A Phase 2, Randomized, Double-blind, Placebo-controlled Study Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Two Dose Levels of Belcesiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

Published: 18-03-2021
Last updated: 17-01-2025

Primary objectives:Cohort 1 and 21. To evaluate the safety and tolerability of multiple doses of belcesiran in patients with AATLD2. To characterize the pharmacodynamics of belcesiran in patients with AATLDCohort 3 1. To characterize the…

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

Summary

ID

NL-OMON55922

Source
ToetsingOnline

Brief title
DCR-A1AT-201

Condition

- Hepatic and hepatobiliary disorders

Synonym
Alpha-1 antitrypsin deficiency-associated liver disease, liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Dicerna Pharmaceuticals, Inc., a wholly owned subsidiary of Novo Nordisk
Source(s) of monetary or material Support: Dicerna Pharmaceuticals;Inc.

Intervention

Keyword: alpha-1 antitrypsin deficiency, Alpha-1 antitrypsin deficiency-associated liver disease, Belcesiran, PiZZ

Outcome measures

Primary outcome

Primary outcomes

Cohort 1 and 2:

1. The incidence and nature of treatment emergent adverse events (TEAEs), and

the change from Baseline in pulmonary function tests (PFTs), 12-lead ECGs,

physical examination findings, vital signs, and clinical laboratory tests.

2. Changes from baseline to weeks 24 (Cohort 1)/48 (Cohort 2) in serum AAT

protein concentrations

Cohort 3:

1. Change from baseline to week 24 in serum Z-AAT protein levels

2. Change from baseline to week 24 in liver Z-AAT protein levels

Secondary outcome

1. Pharmacokinetics profile of belcesiran

2. Change from Baseline up until week 96 in liver fibrosis

3. Change from Baseline up until week 96 in diastase-resistant PAS-positive AAT

globules

Study description

Background summary

Alpha-1 antitrypsin deficiency (AATD) is caused by inherited autosomal mutations in SERPINA1, the gene that encodes the Alpha-1 antitrypsin (AAT) protein. The resultant mutant AAT protein (Z-AAT) is prone to misfolding and aggregation as homopolymers in hepatocytes, rather than secretion into the blood. In individuals homozygous for the Z-allele (known as PiZZ patients), impaired degradation of the aggregated protein leads to putatively toxic accumulation of Z-AAT in the liver (toxic gain-of-function) and exerts continuous stress on the hepatocytes. Over time, this constant stress can lead to liver fibrosis, cirrhosis, and hepatocellular cancer. Currently, there is no treatment for this severe liver disease, also called alpha-1 antitrypsin deficiency-associated liver disease (AATLD), aside from liver transplantation.

The study drug, Belcesiran, uses an RNAi strategy to silence SERPINA1, which reduces the total hepatic Z-AAT expression leading to decreased accumulation of toxic Z-AAT in the liver. Non-clinical studies indicate that without the continuous putative toxic stimulus, the progression of AATLD may be halted, or potentially even reversed by providing the liver an opportunity to heal. Furthermore, the study drug was well tolerated in the ongoing phase 1 study in healthy volunteers.

Study objective

Primary objectives:
Cohort 1 and 2
1. To evaluate the safety and tolerability of multiple doses of belcesiran in patients with AATLD
2. To characterize the pharmacodynamics of belcesiran in patients with AATLD

Cohort 3
1. To characterize the pharmacodynamics of belcesiran in patients with AATLD

Secondary objectives:
1. To characterize the pharmacokinetics of belcesiran in the plasma of patients with AATLD
2. To assess the effect of belcesiran on liver histology in patients with AATLD

Exploratory objectives:
1. To assess the effect of belcesiran on liver stiffness in patients with AATLD

2. To assess the effect of belcesiran on liver fibrosis and/ or inflammation in patients with AATLD

Study design

This is a multiple dose, randomized, placebo-controlled, double-blind study of belcesiran to evaluate the safety, tolerability, PK, and PD in adult patients with PiZZ AATLD (liver fibrosis F1, F2, F3, or F4 in the METAVIR scoring system).

Intervention

The study drug, Belcesiran, uses an RNAi strategy to silence SERPINA1, which reduces the total hepatic Z-AAT expression leading to decreased accumulation of toxic Z-AAT in the liver.

The study will be conducted in 3 parallel cohorts:
1. Cohort 1 (N=8): These subjects will be randomized 3:1 to either belcesiran 210 mg or placebo and a liver biopsy will be performed at week 24 to assess the effect of belcesiran. In addition, participants will have the option to continue treatment for an additional 72 weeks so that the total treatment duration will be 96 weeks.
2. Cohort 2 (N=8): These subjects will be randomized 3:1 to either belcesiran 210 mg or placebo and a liver biopsy will be performed at week 48 to assess the effect of belcesiran. In addition, participants will have the option to continue treatment for an additional 48 weeks so that the total treatment duration will be 96 weeks.
3. Cohort 3 (N=30): These subjects will be randomized 2:1:2:1 to belcesiran 210 mg, the equivalent amount of placebo for belcesiran 210 mg, belcesiran 50 mg or the equivalent amount of placebo for belcesiran 50 mg. Participants will be blinded within each dose level. Participants will have a liver biopsy performed at week 24 to assess the effect of belcesiran and thereafter continue treatment until 96 weeks of treatment have been completed.

After the EOT visit, all participants will be followed up for 48 weeks. If a participant in Cohorts 1 and 2 does not wish to extend the treatment period to 96 weeks, they will proceed to the 48 week follow-up period instead.

Randomization will be stratified based on fibrosis stage (METAVIR Score F1, F2, F3 or F4) in all cohorts.

All Participants in Cohorts 1 to 3 will have the option to undergo a liver biopsy at End of Trial/week 96.

The study drug is administered via a subcutaneous injection.

Study burden and risks

Procedures: medical history, medication and demographics review, PiZZ genotyping, pulmonary X-ray, vital signs (blood pressure, pulse and respiratory rate, and oral temperature), physical examinations (height, weight, BMI and review of body systems), 12-lead ECG, fibroscan and magnetic resonance elastography (MRE), spirometry and diffusion capacity of the lungs for carbon monoxide (DLCO).

Patients should prevent heavy exercise and heavy drinking. They should use effective contraceptive methods and should not donate sperm during the treatment period and for at least 12 weeks after the last dose.

Risks related to study drug:
In the ongoing first-in-human study, the study drug was well tolerated and no severe adverse events (SAEs) and dose-limiting toxicities were reported. Potential risks include exacerbation of emphysema, a decline in lung function, stimulation of expression of receptors leading to cytokine release, inflammation, injection site reactions, elevations of liver function tests, a prolonged activated partial thromboplastin time (aPTT), hepatocellular carcinoma, mild liver toxicity and a transient decrease in sperm motility. All these risks are monitorable and should be reversible after drug discontinuation or could potentially be treated.

Risk related to subcutaneous injection of the study drug:
This injection is associated with pain and may cause vasovagal reactions, allergic reactions, infections, and bleeding.

Blood sampling:
This might cause the subject some slight discomfort and the subject might be bruised for a few days around the area of the needle insertion. There could be some bleeding and vessel damage. There is a slight risk for vessel blockage, inflammation and infection in the area where the needle is inserted. Some people become dizzy when providing blood sample.

Percutaneous liver biopsy:
Milder and more common risks include pain and bruising at the biopsy or incision site. More serious complications include prolonged bleeding from the biopsy or incision site, internal bleeding (which may require hospitalization, transfusion, and sometimes surgery or another procedure to stop the bleeding), infection of the biopsy site or incision site that may cause sepsis, and pneumothorax, hemothorax, or puncture of other organs. The overall risk of serious complications following liver biopsy is approximately 1%. The risks are minimized through the selection of suitable subjects through eligibility criteria and by the safety precautions outlined in the Liver Biopsy Manual. The low risk of respiratory compromise in the elective setting of procedural

sedation and anesthesia is minimized through the standard-of-care monitoring and the presence of a healthcare provider with the knowledge and skills to recognize and treat airway complications.

Benefit:
Currently, there is no treatment for AATLD. Non-clinical studies indicate that belcesiran may halt or even reverse the progression of AATLD.

The risk-benefit profile of belcesiran is favorable.

Contacts

Public
Dicerna Pharmaceuticals, Inc., a wholly owned subsidiary of Novo Nordisk

Hayden Avenue 75
Lexington MA 02421
US
Scientific
Dicerna Pharmaceuticals, Inc., a wholly owned subsidiary of Novo Nordisk

Hayden Avenue 75
Lexington MA 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age 18 to 75 years, inclusive, at the time of signing the informed consent

form (ICF).
2. Documented diagnosis of PiZZ-type AATD, confirmed by genotyping. Historical genotyping data may be used, if available.
3. AATLD, with a liver fibrosis score categorized as F1, F2, F3, or F4 in the METAVIR scoring system, documented by liver biopsy during Screening.
4. Post-bronchodilator FEV1> 45% of predicted at Screening
5. Participants receiving augmentation therapy on a regular basis and intending to continue augmentation therapy during the study are eligible to participate.
6. Estimated glomerular filtration rate at Screening >= 60 mL/min/1.73
7. Non-smokers (defined as having not smoked cigarettes daily for at least the preceding12 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, including use of e-cigarettes. Participants may be on nicotine replacement (patch or gum). A positive urine cotinine result due to nicotine replacement is acceptable for enrollment at the discretion of the Investigator.
8. Male or female:
- Male: A male participant with a partner of childbearing potential must agree to use contraception, as detailed in Section 10.4.2 of the Protocol, during the treatment period and for at least 12 weeks after the last dose of study intervention and refrain from donating sperm during this period. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Female: A female participant is eligible to participate if she is not pregnant and not breastfeeding. Women of childbearing potential (WOCBP) must be using a highly effective method of contraception, as defined in Section 10.4.1. of the Protocol.
9. Capable of giving signed informed consent, which includes compliance with the requirements (including consent to undergo paired liver biopsies) and restrictions listed in the ICF and in the protocol.

Exclusion criteria

Medical Conditions
1. Any condition which, in the investigator's opinion might jeopardize participant's safety or compliance with the protocol.
2. History of chronic liver disease other than non-alcoholic fatty liver disease from any cause other than PiZZ-type AATD.
3. Child-Pugh Score B or C
4.History of one single severe exacerbation of underlying lung disease in the past year prior to randomization. A severe exacerbation is defined as an exacerbation that requires hospitalization or a visit to the emergency room.
5. History of rapid decline in pulmonary function, as assessed by the Investigator.
6. Known or suspected abuse of drugs in the opinion of the Investigator.
7. Known or suspected excessive consumption of alcohol (>= 21 units of alcohol

per week in men and >= 14 units of alcohol per week in women; where a "unit" of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1 ounce shot of hard liquor as defined by the World Health Organization)
8. Any of the following: myocardial infarction, stroke, classification of heart failure New York Heart Association (NYHA) Class IV, hospitalization for unstable angina pectoris or transient ischaemic attack within the past 90 days prior to the day of screening (V2A) and between screening and randomization.
9. History of malignancy, unless the malignancy (other than hepatocellular or lung cancer) has been in complete remission off chemotherapy and without additional medical or surgical interventions within the preceding 5 years, or unless the malignancy has been an adequately treated skin cancer (other than melanoma) or, superficial bladder tumor, or in situ cervical cancer in the preceding 1 year.

Prior/Concomitant Therapy
10. Use of an RNAi drug at any time.
11. History of one or more of the following reactions to an oligonucleotide-based therapy:
a. severe thrombocytopenia (platelet count < 100,000/ mm3)
b. hepatotoxicity, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN or INR > 1.5
c. severe flu-like symptoms leading to discontinuation of therapy
d. localized skin reaction from the injection (graded severe) leading to discontinuation of therapy
e. coagulopathy/clinically significant prolongation of clotting time

Prior/Concurrent Clinical Study Experience
12. Participation in any clinical study in which they received an IMP within 4 months (or 5 times the half-life, whichever is longer) before Screening

Diagnostic assessments
13. AST and ALT > 5 × ULN at Screening For individuals with any serum aminotransferase elevation > 2 × ULN, autoimmune hepatitis should be ruled out through the appropriate screening tests, which may include total IgG or gamma-globulin levels and/or serologic markers (antinuclear antibodies, anti-smooth-muscle antibodies at a titer of at least 1:40, anti-liver/kidney microsomal-1 antibodies, anti-liver cytosol antibody [anti-LC 1], or antisoluble liver/liver pancreas [anti-SLA/LP] antibodies).
14. alkaline phosphatase (ALP) 2 × ULN at Screening
15. Serum AFP value > 100 ng/mL at Screening If AFP at screening is > ULN but < 100 ng/mL, the participant is still eligible if an appropriate hepatic imaging study reveals no lesions
16. Positive screening for antimitochondrial antibodies (only required if primary biliary cirrhosis is suspected)
17. Platelets < 100,000/mm3 at Screening
18. international normalized ratio (INR) > 1.6 × ULN at Screening

19. Positive screening for Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) antibodies, or human immunodeficiency virus (HIV)1 and 2 antibodies. If a participant has been tested in the past 3 months, medical record documentation of this testing can be used for eligibility.
NOTE: In participants with previous treatment for hepatitis C with direct-acting HCV medication and seropositivity for HCV, or in participants with prior infection and spontaneous resolution, HCV RNA must be undetectable (at least two negative HCV RNA tests at least 12 weeks apart), and the HCV infection must have been resolved or cured > 3 years prior to enrollment.

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:	Completed
Start date (anticipated):	01-09-2022
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO

Date:	18-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	09-08-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-10-2023
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-12-2023
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	EUCTR2020-003313-35-NL
CCMO	NL76935.000.21

Study results

Date completed:	08-12-2023
Results posted:	03-10-2024
Actual enrolment:	1

First publication
13-09-2024