A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients With Hemophilia A or B, Without Inhibitory Antibodies to Factor VIII or IX

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The ATLAS-A/B trial (ALN-AT3SC-004) is a multicenter, multinational, randomized, openlabel Phase 3 study designed to demonstrate the efficacy and safety of fitusiran in patients with hemophilia A or B without inhibitory antibodies to FVIII or FIX...

Ethical review	Not approved
Status	Will not start
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON46599

Source
ToetsingOnline

Brief title
ATLAS ALN-AT3SC-004

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Hemophilia A or B

Research involving
Human

Sponsors and support

Primary sponsor: Alnylam Pharmaceuticals, Inc.

Source(s) of monetary or material Support: Alnylam Pharmaceuticals;Inc.

Intervention

Keyword: fitusiran, hemophilia A or B

Outcome measures

Primary outcome

Objectives

Primary

* To evaluate the efficacy of fitusiran compared to on-demand treatment with

factor concentrates, as determined by the frequency of bleeding episodes

Secondary outcome

Secondary

* To evaluate the efficacy of fitusiran compared to on-demand treatment with

factor concentrates, as determined by:

- The frequency of spontaneous bleeding episodes

- The frequency of joint bleeding episodes

- Health-related quality of life (HRQOL) in patients *17 years of age

* To determine the frequency of bleeding episodes during the onset period

* To characterize the safety and tolerability of fitusiran

Study description

Background summary

Hemophilia is a rare bleeding problem in which blood does not clot normally. This means that people with hemophilia may bleed for longer periods of time after an injury or, they may develop bleeds spontaneously. This happens because people with hemophilia have little or none of certain clotting factors.

Clotting factors are proteins in the blood that help the body to stop bleeding by forming a blood clot.
Fitusiran may make it possible to prevent or reduce the frequency of hemophilia-related bleeding in patients with hemophilia

Study objective

The ATLAS-A/B trial (ALN-AT3SC-004) is a multicenter, multinational, randomized, openlabel Phase 3 study designed to demonstrate the efficacy and safety of fitusiran in patients with hemophilia A or B without inhibitory antibodies to FVIII or FIX who are currently treated with on-demand factor concentrates.

The primary objective is to assess the efficacy of fitusiran on prevention or reduction of bleeding episodes. Secondary objectives are to assess the efficacy of fitusiran on: the number and type of bleeding episodes; HRQOL; and to determine the safety and tolerability of fitusiran. Blinding is not considered feasible for this study since the differences in treatment for each study arm cannot be blinded. The open-label, randomized study design is justified because safety monitoring of theoretical risks such as transaminitis or thrombosis can be objectively verified by laboratory monitoring or objective visualization, eg, ultrasound or CT. Therefore the safety monitoring of the studied population does not require blinding. The primary endpoint of the study is ABR in the fitusiran efficacy period (Day 29 to EOS). ABR is a well-established endpoint that has been used as the primary endpoint in global approvals of factor replacement and bypassing agent products. Secondary endpoints characterize ABR in the treatment period, annualized spontaneous and joint bleeding rates, change in Haem-A-QOL score in patients *17 years of age, ABR in the onset period, and the overall safety profile.
Characterization of bleeding episodes is clinically relevant to assess overall bleeding episode protection. Joint bleeding episodes result in pain and hemarthrosis, leading to progressive joint destruction, and hence are important to assess. Haem-A-QOL is a hemophilia-specific HRQOL survey instrument that has been validated in other hemophilia clinical trials and is considered the most appropriate HRQOL tool for this study. The study population will be comprised of males *12 years of age; it is appropriate to study fitusiran in adolescents (patients *12 to <18 years of age) because the pathophysiology of disease progression and bleeding episode management is the same as adults and self-management of hemophilia typically begins at 12 years of age.[4] A similar study in hemophilia patients with inhibitors (ALN-AT3SC-003) is being conducted concurrently to this study. To protect against bias, patients will be assigned to fitusiran (fitusiran treatment arm; N=80) or on-demand factor concentrate therapy (on-demand arm; N=40) by stratified randomization. The onset period duration reflects modeling data that estimates it takes approximately 28 days to reach the therapeutic target range in the majority of patients. Efficacy of fitusiran will be assessed over the remaining 8 months of the study (Day 29 to Month 9). In the event of a breakthrough bleeding

episode, on-demand use of factor concentrates will be permitted throughout the entire study duration (see Section 6.3.1).

Study design

A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, without Inhibitory Antibodies to Factor VIII or IX

Study Design The ATLAS-A/B trial (ALN-AT3SC-004) is a multicenter, multinational, randomized, open-label Alnylam Pharmaceuticals Confidential 5 ALN-AT3SC (fitusiran) Clinical Study Protocol ALN-AT3SC-004 16 November 2017

Phase 3 study designed to evaluate the efficacy and safety of fitusiran in male patients aged *12 years, with hemophilia A or B without inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who are not receiving prophylactic therapy.
Eligible patients will be randomized in a 2:1 ratio to:
* Fitusiran treatment arm: Fitusiran 80 mg administered subcutaneously (SC) as prophylaxis once monthly, with use of on-demand factor concentrates for treatment of breakthrough bleeding episodes
* On-demand arm: On-demand factor concentrates for treatment of breakthrough bleeding episodes
On-demand use of factor concentrates is defined as the use of these agents as needed for episodic bleeding, and not on a regular regimen intended to prevent spontaneous bleeding. Throughout the study, patients in the fitusiran treatment arm may receive on-demand treatment for breakthrough bleeding episodes with factor concentrates, as appropriate.
Bleeding events and doses of factor concentrates administered during the conduct of the study will be recorded in an eDiary. Safety, quality of life, pharmacodynamic, and pharmacokinetic data will also be collected.
All patients will be treated for a total of 9 months; patients randomized to the fitusiran treatment arm will receive a total of 9 SC injections of fitusiran. Because the full PD effect of fitusiran is not achieved until approximately 28 days after receiving the first dose, efficacy will be assessed during the
remaining 8 months on study (Day 29 to Month 9).
An independent data monitoring committee (DMC) will oversee the safety and overall conduct of this study. The DMC will perform periodic reviews of data during the course of the clinical trial, and on an ad hoc basis for review of emergent safety data, as defined in the DMC Charter for this clinical trial.
Patients from both the fitusiran and on-demand treatment arms who complete the study may be eligible for participation in an open-label extension study.
Following final fitusiran dose, in the fitusiran treatment arm patients who do not enroll in the extension study, AT level will be monitored at monthly intervals until returning to an activity level of approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the

study Medical Monitor.

Intervention

Diagnosis and Main Eligibility Criteria
This study will include males with severe hemophilia A or B without inhibitors (defined as Nijmegen modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening), aged *12 years, who have had a minimum of 6 bleeding episodes requiring on-demand treatment with factor concentrates within the last 6 months prior to Screening. Diagnosis of severe hemophilia A or B will be based on a central laboratory measurement or documented medical record evidence of FVIII level <1% or FIX level *2%.

Investigational Product, Dose and Mode of Administration
Fitusiran is an SC administered GalNAc-conjugated siRNA targeting liver-expressed messenger RNA (mRNA) for AT. Patients randomized to the fitusiran treatment arm will receive open-label fitusiran 80 mg as an SC injection once monthly for a total of 9 months; dosing will begin on Day 1 of the treatment period.

Reference Therapy, Dose and Mode of Administration
Patients in the on-demand arm will receive on-demand factor concentrate therapy per Investigator discretion to treat bleeding episodes from Day 1 through end of study. The protocol will recommend guidance for patients in the fitusiran treatment arm to use reduced initial doses of factor concentrates for breakthrough bleeding episodes during the fitusiran efficacy period.

Duration of Treatment
The duration of treatment with fitusiran is 9 months. The estimated total time on study, inclusive of screening, for each patient is up to 11 months for patients who enroll in the extension study and
patients in the on-demand arm. The total time on study may be up to 17 months in fitusiran treatment arm patients who do not enroll in the extension study due to the requirement for an additional 6 months of follow-up for monitoring of AT levels.

Study burden and risks

please check the schedule of event in the protocol and section intervention above

Contacts

Public
Alnylam Pharmaceuticals, Inc.

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Cambridge MA 02142
US
Scientific
Alnylam Pharmaceuticals, Inc.

300 Third street
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

5.1. Inclusion Criteria
Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the
study:
1. Males *12 years of age.
2. Severe hemophilia A or B without inhibitors evidenced by:
a. A central laboratory measurement or documented medical record evidence of
FVIII <1% or FIX level *2% at Screening.
b. On-demand use of factor concentrate to manage bleeding episodes for at least the last 6 months prior to Screening, and meet each of the following criterion:
* Nijmegen modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening
* No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening

* No history of immune tolerance induction therapy within the last 3 years prior to Screening
3. A minimum of 6 bleeding episodes requiring factor concentrate treatment within the last 6 months prior to Screening.
4. Willing and able to comply with the study requirements and to provide written informed consent and assent in the case of patients under the age of legal consent, per local and national requirements.

Exclusion criteria

5.2. Exclusion Criteria
Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in
the study:
1. Known co-existing bleeding disorders other than hemophilia A or B, ie, Von Willebrand*s disease, additional factor deficiencies, or platelet disorders.
2. Current use of factor concentrates as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes.
3. AT activity <60% at Screening as determined by central laboratory measurement.
4. Presence of clinically significant liver disease, or as indicated by any of the conditions below:
a. INR >1.2;
b. ALT and/or AST >1.5× upper limit of normal reference range (ULN);
c. Total bilirubin >ULN (>1.5 ULN in patients with Gilbert*s Syndrome);
d. History of portal hypertension, esophageal varices, or hepatic encephalopathy;
e. Presence of ascites by physical exam
5. Hepatitis C virus antibody positive, except patients with a history of HCV infection who meet both conditions a. and b.:
a. Completed curative treatment at least 12 weeks prior to enrollment and attained sustained virologic response as documented by a negative HCV RNA at screening, or they have spontaneously cleared infection as documented by negative HCV RNA at Screening.
b. No evidence of cirrhosis according to one of the following assessments:
* FibroScan <12.5 kPa (where available), or
* FibroTest score <0.75 and APRI <2 (if FibroScan unavailable)
6. Presence of acute hepatitis, ie, hepatitis A, hepatitis E.
7. Presence of acute or chronic hepatitis B infection (IgM anti-HBc antibody positive or HBsAg positive).
8. Platelet count *100,000/*L.
9. Presence of acute infection at Screening.
10. Known to be HIV positive with CD4 count <200 cells/*L.
11. Estimated glomerular filtration rate *45 mL/min/1.73m
2
(using the Modification of Diet
in Renal Disease [MDRD] formula).

12. Co-existing thrombophilic disorder, as determined by presence of any of the below as identified at central laboratory (or via historical results, where available):
a. FV Leiden (homozygous or heterozygous)
b. Protein S deficiency
c. Protein C deficiency
d. Prothrombin mutation (G20210A; homozygous or heterozygous)
13. History of antiphospholipid antibody syndrome.
14. History of arterial or venous thromboembolism, atrial fibrillation, significant valvular disease, myocardial infarction, angina, transient ischemic attack, or stroke. Patients who have experienced thrombosis associated with indwelling venous access may be enrolled.
15. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin that has been successfully treated.
16. Any condition (eg, medical concern), which in the opinion of the Investigator, would make the patient unsuitable for dosing on Day 1 or which could interfere with the study compliance, the patient*s safety and/or the patient*s participation in the completion of the treatment period of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to hemophilia identified by key laboratory abnormalities or medical history.
17. At Screening, anticipated need of surgery during the study or planned surgery scheduled to occur during the study.
18. Completion of a surgical procedure within 14 days prior to Screening, or currently receiving additional factor infusion for postoperative hemostasis.
19. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
20. Inadequate venous access, as determined by the Investigator, to allow the blood draws required by the study protocol.
21. History of intolerance to SC injection(s).
22. Current or future participation in another clinical study, scheduled to occur during this study, involving an investigational product other than fitusiran or investigational device; in order to participate in this study, patient must discontinue the investigational product at least 30 days (or 5× the investigational product half-life, whichever is longer) prior to dosing (Day 1).
23. Current or prior participation in a gene therapy trial.
24. History of alcohol abuse within the 12 months before Screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits (approximately 1 fluid ounce) = * pint of beer [approximately 284 mL]).

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fitusiran (INN)
Generic name:	ALN-AT3SC

Ethics review

Approved WMO

Date:	26-03-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	17-05-2018
Application type:	First submission
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	EUCTR2016-001464-11-NL
ClinicalTrials.gov	NCT03417245
CCMO	NL63022.000.18