last IMP administration (for details on contraception refer to Appendix 6).
11. The patient has given written informed consent, prior to any study-related procedures that are not part of normal medical care.
PART II
(as in part 1 except for the HHT severity criteria and COVID rules):
1. Completion of Part I of the study, through the End of Study Visit (Visit 12), within the previous 8 months.
2. All adverse events or serious adverse events occurring during Part I of the study have resolved.
3. The patient has given written informed consent, prior to any study related procedures that are not part of normal medical care.
4. Glycosylated haemoglobin (HbA1c) =6.0% in patients without established diagnosis of diabetes.

5. Fasting plasma glucose (FPG) or non-fasting plasma glucose =5.6 mmol/L in patients without established diagnosis of diabetes mellitus.
(Note: a single value measured <5.6 mmol/L between signing informed consent and beginning treatment on Part II of the study satisfies this criterion.)
6. A female patient is eligible to participate if she is neither pregnant nor nursing, and of non-childbearing potential or agrees to use highly effective methods of birth control throughout the Treatment period until 30 days after last IMP administration.
7. Male patients must agree to use two (2) reliable and acceptable methods of contraception with their female partner and refrain from donating sperm throughout the Treatment period until 30 days after last IMP administration.

Exclusion criteria

PART I:
1. Patients with type 1 diabetes or uncontrolled type II diabetes (insulin or non-insulin dependent).
2. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
a. Concomitant clinically relevant cardiac findings, e.g., sustained ventricular tachycardia, and clinically significant second- or third-degree atrioventricular block without a pacemaker;
b. History of familial long QT syndrome or known family history of Torsades de Pointes;
c. Resting QTcF >=450 msec (male) or >=460 msec (female);
d. Concomitant use of agents known to prolong the QT interval.
3. Grade 2 hypertension untreated (systolic blood pressure >=140 mmHg and/or diastolic blood pressure >=90 mmHg). Note that hypertension should be diagnosed according to standard clinical criteria and isolated blood pressure measurements above these values is not exclusionary.
4. Active COVID-19 infection confirmed by either polymerase chain reaction (PCR) or rapid antigen test. COVID-19 testing is not required for eligibility unless, in the opinion of the investigator, the patient is displaying symptoms concerning for acute COVID-19 infection.
Note: The COVID test does not need to be repeated at Screening in case a test was performed in last 72 hours and lab results/data source shared with the site. In case of positive test, a negative test is needed within 2 weeks for the patient to be eligible. If active infection (confirmed by PCR or rapid antigen test) persists after 2 weeks, patients will not be eligible
5. Administration of live attenuated vaccine within 12 weeks of first IMP dose.
6. Administration of other vaccines, excluding COVID-19 and live-attenuated vaccines, within 14 days of first IMP dose.
7. Patients with active uncontrolled infection or known to be serologically positive for human immunodeficiency virus (HIV), hepatitis B (except after vaccination) or hepatitis C infection.

8. Patients with any other severe, progressive, or uncontrolled acute or chronic medical or psychiatric condition or clinical laboratory abnormalities that may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and, in the Investigator*s opinion, would make the patient inappropriate for entry in this study.
9. History of malignancy of any organ system, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases; with the exception of patients with removal of uncomplicated basal cell carcinoma, who may take part in the study.
10. Presence of ANY of the following laboratory abnormalities:
a. Platelets <=100 × 109/L;
b. Absolute neutrophil count <=1.5 × 109/L;
c. Substantive renal disease (estimated Glomerular Filtration Rate [eGFR] <=60 mL/min/1.73m2 calculated using the MDRD Glomerular Filtration Rate [GFR] equation);
d. Abnormal liver function tests such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria: ALT, AST, alkaline phosphatase, or serum bilirubin must NOT exceed 1.5 times upper limit of normal (ULN).
11. Any surgical or medical condition which might significantly alter the absorption of the study drug (e.g., major GI tract surgery such as gastrectomy, gastroenterostomy, bowel resection, or short bowel syndrome).
12. Recent procedures on nasal telangiectases (<6 weeks).
13. Patients who require therapeutic anticoagulation.
14. Use of drugs with anti-angiogenic properties, notably, but not limited to bevacizumab, pazopanib, tamoxifen, thalidomide, lenalidomide, pomalidomide, raloxifene, bazedoxifene in the past 8 weeks and doxycycline in the past 4 weeks.
15. Patients receiving oral tranexamic acid or epsilon-aminocaproic acid unless they are on a stable dose for at least last 1 month, which will also need to be continued during the entire duration of the study. Use of additional doses given acutely in the setting of an emergent bleed are allowed.
16. Patients currently being treated with drugs known to be P-gp inhibitors, and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment.
17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) urine test.
18. Patients who participate in another clinical trial at the time of screening or within 4 weeks prior to Screening or within 5 half-lives of IMP administered in the previous trial (whichever is longer) prior to the expected date of the first dosing.
PART II
Please refer to the study protocol v4.0 for all the details on new exclusion criteria for part II

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-01-2022
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VAD044
Generic name:	VAD044

Ethics review

Approved WMO Date:	28-04-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-07-2022
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-06-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-07-2023
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2022-000160-22-NL
CCMO	NL80807.058.22