A Prospective Phase III Multi-center, 2-Year Placebo Controlled, Double Blind Study to Evaluate the Efficacy and Safety of *Kamada-AAT for Inhalation* 80 mg per day in Adult Patients with Congenital Alpha-1 Antitrypsin Deficiency with Moderate and Severe Airflow Limitation (40% <= FEV1 <= 80% of predicted; FEV1/SVC <= 70%), Followed by a 2-Year Open-Label Extension

Published: 15-05-2019
Last updated: 19-08-2024

Primary Objective (Double Blind)To assess the efficacy of Kamada-AAT for Inhalation administered at a dose of 80 mg daily versus (vs) placebo, with efficacy measured by FEV1 post bronchodilator change from baseline at 104 weeks. OLE Objectives1. To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital respiratory tract disorders
Study type	Interventional

Summary

ID

NL-OMON55372

Source
ToetsingOnline

Brief title
Kamada-AAT (Inhaled)- 008

Condition

- Congenital respiratory tract disorders

Synonym
AATD, congenital lung disease

Research involving
Human

Sponsors and support

Primary sponsor: Kamada Ltd.
Source(s) of monetary or material Support: Kamada Ltd.

Intervention

Keyword: Congenital Alpha-1 Antitrypsin Deficiency, Kamada-AAT, Phase 3

Outcome measures

Primary outcome

DB period

FEV1 (L) post bronchodilator change from baseline at 104 weeks.

OLE period

1. FEV1 (L) post bronchodilator change from DB baseline at OLE 104

weeks (total 208 weeks), and from OLE baseline at OLE 104 weeks (total 104

weeks of open label treatment), stratified by treatment during the DB part.

2. Change from DB at OLE 104 weeks (total 208 weeks of treatment),

and from OLE baseline at OLE 104 weeks (total 104 weeks), in CT

densitometry whole-lung 15th percentile lung density (PD15) at total

lung capacity (TLC), stratified by treatment during the DB part.

3. Change from OLE baseline over 104 weeks of open-label treatment in Post

bronchodilator FEV1 % of predicted, FEV1/FVC %, as well as in postbronchodilator volumes (body plethysmography) and diffusion (DLCO), stratified by treatment during the DB part.

4. BODE index score and 6MWT and MMRC dyspnea score from OLE baseline over 104 weeks of open-label treatment stratified by treatment during the DB part.

5. Quality of life score as measured by the COPD assessment tool (CAT) and EQ-5D-5L from OLE baseline over 104 weeks of open-label treatment, stratified by treatment during the DB part.

6. Desmosine level in plasma from OLE baseline over 104 weeks of open label treatment, stratified by treatment during the DB part.

Secondary outcome

DB period

1. Change from baseline over 104 weeks of treatment in CT densitometry whole-lung 15th percentile lung density (PD15) at total lung capacity (TLC).

2. Change from baseline over 104 weeks of treatment in Post bronchodilator spirometry measures

a. FEV1 % of predicted

b. FEV1/FVC%

3. Exacerbations; annual rate by severity, and duration.

4. Change from baseline over 104 weeks of treatment in 6-minute walk test (6MWT).

Study description

Background summary

AATD is a hereditary (genetic) condition which affects the body ability to produce the protein alpha1-antitrypsin (AAT). In healthy individuals, AAT is produced naturally by the body (mainly by the liver cells) and is carried to the lungs in the blood. In Alpha-1 deficient patients, the level of AAT in blood is low or the protein is not active. In some but not all people with AATD, this deficiency leads to Chronic Obstructive Pulmonary Disease (COPD), a worsening lung condition.
At the moment there is no treatment for AATD yet. Currently only medicines are given to reduce the symptoms. In this study, the study drug, Kamada-AAT for inhalation will be tested to examine if this could be used in the future to treat this condition.
The study drug, Kamada-AAT for inhalation or placebo will be inhaled once daily. Until January 2020, more than 230 patients have received Kamada-AAT for inhalation in the course of a clinical study.

Study objective

Primary Objective (Double Blind)
To assess the efficacy of Kamada-AAT for Inhalation administered at a dose of 80 mg daily versus (vs) placebo, with efficacy measured by FEV1 post bronchodilator change from baseline at 104 weeks.

OLE Objectives
1. To assess the long-term safety of Kamada-AAT for Inhalation for up to 208 weeks of treatment.
2. To assess the long-term efficacy of Kamada-AAT for Inhalation, as measured by FEV1 post bronchodilator for up to 208 weeks of treatment.
3. To assess the long-term efficacy of Kamada-AAT for Inhalation, as measured by CT densitometry change for up to 208 weeks of treatment.

Secondary Objective
To assess the efficacy of Kamada-AAT for Inhalation administered at a dose of 80 mg daily vs placebo, as measured by computed tomography (CT) densitometry change from baseline at 104 weeks.
Safety Objectives
1. To assess the safety of Kamada-AAT for Inhalation administered at a dose of 80 mg daily vs placebo.
2. To assess immunogenicity of Kamada-AAT for Inhalation and characterize the effect of anti-drug antibodies (ADA) on drug levels in plasma.

First (Safety) Cohort Objective
To assess the safety of Kamada-AAT for Inhalation administered at a dose of 80

mg vs placebo once daily during the first 24 weeks of treatment.

Study design

This is a prospective Phase III multi-center, 2-Year placebo-controlled, double-blind (DB) study to evaluate the efficacy and safety of *Kamada-AAT for Inhalation* 80 mg per day during two years in adult patients with congenital AAT Deficiency with moderate airflow limitation (40% <= FEV1 <= 80% and FEV1/SVC <= 70%), Followed by a 2-Year Open-Label Extension and with no history of two or more moderate or one or more severe exacerbations of COPD during the past year.

Patients will be enrolled into the study in two consecutive cohorts, namely the first (safety) cohort and the second cohort.

First (Safety) Cohort: Approximately sixty (60) patients randomized 1:1 AAT: placebo will constitute the first (safety) cohort.
A DSMB safety assessment will be performed after all first (safety) cohort patients complete 24 weeks. The DSMB will then make a recommendation to the sponsor as to continuation of the study, based on stopping rules. The recommendation will be submitted to the FDA by the sponsor.
An interim analysis for futility will be conducted at the time of the safety assessment and the DSMB may recommend to stop the study for futility. The rules for recommendations will be provided in the DSMB Charter and the Statistical Analysis Plan (SAP).
Second cohort: 160 additional patients (total sample size of 220 for the primary analysis) will be randomized 1:1 to either AAT 80 mg or placebo once daily. All patients will be evaluated for efficacy and safety of AAT vs placebo for 104 weeks. Safety will be folowed up for 4 weeks after last dose. Post bronchodilator spirometry and anti-AAT antibody titers (ADA/nADA) will be followed for 26 weeks from the last dose.

Study periods
All study patients will undergo the following study periods:
Screening - Consenting patients will be evaluated for eligibility and undergo screening procedures Eligible patients will continue to the run-in.
Run-in - Eligible patients will be treated by inhalation with normal saline 5 mL once daily for 4 weeks and document inhalation use and daily symptoms using an eDiary. At the end of the run-in period, patients who meet eligibility criteria for compliance with inhalation use and e-Diary completion during run-in will be randomized.
Treatment - Patients will be randomized 1:1 to AAT vs. placebo. All randomized patients will be treated for 104 weeks by daily inhalation.
Open-Label Extension (OLE) - Patients will be offered to participate in the open-label extension period to receive AAT for inhalation for an additional 104 weeks (2 years).
Follow up - Safety will be followed up for 4 weeks after the last dose. Post bronchodilator spirometry and anti-AAT antibody titers (ADA/nADA) will be

followed for 26 weeks from the last dose. The follow up is not part of the efficacy analysis period.

Intervention

Active Product: Alpha-1 Proteinase Inhibitor (Alpha-1 Antitrypsin) (human A1PI)
Dosage form: Nebulizer solution 2% AAT
Dosage frequency: Once daily preferably in the afternoon/evening
Mode of Administration: Inhalation using the eFlow Nebulizer

Control: Placebo (phosphate buffer solution with Tween)
Dosage form: Nebulizer solution
Dosage frequency: Once daily preferably in the afternoon/evening
Mode of Administration: Inhalation using the eFlow Nebulizer

Study burden and risks

The study is expected to last approximately 134 weeks (about 2 and a half years) and consists of a screening visit, a run-in period of 4 weeks, a treatment period of 104 weeks (2 years) and 26 weeks of follow-up. Patient will need to come to the study site at least 14 times during the study. A visit will take between 4 and 7 hours.
Please refer to appendix C in the patient information to see all tests and procedures that will be done during the study.

During the study, patients may have adverse events, discomforts and risks from the study drug and from the study procedures. All participants in the study will be watched carefully for any side effects; however, there may be risks to being in this study that are unknown and cannot be predicted. The study team may give medicines to help reduce side effects. These side effects may be mild or serious. In some cases, these side effects might be long lasting or permanent and may even be life threatening.

Patients may or may not receive direct medical benefit from participating in this study. the AAT symptoms may return or worsen at any time during this study. If the study is successful, inhalation of AAT may become a new treatment option, which is less invasive than the current IV option.

Contacts

Public
Kamada Ltd.

Holtman St, Science Park 2

Rehovot 7670402
IL
Scientific
Kamada Ltd.

Holtman St, Science Park 2
Rehovot 7670402
IL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Double-Blind Period

1. Diagnosis of severe AAT deficiency, i.e. patients with either Pi(ZZ), Pi(Z/Null), or Pi(Null/Null) genotypes confirmed by genotype blood test documented prior to screening.
2. Serum AAT levels <= 11 µM at screening.
3. Lung disease with clinical evidence of airflow limitation (post bronchodilator FEV1/SVC<=70%) at screening.
4. 40% <= FEV1 <= 80% of predicted post-bronchodilator at screening.
5. Patients who are either naïve or washed out of any AAT treatment for at least 8 weeks prior to randomization.
6. Age between 18 to 65 years inclusive at screening.
7. Able to read and sign informed consent and willing to participate in the study.
8. Males or non-pregnant, non-lactating females whose screening pregnancy test is negative, who are willing to use contraceptive methods for the duration of the study, or who are postmenopausal, or surgically sterilized.
9. Study medication use for at least 20 out of the 28 days of run-in, as recorded in the study nebulization PARI Track data.
10. Demonstrated ability to complete eDiary for at least 20 out of the first 28

days of run-in.

Open-Label Period

1. Patients who completed 104 weeks of DB study treatment and attended the end of treatment visit.
2. Patients who completed the DB period and attended follow-up visits are eligible for the OLE provided that they comply with all other OLE eligibility criteria.
3. Consenting to continue study participation in the OLE phase.
4. Agree to continue using contraceptive methods deemed reliable by the investigator for an additional 2 years, unless post-menopausal or surgically sterilized.

Exclusion criteria

Double-Blind Period

1. Immunoglobulin A (IgA) absolute deficiency defined as serum IgA levels< 0.05 g/L.
2. History of life-threatening transfusion reaction(s), allergy, anaphylactic reaction, or systemic response to human plasma-derived products.
3. Two or more moderate or any severe exacerbation(s) within the year prior to baseline.
4. A moderate exacerbation within 6 weeks prior to baseline.
5. Use of oral or parenteral glucocorticoids in doses above 10 mg of prednisone daily or equivalent generics (substance and dose).
6. Clinically significant inter-current illnesses (except for respiratory or liver disease secondary to AAT deficiency), including cardiac, hepatic, renal, endocrine, neurological, hematological, neoplastic, immunological, skeletal, or other. Patients might be included after consultation with the treating physician and the sponsor if, in the opinion of the Investigator, their condition will not interfere with the safety, compliance or other aspects of this study.
7. Hospitalization for any cause 6 weeks prior to screening.
8. History of lung or liver transplant.
9. On any thoracic or hepatic surgery waiting list.
10. Any lung surgery within the past two years (including bronchoscopic lung volume reduction).
11. Any smoking within the year prior to screening.
12. Evidence of alcohol abuse or history of alcohol abuse, or use of illegal drugs and/or abuse of legally prescribed drugs in the last 5 years prior to screening.
13. Acute or chronic hepatitis (hepatitis A, hepatitis B, hepatitis C), or positive human immunodeficiency virus (HIV) serology.

14. Signs of significant abnormalities in serum hematology, serum chemistry, serum inflammatory / immunogenic markers and urinalysis per investigator judgment, taking into considerations the potential effects of the AAT deficiency.
15. Signs of significant abnormalities in ECG per investigator judgment at screening.
16. Presence of psychiatric/ mental disorder or any other medical disorder that might impair the patient*s ability to give informed consent or to comply with the requirements of the study protocol. If, in the opinion of the Investigator, the condition will not interfere with the compliance or other aspects of this study, the patient might be included after consultation with the treating physician and the sponsor.
17. Participation in another clinical trial involving investigational medication or interventional treatment within 30 days and/or last dose 5 half-lives prior to screening visit.
18. Inability to attend scheduled clinic visits and/or comply with study protocol.
19. Any other factor that, in the opinion of the investigator, would prevent the patient from complying with the requirements of the protocol.

Open-Label Period

1. Any adverse event(s) in the DB period and/or medical condition that, in the opinion of the investigator, might prevent the patient from safely participating in the OLE period of the study, including but not limited to:
a. Occurrence of a life-threatening allergy, anaphylactic reaction, or systemic response to human plasma derived products.
b. Received lung transplant, entered a waiting list for lung transplantation, or underwent lung surgery. The investigator should consult the sponsor before inclusion of any patient with a significant condition if the investigator believes that it will not pose an unacceptable risk for the patient.
2. Evidence of alcohol abuse or history of alcohol abuse or illegal and/or legally prescribed drugs, within the DB study or since the DB study.
3. Any smoking within the DB study or since the DB study.
4. Pregnancy or lactation.
5. Participation in another clinical trial since termination of participation in the DB period.
6. Inability to attend scheduled clinic visits and/or comply with study protocol.
7. Any other factor that, in the opinion of the investigator, would prevent the patient from complying with the requirements of the protocol or would jeopardize the safety of the patient.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-10-2019
Enrollment:	70
Type:	Actual

Medical products/devices used

Generic name:	eFlow® nebuliser system
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Kamada-AAT for inhalation
Generic name:	Kamada-AAT for inhalation

Ethics review

Approved WMO

Date:	15-05-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	30-09-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	03-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	23-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	08-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	02-11-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	17-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	30-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	22-11-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	26-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	09-04-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	10-06-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	06-08-2024
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	EUCTR2019-000602-30-NL
CCMO	NL69564.058.19