ALN-AAT02-001 EudraCT Results Summary

Title of Trial:	A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Single-ascending and Multiple-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-AAT02 in Healthy Adult Subjects and Patients With ZZ Type Alpha-1 Antitrypsin Deficiency Liver Disease
EudraCT Number:	2018-001362-41
End of Trial Date:	25-June-2020
Protocol Number:	ALN-AAT02-001

2. SYNOPSIS

Name of Sponsor/Company: Alnylam Pharmaceuticals, Inc.

Name of Finished Product: ALN-AAT02

Name of Active Ingredient: ALN-AAT02

Title of Study: A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Single-ascending and Multiple-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-AAT02 in Healthy Adult Subjects and Patients with ZZ Type Alpha-1 Antitrypsin Deficiency Liver Disease

Study center(s):

Healthy subjects were randomized at 1 study center in the United Kingdom (UK).

Publications (reference):

Not applicable.

Studied period (years):

Study initiation date: 05 December 2018

Study completion date: 25 June 2020

Phase of development:

Phase 1/2

Objectives:

Primary:

- To evaluate the safety and tolerability of single or multiple doses of ALN-AAT02 when administered to healthy adult subjects and patients with ZZ type of alpha-1 antitrypsin deficiency (PiZZ) AAT deficiency liver disease

Secondary:

- To assess the effect of ALN-AAT02 on serum levels of alpha-1 antitrypsin (AAT) protein in healthy adult subjects and PiZZ patients
- To characterize the pharmacokinetics (PK) of ALN-AAT02 in healthy adult subjects and PiZZ patients

Exploratory:

- [redacted]

Methodology:

This was a multicenter, randomized, double-blind, placebo-controlled Phase 1/2 study designed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of subcutaneously (SC) administered ALN-AAT02 in healthy adult subjects and patients with PiZZ liver disease in 2 sequential phases:

- Part A: Single ascending dose (SAD) phase in healthy adult subjects
- Part B: Multiple ascending dose (MAD) phase in adult PiZZ patients with biopsy proven alpha-1 antitrypsin deficiency (AATD)-associated liver disease (ie, presence of intrahepatocytic periodic acid Schiff base staining [PAS-positive] AAT globules), but without severe hepatic fibrosis

A Scientific Review Committee (SRC) performed ongoing reviews of safety, tolerability, and available PD and PK data collected in the study to protect the safety of study participants. The SRC made the decision to escalate to the next dose level in Part A based upon review of the safety data from the preceding dose cohort and to proceed from Part A to Part B based upon accumulated safety data from the Part A cohorts upon completion of dosing.

Part A: Single-Ascending Dose Phase

Eligible healthy adult subjects were enrolled in 1 of 4 SAD cohorts (0.3, 1.0, 3.0, and 6.0 mg/kg). Each cohort included 8 healthy subjects randomized 6:2 to receive a single SC dose of ALN-AAT02 or placebo on Day 1. Healthy subjects were discharged from the clinical study center on Day 2 after completing 24-hour postdose assessments and returned on an outpatient basis from Day 3 through the last postdose follow-up visit on Day 85 for safety, tolerability, PK, and PD monitoring. ALN-AAT02-treated healthy subjects whose AAT values at Day 85 were <80% of their mean pretreatment value and below the reference range lower limit of normal (LLN) were monitored every 84±7 days (extended follow-up visit, beginning on Day 169±7 days) for safety until their AAT values met 1 of the following 3 criteria:

1. AAT values reached ≥80% of their mean pretreatment value
2. AAT values >LLN
3. Subject had been followed for 12 months after study drug administration and their blood AAT values exceeded 0.49 g/dL, the level above which AAT was considered to exert its protective anti-protease function.

On 11 August 2020, the Sponsor made the decision to discontinue the study after the completion of Part A. Part A of the study was terminated earlier than stipulated in the protocol due to the inability to complete the planned follow-up due to coronavirus disease 2019 (COVID-19)-related

restrictions in the UK. This was deemed appropriate given that all subjects had been followed for at least 12 months since their dose of ALN-AAT02, had no ongoing adverse events, and were exhibiting trends towards recovery of serum AAT levels.

Part B: Multiple-Ascending Dose Phase

PiZZ patients with biopsy-proven AATD-associated liver disease (ie, presence of intrahepatocytic periodic acid Schiff base staining [PAS-positive] AAT globules) but without severe hepatic fibrosis (corresponding to an Ishak fibrosis score of <4) were planned to be enrolled in 2 dose escalation multiple-dose cohorts, Cohort 1 and Cohort 2.

No PiZZ patients were enrolled in Part B; therefore, the clinical efficacy of ALN-AAT02 was not evaluated in patients with PiZZ due to the discontinuation of the study.

Number of healthy subjects and patients (planned and analyzed):

Part A

Planned: 32 subjects

Enrolled and randomized: 32 subjects

Analyzed: 32 subjects

Part B

No PiZZ patients were enrolled.

Diagnosis and main criteria for inclusion:

Part A: Healthy adults (18 to 65 years of age) who were nonsmoker ≥5 years before screening with a body mass index of 18 to 30 kg/m^2 , normal AAT levels, forced expiratory volume in 1 second (FEV_1) ≥85% of predicted, FEV_1/forced vital capacity (FVC) ratio ≥0.7, and within normal limits or with no clinically significant abnormalities in electrocardiogram (ECG) in the opinion of the Investigator.

Part B: No PiZZ patients were enrolled due to study discontinuation.

Test product, dose and mode of administration, batch number:

ALN-AAT02 is an investigational agent composed of a synthetic, small interfering RNA (siRNA) targeting AAT messenger RNA and covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand. It is designed to suppress liver production of Z-variant alpha-1 antitrypsin (Z-AAT) protein, which is hypothesized to permit physiological clearance of the accumulated, polymerized Z-AAT protein from hepatocytes, permitting stabilization and potentially reversal of liver fibrosis in individuals with PiZZ AATD. ALN-AAT02 was supplied as a sterile solution for injection that contains 189 mg/mL ALN-AAT02 (equivalent to 200 mg/mL, sodium form) formulated in water for injection. ALN-AAT02 was administered at doses from 0.3 mg/kg to 6 mg/kg as an SC injection.

The lot number for ALN-AAT02 administered in this study was 0000503530.

Duration of treatment:

Part A: Healthy subjects were treated with 1 dose of ALN-AAT02 or placebo on Day 1.

Reference therapy, dose and mode of administration, batch number:

Placebo consisted of SC-administered sodium chloride 0.9% w/v, which was supplied by the clinical study center.

Criteria for evaluation:

Efficacy:

The PD assessment was the change from baseline in serum levels of AAT in healthy subjects over the course of the study. Blood samples were collected for PD assessment.

Pharmacokinetics:

Blood and urine samples were collected to determine the PK profile of ALN-AAT02 [redacted]. The following major plasma PK parameters were calculated when applicable:

- Maximum observed plasma concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Area under the plasma concentration versus time curve (AUC)
- Apparent terminal elimination half-life ($t_{½}$)
- Fraction eliminated in urine (f_e)
- Mean renal clearance (CL_R)

Anti-drug antibodies:

Blood samples were collected and analyzed for the presence of anti-drug antibodies (ADA).

Safety:

Safety was evaluated based on frequency of treatment-emergent adverse events (AEs) and any abnormalities in clinical laboratory tests; vital signs; physical examination, ECG, and pulmonary function testing.

Statistical methods:

The sample size was based on feasibility considerations, not power calculations.

The following analysis sets were defined:

- Safety Analysis Set: All subjects who received any amount of study drug, grouped according to the treatment actually received.
- PD Analysis Set: All subjects who received at least one dose of study drug and who had at least 1 postdose blood sample for the determination of serum AAT.
- PK Analysis Set: All subjects who received any amount of study drug and have at least 1 postdose blood or urine sample for PK parameters and had evaluable PK data.

Subject disposition, demographics, and baseline characteristics were summarized and listed.

Efficacy

Pharmacodynamics

In Part A, the efficacy endpoint was the change from baseline in serum levels of AAT in healthy adult subjects over the course of the study.

The level and relative change from baseline in serum AAT were summarized descriptively at each scheduled visit and also plotted over time. These analyses were performed by treatment cohort.

Pharmacokinetics

Plasma and urine PK concentration data of ALN-AAT02 [redacted] were summarized at each scheduled time point by dose level using descriptive statistics.

Pharmacokinetic parameters of ALN-AAT02 included, but not limited to, maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration versus time curve, apparent clearance, apparent terminal elimination half-life, fraction eliminated in urine, and amount of full-length drug excreted in urine.

Pharmacokinetic analyses were conducted using noncompartmental methods; PK parameters were calculated using a validated version of Phoenix® WinNonlin.

Safety

All safety analyses were performed using the Safety Analysis Set and presented by treatment cohort and overall subjects. Safety parameters, including AEs, clinical laboratory evaluations, vital signs, and ECGs were summarized descriptively.

Summary – Conclusions

Efficacy Results:

Pharmacodynamic and Pharmacokinetic Conclusions in Healthy Subjects

- ALN-AAT02 led to rapid, dose-dependent, and sustained reductions of serum AAT levels. Initial AAT decline was observed at Day 8 postdose, with peak AAT reduction observed at Day 43 to Day 57 for all dose groups, and the peak reduction was maintained through Day 85 for doses ≥1 mg/kg.
- Reduction of serum AAT was observed over an extended period of time for doses ≥3 mg/kg. At the time of last observation (Day 336) for remaining subjects in the dose groups of 3 mg/kg and 6 mg/kg, mean AAT changes of -58.5% and -62.9% from baseline were observed, respectively.
- Slightly higher than dose proportional increase in ALN-AAT02 was observed over the single dose range tested. Mean $t_{½}$ of ALN-AAT02 in plasma ranged from 4.2 hours to 6.3 hours.

Antidrug Antibodies Conclusion

- No healthy subject had a confirmed positive ADA result.

Safety Results:

ALN-AAT02 was well-tolerated in healthy subjects who received a single dose in Part A, with the following safety conclusions:

- Adverse events were reported in 66.7% of ALN-AAT02-treated healthy subjects and 75.0% of placebo-treated healthy subjects. There were no deaths, no serious adverse events (SAEs), and no AEs that led to discontinuation or withdrawal from the study.
- The only AE reported in ≥15% of subjects for both placebo (25%, 2 of 8 subjects) and overall ALN-AAT02 group (16.7%, 4 of 24 subjects) was upper respiratory tract infection. Other AEs reported in 2 or more (≥5%) ALN-AAT02-treated subjects were diarrhea, seasonal allergy, headache, and epistaxis.
- The majority of ALN-AAT02 and placebo-treated healthy subjects had AEs that were mild in severity. One (4.2%) healthy subject in the 1 mg/kg ALN-AAT02 cohort had a transient, nonserious AE of transaminases increased that was moderate in severity. On laboratory analysis, the healthy subject had creatine kinase (CPK) of 42×upper limit of normal (ULN), alanine aminotransferase (ALT) of 3.7×ULN and aspartate aminotransferase (AST) of 6.0×ULN. Alkaline phosphatase and total bilirubin were normal. The event was assessed as not related to ALN-AAT02 and the elevations were determined to be of skeletal muscle injury.
- Two (8.3%) ALN-AAT02-treated healthy subjects had related AEs of transient headache and exertional dyspnoea, both of which were mild in severity.
- There were no injection site reactions (ISRs).
- There were no clinically significant changes in hematologic parameters, liver function tests, blood chemistry parameters, renal function parameters, coagulation parameters vital signs, and physical examination related to ALN-AAT02.
- Two subjects (1 mentioned above) had liver function test (LFT) elevations >5×ULN which were not considered related to study drug. No healthy subjects had elevations that met Hy's Law criteria.
- There were no clinically significant changes in ECG, including no prolongation of corrected QT (QTc) interval.
- There were no clinically significant changes in spirometry parameters, and no healthy subjects in any cohorts had a FEV_1/FVC ratio <0.7.

Conclusion:

[redacted]

Date of the report: 04 January 2021