A Placebo-Controlled, Multi-dose, Phase 2 Study to Determine the Safety, Tolerability and Pharmacodynamic Effect of ARO-AAT in Patients with Alpha-1 Antitrypsin Deficiency (AATD) (SEQUOIA)

Published: 20-06-2019
Last updated: 10-04-2024

Primary Objective:• To select a single dose for use in later stage development based on a combined evaluation of safety and pharmacodynamic effects of ARO-AAT

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON54898

Source
ToetsingOnline

Brief title
AROAAT2001

Condition

- Hepatic and hepatobiliary disorders

Synonym
alpha-1

Research involving
Human

Sponsors and support

Primary sponsor: Arrowhead Pharmaceuticals Inc.
Source(s) of monetary or material Support: pharmaceutische industrie

Intervention

Keyword: Alpha-1 Antitrypsin Deficiency, ARO-AAT

Outcome measures

Primary outcome

Primary Endpoint:

• Percent change from baseline at Week 16 in serum Z-AAT

Secondary outcome

Secundary endpoints:

• Safety of ARO-AAT versus placebo based on frequency of adverse events (AEs) at Week 16 and over time through End of Study (EOS)

• Absolute and percent change from baseline in total liver Z-AAT (insoluble + soluble) protein at post-dose biopsy visit

• Absolute and percent change from baseline in liver Z-AAT soluble protein at postdose biopsy visit

• Absolute and percent change from baseline in liver Z-AAT insoluble protein at postdose biopsy visit

• Absolute and percent change from baseline in liver function tests including ALT, AST, alkaline phosphatase, GGT, total bilirubin, direct bilirubin and INR at Week 16 and over time through EOS

• Absolute and percent change in serum Z-AAT over time through EOS

• Change over time in pharmacokinetic measurements of ARO-AAT at timepoints

specified in the Schedule of Assessments

Study description

Background summary

Alpha-1 antitrypsin deficiency is an autosomal co-dominant genetic disorder with a prevalence range of 1/1500-1/5000 that causes early pulmonary disease in adults and liver disease in children and adults (Nelson et al, 2012). Alpha-1-antitrypsin (AAT) is a 52 kDa circulating glycoprotein protease inhibitor of the serpin family. The primary function of AAT is to inhibit neutrophil elastase to prevent excessive elastase-induced tissue damage.

Normally, AAT is synthesized primarily in hepatocytes and several grams daily are secreted directly into the serum. In lung parenchyma, AAT is critical for protection of alveolar interstitial elastin from degradation by neutrophil elastase. A lack of adequate levels of functional AAT leads to damage of lung elastin by neutrophil elastase and the development of early emphysema. It generally takes decades for lung disease to manifest and usually requires additional environmental insult, usually cigarette smoking. Low plasma AAT levels that lead to pulmonary disease in individuals homozygous for the Z mutation (PiZZ) are not from a lack of synthesis (except in null/null patients) but from a disruption of its processing and secretion by hepatocytes. AAT is normally secreted in monomeric form, but the mutant AAT protein (Z-AAT) synthesized by PiZZ individuals contains a single point mutation that results in low secretion, accumulation and polymer formation in hepatocytes leading to liver disease. Lung disease is frequently treated with AAT replacement therapy, and fewer than 10,000 patients are on replacement or *augmentation* therapy in the U.S. (Stoller et al, 2012). However, augmentation therapy does nothing to treat liver disease, and no specific therapy is available for AATD-associated liver disease.

In clinical practice, over 90% of AAT deficiency is due to the PiZZ genotype (DeSerres et al, 2012). PiZZ adult patients may initially present with clinical signs of pulmonary disease such as dyspnea, cough, chronic bronchitis, or they may initially present with signs of liver disease such as elevated transaminases or bilirubin, hepatitis, or cirrhosis (American Thoracic Society/European Respiratory Society 2003). Pediatric patients typically present with clinical symptoms of liver disease, which may include asymptomatic chronic hepatitis, failure to thrive, poor feeding or hepatomegaly and splenomegaly. However, disease natural history in both pediatric and adult patients is variable.

A 2018 publication by Clark et al., examined 94 PiZZ adults using liver biopsy and various other noninvasive measures of liver disease (e.g. transient elastography, FIB-4). In this cohort, the prevalence of clinically significant liver disease (>=F2) was 35.1%. The presence of accumulated Z-AAT globules, portal inflammation and hepatocellular degeneration were associated with clinically significant fibrosis. Similarly, accumulation of Z-AAT globules, portal inflammation and hepatocellular degeneration are seen on histologic evaluation of the PiZ mouse model liver.

Study objective

Primary Objective:
• To select a single dose for use in later stage development based on a combined evaluation of safety and pharmacodynamic effects of ARO-AAT

Study design

A multi-center, multi-dose placebo-controlled Phase 2 study will be conducted to evaluate the safety, efficacy and tolerability of the investigational product, AROAAT, administered subcutaneously to patients with AATD.

Intervention

The study will test three dose levels compared to placebo. Patients who have signed an IRB/EC approved informed consent and have met all the protocol eligibility criteria during Screening
will be assigned to one of three cohorts and be randomized 2:1 (active: placebo) within each
cohort. The three cohorts of the study are as follows:
• Cohort 1: 25 mg dose of ARO-AAT or placebo
• Cohort 2: 100 mg dose of ARO-AAT or placebo
• Cohort 3: 200 mg dose of ARO-AAT or placebo
Within each cohort, requirements for biopsies, dosing schedules, and SOA will be determined based on the patient*s fibrosis score during Screening.

Patients with no evidence of fibrosis
Patients who have a documented biopsy showing no evidence of fibrosis within 1 year of the Screening visit will not require liver biopsy at any point during the study. Patients without fibrosis at screening will receive two doses of ARO-AAT or placebo on Day 1 and Week 4, as per the Schedule of Assessments. Following their Week 4 dose, these patients remain in the study with regular visits per the SOA until Week 64.

Patients with evidence of fibrosis
Patients who have a pre-dose biopsy showing evidence of fibrosis (without definitive cirrhosis) during Screening will have post-dose biopsy performed at

Week 48. If a patient is beyond Week 48 at the time of IRB/EC approval of Protocol v4.0, then the post-dose biopsy will occur
at Week 72 or 96. The study will end when the last patient with fibrosis reaches Week 48 visit. Patients with evidence of fibrosis at Screening will receive a dose on Day 1, Week 4, and Week 16, then every 12 weeks for up to 15 doses total.

Study burden and risks

See also E9 and E9a

Liver biopsies are the greatest burden on the participants. However, the effectiveness of the study drug cannot be demonstrated without these liver biopsies.

There is also a risk of a decrease in lung function, which may require augmentation therapy. The sponsor has therefore taken a number of risk mitigation measures as described in the reply letter of 14 August 2019 to the CCMO.

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. Male or non-nursing female patients 18-75 years of age, inclusive, at the time of
Screening with previous diagnosis of PiZZ genotype Alpha-1 Antitrypsin Deficiency.
PiZZ diagnosis from source verifiable medical records is permitted. Otherwise, patients
must undergo PiZZ confirmatory testing at Screening. PiMZ or PiSZ genotypes are not
permitted.
2. Able and willing to provide written informed consent prior to the performance of any
study specific procedures.
3. Liver biopsy indicating a liver fibrosis score less than F4 based on local pathologist read.
a. A patient with no fibrosis may participate based in a previous biopsy conducted
within one year if a source verifiable medical record specifies no evidence of fibrosis.
4. A 12-lead ECG at Screening that, in the opinion of the Investigator, has no new acute
abnormalities (e.g., new onset atrial fibrillation) that compromise patient*s safety in this
study. Stable disease (e.g., stable atrial fibrillation) is acceptable.
5. Non-smoker (defined as does not smoke cigarettes daily for at least 12 months) with
current non-smoking status confirmed by urine cotinine at screening AND any previous
smoking history prior to 12 months must be < 15 pack years. Patients may be on nicotine
replacement (patch or gum). e-cigarettes (vapor) is not permitted. A positive urine
cotinine result due to nicotine replacement is acceptable for enrollment at the discretion
of the Investigator.
6. Use highly effective contraception during the study and for 3 months following the last
dose of ARO-AAT. Males must not donate sperm for at least 3 months post last

dose of
study treatment. Females of childbearing potential must have a negative urine pregnancy
test at Screening and on Day 1 pre-dose. Females not of childbearing potential must be
post-menopausal (defined as cessation of regular menstrual periods for at least 12 months
without an alternative medical cause), confirmed by follicle-stimulating hormone (FSH)
consistent with post-menopausal state based on lab reference ranges.
* Using twice the normal protection of birth control by using a condom AND one other
form of either birth control pills (The Pill), depot or injectable birth control, IUD
(Intrauterine Device), birth Control Patch (e.g., Ortho Evra), NuvaRing®, OR
Surgical sterilization as a single form of birth control: i.e., tubal ligation, hysterectomy, bilateral oophorectomy, vasectomy or equivalently effective surgical
form of birth control, is acceptable.
* True abstinence for the duration of the study and 12 weeks after the dose of AROAAT
is acceptable only when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered *true* abstinence and are not acceptable methods of contraception.
* All laboratory tests used as inclusion criteria may be repeated once and the repeat value may
be used for inclusion purposes.

Exclusion criteria

1. INR >= 1.2 at Screening (one retest permitted). If based on opinion of Investigator and/or
prescribing physician patient is appropriate for anticoagulant holiday, patient may stop
taking anticoagulant for an appropriate washout period and if indicated a repeat INR
within < 1.2 would be acceptable. Vitamin K may be used for reversal. If INR is not
indicated (direct thrombin inhibitors or Xa inhibitors) then appropriate washout period
alone may be acceptable. (Note: Anti-platelet agents, aspirin, clopidogrel or NSAIDS are
acceptable but must be held 7 days before and 7 days after liver biopsy)

2. Platelet count < 150 x 109/L at Screening (one retest permitted)
3. ALT and AST levels > 250 U/L at Screening (one retest permitted)
4. eGFR < 60ml/min/1.73m2 at Screening (one retest permitted)
5. FEV1 <65% of predicted (preferentially post-bronchodilatory reading) at Screening (one
retest permitted)
6. Recent (last 3 months) pneumonia or lower respiratory infection (which must be
verifiable from the medical record). Patient reported infection is not sufficient to meet
this criterion.
7. Unavoidable exposure to inhaled environmental toxins that in the clinical judgement of
the Investigator could impair pulmonary function significantly over the course of the
study.
8. Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)
9. Seropositive for HBV (HBsAg positive at Screening) or HCV (detectable HCV RNA at
Screening). Cured HCV (positive antibody test without detectable HCV RNA is acceptable).
10. Uncontrolled hypertension (Systolic BP > 170 and diastolic BP >100 mmHg at Screening). Patients may rescreen once BP is successfully controlled.
11. A history of torsades de pointes, ventricular rhythm disturbances (e.g., ventricular
tachycardia or fibrillation), untreated heart block (excluding first-degree block, being PR
interval prolongation only), congenital long QT syndrome or new acute ST segment elevation or depression or new acute Q wave on ECG. Stable atrial dysrhythmias (e.g.,
stable atrial fibrillation) are acceptable.
12. 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 Screening
13. History of malignancy within the last 1 year except for adequately treated basal cell
carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical
cancer. Patients with other curatively treated malignancies who have no evidence of
metastatic disease and >1-year disease-free interval may be entered following approval
by the Medical Monitor
14. History of major surgery within the prior 1 month prior to Screening

15. Regular use of alcohol within one month prior to the Screening visit (i.e., more than 14
units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40%
alcohol])
16. Use of illicit drugs (such as cocaine, phencyclidine [PCP]) within 1 year prior to the
Screening visit or positive urine drug screen at Screening (a urine drug screen positive for
benzodiazepines, opioids or THC is acceptable for enrollment at the discretion of the
Investigator). The patient may still be eligible at discretion of Medical Monitor and
Investigator if positive urine drug screen is due to a prescription medication.
17. Use of an investigational agent or device within 30 days prior to dosing or current
participation in an investigational study involving a therapeutic intervention. Patients
who have participated in the ARCAAT-1001 study or observational studies are
acceptable. Patients previously enrolled in but no longer enrolled in gene therapy studies
are acceptable. Patients receiving AAT augmentation therapy as part of a post-marketing
study or other access program for approved therapies are acceptable.
18. Blood donation (>=500 mL) within 7 days prior to study treatment administration.
19. Any concomitant medical or psychiatric condition or social situation that would make it
difficult to comply with protocol requirements or put the patient at additional safety risk.
Patients with NASH, NAFLD, metabolic syndrome, well controlled diabetes mellitus
(even if on insulin) or hemochromatosis are acceptable if disease is stable and does not
pose a significant threat to patient participation. Patients enrolled with NASH should
have no plans to undergo bariatric surgery or have initiated or plan to initiate
pharmaceutical therapy for NASH (such as Vitamin E or pioglitazone) during the course
of the study.
20. A history of thromboembolic disease (including deep vein thrombosis or pulmonary
embolism), myocardial infarction, stroke within three (3) months of screening.
21. Any other condition or finding of clinical relevance at Screening, that in the opinion of
the Investigator would render the patient unsuitable for enrollment or could interfere with
participating in and completing the study.

22. Previous diagnosis of definitive liver cirrhosis based on biopsy or complications of
cirrhosis (e.g., varices, ascites, hepatic encephalopathy) based on source verifiable
medical record.
23. Patients who have undergone lung or liver transplant for AATD are excluded.
Note: Sponsor Medical Monitor has the option to exclude the enrollment of a patient if, based
upon the patient*s medical history or Screening results, it is felt that a patient*s safety may be at
risk.
* All laboratory tests used as exclusion criteria may be repeated once and the repeat value may be used for exclusion purposes.

Study design

Design

Study phase:	2
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):	21-10-2020
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	20-06-2019

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-11-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2022
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	EUCTR2018-003385-14-NL
CCMO	NL69848.000.19