A Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of LAM-001 in Patients with Lymphangioleiomyomatosis

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Primary:* To assess the safety and tolerability of LAM-001 administered daily by dry powder inhaler (DPI) for 14 days in patients with lymphangioleiomyomatosis (LAM) (Period 1).* To assess the longer-term safety and tolerability of LAM-001…

Ethical review	Approved WMO
Status	Completed
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON48177

Source
ToetsingOnline

Brief title
LAM-001-LAM-CLN03

Condition

- Bronchial disorders (excl neoplasms)

Synonym
LAM (layman□s term) and Lymphangioleiomatosis

Research involving
Human

Sponsors and support

Primary sponsor: AI Therapeutics

Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: LAM-001, Lymphangioleiomyomatosis, Phase 1

Outcome measures

Primary outcome

Pharmacokinetic Endpoints

The following are the primary rapamycin PK endpoints:

* Cmax: Period 1, Days 1 and 14; Period 2, Day 84

* AUC0-24: Period 1, Days 1 and 14; Period 2, Day 84

* AUC0-t: Period 1, Days 1 and 14; Period 2, Day 84

Secondary outcome

Exploratory Biomarker Endpoints

The endpoints for VEGF-D and other biomarkers are absolute concentration,

changes over time, and variability.

Efficacy Endpoints

Not applicable.

Safety Endpoints

* AE monitoring and recording

* Clinical laboratory results (hematology, serum chemistry, and urinalysis)

* PFTs

* 6MWT

* Vital sign measurements (systolic and diastolic blood pressures, heart rate,

respiratory rate, and body temperature)

* Resting pulse oximetry

* 12-lead ECG results

* Physical examination findings

Study description

Background summary

There is a compelling rationale to determine if direct administration of inhaled rapamycin (LAM-001) into the lungs can deliver a dose that suppresses inappropriate mTOR signaling over long periods to slow or halt decline in lung function and cystic lung destruction without the systemic toxicities that occur with oral rapamycin administration.
The rationale for LAM-001 development is the hypothesis that direct dosing of rapamycin to the lungs will allow similar or improved efficacy at lower systemic availability and a corresponding lower systemic toxicity in comparison to oral administration, as treatment of LAM requires chronic therapy.
See also protocol background and rationale.

Study objective

Primary:
* To assess the safety and tolerability of LAM-001 administered daily by dry powder inhaler (DPI) for 14 days in patients with lymphangioleiomyomatosis (LAM) (Period 1).
* To assess the longer-term safety and tolerability of LAM-001 administered daily by DPI for up to 12 weeks in patients with LAM (Period 2).

Secondary:
* To assess the systemic exposure of LAM-001 administered daily by DPI for 14 days in patients with LAM (Period 1).
* To assess the systemic exposure of LAM-001 administered daily by DPI for up to 12 weeks in patients with LAM (Period 2).

Exploratory:
* To explore the feasibility and variability of assessing vascular endothelial growth factor-

Study design

This is a Phase 1b multicenter, open-label, repeat-dose study to be conducted in patients with LAM.
The SRC will oversee this study.

Period 1: An initial cohort of 6 patients is planned. A sentinel patient will be enrolled at a dose of 100 *g LAM-001 and be assessed before opening dosing to additional patients. Only after the SRC has reviewed the safety and PK data through Day 14 for the sentinel patient will approval be given to allow dosing of the remaining 5 patients in the cohort. The assessments for the sentinel patient will be the same as those for the other patients.
Including the screening period (up to 4 weeks), dosing (2 weeks), and follow up for PK blood collection (4 weeks after the final dose), the study duration for an individual patient in Period 1 will be up to 10 weeks.

Period 2: After an individual patient completes Period 1, provided continued dosing is approved by the SRC and drug supply is adequate, they have the option to continue into Period 2, and receive up to 12 weeks of additional daily dosing. An additional cohort of up to 6 patients may be enrolled directly into Period 2 of the study. Including the screening period, if applicable (4 weeks), treatment (up to 12 weeks), and follow up for PK blood collection (4 weeks after the final dose), the study duration for an individual patient in Period 2 will be up to 20 weeks

Intervention

Capsules of LAM-001 will contain 100 *g (up to a maximum of 200 *g) of rapamycin formulated in hydroxypropyl methyl cellulose dry-powder capsules, using lactose as the excipient.

Study burden and risks

The subject will need to complete following procedures:

Health and Medical questions (4 times in period 1, 6 times in period 2)
Completion of diary each day.

See overview in protocol.

Side effects related to the study:
The study drug will be given at a different form (inhaler). The most common side effects known are the ones that were occurred in LAM patients taken it orally:
* wounds in the mouth
* diarrhoea
* abdominal pain
* nausea

* common cold
* acne
* chest pain
* swelling of tissues, usually in the lower limbs, due to a build up of fluids
* upper respiratory tract infection
* headache
* dizziness
* muscle pain
* increased cholesterol in the blood
* weight decrease

More serious reported side effects:
* swelling of the pouch around the heart and abnormal heart rhythm
* high heart rate and accumulation of fluids due to kidney damage

Common side effects in transplant patients:
* infections: pneumonia (lung infection), fungal infection, viral infection, bacterial infection, herpes simplex infection, urinary tract infection
* blood disorders: low platelets (tiny round blood cells that help your body form clots to stop bleeding) in the blood and possibly an increased risk of unexpected bleeding or increased bruising, low red blood cells in the blood, low white blood cells in the blood
* metabolic disorders (illnesses): low level of potassium (K+) in the blood serum, low level of phosphate in the blood serum, high lipids (including high cholesterol), high triglycerides, high blood sugar, diabetes mellitus
* headache
* high heart rate
* high blood pressure
* increase of lymphatic fluid within the body
* digestive illnesses: abdominal (stomach or gut) pain, constipation, diarrhoea, nausea
* skin disorders: rash, acne
* joint pain
* reduced or decreased kidney function
* menstrual disorder
* general disorders: swelling of tissues, usually in the lower limbs, due to the build up of fluids, fever, generalised (located in a specific place) pain, slower capability to heal wounds or cuts
* investigations: increased blood creatinine, increased blood lactate dehydrogenase (a general sign of tissue and cellular damage), abnormal liver function test

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

1. The patient is independently capable of providing informed consent and provides signed informed consent, witnessed by clinic staff, before any study-related assessments or procedures are performed.
2. The patient is female and from 18 to 70 years of age, inclusive, with a body mass index from 18.0 to 32.0 kg/m2, inclusive, at the time of screening (Visit 1)
a. Patients cannot be pregnant or lactating/breast feeding and must be surgically sterile, postmenopausal (no menses for the previous 12 months), or practicing a highly effective method of birth control as described in this protocol. Acceptable methods of birth control are: certain types of hormonal contraception (eg, birth control pill, injection, implant, transdermal patch, or vaginal ring. Progestin-based contraception is allowed. Only low dose estrogen-containing contraceptives are allowed [estrogen dose between 10 and 25 *g]), intrauterine device, tubal ligation (tied tubes), or a partner with a

vasectomy. High dose estrogen containing contraceptives are not allowed in this study. Gonadotropin-releasing hormone agonist contraceptives are not allowed in this study.
b. Patients must not be planning to become pregnant during the study and agree to use highly effective contraception for at least 90 days after the last dose of study drug.
3. The patient has a confirmed diagnosis of LAM as determined by prior clinical evaluation, including compatible chest CT AND one of the following:
a. Biopsy (lung, abdominal mass, lymph node, or kidney) or cytology (from thoracic or abdominal sources that show HMB45 positive staining of spindles/epithelioid cells); OR
b. Tuberous sclerosis, angiomyolipoma (diagnosed by prior high resolution chest CT, magnetic resonance imaging, ultrasonography, or biopsy); OR
c. Chylous pleural effusion, as verified by thoracentesis (without other etiology); OR
d. Serum VEGF-D level *800 pg/mL as part of the previous diagnostic evaluation.
4. The patient's pulmonary symptoms and lung function have been stable, as judged by the investigator, over the 3 months before Visit 1.
5. The patient has the ability to perform study procedures, including correct use of the RS01 DPI and the spirometry maneuvers.
6. The patient agrees to comply with all protocol requirements.

Exclusion criteria

1. The patient has a pre-bronchodilator FEV1 of *60% of predicted during the screening or baseline visits.
2. The patient has used mTOR inhibitors (e.g., rapamycin, everolimus) within 90 days before Visit 1.
3. The patient is considered likely to need oral rapamycin or another mTOR inhibitor within 6 months following Visit 1, in the opinion of the investigator.
4. The patient has had a pneumothorax within the 2 months before Visit 1.
5. The patient is a smoker. Patients will be defined as ex smokers and eligible for participation in the study if they have not consumed tobacco products or other forms of nicotine replacement therapy for at least 6 months before Visit 1.
6. The patient has a concurrent significant respiratory disease, including any of the following:
a. Confirmed or suspected smoking-related chronic obstructive pulmonary disease.
b. Other significant respiratory disorder including, but not limited to,

pulmonary hypertension, cor pulmonale, pulmonary fibrosis, or bronchiectasis.
c. Previous lung transplantation or is active on a transplant list.
7. The patient requires regular use of inhaled corticosteroids.
8. The patient has significant or uncontrolled disease of any organ system, including psychological illness, that is likely to interfere with the study conduct, patient safety, or the interpretation of study evaluations, as determined by the investigator, including but not limited to the following:
a. Unstable angina, myocardial infarction, previous history of pericarditis, or cerebrovascular event within the past 12 months before screening or uncontrolled hypertension or arrhythmia.
b. Uncontrolled dyslipidemia.
c. Poorly controlled diabetes mellitus, as evidenced by hemoglobin A1c >8.5%.
d. Known history of human immunodeficiency virus or chronic viral hepatitis infection
e. Diagnosed with active or untreated latent tuberculous infection or active pulmonary nontuberculous mycobacterial infection. A tuberculosis screening test is not required. Patients who completed a course of antituberculous therapy at least 1 year before screening with no clinical or radiological evidence of disease recurrence may be eligible for screening.
f. History of malignancy or treatment for malignancy in the 2 years before screening. Patients who have received curative treatment with resection of nonmelanoma skin cancer or with in situ carcinoma of the cervix may be eligible.
9. The patient has a known allergy to rapamycin or has previously discontinued rapamycin due to pulmonary or other safety concerns.
10. The patient has a history of severe milk protein allergy (patients with lactose intolerance are eligible).
11. The patient requires supplemental oxygen therapy as either longterm oxygen therapy or as required ambulatory oxygen.
12. The patient has a significantly abnormal laboratory result at Visit 1, including any of the following:
a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × upper limit of normal (ULN)
b. Hemoglobin <100 kg/m3
c. Platelets <120,000/mm3
d. Absolute neutrophil count <1,500/mm3
e. Total white blood cell count <4,000/mm3
f. Serum creatinine >1.5 mg/dL
13. The patient has significantly abnormal ECG results at Visit 1. The investigator will use clinical judgment when assessing the significance of ECG abnormalities. The investigator is encouraged to discuss the enrollment of these patients with the study medical monitor in cases of uncertainty.
14. The patient has an intercurrent infection that has not adequately

resolved within 2 weeks prior to Visit 1. Patients experiencing an infection during the screening period should be treated appropriately and may be rescreened after the infection has resolved.
15. The patient has had recent surgery that involved entry into a body cavity or required 3 or more sutures within 4 weeks prior to Visit 1.
16. The patient is unable or unwilling to attend the scheduled clinic visits or agree to home healthcare follow-up.
17. The patient has participated in another investigational study involving any investigational product (i.e., study drug, biologic, device) within 30 days or 6 half-lives, whichever is longer, before the planned date of the first dose of study drug.
18. The patient has used any medications not allowed in the study, as they may impact the PK of LAM-001 or other medications.
19. The patient has used estrogen-containing medications within 30 days of Visit 1. Exception: continuation of low- dose estrogen-containing contraceptives (estrogen dose between 10 and 25 *g) is allowed if the patient has been taking them for a minimum of 30 days before Visit 1.
20. The patient is an employee or first-degree relative of sponsor, PPD, or study site personnel or is considered vulnerable by local regulations (e.g., is imprisoned or institutionalized).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-12-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	LAM-001 (Sirolimus)
Generic name:	LAM-001 (Sirolimus)

Ethics review

Approved WMO Date:	15-10-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-11-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2017-005071-33-NL
CCMO	NL67634.041.18

Study results

Date completed: 21-02-2019

Results posted: 08-08-2019

First publication
09-07-2019