A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, with Inhibitory Antibodies to Factor VIII or IX

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1.3. Study Design Rationale The ATLAS-INH trial (ALN-AT3SC-003) is a multicenter, multinational, randomized, openlabel Phase 3 study designed to demonstrate the efficacy and safety of fitusiran in patients with haemophilia A or B with inhibitory…

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

Summary

ID

NL-OMON46748

Source
ToetsingOnline

Brief title
ATLAS ALN-AT3SC-003

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

Primary

* Annualized Bleeding Rate (ABR) in the fitusiran efficacy period and the BPA

prophylaxis period

Secondary outcome

Secondary

* Annualized spontaneous bleeding rate in the fitusiran efficacy period and

the BPA prophylaxis period

* Annualized joint bleeding rate in the fitusiran efficacy period and the BPA

prophylaxis period

* Change in Haem-A-QOL score in the fitusiran treatment period

* ABR in the fitusiran onset period

* ABR in fitusiran treatment period

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. Some people with hemophilia also develop *inhibitors*

against their standard factor treatment. *Inhibitors* are antibodies (a type of protein made by your immune system) that stop your factor treatment from working, which makes forming blood clots even more difficult.

Fitusiran may make it possible to prevent or reduce the frequency of hemophilia-related bleeding in patients with hemophilia.

Study objective

1.3. Study Design Rationale
The ATLAS-INH trial (ALN-AT3SC-003) is a multicenter, multinational, randomized, openlabel Phase 3 study designed to demonstrate the efficacy and safety of fitusiran in patients with haemophilia A or B with inhibitory antibodies to FVIII or FIX who are
Currently treated with ondemand BPAs.

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 ofbleeding episodes; HRQOL; and to determine the safety and tolerability of fitusiran.
Blinding is not considered feasible for this study since 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 BPA 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.[6] A similar study in hemophilia patients without inhibitors (ALN-AT3SC-004) is being conducted concurrently to this study.
To protect against bias, patients will be assigned to fitusiran (fitusiran treatment arm; N=36) or on-demand BPA therapy (on-demand arm; N=18) 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 BPAs will be permitted
throughout the entire study duration (see Section 6.3.1).

Study design

an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B with inhibitory antibodies to factor VIII or IX previously receiving bypassing agent prophylaxis.

Study Design
The ATLAS-PPX trial (ALN-AT3SC-009) is a multicenter, multinational, open label, Phase 3 study designed to evaluate the efficacy and safety of fitusiran in male patients, aged *12 years, with hemophilia A or B, with inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who have
switched from prior bypassing agent (BPA) prophylaxis.
The study has 3 periods:
* 6-Month BPA prophylaxis period in which patients will continue their prestudy, regularly scheduled prophylaxis regimen with BPAs
* 1-Month onset period in which patients receive their first dose of 80 mg fitusiran while continuing their BPA prophylaxis for up to 7 days
* 6-Month fitusiran efficacy period in which patients receive 80 mg fitusiran as a once monthly prophylaxis Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period.
Bleeding events and doses of BPAs 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.
Following the screening and prophylaxis periods, all patients will be treated with fitusiran for a total of 7 months and will receive 7 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 final 6 months of the fitusiran treatment period (Day 29 to Month 7).
Throughout the study, patients may receive on-demand treatment for breakthrough bleeding episodes with BPAs.

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 who complete the study may be eligible for participation in an open-label extension study. For patients who do not enroll in the extension study, AT activity level will be monitored at monthly intervals following the final fitusiran dose until activity levels return to 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 with inhibitors, aged *12 years, who have been prescribed prophylactic treatment with BPAs for at least 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%. Patients with inhibitors must have used BPAs on demand to manage bleeding episodes for at least the last 6 months prior to Screening and must meet one of the following Nijmegen-modified Bethesda assay results criteria: 1) Inhibitor titer of *0.6 BU/mL at Screening, OR 2) Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers *0.6 BU/mL, OR 3) Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response. A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening is required.

Investigational Product, Dose and Mode of Administration
Fitusiran is a subcutaneously (SC) administered GalNAc-conjugated siRNA targeting liver-expressed messenger RNA (mRNA) for AT.
Patients will receive open-label fitusiran 80 mg as an SC injection once monthly, for a total of 7 months; dosing will begin on Day 1 of the fitusiran treatment period.

Reference Therapy, Dose and Mode of Administration
During the BPA prophylaxis period, patients will continue BPA prophylaxis as treatment for hemophilia on a regimen consistent with recommendations in the approved prescribing information, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding.
Dose and mode of administration will be per Investigator discretion; bleeding episode management should be per the local standard practice for episodic use of BPAs and as per Investigator discretion.
Patients will continue to receive BPA prophylaxis for the first 7 days of the onset period. Subsequently, breakthrough bleeding episodes will be treated with on-demand BPA therapy as necessary per the bleeding episode management guidelines.

Reference Therapy, Dose and Mode of Administration
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Study burden and risks

Fitusiran can increase the risk of developing blood clots by raising the AT-level in the blood.
The use of factor or bypassing agents while fitusiran is administered can increase the risk on developing blood clots even further. Blood clots can cause problems in the functioning of organs (e.g. lungs, heart, brain and kidneys), or cause swelling and pain in the arms or legs. In many cases blood clots are treatable with blood thinning medication, but sometimes blood clots can cause serious problems or death. In a clinical study with firusiran one patient developed a blood clot during treatment that resulted in death, and taking factor while receiving fitusiran may have been related to this event.

Risk on changes in liver function
As fitusiran is designed to go to the liver, there is a potential for changes in liver function tests. Abnormal liver tests have been seen in humans treated with fitusiran. Most of these cases have been mild and returned to normal.

Risk on bleeding
Subjects who are receiving fitusiran may be asked to use lower doses of factor or BPA than they are used to for treating bleeding events.

Contacts

Public
Alnylam Pharmaceuticals Inc.

300 Third Street
Cambridge MA 02142
US
Scientific

Alnylam Pharmaceuticals Inc.

300 Third Street
Cambridge MA 02142
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

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 with 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 bypassing agents to manage bleeding episodes for at least the last 6 months prior to Screening, and meet one of the following Nijmegen-modified Bethesda assay results criteria:
* Inhibitor titer of <=0.6 BU/mL at Screening, or
* Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers <=0.6 BU/mL, or
* Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response
3. A minimum of 6 bleeding episodes requiring bypassing agent 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

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 participation in immune tolerance induction therapy (ITI)
3. Current use of bypassing agents as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes.
4. AT activity <60% at Screening, as determined by central laboratory measurement.
5. 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
6. 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)
7. Presence of acute hepatitis, ie, hepatitis A, hepatitis E.
8. Presence of acute or chronic hepatitis B infection (IgM anti-HBc antibody positive or HBsAg positive).
9. Platelet count =100,000/µL.
10. Presence of acute infection at Screening.
11. Known to be HIV positive with CD4 count <200 cells/µL.
12. Estimated glomerular filtration rate =45 mL/min/1.73m2 (using the Modification of Diet in Renal Disease [MDRD] formula).
13. 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 mutation (homozygous or heterozygous)
b. Protein S deficiency
c. Protein C deficiency
d. Prothrombin mutation (G20210A; homozygous or heterozygous)
14. History of antiphospholipid antibody syndrome.
15. 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.
16. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin that has been successfully treated.

17. 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.
18. At Screening, anticipated need of surgery during the study or planned surgery scheduled to occur during the study.
19. Completion of a surgical procedure within 14 days prior to Screening, or currently receiving additional bypassing agent infusion for postoperative hemostasis.
20. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
21. Inadequate venous access, as determined by the Investigator, to allow the blood draws required by the study protocol.
22. History of intolerance to SC injection(s).
23. Current or future participation in another clinical study, scheduled to occur during this study, involving an investigational product other than fitusiran or an investigational device; in order to participate in this study, patient must discontinue the investigational product or investigational device at least 30 days (or 5× the investigational product halflife, whichever is longer) prior to dosing (Day 1).
24. Current or prior participation in a gene therapy trial.
25. 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
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fitusiran
Generic name:	Fitusiran

Ethics review

Approved WMO

Date:	03-05-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	24-07-2018
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	EUCTR2016-001463-36-NL
ClinicalTrials.gov	NCT03417102
CCMO	NL63088.000.18