A Double-Blind, Placebo-Controlled, Dose-Escalating, Phase 1 Study to Determine the Safety, Tolerability, Pharmacokinetics and Effect on Circulating Alpha-1 Antitrypsin Levels of ARC-AAT in Healthy Volunteer Subjects and in Patients with Alpha-1 Antitrypsin Deficiency (AATD)

Published: 10-07-2015
Last updated: 19-04-2024

The primary objective of the study is Study to determine the Safety, Tolerability, Pharmacokinetics and Effect on Circulating Alpha-1 Antitrypsin Levels of ARC-AAT in Patients with Alpha-1 Antitrypsin Deficiency (AATD)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON44026

Source
ToetsingOnline

Brief title
ARCAAT-1001

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Alpha-1 Antitrypsin deficiency; A1AT

Research involving
Human

Sponsors and support

Primary sponsor: Arrowhead Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Arrowhead Research Corporation

Intervention

Keyword: alpha-1 antitrypsin deficiency (AATD), ARC-AAT, double blind, placebo controlled

Outcome measures

Primary outcome

Primary Objectives:

• To determine the safety and tolerability of escalating dose concentrations of

ARC-AAT Injection

• To evaluate the pharmacokinetics of ARC-AAT Injection at different doses

• To determine the effect of ARC-AAT Injection on circulating levels of alpha-1

antitrypsin

Secondary outcome

Secondary Objectives:

• To determine dose level with >30% KD and the dose level with >=90% KD of AAT

on or before Day 22 (± 1 day) when compared to pre-dose geometric mean baseline

AAT level in healthy volunteers

• To determine dose level with 3 of 6 patients in AATD a cohort achieving > 90%

KD at Day 29 (± 1 day)

• Time for serum alpha-1 antitrypsin levels to return to baseline (± 15% from

geometric mean baseline)

• To evaluate the effect of ARC-AAT Injection on cytokines (interleukin-6

[IL-6], monocyte chemoattractant protein 1 [MCP-1], tumor necrosis factor-alpha

[TNFalpha], interleukin-8 [IL-8], interleukin-1beta [IL-1beta], interferon

alpha [IFNalpha], IL-10, IL-12 (p40), IL-12 (p70), macrophage inflammatory

protein-1alpha [Mip 1alpha]

• To evaluate the effect of ARC-AAT Injection on complement factors Bb and

CH50, C5a, C4a, C3a

Study description

Background summary

Alpha 1-antitrypsin (AAT) is a protein that is synthesized mainly in the liver, and especially inhibits the action of the enzyme elastase. Alpha-1 antitrypsin deficiency (AATD) is an inherited disorder that causes early lung disease in adults and liver disease in children and adults. Normal AAT is produced mainly in liver cells and daily a few grams are directly secreted into the blood circulation. However, low blood levels of AAT occur due to a type ZZ mutation in the alpha-1-antitrypsin gene. This mutation causes the production of alpha-1-antitrypsin protein that is lumping in the liver cells. The scientific word for lumping is polymerization. This lumping prevents the release of alpha-1-antitrypsin into the blood circulation, instead it accumulates in the liver cells.
Due to the accumulation of type ZZ alpha-1-antitrypsin protein in the liver patients can develop progressive liver disease leading to cirrhosis, hepatocellular carcinoma and morbidity and mortality. There is no specific treatment available to prevent the progression of AATD-associated liver diseases.
The goal of treatment with AAT-ARC injection is the prevention of liver damage and fibrosis as a result of Z-AAT-protein accumulation. Z-AAT protein accumulation in the liver leads to inflammation. It is important that this accumulation will be reduced, since it is clear that the mutant protein is the cause of progressive liver disease in patients AATD.
The prevention of the formation of the mutant protein is the logical approach for the treatment of AATD-associated liver disease. This is supported by the absence of liver disease in patients with AATD null / null genotypes. These

rare patients have a complete lack of AAT production. They present themselves with pulmonary disease, but because they have no liver production or accumulation of mutant AAT protein, they are devoid of liver disease.
It is expected that elimination of mutant protein accumulation in liver cells can stop the progression of liver disease.

Study objective

The primary objective of the study is Study to determine the Safety, Tolerability, Pharmacokinetics and Effect on Circulating Alpha-1 Antitrypsin Levels of ARC-AAT in Patients with Alpha-1 Antitrypsin Deficiency (AATD)

Study design

A Double-Blind, Placebo-Controlled, Dose-Escalating Study.

Intervention

Part A of the study has been completed. Following safety data review the Data Safety Committee approved progressing into part B at a starting level of 2.0mg/kg API. will consist of seven cohorts with escalating dose levels 6 participants per cohort (4 active and 2 placebo, randomized).

A single intravenous dose will be evaluated in the following concentrations

• Dose 2.0 (mg / kg API)
• Dose 4.0 (mg / kg API)
• Dose 6.0 (mg / kg API)
• Dose 8.0 (mg / kg API)

The first cohort will begin the administration of ARC-AAT or placebo injection to two simultaneous start-up of participants. Following the evaluation of the participants on Day 3, and if there are no serious concerns about safety, the remaining participants may be treated.
Dose Increase will continue until a DLT occurs which is considered to be possibly or probably related to study medication by either the investigator or the DSC or when a> 90% reduction in serum alpha-1 antitrypsin values **of the geometric output level seen in at least 3 of the 6 patients in a cohort or Day 29 (± 1 day).

Study burden and risks

Study Assessments:

Participants will undergo the following evaluations at regular intervals during the study (refer to Schedule of Assessments): medical history, physical

examinations, bee venom allergy blood test, vital sign measurements (blood pressure, temperature, heart rate, respiratory rate), weight, adverse events monitoring, ECGs, pregnancy test (females), concurrent medication, pulmonary function testing (Spirometry including FEV1, VC, FEV1/VC and DLCO) and sample collection for hematology, coagulation, chemistry, PK, complement, cytokines, drug screens, serum alpha-1 antitrypsin levels, and urinalysis. Continuous monitoring by ECG telemetry will be utilized from approximately 8 hours pre-dose through up to 24 hours post-dose, starting at Cohort 2.

Study visits will occur at Screening (Day -60 to -2) and Days -1, 1, 2, 3, 8, 15 (± 1 day), 22 (± 1 day) and 29 (± 1 day)/EOS. Following Day 29, participants will have additional bi-weekly AAT level testing until serum AAT levels have returned to a post-dose level > 90 mg/dL (16.6 microM) in healthy volunteers or within 15% of the geometric mean baseline level for each participant. Participants being monitored every two weeks for AAT level return to baseline will have additional pulmonary function testing monthly. A telephone follow-up will occur on Day 90 to verify compliance with contraceptive measures and absence of any known pregnancy. Clinically significant changes including adverse events will be followed until resolution is achieved or until medically stable.

During the Screening window, AAT levels will be taken at 2 time points at least 5 days apart, and subsequently on Day -1 in order to establish a baseline.

Safety Assessments:
Safety assessments will include: adverse events (AEs)/serious adverse events (SAEs), physical examinations, vital sign measurements (blood pressure, temperature, heart rate, and respiratory rate), ECGs, telemetry, pulmonary function testing, clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation due to toxicity. Safety assessments will be performed at specified time points (as described in the Schedule of Assessments) as well as prior to study completion.

At each visit, participants will be asked about concomitant medication/therapy and will be instructed to volunteer any information regarding AEs and SAEs that they may have experienced by asking open-ended questions (e.g., *How do you feel?*).

The AE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-emergent AEs will be those defined as following dose administration, or in the event onset preceded dose administration, those AEs with severity or frequency increasing post-dose. All AEs that occur during the AE reporting period specified in the protocol must be reported to Arrowhead, regardless of the relationship of the AE to study treatment. For this trial, the investigator should evaluate the relatedness of an AE to investigational product using three categories: Not Related, Possibly Related and Probably Related. Laboratory abnormalities will be

reported as an AE if considered clinically significant by the investigator. Any known untoward event that occurs beyond the AE reporting period that the Investigator considers possibly or probably related to study treatment will be reported to Arrowhead as an AE.
Pharmacokinetics:
Plasma concentrations for ARC-AAT Injection product constituents (MLP, chol-UNA) concentrations at each dose level will be collected pre-dose, 5 minutes, and 0.5, 1, 3, 6, 24, and 48 hours following the end of infusion.

Pharmacodynamics:
The following PD measures will be collected for each dose and treatment group:

• Cytokines panel (IL-6, MCP-1, TNF-alpha, IL-8, IL-1beta, IFN-alpha, IL-10, IL-12 (p40), IL-12 (p70) and Mip-1alpha): pre-dose, 0.5, 2, 6, 24 and 48 hours post-dose.
• Quantitative serum alpha-1 antitrypsin levels: Screening (at 2 time points at least 5 days apart) and on Days -1, 3, 8, 15 (± 1 day), 22 (± 1 day), 29 (± 1 day) and bi-weekly (+2 days) if AAT levels have not returned to > 90 mg/dL (16.6 microM) in healthy volunteers or within 15% of geometric mean baseline in any participant by Day 29 (± 1 day).
• Complement panel (CH50 [serum], C5a, C4a, C3a and Bb [EDTA plasma]): pre-dose, 0.5, 2, 6, 24 and 48 hours post-dose.

Allergenicity:
Bee venom allergy (IgE test) at Screening and on Day 29 (± 1 day).

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

Inclusion Criteria for Part B
To be eligible for randomization, participants must meet all of the following inclusion criteria:
1. Male or female patients 18-70 years of age, inclusive, at the time of Screening with previous diagnosis of PiZZ genotype (or PiZ phenotype if genotype is not available) Alpha-1 Antitrypsin Deficiency not receiving alpha-1 antitrypsin augmentation therapy for more than 4 weeks.
2. Able and willing to provide written informed consent prior to the performance of any study specific procedures
3. Participants with a BMI between 18.0 and 35.0 kg/m2, inclusive. Participants with BMI between 15-18 kg/m2 or between 30-40 kg/m2 may be enrolled at the PI's discretion in consultation with Sponsor depending on co-morbidities.
4. A 12-lead ECG at Screening and pre-dose assessment that, in the opinion of the investigator, has no abnormalities that compromise participant*s safety in this study
5. Non-nursing females
6. Non-smoker (not a daily cigarette smoker) for at least three years with current non-smoking status confirmed by urine cotinine at screening
7. Participants using highly effective, double barrier contraception (both male and female partners) during the study and for 3 months following the dose of ARC-AAT. Males must not donate sperm for at least 3 months post-dose of the last study treatment. Male partners of female patients and female partners of male patients must also use contraception, if they are of childbearing potential. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day -1. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level > 40 mIU/mL.
- Using twice the normal protection of birth control by using a condom AND one other form of the following:
* Birth control pills (The Pill)
* Depot or injectable birth control
* IUD (Intrauterine Device)

* Birth Control Patch (e.g., Othro Evra)
* NuvaRing®
* Surgical sterilization. i.e., tubal ligation or hysterectomy for women or vasectomy for men;Rhythm methods will not be considered as highly effective methods of birth control. Subject abstinence for the duration of the study and three months after the dose of ARC-AAT is acceptable only when this method is in alignment with the normal lifestyle of the patient.
8. Participants who are willing and able to comply with all study assessments and adhere to the protocol schedule
9. Must have suitable venous access for blood sampling
10. No abnormal finding of clinical relevance at the Screening evaluation
11. ALT, AST levels at Screening less than 3 times the upper limit
12. Creatinine levels within normal range at Screening

Exclusion criteria

Exclusion Criteria for Part B
A potential participant will be excluded from the study if any of the following criteria apply:
1. Any recent (within last 6 weeks) transfusion of fresh frozen plasma, platelets, or packed red blood cells, or anticipated need for transfusion during the study period
2. Acute signs of hepatitis/other severe infection (e.g. fever, jaundice with associated nausea, vomiting, abdominal pain) within 4 weeks of Screening and/or at baseline
3. Use of concurrent anticoagulants (anti-platelet agent aspirin is accetable)
4. A depot injection or an implant of any drug other than birth control within 3 months prior to administration of study treatment
5. A history of poorly controlled autoimmune disease or any history of autoimmune hepatitis
6. Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)
7. Seropositive for HBV or HCV, and/or a history of delta virus hepatitis
8. Uncontrolled hypertension (BP > 150/100 mmHg at Screening)
9. A history of torsades de pointes, ventricular rhythm disturbances (e.g., ventricular tachycardia or fibrillation), pathologic sinus bradycardia (<50 bpm), heart block (excluding first-degree block, being PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG. Participants with a history of atrial arrhythmias should be discussed with the Medical Monitor
10. A family history of congenital long QT syndrome or unexplained sudden cardiac death
11. Symptomatic heart failure (per NYHA guidelines), unstable angina, myocardial infarction, severe cardiovascular disease (ejection fraction < 20%, transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to study entry
12. History of malignancy within the last 5 years except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Participants with other curatively treated malignancies who have no evidence of metastatic disease and >2 year disease-free interval may be entered following approval by the Medical Monitor
13. History of major surgery within 2 months of Screening
14. Regular use of alcohol within one month prior to the Screening visit (i.e., more than

fourteen units of alcohol per week)
15. Evidence of acute inflammation, sepsis or hemolysis or clinical evidence of lower respiratory tract infection
16. Diagnosis of significant psychiatric disorder that would inhibit participation in study
17. Use of illicit drugs (such as cocaine, phencyclidine [PCP] and crack) within 1 year prior to the Screening visit or positive urine drug screen at Screening (a urine drug screen positive for benzodiazepines, opioids or marijuana is accepted and at the discretion of the PI).
18. History of allergy to bee venom
19. Use of an investigational agent or device within 30 days prior to dosing or current participation in an investigational study
20. Clinically significant history or presence of any gastrointestinal pathology (e.g., chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g., diarrhea, vomiting), liver or kidney disease, Gilbert*s syndrome, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs
21. Any clinically significant history or presence of poorly controlled or decompensated neurological, endocrinal, cardiovascular, pulmonary, hematological, immunologic, psychiatric, metabolic or other uncontrolled systemic disease
22. Blood donation (500 mL) within 7 days prior to study treatment administration. Donation or loss of whole blood (excluding the volume of blood that will be drawn during the Screening procedures of this study) prior to administration of the study treatment as follows: 50 mL to 499 mL of whole blood within 30 days, or more than 499 mL of whole blood within 56 days prior to study treatment administration
23. History of fever (defined as >38.0ºC/100.4ºF) within 2 weeks of Screening
24. Any concomitant medical or psychiatric condition or social situation that would make it difficult to comply with the protocol requirements or put the participant at additional safetyu risk.
25. Excessive exercise/physical activity within 3 days before and after dosing.
26. A history of thromboembolic disease (including deep vein thrombosis or pulmonary embolism), stroke within six (6) months of baseline and/or concurrent anticoagulant medication(s)
27. Participants who are unable to return for all scheduled study visits.
28. Any other condition, that in the opinion of the investigator would render the participant unsuitable for enrollment, or could interfere with the participant participating in and completing the study.

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:	Recruitment stopped
Start date (anticipated):	13-01-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ARC-AAT
Generic name:	-

Ethics review

Approved WMO Date:	10-07-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-10-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2016
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	18-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2015-001147-36-NL
ClinicalTrials.gov	NCT02363946
CCMO	NL53505.000.15