

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219019Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	219019
Priority or standard	STANDARD
Submit date(s)	3/28/2024
Received date(s)	3/28/2024
PDUFA goal date	3/29/2025
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	Electronic Stamp
Established/proper name	Fitusiran
(Proposed) proprietary name	QFITLIA (fitusiran)
Pharmacologic class	Antithrombin-directed small interfering ribonucleic acid (siRNA)
Other product name(s)	SAR439774 or ALN-AT3SC
Applicant	GENZYME CORP
Dosage form(s)/formulation(s)	INJECTION, SOLUTION
Dosing regimen	The starting dose of fitusiran is 50 mg once every 2 months. The dose should be adjusted if needed, to maintain antithrombin (AT) activity between 15-35%. (b) (4)
Applicant-proposed indication(s)/population(s)	Indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.
SNOMED CT code for proposed indication disease term(s)¹	41788008
Regulatory action	Approval
Approved dosage (if applicable)	The starting dose of fitusiran is 50 mg once subcutaneously every 2 months. The dose should be adjusted, if needed, to maintain AT activity between 15-35%. Monitor AT activity using an FDA-cleared test.
Approved indication(s)/population(s) (if applicable)	Fitusiran is an antithrombin-directed small interfering ribonucleic acid indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.
SNOMED CT code for approved indication disease term(s)¹	41788008

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AAV	adeno-associated virus
AC	advisory committee
ABR	annualized bleeding rate
ADA	antidrug antibody
ADL	associate director for labeling
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AR	adverse reaction
ASPGR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AT	antithrombin
AT-DR	antithrombin-based dose regimen
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve estimated to infinity
AUC_{last}	area under the concentration-time curve to the last measurable concentration
BPA	bypassing agent
CDER	Center for Drug Evaluation and Research
CFC	clotting factor concentrate
C_{max}	maximum plasma concentration
CVST	cerebral venous sinus thrombosis
CYP	cytochrome P450 enzyme
DILI	drug-induced liver injury
FDA	Food and Drug Administration
FIX	factor IX
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FVIII	factor VIII
FX	factor X
GLP	good laboratory practice
HA	hemophilia A
Haem-A-QOL	Haemophilia Quality of Life Questionnaire for Adults
HAwI	hemophilia A with inhibitors
HB	hemophilia B
HBwI	hemophilia B with inhibitors
HD	high dose
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation

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IND	investigational new drug
ITT	intent-to-treat
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measure analysis
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
NDA	new drug application
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PFP	prefilled pen
PI	Prescribing Information
PK	pharmacokinetic
PopK-PD	population kinetic-pharmacodynamic
PRO	patient-reported outcome
PT	preferred term
QM	once monthly
QW	once weekly
Q2M	once every 2 months
rCYP	recombinant cytochrome P450 enzyme
RISC	RNA-induced silencing complex
SA	sensitivity analyses
SAE	serious adverse event
SC	subcutaneous
siRNA	double-stranded small interfering ribonucleic acid
SOC	standard-of-care
TEAE	treatment-emergent adverse event
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TK	toxicokinetic
ULN	upper limit of normal
WT	wild-type

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

The Applicant, Genzyme Corporation, submitted an NDA for fitusiran (trade name QFITLIA), an antithrombin (AT)-directed small interfering ribonucleic acid, for the following indication: routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors. The proposed starting dosage is 50 mg once subcutaneously (SC) every 2 months. The dose should be adjusted, if needed, to maintain AT activity in the range of 15 to 35%.

The Applicant conducted two adequate and well-controlled trials, in which fitusiran prophylaxis use at 80 mg once monthly (QM) demonstrated a substantial improvement in the annualized bleeding rate (ABR) compared to on-demand treatment in subjects with hemophilia A with inhibitors (HAwI) and hemophilia B with inhibitors (HBwI) (Study EFC14768), and subjects with hemophilia A without inhibitors (HA) and hemophilia B without inhibitors (HB) (Study EFC14769). During development, to mitigate the risk of thrombotic events, an antithrombin-based dose regimen (AT-DR) targeting an AT activity range of 15 to 35% was implemented. Subjects in the single-arm extension study (Study LTE15174), who used the to-be-marketed fitusiran AT-DR, were compared to the on-demand control arms from the randomized controlled parent studies (Study EFC19768 and Study EFC14769). We concluded that this comparison was also an adequate and well-controlled investigation and that it confirmed that the efficacy of fitusiran is preserved with the AT-DR.

Fitusiran has serious risks of thromboembolic events and gallbladder disease (including cholecystitis, cholelithiasis, and the need for cholecystectomy in some patients). These risks and mitigation recommendations will be described in a boxed warning. Hepatotoxicity is also a serious risk that will be described in a Warning and Precaution with recommendations for liver test monitoring. The incidence of these risks appears lower with the use of the AT-DR dose regimen. Contemporaneously with fitusiran's approval, the Center for Devices and Radiological Health (CDRH) is clearing a companion diagnostic assay so healthcare providers can accurately assess AT activity and adjust the fitusiran dose and frequency of administration, as needed, to target AT activity of 15 to 35%, which is essential for the safe and effective use of fitusiran.

The application was reviewed by a multidisciplinary review team. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit-risk profile is favorable as described in the Benefit-Risk Framework ([Table 2](#)). For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document, consult reviews (e.g., Drug-Induced Liver Injury team consultation), CDRH assessment of the AT assay, and the product quality review.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations. These included Study EFC14768 in subjects with HAwI and HBwI and Study EFC14769 in subjects with HA and HB as well as the comparison of subjects dosed with the AT-DR in Study LTE15174 with those in the on-demand control arms of Study EFC14768 and EFC14769.

Study EFC14768 was a randomized, multicenter, open-label clinical study in 57 adult and adolescent males (aged ≥ 12 years) with hemophilia A or B with inhibitors who previously received on-demand treatment with bypassing agents (BPAs) for bleeding. Eligible patients were randomized in a 2:1 ratio to receive fitusiran prophylaxis 80 mg SC QM (N=38) or BPA on demand for treatment of breakthrough bleeding episodes (N=19) for 9 months. In the fitusiran prophylaxis arm (80 mg QM), there was a 91% reduction in ABR for treated bleeds compared to the BPA on-demand arm (p value<0.0001) in the efficacy period, demonstrating that fitusiran prophylaxis at 80 mg QM provided a substantial reduction in bleeding compared to on-demand treatment with BPAs in subjects with HAwI and HBwI.

Study EFC14769 was a randomized, multicenter, open-label clinical study in 120 adult and adolescent males (aged ≥ 12 years) with hemophilia A or B without inhibitors who previously received on-demand treatment with clotting factor concentrates (CFCs) for bleeding. Eligible patients were randomized in a 2:1 ratio to receive fitusiran prophylaxis 80 mg SC once monthly (N=80) or CFCs on demand to treat bleeding episodes (N=40) for 9 months. In the fitusiran prophylaxis arm (80 mg QM), there was a 90% reduction in ABR for treated bleeds compared to the factor on-demand arm (p value<0.0001) in the efficacy period, demonstrating that fitusiran prophylaxis at 80 mg QM provided a substantial reduction in bleeding compared to on-demand treatment with CFCs in subjects with HA and HB without inhibitors.

Although fitusiran was originally developed as an 80 mg QM fixed dose regimen, the dose regimen was subsequently modified to an AT-DR after observing multiple thrombotic events and determining that the risk of thrombosis was increased with persistent AT levels <15%. The efficacy of fitusiran AT-DR treatment was assessed by comparing the fitusiran AT-DR treatment data from the long-term extension Study LTE15174 to the control data from studies EFC14768 and EFC14769. Of the 227 enrolled subjects in the long-term extension study, 78 subjects had inhibitors (HAwI=59 and HBwI=19) and 149 subjects did not have inhibitors (HA=115 and HB=34). In subjects with inhibitors treated with fitusiran, there was a 73% reduction (p-value<0.0006) in the estimated ABR for treated bleeds in the primary efficacy period compared to those treated with BPA on demand from the control data. In subjects without inhibitors, there was a 71% reduction (p-value<0.0001) in the estimated ABR for treated bleeds in subjects treated with fitusiran in the primary efficacy period compared to those treated with CFCs on-demand from the control data. In summary, the AT-DR provides substantial reduction in bleeding compared to on-demand treatment, consistent with the efficacy data from the 80 mg QM dose regimen.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Hemophilia A (HA) is an X-linked recessive disorder caused by mutations in the FVIII gene, which results in severe deficiency or absence of the clotting protein factor VIII. HA occurs in approximately 1 in 5,000 live male births. Patients are at increased risk for minor and serious bleeding, including life-threatening spontaneous or traumatic bleeding. Disease manifestations include mucosal bleeding, easy bruising, soft tissue and muscle bleeds, hemarthrosis, and excessive bleeding with procedures or trauma. Bleeding can occur in vital organs (including the brain). Adults commonly experience hemophilic arthropathy due to recurrent joint bleeds, which is associated with significant disease morbidity. • Hemophilia B (HB) is an X-linked recessive disorder caused by mutations in the FIX gene, which results in severe deficiency or absence of the clotting protein factor IX. HB occurs in approximately 1 in 30,000 live male births. Deficient factor IX levels result in an increased risk for minor and serious bleeding, including life-threatening spontaneous or traumatic bleeding. Disease manifestations of HB are the same as HA. • One of the most serious complications of HA and HB is development of inhibitors to factors, which is associated with the use of factor replacement. Approximately 30-35% of patients with HA and 5-15% of patients with HB develop inhibitors. Patients with inhibitors often experience increased disease morbidity and mortality because the bleeding is more difficult to prevent or treat.	Hemophilia A (congenital factor VIII deficiency) with or without FVIII inhibitors and hemophilia B (congenital factor IX deficiency) with or without FIX inhibitors are serious chronic diseases with significant morbidity and mortality due to bleeding. Patients with inhibitors tend to have a worse disease course.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- The goal of treatment in hemophilia is to prevent bleeding, improve joint function, relieve pain, and to assist the patient in continuing/resuming normal activities of daily living. - Current treatment options for patients with hemophilia A or B without inhibitors include either episodic IV infusion of the missing factor (FVIII or FIX) in response to symptoms of a bleed (“on-demand”) or scheduled prophylactic factor (FVIII or FIX) administration to prevent bleeds from occurring. - Prophylactic treatment in patients with severe hemophilia with replacement factor VIII or IX, has been proven to reduce the frequency of bleeding events and joint destruction; however, it requires lifelong IV infusion every 1 to 2 weeks, resulting in treatment burden, incomplete adherence, and complications associated with indwelling catheters (e.g., infection, thrombosis). These products can also lead to inhibitor formation: - Neutralizing alloantibodies (inhibitors) develop with exposure to exogenous factor and block the activity of factor VIII or IX. Approximately 30% of patients with HA and 1-15% of patients with HB will develop inhibitors against infused FVIII or FIX. - Immune tolerance induction (ITI) is used to eradicate the inhibitor, but this is only successful in 60-80% of cases in patients with HAwI and 15-30% of patients with HBwI. - Available non-factor-replacement therapies for hemophilia A or B include: - Emicizumab (HEMLIBRA) is a bispecific factor-IXa- and factor-X-directed antibody that was FDA-approved in 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with or without inhibitors. Emicizumab is administered weekly up to every 4 weeks by SC injection. Emicizumab has a boxed warning for thrombotic microangiopathy and thromboembolism associated with concomitant use of activated prothrombin complex concentrate (aPCC). - Marstacimab (HYMPAVZI) is a tissue factor pathway inhibitor (TFPI) antagonist that was FDA-approved in 2024 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with HA and HB without inhibitors. Marstacimab is a weekly SC injection. Marstacimab has a risk of hypersensitivity reactions, in addition to thromboembolic events.	The effectiveness of available therapy for prophylactic treatment of bleeds varies. There is a need for additional safe and effective therapies to prevent or reduce bleeding in patients with HA and HB with and without inhibitors. Treatment with factor replacement can result in significant treatment burden, including need for IV catheters, risks of infections and thrombosis, and development of inhibitors. There is also need for available therapies that can be dosed less frequently and by a more convenient route of administration (such as SC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Concizumab (ALHEMO) is a TFPI antagonist that was FDA-approved in 2024 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with HAwI and HBwI. Concizumab is a daily SC injection. Concizumab has a risk of hypersensitivity reactions, in addition to thromboembolic events. - Gene therapy options are FDA-approved for patients with HA and HB; however, not all patients are candidates. - FDA-approved bypassing agents are used to prevent or control bleeding in patients with inhibitors. aPCC is indicated to control and prevent bleeding episodes in patients with HAwI and HBwI. Recombinant activated coagulation factor VII (rFVIIa) is indicated for the treatment of bleeding episodes in patients with HAwI and HBwI. Efficacy of these products can be variable, and they carry a boxed warning for thrombosis.	
Benefit	- Studies EFC14768 and EFC14769 were multicenter, open-label clinical trials, in which patients with HA or HB with or without inhibitors were randomized 2:1 to fitusiran 80 mg QM or on-demand therapy. Both studies showed a statistically significant reduction in ABR for treated bleeds with fitusiran compared to on-demand therapy. - Study LTE15174 was a long-term extension study in which 227 subjects with HA or HB with or without inhibitors, who previously received fitusiran in EFC14768 or EFC14769, rolled over and received fitusiran AT-DR. Efficacy of fitusiran AT-DR was established by comparison of data from patients in the extension study LTE15174 with data from patients in the control arms of the parent studies. - In subjects with inhibitors treated with fitusiran prophylaxis, there was a substantial reduction in mean ABR for treated bleeds: 5.1 with 95% CI (2.8, 9.5) for AT-DR compared to 19.1 with 95% CI (11.8, 31.0) for on-demand BPA, with a resultant 73% reduction in estimated ABR for the fitusiran AT-DR compared to on-demand BPA (p=0.0006). - In subjects without inhibitors treated with fitusiran prophylaxis, there was a substantial reduction in mean ABR for treated bleeds: 9.0 with 95% CI (5.6, 14.5) for AT-DR compared to 31.4 with 95% CI (20.5, 48.2) for on-demand BPA, with a resultant 71% reduction in estimated ABR for the fitusiran AT-DR compared to CFC on-demand (p<0.0001).	Fitusiran AT-DR routine prophylaxis compellingly reduces the frequency of bleeding episodes in subjects with HA or HB with or without inhibitors when compared with on-demand BPA (in those with inhibitors) or on-demand CFCs (in those without inhibitors). The prevention and/or reduction of bleeding is a clinical benefit, expected to reduce the morbidity and mortality associated with hemophilia, including joint damage and hemorrhagic stroke. Fitusiran offers the additional convenience of less frequent dosing (every 1 to 2 months) by subcutaneous route.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Similar reductions in the magnitude of bleeding were reported in the estimated annualized spontaneous bleeding rate (AsBR) and estimated annualized joint bleeding rate (AjBR) in the fitusiran AT-DR group for both the inhibitor and noninhibitor groups. - In the inhibitor group, the mean AsBR for treated bleeds in the AT-DR group was 3.1 with 95% CI (1.8, 5.4) compared to 17.1 with 95% CI (9.9, 29.6) for on-demand BPA, with an estimated ABR reduction of 82% ($p < 0.0001$). The mean AjBR for treated bleeds was 4.0 with 95% CI (2.5, 6.2) in the fitusiran AT-DR group compared to 14.4 with 95% CI (9.0, 23.1) for on-demand BPA, with a 73% reduction in estimated ABR with fitusiran AT-DR ($p = 0.0001$). - In the noninhibitor group, the AsBR for treated bleeds in the AT-DR group was 5.4 with 95% CI (3.7, 8.0) compared to 21.0 with 95% CI (14.0, 31.6) for on-demand BPA, with an estimated ABR reduction of 74% ($p < 0.0001$). The AjBR for treated bleeds was 6.2 with 95% CI (4.2, 9.2) in the fitusiran AT-DR group compared to 21.6 with 95% CI (14.6, 31.9) for on-demand BPA, with a 71% reduction in the estimated ABR with fitusiran AT-DR ($p < 0.0001$).	
Risk and risk management	- Fitusiran was originally developed as an 80 mg QM dose; however, due to serious events of thrombosis associated with persistent AT activity $< 15\%$, the dosing regimen was modified to an AT-DR, targeting AT activity 15-35%. - Fitusiran's safety was evaluated primarily in 286 subjects who received fitusiran on the AT-DR. - There were no fatal adverse events on the AT-DR. - Serious adverse reactions occurred in 1.4% of subjects; the most common serious adverse reaction was cholecystitis ($N = 2$). - Adverse reactions leading to permanent discontinuation of fitusiran occurred in 1.4% of subjects and included liver injury, postoperative deep vein thrombosis, cerebral infarction, and pruritus. - Adverse reactions leading to dosage interruptions of fitusiran occurred in 0.7% patients and included increased serum transaminases.	The safety data submitted were sufficient to characterize the toxicity profile of fitusiran. The major risks of fitusiran include thrombotic events, gallbladder events, and hepatotoxicity, all of which appear to be reduced with the AT-DR compared to fixed-dosing. It is essential that patients maintain AT activity 15-35%, necessitating the contemporaneous approval of a companion diagnostic for measuring AT activity. The risk of thromboembolism with the use of fitusiran will be included in a Boxed Warning, together with mitigation strategies (e.g., noting use of the fixed dosing regimen is not approved, need to target AT activity 15-35%,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The most common adverse reactions (≥10%) were viral infection (29%), nasopharyngitis (26%), and bacterial infection (11%). Other reported adverse reactions (≥5%) included hepatic injury (8%), arthralgia (8%), prothrombin fragment 1.2 increased (7%), injection site reaction (6%), headache (5%), and cough (5%). • There are several risks that should be included in the Warnings and Precautions section and Boxed Warning of the United States Prescribing Information (USPI). These risks were identified from the pooled safety population, which includes exposure to fitusiran at fixed doses and the AT-DR (n=355). 1. Thromboembolic events were an adverse event of special interest based on the mechanism of action of fitusiran and the thrombotic events observed in the fitusiran fixed dosing regimen. Thrombotic events were reported in 7 subjects (2.6%) receiving fitusiran 80 mg QM prophylaxis, including a fatal cerebral venous sinus thrombosis event, and in 4 subjects (1.4%) receiving the AT-DR regimen. The risk of thrombosis was greater in patients with persistent AT activity <15%, when bleed management guidelines were not followed in the post-operative setting, with an indwelling venous catheter, and with use of the 80 mg once monthly dosing (not the approved dosing). Monitoring of AT activity using an FDA-cleared test (approved contemporaneously as a companion diagnostic) and targeting AT in the range of 15-35% is recommended to reduce the risk of thrombosis. 2. A risk of acute and recurrent gallbladder disease was identified. In the fitusiran development program, 17% of subjects receiving the fixed dose once monthly regimen experienced gallbladder events, 11 of whom (24%) underwent cholecystectomy. Gallbladder events were reported in 3.8% of subjects receiving the AT-DR, one of whom underwent cholecystectomy. All but one of the patients who underwent cholecystectomy resumed treatment after surgery. One subject who started on fixed dosing experienced cholangitis and pancreatitis caused by gallstone disease more than a year after cholecystectomy while receiving AT-DR dosing. 3. Hepatotoxicity was identified as a risk with the use of fitusiran. On the 80 mg once a month fixed dose regimen, alanine transaminase (ALT) and aspartate transaminase (AST) elevations above 3 times	and need to follow bleeding management guidelines). Fitusiran has a unique and unexpected risk of acute and recurrent gallbladder disease, which resulted in the need for surgical intervention in some subjects. Even routine surgeries in patients with hemophilia can be challenging due to bleeding complications. It is critical that prescribers are aware of this risk before prescribing fitusiran in order to identify signs/symptoms early and to consider whether fitusiran is the appropriate option for their patient. Therefore, this risk will be included in a Boxed Warning, together with mitigation strategies (e.g., considering alternative treatment for hemophilia in patients with a history of symptomatic gallbladder disease; considering interruption or discontinuation of fitusiran if gallbladder disease occurs). The risk of hepatotoxicity will be described in a Warning and Precaution, together with mitigation strategies (e.g., monitoring liver tests, potential need to interrupt or discontinue fitusiran). We will also require enhanced pharmacovigilance for thrombotic events, hepatotoxicity, and gallbladder disease (including cholelithiasis and cholecystitis) to further monitor these risks in the postmarketing setting.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the upper limit of normal (ULN) occurred in 13 subjects (31.7%) with hemophilia with inhibitors and 14 subjects (17.7%) with hemophilia without inhibitors compared to no events in the control group. A Hy's law event occurred on the 80 mg QM dose. On the AT-DR, a total 3.4% subjects exposed to fitusiran had at least one ALT value three or more times the ULN. 4. Although these major risks appear lower with the AT-DR, one important limitation is that only patients who tolerated and completed the parent studies using the fixed-dose regimen were eligible for the AT-DR.	

Abbreviations: ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; ALT, alanine aminotransferase; aPCC, activated prothrombin complex concentrate; AsBR, annualized spontaneous bleeding rate; AST, aspartate aminotransferase; AT, antithrombin; AT-DR, antithrombin-based dose regimen; CFC, clotting factor concentrate; FIX, factor IX; FVIII, factor VIII; HA, hemophilia A; HAwI, hemophilia A with inhibitors; HB, hemophilia B; HBwI, hemophilia B with inhibitors; ITI, immune tolerance induction; IV, intravenous; QM, once monthly; rFVIIa, recombinant activated coagulation factor VII; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; ULN, upper limit of normal; USPI, United States Prescribing Information

2.2. Conclusions Regarding Benefit-Risk

Hemophilia is a rare, serious, and chronic hematologic disorder caused by an inherited deficiency in factor VIII (hemophilia A) or factor IX (hemophilia B), leading to an increased risk of minor and life-threatening bleeding. Therapy is either given on demand, in which the replacement factor or BPA is given at the time of bleeding, or as prophylaxis, in which the therapy is continuously administered to prevent bleeding from occurring. Treatment with clotting factor concentrate can lead to inhibitor development, a serious complication in which bleeding is more difficult to manage. Newer treatments are available for patients depending on the hemophilia subtype and presence or absence of inhibitors, including emicizumab, marstacimab, and concizumab. Despite available therapies, new treatment options are needed.

The efficacy data for fitusiran prophylaxis demonstrate a large, compelling reduction in ABR using AT-DR compared to on-demand treatment with BPA (in those with hemophilia A or B with inhibitors) and compared to CFC (in those with hemophilia A or B without inhibitors). The prevention of bleeding, a clinical benefit, is expected to reduce the morbidity and mortality associated with hemophilia. Fitusiran has the added benefit of every 1- to 2-month SC dosing, based on the AT level; a less frequent administration of the drug is beneficial for patients who may take it lifelong.

The risks of fitusiran can adequately be described with labeling. Thrombotic events and acute and recurrent gallbladder disease will be included in a Boxed Warning and the risk of hepatotoxicity will be included in the Warnings and Precautions. The incidence of these three risks was lower with the AT-DR compared to the non-approved fixed-dosing regimen; therefore, monitoring of AT activity and targeting AT activity in the range of 15-35% is essential for the safe and effective use of fitusiran. An FDA-cleared AT activity assay is being contemporaneously approved with fitusiran as a companion diagnostic. These risks are further mitigated with instructions in labeling (e.g., need to follow bleed management guidelines to reduce thrombotic risks; need to consider alternative hemophilia therapy in patients with a history of symptomatic gallbladder disease; need to monitor liver tests while on treatment) and will be communicated to patients in a Medication Guide.

The large benefit of fitusiran on reducing bleeding outweighs the identified risks when the mitigation approaches described in labeling are followed, providing another useful treatment option for patients with this serious, life-threatening disease. Labeling recommends use of fitusiran by healthcare providers experienced in the treatment of hemophilia, who are the most likely prescribers. These prescribers are well-versed in managing these complex diseases and determining the best treatment option for their specific patients considering the benefits and risks of the available therapies.

II. Interdisciplinary Assessment

3. Introduction

Fitusiran (proprietary name QFITLIA), a new molecular entity, is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of antithrombin (AT) messenger RNA (mRNA) through RNA interference, reducing plasma AT levels. AT is a serine protease inhibitor that inactivates thrombin (factor IIa) and factor Xa, along with other enzymes in the coagulation system. Lower plasma AT protein levels lead to increases in thrombin generation and an improved ability to form stable clots. Fitusiran acts independently from factor VIII (FVIII) and factor IX (FIX), and thus would not be expected to result in the formation of factor-neutralizing antibodies.

The Applicant proposes the following indication: for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A (HA) (congenital factor VIII deficiency) with or without factor VIII inhibitors, or hemophilia B (HB) (congenital factor IX deficiency) with or without factor IX inhibitors.

The proposed dosing regimen is 50 mg subcutaneously once every 2 months, with dose adjustments to maintain AT activity between 15 and 35% using an FDA-authorized AT activity assay.

Disease Background

Congenital hemophilia is a rare X-linked bleeding disorder caused by deficiencies of FVIII in HA and FIX in HB. Patients with HA or HB have a deficiency in the prothrombinase complex, essential for the conversion of prothrombin to thrombin, which is crucial for hemostasis ([Sidonio et al. 2023](#)). HA and HB occur in all racial and ethnic groups and are due to missense, nonsense, or deletions in *F8* or *F9*, respectively. The prevalence of HA is estimated at 24.6 cases per 100,000 male births, while HB prevalence is estimated at 5 cases per 100,000 male births; in both HA and HB, approximately 30 to 40% of cases are sporadic, or born to a noncarrier mother ([Seaman et al. 2021](#); [Sidonio and Malec 2021](#)). The severity of hemophilia is correlated with residual factor levels, with mild defined as between 5 and less than 40% FVIII or FIX activity, moderate as between 1 to less than 5% activity, and severe as less than 1% activity ([Srivastava et al. 2020](#)). Severe disease occurs in roughly 30% of HB and 40% of HA. Inhibitors to FIX occur in 5 to 15% of severe HB, whereas inhibitors to FVIII occur in 30% of severe HA. Differences in severity and inhibitor development between HA and HB are related to the differences in the size of the respective genes, and the types of genetic lesions that differ between HA and HB ([Castaman and Matino 2019](#)).

Clinical hallmarks of severe hemophilia are spontaneous or traumatic joint, soft tissue, and muscle hemorrhages ([Sidonio et al. 2023](#)), and prolonged and potentially fatal hemorrhage after trauma or surgery. In patients with HA or HB, neutralizing antibodies known as FVIII or FIX inhibitors, respectively, may develop, rendering exogenous factor replacement ineffective. The main risk factors for inhibitor development are hemophilia severity, *F8/F9* genotype, and

cumulative exposure to FVIII and FIX concentrates ([Rezende et al. 2024](#)). Individuals with hemophilia with inhibitors are more difficult to treat in response to bleeding events, leading to a higher rate of progressive joint disease from frequent joint bleeds and increased risk of death from uncontrolled bleeding.

The goal of treatment in severe hemophilia is to prevent or minimize the occurrence of bleeding to improve joint function, alleviate pain, and help the patient to continue/resume regular daily activities. Treatment with replacement factor can either be in response to a bleeding event (“on-demand”) or scheduled to prevent bleeds by maintaining factor levels in a protective range (prophylactic treatment). There is significant evidence that prophylactic treatment in children with severe hemophilia prevents bleeding episodes and the associated joint damage ([Manco-Johnson et al. 2007](#)). In individuals with severe hemophilia, an early start of treatment with long-term prophylaxis is reported to reduce bleeding frequency and subsequent chronic joint disease and result in better quality of life, and is recommended by international hemophilia care organizations ([Srivastava et al. 2020](#); [Rezende et al. 2024](#)). The choice of regimens (i.e., on-demand or prophylaxis) is multifactorial and may be based on frequency and severity of bleeding, patient preference and lifestyle, and regional/geographic standard of care. The World Federation of Hemophilia strongly recommends prophylactic treatment for patients with severe hemophilia A or B with or without inhibitors to prevent bleeds at all times. Prophylaxis should be individualized (adjusting prophylaxis dose/frequency or both), taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference ([Konkle et al. 2019](#)).

The treatment options for severe hemophilia have advanced from plasma-derived factor replacement to recombinant factor replacement, extended half-life recombinant factor replacement, non-factor-replacement therapy, and gene therapy. Annualized bleeding rate (ABR) has become the primary outcome measure to demonstrate the success of treatment products for severe hemophilia ([Konkle et al. 2019](#)). ABR is a clinically meaningful endpoint, as a reduction in bleeding events is important to patients by decreasing risk of mortality and organ and tissue damage, including joint damage, and allowing greater activity that might otherwise be limited due to risk of trauma and bleeding.

Current Therapeutic Options

The current prophylaxis treatment options for patients with severe HA or HB without inhibitors include:

1. Prophylactic treatment with replacement factors, which has been proven to reduce the frequency of bleeding events; however, this approach requires frequent IV infusion, resulting in high treatment burden, incomplete adherence, complications associated with indwelling catheters (e.g., infection, thrombosis) and can lead to the development of factor inhibitors. Replacement factor therapy includes both plasma-derived factor concentrates and recombinant factor concentrates.
2. Non-factor-replacement therapies have been designed to provide an alternative to conventional replacement treatment and either increase thrombin generation through the inhibition of naturally occurring anticoagulants, or by mimicking the action of factor VIII. These agents are designed to work in the prophylaxis context, are not indicated for

management of acute bleeding episodes, and are typically dosed subcutaneously on either weekly or monthly schedules.

- a. Emicizumab (Hemlibra) subcutaneous (SC) injection is a bispecific FIXa- and factor X (FX)-directed antibody, approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with HA with and without inhibitors. The emicizumab product label ([Genentech 2024](#)) contains a boxed warning that states cases of thrombotic microangiopathy and thrombotic events were reported when, on average, a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving emicizumab prophylaxis.
 - b. Marstacimab (Hymravzi) is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with HA or HB without inhibitors. Dosing is weekly SC. Thromboembolic events may occur and are listed in warnings and precautions ([Pfizer Laboratories Div Pfizer Inc 2025](#)).
3. Adeno-associated virus (AAV)-based gene therapy introduces an AAV vector that inserts a functional copy of the missing clotting factor gene into patients' hepatocytes so that clotting factor can be expressed ([Deshpande et al. 2024](#)). Advantages of gene therapy include a one-time infusion and factor expression levels that provide excellent prophylaxis. Although these therapies appear to have few serious adverse events, a notable toxicity of hepatotropic AAV-based gene therapy is liver toxicity, which can result in loss of transgene expression of factor.

The current prophylaxis treatment options for patients with severe HA or HB without inhibitors is detailed in [Table 3](#).

Table 3. Approved Products Indicated for Prophylaxis in Severe Hemophilia Without Inhibitors

Product	Prophylaxis (P)			
	On-Demand (OD)	FDA Approval	Hemophilia A Indication	Hemophilia B Indication
Factor Replacement Products				
FVIII products*	P, OD	2000-2023	X	
FIX products*	P, OD	1997-2017		X
Non-Factor-Replacement Products				
Hemlibra (emicizumab)	P	2017	X	
Hymravzi (marstacimab)	P	2024	X	X
Gene Therapy Products				
Hemgenix (etranacogene dezaparvovec-drlb)	P	2022		X
Roctavian (valoctocogene roxaparvovec-rvox)	P	2023	X	
Beqvez (fidanacogene elaparvovec-dzkt)	P	2024		X

Source: Clinical Reviewer

*12 factor VIII replacement products and 6 factor IX replacement products are approved since 1997.

Abbreviations: FIX, factor IX; FVIII, factor VIII; OD, on demand; P, prophylaxis

The current prophylaxis treatment options for patients with severe hemophilia A with inhibitors (HAwI) or hemophilia B with inhibitors (HBwI) include:

4. Non-factor-replacement therapies
- a. Emicizumab (Hemlibra) is also approved for HAwI; see description of the product above.
 - b. Concizumab (Alhemo) is a TFPI antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with HA or HB with inhibitors. Alhemo is dosed daily via SC injection. Thromboembolic events may occur and are listed as a warning in the label ([Novo Nordisk 2024](#)).
5. Bypassing agents, including recombinant activated factor VII or activated prothrombin complex concentrates, are limited by short half-lives requiring daily IV infusion and by cost. Bypassing agents can be used for prophylaxis in both HA and HB with inhibitors. Bypassing agents are also associated with thrombotic risk.

The current prophylaxis treatment options for patients with severe HAwI or HBwI is outlined in [Table 4](#).

Table 4. Approved Products Indicated for Prophylaxis in Severe Hemophilia With Inhibitors

Product	Prophylaxis (P) On Demand (OD)	FDA Approval	Hemophilia A	Hemophilia B
			With Inhibitors Indication	With Inhibitors Indication
Bypassing Agents				
FEIBA (anti-inhibitor coagulant complex)	P, OD	1986	X	X
Novoseven RT (coagulation factor VIIa, recombinant)	OD	1999	X	X
Sevenfact (coagulation factor VIIa recombinant-jncw)	OD	2020	X	X
Non-Factor-Replacement Products				
Hemlibra (emicizumab)	P	2017	X	
Alhemo (concizumab)	P	2024	X	X

Source: Clinical Reviewer
Abbreviations: FIX, factor IX; FVIII, factor VIII; OD, on demand; P, prophylaxis

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Demonstration of Benefit of Fitusiran: Antithrombin-Based Dose Regimen Efficacy Data From the Long-Term Extension Study Compared to Control Data From Randomized Parent Studies

3.1.2. Key Safety Review Issues

3.1.2.1. Thrombotic Events

3.1.2.2. Acute and Recurrent Gallbladder Disease

3.1.2.3. Hepatotoxicity

3.2. Approach to the Clinical Review

[Table 5](#) provides an overview of the clinical studies conducted to support the benefit-risk assessment of fitusiran for subjects with HA and HB with and without inhibitors.

Results from subjects with HA and HB with and without inhibitors from the parent studies EFC14768 and EFC14769, and the extension study LTE15174 formed the primary basis for the assessment of efficacy. The primary assessment of efficacy for the fitusiran 80 mg QM dosage was based on the parent studies, EFC14768 and EFC14769. The assessment of efficacy for the AT-DR was based on a comparison of efficacy data from subjects who received the AT-DR during the single arm extension study LTE15174 to those who used on demand treatment during the parent studies EFC14768 and EFC14769.

The assessment of risk for the fitusiran AT-DR was primarily based on pooled analyses of subjects who received the AT-DR from Studies LTE15174, LTE14762, and EFC15110 (N=286). Additionally, assessment of risk was based on data from a pooled safety set comprising all adverse events occurring in subjects with HA or HB with or without inhibitors while receiving any dosage of fitusiran in a clinical study (N=335).

See [Figure 20](#), Section [12](#) for the timeline of clinical studies in relation to AT-DR across the fitusiran development program.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

Fitusiran is an antithrombin-directed small interfering ribonucleic acid indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.

2. SEE was established with

a. Adequate and well-controlled clinical investigation(s):

- i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
- ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

- c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

3. Complete response, if applicable

- a. ☐ SEE was established
- b. ☐ SEE was not established (if checked, omit item 2)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#))

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([May 1998](#))

³ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#))

Table 5. Clinical Trials Submitted¹ in Support of Efficacy and Safety Determinations for Fitusiran

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
EFC14768	Males aged ≥12 years with severe hemophilia A or B with inhibitors	Control Type: On-demand treatment with BPA	Drug (established name): Fitusiran	Primary: ABR in the efficacy period	Planned: 54	Centers: 26
		Randomization: Stratified randomization	Dose: Fitusiran 80 mg QM or BPA on-demand	Secondary: See footnotes ²	Actual: 57	Countries: 12
		Randomization Ratio: 2:1	Number treated: Fitusiran N=41, BPA N=19			
		Blinding: Open label				
		Biomarkers: No biomarkers	Duration (quantity and units): 9 months			
		Innovative design features: None				
EFC14769	Males aged ≥12 years with severe hemophilia A or B without inhibitors	Control Type: on-demand treatment with CFC	Drug (established name): Fitusiran	Primary: ABR in the efficacy period	Planned: 120	Centers: 42
		Randomization: Stratified randomization	Dose: Fitusiran 80 mg QM or Factor on-demand	Secondary: See footnotes ³	Actual: 120	Countries: 18
		Randomization Ratio: 2:1	Number treated: Fitusiran N=79, Factor N=40			
		Blinding: Open label				
		Biomarkers: No biomarkers	Duration (quantity and units): 9 months			
		Innovative design features: None				

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
EFC15110	Males aged ≥12 years with severe hemophilia A or B with or without inhibitors receiving factor/BPA prophylaxis	Control Type: No treatment concurrent (single-arm switching study, baseline control) Randomization: No randomization (single-arm) Randomization Ratio: No randomization (single-arm) Blinding: Open label Biomarkers: Biomarker to modify dose Innovative design features: None	Drug (established name): Fitusiran Dose: Factor/BPA prophylaxis before switching to fitusiran 80 mg QM until the dose pause. After dosing resumed, fitusiran 50 mg Q2M (to target an AT level of 15% to 35%) Number treated: Fitusiran N=69, Factor/BPA N=78 Duration (quantity and units): 6 months Factor/BPA then 7 months fitusiran	Primary: ABR during the factor/BPA prophylaxis period and the efficacy period Secondary: See footnotes ⁴	Planned: 99 screened Actual: 80	Centers: 32 Countries: 15

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
LTE15174	Adult males who completed EFC14768, EFC14769, or EFC15110	Control Type: No treatment concurrent (single-arm)	Drug (established name): Fitusiran	Primary: Not applicable as the primary objective is to evaluate the long-term safety and tolerability of fitusiran. Secondary: See footnotes ⁵	Planned: 293 screened	Centers: 79
	Chinese males aged ≥12 years with severe hemophilia A or B with or without inhibitors enrolled directly into LTE15174	Randomization: No randomization (single-arm)	Dose: Initially, fitusiran 80 mg QM until the dose pause. When dosing resumed, fitusiran 50 mg Q2M, 50 mg QM, 80 mg QM, 20 mg Q2M, or 20 mg QM to target an AT level of 15% to 35%		Actual: 281	Countries: 20
		Randomization Ratio: No randomization (single-arm)				
		Blinding: Open label	Number treated: 281			
		Biomarkers: Biomarker to modify dose	Duration (quantity and units): Up to 76 months			
		Innovative design features: None				

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
LTE14762	Adult males with moderate or severe hemophilia who completed TDR14767, a PK study with SAD and MAD portions	Control Type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Randomization Ratio: No randomization (single-arm) Blinding: Open label Biomarkers: Biomarker to modify dose Innovative design features: None	Drug (established name): Fitusiran Dose: Initially fitusiran 50 mg QM or 80 mg QM until the dose pause, then 50 mg Q2M, 50 mg QM, or 80 mg QM to target an AT level of 15% to 35% Number treated: 34 Duration (quantity and units): Up to 84 months	Primary: Not applicable as the primary objective is to evaluate the long-term safety and tolerability of fitusiran. Secondary: See footnotes ⁶	Planned: Maximum of 51 subjects who enrolled in TDR14767 Actual: 34	Centers: 13 Countries: 5

Source: Clinical Study Report and adsl.xpt

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² Secondary endpoints EFC14768: ABR in the efficacy period (key secondary; US protocol); ABR in the treatment period (global protocol); annualized spontaneous bleeding rate in the efficacy period; annualized joint bleeding rate in the efficacy period; change in Haem-A-QoL physical health score and total score in the treatment period; ABR in the onset period; incidence, severity, seriousness, and relatedness of AEs

³ Secondary endpoints EFC14769: ABR in the efficacy period (key secondary; US protocol); ABR in the treatment period (global protocol); annualized spontaneous bleeding rate in the efficacy period; annualized joint bleeding rate in the efficacy period; change in Haem-A-QoL physical health score and total score in the treatment period; ABR in the onset period; incidence, severity, seriousness, and relatedness of AEs

⁴ Secondary endpoints EFC15110: ABR in treatment period (Global protocol); ABR in the onset period; annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period; annualized joint bleeding rate in the fitusiran efficacy period and the factor or BPA prophylaxis period; change in Haem-A-QoL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period

⁵ Secondary endpoints LTE15174: ABR in the treatment period; annualized spontaneous bleeding rate in the treatment period; annualized joint bleeding rate in the treatment period; change in Haem-A-QoL physical health score in the treatment period (in subjects ≥17 years of age)

⁶ Secondary endpoints LTE14762: ABR during the efficacy period; annualized spontaneous bleeding rate during the efficacy period; annualized joint bleeding rate during the efficacy period; time intervals between bleeding events; annualized weight-adjusted consumption of factor VIII, factor IX and BPA; QoL measured by EuroQoL 5-dimension 5 level (EQ-5D-5L) score; QoL measured by Haem-A-QoL; AT activity level over time; thrombin generation over time; plasma PK parameters of fitusiran; urine PK parameters of fitusiran
Abbreviations: ABR, annualized bleeding rate; AE, adverse event; AT, antithrombin; BPA, bypassing agents; Haem-A-QoL, haemophilia quality of life questionnaire for adults; No., number; PK, pharmacokinetics; Q2M, every-other-month dosing; QM, monthly dosing; QoL, quality of life

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		See 16.5.
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☒	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (Qualitative studies from literature)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

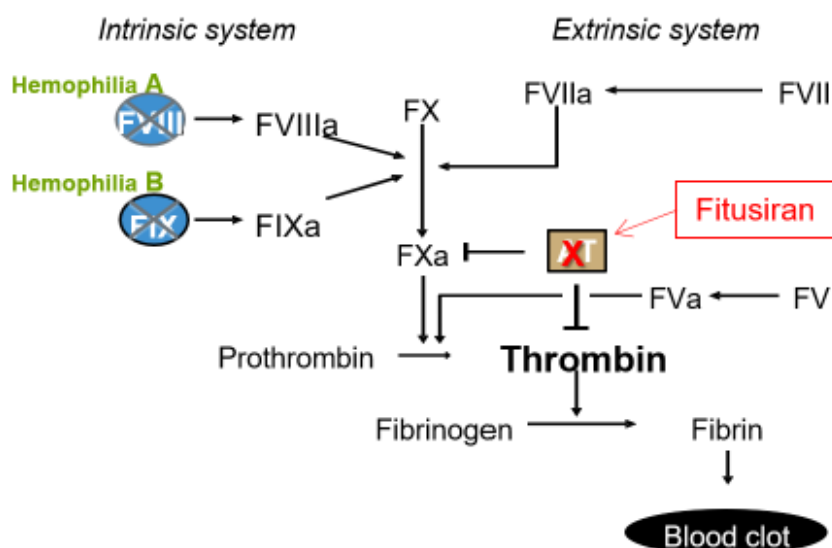
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Hemophilia A and hemophilia B are inherited X-linked genetic bleeding disorders characterized by a deficiency in blood clotting factors in the intrinsic coagulation pathway, which causes an increased risk of bleeding in affected patients. Antithrombin (AT) is a liver-expressed anticoagulant protein that is the major endogenous inhibitor of the coagulation factor thrombin. Fitusiran (AD-57213 or ALN-AT3SC) is a synthetic double-stranded small interfering RNA (siRNA), designed to suppress liver production of AT as a strategy to rebalance the coagulation cascade by increasing thrombin generation to improve hemostasis in individuals with hemophilia. Fitusiran contains a conjugated triantennary N-acetylgalactosamine (GalNAc) sugar ligand that binds to the asialoglycoprotein receptor (ASGPR) on hepatocytes ([Cummings and](#)

[McEver 2009](#)). Upon binding, the ASPGR-fitusiran complex is internalized and processed in endosomes, where fitusiran is loaded onto the RNA-induced silencing complex (RISC), which guides fitusiran to the target AT mRNA sequence (transcribed from the *SERPINC1* gene) and utilizes RNA interference mechanisms to specifically target/degrade AT mRNA. Reduced AT mRNA levels result in lowered plasma AT protein levels, increased thrombin generation potential, and improved ability to form stable clots ([Figure 1](#)).

Figure 1. Mechanism of Action of Fitusiran



Source: Applicant's Application Orientation Meeting
Coagulation model depicting two separate initiations, intrinsic (contact) and extrinsic pathways, which ultimately merge at the level of factor Xa (common pathway). In hemophilia A and B, the lack of FVIII and FIX, respectively, leads to a decrease in thrombin potential, resulting in a bleeding phenotype.
Abbreviations: F, factor

5.1.1. In Vitro Characterization of Fitusiran

To establish the proof of concept for fitusiran as a potential treatment for hemophilia, a series of in vitro and in vivo pharmacology studies was conducted by the Applicant. The ability of fitusiran to reduce AT mRNA, protein, and activity levels was characterized in vitro using HepG2 cells (immortalized human liver cells) and evaluated in vivo using various wild-type (WT) species, transgenic mouse models of hemophilia A (HA) and B (HB), an HA dog model (genetic), and an HA monkey model (anti-FVIII antibody). The specificity of fitusiran for the AT mRNA was evaluated using bioinformatics methodology and in vitro in HepG2 cells.

5.1.2. In Vitro Pharmacological Activity of Fitusiran

Addition of fitusiran to HepG2 cells in vitro resulted in a dose-dependent inhibition of AT mRNA levels with a half maximal inhibitory concentration of 49.6pM. There was no appreciable off-target inhibition detected for any of the eight potential off-target transcripts identified by bioinformatics analyses and tested in HepG2 cells at up to 10nM fitusiran, which supported the specificity of fitusiran for the AT mRNA. Refer to Section [13](#) for additional details on these studies.

5.1.3. In Vivo Proof of Concept Animal Model Data

Fitusiran is pharmacologically active in mice, rats, dogs, and cynomolgus monkeys, as the AT mRNA target sequence is fully conserved (mice, rats, monkeys) or highly conserved (dogs) with the human sequence. AT levels were assessed following single and repeated subcutaneous administrations of fitusiran in WT mice and healthy monkeys, and in mouse, monkey, and dog models of hemophilia. In WT mice, single SC doses of fitusiran >10 mg/kg led to dose-dependent AT suppression exceeding 80%. Consistent with the long tissue residence typical of siRNA drugs, AT mRNA suppression was maintained for at least 28 days postdosing. A single SC dose of fitusiran up to 2 mg/kg in healthy monkeys resulted in AT protein reductions of up to 70%. Further AT reductions up to 80% were observed following 6 months of repeated monthly dosing. Consistent with the intended therapeutic mechanism, reduction of AT was associated with increased thrombin generation. These data confirmed the ability of fitusiran to hit the intended target in vivo and suggested that a less frequent dosing regimen might be suitable for the intended hemophilia patient population.

Mouse models of hemophilia have been generated by disruption of the genes encoding clotting factor VIII (modeling hemophilia A) or factor IX (modeling hemophilia B). These models exhibit bleeding tendencies similar to those observed in humans with hemophilia ([Sabatino et al. 2012](#)). A single SC administration of fitusiran up to 30 mg/kg in hemophilia A (factor VIII knockout) mice resulted in a dose-dependent suppression of AT expression of >80% at ≥ 10 mg/kg when compared to untreated HA mice. Similarly, a single-dose SC administration of fitusiran up to 30 mg/kg fitusiran in hemophilia B (factor IX knockout) mice resulted in a dose-dependent suppression of AT of up to 90% compared to untreated HB mice. A dose-related increase in endogenous thrombin up to 155% was observed at 30 mg/kg in HB mice when compared to control HB mice, predicting an improved ability of the hemophilia mice to form clots. Fitusiran activity was sustained for the duration of a 26-week repeat-dose study in HA mice; once-weekly administration of fitusiran up to 30 mg/kg/week resulted in a significantly decreased activated partial thromboplastin time of up to 60% and up to 90% suppression of plasma AT protein levels compared to control HA mice. Studies in mouse hemophilia models provided important proof of concept data and supported the initiation of clinical development of fitusiran for the treatment of hemophilia. The HA and HB mouse proof of concept data were further corroborated by studies in a genetic dog model of HA and in an HA monkey model where hemophilia was induced using an anti-FVIII monoclonal antibody (MAb). Details of these studies can be found in Section [13](#).

Functional improvements in hemostatic endpoints in HA (factor VIII knockout) mice were assessed using the microvessel laser injury method to compare the ability to form clots in fitusiran-treated versus untreated animals. HA mice were given a single SC administration of fitusiran up to 30 mg/kg prior to injury. Ten days later, the cremaster muscle was injured by laser to induce bleeding. A dose-related increase in the accumulation of platelets and fibrin and improved thrombus formation within 3 minutes were observed in fitusiran-treated HA mice, while no clotting was detected in PBS-treated HA mice. Stable thrombus formation was similarly demonstrated in HB (factor IX knockout) mice using the same methodology. These studies in clinically relevant mouse models link the fitusiran mechanism of action data (decreased AT mRNA, protein expression, and activity) with the desired clinical outcome of reduced clotting times in the presence of injury and suggest that fitusiran can be used prophylactically in the clinic (as opposed to use as a rescue treatment).

Overall, fitusiran administration in healthy animals and hemophilia animal models resulted in dose-dependent decreases in AT mRNA, protein, and activity; decreased activated partial thromboplastin time; and increased endogenous thrombin formation, which supported the proposed mechanism of action. Fitusiran caused sustained reductions of AT mRNA that were anticipated based on the long tissue residence times observed with other siRNA drugs in animals and humans; these data supported the development of less frequent clinical dosing regimens (e.g., once every 8 weeks). Administration of fitusiran prior to laser injury in hemophilia mice led to consistent clot formation at the injury site, demonstrating the desired functional improvement in clinically relevant hemophilia models with real world implications; these data support a plausible mechanism of action by which fitusiran may prevent or reduce the frequency of bleeding episodes. Overall, the results from the studies support the therapeutic rationale for the use of fitusiran as a potentially effective treatment for patients with hemophilia A or B.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 7. Summary of Clinical Pharmacology and Pharmacokinetics

Table 11. Summary of Clinical Pharmacology and Pharmacokinetics																
Characteristic	Drug Information															
	Pharmacologic Activity															
Established pharmacologic class (EPC)	Fitusiran is an antithrombin-directed small interfering ribonucleic acid															
Mechanism of action	Fitusiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of antithrombin (AT) messenger RNA through RNA interference, which results in a reduction of plasma AT levels.															
Active moieties	Fitusiran siRNA solution for SC administration															
QT prolongation	A thorough QT (TQT) study was not conducted in humans with fitusiran because data from nonclinical and clinical studies provide the totality of evidence that fitusiran is not associated with QTc prolongation up to 80 mg QM.															
	General Information															
Bioanalysis	Plasma fitusiran concentration was quantified using a validated liquid chromatography with fluorescence detection (LC-FD) method															
Healthy subjects versus patients	Based on the population PK analysis, hemophilia type and inhibitor status do not impact the PK of fitusiran.															
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	The plasma PK parameters of fitusiran following 20 and 50 mg are shown below: <table><tr><td>Dose 20 mg: Parameter</td><td>Mean±SD</td><td>Dose 50 mg: Parameter</td><td>Mean±SD</td></tr><tr><td>AUC</td><td>491±83.8 ng*h/mL</td><td>AUC</td><td>1290±377 ng*h/mL</td></tr><tr><td>C_{max}</td><td>34.4±10.1 ng/mL</td><td>C_{max}</td><td>84.1±58.7 ng/mL</td></tr></table> In the majority of subjects, fitusiran concentrations in plasma were below the LLOQ (0.2 ng/mL) by 24 to 48 hours postdose. Model-derived individual steady-state exposures for subjects with hemophilia from four phase 3 studies are provided in Appendix 11 of the Population Pharmacokinetic Study Report POH1086.				Dose 20 mg: Parameter	Mean±SD	Dose 50 mg: Parameter	Mean±SD	AUC	491±83.8 ng*h/mL	AUC	1290±377 ng*h/mL	C _{max}	34.4±10.1 ng/mL	C _{max}	84.1±58.7 ng/mL
Dose 20 mg: Parameter	Mean±SD	Dose 50 mg: Parameter	Mean±SD													
AUC	491±83.8 ng*h/mL	AUC	1290±377 ng*h/mL													
C _{max}	34.4±10.1 ng/mL	C _{max}	84.1±58.7 ng/mL													
Range of effective dose(s) or exposure	The starting dose is 50 mg Q2M. If needed, the starting dose can be escalated or de-escalated depending on whether the subject's AT activity is >35% or <15%, respectively. The modified doses include 50 mg QM, 20 mg Q2M, 20 mg QM, 10 mg Q2M, or 10 mg QM.															
Maximally tolerated dose or exposure	No maximum tolerated dose was identified. The highest dose studied was 80 mg QM.															
Dose proportionality	Fitusiran exhibited a dose-proportional increase in plasma exposure over the dose range of 20 to 50 mg following single-dose SC administration.															
Accumulation	No accumulation of fitusiran was observed following multiple once weekly (QW) or QM doses, as fitusiran is short-lived in plasma.															
Time to achieve steady state	From a pharmacodynamic standpoint, regardless of the dose regimen, >99% of subjects are expected to reach steady state AT activity levels within 23 weeks following initiation of fitusiran dosing or following dose escalation or de-escalation.															

NDA 219019
QFITLIA (fitusiran)

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial/study formulations	A single-dose vial/syringe formulation was used in phase 1-3 studies, but a prefilled pen (PFP) was introduced during long-term extension Study LTE15174 for administration of 50-mg doses in recognition that some subjects might prefer its convenience. The Applicant intends to market both vial/syringe and PFP presentations (each single-dose vial is designed to deliver 20 mg of fitusiran in 0.2 mL, or 10 mg of fitusiran in 0.1 mL, and each PFP is designed to deliver a 50-mg fixed dose of fitusiran in 0.5 mL). The statistical comparisons show that the resulting PK parameters (C_{max} , AUC_{0-t} , $AUC_{0-infinity}$) and observed annualized bleeding rate (ABR) are comparable between these two presentations (see Section 6.1.4.4).
Bioavailability T_{max} Food effect (fed/fasted) Geometric least square mean and 90% CI	Absorption Fitusiran is absorbed rapidly following SC administration. Absolute bioavailability is not known. 2 to 4 hours N/A as fitusiran is administered via SC injection.
Volume of distribution Plasma protein binding Drug as substrate of transporters	Distribution 431 L for 20 mg, 570 L for 50 mg 96.6% at clinically relevant exposure (0.5 µg/mL) Fitusiran is not a substrate for CYP450 enzymes or drug transporters.
Mass balance results Clearance Half-life Metabolic pathway(s) Primary excretion pathways (% dose)	Elimination N/A Mean apparent clearance (CL/F) is 50.8 L/h after a 50-mg dose. 5.57 h for 20 mg, 7.98 h for 50 mg Fitusiran is metabolized by endo- and exonucleases to oligonucleotides of varying lengths, which are further metabolized to oligonucleotides of even shorter lengths. The mean fraction of fitusiran dose excreted in urine (0 to 24 hours postdose) after a 50-mg dose is 14.6%.

Characteristic	Drug Information
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	Based on PopPK analysis, body weight and age were identified as statistically significant covariates in subjects with hemophilia, but the magnitude of the effect (<25% on fitusiran PK) is not considered to be clinically relevant (fitusiran effect is driven by fitusiran concentrations in liver rather than plasma).
Age	See above
Renal impairment	No dedicated study has been conducted to evaluate the impact of renal impairment. The PopPK analysis using clinical trial data from subjects with estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m ² identified eGFR as a statistically significant covariate in subjects with hemophilia, but the magnitude of the effect (<25% on fitusiran plasma PK) is not considered to be clinically relevant (fitusiran effect is driven by fitusiran concentrations in liver, rather than plasma).
Hepatic impairment	No dedicated study has been conducted to evaluate the impact of hepatic impairment. There was no clinical experience of fitusiran in subjects with hepatic impairment, as the clinical development program excluded subjects with clinically significant liver disease, or with ALT and/or AST >1.5× upper limit of normal reference range (ULN) or total bilirubin > ULN. Given the risk for hepatotoxicity, the review team recommends “avoid use” in patients with all degrees of hepatic impairment (Child-Pugh A, B and C).
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	At clinically relevant concentrations, fitusiran is unlikely to be an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, or to be an inducer of CYP1A2, CYP2B6, or CYP3A4.
Inhibition/induction of transporter systems	At clinically relevant concentrations, fitusiran is unlikely to be an inhibitor of major efflux transporters, including P-gp, BCRP, and BSEP, or major uptake transporters.
	<i>Immunogenicity (if Applicable)</i>
Bioanalysis	Antidrug antibodies (ADAs) against fitusiran were assayed using ELISA. No assay for neutralizing antibody (NAb) was developed.
Incidence	During fitusiran treatment (up to 250 weeks) in four pivotal studies, 10 out of 290 adults with hemophilia (3.4%) developed ADAs. All subjects had low ADA titers and the majority of subjects had transient ADAs.
Clinical impact	There was no identified clinically significant effect of ADAs on pharmacokinetics, pharmacodynamics, safety, or effectiveness of fitusiran.

Source: Clinical Pharmacology Reviewer

Abbreviations: ABR, annualized bleeding rate; ADA, antidrug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, antithrombin; AUC, area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; ELISA, enzyme-linked immunosorbent assay; LC-FD, liquid chromatography with fluorescence detection; N/A, not applicable; P-gp, P-glycoprotein; PFP, prefilled pen; PK, pharmacokinetics; PopPK, population pharmacokinetics; Q2M, every 2 months; QM, once monthly; QTc, corrected QT interval; QW, once weekly; SC, subcutaneous; SD, standard deviation; siRNA, small interfering ribonucleic acid; time to maximum plasma concentration; T_{max}, TQT, thorough QT; ULN, upper limit of no

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Applicant's Proposed Dosing Regimen

The proposed starting dose of fitusiran is 50 mg once subcutaneously every 2 months (Q2M) and then, if needed, the dose can be escalated or de-escalated to maintain the AT activity in the range of 15 to 35%. The doses include 50 mg QM, 20 mg Q2M, or 20 mg QM based on AT activity levels. AT activity must be measured using an FDA-cleared AT activity assay (under review by the Center for Devices and Radiological Health as a Companion Diagnostic). No dose adjustment from 50 mg Q2M is needed if AT activity levels are maintained between 15 to 35%. AT activity should be measured prior to initiation of fitusiran (b) (4)

After a dose modification, AT measurements should be restarted. The Agency made recommendations to add a 10 mg Q2M dose (described in Section 6.1.4.1) and also to update the frequency and timing of AT activity measurement (described in Section 6.1.4.2) in Section 2 of the USPI.

6.1.2. Selection of Initial Dosing Regimen for Parent Phase 3 Studies

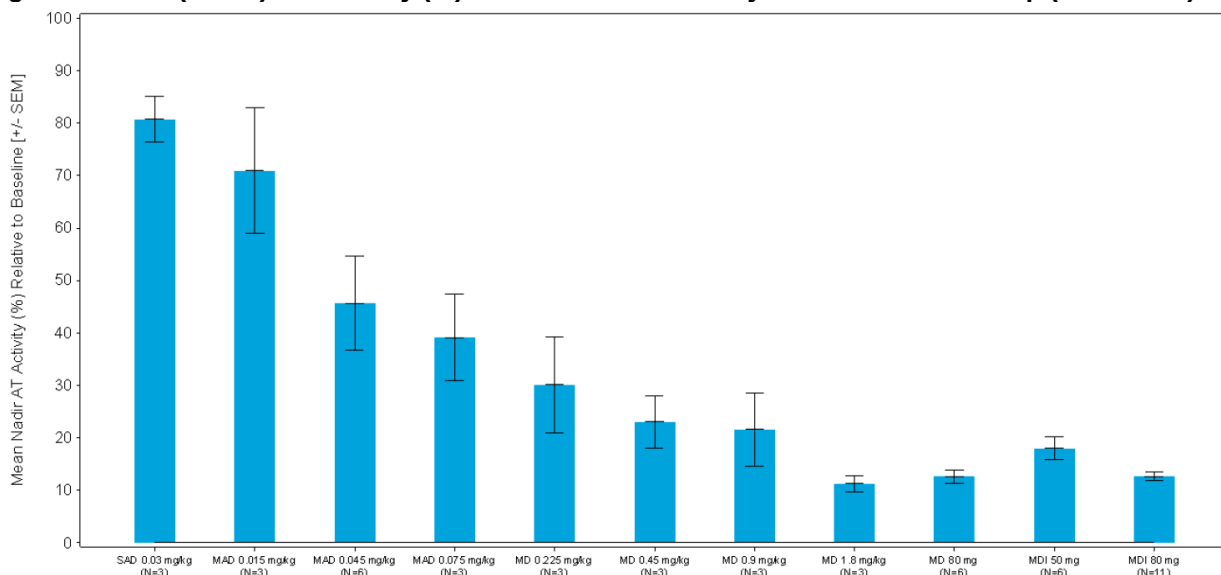
Selection of the Initial 80 mg QM Dose Regimen

The Applicant's selection of the initial 80 mg QM dosing regimen for the phase 3 study was based on the results of phase 1 study TDR14767 (ALN-AT3SC-001) as well as modeling and simulation. Due to an observed disconnect between fitusiran plasma pharmacokinetic (PK) and AT activity, predicted fitusiran concentrations in the liver RISC (based on allometrically scaled total liver PK parameters from rat liver PK) and observed clinical PD values (AT activity) were utilized for the development of a population kinetic-pharmacodynamic (PopK-PD) model. The Applicant's PopK-PD modeling and simulation analyses appeared reasonable for guiding dosing regimen development. Refer to Section 14 Pharmacometrics Assessment for detailed evaluation of this model.

The phase 1 study TDR14767 (ALN-AT3SC-001) evaluated once-weekly (QW) and QM regimens, both as body-weight-based (mg/kg) doses and as fixed (mg) doses. The tolerability and safety of fitusiran in the phase 1 study were evaluated in 3 healthy subjects after a single SC administration of 0.03 mg/kg, and in 42 subjects with hemophilia A or B after either three QW doses ranging from 0.015 to 0.075 mg/kg, three QM doses ranging from 0.225 to 1.8 mg/kg, or three QM doses of 50 or 80 mg. A dose-dependent reduction in AT activity from baseline was observed at all dose levels (Figure 2). Among tested doses, 50-mg and 80-mg fitusiran doses demonstrated generally similar safety profiles and reduction in AT activity.

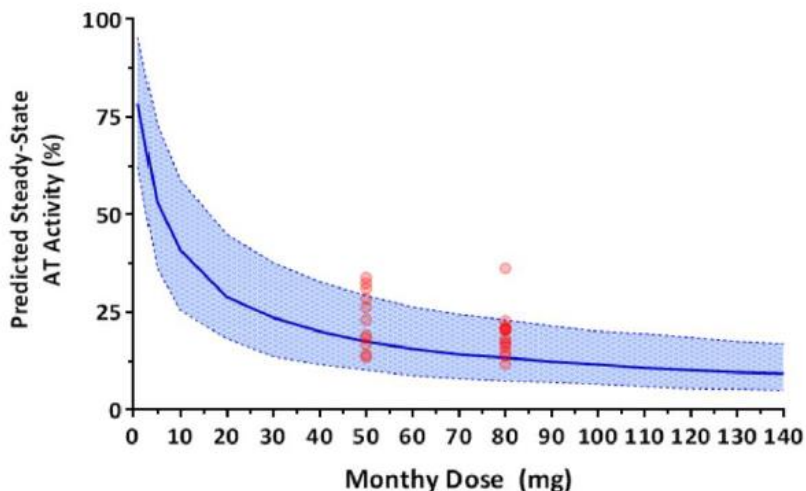
In addition to the observed dose-AT-activity relationship, the Applicant conducted an exploratory PopK-PD analysis to evaluate reduction in AT activity over a fitusiran dose range of 1 to 140 mg. The results showed that with doses greater than 80 mg fitusiran, only a small incremental change in AT activity was predicted ([Figure 3](#)).

Figure 2. Mean ($\pm$ SEM) AT Activity (%) Relative to Baseline by Fitusiran Dose Group (TDR14767)



Abbreviations: AT=antithrombin; MAD=multiple ascending dose; MD=multiple dose; MDI= multiple dose with inhibitors; N=total number of subjects; SAD=single ascending dose; SEM=standard error of the mean.
Source: Figure 10, TDR14767 CSR

Figure 3. Median (90% Prediction Interval) Dose-AT Activity Relationship for Fitusiran

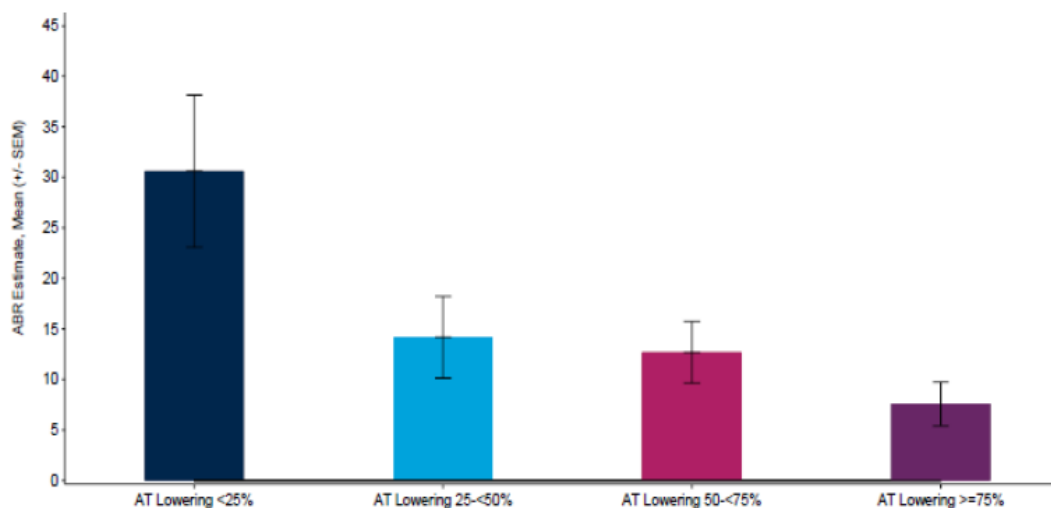


Solid blue line, Median AT activity response; shaded area, 90% prediction interval; symbols, mean steady-state AT activity observations calculated using data points between day 29 after first dose and day 57 after last dose for each individual participant who was part of long term extension study, LTE14762.

Source: Module 5.3.3.5 Population PK Study Reports, Study POH1133 [Figure 21].

Based on evaluation of the mean annualized bleeding rate (ABR) by AT activity quartile observed in the phase 1 study TDR14767 (ALN-AT3SC-001), it was determined that an AT activity reduction of >75% showed maximal effect in controlling bleeding, as shown in [Figure 4](#) below.

Figure 4. Mean ($\pm$ SEM) Annualized Bleed Rate by AT Quartile in Phase 1 Study TDR14767



Abbreviations: ABR, annualized bleed rate; AT, antithrombin; SEM, standard error of the mean.

Source: Module 5.3.3.2 Study TDR14767 [Figure 12].

PopK-PD simulations to predict AT reduction at steady state indicated that 50 mg QM dosing would result in 87% of subjects achieving >75% AT reduction, while 80 mg QM dosing would result in 98% of subjects achieving >75% AT reduction (POH1133).

Based on the totality of available observed and simulated data, the Applicant chose the initial 80 mg QM fitusiran dose for the phase 3 studies (EFC14768, EFC14769, EFC15110), with the goal of achieving maximal pharmacodynamic (PD) activity (AT reduction) with low intersubject variability.

6.1.3. Development of AT-DR

The fitusiran phase 3 program was initiated at a fixed dose regimen of 80 mg QM, and later adjusted to an AT-based dosing regimen (AT-DR).

The efficacy and mean AT levels with fitusiran 80 mg QM treatment compared with on-demand treatment with BPAs or CFCs, or compared with prior BPA/CFC prophylaxis are summarized in [Table 8](#) below.

Table 8. Efficacy and Mean AT Levels of the 80 mg QM Regimen in Three Parent Phase 3 Studies

	EFC14768 HA/B w/ inhibitor	EFC14769 HA/B w/o inhibitor	EFC15110 All 4 subtypes
Comparator	Fitusiran 80 mg prophylaxis vs on-demand BPAs N=60	Fitusiran 80 mg prophylaxis vs on-demand CFCs N=120	Fitusiran 80 mg prophylaxis vs CFC/BPA prophylaxis N=80
Efficacy	91% reduction in bleeding rates compared with on-demand BPAs ($p<0.0001$); Median ABR was 0.0	90% reduction in bleeding rates compared with on-demand CFCs ($p<0.0001$); Median ABR was 0.0	61% reduction in bleeding rates compared with prior BPA/CFC prophylaxis ($p=0.0008$); Median ABR was 0.0
Mean AT levels (SD)	10.7% (2.9)	11.8% (4.0)	11.0% (2.5)

Source: Applicant's Orientation Meeting Slides

Abbreviations: ABR, annualized bleeding rate; AT, antithrombin; BPA, bypassing agent; CFC, clotting factor concentrate; HA/B, hemophilia A or B; SD, standard deviation

One potential concern with the 80 mg QM dose is that the mean AT levels are close to 10% with fitusiran treatment. Clinical data suggested that the risk of serious thrombotic events may be greater with persistent AT levels <10%.

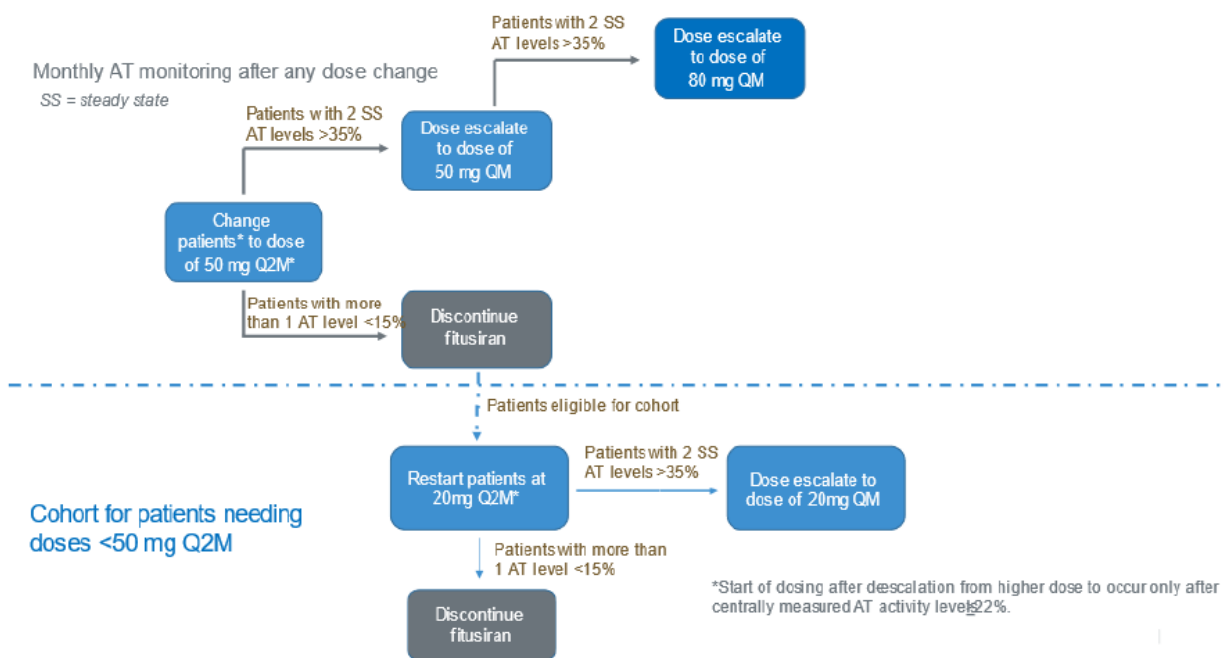
In October 2020, when the phase 1/2 study (LTE14762), the three parent phase 3 studies (EFC14768, EFC14769, EFC15110), and the phase 3 long-term extension (LTE) study (LTE15174) were ongoing, the Applicant placed a voluntary pause on ongoing clinical trials to evaluate the risk of the 80 mg QM regimen, due to concerns regarding thrombotic events potentially related to fitusiran.

After analyzing the role of AT reduction and associated risk of thrombotic events as well as bleeding episodes, the Applicant revised the dosing regimen to AT-DR with a target AT activity of 15 to 35%. The 15% AT activity was set as the lower threshold because clinical data as of October 2020 suggested that the risk of serious thrombotic events may be greater with AT levels <10%, while AT activity from 15% to 25% was deemed to preserve efficacy. The AT activity 35% was set as the upper threshold because data as of October 2020 suggested that AT levels <25% (>75% AT reduction) showed maximal effect in controlling bleeding, and the upper bounds of the 95% and 90% confidence intervals (CIs) of effective AT levels (25%) were 35.5% and 34.2%, respectively.

With the identification of AT target thresholds (15 to 35% of normal AT activity), the Applicant performed modeling and simulation to identify the doses to achieve this target range. Based on the simulation results, the starting dose was revised to 50 mg Q2M (instead of 80 mg QM), with an option to sequentially escalate to 50 mg QM and 80 mg QM in case of AT activity >35% and options to decrease the dose or discontinue fitusiran for AT levels less than 15%. This revised AT-based dosing regimen was implemented in December 2020 across studies (except EFC14768 and EFC14769, which were nearly complete at the time of the voluntary dosing pause). After implementation of the AT-DR, the observed number of subjects who had to discontinue fitusiran treatment due to AT activity levels <15% exceeded predictions. Therefore, based on additional simulations, the lower dose of 20 mg Q2M was identified, with the option to escalate to 20 mg QM in case of AT activity >35%. This lower dose regimen was subsequently implemented in the

long-term extension part of Study LTE15174. The final AT-DR employed in Study LTE15174 is depicted in [Figure 5](#) below.

Figure 5. Final Revised AT-Based Fitusiran Dose Regimens (LTE15174)



Source: Module 5.3.5.2 Study LTE15174 Appendix 16.1.1 [Protocol].

Abbreviations: AT, antithrombin; LTE, long-term extension; Q2M, every 2 months; QM, once monthly; SS, steady state

During the parent phase 3 studies and LTE15174, the Applicant found that escalation to 80 mg QM did not seem necessary, because none of the subjects who started dosing at 50 mg Q2M required dose escalation beyond 50 mg QM up to 80 mg QM. Therefore, in the final proposed AT-DR, the Applicant kept the AT-DR implemented since December 2020, but removed the option of escalating to 80 mg QM.

6.1.4. Evaluation of AT-DR

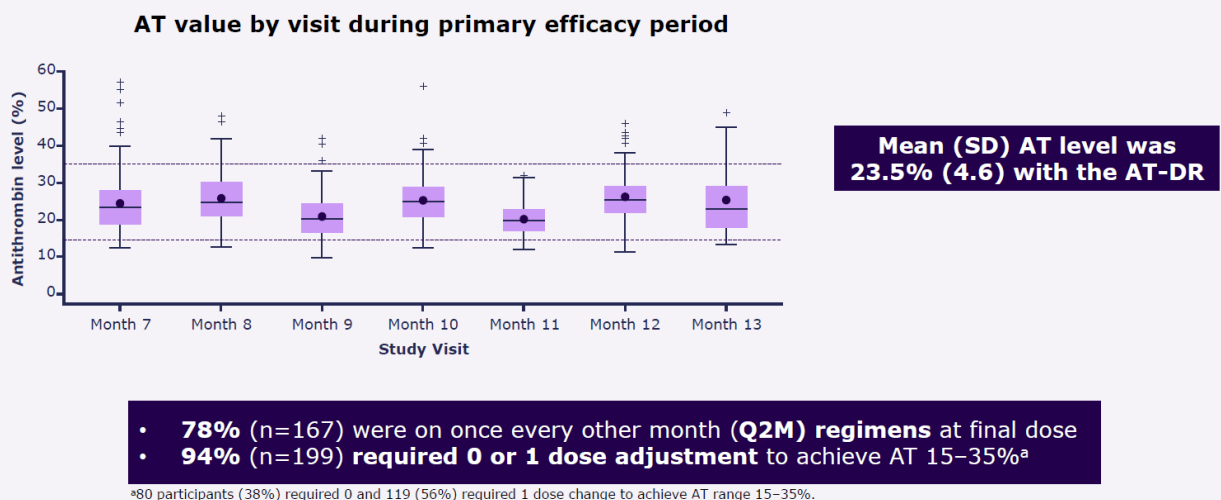
AT-DR Is Supported by Positive Efficacy and Safety Results

The efficacy and safety evaluation supporting the AT-DR is discussed in detail in Section [6.2](#) and Sections [7.4](#) to [7.6](#).

AT-DR Is Effective in Maintaining AT Activity in the Target 15 to 35% Range

As shown in [Figure 6](#) below, in Study LTE15174, the target AT range of 15 to 35% could be achieved with the AT-DR, and 94% of subjects required 0 or 1 dose adjustment to achieve the target AT activity range.

Figure 6. AT Value by Visit During Primary Efficacy Period in LTE15174



Source: Applicant's Orientation Meeting Slides

Abbreviations: AT, antithrombin; AT-DR, antithrombin-based dosing regimen; LTE, long-term extension; Q2M, every 2 months; SD, standard deviation

AT-DR with the lowest dose option of 20 mg Q2M resulted in additional subjects reaching the target AT range at steady state, but a lower dose option is needed to keep more subjects on treatment.

[Table 9](#) shows the observed and simulated subject distribution across the evaluated dose regimens. Both the observed and simulated subject distribution showed that 50 mg Q2M resulted in the largest percentage of subjects reaching the target AT activity range 15 to 35% at steady state. Thus, a starting dose of 50 mg Q2M was determined to be appropriate because it would allow the highest percentage of subjects to start fitusiran treatment at the dose which would enable them to achieve AT activity target sooner than other options.

Table 9. Observed and Simulated Subject Distribution Across Recommended Dose Regimens

Dose Regimen Population	50 mg Q2M	50 mg QM	20 mg Q2M	20 mg QM	Discontinued (AT < 15%)
Observed distribution of participants (N=283)	40.6% (115/283)	15.9% (45/283)	29.7% (84/283)	2.1% (6/283)	11.7% (33/283)
Simulated population distribution of participants (N=1203)	48.04% (578/1203)	19.6% (236/1203)	20.1% (242/1203)	1.41% (17/1203)	10.8% (130/1203)

Abbreviations: AT = antithrombin, QM = once every month, Q2M = once every two months.

Source: Table 23, Summary of Clinical Pharmacology

While the majority of actual and virtual subjects were able to maintain target AT range with AT-DR, 11.7% of actual subjects and 10.8% of virtual subjects had to discontinue fitusiran treatment due to AT levels dropping below 15%, even with a dose reduction to 20 mg Q2M. This proportion was further revised to be about 7% based on an updated simulation methodology that

was agreed upon between the review team and the Applicant. Nevertheless, it presented a need to explore the possibility of providing a dosing option lower than 20 mg Q2M for patients who may have otherwise discontinued fitusiran treatment due to AT activity <15%.

6.1.4.1. Recommendation for Adding 10 mg Q2M for Patients Whose AT Level Drops Below 15%

The review team simulated AT activity at Week 76 (close to trough) for two regimens: 10 mg Q2M and 15 mg Q2M. [Table 10](#) shows that approximately 6% (out of the 7% discontinued due to AT <15%) of virtual subjects could remain on treatment with the addition of a 10 mg Q2M regimen. The 10 mg Q2M regimen is expected to result in relatively more patients remaining on treatment than 15 mg Q2M for patients with at least one AT activity <15% following 20 mg Q2M. The lower dose option of 10 mg Q2M will be an added dosage option in product labeling.

Table 10. Distribution of Virtual Patients After Taking the Lower Dose 10 mg Q2M vs. 15 mg Q2M

AT Activity Range at Week 76 (Close to Trough)	Percent of Total Virtual Patients [%]	
	10 mg Q2M	15 mg Q2M
Any measurement <15%	1.13	2.75
Any measurement >35%	0	0
All measurements 15-35%	5.88	4.26

Source: Reviewer's analysis

Abbreviations: AT, antithrombin; Q2M, every 2 months

6.1.4.2. Changes to Proposed AT Monitoring Plan for Dose De-Escalation

The review team revised the Applicant's proposed AT monitoring and dose adjustment instructions (see Section [14.5.4](#) Evaluation of AT monitoring program). Specifically, changes were made to measure AT activity at Weeks 4 (Month 1), 12 (Month 3), and 20 (Month 5) that coincide with the lowest (nadir) AT activity (4 weeks post-dose) following Q2M or QM dosing to aid in dose de-escalation decisions. A measurement at Week 24 (Month 6) was recommended to capture the pre-dose AT activity to aid in dose escalation decisions. The revised instructions are shown below:

Measure AT activity prior to initiation of QFITLIA using an FDA-authorized test. Do not initiate QFITLIA dosing if AT activity is <60% at baseline, (b) (4)

Measure AT activity at Weeks 4 (Month 1), 12 (Month 3), 20 (Month 5) and 24 (Month 6) following the starting dose and after any dose modification.

- If any AT activity is <15%, a dose reduction is required, the lower dose should be initiated 3 months after the prior dose.
- If AT activity is >35% after 6 months, or if the subject has not achieved satisfactory bleed control, dose escalation should be considered.

Once the subject's target dose is identified based on AT activity 15 to 35%, (b) (4)
measure AT activity annually. Additional measurements can be considered (b) (4)

6.1.4.3. Dosing in Adolescents

The use of fitusiran in adolescents with hemophilia A and B is supported by the three randomized phase 3 studies (EFC14768, EFC14769, EFC15110) and one open-label long-term extension study (LTE15174). A total of 60 adolescents were evaluated in the clinical studies. The dosing used in adolescents was the same as used in adults. No differences in efficacy were observed between the adolescent subgroup and the overall population (see Sections [6.2.1.5](#) and [6.2.2.5](#), efficacy subgroup analysis). In general, the adverse reactions in fitusiran-treated adolescent subjects were similar in type to those seen in adult subjects with hemophilia A or B, with or without inhibitors (see Section [7.5.2.9](#) safety subgroup analysis).

The PopPK analysis also showed that age (12 to 71 years) did not have a significant effect on the PK of fitusiran ([Table 11](#)).

Table 11. Mean (SD) [CV%] Empirical Bayes Fitusiran Exposure Estimates (Dose-Normalized) By Age

Participants	Age	N	C _{max} (ng/mL/mg)	AUC (ng.h/mL/mg)
Adolescents	<18	63	1.65 (0.607) [36.9%]	24.9 (5.01) [20.1%]
Adults	18 to 64	225	1.46 (0.68) [46.5%]	26.0 (7.35) [28.3%]
Elderly	≥65	3	1.33 (0.633) [47.7%]	28.2 (2.19) [7.77%]

Abbreviation: N: number of patients without excluding the discontinued patients; ADA: antidrug antibody; AUC: area under the concentration time curve from 0 to Day 60 days; C_{max}: maximum concentration; eGFR: estimated glomerular filtration rate.

Note: Analysis performed using data from Phase 3 studies (EFC14768, EFC14769, EFC15110, and LTE15174)

Source: Summary of Clinical Pharmacology, Table 27

Therefore, the Applicant's proposal for dosing in adolescent subjects, i.e., ≥12 age <18 years, using the AT-DR is acceptable.

6.1.4.4. Bridging of Phase 3 to the To-Be-Marketed Product Presentations

The vial/syringe formulation was used in phase 1 to 3 studies, but a prefilled pen (PFP) was introduced during LTE15174 for administration of 50-mg doses in recognition that some subjects might prefer its convenience. The Applicant proposes both vial/syringe and PFP formulations in the label (each PFP is designed to deliver a fixed dose of 50 mg of fitusiran in 0.5 mL, and each vial is designed to deliver 20 mg of fitusiran in 0.2 mL). Patients on 50 mg having to decrease the dose to 20 mg should switch from the PFP to vial/syringe presentation. A scientific bridge between PFP and vial/syringe presentations was established from a PK and efficacy perspective.

From a PK perspective, comparison of fitusiran PK administered via the PFP and vial/syringe was performed as part of phase 3 study LTE15174. In Study LTE15174, 12 subjects were first administered the 50-mg fitusiran dose using the glass vial with syringe, and then the next dose of 50 mg was administered with PFP. Eleven subjects completed both glass vial with syringe and PFP dose administrations. As shown in [Table 12](#) below, the two formulations were bioequivalent with the 90% CIs of maximum plasma concentration, area under the concentration-time curve to

the last measurable concentration (AUC_{last}) and area under the concentration-time curve estimated to infinity (AUC_{∞}) falling within the bioequivalence acceptance range of 80 to 125%.

Table 12. Statistical Comparison in PK Parameters Between Vial/Syringe and PFP

PK parameter	Point Estimate	90% Confidence Interval
C_{max}	0.98	(0.83 to 1.15)
AUC_{last}	0.97	(0.83 to 1.13)
AUC_{∞}	0.97	(0.86 to 1.11)

Source: Table 7, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; PFP, prefilled pen

From an efficacy perspective, the two formulations resulted in comparable observed ABR in Study LTE15174, as shown in [Table 13](#) below. This table shows the number of subjects who used both vial and PFP formulations in LTE15174.

Table 13. Comparison in Observed ABR Between Vial/Syringe and PFP

Observed ABR	Vial (n=83)	PFP (n=83)
Mean (SD)	6.8 (8.9)	7.1 (9.3)
Median	3.2	3.6
Q1; Q3	0.0; 8.1	0.0; 12.3

Source: Module 5.3.5.3. Integrated Summary of Efficacy Appendix 4, Section 4.12.1

Note: Only subjects who purely took 50 mg fitusiran and used both vial and PFP devices

Abbreviations: ABR, annualized bleeding rate; PFP, prefilled pen; Q1, first quartile; Q3, third quartile; SD, standard deviation

Overall, the proposed AT-DR, with the addition of the 10-mg lower dose option and revised AT monitoring plan, is reasonable from a clinical pharmacology perspective.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

In support of the proposed indication, the Applicant initially conducted three phase 3 parent studies (i.e., EFC14768 [ATLAS-INH], EFC14769 [ATLAS-A/B], and EFC15110 [ATLAS-PPX]) using a fixed fitusiran dose of 80 mg monthly to evaluate the efficacy of fitusiran in adults and adolescents with hemophilia A or B with or without inhibitors. Study EFC14768 was a randomized, open-label, controlled trial in subjects with hemophilia A or B with inhibitors. Study EFC14769 was a randomized, open-label, controlled trial in subjects with hemophilia A or B without inhibitors. Study EFC15110 was a single-arm trial in subjects with hemophilia A or B with or without inhibitors who were switched to fitusiran from factor or BPA prophylaxis.

In October 2020, the Applicant received reports of nonfatal vascular thrombotic events in subjects on fitusiran in the ongoing phase 3 program. Pending further assessment of these events, and in accordance with the recommendations of an external, independent Data Monitoring Committee and Scientific Steering Committee, the Applicant decided to voluntarily pause dosing and enrollment in all ongoing phase 3 clinical studies using the 80 mg QM regimen as of October 30, 2020, and notified the Agency on November 2, 2020. The original statistical analysis

plan for summary of clinical efficacy/integrated summary of effectiveness was submitted on December 24, 2020.

The Applicant proposed a revised dose regimen and restarted the evaluation of the drug in a long-term extension study (LTE15174 [ATLAS-OLE]). The fitusiran treatment period of the two parent phase 3 studies EFC14768 and EFC24769, was completed as of January 26, 2021. Following completion of these parent studies, subjects rolled over into the long-term extension study. Subjects who have not completed study EFC15110 will also roll into the long-term extension study after study completion. The revised dose (AT-DR) in the long-term extension study consists of a starting dose of 50 mg Q2M, with options to escalate to 50 mg QM and 80 mg QM, and to de-escalate to 20 mg Q2M and 20 mg QM. The dose administered is determined on an individual basis in order to maintain AT level between 15 to 35%.

When this new dosing regimen was implemented, Studies EFC14768 and EFC14769 were near completion; thus, the AT-DR was not implemented in either of these studies. In switching to Study EFC15110, the 50 mg Q2M dose was implemented in 2 subjects. The AT-DR was fully implemented in the extension Study LTE15174. Due to the change in dosing regimen, efficacy of fitusiran AT-DR was established by a comparison of data from subjects in the extension study LTE15174 with the data from subjects in the control arms of the parent studies.

Pool A (HA or HB With Inhibitor) and On Demand Therapy: Intersubject Comparison

Treatment Arm

AT-DR fitusiran treatment data were generated from the extension Study LTE15174. Only AT-DR fitusiran treatment data from subjects in Study LTE15174 who were randomized to the fitusiran arm in Study EFC14768 (with inhibitor population) were used in the primary analysis (see [Figure 7](#)).

Control Data

BPA control data were taken from the original phase 3 Study EFC14768. Control data from subjects who were randomized to the BPA arm in Study EFC14768 were used in the primary analysis (see [Figure 7](#)).

Pool B (HA or HB Without Inhibitor) and On Demand Therapy: Intersubject Comparison

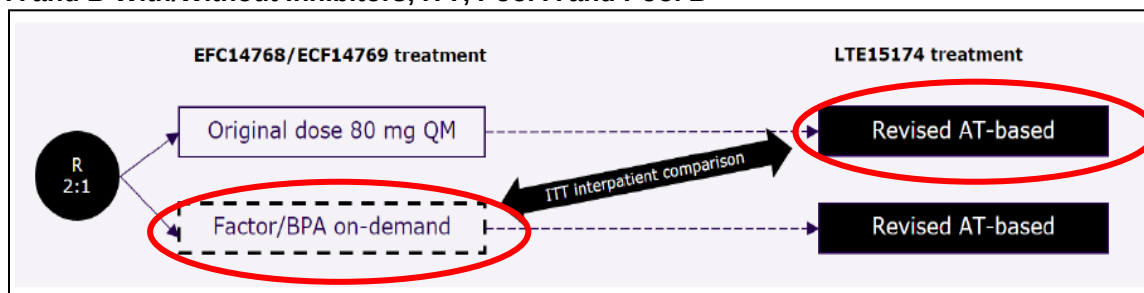
Treatment Arm

AT-DR fitusiran treatment data were generated from the extension Study LTE15174. Only AT-DR fitusiran treatment data from subjects who were randomized to the fitusiran arm in Study EFC14769 (without inhibitor population) were used in the primary analysis (see [Figure 7](#)).

Control Data

Factor on demand control data were taken from the original phase 3 Study EFC14769. Control data from subjects who were randomized to the factor on demand arm in Study EFC14769 were used in the primary analysis (see [Figure 7](#)).

Figure 7. Efficacy Comparison of Fitusiran Prophylaxis vs. Factor/BPA On-Demand in Hemophilia A and B With/Without Inhibitors, ITT, Pool A and Pool B



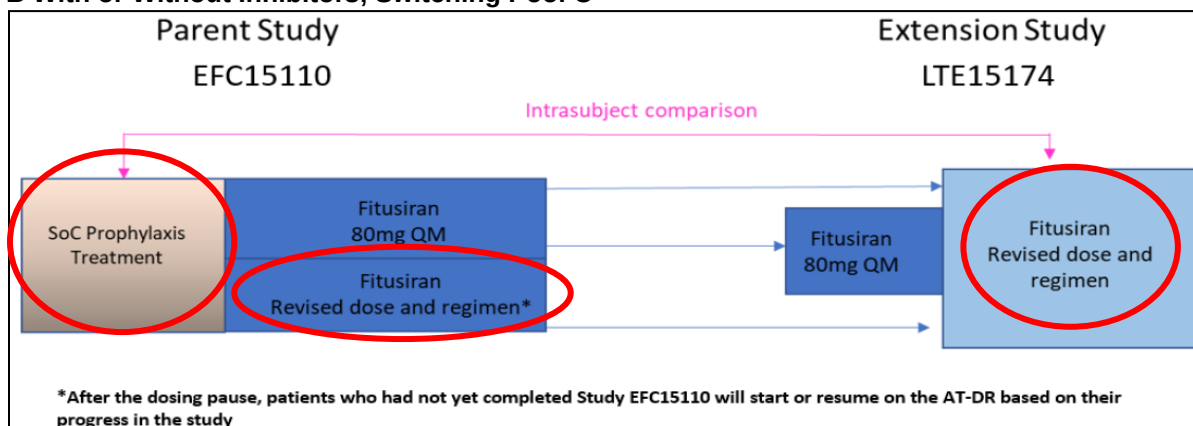
Source: Summary of Clinical Efficacy Hemophilia A and B, Figure 3

Abbreviations: AT, antithrombin; BPA, bypassing agent; ITT, intent-to-treat; QM, once monthly

Pool C (HA and HB with and without inhibitor on prior prophylaxis): intrasubject comparison ([Figure 8](#)).

- **Treatment arm:** AT-DR fitusiran treatment data were generated from both the extension study LTE15174 and from the 2 AT-DR subjects in Study EFC15110.
- **Control arm:** Standard-of-care (SOC) prophylaxis control data were generated from the baseline control period of Study EFC15110 before all subjects were switched to fitusiran.

Figure 8. Efficacy Comparison of Fitusiran Prophylaxis vs. SOC Prophylaxis in Hemophilia A and B With or Without Inhibitors, Switching Pool C



Source: Summary of Clinical Efficacy Hemophilia A and B, Figure 4.

*The figure does not include the two subjects in study EFC15110 that received AT-DR dosing

Abbreviations: AT-DR, antithrombin-based dosing regimen; QM, once monthly; SoC, standard of care

Pool C was not adequately powered for the analysis of ABR and did not have formal hypothesis testing for either superiority or noninferiority of fitusiran. Therefore, data from Pool C are considered descriptive in nature only.

The data and analysis of Pool C are discussed in Section [16.4](#).

The adequacy of Pool A and Pool B for demonstrating the benefit of fitusiran prophylaxis (i.e., comparing the AT-DR efficacy data from the long-term extension study to the control data from the randomized parent studies), is discussed in Section [6.3.1](#).

Analysis periods are defined in [Table 14](#). The endpoint analyses are performed for Pools A, B, and C separately.

Table 14. Definition of Analysis Periods for Integrated Efficacy Pools

Period	Definition ^a
Dose adjustment period ^b	Dose Restart Day 1 to Dose Restart Day 168
Primary efficacy period	Dose Restart Day 169 to Dose Restart Day 364
Treatment period	Dose adjustment period plus primary efficacy period
Control periods in EFC14768/EFC14769/ EFC15110 ^c	Pool A and B: EFC14768/EFC14769 Day 1 to EFC14768/EFC14769 Day 246 Pool C: enrollment date in EFC15110 to the earliest of [enrollment date +167 days, 1 day before first fitusiran dose date] in EFC15110

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 4

^a The dose restart day refers to the date of the first fitusiran dose on the revised AT-DR after the dose pause.

^b The dose adjustment period corresponds to the first 6 months of dosing after the voluntary dosing pause. During this 6-month period, study subjects restarted fitusiran, targeting AT levels of 15 to 35% through individual dose adjustment according to the revised AT-DR in their respective study protocol. By the end of the 6-month period, the majority of study subjects reached AT-steady state and were on a stable dose. Therefore, the primary efficacy period represents the subsequent 6 months when study subjects were generally at steady state and steady dose.

^c For Pool A and B (EFC14768/EFC14769): subjects randomized to BPA/Factor On-demand arms were considered. For Pool C (EFC15110): all subjects who completed factor or BPA prophylaxis period and received any dose of fitusiran were considered. Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent

6.2.1. Pool A — Subjects With HAwI or HBwI, Previously on BPA On-Demand Therapy

Pooling Strategy

Table 15. Pooling Strategy for Integrated Summary of Efficacy, Pool A

Studies	Populations	Treatment Comparisons	Subject Data for Inclusion
EFC14768 & LTE15174	Inhibitor Hem A & Hem B	Fitusiran prophylaxis vs. BPA on-demand	For fitusiran prophylaxis: 13 months of treatment period since first AT-DR dose after dose pause in LTE15174 ^a . For BPA on-demand: 9 months of control period in EFC14768.

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 3.

^a 13-month treatment period was from the Dose Restart Day 1 to the end of month 12. The Dose Restart Day 1 was the start of Month 0. One month =28 days.

Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; Hem, hemophilia

6.2.1.1. Design, Pool A

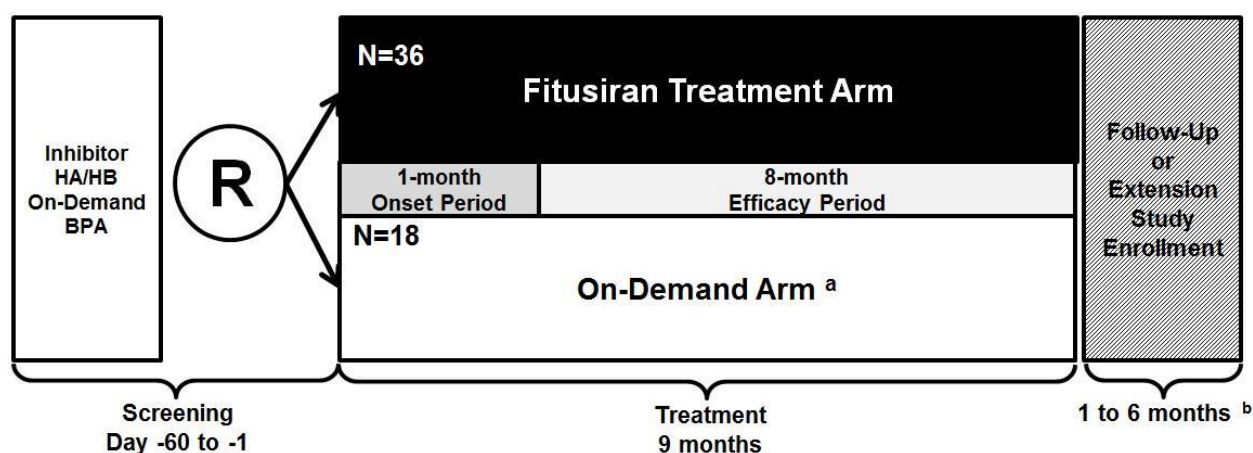
The control arm for Pool A was from Study ATLAS-INH (EFC14768) and is described below first. The treatment arm, which used fitusiran AT-DR, was from the extension Study ATLAS-OLE (LTE15174) and is described second.

ATLAS-INH (EFC14768)

ATLAS-INH (EFC14768) was a multicenter, randomized, open-label study in male subjects aged ≥12 years, with hemophilia A or B and inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who were not receiving prophylactic therapy. The study design is shown in [Figure 9](#). An open-label study design was considered acceptable by the review team, as blinding would not be feasible given differences in treatment regimens and differences in treatment for breakthrough bleeds for each study arm. Subjects were randomized in a 2:1 ratio to either fitusiran 80 mg administered SC as prophylaxis once monthly or on-demand BPAs. Fitusiran-treated subjects

could also receive on-demand BPAs for treatment of breakthrough bleeding episodes. On-demand use of BPAs was defined as the use of these agents, as needed, for episodic bleeding, and not as a regular regimen intended to prevent spontaneous bleeding. For subjects in the BPA on-demand arm (i.e., those not receiving fitusiran), bleeding management therapy with BPAs was managed based on the local standard practice for treating hemophilia subjects with inhibitors, as routinely administered by the physician. Randomization was stratified by the number of bleeding episodes in the 6 months prior to screening (≤ 10 versus > 10). All subjects were treated for 9 months, and upon completion, eligible for participation in an open-label extension study (Study LTE15174). See a detailed description of the study design and bleed management guidelines in Section 15.1.

Figure 9. Study Design, EFC14768



Source: Applicant's Clinical Study Protocol for ATLAS-INH

^a On-demand local BPA as routinely prescribed by physician per local standard practice.

^b Fitusiran treatment arm subjects who do not enroll in the extension study: AT activity level was 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.

Abbreviations: BPA, bypassing agent; HA/HB, hemophilia type A / hemophilia type B; R, randomized

Study LTE15174 (ATLAS-OLE)

Study LTE15174 (ATLAS-OLE) was a multicenter, open-label extension study in male subjects aged ≥ 12 years, with hemophilia A or B, with or without inhibitory antibodies to FVIII or FIX. The study included subjects who had completed any of the fitusiran phase 3 hemophilia A or B studies (Study EFC14768, Study EFC14769, and Study EFC15110, also referred to as “parent” studies) to continue to be evaluated for long-term safety and efficacy. Additionally, this study collected efficacy data for the AT-DR. Initially, subjects received a fixed dose of fitusiran 80 mg QM. Following the dosing pause for cases of thrombotic events in October 2020, subjects were switched to the AT-DR. The estimated total time on the study for a subject who started fitusiran treatment before the 2020 dosing pause is up to 90 months, and up to 62 months for a subject who started fitusiran treatment after the lifting of the pause. Bleeding episodes were treated per Bleed Management Guidelines and management during surgery is outlined in Section 15. Use of prothrombin complex concentrates and emicizumab were not permitted during the study. A detailed study design is described in Section 15.3. For Pool A, the fitusiran-treated subjects who were used from LTE15174 were those with HAwI or HBwI who were originally randomized to fitusiran in Study EFC14768 and who received AT-DR during Study LTE15174.

6.2.1.2. Objectives and Endpoints, Pool A

Objectives

The primary objective was to evaluate the efficacy of fitusiran treatment at the revised AT-DR compared to on-demand treatment with BPAs, as determined by the frequency of bleeding episodes.

Endpoints

The primary efficacy endpoint was annualized bleeding rate (ABR) for treated bleeds in the fitusiran primary efficacy period compared to the control period (refer to [Table 14](#) in Section [6.2](#) for the definition of analysis periods). The number of bleeding episodes was annualized for each subject using the following formula: $\text{ABR for treated bleeds} = \frac{\text{total number of bleeding episodes}}{\text{total number of days in the respective period}} \times 365.25$. Treated bleeds were defined as bleeding episodes that required administration of factor concentrates or BPA infusion for management, e.g., hemarthrosis, muscle, or mucosal bleeding.

The key secondary endpoints are listed below:

1. Annualized treated spontaneous bleeding rate (AsBR) in the primary efficacy period and the control period.
2. Annualized treated joint bleeding rate (AjBR) in the primary efficacy period and the control period.
3. Change in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain score in the primary efficacy period and the control period.
4. Time to first treated bleeding episode in the primary efficacy period and control period (this endpoint was not included in the testing hierarchy of the parent Study EFC14768).

Haem-A-QoL Physical Health Domain Score

The Haem-A-QoL Physical Health domain is a 5-item domain in the 46-item Haem-A-QoL, a patient-reported outcome (PRO) instrument. The Physical Health domain is designed to assess patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement and difficulty walking far). Each item is rated on a 5-point verbal rating scale ranging from “Never” to “All the time.” The recall period is the previous 4 weeks. The Haem-A-QoL was administered by paper at baseline, and month 9.

Endpoints for Study EFC14768 are described in Section [15.1](#).

6.2.1.3. Eligibility Criteria, Pool A

Eligibility criteria for Study EFC14768 are described below. Study LTE15174 included subjects who completed a previous parent phase 3 clinical study of fitusiran and had central AT activity level $\geq 22\%$ (prior to dosing).

Study EFC14768

Key Inclusion Criteria

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 $\leq 2\%$ at Screening.
 - b. On-demand use of BPAs to manage bleeding episodes for at least the last 6 months prior to Screening, and meeting one of the following Nijmegen-modified Bethesda assay results criteria:
 - i. Inhibitor titer of ≥ 0.6 BU/mL at Screening, or
 - ii. Inhibitor titer of < 0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers ≥ 0.6 BU/mL, or
 - iii. Inhibitor titer of < 0.6 BU/mL at Screening with medical record evidence of anamnestic response.
3. A minimum of 6 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening.

Key Exclusion Criteria

1. Known coexisting bleeding disorders other than hemophilia A or B, e.g., Von Willebrand's disease, additional factor deficiencies, or platelet disorders.
2. Current participation in immune tolerance induction therapy.
3. Current use of BPAs as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes.
4. AT activity $< 60\%$ at Screening, as determined by central laboratory measurement, in order to exclude patients with underlying congenital AT deficiency and to decrease the risk of excessively low AT activity levels.
5. Presence of clinically significant liver disease.
6. Estimated glomerular filtration rate ≤ 45 mL/min/1.73 m² (using the Modification of Diet in Renal Disease formula).
7. Coexisting thrombophilic disorder.
8. History of arterial or venous thromboembolism.

6.2.1.4. Statistical Analysis Plan, Pool A

Analysis of the Primary Endpoint

The primary endpoint was analyzed using a negative binomial model with the number of bleeding episodes as the response variable, and treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , > 10) as fixed effects. The logarithm of the

duration (in years) that each subject spent in each study period matching the bleeding episode data being analyzed (i.e., treatment period from Study EFC15174 and control period from Study EFC14768) were included as an offset variable to account for unequal follow-up time due to different durations of the treatment and control periods, early withdrawal, surgery, etc.

Analysis of Key Secondary Endpoints

Annualized Treated Spontaneous Bleeding Rate

The same primary analysis method for the primary endpoint was used for this key secondary endpoint.

Annualized Treated Joint Bleeding Rate

The same primary analysis method for the primary endpoint was used for this key secondary endpoint.

Change in Haem-A-QoL Physical Health Domain Score

Change from baseline in Haem-A-QoL Physical Health domain score (in subjects ≥ 17 years of age) in the control period and primary efficacy period were analyzed using a mixed model for repeated measure analysis (MMRM) with robust sandwich covariance matrix, with fixed effects, visit of study period (one postbaseline in control period and two postbaselines in primary efficacy period), the randomization strata of number of bleeding episodes in the 6 months prior to EFC14768 study entry, and baseline Haem-A-QoL Physical Health domain score. We show the Haem-A-QoL Physical Health results for completeness but do not consider the findings reliable for reasons discussed later in this review.

Time to First Treated Bleeding Episode

The risk of bleeding in the primary efficacy period and control period was compared using a Cox proportional hazards regression model. For intent-to-treat (ITT) Pool A, treatment arm and randomization strata of number of bleeding episodes (≤ 10 , > 10) in the 6 months prior to EFC14768 study entry were fixed effects.

Multiple Testing Strategy

To control the familywise error rate at an alpha level of 0.05 in the testing of the primary and key secondary endpoints for each pool, a hierarchical testing approach was used. For ITT pool A, the endpoints were tested in the following order ([Table 16](#) below):

Table 16. Multiplicity Adjustment, ITT, Pool A

Endpoints	2-Sided Alpha
1. ABR for treated bleeds in the primary efficacy period and control period	0.05
2. Annualized treated spontaneous bleeding rate in the primary efficacy period and control period	0.05
3. Annualized treated joint bleeding rate in the primary efficacy period and control period	0.05
4. Change in Haem-A-QoL Physical Health domain score in the primary efficacy period and control period	0.05
5. Time to first treated bleeding episode in the primary efficacy period and control period	0.05

Source: FDA reviewer summary

Abbreviations: ABR, annualized bleeding rate; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITT, intent-to-treat

If testing of any of the endpoints was not statistically significant, formal testing of subsequent endpoints would be stopped and the null hypothesis for subsequent tests would not be rejected.

Note that Endpoints #1 to #4 in Table 9 were prespecified primary and key secondary endpoints in the protocol of the parent study EFC147689. However, the endpoint of the time to first treated bleeding episode (Endpoint #5) in the primary efficacy period and control period was not prespecified as a key secondary endpoint. Therefore, the review team does not consider it as a prespecified multiplicity-adjusted endpoint for the Pool A analysis. As a result, the endpoint of time to first treated bleeding episode in the primary efficacy period will not be used to support a labeling claim of fitusiran AT-DR.

Handling of Intercurrent Events and Missing Data

Inclusion of bleeding events during the intercurrent events, such as perioperative period, after fitusiran treatment discontinuation, or use of other medications influencing hemostasis ([Table 17](#)) could significantly bias the evaluation of the effect of fitusiran and make treatment comparisons difficult to interpret. To avoid potential selection bias, a combination of on-treatment and hypothetical strategies were used to deal with intercurrent events ([Table 18](#)).

Table 17. Intercurrent Events

Event	Description
I. Dose interruption periods	a) If the gap between the last dose date of the parent study (EFC14768/EFC14769/EFC15110) on a new dose regimen and the first dose date of the extension study (LTE15174) was >84 days: exclude events occurring on dates starting from the date of the last dose in the parent study +29 days, up to the date of the first dose in Study LTE15174+28 days. For subjects whose last dose of the parent study/dose of the extension study was on a 50 mg Q2M schedule, the “28 days” adjustment was replaced with 56 days. The period of >84 days was prespecified to represent 2 consecutive missed doses (56 days) with one additional dosing interval (28 days). Such a pause in dosing was expected to result in antithrombin (AT) recovery to a level that would no longer reflect the efficacy of the drug. b) Gaps from eDiary deactivation date in Study EFC15110 to eDiary reactivation date in LTE15174. This was only applicable to Pool C. c) Permanent fitusiran treatment discontinuation during the dose adjustment period due to low AT level: - Permanent fitusiran treatment discontinuation at 50 mg Q2M. - Permanent fitusiran treatment discontinuation at 20 mg Q2M. d) Permanent fitusiran treatment discontinuation during the primary efficacy period: Exclude events occurring on any dates starting from the date of the last dose within the primary efficacy period +29 days for on-treatment strategy. Permanent fitusiran treatment discontinuation during the dose adjustment period due to reasons other than low AT level. For subjects whose last dose was on 50 mg/20 mg Q2M schedule, the “29 days” adjustment was replaced with 57 days. e) Gaps from eDiary deactivation date to reactivation date for subjects who had no eDiary available during the re-enrollment period from core study to low-dose cohort in LTE15174 study. f) Gap in dosing at the original dose regimen (ODR) of 80 mg QM due to operational reasons prior to enrolling into the LTE15174 at the ODR. (Note: this is not applicable to the primary analysis).
II. Perioperative period of major surgery	The perioperative period of major surgery and major trauma was defined as the day of the surgery or trauma through the final day on which supplemental hemostatic or antithrombotic treatments were administered as part of the perioperative treatment plan.
III. Perioperative period of minor surgery	The perioperative period of minor surgery was defined like the perioperative period of major surgery (see above) or to 72 hours from the end of surgery, whichever was later.
IV. Period of Antithrombin Treatment	Defined as the first day of antithrombin treatment through the final day on which antithrombin or other anticoagulant therapies were administered +5 half-lives.
V. After treatment with emicizumab (Hemlibra®)	Prophylactic treatments with factor/BPA usage were excluded from this intercurrent event due to two considerations: factor/BPA use on any day during the perioperative period were allowed per protocol and this period was already accounted for in II and III; any prophylactic usage of factor/BPA current with fitusiran treatment outside of the perioperative period for Pool A & B or outside of the perioperative period and control period for Pool C was prohibited.

Event	Description
VI. Subjects exit program	Subjects exit the program before Dose Restart Day 1 of fitusiran with a new dose regimen. This includes subjects who withdraw from the parent study or extension study before Dose Restart Day 1, and subjects who completed the parent study without any exposure to the new dose regimen and did not roll over to the extension study.

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 5.
Abbreviations: BPA, bypassing agent; Q2M, every 2 months; QM, once monthly

The primary analysis estimand was based on a combination of on treatment and hypothetical strategies.

For subjects who were followed up in either the control or treatment period, the on-treatment strategy was considered of greatest relevance in assessing the primary objective. Bleeding episodes during intercurrent events I(a), I(b), I(d), I(e), and II through V were excluded from this analysis.

The hypothetical strategy for subjects who received at least one dose of the AT-DR but permanently discontinued treatment during the dose adjustment period due to low AT level (intercurrent event I(c)) was used to address the scientific question concerning the outcomes if these subjects had continued the treatment and been followed until the end of the primary efficacy period. The current clinical development plan under the AT-DR was to evaluate the safety and efficacy when the AT level was between 15 and 35%. Per protocol, subjects who had two AT levels below 15% were required to de-escalate to a lower dose or permanently discontinue fitusiran treatment to mitigate vascular thrombotic risk. Available clinical data suggested that lower AT levels were associated with improved ABR. For those subjects who permanently discontinued fitusiran treatment due to AT levels below 15%, directly using bleeding data from such subjects may create a bias to artificially improve the overall fitusiran ABR. Rather, it was hypothesized that those subjects may have an ABR similar to other subjects with AT levels at 15 to 35%. Therefore, the approach of missing at random was adopted.

The hypothetical strategy for subjects who exit the program before Restart Day 1 of fitusiran with the AT-DR (intercurrent event VI) was considered to address the scientific question concerning the outcomes if these subjects had remained in the program, received the new regimen, and were followed until the end of the primary efficacy period.

Table 18. Strategies to Address Intercurrent Events of the Estimand of the Primary Analysis

Intercurrent Events	Strategy
I(a), I(b), I(d), I(e), II to V	On-treatment
I(c), VI	Hypothetical

Source: ISE SAP, Section 2.7.1.1
Abbreviations: ISE, integrated summary of effectiveness; SAP, statistical analysis plan

Handling of Missing Data in the Primary Analysis

For subjects who received at least one dose of fitusiran after dose pause and permanently discontinued treatment during the dose adjustment period, if the permanent treatment discontinuation was not due to low AT level, the dose adjustment period was counted as the primary efficacy period, available bleeding episode data starting from the Dose Restart Day 1 visit to end of study was used, and intercurrent events I(a), I(b), I(d), I(e), and II to V ([Table 17](#)) would apply.

No imputation of missing data in the control period was performed for subjects who withdrew in the control period.

For the primary efficacy period, unobserved data due to intercurrent event I(c) and VI were addressed as follows:

- For subjects who received no dose of fitusiran under the AT-DR but at least one dose of fitusiran (i.e., 80 mg QM) before dose pause, or who received no dose of fitusiran under either the initial regimen (i.e., 80 mg QM) or AT-DR, the unobserved bleeding data during the primary efficacy period (Dose Restart Day 169 to Dose Restart Day 364) were imputed via a multiple imputation (MI) method with a missing at random (MAR) assumption based on observed bleeding data from Dose Restart Day 169 to Dose Restart Day 364 for subjects who were randomized to the fitusiran arm in EFC14768/EFC14769 study or exposed to fitusiran in EFC15110 study, and also dosed after the dose adjustment period, with on-treatment strategy applied to intercurrent events I(a), I(b), I(d), I(e), II to V.
- For subjects who permanently discontinued fitusiran during the dose adjustment period due to low AT level, the unobserved bleeding data during the primary efficacy period were imputed via MI method with MAR assumption based on observed bleeding data from the primary efficacy period for subjects who were randomized to the fitusiran arm in EFC14768/EFC14769 study or exposed to fitusiran in EFC15110 study, and also dosed with 20 mg of fitusiran during the primary efficacy period, with on-treatment strategy applied to intercurrent events I(a), I(b), I(d), I(e), II to V.

6.2.1.5. Results of Analyses, Pool A

Subject Disposition

ITT Pool A was comprised of fitusiran-treated subjects in Study LTE15174 and on-demand BPA-treated subjects in Study EFC14768 maintaining the original randomization either to fitusiran or on-demand BPA. Thirty-five (92.1%) subjects were enrolled and entered the fitusiran prophylaxis arm in the treatment period (dose resumption Day 1 to Day 364). There were 31 (81.6%) subjects who completed the study period and 4 (10.5%) who did not. Four (10.5%) subjects discontinued the study because more than 1 AT measured <15% ([Table 19](#)).

Table 19. Subject Disposition, ITT, Pool A

n(%)	BPA On Demand (N=19)	Fitusiran Prophylaxis (N=38)
Number of subjects randomized	19 (100)	38 (100)
Enrolled and entered study period	19 (100)	35 (92.1)
Completed the study period	19 (100)	31 (81.6)
Did not complete the study period	0	4 (10.5)
More than 1 AT measurement <15%	NA	4 (10.5)
Did not enter the study period	NA	3 (7.9)
Entered study period but discontinued treatment during the dose adjustment period	NA	4 (10.5)
Discontinued treatment due to low AT levels during the dose adjustment period	NA	4 (10.5)

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 36
Abbreviations: AT, antithrombin; BPA, bypassing agent; ITT, intent-to-treat; NA, not applicable

Demographic and Baseline Characteristics

Table 20. Baseline Demographic and Clinical Characteristics, Pool A

Baseline Characteristics	Pool A (noninhibitor population)		
Characteristic	BPA On Demand (N=19)	Fitusiran AT-DR (N=38)	ALL (N=57)
Sex (male), n (%)	19 (100)	38 (100)	57 (100)
Median age (years) (range)	28 (16-63)	26.5 (13-53)	27 (13-6)
Race, n (%)	Black: 0 White: 6 (31.6) Asian: 13 (68.4)	Black: 0 White: 10 (26.3) Asian: 26 (68.4)	Black: 0 White: 16 (28.1) Asian: 39 (68.4)
Region, n (%)	North America: 0 Europe: 4 (21.1) Asia: 13 (68.4)	North America: 6 (15.8) Europe: 7 (18.4) Asia: 25 (65.8)	North America: 6 (10.5) Europe: 11 (19.3) Asia: 38 (66.7)
Hemophilia A, n (%)	16 (84.2)	29 (76.3)	45 (78.9)
Hemophilia B, n (%)	3 (15.8)	9 (23.7)	12 (21.1)
Bleeds within previous 6 months (range)	10.0 (6-40)	9.5 (6-40)	10 (6-40)

Source: Applicant's Summary of Clinical Efficacy

Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; N, number of subjects in treatment group; n, number of subjects with given characteristic

The small sample size of HBwI subjects (N=12) compared to HA wI subjects (N=45) is expected as HA is more common than HB, with a prevalence of one in 5,000 male live births compared to one in 30,000, respectively ([Castaman and Matino 2019](#)).

The majority of subjects enrolled in Pool A (nearly 90%) were not from the United States. This is expected, as standard of care in the United States has shifted to use of prophylaxis factor replacement for bleeding, rather than on-demand factor therapy. The efficacy outcomes in ex-U.S. patients are expected to be the same as U.S. patients, as there are no known demographic factors that should alter the response to study drug. In addition, when treating patients with hemophilia, clinical practice can vary; however, the pathophysiology of hemophilia does not differ based on country. Therefore, based on the mechanism of action of fitusiran, there is no rationale for a difference in efficacy based on race or geographic region.

Additional baseline characteristics are described in Section [16.1](#).

Analysis of the Primary Endpoint

Pool A met its primary efficacy objective of superiority of fitusiran prophylaxis over BPA on demand in reducing ABR for treated bleeds. The estimated ABR was 19.1 (95% CI: 11.8, 31.0) for the BPA on demand group and 5.1 (95% CI: 2.7, 9.5) for the fitusiran prophylaxis (AT-DR) group, with a rate ratio of 0.27 (95% CI: 0.13, 0.57; p=0.0006). Results for the primary efficacy endpoint analysis are summarized in [Table 21](#). There was no pre-planned formal comparison between the fitusiran 80-mg dose and the AT-DR. The parent study efficacy results for the 80 mg QM dose are also included in the table for reference. The Applicant's primary analysis results were confirmed by the FDA statistical review team.

Table 21. Summary of Annualized Bleeding Rates for Treated Bleeds, Primary Analysis, ITT, Pool A

Parameter	BPA On Demand (N=19)	Fitusiran Prophylaxis (AT-DR) (N=38)	Fitusiran Prophylaxis (80 mg QM) (N=38)
Estimated ABR (95% CI)	19.1 (11.8, 31.0)	5.1 (2.8, 9.5)	2.0 (1.3, 3.1)
Rate ratio (95% CI)		0.27 (0.13, 0.57)	0.11 (0.06, 0.21)
P-value		0.0006 ^a	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 10 and 45; Statistical Review team's analysis.

^a P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , > 10) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable (p-value versus null hypothesis of ratio =1).

Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CI, confidence interval; ITT, intent-to-treat; QM, once monthly administration

Sensitivity analyses (SA) were conducted using the methods of MI, including copy reference (SA 1), zero-inflated negative binomial model (SA 2), and Nonparametric van Elteren test (SA 3). The results from these sensitivity analyses showed that the primary efficacy results in Pool A were robust ([Table 22](#)). These trends of the associated rate ratio with 95% CI were consistent with the results of the primary analysis, especially with the copy reference approach, which used a conservative control-based imputation for missing data in the treatment arm.

Table 22. Sensitivity Analyses, ITT, Pool A

Sensitivity Analyses (SA)	Rate Ratio (95% CI)	p-Value (Nominal)
SA 1 ^a	0.38 (0.19, 0.78)	p =0.008
SA 2 ^b	0.33 (0.16, 0.69)	p =0.003
SA 3 ^c		p<0.0001

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 51; Statistical Reviewer's analysis.

^a Sensitivity analysis 1 was conducted to further assess the impact of missing data defined for the primary analysis with copy reference (CR) approach.

^b Sensitivity analysis 2 was conducted to address the concern of potential excessive zero bleeding events using a zero-inflated negative binomial model.

^c Sensitivity analysis 3 was conducted to check robustness of hypothesis testing using a nonparametric van Elteren test.

Abbreviations: CI, confidence interval; CR, copy reference; ITT, intent-to-treat; SA, sensitivity analysis

Analysis of the Key Secondary Endpoints

The Applicant's primary analysis results (fitusiran prophylaxis AT-DR versus BPA on demand) for the key secondary endpoints and supportive efficacy results (fitusiran prophylaxis 80 mg QM versus BPA on-demand) are summarized below ([Table 23](#) to [Table 26](#)). The FDA statistical review team confirmed the Applicant's results of these four key secondary endpoints under the prespecified testing hierarchy. Significant differences in favor of fitusiran prophylaxis were observed in the key secondary endpoints of AsBR and AjBR, but not in the third key secondary endpoint, change in Haem-A-QoL Physical Health domain score in ITT Pool A, under the testing hierarchy.

Table 23. Summary of Annualized Treated Spontaneous Bleeding Rates, ITT, Pool A

Parameter	BPA On Demand (N=19)	Fitusiran Prophylaxis (AT-DR) (N=38)	Fitusiran Prophylaxis (80 mg QM) (N=38)
Estimated AsBR (95% CI)	17.1 (9.9, 29.6)	3.1 (1.8, 5.4)	0.9 (0.5, 1.6)
Rate ratio (95% CI)		0.18 (0.08, 0.39)	0.06 (0.03, 0.12)
p-Value		<0.0001 ^a	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 12 and 60; Statistical Review team's analysis.

^a P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable.

Abbreviations: AsBR, annualized spontaneous bleeding rate; AT-DR, antithrombin-based dosing regimen; BPA, bypassing agent; CI, confidence interval; ITT, intent-to-Treat; QM, once monthly administration

Table 24. Summary of Annualized Treated Joint Bleeding Rates, ITT, Pool A

Parameter	BPA On-Demand (N=19)	Fitusiran Prophylaxis (AT-DR) (N=38)	Fitusiran Prophylaxis (80 mg QM) (N=38)
Estimated AjBR (95% CI)	14.4 (9.0, 23.1)	4.0 (2.5, 6.2)	1.4 (0.8, 2.3)
Rate ratio (95% CI)		0.27 (0.14, 0.53)	0.10 (0.05, 0.21)
p-Value		0.0001 ^a	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 12 and 57; Statistical Review team's analysis.

^a P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable.

Abbreviations: CI, confidence interval; AjBR, annualized joint bleeding rate; AT-DR, antithrombin-based dosing regimen; BPA, bypassing agent; ITT, intent-to-Treat; QM, once monthly administration

Table 25. Summary of Haem-A-QOL Physical Health Domain Score Relative to Baseline Reductions, Subjects ≥ 17 Years of Age, ITT, Pool A

Parameter	BPA On-Demand (N=18)	Fitusiran Prophylaxis (AT-DR) (N=32)	Fitusiran Prophylaxis (80 mg QM) (N=32)
LS Mean (95% CI)	-5.0 (-9.2, -0.8)	-8.7 (-17.1, -0.4) ^{a,b}	-30.7 (-36.9, -24.4) ^c
LS Mean difference (95% CI)		-3.7 (-13.3, 6.0) ^{a,b}	-28.7 (-39.1, -18.4) ^c
p-Value		0.45 ^{a,b}	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 13 and 63; Statistical Review team's analysis.

^a The LS mean and mean difference (95% C.I.) were estimated by mixed-effect model with repeated measures (MMRM) with robust sandwich covariance matrix, and fixed effects of treatment visit (one postbaseline in control period and two post baselines in primary efficacy period), the randomization strata of number of bleeding episodes in the 6 months prior to EFC14768 and baseline score.

^b The Multiple imputation (MI) method was used to impute missing values at Month 6 and Month 12. The method assumes that the data are Missing at Random (MAR) and is based on observed data collected during the primary efficacy period. Only subjects aged 17 years or older in the ITT were included. The analysis excluded subjects who received at least one dose of fitusiran and those whose permanent treatment discontinuation was due to low AT levels during the dose adjustment period. For subjects with missing data, the last non-missing value after Dose Restart Day 1 was used for analysis. Month 12 data are imputed using LOCF (Last observation carried forward) from Month 6 data.

^c ANCOVA model includes treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) as fixed effects, baseline score as a covariate.

Abbreviations: ANCOVA, analysis of covariance; AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CI, confidence interval; ITT, Intent-to-Treat; Haem-A-QOL, Haemophilia Quality of Life Questionnaire; LOCF, last observation carried forward; LS, least square; MAR, missing at random; MI, multiple imputation; QM, once monthly administration

Table 26. Summary of Time to First Treated Bleeding Episode, ITT, Pool A

Parameter	BPA On Demand (N=19)	Fitusiran Prophylaxis (AT-DR) (N=38)
KM estimate of event	0.95 (0.79, 1.00)	0.63 (0.47, 0.80)
KM estimate of no event	0.05 (0.00, 0.21)	0.37 (0.20, 0.53)
Hazard ratio (95% CI)		0.21 (0.11, 0.42) ^a
Nominal p-value		<0.0001 ^a

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 66; Statistical Review team's analysis.

^a Hazard ratio and p-value were from Cox proportional hazards regression with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) as fixed effects.

Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CI, confidence interval; ITT, intent-to-treat; KM, Kaplan-Meier

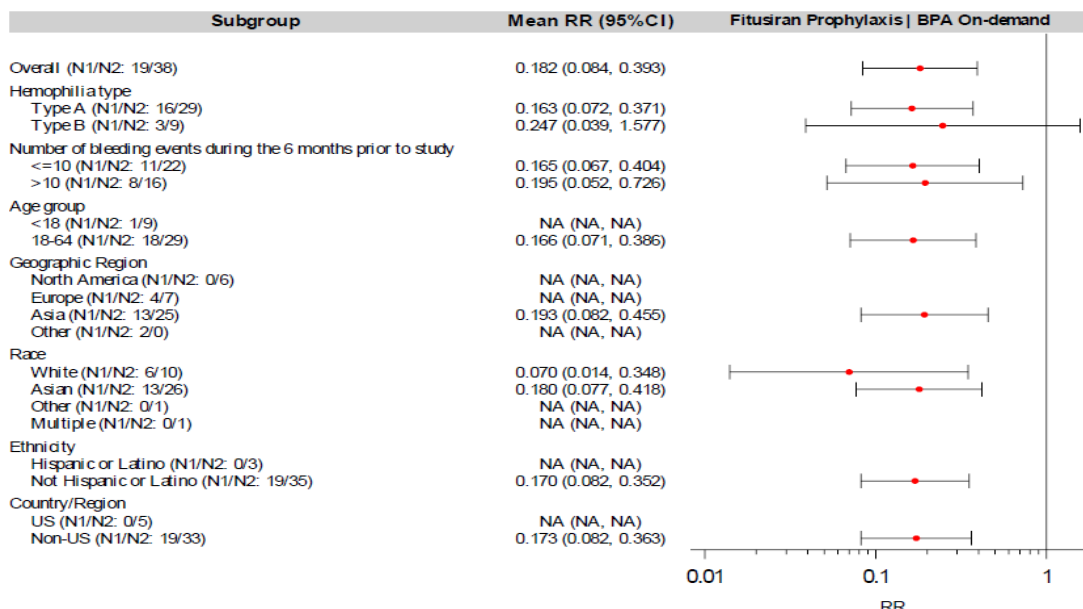
In addition to a nonsignificant p-value, the FDA review team had concerns about the interpretability for the PRO data of Haem-A-QOL Physical Health domain score given the lack of baseline values and other limitations. For details, please refer to Section 16.5. The fourth key secondary endpoint of the time to first treated bleeding episode should be considered exploratory only, since the prior endpoint in the testing hierarchy, Haem-A-QOL Physical Health domain score, failed to yield a significant p-value. Further, this endpoint was not proposed in the parent study EFC14768. In addition, while it is clearly beneficial to reduce the number of treated bleeds, it is not clear whether reducing the time to first treated bleed is a clinically meaningful endpoint. (b) (4)

(b) (4)

Subgroup Analysis of the Primary Endpoints

Subgroup analyses were conducted to assess the potential for differences in the treatment effect of fitusiran prophylaxis compared to BPA on-demand across various demographic and clinical characteristic groups. Overall, the treatment effect was consistent across baseline subgroups, including hemophilia type, prior bleeding events, age group, race, and ethnicity. Of note, these subgroup analyses are limited by the small numbers of subjects, so the results should be interpreted with caution.

Figure 10. Forest Plot of Estimated Annualized Bleeding Rate Ratio (95% CI) by Subgroups, ITT, Pool A



Source: Summary of Clinical Efficacy Hemophilia A and B, Figure 15; Statistical Review team's analysis.
N1 represent number of subjects in control period. N2 represent number of subjects in primary efficacy period.
Abbreviations: BPA, bypassing agent; ITT, intent-to-treat; RR, rate ratio

The subgroup analyses described above should be interpreted with caution given the small sample size. For example, the CI for HBwI population is wide and crosses 1; however, based on the mechanism of action of the drug (which acts independent of factors VIII and IX) and the pathophysiology of the disease, it is not expected for patients with HAwI and HBwI to respond differently to fitusiran. Likely, the difference in ABR is due to small sample size in the subgroup (N=9). With less than 10% of data from U.S. subjects (i.e., 5/57), the mean rate ratio (RR; 95% CI) was not estimable for this geographic region, although the observed mean (±SD) ABR for treated bleeds on fitusiran for the five U.S. subjects in the ITT Pool A was similar to the overall population: 4.8 (5.53) versus 4.4 (5.45).

6.2.2. Pool B — Subjects With HA or HB Without Inhibitors, Previously on Factor On-Demand Therapy

Pooling Strategy

Table 27. Pooling Strategy for Integrated Summary of Efficacy, ITT, Pool B

Studies	Populations	Treatment	Subject Data for Inclusion
		Comparisons	
EFC14769 & LTE15174	Without inhibitor Hem A & Hem B	Fitusiran prophylaxis vs. factor on-demand	For fitusiran prophylaxis: 13 months treatment period since first AT-DR dose after dose pause in LTE15174 ^a . For factor on-demand: 9 months control period in EFC14769.

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 3.

^a 13-month treatment period is from the Dose Restart Day 1 as defined in Section 2.5 to the end of month 12. The Dose Restart Day 1 is the start of Month 0. One month = 28 days.

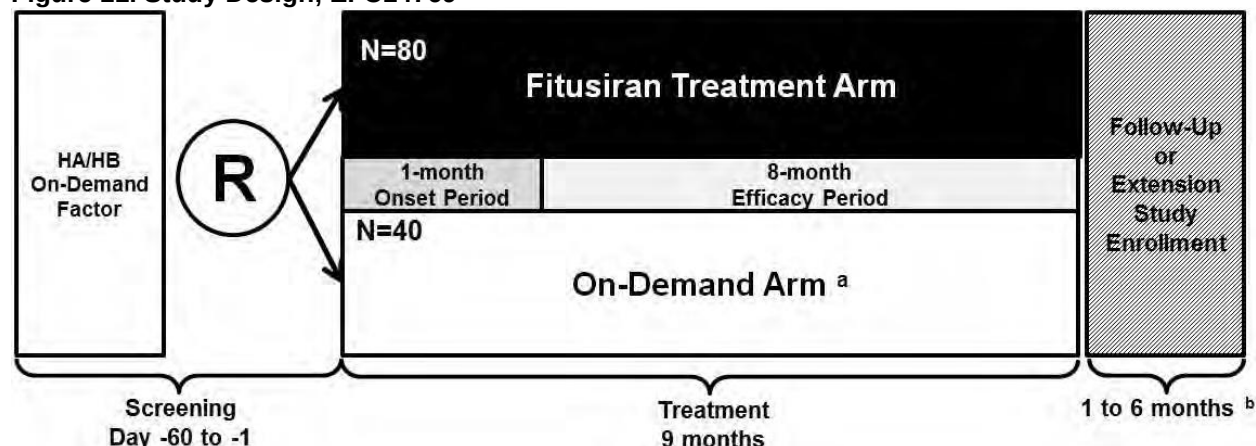
Abbreviations: Hem, hemophilia; ITT, intent-to-treat

6.2.2.1. Design, Pool B

The control arm for Pool B was from Study ATLAS-A/B (EFC14769) described below. The treatment arm was from the extension Study ATLAS-OLE (LTE15174). For Pool B, the fitusiran-treated subjects who were included from LTE15174 were those with hemophilia A or B without inhibitors who were originally randomized to fitusiran in Study EFC14769 and who received AT-DR during Study LTE15174.

ATLAS-A/B (EFC14769) was a multicenter, randomized, open-label study in male subjects aged ≥ 12 years, with hemophilia A or B without inhibitory antibodies to FVIII or FIX, who were not receiving prophylactic therapy. The study design is shown in [Figure 11](#). Subjects were randomized in a 2:1 ratio to either fitusiran 80 mg SC as prophylaxis once monthly or to on-demand factor concentrates. The study allowed use of on-demand factor concentrates in the fitusiran-treated subjects 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. For subjects in the fitusiran treatment arm who developed breakthrough bleeding episodes, bleeding management guidelines were followed as outlined in [Section 15](#). Randomization was stratified by the number of bleeding episodes in the 6 months prior to Screening (≤ 10 versus >10) and hemophilia type (hemophilia A or B). All subjects were treated for 9 months and upon completion, eligible for participation in an open-label extension study. See a detailed description of the study design in [Section 15.2](#).

Figure 11. Study Design, EFC14769



Source: Applicant's Clinical Study Protocol for EFC14769

^a On-demand factor concentrates as routinely prescribed by physician per local standard practice.

^b Fitusiran treatment arm subjects who do not enroll in the extension study: AT activity level was 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.

Abbreviations: AT, antithrombin; HA/HB, hemophilia type A / hemophilia type B; R, randomized

The Study design for Study ATLAS-OLE (LTE15174) is described above in Section [6.2.1.1](#).

6.2.2.2. Objectives and Endpoints, Pool B

Objectives

The primary objective was to evaluate the efficacy of fitusiran treatment with the revised AT-DR compared to factor on demand, as determined by the frequency of bleeding episodes.

The secondary objective was to evaluate the efficacy of fitusiran compared to factor on demand, as determined by the frequency of treated spontaneous bleeding episodes, the frequency of treated joint bleeding episodes, health-related quality of life in subjects ≥ 17 years of age, and time to first treated bleeding episode.

Endpoints

The primary efficacy endpoint was ABR of treated bleeds in the fitusiran primary efficacy period compared to the control period ([Table 14](#)).

The key secondary endpoints are listed below:

1. Annualized treated spontaneous bleeding rate (AsBR).
2. Annualized treated joint bleeding rate (AjBR).
3. Change in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain score. This instrument is described in Section [6.2.1.2](#). (b) (4)
4. Time to first treated bleeding episode (not proposed in parent Study EFC14769).

Endpoints for Study EFC14769 are described in Section [15.2](#).

6.2.2.3. Eligibility Criteria, Pool B

Eligibility criteria for Study EFC14769 are described below. Study LTE15174 included subjects who completed a previous parent phase 3 clinical study of fitusiran and had central AT activity level $\geq 22\%$ (prior to dosing).

ATLAS-A/B (EFC14769)

Key Inclusion Criteria

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 $\leq 2\%$ at Screening.
 - b. On-demand use of factor concentrate to manage bleeding episodes for at least the last 6 months prior to Screening, and meeting each of the following criterion:
 - i. Nijmegen modified Bethesda assay inhibitor titer of < 0.6 BU/mL at Screening.
 - ii. No use of BPAs to treat bleeding episodes for at least the last 6 months prior to Screening.
 - iii. 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.

Key Exclusion Criteria

Key exclusion criteria are the same as Pool A as described in Section [6.2.1.3](#).

6.2.2.4. Statistical Analysis Plan, Pool B

Analysis of the Primary Endpoint

The primary endpoint was analyzed using a negative binomial model with the number of bleeding episodes as the response variable, and randomization arm, the randomization strata of number of bleeding episodes in the 6 months prior (≤ 10 , > 10), and hemophilia type as fixed effects. The logarithm of the duration (in years) that each subject spent in each study period matching their bleeding episode data (i.e., treatment period from Study EFC15174 and control period from EFC14769) was included as an offset variable to account for unequal follow-up time due to different durations of the treatment and control periods, early withdrawal, surgery, etc.

Analysis of Key Secondary Endpoints

Annualized Treated Spontaneous Bleeding Rate

The same primary analysis for the primary endpoint was used for this key secondary endpoint.

Annualized Treated Joint Bleeding Rate

The same primary analysis for the primary endpoint was used for this key secondary endpoint.

Change in Haem-A-QoL Physical Health Domain Score

Change from baseline in Haem-A-QoL Physical Health domain score (in subjects ≥ 17 years of age) in the control period and primary efficacy period was analyzed using an MMRM with robust sandwich covariance matrix, with fixed effects, visit of study period (one postbaseline in control period and two postbaselines in primary efficacy period), randomization strata of number of bleeding episodes in the 6 months prior to EFC14769 study entry, randomization strata of hemophilia type, and baseline Haem-A-QoL Physical Health domain score. We show the Haem-A-QoL Physical Health results for completeness but do not consider the findings reliable because of several limitations discussed in Section [16.5](#).

Time to First Treated Bleeding Episode

The risk of bleeding in the primary efficacy period and control period was compared using a Cox proportional hazards regression model. For ITT Pool B, treatment arm and randomization strata of number of bleeding episodes in the 6 months prior to EFC14769 study entry were fixed effects.

Multiple Testing Strategy

To control the familywise error rate at the alpha level of 0.05 in the testing of the primary and key secondary endpoints for each pool, a hierarchical testing approach was used. For ITT Pool B, the endpoints were tested in the order based on primary analysis of the endpoints as described in [Table 10](#). If testing of any of the endpoints was not statistically significant, formal testing of subsequent endpoints would be stopped and the null hypothesis for subsequent tests would not be rejected.

Handling of Intercurrent Events and Missing data

The handling method of intercurrent events and missing data for Pool B were the same as described in Pool A. See Section [6.2.1.4](#) for further details.

6.2.2.5. Results of Analyses, Pool B

Subject Disposition

ITT Pool B was comprised of subjects in Study LTE15174 and Study EFC14769 maintaining the original randomization either to fitusiran or on-demand factor replacement. Subject disposition is described in [Table 28](#) below.

Table 28. Subject Disposition, ITT, Pool B

n(%)	Factor On Demand (N=40)	Fitusiran Prophylaxis (N=80)
Number of subjects randomized	40 (100)	80 (100)
Enrolled and entered study period	40 (100)	68 (85.0)
Completed the study period	37 (92.5)	62 (77.5)
Did not complete the study period	3 (7.5)	6 (7.5)
Adverse Event	1 (2.5)	2 (2.5)
Protocol violation	1 (2.5)	0
Subject withdrew consent	1 (2.5)	0
More than 1 AT measurement <15%	0	4 (5.0)
Did not enter the study period*	NA	12 (15.0)
Entered study period but discontinued treatment during the dose adjustment period	NA	3 (3.8)
Discontinued treatment due to low AT levels during the dose adjustment period	NA	3 (3.8)

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 37

*refers to subjects who discontinued the study prior to Dose Restart Day 1 and is only applicable for fitusiran prophylaxis arm.

Abbreviations: AT, antithrombin; ITT, intent-to-treat; NA, not applicable

The lower completion rate in the fitusiran prophylaxis arm compared to the on-demand arm is reflective of the higher rate of subjects who did not enter the study period for Study LTE15174.

Demographic and Baseline Characteristics

Table 29. Baseline Demographic and Clinical Characteristics, Pool B

Characteristic	Factor On Demand (N=40)	Fitusiran AT-DR (N=80)	All (N=120)
Sex (male), n (%)	40 (100)	80 (100)	120 (100)
Median age (years) (range)	33.5 (12-60)	30 (12-68)	31 (12-68)
Race, n (%)	Black: 0 White: 12 (30.0) Asian: 28 (70.0)	Black: 2 (2.5) White: 33 (41.3) Asian: 43 (53.8)	Black: 2 (1.7) White: 45 (37.5) Asian: 71 (59.2)
Region, n (%)	North America: 3 (7.5) Europe: 8 (20.0) Asia: 27 (67.5)	North America: 4 (5.0) Europe: 24 (30.0) Asia: 43 (53.8)	North America: 7 (5.8) Europe: 32 (26.7) Asia: 70 (58.3)
Hemophilia A, n (%)	31 (77.5)	62 (77.5)	93 (77.5)
Hemophilia B, n (%)	9 (22.5)	18 (22.5)	27 (22.5)
Previous bleeds (6 months) (range)	10 6-30	10 6-40	10 6-40

Source: Applicant's Summary of Clinical Efficacy

Abbreviations: AT-DR, antithrombin-based dose regimen; N, number of subjects in treatment group; n, number of subjects with given characteristic

The small sample size of HB subjects (N=27) compared to HA subjects (N=93) is expected as HA is more common than HB.

The majority of subjects enrolled in Pool B (nearly 80%) were not from the United States. This is expected as standard of care in the United States has shifted to use of prophylaxis factor replacement for bleeding, rather than on-demand factor therapy. The efficacy outcomes in ex-U.S. patients are expected to be similar to those in U.S. patients as there are no known demographic factors that should alter the response to study drug. In addition, when treating patients with hemophilia, clinical practice can vary; however, the pathophysiology of hemophilia

does not differ based on country. Therefore, based on the mechanism of action of fitusiran, there is no rationale for a difference in efficacy based on race or geographic region.

Additional baseline characteristics are described in Section [16.2](#).

Analysis of the Primary Endpoint

The study demonstrated a statistically significant reduction in ABR for treated bleeds with fitusiran prophylaxis compared to factor on-demand treatment in the primary efficacy period. The estimated ABR was 31.4 (95% CI: 20.5, 48.2) for the factor on-demand group and 9.0 (95% CI: 5.6, 14.5) for fitusiran prophylaxis with AT-DR. Results for the primary efficacy endpoint analysis are summarized in [Table 30](#). There was no pre-planned formal comparison of ABR for treated bleeds between subjects who received fitusiran 80 mg prophylaxis and AT-DR fitusiran prophylaxis. The comparison results of 80 mg QM vs. factor on demand from the parent study are also presented in the table for reference. The Applicant's primary analysis results were confirmed by the FDA statistical review team.

Table 30. Summary of ABR for Treated Bleeds, Primary Analysis, Pool B

Parameter	Factor On Demand (N=40)	Fitusiran Prophylaxis (AT-DR) (N=80)	Fitusiran Prophylaxis (80 mg QM) (N=80)
Estimated ABR (95% CI)	31.4 (20.5, 48.2)	9.0 (5.6, 14.5)	4.1 (3.1, 5.3)
Rate ratio (95% CI)		0.29 (0.18, 0.47)	0.13 (0.09, 0.19)
p-Value		<0.0001 ^a	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 16 and 47; Statistical Review team's analysis.

^a P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) and randomization strata of hemophilia type (A, B) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable.

Abbreviations: ABR, annualized bleeding rate; AT-DR = Antithrombin - based dose regimen; CI = confidence interval.; QM = once monthly administration

Sensitivity analyses (SA) were conducted using the methods of MI, including copy reference (SA 1), zero-inflated negative binomial model (SA 2) and Nonparametric van Elteren test (SA 3), which showed that the primary efficacy results in Pool B were robust. The rate ratios (95% CI) in SA 4 and SA 5 were 0.41 (0.26, 0.65) and 0.35 (0.22, 0.54), respectively ([Table 31](#)). These findings were consistent with the results of the primary analysis, especially with the copy reference approach, which is a conservative control.

Table 31. Sensitivity Analyses, ITT, Pool B

Sensitivity Analyses (SA)	Rate Ratio (95% CI)	p-Value (Nominal)
SA 1	0.41 (0.26, 0.65)	p = 0.0002
SA 2	0.35 (0.22, 0.54)	p < 0.0001
SA 3		p < 0.0001

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 52; Statistical Review team's analysis.

^a Sensitivity analysis 1 was conducted to further assess the impact of missing data defined for the primary analysis with copy reference (CR) approach.

^b Sensitivity analysis 2 was conducted to address the concern of potential excessive zero bleeding events using a zero-inflated negative binomial model with.

^c Sensitivity analysis 3 was conducted to check robustness of hypothesis testing using a nonparametric van Elteren test.

Abbreviations: CI, confidence interval; CR, copy reference; ITT, intent-to-treat; SA, sensitivity analysis

Analysis of the Key Secondary Endpoints

The Applicant's primary efficacy results for the key secondary endpoints are summarized below (Table 32 to Table35). The Applicant's primary efficacy results for the four key secondary endpoints under a testing hierarchy were confirmed by the FDA Statistical review team. Statistically significant differences in favor of fitusiran prophylaxis were observed in all these key secondary endpoints under the testing hierarchy. However, the review team has concerns regarding the interpretation of the PRO endpoint, change from baseline in Haem-A-QoL Physical Health domain score (in subjects ≥ 17 years of age). See further in discussion in Section 16.5.

Table 32. Summary of Annualized Treated Spontaneous Bleeding Rates, Pool B

Parameter	Factor On Demand (N=40)	Fitusiran Prophylaxis (AT-DR) (N=80)	Fitusiran Prophylaxis (80 mg QM) (N=80)
Estimated AsBR (95% CI)	21.0 (14.0, 31.6)	5.4 (3.7, 8.0)	1.8 (1.2, 2.7)
Rate ratio (95% CI)		0.26 (0.16, 0.42)	0.08 (0.05, 0.14)
p-Value		<0.0001	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 18 and 58; Statistical Review team's analysis.

^a P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) and randomization strata of hemophilia type (A, B) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable.

Abbreviations: CI, confidence interval; AsBR, annualized spontaneous bleeding rate; AT-DR, antithrombin-based dosing regimen; BPA, bypassing agent; ITT, intent-to-Treat; QM, once monthly administration

Table 33. Summary of Annualized Treated Joint Bleeding Rates, Pool B

Parameter	Factor On-Demand (N=40)	Fitusiran Prophylaxis (AT-DR) (N=80)	Fitusiran Prophylaxis (80 mg QM) (N=80)
Estimated AjBR (95% CI)	21.6 (14.6, 31.9)	6.2 (4.2, 9.2)	2.3 (1.6, 3.3)
Rate ratio (95% CI)		0.29 (0.17, 0.48)	0.10 (0.06, 0.16)
p-value		<0.0001	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 18 and 61; Statistical Review team's analysis.

P-value from a negative binomial model with treatment arm and randomization strata of number of bleeds in the 6 months prior to study (≤ 10 , >10) and randomization strata of hemophilia type (A, B) as fixed effects. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed was an offset variable

Abbreviations: AjBR, annualized joint bleeding rate; AT-DR, antithrombin-based dosing regimen; BPA, bypassing agent; CI, confidence interval; ITT, intent-to-Treat; QM, once monthly administration

Table 34. Summary of Haem-A-QOL Physical Health Domain Score Relative to Baseline Reductions, Subjects ≥17 Years of Age, Pool B

Parameter	Factor On Demand (N=38)	Fitusiran Prophylaxis (AT-DR) (N=72)	Fitusiran Prophylaxis (80 mg QM) (N=72)
LS mean (95% CI)	-3.8 (-8.7, 1.1)	-12.0 (-18.1, -5.9) ^{a,b}	-23.1 (-28.0, -18.1) ^c
LS mean difference		-8.2 (-15.3, -1.1)	-19.8 (-27.0, -12.5) ^c
p-value		0.025 ^{a,b}	

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 19 and 64; Statistical Review team's analysis.

^a The LS mean and mean difference (95% CI) are estimated by mixed-effect model with repeated measures (MMRM) with robust sandwich covariance matrix, and fixed effects of treatment visit (one postbaseline in control period and two postbaselines in primary efficacy period), the randomization strata of number of bleeding episodes in the 6 months prior to EFC14769, randomization strata of hemophilia type (A versus B), and baseline score.

^b The Multiple imputation (MI) method was used to impute missing values at Month 6 and Month 12. The method assumes that the data are Missing at Random (MAR) and is based on observed data collected during the primary efficacy period. Only subjects aged 17 years or older in the ITT were included. The analysis excluded subjects who received at least one dose of fitusiran and those whose permanent treatment discontinuation was due to low AT levels during the dose adjustment period. For subjects with missing data, the last non-missing value after Dose Restart Day 1 was used for analysis. Month 12 data are imputed using LOCF (Last observation carried forward) from Month 6 data.

^c ANCOVA model includes treatment arm, randomization strata of number of bleeds in the 6 months prior to study (≤10, >10) and randomization strata of hemophilia type (A versus B) as fixed effects, baseline score as a covariate.

Abbreviations: ANCOVA, analysis of covariance; AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CI, confidence interval; Haem-A-QOL, Haemophilia Quality of Life Questionnaire; ITT, Intent-to-Treat; LOCF, last observation carried forward; LS, least square; MAR, missing at random; MI, multiple imputation; QM, once monthly administration

Table 35. Summary of Time to First Treated Bleeding Episode, Pool B

Parameter	Factor On Demand (N=40)	Fitusiran Prophylaxis (AT-DR) (N=80)
KM estimate of event	1.00 (NA, NA)	0.74 (0.62, 0.84)
KM estimate of no event	0.00 (NA, NA)	0.26 (0.16, 0.38)
Hazard ratio (95% CI)		0.19 (0.12, 0.30) ^a
p-Value		<0.0001 ^a

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 67; Statistical Review team's analysis.

^a Hazard ratio and p-value are from Cox proportional hazards regression with treatment arm, randomization strata of number of bleeds in the 6 months prior to study (≤10, >10) and hemophilia type (A, B) as fixed effects.

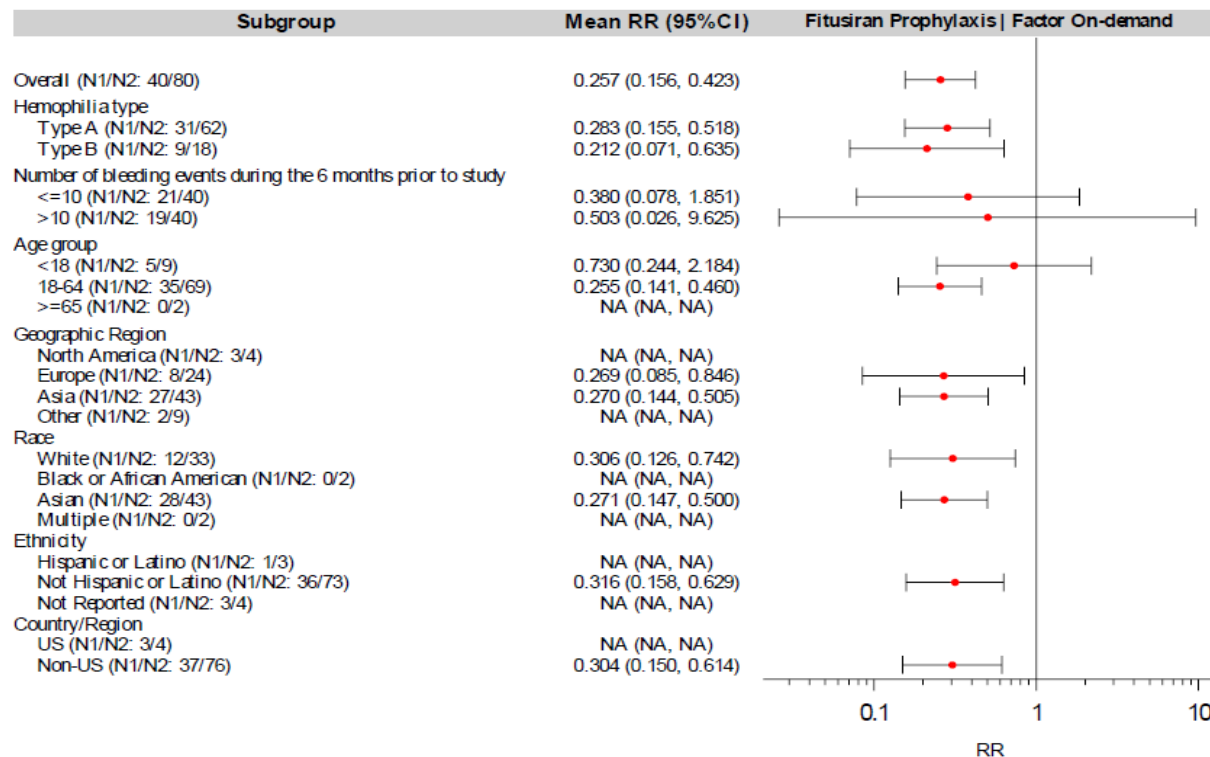
Abbreviations: AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CI, confidence interval; ITT, intent-to-treat; KM, Kaplan-Meier

In contrast to the Pool A population, for the noninhibitor population in Pool B, the PRO endpoint did reach statistical significance however the review team had concerns about the interpretability for the PRO data, Haem-A-QOL Physical Health domain score, considering the open-label design of the study and lack of baseline values. For details, please refer to Section 16.5. Further, the fourth key secondary endpoint of the time to first treated bleeding episode was not proposed in parent study EFC14769, and is not considered clinically meaningful. (b) (4)

Subgroup Analysis of the Primary Endpoint

Subgroup analyses were conducted to assess the potential for differences in the treatment effect of fitusiran prophylaxis compared to factor on demand across various demographic and clinical characteristic groups. Overall, the treatment effect was consistent across baseline subgroups, including hemophilia type, prior bleeding events, age group, race, and ethnicity (Figure 12).

Figure 12. Forest Plot of Estimated Annualized Bleeding Rate Ratio (95% CI) by Subgroups, ITT, Pool B



Source: Summary of Clinical Efficacy Hemophilia A and B, Figure 16; Statistical Review team's analysis.
N1 represent number of subjects in control period. N2 represent number of subjects in primary efficacy period.
Abbreviations: BPA, bypassing agent; ITT, intent-to-treat; NA, not applicable; RR, rate ratio

There were only a few U.S. subjects. In Pool B, 7/120 subjects were from the United States; 4 were in the fitusiran prophylaxis treatment arm and 3 were in the Factor on-demand control arm. The mean rate ratio (RR; 95% CI) cannot be estimated given the small size of the U.S. subgroup. Mean (±SD) ABR for treated bleeds for U.S. subjects: factor on demand: 15.0 (12.74) and fitusiran: 6.8 (4.68). Mean (±SD) ABR for treated bleeds for overall population: factor on demand 31.3 (25.15) and fitusiran 8.3 (9.22).

6.3. Key Efficacy Review Issues

6.3.1. Demonstration of Benefit of Fitusiran: Antithrombin-Based Dose Regimen Efficacy Data From the Long-Term Extension Study Compared to Control Data From Randomized Parent Studies

Issue

The parent randomized controlled phase 3 studies were nearly completed when the Applicant switched to the AT-DR, the to-be-marketed dose of fitusiran. To assess the efficacy of the AT-DR, the Applicant compared the efficacy data from the long-term extension study (LTE15174), which implemented the AT-DR, to the control arms of the parent studies (EFC14768 and

EFC14769). The review team examined whether this approach is adequate to establish the effectiveness of the AT-DR.

Background

Dosing in the phase 3 studies, EFC14768, EFC14769, and EFC15110 (referred to as parent studies in the rest of the section), was initiated with fitusiran at 80 mg QM. To mitigate the risk of thrombotic events, the AT-DR targeting an AT activity range of 15 to 35% was implemented when the parent studies were nearly completed. The AT-DR was fully implemented in the extension study, LTE15174.

The efficacy of fitusiran AT-DR treatment was assessed by comparing the fitusiran AT-DR treatment data from the long-term extension study LTE15174 to the control data from the parent studies (see [Figure 7](#)). This approach was discussed during the IND stage of development. At the Type C Guidance Meeting on September 18, 2023, and in a May 15, 2024, information request, the Agency raised the concern whether the time lag (approximately 2 years) between the parent studies and the extension study LTE15174 introduces additional confounding factors and ultimately reduces the confidence that this approach can establish effectiveness for the proposed AT-DR for fitusiran.

Assessment

The Applicant and the FDA clinical and statistical review team conducted thorough evaluations to assess the comparability between the control arm data from the parent studies and the fitusiran AT-DR data from the extension study.

Pathophysiology

The pathophysiology of severe hemophilia allows for a comparison between control and intervention groups across time. Congenital severe hemophilia typically presents in infancy and throughout the lifespan of a given patient. The clinical hallmark of severe hemophilia is spontaneous bleeding that requires lifelong treatment, including both prophylaxis and on-demand therapies for breakthrough bleeding events. In the control on-demand group, episodic treatment with CFC or BPA does not alter the course of the disease, and for that reason, the individual bleeding phenotype is not anticipated to change in the absence of prophylactic intervention over the study duration. Therefore, the use of the control group in the parent studies is adequate and not impacted by the time lag.

Baseline Characteristics

The parent studies' baseline characteristics, including medical and surgical history at time of enrollment, concomitant medications, and prior hemophilia-directed therapies (e.g., CFC/BPA, prohibited medications, bleed management, etc.), were comparable between the active and control arms. No significant changes were observed in reported medical history or concomitant medications within the relatively short timeframe in which subjects were enrolled in the fitusiran parent and extension clinical studies. Bleed management guidelines were followed in all studies.

Carryover Benefit From Prior Treatment With Fitusiran (i.e., Fitusiran Original Dosing Regimen of 80 mg QM)

Influence From Prior Exposure to Fitusiran

In the extension study LTE15174, among 11 participants who were never exposed to the original dose regimen, the estimated mean (95% CI) annualized bleed rate (ABR) for treated bleeds was lower than the overall AT-DR participants [1.49 (0.58, 3.85) vs. 6.41 (5.31, 7.74)] with nonoverlapped CI, suggesting that there was no positive influence from prior exposure to the original dose regimen for the estimated efficacy for AT-DR. In addition, the primary efficacy assessment occurred after a 6-month period in which study participants restarted fitusiran, targeting AT levels of 15-35%. By the end of the 6-month period, the majority of study participants reached AT-steady state and were on a stable dose. Therefore, as participants were on a steady state of fitusiran, it is unlikely that the prior exposure to fitusiran at the 80mg fixed dose had an influence on efficacy outcomes.

Imbalanced Dropout Rate Between Treatment Arms

The dropout rate is 15% to 22% higher in the fitusiran AT-DR treatment arm from the extension study LTE15174 in subjects originally randomized to fitusiran in the parent studies compared to the control arm from parent studies. The time lag between the extension study and the parent studies may have a considerable contribution to the imbalanced dropout rate between arms (please refer to the disposition tables for Pools A, B and C in Section [6.2](#) for further information). Per the FDA statistical review team's recommendation, the Applicant conducted several sensitivity analyses for ABR in Pools A and B to impute the missing data due to different reasons, including a copy reference approach, which is a conservative control-based imputation that imputes unobserved bleeding data during the primary efficacy period (Dose Restart Day 169 to Dose Restart Day 364) using the control period data distribution in the corresponding parent study. These analyses were consistent with the primary analysis (for details, see the sensitivity analysis results for the primary endpoint in Section [6.2.1.5](#) and [6.2.2.5](#)), showing that the primary efficacy results for the primary efficacy endpoint ABR for treated bleeds are robust. The missing data and dropouts did not affect the final efficacy conclusion. Additional reassurance is provided by the large treatment effect size in which the p-value of the primary efficacy endpoint (ABR for treated bleeds) was <0.001, for both subjects with and without inhibitors.

Impact of Unknown and Known Confounders

Randomization

Although known confounders appear to be generally balanced between the two treatment arms in the pooled data (please refer to the baseline demographics and clinical characteristics tables in Section [6.2](#)), unknown confounders can only be balanced through randomization. To balance the treatment and control groups for the unknown confounders, the Applicant followed the FDA statistical review team's recommendation to maintain the original randomization used in the parent studies for the pooled analyses, i.e., the fitusiran new dose regimen arm should only include subjects who were randomized to the fitusiran arm in the parent study. The efficacy analyses were conducted according to the intent-to-treat (ITT) principle, preserving the randomization in the parent studies.

Intrasubject Comparison

Unknown confounders were further evaluated in a supplementary analysis using intrasubject comparison where the individual serves as their own control. For subjects who were randomized to the control arm in the parent study EFC14768 or EFC14769 and received at least one dose of fitusiran under the revised AT-DR in LTE15174, their fitusiran AT-DR treatment data from the extension study LTE15174 were compared with their own control data from the parent studies ([Table 36](#)). The results of the analysis reached a conclusion consistent with the primary analysis.

Table 36. Intrasubject Comparison of Annualized Bleeding Rates for Treated Bleeds Based on On-Treatment Strategy^a: Fitusiran Prophylaxis in Primary Efficacy Period vs. On-Demand in Control Period, Intrasubject Comparison^b Set, Pool A and Pool B

Pool	Result	On-Demand	Fitusiran AT-DR
Pool A	Number of subjects	16	16
	Estimated ABR (95% CI)	18.6 (13.5, 25.7)	2.8 (1.6, 5.1)
	Rate ratio ^c (95% CI)		0.15 (0.09, 0.26)
	Nominal p-value ^d		<0.0001
Pool B	Number of subjects	33	33
	Estimated ABR (95% CI)	34.3 (25.7, 45.8)	6.0 (3.6, 10.0)
	Rate ratio (95% CI)		0.18 (0.11, 0.27)
	Nominal p-value		<0.0001

Source: Summary of Clinical Efficacy Hemophilia A and B

^a The bleeds analysis is based on the combination of on-treatment strategy, which included the treated bleeding events in the follow-up duration and excluded the treated bleeding events in the intercurrent events.

^b The intrasubject comparison set for Pool A/Pool B are all EFC14768/EFC14769 enrolled subjects who were randomized to the on-demand arm, and rolled over to LTE15174 and were exposed at least one dose of fitusiran under the revised dose regimen after the dosing pause. Participants who were not dosed in the primary efficacy period were excluded from the analysis.

^c Fitusiran rate divided by factor on-demand rate.

^d Nominal p-value from a repeated negative binomial model.

Abbreviations: ABR, annualized bleeding rate; AT-DR, Antithrombin Dosing Regimen; CI, confidence interval.

The FDA statistical review team further explored whether there is consistency in responses between the fitusiran AT-DR, the fitusiran 80 mg QM dose, and the control data ([Table 37](#)). Note that the pooled analysis for AT-DR and the original 80 mg QM dosing regimen analysis shared the same control data. The table below summarizes the estimated ABR (95% CI) for the primary endpoint, ABR for treated bleeds, for the control arm, fitusiran AT-DR treatment arm and fitusiran original dosing regimen treatment arm and corresponding p-values for each treatment arm compared with the control arm. Please refer to Section 6.2 for the full details on the analyses results for efficacy endpoints.

Table 37. Summary of Analysis Results for the Primary Endpoint ABR for Treated Bleeds for the Fitusiran Original Dosing Regimen 80 mg QM Treatment and Fitusiran AT-DR Treatment Compared to the Control Treatment, ITT, Study EFC14768/Pool A and Study EFC14769/Pool B

Study	Parameters	Control	Fitusiran AT-DR	Fitusiran Original Dosing Regimen (80 mg QM)
Study EFC14768/Pool A (n _c /n _t =19/38)	ABR (95% CI) p-value for rate ratio of fitusiran vs. control	19.1 (11.8, 31.0)	5.1 (2.8, 9.5) (p=0.0006)	2.0 (1.3, 3.1) (p<0.0001)
Study EFC14769/Pool B (n _c /n _t =40/80)	ABR (95% CI) p-value for rate ratio of fitusiran vs. control	31.4(20.5, 48.2)	9.0 (5.6 14.5) (p<0.0001)	4.1 (3.1, 5.4) (p<0.0001)

Source: Summary of Clinical Efficacy Hemophilia A and B; Clinical Study Report for Study EFC14768; Clinical Study Report for Study EFC14769; Clinical Study Report for Study EFC15110.

Abbreviations: ABR, annualized bleeding rate; AT, Antithrombin; CI, confidence interval; DR, dosing regimen; FAS, full analysis set; ITT, intent-to-Treat; n_c, number of subjects in the control arm; n_t, number of subjects in the treatment arm; QM, once monthly administration.

For Pools A & B, despite the reduction in estimated effect size in the fitusiran AT-DR arm compared to the fitusiran original 80 mg QM dosing regimen arm, the ABR in the fitusiran AT-DR arm is still significantly lower than that of the control arm with small p-values (p<0.001), showing that the efficacy of fitusiran is maintained under the reduced dose compared to BPA/CFC on-demand treatment.

Conclusion

In summary, the review team determined that the approach of comparing efficacy data from the long-term extension study which used the AT-DR, to the control arms in the parent studies was acceptable for establishing the effectiveness of the AT-DR.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The safety of fitusiran was assessed in good laboratory practice repeat-dose toxicology studies in healthy animals (rats and monkeys) and in animal models of hemophilia (mice, dogs, and monkeys). Animal studies were conducted using the subcutaneous route of administration, which is consistent with the intended clinical route. To ensure continuous exposure and account for differences in tissue exposure half-lives, animals were generally dosed more often (once weekly) than the clinical dosing schedule (once per month or once every other month). Small interfering RNA drugs, including fitusiran, show prolonged tissue residence times (e.g., weeks to months), but have short intermittent plasma exposure (e.g., hours). Because of this, the relationship of fitusiran blood exposures (i.e., AUC) to tissue levels remains uncertain. To account for this, animal-to-human safety margins described herein are based on dose comparisons (instead of plasma exposures), which have been corrected to reflect the total fitusiran dose over time (i.e., mg/kg/month) and further adjusted for body surface area (BSA) differences between species.

Fitusiran was pharmacologically active in the common laboratory strains of rats and monkeys that were utilized in standard toxicology studies. Because these species exhibit normal clotting ability at baseline, toxicity studies with fitusiran in healthy animals were anticipated to overestimate clotting risk to hemophilia patients. However, such studies are still anticipated to provide valuable information, especially for off-target safety assessment. To address the limitations of studies in healthy animals, the Applicant conducted extensive studies in animal models of hemophilia, which provided a more relevant physiological system with which to assess on-target risk for patients with hemophilia. Off-target risk was assessed in both healthy animals and hemophilia animal models. Key nonclinical safety findings and their potential clinical relevance are discussed below (and we refer to the detailed nonclinical study summaries in Section [13.1](#) of this review).

Exaggerated Pharmacology/Thrombosis in Healthy Animals

A major risk of fitusiran is anticipated to be excessive clotting related to exaggerated pharmacology. To begin to characterize this risk, healthy rats were subcutaneously administered fitusiran at up to 1 mg/kg/week for 26 weeks (representing doses below the maximum recommended human dose [MRHD] based on BSA extrapolation). Deaths due to systemic thrombosis occurred at 1 mg/kg/week, a dose that decreased AT protein levels by up to 80% (AT activity not measured). Lower doses resulting in AT protein reductions up to 70% were tolerated. In a shorter, 7-week study, rats were given up to 3 mg/kg/week (representing 2 times the MRHD based on BSA comparisons). The 3 mg/kg/week dose was not tolerated due to systemic clotting, where AT activity and protein levels were decreased up to 91% and 83%, respectively; lower doses that reduced AT activity by up to 88% and AT protein up to 82% were tolerated.

In monkeys with normal coagulation at baseline, fitusiran administration at up to 0.5 mg/kg/week (representing a dose below the MRHD based on BSA comparisons) for 39 weeks decreased AT protein and activity up to 74% and 71%, respectively, and all doses were well-tolerated. Fitusiran administered to monkeys for 7 weeks at up to 1 mg/kg/week (representing approximately 2 times the MRHD based on BSA comparisons) decreased AT activity and protein by up to 83% and 84%, respectively, and deaths occurred that were attributed to systemic clotting. Lower doses resulting in AT protein and AT activity reductions up to 60% were tolerated.

Overall, in healthy animals with normal clotting at baseline, fitusiran was generally tolerated so long as AT protein levels remained >10% and activity levels remained >20%. These data highlight the lower limits of AT protein and activity reductions in healthy animals and underscore the potential limitations of safety assessments with fitusiran in animals with normal clotting at baseline.

Exaggerated Pharmacology/Thrombosis in Hemophilia Animal Models

An important question was whether the hemophilia condition might prevent excessive clotting with fitusiran, compared to animals with normal clotting at baseline. To address this, fitusiran was tested in various hemophilia animal models.

Transgenic hemophilia A (HA) mice were administered fitusiran at up to 30 mg/kg/week (approximately 12 times the MRHD based on BSA comparisons) for 26 weeks. AT protein levels were reduced up to 90% (AT activity not measured), but deaths were only observed in

untreated control HA mice (caused by hemophilia-related bleeding). Fitusiran administration reduced deaths significantly; only 6% of HA mice given fitusiran died, compared to 40% of untreated control HA mice.

A 4-week pharmacodynamic study was conducted using HA dogs (a genetic model) administered fitusiran by subcutaneous injection of up to 10 mg/kg/week (a dose representing 26 times the MRHD based on BSA comparisons). At 90% AT activity reduction (AT protein levels not measured), a dog was euthanized with evidence of systemic clotting, but AT activity reductions up to 70% were well-tolerated at 8 times the MRHD (based on BSA comparisons).

In a monkey study, fitusiran was administered to healthy animals at up to 0.5 mg/kg/week (representing a dose below the MRHD based on BSA comparisons) for 6 weeks, which was followed on Day 43 by induction of an HA phenotype using an antihuman Factor VIII antibody. Fitusiran was well tolerated in monkeys prior to the induction of HA, where AT activity was decreased up to 80% with no evidence of thrombosis. Induction of HA in monkeys on Day 43 resulted in a normalization of thrombin generation at the 0.5 mg/kg/week dose (representing a dose below the MRHD based on BSA comparisons). A disadvantage of this model was that the fitusiran dose was limited (to below the clinical dose) to prevent thrombosis prior to administration of the FVIII antibody.

Taken together, studies in animal models of hemophilia underscored the utility of employing nontraditional species/strains in both pharmacodynamic *and* toxicology studies, both of which contributed important safety information. Overall, these data strongly suggested that animal models of hemophilia were less sensitive to exaggerated pharmacology with fitusiran compared to animals with normal clotting at baseline. In contrast to the induction of clotting seen in healthy animals, fitusiran was generally found to be protective (of bleeding) in animal models of hemophilia along with low risk of excessive clotting at clinically relevant exposures.

Hepatobiliary Toxicity

Subcutaneous administration of fitusiran in animals was characterized by rapid hepatic deposition and slow hepatic clearance, which is typical of GalNAc-conjugated liver-targeted siRNA drugs. Indeed, liver fitusiran concentrations were in vast excess of those measured in other tissues, and liver tissue half-life (~60 hours) greatly exceeded that measured in the plasma (1 to 3 hours). The liver was also a clear target organ of toxicity across the fitusiran nonclinical program. Given that the liver is both the primary site of fitusiran distribution and pharmacodynamic activity, it was important to assess whether fitusiran was directly hepatotoxic. Animal studies consistently showed minimal to moderate hepatic necrosis and bile duct dilatation at the highest doses in the presence of extensive systemic clotting. It is unclear how these biliary tract findings in rats may translate to the human gallbladder. Residual uncertainty regarding a clinical risk of hepatobiliary toxicity should be based on clinical trial data.

Hypersensitivity Reactions

Fitusiran increased the incidence of hypersensitivity reactions (skin redness/dryness/scab/discharge at the injection site) in rats and monkeys at all doses tested. However, given potential differences between animals and humans, any potential labeling of a risk of hypersensitivity reactions should be based on clinical trial data.

Reproductive and Developmental Effects

Fitusiran was not tested in reproduction studies in female animals because hemophilia A and B occur almost exclusively in males. In the absence of such data, the use of effective contraceptive measures by female patients with hemophilia should be encouraged during treatment with fitusiran. Fitusiran did not adversely impact male fertility and did not negatively impact early embryonic development in a 26-week repeat-dose chronic toxicity study in rats where male rats were dosed at up to 1 mg/kg/week (a dose below the MRHD based on BSA comparisons) for 16 weeks and then mated with untreated females.

Clinical Safety Margins

Fitusiran, like other GalNAc conjugated siRNAs, is quickly cleared from the plasma and taken up by the liver and to a lesser extent other tissues. In this context, plasma exposure levels may inadequately reflect total tissue exposure levels over time. Therefore, clinical safety margins shown in [Table 38](#) below reflect total fitusiran doses over time, with additional corrections for body surface area differences between species.

Table 38. Fitusiran Safety Margins

Species/ Model	Duration	NOAEL ¹ Dose Based on Thrombosis (mg/kg/week)	Percent Reduction in AT Activity	Percent Reduction in AT Protein	Clinical Safety Margins ² for Thrombosis
Healthy rats	26 weeks	0.5	-	70	<1-fold
Healthy monkeys	39 weeks	0.5	74	71	<1-fold
Hemophilia A mice	26 weeks	30	-	90	12-fold
Hemophilia A dogs	4 weeks	3	70	-	8-fold

Source: FDA analysis.

¹ No-observed-adverse-effect level, the highest dose tested that produced no evidence of systemic thrombosis.

² Safety margins were calculated based on a maximum clinical dose of 50 mg administered once monthly.

Abbreviations: AT, antithrombin; NOAEL, no-observed-adverse-effect level

Risk Summary and Recommendation

Studies of fitusiran in animal models of hemophilia suggested reduced risk of excessive clotting at clinically relevant doses compared to healthy animals. Hepatotoxicity in animal studies was observed with fitusiran at high doses in the presence of severe systemic clotting. Adverse skin reactions were observed at the subcutaneous injection site with fitusiran in animals, but clinical risk should be based on clinical trial data. No developmental or reproduction studies were conducted in female animals administered fitusiran because hemophilia A and B occur almost exclusively in males. Fitusiran did not adversely impact male fertility or reproductive performance, and conceptuses from dosed males were normal.

Overall, the nonclinical data support the marketing approval of fitusiran for the treatment of hemophilia. Regarding specific risks identified, and for product labeling, while animal models helped characterize the risks of excessive thrombosis, hepatobiliary toxicity, and injection site hypersensitivity reactions, the product label should emphasize clinical trial data. Data obtained from fertility and early embryonic development studies conducted using male animals given fitusiran should be described in Section 13.1 of the product label (refer also to Section [8.4](#) of this review). No animal data are recommended for inclusion in Section [13.2](#) (Animal Toxicology) of the product label. Finally, based on extensive review of the nonclinical program for fitusiran, the

Pharmacology/Toxicology review team did not identify deficiencies that preclude approval of fitusiran for the treatment of hemophilia A and B with or without inhibitors.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential risks or safety concerns were reviewed based on known information from approved non-factor-replacement therapies emicizumab, marstacimab and concizumab. Approved non-factor-replacement products increase thrombin generation by enhancing procoagulants (anti-FIXa/FX bispecific antibody in the case of emicizumab), or by inhibiting anticoagulant pathways (antithrombin siRNA therapy in the case of fitusiran, and anti-TFPI antibodies in the case of concizumab and marstacimab). Increases in thrombin generation are associated with thrombotic risk, and this risk is included in the USPI Warnings and Precautions sections of HEMLIBRA (emicizumab) ([Genentech 2024](#)), HYMPAVZI (marstacimab) ([Pfizer Laboratories Div Pfizer Inc 2025](#)), and ALHEMO (concizumab) ([Novo Nordisk 2024](#)) labels. A box warning in the HEMLIBRA USPI relates the risk of thrombotic microangiopathy and thrombotic events when a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis ([Genentech 2024](#)). Section [7.1](#) discusses the risk of thromboembolic events in the fitusiran development program.

Fitusiran is an siRNA, conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, fitusiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for antithrombin. Potential risks or safety concerns were reviewed based on known information from approved hepatic targeted siRNA therapies ONPATRO (patisiran) ([Alnylam Pharmaceuticals 2023a](#)), GIVLAARI (givosiran) ([Alnylam Pharmaceuticals 2024b](#)), OXLUMO (lumasiran) ([Alnylam Pharmaceuticals 2023b](#)), LEQVIO (inclisiran) ([Novartis Pharmaceuticals Corporation 2024](#)), and AMVUTTRA (vutrisiran) ([Alnylam Pharmaceuticals 2024a](#)). Transaminase elevations (alanine aminotransferase [ALT]) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients treated with GIVLAARI, and hepatic toxicity is listed in the Warnings and Precautions section of the USPI. Section [7.3](#) discusses the risk of hepatotoxicity observed in the fitusiran development program.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Fitusiran is not currently approved or marketed in the United States or in any country.

7.4. FDA Approach to the Safety Review

The primary safety assessment for the intended population of subjects with HA or HB with or without inhibitors was based on a pooled analysis of 286 subjects who received fitusiran AT-DR during the fitusiran developmental program. These individuals include subjects who received the AT-DR during studies EFC15110 (N=2), LTE14762 (N=18), and LTE15174 (N=269). Study EFC15110 was an open-label switching study in subjects with HA or HB with or without

inhibitors, previously on BPA/factor prophylaxis. Study LTE14762 was an open-label long-term extension study in subjects with HA or HB with or without inhibitors who were previously enrolled in a phase 1 study (TDR14767). Study LTE15174 was an open-label extension study in subjects with HA or HB with or without inhibitors who were previously enrolled in a phase 3 parent study (see [Table 5](#) in Section [3.3](#) for further details).

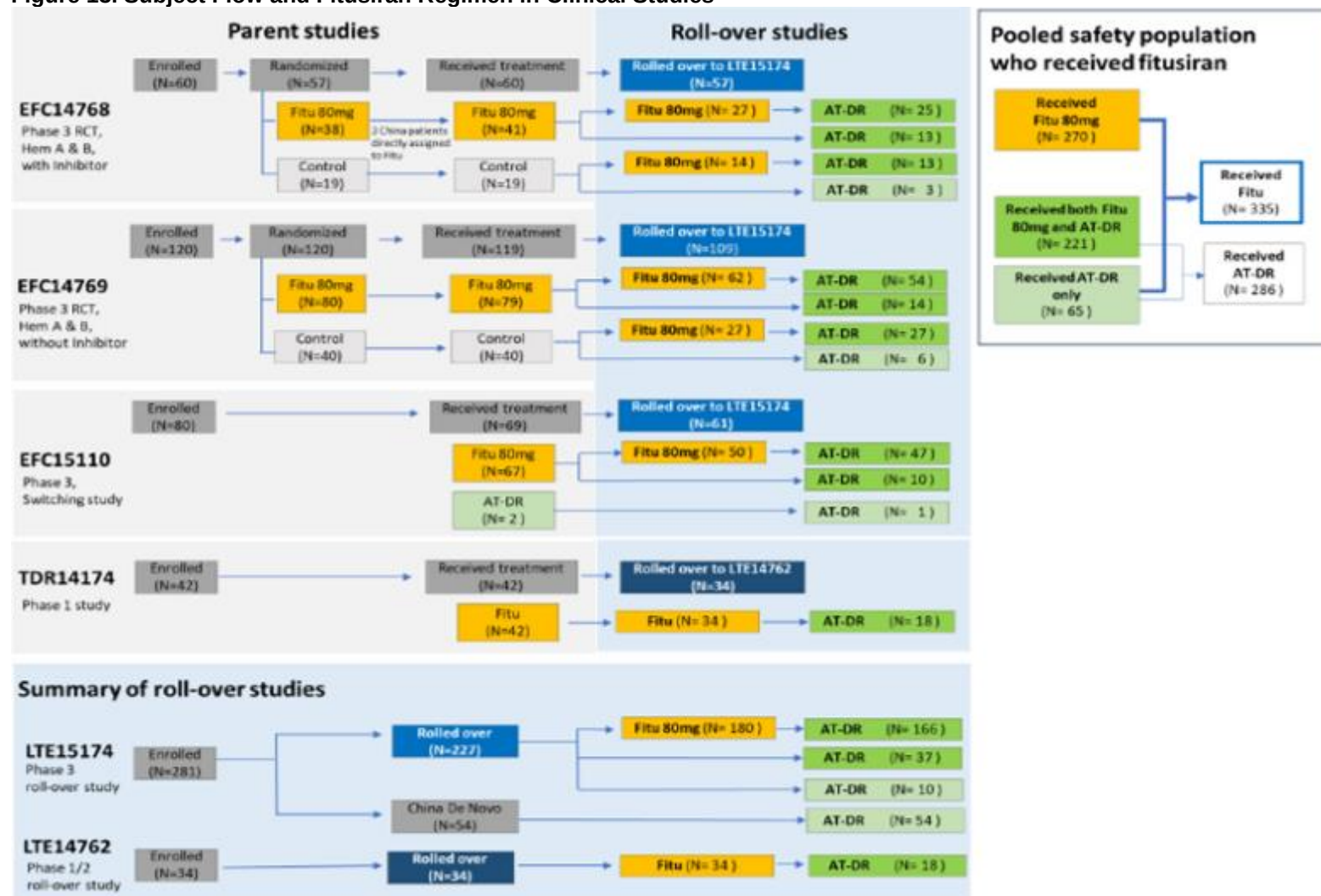
To support the analysis of safety, pooled safety assessments was based on data derived from a total of 335 unique subjects who received at least one dose of fitusiran (whether on the non-AT-DR dose or AT-DR dose) while enrolled in studies LTE14762, EFC14768, EFC14769, EFC15110, and LTE15174. Safety results from these studies were only described when applicable. [Figure 13](#) shows the subject flow and fitusiran dose in the safety population.

A supportive assessment of safety was also conducted for the randomized controlled studies EFC14768 and EFC14769, separately, in order to understand the safety profile of fitusiran compared to a concurrent control (on-demand therapy). The safety results should be interpreted with the understanding that this is based on the 80 mg QM dose regimen, which is a higher dose than the AT-DR. These results are presented in Section [17](#).

Further, an exploratory assessment of safety was conducted comparing safety results of subjects who received the AT-DR in LTE15174 who were originally randomized to the fitusiran 80 mg QM dose in studies EFC14768 and EFC14769 to the control on-demand arm from studies EFC14768 and EFC14769. Results are provided in Section [17](#).

Adverse events of special interest identified by the Agency were thrombosis, hepatotoxicity, and gallbladder disease. The Drug-Induced Liver Injury (DILI) Team was consulted to examine safety signals of gallbladder disease and hepatotoxicity.

Figure 13. Subject Flow and Fitusiran Regimen in Clinical Studies



Source: Applicant Summary of Clinical Safety

Abbreviations: AT-DR, antithrombin-based dose regimen; fitu, fitusiran; hem, hemophilia; RCT, randomized controlled trial

Clinical study data were independently analyzed by the Agency. Clinical data scientists (CDSs) from the Division of Biomedical Informatics generated the safety tables and figures. These include safety tables and figures for subject disposition, exposure data, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs). Additional exploration and analysis of TEAEs were performed by the clinical reviewer using JMP, JMP Clinical, and the Office of Computational Science Medical Dictionary for Regulatory Activities (MedDRA)-based Adverse Event Diagnostics tool.

The Applicant's translations of verbatim terms to the MedDRA (version 25.1) preferred terms (PTs) for TEAEs were reviewed and found to be acceptable. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

TEAEs were defined as any adverse event after receiving a dose of the study drug. TEAEs were collected after the last administration of fitusiran, until AT activity levels returned to at least 60%. All adverse events (AEs) in the reviewed trials were graded by investigators using the terms mild (asymptomatic or mild symptoms, intervention not indicated), moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living), and severe (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; life-threatening; or death).

TEAEs were analyzed at all levels of the MedDRA hierarchy and using FDA Medical Queries (FMQ) narrow. FMQ (narrow) are a collection of approximately 110 standardized groups, where each group comprises adverse event terms that reflect a specific medical concept. Each FMQ term is composed of one or more PTs. FMQs are not mutually exclusive; that is, an individual preferred term (PT) may be counted in more than one FMQ. When reporting FMQ analyses, all FMQs, including overlapping terms, are included in the presentation of the data in this review. In addition, not all PTs are included in an FMQ. To assure that all potential safety signals are identified, analysis of all reported TEAEs not included in at least one FMQ were identified and analyzed.

Review of safety was based upon:

- Clinical Study Reports for studies
- Protocols for studies
- Data sets for the populations from clinical studies described above (data cutoff June 14, 2023)
- Summary of clinical safety
- 120-day safety update (data cutoff March 1, 2024)
- Subject narratives
- Case report forms
- Case report forms and narratives were provided and reviewed for SAEs, and adverse events of special interest

7.5. Adequacy of the Clinical Safety Database

The exposure for the primary safety population AT-DR period is shown in [Table 39](#). The median duration of exposure to AT-DR was 96 (range 72.7 to 117.9) weeks. Approximately 84% of subjects were exposed to fitusiran AT-DR for 50 weeks or longer, with a total exposure to the AT-DR of 486 subject-years.

The size of the safety database is considered adequate for a comprehensive safety assessment of fitusiran for the proposed indication, subject population, dosage regimen, and duration, given the rarity of hemophilia, and is consistent with other drug development programs for severe hemophilia.

Table 39. Duration of Exposure, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia		Total N=111	Hemophilia		Total N=175	N=286
	A N=87	B N=24		A N=134	B N=41		
Duration of treatment, weeks							
Mean (SD)	84.3 (33.6)	91.9 (36.9)	86 (34.3)	89.7 (32.9)	92.4 (29.2)	90.4 (32)	88.7 (32.9)
Median (Q1, Q3)	91.1 (69.3, 114.6)	106.9 (72.5, 119.9)	95.7 (69.3, 117.3)	100.4 (77.6, 119.5)	99.1 (80.1, 116)	99.1 (79.1, 118)	96.3 (72.7, 117.9)
Min, max	8, 128	16, 128	8, 128	8, 127	8, 121.9	8, 127	8, 128
Total exposure (person-years)	141	42	183	230	73	303	486
Subjects treated, by duration, n (%)							
<12 weeks	3 (3.4)	0	3 (2.7)	4 (3.0)	1 (2.4)	5 (2.9)	8 (2.8)
≥12 to <26 weeks	5 (5.7)	3 (12.5)	8 (7.2)	4 (3.0)	1 (2.4)	5 (2.9)	13 (4.5)
≥26 to <50 weeks	9 (10.3)	1 (4.2)	10 (9.0)	13 (9.7)	3 (7.3)	16 (9.1)	26 (9.1)
≥50 to <100 weeks	39 (44.8)	6 (25.0)	45 (40.5)	46 (34.3)	16 (39.0)	62 (35.4)	107 (37.4)
≥100 to <150 weeks	31 (35.6)	14 (58.3)	45 (40.5)	67 (50.0)	20 (48.8)	87 (49.7)	132 (46.2)
≥150 weeks	0	0	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 128 weeks.

Abbreviations: AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.5.1. Safety Results

Fitusiran has a serious risk of thromboembolism, similar to other approved drugs for patients with hemophilia; however, fitusiran also has serious risks of gallbladder disease and hepatotoxicity. Overall, few subjects had serious adverse reactions or required drug discontinuation or dose interruption on the AT-DR. Safety analysis showed fitusiran to have an acceptable safety profile in subjects with either HA or HB, with or without inhibitors. No new safety concerns were identified in the 120-day safety update. As the AT-DR was implemented in

mainly long-term extension studies, the study design did not allow for randomized controlled safety data.

Key safety findings of adverse event analyses of the AT-DR are:

- There were no fatal adverse events on the AT-DR.
- Serious adverse events (SAEs) occurred in 14.3% in subjects who received the AT-DR. The most common SAEs were hemorrhage (8.7%), which is most likely related to the underlying disease and unlikely to be related to fitusiran based on its mechanism of action and disease of study. Serious adverse reactions considered related to fitusiran occurred in 1.4% of subjects and included pancreatitis, cholecystitis, cholangitis, alanine aminotransferase increased, aspartate aminotransferase increased, and embolic stroke.
- Rates of drug interruption and drug discontinuation were low. In total, two subjects (0.7%) experienced TEAEs that led to drug interruption. Both events leading to drug interruption were due to elevated liver enzymes and were determined to be related to fitusiran. Five subjects (1.7%) experienced TEAEs that led to permanent discontinuation of fitusiran. Adverse reactions leading to drug discontinuation included liver injury, postoperative deep vein thrombosis, cerebral infarction, and pruritus.
- A total of 83.2% of subjects experienced a TEAE. The most common adverse reactions (>10%) were viral infection (29%), nasopharyngitis (26%), and bacterial infection (11%). Less common adverse reactions were hepatic injury, arthralgia, prothrombin fragment 1.2 increased, injection site reaction, headache, cough, dyspepsia and abdominal pain.

7.5.2. Safety Results, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

7.5.2.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

[Table 40](#) summarizes the overall safety results in the pooled trials LTE15174, LTE14762 and EFC15110, AT-DR period, based on frequency analysis. Most TEAEs were reported as mild or moderate in severity, and 9.8% of subjects had a reported severe TEAE. There were no TEAEs leading to death. SAEs were reported in 14.3% of subjects; however, many of these were related to hemorrhagic events, due to underlying hemophilia. There were five TEAEs that led to permanent discontinuation of the study drug, and two TEAEs leading to drug interruption. Overall, there did not appear to be a difference in overall TEAEs based on hemophilia A or B nor inhibitor or noninhibitor subtypes.

Table 40. Overview of Adverse Events, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Event Category	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87	N=24	N=111	N=134	N=41	N=175	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
SAE	16 (18.4)	4 (16.7)	20 (18.0)	14 (10.4)	7 (17.1)	21 (12.0)	41 (14.3)
SAEs with fatal outcome	0	0	0	0	0	0	0
Life-threatening SAEs	1 (1.1)	0	1 (0.9)	0	1 (2.4)	1 (0.6)	2 (0.7)
SAEs resulting in substantial disruption of normal life functions	1 (1.1)	0	1 (0.9)	0	1 (2.4)	1 (0.6)	2 (0.7)
AE leading to permanent discontinuation of study drug	1 (1.1)	1 (4.2)	2 (1.8)	3 (2.2)	0	3 (1.7)	5 (1.7)
AE leading to dose modification of study drug	2 (2.3)	0	2 (1.8)	0	0	0	2 (0.7)
AE leading to interruption of study drug	2 (2.3)	0	2 (1.8)	0	0	0	2 (0.7)
AE leading to reduction of study drug	0	0	0	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0	0	0	0
Any AE	75 (86.2)	18 (75.0)	93 (83.8)	108 (80.6)	37 (90.2)	145 (82.9)	238 (83.2)
Severe and worse	11 (12.6)	2 (8.3)	13 (11.7)	9 (6.7)	6 (14.6)	15 (8.6)	28 (9.8)
Moderate	31 (35.6)	11 (45.8)	42 (37.8)	52 (38.8)	19 (46.3)	71 (40.6)	113 (39.5)
Mild	33 (37.9)	5 (20.8)	38 (34.2)	47 (35.1)	12 (29.3)	59 (33.7)	97 (33.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off for NDA. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater.

Duration is up to 128 weeks.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.5.2.2. Deaths, Pooled Analyses, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

No deaths were reported in Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period.

In supportive safety analyses, two subjects died while receiving the original fitusiran dosing regimen (80 mg every month). Brief subject narratives are provided below.

1. Subject (b) (6) was a 48-year-old white male with hemophilia A with inhibitors and a complicated medical history including hepatitis C and HIV. The subject completed parent study EFC14769 and developed a TESAE of "metastases to peritoneum" while participating in extension study LTE15174. The subject was diagnosed with metastatic adenocarcinoma (primary unknown). The subject's death due to metastatic adenocarcinoma occurred approximately 6 months after enrolling into extension Study LTE15174. This event

is not considered related to fitusiran, as there is no evidence that fitusiran increases the risk of malignancy. Hepatitis C can increase the risk of hepatocellular carcinoma, although it is unclear whether the liver was the source of the subject's cancer.

2. Subject (b) (6) was a 25-year-old white male with hemophilia A without inhibitors who completed Study TDR14767 and enrolled in extension Study LTE14762. The subject experienced a TEAE of cerebral venous sinus thrombosis (CVST) that resulted in a fatal outcome. On Day 452, the study subject received his last dose of fitusiran before the start of the event of cerebral venous sinus thrombosis. During the long-term extension study (date not specified), the subject received three doses of factor VIII for hip pain, with doses of 31 IU/kg to 46 IU/kg. About 1 week later, the study subject presented with severe headache, vomiting, and fever, and was subsequently admitted to the hospital (40 days after the last dose of fitusiran). While initially suspected to have viral meningitis, a computed tomography scan performed to evaluate the headache was read as a subarachnoid hemorrhage, and the study subject was treated with replacement factor therapy two to three times daily. The subject subsequently deteriorated and died. Postmortem independent neuro-radiology consultants determined that the initial neuroimaging revealed it was a CVST (not subarachnoid hemorrhage) that led to the subject's initial presentation and subsequent cerebral edema and death.

While the CVST event basis is multifactorial, related to recent factor administration and potential infection, the event is also likely related to fitusiran, given its long pharmacodynamic half-life. Following this event, the Applicant implemented Bleed Management Guidelines which include delineation of the use and dose of FVIII when treating breakthrough bleeds. See Section 7.1 for further discussion on thrombosis risk.

7.5.2.3. Serious Treatment-Emergent Adverse Events, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period.

The frequency of SAEs was 14.3% in subjects who received the AT-DR. [Table 41](#) provides a frequency analysis of serious TEAEs by preferred terms and [Table 42](#) provides a frequency analysis by FMQs that occurred during the AT-DR period. The most common SAE was hemorrhage, which occurred in 8.7% of subjects, most likely related to hemophilia and unlikely to be related to treatment with fitusiran based on its procoagulant mechanism of action.

Serious adverse reactions related to fitusiran occurred in 1.4% of subjects and included pancreatitis, cholecystitis, cholangitis, alanine aminotransferase increased, aspartate aminotransferase increased, and embolic stroke. Subject narratives are summarized below. See Section 7.2 for a discussion of acute gallbladder disease (including cholecystitis, cholelithiasis, and related complications), Section 7.3 for a discussion of hepatotoxicity, and Section 7.1 for a discussion of embolic stroke. Of note, adverse events that occurred perioperatively were not considered SAEs per the Applicant.

There was one event of pneumonitis. This was not considered related to fitusiran as it occurred on day 606 of the study and the subject recovered after receiving antiviral and antibiotics. Fitusiran was not interrupted or discontinued.

Table 41. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

System Organ Class Preferred Term	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A N=87 n (%)	Hemophilia B N=24 n (%)	Total N=111 n (%)	Hemophilia A N=134 n (%)	Hemophilia B N=41 n (%)	Total N=175 n (%)	
Any SAE	16 (18.4)	4 (16.7)	20 (18.0)	14 (10.4)	7 (17.1)	21 (12.0)	41 (14.3)
Blood and lymphatic system disorders (SOC)	0	1 (4.2)	1 (0.9)	0	0	0	1 (0.3)
Increased tendency to bruise	0	1 (4.2)	1 (0.9)	0	0	0	1 (0.3)
Gastrointestinal disorders (SOC)	4 (4.6)	1 (4.2)	5 (4.5)	5 (3.7)	3 (7.3)	8 (4.6)	13 (4.5)
Anal fissure	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Duodenal ulcer hemorrhage	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Intra-abdominal hemorrhage	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Melaena	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Volvulus	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Gastric hemorrhage	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Gastric ulcer	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Gastrointestinal hemorrhage	0	0	0	2 (1.5)	0	2 (1.1)	2 (0.7)
Hematochezia	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Hemoperitoneum	0	1 (4.2)	1 (0.9)	0	0	0	1 (0.3)
Pancreatitis	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Tongue hematoma	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Tooth malformation	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Hepatobiliary disorders (SOC)	1 (1.1)	0	1 (0.9)	1 (0.7)	1 (2.4)	2 (1.1)	3 (1.0)
Cholangitis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Cholecystitis	0	0	0	1 (0.7)	1 (2.4)	2 (1.1)	2 (0.7)
Infections and infestations (SOC)	3 (3.4)	0	3 (2.7)	3 (2.2)	1 (2.4)	4 (2.3)	7 (2.4)
Bronchitis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
COVID-19 pneumonia	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Pneumonia	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
COVID-19	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Large intestine infection	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Staphylococcal infection	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Tooth abscess	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Injury, poisoning and procedural complications (SOC)	0	1 (4.2)	1 (0.9)	0	1 (2.4)	1 (0.6)	2 (0.7)
Road traffic accident	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Subcutaneous hematoma	0	1 (4.2)	1 (0.9)	0	0	0	1 (0.3)
Investigations (SOC)	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Alanine aminotransferase increased	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Aspartate aminotransferase increased	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders (SOC)	5 (5.7)	3 (12.5)	8 (7.2)	2 (1.5)	1 (2.4)	3 (1.7)	11 (3.8)
Hemarthrosis	2 (2.3)	2 (8.3)	4 (3.6)	0	1 (2.4)	1 (0.6)	5 (1.7)
Limb mass	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Muscle hemorrhage	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Rotator cuff syndrome	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Hematoma muscle	0	2 (8.3)	2 (1.8)	1 (0.7)	0	1 (0.6)	3 (1.0)
Hemophilic arthropathy	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)

System Organ Class Preferred Term	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Large intestine benign neoplasm	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Hepatocellular carcinoma	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Nervous system disorders (SOC)	1 (1.1)	0	1 (0.9)	1 (0.7)	1 (2.4)	2 (1.1)	3 (1.0)
Hemorrhage intracranial	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Embolic stroke	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Subarachnoid hemorrhage	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Renal and urinary disorders (SOC)	4 (4.6)	2 (8.3)	6 (5.4)	0	3 (7.3)	3 (1.7)	9 (3.1)
Hematuria	2 (2.3)	2 (8.3)	4 (3.6)	0	3 (7.3)	3 (1.7)	7 (2.4)
Hemorrhage urinary tract	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Hydronephrosis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Renal hemorrhage	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders (SOC)	2 (2.3)	0	2 (1.8)	0	0	0	2 (0.7)
Asthma	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Pneumonitis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Social circumstances (SOC)	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Pregnancy of partner	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off for NDA. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is up to 128 weeks.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; incl, including; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

Table 42. Subjects With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Gastrointestinal disorders (SOC)							
Pancreatitis	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Hepatobiliary disorders (SOC)							
Cholecystitis	0	0	0	1 (0.7)	1 (2.4)	2 (1.1)	2 (0.7)
Hepatic injury	0	0	0	0	1 (2.4)	1 (0.6)	1 (0.3)
Infections and infestations (SOC)							
Bacterial infection	1 (1.1)	0	1 (0.9)	2 (1.5)	2 (4.9)	4 (2.3)	5 (1.7)
Pneumonia	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Viral infection	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Purulent material	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders (SOC)							
Tendinopathy	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A N=87 n (%)	Hemophilia B N=24 n (%)	Total N=111 n (%)	Hemophilia A N=134 n (%)	Hemophilia B N=41 n (%)	Total N=175 n (%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Nervous system disorders (SOC)							
Stroke and TIA	0	0	0	1 (0.7)	1 (2.4)	2 (1.1)	2 (0.7)
Respiratory, thoracic and mediastinal disorders (SOC)							
Bronchospasm	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Pneumonitis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Vascular disorders (SOC)							
Hemorrhage	11 (12.6)	4 (16.7)	15 (13.5)	5 (3.7)	5 (12.2)	10 (5.7)	25 (8.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off for NDA. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is up to 128 weeks.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; FMQ, FDA medical query; incl, including; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

Selected SAE Narratives Considered To Be Serious Adverse Reactions

- Subject (b) (6) was a 50-year-old male with HA with inhibitors and a history of diabetes mellitus, hypertension and hepatitis C who experienced an SAE of **cholangitis**. On Day 777 of Study LTE15174, he presented with symptoms of pancreatitis. Imaging showed obstruction due to a common bile duct stone. The subject was hospitalized and diagnosed with obstructive cholangitis, and 4 days later underwent pancreatobiliary sphincterotomy. The subject was treated with recombinant factor VIIa at the time of surgery. Fitusiran dose had been interrupted before the SAE of cholangitis due to a prior event of aspartate aminotransferase (AST) increase on Day 677 and was resumed 2 days after the sphincterotomy, and the subject remains on fitusiran. The review team assessed this SAE as likely to be related to fitusiran based on the association of fitusiran and development of gallbladder disease (see Section 7.6.2).

- Subject (b) (6) was a 27-year-old male with hemophilia who experienced a SAE of **cholecystitis**. On Day 52 of LTE15174, the subject developed biliary colic and was admitted to hospital. A CT scan with contrast showed no visible gallstones. Magnetic resonance cholangiopancreatography showed dilated intrahepatic bile ducts, but no gallstones. On Day 56, the study subject recovered from the event of biliary colic and was discharged from the hospital on the same day. Fitusiran was permanently discontinued due to the event of biliary colic and the last dose was administered on Day 114. On Day 230 (116 days after the last dose of fitusiran), the study subject recovered from the event of biliary colic. The review team assessed this SAE as likely to be related to fitusiran based on the association of fitusiran and development of gallbladder disease (see Section 7.6.2).
- Subject (b) (6) was a 27-year-old male who experienced the SAEs of **cholecystitis, alanine aminotransferase increased, aspartate aminotransferase increased, and pancreatitis**. On Day 136 of LTE15174, he experienced symptoms of cholecystitis, and an ultrasound showed gallbladder stones. On Day 151, AEs of ALT increased (ALT >3×ULN at 411 IU/L (normal range: 0 to 41 IU/L, baseline value: 12 IU/L [normal range: 10 to 40 IU/L]), aspartate aminotransferase increased (AST >3×ULN at 467 IU/L (normal range: 0 to 40 IU/L, baseline value: 13 IU/L [normal range: 10 to 43 IU/L]), pancreatitis, and cholecystitis were reported and the subject was hospitalized. The study subject was discharged from the hospital on Day 156. On Day 217, the subject was readmitted to hospital with symptoms of abdominal pain, and an ultrasound of the gallbladder showed multiple subcentimetric stones in the gallbladder lumen. The subject recovered from the SAEs of alanine aminotransferase increased, aspartate aminotransferase increased, and pancreatitis. Fitusiran was continued without interruption. The review team considers that fitusiran is related to the SAEs of cholecystitis, alanine aminotransferase increased, aspartate aminotransferase increased, and pancreatitis as acute gallbladder disease has been identified as serious adverse reactions with fitusiran (see Section 7.6.2).
- Subject (b) (6) is a 54-year-old male with hemophilia who experienced an SAE of **embolic stroke**. The subject had a history of hypertension, hyperlipidemia, and diabetes. The subject was initially on fitusiran 80 mg QM during Study EFC14769, and then transitioned to the AT-DR in Study LTE15174. On Day 327, the fitusiran dose was reduced to 50 mg Q2M based on AT levels. On Day 508, fitusiran was permanently discontinued due to persistently low AT levels. On Day 673 (165 days after the last dose of fitusiran), the subject developed acute symptoms of lightheadedness and dizziness in the setting of elevated blood pressure, and subsequent slurring of speech and loss of strength in the right arm and leg. He was hospitalized. MRI showed acute nonhemorrhagic infarcts in the left corona radiata and ganglio-capsular region, chronic ischemic changes in the bilateral fronto-parietal region, and chronic lacunar infarcts in bilateral ganglio-capsular region. On Day 687 (179 days after the last dose of fitusiran), the study subject recovered from the event embolic stroke and was discharged from the hospital. Given the multiple risk factors for stroke, it is difficult to discern if fitusiran contributed to the event. Due to the mechanism of action of fitusiran and fitusiran's long pharmacodynamic half-life, it is possible that fitusiran increased the thrombotic risk. While the subject had discontinued the drug 165 days prior to the event, the subject had discontinued fitusiran due to AT <15%, a strong risk factor for thrombosis. At the time of the event, the AT level was 36%.

7.5.2.4. Adverse Events Leading to Treatment Discontinuation, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period.

During the AT-DR period, there were two subjects (0.7%) who experienced TEAEs that led to drug interruption. Both events leading to drug interruption were due to elevated liver enzymes and were determined to be related to fitusiran (see Section [7.6.3](#) for further discussion on hepatotoxicity). In total, five subjects (1.7%) experienced TEAEs that led to permanent discontinuation of fitusiran. Adverse reactions leading to drug discontinuation included liver injury, postoperative deep vein thrombosis, cerebral infarction, and pruritus. Subject narratives are summarized below. Risk of thrombosis with fitusiran is further discussed in Section [7.6.1](#).

Subject narratives for TEAEs leading to drug interruption:

1. Subject (b) (6) experienced transaminases increased (PT). The study subject was a 35-year-old male with HA and a history of hepatitis C. On Day 1515 of LTE14762, ALT was 531 IU/L (normal range: 0 to 50 IU/L) and AST was 288 IU/L (normal range: 0 to 50 IU/L). These elevations were associated with an episode of alcohol consumption as reported by the study subject. Fitusiran was interrupted with the last dose given on Day 1480. The subject was instructed to abstain from alcohol; no other corrective treatment was given. The transaminases returned to the normal range by Day 1564, and fitusiran was restarted on Day 1564. The liver enzymes remained normal until Day 1955 when ALT was $>3\times$ ULN, with ALT at 309 IU/L (normal range: 10 to 40 IU/L) and AST at 139 IU/L (normal range: 10 to 43 IU/L). No further details regarding the event were provided. The subject interrupted fitusiran and subsequently withdrew from the study.
2. Subject (b) (6) experienced aspartate aminotransferase increased (PT) which led to drug interruption. See Section [7.6.3](#) for further details.

Subject narratives of TEAEs leading to permanent drug discontinuation:

1. Subject (b) (6) was a 20-year-old male with HA who permanently discontinued fitusiran after a TEAE of liver injury on Day 56 of LTE15174, after his first dose of fitusiran (50 mg Q2M). On Day 56, LFTs showed AST at 164 IU/L (normal range: 15 to 40 IU/L, baseline value: 24 IU/L), ALT at 624 IU/L (normal range: 9 to 50 IU/L, baseline value: 35 IU/L [normal range: 10 to 40 IU/L]). Alkaline phosphatase (ALP), bilirubin, and gamma glutamyl transferase were within the normal range. On Day 135, the study subject recovered from the event of liver injury with AST at 28 IU/L and ALT at 44 IU/L. This event is considered related to fitusiran.
2. Subject (b) (6) permanently discontinued fitusiran after a TEAE of cerebral infarction. The subject was a 26-year-old male with HB with inhibitors and a history of type 2 diabetes, dyslipidemia, hepatic steatosis, obstructive sleep apnea, and nephrotic syndrome. The subject was evaluated on Day 219 of LTE15174 for vertigo and an MRI revealed evidence of a cerebral infarction in the right temporal lobe and cerebellum, though acuity could not be determined. The subject received the last dose of fitusiran (50 mg Q2M) on Day 226. The review team considers that while the subject had cardiovascular risk factors for stroke, given the mechanism of action of fitusiran to increase thrombotic risk, its role in the causation of the event cannot be ruled out.

3. Subject (b) (6) discontinued fitusiran after a TEAE of hepatocellular carcinoma. The subject was a 61-year-old male with HA and a history of hepatitis C. On Day 2340 of study LTE14762, the subject experienced a TEAE of hepatocellular carcinoma after investigation of elevated alkaline phosphatase and bilirubin. The last dose of fitusiran was Day 2309. The review team considers that fitusiran is unrelated to the event of hepatocellular carcinoma, as there is no mechanistic reason for fitusiran to cause malignancies and hepatitis C is a strong risk factor for hepatocellular carcinoma.
4. Subject (b) (6) permanently discontinued fitusiran after a TEAE of pruritis. The subject was a 47-year-old with HA and a history of pruritus, who on Day 627 of LTE15174, while receiving the AT-DR (dose 50 mg Q2M), developed worsening pruritus. Fitusiran was discontinued on Day 624. At the time of the cutoff date, the study subject had not recovered from the event of pruritus. As the pruritus worsened with fitusiran, it is possible fitusiran contributed to this adverse event.
5. Subject (b) (6) was a 40-year-old male with HA who permanently discontinued fitusiran due to an AE of deep vein thrombosis postoperative. On Day 1140 of LTE15174, the subject underwent a left total knee replacement. On Day 1148, he had a peripherally inserted central venous catheter. On Day 1155, he developed pain and swelling of the left leg and venous doppler ultrasound showed extensive thrombosis of the left common femoral, popliteal, and calf veins. The subject received anticoagulation with apixaban, and fitusiran was discontinued, with the last dose (50 mg QM) administered on Day 1148. The event of thrombosis is considered related to fitusiran based on the mechanism of action of the drug. Recent orthopedic surgery and the central line likely further increased the risk of thrombosis.

7.5.2.5. Treatment-Emergent Adverse Events, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

[Table 43](#) lists the adverse events by PT and [Table 44](#) lists adverse events by FMQ from the Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period. A total of 83.2% of subjects experienced a TEAE. The most common TEAEs were viral infection (29%), nasopharyngitis (26%), and bacterial infection (11%). While it is not expected based on the mechanism of action of fitusiran for there to be an increased risk of infections, on further analyses of the randomized controlled studies (Studies EFC14768 and EFC14769), the rates of viral infection, nasopharyngitis, and bacterial infections were significantly higher in the fitusiran arm compared to the on-demand arm (see Section [17.1](#) of the review). Therefore, the clinical team considered these TEAEs as likely related to fitusiran. The next most common TEAEs were hemorrhage (10%), hepatic injury (9%), arthralgia (8%), pyrexia (7%), diarrhea (6%), pain in extremity (6%), prothrombin fragment 1.2 increased (6%), injection site reaction (5%), cough (5%), and headache (5%). Elevated prothrombin 1.2 levels can indicate an increased risk for thrombosis ([Ota et al. 2008](#)). Adverse events of pyrexia, diarrhea and pain in extremity did not occur at higher rates in the fitusiran arms compared to on-demand arms in randomized controlled trials, therefore, these events were not considered adverse reactions. Urticaria was reported in two subjects (0.7%). It is unclear if the events of urticaria were related to fitusiran due to limited details regarding the events. However, both subjects continued fitusiran without interruption, and similar rates of urticaria were seen in control and fitusiran arms in randomized controlled trials (see Section [17.1](#) for further details). The review team considered hemorrhage unrelated to

fitusiran as it is related to the underlying disease. Of note, there was a single event of mild angioedema (lip swelling). This was not considered related to fitusiran as it occurred on day 971 of the study and the fitusiran dose was not interrupted.

Table 43. Subjects With Common Adverse Events Occurring at ≥5% Frequency, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Preferred Term	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophili a A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Any AE	75 (86.2)	18 (75.0)	93 (83.8)	108 (80.6)	37 (90.2)	145 (82.9)	238 (83.2)
Upper respiratory tract infection	20 (23.0)	2 (8.3)	22 (19.8)	19 (14.2)	2 (4.9)	21 (12.0)	43 (15.0)
COVID-19	18 (20.7)	7 (29.2)	25 (22.5)	17 (12.7)	4 (9.8)	21 (12.0)	46 (16.1)
Alanine aminotransferase increased	10 (11.5)	0	10 (9.0)	7 (5.2)	3 (7.3)	10 (5.7)	20 (7.0)
Prothrombin fragment 1.2 increased	9 (10.3)	3 (12.5)	12 (10.8)	5 (3.7)	0	5 (2.9)	17 (5.9)
Pyrexia	8 (9.2)	2 (8.3)	10 (9.0)	5 (3.7)	4 (9.8)	9 (5.1)	19 (6.6)
Arthralgia	7 (8.0)	5 (20.8)	12 (10.8)	8 (6.0)	3 (7.3)	11 (6.3)	23 (8.0)
Cough	6 (6.9)	3 (12.5)	9 (8.1)	3 (2.2)	3 (7.3)	6 (3.4)	15 (5.2)
Nasopharyngitis	4 (4.6)	5 (20.8)	9 (8.1)	10 (7.5)	2 (4.9)	12 (6.9)	21 (7.3)
Influenza	3 (3.4)	2 (8.3)	5 (4.5)	8 (6.0)	2 (4.9)	10 (5.7)	15 (5.2)
Headache	2 (2.3)	6 (25.0)	8 (7.2)	4 (3.0)	3 (7.3)	7 (4.0)	15 (5.2)
Pain in extremity	2 (2.3)	1 (4.2)	3 (2.7)	9 (6.7)	6 (14.6)	15 (8.6)	18 (6.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off for NDA. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater.

Duration is up to 128 weeks.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SARS, severe acute respiratory syndrome

Table 44. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Blood and lymphatic system disorders (SOC)							
Leukopenia	5 (5.7)	0	5 (4.5)	1 (0.7)	1 (2.4)	2 (1.1)	7 (2.4)
Anemia	3 (3.4)	1 (4.2)	4 (3.6)	2 (1.5)	1 (2.4)	3 (1.7)	7 (2.4)
Thrombocytopenia	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Cardiac disorders (SOC)							
Systemic hypertension	7 (8.0)	0	7 (6.3)	3 (2.2)	2 (4.9)	5 (2.9)	12 (4.2)
Arrhythmia	2 (2.3)	4 (16.7)	6 (5.4)	2 (1.5)	0	2 (1.1)	8 (2.8)
Myocardial ischemia	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Palpitations	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Tachycardia	0	1 (4.2)	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Ear and labyrinth disorders (SOC)							
Vertigo	1 (1.1)	1 (4.2)	2 (1.8)	0	0	0	2 (0.7)
Endocrine disorders (SOC)							
Hyperglycemia	1 (1.1)	1 (4.2)	2 (1.8)	1 (0.7)	3 (7.3)	4 (2.3)	6 (2.1)
Gastrointestinal disorders (SOC)							
Diarrhea	5 (5.7)	3 (12.5)	8 (7.2)	6 (4.5)	2 (4.9)	8 (4.6)	16 (5.6)
Abdominal pain	2 (2.3)	4 (16.7)	6 (5.4)	6 (4.5)	2 (4.9)	8 (4.6)	14 (4.9)
Constipation	2 (2.3)	3 (12.5)	5 (4.5)	1 (0.7)	1 (2.4)	2 (1.1)	7 (2.4)
Nausea	1 (1.1)	3 (12.5)	4 (3.6)	1 (0.7)	0	1 (0.6)	5 (1.7)
Pancreatitis	1 (1.1)	0	1 (0.9)	0	1 (2.4)	1 (0.6)	2 (0.7)
Vomiting	1 (1.1)	4 (16.7)	5 (4.5)	4 (3.0)	0	4 (2.3)	9 (3.1)
Dyspepsia	0	2 (8.3)	2 (1.8)	4 (3.0)	1 (2.4)	5 (2.9)	7 (2.4)
General disorders and administration site conditions (SOC)							
Pyrexia	8 (9.2)	2 (8.3)	10 (9.0)	5 (3.7)	4 (9.8)	9 (5.1)	19 (6.6)
Dizziness	1 (1.1)	1 (4.2)	2 (1.8)	3 (2.2)	0	3 (1.7)	5 (1.7)
Fatigue	1 (1.1)	2 (8.3)	3 (2.7)	3 (2.2)	1 (2.4)	4 (2.3)	7 (2.4)
Peripheral edema	1 (1.1)	0	1 (0.9)	2 (1.5)	2 (4.9)	4 (2.3)	5 (1.7)
Fall	0	0	0	5 (3.7)	0	5 (2.9)	5 (1.7)
Local administration reaction	0	6 (25.0)	6 (5.4)	7 (5.2)	2 (4.9)	9 (5.1)	15 (5.2)
Hepatobiliary disorders (SOC)							
Hepatic injury	11 (12.6)	0	11 (9.9)	11 (8.2)	4 (9.8)	15 (8.6)	26 (9.1)
Cholecystitis	2 (2.3)	0	2 (1.8)	2 (1.5)	1 (2.4)	3 (1.7)	5 (1.7)
Immune system disorders (SOC)							
Angioedema	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Infections and infestations (SOC)							
Viral infection	28 (32.2)	9 (37.5)	37 (33.3)	36 (26.9)	10 (24.4)	46 (26.3)	83 (29.0)
Nasopharyngitis	27 (31.0)	8 (33.3)	35 (31.5)	36 (26.9)	4 (9.8)	40 (22.9)	75 (26.2)
Bacterial infection	13 (14.9)	3 (12.5)	16 (14.4)	12 (9.0)	3 (7.3)	15 (8.6)	31 (10.8)
Pneumonia	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Purulent material	1 (1.1)	2 (8.3)	3 (2.7)	1 (0.7)	0	1 (0.6)	4 (1.4)
Fungal infection	0	1 (4.2)	1 (0.9)	2 (1.5)	2 (4.9)	4 (2.3)	5 (1.7)
Metabolism and nutrition disorders (SOC)							
Lipid disorder	1 (1.1)	1 (4.2)	2 (1.8)	1 (0.7)	3 (7.3)	4 (2.3)	6 (2.1)

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	N=286 n (%)
	N=87 n (%)	N=24 n (%)	N=111 n (%)	N=134 n (%)	N=41 n (%)	N=175 n (%)	
Musculoskeletal and connective tissue disorders (SOC)							
Arthralgia	7 (8.0)	5 (20.8)	12 (10.8)	8 (6.0)	3 (7.3)	11 (6.3)	23 (8.0)
Arthritis	5 (5.7)	0	5 (4.5)	4 (3.0)	2 (4.9)	6 (3.4)	11 (3.8)
Back pain	2 (2.3)	3 (12.5)	5 (4.5)	5 (3.7)	1 (2.4)	6 (3.4)	11 (3.8)
Tendinopathy	2 (2.3)	0	2 (1.8)	5 (3.7)	2 (4.9)	7 (4.0)	9 (3.1)
Fracture	1 (1.1)	1 (4.2)	2 (1.8)	1 (0.7)	1 (2.4)	2 (1.1)	4 (1.4)
Gout	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Myalgia	0	1 (4.2)	1 (0.9)	1 (0.7)	1 (2.4)	2 (1.1)	3 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Nervous system disorders (SOC)							
Headache	2 (2.3)	6 (25.0)	8 (7.2)	4 (3.0)	3 (7.3)	7 (4.0)	15 (5.2)
Seizure	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Dysgeusia	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Paresthesia	0	1 (4.2)	1 (0.9)	1 (0.7)	1 (2.4)	2 (1.1)	3 (1.0)
Stroke and TIA	0	1 (4.2)	1 (0.9)	1 (0.7)	1 (2.4)	2 (1.1)	3 (1.0)
Psychiatric disorders (SOC)							
Depression	1 (1.1)	0	1 (0.9)	0	1 (2.4)	1 (0.6)	2 (0.7)
Insomnia	0	0	0	2 (1.5)	1 (2.4)	3 (1.7)	3 (1.0)
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	4 (4.6)	0	4 (3.6)	2 (1.5)	0	2 (1.1)	6 (2.1)
Respiratory, thoracic and mediastinal disorders (SOC)							
Cough	6 (6.9)	3 (12.5)	9 (8.1)	3 (2.2)	3 (7.3)	6 (3.4)	15 (5.2)
Bronchospasm	4 (4.6)	0	4 (3.6)	3 (2.2)	1 (2.4)	4 (2.3)	8 (2.8)
Pneumonitis	1 (1.1)	0	1 (0.9)	0	0	0	1 (0.3)
Dyspnea	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)
Skin and subcutaneous tissue disorders (SOC)							
Rash	2 (2.3)	0	2 (1.8)	7 (5.2)	4 (9.8)	11 (6.3)	13 (4.5)
Urticaria	1 (1.1)	0	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Erythema	0	1 (4.2)	1 (0.9)	3 (2.2)	1 (2.4)	4 (2.3)	5 (1.7)
Pruritus	0	1 (4.2)	1 (0.9)	5 (3.7)	1 (2.4)	6 (3.4)	7 (2.4)

System Organ Class FMQ (Narrow)	Inhibitor			Noninhibitor			Overall N=286 n (%)
	Hemophilia A N=87 n (%)	Hemophilia B N=24 n (%)	Total N=111 n (%)	Hemophilia A N=134 n (%)	Hemophilia B N=41 n (%)	Total N=175 n (%)	
Vascular disorders (SOC)							
Hemorrhage	11 (12.6)	6 (25.0)	17 (15.3)	8 (6.0)	5 (12.2)	13 (7.4)	30 (10.5)
Thrombosis	0	1 (4.2)	1 (0.9)	1 (0.7)	0	1 (0.6)	2 (0.7)
Thrombosis arterial	0	1 (4.2)	1 (0.9)	0	0	0	1 (0.3)
Thrombosis venous	0	0	0	1 (0.7)	0	1 (0.6)	1 (0.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off for NDA. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater.

Duration is up to 128 weeks.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; FMQ, FDA medical query; incl, including; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

7.5.2.6. Laboratory Findings, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Routine monitoring of blood and urine, including complete blood count, clinical chemistries, and hepatic and renal evaluations, were obtained regularly at prespecified points throughout the studies. This section presents a frequency-based analysis of laboratory assessments.

Chemistries

[Table 45](#) presents a frequency-based analysis of laboratory assessments using objective laboratory data. There were no significant changes in laboratory assessments for sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, or albumin.

Low glucose levels occurred in 16.1% of study subjects. Most low glucose levels were level 1 and not associated with a continuous trend. High random glucose levels occurred in 6% of study subjects. Sustained elevated glucoses were in study subjects who had a concurrent diagnosis of diabetes mellitus. Of note, glucose levels were not fasting. There was no pattern of either low or high glucose based on hemophilia type or inhibitor status.

Increases in creatinine $\geq 2\times$ baseline occurred in 4.2% of subjects; however, these were not sustained increases. Reductions in eGFR of $\geq 50\%$ from baseline occurred in 3 individuals. These cases were reviewed, and the reductions were not sustained and recovered to baseline.

Overall, no clinically relevant chemistry laboratory findings were identified. Most abnormal laboratory values were not sustained and were associated with underlying comorbidities. In addition, while there appear to be outliers for hypokalemia and hypophosphatemia in this analysis, no imbalance was seen for fitusiran vs. on demand treatment in the randomized, controlled parent studies.

Table 45. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	N=286 n/N _w (%)
Sodium, low (mEq/L)							
Level 1 (<132)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Level 2 (<130)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Level 3 (<125)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	0/134 (0)	0/41 (0)	0/175 (0)	1/285 (0.4)
Sodium, high (mEq/L)							
Level 1 (>150)	4/86 (4.7)	0/24 (0)	4/110 (3.6)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	5/285 (1.8)
Level 2 (>155)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Level 3 (>160)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	0/134 (0)	0/41 (0)	0/175 (0)	1/285 (0.4)
Potassium, low (mEq/L)							
Level 1 (<3.6)	23/86 (26.7)	12/24 (50.0)	35/110 (31.8)	32/134 (23.9)	8/41 (19.5)	40/175 (22.9)	75/285 (26.3)
Level 2 (<3.4)	8/86 (9.3)	3/24 (12.5)	11/110 (10.0)	9/134 (6.7)	1/41 (2.4)	10/175 (5.7)	21/285 (7.4)
Level 3 (<3)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	3/285 (1.1)
Potassium, high (mEq/L)							
Level 1 (>5.5)	2/86 (2.3)	1/24 (4.2)	3/110 (2.7)	0/134 (0)	2/41 (4.9)	2/175 (1.1)	5/285 (1.8)
Level 2 (>6)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Level 3 (>6.5)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Chloride, low (mEq/L)							
Level 1 (<95)	4/86 (4.7)	0/24 (0)	4/110 (3.6)	2/134 (1.5)	1/41 (2.4)	3/175 (1.7)	7/285 (2.5)
Level 2 (<88)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	0/134 (0)	0/41 (0)	0/175 (0)	1/285 (0.4)
Level 3 (<80)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Chloride, high (mEq/L)							
Level 1 (>108)	9/86 (10.5)	0/24 (0)	9/110 (8.2)	3/134 (2.2)	1/41 (2.4)	4/175 (2.3)	13/285 (4.6)
Level 2 (>112)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Level 3 (>115)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Bicarbonate, low (mEq/L)							
Level 1 (<20)	41/86 (47.7)	7/24 (29.2)	48/110 (43.6)	49/134 (36.6)	17/41 (41.5)	66/175 (37.7)	114/285 (40.0)
Level 2 (<18)	13/86 (15.1)	1/24 (4.2)	14/110 (12.7)	13/134 (9.7)	9/41 (22.0)	22/175 (12.6)	36/285 (12.6)
Level 3 (<15)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	3/134 (2.2)	0/41 (0)	3/175 (1.7)	4/285 (1.4)
Bicarbonate, high (mEq/L)							
Level 3 (>30)	9/86 (10.5)	1/24 (4.2)	10/110 (9.1)	12/134 (9.0)	1/41 (2.4)	13/175 (7.4)	23/285 (8.1)

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	N=286 n/N _w (%)
Glucose, low (mg/dL)							
Level 1 (<70)	21/86 (24.4)	4/24 (16.7)	25/110 (22.7)	16/134 (11.9)	5/41 (12.2)	21/175 (12.0)	46/285 (16.1)
Level 2 (<54)	4/86 (4.7)	1/24 (4.2)	5/110 (4.5)	4/134 (3.0)	0/41 (0)	4/175 (2.3)	9/285 (3.2)
Level 3 (<40)	0/86 (0)	0/24 (0)	0/110 (0)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	1/285 (0.4)
Glucose, fasting, high (mg/dL)							
Level 1 (≥100 to 125)	2/2 (100)	0/0 (NA)	2/2 (100)	0/0 (NA)	0/0 (NA)	0/0 (NA)	2/2 (100)
Level 2 (≥126)	0/2 (0)	0/0 (NA)	0/2 (0)	0/0 (NA)	0/0 (NA)	0/0 (NA)	0/2 (0)
Glucose, random, high (mg/dL)							
Level 2 (≥200)	5/86 (5.8)	1/24 (4.2)	6/110 (5.5)	9/134 (6.7)	2/41 (4.9)	11/175 (6.3)	17/285 (6.0)
Level 3 (>250)	3/86 (3.5)	1/24 (4.2)	4/110 (3.6)	6/134 (4.5)	1/41 (2.4)	7/175 (4.0)	11/285 (3.9)
Calcium, low (mg/dL)							
Level 1 (<8.4)	5/86 (5.8)	0/24 (0)	5/110 (4.5)	5/134 (3.7)	2/41 (4.9)	7/175 (4.0)	12/285 (4.2)
Level 2 (<8)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	2/134 (1.5)	1/41 (2.4)	3/175 (1.7)	6/285 (2.1)
Level 3 (<7.5)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	1/41 (2.4)	1/175 (0.6)	3/285 (1.1)
Calcium, high (mg/dL)							
Level 1 (>10.5)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	10/134 (7.5)	3/41 (7.3)	13/175 (7.4)	14/285 (4.9)
Level 2 (>11)	0/86 (0)	0/24 (0)	0/110 (0)	2/134 (1.5)	0/41 (0)	2/175 (1.1)	2/285 (0.7)
Level 3 (>12)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Magnesium, low (mg/dL)							
Level 1 (<1.5)	1/3 (33.3)	0/0 (NA)	1/3 (33.3)	0/2 (0)	0/3 (0)	0/5 (0)	1/8 (12.5)
Level 2 (<1.2)	0/3 (0)	0/0 (NA)	0/3 (0)	0/2 (0)	0/3 (0)	0/5 (0)	0/8 (0)
Level 3 (<0.9)	0/3 (0)	0/0 (NA)	0/3 (0)	0/2 (0)	0/3 (0)	0/5 (0)	0/8 (0)
Magnesium, high (mg/dL)							
Level 1 (>2.3)	0/3 (0)	0/0 (NA)	0/3 (0)	0/2 (0)	1/3 (33.3)	1/5 (20.0)	1/8 (12.5)
Level 2 (>4)	0/3 (0)	0/0 (NA)	0/3 (0)	0/2 (0)	0/3 (0)	0/5 (0)	0/8 (0)
Level 3 (>7)	0/3 (0)	0/0 (NA)	0/3 (0)	0/2 (0)	0/3 (0)	0/5 (0)	0/8 (0)
Phosphate, low (mg/dL)							
Level 1 (<2.5)	24/86 (27.9)	3/24 (12.5)	27/110 (24.5)	37/134 (27.6)	10/41 (24.4)	47/175 (26.9)	74/285 (26.0)
Level 2 (<2)	6/86 (7.0)	2/24 (8.3)	8/110 (7.3)	10/134 (7.5)	4/41 (9.8)	14/175 (8.0)	22/285 (7.7)
Level 3 (<1.4)	0/86 (0)	0/24 (0)	0/110 (0)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	1/285 (0.4)
Albumin, low (g/dL)							
Level 1 (<3.1)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	0/41 (0)	0/175 (0)	2/285 (0.7)
Level 2 (<2.5)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Level 3 (<2)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	N=286 n/N _w (%)
Creatinine, high (mg/dL)							
Level 1 ($\geq 1.5 \times$ baseline)	22/86 (25.6)	8/24 (33.3)	30/110 (27.3)	17/134 (12.7)	4/41 (9.8)	21/175 (12.0)	51/285 (17.9)
Level 2 ($\geq 2 \times$ baseline)	5/86 (5.8)	3/24 (12.5)	8/110 (7.3)	3/134 (2.2)	1/41 (2.4)	4/175 (2.3)	12/285 (4.2)
Level 3 ($\geq 3 \times$ baseline)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
eGFR, low (ml/min/1.73 m ²)							
Level 1 ($\geq 25\%$ decrease)	18/86 (20.9)	4/23 (17.4)	22/109 (20.2)	17/134 (12.7)	6/41 (14.6)	23/175 (13.1)	45/284 (15.8)
Level 2 ($\geq 50\%$ decrease)	1/86 (1.2)	1/23 (4.3)	2/109 (1.8)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	3/284 (1.1)
Level 3 ($\geq 75\%$ decrease)	0/86 (0)	0/23 (0)	0/109 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/284 (0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 128 weeks.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: AT-DR, antithrombin-based dose regimen; CPK, creatine phosphokinase; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data

Hematology Laboratory Findings

Frequency of abnormal laboratory values for hematology assessments are shown in [Table 46](#). No significant differences in abnormal laboratory values occurred across the hemophilia subtypes or inhibitor status. Changes in hemoglobin likely were related to the subjects' bleeding profile.

Overall, no clinically relevant laboratory findings were identified. The majority of abnormal laboratory values were not sustained and were associated with underlying comorbidities. In addition, while there appears to be outliers of low white blood cell counts, low neutrophil counts and low lymphocyte counts in this analysis, no imbalance was seen for fitusiran vs. on demand treatment in the randomized, controlled parent studies.

**Table 46. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials
LTE15174, LTE14762, and EFC15110, AT-DR Period**

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total Hemophilia N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	N=286 n/N _w (%)
<i>Complete blood count</i>							
WBC, low (10 ³ cells/μL)							
Level 1 (<3.5)	12/86 (14.0)	2/24 (8.3)	14/110 (12.7)	12/134 (9.0)	9/41 (22.0)	21/175 (12.0)	35/285 (12.3)
Level 2 (<3)	5/86 (5.8)	2/24 (8.3)	7/110 (6.4)	5/134 (3.7)	4/41 (9.8)	9/175 (5.1)	16/285 (5.6)
Level 3 (<1)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
WBC, high (10 ³ cells/μL)							
Level 1 (>10.8)	14/86 (16.3)	7/24 (29.2)	21/110 (19.1)	13/134 (9.7)	6/41 (14.6)	19/175 (10.9)	40/285 (14.0)
Level 2 (>13)	8/86 (9.3)	1/24 (4.2)	9/110 (8.2)	4/134 (3.0)	2/41 (4.9)	6/175 (3.4)	15/285 (5.3)
Level 3 (>15)	5/86 (5.8)	0/24 (0)	5/110 (4.5)	1/134 (0.7)	1/41 (2.4)	2/175 (1.1)	7/285 (2.5)
Hemoglobin, low (g/dL)							
Level 2 (>1.5 g/dL dec. from baseline)	15/86 (17.4)	4/24 (16.7)	19/110 (17.3)	24/134 (17.9)	7/40 (17.5)	31/174 (17.8)	50/284 (17.6)
Level 3 (>2 g/dL dec. from baseline)	12/86 (14.0)	2/24 (8.3)	14/110 (12.7)	20/134 (14.9)	6/40 (15.0)	26/174 (14.9)	40/284 (14.1)
Hemoglobin, high (g/dL)							
Level 2 (>2 g/dL inc. from baseline)	37/86 (43.0)	12/24 (50.0)	49/110 (44.5)	30/134 (22.4)	8/40 (20.0)	38/174 (21.8)	87/284 (30.6)
Level 3 (>3 g/dL inc. from baseline)	19/86 (22.1)	4/24 (16.7)	23/110 (20.9)	8/134 (6.0)	2/40 (5.0)	10/174 (5.7)	33/284 (11.6)
Platelets, low (10 ³ cells/μL)							
Level 1 (<140)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	13/134 (9.7)	2/41 (4.9)	15/175 (8.6)	18/285 (6.3)
Level 2 (<125)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	11/134 (8.2)	0/41 (0)	11/175 (6.3)	12/285 (4.2)
Level 3 (<100)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	2/285 (0.7)
<i>WBC differential</i>							
Lymphocytes, low (10 ³ cells/μL)							
Level 1 (<1)	17/86 (19.8)	3/24 (12.5)	20/110 (18.2)	20/134 (14.9)	3/41 (7.3)	23/175 (13.1)	43/285 (15.1)
Level 2 (<0.75)	7/86 (8.1)	2/24 (8.3)	9/110 (8.2)	4/134 (3.0)	1/41 (2.4)	5/175 (2.9)	14/285 (4.9)
Level 3 (<0.5)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	1/41 (2.4)	1/175 (0.6)	3/285 (1.1)
Lymphocytes, high (10 ³ cells/μL)							
Level 1 (>4)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	5/134 (3.7)	0/41 (0)	5/175 (2.9)	7/285 (2.5)
Level 2 (>10)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Level 3 (>20)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
Neutrophils, low (10 ³ cells/μL)							
Level 1 (<2)	19/86 (22.1)	6/24 (25.0)	25/110 (22.7)	42/134 (31.3)	15/41 (36.6)	57/175 (32.6)	82/285 (28.8)
Level 2 (<1)	6/86 (7.0)	0/24 (0)	6/110 (5.5)	3/134 (2.2)	4/41 (9.8)	7/175 (4.0)	13/285 (4.6)
Level 3 (<0.5)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	0/134 (0)	1/41 (2.4)	1/175 (0.6)	4/285 (1.4)

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n/N _w (%)	N=24 n/N _w (%)	N=111 n/N _w (%)	N=134 n/N _w (%)	N=41 n/N _w (%)	N=175 n/N _w (%)	N=286 n/N _w (%)
Eosinophils, high (10 ³ cells/μL)							
Level 1 (>0.65)	19/86 (22.1)	5/24 (20.8)	24/110 (21.8)	21/134 (15.7)	5/41 (12.2)	26/175 (14.9)	50/285 (17.5)
Level 2 (>1.5)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	4/285 (1.4)
Level 3 (>5)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
<i>Coagulation studies</i>							
PT, high (sec)							
Level 1 (>1.1× ULN)	24/86 (27.9)	17/24 (70.8)	41/110 (37.3)	29/134 (21.6)	24/41 (58.5)	53/175 (30.3)	94/285 (33.0)
Level 2 (>1.3× ULN)	1/86 (1.2)	2/24 (8.3)	3/110 (2.7)	2/134 (1.5)	3/41 (7.3)	5/175 (2.9)	8/285 (2.8)
Level 3 (>1.5× ULN)	1/86 (1.2)	2/24 (8.3)	3/110 (2.7)	1/134 (0.7)	2/41 (4.9)	3/175 (1.7)	6/285 (2.1)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 128 weeks.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: AT-DR, antithrombin-based dose regimen; dec., decrease; inc., increase; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

[Table 47](#) presents abnormal liver laboratory findings by maximum worsening grade.

[Figure 14](#) shows the change over time from baseline for ALT, [Figure 15](#) for AST and [Figure 16](#) for total bilirubin.

[Table 158](#) (Section [17](#) Clinical Safety) shows the liver test excursions from normal and mean change over time in Studies EFC14768 and EFC14769. In these analyses, there is a higher prevalence of ALT excursions greater than 3× ULN, and higher mean ALT values over the study time compared to the on-demand controls.

Hepatotoxicity was identified as serious safety signal; see further discussion in Section [7.6.3](#).

Table 47. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Laboratory Parameter	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	N=286 n/N _w (%)
Alkaline phosphatase, high (U/L)							
Level 1 (>1.5× ULN)	8/86 (9.3)	2/24 (8.3)	10/110 (9.1)	13/134 (9.7)	5/41 (12.2)	18/175 (10.3)	28/285 (9.8)
Level 2 (>2× ULN)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	4/134 (3.0)	1/41 (2.4)	5/175 (2.9)	7/285 (2.5)
Level 3 (>3× ULN)	0/86 (0)	0/24 (0)	0/110 (0)	2/134 (1.5)	0/41 (0)	2/175 (1.1)	2/285 (0.7)
Alanine aminotransferase, high (U/L)							
Level 1 (>3× ULN)	4/86 (4.7)	1/24 (4.2)	5/110 (4.5)	3/134 (2.2)	2/41 (4.9)	5/175 (2.9)	10/285 (3.5)
Level 2 (>5× ULN)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	1/134 (0.7)	1/41 (2.4)	2/175 (1.1)	5/285 (1.8)
Level 3 (>10× ULN)	2/86 (2.3)	0/24 (0)	2/110 (1.8)	0/134 (0)	1/41 (2.4)	1/175 (0.6)	3/285 (1.1)
Aspartate aminotransferase, high (U/L)							
Level 1 (>3× ULN)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	3/134 (2.2)	2/41 (4.9)	5/175 (2.9)	8/285 (2.8)
Level 2 (>5× ULN)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	1/134 (0.7)	1/41 (2.4)	2/175 (1.1)	3/285 (1.1)
Level 3 (>10× ULN)	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	1/41 (2.4)	1/175 (0.6)	1/285 (0.4)
Bilirubin, total, high (mg/dL)							
Level 1 (>1.5× ULN)	9/86 (10.5)	5/24 (20.8)	14/110 (12.7)	16/134 (11.9)	4/41 (9.8)	20/175 (11.4)	34/285 (11.9)
Level 2 (>2× ULN)	3/86 (3.5)	0/24 (0)	3/110 (2.7)	7/134 (5.2)	1/41 (2.4)	8/175 (4.6)	11/285 (3.9)
Level 3 (>3× ULN)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	2/134 (1.5)	0/41 (0)	2/175 (1.1)	3/285 (1.1)

Source: adlb.xpt; Software: R

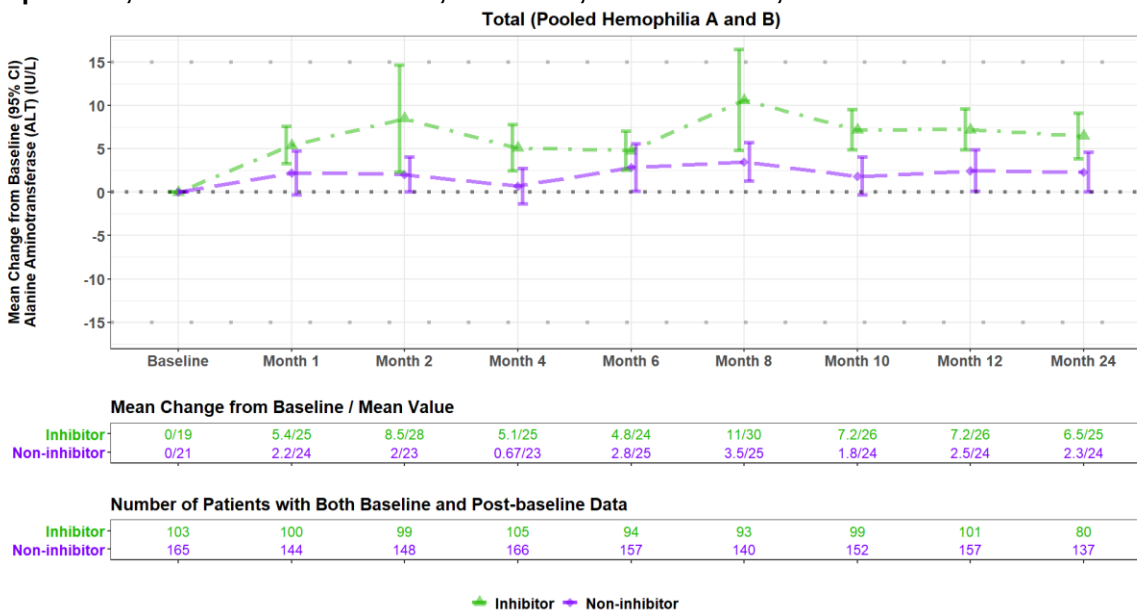
Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 128 weeks.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Figure 14. Mean Alanine Aminotransferase Data Change From Baseline Over Time, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period.

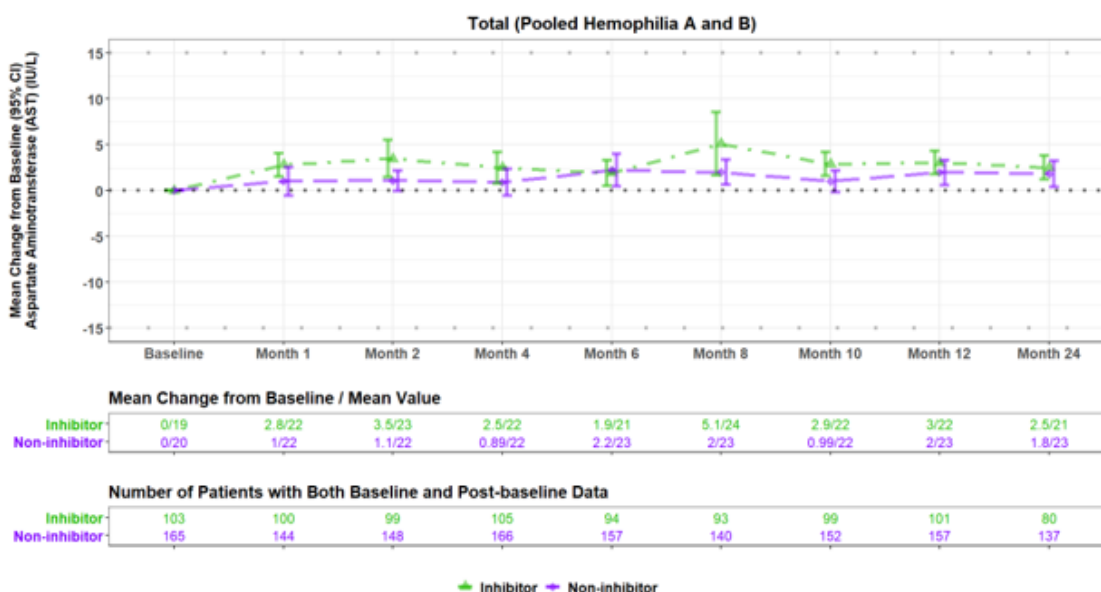


Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups. Only central laboratory data are included in the analysis.

Abbreviations: ALT, alanine aminotransferase; LTE, long-term extension

Figure 15. Mean Aspartate Aminotransferase Data Change From Baseline Over Time, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

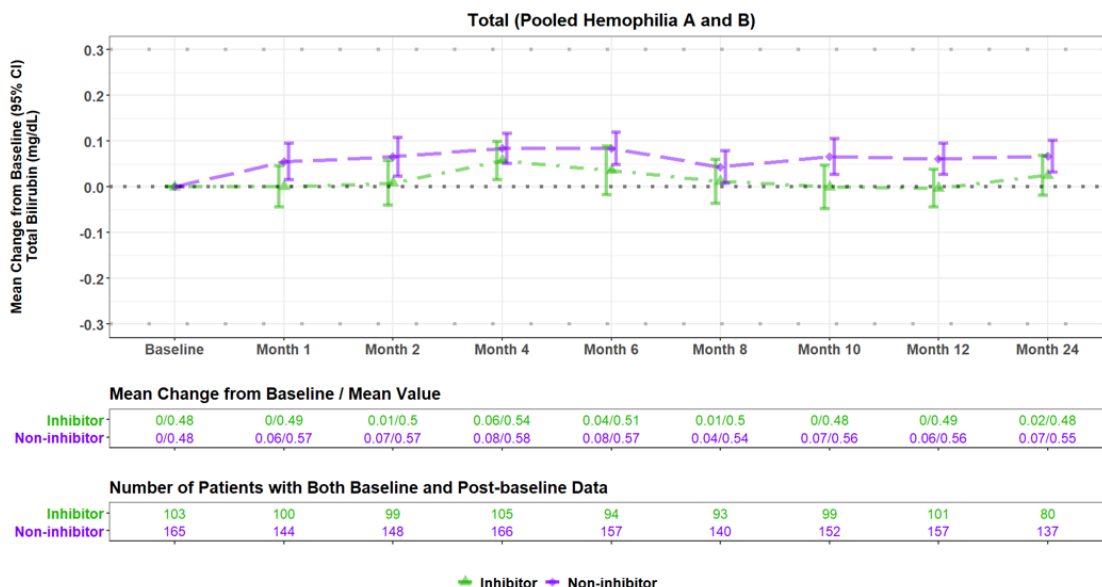


Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups. Only central laboratory data are included in the analysis.

Abbreviations: AST, aspartate aminotransferase; AT-DR, antithrombin-based dose regimen; LTE, long-term extension

Figure 16. Mean Total Bilirubin Data Change From Baseline Over Time, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period



Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Only central laboratory data are included in the analysis.

Abbreviations: AT-DR, antithrombin-based dose regimen; CI, confidence interval; Intl., international; LTE, long-term extension

7.5.2.7. Assessment of Drug-Induced Liver Injury, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

eDISH plots for hepatocellular injury are presented in [Figure 17](#) and [Figure 18](#). Two subjects met potential Hy's Law criteria and are presented below. Upon further investigation, both cases were determined to be unlikely DILI due to fitusiran. In the pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period, there was no case of confirmed DILI.

- Subject (b) (6) was a 50-year-old male with HA with inhibitors and a history of diabetes mellitus, hypertension, and hepatitis C, who was enrolled in Study EFC014768 at 80 mg QM, and then rolled over to Study LTE15174. On Day 777 of Study LTE15174 (Day 1030 since the initiation of fitusiran in Study EFC14768), he presented with symptoms of pancreatitis. Imaging showed obstruction due to a common bile duct stone. The subject was hospitalized on Day 778, was diagnosed with obstructive cholangitis, and on Day 782 underwent pancreatobiliary sphincterotomy. Liver tests around this time were significant for an ALT >10× ULN and bilirubin >2× ULN. On Day 786, the study subject recovered from the events of cholangitis and obstructive pancreatitis, and liver tests normalized. Fitusiran had been previously held on Day 677 due to AST elevation and then was resumed Day 784 at 20 mg Q2M and there was no recurrence of elevated liver enzymes. This case is unlikely DILI due to intervening obstructive biliary disease as the cause of ALT and bilirubin increase, and resolved with endoscopic retrograde cholangiopancreatography with no recurrence with drug rechallenge.

- Subject (b) (6) was a 44-year-old male with HA without inhibitors who on Day 589 of Study LTE15174 developed AST $>6\times$ ULN, ALT $2.9\times$ ULN, and bilirubin of $2\times$ ULN. There were exposures to alcohol, a cold medication, and protein powder, which were likely the etiology of liver abnormalities. Liver tests normalized 1 week later, and the subject remained on fitusiran treatment.

In the original fitusiran dosing of 80 mg SQ QM, ALT elevations $>3\times$ ULN and potential cases of Hy's Law were observed more frequently than in the AT-DR dosing period. The DILI consult team performed an in-depth analysis of both DILI and gallbladder disease across the fitusiran development program, including the original dosing regimens used in studies EFC14768, EFC14769, EFC15110, and LTE14762; refer to the finalized DILI consult in DARRTS for the full analysis and Section 7.6.3 for further discussion.

Table 48. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Quadrant	Inhibitor			Noninhibitor			Overall
	Hemophilia Hemophilia			Hemophilia Hemophilia			
	A	B	Total	A	B	Total	
	N=87	N=24	N=111	N=134	N=41	N=175	
	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	N=286 n/N _w (%)
Potential Hy's Law (right upper)	1/86 (1.2)	0/24 (0)	1/110 (0.9)	1/134 (0.7)	0/41 (0)	1/175 (0.6)	2/285 (0.7)
Cholestasis (left upper)	2/86 (2.3)	1/24 (4.2)	3/110 (2.7)	6/134 (4.5)	1/41 (2.4)	7/175 (4)	10/285 (3.5)
Temple's corollary (right lower)	3/86 (3.5)	1/24 (4.2)	4/110 (3.6)	4/134 (3)	2/41 (4.9)	6/175 (3.4)	10/285 (3.5)
Total	6/86 (7)	2/24 (8.3)	8/110 (7.3)	11/134 (8.2)	3/41 (7.3)	14/175 (8)	22/285 (7.7)

Source: adlb.xpt; Software: R

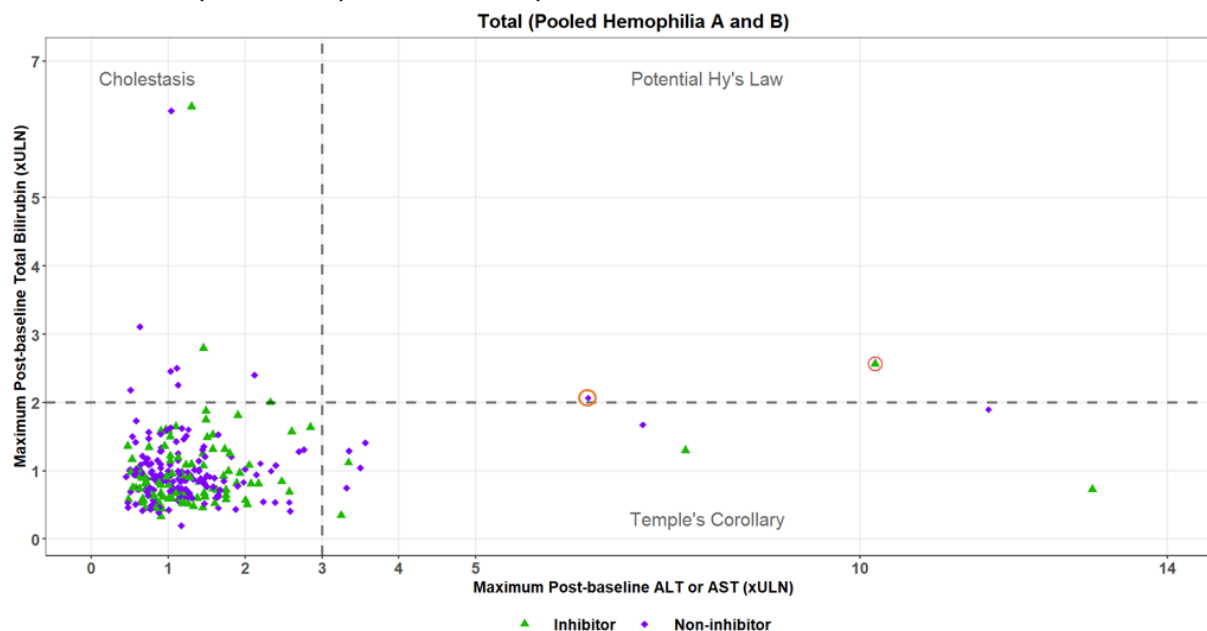
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding $2\times$ ULN after a postbaseline ALT or AST equal to or exceeding $3\times$ ULN.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT-DR, antithrombin-based dose regimen; DILI, drug-induced liver injury; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Figure 17. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

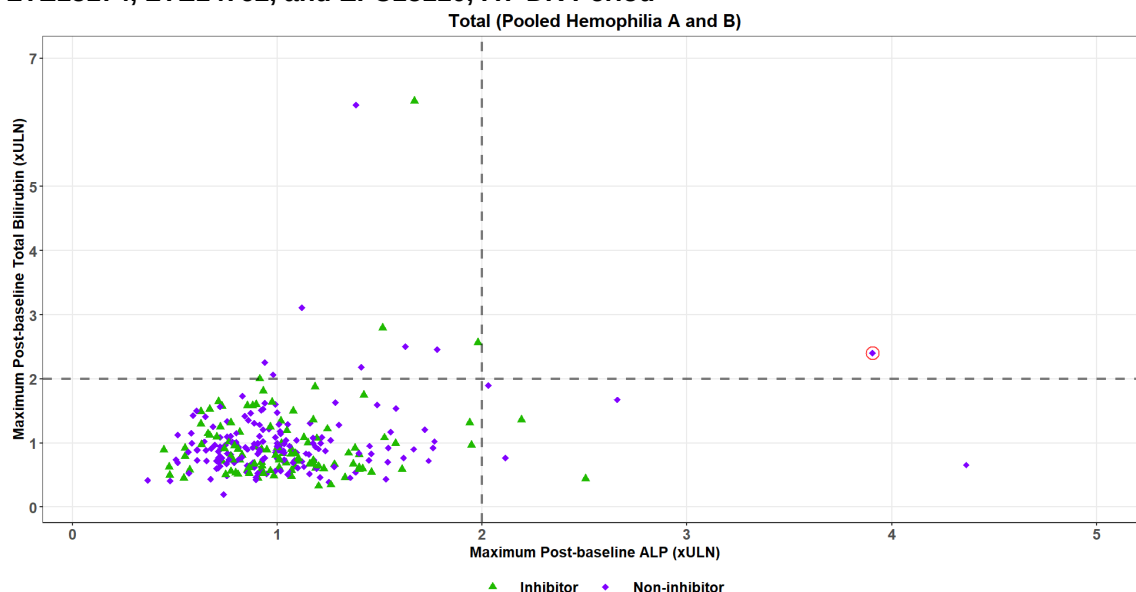
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT-DR, antithrombin-based dose regimen; LTE, long-term extension; ULN, upper limit of normal

[Figure 18](#) presents the cholestatic drug-induced liver injury screening plot. The single case of potential cholestatic DILI was identified in Subject (b) (6). The ALP was chronically elevated, and the total bilirubin was elevated for only one reading. The subject was receiving 50 mg Q2M, which was not interrupted, and the subject remained on fitusiran.

Figure 18. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.

A potential cholestatic DILI case (red circled) was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Cholestatic DILI Screening Plot ..."

Abbreviations: ALP, alkaline phosphatase; AT-DR, antithrombin-based dose regimen; DILI, drug-induced liver injury; LTE, long-term extension; ULN, upper limit of normal

7.5.2.8. Vital Signs, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

[Table 49](#) shows the frequency of maximum systolic blood pressure ≥ 140 mm Hg to be 20.4% overall in the Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period. [Figure 19](#) shows that the population mean systolic blood pressure fluctuates about the baseline and does not consistently rise in either the inhibitor or noninhibitor population.

Moreover, the fluctuations are between 1 to 3 mm Hg above and below the baseline, and not clinically significant. The prevalence of maximum systolic blood pressure changes reflects the baseline cohort hypertension prevalence, which is 11.9%. Similar percentages of systolic blood pressure ≥ 140 mmHg were reported in both the fitusiran and on demand treatment arms of Studies EFC14768 and EFC14769.

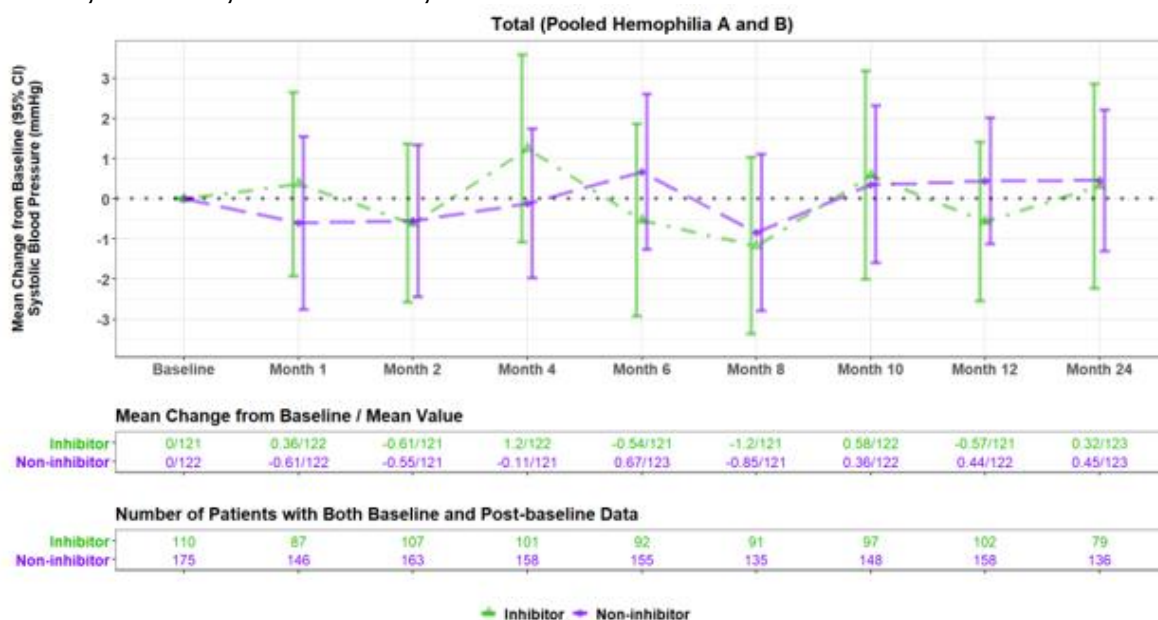
Table 49. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Systolic Blood Pressure (mm Hg)	Inhibitor			Noninhibitor			Overall
	Hemophilia A N=87 n/N _w (%)	Hemophilia B N=24 n/N _w (%)	Total N=111 n/N _w (%)	Hemophilia A N=134 n/N _w (%)	Hemophilia B N=41 n/N _w (%)	Total N=175 n/N _w (%)	
<90	0/86 (0)	0/24 (0)	0/110 (0)	0/134 (0)	0/41 (0)	0/175 (0)	0/285 (0)
≥90	86/86 (100)	24/24 (100)	110/110 (100)	134/134 (100)	41/41 (100)	175/175 (100)	285/285 (100)
≥120	79/86 (91.9)	22/24 (91.7)	101/110 (91.8)	119/134 (88.8)	39/41 (95.1)	158/175 (90.3)	259/285 (90.9)
≥140	10/86 (11.6)	9/24 (37.5)	19/110 (17.3)	33/134 (24.6)	6/41 (14.6)	39/175 (22.3)	58/285 (20.4)
≥160	0/86 (0)	1/24 (4.2)	1/110 (0.9)	5/134 (3.7)	0/41 (0)	5/175 (2.9)	6/285 (2.1)
≥180	0/86 (0)	1/24 (4.2)	1/110 (0.9)	0/134 (0)	0/41 (0)	0/175 (0)	1/285 (0.4)

Source: advs.xpt; Software: R

Abbreviations: AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Figure 19. Mean Change From Baseline Systolic Blood Pressure, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period



Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: AT-DR, antithrombin-based dose regimen; CI, confidence interval; LTE, long-term extension

7.5.2.9. Subgroups, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

An overview of TEAEs by demographic subgroup is summarized in [Table 50](#). The incidence of overall TEAEs did not appear to meaningfully differ between the subgroups of Age group 12 to <18 versus Age group 18 to 64, or the subgroups of Race Asian versus White. The small sizes of all other subgroups limit further assessment.

Table 50. Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Trials LTE15174, LTE14762, and EFC15110, AT-DR Period

Characteristic	Inhibitor			Noninhibitor			Overall
	Hemophilia A	Hemophilia B	Total	Hemophilia A	Hemophilia B	Total	
	N=87 n/Ns (%)	N=24 n/Ns (%)	N=111 n/Ns (%)	N=134 n/Ns (%)	N=41 n/Ns (%)	N=175 n/Ns (%)	N=286 n/Ns (%)
Sex							
Male	75/87 (86.2)	18/24 (75.0)	93/111 (83.8)	108/134 (80.6)	37/41 (90.2)	145/175 (82.9)	238/286 (83.2)
Age group, years							
12 to <18	14/16 (87.5)	9/11 (81.8)	23/27 (85.2)	20/22 (90.9)	10/11 (90.9)	30/33 (90.9)	53/60 (88.3)
18 to 64	60/70 (85.7)	9/13 (69.2)	69/83 (83.1)	87/111 (78.4)	26/29 (89.7)	113/140 (80.7)	182/223 (81.6)
≥65	1/1 (100)	0/0 (NA)	1/1 (100)	1/1 (100)	1/1 (100)	2/2 (100)	3/3 (100)
Age group ≥75, years							
≥75	0/87 (0)	0/24 (0)	0/111 (0)	0/134 (0)	0/41 (0)	0/175 (0)	
Race							
Asian	51/59 (86.4)	8/11 (72.7)	59/70 (84.3)	60/80 (75.0)	17/19 (89.5)	77/99 (77.8)	136/169 (80.5)
Black or African American	0/0 (NA)	0/1 (0)	0/1 (0)	1/2 (50.0)	0/0 (NA)	1/2 (50.0)	1/3 (33.3)
White	24/28 (85.7)	8/10 (80.0)	32/38 (84.2)	40/44 (90.9)	20/22 (90.9)	60/66 (90.9)	92/104 (88.5)
Multiple	0/0 (NA)	0/0 (NA)	0/0 (NA)	1/2 (50.0)	0/0 (NA)	1/2 (50.0)	1/2 (50.0)
Not reported	0/0 (NA)	0/0 (NA)	0/0 (NA)	5/5 (100)	0/0 (NA)	5/5 (100)	5/5 (100)
Other	0/0 (NA)	2/2 (100)	2/2 (100)	1/1 (100)	0/0 (NA)	1/1 (100)	3/3 (100)
Ethnicity							
Hispanic or Latino	0/0 (NA)	2/2 (100)	2/2 (100)	0/0 (NA)	3/3 (100)	3/3 (100)	5/5 (100)
Not Hispanic or Latino	72/84 (85.7)	15/21 (71.4)	87/105 (82.9)	98/124 (79.0)	33/37 (89.2)	131/161 (81.4)	218/266 (82.0)
Not reported	3/3 (100)	1/1 (100)	4/4 (100)	10/10 (100)	1/1 (100)	11/11 (100)	15/15 (100)
Is in United States							
United States	0/0 (NA)	5/6 (83.3)	5/6 (83.3)	2/3 (66.7)	3/3 (100)	5/6 (83.3)	10/12 (83.3)
Non-United States	75/87 (86.2)	13/18 (72.2)	88/105 (83.8)	106/131 (80.9)	34/38 (89.5)	140/169 (82.8)	228/274 (83.2)

Source: adae.xpt; Software: R

Abbreviations: AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6. Key Safety Review Issues

7.6.1. Thrombotic Events

Issue

Fitusiran was originally developed as an 80 mg QM fixed dose, however, due to serious events of thrombosis, including a thrombosis-related fatality, the dosing regimen was modified to the AT-DR. The risk of thrombotic events was assessed in both subjects who received the original 80 mg QM dosing regimen and the AT-DR.

Background

Fitusiran is an siRNA that causes degradation of AT mRNA through RNA interference, which results in a reduction of plasma AT protein levels, reduced AT activity, and increased thrombin generation. The mechanism of action of fitusiran to increase thrombin generation inherently increases the ability to make clots, which can increase thrombosis risk through excessive pharmacologic effect. In the hemophilia context, increasing clot formation is beneficial due to underlying pathological bleeding risk, but there is a careful balance between sufficient antithrombin suppression to prevent bleeding and avoidance of the risk of thrombosis, which is associated with significant morbidity and mortality. Thromboembolic events are a common complication in congenital antithrombin deficiency, in which AT activity ranges from 40 to 60% ([Patnaik and Moll 2008](#)). Thrombosis formation was observed in nonclinical studies with fitusiran (see Section [7.1](#)).

Mitigation of potential thrombotic risks in the fitusiran development program included exclusion of subjects with severe hemophilia with significant thrombosis history or known thrombophilia disorder, and implementation of bleed management guidelines (BMG), which include recommendations to guide investigators on the use of factor replacement products or bypassing products during acute bleeding events and during surgical procedures. Bleed management guidelines are described in detail in Section [15](#). At the close of the controlled studies EFC14768, EFC14769, and EFC15110, an analysis of thrombotic events and correlation with AT activity led to institution of the AT-DR to target antithrombin levels between 15 to 35%. Per the Applicant, persistent AT levels <10% increases the risk of thromboembolic events.

Assessment

In total, 11 out of 335 subjects (3.3%) experienced a thrombotic event in the fitusiran clinical development program. Of the subjects who experienced thrombotic events, 7 out of 270 subjects (2.6%) had a thrombotic event while receiving the original 80-mg dose regimen and 4 out of 286 (1.4%) subjects had a thrombotic event on the AT-DR. No subjects in the on-demand (control) arms in the randomized controlled trials (studies EFC14768 and EFC14769) experienced a thrombotic event. A summary of the subjects with thrombotic events while receiving fitusiran is described in [Table 51](#) below, and full subject narratives from all 11 subjects are in Section [17.3](#). It is notable that both arterial and venous thrombotic events were reported, including atypical events such as spinal vein thrombosis and thrombosis of the papilla of the eye. Events typically occurred after subjects had been taking fitusiran for over >5 months (range 57 to 1147 days on fitusiran). Almost all subjects had risk factors at baseline (e.g., hypertension, diabetes, smoking history, recent surgery, central line, history of thrombosis), however, the strongest risk factors appear to be recent administration of factor or bypassing factor agent, and persistent AT levels <15%. The risk of thrombosis remains for several months after discontinuing fitusiran, as it may take 6 months for AT activity to recover to >60%.

Table 51. Summary of Thrombotic Events in Fitusiran Clinical Studies

Subject/ Study	Diagnosis/ Age (Years)	Thrombosis Risk Factors	Relevant Concomitant Therapy	Fitusiran Dose	AT Level*	Thrombotic Event	Reviewer Interpretation
(b) (6)	HBwl/17	Medical Hx: prior thrombosis and malabsorption Current central line infection and hospitalization	Factor VIII, with doses 31 IU/kg- 46 IU/kg	80 mg QM	Day 57=11.9%	DVT, subclavian vein thrombosis on study day 63	While the subject had multiple risk factors for thrombosis, including recent factor administration, given the AT level <15% fitusiran likely contributed to event.
	HAwl/19	None.	None.	80 mg QM	Day 197=11.6%	Spinal vein thrombosis on study day 204	Likely related to fitusiran, no other risk factors and AT level <15%.
	HA/36	Medical Hx: prior thrombosis, DM, HTN, hyperlipidemia, smoker	Factor VIII, with doses 31 IU/kg- 46 IU/kg	80 mg QM	Day 169=6%	CVA on day 160	Likely related to fitusiran, while multiple risk factors, including recent factor administration, AT level <15%.
	HAwl/56	Medical Hx: HTN	None.	80 mg QM	Day 246=11%	Thrombosis on the papilla of left eye, symptoms began on day 247 (last dose of fitusiran 77 days prior)	Likely related to fitusiran, AT level <15%.
	HA/25	Medical Hx: hepatitis C, smoker	Factor VIII, with doses 31 IU/kg- 46 IU/kg	80 mg QM	Day 452=11.6%	CVST, symptoms began on day 482, subject died due to CVST	While the subject had risk factors for thrombosis, AT level <15% and had received high factor doses, event likely related to fitusiran.

Subject/ Study	Diagnosis/ Age (Years)	Thrombosis Risk Factors	Relevant Concomitant Therapy	Fitusiran Dose	AT Level*	Thrombotic Event	Reviewer Interpretation
(b) (6)	HBwl/24	Medical Hx: Factor IX inhibitor developed as an infant, failed desensitization therapy, and developed nephrotic syndrome after immunosuppression; required frequent VIIa therapy for L elbow target joint prior to fitusiran treatment	None.	80 mg QM	Day 671=12.9%	Incidental finding of right atrial thrombosis on day 679	Difficult to attribute given unknown date when the thrombosis formed, likely fitusiran contributed, while multiple risk factors AT level <15%
	HA/62	Medical Hx: hepatitis C, HIV	None.	80 mg QM	Day 454=2%	Cerebral artery embolism on day 436	Likely related to fitusiran, while multiple risk factors AT level <15%
	HA/51	Medical Hx: HTN, DM, hepatitis C	None.	50 mg Q2M	Day 619=36%	Embolitic stroke on day 673 (last dose of fitusiran 165 days prior)	Difficult to attribute given multiple risk factors and fitusiran had been discontinued and AT levels >35%. However, fitusiran was discontinued due to persistent levels <15% and had not returned to baseline values.
	HBwl/13	Medical Hx: multiple thrombotic events Recent inguinal hernia surgery with drain placement (5 days prior to event)	None.	50 mg Q2M	Day 678=23%	Venous thrombosis (moderate) (left axillary, brachial and basilic vein) on day 687	Difficult to attribute given multiple risk factors and AT level >15% (although not in normal range), however as fitusiran was continued during surgery it could have contributed.

Subject/ Study	Diagnosis/ Age (Years)	Thrombosis Risk Factors	Relevant Concomitant Therapy	Fitusiran Dose	AT Level*	Thrombotic Event	Reviewer Interpretation
(b) (6)	HA/43	Medical Hx: Hepatitis C, HTN, obesity Recent orthopedic surgery and central line placement (15 days prior to event)	None.	50 mg QM	Day 1147=15%	Deep vein thrombosis postoperative on day 1155	Difficult to attribute given multiple risk factors, however as recent AT level was at the lowest end of the target range, fitusiran likely further increased this risk.
	HBwl/27	Medical Hx: type 2 diabetes, dyslipidemia, nephrotic syndrome	None.	50 mg Q2M	Day 226=20%	Cerebral infarction on day 224	Difficult to attribute given multiple risk factors, and AT level is in target range, however it is likely that fitusiran contributed to the event due to MOA.

Source: Clinical reviewer

*AT level closest to the event

Abbreviations: AT, antithrombin; CVA, cerebrovascular accident; CVST, cerebral venous sinus thrombosis; DM, diabetes mellitus; DVT, deep vein thrombosis; HA, hemophilia A; HAwI, hemophilia A with inhibitor; HB, hemophilia B; HBwl, hemophilia B with inhibitor; HTN, hypertension; Hx, history; L, left; MOA, mechanism of action; Q2M, every 2 months; QM, once monthly

Conclusion

Patients exposed to fitusiran are at increased risk of thrombosis due to excessive pharmacologic effect. While implementing bleed management guidelines and reducing fitusiran exposure such that the AT activity range is targeted to between 15 to 35% appears to have decreased the rate of thrombotic events, the risk clearly remains, in particular in the setting of additional risk factors for thrombosis, including high doses of factor administration and persistent AT levels <15%. The risk of thromboembolism should be included as a boxed warning, as knowledge of this risk is necessary prior to a prescriber administering the drug. Patients with a history of thrombosis or significant risk factors for thrombosis will need to consider the benefit/risk profile of the drug, and it is imperative for prescribers to follow bleed management guidelines. With labeling which includes bleed management guidelines, this risk can be mitigated.

7.6.2. Acute and Recurrent Gallbladder Disease

Issue

Fitusiran has a significant risk of acute and recurrent gallbladder disease. Subjects in clinical trials required surgical intervention and had complications such as pancreatitis. The risk of acute and recurrent gallbladder disease was assessed in subjects who received the original dosing regimen and the AT-DR.

This review issue was largely assessed by the DILI team from the Division of Hepatology and Nutrition; please see the finalized consult review in DARRTS dated March 21, 2025.

Background

Patients with hemophilia are not typically at increased risk for gallbladder disease. In addition, gallbladder disease was not identified as an adverse reaction during the clinical development programs of other approved siRNA products. Therefore, it was an unexpected finding when a significant number of subjects developed gallbladder disease and related complications in this development program.

Biliary tract abnormalities of biliary hyperplasia and bile duct dilation were noted in mice treated with fitusiran (see Section [13.2.5](#)). However, biliary tract abnormalities were not observed across animal studies.

Assessment

In the fitusiran development program, 51 (15.2%) subjects experienced a gallbladder TEAE after receiving at least one dose of fitusiran. Of the 51 subjects who experienced a gallbladder event, the most common event was cholelithiasis (47.1%), followed by cholecystitis (33.3%), chronic cholecystitis (11.8%), gallbladder polyp (11.8%), acute cholecystitis (7.8%), biliary colic (5.9%), gallbladder enlargement (5.9%), cholestasis (3.9%), cholangitis (2%), and biliary dyskinesia (2%). The majority of events were moderate in severity. Gallbladder TEAEs were graded mild in 12 subjects (23.5%), moderate in 36 subjects (70.6%) and severe in 9 subjects (17.6%). Frequency of gallbladder TEAEs are described below by dosing cohort.

Frequency of Gallbladder Events in Pooled Safety Databases

Original 80 mg QM Dose Cohort

46/270 (17.3%) of subjects experienced gallbladder events.

- Study 14768: 6/41 (14.6%) subjects in the fitusiran treatment arm and 0/19 in the on-demand control arm.
- Study 14769: 7/79 (8.8%) subjects in the fitusiran treatment arm and 0/40 in the on-demand control arm.
- Study 15110: 10/67 (14.9%) subjects during the fitusiran treatment period and 0/78 subjects during the control period of 15110.

AT-DR Cohort

11/286 (3.8%) of subjects experienced 15 acute gallbladder events, including cholelithiasis (4), cholecystitis (3), gallbladder polyp (3), cholecystitis acute (2), cholangitis (1), cholecystitis chronic (1), and gallbladder enlargement (1).

Cholecystectomy

Across the 335-subject safety database from the entire fitusiran exposed population, 12 individuals (all on fitusiran) underwent a cholecystectomy (3.6%). Nine of these individuals experienced an SAE of cholecystitis/cholelithiasis before the cholecystectomy, and one experienced an SAE of cholangitis and pancreatitis caused by gallstone disease more than a year after cholecystectomy. Most subjects (11 of 12) did not interrupt fitusiran prior to the procedure; however, all subjects received factor concentrate or a bypassing agent perioperatively.

Of the 12 subjects on fitusiran who underwent cholecystectomy, 11 subjects were receiving a fixed dose of fitusiran, and one was on AT-DR (20 mg Q2M). Eleven of these 12 subjects continued fitusiran after cholecystectomy. One subject experienced cholangitis and pancreatitis caused by gallstone disease more than two years after cholecystectomy and while on the AT-DR dose regimen. The average time to receiving a cholecystectomy was 417 days (range 57 to 1035). [Table 164](#) (Section [17.4](#)) shows the demographics and associated AEs in the cholecystectomy cohort.

Conclusion

Gallbladder events only occurred in severe hemophilia patients exposed to fitusiran in clinical studies; none were reported in the control subjects. Gallbladder events were less common on the AT-DR dosing (3.8%) compared to the original 80 mg fixed dose regimen (17.3%), suggesting a fitusiran dose effect. However, this observation may be subject to selection. Most subjects on AT-DR dosing had first been dosed with the original 80 mg regimen. Their ability to stay in the study and change to the AT-DR dosing was therefore contingent on their ability to tolerate the original dosing, leading to potential selection bias in safety evaluation of the AT-DR dosing.

The proportion of subjects who required cholecystectomy after they developed gallbladder disease is concerning for this patient population. Patients with hemophilia are prone to bleeding, which can increase the risk of surgical procedures.

Acute and recurrent gallbladder disease should be included in a boxed warning in the label to alert prescribers of this risk prior to drug administration. Prescribers should consider this risk for patients at high risk for gallbladder disease, or high risk for surgical procedures. With labeling, acute and recurrent gallbladder disease risk can be mitigated. Enhanced pharmacovigilance for gallbladder disease will be recommended.

7.6.3. Hepatotoxicity

Issue

Fitusiran has a significant risk of hepatotoxicity identified with the original 80-mg dose, as evidenced by a high incidence of ALT elevations greater than 3× ULN and a Hy's law case. The risk of hepatotoxicity was assessed in subjects who received the original dosing regimen and the AT-DR. This review issue was largely assessed by the DILI team from the Division of Hepatology and Nutrition; please see the finalized consult review in DARRTS dated March 21, 2025.

Background

Fitusiran targets the liver by active uptake via the ASPGR expressed on hepatocytes. Fitusiran inhibits hepatocyte AT production through RNA interference on the *SERPINC1* gene, leading to its degradation by RNA-induced silencing complex and preventing translation of gene expression and function. The Division of Applied Regulatory Science (DARS) found no evidence that the knockdown of AT production would cause hepatotoxicity. Animal studies indicate minimal to moderate liver toxicity potential with findings of liver cell necrosis and bile duct dilatation at the highest dose exposures; however, there were differences in species. Only about 10% of the administered dose is accounted for in excretion studies, and the rest of the product may be retained in the liver, but how much is in smaller nucleotide forms (metabolites) that may be recycled for use by the body is unknown. See the DILI consult review for further details.

FDA has approved several siRNAs that inhibit hepatic mRNA translation by targeted uptake by the ASPGR (see Section 7.2 for further discussion). Of the hepatic targeted siRNAs, givosiran has hepatotoxicity listed as a Warning in the label ([Alnylam Pharmaceuticals 2024b](#)).

Assessment

Overall, 66 out of 335 subjects (19.7%) who received fitusiran met DILI reporting requirements.

Original Dose Regimen

In the parent studies (fitusiran 80 mg QM dose regimen), ALT and AST elevations above 3 times the upper limit of normal (ULN) occurred in 13 subjects (31.7%) with hemophilia with inhibitors (Study EFC14769) and 14 subjects (17.7%) with hemophilia without inhibitors (Study EFC14768), compared to no events of AST/ALT elevation greater than 3× ULN in the on-demand control groups from either study. See [Table 52](#) and [Table 53](#) below for liver enzyme abnormalities by study. Subjects treated with fitusiran 80 mg in the open-label study EFC15110 had ALT elevations greater than 3× ULN at similar rates seen in fitusiran subjects treated in Study EFC14768 and EFC14769.

Table 52. Frequency of Hepatic Safety Laboratory Parameter Elevations at Any Postbaseline Visit by Treatment Arm, Safety Population, Study EFC14769

Laboratory Abnormality	Fitusiran N=79 n (%)	On-Demand N=40 n (%)	Risk Difference (%) (95% CI)
ALT			
≥1× ULN	68/79 (86.1)	15/39 (38.5)	47.6 (29.7, 63.1) *
≥3× ULN	14/79 (17.7)	0/39 (0)	17.7 (8.2, 27.6) *
≥5× ULN	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
≥10× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
≥20× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
AST			
≥1× ULN	54/79 (68.4)	10/39 (25.6)	42.7 (24.0, 57.9) *
≥3× ULN	5/79 (6.3)	1/39 (2.6)	3.8 (-7.4, 12.0)
≥5× ULN	3/79 (3.8)	0/39 (0)	3.8 (-5.4, 10.6)
≥10× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
≥20× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
ALP			
≥2× ULN	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
≥3× ULN	1/79 (1.3)	0/39 (0)	1.3 (-7.8, 6.9)
Total bilirubin			
≥2× ULN	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
≥5× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
≥8× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
Direct bilirubin			
≥2× ULN	4/79 (5.1)	0/39 (0)	5.1 (-4.1, 12.3)
≥5× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
GGT			
≥2× ULN	12/79 (15.2)	4/39 (10.3)	4.9 (-9.9, 16.7)
INR			
≥1.5× ULN	2/79 (2.5)	1/39 (2.6)	-0.0 (-10.9, 6.7)
≥3× ULN	0/79 (0)	1/39 (2.6)	-2.6 (-13.2, 2.2)
≥5× ULN	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)

Source: DILI Team Consult Review.

The frequency represented here are based on peak levels.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Table 53. Frequency of Hepatic Safety Laboratory Parameter Elevations at Any Postbaseline Visit by Treatment Arm, Safety Population, Study EFC14768

Laboratory Abnormality	Fitusiran N=41 n (%)	On-Demand N=19 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	37/41 (90.2)	5/19 (26.3)	63.9 (38.8, 80.8) *
>=3X ULN	13/41 (31.7)	0/19 (0)	31.7 (13.1, 47.1) *
>=5X ULN	3/41 (7.3)	0/19 (0)	7.3 (-10.2, 19.6)
>=10X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
>=20X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
AST			
>=1X ULN	35/41 (85.4)	1/19 (5.3)	80.1 (57.9, 90.3) *
>=3X ULN	5/41 (12.2)	0/19 (0)	12.2 (-5.5, 25.7)
>=5X ULN	2/41 (4.9)	0/19 (0)	4.9 (-12.5, 16.3)
>=10X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
>=20X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
ALP			
>=2X ULN	3/41 (7.3)	0/19 (0)	7.3 (-10.2, 19.6)
>=3X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
Total Bilirubin			
>=2X ULN	2/41 (4.9)	0/19 (0)	4.9 (-12.5, 16.3)
>=5X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
>=8X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
Direct Bilirubin			
>=2X ULN	1/41 (2.4)	0/19 (0)	2.4 (-14.8, 12.7)
>=5X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
GGT			
>=2X ULN	10/41 (24.4)	1/19 (5.3)	19.1 (-2.7, 35.6)
INR			
>=1.5X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
>=3X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)
>=5X ULN	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)

Source: DILI team consult review

The frequency represented here are based on peak levels.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Two potential Hy's law cases from eDISH plots were identified from the three parent studies EFC15110, EFC14678 and EFC14679. One subject ((b) (6)) was determined by the DILI team to be highly likely due to fitusiran. The other subject ((b) (6)) was later found to have an erroneous bilirubin value and, therefore, did not meet Hy's law but was still assessed as probable DILI. Both subject narratives are provided below. [Table 55](#) summarizes all cases that met potential Hy's law in the entire fitusiran clinical development program.

- Subject (b) (6) was a 19-year-old with HA, receiving 80 mg QM fitusiran, who had normal liver enzymes at baseline and developed DILI that was highly likely due to fitusiran. On Day 42 he had an adverse event of ALT increase (4 to 5× ULN) after the second

dose of fitusiran 80 mg. Liver enzymes improved with drug interruption. The subject was restarted on dosing and experienced concomitant rise in his liver tests. On Day 198, the subject met Hy's law criteria with a TB $>2\times$ ULN and ALT $7\times$ ULN. There were no concomitant medications. Fitusiran was discontinued and the subject's liver tests improved.

- Subject (b) (6) was an 18-year-old with HB, receiving 80 mg QM, who had normal liver enzymes at baseline and developed probable DILI. On Day 110 the subject experienced an adverse event of ALT increased that was $3\times$ ULN. Evaluation for alternative causes of ALT increase was negative and the subject was not taking any other concomitant medications. Fitusiran was interrupted with improvement in liver tests. Fitusiran was reinitiated on Day 281 and a small but not clinically significant increase in ALT was observed. The subject remained on fitusiran in the long-term extension study.

AT-DR Regimen

ALT $>3\times$ ULN was less common in the AT-DR period compared to the 80 mg QM dose regimen.

[Table 54](#) shows an analysis conducted by the DILI team of 267 individuals from the AT-DR period compared to 59 individuals from the control, on-demand arms of studies EFC14678 and EFC14679. The frequency of ALT $\geq 3\times$ ULN in the AT-DR period of Study LTE15174 was 3.4% (9/266 fitusiran AT-DR treated subjects) and higher than the 0% frequency in the 59 on-demand control subjects (note that there were approximately $4.5\times$ more AT-DR treated subjects than on-demand subjects). See [Table 54](#) below for liver abnormalities seen in the AT-DR period, compared to on-demand arms in the original parent studies. The onset for initial ALT elevations exceeding $3\times$ ULN had a median onset of 42.5 days after initial dosing (range 14 to 365 days). There were two potential Hy's law cases identified by eDISH plots (subject (b) (6) and (b) (6)) in the AT-DR period of Study LTE15174. Subject narratives and eDISH plots are described in Section [7.5.2.7](#) and a summary of events are described in [Table 55](#).

Table 54. Frequency of Hepatic Safety Laboratory Parameter Elevations at Any Postbaseline Visit by Treatment Arm, Safety Population, Studies LTE15174 (AT-DR) and EFC14768/14769 (On-Demand)

Laboratory Abnormality	Fitusiran N=267 n (%)	On-Demand N=59 n (%)	Risk Difference (%) (95% CI)
ALT			
≥1× ULN	143/266 (53.8)	20/58 (34.5)	19.3 (5.1, 31.9) *
≥3× ULN	9/266 (3.4)	0/58 (0)	3.4 (-2.9, 6.3)
≥5× ULN	4/266 (1.5)	0/58 (0)	1.5 (-4.7, 3.8)
≥10× ULN	3/266 (1.1)	0/58 (0)	1.1 (-5.1, 3.3)
≥20× ULN	0/266 (0)	0/58 (0)	0.0 (-6.2, 1.4)
AST			
≥1× ULN	87/266 (32.7)	11/58 (19.0)	13.7 (0.7, 23.9) *
≥3× ULN	7/266 (2.6)	1/58 (1.7)	0.9 (-6.6, 4.1)
≥5× ULN	3/266 (1.1)	0/58 (0)	1.1 (-5.1, 3.3)
≥10× ULN	1/266 (0.4)	0/58 (0)	0.4 (-5.9, 2.1)
≥20× ULN	0/266 (0)	0/58 (0)	0.0 (-6.2, 1.4)
ALP			
≥2× ULN	7/266 (2.6)	0/58 (0)	2.6 (-3.6, 5.3)
≥3× ULN	2/266 (0.8)	0/58 (0)	0.8 (-5.5, 2.7)
Total bilirubin			
≥2× ULN	12/266 (4.5)	0/58 (0)	4.5 (-1.8, 7.7)
≥5× ULN	2/266 (0.8)	0/58 (0)	0.8 (-5.5, 2.7)
≥8× ULN	0/266 (0)	0/58 (0)	0.0 (-6.2, 1.4)
Direct bilirubin			
≥2× ULN	19/266 (7.1)	0/58 (0)	7.1 (0.8, 10.9) *
≥5× ULN	2/266 (0.8)	0/58 (0)	0.8 (-5.5, 2.7)
GGT			
≥2× ULN	28/266 (10.5)	5/58 (8.6)	1.9 (-8.6, 8.6)
INR			
≥1.5× ULN	5/266 (1.9)	1/58 (1.7)	0.2 (-7.3, 3.1)
≥3× ULN	1/266 (0.4)	1/58 (1.7)	-1.3 (-8.8, 0.8)
≥5× ULN	0/266 (0)	0/58 (0)	0.0 (-6.2, 1.4)

Source: DILI Team Consult Review

The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For subjects with chronic liver disease, cutoff should be established using multiples of baseline (e.g., 2×, 3×, 5×).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; LTE, long-term extension; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Table 55. Summary of Putative Cases of Hy's Law, Studies EFC14768, EFC14769, EFC15110, and AT-DR Period of LTE15174

Subject/ Study	Diagnosis/ Age (Years)	Medical History	Fitusiran Dose at Hy's Law Event	DILI Event	Fitusiran Interruption or Discontinuation	DILI Reviewer Interpretation
(b) (6)	HA/19	None	80 mg QM	Study day: 42 ALT >4-5× ULN Study day: 198 ALT 7× ULN and TB >2× ULN	ALT improved with interruption, fitusiran ultimately discontinued	Highly likely for DILI, positive dechallenge after hold, then positive rechallenge on redosing. Subject recovered with drug discontinuation. No alternative etiology identified.
	HB/18	None.	80 mg QM	Study Day: 110 ALT >3× ULN	ALT improved with interruption	Probable DILI due to onset after initiation, improvement after dechallenge. Rechallenge tolerated and subject completed study. No alternative etiology identified.
	HAwI/50	Diabetes mellitus, hypertension, hepatitis C	50 mg Q2M	Study day: 1030 ALT >10× ULN Bilirubin >2× ULN In setting of obstructive gallstone pancreatitis	Fitusiran interrupted, ultimately continued	Unlikely DILI due to intervening obstructive biliary disease as cause of ALT and bilirubin increase; resolved with ERCP, and no recurrence with rechallenge.
	HA/44	None	50 mg Q2M	Study day: 589 ALT 2.9× ULN, Bilirubin 2× ULN	Fitusiran continued	Unlikely DILI due to resolution of enzymes, rechallenge without recurrence. Recent exposure to alcohol, cold medication, and protein powder likely basis of transient ALT rise

Source: Clinical reviewer and DILI consult review

Abbreviations: ALT, alanine aminotransferase; DILI, drug-induced liver injury; ECRP, endoscopic retrograde cholangiopancreatography; HA, hemophilia A; HAwI, hemophilia A with inhibitor; HB, hemophilia B; LTE, long-term extension; Q2M, every 2 months; QM, once monthly; TB, total bilirubin; ULN, upper limit of normal

Conclusion

The below conclusion is adapted from the DILI consult review.

Fitusiran use was associated with an increased incidence of liver test elevations in treated subjects compared to controls. The risk of hepatotoxicity is greater in the 80-mg original dosing compared to the AT-DR dosing. There was one Hy's law case (Study subject (b) (6) that was highly likely for DILI on the original 80-mg dose. This subject recovered with timely drug discontinuation, but the case indicates that the rise in liver enzymes associated with fitusiran can lead to liver injury with impairment of hepatic function, rather than being benign elevation in aminotransaminases.

On the AT-DR, the incidence of ALT elevations was lower. The dose subjects received was lower (50 mg or 20 mg QM or Q2M) compared to the 80 mg QM in the original studies, indicating the liver injury may be partly dose-dependent. While the incidence of ALT elevation was lower in the AT-DR, the risk of hepatotoxicity was not eliminated. Furthermore, there was no control group for the AT-DR dosing, and the majority of subjects on the AT-DR dose were those who had tolerated the 80-mg dose, such that interpretation of the experience on the AT-DR is confounded by selection bias. Those on the original dosing regimen who tolerated the drug and were able to stay on it would have likely been less likely to have an issue on an even lower dose seen in AT-DR.

Hepatotoxicity should be included as a Warning in the label to closely monitor patients for hepatic injury by monitoring liver blood tests monthly for 6 months and as clinically indicated thereafter, and to direct discontinuation with suspected DILI injury. While prompt discontinuation is not possible, given dosing is QM or Q2M, early recognition with monitoring liver enzymes should decrease the risk of serious liver injury. With labeling, including prescribing the AT-DR, hepatotoxicity risk can be mitigated. Enhanced pharmacovigilance for hepatotoxicity will be recommended.

8. Therapeutic Individualization

8.1. Intrinsic Factors

The Applicant performed PopPK analysis using pooled data from all 6 clinical studies to evaluate the effects of intrinsic factors on the plasma PK and PD of fitusiran. The evaluated intrinsic factors included age, body weight, hemophilia type (hemophilia A or B), inhibitor status (inhibitor or noninhibitor), and race. A summary of the PopPK analysis can be found in the Pharmacometrics Assessment in Section [14](#) below.

PopPK analysis showed that hemophilia type and inhibitor status do not impact fitusiran plasma PK. Body weight, race (Asian versus non-Asian), eGFR, albumin, and bilirubin were identified as statistically significant covariates in subjects with hemophilia, but the magnitude of the effect (<25% on fitusiran plasma PK) is not considered to be clinically relevant (fitusiran effect is driven by fitusiran concentrations in liver, rather than plasma).

Hepatic Impairment

There was no clinical experience of fitusiran in subjects with hepatic impairment, as the clinical development program excluded subjects with clinically significant liver disease, or with ALT and/or AST $>1.5\times$ upper limit of normal reference range (ULN) or total bilirubin $> \text{ULN}$. The Applicant did not conduct a dedicated clinical study to evaluate the impact of hepatic impairment on fitusiran PK/PD. The review team recommends “avoid use” of fitusiran in patients with all degrees of hepatic impairment (Child-Pugh Class A, B, and C). This recommendation is due to the known risk of hepatotoxicity with fitusiran, and patients with cirrhosis are at a greater risk of decompensation if they have a gallbladder event and require cholecystectomy.

8.2. Extrinsic Factors

The Applicant conducted a number of in vitro studies with human matrices to assess the potential for drug interactions mediated by drug metabolizing enzymes and transporters. These studies showed that fitusiran is unlikely to interact with drug-metabolizing enzymes and transporters and, therefore, the potential for drug interaction at clinically relevant concentrations is very low (see Section [14.1](#) for details). Thus, no clinical drug interactions studies were conducted by the Applicant.

8.3. Plans for Pediatric Drug Development

Fitusiran will be approved for pediatric patients 12 years and older, as this age group was included in the clinical trials used to demonstrate efficacy and safety of fitusiran. The Applicant is currently conducting Study EFC15467, an open-label dose finding study in subjects with hemophilia A and B aged 1 to <12 years. The results of this study may be used to inform pediatric labeling for younger patients in the future.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The following nonclinical information was used in support of the indicated labeling sections. Additional nonclinical details are in Section [13.1](#).

Animal Data

Animal reproductive and developmental toxicology studies have not been conducted with fitusiran, as the intended population is males with hemophilia, and the clinical development program was conducted exclusively in males. Hemophilia A and B are X-linked recessive inherited bleeding disorders primarily affecting males (99%), and the likelihood of women of childbearing potential receiving fitusiran is very low. There were no adverse effects of fitusiran on male fertility or reproductive performance parameters assessed in Sprague-Dawley rats in the 26-week repeated dose chronic toxicity study. It is not known whether fitusiran can adversely impact the development of an embryo/fetus when administered to a pregnant woman.

(b) (4)

(b) (4) Additional detailed information is available in Section [13](#).

Table 56. Nonclinical Data for Product Labeling

Labeling Section	Nonclinical Data
8.1 Pregnancy	There are no available data on QFITLIA use in pregnant women to evaluate for a drug-associated risk of major birth defects, and miscarriage or other adverse maternal or fetal outcomes. Reproduction studies in pregnant animals have not been conducted with fitusiran based on the target population being limited to male subjects. It is not known whether QFITLIA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. QFITLIA should be used during pregnancy only if the potential benefit for the mother outweighs the potential risks, including those to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes; In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.
8.2 Lactation	There are no data on the presence of fitusiran or its metabolite in human milk, the effects on the breastfed child, or the effects on milk production. It is not known whether or not QFITLIA is safe for use during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QFITLIA and any potential adverse effects on the breastfed infant from QFITLIA or from the underlying maternal condition.
8.3 Females and Males of Reproductive Potential	Contraception <i>Females</i> Use of QFITLIA in women using hormonal contraceptives may increase the risk of thrombotic events. Estrogen based hormonal contraceptives are an established risk factor for thrombosis in women with inherited AT deficiency. Advise patients using hormonal contraceptives to use an alternative nonhormonal contraception prior to starting treatment with and while receiving QFITLIA.

Labeling Section	Nonclinical Data
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	(b) (4) In a 2-year carcinogenicity study in Sprague Dawley rats, fitusiran was not carcinogenic up to the highest dose tested following subcutaneous administration at doses of 0.03, 0.1 or 0.3 mg/kg/week in males and 0.1, 0.3, or 1 mg/kg/week in females. All doses in males and females were below the maximum recommended human dose (MRHD) of 50 mg per month based on body surface area (BSA) comparisons. Fitusiran was not carcinogenic in Tg-rasH2 mice following subcutaneous administration for 26 weeks at doses of 0.05, 0.15, or 0.5 mg/kg/week in males and 0.025, 0.08, or 0.25 mg/kg/week in females. Fitusiran was not mutagenic or clastogenic in a battery of genetic toxicity studies (i.e., in vitro bacterial reverse mutation assay, in vitro chromosomal aberration assay in human peripheral blood lymphocytes; in vivo bone marrow micronucleus test in rats). (b) (4) In a chronic repeat dose toxicology study in Sprague-Dawley rats, fitusiran-treated males were cohabitated with fitusiran-naïve females following subcutaneous administration at doses of 0.25, 0.5, or 1 mg/kg/week for 16 weeks. No adverse effects on male fertility endpoints were observed. All doses used in males were below the MRHD based on BSA comparisons. (b) (4)

Source: Fitusiran Prescribing Information
Abbreviations: AT, antithrombin; AUC, area under the plasma concentration-time curve; BSA, body surface area; MRHD, maximum recommended human dose

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed the application with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective; see finalized Integrated Quality Reviews in DARRTS dated January 17th, 2025 and March 26, 2025. A shelf life of 36 months is granted for the 20 mg drug product in a 0.2 mL single-dose vial (100 mg/mL) when stored either at 2°C to 8°C (36°F to 46°F) or at 15°C to 30°C (59°F to 86°F). A shelf life of 24 months is granted for the 50 mg drug product in a 0.5 mL single-dose prefilled pen (100 mg/mL) when stored at 2° C to 8° C. The 50 mg drug product may be stored at 15°C to 30°C (59°F to 86°F) for a single period of up to 3 months at the end of storage within the shelf life of 24 months.

9.1. Device or Combination Product Considerations

Fitusiran is provided as a clear, colorless to pale yellow solution for injection either as a 50 mg/0.5 mL prefilled pen for single use for cutaneous administration or as a 20 mg/0.2 mL

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single-dose vial for injection. Each single-dose vial is designed to deliver 20 mg of fitusiran in 0.2 mL or 10 mg of fitusiran in 0.1 mL. Fitusiran is available in cartons containing one prefilled pen or vial.

The Center for Devices and Radiological Health was consulted for evaluation of this product and found the product approvable.

AT Assay

Maintaining AT activity 15-35% is essential for safe and effective use of fitusiran. The Center for Devices and Radiological Health evaluated the INNOVANCE Antithrombin assay that the Applicant is proposing for monitoring AT activity. This assay will be FDA-authorized as a Companion Diagnostic on the date of drug approval.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Clinical trials were conducted in compliance with Good Clinical Practice, as required by the International Council for Harmonisation (ICH) *E6 Guideline for Good Clinical Practice* ([November 2016](#)). The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation by the Applicant.

A clinical site inspection consult review was completed by Dr. Anthony Orenica in the Office of Scientific Investigations and is summarized in Section [22](#). The results of the clinical site inspections and Applicant inspection support the conclusion that the trials were conducted adequately, and that the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. A Financial Disclosure summary review is located in Section [25](#).

11. Advisory Committee Summary

The application did not raise efficacy or safety issues requiring external expert advice. Therefore, an advisory committee meeting was not convened to discuss this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

Fitusiran was granted orphan drug designation (ODD) on August 16, 2013, for the treatment of hemophilia A (ODD #13-4028) and August 12, 2013, for the treatment of hemophilia B (ODD #13-4029).

Fitusiran was granted fast track designation (FTD) on December 23, 2020, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B with or without factor VIII or IX inhibitors.

Fitusiran was granted breakthrough therapy designation (BTD) on December 6, 2023, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B with factor IX inhibitors.

On June 26, 2015, the Sponsor submitted a new IND under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (IND 125632). Prior to the IND submission, one type B meeting was held on April 23, 2015, to discuss the Sponsor's overall chemistry, manufacturing, and controls, nonclinical data, and preliminary results from the ongoing phase 1 clinical study.

On July 24, 2015, the Applicant was advised that the 30-day safety review of the application had concluded and that the study could proceed with their proposed clinical investigation for the treatment of patients with moderate to severe hemophilia A.

On May 10, 2016, an End-of-Phase 2 meeting was held to discuss the Sponsor's nonclinical development plan and proposals for the planned phase 3 trials.

On September 28, 2016, a carcinogenicity special protocol assessment request was submitted, and on November 2, 2016, an agreement communication was issued. On November 22, 2016, another carcinogenicity special protocol assessment request was submitted, and on December 21, 2016, an agreement communication was issued.

On May 9, 2017, a prephase 3 meeting was held to discuss the proposed development of the phase 3 program in support of a marketing application for fitusiran.

On September 8, 2017, the Sponsor was notified that all studies included in IND 125632 were being placed on full clinical hold based on the occurrence of a fatal case of cerebral venous sinus thrombosis reported for one of the subjects (27-year-old male with hemophilia A) from Bulgaria in Study ALN-AT3SC-002. On November 8, 2017, a Type A meeting was held to gain concurrence on the Sponsor's proposal for additional measures to mitigate the risk of thrombosis and to remove the clinical hold on studies with fitusiran following implementation of these measures and IRB approval of the amended clinical study protocols. The Sponsor proposed to amend the study to limit the subject population to hemophilia A and B subjects with inhibitors only. On December 14, 2017, the full clinical hold was removed after the Bleed Management Guide (BMG) was revised.

On January 26, 2018, preliminary comments were sent for a type C meeting request to discuss the combination product development of fitusiran, including development of the proposed (b) (4) autoinjector and clinical bridging plan, as well as the proposed prefilled syringe with safety

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QFITLIA (fitusiran)

device (PFS-S) human factors validation study approach and protocol. On January 30, 2018, the meeting scheduled for January 31, 2018, was canceled because the preliminary responses were clear, and no further discussion was needed.

On October 30, 2020, the Sponsor voluntarily paused dosing to implement the antithrombin-based dose regimen (AT-DR) dose regimen due to analysis of thrombotic events.

On December 10, 2020, the Sponsor resumed Studies EFC14768, EFC14769, EFC15110, LTE14762, and LTE15467, and introduced the AT-DR dose regimen.

On November 29, 2021, the proprietary name QFITLIA was conditionally approved for fitusiran after a June 19, 2021, denial of the proposed name (b) (4).

On June 7, 2022, Written Responses were issued to discuss the strategy intended to support registration of the prefilled pen for fitusiran.

On June 4, 2023, Type C Written Responses was issued to discuss the NDA format in advance of a pre-NDA meeting for fitusiran.

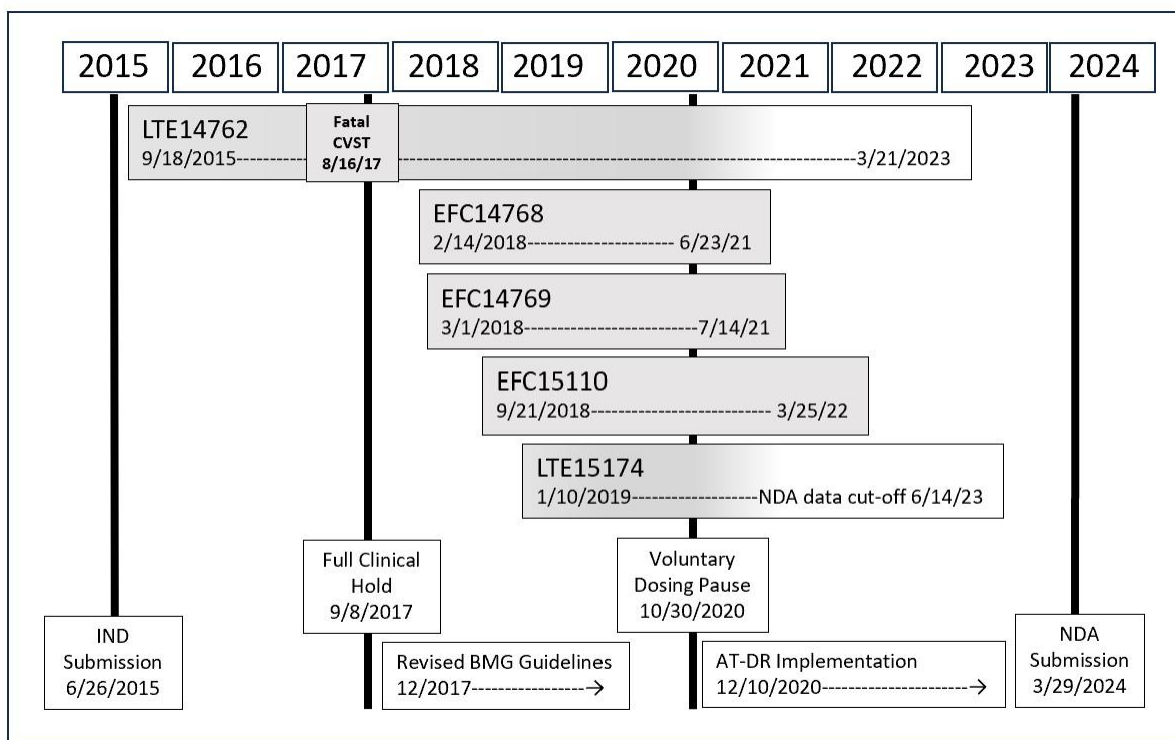
On September 18, 2023, a Type C guidance meeting was held to discuss the Sponsor's plans to submit an NDA for fitusiran. FDA converted the requested pre-NDA meeting to a Type C meeting because FDA did not have sufficient information to determine whether the Sponsor's proposed clinical data package was sufficient for filing. FDA provided feedback on the Sponsor's proposed approach to demonstrating efficacy and safety of fitusiran for the proposed indication.

On March 19, 2024, a pre-NDA meeting was held to discuss FDA's concurrence regarding the Sponsor's plan to submit an NDA in March/April 2024 and to discuss the clinical data package to support the filing and review of the planned NDA, the proposed indication in the label, and planned NDA regulatory milestones.

On March 28, 2024, the Applicant submitted an NDA for fitusiran to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia A or B, with or without factor VIII or IX inhibitors. The recommended dose regimen for fitusiran is a starting dose of 50 mg once every 2 months (Q2M), which may be escalated to 50 mg once monthly (QM) or de-escalated to 20 mg QM or Q2M based on antithrombin (AT) levels.

[Figure 20](#) shows a timeline of the fitusiran development program, and description of these studies is provided in [Table 5](#).

Figure 20. Clinical Development and Regulatory History of Fitusiran



Source: Clinical Reviewer

Fitusiran dosing is identified by the background color of the study. Gray represents non-AT-DR dosing, white represents AT-DR dosing and a gray-white gradient represents approximately when the non-AT-DR dosing regimen was switched to the AT-DR dosing regimen during the study.

Abbreviations: AT-DR, antithrombin-based dose regimen; BMG, Bleeding Management Guide; CVST, cerebral venous sinus thrombosis

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

A review of each individual study is provided in Section [13.2](#). Refer to Section [7.1](#) for a summary review of potential risks or safety concerns based on nonclinical data and Section [5.1](#) for nonclinical assessment of potential effectiveness.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Primary Pharmacology

Pharmacological activity of fitusiran was examined in hemophilia A and B animal models. Fitusiran was effective at enhancing coagulation and bleeding in these models, supporting the proposed prophylactic benefits of fitusiran. The summaries of these studies are shown in [Table 57](#).

Table 57. Tabulated In Vitro and In Vivo Pharmacology Studies With Fitusiran

Study Details	Findings																												
Primary target sequence conservation across various species (per summary materials contained in the Applicant's submission)	Fitusiran is pharmacologically active in mice, rats, cynomolgus monkeys, and dogs because the sequences of antithrombin mRNAs (derived from the <i>SERPINC1</i> genes) are highly conserved across species. The dog sequence contains a single nucleotide mismatch compared to others. Treatment with fitusiran demonstrated exaggerated pharmacodynamic effects of antithrombin suppression in all four healthy animal species																												
Study No: BIO-12020 Pharmacodynamic evaluation of fitusiran in wild-type mice following single subcutaneous injection (4 M/dose group) Dose: PBS, 0.3, 1, 3, 10 and 30 mg/kg	A single SC dose of fitusiran to wild-type mice led to dose-dependent AT suppression (as measured by decreases in mRNA, antigen levels, and activity) of approximately 50% at 1 mg/kg on Day 3 postdose, and maximum AT protein suppression up to 95% at doses up to 30 mg/kg by Day 10. Greater than 80% AT suppression was maintained for approximately 28 days postdose at ≥ 10 mg/kg. Figure 21. Reduction of AT After Single Dose SC Administration of Fitusiran in Wild-Type Mice <table><thead><tr><th>Dose (mg/kg)</th><th>mRNA (Relative to PBS)</th><th>Activity (Relative to PBS)</th><th>Antigen (Relative to PBS)</th></tr></thead><tbody><tr><td>PBS</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>0.3</td><td>~0.85</td><td>~0.82</td><td>~0.92</td></tr><tr><td>1</td><td>~0.60</td><td>~0.58</td><td>~0.45</td></tr><tr><td>3</td><td>~0.30</td><td>~0.25</td><td>~0.25</td></tr><tr><td>10</td><td>~0.10</td><td>~0.05</td><td>~0.08</td></tr><tr><td>30</td><td>~0.05</td><td>~0.05</td><td>~0.05</td></tr></tbody></table> Source: from Applicant's submission Abbreviations: AT, antithrombin; mRNA, messenger RNA; PBS, phosphate-buffered saline; SC, subcutaneous	Dose (mg/kg)	mRNA (Relative to PBS)	Activity (Relative to PBS)	Antigen (Relative to PBS)	PBS	1.0	1.0	1.0	0.3	~0.85	~0.82	~0.92	1	~0.60	~0.58	~0.45	3	~0.30	~0.25	~0.25	10	~0.10	~0.05	~0.08	30	~0.05	~0.05	~0.05
Dose (mg/kg)	mRNA (Relative to PBS)	Activity (Relative to PBS)	Antigen (Relative to PBS)																										
PBS	1.0	1.0	1.0																										
0.3	~0.85	~0.82	~0.92																										
1	~0.60	~0.58	~0.45																										
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10	~0.10	~0.05	~0.08																										
30	~0.05	~0.05	~0.05																										

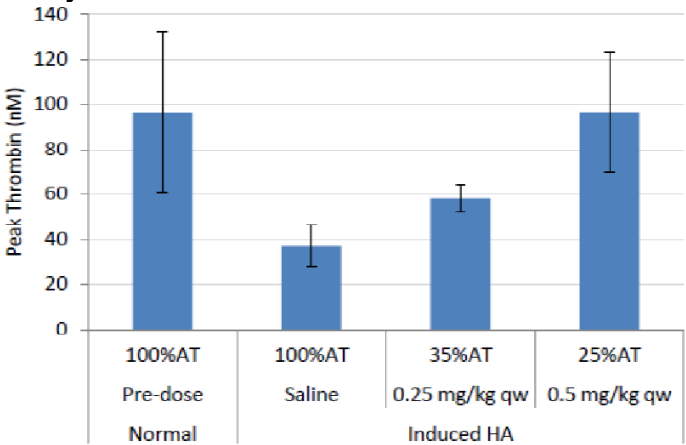
Study Details	Findings																									
Study No: BIO-12024 Pharmacodynamic Evaluation of Fitusiran in Hemophilia A Factor VIII ^{-/-} Knockout Mice Following Single Subcutaneous Injection (4 M +4 F/dose group) Dose: PBS, 1, 3, 10 and 30 mg/kg	A single SC injection of fitusiran at 3, 10 or 30 mg/kg given to hemophilia A mice resulted in a dose dependent suppression of AT (as measured by decreases in mRNA, antigen levels, and activity) of approximately 80-85% at 30 mg/kg on Day 3 postdose compared to the PBS control. The study demonstrated the anticipated pharmacodynamic effect of fitusiran in a hemophilia A disease mouse model.																									
Study No: BIO-13004 Evaluation of Thrombin Generation in Hemophilia B Factor IX Knock-Out Mice After Single Dose of Fitusiran (3 M/dose group) Dose: PBS, 1, 3, 10 and 30 mg/kg	A single SC dose of 1, 3, or 30 mg/kg fitusiran administered to male HB mice resulted in a dose-dependent suppression of plasma AT levels up to 90% compared to the PBS control on Day 10 postdose. Dose-related increases of up to 155% in endogenous thrombin generation were observed when compared to PBS controls. The study demonstrated that fitusiran is capable of prolonged AT suppression and promoting enhanced thrombin generation following a single SC dose in the hemophilia B mouse model.																									
Study No: BIO-13005 and BIO-13006 Effect of Fitusiran in Microvessel Laser Injury Model of Hemostasis in Mice with Hemophilia A/ (5-6 M/dose group) Dose: PBS, 1, 3, and 30 mg/kg 2 M/dose group Dose: PBS and 30 mg/kg	A microvessel laser injury model was used to compare stable hemostatic clot formation in treated versus untreated hemophilia A and hemophilia B mice. A single SC dose of 1 or 30 mg/kg fitusiran administered to Factor VIII^{-/-} knockout mice with hemophilia A (HA) on Day 0 led to a dose-dependent and rapid (180 seconds) accumulation of platelets and fibrin after acute injury induced on Day 10. The formation of thrombus was observed at all laser injury sites (55/55 sites) in all animals treated with fitusiran, which correlated with dose-related decreased liver AT mRNA levels (up to 93% at the 30 mg/kg dose). Table 58. Stable Thrombus Formation in HA Mice Treated With Fitusiran <table><tr><th>Group</th><th>Animals (N)</th><th>Injuries (N)</th><th>Stable Thrombus (N)</th><th>Percent AT mRNA in Liver</th></tr><tr><td>WT</td><td>5</td><td>25</td><td>25</td><td>100%</td></tr><tr><td>HA+PBS</td><td>5</td><td>25</td><td>0</td><td>100%</td></tr><tr><td>HA +1 mg/kg fitusiran</td><td>5</td><td>25</td><td>25</td><td>50%</td></tr><tr><td>HA +30 mg/kg fitusiran</td><td>5</td><td>30</td><td>30</td><td>7%</td></tr></table> Source: Reviewer generated table based on the Applicant's submission Abbreviations: AT, antithrombin; HA, hemophilia A; mRNA, messenger RNA; PBS, phosphate-buffered saline; WT, wild-type Stable thrombus formation was observed at all sites of injury (55/55 injury sites) in the fitusiran-treated laser injury HA mice animals) and all laser injury HB animals (6/6). These studies demonstrated the protective activity of a single fitusiran dose given prophylactically to clinically relevant animal models of hemophilia in reducing the bleeding time, which correlated with AT suppression.	Group	Animals (N)	Injuries (N)	Stable Thrombus (N)	Percent AT mRNA in Liver	WT	5	25	25	100%	HA+PBS	5	25	0	100%	HA +1 mg/kg fitusiran	5	25	25	50%	HA +30 mg/kg fitusiran	5	30	30	7%
Group	Animals (N)	Injuries (N)	Stable Thrombus (N)	Percent AT mRNA in Liver																						
WT	5	25	25	100%																						
HA+PBS	5	25	0	100%																						
HA +1 mg/kg fitusiran	5	25	25	50%																						
HA +30 mg/kg fitusiran	5	30	30	7%																						

Study Details	Findings																																														
Study No AT3-NCD14-008: A 26-Week Repeat Subcutaneous Injection Toxicity Study in the Transgenic Hemophilia A Mouse/ GLP: Yes Dose: 0, 10 and 30 mg/kg/week 35 M +35 F/dose group	Once-weekly repeated SC administration of fitusiran at 10 or 30 mg/kg/week to HA mice for 26-weeks led to durable AT suppression and reduced activated partial thromboplastin time (aPTT) at both doses. Table 59. Summary of Activated Partial Thromboplastin Time in Male and Female Mice With HA Compared to Control Mice With HA <table><tr><th rowspan="3">Study Day</th><th colspan="4">Dose (mg/kg/week)</th></tr><tr><th colspan="2">10</th><th colspan="2">30</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>Day 93</td><td>-60%***</td><td>-60%</td><td>-56%***</td><td>-53%</td></tr><tr><td>Day 184</td><td>-50%*</td><td>-53%</td><td>-51%*</td><td>-60%*</td></tr></table> Source: Reviewer generated table from Applicant's submission Significantly different from control group: * p≤0.05 *** p≤0.001 (Dunn or Dunnett) Abbreviations: F, female; HA, hemophilia A; M, male Table 60. Mean AT Protein (Relative to Saline Control) in Male and Female Mice With HA <table><tr><th rowspan="3">Study Day</th><th colspan="4">Dose (mg/kg/week)</th></tr><tr><th colspan="2">10</th><th colspan="2">30</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>Day 93</td><td>-92%</td><td>-89%</td><td>-92%</td><td>-89%</td></tr><tr><td>Day 184</td><td>-81%</td><td>-79%</td><td>-89%</td><td>-88%</td></tr></table> Source: Reviewer generated table from Applicant's submission Abbreviations: AT, antithrombin; F, female; HA, hemophilia A; M, male These studies with mouse models of hemophilia demonstrate the evidence of pharmacologic activity when treated with fitusiran following single or repeat dose SC administration.	Study Day	Dose (mg/kg/week)				10		30		M	F	M	F	Day 93	-60%***	-60%	-56%***	-53%	Day 184	-50%*	-53%	-51%*	-60%*	Study Day	Dose (mg/kg/week)				10		30		M	F	M	F	Day 93	-92%	-89%	-92%	-89%	Day 184	-81%	-79%	-89%	-88%
Study Day	Dose (mg/kg/week)																																														
	10		30																																												
	M	F	M	F																																											
Day 93	-60%***	-60%	-56%***	-53%																																											
Day 184	-50%*	-53%	-51%*	-60%*																																											
Study Day	Dose (mg/kg/week)																																														
	10		30																																												
	M	F	M	F																																											
Day 93	-92%	-89%	-92%	-89%																																											
Day 184	-81%	-79%	-89%	-88%																																											

Study Details	Findings																																													
Study No.: BIO-13023 Single or Repeat Dose Administration of Fitusiran in Cynomolgus Monkeys Dose: 0.1, 1, 3, 10, 30 mg/kg (single) 3M/dose group	Cynomolgus monkeys received single doses of 0.1, 1, 3, 10, 30 mg/kg or 3 weekly doses of 30 mg/kg fitusiran (AD-57213). Single SC administration showed a dose-dependent, durable lowering of AT protein levels at 1, 3, 10, and 30 mg/kg fitusiran. No pharmacologic activity was observed at 0.1 mg/kg with ~50% and >70% AT suppression for ~30 days at 1 mg/kg and 10 mg/kg, respectively. Single SC administration at 30 mg/kg showed minimal decreased mean fibrinogen (FIB) concentration and aPTT on Day 37 (-36% and -21% respectively compared to Day -8 pretreatment). These changes correlated with increased D-Dimer concentrations peaking between Days 15 and 37 (peaks between 166% and 830%, individual values compared to pretreatment), decreased AT concentrations ($\geq 90\%$), and increased thrombin generation levels. Figure 22. AT Suppression After Single Dose of Fitusiran in Monkeys <table><caption>Estimated data for Figure 22: Relative serum AT (Predose=1)</caption><thead><tr><th>Days post dose</th><th>30mg/kg</th><th>10mg/kg</th><th>3 mg/kg</th><th>1 mg/kg</th></tr></thead><tbody><tr><td>-14</td><td>1.0</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>-4</td><td>1.0</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>6</td><td>0.5</td><td>0.8</td><td>1.0</td><td>1.0</td></tr><tr><td>16</td><td>0.1</td><td>0.2</td><td>0.4</td><td>0.5</td></tr><tr><td>26</td><td>0.1</td><td>0.2</td><td>0.3</td><td>0.4</td></tr><tr><td>36</td><td>0.2</td><td>0.3</td><td>0.5</td><td>0.5</td></tr><tr><td>46</td><td>0.2</td><td>0.6</td><td>0.7</td><td>0.8</td></tr><tr><td>56</td><td>0.4</td><td>0.9</td><td>1.1</td><td>1.2</td></tr></tbody></table> Source: from Applicant's submission AT protein concentration from individual animals were normalized to their respective individual predose serum concentration at each time point. Each graphical data point represents the remaining AT for the group mean (N=3 animals, samples assayed in technical triplicates $\pm$ standard deviation). Abbreviation: AT, antithrombin Repeated once-weekly administration of fitusiran for 3 weeks at 30 mg/kg was not tolerated, resulting in mortality in 3/3 animals due to moderate to severe thrombosis, which was primarily seen in the pulmonary vasculature, and/or moderate or severe right atrial thrombosis in the heart. More than 95% suppression of AT levels was maintained during the dosing period, which correlated with decreased AT mRNA levels in the liver. Hematological changes of marked increased D-Dimer values (peaks up to 3,887% and 36,259%), decreased red blood cell parameters, platelet counts, and/or FIB concentrations, were considered related to the exaggerated pharmacological effects of fitusiran. This study demonstrated durable pharmacological activity of fitusiran in normal monkeys at doses up to 30 mg/kg (12 times the MRHD based on BSA comparisons) following single dose.	Days post dose	30mg/kg	10mg/kg	3 mg/kg	1 mg/kg	-14	1.0	1.0	1.0	1.0	-4	1.0	1.0	1.0	1.0	6	0.5	0.8	1.0	1.0	16	0.1	0.2	0.4	0.5	26	0.1	0.2	0.3	0.4	36	0.2	0.3	0.5	0.5	46	0.2	0.6	0.7	0.8	56	0.4	0.9	1.1	1.2
Days post dose	30mg/kg	10mg/kg	3 mg/kg	1 mg/kg																																										
-14	1.0	1.0	1.0	1.0																																										
-4	1.0	1.0	1.0	1.0																																										
6	0.5	0.8	1.0	1.0																																										
16	0.1	0.2	0.4	0.5																																										
26	0.1	0.2	0.3	0.4																																										
36	0.2	0.3	0.5	0.5																																										
46	0.2	0.6	0.7	0.8																																										
56	0.4	0.9	1.1	1.2																																										

Study Details	Findings
Study No: BIO-13025A Repeat Dose Pharmacology Study in Cynomolgus Monkeys by Subcutaneous Doses of Fitusiran with a 4-week Recovery 3M/dose group	The study evaluated different repeated dose regimens in monkeys (three males/group) of once weekly (QW) or once every other weekly (Q2W) dosing, as follows: g) QW at 0.5 for 8 doses or 0.125 mg/kg for 13 doses h) Q2W at 1 for 4 doses or 0.25 mg/kg for 13 doses i) QW at 1.5 mg/kg for 6 doses j) Q2W at 3 mg/kg for 3 doses Cumulative weekly doses of 0.5 mg/kg or 1 mg/kg resulted in approximately 90% suppression of AT activity, and a steady-state AT suppression level of ~50% and ~65% at lower doses of 0.125 mg/kg and 0.25 mg/kg, respectively. Animals dosed at a higher cumulative weekly dose of 1.5 mg/kg (1.5 mg/kg QW or 3 mg/kg Q2W) had >90% AT suppression. Reduction of AT was associated with increased thrombin generation, with a roughly 3-fold increase in peak thrombin over baseline levels at approximately 80% AT reduction. The data showed a strong correlation between the peak thrombin values and the levels of AT. Unscheduled deaths occurred in two monkeys at 3 mg/kg Q2W after 3 doses, which were caused by platelet depletion resulting from systemic clotting, which paradoxically led to severe systemic hemorrhage. These findings were consistent with the effects of the excessively suppressed AT activity of >90% and increase in D-Dimer values compared to predose. Monkeys given 1.5 mg/kg QW survived; clinical signs included swelling of the left leg and groin/inguinal areas, inguinal area redness, left leg lameness, decreased activity, small feces, paleness, and decreased food consumption. Changes in platelet counts were observed at 1.5 and 3 mg/kg, consistent with increased platelet consumption and a compensatory regenerative rebound response. This study demonstrated durable pharmacological activity with repeat dosing up to 1.5 mg/kg (2× the MRHD based on BSA comparisons).
Study No: BIO-14035 A 6-Month Pharmacodynamic Evaluation of Fitusiran Following Once Monthly Subcutaneous Injection of Cynomolgus Monkeys Doses: 0.5,1 and 2 mg/kg 3M/dose group	Animals administered 0.5 and 1 mg/kg were dosed on Days 1, 29, 57, 85, 113, and 141. Animals administered 2 mg/kg were dosed on Days 1, 29, and 57. Once-monthly doses of 0.5, 1 and 2 mg/kg fitusiran were well-tolerated and led to a dose-dependent reduction in AT activity of 30%, 40% and 70%, respectively. Repeated SC administration once monthly for 6 months led to further AT reduction of 40% at 0.5 mg/kg, 50% at 1 mg/kg and AT reduction of 80% at 2 mg/kg for 3 months. Reductions of AT increased thrombin generation and suggested a similar sustained suppression of AT, e.g., via a monthly clinical dosing regimen, may be effective in the intended patient population. Administration of fitusiran by once-monthly subcutaneous injection was well tolerated in monkeys at the highest dose of 2.0 mg/kg/month (3× the MRHD based on BSA comparisons).

Study Details	Findings																																																				
Study No: BIO-13026 Repeat Subcutaneous Injection Efficacy Study in the Cynomolgus Monkey Induced HA Model Doses: 0, 0.25 and 0.5 mg/kg 2 M +2 F/dose group	Six weeks of once-weekly fitusiran dosing suppressed AT activity by 65% and 75% at 0.25 and 0.5 mg/kg, respectively, in monkeys when compared to pretreatment. After the establishment of steady state AT suppression, severe hemophilia was transiently induced with a single intravenous dose (20,000 BU/kg) of an anti-Factor VIII antibody, which decreased FVIII activity and increased clotting times. Figure 23. AT Activity in Monkeys With Induced Hemophilia <table><caption>Estimated data for Figure 23: AT Activity in Monkeys With Induced Hemophilia</caption><thead><tr><th>Days post first dose</th><th>Saline (Relative AT Activity)</th><th>0.25 mg/kg (Relative AT Activity)</th><th>0.5 mg/kg (Relative AT Activity)</th></tr></thead><tbody><tr><td>-5</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>0</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>5</td><td>1.0</td><td>1.0</td><td>1.0</td></tr><tr><td>10</td><td>0.9</td><td>0.85</td><td>0.65</td></tr><tr><td>15</td><td>1.0</td><td>0.65</td><td>0.4</td></tr><tr><td>20</td><td>0.9</td><td>0.5</td><td>0.25</td></tr><tr><td>25</td><td>1.0</td><td>0.45</td><td>0.2</td></tr><tr><td>30</td><td>1.05</td><td>0.4</td><td>0.2</td></tr><tr><td>35</td><td>1.05</td><td>0.35</td><td>0.2</td></tr><tr><td>40</td><td>1.1</td><td>0.4</td><td>0.2</td></tr><tr><td>45</td><td>1.1</td><td>0.4</td><td>0.25</td></tr><tr><td>50</td><td>1.0</td><td>0.4</td><td>0.25</td></tr></tbody></table> Source: from Applicant's submission Protein levels from individual animals at each time point were normalized to their respective individual predose level (average of three predose values). Abbreviation: AT, antithrombin Analysis of plasma samples collected 4 hours post antibody dose demonstrated a fitusiran dose-dependent increase in thrombin generation, with the 0.5 mg/kg achieving peak thrombin values equivalent to those in the noninduced, prehemophilic state, suggestive of normalization of thrombin generation. Higher doses of fitusiran could not be administered as they were not anticipated to be tolerated.	Days post first dose	Saline (Relative AT Activity)	0.25 mg/kg (Relative AT Activity)	0.5 mg/kg (Relative AT Activity)	-5	1.0	1.0	1.0	0	1.0	1.0	1.0	5	1.0	1.0	1.0	10	0.9	0.85	0.65	15	1.0	0.65	0.4	20	0.9	0.5	0.25	25	1.0	0.45	0.2	30	1.05	0.4	0.2	35	1.05	0.35	0.2	40	1.1	0.4	0.2	45	1.1	0.4	0.25	50	1.0	0.4	0.25
Days post first dose	Saline (Relative AT Activity)	0.25 mg/kg (Relative AT Activity)	0.5 mg/kg (Relative AT Activity)																																																		
-5	1.0	1.0	1.0																																																		
0	1.0	1.0	1.0																																																		
5	1.0	1.0	1.0																																																		
10	0.9	0.85	0.65																																																		
15	1.0	0.65	0.4																																																		
20	0.9	0.5	0.25																																																		
25	1.0	0.45	0.2																																																		
30	1.05	0.4	0.2																																																		
35	1.05	0.35	0.2																																																		
40	1.1	0.4	0.2																																																		
45	1.1	0.4	0.25																																																		
50	1.0	0.4	0.25																																																		

Study Details	Findings
	Figure 24. Normalization of Thrombin Generation in Induced Hemophilic Monkeys  Source: from Applicant's submission Figure 24 shows baseline AT activities in normal monkeys (100% AT), and in induced hemophilia A monkeys given weekly doses of saline (100% AT), 0.25 mg/kg (reduced AT to 35% of normal), and 0.5 mg/kg (reduced AT to 25% of normal) fitusiran. Peak thrombin values were determined using a thrombin generation assay on plasma samples collected 4 hours post anti-FVIII antibody dose. Normal control peak thrombin values determined in predose, noninduced plasma samples. AT protein activity was measured following SC injection of fitusiran in cynomolgus monkeys (n=3 per group) at 0.25 mg/kg or 0.5 mg/kg/week for 6 doses. Each graphical data point represents the group average peak thrombin (assayed in technical triplicates) ±standard deviation. Normal control peak thrombin data represent the mean of 3 predose values for all 12 animals (n=36) ±standard deviation. Abbreviations: AT, antithrombin; FVIII, Factor VIII; HA, hemophilia A; SC, subcutaneous; qw, once weekly
Study No BIO-13028 Single Dose Pharmacology Study of Fitusiran in Male Beagle Dogs Doses: 0, 1, 3 and 10 mg/kg 3M/dose group	Single SC doses of fitusiran at 0, 1, 3 or 10 mg/kg were administered to male beagle dogs (n=3/per dose). Dose-dependent AT suppression was observed with a maximum of >90% at 10 mg/kg on Day 22 that was maintained up to Day 40 post dose in wild-type dogs. Platelet counts were decreased at 10 mg/kg (7 times the MRHD based on BSA comparisons). One high-dose dog was euthanized on Day 22 coincident with a 60% decrease in platelet count compared to the predose baseline. This animal presented with apparent blood in urine and feces, emesis, and pale mucous membranes, suggesting signs of consumptive coagulopathy.
Pharmacology of Fitusiran in Hemophilia A (HA; arising from factor VIII intron 22 inversion) Dogs After Single and Repeat Dosing/BIO- 13027 4 F with washout periods Doses: 1, 1.5, 3, or 10 mg/kg	Single or once-weekly repeated dosing of fitusiran at 1.5, 3 or 10 mg/kg for 4 weeks to hemophilia A female dogs resulted in a dose-dependent inhibition of AT activity up to 85% after the final dose. Analysis of plasma thrombin suggested treatment with fitusiran increased thrombin compared to predose values.

Source: Applicant's submission

Abbreviations: aPTT, activated partial thromboplastin time; AT, antithrombin; BSA, body surface area; F, female; FIB, fibrinogen; GLP, good laboratory practice; HA, hemophilia A; M, male; MRHD, maximum recommended human dose; mRNA, messenger RNA; PBS, phosphate-buffered saline; Q2W, every other week; QW, once weekly; SC, subcutaneous

13.2.2. Secondary Pharmacology

Table 61. Assessment for Off-Target Effects of Fitusiran

Study Details	Findings
Study No: BIO-13007 Study Title: In Vitro "Off-Target" Analysis of ALN-57213, the SERPINC1-Targeting siRNA Component of ALN-AT3	Addition of fitusiran to a human hepatoma cell line (HepG2) in vitro at concentrations ranging from 35.7fM to 10nM resulted in a dose-dependent inhibition of endogenous antithrombin (AT) mRNA levels with an IC₅₀ of 49.6pM. The 19-mer core sequence of A-116861, the antisense strand of fitusiran, was evaluated for off-target potential by conducting a comprehensive search against the human transcriptomes within the human NCBI Refseq dataset. There were a total of 9 mRNA sequences predicted as potentially possessing off-target potential. These 9 transcripts were then assessed experimentally. No IC₅₀ values were calculable for 8 of the 9 off-target transcripts at up to 10nM fitusiran. An IC₅₀ near 10nM was calculated for the remaining transcript, which suggests a 200-fold difference between fitusiran's "on-target" binding and the most sensitive "off-target" transcript.
Analysis of Human for polymorphism variations in support of Fitusiran/BIO15011	A search of the NCBI dbSNP identified a single SNP within the AT gene <i>SERPINC1</i> transcript NM_000488. The estimated frequency of rs144084678 SNP in the broader human population is <1/0.0002 that appears to fall outside the critical target recognition of fitusiran, suggesting negligible target impact. Bioinformatic analysis (Study no. BIO-13007) conducted to identify siRNAs targeting the human <i>SERPINC1</i> transcript in the NCBI Gene database showed no off-target suppression up to concentrations of 10nM, confirming the specificity of fitusiran to <i>SERPINC1</i> (IC₅₀ of 49.6pM or 0.0496nM).

Source: Applicant's submission

Abbreviations: AT, antithrombin; dbSNP, Single-Nucleotide Polymorphism database; IC₅₀, half maximal inhibitory concentration; mRNA, messenger RNA; NCBI, National Center for Biotechnology Information; siRNA, small interfering RNA; SNP, single-nucleotide polymorphism

13.2.3. Safety Pharmacology

Descriptions of safety pharmacology assessments are described below.

Table 62. Summary of Safety Pharmacology Studies and Findings

Study Details	Findings										
Study No: PAT0287 Study Title: Effect of Fitusiran on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	Fitusiran did not inhibit hERG at up to 10µM in a GLP-compliant study. The positive control induced statistically significant hERG inhibition confirming the sensitivity and validity of the test system to hERG inhibition. Table 63. hERG Channel Current Inhibition by Fitusiran <table><tr><th>Human Cardiac Ion Channel</th><th>Vehicle Control</th><th>Fitusiran (1µM)</th><th>Fitusiran (10µM)</th><th>Terfenadine (60nM)</th></tr><tr><td>hERG</td><td>1.6±0.8%</td><td>1.5±0.3%</td><td>3.4±0.2</td><td>84.6±3.9%</td></tr></table> Source: Reviewer Constructed Table The data suggest that the risk of fitusiran affecting cardiovascular function through hERG inhibition in humans is negligible at clinically relevant concentrations. There were no clinically significant ECG abnormalities reported in clinical trials with fitusiran.	Human Cardiac Ion Channel	Vehicle Control	Fitusiran (1µM)	Fitusiran (10µM)	Terfenadine (60nM)	hERG	1.6±0.8%	1.5±0.3%	3.4±0.2	84.6±3.9%
Human Cardiac Ion Channel	Vehicle Control	Fitusiran (1µM)	Fitusiran (10µM)	Terfenadine (60nM)							
hERG	1.6±0.8%	1.5±0.3%	3.4±0.2	84.6±3.9%							
Study No: ALN-AT3SC A Cardiovascular and Respiratory Safety Pharmacology Study in Cynomolgus Monkey Using Telemetry Doses: 0, 1, 3, or 10 mg/kg 0, 3 M/dose group	In a GLP safety pharmacology study that evaluated both cardiovascular and respiratory function, male telemetered cynomolgus monkeys were subcutaneously administered a single dose of vehicle (0.9% sodium chloride for injection), 1, 3, or 10 mg/kg of fitusiran. There were no fitusiran-related changes up to 72 hours postdose in systemic blood pressure parameters, heart rate, electrocardiographic intervals, or body temperature at SC doses up to 10 mg/kg (HED 194 mg/day or 4 times the MRHD based on BSA comparisons). There were no effects on respiratory rate or blood gas parameters at timepoints up to 24 hours postdose. Plasma exposures (C_{max} 3490 ng/mL, Day 1) at the 10 mg/kg dose in male monkeys, exceeded the C_{max} (84.1 ng/mL) at the MRHD (50 mg) by approximately 42-fold. Taken together, these results did not identify any cardiovascular or respiratory risk associated with fitusiran exposure.										

Source: Applicant's submission

Abbreviations: C_{max} , maximum plasma concentration; ECG, electrocardiogram; GLP, good laboratory practice; HED, human equivalent dose; M, male; MRHD, maximum recommended human dose; SC, subcutaneous

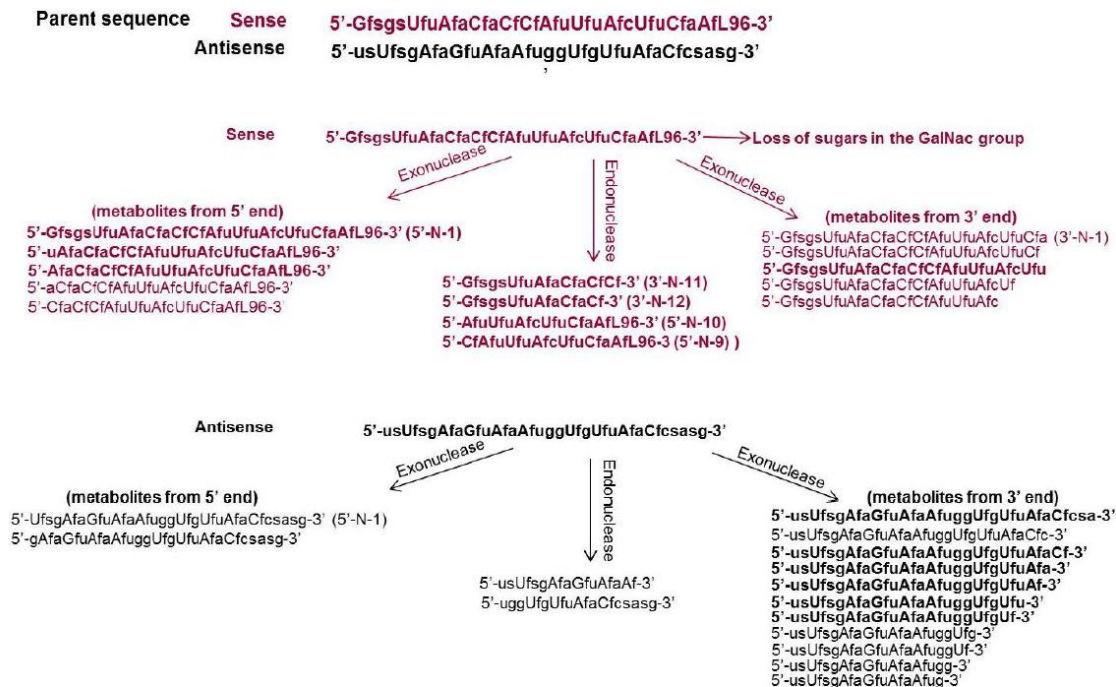
13.2.4. Absorption, Distribution, Metabolism, and Excretion/Pharmacokinetics Studies

Table 64. Summary of ADME/PK Studies

Type of Study	Major Findings
Absorption	
Study No:AT3-NCD13-006, AT3-NCD12-007 Species: Rats (9M +9F/dose group) Dose: 0.3, 1, 3 mg/kg Species: Monkeys (3M +3F/dose group) Dose: 0.1, 0.3, 1 mg/kg. Repeat once weekly SC dosing	Fitusiran was rapidly absorbed in both rats and monkeys. The plasma concentrations of fitusiran peaked at 0.5 hours in rats and 1-2 hours in monkeys and rapidly declined followed by distribution to tissues. The subcutaneous bioavailability was 33% in rats and 19% in monkeys at a dose of 3 mg/kg. The plasma terminal elimination was 1 hour in rats and 3.64 hours in monkeys.
Distribution	
Study No: LPR1221 Binding of Fitusiran to Mouse, Rat, Dog, Monkey, and Human Plasma Proteins Concentrations: 0.5, 1 5, 10, or 50 µg/mL.	The percent protein binding of fitusiran decreased with increasing drug concentrations. There was no apparent difference in plasma protein binding among the different species tested. The mean percentage of fitusiran plasma protein binding ranged from 93.4% to 47.3% for mouse plasma, 99.2% to 69.1% for rat plasma, 95.2% to 58.9% for dog plasma, 98.0% to 83.6% for monkey plasma, and 96.6% to 52.4% for human plasma over the concentration range of 0.5 to 50 µg/mL. Fitusiran has a very short half-life in plasma as it is rapidly cleared and distributed to tissues. Thus, the of plasma protein binding is unlikely to impact safety of the drug.
Study no: AT3-NCD13-002, AT3-NCD14-009 Species: Rats Dose 3 mg/kg Single dose IV or SC dosing Dose: 0.25, 0.5, or 1 mg/kg/week. Repeat SC doing for 26 weeks.	Fitusiran distributed mainly to liver (the primary target organ of pharmacology), followed by kidney and spleen. Following single IV dose administration of fitusiran at 3 mg/kg, the percentage of the dose in the liver and kidney were 29.1% and 2.39% after 1 hour, respectively. Following single SC administration of 3 mg/kg, the highest percentage of the dose was observed in the liver and kidney: 36.2% (after 4 h) and 1.03% (after 180 h), respectively. The liver tissue terminal elimination half-life ($t_{1/2}$) was approximately 55 hours and 60 hours by IV and SC, respectively. Exposures in other tissues (e.g., brain, thymus, thyroid, and heart) were negligible. After repeat SC administration to rats, limited accumulation was observed in liver; however, several-fold increase in fitusiran exposure was noted in the kidney.
Metabolism	
Study No: BA13003 In vitro: Matrix: serum and S9 liver fractions from mouse, rat, dog, monkey, and human. In vivo Matrix: Plasma and liver Species: Mice, dose 25 mg/kg Rat, dog and monkey, 3 mg/kg	Fitusiran is metabolized by sequential loss of the three sugar moieties and GalNAc linkers from the GalNAc group from the sense strand. The antisense strand of fitusiran is metabolized to AS(N-1)3' in in vivo plasma and liver samples consistent with in vitro liver samples. The sense strand was metabolized to form major metabolites, S(N-10)5' and S(N-11)3' by endonuclease metabolism and S(N-3)3' by exonuclease metabolism in in vitro liver S9 fractions while it was metabolized to S(N-1)5' as major metabolite in in vivo liver samples. Based on the metabolites identified in the in vitro and in vivo studies for the antisense and sense strands, the following metabolic pathways have been proposed by the Applicant for fitusiran.

Type of Study	Major Findings

Figure 25. Proposed Metabolic Scheme of Fitusiran



Source: Applicant's submission

Source: Applicant's submission
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; F, female; GalNAc, N-acetylgalactosamine; IV, intravenous; M, male; SC, subcutaneous

13.2.4.1. Excretion

Excretion of fitusiran was evaluated in a single subcutaneous (SC) dose of 3 mg/kg in rats (Study no. AT3-NCD13-002). Approximately 4.67% of the dose administered (3 mg/kg) was recovered in the urine over 8 weeks, with most of the dose (~3.75%) recovered in the first 24 hours postdose. Fecal excretion of fitusiran has not been evaluated. In subjects with hemophilia, mean recovery of intact fitusiran in 0 to 24 hours urine was 14.6% at the recommended dose of 50 mg.

13.2.5. Toxicology

13.2.5.1. General Toxicology

Repeat-dose toxicology studies were conducted in healthy rats for up to 26 weeks, healthy monkeys for up to 39 weeks, and in hemophilia mice for up to 26 weeks. Fitusiran is pharmacologically active in mice, rats, monkeys, and dogs because the antithrombin mRNA sequences are highly conserved across species. Animals were dosed once weekly by the SC route. Key findings from these studies are summarized below.

13.2.5.1.1. A 26-Week Subcutaneous Injection Toxicity, Toxicokinetic, and Fertility and Early Embryonic Development (to Implantation) Study in the Rat Followed By a 13-Week Recovery Period (AT3-NCD14-009)

Key Study Findings

Toxicity

- Once-weekly SC administration of fitusiran for 26 weeks was well tolerated by female rats up to 1 mg/kg/week and by male rats up to 0.5 mg/kg/week.
- Unscheduled deaths occurred in 5/5 males at 1 mg/kg/week. The cause of deaths was excessive clotting (leading to platelet reductions and, paradoxically, systemic hemorrhage), necrosis, and/or thrombosis in various organs and tissues, consistent with the exaggerated pharmacology of fitusiran.
- In surviving animals, microscopic findings were observed at the injection site secondary to the experimental procedure (needle trauma associated with the injection procedure), that resolved by the end of the recovery period.
- Dose-related decreases in antithrombin protein levels were observed during the dosing period consistent with the pharmacology of fitusiran.
- The no observed adverse effect level (NOAEL) was the high dose (HD) of 1 mg/kg/week in females, based on the absence of toxicity, and the MD of 0.5 mg/kg/week in males, based on severe clotting. Both doses represent doses below the maximum recommended human dose (MRHD) of 50 mg per month based on BSA comparisons.

Juvenile Toxicity

There were no drug-related adverse effects on growth or physical development in juvenile rats given up to 1 mg/kg/week fitusiran by once-weekly SC dosing up to Day 58 (equivalent to week 4 to 8 age). The NOAEL in juvenile rats was 1 mg/kg/week (below the MRHD of 50 mg per month based on BSA comparisons), based on no adverse findings up to 1 mg/kg/week.

Reproductive Performance

There were no fitusiran-related impacts on male fertility or early embryonic development up to 1 mg/kg/week. The NOAEL for male reproductive effects was 1 mg/kg/week (below the MRHD of 50 mg per month based on BSA comparisons).

Table 65. Study Information, ALN-AT3SC

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and Frequency of Dosing:	0, 0.25, 0.5, or 1 mg/kg/week (Lot No. P02214). The dose levels were selected based on mortality at 3 mg/kg, the NOAEL of 1 mg/kg in a 7-week study (AT3-NCD13-006), and the findings from a 4-week repeat dose range study in juvenile rats that showed fitusiran was tolerated at ≤1 mg/kg (AT3-NCD14-005).

Study Features and Methods	Details
Route of administration:	SC
Formulation/vehicle:	0.9% Sodium Chloride for Injection, USP
Species/strain:	Sprague-Dawley rats
Number/sex/group:	10/sex for necropsy on Day 58 (terminal euthanasia juvenile), Day 184 (terminal euthanasia main) and Day 275 (recovery euthanasia). Ten males/group from each Main and Recovery population (total of 20 males/group) were selected for the cohabitation phase of the study.
Age:	4 weeks age starting with juvenile animal toxicity study
Satellite groups/unique design:	Toxicokinetics: 3/sex in the control and 30/sex in the toxicokinetic study.
	Twenty (20) naïve untreated females/group were used for fertility and early embryonic development phase. Treated males were cohabitated with untreated female rats after 16 doses.
	Effects on juvenile toxicity were assessed after 8 weeks of dosing (9 total doses)
Deviations from study protocol:	None that affected the interpretation of the results

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; USP, United States Pharmacopeia

Table 66. Observations and Results, ALN-AT3SC

Parameters	Major Findings
Mortality	Unscheduled deaths occurred in male rats: 1 each in control, LD, and MD, and 10 in HD. The HD males 4029, 4033, 4034, 4113, and 4123 were found dead on Days 175, 49, 78, 110 and 110, respectively. Cause of deaths in 5/5 at high dose in the main study was considered related to the exaggerated pharmacology of fitusiran and consisted of systemic clotting (which led to platelet reductions and, paradoxically, to minimal to marked systemic hemorrhage). Clinical signs noted in one male (#4123) at HD included decreased activity, shallow breathing, and cold to the touch prior to death. Cause of deaths in control was not determined, and the deaths in LD and MD were not fully investigated. Five male rats that were found dead in the TK study were either not fully investigated (2/5) or associated with blood collection procedures. Macroscopic findings correlated with hemorrhage at 1 mg/kg/week including swelling, thickened or mass in subcutis, thymus, adipose tissue, enlargement of various lymph nodes, prostate, adrenal, tongue, abnormal consistency-firm prostate, seminal vesicle, dark focus in lungs, epididymis, various lymph nodes, stomach, subcutis, thymus, material accumulation-clot in skeletal muscle, pelvic body cavity, and pancreas. Microscopic findings in the unscheduled deaths included minimal to marked hemorrhage/thrombosis/necrosis in multiple organ and tissues.

Parameters	Major Findings				
Mortality					

Table 67. Fitusiran-Related Microscopic Findings in Unscheduled Deaths in Males From the Main Study at HD (1 mg/kg/week; n=3)

Microscopic Findings	Grade	Incidence	Microscopic Findings	Grade	Incidence
Adipose tissue			Liver		
Hemorrhage	Mild	1	Necrosis	Minimal	1
	Moderate	1		Mild	1
Body cavity, nasal			Thrombosis	Minimal	1
Hemorrhage	Moderate	2	Hemorrhage	Minimal	2
Body cavity, pelvic			Hyperplasia; biliary	Minimal	1
Hemorrhage	Moderate	1	Lung		
Brain			Hemorrhage	Mild	1
Hemorrhage	Minimal	1		Moderate	1
	Mild	1	Thrombosis	Minimal	1
Eye				Marked	1
Hemorrhage	Moderate	1	Lymph node		
GALT			Hemorrhage	Moderate	1
Necrosis; lymphoid	Mild	1		Marked	1
Gland, adrenal			Lymph node, axillary		
Hemorrhage	Minimal	3	Hemorrhage	Moderate	2
	Mild	1		Marked	1
Gland, prostate			Necrosis; lymphoid	Minimal	1
Hemorrhage	Marked	1		Mild	1
Gland, pituitary			Lymph node, deep cervical		
Hemorrhage	Mild	1	Hemorrhage	Mild	2
Gland, salivary				Moderate	2
Hemorrhage	Mild	1	Lymph node, mandibular		
Gland, seminal vesicle			Hemorrhage	Moderate	3
Hemorrhage	Marked		Necrosis	Minimal	1
Heart			Lymph node, superficial cervical		
Hemorrhage	Mild	2	Hemorrhage	Moderate	1
	Moderate	1	Lymph node, mesenteric		
Thrombosis	Marked	1	Hemorrhage	Moderate	1
Kidney				Marked	1
Cast	Minimal	1	Necrosis; lymphoid....	Minimal	1
	Mild	1	Vessel, blood axillary		
	Marked	1	Thrombosis	Marked	1
Hemorrhage	Minimal	1	Infiltration, mononuclear cell	Minimal	1
	Mild	1	Tubular intraepithelial eosinophilic droplet; multifocal	Mild	2
				Marked	1
Lymph node, superficial cervical			Subcutis		
Hemorrhage	Moderate	1	Hemorrhage	Moderate	1
	Marked	1		Marked	1
Necrosis; lymphoid....	Minimal	1	Thrombosis	Mild	1
Pancreas			Testis		
Hemorrhage	Marked	1	Degeneration/atrophy, tubular; unilateral, focal	Minimal	1
Edema			Thymus		
Skeletal muscle			Hemorrhage	Minimal	2
Hemorrhage	Mild	1		Mild	1
Site, injection			Necrosis, lymphoid	Moderate	1
Infiltration, mononuclear cell; perivascular	Minimal	1		Mild	1

Parameters	Major Findings					
	Microscopic Findings	Grade	Incidence	Microscopic Findings	Grade	Incidence
	Small intestine, duodenum			Tongue		
	Hemorrhage	Minimal	1	Hemorrhage	Minimal	1
	Spleen			Thrombosis	Moderate	1
	Pigmentation	Minimal	1	Trachea		
	Depletion; lymphoid	Minimal	1	Inflammation	Minimal	1
		Mild	1	Urinary bladder		
	Seminal vesicle			Hemorrhage	Marked	1
	Hemorrhage	Minimal	1			
		Mild	1			

Source: Reviewer generated table from Applicant's submission
Abbreviation: HD, high dose

Clinical signs	Unscheduled deaths: Decreased activity, shallow breathing and cold to the touch in male #4123.

Surviving animals: Skin redness/dryness/scab/discharge, thin cover, or staining of the fur were observed at all fitusiran-dosed groups and controls. Dose-related increased incidence of hypersensitivity was observed in fitusiran treated females compared to males.

Table 68. Incidence of Fitusiran-Related Hypersensitivity in Rats

Finding	Dose (mg/kg/week)							
	Males				Females			
	0	0.25	0.5	1.0	0	0.25	0.5	1.0
Hypersensitivity	28	48	52	37	31	66	117	229

Source: Reviewer generated table from Applicant's submission

Local irritation	There was transient slight erythema noted in individual male rats at all doses including control, and two females at MD dose throughout the dosing phase without dose relationship, and therefore not considered related to fitusiran administration.
Body weights	There were no notable changes in body weights and body weight gains in males or females related to fitusiran treatment up to 1 mg/kg/week.
Food consumption	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology, coagulation, clinical chemistry, urinalysis	No fitusiran-related effects were observed on Day 58 (juvenile), Day 184 (end of main study), or Day 275 (recovery). There were no apparent increases in the liver enzymes observed in surviving animals treated with fitusiran on Day 58, Day 184, and Day 275.

Parameters	Major Findings
Antithrombin protein	Dose-related decrease in antithrombin protein levels (measured with ELISA) were observed in males and females throughout the dosing period and returned to baseline following a 13-week recovery period (Day 275), consistent with the mechanism of action of fitusiran. The decreases were higher in males (-50% to -80%) than females (-10% to -50%) relative to respective control groups.

Table 69. Mean Percent AT Protein (Relative to Saline Control) in Male and Female Rats

Study Day	Dose (mg/kg/week)					
	0.25		0.5		1.0	
	M	F	M	F	M	F
Day 56	-47	-24	-68	-33	-79	-52
Day 84-86	-48	-23	-67	-28	-81	-48
Day 175	-35	-13	-69	-26	-82	-48
Day 275	+0.5	+11	-3	+2	-3	+8

Source: Reviewer generated table from Applicant's submission
Abbreviations: AT, antithrombin; F, female; M, male

Tissue TK Parameters (Liver, Kidney, and Spleen)	High concentrations of fitusiran were detected in liver and kidney tissues from the main study animals on Day 58 and Day 184, and in kidney tissues at Day 275. Liver concentrations were higher on Day 58, while kidney concentrations were higher on Day 184. Fitusiran levels were $\leq$ LLOQ for most spleen tissue samples. Accumulation ratio values in liver ranged from 1.06 to 1.27 for C_{max} and from 0.521 to 4.10 for AUC_{0-t} . Accumulation ratio values in kidney ranged from 16.0 to 18.9 for C_{max} and from 115 to 1619 for AUC_{0-t} . Despite high concentrations in these tissues, there were no fitusiran-related toxicities in the liver and kidney in surviving animals up to 1 mg/kg/week. However, evidence of hepatobiliary toxicity was observed in the 7-week GLP repeat dose study in rats at 3 mg/kg/week (AT3-NCD13-006) and hemophilia dogs at intolerable doses (BIO-013027).

Table 70. Mean Fitusiran Liver Tissue Concentrations (ng/g), – Main Study Groups on, Days 58, 184, and 275 of Necropsy

Fitusiran Dose (mg/kg)	Sex	Necropsy Day		
		58	184	275
		(n=10 Animals per Sex)	(n=3 Animals per Sex)	(n=3 Animals per Sex)
0	M	NC	NC	NC
	F	NC	NC	NC
0.25	M	1843±246	1262±160	NC
	F	1185±260	580± NA	NC
0.5	M	3377±351	2350±799	NC
	F	2183±357	1517±497	NC
1.0	M	6115±675	5106±871	NC
	F	4824±653	3351±244	NC

Source: Applicant's submission
Abbreviations: F, female; M, male; NA, not applicable; NC, not calculated for values below Lower Limit of Quantification

Parameters	Major Findings

Table 71. Mean Fitusiran Kidney Tissue Concentrations (ng/g), Main Study Groups, Days 58, 184, and 275 of Necropsy

Fitusiran Dose (mg/kg)	Sex	Necropsy Day		
		58 (n=10 Animals per Sex)	184 (n=3 Animals per Sex)	275 (n=3 Animals per Sex)
0	M	NC	NC	NC
	F	NC	NC	NC
0.25	M	1526±338	1983±503	132* ± NA
	F	1343±357	1188±129	96.2* ± NA
0.5	M	2017±249	3748±605	627±NA
	F	1949±241	1851±207	186* ± NA
1.0	M	2994±351	6954±1724	593±605
	F	3587±525	4697±407	504±158

Source: Applicant's submission

*Mean value of n=1

Abbreviations: F, female; M, male; NA, not applicable; NC, not calculated for values below Lower Limit of Quantification

Bone Marrow Evaluation	No differences were observed in the myeloid:erythroid (M:E) ratios in the 300-cell bone marrow differential count, and there were no observations in the maturation of the hematopoietic cell lineages on Day 58 or at the end of the main (Day 184) and recovery (Day 275) periods related to the administration of fitusiran.
Gross pathology	There were no gross findings related to fitusiran in the main or recovery studies.
Organ weights	There were no fitusiran-related organ weight changes in the main or recovery studies (Days 58, 184, and 275).
Histopathology	The most frequent microscopic changes at the scheduled necropsy observed at the subcutaneous injection site were minimal to mild perivascular mononuclear cell infiltration, minimal myofiber degeneration, minimal to moderate acute hemorrhage, and minimal subacute inflammation on Day 58 and Day 184. These changes were not considered to be related to fitusiran based on similar incidence and severity in control and treated animals. They were considered secondary to the experimental procedure (needle trauma associated with the injection procedure). Increased incidence of tubular testicular degeneration and marked oligospermia were observed in MD and HD on Day 58, and in HD on Day 184. At the end of the recovery period, Day 275, the testis findings appeared to resolve, however, marked oligospermia was present in one recovery animal at HD. Findings of increased incidence of minimal to mild rosette in the eye were noted at HD in males on Day 58, and in one male and one female on Day 184 and Day 275. In short-term single-dose studies (Study No. AT3-NCD12-001 and Study AT3-NCD12-002), findings of porphyrin staining (eyes, nose, paws) were observed at ≥3 mg/kg. No data on the distribution of fitusiran in the eyes were provided. Thus, the toxicological significance of this finding could be related to systemic toxicity due to exaggerated pharmacology of fitusiran. There were findings in pancreas at terminal necropsy in one male at HD with mild acinar cell atrophy, in one control male, and in one HD female at recovery necropsy. Additional findings at recovery necropsy included minimal hemorrhage, and mild inflammation in males at HD. Findings in pancreas were also observed in the 7-week repeat dose rat study with adverse atrophy/single cell necrosis and/or hemorrhage at 3 mg/kg/week (unscheduled deaths), and mild acinar atrophy in the

Parameters	Major Findings
	39-week monkey study in 1 male at HD (0.5 mg/kg/week). These findings are considered likely related to fitusiran treatment based on consistent findings in multiple studies/species.
Histopathology	

Table 72. Incidence of Fitusiran-Related Histopathology Findings in Rats

		Dose (mg/kg/week)							
Finding	Grade	Males				Females			
		0	0.25	0.5	1.0	0	0.25	0.5	1.0
Day 58									
Number of animals		10	10	10	10	10	10	10	10
Bone									
Hemorrhage	minimal	.	.	.	.	.	.		1
Bone, femur									
Hemorrhage	minimal	0	.	.	1	0	.	.	0
Infiltration,	minimal	0	.	.	1	0	.	.	0
mixed cell	mild	0	.	.	1	0	.	.	0
Eye									
Rosette, retina	minimal	1	.	.	2	0	.	.	0
	mild	0	.	.	1	0	.	.	0
Site, injection									
Hemorrhage	minimal	1	.	1	0	1	.	0	0
	mild	0	.	0	0	0	.	1	0
Inflammation;	moderate	0	.	0	0	1	.	0	0
subacute									
Infiltration,	minimal	7	.	0	4	2	.	1	2
mononuclear	mild	1	.	0	0	1	.	0	0
cell;									
perivascular									
Day 184									
Number of animals		20	20	20	16	20	20	20	20
Bone, femur									
Degeneration;	minimal	0	.	.	1	0	.	.	0
cartilage									
Epididymis									
Oligo/aspermia	marked	1	1	2	2	NA	NA	NA	NA
Eye									
Degeneration;	mild	0	.	.	0	0	1	.	0
lens									
Degeneration;	marked	0	.	.	0	0	1	.	0
retina									
Rosette; retina	minimal	2	.	.	1	1	0	.	1
	mild	0	.	.	1	0	0	.	0
Macrophage	minimal	0	.	.	0	0	1	.	0
aggregation									
Pancreas									
Atrophy; acinar	mild	0	.	.	1	0	.	.	0

Parameters	Major Findings									
	Finding	Grade	Dose (mg/kg/week)							
			Males				Females			
			0	0.25	0.5	1.0	0	0.25	0.5	1.0
Site, injection	Hemorrhage	minimal	1	1	1	2	2	3	1	0
		mild	1	1	1	2	1	0	0	0
		moderate	1	0	0	0	0	0	0	0
	Inflammation; subacute	minimal	3	0	0	2	1	2	0	3
	Infiltration, mononuclear cell; perivascular	minimal	12	2	1	8	11	2	0	10
	Degeneration; myofiber	minimal	7	1	0	1	3	3	1	3
	Granuloma	minimal	1	0	0	0	0	0	0	0
	Crust	mild	0	0	1	0	0	0	0	0
	Testis									
	Degeneration/atrophy, tubular	minimal	0	0	0	2	NA	NA	NA	NA
Day 275		mild	1	0	0	0	NA	NA	NA	NA
		marked	1	1	2	1	NA	NA	NA	NA
		severe	0	1	0	0	NA	NA	NA	NA
	Number of animals		9	10	10	9	10	10	10	10
	Epididymis	severe	1	.	.	0	NA	NA	NA	NA
	Oligo/aspermia	marked	0	.	.	1	NA	NA	NA	NA
	Eye									
	Rosette; retina	minimal	0	.	.	1	0	.	.	1
	Pancreas									
	Atrophy; acinar	mild	1	.	.	0	0	.	.	1
	Hemorrhage	minimal	0	.	.	1	0	.	.	0
	Inflammation	mild	0	.	.	1	0	.	.	0
	Spleen									
	Increased hematopoiesis	moderate	0	0	0	0	0	.	.	1
	Source: Reviewer generated table from Applicant's submission									
	.' Not examined									
	Abbreviation: NA, not applicable									

Toxicokinetic	Fitusiran concentrations were ≤LLOQ of 50.0 ng/mL for LD (0.25 mg/kg) on Days 1, 92, and 183, and for MD (0.5 mg/kg) on Day 1. Exposure to fitusiran (C_{max} and AUC) generally increased with the increase in dose level from 0.5 to 1 mg/kg on Days 92 and 183. Sex differences in exposure were generally less than 2-fold, except for the AUC in males, 3.7-fold, and 2.7-fold higher at 0.5 mg/kg/week on Day 92 and Day 183, respectively. Plasma concentrations reflect rapid clearance and uptake by tissues (primarily liver and kidney) indicating shorter AUC distribution phase.

Parameters	Major Findings

Table 73. Toxicokinetic Parameters for Fitusiran in Rat Plasma, Days 1, 92, and 183

Parameter	Day	Dose (mg/kg/week)					
		0.25		0.5		1	
		M	F	M	F	M	F
AUC _{0-t} (ng·h/mL)	1	NC	NC	NC	NC	77.8	117
C _{max} (ng/mL)	1	NC	NC	NC	NC	136	217
T _{max} (hr)	1	NC	NC	NC	NC	0.5	0.5
AUC _{0-t} (ng·h/mL)	92	NC	NC	505	135	347	647
C _{max} (ng/mL)	92	NC	NC	102	160	286	216
T _{max} (hr)	92	NC	NC	8.0	0.5	0.5	0.5
AUC _{0-t} (ng·h/mL)	183	NC	NC	65.0	27.0	236	117
C _{max} (ng/mL)	183	NC	NC	125	105	156	199
T _{max}	183	NC	NC	1.0	0.5	1.0	1.0

Source: Reviewer generated table from Applicant's submission
Due to the lack of a distinct plasma elimination phase, $t_{1/2}$, CL/F, and Vz/F could not be calculated.
Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; NC, not calculated due to values being below the lower limit of quantification; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution

Juvenile growth and physical development phase Day 58	There were no fitusiran-related effects on bone length (tibia and femur) or on growth of the animals (crown-rump measurement) in juvenile rats up to 1 mg/kg/week. Sexual maturation (vaginal opening or balano-preputial skinfold separation) was normal for the treated males and females.
Spermatogenic cycle assessment	Following weekly SC administration of fitusiran for a total of 16 weeks in juvenile male Sprague Dawley rats (initiation at approximately 4 weeks), there were no treatment-related effects on sperm morphology and motility, and histopathological evaluation of testes showed no changes in fitusiran-treated animals compared to control on Days 58 (juvenile), 184 (terminal), and 285 (recovery).
Male reproductive performance	There were no adverse effects of fitusiran on male reproductive performance.

Table 74. Male Reproductive Performance

Dose (mg/kg/week)	0	0.25	0.5	1.0
Mean no. days prior to mating	2.2	2.6	1.9	2.2
No. of males that mated	20	20	19	18
No. of males producing a pregnancy	20	20	19	17

Source: Applicant's submission

Parameters	Major Findings
Estrous cycles/parental performance	There were no effects on estrous cycle and prenatal performance in rats.

Table 75. Summary of Estrous Cycles and Parental Performance in Rats

Dose mg/kg/week	Days in Estrus*	# of Cycles Seen**	Number Females Pregnant	Mating Index (%)	Fertility Index (%)	Conception Rate (%)
0	4.5	3.8	20	100	100	100
0.25	4.5	3.8	20	100	100	100
0.5	4.4	3.5	19	95	95	100
1.0	4.6	3.9	17	100	94.4	94.4

Source: Applicant's submission

* Includes only the days in estrous

** Includes actual cycles seen in estrous and the "unseen" cycles determined

Ovarian and uterine parameters – naive females

Table 76. Summary of Mean Number Ovarian and Uterine Findings in Rats

Finding	Dose (mg/kg/week)			
	0	0.25	0.5	1.0
Corpora lutea	16.5	16.3	15.9	16.7
Implantations	15	15.4	15.1	15.5
Preimplantation loss	10.2	5.48	4.46	7.78
Live conceptuses	14.2	14.6	14.3	14.7
Resorptions	0.8	0.8	0.8	0.8
Postimplantation loss	5.47	4.92	6.14	5.38

Source: Applicant's submission

Source: Applicant's submission

Abbreviations: AT, antithrombin; AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; ELISA, enzyme-linked immunosorbent assay; F, female; GLP, good laboratory practice; HD, high dose; LD, low dose; LLOQ, lower limit of quantification; M, male; M:E, myeloid:erythroid; MD, mid dose; TK, toxicokinetics

13.2.5.1.2. A 39-Week Subcutaneous Injection Toxicity and Toxicokinetic Study in the Cynomolgus Monkey Followed by a 13-Week Recovery Period (AT3-NCD14-007)

Key Study Findings

- Once-weekly SC administration of fitusiran for 39 weeks was well tolerated by male and female monkeys up to the highest dose of 0.5 mg/kg/week.
- Fitusiran-related toxicities included elevated D-dimer values at all doses during the dosing period that correlated with decreases in AT levels and tended to recover at the end of recovery period.
- The NOAEL was determined to be the HD, 0.5 mg/kg/week, for both males and females, based on absence of adverse fitusiran-related effects, which is lower than the MRHD of 50 mg per month based on BSA comparisons.

Table 77. Study Information, AT3-NCD14-007

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 0.15, 0.3, or 0.5 mg/kg/week (Lot No P02214) The dose levels were selected based on mortality at 1 mg/kg, and the NOAEL of 0.3 mg/kg/week in a 7-week study (AT3-NCD12-007)
Route of administration	SC
Formulation/vehicle	0.9% Sodium Chloride for Injection, USP.
Species/strain	Cynomolgus monkey
Number/sex/group	6
Age	3 to 3.5 years old
Satellite groups/unique design	None
Deviation from study protocol	None that affected the interpretation of the results

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; USP, United States Pharmacopeia

Table 78. Observations and Results, AT3-NCD14-007

Parameters	Major Findings
Mortality	None
Clinical signs	Skin redness/dryness/scab, thin cover or staining of the fur, and occasional occurrences of liquid/soft feces were noted in all dose groups, including control, and considered incidental and unrelated to fitusiran due to their low incidence and/or lack of dose relationship.
Body weights	Unremarkable
Local irritation assessment	Unremarkable
Neurological examination	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology, clinical chemistry, urinalysis	Unremarkable on Days 92, 183, and 274, and following 13-week recovery period.
D-dimer	Nonadverse dose-related increased D-dimer levels were observed in males at ≥ 0.3 mg/kg/week and females at ≥ 0.15 mg/kg/week on Day 92, and at all dose levels with no dose response on Day 183. The D-dimer levels stayed elevated in females on Day 274 and tended to recover following the recovery period. Elevated D-dimer concentrations were also observed in an exploratory single-dose pharmacodynamic study (Study No. BIO-13023), and 7-week repeat-dose toxicity study (Study no. AT3-NCD12-007) in monkeys that were adverse (>500 -fold). These findings were correlated with decreased platelet counts, decreased FIB values, and thrombosis consistent with the intended procoagulant effects of target antithrombin protein suppression. Increases in fibrin D-Dimer have been reported in clinical studies with fitusiran.

Parameters	Major Findings

Table 79. Mean Percent D-Dimer (µg/mL) in Fitusiran-Treated Animals Compared to Control Animals

Study Day	Dose (mg/kg/week)					
	0.15		0.3		0.5	
	M	F	M	F	M	F
Day 92	-2	+15	+46	+37	+73*	+80
Day 183	+46	+168	+8	+27	+31	+151
Day 274	+2	+77	-13	+56	+45	+110
Day 365	-14	-20	-19	-3	+40	-63

Source: Reviewer generated table from Applicant's submission
Abbreviation: F, female; M, male

Antithrombin protein	Dose-related decreases in antithrombin levels were observed in males and females throughout the dosing period and returned to baseline following a 13-week recovery period (Day 365), consistent with mechanism of action of fitusiran. The decreases were larger in males (-30% to -70%) than females (-10% to -60%) relative to respective control groups.

Table 80. Mean Percent AT Protein (Relative to Saline Control) in Male and Female Monkeys

Study Day	Dose (mg/kg/week)					
	0.15		0.3		0.5	
	M	F	M	F	M	F
Day 92	-34	-10	-46	-34	-59	-56
Day 183	-45	-29	-58	-45	-71	-61
Day 274	-57	-27	-63	-53	-74	-64
Day 365	-12	+2	-8	+8	-16	+38

Source: Reviewer generated table from Applicant's submission
Abbreviations: AT, antithrombin; F, female; M, male

Antithrombin activity	Dose-related decreases in antithrombin activity (as evaluated by ELISA) were observed in males and females throughout the dosing period and returned to baseline following the 13-week recovery period (Day 365), consistent with the mechanism of action of fitusiran. The decreases were larger in males (-40% to -70%) than females (-20% to -60%) relative to respective control groups.

Table 81. Mean Percent AT Activity (Relative to Saline Control) in Male and Female Monkeys

Study Day	Dose (mg/kg/week)					
	0.15		0.3		0.5	
	M	F	M	F	M	F
Day 92	-43	-23	-56	-52	-66	-60
Day 183	-38	-22	-55	-46	-63	-56
Day 274	-48	-27	-54	-53	-71	-59
Day 365	+2	+8	+8	+6	+1	+1

Source: Reviewer generated table from Applicant's submission
Abbreviations: AT, antithrombin; F, female; M, male

Parameters	Major Findings																																																																																																																																																														
Gross pathology	Table 82. Incidence of Fitusiran-Related Macroscopic Findings in Monkeys at Terminal and Recovery Necropsy <table><tr><th rowspan="3">Finding</th><th colspan="8">Dose (mg/kg/week)</th></tr><tr><th colspan="4">Males</th><th colspan="4">Females</th></tr><tr><th>0</th><th>0.15</th><th>0.3</th><th>0.5</th><th>0</th><th>0.15</th><th>0.3</th><th>0.5</th></tr><tr><td>Number of animals</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td></tr><tr><td colspan="9">Day 275</td></tr><tr><td>Epididymis Small</td><td>1</td><td>1</td><td>1</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Gland, prostate Small</td><td>1</td><td>1</td><td>1</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Gland, seminal vesicle Small</td><td>1</td><td>1</td><td>1</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Site, injection Focus; dark</td><td>1</td><td>1</td><td>0</td><td>0</td><td>1</td><td>1</td><td>2</td><td>2</td></tr><tr><td>Testis Small</td><td>1</td><td>1</td><td>2</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td colspan="9">Day 365</td></tr><tr><td>Epididymis Small</td><td>0</td><td>0</td><td>1</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Nodule</td><td>0</td><td>1</td><td>0</td><td>0</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Gland, prostate Small</td><td>0</td><td>1</td><td>1</td><td>2</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Gland, seminal vesicle Small</td><td>0</td><td>1</td><td>1</td><td>2</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Site, injection Focus; dark</td><td>1</td><td>0</td><td>1</td><td>1</td><td>0</td><td>1</td><td>1</td><td>0</td></tr><tr><td>Testis Small</td><td>0</td><td>0</td><td>1</td><td>1</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr></table> Source: Reviewer generated table from Applicant's submission Abbreviation: NA, not applicable								Finding	Dose (mg/kg/week)								Males				Females				0	0.15	0.3	0.5	0	0.15	0.3	0.5	Number of animals	3	3	3	3	3	3	3	3	Day 275									Epididymis Small	1	1	1	1	NA	NA	NA	NA	Gland, prostate Small	1	1	1	1	NA	NA	NA	NA	Gland, seminal vesicle Small	1	1	1	1	NA	NA	NA	NA	Site, injection Focus; dark	1	1	0	0	1	1	2	2	Testis Small	1	1	2	1	NA	NA	NA	NA	Day 365									Epididymis Small	0	0	1	1	NA	NA	NA	NA	Nodule	0	1	0	0	NA	NA	NA	NA	Gland, prostate Small	0	1	1	2	NA	NA	NA	NA	Gland, seminal vesicle Small	0	1	1	2	NA	NA	NA	NA	Site, injection Focus; dark	1	0	1	1	0	1	1	0	Testis Small	0	0	1	1	NA	NA	NA	NA
Finding	Dose (mg/kg/week)																																																																																																																																																														
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	0	0.15	0.3	0.5	0	0.15	0.3	0.5																																																																																																																																																							
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Day 275																																																																																																																																																															
Epididymis Small	1	1	1	1	NA	NA	NA	NA																																																																																																																																																							
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Site, injection Focus; dark	1	1	0	0	1	1	2	2																																																																																																																																																							
Testis Small	1	1	2	1	NA	NA	NA	NA																																																																																																																																																							
Day 365																																																																																																																																																															
Epididymis Small	0	0	1	1	NA	NA	NA	NA																																																																																																																																																							
Nodule	0	1	0	0	NA	NA	NA	NA																																																																																																																																																							
Gland, prostate Small	0	1	1	2	NA	NA	NA	NA																																																																																																																																																							
Gland, seminal vesicle Small	0	1	1	2	NA	NA	NA	NA																																																																																																																																																							
Site, injection Focus; dark	1	0	1	1	0	1	1	0																																																																																																																																																							
Testis Small	0	0	1	1	NA	NA	NA	NA																																																																																																																																																							
Organ weights	There were no fitusiran-related organ weight changes noted at the termination of the main or recovery study animals.																																																																																																																																																														

Parameters	Major Findings
Histopathology	Injection site findings (acute hemorrhage and/or presence of inflammatory cells) were similar in control and treated animals from all dose groups and were considered secondary to the experimental procedures (i.e., subcutaneous injection). Effects on male reproductive organs were observed that included mild to severe immaturity in epididymis, prostate gland, and seminal vesicle gland at ≥ 0.15 mg/kg/week and marked to severe immaturity in testis in control and fitusiran-treated animals consistent with small size of the male reproductive organs at the end of recovery necropsy. However, the organ weights relative to body weight either show no change or increase. These findings are likely related to differences in the sexual maturity of the monkeys, therefore were considered unrelated to administration of fitusiran. Additional nonadverse findings included effects on pancreas including minimal angiectasis of islet of Langerhans in a male (LD) and a female (MD) on Day 184 and mild acinar atrophy with ductular hyperplasia in male at HD on day 365 (recovery). Acinar atrophy was also noted in rats in the 26-week chronic study and considered adverse (atrophy/single cell necrosis, hemorrhage at $5\times$ MRHD) in the 7-week rat study. Although this finding is seen infrequently as a background finding in cynomolgus monkeys, relationship to fitusiran cannot be excluded in light of similar findings in rats.

Table 83. Incidence of Fitusiran-Related Histopathology Findings in Monkeys at Terminal and Recovery Necropsy

Finding	Severity	Dose (mg/kg/week)							
		Males				Females			
		0	0.15	0.3	0.5	0	0.15	0.3	0.5
Day 275 (terminal)									
Number of animals		3	3	3	3	3	3	3	3
GALT									
Hemorrhage	minimal	0	0	1	0	0	0	0	0
Heart									
Inflammation, vascular/perivascular	minimal	0	0	0	1	0	0	0	0
Pancreas									
Angiectasis; islet of Langerhans	minimal	0	1	0	0	0	0	1	0
Testis									
Degeneration; seminiferous tubule	mild	0	0	1	0	NA	NA	NA	NA
Thymus									
Hemorrhage	minimal	0	1	1	0	0	1	0	1
Day 365 (recovery)									
Number of animals		3	3	3	3	3	3	3	3
Epididymis									
Immaturity	mild	0	1	0	1	NA	NA	NA	NA
	severe	0	0	1	1	NA	NA	NA	NA
Necrosis	mild	0	1	0	0	NA	NA	NA	NA

Parameters		Major Findings							
Finding	Severity	Dose (mg/kg/week)							
		Males				Females			
		0	0.15	0.3	0.5	0	0.15	0.3	0.5
Gland prostate									
Immataturity	minimal	0	1	0	0	NA	NA	NA	NA
	mild	1	1	0	0	NA	NA	NA	NA
	moderate	0	0	0	1	NA	NA	NA	NA
	marked	0	0	0	1	NA	NA	NA	NA
	severe	0	0	1	0	NA	NA	NA	NA
Gland, seminal vesicle	mild	1	1	0	0	NA	NA	NA	NA
Immataturity	minimal	0	1	0	0	NA	NA	NA	NA
	mild	0	1	0	0	NA	NA	NA	NA
	moderate	0	0	0	1	NA	NA	NA	NA
	marked	0	0	0	1	NA	NA	NA	NA
	severe	0	0	1	0	NA	NA	NA	NA
Pancreas									
Atrophy; acinar	mild	0	0	0	1	0	0	0	0
Testis									
Immataturity	marked	1	0	0	1	NA	NA	NA	NA
	severe	1	1	2	1	NA	NA	NA	NA

Source: Reviewer generated table from Applicant's submission

Abbreviations: GALT, gut-associated lymphoid tissue; NA, not applicable

Toxicokinetic	Fitusiran concentrations were $\leq$ LLOQ of 50.0 ng/mL for LD (0.15 mg/kg) and MD (0.3 mg/kg) on Days 1, and 274.

Table 84. Toxicokinetic Parameters for Fitusiran in Monkey Plasma Following Q1W Administration for 39 Weeks

		Dose (mg/kg/week)						
Parameter	Day	0.15		0.3		0.5		Overall
		M	F	M	F	M	F	
T _{max} (hr)	1	NC	NC	NC	NC	1.2	1.2	1.2
C _{max} (ng/mL)	1	NC	NC	NC	NC	80.4	78.1	79.3
AUC _{0-t} (ng·h/mL)	1	NC	NC	NC	NC	117	105	111
T _{max}	274	NC	NC	NC	NC	1.5	1.2	1.3
C _{max} (ng/mL)	274	NC	NC	NC	NC	66.2	68.4	67.8
AUC _{0-t} (ng·h/mL)	274	NC	NC	NC	NC	139	87.1	102

Source: Reviewer generated table from Applicant's submission

Due to the lack of a distinct plasma elimination phase, t_{1/2}, CL/F, and Vz/F could not be calculated.

Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; NC, not calculated due to values being below the lower limit of quantification; Q1W, once weekly; t_{1/2}, half-life; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution

Source: Applicant's submission

Abbreviations: ELISA, enzyme-linked immunosorbent assay; LD, low dose; LLOQ, lower limit of quantification; MD, mid dose; MRHD, maximum recommended human dose; Q1W, once weekly

Good laboratory practice (GLP)-compliant 7-week repeat dose toxicology studies in rats and monkeys were reviewed for fitusiran-related findings that were not observed in the chronic studies in rats and monkeys.

13.2.5.1.3. A 7-Week Repeat Subcutaneous Injection Toxicity and Toxicokinetic Study in the Albino Rat With a 2-Month Recovery Period (AT3-NCD13-006)

Key Findings

- Unscheduled deaths occurred in seven male and six female rats at the HD of 3 mg/kg/week, which were caused by the exaggerated pharmacology of fitusiran (thrombosis in various organs and tissues), which led to platelet reductions and paradoxical systemic hemorrhage.
- Hepatobiliary toxicity was observed in some animals at the high dose, consisting of elevated liver enzymes and adverse histopathology findings that were associated with extensive and prolonged pharmacodynamic activity of fitusiran that led to systemic thrombosis and/or hemorrhage at >80% reduction in AT protein levels.
- A NOAEL of 1 mg/kg/week was considered based on deaths and adverse toxicities at 3 mg/kg/week (less than the MRHD of 50 mg per month based on BSA comparisons).

Table 85. Study Information, AT3-NCD13-006

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 0.3, 1, or 3 mg/kg once weekly
Route of administration	SC
Formulation/vehicle	0.9% Sodium Chloride for Injection, USP
Species/strain	Sprague-Dawley rats
Number/sex/group	15
Age	8 weeks old
Toxicokinetics	3/sex in control and 9/sex in treatment

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; SC, subcutaneous; USP, United States Pharmacopeia

Unscheduled Euthanasia

Seven males and six females given fitusiran at 3 mg/kg were found dead or euthanized on days ranging from 7 to 11 and 16 to 34, respectively. Because of the earlier mortalities and adverse clinical signs in the males at 3 mg/kg/week, this entire group was terminated and necropsied on Days 15 and 16, along with 3 control-group males. Histopathology evaluations were performed only on the unscheduled animals from the main study and not on the animals from the toxicokinetic (TK) study.

- Clinical signs prior to death included decreased activity, cold to touch; swollen firm areas (e.g., hind paws, cranium, ventral cervical), swollen soft areas (e.g., ventral cervical, cranium, tongue, forelimbs, hind paws), red/black fur staining (e.g., around eyes, forelimbs, head, muzzle, urogenital); labored/shallow breathing; thin fur; and dry skin on tail.
- Clinical pathology parameters in 1 male and 2 female rats compared to control on Day 15/16 showed decreases in platelets (-68%), reticulocytes (-40%), and lymphocytes (-38%), and increases in neutrophils (+390%), WBC (+48%), monocytes (+133%). Changes in coagulation included activated partial thromboplastin time (aPTT) (+37%) and FIB concentration (+22%). Clinical chemistry changes showed slight increases in alanine

aminotransferase (ALT) (+54%) and alkaline phosphatase (ALP) (+77%) activity, with increased total bilirubin concentrations (+128%).

- Clinical pathology findings correlated with microscopic findings in the liver (single cell necrosis, increased mitoses, mononuclear infiltration, and effects of biliary duct hyperplasia or dilation). Dosing was discontinued for the remaining HD males, and they were sacrificed on Day 15/16. Additional hematology findings included marked platelet clumps in female rat 4006.
- Macroscopic findings correlated with hemorrhage and/or edema and thrombosis and included dark discoloration/focus in several organs including adrenals, kidneys, lymph nodes (mandibular, mesenteric), testis, and thymus. In addition, the subcutis was thickened with or without dark discoloration. In Animal No. 4503, the tongue was thickened and dark. In Animal No. 4005, the penis was protruded, thickened, and dark. The gross changes described above usually correlated with hemorrhage microscopically. Dark fluid/material (compatible with blood) was seen in the urinary bladder, muscle, and thymus of a few rats. In one rat (No. 4006) there was a dilatation of the bile duct.
- Microscopic findings included hemorrhage, necrosis, edema, and/or thrombosis in various organs and tissues (e.g., nasal cavity, larynx, lungs, trachea, brain, eye, mandibular lymph node, penis, prostate, subcutis, and tongue), and liver changes recorded in few animals including single cell necrosis, increased mitoses and biliary (biliary duct) hyperplasia, and lymphoid necrosis/depletion in lymph nodes (mandibular and mesenteric), GALT, spleen, and thymus.

Table 86. Fitusiran-Related Unscheduled Deaths in Rats at 3.0 mg/kg/week

Sex	Animal # (Group)	Day of FDI/ Mortality UE	Gross or Microscopic Findings
M	4003 (main)	7 FD	Hemorrhage and/or necrosis in heart, kidney, larynx, lymph nodes, skeletal muscle, subcutis edema, testis, thymus, liver; biliary hyperplasia, single cell necrosis and increased mitosis in liver
M	4005 (main)	13 FD	Hemorrhage and/or necrosis in liver, kidney, penis, thymus; thrombosis in penis.
M	4006 (main)	13 UE	Hemorrhage in brain, lymph nodes; necrosis in liver, pancreas, thymus, and thrombosis in brain, larynx, tongue with edema, hyperplasia in the liver and dilation of bile duct
M	4016 (TK)	12 FD	No data/subcutis thick; pale, swelling, ventral cervical
M	4019 (TK)	13 FD	No data/subcutis thick; pale, swelling, ventral cervical
M	4020 (TK)	11 FD	No data/no observation found
M	4021 (TK)	11 UE	No data/no observation found
F	4503 (main)	16 UE	Hemorrhage in larynx, subcutis, tongue, lymph nodes; necrosis in tongue; thrombosis in tongue with edema, subcutis; biliary hyperplasia in the liver
F	4505 (main)	34 FD	Hemorrhage in heart, kidney, larynx, lung, lymph nodes; necrosis in lymph nodes, thymus; thrombosis in larynx, lung, eye.
F	4507 (main)	22 UE	Hemorrhage in kidney, lung, lung, lymph nodes, subcutis, thymus; necrosis in thymus; thrombosis in trachea.
F	4512 (recovery)	15 FD	Hemorrhage in lung, subcutis; necrosis in liver, lymph nodes, thymus; thrombosis in lymph nodes; biliary hyperplasia in the liver

Sex	Animal # (Group)	Day of FD/ Mortality UE	Gross or Microscopic Findings
F	4514 (recovery)	20 FD	Hemorrhage in in thymus, skeletal muscle, and trachea; necrosis in lymph nodes, thymus; thrombosis in lymph nodes and thymus
F	4518 (TK)	35 UE	No data/subcutis thick; pale, swelling, cervical

Source: reviewer generated the table from Applicant's submission

Abbreviations: F, female; FD, found dead; M, male; TK, toxicokinetics; UE, unscheduled euthanasia

Early Euthanasia (Day 15/16)

Microscopic findings in scheduled euthanasia of HD males included minimal to moderate hemorrhage and/or thrombosis in multiple organs including brain, lung, pancreas, and femorotibial joint.

Compared to control on Day 44, mild to moderate increases in neutrophil (+68%), lymphocyte (+42%) and monocyte (+100%) counts, reflected in total white blood cell counts (+48%), increases in aspartate aminotransferase (AST) (+117%), ALT (+184%), ALP (+45%), with mild to marked increases in total bilirubin (+372%), cholesterol (+26%), triglyceride (+29%), and globulin (+20%) concentrations were observed at 3 mg/kg/week correlated with histological findings in the liver with minimal to moderate necrosis (focal to multifocal), minimal single cell necrosis, minimal to moderate biliary hyperplasia, minimal portal mononuclear cell infiltration, and minimal increased mitoses.

Scheduled Euthanasia (Day 44)

Clinical signs: Hypersensitivity to the touch, skin redness/dryness/scab, and thin cover or staining of the fur were noted in males at 0.3 and 1 mg/kg/week.

Minimal increases in ALP in females at 0.3 (+14%), and 1 mg/kg (+14%) resolved at the end of the recovery period. Histopathology findings included minimal brain hemorrhage in one male at 1 mg/kg and minimal thrombosis in the lungs in two males at 0.3 mg/kg, one male and one female at 1 mg/kg, and one female at 3 mg/kg, and minimal thrombosis of the larynx in one female at 3 mg/kg/week was observed.

Table 87. Fitusiran-Related Histopathology Findings in Rats in the 7-Week Repeat Dose Toxicology Study

Finding		Severity	Dose (mg/kg/week)								
			0 (Control)		0.3		1.0		3.0		
			M	F	M	F	M	F	M	F	
Scheduled Euthanasia											
Day 15/16											
Number of animals			3	NA	NA	NA	NA	NA	12	NA	
Brain											
Hemorrhage			Moderate	0	NA	NA	NA	NA	NA	1	NA
Necrosis			Minimal	0	NA	NA	NA	NA	NA	1	NA
Dilatation; ventricular			Marked	0	NA	NA	NA	NA	NA	1	NA
Thrombosis (meningeal)			Mild	0	NA	NA	NA	NA	NA	1	NA
Lymph node, mandibular											
Hemorrhage			Minimal to moderate	0	NA	NA	NA	NA	NA	2	NA
Thrombosis			Minimal	0	NA	NA	NA	NA	NA	1	NA

Finding	Severity	Dose (mg/kg/week)							
		0 (Control)		0.3		1.0		3.0	
		M	F	M	F	M	F	M	F
Liver									
Single cell necrosis (focal to multifocal)	Minimal	0	NA	NA	NA	NA	NA	2	NA
Necrosis	Minimal to mild	0	NA	NA	NA	NA	NA	5	NA
Hyperplasia; biliary	Moderate to mild	0	NA	NA	NA	NA	NA	10	NA
Portal infiltration, mononuclear cell	Minimal	0	NA	NA	NA	NA	NA	4	NA
Increased mitoses	Minimal	0	NA	NA	NA	NA	NA	3	NA
Bile duct dilatation		0	NA	NA	NA	NA	NA	1	NA
Lung									
Hemorrhage	Minimal	1	NA	NA	NA	NA	NA	1	NA
Thrombosis	Mild	0	NA	NA	NA	NA	NA	1	NA
Pancreas									
Atrophy	Mild	0	NA	NA	NA	NA	NA	2	NA
Hemorrhage	Minimal	0	NA	NA	NA	NA	NA	1	NA
Necrosis, single cell	Minimal	0	NA	NA	NA	NA	NA	4	NA
Femorotibial joint									
Mixed cell inflammation		0	NA	NA	NA	NA	NA	1	NA
Thrombosis		0	NA	NA	NA	NA	NA	1	NA
Thymus									
Hemorrhage	Minimal	0	NA	NA	NA	NA	NA	1	NA
Necrosis; lymphoid	Minimal	0	NA	NA	NA	NA	NA	1	NA
Day 44									
Brain									
Hemorrhage	Minimal	0	0	0	0	1	0	NA	0
Larynx									
Thrombosis	Minimal	0	0	0	0	0	0	NA	1
Infiltration, mononuclear	Minimal	0	0	0	0	0	0		1
Liver									
Vacuolation; hepatocellular	Minimal	0	1	1	1	1	1	NA	2
	Mild	0	0	0	1	1	0		0
Necrosis	Minimal	0	0	1	0	0	0		0
	Mild	0	0	1	0	0	0		0
Lung									
Hemorrhage	Minimal	0	0	2	0	0	1	NA	1
	Mild	0	0	0	0	1	0		0
Thrombosis	Minimal	0	0	0	0	1	1		0
Macrophage aggregation	Minimal	0	0	1		1	1		0

Source: Reviewer generated table from Applicant's submission
Abbreviations: F, female; M, male; NA, not applicable

Scheduled 2-Month Recovery Euthanasia (Day 100)

There were no fitusiran-related gross pathology, organ weight changes, or microscopic findings observed at the end of recovery period.

Table 88. Mean Percent AT Protein (Relative to Saline Control) in Male and Female Rats

Study Day	Dose (mg/kg/week)					
	0.3		1		3	
	M	F	M	F	M	F
Day 15/16 ^a	N/A	N/A	N/A	N/A	-83%	N/A
Day 44 ^b	-59	-16	-82	-39	N/A	-80
Day 100 ^c	+3	+11	+0.5	-2	N/A	-3

Source: Reviewer generated table from Applicant's submission

^a Males at 3 mg/kg were euthanized early on Days 15/16 due to adverse events. Three control male animals were sacrificed on Day 16 to provide concurrent comparator.

^b Day 44: N=7 for male control and females at 3 mg/kg/week; other groups N=10

^c Day 100: N=3 for females at 3 mg/kg/week; other groups N=5

Abbreviations: AT, antithrombin; F, female; M, male

Table 89. Mean Percent AT Activity (Relative to Saline Control) in Male and Female Rats

Study Day	Dose (mg/kg/week)					
	0.3		1		3	
	M	F	M	F	M	F
Day 15/16 ^a	N/A	N/A	N/A	N/A	-91	N/A
Day 44 ^b	-62	-23	-88	-56	N/A	-83
Day 100 ^c	-3.1	-4	+5	-7	N/A	-4

Source: Reviewer generated table from Applicant's submission

^a 3 mg/kg/week males (N=12) along with the first 3 control males for comparison purposes were euthanized on Day 15/16 due to early mortalities and adverse events observed in the high dose group.

^b Day 44: N=7 for male control and females at 3 mg/kg/week; other groups N=10

^c Day 100: N=3 for females at 3 mg/kg/week; other groups N=5

Abbreviations: AT, antithrombin; F, female; M, male

Toxicokinetic Profile

Based on exposure (AUC_{0-t} and maximum plasma concentration [C_{max}]) at 0.3 and 1 mg/kg/week, there was no sex difference observed in the TK parameters. The exposure to fitusiran increased approximately in a dose-proportional manner over the dose range. The time to maximum concentration was 0.5 hours after SC administration.

Table 90. Summary of Toxicokinetic Parameters of Fitusiran in Rat Plasma Following 7 Weekly SC Administrations on Day 43

Study Day	Dose (mg/kg/week)							
	0.3			1.0			3.0	
	M	F	M+F	M	F	M+F	M	F
AUC_{0-t} (ng·h/mL)	90	50	70	340	230	285	N/A	800 ^a
C_{max} (ng/mL)	40	40	40	150	140	145	N/A	440 ^a
Apparent $t_{1/2}$ (h)	1.19	NR	1.19	1.75	0.92	1.3	NA	1.05
T_{max} (h)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	NA

Source: Reviewer generated table from Applicant's submission

^a Values are for females only; males were euthanized on Days 15/16

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; F, female; M, male; SC, subcutaneous; $t_{1/2}$, half-life; T_{max} , time to maximum plasma concentration

13.2.5.1.4. A 7-Week Repeat Subcutaneous Injection Toxicity and Toxicokinetic Study in the Cynomolgus Monkey With a 2-Month Recovery Period (AT3-NCD12-007)

Key Findings

- Unscheduled deaths occurred in two male monkeys at 1 mg/kg/week with progressive increases in D-dimer values, decrease in fibrinogen, and decrease in platelets (in one monkey) associated with moderate multifocal cerebral necrosis with hemorrhage and moderate thrombosis or minimal pulmonary vessel thrombosis following second dose administration.
- A NOAEL of 1 mg/kg/week was considered based on deaths and adverse toxicities at 3 mg/kg/week (2 times the MRHD of 50 mg per month based on BSA comparisons).

Table 91. Study Information, AT3-NCD12-007

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 0.1, 0.3, or 1 mg/kg once weekly
Route of administration	SC
Formulation/vehicle	0.9% Sodium Chloride for Injection, USP.
Species/strain	Cynomolgus monkeys
Number/sex/group	3
Age	2-3 years old
Toxicokinetics	3/sex in control and 9/sex in treatment

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; SC, subcutaneous; USP, United States Pharmacopeia

Unscheduled Euthanasia

Two male monkeys given fitusiran at high dose 1 mg/kg were found dead on Day 22 (4001) and Day 35 (4004). Both animals had changes in coagulation parameters related to fitusiran treatment. Clinical signs included soft swelling of the ventral cervical and cranial regions.

- Animal #4001 showed progressive increases in D-dimer on Day 15 and 22 (26% to 543%), minimal to mild decreases in fibrinogen concentration (-8% to -26%), and a moderate decrease in platelet count (-58%) compared to individual pretreatment values.
- Animal #4004 had progressive increases in D-dimer (31% to 386% individual values compared to second prestudy value) and mild decreases in fibrinogen concentration (-18% to -26%) between Days 15 and 29, and no noticeable change in platelet count compared to individual pretreatment values.
- These findings correlated macroscopically with moderate multifocal cerebral necrosis with hemorrhage and moderate thrombosis in animal 4004 and chronic and minimal pulmonary vessel thrombosis in animal 4001.

In surviving animals, clinical observations of skin redness/dryness/scab and thin cover or staining of the fur were observed in all dose groups. Clinical pathology findings included minimal to mild increases in D-dimer values in males at ≥ 0.1 mg/kg (83% to 598%) and in females at ≥ 0.3 mg/kg (55% to 139%) compared to control on Day 44, and mild decreases in FIB

at 1.0 mg/kg (-21% to -33% compared to pretreatment values) correlated with decreases in AT protein and activity levels.

Table 92. Mean Percent D-Dimer Values in Monkeys

Study Day	Dose (mg/kg/week)					
	0.1		0.3		1	
	M	F	M	F	M	F
Day 44	+83	-2.6	+107	+55	+598*	+139*
Day 100	+3	-32	+108	+23	-16	+69

Source: Reviewer generated table from Applicant's submission

* = p≤0.05

Abbreviations: F, female; M, male

Dose-related decreases in AT protein and AT activity levels were observed on Day 44 and recovered by Day 100 (recovery). Dose-related AT activity levels correlated with thrombin generation time at doses ≥0.1 mg/kg/week by the end of dosing period and returned to baseline following the 2-month recovery period. The D-dimer concentrations remained elevated for 1 male at 0.3 mg/kg/week (up to 67%) on Days 72 and 100; other monkeys had no appreciable changes in D-dimer concentrations during the recovery period.

Table 93. Mean Percent Antithrombin Protein Values in Monkeys

Study Day	0.1		0.3		1	
	M	F	M	F	M	F
Day 44	-24	-25	-47***	-56*	-84***	81***
Day 100	+13	+6	+13	-13	+12	-0.9

Source: Reviewer generated table from Applicant's submission

* = p≤0.05; ** = p≤0.01; *** = p≤0.001

Abbreviations: F, female; M, male

Table 94. Mean Percent Antithrombin Activity Values in Monkeys

Study Day	Dose (mg/kg/week)					
	0.1		0.3		1	
	M	F	M	F	M	F
Day 44	-36	-39	-50	-60	-83	-81
Day 100	-3	-2	-5	-9	-14	-13

Source: Reviewer generated table from Applicant's submission

Abbreviations: F, female; M, male

Table 95. Mean Percent Thrombin Generation Peak Height Values

Study Day	Dose (mg/kg/week)					
	0.1		0.3		1	
	M	F	M	F	M	F
Day 44	+54	+26	+44	+69	+260	+189
Day 100	-18	-3	-31	+12	+11	+26

Source: Reviewer generated table from Applicant's submission

Abbreviations: F, female; M, male

Antidrug antibodies (ADAs) were not detected in any monkey administered fitusiran at doses ranging from 0.1 to 1.0 mg/kg/week during the dosing period or following an 8-week recovery period.

Transient, nonadverse, slight increases in plasma concentrations of complement factors, Bb (up to 1.6-fold), C3a (up to 1.6-fold), and cytokines IL-6 (up to 5.4-fold) and/or TNF-alpha (up to 3.2-fold) were observed in individual animals. For complement factors, no overall trend in group means and no statistically significant changes were observed for either sex after fitusiran administration. The relationship of IL-6 and TNF-alpha to administration of fitusiran was unclear based on the lack of any dose-dependent trend in responses, the small magnitude, and the low incidence of the increases.

Histopathology findings on day 44 at 1 mg/kg/week included minimal or mild focal thrombosis and mononuclear cell inflammation in the lung in one male and one female monkey, likely an on-target pharmacological effect of fitusiran.

Table 96. Fitusiran-Related Histopathology Findings in Monkeys in the 7-Week Repeat-Dose Toxicology Study

Finding	Dose (mg/kg/week)							
	0 (Control)		0.1		0.3		1.0	
	M	F	M	F	M	F	M	F
Day 44 (Main)								
Number of animals	3	3	3	3	3	3	2	3
Kidney, liver, stomach, colon								
Vascular/perivascular mononuclear cell inflammation	0	0	0	1	0	0	0	0
Lung								
Focal thrombosis	0	0	0	0	0	0	1	1
Inflammation, mononuclear cell	1	0	0	0	0	0	1	1
Day 100 (Recovery)								
Number of animals	3	3	3	3	3	3	2	3
Liver								
Vascular/perivascular inflammation	0	0	0	0	0	0	1	0

Source: Reviewer generated table from Applicant's submission

Abbreviations: F, female; M, male

Toxicokinetics

The mean C_{max} and AUC_{0-t} values for fitusiran were comparable between male and female animals following subcutaneous administration. There was no apparent accumulation of fitusiran after repeated once-weekly administration on Days 1 and 43.

Table 97. Toxicokinetic Parameters for Fitusiran in Monkey Plasma Following Q1W for 7 Weeks

Parameter	Day	Dose (mg/kg/week)					
		0.1		0.3		1.0	
		M	F	M	F	M	F
$t_{1/2}$ (h)	1	3.47	3.02	2.52	2.34	2.04	2.20
T_{max} (hr)	1	1.17	1.17	1.50	1.58	1.33	1.33
AUC_{0-t} (ng·h/mL)	1	38.7	36.7	167	167	687	629
C_{max} (ng/mL)	1	15.3	13.9	39.3	41.1	142	141
$t_{1/2}$ (h)	43	4.61	3.64	2.14	2.03	2.72	2.05
T_{max} (hr)	43	1.08	1.21	1.67	1.67	2.00	2.20
AUC_{0-t} (ng·h/mL)	43	30.7	34.6	159	155	581	570
C_{max} (ng/mL)	43	10.0	11.1	42.7	41.1	120	131

Source: Reviewer generated table from Applicant's submission

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; F, female; M, male; $t_{1/2}$, half-life; T_{max} , time to maximum plasma concentration

13.2.5.2. Other Toxicology Studies

13.2.5.2.1. A 26-Week Repeat Subcutaneous Injection Toxicity Study in the Transgenic Hemophilia A Mouse (AT3-NCD14-008)

Key Findings

- Unscheduled deaths occurred in control untreated hemophilia mice (40%), and in fitusiran treated hemophilia mice 10 (3%) and 30 (8.5%) mg/kg/week caused by hemorrhage mainly at the injection site, associated with hemophilia condition.
- Fitusiran-related findings included dose-related decreases in AT protein levels and decreases in aPTT at both fitusiran dose levels, supporting the reduced incidence of mortality/morbidity secondary to hemorrhage in fitusiran-treated groups.
- The study demonstrates therapeutic benefit of fitusiran in hemophilia A mice when compared to untreated hemophilia mice.
- A NOAEL could not be determined because of unscheduled deaths at both fitusiran doses evaluated in this study.

Table 98. Study Information, AT3-NCD14-008

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 10 or 30 mg/kg once weekly
Route of administration	SC
Formulation/vehicle	0.9% Sodium Chloride for Injection, USP.
Species/strain	Male mice (B6;129S4-F8tm1Kaz/J) mice with hemophilia A
Number/sex/group	35
Age	6 to 8 weeks old
Toxicokinetics	Not conducted

Source: Applicant's submission
Abbreviations: SC, subcutaneous; USP, United States Pharmacopeia

Unscheduled deaths occurred in 40% of control mice (11/35 males and 15/35 females) and 6% of fitusiran-treated animals (1 male and 1 female at 10 mg/kg [3%], and 3 males and 3 females at 30 mg/kg [8.5%]). Findings included hemorrhage at injection site, intestine, nasal cavity, spinal cord, and subcutis in the control and injection site, ear, subcutis in the fitusiran-treated mice, suggesting bleeding in association with hemophilia condition. Clinical signs noted prior to death in control animals and fitusiran-treated mice included decreased activity, weakness, partly closed eyes, cold to touch, suspected dehydration, hunched posture, and labored breathing. Mortality attributed to lethal hemorrhage in the control group correlated with the hemostatic disease condition in this strain of mice.

Coagulation

A decrease in aPTT and statistically significant decrease in males was observed at both doses on Day 93 and Day 184.

Table 99. Percent Activated Partial Thromboplastin Time in Male and Female HA Mice Compared to Control HA Mice

Study Day	Dose (mg/kg/week)			
	10		30	
	M	F	M	F
Day 93	-60***	-60	-56***	-53
Day 184	-50*	-53	-51*	-60*

Source: Reviewer generated table from Applicant's submission

Significantly different from control group: * p≤0.05 *** p≤0.001 (Dunn or Dunnett)

Abbreviations: F, female; HA, hemophilia A; M, male

A significant decrease in AT protein was observed at both fitusiran dose levels compared to control.

Table 100. Mean Percent AT Protein (Relative to Saline Control) in Male and Female HA Mice

Study Day	Dose (mg/kg/week)			
	10		30	
	M	F	M	F
Day 93	-92	-89	-92	-89
Day 184	-81	-79	-89	-88

Source: Reviewer generated table from Applicant's submission

Abbreviations: AT, antithrombin; F, female; HA, hemophilia A; M, male

There were no fitusiran-related findings/changes in hematology, clinical chemistry, organ weights, or gross pathology in fitusiran-treated hemophilia A (HA) mice.

Histopathology findings in the surviving animals included minimal to mild pigmented macrophages consistent with hemosiderin in the mandibular lymph nodes in both control and fitusiran-treated mice, suggesting bleeding. The pigmentation in the lymph nodes is most likely hemoglobin degradation following hemorrhage in these hemophiliac mice and was not considered to be a direct effect of fitusiran. Other findings included minimal hepatocellular necrosis (males only), and minimal to mild Kupffer cell pigmentation in HD male and female mice.

Table 101. Incidence of Fitusiran-Related Histopathology Findings in Hemophilia A Mice Following 14 and 27 Weekly Dose Administrations

Finding		Grade	Dose (mg/kg/week)					
			Males			Females		
			0#	10	30	0#	10	30
Day 93								
Number of animals			9	9	10	8	10	8
Lymph node, mandibular								
Pigmented macrophage		Minimal	5	4	3	4	2	6
		Mild	0	0	0	0	2	0
Site, injection								
Ulceration		Minimal	0	0	0	0	0	1
Infiltration, mixed cell		Minimal	6	7	7	5	6	4
		Mild	0	0	0	3	3	2
		Moderate	0	0	0	0	1	0
Pigmented macrophage		Minimal	0	1	1	2	0	1
		Mild	1	0	0	1	0	0
Vacuolation; macrophage		Minimal	0	1	1	0	0	3

		Dose (mg/kg/week)					
		Males			Females		
Finding	Grade	0 [#]	10	30	0 [#]	10	30
Day 184							
Number of animals		13	25	22	12	24	24
Liver							
Necrosis, hepatocellular	Minimal	0	1	1	0	0	0
Pigmentation; Kupffer cell	Minimal	0	0	0	0	0	1
	Mild	0	0	1	0	0	1
Hyperplasia, bile duct	Mild	0	0	0	0	1	0
Lymph node, axillary							
Pigmented macrophage	Minimal	1	-	3	1	-	5
	Mild	1	-	0	1	-	0
Lymph node, cervical	Minimal	2	-	3	3	-	6
Lymph node, mandibular							
Pigmented macrophage	Minimal	4	8	9	3	7	9
	Mild	0	0	0	0	2	0
Site, injection							
Hemorrhage	Minimal	0	1	2	0	2	1
	Mild	1	0	0	3	2	0
	Moderate	0	0	0	0	1	0
Infiltration, mixed cell	Minimal	6	12	16	7	19	18
	Mild	0	2	2	2	3	2
Pigmented macrophage	Minimal	0	0	2	2	3	1
	Mild	0	1	0	0	1	0
Vacuolation; macrophage	Minimal	1	3	1	1	1	1
Testis							
Degeneration; seminiferous tubule	Marked	0	0	1	NA-	NA	NA
Thymus							
Hemorrhage	Minimal	0	.	1	2	0	4
Decreased cellularity; lymphoid	Minimal	0	.	0	2	0	6
	Mild	1	.	0	2	0	1
	Moderate	0	.	1	0	0	0
	Marked	0	.	1	0	0	0

Source: Reviewer generated table from Applicant's submission

untreated control hemophilia mice.

Abbreviation: NA, not applicable

Table 102. Toxicological Effects of Fitusiran in Dogs With Hemophilia A

Type of Study	Major Findings
Study No: BIO-13027	Although this study was designed to assess the pharmacodynamic activity in female HA dogs (see primary pharmacology section), routine hematology and clinical chemistry parameters and limited histopathology were assessed. Fitusiran at 10 mg/kg/week in dogs was not tolerated after the 4 th dose, producing adverse liver and kidney findings including increases in ALP (32 to 93-fold), ALT (34 to 93-fold), AST (12 to 18-fold), and total bilirubin (2 to 110-fold) and decrease in platelets (33 to 82%).
Study Title: Pharmacology of Fitusiran in Hemophilia A Dogs After Repeat SC Dosing	Based on the degree of fitusiran-related clinical pathology parameter changes, two dogs with HA were humanely euthanized 17 days after the 4 th dose of 10 mg/kg/week (26 times the MRHD of 50 mg per month based on BSA comparisons); macroscopic findings included both livers with abnormal appearance (discolored, mottled, pitted). There was no evidence of thrombosis or hemorrhage in the mesenteric vasculature. Microscopic findings were observed in the liver and kidney. Gallbladders were not evaluated. Liver: minimal to mild hepatocellular degeneration/necrosis and mild to moderate inflammation in both dogs; moderate acute/chronic hemorrhage, and/or sinusoidal congestion. There was no evidence of thrombosis or fibrin clots in the liver. Kidneys: minimal tubular degeneration and/or necrosis, minimal regeneration, and minimal dilatation, minimal tubule epithelia pigment (presumably hemosiderin).

Source: Applicant's submission

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BSA, body surface area; HA, hemophilia A; MRHD, maximum recommended human dose; SC, subcutaneous

13.2.5.2.2. Genetic Toxicology

Table 103. Summary of Genetic Toxicology Studies

Study No./ Study Title.	Key Study Findings
Study No: X4P-001-TOX-019/ In vitro reverse mutation assay in bacterial cells	Fitusiran was not mutagenic in a standard and valid GLP-compliant bacterial reverse mutation assay up to 5000 µg/plate.
Study No. AT3-NCD13-010/ In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes	Fitusiran tested negative in a standard and valid GLP-compliant in vitro chromosome aberration assay in human peripheral lymphocytes up to 500 µg/mL.
Study No: AT3-NCD14-006/ In vivo Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow	Fitusiran tested negative in a standard and valid GLP-compliant in vivo rat bone marrow micronucleus assay up to 30 mg/kg (maximum tolerated dose) at 24 h and 48 h postdose following single-dose SC administration.

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; IND, investigational new drug; MNB, micronucleated binucleated; S9, mammalian liver postmitochondrial fraction

Table 104. Summary of Genetic Toxicology Studies of Impurities

Study No./ Study Title.	Key Study Findings
Study No: MAR0230 Study Title: Fitusiran - In Silico Mutagenicity Hazard Assessment of Impurities GLP: No Potential and actual impurities were investigated for structural alerts for mutagenicity using two (quantitative) structure-activity relationship (QSAR) in silico systems, DEREK, and Leadscope.	Two potential mutagenic Class 1 impurities were identified through quantitative structure-activity relationship (QSAR) from a mutagenic impurities risk assessment. These impurities were (b) (4) and (b) (4). However, these impurities were not detected in the investigation of 6 representative drug substance batches manufactured at commercial scale. The levels of (b) (4) and (b) (4) in the fitusiran drug substance batches were below the limit of detection (LOD) of (b) (4) ppm. The Applicant noted that these impurities will be controlled to a Threshold of Toxicological Concern-based acceptable intake of a mutagenic impurity of 1.5 µg per person per day.
Study nos. AT3-NCD14-010 and AT3-GLP16-021 5-week repeat-dose toxicity studies in rats with fitusiran	Five-week repeat-dose toxicity studies were conducted in rats to evaluate novel impurities of fitusiran to be used in the chronic toxicity studies and clinical trials during development. (drug substance (DS) lot 207305 (Drug Product [DP] Batch No. P02214 or DS lot 207068 (DP Batch No. P02314). A total of 6 relative retention times (RRT) impurity groups were identified based on analytical methods. There were no new toxicities related to impurities in the 5-week rat studies at (b) (4) mg/kg/week with both DS lots used in the DP batches.

Source: Applicant's submission

Abbreviations: DEREK, Deductive Estimation of Risk from Existing Knowledge; DP, drug product; DS, drug substance; GLP, good laboratory practice; LOD, limit of detection; QSAR, quantitative structure-activity relationship; RRT, relative retention times

Qualification of Impurities

The toxicity of the DS lot 207305 (Drug Product [DP] Batch No. P02214) was evaluated in three chronic repeat-dose GLP subcutaneous toxicity studies: 1) a 26-week study in HA mice (study No. AT3-NCD14-008); 2) a 26-week study in rats (study No. AT3-NCD14-009); and 3) a 39-week study in cynomolgus monkeys (AT3-NCD14-007). Doses of fitusiran ≥ 1 mg/kg/week caused mortality in rats and monkeys caused by exaggerated pharmacology that resulted in significantly lower NOAELs (b) (4) mg/kg/week) that were below the MRHD of 50 mg per month based on BSA comparisons. The Applicant utilized the toxicology data from the 26-week study in mice with HA that provided an evaluation of safety relative to dosing of patients with hemophilia. In the 26-week toxicology study with hemophilia mice, a NOAEL was not determined based on unscheduled deaths at both fitusiran doses evaluated in this study (3% at 10 mg/kg/week and 8.5% at 30 mg/kg/week). However, these deaths were predominantly attributed to the inherent hemophilia condition and were not considered related to fitusiran or the impurities present in the lot, as there were more deaths in vehicle-control hemophilia mice (40%). Both doses of fitusiran were effective pharmacologically when compared to vehicle-dosed control animals, and treatment resulted in fewer deaths and the anticipated pharmacodynamic activity, which supports the use of this study for impurity qualification.

The safety margins (animal:human) of the impurities in the drug substance were estimated using the highest dose in the study, 30 mg/kg. The safety margins for the impurities at the percentage proposed acceptance criteria are (b) (4)-fold higher. Therefore, the proposed impurity levels in drug substance are considered adequately qualified from a nonclinical perspective.

Table 105. Drug Substance Impurity Qualification Based on 26-Week Toxicology Study in Hemophilia Mice

Impurity	DS Impurity in Tox Study	DS Impurity Amount (in mg/kg/Week) at 30 mg/kg/Week (HD) ^a (Amount Corrected for By-Monthly Dosing Interval) ^a	DS Proposed Acceptance Criteria (%)	DS Impurity Amount at Human 50-mg Dose (mg/kg/month) ^b	Animal:Human Margin ^c (b) (4)
[Redacted Table Content]					

Source: Reviewer generated table from Applicant's submission

(b) (4)

Abbreviations: DP, drug product; DS, drug substance; HD, high dose; tox, toxicology

13.2.5.3. Carcinogenicity Studies

Study No/ Study Title: ALN-AT3SC: A 2-Year Subcutaneous Injection Carcinogenicity Study in Rats

Good laboratory practice (GLP) compliance: Yes

Key Study Findings

In agreement with doses recommended by CDER's Executive Carcinogenicity Assessment Committee, Sprague Dawley rats were administered fitusiran at subcutaneous doses of 0, 0.03, 0.1, or 0.3 mg/kg/week to males and 0, 0.1, 0.3, or 1 mg/kg/week to females once weekly for 2 years. The highest doses were based on mortality due to hemorrhagic thrombosis at ≥ 1 mg/kg in males and at 3 mg/kg in females in a 26-week and a 7-week repeat dose toxicity study, respectively. The survival rate in fitusiran-treated groups was comparable to control groups. There were no dose-dependent or statistically significant fitusiran-related neoplastic findings noted in either male or female rats up to the highest dose tested. All fitusiran dose levels tested in male and female rats were below the MRHD based on BSA comparisons.

Adequacy of Carcinogenicity Study

The Committee concluded that the 2-year carcinogenicity study conducted in Sprague-Dawley rats with fitusiran was adequate and there was no evidence of drug-related neoplasms in male or female rats.

Study No/ Study Title: AT3-GLP17-001 / ALN-AT3SC: A 26-Week Subcutaneous Injection Carcinogenicity Study in TgRasH2 Mice

Good laboratory practice (GLP) compliance: Yes

Key Study Findings

In agreement with doses recommended by CDER's Executive Carcinogenicity Assessment Committee, Tg.RasH2 mice were administered fitusiran at subcutaneous doses of 0, 0.05, 0.15, or 0.5 mg/kg/week to males and 0, 0.025, 0.08, or 0.25 mg/kg/week to females once weekly for 26 weeks. The highest doses were selected based on body weight gain decrements in a dose range finding study in wild-type littermates. A positive control group of Tg.RasH2 mice was administered a single intraperitoneal dose of N-methyl-N-nitrosourea (MNU) at 75 mg/kg on Day 1. The survival rate in fitusiran-treated animals was comparable to control animals. No statistically significant increases in dose-response relationships or pairwise comparisons were observed for neoplastic findings after exposure to doses of fitusiran up to 0.5 mg/kg. The positive control MNU induced increased incidences of malignant squamous cell carcinoma and papilloma of the stomach in male and female RasH2 mice relative to control.

ECAC Conclusions

The Committee concluded that the 26-week carcinogenicity study conducted in Tg.RasH2 mice with fitusiran was adequate and there was no evidence of drug-related neoplasms in male and female mice.

13.2.5.4. Reproductive Toxicology

No reproductive and developmental toxicity studies were conducted with fitusiran in female animals because the intended population is almost exclusively male, and the clinical development program was conducted exclusively in males. Hemophilia A and B are X-linked recessive inherited bleeding disorders predominantly affecting males (99%), and the likelihood of women of childbearing potential receiving fitusiran is very low; therefore, only a male fertility study was integrated into the 26-week repeated dose chronic toxicity study in rats. There were no fitusiran-related effects on male fertility and early embryonic development up to 1 mg/kg/week (below the MRHD based on BSA comparisons). It is not known whether fitusiran can adversely impact the development of embryo/fetus when administered to a pregnant woman. Only male subjects were enrolled in clinical trials with fitusiran. (b) (4)

Female Fertility and Early Embryonic Development

Because hemophilia is primarily an X-linked disease, no embryo-fetal toxicity studies in rats and rabbits have been performed.

Juvenile Animal Studies

Non-GLP range finding (AT3-DSM16-001) and repeat-dose tolerability (AT3-NCD14-005) studies in juvenile rats were conducted. Four-day-old pups (n=8/sex/group) were administered fitusiran by SC administration with doses of 0, 1, 3, or 10 mg/kg/week ×4 or 0, 0.5, and 1.0 mg/kg/week ×5.

Results

Study AT3-DSM16-001: At 10 mg/kg/week, mortality was observed in 7 pups (6 males and 1 female) occurring between Study Days 19 and 28, due to jugular venipuncture or head trauma based on swelling or clotting in the ventral cervical region (4 pups) or in the cranial cavity (1 of those 4 pups) likely due to the pharmacological effect of fitusiran. One pup had poor and/or deteriorating condition that led to unscheduled euthanasia, likely due to unilateral findings of irregular surface and mottled discoloration in the kidney. The cause of the death was undetermined for the remaining two pups.

Clinical signs in these moribund pups included abnormal gait, decreased activity, cold to touch, incoordination, eyes partly closed, skin pallor, and labored breathing. Decreased body weight gains were noted at 10 mg/kg/week.

Toxicokinetics

Plasma

Plasma TK parameters at 1 mg/kg/week were below the lower limit of quantitation on Days 4 postpartum (PP) and 25 PP. There were no sex differences in exposure (C_{max} and AUC); the data are presented for males and females combined.

Table 106. Plasma TK Parameters of Fitusiran in Juvenile Rats

Parameter	PP Day	Dose (mg/kg/week)		
		1	3	10
		M+F	M+F	M+F
T_{max}	4 (First dose)	NC	1.0	1.0
C_{max} (ng/mL)	4 (First dose)	NC	145	1650
AUC_{0-t} (ng·h/mL)	4 (First dose)	NC	175	1760
T_{max}	25 (Last dose)	NC	0.5	0.5
C_{max} (ng/mL)	25 (Last dose)	NC	141	625
AUC_{0-t} (ng·h/mL)	25 (Last dose)	NC	176	1020

Source: Reviewer generated table from Applicant's submission

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; F, female; M, male; NC, not calculated as plasma values at 1 mg/kg/week were below the limit of quantitation (<50.0 ng/mL); PP, postpartum; TK, toxicokinetics; T_{max} , time to maximum plasma concentration

Liver

Fitusiran exposure (C_{max} and AUC) in the liver increased dose-proportionally for 1, 3, and 10 mg/kg. The exposure to fitusiran in the liver was several fold higher when compared to plasma concentrations consistent with adult rats. Liver tissue samples were not analyzed for AT protein levels.

Table 107. Liver Exposure to Fitusiran in Juvenile Rats

Parameter	Day	Dose (mg/kg/week)		
		1	3	10
		M+F	M+F	M+F
T _{max}	25	6	6	15
C _{max} (ng/mL)	25	3450	17000	32700
AUC _{0-t} (ng·h/mL)	25	62900	289000	628000

Source: Reviewer generated table from Applicant's submission

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; F, female; M, male; T_{max}, time to maximum plasma concentration

Study AT3-NCD14-005: Five weekly SC administrations of fitusiran up to 1 mg/kg/week were well tolerated. There were no adverse findings in clinical signs, body weights, and clinical pathology parameters including hematology, clinical chemistry, and coagulation in fitusiran-treated juvenile rats compared to control juvenile rats. On Day 30, AT protein concentrations were decreased in a dose-dependent manner in both males and females at both fitusiran concentrations. The NOAEL was considered at 1 mg/kg/week in juvenile rats in repeat dose SC administration for 5 weeks.

Table 108. Local Tolerance Study

Study Type/ Study No	Key Study Findings
Local Tolerance	
ALN-AT3SC: A Single Dose Subcutaneous Local Tolerability Study in Male New Zealand White Rabbit	There were no findings of erythema at 50 or 200 mg/site or edema at 50 mg/site. At 200 mg/site, increased incidence of slight edema was observed in all 3 animals between 1-4 hours postinjection compared to control, that resolved 6 hours postinjection. Gross pathology findings included dark focus at the injection site in 2 animals at 50 mg/site, correlated histologically with minimal focal subcutaneous hemorrhage likely related to procedure. Nonadverse histopathology findings were observed at the injection site in 2 animals at 200 mg/site that included minimal multifocal mixed (neutrophilic and histiocytic) cell inflammation in the subcutaneous tissues or minimal focal thrombosis of a deep dermal blood vessel, and mild multifocal neutrophilic inflammation in the epidermis (surface and follicular), and dermis, correlated with edema.
Fitusiran was administered as a single SC injection in the lumbar area of male New Zealand rabbits (n=3/group) at 0, 50 mg/site or 200 mg/site using 2 mL dosing volume	
	Overall, single SC administration of fitusiran up to 200 mg/site was well tolerated by New Zealand rabbits.
Immunotoxicity	
Evaluation of AD-57213 Cytokine Induction in an in vitro Human Whole Blood Assay/BIO13003	The mean cytokine responses to fitusiran transfected to human whole blood at 300nM were less than 2-fold higher than medium alone for all 13 cytokines (IL-1β, IL-RA, IL-6, IL-8, IL-10, IL-12 (p70), granulocyte colony-stimulating factor (G-CSF), IFN-γ, interferon-inducible protein 10 (IP-10), macrophage inflammation protein 1 alpha (MIP-1α), macrophage inflammation protein 1 beta (MIP-1β), monocyte chemoattractant protein 1 (MCP-1) and TNF-α measured for the four human donors. Thus, fitusiran was not considered to induce these cytokine or chemokines.
A DOTAP mock-transfection control was also included as a transfection control.	

Study Type/ Study No	Key Study Findings
Study No: INV-NCD12-023 Study Title: A Single Dose (subcutaneous injection) Exploratory immunostimulation study of Fitusiran in the male CD-1 mouse.	In an immune stimulation study of fitusiran in male CD-1 mice (n=5/dose) following single SC injection of fitusiran at doses 0, 10, 30 or 100 mg/kg, all animals survived through scheduled necropsy on Day 1. No significant fitusiran-related increases in mouse cytokine parameters (G-CSF, IL-6, IP-10, KC, MCP-1, and TNF-α using Millipore Mouse 6-Plex Cytokine Kits and the Bio-Plex® Suspension Array (Luminex) system) were noted up to 100 mg/kg 4 hours postdose.

Source: Applicant's submission
Abbreviations: ALN-AT3SC, fitusiran; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; IP, interferon-inducible protein; KC, keratinocyte chemoattractant; MCP, monocyte chemoattractant protein; MIP, macrophage inflammation protein; RA, receptor antagonist; SC, subcutaneous; TNF, tumor necrosis factor

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Distribution Study

14.1.1.1. Study AT3-RS13-001: Plasma Protein Binding of Fitusiran

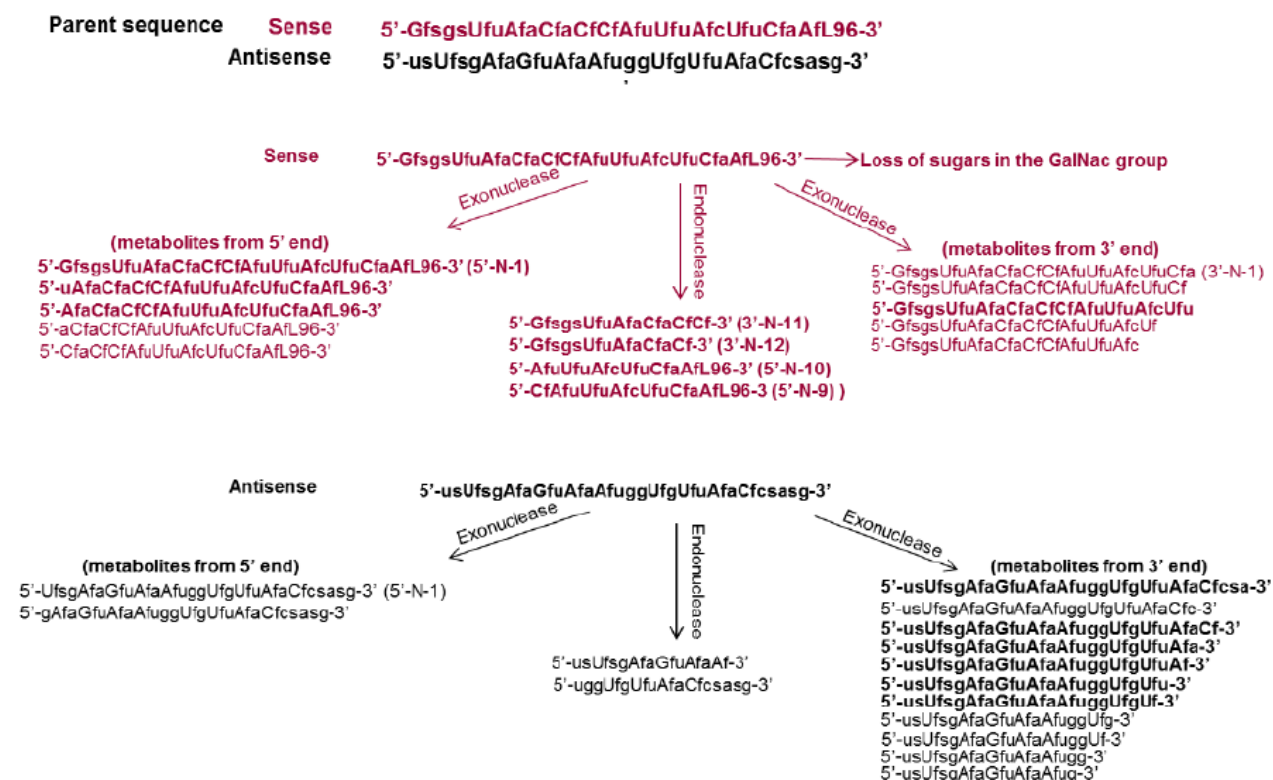
The Applicant evaluated the binding of fitusiran to animal (mouse, rat, monkey, dog) and human plasma proteins. Briefly, as detailed in the nonclinical study report LPR1221 (submitted on September 16, 2024, Module 4.2.2.3), in vitro human plasma protein binding of fitusiran at concentrations of 0.5, 1, 5, 10, 25, and 50 µg/mL was 96.6%, 95.6%, 90.2%, 83.9%, 78.7% and 52.4% respectively.

14.1.2. Metabolism and Transport Characterization, and Drug-Drug Interaction Studies

14.1.2.1. In Vitro Metabolic Stability Study BA13003

Study BA13003 evaluated the in vitro metabolic stability of fitusiran in mouse, rat, dog, monkey, and human serum and liver S9 fractions, and conducted its in vitro and in vivo metabolic profiling. The proposed metabolic pathway of fitusiran is presented in [Figure 26](#) below.

Figure 26. Proposed Metabolic Pathway of Fitusiran



Source: Figure 7, Summary of Clinical Pharmacology Studies

14.1.2.2. Study MET0981: Evaluation of the Percentage of N-1 Metabolite in Clinical Samples

Study MET0981 evaluated fitusiran N-1 metabolite in human plasma samples from phase 1 study ALN-AT3SC-001. The objective of this study was to obtain an estimation of the percentage of N-1 metabolite in human plasma by retrospectively reanalyzing select chromatograms from the fitusiran pharmacokinetic (PK) sample analysis in Study TDR14767 (ALN-AT3SC-001).

The evaluation included: (i) analyzing HPLC chromatograms which had already been generated as part of fitusiran analysis in PK samples from Study TDR14767 (ALN-AT3SC-001), (ii) identification of N-1 metabolite as a peak distinct from fitusiran, and (iii) reprocessing of the chromatograms to integrate the N-1 peak areas for comparison with fitusiran peak areas. Noncompartmental pharmacokinetic analysis was then performed on the chromatogram peak areas to generate area under the concentration-time curve to the last measurable concentration (AUC_{last}) values for 16 subjects who had received 3 fitusiran SC doses at 80 mg QM, and the amount of N-1 metabolite relative to fitusiran was estimated from the ratio of N-1 metabolite AUC_{last} /fitusiran AUC_{last} .

The data indicated that after repeated SC administration of fitusiran at 80 mg QM, the N-1 metabolite is present in plasma at levels <10% of intact fitusiran (N-1 metabolite/fitusiran = $5.26 \pm 0.98\%$). No sample analysis or reanalysis to specifically quantitate N-1 metabolite was performed for any clinical sample. In addition, it could not be ascertained

whether the N-1 metabolite identified in the HPLC chromatograms was the AS(N-1)3' or AS(N-1)5' metabolite. However, based on in vitro metabolic stability studies and metabolite profiling of in vitro human serum and liver S9 fractions, the N-1 metabolite in human plasma was expected to be the AS(N-1)3' metabolite.

14.1.2.3. Study 319N-1520: CYP450 Isoforms Involved in the Metabolism of Fitusiran

Study 319N-1520 evaluated the potential human CYP450 isoforms involved in the metabolism of ALN-AT3SC using cDNA-expressed enzymes. The objective of this study was to identify if any of the cytochrome P450 enzymes (CYP) are involved in the metabolism of fitusiran by using a panel of recombinant cytochrome P450 enzymes (rCYPs).

In this study, fitusiran was incubated in triplicate with individual rCYPs: rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, rCYP3A4 and rCYP3A5. The reaction mixture consisted of a specific rCYP, 100mM potassium phosphate buffer (pH 7.4), 1mM NADPH, and fitusiran at 2 concentrations, 800 ng/mL and 8,000 ng/mL. Reactions with fitusiran were terminated at 0 and 45 minutes with ice-cold methanol (1:1 v/v) and with the positive controls at 30 minutes with ice-cold acetonitrile containing internal standard (1:1 v/v). Probe substrates for each of the rCYP enzymes were included in the study as positive controls. The negative control incubations consisted of fitusiran with rCYPs but without NADPH. Fitusiran was analyzed by liquid chromatography-time of flight-mass spectrometry (LC-TOF-MS). Positive control substrates were analyzed by ultra-high-performance liquid chromatography-mass spectrometry/mass spectrometry (UHPLC-MS/MS). Peak area ratios were used to calculate the percent parent drug remaining at 45 or 30 minutes.

The results showed that the percentage of fitusiran remaining after 45 minutes ranged from ~90% to ~100% for all rCYPs tested in the presence of NADPH. In contrast, positive control incubations showed significant metabolism as parent compound was depleted for rCYP2C9, rCYP2D6, and rCYP3A4/5, with 35.9% to 68.0% remaining for the other rCYPs tested.

These results indicated that fitusiran is not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5.

14.1.2.4. Study AT3-NCD13-014 (CYP Inhibition)

Study AT3-NCD13-014 evaluated the inhibitory potential of fitusiran against eight principal human CYP isozymes using human liver microsomes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

In this study, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 activity was investigated using phenacetin, coumarin, bupropion, amodiaquine, tolbutamide, S-mephenytoin, and dextromethorphan as probe substrates, respectively. CYP3A4/5 activity was investigated using both midazolam and testosterone as probe substrates. The inhibitory activity was evaluated using pooled human liver microsomes and was measured at 10 fitusiran concentrations (0 to 10,000 µg/mL), in triplicate. Reaction was initiated by addition of NADPH and following incubation at 37°C (3 to 30 minutes for different probe substrates). The reaction was terminated by addition of acetonitrile. The metabolites of the probe substrates in pooled

samples (acetaminophen for CYP1A2, 7-hydroxycoumarin for CYP2A6, hydroxybupropion for CYP2B6, N-desethylamodiaquine for CYP2C8, 4-hydroxytolbutamide for CYP2C9, 4'-hydroxymephenytoin for CYP2C19, dextrophan for CYP2D6, 6 β -hydroxytestosterone and 1'-hydroxymidazolam for CYP3A4/5) were measured using electrospray ionization techniques.

Results

There were no changes in activity as compared to the vehicle control for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (both midazolam and testosterone as substrates), indicating that fitusiran was not an inhibitor of any of these CYPs. Fitusiran showed inhibition of CYP2C8, with a calculated half maximal inhibitory concentration (IC₅₀) value for fitusiran of ~800 μ g/mL, indicating that fitusiran was not an inhibitor of CYP2C8 enzymes at clinically relevant concentrations (mean maximum plasma concentration at the highest recommended clinical dose of 50 mg is 84.1 ng/mL [LTE15174], which is ~9500-fold lower than the CYP2C8 IC₅₀ value). The calculated IC₅₀ values for positive controls were consistent with reported literature values.

To summarize, fitusiran is unlikely to inhibit any of these tested CYPs at clinically relevant concentrations.

14.1.2.5. Study 319N-1517 (CYP Induction)

Study 319N-1517 evaluated the potential of fitusiran to induce CYP1A2, CYP2B6 and CYP3A4 in sandwich cultured human hepatocytes.

Evaluation of the degree of CYP induction was performed by the following two methods: (i) measurement of mRNA levels by reverse transcription-polymerase chain reaction (TaqMan), and (ii) measurement of enzyme activities using isoform-specific probe substrates. Cultured human hepatocytes from three separate adult donors were cultured on collagen-coated plates and incubated with vehicle alone, positive and negative control compounds, or fitusiran for 48 or 72 hours (mRNA and enzyme activities, respectively). Fitusiran was evaluated at 4 concentrations: 0.005, 0.25, 2.5, and 25 μ g/mL. Activity levels of CYP1A2, CYP2B6, and CYP3A4 were measured in situ with a cocktail of phenacetin, bupropion, and midazolam using qualified liquid chromatography-tandem mass spectrometry (LC MS/MS) methods (details in 319N-1517). The criteria for positive CYP induction were increases in mRNA levels 2-fold above the vehicle control or enzyme activity $\geq$ 40% (or 0.4-fold) of the relevant positive control induction.

Results

Hepatocytes treated with fitusiran showed no statistically significant increase in CYP1A2, CYP2B6, or CYP3A4 mRNA levels at the concentrations tested, and no increased CYP1A2, CYP2B6, or CYP3A4 enzyme activity under the conditions utilized in this study. Based on these results, fitusiran appeared unlikely to be a CYP inducer at concentrations that were at or below 25 μ g/mL (mean maximum plasma concentration at the highest recommended clinical dose of 50 mg is 84.1 ng/mL [LTE15174], which is ~300-fold lower than the highest concentration of 25 μ g/mL tested in this study).

To summarize, fitusiran is unlikely to induce any of these tested CYPs at clinically relevant concentrations.

14.1.2.6. Study Alnylam-03-22Jul2016: Transporter Inhibition and Substrate Evaluations

Study Alnylam-03-22Jul2016 evaluated whether fitusiran is a substrate and inhibitor of efflux and uptake transporters, through in vitro interaction studies of fitusiran with human BSEP, BCRP and MDR1 efflux (ABC) transporters, and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters. The objective of this study was to evaluate potential interaction of fitusiran with 11 human efflux and uptake transporters. The transporters evaluated, assays performed, and fitusiran concentrations tested are summarized in [Table 109](#).

Table 109. Transporters Studied and Transporter Assays

Transporter Type	Transporter	Assays for each transporter ^a	Fitusiran concentrations tested (µg/mL ^b)
ABC (Efflux) Transporters	BCRP	Vesicular transport inhibition assay	48.7 and 487
	BSEP	Vesicular transport substrate assay	0.487, 4.87, 48.7 and 487
	MDR1		
SLC (Uptake) Transporters	MATE-1		
	MATE2-K		
	OAT1	Uptake transporter inhibition assay	48.7 and 487
	OAT3	Uptake transporter substrate assay	0.487, 4.87, 48.7 and 487
	OATP1B1		
	OATP1B3		
	OCT1 ^c		
	OCT2		

Abbreviations: ABC, ATP-binding cassette; BCRP, Breast cancer resistance protein; BSEP, Bile salt export pump; MDR1, Multidrug resistance protein 1; MATE, Multidrug and toxin extrusion transporter; OAT, Organic anion transporter; OATP, Organic anion-transporting polypeptide; OCT, Organic cation transporter; SLC, Solute carrier.

^a Two assays (inhibition assay and substrate assay) were conducted for each transporter, unless otherwise specified.

^b Fitusiran concentrations are expressed as µM (0.03 to 30 µM) in study report (Alnylam-03-22Jul2016).

^c Inhibition assay only performed for OCT1.

Source: Table 5, Summary of Clinical Pharmacology Studies

In this study, vesicular transport inhibition and substrate assays were performed with inside-out membrane vesicles prepared from cells overexpressing human ATP-binding cassette (ABC) transporters in human embryonic kidney cell line 293 (HEK293). Uptake transporter inhibition and substrate assays were performed using Madin Darby canine kidney cells II (MDCKII) or HEK293 cells stably expressing the respective uptake transporters.

Results

Vesicular Transport Inhibition Assays

Fitusiran did not influence the BCRP-, BSEP-, and multidrug resistance protein 1 (MDR-1)-mediated probe substrate accumulation at the concentrations evaluated.

Vesicular Transport Substrate Assays

ATP-dependent accumulation of fitusiran was similar in the presence of ATP and AMP, indicating no active accumulation of fitusiran in transporter (BCRP, BSEP and MDR1) expressing or control vesicles.

Uptake Transporter Inhibition Assays

Fitusiran inhibited the organic cation transporter (OCT)2-mediated metformin transport by 24% at 487 µg/mL. Fitusiran did not influence the multidrug and toxin extrusion transporter (MATE)1-, MATE2-K-, organic anion-transporting polypeptide (OATP)1B1-, OATP1B3-, organic anion transporter (OAT)1-, OAT3- and OCT1-mediated probe substrate accumulation at the applied concentrations.

Uptake Transporter Substrate Assays

Accumulation of fitusiran was similar in the OAT1-, OAT3- and OCT2-expressing and the control cells, indicating no active accumulation of fitusiran. Transporter-specific accumulation of fitusiran was observed in cells expressing OATP1B1 (2.45-fold at 487 µg/mL), OATP1B3 (2.51-fold at 487 µg/mL), MATE1 (2.24-fold at 48.7 µg/mL) and MATE2-K (8.64-fold at 48.7 µg/mL, 2.39-fold at 4.87 µg/mL, and 0.81-fold at 0.487 µg/mL). These results indicated that fitusiran was likely a substrate of MATE2-K uptake transporters at high concentrations, but probably not at clinically relevant concentrations (no accumulation observed at 0.487 µg/mL [487 ng/mL], which is 5.79-fold higher than the mean maximum plasma concentration of 84.1 ng/mL observed at the highest recommended clinical dose of 50 mg [LTE15174]).

To summarize, fitusiran is unlikely to be a substrate or inhibitor of the tested efflux and uptake transporters at clinically relevant concentrations.

14.2. In Vivo Studies

14.2.1. Single Ascending Dose and Multiple Ascending Dose PK Study in Healthy Subjects

14.2.1.1. Phase 1 Study TDR14767

Study TDR14767 was a phase 1 single ascending dose and multiple ascending dose safety, tolerability, and pharmacokinetics study of subcutaneously administered fitusiran in healthy adult volunteers and hemophilia A or B subjects (moderate or severe hemophilia). The primary objective was to evaluate the safety and tolerability of fitusiran when administered to healthy adult male subjects and when administered to male subjects with moderate or severe hemophilia A or B.

Study Design

This study consisted of 4 parts: Part A, a single-ascending-dose phase in healthy subjects; Part B, a multiple-ascending-dose phase in subjects with moderate or severe hemophilia A or B; Part C, an exploratory multiple-dose phase in male subjects with moderate or severe hemophilia A or B; and Part D, a multiple-dose phase in subjects with moderate or severe hemophilia A or B with inhibitors.

The doses were: Part A: 0.03 mg/kg (single dose); Part B: 0.015, 0.045, or 0.075 mg/kg once weekly (QW) (total of 3 doses); Part C: 0.225, 0.45, 0.9, or 1.8 mg/kg, or 80 mg QM (total of 3 doses); Part D: 50 or 80 mg QM (total of 3 doses). A total of 46 subjects were enrolled (45 treated with fitusiran, 1 placebo).

Intensive PK sampling was performed in Part A (healthy subjects) following a single dose of fitusiran, in Part B (subjects with hemophilia A or B) after the first (Day 0) and third QW (Day 14) dose of fitusiran, and in Parts C and D (subjects with hemophilia A or B) after the first (Day 0) and third QM (Day 56) dose of fitusiran. PK sampling timepoints were: predose, then 0.083, 0.167, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 168 hours postdose for 0.015- to 0.075-mg/kg dose cohorts; and predose, then 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose for 0.225-mg/kg to 1.8-mg/kg and 50- and 80-mg dose cohorts. Urine samples for PK analysis were collected from 0 to 6, 6 to 12, and 12 to 24 hours after the first and last doses.

Samples for AT and thrombin generation (TG) measurements were collected at the following timepoints: Part A (single dose): at screening, on Day (D)0 (predose/baseline), then D1, D2, D3, D7, D10, D14, D21, D28, D42, and D56; Part B (3×QW doses): at screening, on D0 (predose/baseline), then D1, D2, D3, D7 (predose), D8, D9, D14 (predose), and D15; Parts C and D (3×QM doses): at screening, on D0 (predose/baseline), then D1, D7, D14, D28 (predose), D29, D42, D56 (predose), D57, D70, D84, D98, and D112. All samples for ADA assessment were collected at predose/trough time points on D0 (Part A), D0, D7, and D14 (Part B), and D0, D28, and D57 (Parts C and D).

Results

Plasma Pharmacokinetics

Fitusiran plasma PK parameters following single SC administration of fitusiran to healthy volunteers at 0.03 mg/kg (Part A), to subjects with hemophilia after single and multiple (n=3) doses at 0.015 to 0.045 mg/kg QW (Part B), at 0.225 to 1.8 mg/kg and 80 mg QM (Part C), and 50 and 80 mg QM (Part D), are presented in [Table 110](#) (single dose data) and [Table 111](#) (multiple dose data).

Table 110. Summary of Fitusiran Plasma Pharmacokinetic Parameters Following Single SC Administration (Day 0) to Adult Healthy Volunteers and Subjects With Hemophilia, Study TDR14767

Population	Study Part	Dose	Statistic	C _{max} (ng/mL)	AUC _{last} (h•ng/mL)	AUC _∞ (h•ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _d /F (L)
Healthy volunteers	A	0.03 mg/kg	N	3	3	3	3	3	3	3
			Geometric Mean	3.877	43.20	46.04	5.24	4.16 0	54.11	324.7
			CV(%)	18.1	19.6	17.7	21.7	36.8	17.4	47.7
Hemophilia	B	0.015 mg/kg	N	3	3	2	3	2	2	2
			Geometric Mean	2.350	18.27	15.57	3.20	3.07 3	73.96	326.9
			CV(%)	43.9	51.7	NC	35.4	NC	NC	NC
		0.045 mg/kg	N	5	5	4	5	4	4	4
			Geometric Mean	4.290	46.08	82.22	5.15	4.85 3	45.25	317.1
			CV(%)	55.9	57.1	25.6	21.9	22.7	43.9	14.6
		0.075 mg/kg	N	3	3	1	3	1	1	1
			Geometric Mean	11.21	141.5	170.0	7.56	4.16 0	39.30	236.0
			CV(%)	22.7	13.9	NC	43.3	NC	NC	NC
Hemophilia	C	0.225 mg/kg	N	3	3	2	3	2	2	2
			Geometric Mean	25.23	341.0	298.4	4.58	4.46 4	60.35	389.0
			CV(%)	21.5	35.6	NC	88.2	NC	NC	NC
		0.45 mg/kg	N	3	3	2	3	2	2	2
			Geometric Mean	30.48	346.8	276.1	5.24	3.15 2	117.0	532.4
			CV(%)	40.1	61.9	NC	75.5	NC	NC	NC
		0.9 mg/kg	N	3	3	3	3	3	3	3
			Geometric Mean	122.7	1480	1524	4.58	4.10 7	45.07	267.0
			CV(%)	15.6	11.8	11.1	24.7	23.6	11.4	31.4
		1.8 mg/kg	N	3	3	3	3	3	3	3
			Geometric Mean	263.4	6025	6125	4.58	4.68 1	20.52	138.1
			CV(%)	43.7	65.9	64.6	24.7	28.7	56.1	60.2
		80 mg	N	6	6	6	6	6	6	6
			Geometric Mean	148.6	2086	2206	3.80	5.27 2	36.22	275.5
			CV(%)	24.0	73.8	69.1	31.8	29.3	36.6	47.6

Population	Study Part	Dose	Statistic	C _{max} (ng/mL)	AUC _{last} (h•ng/mL)	AUC _∞ (h•ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)
Hemophilia	D ^a	50 mg	N	6	6	4	6	4	4	4
			Geometric Mean	85.36	1053	1109	3.83	3.41 7	45.10	222.2
			CV(%)	42.1	39.8	45.4	79.4	37.6	56.1	95.6
		80 mg	N	11	9 ^b	7 ^b	11	9	9	9
			Geometric Mean	142.9	1743 ^b	1983 ^b	3.70	5.04 9	19.96	145.5
			CV(%)	37.3	59.0 ^b	56.1 ^b	49.2	34.2	62.7	77.1

Abbreviations: AUC_∞, area under the concentration-time curve extrapolated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; NC, not calculated; PK, pharmacokinetic; t_{1/2}, terminal elimination half-life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

^a Participants with inhibitors

^b Two participants in the 80 mg cohort in Part D on Day 0 had aberrant AUC_{last} and AUC_∞ values which were not supported by the concentration-time data for these 2 participants, nor were they consistent with the corresponding Day 56 data. In the data presented above, those 2 participants were excluded from the Day 0 descriptive statistics. For transparency, the Day 0 AUC_{last} value for N=11 (ie, including the 2 aberrant values) was 3166 ng.h/mL with a CV of 195.2%, and the Day 0 AUC_∞ value for N=9 (ie, including the 2 aberrant values) was 4011 ng.h/mL with a CV of 177.6%.

Source: Table 6, Summary of Clinical Pharmacology Studies
Abbreviations: SC, subcutaneous

Table 111. Summary of Fitusiran Plasma Pharmacokinetic Parameters Following Multiple SC Administrations to Adult Subjects With Hemophilia, Study TDR14767

Population	Study Part/Day [Regimen]	Dose	Statistic	C _{max} (ng/mL)	AUC _{last} (h•ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)
Hemophilia	Part B/ Day 14	0.015 mg/kg [QW]	N	2	2	2	2	2	2
			Geometric Mean	4.205	23.43	2.00	2.389	41.54	143.5
			CV(%)	NC	NC	NC	NC	NC	NC
		0.045 mg/kg [QW]	N	6	6	6	5	5	5
			Geometric Mean	9.252	103.5	3.03	4.260	28.79	177.3
			CV(%)	71.1	36.4	68.9	25.0	43.3	69.3
		0.075 mg/kg [QW]	N	3	3	3	1	1	1
			Geometric Mean	16.46	166.0	3.17	5.670	20.20	165.0
			CV(%)	93.6	60.6	78.7	NC	NC	NC
	Part C/ Day 56	0.225 mg/kg [QM]	N	3	3	3	3	3	3
			Geometric Mean	18.25	179.2	3.23	4.342	86.18	538.7
			CV(%)	105.8	97.2	32.6	72.3	102.1	143.5
		0.45 mg/kg [QM]	N	3	3	3	3	3	3
			Geometric Mean	50.46	659.0	5.33	5.081	47.89	350.8
			CV(%)	2.0	17.2	19.2	32.9	27.3	53.4

NDA 219019
QFITLIA (fitusiran)

Population	Study Part/Day	Dose [Regimen]	Statistic	C _{max} (ng/mL)	AUC _{last} (h•ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)
		0.9 mg/kg [QM]	N	3	3	3	2	2	2
			Geometric Mean	85.46	1168	5.77	4.152	60.03	359.9
			CV(%)	20.7	24.9	33.3	NC	NC	NC
		1.8 mg/kg [QM]	N	3	3	3	1	1	1
			Geometric Mean	229.2	2669	5.00	4.610	38.00	253.0
			CV(%)	71.6	27.6	57.4	NC	NC	NC
		80 mg [QM]	N	5	5	5	5	5	5
			Geometric Mean	139.9	1746	4.44	5.554	42.63	341.5
			CV(%)	11.5	17.7	20.2	21.9	23.4	8.2
	Part D/ Day 56	50 mg [QM]	N	6	6	5	5	5	5
			Geometric Mean	96.50	1118	4.06	4.343	41.36	259.2
			CV(%)	34.3	29.5	75.2	34.9	29.6	59.1
		80 mg [QM]	N	11	11	11	10	10	10
			Geometric Mean	157.1	1768	3.60	5.178	43.26	323.0
			CV(%)	32.9	23.1	67.7	25.2	22.1	44.6

Abbreviations: AUC_{last}, area under the concentration-time curve to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; NC, not calculated; PK, pharmacokinetic; t_{max}, time to maximum plasma concentration; t_{1/2}, terminal elimination half-life; V_z/F, apparent volume of distribution.

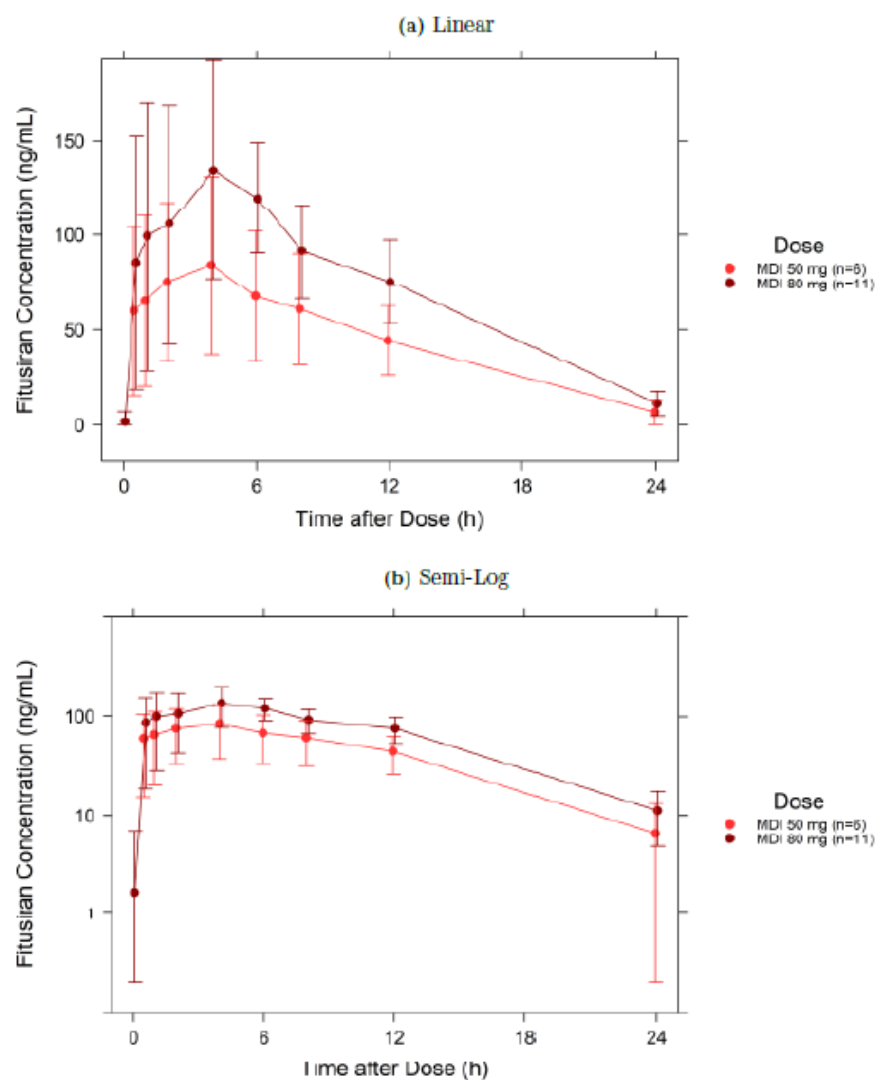
Source: Table 7, Summary of Clinical Pharmacology Studies

Abbreviations: SC, subcutaneous; QM, once monthly

Overall, the PK data indicate that following SC administration to subjects with hemophilia, fitusiran exposures (C_{max}, AUC) increased with dose on both PK assessment days 0 and 56 (after first and third dose); plasma half-lives were similar on Day 0 (~3 to 5 hours) and Day 56 (~2 to 6 hours). Because plasma half-life was very short relative to the dosing interval (QW or QM), no significant accumulation was expected, and the data showed no fitusiran accumulation with monthly dosing.

Dose proportionality evaluations indicated that fitusiran exposure increased approximately dose proportionality on Day 0 and Day 56. Representative examples of fitusiran concentration-time profiles are shown for 50 and 80 mg QM doses (Part D) in [Figure 27](#) (Day 0) and [Figure 28](#) (Day 56).

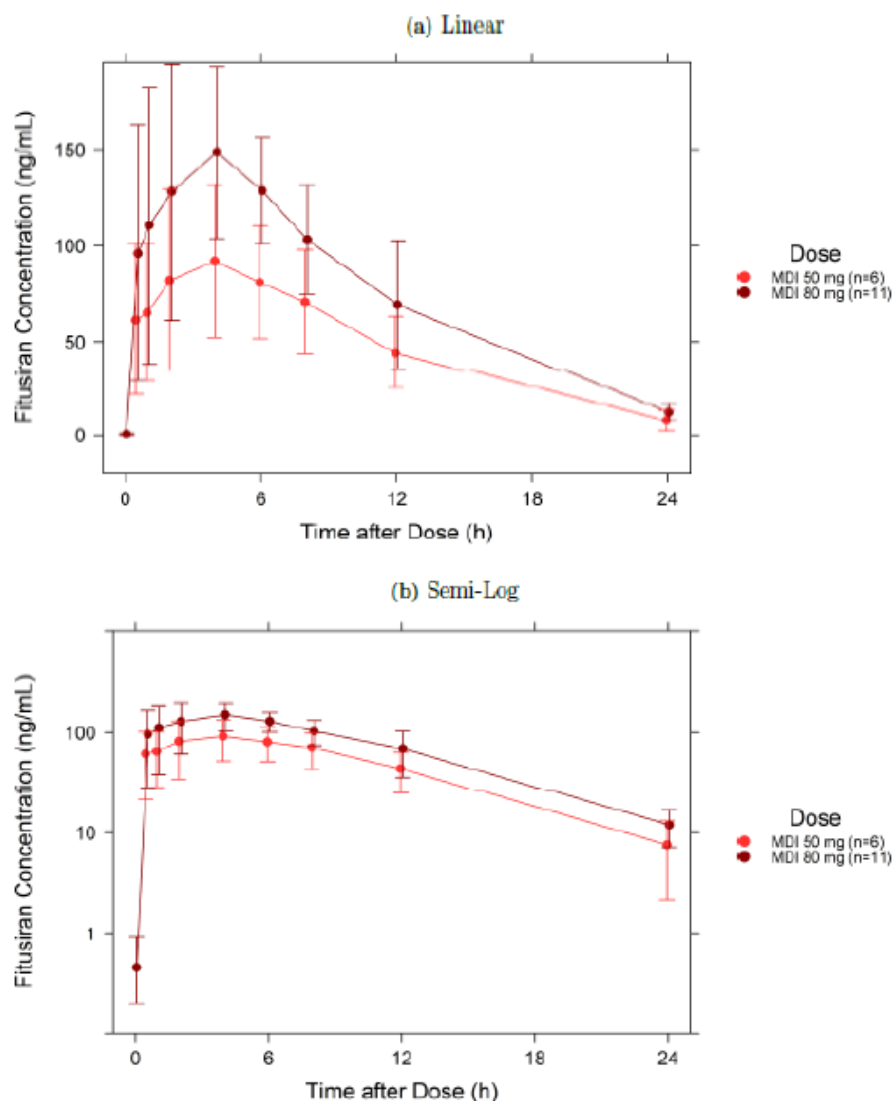
Figure 27. Mean ($\pm$ SD) Plasma Concentration-Time Profiles on Day 0 (After First Dose) in Hemophilia Subjects, Study TDR14767, Part D



Source: Figure 8, Summary of Clinical Pharmacology Studies

Abbreviations: MDI, multiple-dose part (Part D) in subjects with inhibitors; SC, subcutaneous

Figure 28. Mean ($\pm$ SD) Plasma Concentration-Time Profiles on Day 56 (After Third QM dose) in Hemophilia Subjects, Study TDR14767, Part D



Source: Figure 9, Summary of Clinical Pharmacology Studies

Abbreviations: MDI, multiple-dose part (Part D) in subjects with inhibitors; QM, once monthly; SC, subcutaneous

Urine Pharmacokinetics

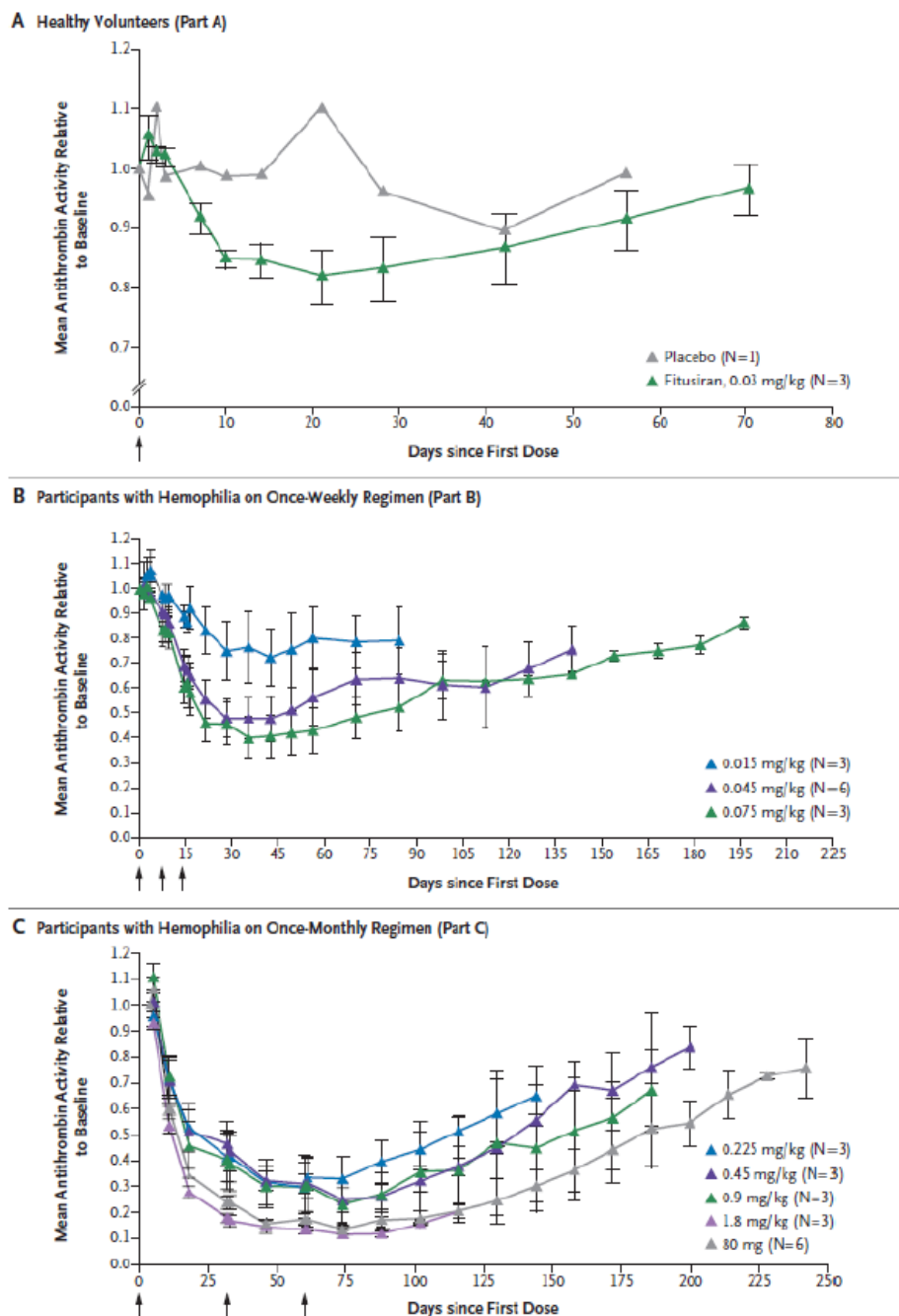
Urinary excretion could not be determined in many subjects due to missing urine volumes. Among the 3 subjects with urine excretion data in Part C (Day 56) who received 1.8 mg/kg (n=1) or 80 mg (n=2), fraction excreted (f_e , presented as % of administered dose) was similar across the 3 subjects (9.8% to 14.0%). In Part D, geometric mean f_e (N=9) was 17.0% on Day 56, with a CV of 54%.

Pharmacodynamics (Plasma AT and TG)

Plasma AT-time profiles of mean AT activity after fitusiran administration, normalized to baseline AT levels, for Parts A, B and C are presented in [Figure 29](#), and for Part D (subjects with inhibitors) in [Figure 30](#).

Fitusiran treatment resulted in a dose-dependent decrease in plasma AT. AT reduction was measurable at 7 days postdose, reaching a maximum after ~28 days, and was sustained between monthly doses at the dose levels tested. The higher monthly doses evaluated (1.8 mg/kg QM and 50 mg and 80 mg QM in Parts C and D) resulted in >80% AT reduction.

Figure 29. Mean ($\pm$ SEM) Plasma Antithrombin-Time Profiles Following Fitusiran Administration in Healthy Subjects (Part A) and Subjects With Hemophilia (Parts B and C), Study TDR14767

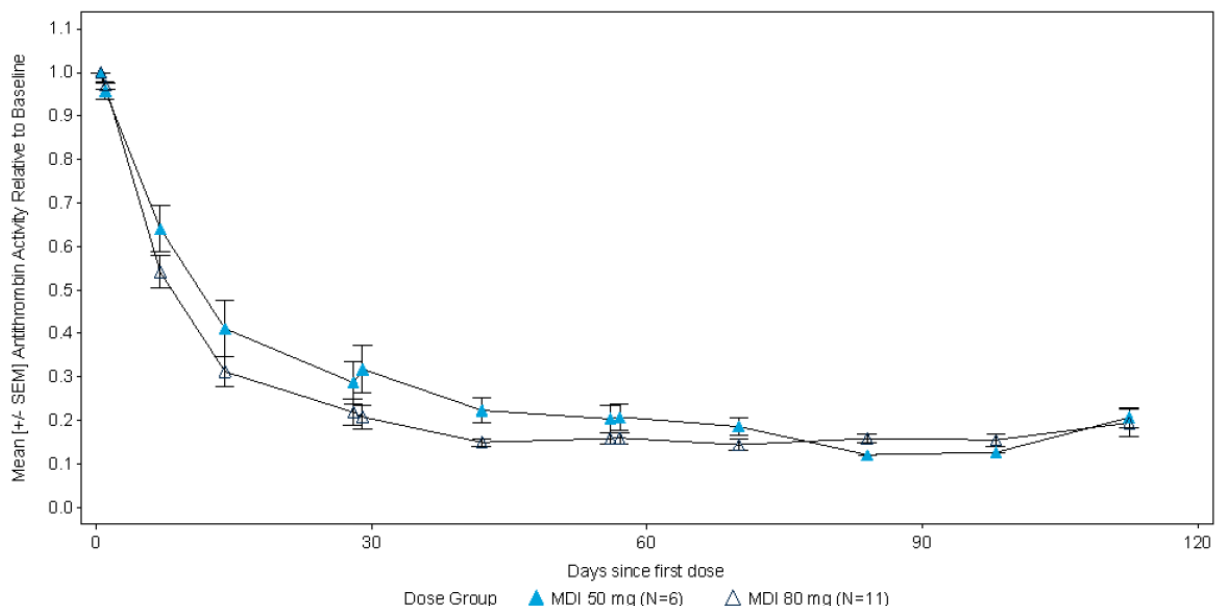


The arrows below the graphs indicate the timing of fitusiran dosing.

Source: (29).

Source: Figure 10, Summary of Clinical Pharmacology Studies
Abbreviation: SEM, standard error of the mean

Figure 30. Mean ($\pm$ SEM) Plasma Antithrombin-Time Profiles Following Fitusiran Administration in Subjects With Hemophilia, Study TDR14767, Part D



Abbreviations: MDI, multiple dose with inhibitors; n, total number of subjects; SEM, standard error of the mean.

Note: Baseline was the average of all predose measurements within 60 days of first dose. Baseline value was plotted as Day 0.

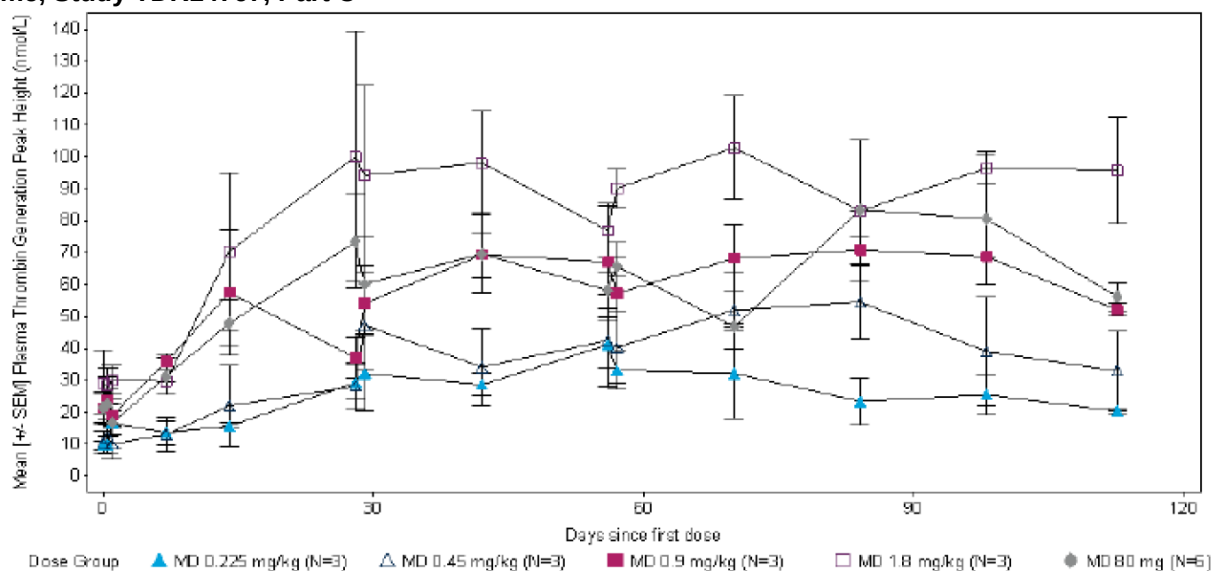
Source: TDR14767 [ALN-AT3SC-001] CSR

Source: Figure 11, Summary of Clinical Pharmacology Studies

Time taken for recovery of AT activity after the last (third) dose was generally dose-dependent. For example, based on a visual evaluation of Part C data ([Figure 10](#)), the time taken for mean AT activity from the 0.225-mg/kg dose group to return to ~50% of starting levels is ~28 days (from Day 84 [trough activity for third dose] to ~Day 112), whereas time taken for mean AT activity from the 80-mg dose group to return to ~50% of starting levels is ~98 days (from Day 84 [trough activity for third dose] to ~Day 182).

[Figure 31](#) shows thrombin generation peak height (nmol/L) by dose group for Part C (representative example).

Figure 31. Mean ($\pm$ SEM) Plasma Thrombin Generation Peak Height (nmol/L) by Dose Group Over Time, Study TDR14767, Part C



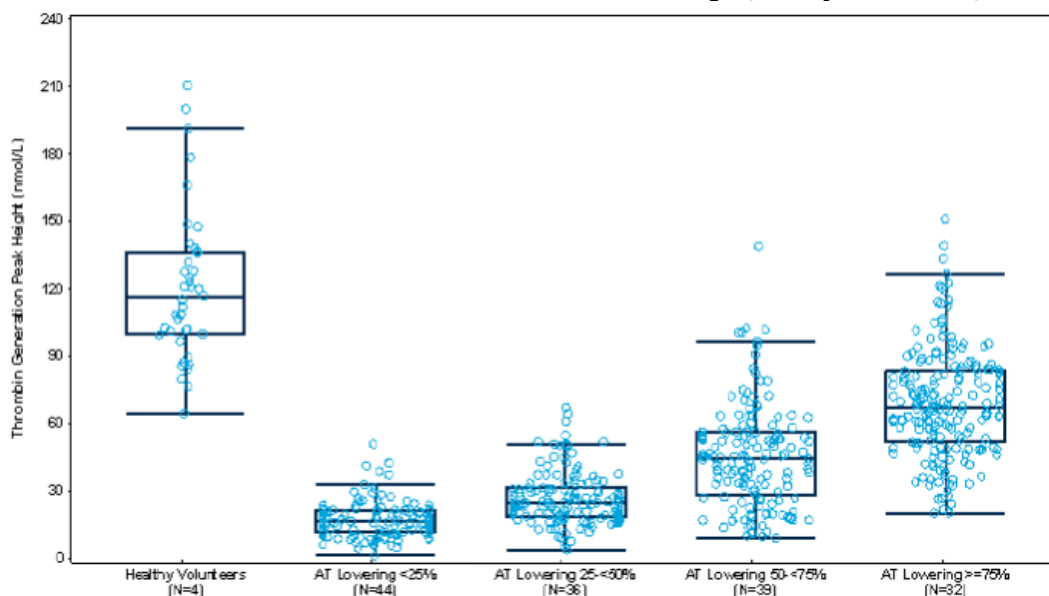
Abbreviations: MD, multiple dose; N, total number of subjects; SEM, standard error of the mean.

Source: TDR14767 (ALN-AT3SC-001) CSR.

Source: Figure 12, Summary of Clinical Pharmacology Studies

The relationship between AT reduction and thrombin generation is shown in [Figure 32](#). TG increases were associated with AT reduction. There was an association between peak TG and the degree of AT reduction with the highest peak TG associated with AT reduction $\geq 75\%$. Peak TG values achieved at AT reduction $\geq 75\%$ were comparable to those observed in the lower end of the normal range in healthy subjects, with values not exceeding the normal range.

Figure 32. Jitter Box Plot of Thrombin Generation Peak Height, Study TDR14767, All Study Parts



Abbreviations: AT, antithrombin; N=total number of subjects.

Note: Data are from Parts A, B, C, and D of Study TDR14767 (ALN-AT3SC-001). Points represent peak thrombin values obtained while participants had the corresponding AT lowering. Peak thrombin values obtained within 48 hours of factor consumption are excluded. The vertical lines represent the most extreme point within 1.5 interquartile ranges. The bottom and top edges of the box indicate intra-quartile range. The line inside the box indicates the median value.

Source: TDR14767 (ALN-AT3SC-001) CSR.

Source: Figure 13, Summary of Clinical Pharmacology Studies

Immunogenicity

No subject developed treatment-induced ADA. Among the treated subjects (n=46), 1 subject in Part B (0.015-mg/kg dose group) had positive ADA results both at baseline and throughout the study. ADA titers in this subject were: predose =400, Day 7=200, and Day 70=400. The PK and pharmacodynamic (PD) parameters for this subject were within the variability observed in other dose groups.

14.2.2. PK/PD Studies in Patients (Five Studies)

14.2.2.1. Phase 1/2 Study LTE14762

Study LTE14762 was a phase 1/2 long term extension study (up to 7 years) in adult subjects with hemophilia who had completed the phase 1 study TDR14767. The primary objective was to evaluate the long-term safety and tolerability of fitusiran in male subjects with moderate or severe hemophilia A or B.

Study Design

This study was an open-label extension study. As mentioned above, Study TDR14767 was conducted in 4 parts. Subjects from Part B rolled over into the LTE1462 study after completing Day 70 in the parent study. Subjects from Parts C and D were expected to roll over into the LTE14762 study approximately 1 month after completing the 3 monthly doses of study drug in the parent study, thereby maintaining their monthly dosing schedule.

Therefore, the fitusiran doses evaluated in this study were 50 mg and 80 mg SC, which were the doses evaluated in the parent study TDR14767. Doses in this study were initially administered in terms of fitusiran sodium salt, but later as fitusiran free acid. Dosing frequency during the period that PK samples were collected (up to 2 years from enrollment) was QM. A dosing pause period for the original dose and regimen was implemented on October 30, 2020, due to thrombotic events observed in other clinical studies within the fitusiran clinical program. Later, a 50 mg Q2M regimen was introduced as part of a risk mitigation strategy against potential thrombotic events since November 25, 2020.

Intensive plasma PK sampling was performed on Day 1, Day 361 (Month 12), and Day 721 (Month 24). The sampling timepoints were: predose, then 0.5, 2, 4, 8, and 24 hours postdose. Urine samples (0 to 6, 6 to 12, and 12 to 24 hours) were collected on Day 721.

Samples for AT activity and TG measurements were collected at the following timepoints: (i) subjects who remained on original dose regimen: D1, then monthly up to Month (M) 24, then M30, M36, M42 and M48; (ii) subjects who changed to modified dose regimen: D1 (day of dose restart), then monthly from post-restart (PR) M1 to PRM12, then PRM16, PRM20, PRM24, PRM28, PR M32, and PRM36. All AT and TG samples were collected predose.

Samples for ADA evaluation were collected on D1, M1, M2, M3, M6, M9, M12, M15, M18, M21, M24, M36, M48, M60, M72, and M84 for the original dose regimens, and PRD1, PRM6, PRM12, PRM24, and PRM36 for the post-restart dose regimens. All ADA samples were collected predose.

Results

Pharmacokinetics

Fitusiran plasma PK parameters following SC administration on Day 1, Day 361, and Day 721 at 50 mg QM and 80 mg QM are presented in [Table 112](#) and [Table 113](#) respectively.

Table 112. Summary of Fitusiran Plasma Pharmacokinetic Parameters Following Single and Multiple SC Administrations at 50 mg QM to Adult Subjects With Hemophilia, Study LTE14762

PK Parameters Mean ± SD (Geometric Mean) [CV%]	Time ^a		
	Day 1	Day 361 (± 7 days) (Month 12)	Day 721 (± 7 days) (Month 24)
N	14	9	2
t _{max} ^b (h)	3.97 (0.50, 8.08)	4.02 (2.00, 8.00)	4.00 (4.00, 4.00)
C _{max} (ng/mL)	86.8±44.1 (71.7) [51]	75.2±50.3 (63.1) [67]	62.5±35.3 (57.2) [57]
AUC _{last} (ng.h/mL)	1110±486 (883) [44]	961±551 (835) [57]	935±550 (850) [59]
AUC _∞ (ng.h/mL)	1470±441 (1420) [30] ^c	356±NC (356) [NC] ^e	NA ^f
t _{1/2} (h)	5.19±1.61 (4.97) [31] ^d	3.91±NC (3.91) [NC] ^e	NA ^f
CL/F (L/h)	37.6±13.6 (36.0) [36] ^c	143±NC (143) [NC] ^e	NA ^f
Vss/F (L)	283±155 (256) [55] ^c	834±NC (834) [NC] ^e	NA ^f
Recovery in 0-24 h urine (f _e (%))	NA	NA	10.7±4.08 (10.3) [38]

Abbreviations: AUC_∞: area under the concentration versus time curve extrapolated to infinity; AUC_{last}: area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last}; CL/F: apparent total body clearance after a single extravascular dose of the drug from plasma; C_{max}: maximum observed concentration; f_e: fraction of the dose excreted in urine over the collection interval; NA = not applicable; NC: not calculable; t_{max}: time to reach the maximum concentration; t_{1/2}: terminal elimination half-life; Vss/F: apparent volume of distribution at the steady state after single extravascular dose.

^a Time from enrollment in LTE14762 study. (LTE14762 subjects had previously received fitusiran doses (at different dose levels) in Phase 1 study TDR14767 [ALN-AT3SC-001]).

^b Median (min-max).

^c N=4

^d N=5

^e N=1

^f N=0

Source: Table 8, Summary of Clinical Pharmacology Studies

Abbreviations: LTE, long-term extension; QM, once monthly; SC, subcutaneous

Table 113. Summary of Fitusiran Plasma Pharmacokinetic Parameters Following Single and Multiple SC Administrations at 80 mg QM to Adult Subjects With Hemophilia, Study LTE14762

PK Parameters Mean ± SD (Geometric Mean) [CV%]	Time ^a		
	Day 1	Day 361 (± 7 days) (Month 12)	Day 721 (± 7 days) (Month 24)
N	17	10	9
t _{max} ^b (h)	4.00 (2.00, 8.07)	6.00 (2.02, 8.03)	7.83 (4.05, 8.00)
C _{max} (ng/mL)	168±74.6 (153) [44]	149±53.2 (141) [36]	155±87.9 (134) [57]
AUC _{last} (ng.h/mL)	2130±769 (2010) [36]	2020±708 (1910) [35]	2070±917 (1890) [44]
AUC _∞ (ng.h/mL)	2230±641 (2160) [29] ^c	2860±NC (2860) [NC] ^d	NA ^e
t _{1/2} (h)	5.90±3.83 (5.16) [65] ^c	4.94±NC (4.94) [NC] ^d	NA ^e
CL/F (L/h)	38.8±12.7 (37.5) [33] ^c	28.3±NC (28.3) [NC] ^d	NA ^e
Vss/F (L)	390±348 (301) [89] ^c	204±NC (204) [NC] ^d	NA ^e
Recovery in 0-24 h urine (f _e [%])	NA	NA	12.6±4.92 (11.5) [39] ^f

Abbreviations: AUC_∞: Area Under the concentration versus time Curve extrapolated to infinity; AUC_{last}: Area Under the concentration versus time Curve calculated using the trapezoidal method from time 0 to the real time t_{last}; CL/F: apparent total body clearance after a single extravascular dose of the drug from plasma; C_{max}: maximum observed concentration; f_e: fraction of the dose of drug excreted in urine over a collection interval; NA = Not Applicable; NC: Not Calculated; t_{max}: time to reach the maximum concentration; t_{1/2}: terminal elimination half-life; Vss/F: apparent volume of distribution at the steady state after single extravascular dose.

^a Time from enrollment in this (LTE14762) study. (LTE14762 subjects had previously received fitusiran doses (at different dose levels) in Phase 1 study ALN-AT3SC-001).

^b Median (min-max).

^c N=3

^d N=1

^e N=0

^f N=7

Source: Table 9, Summary of Clinical Pharmacology Studies

Abbreviations: LTE, long-term extension; QM, once monthly; SC, subcutaneous

Pharmacodynamics

Monthly dosing with fitusiran (original dose and regimen, PD Set 1) resulted in a change in AT activity to 14.4% of baseline starting at Month 1 and persisting over several months. In the revised AT-DR regimen (PD Set 2), the change in AT activity was 23.3% of baseline. There were 3 subjects who discontinued the study because their AT levels were <15%. The rest of the AT activity levels were maintained between 15 to 35%.

Consistent with fitusiran's mechanism of action, TG increased with AT lowering, reaching a peak mean of 74.42nM by endpoint evaluation that remained elevated during the course of fitusiran treatment for the overall subjects in PD Set 1. In PD Set 2, TG reached a mean of 88.08nM.

Immunogenicity

Two subjects developed treatment-induced ADA; one was positive at one timepoint (Month 10) with a titer of 200, and the other was positive at Month 48, Month 60, and Month 72, with a titer of 400 at Month 48 and 100 (equivalent to minimum required dilution [MRD] of the assay) at the other timepoints.

14.2.2.2. Phase 3 Pivotal Study EFC14768

Study EFC14768 was a phase 3 study to evaluate the efficacy and safety of fitusiran in subjects with hemophilia A or B, with inhibitory antibodies to Factor VIII or IX. The primary objective was to evaluate the efficacy of fitusiran compared to on-demand treatment with BPAs, as determined by the frequency of bleeding episodes.

Study Design

Sixty subjects were enrolled in this study, 41 on fitusiran and 19 on bypassing agents (BPA) on demand). PK and PD samples were only collected from the fitusiran-treated subjects.

The fitusiran SC dose evaluated in this study was 80 mg QM, except in 3 subjects from mainland China who received a single first dose of 50 mg, before being switched to 80 mg QM.

Fitusiran treatment duration was 9 months.

Intensive PK sampling (predose, then 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose) was performed after the first fitusiran dose in East Asian subjects, whilst sparse PK samples (4 hours postdose and trough) were collected from all subjects at visits specified in the study protocol. Urine samples for PK analysis were collected at 0 to 6, 6 to 12, and 12 to 24 hours after the first fitusiran dose.

Samples for AT activity and TG measurements were collected at screening, then D1 (baseline), D2 (East Asian only), D8 (East Asian only), D15, D29 (M1), D43, D57 (M2), then monthly up to M9. All AT and TG samples, except D2, D8, and D15, were collected predose. Sampling timepoints for ADA analysis in phase 3 studies are summarized in Section [14.4.1](#)

Results

Pharmacokinetics

A summary of single-dose PK parameters is presented in [Table 114](#).

Table 114. Summary of Fitusiran Plasma PK Parameters on Day 1 Following the First SC Administration at 50 and 80 mg to East Asian Subjects, Study EFC14768

Day 1 PK Parameters Mean $\pm$ SD (Geometric Mean) [CV%]	Dose (mg)	
	50 mg	80 mg
N	3	5
$t_{\max}^a$ (h)	3.93 (0.48-7.85)	1.88 (0.50-5.93)
$C_{\max}$ (ng/mL)	109 $\pm$ 42.8 (104) [39]	152 $\pm$ 103 (132) [68]
AUC_{last} (ng.h/mL)	1350 $\pm$ 497 (1300) [37]	1960 $\pm$ 1040 (1750) [53]
AUC_{∞} (ng.h/mL)	1660 $\pm$ NC ^b (NC) [NC]	2260 $\pm$ 1040 (2080) [46]
$t_{1/2}$ (h)	6.97 $\pm$ NC ^b (NC) [NC]	7.94 $\pm$ 3.88 (7.02) [49]
CL/F (L/h)	33.6 $\pm$ NC ^b (NC) [NC]	41.5 $\pm$ 17.1 (38.4) [41]
V_{ss}/F (L)	380 $\pm$ NC ^b (NC) [NC]	570 $\pm$ 351 (471) [62]
Recovery in 0-24 h urine (f_e (%))	NC ^c	13.9 $\pm$ 4.84 (13.1) [35]

Abbreviations: AUC_{last} , area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last} ; AUC_{∞} , area under the concentration versus time curve extrapolated to infinity; CL/F, apparent total body clearance after a single extravascular dose of the drug from plasma; $C_{\max}$, maximum observed concentration; f_e , fraction of the administered dose excreted in urine as parent drug, over a collection interval; NC, not calculated; $t_{\max}$, time to reach maximum concentration; $t_{1/2}$, terminal elimination half-life; V_{ss}/F , apparent volume of distribution at steady state after single extravascular dose.

^a Median (min-max)

^b N=2

^c Urine samples from 50 mg dose were not analyzed for fitusiran concentrations

Source: Table 10, Summary of Clinical Pharmacology Studies

Abbreviations: PK, pharmacokinetics; SC, subcutaneous

Increases in systemic exposure with dose were approximately dose proportional, with a 1.4- to 1.5-fold increase in mean $C_{\max}$ and AUCs for the 1.6-fold increase in dose from 50 mg to 80 mg, respectively.

A summary of plasma concentrations at 4 hours postdose (C4h) is provided in [Table 115](#) below. C4h values were similar between Non-East Asian and East Asian subjects on Days 1 and 197.

Table 115. Summary of Fitusiran Plasma Concentrations at 4 Hours Postdose and Trough Following SC Administration at 80 mg QM, Study EFC14768

PK Parameter	Fitusiran concentrations (ng/mL)		
	Mean ± SD		
	(Geometric Mean) [CV%]		
Population	Non-East Asian ^a	East Asian ^b	All ^c
N	33	8	41
4 hour concentration – Day 1 (after first dose)	130 ± 54.1 ^d (119) [42]	115 ± 86.1 ^k (95.7) [75]	128 ± 58.1 ^k (116) [46]
4 hour concentration – Day 197 (after eighth dose)	117 ± 57.4 ^e (103) [49]	155 ± 144 (115) [92]	126 ± 83.9 (106) [67]
Pre-dose (pre-first dose)	<LLOQ ± 0.00 ^f (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]

Source: Table 33, Summary of Clinical Pharmacology Studies

^a All subjects except those from East Asian (mainland China, Japan, South Korea, and Taiwan) sites.

^b Subjects from East Asian sites, excluding Day 1, 4 hour, and Day 29 C_{trough} data from the 3 Chinese subjects (Chinese subjects received a first dose of 50 mg followed by subsequent doses of 80 mg).

^c All 80 mg subjects from all sites combined.

^d N=32

^e N=27

^f N=32

^k N=5

Abbreviations: C_{trough}, minimum concentration (concentration just before administration of next dose); CV, coefficient of variation; LLOQ, lower limit of quantification (0.2 ng/mL); NA, not applicable; NC, not calculated; PK, pharmacokinetics; QM, once monthly; SC, subcutaneous; SD, standard deviation

Pharmacodynamics

Monthly dosing with fitusiran resulted in a sustained reduction of AT activity, reaching 15.9% of baseline by Day 29. Consistent with fitusiran's mechanism of action, TG increased with AT reduction, reaching a peak mean of 46.7nM by Day 43 (540% change from baseline) that remained elevated during the course of fitusiran treatment, thus indicating persistent and sustained improvement of coagulation potential.

Immunogenicity

One subject developed treatment-induced ADA at one timepoint, with a titer of 50, equivalent to minimum required dilution (MRD) of the assay, indicating that fitusiran has low potential to elicit an immunogenic response.

14.2.2.3. Phase 3 Pivotal Study EFC14769

Study EFC14769 was a phase 3 study to evaluate the efficacy and safety of fitusiran in subjects with hemophilia A or B, without inhibitory antibodies to Factor VIII or IX. The primary objective was to evaluate the efficacy of fitusiran compared to on-demand treatment with factor concentrates, as determined by the frequency of bleeding episodes.

Study Design

In this study, 120 subjects were enrolled, with 79 on fitusiran and 40 on factor (on demand). PK and PD samples were only collected from the fitusiran-treated subjects. The fitusiran dose

evaluated in this study was 80 mg (free acid) QM, and fitusiran treatment duration was 9 months. Intensive PK sampling was performed after the first fitusiran dose in East Asian subjects, while sparse PK samples (4 h postdose and trough) were collected from all subjects. PK, PD (AT and TG) and ADA timepoints were the same as in Study EFC14768.

Results

Pharmacokinetics

A summary of single-dose PK parameters is presented in [Table 116](#).

Table 116. Summary of Fitusiran Plasma PK Parameters on Day 1 Following the First SC Administration at 80 mg to East Asian Subjects, Study EFC14769

Day 1 PK Parameters Mean ± SD (Geometric Mean) [CV%]	
N	17
$t_{\max}^a$ (h)	4.00 (0.50-12.00)
$C_{\max}$ (ng/mL)	185 ± 115 (160) [62]
AUC_{last} (ng.h/mL)	2020 ± 593 (1940) [29]
AUC_{∞} (ng.h/mL)	2410 ± 474 (2380) [20] ^b
$t_{1/2}$ (h)	7.33 ± 5.63 (5.90) [77] ^c
CL/F (L/h)	34.2 ± 5.94 (33.7) [17] ^b
Vss/F (L)	314 ± 135 (287) [43] ^b
Recovery in 0-24 h urine (fe (%))	11.1 ± 5.39 (9.52) [49] ^d

Abbreviations: AUC_{last} , area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last} ; AUC_{∞} , area under the concentration versus time curve extrapolated to infinity; CL/F, apparent total body clearance after a single extravascular dose of the drug from plasma; $C_{\max}$, maximum observed concentration; f_e , fraction of the administered dose excreted in urine as parent drug, over a collection interval; NC, not calculated; $t_{\max}$, time to reach maximum concentration; $t_{1/2}$, terminal elimination half-life; Vss/F, apparent volume of distribution at steady state after single extravascular dose.

^a Median (min-max)

^b N=10

^c N=12

^d N=16

Source: Table 11, Summary of Clinical Pharmacology Studies

Abbreviations: max, maximum; min, minimum; PK, pharmacokinetics; SC, subcutaneous

The PK data obtained from sparse plasma PK sampling (C4h) following 80 mg QM administration of fitusiran to all subjects (non-East Asian and East Asian) are provided in [Table 117](#). The data indicated that there were no overt differences in mean 4-hour postdose fitusiran concentrations between non-East Asian and East Asian subjects.

Table 117. Summary of Fitusiran Plasma Concentrations at 4 Hours Postdose and Trough Following SC Administration at 80 mg QM, Study EFC14769

PK Parameter	Fitusiran concentrations (ng/mL) Mean ± SD (Geometric Mean) [CV%]		
	Non-East Asian ^a	East Asian ^b	All ^c
N	62	17	79
4 hour concentration – Day 1 (after first dose)	104 ± 67.9 (81.9) [66] ^d	156 ± 124 (125) [80]	115 ± 86.0 (90.2) [74]
4 hour concentration – Day 197 (after eighth dose)	103 ± 64.8 (85.7) [63] ^e	125 ± 75.1 (106) [60] ^j	108 ± 67.3 (89.9) [63]
Pre-dose (pre- first dose)	<LLOQ ± 0.00 (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]

Source: Table 34, Summary of Clinical Pharmacology Studies

^a All subjects except those from East Asian (China, Japan, South Korea, and Taiwan) sites.

^b All subjects from East Asian (China, Japan, South Korea, and Taiwan) sites

^c All subjects from all sites combined.

^d N=58

^e N=56

^j N=16

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification (0.2 ng/mL); NA, not applicable; NC, not calculated; QM, once monthly; SC, subcutaneous; SD, standard deviation

Pharmacodynamics

Monthly dosing with fitusiran resulted in a sustained reduction of AT activity levels, reaching 17.9% of the baseline by Day 29. Consistent with fitusiran's mechanism of action, TG increased with AT reduction, reaching a peak mean of 40.7nM by Day 225 (703.36% change from baseline) that remained elevated during the course of fitusiran treatment, thus indicating improvement of persistent and sustained TG potential.

Immunogenicity

Four subjects from the fitusiran prophylaxis group developed treatment-induced ADA at one or more timepoints. Three subjects from the factor on-demand arm were also positive at one or more timepoints. ADA titer in each case was 50 (equivalent to MRD of the assay).

14.2.2.4. Phase 3 Pivotal Study EFC15110

Study EFC15110 was an open-label, multinational switching study to describe the efficacy and safety of fitusiran prophylaxis in subjects with hemophilia A and B previously receiving factor or bypassing agent prophylaxis. The primary objective was to characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving factor concentrate or bypassing agent (BPA) prophylaxis.

Study Design

PK and PD samples were only collected during the fitusiran treatment phase of the study.

Fitusiran doses evaluated in this study were 80 mg QM and 50 mg Q2M (administered in terms of free acid), and fitusiran treatment duration was 7 months. Intensive PK sampling was performed after the first fitusiran dose in East Asian subjects. Sparse PK samples (4 hours postdose and trough) were collected from all subjects. Since the change in dose regimen from 80 mg QM to 50 mg Q2M, introduced as part of a risk mitigation strategy against potential thrombotic events, was only made towards the end of the study when the majority of subjects had already completed their 7-month fitusiran treatment period, all the PK data from this study are with the 80 mg QM dose.

Sample collection timepoints for intensive and sparse plasma PK and urine PK analyses from East Asian subjects after the first fitusiran dose were the same as in Study EFC14768. Samples for AT activity and TG measurements were collected at screening, then D1 (baseline), D2 (East Asian only), D8 (East Asian only), D15, D29 (M1), D43, D57 (M2), then monthly up to M7. All AT and TG samples, except D2, D8, and D15, were collected predose. Sampling timepoints for ADA analysis in phase 3 studies are summarized in Section [14.4.1](#).

Results

Pharmacokinetics

A summary of single-dose PK parameters is presented in [Table 118](#). The data indicated that, following fitusiran administration at 80 mg QM, mean plasma PK parameters and recoveries of fitusiran in 0 to 24 h urine were similar in East Asian subjects with and without inhibitors.

Table 118. Summary of Fitusiran Plasma PK Parameters on Day 1 Following the First SC Administration at 80 mg to Subjects With and Without Inhibitors in East Asian Subjects, Study EFC15110

Day 1 PK Parameters Mean ± SD (Geometric Mean) [CV%]	Inhibitor Status	
	With Inhibitors	Without Inhibitors
N	3	13
t _{max} ^a (h)	5.95 (5.63 ,7.58)	6.00 (1.00 ,8.00)
C _{max} (ng/mL)	206±72.1 (196) [35]	186±73.3 (175) [39]
AUC _{last} (ng.h/mL)	2670±777 (2590) [29]	2270±623 (2190) [27]
AUC _∞ (ng.h/mL)	2520±508 (2490) [20] ^b	2560±511 (2510) [20] ^c
t _{1/2} (h)	6.28±1.23 (6.22) [20] ^b	6.25±2.50 (5.78) [40] ^c
CL/F (L/h)	32.4±6.54 (32.1) [20] ^b	32.7±8.10 (31.9) [25] ^c
Vss/F (L)	372±117 (363) [31] ^b	352±141 (325) [40] ^c
Recovery in 0-24 h urine (fe (%))	21.6±7.38 (20.6) [34]	17.3±12.0 (14.6) [70]

Abbreviations: AUC_{last}, area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last}; AUC_∞, area under the concentration versus time curve extrapolated to infinity; CL/F, apparent total body clearance after a single extravascular dose of the drug from plasma; C_{max}, maximum observed concentration; fe, fraction of the administered dose excreted in urine as parent drug, over a collection interval; NC, not calculated; t_{max}, time to reach maximum concentration; t_{1/2}, terminal elimination half-life; Vss/F, apparent volume of distribution at steady state after single extravascular dose.

^a Median (min-max)

^b N=2

^c N=9

Source: Table 12, Summary of Clinical Pharmacology Studies
Abbreviations: PK, pharmacokinetics; SC, subcutaneous

The PK data obtained from sparse plasma PK sampling (C4h) following 80 mg QM administration of fitusiran to all subjects (non-East Asian + East Asian), or East Asian subjects, with and without inhibitors, are provided in [Table 119](#) and [Table 120](#). Further, there was no significant difference in mean 4-hour postdose fitusiran concentrations between non-East Asian and East Asian subjects with or without inhibitors (data not shown).

Table 119. Summary of Fitusiran Plasma Concentrations at 4 Hours Postdose and at Trough Following SC Administration at 80 mg QM to Subjects (Non-East Asian + East Asian) With and Without Inhibitors, Study EFC15110

PK Parameter	Fitusiran concentrations (ng/mL)		
	Mean ± SD (Geometric Mean) [CV%]		
Inhibitor Status	With Inhibitors	Without Inhibitors	All
N	20	44	64
4 hour concentration – Day 1 (after first dose)	126±73.6 (111) [59]	126±68.5 (111) [54]	126±69.5 (111) [55]
4 hour concentration – Day 141 (after 6th dose)	135±65.1 (121) [48]	137±76.6 (119) [56]	136±72.2 (120) [53]
Pre-dose (pre-first dose)	<LLOQ ± 0.00 (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]	<LLOQ ± 0.00 (NA) [NC]

Source: Table 35, Summary of Clinical Pharmacology Studies

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification (0.2 ng/mL); NA, not applicable; NC, not calculated; QM, once monthly; SC, subcutaneous; SD, standard deviation

Table 120. Summary of Fitusiran Plasma Concentrations at 4 Hours Postdose and at Trough Following SC Administration at 80 mg QM to East Asian Subjects With and Without Inhibitors, Study EFC15110

PK Parameter	Fitusiran concentrations (ng/mL)		
	Mean ± SD (Geometric Mean) [CV%]		
Population	East Asian ^a		
Inhibitor Status	With Inhibitors	Without Inhibitors	All ^b
N	3	13	16
C _{max} at 4 hours – Day 1 (after first dose)	145±78.9 (132) [54]	140±58.8 (128) [42]	141±60.0 (129) [43]
C _{max} at 4 hours – Day 141 (after 6th dose)	174±76.4 (160) [44]	148±85.3 (127) [57] ^c	155±80.5 (135) [52]
Pre-dose (pre-first dose)	<LLOQ ± NC (NA) [NC]	<LLOQ ± NC (NA) [NC]	<LLOQ ± NC (NA) [NC]

Source: Table 37, Summary of Clinical Pharmacology Studies

^a All subjects from East Asian (Japan and South Korea) sites.

^b All East Asian subject with and without inhibitors.

^c N=9, the 4 hours postdose samples for subject (b) (6) on Day 141 were not collected.

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification (0.2 ng/mL); NA, not applicable; NC, not calculated; QM, once monthly; SC, subcutaneous; SD, standard deviation

Pharmacodynamics

Monthly dosing with fitusiran resulted in a sustained reduction of AT levels, reaching 16.6% of baseline by Day 29 that persisted over several months. The lowest AT level reached was 9.4% of baseline at Day 169, with 12.7% for Cohort A (inhibitor) and 7.8% for Cohort B (noninhibitor), respectively.

Consistent with fitusiran's mechanism of action, TG increased with AT reduction, reaching a peak mean of 62.6nM (472% change from baseline) by endpoint evaluation (defined as the last nonmissing postbaseline assessment on or before EOS/ET visit for fitusiran 80 mg prophylaxis period) that remained elevated during the course of fitusiran treatment for the overall subjects. The peak TG levels were 54.1nM (564% change from baseline) for subjects in Cohort A (inhibitor) and 66.5nM (429% change from baseline) for the subjects in Cohort B (noninhibitor), respectively.

Immunogenicity

Two subjects had treatment-induced ADA at one timepoint each. The ADA titer in each case was 50 (equivalent to the MRD of the assay).

14.2.2.5. Phase 3 Pivotal Study LTE15174

Study LTE15174 was an open-label long-term safety and efficacy study of fitusiran in subjects with hemophilia A or B, with or without inhibitory antibodies to factor VIII or IX. This study used the AT-DR. The primary objective was to characterize the long-term safety and tolerability of fitusiran. The primary endpoints of this study were the incidence, severity, relatedness, and seriousness of adverse events (AEs), and laboratory assessments.

Study Design

This study enabled subjects who had completed any of the phase 3 studies of fitusiran to continue to be evaluated for long-term safety and efficacy. It was initially planned as a long-term extension study for subjects from phase 3 studies EFC14768, EFC14769, and EFC15110 at the same dose regimen (80 mg QM) as the parent studies. The majority of subjects from the parent studies had already rolled over into LTE15174 when dosing was temporarily paused to evaluate a revised AT-DR. Unlike the dose regimen in the parent studies, which targeted AT reduction of $\geq 85\%$ in the majority of subjects, the postpause strategy targeted AT activity values between 15% to 35% with fitusiran treatment.

The final dose regimens evaluated in LTE15174 were: 20 mg Q2M, 20 mg QM, 50 mg Q2M, 50 mg QM, and 80 mg QM. All doses were administered in terms of fitusiran free acid. Following the dosing pause, all subjects except 11, who had AT activity of 15 to 35% at 80 mg QM regimen, were restarted on fitusiran treatment at 50 mg Q2M. Of these 11 subjects, 4 later required a dose reduction, but the other 7 remained on the 80 mg QM dose regimen. Subjects who had AT values $>35\%$ after 2 to 3 doses at 50 mg Q2M, were dose escalated to 50 mg QM (and if needed, to 80 mg QM); if they had AT values $<15\%$, they were dose de-escalated to 20 mg Q2M (and if needed, escalated to 20 mg QM from 20 mg Q2M), as appropriate, based on the criteria shown in [Figure 5](#) in section [6.1.3](#). Subjects who had AT activity $<15\%$ at 20 mg Q2M were discontinued from the study.

Fitusiran dosing in all previous clinical studies was conducted using a glass vial and syringe device, and the same device was used to deliver the different doses (20 mg, 50 mg, 80 mg) in this study. In addition, a 50 mg fitusiran prefilled pen (PFP) device was also evaluated in this study.

Intensive PK sampling was performed in the following 3 subgroups of subjects: (a) after the first 50-mg dose in East Asians (at least 12 each from mainland China [mainly de novo subjects] and South Korea, and all subjects [who consented to intensive PK sampling] from Japan and Taiwan), and Non-East Asians (at least 12 subjects from rest of the world [ROW]); (b) after the first 20-mg dose to at least 6 East Asian subjects (from any East Asian country or region [mainland China, Japan, South Korea, Taiwan]), and at least 6 Non-East Asian subjects (from ROW), and (c) 12 subjects (any region of the world) for PK comparison between 50-mg dose administered first using a glass vial and syringe device (all 12 subjects), and at the next dose (Q2M or QM), using a PFP device (all 12 subjects). Eleven (11) subjects completed intensive sampling following administration by both devices. Intensive PK samples were not collected from any of the subjects who remained on the 80 mg QM dose in this study. Sparse PK samples (at 4 hours postdose and trough) were collected from all subjects. Urine PK samples were collected from 7 subjects in the 50 mg Q2M group only.

Sample collection timepoints for intensive and sparse plasma PK and urine PK analyses were the same as for the other phase 3 studies. Details of the AT and TG sampling times for subjects under different dose regimens are provided in the schedule of assessments of LTE15174 protocol, but in general they were: (a) D1 (baseline), D15, D29 (M1), M2, M3, then every 3 months up to M24, then every 6 months up to M48, for subjects who remained on original dose regimen; and (b) PRD1 (day of dose restart), then monthly from PRM1 to PRM12, then every 4 months up to PRM36, then PRM42 and PRM48, for subjects who changed to AT-DR. All AT and TG samples, except Day 15, were collected predose. Sampling timepoints for ADA analysis in phase 3 studies are summarized in Section [14.4.1](#).

Results

Pharmacokinetics

A summary of PK parameters following fitusiran administration at 20 mg Q2M and 50 mg Q2M is presented in [Table 121](#). Increases in systemic exposure with dose were approximately dose-proportional, with a 2.4- to 2.6-fold increase in mean C_{max} and AUCs for the 2.5-fold increase in dose from 20 mg to 50 mg, respectively.

Table 121. Summary of Fitusiran Plasma PK Parameters Following the First SC Administration at 20 mg Q2M and 50 mg Q2M, Study LTE15174

PK Parameters Mean $\pm$ SD (Geometric Mean) [CV%]	Dose Regimen	
	20 mg Q2M	50 mg Q2M
N	6	84
$t_{\max}$ ^a (h)	2.88 (0.50, 4.33)	3.78 (0.42, 11.90)
$C_{\max}$ (ng/mL)	34.4 $\pm$ 10.1 (33.1) [29]	84.1 $\pm$ 58.7 (72.7) [70]
AUC _{last} (ng.h/mL)	451 $\pm$ 85.1 (444) [19]	1090 $\pm$ 372 (1020) [34]
AUC _{∞} (ng.h/mL)	491 $\pm$ 83.8 (484) [17]	1290 $\pm$ 377 (1200) [29] ^c
$t_{1/2}$ (h) ^b	5.57 $\pm$ 2.36 (5.06) [42]	7.98 $\pm$ 4.74 (6.75) [59] ^c
CL/F (L/h)	41.9 $\pm$ 8.39 (41.3) [20]	50.8 $\pm$ 71.1 (41.5) [140] ^c
Vss/F (L)	431 $\pm$ 135 (413) [31]	570 $\pm$ 713 (454) [125] ^c
Recovery in 0-24 h urine (fe (%))	NS	14.6 $\pm$ 16.4 (3.89) [112] ^d

Abbreviations: AUC_{last} = area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last}; AUC _{∞} = area under the concentration versus time curve extrapolated to infinity; C_{max} = maximum observed concentration; t_{1/2} = terminal elimination half-life; CL/F = apparent total body clearance after a single extravascular dose of the drug from plasma; NCA = noncompartmental analysis; NS = No samples collected; t_{max} = time to reach the maximum concentration; Vss/F = apparent volume of distribution at the steady state after single extravascular dose

^a Median (min-max).

^b Terminal half-life (referred to as t_{1/2 β} in study protocol).

^c N=52-58. AUC _{∞} , t_{1/2 β} , CL/F, and/or Vss/F could not be calculated for the other participants.

^d N=4.

Source: Table 13, Summary of Clinical Pharmacology Studies

Abbreviations: LTE, long-term extension; PK, pharmacokinetics; Q2M, every 2 months; SC, subcutaneous

Mean PK parameters presented in [Table 121](#) above are for all subjects (Non-East Asian and East Asian, with and without inhibitors). PK data by individual subgroups (Non-East Asian, with and without inhibitors, and East Asian, with and without inhibitors) are provided in 5.3.5.2 Study LTE15174 Appendix 16.2.5 [16.2.5.4.1].

A summary of the PK data obtained from sparse plasma PK sampling (C4h) by dose group (20 mg Q2M and QM, 50 mg Q2M and QM, and 80 mg QM) is provided in [Table 122](#). C4h summaries by non-East Asian and East Asian subjects, with and without inhibitors are provided in 5.3.5.2 Study LTE15174 Appendix 16.2.5 [16.2.5.4.1].

Table 122. Summary of Fitusiran Concentrations at 4 Hours Postdose and at Trough Following SC Administration at 20 mg Q2M, 20 mg QM, 50 mg Q2M, 50 mg QM, and 80 mg QM, Study LTE15174

Fitusiran Concentrations (ng/mL) Mean ± SD (Geometric Mean) [CV%]	Dose Regimen				
	20 mg Q2M	20 mg QM	50 mg Q2M	50 mg QM	80 mg QM
N (Total) = 600	122	3	257	38	180
4 hours post-dose – Day 1 (after first dose)	25.0±12.1 (22.4) [48] [N=106]	25.0 [N=1] ^a	70.2±41.0 (59.7) [58] [N=223]	NS	120±72.9 (105) [61] [N=169]
4 hours post-dose – Month 6	25.9±15.8 (22.3) [61] [N=75]	31.5, 22.3 [N=2] ^a	62.2±35.5 (53.8) [57] [N=159]	44.0±19.7 (40.0) [45] [N=18]	70.7, 115 [N=2] ^a
4 hours post-dose – Month 12	21.2±9.41 (19.0) [44] [N=50]	NS	52.1±29.4 (45.1) [56] [N=92]	42.2±15.8 (39.6) [38] [N=15]	102±41.2 (94.3) [40] [N=21]
Predose – Day 1 (before first dose)	<LLOQ ±0.0568 (NA) [746] [N=112]	<LLOQ [N=1] ^a	<LLOQ ±0.340 (NA) [729] [N=239]	0.311±0.712 (NA) [229] [N=7]	0.386±1.11 (NA) [287] [N=176]

Source: Table 38, Summary of Clinical Pharmacology Studies

Note: Details of data excluded from descriptive statistics in Table 16, are provided in the LTE15174 CSR. Reasons included: deviation in sample collection time greater than ±15%, abnormal values, sample collection date or time not documented, and for trough samples, no dose administered at the previous visit.

^a For N <3, individual values, rather than descriptive statistics, are provided.

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification (0.2 ng/mL); LTE, long-term extension; NA, not applicable; NS, no samples collected; QM, once monthly; Q2M, every two months; SC, subcutaneous; SD, standard deviation

Overall, the PK data (from both intensive and sparse sampling) indicated that there were no overt differences in PK between non-East Asian and East Asian subjects with or without inhibitors.

Descriptive statistics of the key PK parameters following fitusiran administration by PFP versus glass vial and syringe devices are tabulated in [Table 123](#), and the results from the statistical analysis between the 2 devices (geometric mean ratios and 90% confidence intervals [CI]) are presented in Section [6.1.4.4](#). The data showed that fitusiran exposures following administration of the 50-mg dose with the PFP device were similar to those after the glass vial with syringe device. Geometric mean ratios (and 90% confidence intervals) for C_{max}, AUC_{last}, and AUC_∞ were 0.98 (0.83 to 1.15), 0.97 (0.83 to 1.13), and 0.97 (0.86 to 1.11), respectively.

Table 123. Summary of Fitusiran Plasma PK Parameters Following Administration of 50 mg Fitusiran With Glass Vial With Syringe and Prefilled Pen

PK Parameters Mean $\pm$ SD (Geometric Mean) [CV%]	Device	
	Vial/Syringe	Prefilled Pen
N	12	11
t_{max}^a (h)	2.08 (0.50, 6.03)	0.93 (0.43, 4.50)
C_{max} (ng/mL)	85.2 $\pm$ 32.7 (79.3) [38]	80.9 $\pm$ 27.9 (76.5) [34]
AUC _{last} (ng.h/mL)	1190 $\pm$ 386 (1130) [32] ^b	1160 $\pm$ 420 (1090) [36] ^d
AUC _{∞} (ng.h/mL)	1370 $\pm$ 346 (1330) [25] ^c	1370 $\pm$ 419 (1320) [31] ^e

Abbreviations: AUC_{last} = Area Under the concentration versus time Curve calculated using the trapezoidal method from time 0 to the real time t_{last} , AUC _{∞} = Area Under the concentration versus time Curve extrapolated to infinity, C_{max} = maximum observed concentration, NC = Not Calculated, NCA = noncompartmental analysis, t_{max} = time to reach the maximum concentration

Footnotes:

a Median (min-max).

b N=10, for Participant (b) (6) the 24 hour value was missing, so the parameter AUC_{last} was excluded in the descriptive statistics, and for participant (b) (6) the 24 hour value was an abnormal value and the value was excluded in PK parameter analysis, so the parameter AUC_{last} was excluded in the descriptive statistics.

c N=9, for Participant (b) (6) AUC _{∞} could not be calculated due to poor fit of the linear regression (R^2 adjusted <0.7) and for participants (b) (6) the AUC_{ext} value was exceeded 30%, and therefore the AUC _{∞} was excluded from descriptive statistics.

d N=10, for Participant (b) (6) the 24 hour value was missing, so the parameter AUC_{last} was excluded in the descriptive statistics.

e N=9, for participant (b) (6) AUC _{∞} could not be calculated due to poor fit of the linear regression (R^2 adjusted <0.7) and for participant (b) (6) the AUC_{ext} value was exceeded 30%, and therefore the AUC _{∞} was excluded from descriptive statistics.

Source: Table 39, Summary of Clinical Pharmacology Studies

Abbreviations: Q2M, every 2 months; QM, once monthly; SC, subcutaneous

Pharmacodynamics

The fitusiran revised AT-DR was successful at maintaining AT levels within the targeted AT range. Most subjects were able to achieve AT levels between 15 to 35% with the revised AT-DR. Overall, 200 of 213 rolled-over subjects (93%) required no or 1 dose change to maintain AT activity between 15 to 35%; 167 (78%) subjects were on Q2M regimens. None of the subjects who initiated dosing at 50 mg Q2M needed a dose higher than 50 mg QM to achieve AT activity in the target 15 to 35% range. Of subjects at the lowest dose evaluated (20 mg Q2M), 11.7% repeatedly had AT <15% and thus required fitusiran discontinuation.

Under the revised AT-DR, dosing with fitusiran resulted in a sustained lowering of AT activity levels. The mean (SD) AT level was 23.5% (4.64%) during the Primary Efficacy Period. The results showed that the majority of subjects were within the target AT range of 15 to 35% at steady-state and remained within the range for the duration of the study under the revised AT-DR, regardless of the actual fitusiran dose. Following discontinuation of fitusiran treatment, fitusiran effects (reduced AT activity) persisted over several months. In the majority of subjects AT had recovered to >60% in 6 months.

Immunogenicity

Overall, 4 out of 5 confirmed ADA-positive subjects had treatment-induced ADA, which were generally transient. One subject was ADA-positive only at study entry and not at subsequent timepoints. One subject had persistent treatment-induced ADA with a peak ADA titer of 100 and last titer of 50.

14.3. Bioanalytical Method Validation and Performance

The bioanalytical methods used for fitusiran clinical studies are classified into three categories: PK, PD biomarkers, and ADA assays. Bioanalytical methods were developed in accordance with the ICH and regulatory guidelines.

14.3.1. Bioanalytical Method for PK Assessment

The PK assays included determination of fitusiran concentrations in plasma and urine. An overview of the assay methods used for quantitation of fitusiran plasma and urine concentrations is provided in [Table 124](#).

Table 124. Overview of Pharmacokinetic Assays Used in Fitusiran Clinical Studies

Assay Code	Method	Biological Matrix	LLOQ (ng/mL)	Clinical Study	Assay site	Report Location
TSLS14-334 and addendums 01 and 02	LC-FD	Plasma (K ₂ EDTA)	0.200 ng/mL	TDR14767 (ALN-AT3SC-001), LTE14762, EFC14768, EFC14769, EFC15110, LTE15174	(b) (4)	Module 5.3.1.4
TSLS13-178	LC-FD	Urine	1.00 ng/mL	TDR14767 (ALN-AT3SC-001), LTE14762		Module 5.3.1.4
TSLS13-178 (PDV0075)	LC-FD	Urine	1.00 ng/mL	EFC14768, EFC14769, EFC15110, LTE15174		Module 5.3.1.4
PDV0102	LC-FD	Plasma (K ₂ EDTA)	0.200 ng/mL	Chinese participants in EFC14768, EFC14769, LTE15174		Module 5.3.1.4

Abbreviations: LC-FD = liquid chromatography (LC) with fluorescence detection (FD), LLOQ = lower limit of quantification

Source: Table 3, Summary of Biopharmaceutical Studies and Associated Analytical Methods

The assay validation summaries for fitusiran concentration in two assay sites are presented in Tables 12 and 13 in Summary of Biopharmaceutical Studies and Associated Analytical Methods (Module 2.7). Cross-validation data demonstrated the comparability of the assays between (b) (4) (comparator lab) and (b) (4) (reference lab). The bioanalytical reports of each clinical study, including the performance of calibration standards and QCs in sample analysis, are located in Module 5.3.5.1 (Appendix 16.2.5). The method validation and sample analysis are deemed adequate.

14.3.2. Bioanalytical Method for PD Assessment

The PD assays included analysis of plasma AT activity and/or AT protein levels, thrombin generation (TG), selected cytokines (IL-1 β , IL-1RA, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IP-10, IFN- α , IFN- γ , TNF- α , GM-CSF and G-CSF), factor VIII (FVIII) and factor IX (FIX) inhibitors. The Applicant submitted method validation summaries for the abovementioned PD biomarkers.

An overview of the assay methods used for assessment of PD and biomarkers is provided in [Table 125](#) below.

Table 125. Overview of PD and Biomarker Assays Used in Fitusiran Clinical Studies

Assay Code	Analyte	Method	Biological Matrix	LLOQ	Clinical Study	Assay site	Report Location (CTD Module)
2012-0021-G	AT activity	Chromogenic assay	plasma (citratd)	10%	TDR14767 (ALN-AT3SC-001), LTE14762, EFC14768, EFC14769, EFC15110, LTE15174	(b) (4)	Module 5.3.1.4
BMV0091, addendum 01 and amendment 01	AT activity	Chromogenic assay	plasma (citratd)	10%	Chinese participants in studies EFC14768, EFC14769, LTE15174		Module 5.3.1.4
3000085	AT protein	ELISA	plasma (citratd)	3.13 ng/mL	TDR14767 (ALN-AT3SC-001)		Module 5.3.1.4
2012-0021-I	TG	Calibrated automated thrombogram	plasma (citratd)	NA	TDR14767 (ALN-AT3SC-001), LTE14762, EFC14768, EFC14769, EFC15110, LTE15174		Module 5.3.1.4
2012-0021-J	TG	Calibrated automated thrombogram	plasma (citratd)	NA	TDR14767 (ALN-AT3SC-001)		Module 5.3.1.4
302269	Selected Cytokines	Luminex multiplex ELISA	serum	value varies for different cytokines *	TDR14767 (ALN-AT3SC-001)		Module 5.3.1.4
2012-0021-K	FVIII inhibitor	Nijmegen-Bethesda assay	plasma (citratd)	0.3 NBU/mL	TDR14767 (ALN-AT3SC-001), EFC14768, EFC14769, EFC15110, LTE15174		Module 5.3.1.4
2012-0021-O	FIX inhibitor	Nijmegen-Bethesda assay	plasma (citratd)	0.3 NBU/mL	TDR14767 (ALN-AT3SC-001), EFC14768, EFC14769, EFC15110, LTE15174		Module 5.3.1.4

Abbreviations: AT = Antithrombin; TG = Thrombin Generation, LLOQ = lower limit of quantification, NA = Not applicable

* LLOQ values are different for different cytokines. Refer to 5.3.1.4 [302269].

Source: Table 4, Summary of Biopharmaceutical Studies and Associated Analytical Methods

The method validation for AT activity in human plasma demonstrated acceptable precision, accuracy, dilutional linearity, and drug interference, and established that the method is suitable for quantitation of AT activity in clinical trials. All assay acceptance criteria were met for the assay parameters tested. The lower limit of quantification of the assay was 10.0% and the limit of detection (LOD) was 5.0%. The assay validation summaries for AT activity in two assay sites are presented in [Table 126](#) and [Table 127](#) below. The validation summaries for other PD assays can be found in Module 2.7 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Table 126. Validation Summary for AT Activity Assay in Citrated Plasma ((b) (4))

Test Article	AT activity
Study number	2012-0021-G
Species	Human
Sample Analytical Matrix	Sodium citrated plasma
Type of Assay	Chromogenic assay
Minimum Required Dilution (MRD)	NA
Validated Range	10.0 % (LLOQ) to 135.0% (ULOQ)
Dilution Linearity/Hook Effect	1: 2 and 1:4 dilution with AT buffer were acceptable. Dilution of plasma samples below 10% was not recommended. No hook effect.
Drug Interference	No interference of ALN-AT3SC up to 3 mg/mL
Accuracy and Precision	Accuracy and precision for intra-assay are as follows C0 (very low AT): 13.9%CV, within $\pm 20\%$ bias C1 (low AT): 2.6%CV, within $\pm 20\%$ bias C2 (mid AT): 2.9%CV, within $\pm 20\%$ bias C3 (high AT): 3.7%CV, within $\pm 20\%$ bias Accuracy and precision for inter-assay are as follows C0 (very low AT): 8.8%CV, within $\pm 20\%$ bias C1 (low AT): 2.6%CV, within $\pm 20\%$ bias C2 (mid AT): 1.7%CV, within $\pm 20\%$ bias C3 (high AT): 1.8%CV, within $\pm 20\%$ bias
Selectivity (Normal/Hemolyzed/Lipemic)	NA
Bench Top Stability at Room Temperature	8 hours
Freeze/Thaw (F/T) Stability	Up to 5 F/T cycles
Long Term Stability	Up to 6 months at -60°C to -80°C

Abbreviations: ALN-AT3SC = fitusiran; AT = Antithrombin; F/T = Freeze/Thaw; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification; NA = Not applicable

Source: 5.3.1.4 [2012-0021-G].

Source: Table 15, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 127. Validation Summary for AT Activity Assay in Citrated Plasma ((b) (4))

Test Article	AT activity
Study number	BMV0091
Species	Human
Sample Analytical Matrix	Sodium citrated plasma
Type of Assay	Chromogenic assay
Minimum Required Dilution (MRD)	NA
Validated Range	10.0 % (LLOQ) to 135.0% (ULOQ)
Dilution Linearity/Hook Effect	1: 2 and 1:4 dilution with AT buffer were acceptable. Dilution of plasma samples below 10% was not recommended. No hook effect.
Parallelism	Passed
Drug Interference	No interference of ALN-AT3SC up to 3 mg/mL
Accuracy and Precision	Accuracy and precision for intra-assay are as follows C0 (very low AT): 20.59%CV, within $\pm 20\%$ bias C1 (low AT): 6.63%CV, within $\pm 20\%$ bias C2 (mid AT): 2.28%CV, within $\pm 20\%$ bias C3 (high AT): 2.05%CV, within $\pm 20\%$ bias Accuracy and precision for inter-assay are as follows C0 (very low AT): 12.54%CV, within $\pm 20\%$ bias C1 (low AT): 4.08%CV, within $\pm 20\%$ bias C2 (mid AT): 1.44%CV, within $\pm 20\%$ bias C3 (high AT): 1.30%CV, within $\pm 20\%$ bias
Selectivity (Normal/Hemolyzed/Lipemic)	No interference from hemolyzed matrix and lipemic matrix
Bench Top Stability at Room Temperature	8 hours (480 mins)
Freeze/Thaw (F/T) Stability	Up to 5 F/T cycles
Long Term Stability	Up to 20 months at -60°C to -80°C

Abbreviations: ALN-AT3SC = fitusiran; AT = Antithrombin; F/T = Freeze/Thaw; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification; NA = Not applicable

Source: 5.3.1.4 BMV0091 [CL-MVR-0015], BMV0091 addendum 1 [CL-MVR-0019], and BMV0091 amendment 01.

Source: Table 16, Summary of Biopharmaceutic Studies and Associated Analytical Methods

The bioanalytical reports of each clinical study are located in Module 5.3.5.1 (Appendix 16.2.5). The method validation and sample analysis are deemed adequate.

14.3.3. Bioanalytical Method for ADA Assessment

[Table 128](#) below summarizes the ADA assays, their validation reports, and the respective clinical studies where the specific assays were used. The minimum required dilution (MRD) in the initial ADA validation study 3000481 was 100. This method was used to analyze ADA in the phase 1 study TDR14767 (ALN-AT3SC-001) and phase 1/2 study LTE14762. The MRD in the later assay DOH1645 was optimized to 50 and the assay was used to analyze ADA in phase 3 studies. The DOH1645 assay was also transferred to (b) (4) (ABV0083) to analyze the samples from Chinese subjects.

Table 128. Overview of ADA Assays Used in Fitusiran Clinical Studies

Assay	Validation report	Intended use	MRD	Sensitivity	Clinical studies	Assay Site	Report Location (CTD Module)
ELISA	3000481	ADA screen, confirm, titer	100	NA	TDR14767 (ALN-AT3SC-001)	(b) (4)	Module 5.3.1.4
ELISA	Amended Final Study Report - 3000481 (v3.0)	ADA screen, confirm, titer	100	Screening: 57 ng/mL; Confirmatory: 156 ng/mL	LTE14762		Module 5.3.1.4
ELISA	DOH1645	ADA screen, confirm, titer	50	Screening: 192.74 ng/mL; Confirmatory: 39.10 ng/mL	EFC14768, EFC14769, EFC15110, LTE15174		Module 5.3.1.4
ELISA	ABV0083	ADA screen, confirm, titer	50	Screening: 192 ng/mL	Chinese participants in studies EFC14768, EFC14769, LTE15174		Module 5.3.1.4

Abbreviations: ADA = anti-drug antibodies; ELISA = Enzyme-Linked Immunosorbent Assay; MRD = Minimum required dilution; NA = Not available

Source: Table 5, Summary of Biopharmaceutical Studies and Associated Analytical Methods

Neutralizing antibodies (NAbs) against fitusiran were not examined, because the observed incidence of ADAs was low across fitusiran clinical studies.

The validation demonstrated acceptable inter- and intra-assay accuracy and precision. All assay acceptance criteria were met for the assay parameters tested to establish assay robustness and ruggedness. The results indicated that the method described is suitable for the assessment of ADA. ADA assay validation summaries are presented in Table 23, 24 and 25 in Summary of Biopharmaceutical Studies and Associated Analytical Methods (Module 2.7), for assay 3000481, assay DOH1645 and assay ABV0083, respectively. The method validation and sample analysis are deemed adequate.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

14.4.1. Summary of Clinical Studies

Fitusiran immunogenicity was assessed in all 6 clinical studies listed above. The sampling timepoints in each of the phase 3 studies are listed in [Table 129](#) below. The bioanalytical method for ADA measurement is described in Section 14.3 above. Summaries of ADA data from individual studies are presented in each individual study above. Overall, the results confirm that development of treatment-induced ADA by fitusiran is limited, and ADA status did not have a meaningful effect on fitusiran PK or PD.

Table 129. Assessments and Sampling Timepoints

Study No.	No. of participants enrolled (treated)	Assessment	Timepoints
EFC14768	60	- ADA - PK - Plasma AT	ADA: Predose, M1, M3, M8 PK: Predose on D1, M1, M3, M7, & M8; 4 hours post-dose on D1^a. East Asian participants only also had the following timepoints: +0-24 h on D1 AT: Predose, W2, W4 (M1), W6, M2, M3, M4, M5, M6, M7, M8. East Asian participants only also had the following timepoints: D2, D8
EFC14769	120	- ADA - PK - Plasma AT	ADA: Predose, M1, M3, M8 PK: Predose on D1, M1, M3, M7, & M8; 4 hours post-dose on D1^a. East Asian participants only also had the following timepoints: +0-24 h on D1 AT: Predose, W2, W4 (M1), W6, M2, M3, M4, M5, M6, M7, M8
EFC15110	80	- ADA - PK - Plasma AT	ADA: Predose, M1, M2, M4, M6, M7 PK: Predose on D1, M2, M4, & M6; 4 hours post-dose on D1 & M5. ^a East Asian participants only also had the following timepoints: +0-24 h on D1 AT: Predose, W2, W4 (M1), W6, M2, M3, M4, M5, M6
LTE15174	281	- ADA - PK^b - Plasma AT^b	ADA: Predose on D1, M2, M4, M6, M12, M24, M36 & M48, M60, M72, M76. De novo Chinese patients only: + M1, M3 & M6 PK: Predose D1, D2, M2, M4, M6, M12, M24, M36, M48, & 4 hours post-dose on D1, M12, M24, M36 & M48^a. De novo Chinese patients only: + 0-24h on D1 AT: Predose, M1, M2, M3, M6, M9, M12, M15, M18, M21, M24, M30, M36, M42 & M48. De novo Chinese patients only: +W2

ADA = anti-drug antibody; AT = antithrombin; M = male; PK = pharmacokinetic; AT= antithrombin (PD marker)

^a 4 hour post-dose concentration is equivalent to approximate C_{max}

^b Additional adjustments to sample collection timepoints are provided in (Module 5.3.5.2 Study LTE15174 Appendix 16.1.1 [Protocol])

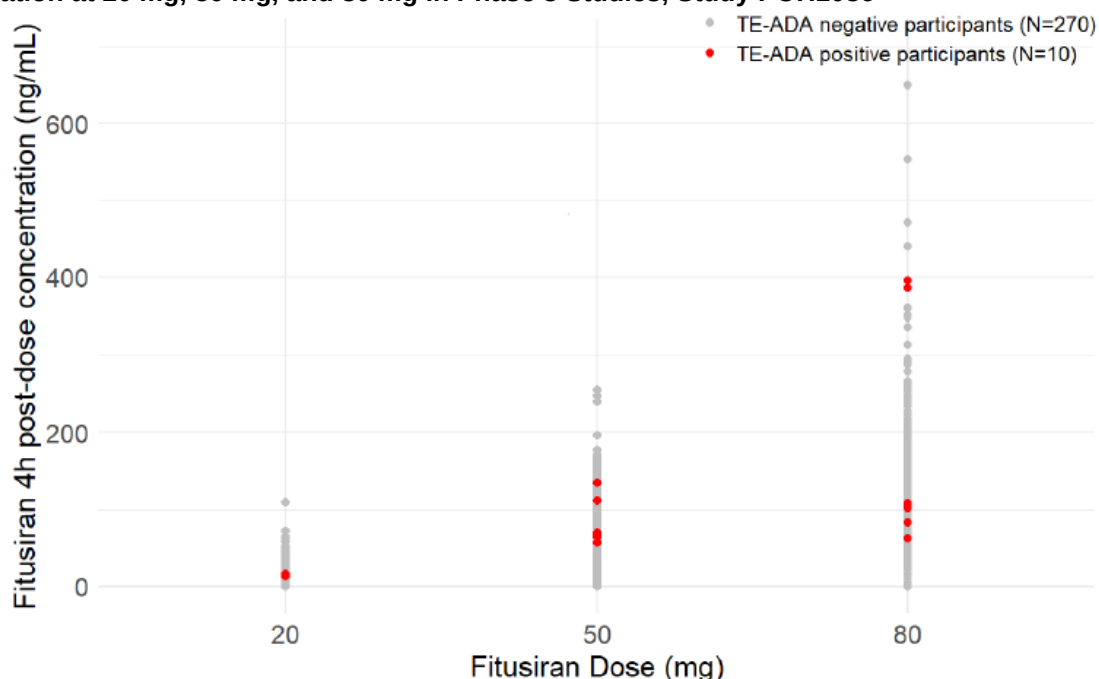
Source: Module 5.3.5.1 [Study EFC14768], Module 5.3.5.1 [Study EFC14769], Module 5.3.5.1 [Study EFC15110], Module 5.3.5.2 [Study LTE15174].

Source: Table 7, Integrated Summary of Immunogenicity, Module 5.3.5.3

ADA Effect on the PK of Fitusiran

A comparison of plasma fitusiran C_{4h} and ADA status, evaluated at the subject level (i.e., treatment-emergent-ADA-positive [TE-ADA-positive] versus treatment-emergent-ADA-negative [TE-ADA negative] subjects), and by dose level in the 20, 50, and 80 mg groups from phase 3 studies, are presented in [Figure 33](#). The PK concentrations for TE-ADA-positive subjects largely overlapped with those for subjects with no treatment-emergent ADAs, indicating a lack of correlation between ADA status and fitusiran concentrations.

Figure 33. Fitusiran Plasma Concentrations (4 Hours Postdose) and ADA Status After Fitusiran Administration at 20 mg, 50 mg, and 80 mg in Phase 3 Studies, Study POH1086



Source: Figure 25, Summary of Clinical Pharmacology Studies

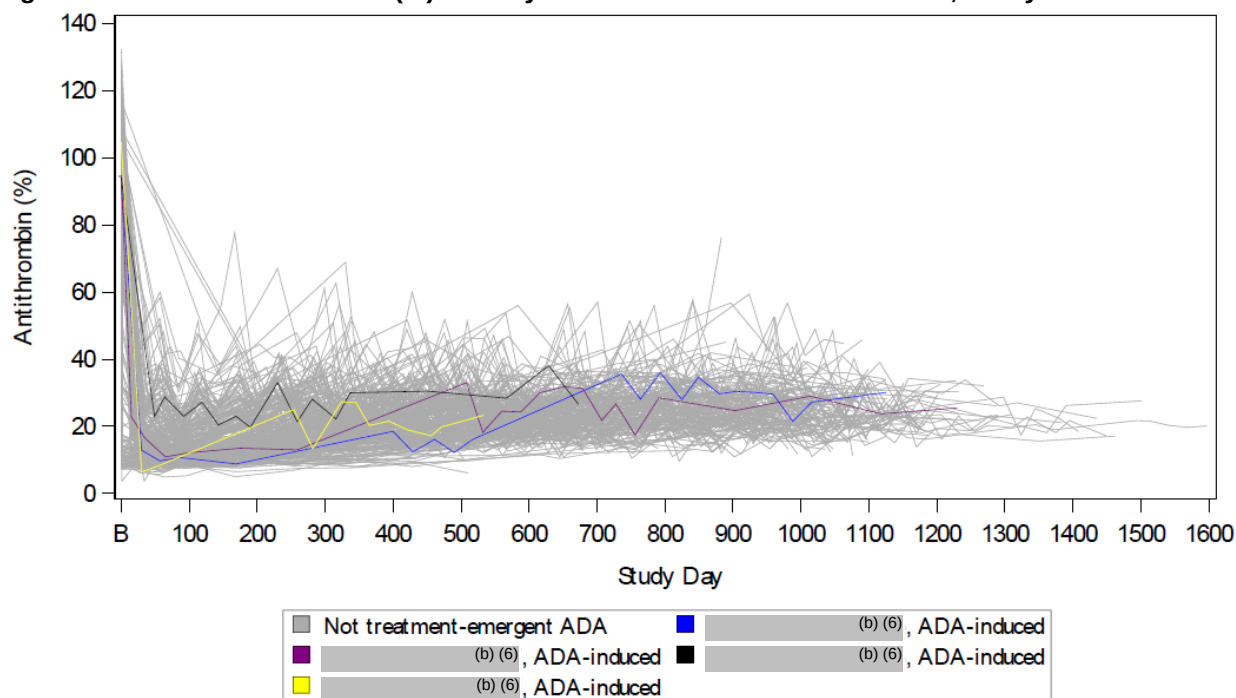
Red data points represent 4 h plasma fitusiran concentrations from subjects who were treatment-emergent ADA positive at any time point (one or more timepoints for each subject) during the fitusiran treatment period. Grey data points represent 4 h plasma fitusiran concentrations from subjects who were treatment-emergent ADA negative (had neither treatment-induced nor treatment-boosted ADA) at all timepoints during the fitusiran treatment period.

Abbreviations: ADA, antidrug antibody; TE-ADA, treatment-emergent antidrug antibody

ADA Effect on the PD of Fitusiran

The impact of ADA on AT activity was evaluated for the 10 subjects who had developed treatment-emergent ADAs during their respective study (all with treatment-induced ADAs) and compared to the subjects who did not develop ADA. Plots of AT activity over time and ADA status of subjects (TE-ADA positive or TE-ADA negative) from each of the four phase 3 studies are presented in Module 5.3.5.3 – Integrated Summary of Immunogenicity. The plot of AT activity and ADA status in LTE15174 is shown below in [Figure 34](#). The AT activity-time profiles for TE-ADA positive subjects largely overlapped with those for subjects with no treatment-emergent ADAs. These results also indicate there was no neutralizing activity associated with development of ADA. In conclusion, ADA did not have any effect on the PD marker, AT activity.

Figure 34. Plot of Antithrombin (%) Activity Level Over Time for ADA Status, Study LTE15174



Source: Figure 11, Integrated Summary of Immunogenicity
Abbreviations: ADA, antidrug antibody; LTE, long-term extension

ADA Effect on Efficacy and Safety of Fitusiran

Given the complexity of hemophilia, no evident impact on annualized bleeding rate (ABR) was associated with ADA as observed among the subjects who developed treatment-emergent ADA and the ABR of the overall study populations.

No new safety findings were identified in subjects who had confirmed positive ADA during the studies. The observed treatment-emergent adverse events (TEAEs) were consistent with those expected of the underlying disease and the known safety profile of fitusiran.

Summary of Immunogenicity Assessment

The clinical findings support that fitusiran has a low immunogenicity risk relative to ADA impact on clinical outcomes. Subjects who developed ADA had a low titer response that did not meaningfully influence PK, PD (AT activity), efficacy as assessed by ABR, or safety parameters when compared to subjects who did not develop ADA.

14.5. Pharmacometrics Assessment

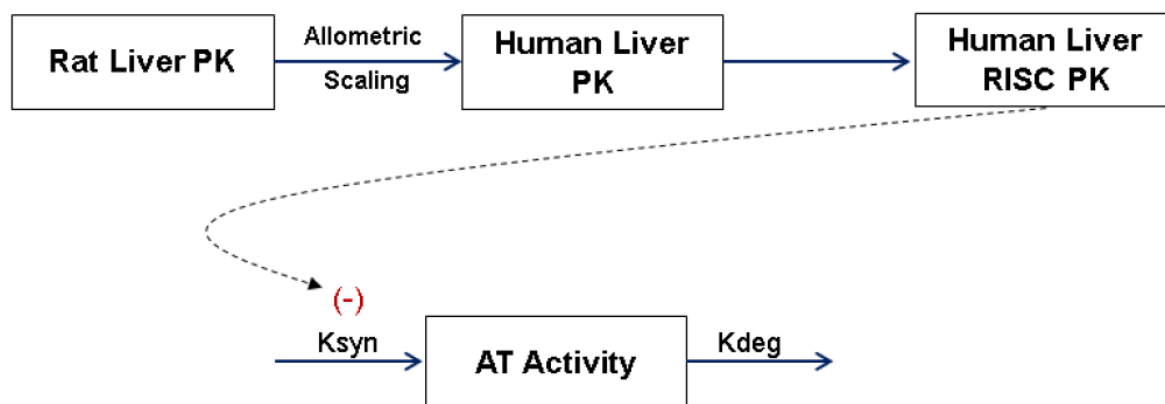
14.5.1. Applicant's Population Kinetic- Pharmacodynamic Model Analysis

Upon single or multiple dose administration of fitusiran in nonhuman primates (NHP) and in man, plasma concentrations decline rapidly and are below the lower limit of quantitation in 1 to 2 days postdose, while suppression of the target protein, antithrombin (AT), is sustained for days,

highlighting the disconnect between plasma concentrations and PD effect. This lack of correlation is to be expected based on the mechanism of action of fitusiran, i.e., (i) the GalNAc-mediated targeted delivery of the double-stranded small interfering ribonucleic acid (siRNA)-conjugate to the liver following subcutaneous administration; (ii) uptake of the siRNA into hepatocytes; and (iii) binding of the antisense strand of the siRNA to the RNA-induced silencing complex (RISC), causing specific degradation of the AT mRNA in the hepatocytes, the primary source of AT production. The time taken for this process to result in measurable decreases in plasma AT levels, including the time for the elimination of preexisting AT, explains the duration of onset of pharmacological effect of fitusiran following administration. Further, since a single RISC-bound antisense strand in the hepatocyte can cause the catalytic degradation of multiple target AT mRNAs, the duration of the pharmacology of fitusiran is significantly longer than what might be estimated based on plasma PK. Based on the biology and mechanism of action, it is clear that liver concentrations of fitusiran are linked to the gradual decrease in serum AT and the ensuing long duration of AT suppression.

Since liver concentrations are not practical to measure in man and were not measured in monkeys at pharmacologic doses of fitusiran, the Applicant used allometric scaling to predict liver concentrations of fitusiran in both NHPs and humans. This is based on other siRNA molecules (where liver biopsies in NHP were collected) with similar physicochemical characteristics to fitusiran, for which observed dose-proportional liver concentrations scale allometrically in rats and monkeys. It was noted that the liver PK of siRNA molecules scale allometrically between species with a clearance exponent of 0.75 and a volume exponent of 1.0. The overall modeling strategy was executed in a stepwise manner as follows: (1) fitusiran liver PK parameters, which were estimated based on fitusiran liver concentrations in rats, were allometrically scaled to humans; (2) fitusiran concentrations in the RISC complex (fitusiran-RISC) were estimated based on scaled liver PK parameters and observed PD; (3) fitusiran-RISC concentrations were linked to AT lowering, with an inhibitory effect on synthesis rate of AT activity. A schematic of the modeling strategy is shown in [Figure 35](#).

Figure 35. Schematic Representation of PopK-PD Modeling Strategy



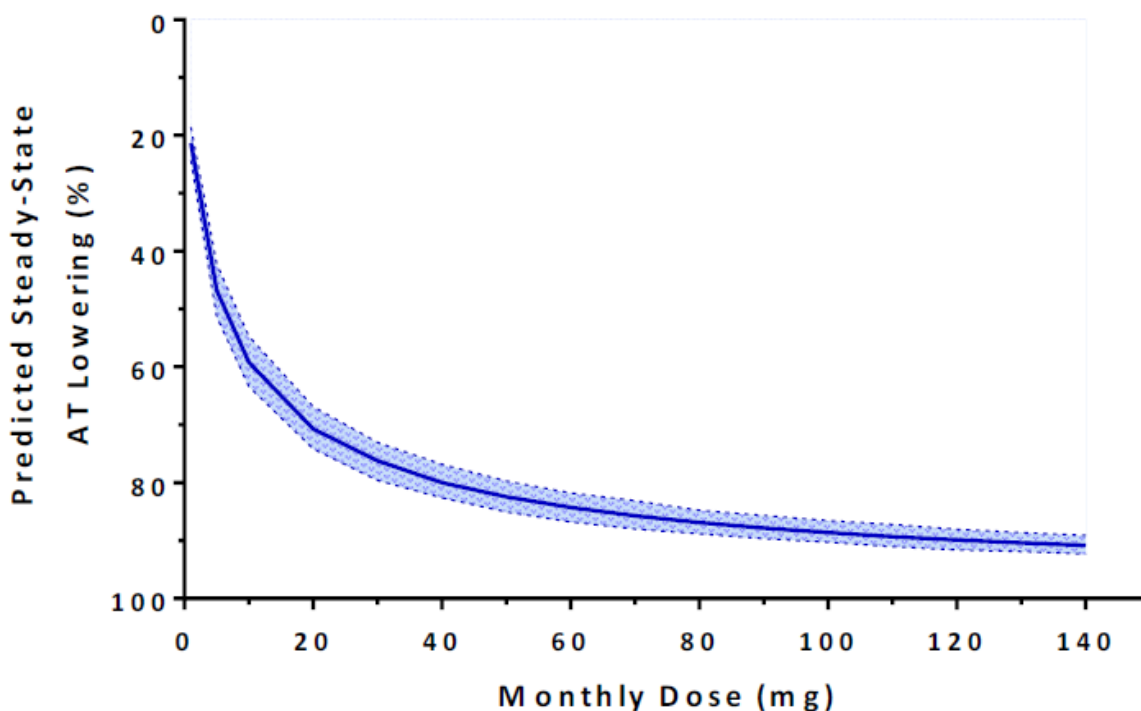
Source: study-poh1133, Figure 6

Abbreviations: AT, antithrombin; Kdeg, degradation rate of AT; Ksyn, synthesis rate of AT; PK, pharmacokinetics; RISC, RNA-induced silencing complex

The fitusiran population kinetic-pharmacodynamic (PopK-PD) model (POH1133) was first developed based on plasma AT activity data from 41 hemophilia A or B subjects enrolled in Study ALN-AT3SC-001 (Parts B, C and D) and ALN-AT3-002. AT activity was measured

biweekly for Study ALN-AT3SC-001, and monthly for Study ALN-AT3SC-002. Fitusiran liver concentrations in rats were allometrically scaled to predict human liver PK. Fitusiran concentrations in the RISC complex (fitusiran-RISC) were predicted based on total liver PK and observed PD, where fitusiran-RISC concentrations had an inhibitory effect on synthesis rate of AT activity. Simulations of steady-state residual AT activity (at 1 month after the fifth dose) in 1000 virtual hemophilia patients receiving monthly doses of fitusiran over a dose range of 1 to 140 mg were conducted to guide the dose selection for pivotal trials. As shown in [Figure 36](#), a sharp decline in mean steady-state AT lowering is predicted as fitusiran dose increases from 1 mg to 20 mg. A further increase in dose from 20 mg to 50 mg shows a less rapid decline in AT activity. At doses greater than 80 mg, the dose-response curve reaches an asymptote, suggesting that any increase in dose beyond 80 mg will cause minimal further decline in AT activity. In addition, less variability in AT lowering is predicted at 80 mg (95th to 5th percentile of 77% to 92%) compared to 50 mg (95th to 5th percentile of 72% to 90%) ([Table 130](#)). The 80 mg QM dosing regimen was selected for later stage clinical trials based on these simulation results as well as the observed safety, efficacy, and pharmacodynamic profile in trial TDR14767.

Figure 36. Mean (90% Confidence Interval) Dose-AT Lowering Relationship for Fitusiran in Virtual Hemophilia Patients Across a Dose Range of 1 mg to 140 mg Administered Monthly



Solid blue line= Mean AT Lowering response, shaded area=90% confidence interval

Source: study-poh1133, Figure 20
Abbreviation: AT, antithrombin

Table 130. Model-Simulated AT Reduction and Variability by Dose, Study POH1133

Dose (mg)	95th Percentile	Median	5th Percentile	Mean (90% CI)
50	71.6	82.5	89.8	82.4 (79.7-85)
80	77.3	86.6	92.3	86.8 (84.7-88.8)
140	83.9	90.8	94.9	90.8 (89.1-92.3)

Source: study-poh1133, Table 6
Abbreviations: AT, antithrombin; CI, confidence interval

In October 2020, when the phase 1/2 (LTE14762), phase 3 (EFC14768, EFC14769, EFC15110), and phase 3 extension (LTE15174) studies were ongoing, concerns regarding thrombotic events potentially related to fitusiran resulted in placing the ongoing clinical studies on a voluntary pause by the Sponsor to evaluate risk factors. All available clinical data were analyzed to assess the potential role of AT reduction and the associated risk of thrombotic events, as well as bleeds. An optimized dose regimen targeting AT activity levels between 15% and 35% was implemented. The rationale for the selection of these targets was based on review of thrombotic event incidence as well as bleeding data at different AT activity levels. The clinical data, along with PopK-PD modeling, was used to assess doses and dose regimens that would achieve and maintain AT activity between 15% and 35%. The PopK-PD model (POH0721) was updated based on data from 45 healthy volunteers and hemophilia A or B subjects enrolled in Study ALN-AT3SC-001 and ALN-AT3SC-002. This dataset included 3 healthy volunteers, 34 subjects with hemophilia A, and 8 subjects with hemophilia B. Amongst the hemophilia subjects, 25 subjects were without inhibitors and 17 subjects were with inhibitors. The updated model structure was identical to the first PopK-PD model. AT activity data until week 24 from phase 3 trials (EFC14768, EFC14769, and EFC15110) were applied to validate the model. Simulation analysis was performed to guide the dose regimen selection which could achieve target AT activity range of 15% to 35%.

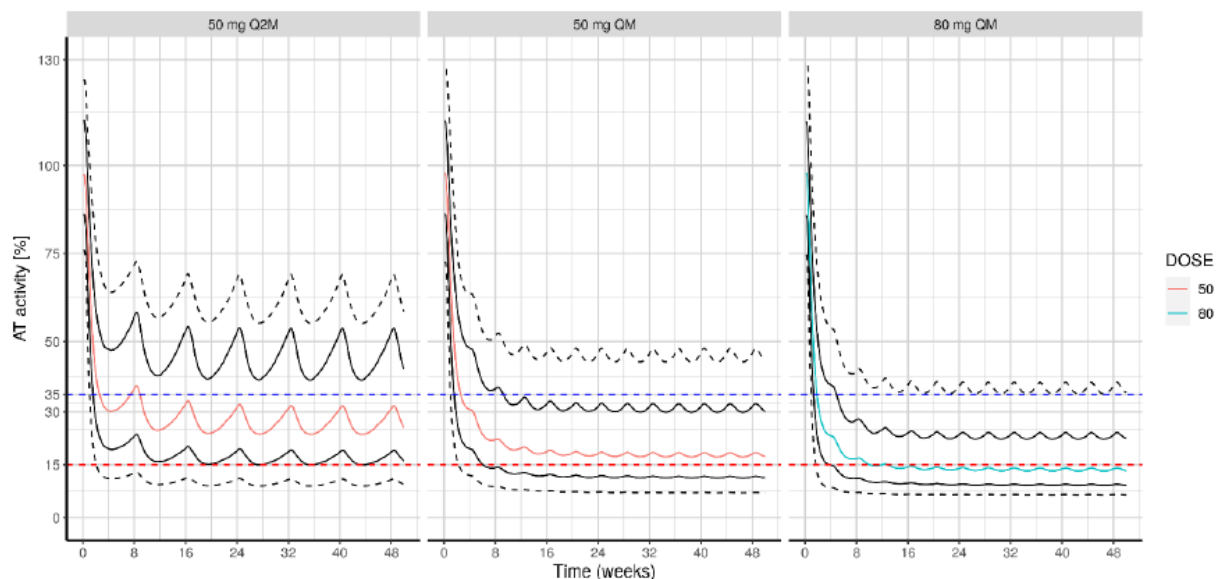
The simulation results showed that with a starting dose of 80 mg QM, the minimum AT activity in virtual subjects could go down to 6.9%, where for the 50 mg Q2M regimen, the minimum AT activity would remain above 10% ([Table 131](#) and [Figure 37](#)). Therefore, based on the simulation results, the starting dose was revised to 50 mg Q2M (instead of 80 mg QM), with an option to sequentially escalate to 50 mg QM and 80 mg QM if AT activity was >35%. This revised dose regimen was implemented in December 2020 across studies (except EFC14768 and EFC14769, which were nearly complete at the time of the voluntary dosing pause).

Table 131. Model-Simulated Antithrombin Activity Percentiles for Different Dosing Regimens, Study POH0721

Regimen	MinAT	TroughAT_5th_SS	TroughAT_Median_SS	TroughAT_95th_SS	PeakAT_5th_SS	PeakAT_Median_SS	PeakAT_95th_SS	MaxAT
50 mg Q2M	10.5	13.9	23.3	39.7	17.87	32.37	56.42	77.5
50 mg QM	7.96	10.3	17.2	29.6	11.36	18.23	31.15	58.5
80 mg QM	6.90	8.91	13.4	22.8	9.11	14.16	23.55	41.7

Source: study-poh0721, Table 4
Abbreviations: AT, antithrombin; Q2M, every 2 months; QM, once monthly; SS, steady state

Figure 37. Model-Simulated AT Activity Profiles for 50 mg QM, 50 mg Q2M, and 80 mg QM, Study POH0721



Colored line is model simulated median AT activity; Black solid lines are model simulated 5th (lower) and 95th (upper) percentile AT activity; Black dashed lines are model simulated minimum (lower) and maximum (upper) AT activity.

Source: study-poh0721, Figure 9

Abbreviations: AT, antithrombin; Q2M, every 2 months; QM, once monthly

The prior PopK-PD model served as a starting point for the current modeling analysis, which aimed to develop a PopK-PD model for fitusiran based on a larger dataset from clinical data that were pooled from phase 1, 2, and 3 studies. A summary of pooled clinical studies included in this PopK-PD analysis is provided in [Table 132](#). A summary of numbers of records excluded and the reason for exclusion is provided in [Table 133](#). The summary statistics of demographic information is shown in [Table 134](#) and [Table 135](#).

Table 132. Summary of AT Activity Data Included in the PopK-PD Model Development

Study	Phase	Number of participants			Number of samples collected		
		Total number of participants	Total number of participants in the analysis dataset	Number of excluded participants	Total number of samples collected	Total number of samples in the analysis dataset	Number of excluded samples
EFC14768	3	41	41	0	923	735	188
EFC14769	3	80	79	1	1708	1498	210
EFC15110	3	69	69	0	1243	1052	191
LTE14762	1/2	34	34	0	2709	2652	57
LTE15174	3	281	281	0	11146	10751	395
TDR14767	1	46	45	1	985	971	14
Total		341 ^a	339 ^a	2[0.6%]	18714	17659	1055[5.6%]

^a Some participants are carried between studies.

Source: study-poh1116, Table 1

Abbreviations: AT, antithrombin; PopK-PD, population kinetics-pharmacodynamics

Table 133. Summary of Number of Excluded Samples From Final PopK-PD Model Dataset

Reason for excluding samples	Number of samples excluded	Percentage of total samples excluded
Participant given placebo	12	0.06%
Missing Dose and observation	1	0.005%
AT data below LLOQ	898	4.8
0 AT value ^a	144	0.77%
Total	1055	5.64%

^a Bioanalytical data was either < LLOQ, not reportable, or not available

Source: study-poh1116, Table 3

Abbreviations: AT, antithrombin; LLOQ, lower limit of quantification; PopK-PD, population kinetics-pharmacodynamics

Table 134. Summary Statistics of Continuous Covariates Included in the Final PopK-PD Dataset

Covariates	Minimum	Q1 ^a	Median	Mean	Q3 ^b	Maximum	SD	N	Missing
AGE [Year]	12	20	27	29.3	36	71	13	339	0 (0.0%)
Body Weight [Kg]	26.7	59.7	70	70.8	82	140	17	339	0 (0.0%)
eGFR [mL/min/1.73 m ²]	54.1	116	141	157	170	656	70	337	2 (0.6%)
ALB [g/L]	38	46	48	47.8	50	55	3.1	339	0 (0.0%)
BILI [μmol/L]	1.52	6.55	8.89	10.3	12.7	44.8	5.8	339	0 (0.0%)
AST [IU/L]	9	17	21	23.1	26	83	9.6	339	0 (0.0%)
ALT [IU/L]	4.1	13	20	24.6	31	118	17	339	0 (0.0%)
ALP [IU/L]	35	71.5	88	108	115	458	64	339	0 (0.0%)
Baseline D-Dimer	0.12	0.21	0.37	69.4	5.61	1460	176	181	158 (46.6%)

Abbreviation: SD: Standard Deviation

^a Q1 represents first quartile

^b Q3 represents third quartile..

Source: study-poh1116, Table 4

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; eGFR, estimated glomerular filtration rate; PopK-PD, population kinetics-pharmacodynamics

Table 135. Summary of Categorical Covariates in the Final PopK-PD Dataset

Covariates	Categories	N	Missing
Race	Caucasian	142 (41.9%)	0 (0.0%)
Race	Black	5 (1.47%)	0 (0.0%)
Race	Asian	181 (53.4%)	0 (0.0%)
Race	Other ^a	11 (3.24%)	0 (0.0%)
Ethnicity	Missing	17 (5.01%)	17 (5.0%)
Ethnicity	Non-Hispanic	315 (92.9%)	17 (5.0%)
Ethnicity	Hispanic	7 (2.06%)	17 (5.0%)
Static antidrug antibody	ADA negative	329 (97.1%)	0 (0.0%)
Static antidrug antibody	Treatment emergent	10 (2.95%)	0 (0.0%)
Type of disease	Healthy volunteer	3 (0.885%)	0 (0.0%)
Type of disease	Hemophilia A	266 (78.5%)	0 (0.0%)
Type of disease	Hemophilia B	70 (20.6%)	0 (0.0%)
Baseline Type of Factor	Missing	6 (1.77%)	6 (1.8%)
Baseline Type of Factor	FVIII	264 (77.9%)	6 (1.8%)
Baseline Type of Factor	FIX	69 (20.4%)	6 (1.8%)
Baseline inhibitor status	Without inhibitors to FVIII or FIX at baseline	214 (63.1%)	0 (0.0%)
Baseline inhibitor status	With inhibitors to FVIII or FIX at baseline	125 (36.9%)	0 (0.0%)

^a For the purpose of the PopK-PD model, Indians and Malaysians have been counted in the 'other' race category.

Source: study-poh1116, Table 5

Abbreviations: ADA, antidrug antibody; F, Factor; PopK-PD, population kinetics-pharmacodynamics

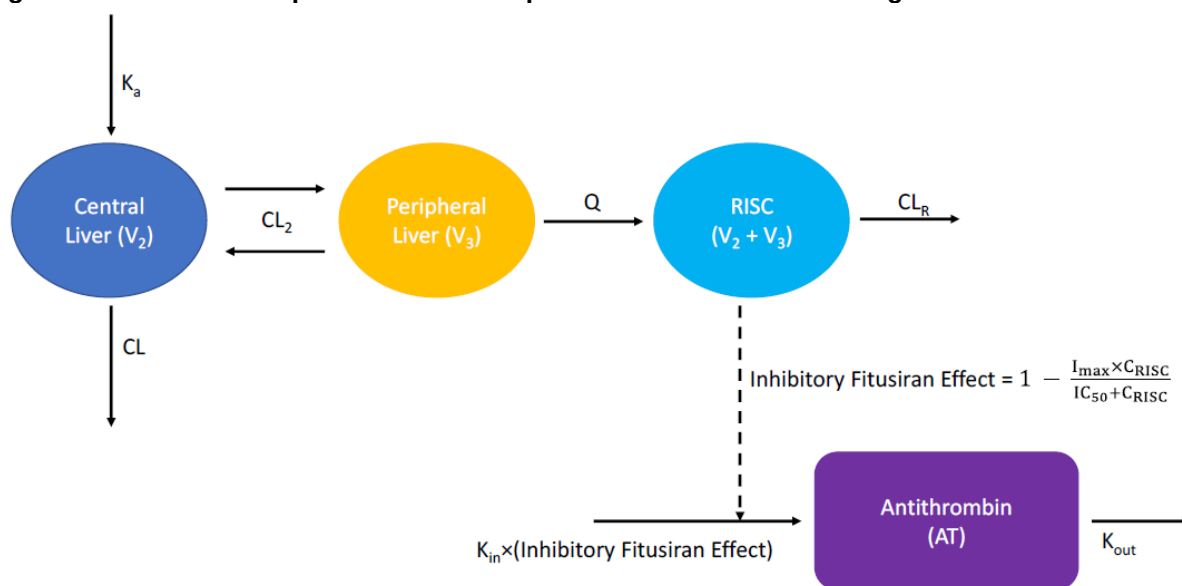
The model structure is shown in [Figure 38](#). Based on the mechanism of action of fitusiran, the liver pharmacokinetic parameters (i.e., absorption rate [Ka], clearance from liver central compartment [CL], liver intercompartmental clearance [CL₂], liver central volume [V₂] and liver peripheral volume [V₃]) were predicted by allometric scaling from rat liver PK and were fixed in the current PopK-PD model. The minimum uptake into RISC compartment (minQ) was fixed to 0.0225 g/h and the volume of RISC compartment (RV), that is V₂+V₃, was fixed to be 9375 g. The bioavailability was set to 1 and the turnover rate of fitusiran from peripheral liver compartment into RISC compartment Q was assumed to be dose-dependent and defined as follows:

Equation 1. Turnover Rate of Fitusiran from Peripheral Liver Compartment into RISC Compartment Q

$$Q = \text{minQ} \times (1 - \text{POP}) + \text{POP} \times Q^{\text{max}} \times \left(\frac{\text{Dose}}{50} \right)^{\theta_Q}$$

Q^{max} is the maximum turnover rate of fitusiran from the peripheral liver compartment and θ_Q is the hill coefficient correlating the impact of dose on the turnover rate of fitusiran from the peripheral compartment. Q^{max} and θ_Q were estimated. POP is a conditional variable where POP=1 if the subject is de-escalated to the 20 mg Q2M dose and POP=0 otherwise. The dynamics of AT activity were described by an indirect response model linking the predicted human liver concentrations to suppression of synthesis rate of AT through an effect compartment representing fitusiran loaded onto RISC. The key parameters for AT dynamics such as CL_R (clearance from RISC compartment), K_{out} (AT elimination rate), K_{in} (AT production rate), I_{max} (maximum inhibition of AT production), and IC₅₀ (RISC concentration for 50% of maximum effect) were estimated.

Figure 38. Schematic Representation of PopK-PD Model for AT Lowering



Abbreviations: C_{RISC} , RNA-induced silencing complex (RISC) concentration of active small interfering RNA; CL , clearance; CL_R , clearance from RISC compartment; IC_{50} , concentration required to produce half-maximal effect of fitusiran; I_{max} , maximum inhibitory effect of fitusiran on K_{in} ; K_a , uptake rate constant to liver; K_{in} , zero-order synthesis rate of AT; K_{out} , first-order degradation rate constant for AT; Q , intercompartmental clearance; Q , turnover rate of fitusiran from peripheral liver compartment into RISC; V_2 , volume of distribution of central liver compartment; V_3 , volume of distribution of peripheral liver compartment

Source: study-poh1116, Figure 2

[Table 136](#) summarizes all covariates that were investigated during the development of the PopK-PD final model. The covariate model development started with a detailed exploratory covariate analysis that aimed to identify: (1) covariate distribution; (2) correlation between covariates; and (3) potential relationship between covariates and PopK-PD model parameters. The result of the exploratory covariate analysis was used as input to formally screen statistically significant covariates in the PopK-PD model. The formal covariate analysis was performed using a stepwise selection procedure. This procedure involves stepwise testing of linear and nonlinear relationships in a forward inclusion (ΔOFV of 6.63, $p < 0.01$ for 1 degree of freedom [DF]) and backwards exclusion (ΔOFV of 10.8, $p < 0.001$ for 1 DF) procedure. The covariate analysis identified statistically significant effects of bilirubin on RISC clearance and RACE on K_{out} , with AT protein being eliminated faster in Asians (i.e., Japan, Korea, China, Taiwan, India, and Malaysia) than the remaining category of race considered in the analysis dataset, i.e., Black, Caucasian, and “other” races (i.e., American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other multiple races, and not reported races).

Table 136. Covariates That Had Been Investigated in PopK-PD Model Development

Covariates	Reason for investigation	PopK-PD model parameters
Bodyweight	Bodyweight may influence AT distributional characteristics	CL _R , IC ₅₀ and K _{out}
Age	AGE may influence AT distributional characteristics	CL _R , IC ₅₀ and K _{out}
Race	RACE may influence AT distributional characteristics	CL _R , IC ₅₀ and K _{out}
Ethnicity	Ethnicity may influence AT distributional characteristics	CL _R , IC ₅₀ and K _{out}
eGFR (estimate Glomerular Filtration Rate)	Assess influence of renal function on AT	CL _R , IC ₅₀ and K _{out}
ALT (Alanine amino transferase)	Assess influence of hepatic function on AT	CL _R , IC ₅₀ and K _{out}
AST (Aspartate amino transferase)	Assess influence of hepatic function on AT	CL _R , IC ₅₀ and K _{out}
ALP (Alkaline phosphatase)	Assess influence of hepatic function on AT	CL _R , IC ₅₀ and K _{out}
ALBUMIN	Assess influence of hepatic function on AT	CL _R , IC ₅₀ and K _{out}
BILIRUBIN	Assess influence of hepatic function on AT	CL _R , IC ₅₀ and K _{out}
Type of disease (i.e., Hemophilia A, Hemophilia B, or healthy volunteer)	Potential for type of disease to influence AT but also potential other population differences	CL _R , IC ₅₀ and K _{out}
ADA (anti-drug antibody)	Assess influence of ADA on AT	CL _R , IC ₅₀ and K _{out}
Baseline D-Dimer	Assess influence of Baseline D-Dimer on AT	CL _R , IC ₅₀ and K _{out}
Baseline Type of Factor	Assess influence of baseline type factor on AT	CL _R , IC ₅₀ and K _{out}
Baseline inhibitor status	Assessing the influence of Baseline inhibitor status on AT	CL _R , IC ₅₀ and K _{out}

Source: study-poh1116, Table 2

Abbreviations: ADA, antidrug antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, antithrombin; CL_R, clearance from RISC compartment; eGFR, estimated glomerular filtration rate; IC₅₀, half maximal inhibitory concentration; K_{out}, first-order degradation rate constant for AT; RISC, RNA-induced silencing complex

The model parameter estimates are summarized in [Table 137](#). All parameters were estimated with relatively good precision. Goodness-of-fit plots demonstrating that the PopK-PD model reasonably captured the data are presented in [Figure 39](#). The PopK-PD model was validated using prediction corrected visual predictive check (pcVPC) that is shown in [Figure 40](#). The final PopK-PD model was able to predict the observed AT activity data reasonably well for both the median and 95th percentile of observations. The model tends to slightly underestimate the 5th percentile of observations.

Table 137. Parameter Estimates of Final PopK-PD Model

Parameter	Description	Units	Population estimate	RSE (relative standard error in %)
K_a	Absorption rate	1/h	0.157 (FIX)	-
V_2	Liver central volume	g	3300 (FIX)	-
V_3	Liver peripheral volume	g	6075 (FIX)	-
CL	Clearance from liver central compartment	g/h	39.6 (FIX)	-
CL_2	Liver inter-compartment clearance	g/h	27.20 (FIX)	-
minQ	Minimum clearance into RISC compartment	g/h	0.0225 (FIX)	-
Q_{max}	Dose dependent clearance into RISC compartment	g/h	0.029	2.3
RV	RISC volume	g	9375 (FIX)	-
CL_R	Clearance from RISC compartment	g/h	11.2	1.6
IC_{50}	RISC concentration for 50% of maximum effect	mg/g	0.0004	4
I_{max}	Maximum inhibition of AT production	-	0.9	0.3
K_{in}	AT production rate	%/h	0.99	2.4
K_{out}	AT elimination rate	1/h	0.01	2.3
F	Dose effect on bioavailability	-	1 (FIX)	-
θ_Q	Hill's coefficient for dose dependent clearance into RISC compartment	-	0.2	10
Inter-individual variability				
Parameter	Description	Units	%CV (shrinkage in %)	RSE (relative standard error in %)
IIV CL_R	IIV on CL_R	-	25.7 (11.8)	7.7
IIV IC_{50}	IIV on IC_{50}	-	61.2 (10.2)	9.3
IIV I_{max}	IIV on I_{max}	-	4 (23.4)	4.6
IIV K_{out}	IIV on K_{out}	-	12 (34)	15
IIV θ_Q	IIV on θ_Q	-	94.5 (52.2)	26

Abbreviations: $CL_R = 11.2 * (1 + 0.01 * (BILI - 9.43))$, $K_{out} = 0.01 * [(1 + 0.12) \text{ if "Other races"}]$, $K_{out} = 0.01 * [(1 + 0.08) \text{ if "Asian"}]$ and $K_{out} = 0.01 * [(1 + 0.064) \text{ if "Black"}]$.

Parameter	Description	Units	Population estimate	RSE (relative standard error in %)
Residual variability				
Parameter	Description	Units	% CV (shrinkage in %)	RSE (relative standard error in %)
EPS1	Proportional error		18.1 (4.2)	0.52
Covariate information				
Parameter	Description	Units	Population estimate	RSE (relative standard error in %)
CL _R BILI	Impact of Bilirubin on CL _R		0.01	7.7
K _{out,other}	Impact of other races on K _{out}		0.12	16
K _{out,ASIAN}	Impact of Asian race on K _{out}		0.08	26
K _{out,BLACK}	Impact of Black race on K _{out}		0.06	125

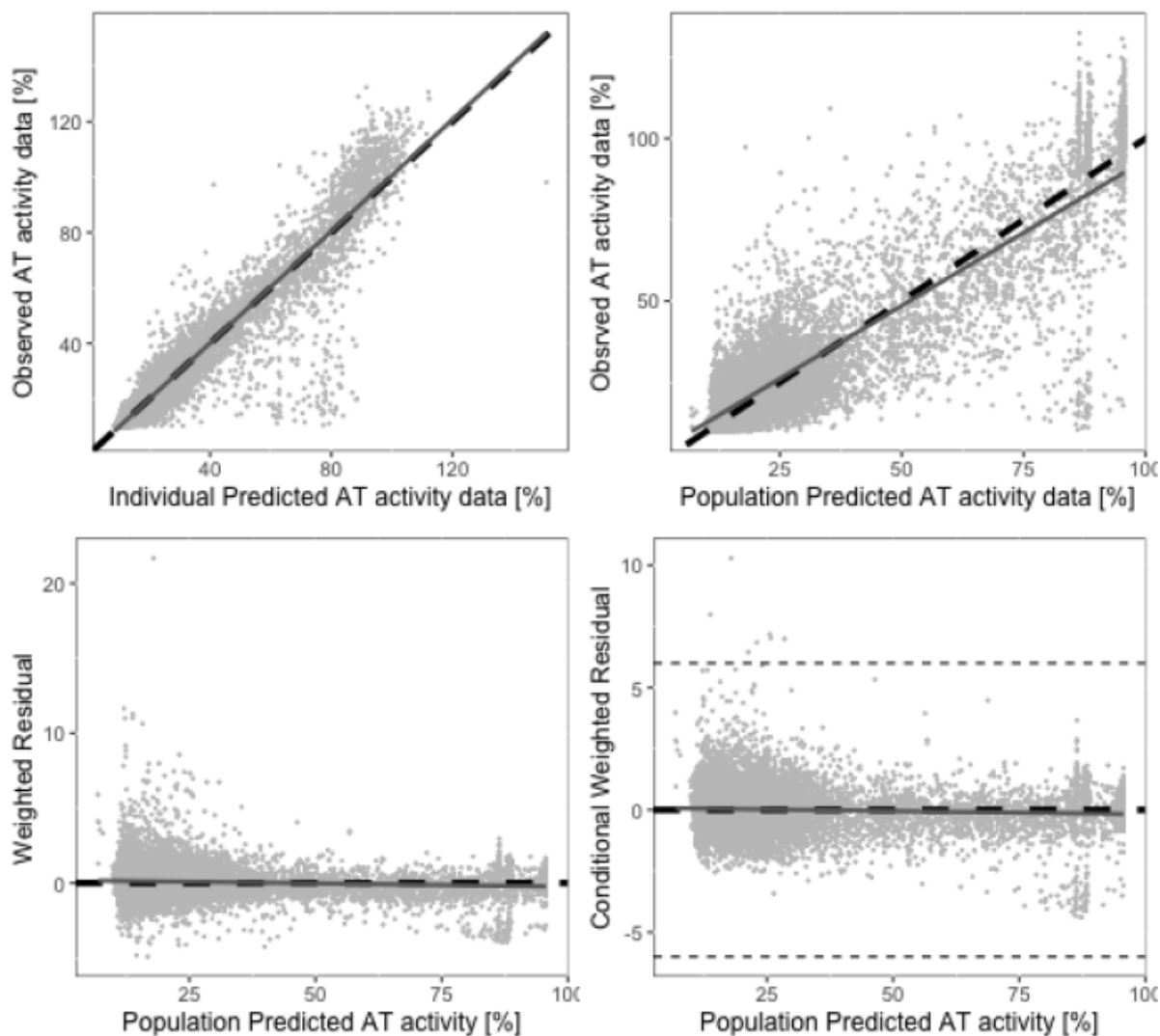
Abbreviations: CL_R= 11.2*(1 + 0.01*(BILI - 9.43)), K_{out}=0.01*[(1+0.12) if "Other races"], K_{out}=0.01*[(1+0.08) if "Asian"] and K_{out}=0.01*[(1+0.064) if "Black"].

Source: study-poh1116, Table 9

Abbreviations: AT, antithrombin; CL, clearance from liver central compartment; CL₂, liver intercompartment clearance; CL_R, clearance from RISC compartment; CV, coefficient of variation; F, dose effect on bioavailability; FIX, Factor IX; IC₅₀, half maximal inhibitory concentration; I_{max}, maximum inhibition of AT production; K_a, absorption rate; K_{in}, AT production rate; K_{out}, AT elimination rate; minQ, minimum clearance into RISC compartment; Q^{max}, dose-dependent clearance into RISC compartment; RISC, RNA-induced silencing complex; RSE, relative standard error; RV, RISC volume; V₂, liver central volume; V₃, liver peripheral volume; θ_Q, Hill's coefficient for dose-dependent clearance into RISC compartment

Figure 39. Goodness-of-Fit Plot of Final PopK-PD Model

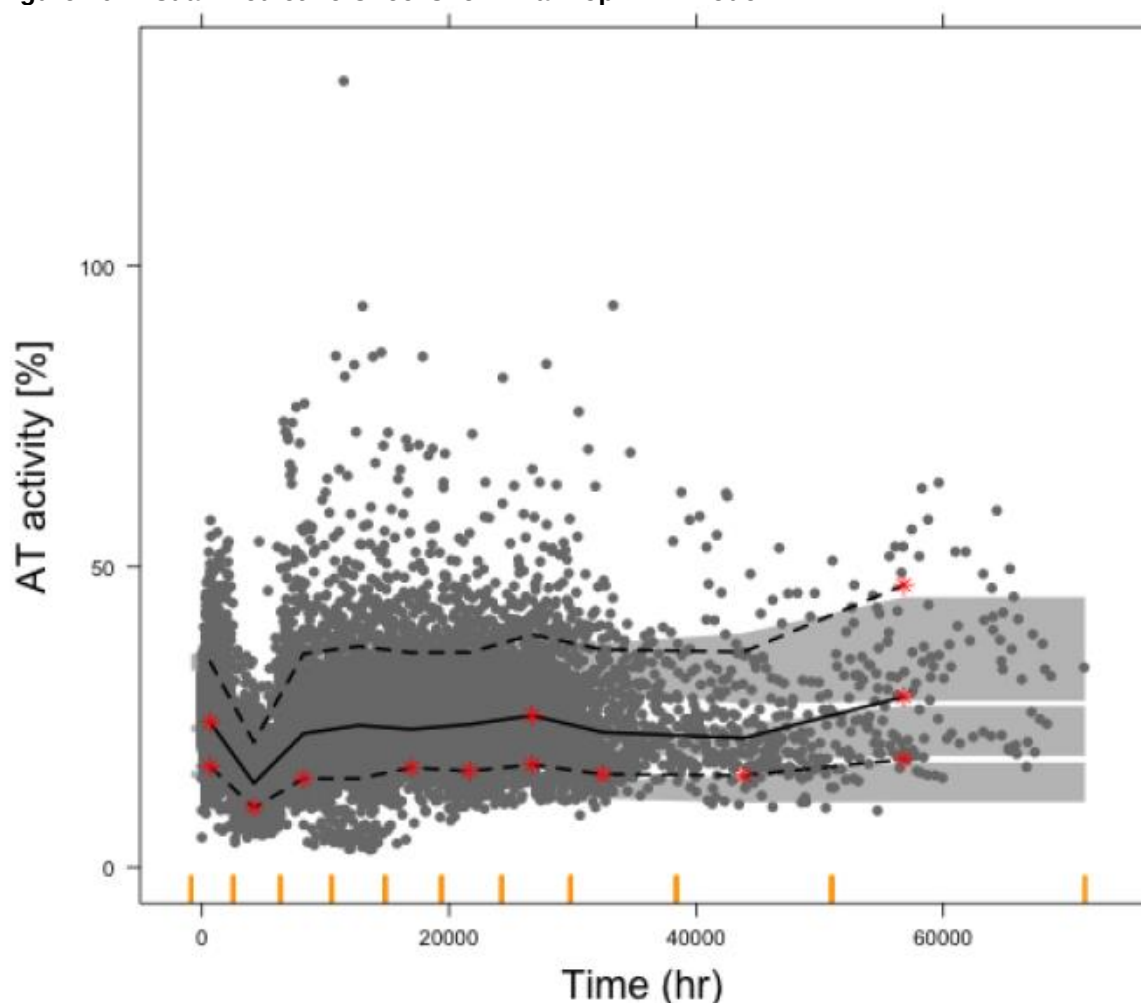
Legend: Dots are individual data; solid lines are smooth lines. In the two plots of the first row, dashed lines are lines of identity, whilst in the two plots of the second-row dashed lines represent zero line



Source: study-poh1116, Figure 18

Abbreviations: AT, antithrombin; PopK-PD, population kinetics-pharmacodynamics

Figure 40. Visual Predictive Checks for Final PopK-PD Model



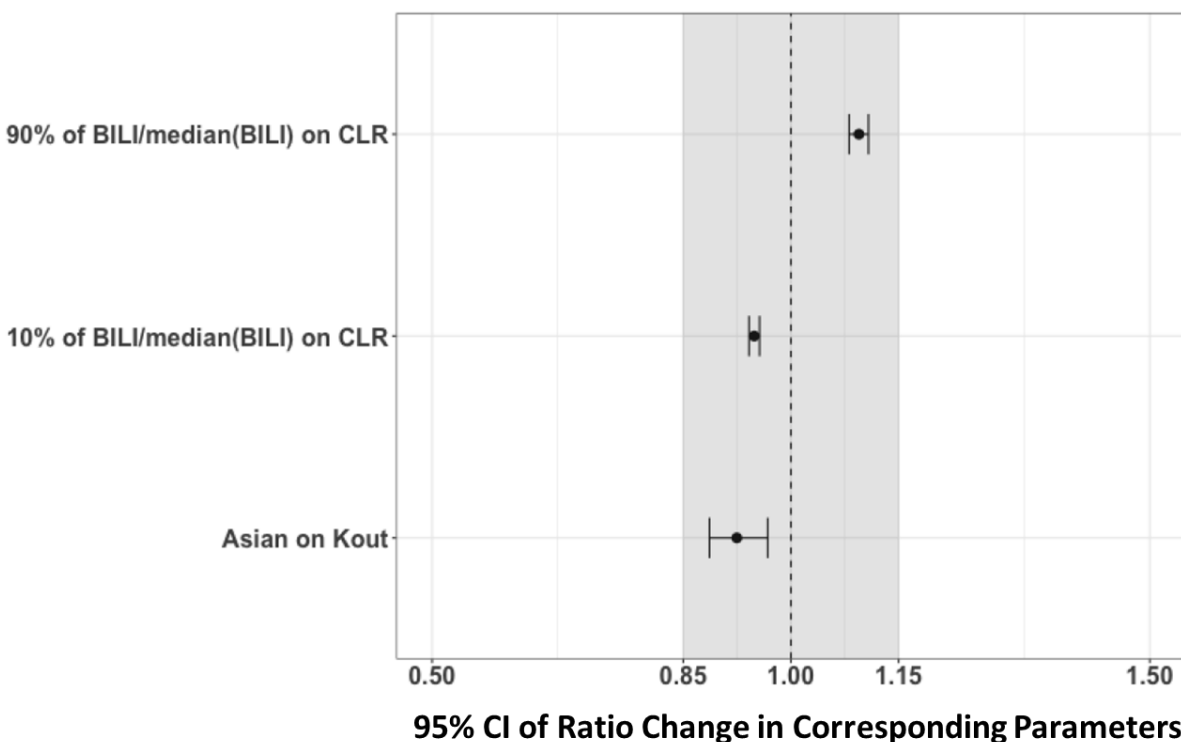
Source: study-poh1116, Figure 19

Grey closed circles represent observations; black line represents median of observations; black dashed lines are 5th and 95th percentiles of observations; grey area represents prediction intervals for median, 5th, and 95th percentile; red asterisks are time points where observations are outside the prediction intervals.

Abbreviations: AT, antithrombin; PopK-PD, population kinetics-pharmacodynamics

The impact of selected statistically significant covariates on PopK-PD model parameters were defined as the ratio between PopK-PD model parameters with and without covariates that were obtained from the estimates of fixed effects (thetas) and parameter precision as derived from parametric bootstrapping. [Figure 41](#) shows the 95% confidence interval of the distribution of the impact of selected statistically significant covariates on model parameters. Overall, the magnitude of the impact of selected significant covariates is less than 25% (i.e., 95% CI of the ratio within [0.85,1.15]).

Figure 41. Impact of Selected Statistically Significant Covariates on PopK-PD Model Parameters

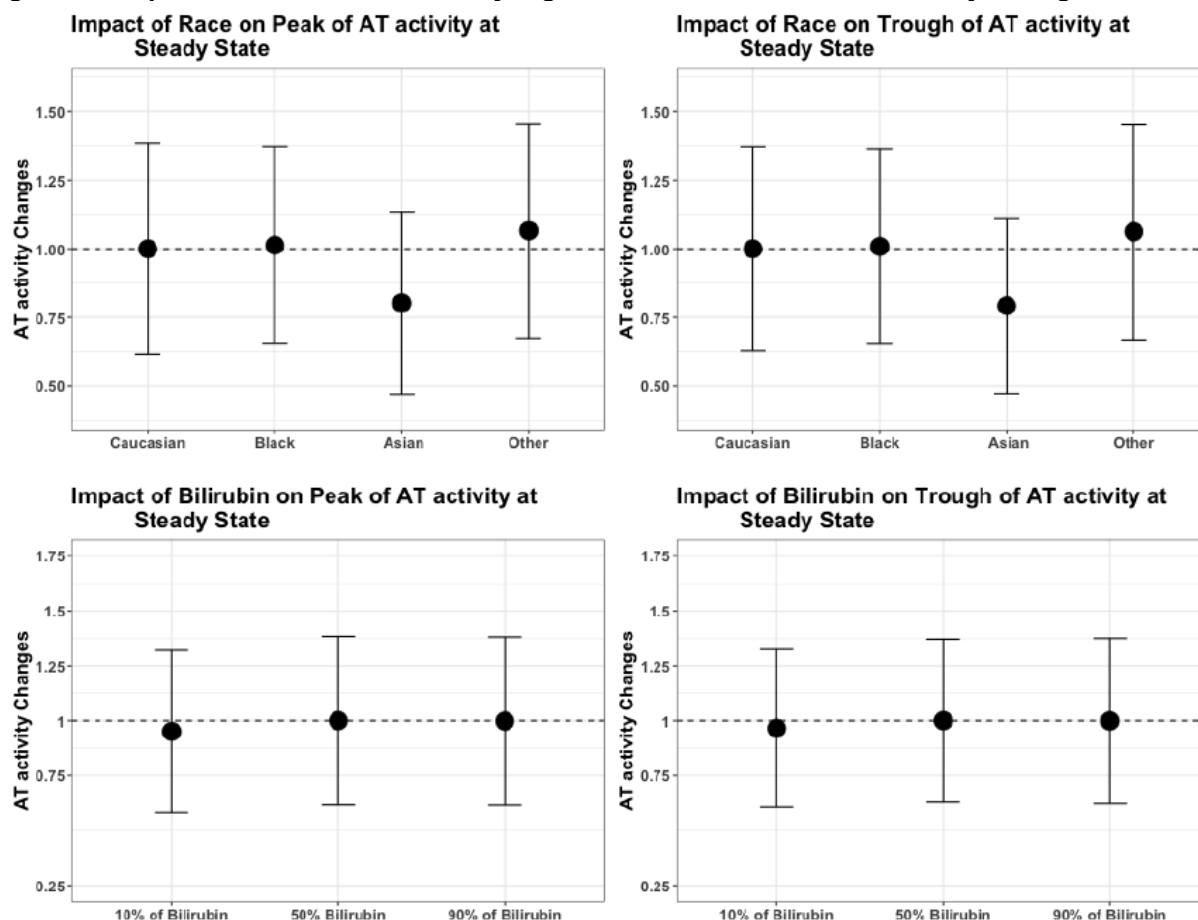


Source: study-poh1116, Figure 20

Abbreviations: AT, antithrombin; BILI, bilirubin; CI, confidence interval; CLR, clearance from RISC compartment; Kout, AT elimination rate; PopK-PD, population kinetics-pharmacodynamics

Simulations were conducted in a large subject population to generate a distribution of AT-activity-versus-time profiles across the population. The impact of covariates was assessed by calculating fold change of steady-state AT peak or trough after 50 mg Q2M dose of a statistically significant covariate value relative to its reference. [Figure 42](#) shows that peak and trough AT activities of Asian subjects at steady state are lower compared to the remaining race categories, with magnitude of median impact less than 25%. The other races (i.e., Caucasian, Black, and others) and bilirubin do not have significant effect on peak and trough AT activity. Overall, the median effect of the selected statistically significant covariates on AT changes are less than 25%.

Figure 42. Impact of Selected Statistically Significant Covariates on AT Activity Change



In all simulations, typical participant is a Caucasian with Bilirubin= 9.43 $\mu\text{mol/L}$.

Source: study-poh1116, Figure 21

Dots and error bars represent the mean and 95% CI of predicted AT activity change. 10%-, 50%-, and 90% of Bilirubin refers to 10th percentile, median, and 90th percentile of the observed bilirubin distribution.

Abbreviations: AT, antithrombin; CI, confidence interval

Simulations were conducted with the PopK-PD model to predict dose distribution based on the proposed AT-based dose regimen. The Agency identified several issues in this simulation analysis and requested a revised simulation. The updated results from the Applicant are shown in [Table 138](#). The model underestimated the percentage of subjects who discontinued the treatment due to AT <15% with 20 mg QM.

Table 138. Distribution of Subjects Across Recommended Fitusiran Dose Regimens at Which Individual Subject AT Activity is Maintained Between 15 and 35%

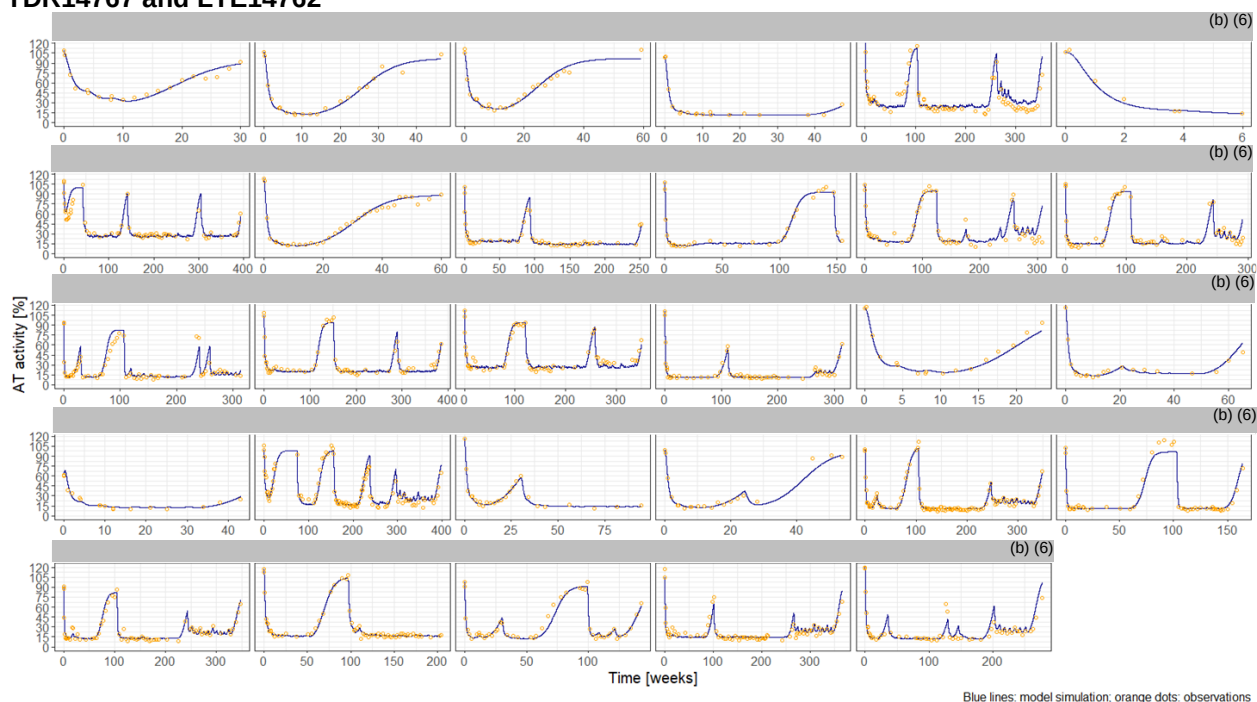
Dose Regimen Population	50 mg Q2M	50 mg QM	20 mg Q2M	20 mg QM	Discontinued (AT<15%)
Observed distribution of participants	40.6%	15.9%	29.7%	2.1%	11.7%
Simulated distribution of patients with etas resampling (Original KPD model)	48.0%	19.6%	20.1%	1.41%	10.8%
Simulated distribution of patients without resampling etas	50.6%	15.3%	25.0%	2.9%	6.1%

Source: Response for Information Request dated on November 4, 2024, Table 1

Abbreviations: AT, antithrombin; KPD, kinetic-pharmacodynamic; Q2M, every 2 months; QM, once monthly

Overall, the Applicant's revised PopK-PD modeling and simulation analyses appear to be reasonable. Approximately 6% of subjects were predicted to discontinue treatment due to AT <15% with 20 mg Q2M, which was lower than the observed 11.7% ([Table 138](#)). This inconsistency between model prediction and observation might be due to the Applicant's simulation approach, which did not consider the carryover effect due to the sustained AT activity inhibition from (1) the 80 mg QM regimen before the voluntary dosing pause; (2) AT-guided dose titration in the trial after the voluntary dosing pause (e.g., 50 mg Q2M de-escalate to 20 mg Q2M). To better evaluate the proposed dosing regimen and AT monitoring program, the reviewer performed independent PopK-PD model simulation analyses. The reviewer's simulation matched with the observed individual AT profile relatively well ([Figure 43](#) and [Figure 44](#)).

Figure 43. Model-Simulated AT Profile vs. Individual Observations for Representative Subjects in TDR14767 and LTE14762



Source: reviewer's analysis

Abbreviations: AT, antithrombin; LTE, long-term extension

Figure 44. Model-Simulated AT Profile vs. Individual Observations for Representative Subjects in EFC14768, EFC14769, LTE15174, and EFC15110



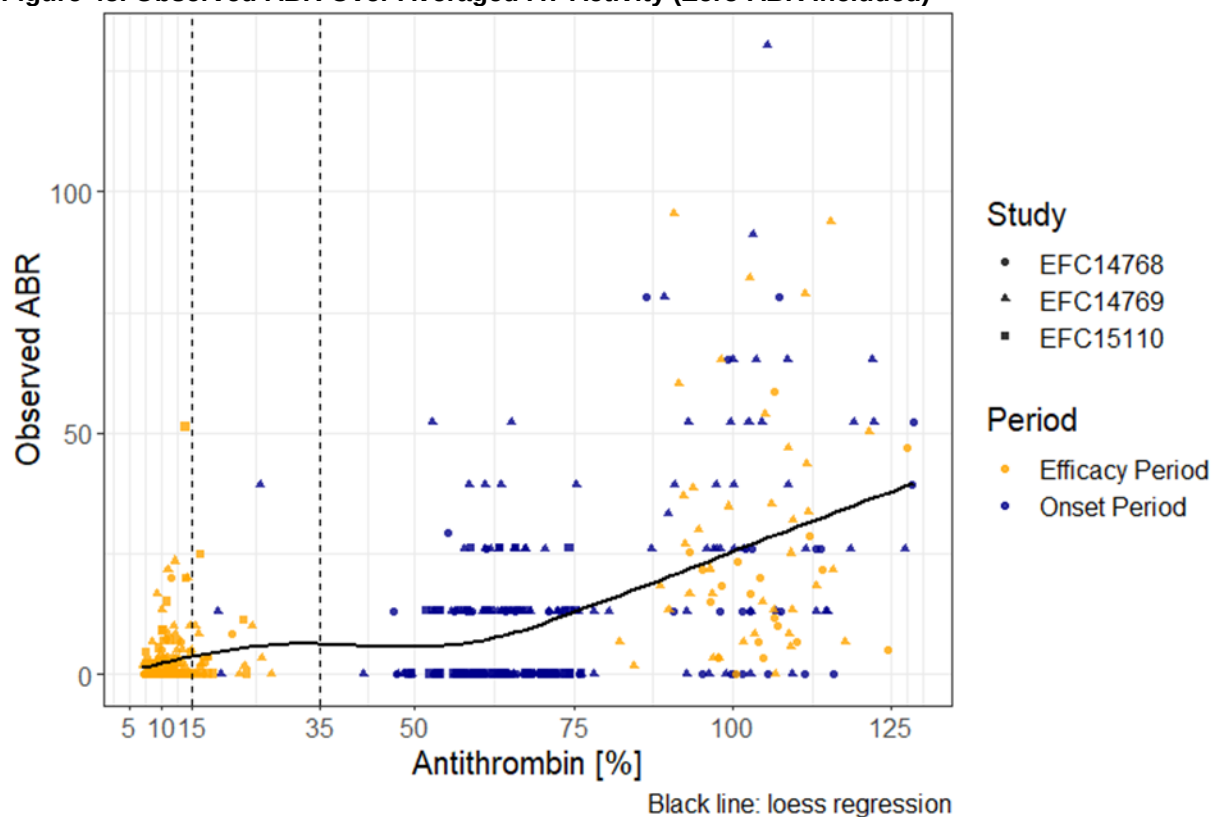
Source: reviewer's analysis

Abbreviations: AT, antithrombin; LTE, long-term extension

14.5.2. Evaluation for the Target AT Activity Range of 15% to 35%

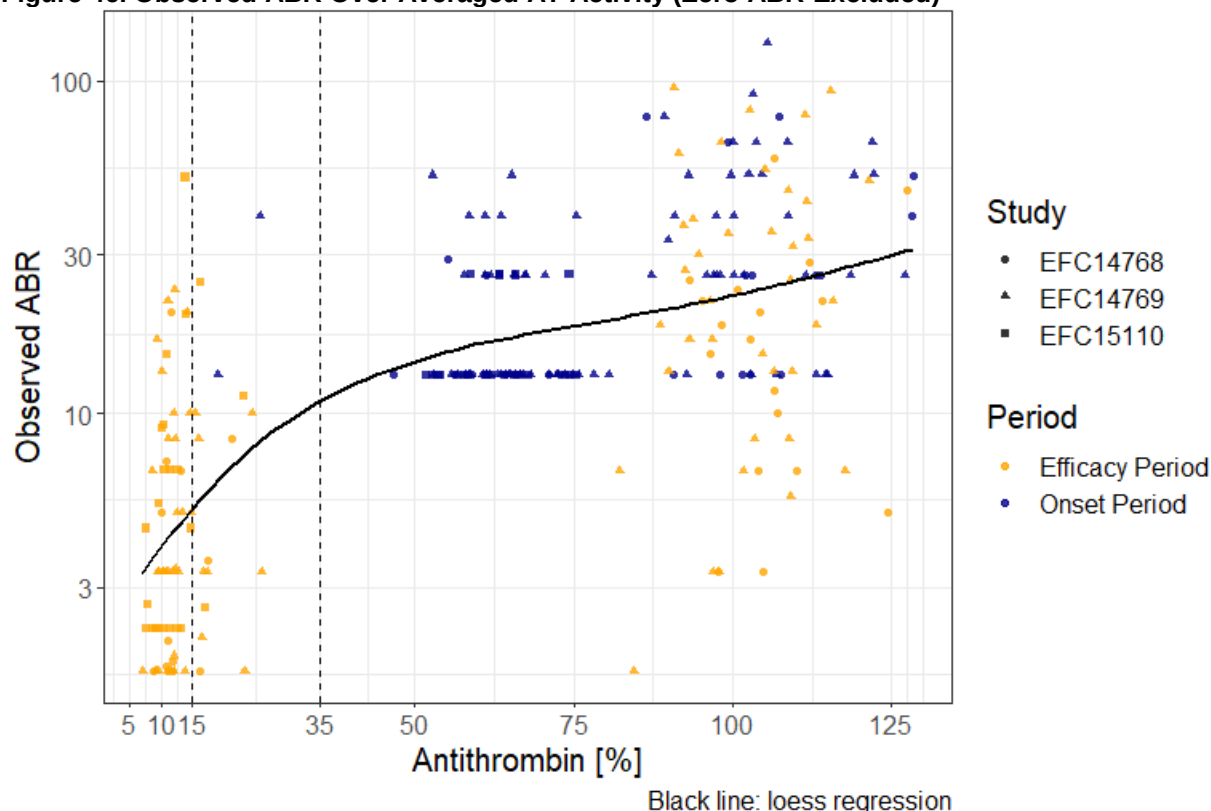
Observed ABR records from 242 subjects in Studies EFC14768 (ITT), EFC14769 (ITT), and EFC15110 with fixed 80 mg QM were used to evaluate the correlation between AT activity and the efficacy endpoint ABR. Observations with the AT-based dosing regimen were not incorporated due to potential confounding by dose titration. The onset period for the 3 trials was the first 28 days. The efficacy period was Day 29 onwards until Month 9 for EFC14769, until Day 246 for EFC14769, and until Month 6 for EFC15110. Due to the limited duration of the onset period, a high number of zero-ABR values was observed. The average AT during the onset and efficacy periods was used to correlate with the observed ABR in the respective periods. The association plots, both with (Figure 45) and without (Figure 46) zero-ABR records, indicated that lower AT activity was potentially associated with lower ABR. However, it is unclear at which level of AT activity the ABR lowering plateaued, as the data did not provide sufficient information. Furthermore, the variability in follow-up duration among trials and between the onset and efficacy periods may have confounded the results.

Figure 45. Observed ABR Over Averaged AT Activity (Zero ABR Included)



Source: reviewer's analysis
Abbreviations: ABR, annualized bleeding rate; AT, antithrombin

Figure 46. Observed ABR Over Averaged AT Activity (Zero ABR Excluded)

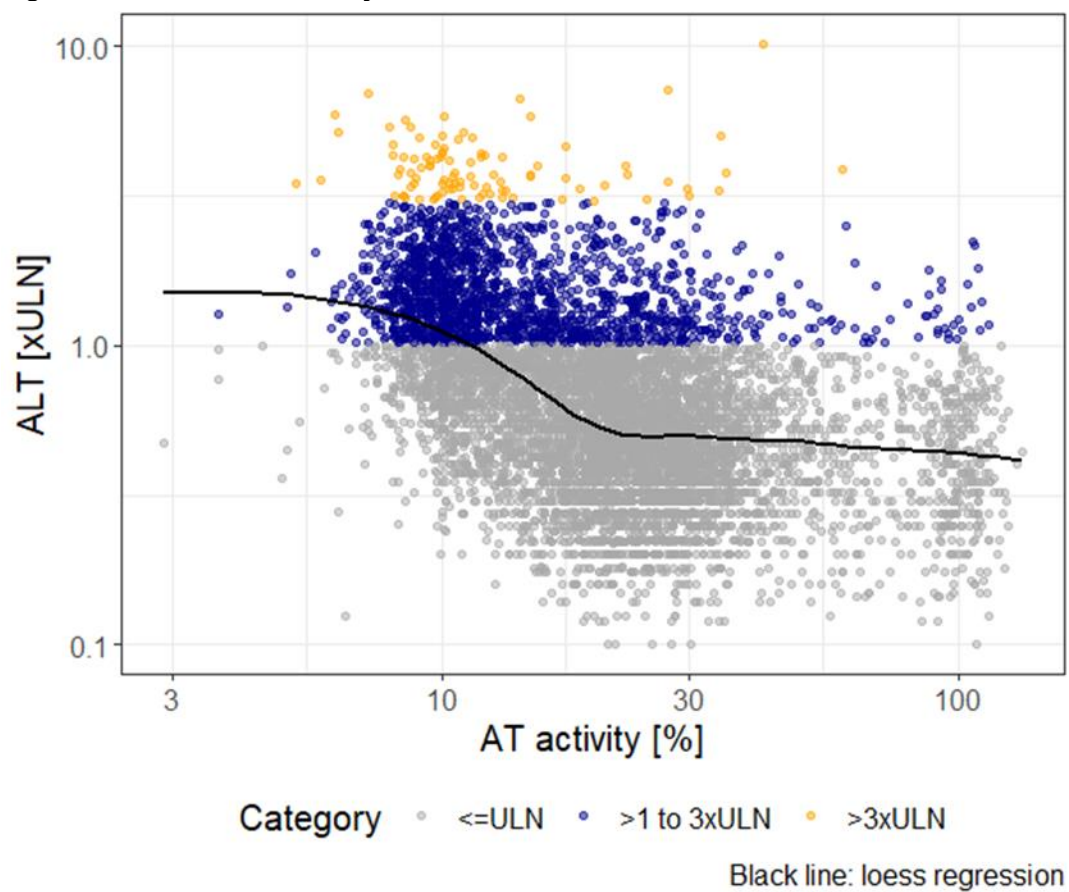


Source: reviewer's analysis

Abbreviations: ABR, annualized bleeding rate; AT, antithrombin

In addition, ALT and AST data from 293 subjects in EFC14768, EFC14769, EFC15110, and LTE15174 were used to explore the correlation between AT activity and ALT/AST elevation. [Figure 47](#) and [Figure 48](#) suggested both ALT and AST elevation were associated with AT activity suppression. Targeting AT activity within the range of 15% to 35% could potentially reduce the percentage of subjects exhibiting $>1\times$ ALT ([Figure 49](#)) and >1 to $3\times$ AST ([Figure 50](#)) levels compared to targeting AT activity below 15%.

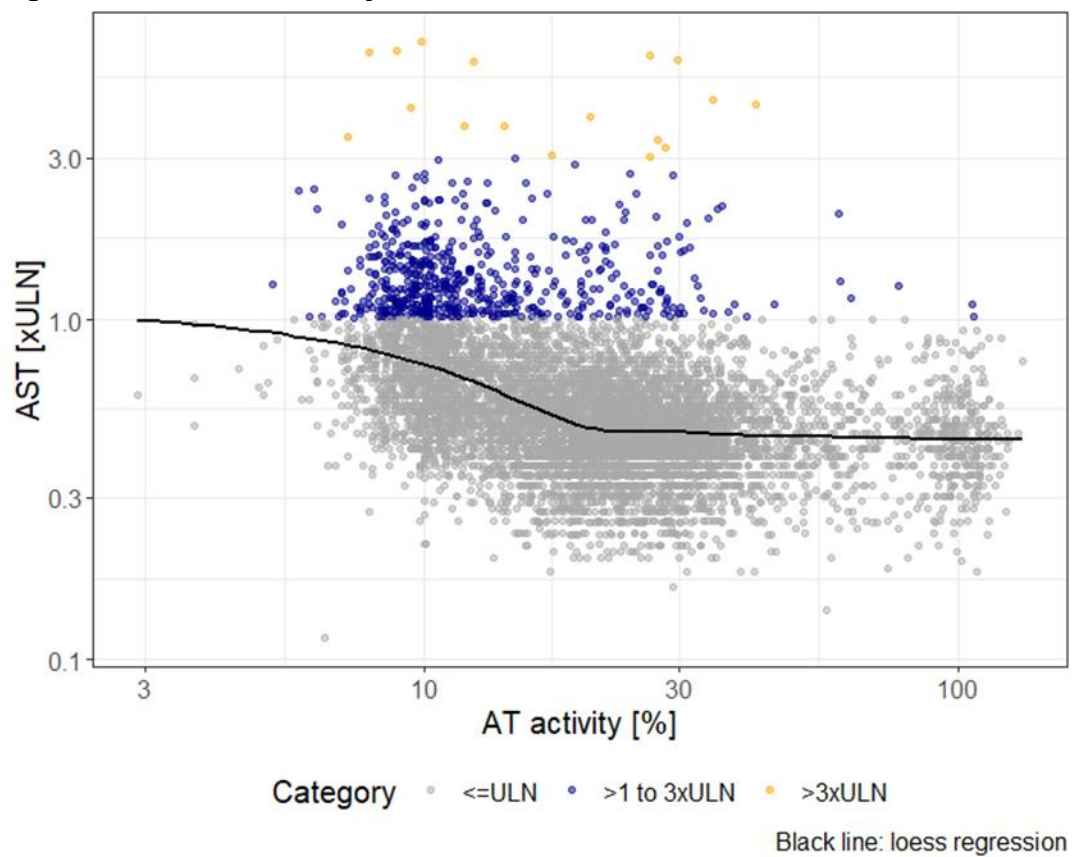
Figure 47. ALT vs. AT Activity



Source: reviewer's analysis

Abbreviations: ALT, alanine aminotransferase; AT, antithrombin; ULN, upper limit of normal

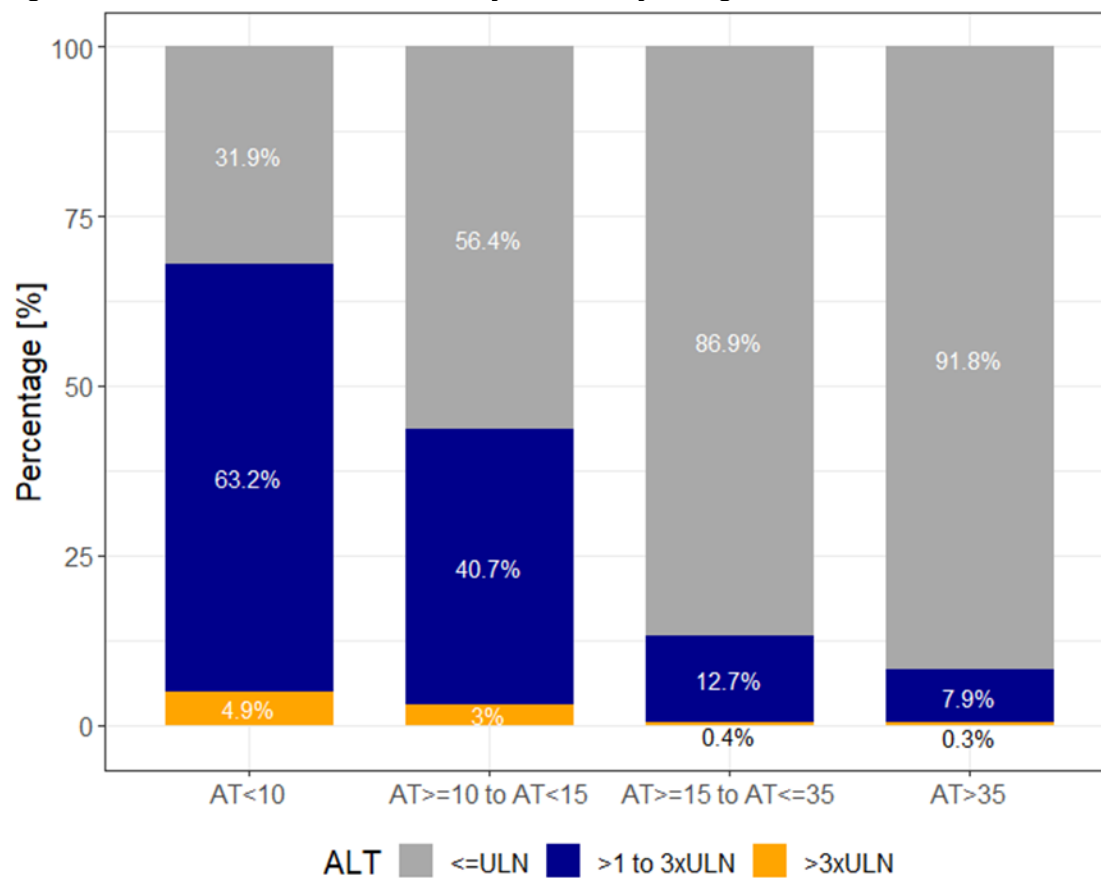
Figure 48. AST vs. AT Activity



Source: reviewer's analysis

Abbreviations: AST, aspartate aminotransferase; AT, antithrombin; ULN, upper limit of normal

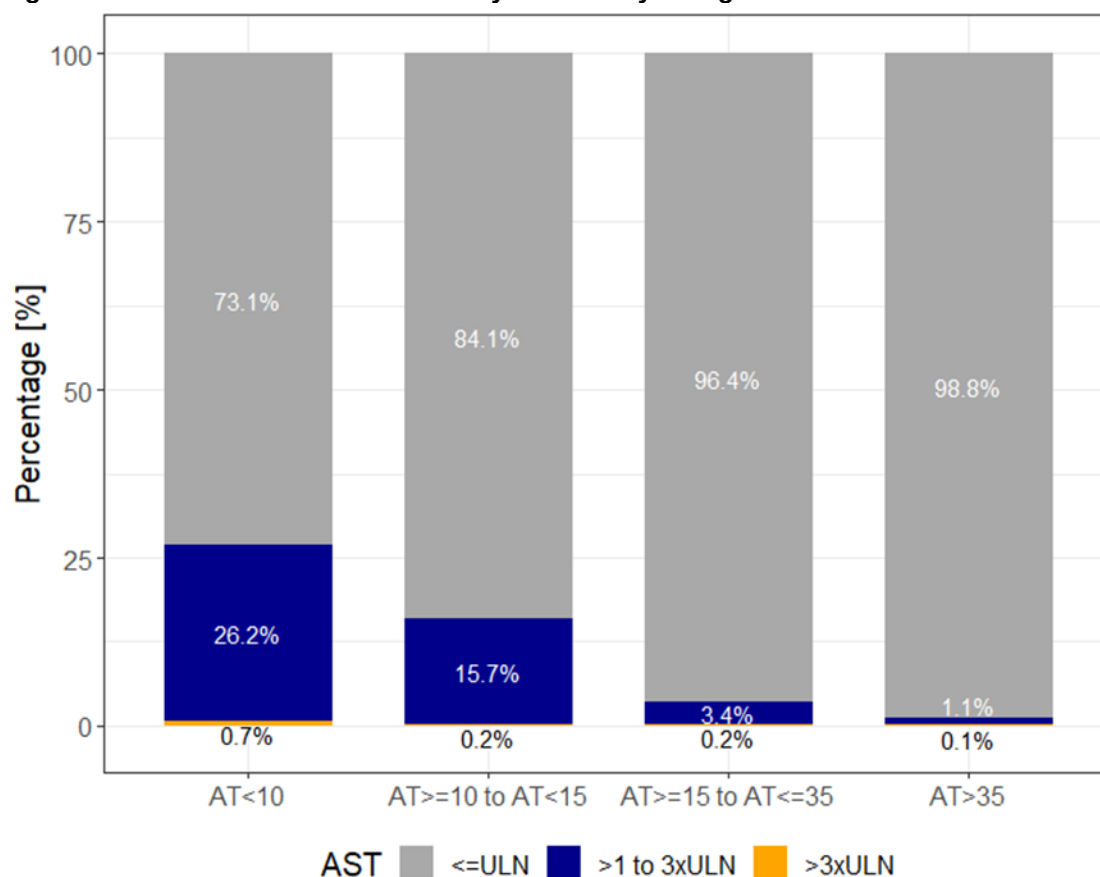
Figure 49. ALT Distribution Stratified by AT Activity Categories



Source: reviewer's analysis

Abbreviations: ALT, alanine aminotransferase; AT, antithrombin; ULN, upper limit of normal

Figure 50. AST Distribution Stratified by AT Activity Categories



Source: reviewer's analysis

Abbreviations: AST, aspartate aminotransferase; AT, antithrombin; ULN, upper limit of normal

In addition to ALT and AST elevation, AT activity below 10% is associated with increased risk for thromboembolic events. Taking these results into consideration, the target AT activity range of 15% to 35% to balance efficacy and safety of fitusiran appears reasonable.

14.5.3. Addition of a Lower 10 mg Q2M Dose for Patients With AT <15% on 20 mg Q2M

In the clinical trials, 11.7% of subjects discontinued treatment due to AT activity <15% with the 20 mg Q2M dosing regimen. However, the majority of subjects, who received 80 mg QM before the voluntary dosing pause, did not exhibit AT levels returning to baseline when starting the AT-based dosing regimen after the dosing pause, which suggested a carryover effect of the 80 mg QM dosing regimen. As a result, the true percentage of subjects discontinuing treatment with the proposed dosing regimen without considering the carryover effect should be less than what was observed. The Applicant estimated that approximately 6% of the total virtual patient population would discontinue treatment due to AT levels below 15% with the 20 mg Q2M regimen. However, the Applicant's simulation approach did not account for the carryover effect following dose titration. The reviewer conducted a PopK-PD simulation that considered the carryover effect due to changes in dosage.

The virtual patient population was generated by resampling each studied subject 10 times and incorporating sampled interindividual variability for corresponding PopK-PD parameters. Dose modification for each virtual patient was based on trough AT levels for down-titration and maximum (predose) AT levels for up-titration. A 6-month AT profile was simulated for each dose level after last dose modification and before next potential dose modification.

The simulation indicated that 54.3% of the total virtual patient population remained on the 50 mg Q2M dosage regimen over time. Furthermore, 13.5% of the total virtual patients up-titrated to 50 mg QM, while 32.3% down-titrated to 20 mg Q2M. Among the patients who were down-titrated to 20 mg Q2M, 22% (representing 7% of the total virtual patient population) exhibited trough AT levels below 15%. To explore a lower dosage regimen that could retain these 7% of patients on fitusiran treatment, the reviewer simulated 10 mg Q2M and 15 mg Q2M using the virtual patients who had AT levels below 15% with the 20 mg Q2M regimen. The results suggested that 5.88% and 4.26% of the total virtual patient population could remain on treatment with the 10 mg Q2M and 15 mg Q2M regimens, respectively. Notably, neither regimen resulted in patients with AT levels exceeding 35%. Consequently, the review team recommended adding 10 mg Q2M as a lower dose option for patients who would otherwise discontinue treatment due to AT levels below 15% with the 20 mg Q2M regimen. The patient distribution with the review-team-proposed dosing regimen is shown in [Figure 51](#).

Figure 51. Patient Distribution After Adding 10 mg Q2M



Source: reviewer's analysis
(): percentage of total virtual patients
Abbreviations: AT, antithrombin; Q2M, every 2 months

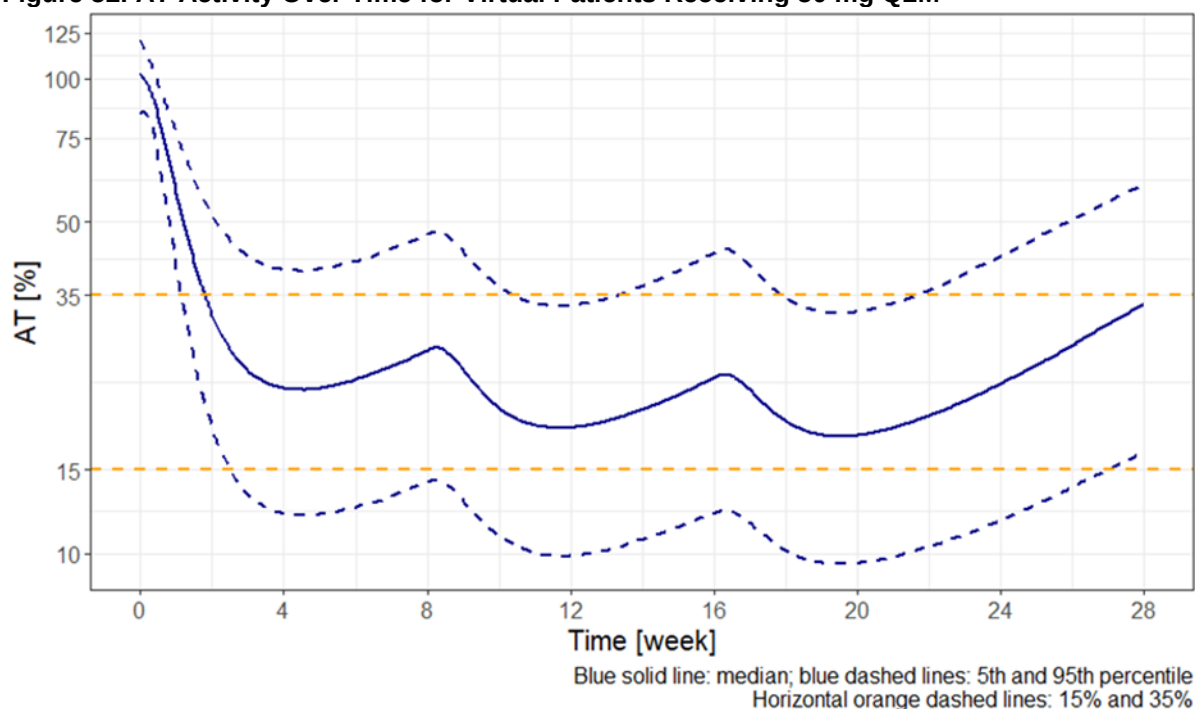
14.5.4. Evaluation of AT Monitoring Program

The Applicant proposed that AT activity be measured prior to initiation of fitusiran treatment and

(b) (4) If AT activity is (b) (4) <15%, then a dose reduction is required, and the lower dose should be initiated 3 months after the prior dose. If AT activity is >35% after 6 months, or if the patient has not achieved satisfactory bleed control, dose modification should be considered. In the clinical trials, subjects with more than one AT activity level <15% within a 12-month period must discontinue fitusiran dosing and may have the option to enroll into the lower dose cohort. Upon the first AT level <15%, the patient must have another AT sample drawn within 1 week of site receipt of the results. If this result is <15%, it was considered the second AT activity level <15%. Dose escalation in the clinical trial was based on 2 steady-state (Month 4, Month 5, and Month 6) AT activity levels >35%. To evaluate the appropriateness of the proposed AT monitoring program, the reviewer performed a PopK-PD simulation.

For the Q2M regimen, AT inhibition reached its maximum approximately 4 weeks after each dose (Month 1, Month 3, and Month 5), whereas the predose AT activity was close to the minimum AT inhibition within each dosing interval ([Figure 52](#)). The dose de-escalation based on the AT activity measured predose every other month led to 14.2% of patients being down-titrated to 20 mg Q2M, whereas down-titration would occur in approximately 32.3% of patients if using the peak effect of fitusiran on AT activity measured at 4 weeks post each dose (Month 1, Month 3, and Month 5) ([Table 139](#)). Considering the severe safety outcome associated with low AT activity, the review team recommended that dose de-escalation be based on AT activity measured at 4 weeks after each dose (Month 1, Month 3, and Month 5) rather than AT activity measured predose every other month. For the QM regimen, the fluctuation of AT activity between maximum and trough AT activity was minimal, and the AT activity measured at each month was close to the maximum AT inhibition ([Figure 53](#)). Additionally, patients on the QM dosing regimen had less concern for low levels of AT. As a result, the review-team-proposed AT monitoring program can be applied to a QM dosing regimen as well.

Figure 52. AT Activity Over Time for Virtual Patients Receiving 50 mg Q2M



Source: reviewer's analysis
Abbreviations: AT, antithrombin; Q2M, every 2 months

Table 139. Distribution of the Virtual Patients Who Required Dose De-Escalation With 50 mg Q2M Based on AT Measurement Either Every Other Month or Measured 4 Weeks Post Each Dosing

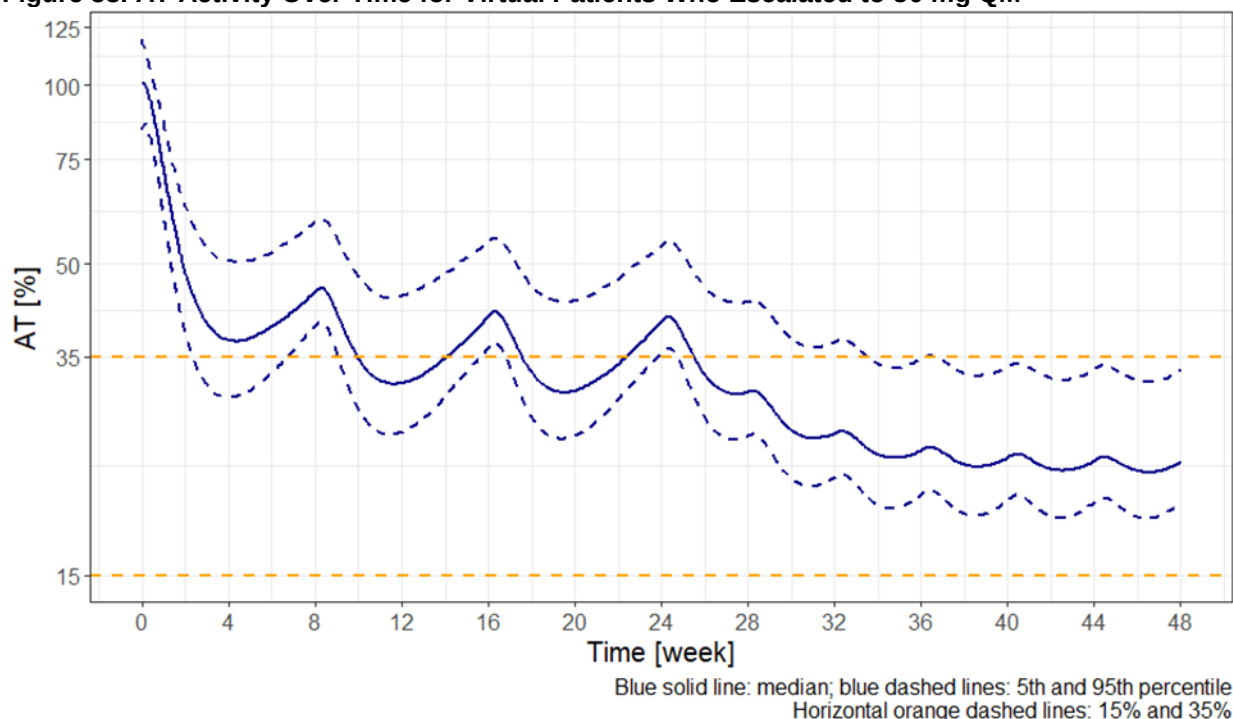
Percentage of total virtual patients		
De-escalation based on	20 mg Q2M	Discontinue due to AT < 15% with 20 mg Q2M
Pre-dose AT	14.2%	1.8%
AT measured at one month post each dose	32.3%	7%

Source: reviewer's analysis

Abbreviations: AT, antithrombin; Q2M, every 2 months

To evaluate the proposed dose escalation rule, the reviewer simulated three scenarios: (1) all 3 predose AT >35%; (2) 2 out of 3 predose AT >35%; (3) at least 1 predose AT >35%. The proposed AT monitoring after 6 months is equivalent to the simulation scenario where 3 predose ATs are required to be >35% since the AT activity gradually decreases over time in each 6-month period and AT at 6 months would be the maximum predose inhibition ([Figure 53](#)). All three scenarios had 0.46% of total virtual patients who had AT >35% after dose escalation. If the dose is escalated with only one predose AT >35%, then there is a potential risk to induce AT below 15% ([Table 140](#)). Based on the simulation results, the proposed dose escalation rule appears to be reasonable.

Figure 53. AT Activity Over Time for Virtual Patients Who Escalated to 50 mg QM



Source: reviewer's analysis
Abbreviations: AT, antithrombin; QM, once monthly

Table 140. Distribution of Virtual Patients Who Escalated to 50 mg QM Based on Three Different Dose Escalation Scenarios

AT activity at week 48	Percent of total virtual patients [%]		
	3 pre-dose AT >35%	2 pre-dose AT >35%	1 pre-dose AT >35%
> 35%	0.46	0.46	0.46
15% - 35%	13	13.9	22.7
< 15%	NA	NA	0.07

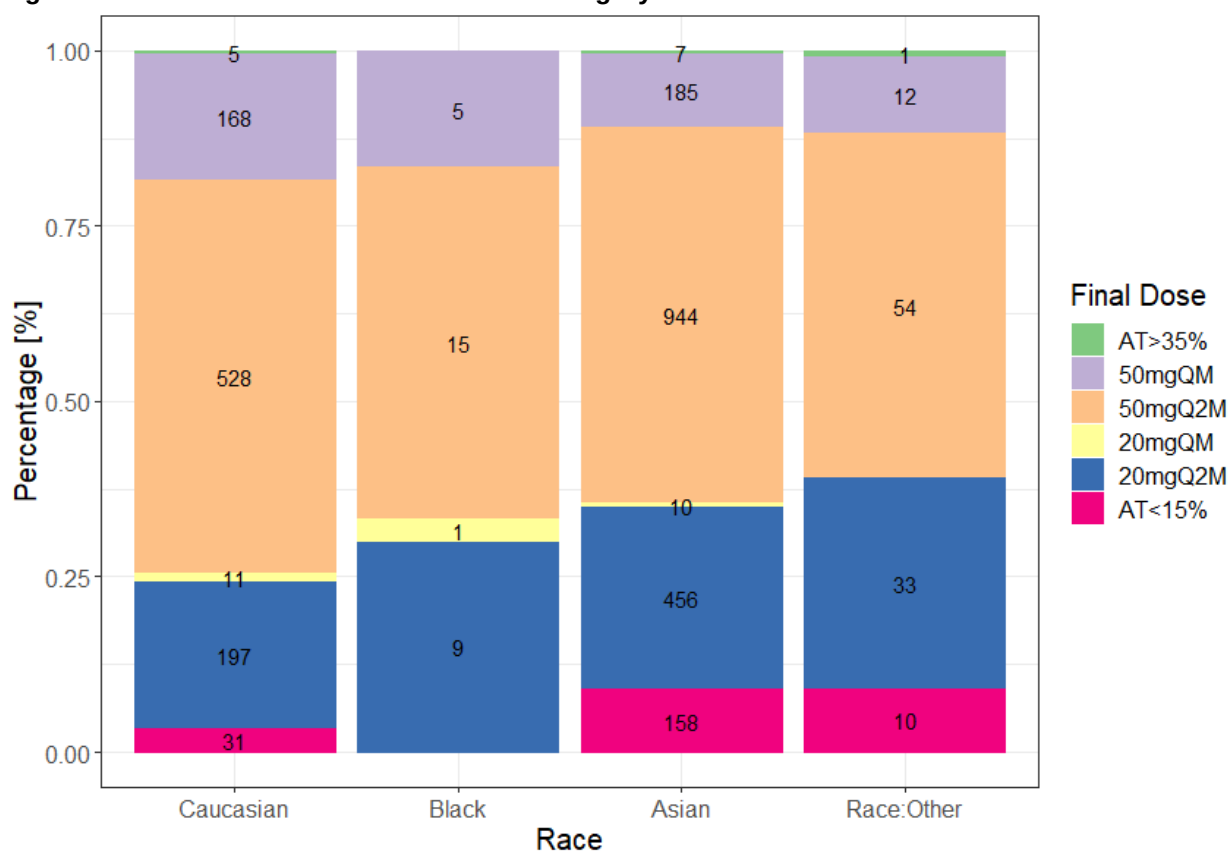
Source: reviewer's analysis
Abbreviations: AT, antithrombin; QM, once monthly

14.5.5. Evaluation of Covariate Effect of Race on AT

In clinical trials, the majority (93.9%) of the subjects who discontinued the drug due to low AT levels were Asians. The covariate effect of race on AT activity was explored using PopK-PD simulation. The original PopK-PD model dataset consists of 41.9% of Caucasian (n=142), 1.5% of Black or African American (n=5), 53.4% of Asian (n=181), and 3.2% of other races (n=11). The virtual patients were resampled from the studied subjects while maintaining the same race

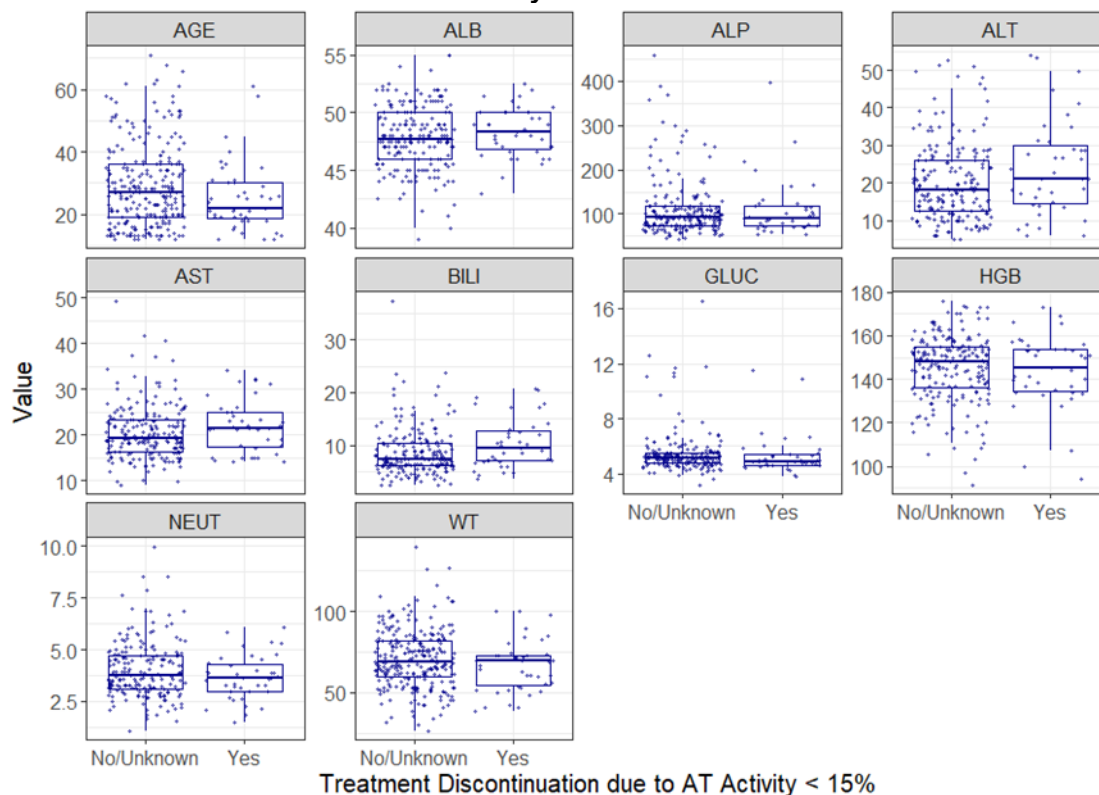
distribution as observed in the trial. The dose distribution stratified by race is shown in [Figure 54](#). The simulation indicated Asian patients had the highest number of treatment discontinuations due to AT <15%. The percentage of Asian patients who discontinued treatment was larger than that of Caucasian patients. The percentage of discontinued patients was comparable between Asian and Race: Other groups. However, the limited number of patients in the Black and Race: Other groups makes it difficult to draw solid conclusions. The higher number of Asian patients who discontinued treatment in the trial was partially due to their larger representation in the studied population. The reviewer did not identify potential confounding factors (including body weight) that were imbalanced between patients who discontinued or remained on treatment ([Figure 55](#)). Since a lower 10 mg Q2M was recommended for all patients, no additional dose adjustment is needed based on race.

Figure 54. Dose Distribution in Each Race Category



Source: Reviewer's analysis
Numbers represent the number of virtual patients for the corresponding category
Abbreviations: AT, antithrombin; Q2M, every 2 months; QM, once monthly

Figure 55. Comparison of Representative Demographic Characteristics and Laboratory Measurements at Baseline Between Patients Who Remained on Treatment and Patients Who Discontinued Treatment Due to AT Activity <15%



Source: Reviewer's analysis

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, antithrombin; BILI, bilirubin; GLUC, glucose; HGB, hemoglobin; NEUT, neutrophil; WT, body weight

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Study EFC14768

Study Title

ATLAS-INH: 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

Study Dates

Study initiation date: February 14, 2018 (date of first subject screened)

Study completion: June 23, 2021 (last subject last visit)

Study Objectives

Primary

To evaluate the efficacy of fitusiran compared to on-demand treatment with BPAs (bypassing agents), as determined by the frequency of bleeding episodes.

Secondary

1. To evaluate the efficacy of fitusiran compared to on-demand treatment with BPAs, as determined by:
 - a. The frequency of spontaneous bleeding episodes.
 - b. The frequency of joint bleeding episodes.
 - c. Health-related quality of life (HRQOL) in subjects ≥ 17 years of age
2. To determine the frequency of bleeding episodes during the onset period (defined as the first 28 days after the first dose of fitusiran, during which the target pharmacodynamic effect is reached).
3. To determine the safety and tolerability of fitusiran.

Study Endpoints

Primary

Annualized Bleeding Rate (ABR) for treated bleeds in the treatment period (defined in Section [6.2](#), [Table 14](#)).

Secondary

1. ABR for treated bleeds in the efficacy period.
2. Annualized treated spontaneous bleeding rate in the efficacy period (defined in Section [6.2](#), [Table 14](#)).
3. Annualized treated joint bleeding rate in the efficacy period.
4. Change in Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) physical health score and total score in the treatment period.

Study Design

The ATLAS-INH (EFC14768) study was a multicenter, multinational, randomized, open-label phase 3 study designed to evaluate the efficacy and safety of fitusiran in male subjects aged ≥ 12 years with hemophilia A or B and inhibitory antibodies to factor FVIII or factor FIX, who are not receiving prophylactic therapy.

Eligible patients were randomized in a 2:1 ratio to either the fitusiran treatment arm, receiving 80 mg administered subcutaneously (SC) as prophylaxis once monthly, with use of on-demand BPAs for treatment of breakthrough bleeding episodes; or the on-demand arm, receiving BPAs for treatment of breakthrough bleeding episodes. Randomization was stratified by the number of bleeding episodes in the 6 months prior to Screening (≤ 10 versus > 10). All subjects were treated

for a total of 9 months; subjects randomized to the fitusiran treatment arm received 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 was assessed during the final 8 months on study (Day 29 to Month 9). Scheduled assessments included monthly physical exams, triglyceride levels, AT activity levels, hematology labs, liver tests, and serum chemistry. Subjects from both the fitusiran and on-demand treatment arms who completed the study were eligible for participation in an open-label extension study.

BPAAs include recombinant factor VIIa, Factors VIII and IX, and activated prothrombin complex concentrates (aPCC).

Breakthrough bleeding is defined as any occurrence of hemorrhage that requires administration of factor concentrates or BPA infusion, e.g., hemarthrosis, muscle, or mucosal bleeding. A spontaneous bleeding episode is a bleeding event that occurs for no apparent or known reason, particularly into the joints, muscles, and soft tissues. A joint bleeding episode is characterized by an unusual sensation in the joint (“aura”) in combination with: (1) increasing swelling or warmth over the skin over the joint; (2) increasing pain; or (3) progressive loss of range of motion or difficulty in using the limb as compared with baseline. A muscle bleed may be characterized by pain, swelling, and loss of movement over the affected muscle group. A target joint is defined as a joint where 3 or more spontaneous bleeding episodes in a single joint within a consecutive 6-month period has occurred; where there have been ≤ 2 bleeding episodes in the joint within a consecutive 12-month period the joint is no longer considered a target joint. A traumatic bleeding episode is one that is caused by a known injury or trauma. Bleeding episodes sustained during sports and recreation were counted as traumatic bleeding episodes.

Bleed Management Guidelines

On-Demand Arm

For subjects not receiving fitusiran (on-demand arm), bleeding management therapy with BPAAs was to be managed based on the local standard practice for treating hemophilia patients with inhibitors, as routinely administered by the physician. Where clinical circumstances allowed, it was recommended that the subject contact the Investigator for all events suspected to be or characteristic of a bleeding episode. If adequate hemostasis did not occur after two doses of BPA, the subject was to contact the site for further instruction. If the subject felt the need to administer doses higher than the subject’s bleeding episode management plan recommended, or at a higher frequency, it was recommended that the subject contact the site.

Fitusiran Treatment Arm

Given the mechanism of action and PD profile of fitusiran, the BPA dose necessary to safely and effectively treat breakthrough bleeding episodes in subjects receiving fitusiran (fitusiran treatment arm) was lower than standardly prescribed (see [Table 141](#) below). This was supported by data from the phase 1 study in which bleeding events were managed with factor or BPA, as well as additional modeling and ex vivo spiking data.

Subjects on fitusiran were provided a written bleed management plan (as described below) with appropriate dosing of BPA for use during Day 1 through 7, as well as a bleed management plan with dosing for Day 8 and beyond. Thereafter the bleed management plan was reviewed and updated at monthly visits, and new written plans were provided to the subject if dosing changed.

Importantly, during the treatment period, subjects were not to use BPA or other hemostatic agents as prophylaxis for bleeding episode prevention, including doses related to anticipated hemostatic challenges such as physical activity.

Day 1 to Day 7

Subjects were to be instructed to call the site prior to administering factor or BPA. Subjects were to continue with their standard BPA regimens.

Day 8 and Beyond

1. Subject was to be instructed to call the study center to discuss symptoms to determine whether or not they were consistent with a bleeding event and to discuss the appropriate factor/BPA dose to use. This interaction between subject and Investigator is recommended prior to the administration of each dose of factor or BPA. Confirmation of bleeds at the study center prior to treatment may be considered.
2. If a determination was made that symptoms required treatment, the recommended treatment algorithm for bleeding episodes is described below:
 - a. A single dose could be administered according to the guidelines in [Table 141](#).
 - b. The subject was to be instructed to reevaluate symptoms in 24 hours for bleeds treated with FVIII, FIX or aPCC and in 2 to 3 hours for bleeds treated with rFVIIa.
 - c. Administration of FIX Extended half-life should not be more frequent than every 5 to 7 days.
3. If a second dose (in the case of FVIII, FIX or aPCC) or a third dose (in the case of rFVIIa) was needed, the subject was to call the study center before dosing.
 - a. Study staff were to consider evaluation and treatment of the subject at the study center and confirmation of bleeds when any repeated doses were needed.
 - b. If more than two doses of FVIII, FIX, or aPCC, or three doses of rFVIIa were needed, the subject was to be seen at the study center within 48 to 72 hours.
4. Doses were not to be administered at less than 24-hour intervals (except rFVIIa as indicated in [Table 141](#)).
5. Doses were not to exceed the protocol maximum recommended dose indicated in [Table 141](#).
6. Consultation with the study Medical Monitor and Clinical Advisor was to be considered for clinical circumstances below, that may warrant AT replacement:
 - a. Doses of factor or BPA higher than those recommended in [Table 141](#)
 - b. Dosing of factor or BPA at decreased intervals than those recommended in [Table 141](#)
 - c. Multiple or repeated doses of factor or BPA
7. Antifibrinolytics were not to be used in combination with factor or BPA.

Table 141. Bleed Management Guidelines by Specific Product

	Factor VIII	Factor IX Standard half- life	Factor IX Extended half- life	aPCC	Recombinant Factor VIIa
Recommended <u>single</u> dose of	10 IU/kg	20 IU/kg	20 IU/kg	30 U/kg	≤45 µg/kg
Single Dose should not exceed	20 IU/kg	30 IU/kg	30 IU/kg	50 U/kg	45 µg/kg
Repeat dose instructions	Mandatory to call the clinical study center prior to second dose Consider evaluation and treatment at the clinical study center (see Section 6.4)				Mandatory to call site prior to third dose
	Should not repeat in less than 24 hours	Should not repeat in less than 24 hours	Should not repeat in less than 5-7 days	Should not repeat in less than 24 hours	Should not repeat in less than 2 hours
	Should be seen at site within 48-72 hours if more than 2 doses are required (see Schedule of Assessments for assessments)				Should be seen at site within 48-72 hours if more than 3 doses are required
For situations requiring higher doses, more frequent administration, multiple repeated doses, discussion with study Medical Monitor and Clinical Advisor is recommended, and AT replacement should be considered.					
Do not use antifibrinolytics in combination with factor or BPA.					

Note: Doses of FVIII and FIX are included for completeness. It is expected that these inhibitor patients will be routinely managed with rFVIIa or aPCC for bleeding episodes. Adjunctive management of bleeding episodes should be carried out per standard of care.

Source: Applicant's Protocol for Study EFC14768

Abbreviations: aPCC, activated prothrombin complex concentrate; AT, antithrombin; BPA, bypassing agent; FIX, factor IX; FVIII, factor VIII; rFVIIa, recombinant factor VII

Perioperative Treatment Plan

In subjects in both the on-demand and fitusiran treatment arms undergoing surgery, a written perioperative treatment plan was reviewed with the study Medical Monitor before conducting the procedure, unless clinical circumstances did not allow. In subjects on fitusiran, the perioperative treatment plans were developed using the same principles as bleed management.

If a fitusiran dose was scheduled to occur on or in close proximity to the day of surgery, or anytime during the perioperative period, the dose should be withheld. The Perioperative Evaluation Period was defined as the day of the surgery through the final day on which supplemental hemostatic or antithrombotic treatments were administered as part of the perioperative treatment plan. Fitusiran dosing could be resumed at the next scheduled visit following the Perioperative Evaluation Period at the discretion of the Investigator. If multiple consecutive doses of fitusiran were withheld, the Investigator was to consult with the study Medical Monitor, who would determine if the subject could continue on study.

15.2. Study EFC14769

Study Title

ATLAS-A/B: 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 Dates

Study initiation date: March 1, 2018

Study completion: July 14, 2021

Study 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

1. To evaluate the efficacy of fitusiran compared to on-demand treatment with factor concentrates, as determined by:
 - a. The frequency of spontaneous bleeding episodes
 - b. The frequency of joint bleeding episodes
 - c. Health-related quality of life (HRQOL) in subjects ≥ 17 years of age
2. To determine the frequency of bleeding episodes during the onset period
3. To determine the safety and tolerability of fitusiran

Study Endpoints

Primary

Annualized Bleeding Rate (ABR) for treated bleeds in the treatment period.

Secondary

1. ABR for treated bleeds in the efficacy period.
2. Annualized treated spontaneous bleeding rate in the efficacy period.
3. Annualized treated joint bleeding rate in the efficacy period.
4. Change in Haem-A-QOL physical health score and total score in the treatment period.

Study Design

The ATLAS-A/B (EFC14769) study was a multicenter, multinational, randomized, open-label phase 3 study designed to evaluate the efficacy and safety of fitusiran in male subjects aged ≥ 12 years, with hemophilia A or B and without inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who are not receiving prophylactic therapy.

Eligible patients were to be randomized in a 2:1 ratio to either the fitusiran treatment arm receiving fitusiran 80 mg administered subcutaneously (SC) as prophylaxis once monthly, with use of on-demand factor concentrates or treatment of breakthrough bleeding episodes, or the on-demand arm with on-demand factor concentrates for treatment of breakthrough bleeding episodes. 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). Subjects from both the fitusiran and on-demand treatment arms who complete the study may be eligible for participation in an open-label extension study.

Breakthrough bleeding definitions, Bleed Management Guidelines, and Perioperative Treatment Plan were the same as Study EFC14768 (See Section [15.1](#) above).

15.3. Study LTE15174

Study Title

ATLAS-OLE: An Open-label, Long-term Safety and Efficacy Study of Fitusiran in Patients with Hemophilia A or B, with or without Inhibitory Antibodies to Factor VIII or IX

Study Dates

Study initiation date: January 10, 2019

Study completion: June 14, 2023

Study Objectives

Primary

To characterize the long-term safety and tolerability of fitusiran.

Secondary

1. To characterize the long-term efficacy of fitusiran as assessed by the frequency of:
 - a. Bleeding episodes
 - b. Spontaneous bleeding episodes
 - c. Joint bleeding episodes
2. To characterize the effects of fitusiran on health-related quality of life measures in subjects ≥ 17 years of age

Study Endpoints

Primary

Incidence, severity, relatedness, and seriousness of AEs, and laboratory assessments.

Secondary

1. Annualized bleeding rate for treated bleeds in the treatment period.
2. Annualized treated spontaneous bleeding rate in the treatment period.
3. Annualized treated joint bleeding rate in the treatment period.
4. Change in Haem-A-QoL physical health score in the treatment period (in subjects ≥ 17 years of age).

Study Design

The ATLAS-OLE (LTE15174) study was a multicenter, multinational, open-label extension study of the long-term safety and efficacy of fitusiran in males ≥ 12 years of age with hemophilia A or B with or without inhibitory antibodies to FVIII or FIX. Subjects from all three parent studies (EFC14768, EFC14769, and ATLAS-PPX) were considered for enrollment.

The study had 3 periods:

- A screening period of up to 60 days (under certain circumstances, screening could be extended beyond 60 days following consultation with the Sponsor).
- An open-label treatment period that could vary depending on the timing of subject's restart after lifting of the dosing pause implemented in Q4 2020 (i.e., subjects were to be dosed up to 48 months after the restart):
 - Subjects that started fitusiran dosing in this study after lifting of the dosing pause were planned to have a maximum treatment duration of 48 months.
 - Subjects that had started fitusiran before the 2020 dosing pause were planned to have a maximum treatment duration of 76 months.
- An approximately 6-month AT follow-up period after the last dose of fitusiran (note that some subjects may have undergone two 6-month AT follow-up periods, one at the end of the core study, i.e., before starting in the low dose cohort, and one at the completion of the whole study).

On-demand factors or BPAs were utilized for treatment of breakthrough bleeding episodes. BPAs include recombinant factor VIIa, Factors VIII and IX, as well as activated prothrombin complex concentrates (aPCC).

Scheduled assessments included monthly physical exams, hematology labs, and serum chemistry. Triglyceride levels, AT activity levels, and liver tests were done monthly for the first half of the study and then every 4 months.

Breakthrough bleeding definitions, Bleed Management Guidelines, and Perioperative Treatment Plan were the same as Study EFC14768.

The AT-DR initially consisted of a starting dose of 50 mg once every 2 months (Q2M) with options to escalate to 50 mg once monthly (QM) or 80 mg QM, or to de-escalate to 20 mg Q2M or 20 mg QM, based on an individual's AT response. The AT-DR was initiated after a voluntary dosing pause in October 2020. In detail, the final AT-DR used in study LTE15174 stated that if at the starting dose of 50 mg Q2M, AT was <15% twice (per central lab), the study subjects would have to discontinue fitusiran administration at this dosing regimen and de-escalate to 20 mg Q2M. If the steady state AT on at least two occasions was >35% (per central lab), the fitusiran dose was to be escalated to 50 mg QM (or 20 mg QM, respectively in the low dose cohort). If 50 mg QM also resulted in AT activity level >35%, then the subject could escalate to 80 mg QM, provided that he had no prior history of central AT activity <15% more than one time during any prior exposure to fitusiran. Subjects previously exposed to fitusiran at a dose of 80 mg monthly with no more than 1 AT activity level <15% at any time during fitusiran treatment (based on at least 3 months of prior AT measurements) had the option to remain on that dose. The Investigator could consider dose escalation on clinical grounds even if the subjects AT values were within 15 to 35% if bleed control was considered inadequate.

Eligibility Criteria

Inclusion Criteria

1. Subject must be at least 12 years of age inclusive, at the time of signing the informed consent.
2. Subjects with severe hemophilia A or B who have completed a phase 3 fitusiran clinical trial.
3. Male - There are no contraceptive requirements for this study except where required by local regulations.
4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the subject's legally authorized representative.

Exclusion Criteria

1. Completion of a surgical procedure within 14 days prior to screening, or currently receiving additional factor concentrate or BPA infusion for postoperative hemostasis.
2. Current participation in immune tolerance induction therapy.
3. Current use of factor concentrate or BPAs as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes. However, subjects requiring factor concentrates or BPAs as prophylaxis during the study dosing pause period, per Investigator's judgement in agreement with the study Medical Monitor, may be permitted to be enrolled.
4. Use of compounds other than factor concentrates or BPAs for hemophilia treatment, including use of emicizumab (Hemlibra[®]) within 6 months prior to screening.
5. Received an investigational drug or device, other than fitusiran, within 30 days of anticipated IMP administration or 5 half-lives of the IMP, whichever is longer.
6. Current or prior participation in a gene therapy trial.

7. ALT and/or AST $>1.5\times$ upper limit of normal reference range (ULN) for subjects who were naïve to fitusiran at study start; ALT and/or AST $>5\times$ ULN for subjects who were in the fitusiran arm in the parent study.
8. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.
9. Any country-related specific regulation that would prevent the subject from entering the study – see Appendix 8 (Section 10.8) (country-specific requirements).
10. Subject not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or subjects potentially at risk of noncompliance to study procedures.
11. Subjects who are dependent on the Sponsor or Investigator (as defined in Section 1.61 of the ICH-Good Clinical Practice E6) ([November 2016](#)).
12. Subjects are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.
13. Any specific situation during study implementation/course that may rise ethics considerations.
14. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

16. Efficacy

16.1. Study EFC14768

Disposition

Of 85 subjects screened, 57 were randomized to study treatment: 19 in the BPA on-demand arm and 38 in the fitusiran prophylaxis arm. There were 3 subjects who were treated but not randomized (due to protocol amendment).

Baseline Disease Characteristics

Table 142. Baseline Disease Characteristics, Study EFC14768

	BPA On-demand (N=19)	Fitusiran 80 mg Prophylaxis (N=38)	All (N=57)
Age at diagnosis (years)			
Number	19	38	57
Mean (SD)	5.4 (9.5)	2.4 (4.8)	3.4 (6.8)
Median	0.7	0.6	0.6
Q1 ; Q3	0.0 ; 9.6	0.5 ; 1.1	0.4 ; 1.6
Min ; Max	0 ; 38	0 ; 21	0 ; 38
Time from diagnosis to randomization (years)			
Number	19	38	57
Mean (SD)	26.5 (14.5)	24.9 (10.3)	25.4 (11.8)
Median	25.8	24.9	25.5
Q1 ; Q3	17.6 ; 34.0	17.0 ; 29.6	17.6 ; 31.1
Min ; Max	2 ; 63	4 ; 53	2 ; 63
Number of bleeding episodes in the last 6 months prior to screening			
Number	19	38	57
Mean (SD)	12.3 (8.2)	12.8 (8.2)	12.6 (8.1)
Median	10.0	9.5	10.0
Q1 ; Q3	7.0 ; 15.0	7.0 ; 16.0	7.0 ; 15.0
Min ; Max	6 ; 40	6 ; 40	6 ; 40
Number of bleeding events groups in the last 6 months prior to screening, n (%)			
Number	19	38	57
≤10	11 (57.9)	21 (55.3)	32 (56.1)
>10 to ≤15	4 (21.1)	7 (18.4)	11 (19.3)
>15 to ≤20	2 (10.5)	5 (13.2)	7 (12.3)
>20 to ≤30	1 (5.3)	3 (7.9)	4 (7.0)
>30 to ≤40	1 (5.3)	2 (5.3)	3 (5.3)
>40	0	0	0
Hemophilia type, n (%)			
Number	19	38	57
Hemophilia A	16 (84.2)	29 (76.3)	45 (78.9)
Hemophilia B	3 (15.8)	9 (23.7)	12 (21.1)
Inhibitor type, n (%)			
Number	19	38	57
Inhibitor	19 (100)	38 (100)	57 (100)
Highest Historical Inhibitor Titer Result ^a			
< 5 BU/mL	1 (5.3)	6 (15.8)	7 (12.3)
Hemophilia A	1 (5.3)	3 (7.9)	4 (7.0)
Hemophilia B	0	3 (7.9)	3 (5.3)
≥ 5 BU/mL	18 (94.7)	32 (84.2)	50 (87.7)
Hemophilia A	15 (78.9)	26 (68.4)	41 (71.9)
Hemophilia B	3 (15.8)	6 (15.8)	9 (15.8)
Non-Inhibitor ^b	0	0	0

	BPA On-demand (N=19)	Fitusiran 80 mg Prophylaxis (N=38)	All (N=57)
Number of target joints at baseline			
Number	19	38	57
Mean (SD)	1.5 (1.4)	1.4 (1.4)	1.4 (1.4)
Median	1.0	1.0	1.0
Q1 ; Q3	0.0 ; 3.0	0.0 ; 2.0	0.0 ; 2.0
Min ; Max	0 ; 4	0 ; 6	0 ; 6
Number of target joints groups at baseline, n(%)			
Number	19	38	57
0	7 (36.8)	12 (31.6)	19 (33.3)
1	3 (15.8)	11 (28.9)	14 (24.6)
2	3 (15.8)	8 (21.1)	11 (19.3)
≥ 3	6 (31.6)	7 (18.4)	13 (22.8)

^aBethesda assay

^bRedundant for this study (all inhibitors) but included for completeness/consistency.

Source: Applicant's CSR

Abbreviations: BPA, bypassing agent; BU, Bethesda units; CSR, clinical study report; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation

Primary Endpoint Results

Fitusiran demonstrated a reduced ABR for treated bleeds in the treatment period. The ABRs estimated based on negative binomial regression model in the treatment period were 2.0 (95% CI: 1.3, 3.1) for the fitusiran prophylaxis arm and 18.8 (95% CI: 11.5, 30.7) for the BPA on-demand arm, corresponding to an 89.2% reduction in the bleeding rate associated with fitusiran prophylaxis during the treatment period (rate ratio of 0.11 [95% CI: 0.06, 0.21], $p < 0.0001$).

Secondary Endpoint Results

There was a significant reduction in the spontaneous estimated ABR for treated bleeds in subjects treated with fitusiran (0.9 [95% CI: 0.5 to 1.6]) compared to those treated with BPA on demand (15.7 [95% CI: 9.3 to 26.5]), corresponding to a 94.4% reduction in the treated spontaneous bleeds associated with fitusiran prophylaxis during the efficacy period (rate ratio of 0.06 [95% CI: 0.03, 0.12], $p < 0.0001$).

The estimated ABR for treated bleeds in joints was 1.3 (95% CI: 0.8, 2.3) and 13.8 (95% CI: 8.0, 23.8) in the fitusiran prophylaxis and BPA on demand arms, respectively, corresponding to a 90.2% reduction in treated joint bleeds associated with fitusiran prophylaxis during the efficacy period (rate ratio of 0.10 [95% CI: 0.05, 0.21], $p < 0.0001$).

Total scores (transformed) of Haem-A-QoL demonstrated overall improvements in perceived QoL in fitusiran prophylaxis arm, with reported LS mean (95% CI) -15.3 (-19.3, -11.2) and -0.4 (-5.7, 4.8) reductions from baseline in the fitusiran prophylaxis and BPA on-demand arms, respectively. The observed LS mean difference was -14.9 (-21.4, -8.3) in favor of fitusiran ($p < 0.0001$).

16.2. Study EFC14769

Disposition

Of 177 subjects screened, 120 were randomized to study treatment: 80 in the fitusiran prophylaxis arm and 40 in the factor on demand arm. Out of 177 subjects screened, 57 were screen failures. There was 1 subject randomized to the fitusiran prophylaxis arm but not treated. The subject voluntarily withdrew his consent from study. There were no subjects who were treated but not randomized.

Baseline Disease Characteristics

Table 143. Baseline Disease Characteristics, Study EFC14769

	Factor On-demand (N=40)	Fitusiran 80 mg Prophylaxis (N=80)	All (N=120)
Age at diagnosis (years)			
Number	40	80	120
Mean (SD)	3.3 (5.3)	2.6 (4.9)	2.8 (5.0)
Median	0.9	0.6	0.6
Q1 ; Q3	0.5 ; 3.6	0.0 ; 2.6	0.1 ; 2.6
Min ; Max	0 ; 25	0 ; 30	0 ; 30
Time from diagnosis to randomization (years)			
Number	40	80	120
Mean (SD)	30.9 (13.6)	31.8 (14.9)	31.5 (14.4)
Median	29.8	29.4	29.4
Q1 ; Q3	19.3 ; 41.2	20.0 ; 43.1	20.0 ; 42.4
Min ; Max	7 ; 57	1 ; 68	1 ; 68
Number of bleeding episodes in the last 6 months prior to screening			
Number	40	80	120
Mean (SD)	11.8 (5.9)	13.1 (7.5)	12.7 (7.0)
Median	10.0	10.0	10.0
Q1 ; Q3	7.0 ; 14.5	8.0 ; 16.5	7.5 ; 16.0
Min ; Max	6 ; 30	6 ; 40	6 ; 40
Number of bleeding events groups in the last 6 months prior to screening, n (%)			
Number	40	80	120
≤10	21 (52.5)	44 (55.0)	65 (54.2)
>10 to ≤15	10 (25.0)	14 (17.5)	24 (20.0)
>15 to ≤20	7 (17.5)	9 (11.3)	16 (13.3)
>20 to ≤30	2 (5.0)	11 (13.8)	13 (10.8)
>30 to ≤40	0	2 (2.5)	2 (1.7)
>40	0	0	0

	Factor On-demand (N=40)	Fitusiran 80 mg Prophylaxis (N=80)	All (N=120)
Hemophilia type, n (%)			
Number	40	80	120
Hemophilia A	31 (77.5)	62 (77.5)	93 (77.5)
Hemophilia B	9 (22.5)	18 (22.5)	27 (22.5)
Number of target joints at baseline			
Number	40	80	120
Mean (SD)	1.4 (1.5)	1.4 (1.3)	1.4 (1.4)
Median	1.0	1.0	1.0
Q1 ; Q3	0.0 ; 2.0	0.0 ; 2.0	0.0 ; 2.0
Min ; Max	0 ; 7	0 ; 5	0 ; 7
Number of target joints groups at baseline, n(%)			
Number	40	80	120
0	11 (27.5)	27 (33.8)	38 (31.7)
1	14 (35.0)	21 (26.3)	35 (29.2)
2	9 (22.5)	16 (20.0)	25 (20.8)
≥ 3	6 (15.0)	16 (20.0)	22 (18.3)

Source: Applicant's CSR

Abbreviations: max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation

Primary Endpoint Results

A reduced ABR for treated bleeds was demonstrated with fitusiran prophylaxis in the treatment period. The ABRs for treated bleeds estimated based on negative binomial regression model were 4.1 (95% CI: 3.1, 5.3) for the fitusiran prophylaxis arm and 31.4 (95% CI: 23.0, 43.0) for the factor on demand arm, corresponding to an 87.0% reduction in the bleeding rate associated with fitusiran prophylaxis during the treatment period (rate ratio of 0.13 [95% CI: 0.09, 0.19], $p < 0.0001$).

Secondary Endpoint Results

There was a significant reduction in the spontaneous estimated ABR for treated bleeds in subjects treated with fitusiran (1.8 [95% CI: 1.2, 2.7]) compared to those treated on-demand (22.0 [95% CI: 14.2, 34.3]), corresponding to a 91.7% reduction in the treated spontaneous bleeds associated with fitusiran prophylaxis during the efficacy period (rate ratio of 0.08 [95% CI: 0.05, 0.14], $p < 0.0001$).

The estimated ABR for treated bleeds in joints was 2.3 (95% CI: 1.6, 3.3) and 23.4 (95% CI: 15.4, 35.7) in the fitusiran prophylaxis and factor on demand arms, respectively, corresponding to a 90.3% reduction in treated joint bleeds associated with fitusiran prophylaxis during the efficacy period (rate ratio of 0.10 [95% CI: 0.06, 0.16], $p < 0.0001$).

The transformed total scores of Haem-A-QoL demonstrated overall improvements in perceived QoL in the fitusiran prophylaxis arm, with a reported LS mean (95% CI) of -9.7 (-12.5, -6.9), compared to the factor on demand arm LS mean of -2.6 (-6.3, 1.0). The LS mean difference was -7.1 (-11.2, -2.9) in favor of fitusiran ($p = 0.0011$).

16.3. Study LTE15174

Exposure

The recommended AT-DR does not include the 80 mg QM dose, as no subjects who initiated treatment at 50 mg Q2M during the phase 3 clinical trials required escalation to 80 mg QM to maintain the target AT range of 15 to 35%. In Study LTE15174, 5 (2.3%) subjects had the 80 mg QM dose as their final dose. Those subjects started the study on 80 mg. Four subjects started at 80 mg and decreased to 50 mg. One subject was escalated to 80 mg and de-escalated to 50 mg by the end of the study. [Table 144](#) below contains the doses, after the dosing pause and dose restart, of the 213 rollover subjects into Study LTE15174 who received at least one dose of fitusiran during the Revised AT-Based Treatment Period.

Table 144. Summary of Study Drug Exposure

	Inhibitor			Non-inhibitor			Overall		
	Hem A (N=56)	Hem B (N=19)	Total (N=75)	Hem A (N=106)	Hem B (N=32)	Total (N=138)	Hem A (N=162)	Hem B (N=51)	Total (N=213)
Total number of actual dose sequence, n(%)									
80mg QM	0	2 (10.5)	2 (2.7)	2 (1.9)	1 (3.1)	3 (2.2)	2 (1.2)	3 (5.9)	5 (2.3)
80mg QM - 50mg Q2M	0	0	0	1 (0.9)	0	1 (0.7)	1 (0.6)	0	1 (0.5)
80mg QM - 50mg Q2M - 50mg QM	0	1 (5.3)	1 (1.3)	0	1 (3.1)	1 (0.7)	0	2 (3.9)	2 (0.9)
80mg QM - 50mg QM	0	0	0	1 (0.9)	0	1 (0.7)	1 (0.6)	0	1 (0.5)
50mg Q2M	13 (23.2)	5 (26.3)	18 (24.0)	47 (44.3)	10 (31.3)	57 (41.3)	60 (37.0)	15 (29.4)	75 (35.2)
50mg Q2M - 50mg QM	7 (12.5)	5 (26.3)	12 (16.0)	14 (13.2)	5 (15.6)	19 (13.8)	21 (13.0)	10 (19.6)	31 (14.6)
50mg Q2M - 50mg QM - 80mg QM - 50mg QM	1 (1.8)	0	1 (1.3)	0	0	0	1 (0.6)	0	1 (0.5)
50mg Q2M - 50mg QM - 50mg Q2M	2 (3.6)	0	2 (2.7)	0	1 (3.1)	1 (0.7)	2 (1.2)	1 (2.0)	3 (1.4)
50mg Q2M - 50mg QM - 20mg Q2M	0	0	0	1 (0.9)	0	1 (0.7)	1 (0.6)	0	1 (0.5)
50mg Q2M - 20mg Q2M	29 (51.8)	6 (31.6)	35 (46.7)	37 (34.9)	14 (43.8)	51 (37.0)	66 (40.7)	20 (39.2)	86 (40.4)
50mg Q2M - 20mg Q2M - 20mg QM	2 (3.6)	0	2 (2.7)	3 (2.8)	0	3 (2.2)	5 (3.1)	0	5 (2.3)
50mg Q2M - 20mg Q2M - 20mg QM - 20mg Q2M	1 (1.8)	0	1 (1.3)	0	0	0	1 (0.6)	0	1 (0.5)
20mg Q2M - 20mg QM	1 (1.8)	0	1 (1.3)	0	0	0	1 (0.6)	0	1 (0.5)

Source: Applicant's CSR for Study LTE15174

Note: Exclude the de-novo subjects who were directly enrolled in LTE15174 from the analysis.

The revised regimen period is from dose restart day 1 to date cut off for interim lock.

Abbreviations: CSR, clinical study report; Hem, hemophilia; Q2M, every 2 months; QM, once monthly

16.4. Pool C — Subjects With HA or HB With or Without Inhibitors, Previously on SOC Prophylaxis

Pooling Strategy

Table 145. Pooling Strategy for Integrated Summary of Efficacy, Pool C

Studies	Populations	Treatment Comparisons	Subject Data for Inclusion
EFC151110 & LTE15174	With and without inhibitor Hem A & Hem B	Fitusiran prophylaxis vs. SOC prophylaxis	For fitusiran prophylaxis: 13 months treatment period since first AT-DR dose after dose pause in LTE15174 ^a . For SOC prophylaxis: 6 months control period in EFC151110 ^b .

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 3.

^a 13-month treatment period is from the Dose Restart Day 1 as defined in Section 2.5 to the end of month 12. The Dose Restart Day 1 is the start of Month 0. One month = 28 days.

^b SOC is Prophylaxis with factor/BPA for Pool C.

Only subjects who were initially included in these studies were compared. De-novo subjects enrolled in China in LTE15174 were excluded from all analyses.

Abbreviations: BPA, bypassing agent; Hem, hemophilia; SOC, standard of care

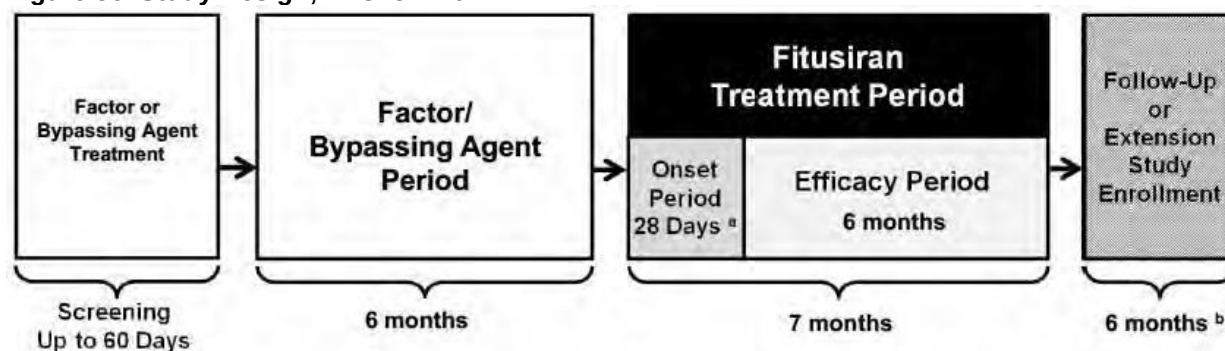
Pool C was not adequately powered for the analysis of ABR for treated bleeds and did not have formal hypothesis testing for either superiority or noninferiority of fitusiran. Therefore, data from Pool C are considered descriptive in nature only.

16.4.1. Design, Pool C

ATLAS-PPX (EFC151110) was a multicenter, open-label study in male subjects aged ≥ 12 years with hemophilia A or B with or without inhibitory antibodies to FVIII or FIX, who switched to fitusiran from prior bypassing agent (BPA, Cohort A) or factor (Cohort B) prophylaxis. The study design is shown in [Figure 56](#).

The study had three periods. There was a 6-month factor or BPA prophylaxis period in which subjects continued their baseline, regularly scheduled prophylaxis regimen with factor concentrates or BPAs. Next, a 1-month onset period in which subjects received their first dose of fitusiran while continuing their factor or BPA prophylaxis for up to 7 days. Then, a 6-month fitusiran efficacy period in which subjects received fitusiran as prophylaxis. Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period. Throughout the study, subjects may have received on-demand treatment for breakthrough bleeding episodes with factors or BPAs, as appropriate. Details on management of breakthrough bleeds are described in Section [15](#). All subjects were treated for 9 months and, upon completion, were eligible for participation in an open-label extension study.

Figure 56. Study Design, EFC151110



Source: Applicant's Clinical Study Protocol for ATLAS-PPX

Note: For subgroup of Cohort A subjects enrolling directly into the fitusiran treatment period, see Figure 2.

Note: For the United States specific requirements, see Section 11.6.1.2.

^a Subjects continued to receive prescribed factor or BPA prophylaxis for the first 7 days of the onset period.

^b Following final fitusiran dose, AT activity level was 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.

Abbreviations: AT, antithrombin; BPA, bypassing agent

The Study design for Study ATLAS-OLE (LTE15174) is described in Section [15.3](#).

16.4.2. Objectives and Endpoints, Pool C

Objectives

The primary objective was to evaluate the efficacy of fitusiran treatment at the revised AT-DR compared to standard-of-care (SOC) prophylaxis as determined by the frequency of bleeding episodes.

The major secondary objectives:

- To characterize the following while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis:
 - The frequency of spontaneous bleeding episodes.
 - The frequency of joint bleeding episodes.
 - Health-related quality of life (HRQOL) in subjects ≥ 17 years of age.
- To characterize the frequency of bleeding episodes during the onset and treatment periods in subjects receiving fitusiran.

Endpoints

The primary efficacy endpoint was annualized bleeding rate (ABR) for treated bleeds in the fitusiran primary efficacy period compared to the control period ([Table 14](#)).

The major secondary endpoints are listed below:

1. Annualized treated spontaneous bleeding rate (AsBR).
2. Annualized treated joint bleeding rate (AjBR).
3. Change in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain score.

16.4.3. Eligibility Criteria, Pool C

Eligibility criteria for Study EFC151110 are described below. Study LTE15174 included subjects who completed a previous parent phase 3 clinical study of fitusiran and had central AT activity level $\geq 22\%$ (prior to dosing).

ATLAS-PPX (EFC151110)

Key Inclusion Criteria

1. Males ≥ 12 years of age.
2. Severe hemophilia A or B as evidenced by:
 - a. A central laboratory measurement at screening or documented medical record evidence of FVIII $< 1\%$ or FIX level $\leq 2\%$.
3. A minimum of 2 bleeding episodes requiring BPA treatment within the last 6 months prior to Screening for patients with inhibitory antibodies to Factor VIII or Factor IX (Cohort A). A minimum of 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening for patients without inhibitory antibodies to Factor VIII or Factor IX (Cohort B).
4. Must meet either the definition of inhibitor or noninhibitor patient as below:
 - a. Inhibitor
 - i. Use of BPAs for prophylaxis and for any 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
 - ii. The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period:
 - Hemophilia B with inhibitory antibody to Factor IX as defined above
 - Not responding adequately to BPA treatment (historical ABR ≥ 20) prior to enrollment
 - In the opinion of the Investigator, with approval of Sponsor Medical Monitor, 6-month BPA prophylaxis period should be omitted.

- b. Noninhibitor
 - i. Use of factor concentrates for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening, and meet each of the following criteria:
 - Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening and
 - No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening and
 - No history of immune tolerance induction therapy within the past 3 years prior to Screening.
5. Prescribed prophylactic treatment (documented in the medical or pharmacy records) of hemophilia with factor concentrates or BPAs for at least 6 months prior to Screening; the regimen must be consistent with the approved prescribing information for the product or local recommendations, allowing for adjustment to individual subject response, and designed to decrease spontaneous bleeding.
6. Adherent to the prescribed prophylactic therapy for at least 6 months prior to Screening per Investigator assessment.

Other Key Exclusion Criteria are the same as Pool A as described in Section [6.2.1.3](#).

16.4.4. Statistical Analysis Plan, Pool C

Analysis Population

The following analysis sets were defined for the statistical analysis:

Full analysis set for Pool C of Study EFC15110 (ATLAS-PPX)/Study LTE15174 (ATLAS-OLE):

- For treatment period: AT-DR fitusiran treatment data were generated from both the extension study LTE15174 and study EFC15110.
- For control period: SOC prophylaxis control data were generated from the control period of the original switching study EFC15110.

Analysis of the Primary Endpoint

The primary efficacy endpoint was annualized bleeding rate (ABR) for treated bleeds.

The primary endpoint was analyzed using a repeated measures negative binomial model. The variable was the number of bleeding episodes. The study period for Switching in Pool C (primary efficacy period or control period) was treated as fixed effects. The robust sandwich covariance matrix constructed to account for within-subject dependence was considered for Switching Pool C. The logarithm of the duration (in years) that each subject spent in each study period matching the bleeding episode data being analyzed was included as an offset variable to account for unequal follow-up time due to early withdrawal, surgery, etc.

Neither the parent study EFC15110 nor Pool C was adequately powered for the analysis of ABR for treated bleeds. Pool C did not have any formal hypothesis to test either superiority or noninferiority of fitusiran prophylaxis compared to prior SOC prophylaxis.

Analysis of Major Secondary Endpoints

Annualized Treated Spontaneous Bleeding Rate

The same analysis method for the primary endpoint was used for this key secondary endpoint.

Annualized Treated Joint Bleeding Rate

The same analysis method for the primary endpoint was used for this key secondary endpoint.

Change in Haem-A-QoL Physical Health Domain Score

Change from baseline in Haem-A-QoL physical health score (in subjects ≥ 17 years of age) in the control period and primary efficacy period were analyzed using a mixed model for repeated measure analysis (MMRM) with robust sandwich covariance matrix, with fixed effects of study period (factor or BPA prophylaxis period and fitusiran treatment period) and baseline Haem-A-QoL Physical Health domain score for each period.

Multiple Testing Strategy

No multiplicity control was provided.

Handling of Intercurrent Events and Missing Data

Handling of intercurrent events and missing data are the same as described for Pool A in Section [6.2.1.4](#).

16.4.5. Results of Analyses, Pool C

Subject Disposition

The population for Pool C was comprised of subjects in Study LTE15174 and Study EFC15110 who switched from SOC prophylaxis to fitusiran prophylaxis. The full analysis set for the SOC prophylaxis arm is comprised of all EFC15110 enrolled subjects who received factor or BPA prophylaxis in Study EFC15110 and any dose of fitusiran. The fitusiran prophylaxis arm is comprised of all subjects who received at least one dose of fitusiran. Fifty-nine (85.5%) subjects were enrolled and entered the fitusiran prophylaxis arm in the treatment period (dose resumption Day 1 to Day 364). There were 54 subjects who received at least one dose of fitusiran who completed the study period and 5 subjects who received at least one dose of fitusiran who did not complete the study period. Of these 5 subjects, one (1.4%) discontinued the study because of adverse events, 2 (2.9%) withdrew consent, and 2 (2.9%) were discontinued because of more than 1 AT measurement $< 15\%$ ([Table 146](#)).

Table 146. Subject Disposition, FAS, Pool C

n(%)	SOC Prophylaxis (N=67)	Fitusiran Prophylaxis (N=69)
Number of subjects	67 (100)	69 (100)
Enrolled and entered study period	67 (100)	59 (85.5)
Completed the study period	67 (100)	54 (78.3)
Did not complete the study period	0	5 (7.2)
Adverse event	0	1 (1.4)
Subject withdrew consent	0	2 (2.9)
More than 1 AT measurement <15%	0	2 (2.9)
Did not enter the study period	NA	10 (14.5)
Entered study period but discontinued treatment during the dose adjustment period	NA	5 (7.2)
Discontinued treatment due to low AT levels during the dose adjustment period	NA	3 (4.3)

Source: Summary of Clinical Efficacy Hemophilia A and B, Table 38
Abbreviations: AT, antithrombin; FAS, full analysis set; SOC, standard of care

Demographic and Baseline Characteristics

Table 147. Baseline Demographic and Clinical Characteristics, Pool C

Characteristic	SOC Prophylaxis (N=67)	Fitusiran Prophylaxis (N=69)
Sex (male), n (%)	67 (100)	69 (100)
Median age (years) (range)	23 12-71	23 12-71
Race, n (%)	White: 44 (65.7) Asian: 20 (29.9) Other: 2 (3) Black: 1 (1.5)	White: 45 (65.2) Asian: 21 (30.4) Other: 2 (2.9) Black: 1 (1.4)
Region, n (%)	Europe: 45 (67.2) Asia: 20 (29.9) Other: 2 (3)	Europe: 46 (66.7) Asia: 21 (30.4) Other: 2 (2.9)
Hemophilia A, n (%)	52 (77.6)	52 (75.4)
Hemophilia B, n (%)	15 (22.4)	17 (24.6)
Noninhibitor, n (%)	46 (68.7)	46 (66.7)
Inhibitor, n (%)	21 (31.3)	23 (33.3)
Previous bleeds (6 months) (median) (range)	4 2-10	5 2-19

Source: Applicant's Summary of Clinical Efficacy
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SOC, standard of care

Analysis of the Primary Endpoint

[Table 148](#) summarizes the annualized bleeding rates (ABR) for treated bleeds in the fitusiran prophylaxis period compared to the SOC prophylaxis period as determined by the Applicant. The estimated ABR was 7.5 (95% CI: 5.6, 10.1) for the SOC prophylaxis period and 5.7 (95% CI: 3.9, 8.2) for the fitusiran prophylaxis (AT-DR) period. The rate ratio (AT-DR prophylaxis/SOC prophylaxis) was 0.75 (95% CI: 0.47, 1.2). There were no formal hypotheses preplanned and the results were exploratory only and should be interpreted with caution. However, the results observed appear descriptively to be similar with both types of prophylaxis. For exploratory purposes, the results of the subjects on prior prophylaxis with a fixed dose of fitusiran in study

EFC15110 were compared to the AT-DR in study LTE15174. The comparison results of 80 mg QM versus SOC prophylaxis from the parent study are also presented in [Table 148](#) for reference.

Table 148. Summary of Annualized Bleeding Rates for Treated Bleeds, Primary Analysis, Pool C/Study EFC151110

ABR	SOC Prophylaxis (N=67)	Fitusiran Prophylaxis (AT-DR) (N=69)	Fitusiran Prophylaxis (80 mg QM) (N=69)
Estimated ABR (95% CI)	7.5 (5.6, 10.1)	5.6 (3.9, 8.2)	3.3 (2.1, 5.2)
Rate ratio (95% CI)		0.75 (0.47, 1.2) ^a	0.44 (0.27, 0.72)

Source: Summary of Clinical Efficacy Hemophilia A and B, Tables 22 and 49; Statistical Review team's analysis.
^a P-value (Nominal) =0.2316 and it was from a repeated negative binomial model with treatment arm as fixed effects, and a robust sandwich covariance matrix is constructed to account for the within subject dependence. The logarithm of the duration that each subject spends in the control or primary efficacy period matching the bleeding event being analyzed as an offset variable.
Abbreviations: ABR, annualized bleeding rate; AT-DR, antithrombin-based dose regimen; CI, confidence interval; QM, once monthly; SOC, standard of care

The FDA review team obtained slightly different efficacy results than described above. The FDA review team derived an estimated ABR for treated bleeds of 5.8 (4.0, 8.4) in the fitusiran period and 7.5 (5.6, 10.1) in the SOC prophylaxis period, with a corresponding rate ratio of 0.77 with a nominal p-value of 0.26. The team sent an information request (IR) on December 5, 2024, to request clarification, and the Applicant responded that the discrepancy in the estimates was numerically small and the overall conclusion remains unchanged. The difference appears to be related to a technical issue in the operating system of running SAS programs.

Subgroup analyses were conducted for the primary endpoint by hemophilia types (i.e., HA or HB) and by different inhibitor cohorts (i.e., with or without inhibitors). In the Type C Meeting, on July 26, 2018, the Division recommended formal statistical testing for study EFC15110 in order to determine the treatment effect of fitusiran in subjects switched from factor or BPA prophylaxis. In addition, the Division recommended to include sufficient numbers of subjects with and without inhibitors, in order for efficacy to be assessed in both populations. However, neither study EFC15110 nor Pool C included formal statistical testing for efficacy endpoints, including the primary efficacy endpoint ABR. The ABRs in different inhibitor cohorts were not prespecified endpoints. In the final statistical analysis plan for study EFC15110, the determination of the sample size for study EFC15110 was based on clinical considerations rather than a power calculation, and the Applicant stated that the p-value should be interpreted with caution.

Although the final clinical study reports for study EFC15110 and Pool C presented superiority testing results for the primary efficacy endpoint ABR, without adequately powered formal statistical testing to detect differences, the analyses are considered exploratory. The Agency notified the Applicant in a Type C Meeting on September 18, 2023, that the results of this study would be descriptive, as there was no prespecified decision rule. Given the exploratory nature of this analysis, results from Pool C will not be included in labeling.

16.5. Patient-Reported Hemophilia-Related Symptoms and Physical Functioning for Pools A and B

The patient-reported outcome (PRO) endpoint of change in Haem-A-QoL Physical Health domain score from baseline was included by the Applicant in the statistical testing hierarchy as the third key secondary endpoint for Pools A and B (b) (4). Analysis of this endpoint for Pool A failed to reach statistical significance, whereas in Pool B, this endpoint did reach statistical significance.

The Haem-A-QoL Physical Health domain is a reasonable option to assess patient-reported hemophilia signs/symptoms (swellings and joint pain) and physical functioning (b) (4). However, in a Type C Guidance meeting on September 18, 2023, the Agency raised the concerns that the open-label design limits interpretation of the PRO, as a subject’s knowledge of treatment assignment may lead to systematic over- or underestimation of the treatment effect, the magnitude of which is unknown. In addition, the Agency informed the Applicant that the 2-year difference between the AT-DR in the long-term extension study also posed challenges in interpretation of the PRO endpoint.

Table 149 briefly summarizes the primary efficacy analysis results for the PRO endpoint change in Haem-A-QoL Physical Health domain score from baseline in Pools A and B. Please refer to Section 6.2 for further details.

Table 149. Primary Efficacy Analysis: Mean Change in Haem-A-QoL Physical Health Domain Score From Baseline to End of Primary Efficacy Period for Fitusiran Prophylaxis, and to the End of Control Period for On-Demand Using MMRM, Subjects ≥17 Years of Age, ITT Set

Pool	Result	On-Demand	Fitusiran AT-DR
Pool A	Number of subjects	18	32
	LS mean (95% CI)	-5.0 (-9.2, -0.8)	-8.7 (-17.1, -0.3)
	LS mean difference (95% CI)		-3.7 (-13.3, 6.0)
	p-value		0.45
Pool B	Number of subjects	38	72
	LS mean (95% CI)	-3.8 (-8.7, 1.1)	-12.0 (-18.1, -5.9)
	LS mean difference (95% CI)		-8.2 (-15.3, -1.0)
	p-value		0.025

Source: Summary of Clinical Efficacy Hemophilia A and B
Missing data in primary efficacy period were imputed under MAR assumption.
Abbreviations: AT-DR, Antithrombin Dosing Regimen; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITT, Intent-to-Treat; LS, least squares; MAR, missing at random; MMRM, mixed-effect model with repeated measures

The following concerns limit the interpretability of the PRO data comparing the fitusiran AT-DR treatment with the control treatment:

Baseline Data

The AT-based dosing regimen does not have any true baseline values (i.e., the transition from fitusiran 80 mg to the AT-based dosing regimen consisted of a variable period that was individualized); as such, it is difficult to compare the data between control and the fitusiran

AT-based dose regimen from an efficacy standpoint. Further, there is no matching control for the AT-based dosed regimen in the primary efficacy period.

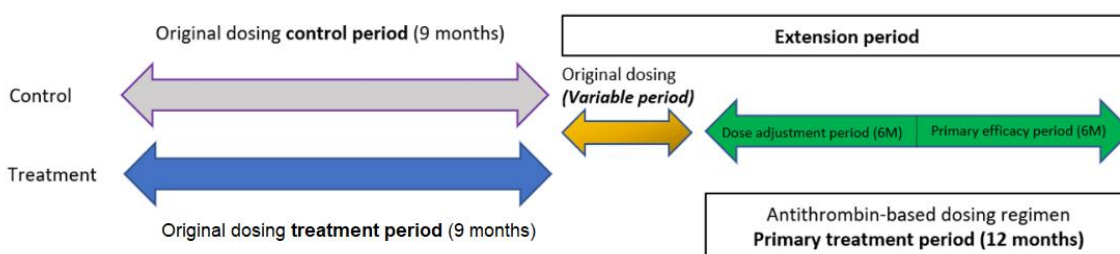
Open-Label Design

The interpretability of PRO data is limited because subjects' knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect, the magnitude of which is unknown. In settings where blinding is not feasible, or there is high likelihood of inadvertent unblinding due to toxicity, lack of blinding will need to be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial. Pool A failed to achieve statistical significance, and Pool B only achieved a marginally significant p-value for the superiority test comparing fitusiran AT-DR treatment with control treatment for the PRO endpoints. The effect sizes in Pools A and B may not be able to account for the bias introduced by the open-label design of the study for PRO endpoints.

Time Lag in the Pooled Analysis

In Pools A and B, the calculation of change from baseline in the fitusiran arm started from Day 1 of the parent studies with the original fitusiran 80 mg QM dose regimen treatment to the end of the primary efficacy period with the fitusiran AT-DR treatment, which involves the period of both the fitusiran 80 mg QM original dosing regimen treatment and the fitusiran AT-DR treatment. The time lag introduces further uncertainty on the estimated treatment effect for the PRO endpoints, with the much longer period of the subjects on fitusiran treatment (i.e., over 21 months, including at least 9 months on fitusiran 80 mg QM plus 12 months on fitusiran AT-DR compared to 9 months for the control treatment) and the higher rate of subject dropout due to the long treatment period for the fitusiran treatment. Please refer to [Figure 57](#) below for the length of each period.

Figure 57. Graphic Illustration of Treatment Periods for Subjects in Pool A and Pool B



Source: DCOA Reviewer's sketch

Robustness of the Primary Analysis Results

[Table 150](#) summarizes the missing pattern for the PRO endpoint in Pools A and B. The missing data rate in the fitusiran AT-DR treatment arm is considerably higher than the on-demand control arm.

Table 150. Missing Pattern for the PRO Endpoint, Subjects ≥17 Years of Age, ITT Set, Pools A and B

Pool	Variable	On-Demand	Fitusiran AT-DR
Pool A	Number of subjects	18	32
	Number of subjects with missing at baseline visit	0	0
	Number of subjects with missing at any postbaseline visit	1 (5.6%)	11 (34.4%)
	Number of subjects with missing at Month 6	NA	7 (21.9%)
	Number of subjects with missing at Month 9	1 (5.6%)	NA
	Number of subjects with missing at Month 12	NA	10 (31.3%)
Pool B	Number of subjects	38	72
	Number of subjects with missing at baseline visit	1 (2.6%)	1 (1.4%)
	Number of subjects with missing at any postbaseline visit	4 (10.5%)	33 (45.8%)
	Number of subjects with missing at Month 6	NA	17 (23.6%)
	Number of subjects with missing at Month 9	4 (10.5%)	NA
	Number of subjects with missing at Month 12	NA	30 (41.7%)

Source: Response to FDA Information Request on November 22, 2024

Abbreviations: AT-DR, antithrombin-based dose regimen; ITT, intent-to-treat; NA, not applicable

In the primary analysis for the PRO endpoint change in Haem-A-QoL Physical Health domain score from baseline using the MMRM approach, no imputation of missing data in the control period was performed for subjects who withdrew in the control period; unobserved data for the primary efficacy period were imputed via multiple imputation method with missing at random (MAR) assumption based on observed data during the primary efficacy period. To evaluate the robustness of the primary analysis result against the approach to handle missing data, the FDA statistical review team requested several sensitivity analyses via information request dated November 22, 2024, for Pools A and B, including:

1. The result of multiple imputation can vary due to reasons such as the selection of imputation method/model under MAR assumption and the selection of seed for the imputation. Furthermore, a multiple imputation for missing data under MAR assumption is not necessary for MMRM analysis since this model already imputes missing data under the MAR assumption. A sensitivity analysis using MMRM approach was conducted based only on the observed data without any imputation for the unobserved data for Pools A and B ([Table 151](#)).

Table 151. Sensitivity Analysis: Mean Change in Haem-A-QoL Physical Health Domain Score From Baseline to End Of Primary Efficacy Period for Fitusiran Prophylaxis, and to the End of Control Period for On-Demand Using MMRM (Based Only on the Observed Data), Subjects ≥17 Years of Age, ITT Set

Pool	Result	On-Demand	Fitusiran AT-DR
Pool A	Number of subjects	18	32
	LS mean (95% CI)	-5.3 (-9.5, -1.1)	-8.4 (-17.2, 0.4)
	LS mean difference (95% CI)		-3.1 (-13.2, 6.9)
	Nominal p-value		0.53
Pool B	Number of subjects	38	72
	LS mean (95% CI)	-4.2 (-9.0, 0.7)	-11.3 (-17.9, -4.7)
	LS mean difference (95% CI)		-7.1 (-14.7, 0.4)
	Nominal p-value		0.064

Source: Response to FDA Information Request on November 22, 2024

Abbreviations: AT-DR, Antithrombin Dosing Regimen; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITT, Intent-to-Treat; LS, least squares; MMRM, mixed-effect model with repeated measures.

2. The MAR assumption cannot be verified since the missing values are not observed. A sensitivity analysis was conducted to impute unobserved data in the primary efficacy period under missing not at random (MNAR) assumptions using a control-based pattern mixture model, which imputes missing data in the treatment arm using the control data distribution (Table 152).

Table 152. Sensitivity Analysis: Mean Change in Haem-A-QoL Physical Health Domain Score From Baseline to End of Primary Efficacy Period for Fitusiran Prophylaxis, and to the End of Control Period for On-Demand Using MMRM, Subjects ≥17 Years of Age, ITT Set

Pool	Result	On-Demand	Fitusiran AT-DR
Pool A	Number of subjects	18	32
	LS mean (95% CI)	-5.2 (-9.3, -1.1)	-7.5 (-14.4, -0.6)
	LS mean difference (95% CI)		-2.3 (-10.6, 6.0)
	Nominal p-value		0.59
Pool B	Number of subjects	38	72
	LS mean (95% CI)	-4.3 (-9.0, 0.3)	-8.4 (-13.9, -2.9)
	LS mean difference (95% CI)		-4.0 (-10.7, 2.6)
	Nominal p-value		0.23

Source: Response to FDA Information Request on November 22, 2024
Missing data imputed via a control-based pattern mixture model.
Abbreviations: AT-DR, Antithrombin Dosing Regimen; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITT, Intent-to-Treat; LS, least squares; MMRM, mixed-effect model with repeated measures.

Pool A failed to achieve statistically significant results in the primary analysis, nor did it achieve nominal significant results in the sensitivity analyses. None of the above sensitivity analyses for Pool B achieved the same conclusion (i.e., nominal p-value<0.05) as the primary analysis results, indicating that the primary analysis result for Pool B is not robust against the approach to handle missing data. The p-value for the primary analysis should be interpreted with caution.

(b) (4)

17. Clinical Safety

17.1. Safety Analysis of Pooled Trials EFC14768 and EFC14769

Trials EFC14768 and EFC14769 are open-label controlled trials that randomized subjects with hemophilia A and B with and without inhibitors, respectively, to receive fitusiran 80 mg SQ QM or on-demand therapy over a 9-month treatment period. High-level safety data are provided below. For dose-related adverse reactions, the safety profile of 80 mg QM could differ from that of the AT-DR, as the 80 mg QM regimen is a higher dose. However, these analyses are useful because they provide randomized, controlled comparisons and could potentially identify safety signals that were not seen in the uncontrolled long-term extension study.

Exposure

[Table 153](#) below shows exposure data for both studies.

Table 153. Duration of Exposure (Study Drug) or Observation in Study (On-Demand), Safety Population, Pooled Trials EFC14768 and EFC14769

Parameter	EFC14768 (Inhibitor)		EFC14769 (Noninhibitor)	
	Fitusiran N=41	On-Demand N=19	Fitusiran N=79	On-Demand N=40
Duration of treatment or observation, weeks				
Mean (SD)	35.8 (1.7)	37.3 (2.3)	35.2 (3.3)	34.4 (8.4)
Median (Q1, Q3)	36 (35.9, 36.6)	37 (36.1, 37.2)	36 (35.7, 36.7)	36.1 (35.9, 36.9)
Min, max	29, 38.7	35, 45.4	17, 37.6	0.1, 41.6
Total exposure or observation (person years)	28	14	53	26
Subjects treated or observed, by duration, n (%)				
<12 weeks	0	0	0	2 (5.0)
≥12 to <24 weeks	0	0	1 (1.3)	1 (2.5)
≥24 to <36 weeks	13 (31.7)	3 (15.8)	23 (29.1)	8 (20.0)
≥36 to <48 weeks	28 (68.3)	16 (84.2)	55 (69.6)	29 (72.5)
≥48 weeks	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Note duration of treatment exposure for study drug subjects (days) = (date of last dose of study drug - date of first dose of study drug) +28. The number 28 is the number of days between two scheduled doses of study drug. Duration of observation for on-demand subjects (days) = (study end date - study start date) +1.

Duration is 9 months.

Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

Overview of Adverse Event Data

An overview of adverse event data is shown in [Table 154](#) below. Serious adverse events (SAEs) were higher in the on-demand arm than the fitusiran arm. Overall, there were low rates of drug discontinuation and dose modification.

Table 154. Overview of Adverse Events, Safety Population, Pooled Trials EFC14768 and EFC14769

Event Category	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	Fitusiran N=41 n (%)	On-Demand N=19 n (%)	Risk Difference % (95% CI)	Fitusiran N=79 n (%)	On-Demand N=40 n (%)	Risk Difference % (95% CI)
SAE	7 (17.1)	5 (26.3)	-9.2 (-34.1, 11.6)	5 (6.3)	5 (12.5)	-6.2 (-20.5, 4.2)
SAEs with fatal outcome	0	0	0.0 (-17.1, 8.7)	0	0	0.0 (-8.8, 4.7)
Life-threatening SAEs	0	0	0.0 (-17.1, 8.7)	0	1 (2.5)	-2.5 (-12.9, 2.3)
SAEs resulting in substantial disruption of normal life functions	0	0	0.0 (-17.1, 8.7)	0	1 (2.5)	-2.5 (-12.9, 2.3)
AE leading to permanent discontinuation of study drug	1 (2.4)	0	2.4 (-14.8, 12.7)	2 (2.5)	0	2.5 (-6.4, 8.8)

Event Category	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	Fitusiran N=41 n (%)	On-Demand N=19 n (%)	Risk Difference % (95% CI)	Fitusiran N=79 n (%)	On-Demand N=40 n (%)	Risk Difference % (95% CI)
AE leading to dose modification of study drug	4 (9.8)	0	9.8 (-7.9, 22.7)	6 (7.6)	0	7.6 (-1.5, 15.6)
AE leading to interruption of study drug	4 (9.8)	0	9.8 (-7.9, 22.7)	6 (7.6)	0	7.6 (-1.5, 15.6)
AE leading to reduction of study drug	0	0	0.0 (-17.1, 8.7)	0	0	0.0 (-8.8, 4.7)
AE leading to dose delay of study drug	0	0	0.0 (-17.1, 8.7)	0	0	0.0 (-8.8, 4.7)
Any AE	38 (92.7)	11 (57.9)	34.8 (12.8, 57.7) *	62 (78.5)	18 (45.0)	33.5 (15.3, 50.3) *
Severe and worse	5 (12.2)	1 (5.3)	6.9 (-13.9, 21.7)	2 (2.5)	3 (7.5)	-5.0 (-17.6, 2.8)
Moderate	17 (41.5)	4 (21.1)	20.4 (-6.1, 41.5)	32 (40.5)	6 (15.0)	25.5 (8.3, 39.8) *
Mild	16 (39.0)	6 (31.6)	7.4 (-19.4, 30.8)	28 (35.4)	9 (22.5)	12.9 (-5.0, 28.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date after the first dose of fitusiran in the fitusiran arm or after the Day 1 visit for the on-demand arm.

Duration is 9 months.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Serious Adverse Events

[Table 155](#) shows the SAEs by system organ class and PT. Only fitusiran-treated patients had SAEs reported in the hepatobiliary disorders SOC (PTs biliary colic, cholecystitis acute, cholecystitis chronic, cholecystitis and cholelithiasis), vascular SOC (PTs thrombosis and subclavian vein thrombosis), and spinal vascular disorder.

Overall, the most prevalent SAEs occurring only in the fitusiran arms in studies EFC14768 and EFC14769, were hepatobiliary disorders (biliary colic, cholecystitis acute, cholecystitis chronic). This mirrored the most prevalent SAEs associated with fitusiran use in the AT-DR open-label study, cholecystitis ([Table 41](#), Section [7.5.2.1](#)).

Table 155. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials EFC14768 and EFC14769

System Organ Class Preferred Term	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On- Fitusiran N=32 n (%)	Demand N=16 n (%)	On- Fitusiran N=9 n (%)	Demand N=3 n (%)	On- Fitusiran N=61 n (%)	Demand N=31 n (%)	On- Fitusiran N=18 n (%)	Demand N=9 n (%)
Any SAE	5 (15.6)	4 (25.0)	2 (22.2)	1 (33.3)	3 (4.9)	2 (6.5)	2 (11.1)	3 (33.3)
Blood and lymphatic system disorders (SOC)	0	0	1 (11.1)	0	0	0	0	0
Anemia	0	0	1 (11.1)	0	0	0	0	0
Eye disorders (SOC)	0	0	0	0	0	1 (3.2)	0	0
Diplopia	0	0	0	0	0	1 (3.2)	0	0

System Organ Class Preferred Term	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On-		On-		On-		On-	
	Fitusiran N=32 n (%)	Demand N=16 n (%)	Fitusiran N=9 n (%)	Demand N=3 n (%)	Fitusiran N=61 n (%)	Demand N=31 n (%)	Fitusiran N=18 n (%)	Demand N=9 n (%)
Gastrointestinal disorders (SOC)	0	1 (6.2)	0	0	0	0	0	0
Retroperitoneal hemorrhage	0	1 (6.2)	0	0	0	0	0	0
Hepatobiliary disorders (SOC)	2 (6.2)	0	0	0	1 (1.6)	0	2 (11.1)	0
Biliary colic	1 (3.1)	0	0	0	0	0	0	0
Cholecystitis acute	1 (3.1)	0	0	0	0	0	0	0
Cholecystitis chronic	1 (3.1)	0	0	0	0	0	0	0
Cholecystitis	0	0	0	0	1 (1.6)	0	0	0
Cholelithiasis	0	0	0	0	0	0	2 (11.1)	0
Infections and infestations (SOC)	1 (3.1)	0	1 (11.1)	0	1 (1.6)	1 (3.2)	0	0
COVID-19	1 (3.1)	0	0	0	0	0	0	0
Hematoma infection	1 (3.1)	0	0	0	0	0	0	0
Device related infection	0	0	1 (11.1)	0	0	0	0	0
Gastroenteritis	0	0	0	0	0	1 (3.2)	0	0
Lower respiratory tract infection	0	0	0	0	1 (1.6)	0	0	0
Vascular device infection	0	0	1 (11.1)	0	0	0	0	0
Injury, poisoning and procedural complications (SOC)	0	2 (12.5)	0	0	0	0	0	1 (11.1)
Humerus fracture	0	0	0	0	0	0	0	1 (11.1)
Subdural hemorrhage	0	0	0	0	0	0	0	1 (11.1)
Tibia fracture	0	0	0	0	0	0	0	1 (11.1)
Tooth fracture	0	1 (6.2)	0	0	0	0	0	0
Traumatic hemorrhage	0	1 (6.2)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders (SOC)	0	1 (6.2)	0	1 (33.3)	0	0	0	1 (11.1)
Hemarthrosis	0	0	0	1 (33.3)	0	0	0	0
Muscle hemorrhage	0	1 (6.2)	0	0	0	0	0	0
Osteoarthritis	0	0	0	0	0	0	0	1 (11.1)
Nervous system disorders (SOC)	1 (3.1)	0	0	0	0	0	0	0
Spinal vascular disorder	1 (3.1)	0	0	0	0	0	0	0
Psychiatric disorders (SOC)	0	0	0	0	0	0	0	1 (11.1)
Suicidal ideation	0	0	0	0	0	0	0	1 (11.1)
Renal and urinary disorders (SOC)	1 (3.1)	0	0	1 (33.3)	0	0	0	0
Hematuria	1 (3.1)	0	0	1 (33.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	0	0	1 (1.6)	0	0	0
Asthma	0	0	0	0	1 (1.6)	0	0	0

System Organ Class Preferred Term	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On-Demand		On-Demand		On-Demand		On-Demand	
	Fitusiran N=32 n (%)	Demand N=16 n (%)	Fitusiran N=9 n (%)	Demand N=3 n (%)	Fitusiran N=61 n (%)	Demand N=31 n (%)	Fitusiran N=18 n (%)	Demand N=9 n (%)
Vascular disorders (SOC)	1 (3.1)	0	1 (11.1)	0	0	0	0	0
Thrombosis	1 (3.1)	0	0	0	0	0	0	0
Subclavian vein thrombosis	0	0	1 (11.1)	0	0	0	0	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date after the first dose of fitusiran in the fitusiran arm or after the Day 1 visit for the on-demand arm.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 9 months.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

[Table 156](#) shows adverse events by system organ class and FMQ narrow. The most common FMQ SOC, hepatobiliary disorder, was reported almost exclusively in fitusiran-treated patients.

Table 156. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials EFC14768 and EFC14769

System Organ Class FMQ (Narrow)	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On-Demand		On-Demand		On-Demand		On-Demand	
	Fitusiran N=32 n (%)	Demand N=16 n (%)	Fitusiran N=9 n (%)	Demand N=3 n (%)	Fitusiran N=61 n (%)	Demand N=31 n (%)	Fitusiran N=18 n (%)	Demand N=9 n (%)
Blood and lymphatic system disorders (SOC)								
Anemia	1 (3.1)	0	1 (11.1)	0	0	0	0	0
Leukopenia	1 (3.1)	0	0	0	0	0	0	0
Cardiac disorders (SOC)								
Systemic hypertension	2 (6.2)	0	0	0	4 (6.6)	3 (9.7)	0	0
Cardiac conduction disturbance	0	0	0	0	1 (1.6)	0	0	0
Endocrine disorders (SOC)								
Hyperglycemia	0	0	0	0	2 (3.3)	1 (3.2)	0	1 (11.1)
Hyperprolactinemia	0	0	0	0	1 (1.6)	0	0	0
Gastrointestinal disorders (SOC)								
Abdominal pain	7 (21.9)	0	1 (11.1)	0	7 (11.5)	0	2 (11.1)	1 (11.1)
Dyspepsia	5 (15.6)	0	1 (11.1)	0	4 (6.6)	0	1 (5.6)	0
Constipation	1 (3.1)	0	0	1 (33.3)	0	0	0	0
Diarrhea	1 (3.1)	0	1 (11.1)	0	1 (1.6)	1 (3.2)	2 (11.1)	0
General disorders and administration site conditions (SOC)								
Pyrexia	2 (6.2)	0	1 (11.1)	0	1 (1.6)	0	0	2 (22.2)
Fall	1 (3.1)	0	1 (11.1)	0	2 (3.3)	0	0	0
Local administration reaction	1 (3.1)	0	3 (33.3)	0	3 (4.9)	0	2 (11.1)	0
Fatigue	0	1 (6.2)	2 (22.2)	0	0	0	0	0
Peripheral edema	0	0	1 (11.1)	0	0	0	1 (5.6)	0

System Organ Class FMQ (Narrow)	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On-		On-		On-		On-	
	Fitusiran N=32 n (%)	Demand N=16 n (%)	Fitusiran N=9 n (%)	Demand N=3 n (%)	Fitusiran N=61 n (%)	Demand N=31 n (%)	Fitusiran N=18 n (%)	Demand N=9 n (%)
Hepatobiliary disorders (SOC)								
Hepatic injury	14 (43.8)	0	1 (11.1)	0	14 (23.0)	1 (3.2)	6 (33.3)	0
Cholecystitis	4 (12.5)	0	0	0	2 (3.3)	0	0	0
Infections and infestations (SOC)								
Nasopharyngitis	6 (18.8)	1 (6.2)	5 (55.6)	0	15 (24.6)	3 (9.7)	3 (16.7)	3 (33.3)
Bacterial infection	5 (15.6)	1 (6.2)	2 (22.2)	0	9 (14.8)	1 (3.2)	1 (5.6)	1 (11.1)
Viral infection	3 (9.4)	1 (6.2)	2 (22.2)	0	4 (6.6)	1 (3.2)	1 (5.6)	1 (11.1)
Purulent material	0	0	1 (11.1)	0	2 (3.3)	0	1 (5.6)	0
Metabolism and nutrition disorders (SOC)								
Lipid disorder	1 (3.1)	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders (SOC)								
Arthralgia	1 (3.1)	0	4 (44.4)	0	1 (1.6)	0	4 (22.2)	1 (11.1)
Arthritis	0	0	0	0	1 (1.6)	0	1 (5.6)	1 (11.1)
Back pain	0	1 (6.2)	1 (11.1)	0	1 (1.6)	1 (3.2)	1 (5.6)	1 (11.1)
Fracture	0	1 (6.2)	0	0	1 (1.6)	0	0	1 (11.1)
Myalgia	0	0	0	0	1 (1.6)	0	1 (5.6)	0
Rhabdomyolysis	0	0	0	0	0	0	0	1 (11.1)
Nervous system disorders (SOC)								
Headache	1 (3.1)	1 (6.2)	5 (55.6)	0	5 (8.2)	0	0	1 (11.1)
Paresthesia	0	1 (6.2)	0	0	0	0	1 (5.6)	0
Psychiatric disorders (SOC)								
Self-harm	0	0	0	0	0	0	0	1 (11.1)
Renal and urinary disorders (SOC)								
Renal & urinary tract infection	2 (6.2)	1 (6.2)	0	0	3 (4.9)	0	0	0
Respiratory, thoracic and mediastinal disorders (SOC)								
Bronchospasm	1 (3.1)	0	0	0	4 (6.6)	0	1 (5.6)	0
Cough	1 (3.1)	0	1 (11.1)	0	5 (8.2)	0	1 (5.6)	0
Skin and subcutaneous tissue disorders (SOC)								
Pruritus	1 (3.1)	0	1 (11.1)	0	4 (6.6)	0	1 (5.6)	0
Rash	1 (3.1)	1 (6.2)	1 (11.1)	0	2 (3.3)	0	0	0
Erythema	0	0	0	0	2 (3.3)	0	0	0
Urticaria	0	1 (6.2)	1 (11.1)	0	0	0	0	0

System Organ Class FMQ (Narrow)	Inhibitor				Noninhibitor			
	Hemophilia A		Hemophilia B		Hemophilia A		Hemophilia B	
	On-Demand		On-Demand		On-Demand		On-Demand	
	Fitusiran N=32 n (%)	Fitusiran Demand N=16 n (%)	Fitusiran N=9 n (%)	Fitusiran Demand N=3 n (%)	Fitusiran N=61 n (%)	Fitusiran Demand N=31 n (%)	Fitusiran N=18 n (%)	Fitusiran Demand N=9 n (%)
Vascular disorders (SOC)								
Hemorrhage	5 (15.6)	2 (12.5)	0	1 (33.3)	3 (4.9)	0	4 (22.2)	0
Thrombosis	1 (3.1)	0	1 (11.1)	0	0	0	0	0
Thrombosis venous	0	0	1 (11.1)	0	0	0	0	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date after the first dose of fitusiran in the fitusiran arm or after the Day 1 visit for the on-demand arm.

Duration is 9 months.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Most Common TEAEs

The most common TEAEs by FMQ are shown in [Table 157](#).

The most common preferred term (PT), hepatic injury, occurred nearly exclusively in the fitusiran treatment arms compared to the on-demand arms, and in each study the risk difference 95% confidence interval did not cross zero. Cholecystitis and dyspepsia were prevalent PTs reported only in the fitusiran treatment arms. Abdominal pain was also mostly reported in the fitusiran treatment arms. Dyspepsia and abdominal pain will be included as clinically relevant adverse reactions.

Table 157. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials EFC14768 and EFC14769

System Organ Class FMQ (Narrow)	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	On-Demand			On-Demand		
	Fitusiran N=41 n (%)	Fitusiran Demand N=19 n (%)	Risk Difference % (95% CI)	Fitusiran N=79 n (%)	Fitusiran Demand N=40 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)						
Anemia	2 (4.9)	0	4.9 (-12.5, 16.3)	0	0	0.0 (-8.8, 4.7)
Leukopenia	1 (2.4)	0	2.4 (-14.8, 12.7)	0	0	0.0 (-8.8, 4.7)
Cardiac disorders (SOC)						
Systemic hypertension	2 (4.9)	0	4.9 (-12.5, 16.3)	4 (5.1)	3 (7.5)	-2.4 (-15.4, 6.4)
Cardiac conduction disturbance	0	0	0.0 (-17.1, 8.7)	1 (1.3)	0	1.3 (-7.6, 6.9)
Endocrine disorders (SOC)						
Hyperglycemia	0	0	0.0 (-17.1, 8.7)	2 (2.5)	2 (5.0)	-2.5 (-14.3, 4.7)
Hyperprolactinemia	0	0	0.0 (-17.1, 8.7)	1 (1.3)	0	1.3 (-7.6, 6.9)

System Organ Class FMQ (Narrow)	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	Fitusiran N=41 n (%)	On- Demand N=19 n (%)	Risk Difference % (95% CI)	Fitusiran N=79 n (%)	On- Demand N=40 n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)						
Abdominal pain	8 (19.5)	0	19.5 (1.4, 34.2) *	9 (11.4)	1 (2.5)	8.9 (-2.4, 18.3)
Dyspepsia	6 (14.6)	0	14.6 (-3.2, 28.6)	5 (6.3)	0	6.3 (-2.7, 14.0)
Diarrhea	2 (4.9)	0	4.9 (-12.5, 16.3)	3 (3.8)	1 (2.5)	1.3 (-9.4, 8.6)
Constipation	1 (2.4)	1 (5.3)	-2.8 (-22.7, 8.4)	0	0	0.0 (-8.8, 4.7)
General disorders and administration site conditions (SOC)						
Local administration reaction	4 (9.8)	0	9.8 (-7.9, 22.7)	5 (6.3)	0	6.3 (-2.7, 14.0)
Pyrexia	3 (7.3)	0	7.3 (-10.2, 19.6)	1 (1.3)	2 (5.0)	-3.7 (-15.4, 2.7)
Fall	2 (4.9)	0	4.9 (-12.5, 16.3)	2 (2.5)	0	2.5 (-6.4, 8.8)
Peripheral edema	1 (2.4)	0	2.4 (-14.8, 12.7)	1 (1.3)	0	1.3 (-7.6, 6.9)
Fatigue	2 (4.9)	1 (5.3)	-0.4 (-20.5, 12.1)	0	0	0.0 (-8.8, 4.7)
Hepatobiliary disorders (SOC)						
Hepatic injury	15 (36.6)	0	36.6 (17.8, 52.0) *	20 (25.3)	1 (2.5)	22.8 (10.4, 34.0) *
Cholecystitis	4 (9.8)	0	9.8 (-7.9, 22.7)	2 (2.5)	0	2.5 (-6.4, 8.8)
Infections and infestations (SOC)						
Nasopharyngitis	11 (26.8)	1 (5.3)	21.6 (-0.5, 38.2)	18 (22.8)	6 (15.0)	7.8 (-8.4, 21.3)
Bacterial infection	7 (17.1)	1 (5.3)	11.8 (-9.4, 27.5)	10 (12.7)	2 (5.0)	7.7 (-5.0, 17.9)
Viral infection	5 (12.2)	1 (5.3)	6.9 (-13.9, 21.7)	5 (6.3)	2 (5.0)	1.3 (-10.8, 10.1)
Purulent material	1 (2.4)	0	2.4 (-14.8, 12.7)	3 (3.8)	0	3.8 (-5.1, 10.6)
Metabolism and nutrition disorders (SOC)						
Lipid disorder	1 (2.4)	0	2.4 (-14.8, 12.7)	0	0	0.0 (-8.8, 4.7)
Musculoskeletal and connective tissue disorders (SOC)						
Arthralgia	5 (12.2)	0	12.2 (-5.5, 25.7)	5 (6.3)	1 (2.5)	3.8 (-7.1, 12.0)
Arthritis	0	0	0.0 (-17.1, 8.7)	2 (2.5)	1 (2.5)	0.0 (-10.6, 6.7)
Myalgia	0	0	0.0 (-17.1, 8.7)	2 (2.5)	0	2.5 (-6.4, 8.8)
Rhabdomyolysis	0	0	0.0 (-17.1, 8.7)	0	1 (2.5)	-2.5 (-12.9, 2.3)
Back pain	1 (2.4)	1 (5.3)	-2.8 (-22.7, 8.4)	2 (2.5)	2 (5.0)	-2.5 (-14.3, 4.7)
Fracture	0	1 (5.3)	-5.3 (-24.9, 3.8)	1 (1.3)	1 (2.5)	-1.2 (-11.8, 4.7)

System Organ Class FMQ (Narrow)	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	Fitusiran N=41 n (%)	On-Demand N=19 n (%)	Risk Difference % (95% CI)	Fitusiran N=79 n (%)	On-Demand N=40 n (%)	Risk Difference % (95% CI)
Nervous system disorders (SOC)						
Headache	6 (14.6)	1 (5.3)	9.4 (-11.7, 24.6)	5 (6.3)	1 (2.5)	3.8 (-7.1, 12.0)
Paresthesia	0	1 (5.3)	-5.3 (-24.9, 3.8)	1 (1.3)	0	1.3 (-7.6, 6.9)
Psychiatric disorders (SOC)						
Self-harm	0	0	0.0 (-17.1, 8.7)	0	1 (2.5)	-2.5 (-12.9, 2.3)
Renal and urinary disorders (SOC)						
Renal & urinary tract infection	2 (4.9)	1 (5.3)	-0.4 (-20.5, 12.1)	3 (3.8)	0	3.8 (-5.1, 10.6)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	2 (4.9)	0	4.9 (-12.5, 16.3)	6 (7.6)	0	7.6 (-1.5, 15.6)
Bronchospasm	1 (2.4)	0	2.4 (-14.8, 12.7)	5 (6.3)	0	6.3 (-2.7, 14.0)
Skin and subcutaneous tissue disorders (SOC)						
Pruritus	2 (4.9)	0	4.9 (-12.5, 16.3)	5 (6.3)	0	6.3 (-2.7, 14.0)
Erythema	0	0	0.0 (-17.1, 8.7)	2 (2.5)	0	2.5 (-6.4, 8.8)
Rash	2 (4.9)	1 (5.3)	-0.4 (-20.5, 12.1)	2 (2.5)	0	2.5 (-6.4, 8.8)
Urticaria	1 (2.4)	1 (5.3)	-2.8 (-22.7, 8.4)	0	0	0.0 (-8.8, 4.7)
Vascular disorders (SOC)						
Thrombosis	2 (4.9)	0	4.9 (-12.5, 16.3)	0	0	0.0 (-8.8, 4.7)
Thrombosis venous	1 (2.4)	0	2.4 (-14.8, 12.7)	0	0	0.0 (-8.8, 4.7)
Hemorrhage	5 (12.2)	3 (15.8)	-3.6 (-27.1, 13.8)	7 (8.9)	0	8.9 (-0.2, 17.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date after the first dose of fitusiran in the fitusiran arm or after the Day 1 visit for the on-demand arm.

Duration is 9 months.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Liver Assessment

Liver enzyme elevations were higher on the 80 mg QM dose regimen, compared to the AT-DR. This is discussed in the safety review issue for hepatotoxicity (see Section 7.6.3 for further discussion).

Table 158. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials EFC14768 and EFC14769

Laboratory Parameter	EFC14768 (Inhibitor)			EFC14769 (Noninhibitor)		
	Fitusiran N=41 n/N _w (%)	On- Demand N=19 n/N _w (%)	Risk Difference % (95% CI)	Fitusiran N=79 n/N _w (%)	On- Demand N=40 n/N _w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5× ULN)	9/41 (22.0)	1/19 (5.3)	16.7 (-5.0, 33.0)	7/79 (8.9)	0/39 (0)	8.9 (-0.4, 17.2)
Level 2 (>2× ULN)	3/41 (7.3)	0/19 (0)	7.3 (-10.2, 19.6)	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
Level 3 (>3× ULN)	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)	1/79 (1.3)	0/39 (0)	1.3 (-7.8, 6.9)
Alanine aminotransferase, high (U/L)						
Level 1 (>3× ULN)	11/41 (26.8)	0/19 (0)	26.8 (8.4, 42.1) *	14/79 (17.7)	0/39 (0)	17.7 (8.2, 27.6) *
Level 2 (>5× ULN)	2/41 (4.9)	0/19 (0)	4.9 (-12.5, 16.3)	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
Level 3 (>10× ULN)	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3× ULN)	4/41 (9.8)	0/19 (0)	9.8 (-7.9, 22.7)	5/79 (6.3)	1/39 (2.6)	3.8 (-7.4, 12.0)
Level 2 (>5× ULN)	2/41 (4.9)	0/19 (0)	4.9 (-12.5, 16.3)	3/79 (3.8)	0/39 (0)	3.8 (-5.4, 10.6)
Level 3 (>10× ULN)	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)	0/79 (0)	0/39 (0)	0.0 (-9.0, 4.7)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5× ULN)	4/41 (9.8)	0/19 (0)	9.8 (-7.9, 22.7)	5/79 (6.3)	0/39 (0)	6.3 (-2.9, 14.0)
Level 2 (>2× ULN)	1/41 (2.4)	0/19 (0)	2.4 (-14.8, 12.7)	2/79 (2.5)	0/39 (0)	2.5 (-6.6, 8.8)
Level 3 (>3× ULN)	0/41 (0)	0/19 (0)	0.0 (-17.1, 8.7)	1/79 (1.3)	0/39 (0)	1.3 (-7.8, 6.9)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 9 months.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

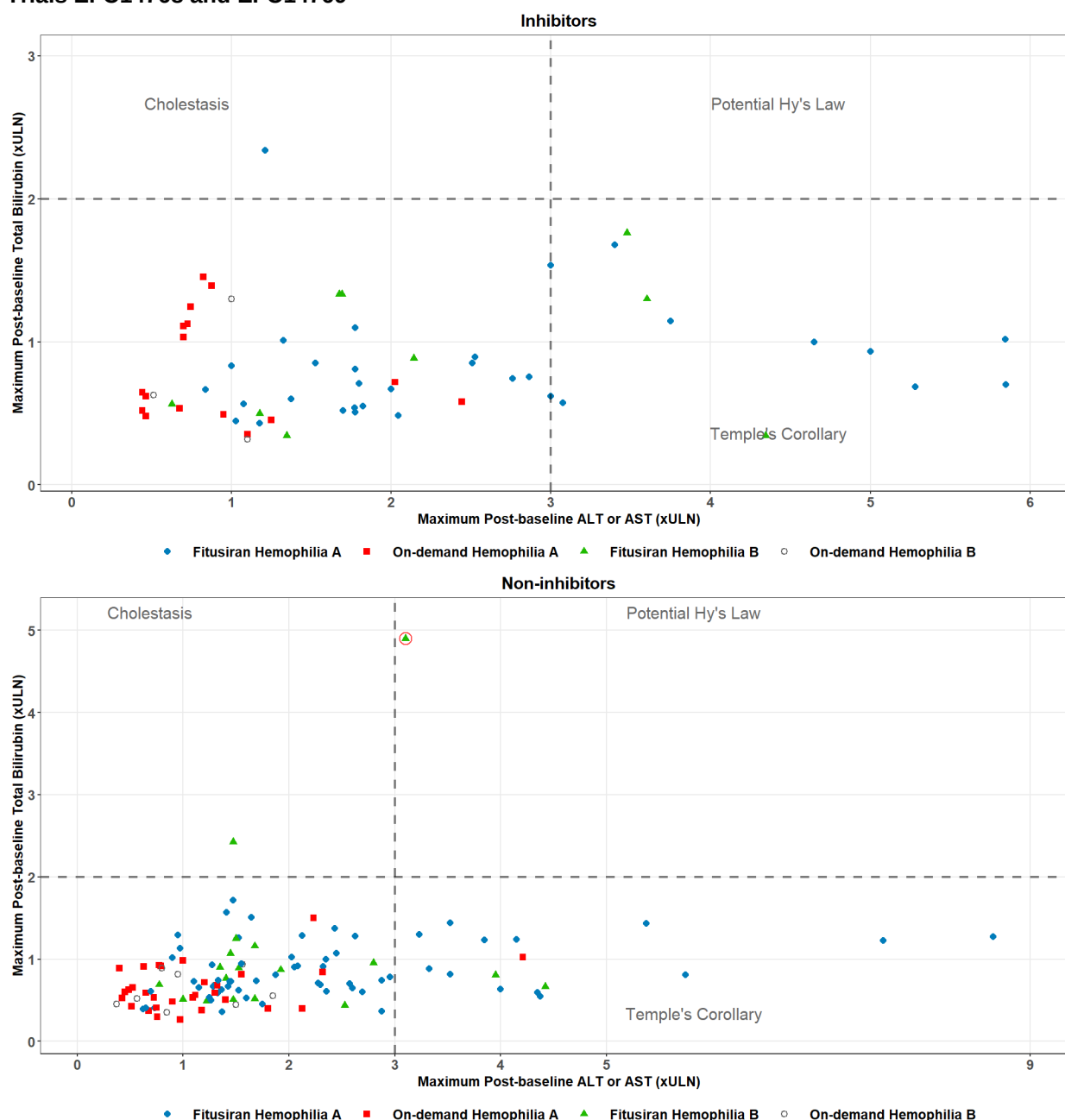
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; ULN, upper limit of normal

[Figure 58](#) shows the eDISH plots for potential Hy's Law cases in the pooled trials EFC14768 and EFC14769. There was one subject, study subject (b) (6), who met the criteria for potential drug-induced liver injury. See Section [7.6.3](#) for the subject narrative and discussion.

Figure 58. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials EFC14768 and EFC14769



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

17.2. Safety Analysis of Pooled Trials EFC14768 and EFC14769 On-Demand Controls and LTE15174 AT-DR Treatment Phase Subjects Originally Randomized to Fitusiran in Parent Study EFC14768 and EFC14769

To further assess potential treatment effects of fitusiran AT-DR, an exploratory analysis compared subjects receiving the AT-DR during LTE15174 (N=103; 35 inhibitor and 68 noninhibitor) with the subjects randomized to the on-demand treatment arm (N=59; 19 inhibitor and 40 noninhibitor) from studies EFC14768 and EFC14769. For this analysis, we only included AT-DR subjects who had originally been randomized to the fitusiran treatment arm in studies EFC14768 and EFC14769. An important limitation of this analysis is that patients on the AT-DR who tolerated the higher dose of fitusiran in the parent studies and then continued into the long-term extension study may not reflect what would occur in patients who are treatment-naïve to fitusiran AT-DR.

Exposure Data

[Table 159](#) shows the duration of exposure to fitusiran AT-DR in Study LTE15174 and exposure to the on-demand treatment in EFC14768 and EFC14769. The mean duration of treatment of 107.2 weeks in the fitusiran AT-DR cohort is longer than the mean duration of 35.4 weeks for the on-demand cohort. In addition, as this analysis is adhering to the original randomization, there are more subjects in the fitusiran AT-DR cohort due to the original 2:1 randomization scheme.

Table 159. Duration of Exposure (Study Drug) or Duration of Observation (On-Demand), Safety Population, Pooled Trials EFC14768, EFC14769, and LTE15174

Parameter	Inhibitor		Noninhibitor		Overall	
	LTE15174	EFC14768	LTE15174	EFC14769	Fitusiran	On-
	Fitusiran AT-DR N=35	On-Demand N=19	Fitusiran AT-DR N=68	On-Demand N=40	AT-DR N=103	Demand N=59
Duration of treatment or observation, weeks						
Mean (SD)	110.1 (11.9)	37.3 (2.3)	105.6 (20.6)	34.4 (8.4)	107.2 (18.2)	35.4 (7.2)
Median (Q1, Q3)	114.1 (108.1, 117.2)	37 (36.1, 37.2)	112.1 (106.7, 116.2)	36.1 (35.9, 36.9)	112.9 (106.9, 116.6)	36.3 (36, 37.1)
Min, max	74.1, 121	35, 45.4	28, 122	0.1, 41.6	28, 122	0.1, 45.4
Total exposure (person years)	74	14	138	26	212	40

Parameter	Inhibitor		Noninhibitor		Overall	
	LTE15174 Fitusiran AT- DR N=35	EFC14768 On-Demand N=19	LTE15174 Fitusiran AT- DR N=68	EFC14769 On-Demand N=40	Fitusiran AT-DR N=103	On- Demand N=59
Subjects treated or observed, by duration, n (%)						
<12 weeks	0	0	0	2 (5.0)	0	2 (3.4)
≥12 to <26 weeks	0	0	0	1 (2.5)	0	1 (1.7)
≥26 to <50 weeks	0	19 (100)	4 (5.9)	37 (92.5)	4 (3.9)	56 (94.9)
≥50 to <100 weeks	4 (11.4)	0	5 (7.4)	0	9 (8.7)	0
≥100 to <150 weeks	31 (88.6)	0	59 (86.8)	0	90 (87.4)	0
≥150 weeks	0	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 128 weeks for the fitusiran group and 36 weeks for the on-demand group.

The revised regimen period is from dose restart Day 1 to data cut off for interim lock and follow-up AT back to 60% whichever comes first.

Abbreviations: AT, antithrombin; AT-DR, antithrombin-based dose regimen; LTE, long-term extension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Overview of Adverse Events

[Table 160](#) shows the overview of adverse events. Given the differences in exposure, the frequencies are reported in an exposure-adjusted incidence rate (EAIR, per 100 person-years). SAEs were lower in the fitusiran treatment cohort than in the on-demand cohort. [Table 161](#) shows subjects with SAEs by SOC and PT. Conclusions are limited by the low numbers of events.

Table 160. Overview of Adverse Events, Safety Population, Pooled Trials EFC14768, EFC14769, and LTE15174

Event Category	Inhibitor		Noninhibitor		Overall		
	LTE15174 Fitusiran AT-DR PY =73.9 N=35	EFC14768 On- Demand PY =13.6 N=19	LTE15174 Fitusiran AT-DR PY =137.7 N=68	EFC14769 On- Demand PY =26.4 N=40	Fitusiran AT-DR PY =211.5 N=103	On-Demand PY =40 N=59	Fitusiran AT-DR vs. On-Demand EAIR Difference (95% CI)
	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	
SAE	8/65.2 (12.3)	5/11.8 (42.3)	6/131.7 (4.6)	5/24.6 (20.3)	14/196.9 (7.1)	10/36.4 (27.4)	-20.3 (-43.6, -7.0) *
SAEs with fatal outcome	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	0/40 (0)	0.0 (-9.6, 1.8)
Life-threatening SAEs	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	1/39.3 (2.5)	-2.5 (-14.4, -0.4) *
SAEs resulting in substantial disruption of normal life functions	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	1/39.3 (2.5)	-2.5 (-14.4, -0.4) *
AE leading to permanent discontinuation of study drug	0/73.9 (0)	0/13.6 (0)	1/137.4 (0.7)	0/26.4 (0)	1/211.3 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
AE leading to dose modification of study drug	1/72.3 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/209.9 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
AE leading to interruption of study drug	1/72.3 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/209.9 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
AE leading to reduction of study drug	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	0/40 (0)	0.0 (-9.6, 1.8)
AE leading to dose delay of study drug	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	0/40 (0)	0.0 (-9.6, 1.8)
Any AE	29/29.7 (97.7)	11/8.7 (125.8)	57/59.1 (96.4)	18/18 (99.9)	86/88.8 (96.9)	29/26.8 (108.3)	-11.5 (-62.0, 28.7)
Severe and worse	5/69.6 (7.2)	1/13 (7.7)	5/132.7 (3.8)	3/25.2 (11.9)	10/202.3 (4.9)	4/38.2 (10.5)	-5.5 (-22.2, 2.1)
Moderate	17/51.4 (33.1)	4/11.9 (33.6)	26/111.7 (23.3)	6/23.9 (25.1)	43/163.1 (26.4)	10/35.8 (27.9)	-1.6 (-25.9, 14.3)
Mild	7/65.7 (10.7)	6/11.6 (51.8)	26/104.5 (24.9)	9/22.6 (39.8)	33/170.1 (19.4)	15/34.2 (43.8)	-24.4 (-53.5, -5.5) *

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off (June 14, 2023) for NDA for the fitusiran group. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater. For the on-demand group, AEs were defined as treatment-emergent if they occurred after the Day 1 visit during studies EFC14768 and EFC14769.

Duration is up to 128 weeks for the fitusiran group and 36 weeks for the on-demand group.

Events occurred during major surgery periods are excluded.

The revised regimen period is from dose restart Day 1 to data cut off for interim lock and follow-up AT back to 60% whichever comes first.

Person-years for the AT-DR group were calculated as the total duration starting from the first dose of AT-DR until the initial occurrence of the event for subjects who experienced an event, or the data cutoff date for subjects who did not. However, for subjects who discontinued earlier, the follow-up period was considered completed once the AT recovered to 60%.

Person-years for the on-demand group were calculated as the total duration starting from the Day 1 visit until the initial occurrence of the event for subjects who experienced an event, or the last day in the study for subjects who did not.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Note that differences are sometimes observed between Table 3 and Table 5 because these tables are derived from different datasets and sometimes differ in definitions or how cases are counted.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with at least one event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event

Serious Adverse Events

[Table 161](#) shows SAEs by SOC and PT. The overall frequency of SAEs was higher in the on-demand treatment group compared to fitusiran; however, most SAEs were reported in only 1-2 subjects, limiting conclusions.

Table 161. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials EFC14768, EFC14769, and LTE15174

System Organ Class Preferred Term	Inhibitor		Noninhibitor		Overall		
	LTE15174 Fitusiran AT-DR PY =73.9 N=35 n/py (EAIR)	EFC14768 On-Demand PY =13.6 N=19 n/py (EAIR)	LTE15174 Fitusiran AT-DR PY =137.7 N=68 n/py (EAIR)	EFC14769 On-Demand PY =26.4 N=40 n/py (EAIR)	Fitusiran AT-DR PY =211.5 N=103 n/py (EAIR)	On-Demand PY =40 N=59 n/py (EAIR)	Fitusiran AT-DR vs. On-Demand EAIR Difference (95% CI)
Any SAE	8/65.2 (12.3)	5/11.8 (42.3)	6/131.7 (4.6)	5/24.6 (20.3)	14/196.9 (7.1)	10/36.4 (27.4)	-20.3 (-43.6, -7.0) *
Eye disorders (SOC)	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.1 (3.8)	0/211.5 (0)	1/39.7 (2.5)	-2.5 (-14.3, -0.4) *
Diplopia	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.1 (3.8)	0/211.5 (0)	1/39.7 (2.5)	-2.5 (-14.3, -0.4) *
Gastrointestinal disorders (SOC)	2/71.1 (2.8)	1/13 (7.7)	2/134.7 (1.5)	0/26.4 (0)	4/205.8 (1.9)	1/39.4 (2.5)	-0.6 (-12.5, 3.2)
Tongue hematoma	0/73.9 (0)	0/13.6 (0)	1/135.6 (0.7)	0/26.4 (0)	1/209.4 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Melaena	1/72.5 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.1 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Hemoperitoneum	1/72.5 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.2 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Tooth malformation	0/73.9 (0)	0/13.6 (0)	1/136.8 (0.7)	0/26.4 (0)	1/210.7 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Retroperitoneal hemorrhage	0/73.9 (0)	1/13 (7.7)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	1/39.4 (2.5)	-2.5 (-14.4, -0.4) *
Hepatobiliary disorders (SOC)	1/72.4 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.1 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Cholangitis	1/72.4 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.1 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Infections and infestations (SOC)	1/73 (1.4)	0/13.6 (0)	1/135.9 (0.7)	1/26.1 (3.8)	2/208.8 (1.0)	1/39.7 (2.5)	-1.6 (-13.3, 1.6)
Large intestine infection	0/73.9 (0)	0/13.6 (0)	1/135.9 (0.7)	0/26.4 (0)	1/209.7 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pneumonia	1/73 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.6 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Gastroenteritis	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.1 (3.8)	0/211.5 (0)	1/39.7 (2.5)	-2.5 (-14.3, -0.4) *
Injury, poisoning and procedural complications (SOC)	0/73.9 (0)	2/13 (15.4)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	3/38.7 (7.7)	-7.7 (-22.8, -2.6) *
Tooth fracture	0/73.9 (0)	1/13.6 (7.4)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	1/40 (2.5)	-2.5 (-14.2, -0.4) *
Traumatic hemorrhage	0/73.9 (0)	1/13 (7.7)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	1/39.4 (2.5)	-2.5 (-14.4, -0.4) *
Humerus fracture	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	1/39.3 (2.5)	-2.5 (-14.4, -0.4) *
Subdural hemorrhage	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	1/39.3 (2.5)	-2.5 (-14.4, -0.4) *
Tibia fracture	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.7 (3.9)	0/211.5 (0)	1/39.3 (2.5)	-2.5 (-14.4, -0.4) *

System Organ Class Preferred Term	Inhibitor		Noninhibitor		Overall		
	LTE15174 Fitusiran AT-DR PY =73.9 N=35	EFC14768 On-Demand PY =13.6 N=19	LTE15174 Fitusiran AT-DR PY =137.7 N=68	EFC14769 On-Demand PY =26.4 N=40	Fitusiran AT- DR PY =211.5 N=103	On-Demand PY =40 N=59	Fitusiran AT-DR vs. On-Demand EAIR Difference (95% CI)
	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	
Musculoskeletal and connective tissue disorders (SOC)	4/69.7 (5.7)	2/13.2 (15.2)	0/137.7 (0)	1/25.9 (3.9)	4/207.4 (1.9)	3/39 (7.7)	-5.8 (-20.7, 0.0)
Limb mass	1/72.2 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/209.8 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Hematoma muscle	1/73.4 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/211 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Hemarthrosis	2/71.9 (2.8)	1/13.2 (7.6)	0/137.7 (0)	0/26.4 (0)	2/209.5 (1.0)	1/39.6 (2.5)	-1.6 (-13.4, 1.6)
Muscle hemorrhage	0/73.9 (0)	1/13.6 (7.4)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	1/39.9 (2.5)	-2.5 (-14.2, -0.4) *
Osteoarthritis	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.9 (3.9)	0/211.5 (0)	1/39.5 (2.5)	-2.5 (-14.4, -0.4) *
Nervous system disorders (SOC)	1/73.2 (1.4)	0/13.6 (0)	1/137.6 (0.7)	0/26.4 (0)	2/210.8 (0.9)	0/40 (0)	0.9 (-8.7, 3.5)
Hemorrhage intracranial	1/73.2 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.9 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Embolic stroke	0/73.9 (0)	0/13.6 (0)	1/137.6 (0.7)	0/26.4 (0)	1/211.5 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Psychiatric disorders (SOC)	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.3 (3.8)	0/211.5 (0)	1/39.9 (2.5)	-2.5 (-14.2, -0.4) *
Suicidal ideation	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.3 (3.8)	0/211.5 (0)	1/39.9 (2.5)	-2.5 (-14.2, -0.4) *
Renal and urinary disorders (SOC)	1/72.6 (1.4)	1/13 (7.7)	1/137.5 (0.7)	0/26.4 (0)	2/210.1 (1.0)	1/39.4 (2.5)	-1.6 (-13.4, 1.6)
Hematuria	1/72.6 (1.4)	1/13 (7.7)	1/137.5 (0.7)	0/26.4 (0)	2/210.1 (1.0)	1/39.4 (2.5)	-1.6 (-13.4, 1.6)
Respiratory, thoracic and mediastinal disorders (SOC)	2/73 (2.7)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	2/210.6 (0.9)	0/40 (0)	0.9 (-8.7, 3.5)
Asthma	1/73.2 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.9 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pneumonitis	1/73.6 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/211.2 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Social circumstances (SOC)	0/73.9 (0)	0/13.6 (0)	1/136.6 (0.7)	0/26.4 (0)	1/210.4 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pregnancy of partner	0/73.9 (0)	0/13.6 (0)	1/136.6 (0.7)	0/26.4 (0)	1/210.4 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off (June 14, 2023) for NDA for the fitusiran group. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater. For the on-demand group, AEs were defined as treatment-emergent if they occurred after the Day 1 visit during studies EFC14768 and EFC14769.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is up to 128 weeks for the fitusiran group and 36 weeks for the on-demand group.

Events occurred during major surgery periods are excluded.

The revised regimen period is from dose restart Day 1 to data cut off for interim lock and follow-up AT back to 60% whichever comes first.

Person-years for the AT-DR group were calculated as the total duration starting from the first dose of AT-DR until the initial occurrence of the event for subjects who experienced an event, or the data cutoff date for subjects who did not. However, for subjects who discontinued earlier, the follow-up period was considered completed once the AT recovered to 60%. Person-years for the on-demand group were calculated as the total duration starting from the Day 1 visit until the initial occurrence of the event for subjects who experienced an event, or the last day in the study for subjects who did not.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with at least one event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event; SOC, system organ class

Most Common Adverse Events

[Table 162](#) shows the adverse events by SOC and FDA Medical Query. Many AEs were reported in only 1-2 subjects, limiting conclusions. More frequently reported AEs of cough, bronchospasm, and rash were reported almost exclusively with fitusiran treatment compared to on-demand treatment, similar to the distribution of these AEs in the randomized controlled trials. The PT viral infection was reported at a higher rate with fitusiran compared to on-demand treatment, like in the randomized controlled trials, although bacterial infection and nasopharyngitis rates were lower with fitusiran, in contrast to that seen in the randomized trials.

Table 162. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials EFC14768, EFC14769, and LTE15174

System Organ Class FMQ (Narrow)	Inhibitor		Noninhibitor		Overall		
	LTE15174	EFC14768	LTE15174	EFC14769	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR
	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR	On-Demand	AT-DR	AT-DR	vs. On-Demand
	PY =73.9 N=35 n/py (EAIR)	PY =13.6 N=19 n/py (EAIR)	PY =137.7 N=68 n/py (EAIR)	PY =26.4 N=40 n/py (EAIR)	PY =211.5 N=103 n/py (EAIR)	PY =40 N=59 n/py (EAIR)	EAIR Difference (95% CI)
Blood and lymphatic system disorders (SOC)							
Leukopenia	3/70.2 (4.3)	0/13.6 (0)	1/136.4 (0.7)	0/26.4 (0)	4/206.6 (1.9)	0/40 (0)	1.9 (-7.7, 5.0)
Anemia	1/72 (1.4)	0/13.6 (0)	1/137.5 (0.7)	0/26.4 (0)	2/209.5 (1.0)	0/40 (0)	1.0 (-8.7, 3.5)
Thrombocytopenia	0/73.9 (0)	0/13.6 (0)	1/136.6 (0.7)	0/26.4 (0)	1/210.4 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Cardiac disorders (SOC)							
Arrhythmia	1/72.6 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.2 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Palpitations	0/73.9 (0)	0/13.6 (0)	1/136.9 (0.7)	0/26.4 (0)	1/210.8 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Myocardial ischemia	1/73.6 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/211.3 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Systemic hypertension	5/71.5 (7.0)	0/13.6 (0)	2/136.4 (1.5)	3/25.2 (11.9)	7/207.9 (3.4)	3/38.8 (7.7)	-4.4 (-19.5, 1.8)
Endocrine disorders (SOC)							
Hyperglycemia	2/73.2 (2.7)	0/13.6 (0)	2/136.5 (1.5)	2/25.3 (7.9)	4/209.7 (1.9)	2/38.9 (5.1)	-3.2 (-16.9, 1.5)
Gastrointestinal disorders (SOC)							
Vomiting	1/72.3 (1.4)	0/13.6 (0)	2/135.7 (1.5)	0/26.4 (0)	3/207.9 (1.4)	0/40 (0)	1.4 (-8.2, 4.2)
Nausea	2/70.7 (2.8)	0/13.6 (0)	1/137.4 (0.7)	0/26.4 (0)	3/208.2 (1.4)	0/40 (0)	1.4 (-8.2, 4.2)
Dyspepsia	0/73.9 (0)	0/13.6 (0)	2/135.4 (1.5)	0/26.4 (0)	2/209.2 (1.0)	0/40 (0)	1.0 (-8.7, 3.5)
Abdominal pain	3/70.7 (4.2)	0/13.6 (0)	4/133.5 (3.0)	1/26.1 (3.8)	7/204.2 (3.4)	1/39.7 (2.5)	0.9 (-10.9, 5.3)
Pancreatitis	1/72.4 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.1 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Constipation	3/71.4 (4.2)	1/13.6 (7.4)	1/135.9 (0.7)	0/26.4 (0)	4/207.2 (1.9)	1/40 (2.5)	-0.6 (-12.3, 3.1)
Diarrhea	1/72.1 (1.4)	0/13.6 (0)	3/135.3 (2.2)	1/26.1 (3.8)	4/207.4 (1.9)	1/39.7 (2.5)	-0.6 (-12.4, 3.1)

System Organ Class FMQ (Narrow)	Inhibitor		Noninhibitor		Overall		
	LTE15174 Fitusiran AT-DR PY =73.9 N=35 n/py (EAIR)	EFC14768 On-Demand PY =13.6 N=19 n/py (EAIR)	LTE15174 Fitusiran AT-DR PY =137.7 N=68 n/py (EAIR)	EFC14769 On-Demand PY =26.4 N=40 n/py (EAIR)	Fitusiran AT-DR PY =211.5 N=103 n/py (EAIR)	On-Demand PY =40 N=59 n/py (EAIR)	Fitusiran AT-DR vs. On-Demand EAIR Difference (95% CI)
General disorders and administration site conditions (SOC)							
Local administration reaction	3/68.3 (4.4)	0/13.6 (0)	3/135.7 (2.2)	0/26.4 (0)	6/204 (2.9)	0/40 (0)	2.9 (-6.7, 6.4)
Fall	0/73.9 (0)	0/13.6 (0)	3/134 (2.2)	0/26.4 (0)	3/207.9 (1.4)	0/40 (0)	1.4 (-8.2, 4.2)
Dizziness	0/73.9 (0)	0/13.6 (0)	1/135.8 (0.7)	0/26.4 (0)	1/209.6 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pyrexia	3/69 (4.3)	0/13.6 (0)	7/129.5 (5.4)	2/25.2 (7.9)	10/198.6 (5.0)	2/38.8 (5.2)	-0.1 (-13.9, 5.7)
Fatigue	2/70 (2.9)	1/12.9 (7.7)	3/136.8 (2.2)	0/26.4 (0)	5/206.8 (2.4)	1/39.3 (2.5)	-0.1 (-12.1, 3.8)
Hepatobiliary disorders (SOC)							
Hepatic injury	1/72.1 (1.4)	0/13.6 (0)	3/134.5 (2.2)	1/26 (3.8)	4/206.6 (1.9)	1/39.6 (2.5)	-0.6 (-12.4, 3.1)
Immune system disorders (SOC)							
Angioedema	0/73.9 (0)	0/13.6 (0)	1/137.2 (0.7)	0/26.4 (0)	1/211 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Infections and infestations (SOC)							
Viral infection	9/64.6 (13.9)	1/13.4 (7.4)	19/116.2 (16.4)	2/25.6 (7.8)	28/180.8 (15.5)	3/39 (7.7)	7.8 (-7.6, 16.7)
Fungal infection	1/72.9 (1.4)	0/13.6 (0)	3/135.4 (2.2)	0/26.4 (0)	4/208.3 (1.9)	0/40 (0)	1.9 (-7.7, 4.9)
Purulent material	1/71.6 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/209.3 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pneumonia	1/73 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/210.6 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Bacterial infection	5/65 (7.7)	1/13.1 (7.6)	6/130.1 (4.6)	2/25.2 (7.9)	11/195.1 (5.6)	3/38.3 (7.8)	-2.2 (-17.6, 4.7)
Nasopharyngitis	7/65.3 (10.7)	1/12.9 (7.7)	18/119.4 (15.1)	6/24.4 (24.6)	25/184.7 (13.5)	7/37.4 (18.7)	-5.2 (-25.6, 6.5)
Metabolism and nutrition disorders (SOC)							
Lipid disorder	0/73.9 (0)	0/13.6 (0)	3/135.8 (2.2)	0/26.4 (0)	3/209.7 (1.4)	0/40 (0)	1.4 (-8.2, 4.2)
Musculoskeletal and connective tissue disorders (SOC)							
Tendinopathy	0/73.9 (0)	0/13.6 (0)	3/133.4 (2.2)	0/26.4 (0)	3/207.3 (1.4)	0/40 (0)	1.4 (-8.2, 4.3)
Arthralgia	4/69.7 (5.7)	0/13.6 (0)	4/133.5 (3.0)	1/26.4 (3.8)	8/203.2 (3.9)	1/40 (2.5)	1.4 (-10.3, 6.0)
Myalgia	0/73.9 (0)	0/13.6 (0)	2/135.7 (1.5)	0/26.4 (0)	2/209.6 (1.0)	0/40 (0)	1.0 (-8.7, 3.5)
Arthritis	0/73.9 (0)	0/13.6 (0)	1/135.5 (0.7)	1/25.9 (3.9)	1/209.3 (0.5)	1/39.5 (2.5)	-2.1 (-13.9, 0.8)
Rhabdomyolysis	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/25.8 (3.9)	0/211.5 (0)	1/39.4 (2.5)	-2.5 (-14.4, -0.4) *
Fracture	1/72.3 (1.4)	1/13.6 (7.4)	0/137.7 (0)	1/25.7 (3.9)	1/209.9 (0.5)	2/39.3 (5.1)	-4.6 (-18.1, -0.6) *
Back pain	1/72.2 (1.4)	1/13.2 (7.6)	2/135.3 (1.5)	2/25.6 (7.8)	3/207.5 (1.4)	3/38.8 (7.7)	-6.3 (-21.3, -0.7) *

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QFITLIA (fitusiran)

System Organ Class FMQ (Narrow)	Inhibitor		Noninhibitor		Overall		
	LTE15174	EFC14768	LTE15174	EFC14769	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR
	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR	On-Demand	AT-DR	AT-DR	vs. On-Demand
	PY =73.9	PY =13.6	PY =137.7	PY =26.4	PY =211.5	PY =40	EAIR Difference
	N=35	N=19	N=68	N=40	N=103	N=59	(95% CI)
	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	
Nervous system disorders (SOC)							
Seizure	1/71.8 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/209.5 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Dysgeusia	0/73.9 (0)	0/13.6 (0)	1/136.2 (0.7)	0/26.4 (0)	1/210.1 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Stroke and TIA	0/73.9 (0)	0/13.6 (0)	1/137.6 (0.7)	0/26.4 (0)	1/211.5 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Paresthesia	0/73.9 (0)	1/13.1 (7.7)	1/137 (0.7)	0/26.4 (0)	1/210.8 (0.5)	1/39.4 (2.5)	-2.1 (-13.9, 0.8)
Headache	3/69.9 (4.3)	1/13.1 (7.7)	2/135.1 (1.5)	1/26.4 (3.8)	5/205 (2.4)	2/39.4 (5.1)	-2.6 (-16.1, 2.3)
Psychiatric disorders (SOC)							
Insomnia	0/73.9 (0)	0/13.6 (0)	1/136.6 (0.7)	0/26.4 (0)	1/210.4 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Self-harm	0/73.9 (0)	0/13.6 (0)	0/137.7 (0)	1/26.3 (3.8)	0/211.5 (0)	1/39.9 (2.5)	-2.5 (-14.2, -0.4) *
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	1/73.6 (1.4)	1/13.1 (7.6)	2/135.8 (1.5)	0/26.4 (0)	3/209.3 (1.4)	1/39.5 (2.5)	-1.1 (-12.9, 2.4)
Respiratory, thoracic and mediastinal disorders (SOC)							
Cough	4/69.7 (5.7)	0/13.6 (0)	3/133.8 (2.2)	0/26.4 (0)	7/203.5 (3.4)	0/40 (0)	3.4 (-6.2, 7.1)
Bronchospasm	2/71 (2.8)	0/13.6 (0)	3/135.3 (2.2)	0/26.4 (0)	5/206.3 (2.4)	0/40 (0)	2.4 (-7.2, 5.7)
Dyspnea	0/73.9 (0)	0/13.6 (0)	1/135.8 (0.7)	0/26.4 (0)	1/209.7 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Pneumonitis	1/73.6 (1.4)	0/13.6 (0)	0/137.7 (0)	0/26.4 (0)	1/211.2 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Skin and subcutaneous tissue disorders (SOC)							
Pruritus	1/73.6 (1.4)	0/13.6 (0)	3/136.6 (2.2)	0/26.4 (0)	4/210.2 (1.9)	0/40 (0)	1.9 (-7.7, 4.9)
Rash	1/73.6 (1.4)	1/13 (7.7)	6/130.4 (4.6)	0/26.4 (0)	7/204 (3.4)	1/39.4 (2.5)	0.9 (-11.0, 5.3)
Erythema	0/73.9 (0)	0/13.6 (0)	1/137.7 (0.7)	0/26.4 (0)	1/211.5 (0.5)	0/40 (0)	0.5 (-9.1, 2.7)
Urticaria	0/73.9 (0)	1/13 (7.7)	0/137.7 (0)	0/26.4 (0)	0/211.5 (0)	1/39.4 (2.5)	-2.5 (-14.4, -0.4) *

System Organ Class FMQ (Narrow)	Inhibitor		Noninhibitor		Overall		
	LTE15174	EFC14768	LTE15174	EFC14769	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR
	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR	On-Demand	Fitusiran AT-DR
	PY =73.9	PY =13.6	PY =137.7	PY =26.4	PY =211.5	PY =40	vs. On-Demand
	N=35	N=19	N=68	N=40	N=103	N=59	EAIR Difference
	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	n/py (EAIR)	(95% CI)
Vascular disorders (SOC)							
Hemorrhage	7/65.3 (10.7)	3/12.4 (24.2)	3/134.3 (2.2)	0/26.4 (0)	10/199.6 (5.0)	3/38.8 (7.7)	-2.7 (-17.9, 3.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with onset or ongoing after fitusiran dose restart and before the data cut off (June 14, 2023) for NDA for the fitusiran group. However, AEs were not considered treatment-emergent if they occurred during the follow-up after a subject's AT value was 60% or greater. For the on-demand group, AEs were defined as treatment-emergent if they occurred after the Day 1 visit during studies EFC14768 and EFC14769.

Duration is up to 128 weeks for the fitusiran group and 36 weeks for the on-demand group.

Events occurred during major surgery periods are excluded.

The revised regimen period is from dose restart Day 1 to data cut off for interim lock and follow-up AT back to 60% whichever comes first.

Person-years for the AT-DR group were calculated as the total duration starting from the first dose of AT-DR until the initial occurrence of the event for subjects who experienced an event, or the data cutoff date for subjects who did not. However, for subjects who discontinued earlier, the follow-up period was considered completed once the AT recovered to 60%. Person-years for the on-demand group were calculated as the total duration starting from the Day 1 visit until the initial occurrence of the event for subjects who experienced an event, or the last day in the study for subjects who did not.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; AT, antithrombin; AT-DR, antithrombin-based dose regimen; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class; TIA, transient ischemic attack

Liver Assessment

While less compared to the 80 mg QM dose regimen, liver enzyme abnormalities also occurred at higher rates in the AT-DR arm compared to on-demand. This issue is discussed in Section [7.6.3](#).

Table 163. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials EFC14768, EFC14769, and LTE15174

Laboratory Parameter	Inhibitor		Noninhibitor		Overall		Fitusiran AT-DR vs. On-Demand Risk Difference % (95% CI)
	LTE15174 Fitusiran AT-DR N=35 n/N _w (%)	EFC14768 On-Demand N=19 n/N _w (%)	LTE15174 Fitusiran AT-DR N=68 n/N _w (%)	EFC14769 On-Demand N=40 n/N _w (%)	Fitusiran AT-DR N=103 n/N _w (%)	On-Demand N=59 n/N _w (%)	
Alkaline phosphatase, high (U/L)							
Level 1 (>1.5× ULN)	7/35 (20.0)	1/19 (5.3)	9/68 (13.2)	0/39 (0)	16/103 (15.5)	1/58 (1.7)	13.8 (5.1, 22.4) *
Level 2 (>2× ULN)	1/35 (2.9)	0/19 (0)	3/68 (4.4)	0/39 (0)	4/103 (3.9)	0/58 (0)	3.9 (-2.5, 9.6)
Level 3 (>3× ULN)	0/35 (0)	0/19 (0)	2/68 (2.9)	0/39 (0)	2/103 (1.9)	0/58 (0)	1.9 (-4.4, 6.8)
Alanine aminotransferase, high (U/L)							
Level 1 (>3× ULN)	1/35 (2.9)	0/19 (0)	1/68 (1.5)	0/39 (0)	2/103 (1.9)	0/58 (0)	1.9 (-4.4, 6.8)
Level 2 (>5× ULN)	1/35 (2.9)	0/19 (0)	0/68 (0)	0/39 (0)	1/103 (1.0)	0/58 (0)	1.0 (-5.3, 5.3)
Level 3 (>10× ULN)	1/35 (2.9)	0/19 (0)	0/68 (0)	0/39 (0)	1/103 (1.0)	0/58 (0)	1.0 (-5.3, 5.3)
Aspartate aminotransferase, high (U/L)							
Level 1 (>3× ULN)	1/35 (2.9)	0/19 (0)	2/68 (2.9)	1/39 (2.6)	3/103 (2.9)	1/58 (1.7)	1.2 (-6.5, 6.8)
Level 2 (>5× ULN)	1/35 (2.9)	0/19 (0)	0/68 (0)	0/39 (0)	1/103 (1.0)	0/58 (0)	1.0 (-5.3, 5.3)
Level 3 (>10× ULN)	0/35 (0)	0/19 (0)	0/68 (0)	0/39 (0)	0/103 (0)	0/58 (0)	0.0 (-6.2, 3.6)
Bilirubin, total, high (mg/dL)							
Level 1 (>1.5× ULN)	9/35 (25.7)	0/19 (0)	11/68 (16.2)	0/39 (0)	20/103 (19.4)	0/58 (0)	19.4 (12.8, 28.1) *
Level 2 (>2× ULN)	3/35 (8.6)	0/19 (0)	6/68 (8.8)	0/39 (0)	9/103 (8.7)	0/58 (0)	8.7 (2.3, 15.8) *
Level 3 (>3× ULN)	1/35 (2.9)	0/19 (0)	2/68 (2.9)	0/39 (0)	3/103 (2.9)	0/58 (0)	2.9 (-3.4, 8.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is up to 128 weeks for the fitusiran group and 36 weeks for the on-demand group.

The revised regimen period is from dose restart Day 1 to data cut off for interim lock and follow-up AT back to 60% whichever comes first.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific evaluation of drug-induced liver injury (DILI), see the figure "Hepatocellular Drug-Induced Liver Injury Screening Plot..."

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AT, antithrombin; AT-DR, antithrombin-based dose regimen; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

17.3. Thrombotic Event Narratives

Subject narratives for thrombotic events are summarized below.

EFC14768, Fitusiran 80 mg QM

1. Subject (b) (6) was a 17-year-old with hemophilia B with inhibitors and a relevant history of pancreatic insufficiency, malabsorption syndrome, prior central catheter infections, and prior deep venous thrombosis of the right upper extremity, who presented on Day 63 with an SAE of **deep vein thrombosis, subclavian vein thrombosis and superficial thrombophlebitis** (PTs). The subject had a recent catheter-device-related infection that occurred on Day 57, which required hospitalization, removal of both an indwelling port and a right-sided PICC line, and extended intravenous antibiotic therapy. The thrombotic event occurred during the hospitalization for the catheter-device infection and extended the hospitalization. The thrombotic event was in the anatomical location of the recent PICC catheter, and imaging showed occlusive thrombus in the right brachial vein, chronic nonocclusive thrombus in the right subclavian vein, and right axillary occlusive thrombus. Fitusiran was continued and the subject completed the study treatment period, with the last dose of fitusiran 80 mg SC QM occurring on Day 239. The clinical review team considers that while there were many ongoing risk factors for DVT, fitusiran likely contributed to the risk of this event.
2. Subject (b) (6) was a 19-year-old who experienced an SAE of **thrombosis (suspected spinal vessel thrombosis)** on Day 204. The subject had a history of hemophilia A with inhibitors. He presented with right hand and bilateral thigh numbness, which progressed to right hand weakness and bilateral leg weakness, requiring aids for ambulation. On Day 228, MRI of the lumbar spine showed nonspecific C6/C7 spinal cord hyperintensity with mild cord expansion, but did not show explicit evidence of hematoma, acute spinal infarct or spinal artery thrombosis, or spinal tumor. A whole-spine MRI showed a focal area of T2 hyperintensity within the spinal cord, centered at C7, consistent with an area of myelopathy. Differential diagnosis included cord ischemia or demyelination. An angiogram was not performed. The subject was treated with antithrombin concentrates on Days 255 and 256, and then on Days 302 to 306. Neurological findings improved gradually over 2 to 3 months following administration of antithrombin concentrates. Fitusiran was stopped, with last dose given (80 mg QM) on Day 204. The review team considers that the most consistent imaging findings were of spinal cord ischemia, and while the nature of the underlying spinal cord process (whether primary thrombotic, infectious or inflammatory) is unclear, vascular insufficiency appears to have played a role. Features of this case suggesting that fitusiran was related were that the symptoms resolved over time without other treatment than fitusiran withdrawal and as antithrombin levels recovered to the normal range, and that vascular insufficiency due to thrombosis is compatible with fitusiran's mechanism of action.

EFC15110, Fitusiran Dose 80 mg QM

1. Subject (b) (6) was a 36-year-old male with a history of hemophilia A without inhibitors, prior deep vein thrombosis, obesity, hypertension, hyperlipidemia, tobacco use, and diabetes mellitus who experienced the SAE of **cerebrovascular accident**. On Day 160 of fitusiran dosing, the subject presented with left-sided paralysis, and imaging showed lesions in the right basal ganglia and corona radiata. A CT angiogram showed occlusion of the M1 division of the right middle cerebral artery. The last dose of fitusiran (80 mg QM) was given on Day 146, and fitusiran was discontinued. The clinical review team recognizes that the subject had many vascular risk factors, but fitusiran contribution is likely.
2. Subject (b) (6) was a 56-year-old male with HA with inhibitors and a history of hypertension and renal calculi, who experienced the SAE of **thrombosis, papilla** of left eye on Day 257. He presented on Day 247 with 95% sudden loss of vision in his left eye, associated with fatigue, headache, and dizziness. MRI did not show vascular or other lesions. Carotid ultrasounds showed a calcified plaque at the right carotid bulb. Eight days later, the subject presented to a neurologist and exam confirmed severe loss of vision and papilledema of the left eye. Prednisolone was started. Three days later, cranial MR venography did not reveal cerebral sinus thrombosis. The neurologist concluded that the episode was due to capillary occlusion of the left papilla, on Day 257. The subject received the last dose of fitusiran on Day 170 (80 mg QM) and remains with vision loss. The review team considers that this acute painful visual loss associated with papilledema likely represents a microvascular arterial or venous thrombotic event, and given the mechanism of action, fitusiran likely contributed.

LTE14762: Fitusiran Dose 80 mg QM

Subject (b) (6) was a 25-year-old White male with hemophilia A without inhibitors who experienced cerebral venous sinus thrombosis that resulted in a fatal outcome (originally reported as PT subarachnoid hemorrhage). The subject narrative can be found in Section [7.5.2.2](#).

LTE15174: Fitusiran dose 80 mg QM

Subject LTE15174 (b) (6) was a 62-year-old with hemophilia A without inhibitors with a past medical history of hepatitis C, prostate cancer post radical prostatectomy 3 years earlier, HIV infection, and bronchiectasis, who experienced a cerebral artery embolism on Day 436. The subject presented with aphasia. MRI showed numerous small infarcts involving the left middle cerebral artery territory with absent flow in the M2 branch. Fitusiran was discontinued. The subject improved but did not fully recover neurologic deficits. The review team considers that while the subject had cardiovascular risk factors of HIV, prior cancer, and bronchiectasis, fitusiran, due to its mechanism of action, is a contributing factor to the cerebral artery aneurysm.

LTE15174: Fitusiran Dose 50 mg Q2M

1. Subject (b) (6) was a 13-year-old male with hemophilia B with inhibitors who experienced a serious TEAE of **venous thrombosis**. Of note, per-protocol TEAEs that occurred during the perioperative period of a major surgery were not considered SAEs. The subject had a prior history of deep venous thrombosis of the vena cava and subclavian vein thrombosis, thrombectomy, and venous angioplasty. On Day 687, he presented with pain in the left upper extremity, and ultrasound of the extremity revealed venous thrombosis of the left axillary, brachial and basilic veins. The event of venous thrombosis was considered serious because it required another admission to the hospital. Of note, the subject had recently undergone right inguinal hernia repair (Day 682), which was complicated by an incision site hematoma that required incision and drainage and drain placement. The subject was treated with argatroban and by Day 690 recovered from both the venous thrombosis and incision hematoma revision and was discharged. The subject continued to receive fitusiran. The clinical review team's assessment is that while the subject was at increased risk of venous thrombosis due to recent hernia surgery with incisional hematoma and revision, and prior venous thrombotic events in the same anatomic region, fitusiran likely increased venous thrombosis risk.
2. Subject (b) (6) was a 40-year-old male with HA who permanently discontinued fitusiran due to the AE of **deep vein thrombosis postoperative**. See subject narrative in Section [7.6.1](#).
3. Subject (b) (6) permanently discontinued after the AE of **cerebral infarction**. See subject narrative in Section [7.6.1](#).
4. Subject (b) (6) was a 54-year-old male with hemophilia who experienced an SAE of **embolic stroke**. The subject narrative can be found in Section [7.6.1](#).

17.4. Acute Gallbladder Events

[Table 164](#) shows the demographic features, fitusiran dosing, and gallbladder AEs in the 12 subjects who underwent cholecystectomy in the fitusiran development program. Most cholecystectomies were performed while subjects were receiving non-AT-DR dose regimens, although one subject had transitioned to AT-DR dosing 589 days before cholecystectomy, and another developed cholangitis and pancreatitis while on AT-DR dosing 889 days after cholecystectomy.

Table 164. Cholecystectomy Events, Studies LTE14762, EFC14768, EFC14769, EFC11510, and LTE15174

Subject ID	Study	Age (Years)/ SAE Fitusiran Dose (Fitusiran exposure day)	AE (Fitusiran Exposure Day)	Cholecystectomy (Fitusiran Exposure Day)
(b) (6)	LTE14762	40/ Cholecystitis (261) Fixed Dose 50 QM ^a Cholecystitis (437)	Cholecystitis (150) Cholecystitis (268)	Day 1025
	LTE14762	28/ Gastritis (298) Fixed Dose 50 QM Cholecystitis (298)	ALT >3× ULN (1430) ALT >3× ULN (1570)	Day 621
	14768	50/ Cholecystitis Chronic (139) Fixed Dose 80 QM Cholangitis (1030) ^b	Cholecystitis (85) Transaminase increase (115)	Day 141
	LTE15174	37/ Fixed Dose 80 QM originally; AT-DR 20 Q2M at cholecystectomy	Cholelithiasis (140) Cholelithiasis (244) Cholelithiasis (1035)	Day 1035
	14769	68/ Cholelithiasis (89) Fixed Dose 80 QM		Day 92
	LTE15174	27/ Cholelithiasis (108) Fixed Dose 80 QM Cholelithiasis (223)	Transaminase increase (109) ALT increase (110) Abdominal pain, upper (173) Biliary dyskinesia (231)	Day 329
	15110	21/ Biliary neoplasm (42) Fixed Dose 80 QM CRP increased (61)	Cholecystitis Chronic (41) ALT increase (48) Cholelithiasis (74) ^c	Day 57
	15110	31/ Cholelithiasis (146) Fixed Dose 80 QM	ALT increase (55) Cholelithiasis (106) Cholecystitis (146)	Day 146
	LTE15174	30/ Cholelithiasis (226) Fixed Dose 80 QM	Cholecystitis (84) Cholecystitis (133)	Day 523
	LTE15174	31/ Cholecystitis (162) Fixed Dose 80 QM	Hyperplastic cholecystopathy (162) AST increased (1127)	Day 415
	LTE15174	52/ Large intestine polyp (99) Fixed Dose 80 QM Cholecystitis chronic (258)	ALT increased (113)	Day 259

NDA 219019
QFITLIA (fitusiran)

Subject ID	Study	Age (Years)/ SAE Fitusiran Dose (Fitusiran exposure day)	AE (Fitusiran Exposure Day)	Cholecystectomy (Fitusiran Exposure Day)
(b) (6)	LTE15174	33/ Fixed Dose 80 QM	Biliary dyskinesia (231)	Day 329

Source: Clinical reviewer

^a Discontinued Fitusiran exposure day 857, 168 days before cholecystectomy

^b Experienced SAE of obstructive cholangitis 889 days after cholecystectomy

^c Experienced cholelithiasis 17 days after cholecystectomy

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LTE, long-term extension; QM, once monthly; SAE, serious adverse event; ULN, upper limit of normal

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

See Section [5.1](#) for mechanism of action of the drug. Drug resistance is not applicable.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A clinical inspection summary was completed by the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations with a final signature date of November 11, 2024. Two clinical investigators, Drs. Savita Rangarajan (India) and Chur-Woo You (South Korea), were inspected.

The Office of Scientific Investigations concluded that, based on the inspections, the study data derived from these clinical sites are considered reliable and are acceptable and that the study data submitted to the Agency for assessment appears acceptable in support of the proposed indication.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 165](#)). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 165. Key Labeling Changes and Considerations

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant's Draft PI
BOXED WARNING	Added Boxed Warning to describe the risks of Thrombotic Events and Acute and Recurrent Gallbladder Disease. These risks are considered crucial for prescribing decisions. Patients developed thrombosis who did not follow bleeding management guidelines on the prescribed dose, so it is important for providers to be aware of this prior to prescribing. In addition, one patient on the 80 mg dose died due to thrombosis. For acute gallbladder disease, a significant proportion of patients developed cholelithiasis/cholecystitis resulting in surgery, and one patient had a complication of pancreatitis. It is important for providers to be aware of this risk prior to prescribing the drug to ensure prompt diagnosis/intervention. In addition, patients with a history of symptomatic gallbladder disease may want to consider alternative therapies.
1 INDICATIONS AND USAGE	Revised "adolescent" to "pediatric" patients and specified the ages of 12 years and over for clarity and per the Pediatric Use guidance.
2 DOSAGE AND ADMINISTRATION	2.1 Added AT activity monitoring recommendations as determined by the FDA-cleared text. Trough AT levels should be monitored at Weeks 4, 12, and 20, which coincide with trough AT levels. 2.2 Revised Table 1 by adding a column for "dosage modification" to reduce the risk of dosing errors. Added Missed Dose instructions. 2.3 Added new subsection to describe Bleed Management. Added "use during surgical interventions."
4 CONTRAINDICATIONS	n/a
5 WARNINGS AND PRECAUTIONS	5.1 Thrombotic Events-Revised to include situations that increase the risk of these events and to clarify mitigating strategies. 5.2. Added a new W&P for Acute and Recurrent Gallbladder Disease (to 5.2 as it's in the Boxed Warning) to describe this serious risk, monitoring recommendations, and mitigation strategies. 5.3 Renamed (b) (4) to "hepatotoxicity" to more accurately describe the risk. Revised the risk in consultation with the DILI team. Mitigating strategies added. Revised (b) (4) and replaced with "avoid use in patients with moderate to severe hepatic impairment." Deleted (b) (4) as none were reported and no basis was provided.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	Added a description of the safety population used in the W&P section [not the same as 6]. Added a description of the exposure for the safety populations. Rounded adverse reaction (AR) rates to whole integer per Adverse Reactions Guidance. Added a description of the serious ARs, ARs leading to permanent discontinuation, ARs leading to dosage interruption, and revised most common ARs list to be c/w changes to Common AR table. (b) (4) . Applied OND Custom Medical Queries to avoid splitting AR terms that are likely to be the same/similar event. Listed the definitions of the grouped terms that were not near-synonyms or synonyms.
7 DRUG INTERACTIONS	Revised proposed Drug Interactions for Concomitant Use of CFC and BPA to explain the basis of the risk.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 and 8.3 Revised to be consistent with the PLLR Guidance. Added the basis of the advice to avoid using hormonal contraceptives. 8.4 Revised to be c/w Pediatric Use Guidance. Added the basis of the pediatric indication. 8.6 Revised to be c/w Geriatric Use Guidance.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	Section omitted as no overdosage information available.
12 CLINICAL PHARMACOLOGY	12.1 Revised to describe the main MoA. 12.2 Revised to be c/w Clin Pharm Labeling Guidance.
13 NONCLINICAL TOXICOLOGY	Revised to provide more detail on carcinogenicity results.
14 CLINICAL STUDIES	Reorganized this section to move description of the studies earlier. Deleted (b) (4) (b) (4) We added a description to explain the efficacy analysis. We describe the demographics of each study, not the extension study. The CDx assay (INNOVANCE) was used during this specific trial, therefore, the specific mention of the device name is appropriate to include here. (b) (4) (b) (4)
17 PATIENT COUNSELING INFORMATION	Revised to reflect changes to FPI (add new W&P, dosage instructions). Removed text regarding (b) (4) (b) (4) (b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	11 Included a description of key physical properties of the drug substance (e.g., appearance, solution pH, solubility). 16 Revised the storage statement for Prefilled Pen as follows, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light."

Source: [Please provide a source for this table.]

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviations: AR, adverse reaction; AT, antithrombin; AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CDx, companion diagnostic; CFC, clotting factor concentrate; c/w, consistent with; DILI, drug-induced liver injury; FPI, full prescribing information; MedDRA, Medical Dictionary for Regulatory Activities; MoA, mechanism of action; OND, Office of New Drugs; PI, Prescribing Information; PLLR, Pregnancy and Lactation Labeling Rule; PRO, patient-reported outcome; SAP, statistical analysis plan; W&P, warning and precaution

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information (PI)
- Medication Guide (MG)
- Instructions for Use for 50 mg Pen (IFU)
- Instructions for Use for 20 mg Vial (IFU)

24. Postmarketing Requirements and Commitments

No postmarketing requirements or postmarketing commitments are recommended.

25. Financial Disclosure

Table 166. Covered Clinical Studies: EFC14768 (ATLAS-INH, ALN-AT3SC-003), EFC14769 (ATLAS-AB, ALN-AT3SC-004), EFC15110 (ATLAS-PPX, ALN-AT3SC-009), and LTE15174 (ALN-AT3SC-005)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 411		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Published Literature

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Guidances for Industry

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

ICH harmonised guideline *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* (November 2016)

Guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Prescribing Information

Prescribing Information: ONPATTRO- patisiran injection, lipid complex. Alnylam Pharmaceuticals. 2023a. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=e87ec36f-b4b4-49d4-aea4-d4ffb09b0970&type=pdf>.

Prescribing Information: OXLUMO- lumasiran injection, solution. Alnylam Pharmaceuticals. 2023b. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=16985a31-f5e4-4557-9266-fc78d4bc5055&type=pdf>.

Prescribing Information: AMVUTTRA- vutrisiran injection. Alnylam Pharmaceuticals. 2024a. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=8db0facb-81b6-4006-9239-27dc6409c5d3&type=pdf>.

Prescribing Information: GIVLAARI- givosiran sodium injection, solution. Alnylam Pharmaceuticals. 2024b. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=167e663c-11e1-497b-a3fc-951d65d58eaa&type=pdf>.

Prescribing Information: HEMLIBRA- emicizumab injection, solution. Genentech. 2024. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=2483adba-fab6-4d1b-96c5-c195577ed071&type=pdf>.

Prescribing Information: LEQVIO- inclisiran injection, solution. Novartis Pharmaceuticals Corporation. 2024. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=6fc0afca-4513-4c35-b594-6544aee29a44&type=pdf>.

Prescribing Information: Alhemo (concizumab-mtci) injection, for subcutaneous use. Novo Nordisk. 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761315s0001bl.pdf.

Prescribing Information: HYMPAVZI- marstacimab-hncq injection, solution. Pfizer Laboratories Div Pfizer Inc. 2025. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=a2cc631e-13a6-40c2-acf9-065ccedfb90a&type=pdf>.

27. Review Team

Table 167. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Bijal Patel
Nonclinical reviewer	Ramadevi Gudi
Nonclinical team leader	Pedro Del Valle
OCP reviewer(s)	Tian Zhou, Yuan Ye
OCP team leader(s)	Sudharshan Hariharan, Jiang Liu
Clinical reviewer	Donna Whyte-Stewart
	Alison Moliterno
Clinical team leader	Carrie Diamond
Biometrics reviewer	Xiaoyu Cai
	Xiaoyan Yin
Biometrics team leader	Yeh-Fong Chen
Cross-discipline team leader	Carrie Diamond
Division director (pharm/tox)	Todd Bourcier
Division director (OCP)	Shirley Seo
Division director (OB)	Yeh-Fong Chen
Deputy Division director (clinical)	Tanya Wroblewski
Office director (or designated signatory authority)	Hylton Joffe

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 168. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Daniel Jansen, Zhengfu Wang, Monica Cooper, Mohan Sapru, Carl Lee, Rose Xu, Sarah Davis, Neal Sweeney Theodore Carver
OPDP	
OSI	Anthony Orendia
OSE/DEPI	Steve Bird
OSE/DMEPA	Shabana Rauf, Millie Shah
OSE/DRISK	Sarah Brant (Katie), Jacqueline Sheppard
DMPP	Susan Redwood, Barbara Fuller
Other	N/A

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-169 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Lola Luo OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lola Luo Digitally signed by Lola Luo Date: 3/27/2025 1:53 PM EDT GUID: 2025327175347				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Theodore Carver OPQAI DPQAI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Theodore Carver Digitally signed by Theodore Carver Date: 3/27/2025 1:54 PM EDT GUID: 2025327175442				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Carrie Diamond OCHEN DNH	Sections: all	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Carrie Diamond		Digitally signed by Carrie Diamond Date: 3/27/2025 2:00 PM EDT GUID: 202532718042		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Secondary Reviewer	Pedro Delvalle OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Pedro Delvalle		Digitally signed by Pedro Delvalle Date: 3/27/2025 2:01 PM EDT GUID: 202532718111		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Ramadevi Gudi OCHEN DPTCHEN	Sections: 5,7,8, and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ramadevi Gudi Digitally signed by Ramadevi Gudi Date: 3/27/2025 2:06 PM EDT GUID: 202532718646				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Xiaoyan Yin OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xiaoyan Yin Digitally signed by Xiaoyan Yin Date: 3/27/2025 2:08 PM EDT GUID: 20253271882				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore Digitally signed by Calvin Elmore Date: 3/27/2025 2:39 PM EDT GUID: 2025327183918				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Microbiology (OPQ) Discipline Secondary Reviewer	Neal Sweeney OPMA DPMAI	Sections: 9. Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Neal Sweeney Digitally signed by Neal Sweeney Date: 3/27/2025 3:08 PM EDT GUID: 20253271984				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Reviewer	Alison Moliterno OCHEN DNH	Sections: Section 3, 3.1, 3.2; Section 7; Section 17	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Alison Moliterno Digitally signed by Alison Moliterno Date: 3/27/2025 5:14 PM EDT GUID: 2025327211437				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Associate Director	Jiang Liu OCP DPM	Sections: 2, 5, 6, 7, 8, 14	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jiang Liu Digitally signed by Jiang Liu Date: 3/28/2025 8:29 AM EDT GUID: 202532812293				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Xiaoyu Cai OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xiaoyu Cai		Digitally signed by Xiaoyu Cai Date: 3/28/2025 9:45 AM EDT GUID: 2025328134513		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Xiaoyu Cai OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xiaoyu Cai		Digitally signed by Xiaoyu Cai Date: 3/28/2025 9:46 AM EDT GUID: 2025328134611		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Tian Zhou OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tian Zhou		Digitally signed by Tian Zhou Date: 3/28/2025 11:09 AM EDT GUID: 202532815959		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Bijal Patel ORO DROCHEN	Sections: Section 12: Regulatory History	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Bijal Patel		Digitally signed by Bijal Patel Date: 3/28/2025 11:11 AM EDT GUID: 2025328151139		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Sejal Kiani ORO DROCHEN	Sections: Section 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sejal Kiani Digitally signed by Sejal Kiani Date: 3/28/2025 11:17 AM EDT GUID: 2025328151730				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Daphney Jean ODES DCOA	Sections: 6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Daphney Jean Digitally signed by Daphney Jean Date: 3/28/2025 11:17 AM EDT GUID: 2025328151757				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Donna Whyte-Stewart OCHEN DNH	Sections: 3, 6, 15, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Donna Whyte-Stewart Digitally signed by Donna Whyte-Stewart Date: 3/28/2025 11:21 AM EDT GUID: 2025328152156				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Donna Whyte-Stewart OCHEN DNH	Sections: 3, 6, 15, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Donna Whyte-Stewart Digitally signed by Donna Whyte-Stewart Date: 3/28/2025 11:22 AM EDT GUID: 2025328152233				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Microbiology (OPQ) Discipline Primary Reviewer	Sarah Davis OPMA DPMIAI	Sections: 9. Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sarah Davis		Digitally signed by Sarah Davis Date: 3/28/2025 11:32 AM EDT GUID: 2025328153227		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sudharshan Hariharan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sudharshan Hariharan		Digitally signed by Sudharshan Hariharan Date: 3/28/2025 11:58 AM EDT GUID: 2025328155824		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Yuan Shen OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuan Shen Digitally signed by Yuan Shen Sign on behalf of Yuan-Li Shen Date: 3/28/2025 12:14 PM EDT GUID: 2025328161438				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Selena Daniels ODES DCOA	Sections: 4, 16.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Selena Daniels Digitally signed by Selena Daniels Date: 3/28/2025 12:14 PM EDT GUID: 2025328161448				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Ye Yuan OCP DPM	Sections: 6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ye Yuan Digitally signed by Ye Yuan Date: 3/28/2025 12:29 PM EDT GUID: 2025328162926				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Theodore Carver OPQAI DPQAI	Sections: 9, 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Theodore Carver Digitally signed by Theodore Carver Date: 3/28/2025 12:39 PM EDT GUID: 2025328163915				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE E DIAMOND
03/28/2025 12:41:53 PM

TANYA M WROBLEWSKI
03/28/2025 12:54:22 PM

HYLTON V JOFFE
03/28/2025 12:57:45 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*: NDA 219019 (IND 125632)
Supporting Document Number/s: 0001
CDER Receipt Date: March 28, 2024
Applicant: Genzyme Corporation, A Sanofi Company
Product: Fitusiran
Pharmacologic Class: Antithrombin-directed small interfering
ribonucleic acid (siRNA)
Indication: Hemophilia A or B with or without factor VIII
or IX inhibitors.
Therapeutic area: Hematology
Clinical Review Division: Division of Non-Malignant Hematology
(DNH)
Pharm/Tox Division: Division of Pharm/Tox for Cardiology,
Hematology, Endocrinology, and Nephrology
(DPT-CHEN)
Reviewer: Ramadevi Gudi, PhD
Team Leader: Pedro DelValle, PhD, Fellow ATS
Project Manager: Bijal R. Patel, MS
Purpose of Review: Study Report Review
Carcinogenicity Study Final Reports
Reviewer Completion Date: August 7, 2024

Template Version: Sep 11, 2020

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Nonclinical Summary

Fitusiran (AD-57213 or ALN-AT3SC) is a chemically synthesized double strand small interfering RNA (siRNA) covalently bound to a triantennary Nacetylgalactosamine ligand (GalNAc) that specifically targets AT messenger RNA to lower production of AT in the liver. Targeting AT mRNA, fitusiran enhances thrombin generation potential and rebalance hemostasis in patients with hemophilia.

The Sponsor submitted final reports for carcinogenicity studies of fitusiran

1. A 26-week study in TgRasH2 mouse [study-at3-glp17-001.pdf](#),
2. A 2-year study in rats [study-car0186.pdf](#).

The mouse and rat tumor data were analyzed by FDA statistician Dr. Hepei Chen [Statistical Review IND 125632 NDA 219019](#).

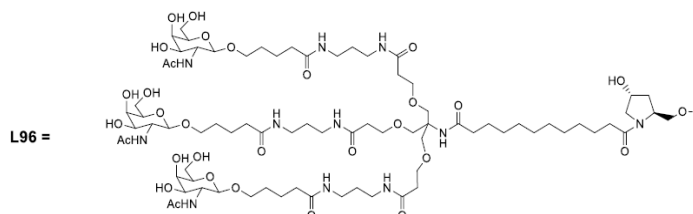
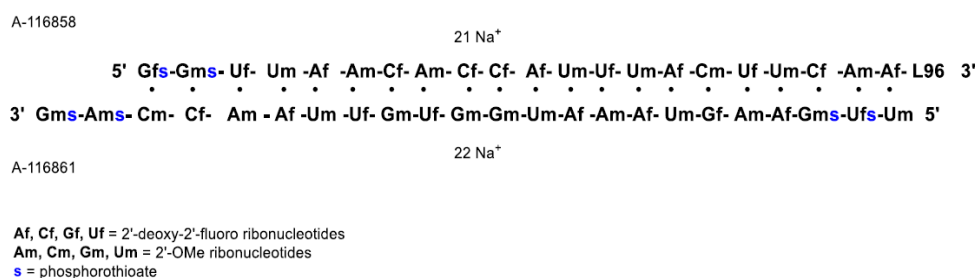
In both studies, fitusiran was administered by subcutaneous injection once weekly. In the mouse study, TgRasH2 mice (n=25/sex/group) were administered fitusiran doses of 0 (0.9 % sodium chloride), 0.05, 0.15, or 0.5 mg/kg/week in males and 0 (0.9 % sodium chloride), 0.025, 0.08, 0.25 mg/kg/week in females. In addition, a positive control group of male and female TgRasH2 mice received a single, intraperitoneal dose of 75 mg/kg N-methyl-N-nitrosourea (MNU) on Day 1. In the rat study, Sprague-Dawley rats were administered fitusiran doses of 0 (0.9% Sodium Chloride), 0.03, 0.1 or 0.3 mg/kg/week in males, and 0 (0.9% Sodium Chloride), 0.1, 0.3 or 1 mg/kg/week in females.

The percent survival in fitusiran treated male and female mice was >96 and 100%, respectively; survival for the mouse vehicle control groups was 96%. Fitusiran was not carcinogenic in mice based on dose response-wise or pairwise comparison analysis conducted by both the Sponsor and the FDA statistical analysis. The positive control group showed statistically significant increased mortality and increases in malignant tumors compared to the vehicle control group. On Day 183, the C_{max} values at 0.5 mg/kg/week and 0.25 mg/kg/week were 24.3 ng/mL and 16.8 ng/mL, respectively, and AUC_{0-t} values were 70.9 ng·h/mL and 28.7 ng·h/mL, respectively. The mouse to human exposure multiples is <1-fold the MRHD based on AUC.

The percent survival in fitusiran treated male and female rats was >25% and >35%, respectively; survival for the vehicle control male and female rats was 33%, respectively. Fitusiran was not carcinogenic in rats based on dose response-wise or pairwise comparison analysis conducted by both the Sponsor and the FDA statistical analysis. On Day 176, in males, the C_{max} and AUC_{0-t} values at 0.3 mg/kg/week were 91.1 ng/mL and 163 ng·h/mL, respectively. In females, the C_{max} and AUC_{0-t} values at 1 mg/kg/week were 190 ng/mL and 372 ng·h/mL, respectively. The rat to human exposure multiples is 1-2-fold the MRHD based on AUC.

Drug Information⁺

Type of Product:	Synthetic small interfering RNA (siRNA)
Code/ Generic Name:	SAR439774, ALN-57213, AD-57213, ALN-AT3SC / Fitusiran
Chemical Name (optional):	There are 3 acceptable conventions for fitusiran: (1) The oligonucleotide chemical name (2) Abbreviated single letter nucleotide code (3) Abbreviated 3 letter nucleotide code
CAS# or UNII (if available):	CAS:1609016-97-8 UNII: Click here to enter text.

Structure or Biochemical Description:**Molecular Formula/ Molecular Weight:**

	Fitusiran (Duplex)	Sense strand (SS)	Antisense strand (AS)
Molecular formula sodium salt	C ₅₂₀ H ₁₆₃₆ F ₂₁ N ₁₇₅ Na ₄₃ O ₃₀₉ P ₄₃ S ₆	C ₂₈₅ H ₃₆₉ F ₁₂ N ₈₅ Na ₂₁ O ₁₆₄ P ₂₁ S ₂	C ₂₃₅ H ₂₆₇ F ₉ N ₈₀ Na ₂₂ O ₁₄₅ P ₂₂ S ₄
Molecular formula free acid	C ₅₂₀ H ₁₆₇₉ F ₂₁ N ₁₇₅ O ₃₀₉ P ₄₃ S ₆	C ₂₈₅ H ₃₉₀ F ₁₂ N ₈₅ O ₁₆₄ P ₂₁ S ₂	C ₂₃₅ H ₂₈₉ F ₉ N ₈₀ O ₁₄₅ P ₂₂ S ₄
Molecular weight sodium salt	17193 Da	9035 Da	8159 Da
Molecular weight free acid	16248 Da	8573 Da	7675 Da

8 Carcinogenicity

8.1 Study Title⁺:

Study no.:	AT3-GLP17-001
Study report location:	4.2.3.4.1
Study initiation date:	February 7, 2017
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	ALN-57213, Lot # P07916, 98.5% (100 mg/mL)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	HD based on body weight decrements in the 28-day dose range findings study; LD and MD based on acceptable intervals.

Reviewer Carcinogenicity Conclusion (negative/positive): Negative

ECAC Carcinogenicity Conclusion: Negative

Tumor Findings:

- There were no fitusiran-related statistically significant increase in the incidence of any neoplasm in RasH2 mice.
- There was no statistically significant dose response relationship and pairwise comparisons in mortality in male or female RasH2 mice.
- The mouse to human exposure multiples is <1-fold (adjusted to bimonthly dosing) at the MRHD based on AUC.
- Positive control, N-Methyl-N-Nitrosourea (MNU) significantly increased incidences of malignant squamous cell carcinoma and papilloma of the stomach in male and female RasH2 mice relative to control. There was a statistically significant higher mortality rate (15/25 males, 17/25 females) for positive control related to tumor findings.

Methods

Doses:	Doses: 0 (0.9 % sodium chloride) Fitusiran doses: Males = 0.05, 0.15, or 0.5 mg/kg/week Females = 0.025, 0.08, 0.25 mg/kg/week Positive control= MNU 75 mg/kg/day
Frequency of dosing:	Vehicle and Fitusiran: Once weekly MNU, Day 1
Number/Sex/Group:	25/Sex/Group for the Main study; 4 or 20/sex/group, for control and fitusiran treatment groups, respectively for toxicokinetic study
Dose volume:	10 mL/kg
Formulation/Vehicle:	Vehicle for fitusiran: 0.9% sodium chloride <u>Vehicle for Positive control (MNU):</u> citrate-buffered saline (pH 4.5)
Route of administration:	SUBCUTANEOUS (fitusiran), Intraperitoneal (MNU)
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	9 weeks old
Comment on Study Design and Conduct:	Toxicokinetic group was included in the study design
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments or early termination occurred.
Dosing Solution Analysis:	Formulation analysis showed concentration verification values were within the specified range except some concentrations on Week 2, 3, 5, 26 and 27 at 0.005, 0.0025, 0.008 mg/mL were within 20% less of the nominal concentrations. These discrepancies were not considered to impact the study outcome.

Study Design

Group No.		No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/week)	
Male	Female	Male	Female		Male	Female
1	1	25	25	Vehicle control	0	0
2	5	25	25	ALN-AT3SC Low	0.05	0.025
3	6	25	25	ALN-AT3SC Mid	0.15	0.08
4	7	25	25	ALN-AT3SC High	0.5	0.25
8	8	25	25	Positive control (MNU)	75 mg/kg	75 mg/kg

Toxicokinetic group included 4 or 20/sex/group, for control and fitusiran treatment groups, respectively.

Anti-drug-antibody measurement 5/sex/group for control and Fitusiran dose groups

N-methyl-N-nitrosourea (MNU) was injected (IP) once at the beginning of the study.

Observations and Results

Mortality

There was no statistically significant dose response relationship and pairwise comparisons in mortality in male or female mice at all groups except for the positive control animals according to the statistical analysis by the FDA statistician.

Table 1: Summary of Unscheduled Deaths in male and female mice

	Control (Vehicle)	LD	MD	HD	Positive control
Male	1 (4%)	0 (0%)	1 (4%)	1 (4%)	15 (60%)
Female	1 (4%)	0 (0%)	0 (0%)	0 (0%)	17 (68%)

LD, MD, and HD= fitusiran 0.05, 0.15, 0.5 mg/kg/week to males and 0.025, 0.08, and 0.25 mg/kg/week to females, respectively

Source: Reviewer's analysis from data submitted to AT3-GLP17-001

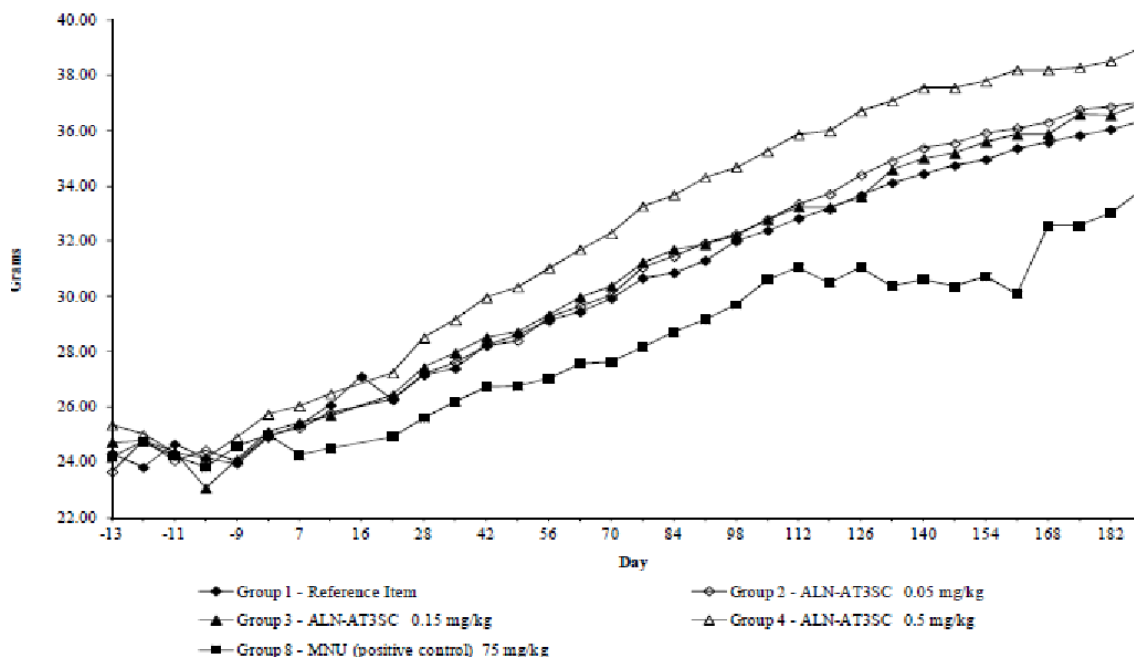
Clinical Signs

There were no fitusiran-related clinical signs observed at any dose.

Body Weights and Food Consumption

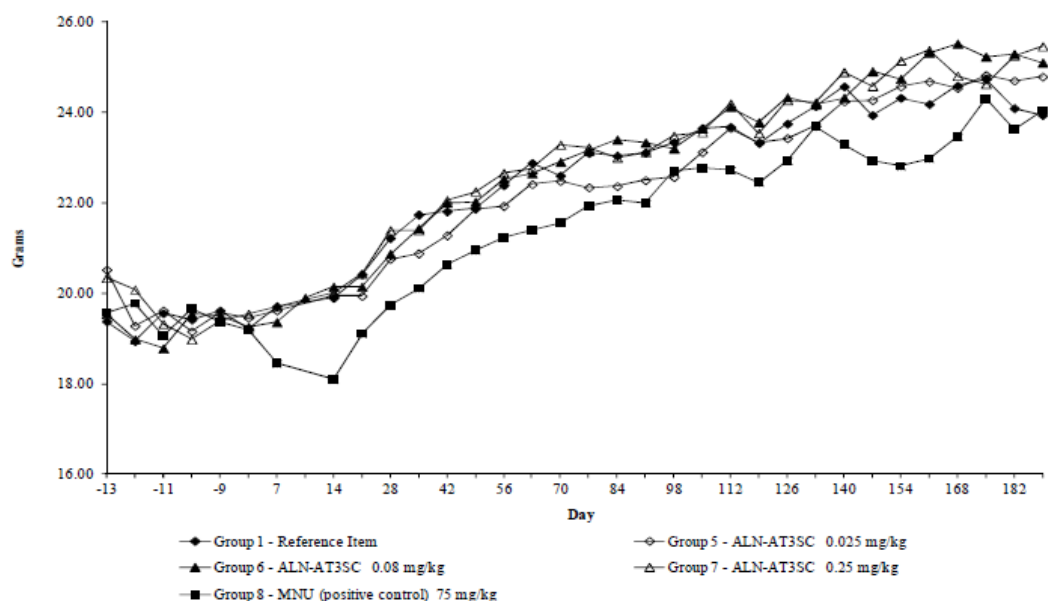
No-fitusiran related decrements in body weights, or food consumption occurred at any dose.

Figure 1: Summary Body Weights in Male Mice



Source: Excerpted from data submitted to study report AT3-GLP17-001

Figure 21: Summary Body Weights in Female Mice



Source: Excerpted from data submitted to study report AT3-GLP17-001

Gross Pathology

There were no fitusiran-related macroscopic findings observed. A low incidence of raised focus, nodules and/or mass observed in the stomach of control or fitusiran administered mice at all dose levels that generally correlated with squamous or glandular hyperplasia. All findings were generally consistent with the usual findings in the strain of Rash2 Tg/WT mice of this age.

Table 2: Summary of Gross Pathology in TgRash2 Mice

	Males					Females				
Dose (mg/kg/week)	0 ^a	0.05	0.15	0.5	75 ^b	0 ^a	0.025	0.08	0.25	75 ^b
Number of mice examined	25	25	25	25	25	25	25	25	25	25
Stomach										
Focus; raised	1	0	0	2	2	0	0	1	0	5
Nodule	0	1	0	0	12	0	1	1	1	10
Mass	0	0	0	2	6	1	1	0	1	2

^a Saline

^b N-Methyl-N-Nitrosourea (MNU) administered on Day 1 only; positive control

Source: Reviewer's analysis from data submitted to AT3-GLP17-001

Histopathology

Peer Review Conducted: Yes ((b) (4))
 Historical Control Provided for Tumor Incidence: Yes

The percentage of carcinoma + adenomas in the lungs lacked dose-response relationship with administration of fitusiran. These tumors are considered spontaneous

and/or incidental with low incidence rate and/or consistent with the tumor profile known for RasH2 Tg/WT mice of this age (Paranjpe et al 2013; Paranjpe et al 2019; Nambiar et al 2012). On the contrary, splenic hemangiosarcomas were observed only in fitusiran-treated mice and the incidence slightly exceeds the maximum range for this tumor type in the historical control data of the Test Facility. Based on the absence of a dose-relationship, these tumors were considered incidental in origin. No statistically significant dose-response relationship and pairwise comparisons in tumor data was noted in the FDA statistical analysis for both male and female mice.

Neoplastic

Table 3: Neoplastic Findings from Scheduled and Unscheduled Necropsies

	Males					Females				
Dose (mg/kg/week)	0 ^a	0.05	0.15	0.5	75 ^b	0 ^a	0.025	0.08	0.25	75 ^b
Number of mice examined	25	25	25	25	25	25	25	25	25	25
LUNG										
Bronchioloalveolar carcinoma	1	0	1	0	0	0	0	0	0	2
Bronchioloalveolar adenoma	4	4	2	3	5	1	1	1	2	3
Adenoma + carcinoma Number of mice / (%)	5 (20)	4 (16)	3 (12)	3 (12)	5 (20)	1 (4)	1 (4)	1 (4)	2 (8)	5 (20)
SPLEEN										
Hemangiosarcoma	0	1	0	2	0	0	2	2	0	0

^a Saline

^b Positive control N-Methyl-N-Nitrosourea (MNU) administered on Day 1 only; positive control

Source: Reviewer's analysis from data submitted to AT3-GLP17-001

Non-Neoplastic

Stomach: Increased incidence of mixed cell infiltration and increased severity in hyperplasia of squamous mucosa was observed in male and female fitusiran-treated mice.

Table 4: Non-Neoplastic Findings from Scheduled and Unscheduled Necropsies

	Males					Females				
Dose (mg/kg/week)	0 ^a	0.05	0.15	0.5	75 ^b	0 ^a	0.025	0.08	0.25	75 ^b
Number of mice examined	25	25	25	25	25	25	25	25	25	25
Stomach										
Infiltration, mixed cell										
minimal	2	4	5	5	1	9	3	5	6	0
mild	1	0	0	1	0	0	0	0	3	0
Hyperplasia; squamous mucosa										
minimal	1	0	0	0	1	0	0	0	0	0

mild	0	0	0	0	3	1	0	0	0	1
moderate	0	1	0	1	2	0	0	0	2	1

^a Saline^b N-Methyl-N-Nitrosourea (MNU) administered on Day 1 only; positive control

Source: Reviewer's analysis from data submitted to AT3-GLP17-001

Toxicokinetics

AUC values were not determined for LD and MD males and LD and HD females on Day 1 and LD males and LD and HD in females on Day 183 because of insufficient measurable blood quantities. As a result, TK interpretation is only being performed on Day 183 results. Exposure on Day 183, as assessed by fitusiran C_{max} values, the increases were generally greater than dose proportional from MD to HD, and in females, they were generally less than dose proportional from LD to MD and greater than dose proportional from MD to HD.

Table 6: Mean Plasma Toxicokinetic Parameters of Fitusiran in hemizygous TgRasH2 mice on Days 1 and 183

Interval (Day)	Dose Group	Dose Level (mg/kg)	Sex	C _{max} (µg/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*µg/mL)	AUC _{0-∞} (h*µg/mL)
1	2	0.05	M	0.00458	0.3	NR	NR
	3	0.15		0.00536	1.0	NR	NR
	4	0.5		0.00334	8.0	0.0380	0.00724
	5	0.025	F	0.000974	0.3	NR	NR
	6	0.08		0.00813	0.3	0.0549	0.0295
	7	0.25		0.0152	0.3	NR	NR
183	2	0.05	M	0.00133	0.3	NR	NR
	3	0.15		0.00683	0.3	0.0675	0.0343
	4	0.5		0.0243	0.3	0.0709	0.0632
	5	0.025	F	0.00154	0.3	NR	NR
	6	0.08		0.00294	1.0	0.0422	0.0205
	7	0.25		0.0168	0.3	NR	0.0287

NR: Not reported due to insufficient measurable concentrations within a profile.

The lower limit of quantitation for concentration analysis was < 0.200 ng/mL.

Source: Excerpted from data submitted to study report AT3-GLP17-001

8.1 Study Title⁺: ALN-AT3SC: A 2-Year Subcutaneous Injection Carcinogenicity Study in Rats

Study no.:	CAR0186
Study report location:	4.2.3.4.1
Study initiation date:	February 7, 2017
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	ALN-57213, Lot # P07916, 98.5% (100 mg/mL)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	HD of 0.3 in males and 1 mg/kg for females based on mortality due to hemorrhagic thrombosis at 1 mg/kg in males and at 3 mg/kg in females. The mid and low doses were selected based on AUC values.

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative**ECAC Carcinogenicity Conclusion (negative/ positive): Negative****Tumor Findings:**

- There were no dose-dependent or statistically significant fitusiran-related neoplastic findings noted in both male and female SD rats.
- The survival rate in fitusiran-treated groups was comparable to control groups.
- The rat to human exposure multiples is 1-2-fold (adjusted based on bimonthly dosing) at the MRHD based on AUC.

Methods

Doses:	Doses: 0 (0.9% Sodium Chloride) Fitusiran doses: Males = 0.03, 0.1 or 0.3 mg/kg/week Females = 0.1, 0.3 or 1 mg/kg/week
Frequency of dosing:	Once weekly
Number/Sex/Group:	60/Sex/Group for the Main study; 4 or 10/sex/group, for control and fitusiran treatment groups, respectively for toxicokinetic study
Dose volume:	2 mL/kg
Formulation/Vehicle:	0.9% Sodium Chloride
Route of administration:	SUBCUTANEOUS
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age:	8 weeks old
Comment on Study Design and Conduct:	Toxicokinetic group was included in the study design
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments or early termination occurred.
Dosing Solution Analysis:	Formulation analysis showed concentration verification values were within the specified range except some concentrations on Week 1 and 5 (0.015 mg/mL), 34 (0.015, 0.05, 0.15, 0.5 mg/mL), 66 (0.5 mg/mL) and 98 (0.05 and 0.15 mg/mL). These discrepancies were not considered to impact the study outcome.

Observations and Results**Mortality**

There were several unscheduled deaths in males and females at all doses including control groups. There was no statistically significant dose response relationship in mortality compared to control groups. Two deaths, one male at MD (0.1 mg/kg/week) and one female at HD (1 mg/kg/week) were related to fitusiran based on necrosis in the brain, associated with the presence of thrombi. Although the frequency is within or slightly higher than the laboratory historical control data, based on the mechanism of action, the deaths are considered related to fitusiran. FDA statistical analysis of survival rate concurred that there was no statistically significant dose-response relationship or pairwise comparisons in mortality for both male and female rats.

Table 7: Summary of Unscheduled Deaths in Rats

	Control (Vehicle)	LD	MD	HD
Male	40 (67%)	45 (75%)	45 (75%)	42 (70%)
Female	40 (67%)	33 (55%)	39 (65%)	34 (57%)

LD, MD, and HD= fitusiran 0.03, 0.1, 0.3 mg/kg/week to males and 0.1, 0.3, 1 mg/kg/week to females, respectively

Due to increased mortality in males receiving 0.03 and 0.1 mg/kg/week all surviving male animals in these dose groups were euthanized during Week 94 and Week 98, respectively, of the study. Due to increased mortality in male and female rats receiving vehicle control (Group 1), all surviving female rats and males receiving 0.3 mg/kg/week were euthanized during Week 93 and Weeks 98/99, respectively of the study. Early termination of all groups in this study was considered to have no impact on the assessment of carcinogenic potential because the number of animals evaluated, and the study duration were consistent with FDA guidances.

Source: Reviewer's analysis of the data submitted to the study report Car0186

The neoplasms observed in unscheduled deaths included mainly pituitary adenoma of the pars distalis in males and females and neoplasms of the mammary gland in females across all groups, commonly encountered neoplasms in rats of this strain and age range. There were no other neoplasms observed unique to fitusiran at any dose group.

Table 8: Common Cause of Death/Moribundity in Preterminal Decedent Animals

Group Dose Level (mg/kg/week)	Males				Females			
	1 0	2 0.03	3 0.1	4 0.3	1 0	5 0.1	6 0.3	7 1
Number of rats examined	40	45	45	42	40	33	39	34
Undetermined	7	14	8	13	4	0	4	1
Accidental (including gavage accident)	0	2	0	0	0	0	0	0
Neoplastic:								
Pituitary gland adenoma, pars distalis	23	21	20	11	22	22	19	17
Pituitary gland carcinoma, pars distalis	1	0	2	0	2	3	4	3
Mammary gland fibroadenoma	0	0	0	1	4	6	3	3
Mammary gland adenocarcinoma	0	0	0	0	3	1	4	4
Hemolymphoid neoplasia	2	2	1	2	2	0	1	1
Skin/Subcutis, fibrosarcoma	1	0	1	3	2	1	1	1
Other neoplastic change	3	5	6	7	1	0	2	2
Non-neoplastic:								
Joint, inflammation, mixed cell	1	0	1	1	0	0	0	1
Other non-neoplastic change	2	1	6	4	0	0	1	1

Source: Source: Excerpted from data submitted to study report Car0186

Clinical Signs

There were no fitusiran-related clinical observations at any dose level.

Body Weights and Food Consumption

There were no fitusiran-related effects on mean body weights or body weight gains, and food consumption.

Gross Pathology

There were no fitusiran-related macroscopic findings observed. There were gross findings in multiple organs that lacked dose response and the incidences were similar across fitusiran treated animals when compared to controls.

Histopathology

Peer Review Conducted: Yes ((b) (4))

Historical Control Provided for Tumor Incidence: Yes

Neoplastic

Neoplastic findings were noted in various tissues including control and fitusiran treated animals. Findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in terminal control and treated animals and, therefore, these findings were considered unrelated to the administration of fitusiran. The Applicant concluded fitusiran was not carcinogenic in Sprague-Dawley rats following weekly subcutaneous injection at ≤ 0.3 mg/kg/week in males and ≤ 1 mg/kg/week in females.

The FDA statistical analysis confirmed there were no statistically significant dose response relationship or pairwise comparisons noted in tumor data for male and female rats.

Table 9: Neoplastic Findings in Terminal Rats

Dose (mg/kg/week)	0 (Control)		0.03	0.1		0.3		1
Sex	M	F	M	M	F	M	F	F
No. of animals examined	20	20	15	15	27	18	21	26
Brain								
Astrocytoma, Malignant	1	0	1	1	1	0	1	1
Granular Cell Tumor, Malignant	0	0	0	1	0	0	0	0
Meningioma, Malignant	0	0	0	1	0	0	0	0
Oligodendroglioma, Malignant	0	0	1	1	0	0	0	0
Gland, Adrenal								
Cortical Adenoma	2	4	2	0	3	3	8	2
Cortical Carcinoma	-	0	-	-	1	-	1	0
Cortical Adenoma/ Cortical Carcinoma	-	4	-	-	4	-	9	2
Pheochromocytoma, Benign	2	2	2	4	0	4	1	1
Pheochromocytoma, Malignant	0	0	0	3	1	1	0	0
Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	2	2	2	7	1	5	1	1
Cervix								
Granular Cell Tumor, Benign	NA	0	NA	NA	0	NA	3	0
Gland, Mammary								
Adenocarcinoma	-	17	-	-	14	-	20	13
Adenoma	2	7	0	0	4	1	7	4
Adenocarcinoma/Adenoma	-	24	-	-	16	-	24	16

Fibroadenoma	0	31	1	0	37	2	27	34
Sarcoma	-	0	-	-	1	-	1	0
Gland, Parathyroid								
Adenoma	2	1	0	0	0	1	0	0
Gland, Pituitary	38		29	34		19		
Adenoma, Pars Distalis	0	35	0	0	34	1	39	31
Adenoma, Pars Intermedia	1	0	0	2	0	0	0	1
Carcinoma, Pars Distalis	1	3	0	2	6	0	4	5
Adenoma, Pars Distalis/ Adenoma, Pars Intermedia/ Carcinoma, Pars Distalis	39	38	29	36	40	20	43	36
Pituicytoma	0	-	0	1	-	0	-	-
Gland, Salivary, Mandibular								
Schwannoma, Benign	0	-	0	1	-	0	-	-
Gland, Thyroid								
C-Cell Adenoma	5	5	6	9	3	8	4	4
C-Cell Carcinoma	0	1	1	2	0	0	0	2
C-Cell Adenoma/ C-Cell Carcinoma	5	6	7	11	3	8	4	6
Follicular Cell Adenoma	2	0	1	1	2	5	1	3
Follicular Cell Carcinoma	1	-	0	0	-	1	-	-
Follicular Cell Adenoma/ Follicular Cell Carcinoma	3	-	1	1	-	5	-	-
Gland, Zymbals								
Carcinoma	0	-	1	0	-	0	-	-
Heart								
Schwannoma, Benign	0	-	1	0	-	0	-	-
Hemolymphoreticular Tissue								
Histiocytic Sarcoma	2	1	1	1	0	2	0	1
Lymphoma, Malignant	2	2	2	1	1	1	1	2
Kidney								
Amphophilic Vacuolar Tubular Adenoma	0	-	0	1	-	0	-	-
Liposarcoma	0	-	1	0	-	0	-	-
Mesenchymal Tumor, Malignant	0	-	0	0	-	1	-	-
Nephroblastoma, Malignant	-	0	-	-	0	-	0	1
Liver								
Cholangioma	-	1	-	-	0	-	0	0
Hepatocellular Adenoma	3	4	0	1	2	3	0	0
Hepatocellular Carcinoma	0	0	0	1	1	1	0	0
Hepatocellular Adenoma/ Hepatocellular Carcinoma	3	4	0	2	3	4	0	0
Lung								
Bronchioloalveolar Adenoma	0	-	0	1	-	0	-	-
Bronchioloalveolar Carcinoma	0	-	0	0	-	1	-	-
Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	0	-	0	0	-	1	-	-
Mesothelioma, Malignant	1	-	0	0	-	0	-	-
Lymph Node, Mesenteric								
Hemangioma	2	0	1	3	0	1	0	1
Muscle, Skeletal								
Fibrosarcoma	0	-	0	1	-	0	-	-
Nerve, Optic								

Schwannoma, Malignant	1	-	0	0	-	0	-	-
Ovary								
Granulosa Cell Tumor, Benign	NA	0	NA	NA	0	NA	0	1
Mixed Sex Cord Stromal Tumor, Benign	NA	0	NA	NA	0	NA	0	2
Pancreas								
Acinar Adenoma	1	3	-	0	-	1	-	-
Islet Cell Adenoma	4	3	0	3	0	4	0	0
Islet Cell Carcinoma	0	0	2	0	0	0	0	1
Islet Cell Adenoma/ Islet Cell Carcinoma	4	3	2	3	0	4	0	
Site, Injection								
Fibroma	1	-	0	0	-	2	-	-
Skin								
Basal Cell Tumor, Benign	0	0	1	0	0	2	1	0
Basal Cell Tumor, Malignant	1	0	0	0	0	1	0	1
Basal Cell Tumor, Benign/ Basal Cell Tumor, Malignant	1	0	1	0	0	3	1	1
Hair Follicle Tumor, Benign	0	-	0	1	-	0	-	-
Keratoacanthoma	2	-	5	0	-	3	-	-
Squamous Cell Carcinoma	1	-	0	0	-	0	-	-
Keratoacanthoma/ Squamous Cell Carcinoma	3	-	5	0	-	3	-	-
Papilloma	1	2	3	2	0	1	0	1
Sebaceous Cell Adenoma	1	-	1	0	-	2	-	-
Small Intestine, Ileum								
Schwannoma, Malignant	0	-	0	1	-	0	-	-
Small Intestine, Duodenum								
Adenoma	-	1	-	-	0	-	0	0
Spleen								
Hemangiosarcoma	0	-	0	1	-	0	-	-
Subcutis								
Fibroma	5	1	6	2	2	7	0	3
Fibrosarcoma	1	2	0	1	1	3	1	2
Fibroma/Fibrosarcoma	6	3	6	3	3	9	1	5
Histiocytic Sarcoma	0	-	0	1	-	0	-	-
Lipoma	0	1	1	1	0	3	1	1
Liposarcoma	0		1	0		0		
Leiomyosarcoma	-	0	-	-	0	-	0	1
Lipoma/Liposarcoma	0	-	2	1	-	3	-	-
Mesenchymal Tumor, Malignant	0	-	0	0	-	1	-	-
Schwannoma, Benign	0	-	2	0	-	0	-	-
Schwannoma, Malignant	2	-	0	0	-	0	-	-
Schwannoma, Benign/ Schwannoma, Malignant	2	-	2	0	-	0	-	-
Thymus								
Thymoma, Benign	-	0	-	0	-	-	1	1
Thymoma, Malignant	0	-	1	0	-	0	-	-
Urinary Bladder								
Transitional Cell Papilloma	1	-	1	1	-	1	-	-
Uterus								

Endometrial Stromal Polyp	NA	5	NA	NA	2	NA	5	5
Endometrial Stromal Sarcoma	NA	0	NA	NA	0	NA	0	1
Endometrial Stromal Polyp/ Endometrial Stromal Sarcoma	NA	5	NA	NA	2	NA	5	6
Leiomyoma	NA	1	NA	NA	0	NA	0	0
Vagina			NA	NA		NA		
Granular Cell Tumor, Benign	NA	0	NA	NA	1	NA	0	1

“-” no data

NA: not applicable

Source: Reviewer constructed table from Sponsor's submission and Statistical analysis report.

Non-Neoplastic

Toxicokinetics

The lower limit of quantitation for concentration analysis was <4 ng/mL as a result concentration analysis from males administered 0.03 mg/kg/week was not performed. According to the Sponsor, inadequate sampling and insufficient data limited estimations of $T_{1/2}$ and AUC. Exposure, as assessed by fitusiran C_{max} values, increased with the increase in dose level from 0.1 to 0.3 mg/kg/dose for males and from 0.1 to 1 mg/kg/dose for females.

Table 10: Toxicokinetic Parameters of fitusiran in Rat Plasma following Once Weekly SC Week 26 (Day 176)

Dose Level (mg/kg/week)	Sex	C _{max} (µg/mL)	AUC _{0-t} (µg·h/mL)	AUC ₀₋₂ (µg·h/mL)	AUC ₀₋₂₄ (µg·h/mL)
0.03	M	NP	NP	NP	NP
0.1	M	0.0224	0.0568	0.0358	0.0693
	F	0.0209	0.0246	0.0246	NC
	MF	0.0216	0.0500	0.0313	0.0648
0.3	M	0.0911	0.163	0.114	0.180
	F	0.0518	0.112	0.0795	NC
	MF	0.0657	0.139	0.0969	0.154
1	F	0.190	0.372	0.276	0.383

M = Male; F = Female

NP Not performed.

NC Not calculated due to the lack of a distinct elimination phase.

Note: Toxicokinetic analysis was not performed on data obtained from males administered 0.03 mg/kg/week as concentrations were sparsely quantifiable and generally below the limit of quantitation. Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

Source: Excerpted from data submitted to study report Car0186

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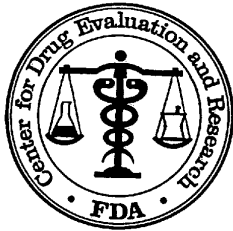
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: IND 125632 / NDA 219019

Drug Name: ALN-AT3SC

Indication: Treatment of Hemophilia A and B

Studies: Carcinogenicity Studies in Rats for 104 weeks and Mice for 26 weeks

Applicant: Study Sponsor for Rat Study:
Sanofi-aventis recherche & développement
1, avenue Pierre Brossolette
91385 Chilly-Mazarin Cedex
France

Study Sponsor for Mouse Study:
Alnylam Pharmaceuticals Inc.
300 Third Street, 3rd Floor
Cambridge, MA 02142
USA

Testing Facility: (b) (4)


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Statistical Reviewer: Dr. Hepei Chen

Medical Division: Division of Pharmacology Toxicology for Cardiology, Hematology,
Endocrinology & Nephrology (DPTCHEN)

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the carcinogenic potential of ALN-AT3SC, when given by subcutaneous injection once weekly for 104 consecutive weeks (total of a 104 doses) to rats, and for 26 weeks (total of 27 doses) to the TgRasH2 hemizygous mouse.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 3, in the experiment there were three treated groups, and one vehicle control group. Two hundred and forty rats of each sex were assigned randomly in size of 60 rats per group. ALN-AT3SC was administered weekly by subcutaneous injection at doses of 0.03, 0.1 or 0.3 mg/kg/week to male rats and 0.1, 0.3 or 1 mg/kg/week to female rats for a total of 104 doses. In this review the three treated groups were referred to as the low, mid, and high dose groups (Group 2, 3, 4 for male rats, and Group 5, 6, and 7 for female rats), respectively. The rats in the vehicle control group (Group 1) were administered with 0.9% Sodium Chloride for injection, USP, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.		No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/week)	
Male	Female	Male	Female		Male	Female
1	1	60	60	Vehicle control	0	0
2	5	60	60	ALN-AT3SC Low	0.03	0.1
3	6	60	60	ALN-AT3SC Mid	0.1	0.3
4	7	60	60	ALN-AT3SC High	0.3	1

Due to the number of survivors, female rats of all groups (Group 1, 5, 6, and 7) and male rats of the low dose group (Group 2) were terminated on week 93/94; male rats of the vehicle control group, and the mid and high dose groups (Group 1, 3 and 4) were terminated on week 98/99.

Evaluations for potential ALN-AT3SC-related effects were based on survival, clinical signs (including presence of palpable masses), body weights, food consumption, hematology parameters, toxicokinetic parameters, macroscopic observations at necropsy, and microscopic examinations. A complete gross pathological examination was performed on all animals, as specified in the Study Plan.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's report, the statistical analyses for mortality Main Study data were performed separately for each sex. The survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals and graphs were produced. Any animal with accidental injury that caused its death or its unscheduled sacrifice, or still alive at the day following the last day of the experimental period were censored in the estimation. The log-rank test was applied to the four groups in order to assess the significance of the overall group effect on mortality data. If this test was found to be significant, then, using dose level scores, the significance of an overall dose-related trend in mortality and pairwise comparisons between the vehicle control group (Group 1) and each of the test item-treated groups (Groups 2, 3, 4, 5, 6 and 7) were evaluated via a Peto's two-sided test (Peto et al., 1980). All statistical tests were conducted at the 5% significance level..

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33%), 15 (25%), 15 (25%), and 18 (30%) in the vehicle control group, the low, mid, and high dose groups for male rats, respectively, and 20 (33%), 27 (45%), 21 (35%), and 26 (43%) for female rats, respectively. There was no ALN-AT3SC-related increase in the incidence of mortalities and no statistically significant changes in mortality.

2.1.2. Tumor data analysis

In the sponsor's analysis, the statistical evaluation of tumor data was done separately for each sex and was limited to subcutis and hemolymphoreticular tissue using all study animals, to all non-secondary neoplastic lesions found in Study Plan-required tissues/sites, and to the combination of hemangiosarcoma findings across whole body. Statistical analyses of histopathological data were conducted according to the requirements specified in the study plan/study plan amendment. Palpable neoplastic lesions found under skin, subcutis, and under Study Plan-required glands were statistically analyzed in a "mortality independent" context according to Peto's onset rate using all study animals. Whereas, non-palpable neoplastic, incidental and fatal findings were statistically analyzed in a "mortality dependent" context according to Peto's prevalence and death rate methods, respectively. For each dataset of interest, Peto's test, using integer dose level scores, was conducted in order to assess significance of tumor rate increase across all groups and in each of Groups 2, 3, 4, 5, 6 and 7 when compared to Group 1.

These multicentric neoplasms were shown as primary tumor only once per animal under the tissue "hemolymphoreticular tissue" in order to present true incidence of the given multicentric neoplasm for each affected animal. The presence of multiple benign tumors of the same type (e.g. several hepatocellular adenomas of the liver located in different lobes) was recorded only once, and the individual locations correlated with gross observations in the individual animal data record.

As per Lin (Lin, 1997), the discrete permutation distribution was used for each statistical test involving a dataset with 10 or less tumor occurrences. All tests were performed at the 5% significance level and, as recommended by the FDA (Guidance for Industry, 2001), are discussed

in the Anatomic Pathology Report according to the tumor prevalence classification (common or rare).

Adjustment for multiple testing:

In the sponsor's report, no specific adjustment for multiple testing was discussed. A tumor type was considered rare if the spontaneous rate was 1% or less based on concurrent control data and historical control data from this facility or reported in the literature, otherwise a tumor type was classified as a common tumor.

Sponsor's findings:

In the sponsor's report, There were no ALN-AT3SC-related neoplastic microscopic findings and no statistical significance for palpable and non-palpable neoplasms.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all four groups (Groups 1, 2, 3, 4 for male rats, and 1, 5, 6, 7 for female rats) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, 4 for male rats, and 1, 5, 6, 7 for female rats using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all four groups in male and female rats, respectively. The intercurrent mortality data of all four groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, 4 for male rats, and 1, 5, 6, 7 for female rats are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33%), 15 (25%), 15 (25%), and 18 (30%) in the vehicle control group, the low, mid, and high dose groups for male rats, respectively, and 20 (33%), 27 (45%), 21 (35%), and 26 (43%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the vehicle control group, and low, mid, and high dose groups, and pairwise comparisons of each of the three treated groups against the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the i -th treatment group R^*_i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the j -th animal in the i -th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the j -th animal in the i -th treatment group, and $tsacr$ is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since $t_{ij} = tsacr$. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij} = 1$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the $tsacr$ should not be affected by the unplanned early terminations. The $tsacr$ should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than $tsacr$, regardless their actual terminal sacrifice time, $tsacr$ was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k , which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data.

Multiple testing adjustment:

For a submission with one two-year study in one species and one short-term study with another species, in order to keep the overall false-positive rate at the nominal level of approximately 10%, as indicated in Table 2, this reviewer used the methodologies suggested in the Expanded Statistical Decision Rules for Interpretations of Results of Rodent Carcinogenicity Studies of Pharmaceuticals by Lin and Rahman (2018).

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this

tumor is considered as the common tumor.

Table 2. Recommended decision rules for controlling the overall false positive rates

	Tests for positive trend alone	Control-high pairwise comparison alone	Tests for positive trend and control-high pairwise comparison jointly
Alternative ICH studies (one two-year study in one species and one short- or medium-term alternative study, two sexes)	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively, in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in the alternative study	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively, in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in the alternative study	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively, in trend test, and at 0.05 and 0.10 significance levels, respectively, in control-high pairwise comparison in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in both trend test and control-high pairwise comparison in the alternative study

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. No statistically significant dose response relationship and pairwise comparisons were noted in tumor data for male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in the experiment there were three treated groups, one vehicle control group, and one positive control group. One hundred and twenty-five TgRasH2 (CByB6F1-Tg(HRAS)2Jic) mice of each sex were assigned randomly in size of 25 mice per group. ALN-AT3SC was administered weekly by subcutaneous injection at doses of 0.05, 0.15, or 0.5 mg/kg/week to male rats, and 0.025, 0.08, 0.25 mg/kg/week to female rats for a total of 27 doses. In this review the three treated groups were referred to as the low, mid, and high dose groups (Group 2, 3, 4 for male rats, and Group 5, 6, and 7 for female rats), respectively. The mice in the vehicle control group (Group 1) were administered once weekly by subcutaneous injection at 0.9% sodium chloride for injection, and handled for the same duration and in the same manner as the treated groups. The positive control group (Group 8) received a single intraperitoneal dose of MNU (N-Methyl-N-Nitrosurea) on Day 1 at 75 mg/kg.

Table 3: Experimental Design in Mouse Study

Group No.		No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/week)	
Male	Female	Male	Female		Male	Female
1	1	25	25	Vehicle control	0	0
2	5	25	25	ALN-AT3SC Low	0.05	0.025
3	6	25	25	ALN-AT3SC Mid	0.15	0.08
4	7	25	25	ALN-AT3SC High	0.5	0.25
8	8	25	25	Positive control (MNU)	75 mg/kg	75 mg/kg

The same clinical examinations, laboratory investigations and pathology procedures used in the rat study were performed in the mouse study.

3.1. Sponsor's analyses

Because the mouse study was conducted by the same testing facility as the rat study, the sponsor used the same methodologies that were used for the analyses of the rat survival and tumor data.

3.1.1. Survival analysis

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), 24 (96%), and 10 (40%) in the vehicle control group, the low, mid, and high dose groups, and the positive control group for male mice, respectively, and 24 (96%), 25 (100%), 25 (100%), 25 (100%), and 8 (32%) for female mice respectively. For both male and female mice, there were no statistically significant differences in the incidence of mortality amongst the groups.

3.1.2. Tumor data analysis

Multiple testing adjustment:

The same multiple testing adjustment used in the rat study was used in the mouse study.

Sponsor's findings:

In the sponsor's report, for both male and female mice, the pairwise comparisons between the positive control group and the vehicle control group showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected. No other statistically significant findings were noted in tumor data for male and female mice.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), 24 (96%), and 10 (40%) in the vehicle control group, the low, mid, and high dose groups, and the positive control group for male mice, respectively, and 24 (96%), 25 (100%), 25 (100%), 25 (100%), and 8 (32%) for female mice respectively. No statistically significant dose response relationship and pairwise comparisons was noted in mortality for both male and female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and 4B in the appendix for male and female mice, respectively. For both male and female mice, the pairwise comparisons between the positive control group and the vehicle control group showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected. No statistically significant dose response relationship and pairwise comparisons in tumor data was noted in the reviewer's analysis for both male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the carcinogenic potential of ALN-AT3SC, when given by subcutaneous injection once weekly for 104 consecutive weeks (total of a 104 doses) to rats, and for 26 weeks (total of 27 doses) to the TgRasH2 hemizygous mouse.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of the experiments, there were three treated groups, and one vehicle control group. Two hundred and forty rats of each sex were assigned randomly in size of 60 rats per group. ALN-AT3SC was administered weekly by subcutaneous injection at doses of 0 (vehicle control), 0.03, 0.1 or 0.3 mg/kg/week to male rats and 0 (vehicle control), 0.1, 0.3 or 1 mg/kg/week to female rats, respectively. The rats in the vehicle control group (Group 1) were administered with 0.9%

Sodium Chloride for injection, USP, and handled for the same duration and in the same manner as the treated groups.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33%), 15 (25%), 15 (25%), and 18 (30%) in the vehicle control group, the low, mid, and high dose groups for male rats, respectively, and 20 (33%), 27 (45%), 21 (35%), and 26 (43%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

In the reviewer's analysis, no statistically significant dose response relationship and pairwise comparisons were noted in tumor data for male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of the experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and twenty-five TgRasH2 (CByB6F1-Tg(HRAS)2Jic) mice of each sex were assigned randomly in size of 25 mice per group. ALN-AT3SC was administered weekly by subcutaneous injection at doses of 0.05, 0.15, or 0.5 mg/kg/week to male rats, and 0.025, 0.08, 0.25 mg/kg/week to female rats for a total of 27 doses. The mice in the vehicle control group (Group 1) were administered once weekly by subcutaneous injection at 0.9% sodium chloride for injection, and handled for the same duration and in the same manner as the treated groups. The positive control group (Group 8) received a single intraperitoneal dose of MNU (N-Methyl-N-Nitrosurea) on Day 1 at 75 mg/kg.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), 24 (96%), and 10 (40%) in the vehicle control group, the low, mid, and high dose groups, and the positive control group for male mice, respectively, and 24 (96%), 25 (100%), 25 (100%), 25 (100%), and 8 (32%) for female mice respectively. No statistically significant finding was noted in mortality for both male and female mice.

In the reviewer's analysis, for both male and female mice, the pairwise comparisons between the positive control group and the vehicle control group showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected. No statistically significant dose response relationship and pairwise comparisons in tumor data was noted in the reviewer's analysis for both male and female mice.

Dr. Hepei Chen.
Mathematical Statistician

Cc: Archival IND 125632 / NDA 219019
Dr. Ramadevi Gudi

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	0 mg/kg/week Vehicle Control		0.1 mg/kg/week Low		0.3 mg/kg/week Mid		1 mg/kg/week High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	6.67	4	6.67	5	8.33	5	8.33
53 - 78	15	31.67	21	41.67	19	40.00	12	28.33
79 - 91	14	55.00	16	68.33	15	65.00	17	56.67
92 - 99	7	66.67	2	71.67	6	75.00	8	70.00
Accidental Death			2	3.33				
Terminal sacrifice	20	33.33	15	25.00	15	25.00	18	30.00
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.7195		0.0816		0.2458		0.6900	
Homogeneity (Log-Rank)	0.3095		0.0762		0.2397		0.6863	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	0 mg/kg/week Vehicle Control		0.03 mg/kg/week Low		0.1 mg/kg/week Mid		0.3 mg/kg/week High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	1	1.67	1	1.67	2	3.33	4	6.67
53 - 78	21	36.67	14	25.00	17	31.67	17	35.00
79 - 91	13	58.33	18	55.00	19	63.33	10	51.67
92 - 93	5	66.67			1	65.00	3	56.67
Terminal sacrifice	20	33.33	27	45.00	21	35.00	26	43.33
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.6912		0.2290		0.9691		0.4400	
Homogeneity (Log-Rank)	0.5569		0.2225		0.9686		0.4339	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.1 mg Low (L) P - VC vs. L	0.3 mg Mid (M) P - VC vs. M	1 mg High (H) P - VC vs. H
Body Cavity, Nasal	Schwannoma, Malignant	1/60 (35) 0.7200	0/60 (27) 0.4355	0/60 (30) 0.4615	0/60 (33) 0.4853
Brain	Astrocytoma, Malignant	1/60 (34) 0.7397	1/60 (28) 0.7033	1/60 (31) 0.7303	0/60 (33) 0.4925
	Granular Cell Tumor, Malignant	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
	Meningioma, Malignant	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
	Oligodendroglioma, Malignant	0/60 (34) 0.5199	1/60 (27) 0.4426	1/60 (31) 0.4769	0/60 (33) NC
Gland, Adrenal	Cortical Adenoma	2/60 (35) 0.2832	2/60 (28) 0.6044	0/60 (30) 0.7139	3/60 (34) 0.4860
	Pheochromocytoma, Benign	2/60 (35) 0.2099	2/60 (28) 0.6044	4/60 (31) 0.2796	4/60 (34) 0.3226
	Pheochromocytoma, Malignant	0/60 (34) 0.2994	0/60 (27) NC	3/60 (31) 0.1029	1/60 (33) 0.4925
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	2/60 (35) 0.1433	2/60 (28) 0.6044	7/60 (32) 0.0561	5/60 (34) 0.2021
Gland, Mammary	Adenoma	2/49 (26) 0.5803	0/48 (22) 0.7119	0/46 (22) 0.7119	1/52 (28) 0.5283
	Fibroadenoma	0/49 (26) 0.1356	1/48 (23) 0.4694	0/46 (22) NC	2/52 (29) 0.2734
Gland, Parathyroid	Adenoma	0/55 (31) 0.5372	1/56 (26) 0.4561	1/57 (29) 0.4833	0/59 (33) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.1 mg Low (L) P - VC vs. L	0.3 mg Mid (M) P - VC vs. M	1 mg High (H) P - VC vs. H
Gland, Pituitary	Adenoma, Pars Distalis	38/60 (51) 0.9980	29/60 (42) 0.6385	34/60 (47) 0.5062	19/60 (41) 0.9947
	Adenoma, Pars Intermedia	0/60 (34) 0.2661	0/60 (27) NC	0/60 (30) NC	1/60 (33) 0.4925
	Carcinoma, Pars Distalis	1/60 (35) 0.6530	0/60 (27) 0.4355	2/60 (32) 0.4659	0/60 (33) 0.4853
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia/ Carcinoma, Pars Distalis	39/60 (52) 0.9977	29/60 (42) 0.6598	36/60 (48) NC	20/60 (42) 0.9941
	Pituicytoma	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
Gland, Salivary, Mandibular	Schwannoma, Benign	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
Gland, Thyroid	C-Cell Adenoma	5/60 (36) 0.2369	6/60 (30) 0.3684	9/60 (34) 0.1548	8/60 (35) 0.2519
	C-Cell Carcinoma	0/60 (34) 0.6189	1/60 (27) 0.4426	2/60 (31) 0.2236	0/60 (33) NC
	C-Cell Adenoma/ C-Cell Carcinoma	5/60 (36) 0.2981	7/60 (30) 0.2509	11/60 (35) 0.0683	8/60 (35) 0.2519
	Follicular Cell Adenoma	2/60 (35) 0.1109	1/60 (27) 0.4022	1/60 (31) 0.4539	4/60 (34) 0.3226
	Follicular Cell Carcinoma	1/60 (34) 0.4630	0/60 (27) 0.4426	0/60 (30) 0.4688	1/60 (33) 0.7463
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	3/60 (35) 0.0925	1/60 (27) 0.5894	1/60 (31) 0.6458	5/60 (34) 0.3382
Gland, Zymbals	Carcinoma	0/60 (34) 0.2720	0/60 (27) NC	0/60 (30) NC	1/60 (34) 0.5000
Heart	Schwannoma, Benign	0/60 (34) 0.5081	1/60 (27) 0.4426	0/60 (30) NC	0/60 (33) NC
Hemolymphoreticular Tissue	Histiocytic Sarcoma	2/60 (35) 0.4172	1/60 (28) 0.4157	1/60 (31) 0.4539	2/60 (33) 0.6705
	Lymphoma, Malignant	2/60 (35) 0.7140	2/60 (29) 0.6189	1/60 (31) 0.4539	1/60 (34) 0.4890

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.1 mg Low (L) P - VC vs. L	0.3 mg Mid (M) P - VC vs. M	1 mg High (H) P - VC vs. H
Kidney	Amphophilic Vacuolar Tubular Adenoma	0/60 (34)	0/60 (27)	1/60 (31)	0/60 (33)
		0.2640	NC	0.4769	NC
	Liposarcoma	0/60 (34)	1/60 (28)	0/60 (30)	0/60 (33)
		0.5040	0.4516	NC	NC
	Mesenchymal Tumor, Malignant	0/60 (34)	0/60 (27)	0/60 (30)	1/60 (34)
		0.2720	NC	NC	0.5000
Liver	Hepatocellular Adenoma	3/60 (36)	0/60 (27)	1/60 (31)	3/60 (34)
		0.2493	0.8202	0.6344	0.6354
	Hepatocellular Carcinoma	0/60 (34)	0/60 (27)	1/60 (31)	1/60 (33)
		0.2001	NC	0.4769	0.4925
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	3/60 (36)	0/60 (27)	2/60 (31)	4/60 (34)
		0.1317	0.8202	0.4281	0.4673
Lung	Bronchioloalveolar Adenoma	0/60 (34)	0/60 (27)	1/60 (31)	0/60 (33)
		0.2640	NC	0.4769	NC
	Bronchioloalveolar Carcinoma	0/60 (34)	0/60 (27)	0/60 (30)	1/60 (33)
		0.2661	NC	NC	0.4925
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	0/60 (34)	0/60 (27)	1/60 (31)	1/60 (33)
		0.2001	NC	0.4769	0.4925
Lymph Node, Mesenteric	Mesothelioma, Malignant	1/60 (35)	0/60 (27)	0/60 (30)	0/60 (33)
		0.7200	0.4355	0.4615	0.4853
	Hemangioma	2/60 (35)	1/60 (27)	3/60 (31)	1/60 (33)
		0.6334	0.4022	0.4415	0.4776
	Fibrosarcoma	0/60 (34)	0/60 (27)	1/60 (31)	0/60 (33)
		0.2640	NC	0.4769	NC
Nerve, Optic	Schwannoma, Malignant	1/60 (35)	0/60 (27)	0/59 (30)	0/60 (33)
		0.7200	0.4355	0.4615	0.4853
Pancreas	Acinar Adenoma	1/60 (35)	0/60 (27)	0/60 (30)	1/60 (33)
		0.4599	0.4355	0.4615	0.7388
	Islet Cell Adenoma	4/60 (35)	0/60 (27)	3/60 (31)	4/60 (34)
		0.2308	0.9061	0.4307	0.6286
	Islet Cell Carcinoma	0/60 (34)	2/60 (28)	0/60 (30)	0/60 (33)
		0.7560	0.1999	NC	NC
	Islet Cell Adenoma/ Islet Cell Carcinoma	4/60 (35)	2/60 (28)	3/60 (31)	4/60 (34)
		0.3843	0.5510	0.4307	0.6286

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.1 mg Low (L) P - VC vs. L	0.3 mg Mid (M) P - VC vs. M	1 mg High (H) P - VC vs. H
Site, Injection	Fibroma	1/60 (34) 0.1725	0/60 (27) 0.4426	0/60 (30) 0.4688	2/60 (33) 0.4886
Skin	Basal Cell Tumor, Benign	0/60 (34) 0.1146	1/60 (27) 0.4426	0/60 (30) NC	2/60 (33) 0.2388
	Basal Cell Tumor, Malignant	1/60 (34) 0.4630	0/60 (27) 0.4426	0/60 (30) 0.4688	1/60 (33) 0.7463
	Basal Cell Tumor, Benign/ Basal Cell Tumor, Malignant	1/60 (34) 0.1032	1/60 (27) 0.6934	0/60 (30) 0.4688	3/60 (33) 0.2954
	Hair Follicle Tumor, Benign	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
	Keratoacanthoma	2/60 (35) 0.5292	5/60 (29) 0.1430	0/60 (30) 0.7139	3/60 (33) 0.4716
	Squamous Cell Carcinoma	1/60 (35) 0.7200	0/60 (27) 0.4355	0/60 (30) 0.4615	0/60 (33) 0.4853
	Keratoacanthoma/ Squamous Cell Carcinoma	3/60 (35) 0.6356	5/60 (29) 0.2528	0/60 (30) 0.8502	3/60 (33) 0.6347
	Papilloma	1/60 (34) 0.6883	3/60 (28) 0.2364	2/60 (31) 0.4649	1/60 (33) 0.7463
	Sebaceous Cell Adenoma	1/60 (34) 0.2562	1/60 (27) 0.6934	0/60 (30) 0.4688	2/60 (33) 0.4886
	Schwannoma, Malignant	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC
	Hemangiosarcoma	0/60 (34) 0.2640	0/60 (27) NC	1/60 (31) 0.4769	0/60 (33) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.1 mg Low (L) P - VC vs. L	0.3 mg Mid (M) P - VC vs. M	1 mg High (H) P - VC vs. H
Subcutis	Fibroma	5/12 (10)	6/11 (9)	2/8 (5)	7/22 (16)
		0.7534	0.3950	0.4266	0.4640
	Fibrosarcoma	1/12 (9)	0/11 (6)	1/8 (6)	3/22 (16)
		0.2326	0.4000	0.6571	0.5423
	Fibroma/Fibrosarcoma	6/12 (11)	6/11 (9)	3/8 (6)	9/22 (17)
		0.6241	0.4650	0.3733	0.3800
	Histiocytic Sarcoma	0/12 (8)	0/11 (6)	1/8 (5)	0/22 (14)
		0.4242	NC	0.3846	NC
	Lipoma	0/12 (8)	1/11 (6)	1/8 (5)	3/22 (14)
		0.1499	0.4286	0.3846	0.2364
	Liposarcoma	0/12 (8)	1/11 (6)	0/8 (5)	0/22 (14)
		0.5758	0.4286	NC	NC
	Lipoma/Liposarcoma	0/12 (8)	2/11 (6)	1/8 (5)	3/22 (14)
		0.2655	0.1648	0.3846	0.2364
	Mesenchymal Tumor, Malignant	0/12 (8)	0/11 (6)	0/8 (5)	1/22 (14)
		0.4242	NC	NC	0.6364
	Schwannoma, Benign	0/12 (8)	2/11 (6)	0/8 (5)	0/22 (14)
		0.8277	0.1648	NC	NC
	Schwannoma, Malignant	2/12 (9)	0/11 (6)	0/8 (5)	0/22 (14)
		0.9358	0.6571	0.6044	0.8577
	Schwannoma, Benign/ Schwannoma, Malignant	2/12 (9)	2/11 (6)	0/8 (5)	0/22 (14)
		0.9748	0.5385	0.6044	0.8577
Testis	Interstitial (Leydig) Cell Adenoma	0/60 (34)	1/60 (27)	0/60 (30)	1/60 (33)
		0.3159	0.4426	NC	0.4925
Thymus	Thymoma, Malignant	0/60 (34)	1/59 (27)	0/59 (30)	0/60 (33)
		0.5081	0.4426	NC	NC
Urinary Bladder	Transitional Cell Papilloma	1/60 (34)	1/60 (27)	1/60 (31)	1/60 (33)
		0.4330	0.6934	0.7303	0.7463

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.03 mg Low (L) P - VC vs. L	0.1 mg Mid (M) P - VC vs. M	0.3 mg High (H) P - VC vs. H
Brain	Astrocytoma, Malignant	0/60 (31) 0.2991	1/60 (33) 0.5156	1/60 (31) 0.5000	1/60 (32) 0.5079
Cervix	Granular Cell Tumor, Benign	0/60 (31) 0.5748	0/60 (33) NC	3/60 (31) 0.1189	0/60 (31) NC
Gland, Adrenal	Cortical Adenoma	4/60 (32) 0.7675	3/60 (34) 0.5347	8/60 (34) 0.2007	2/60 (32) 0.6641
	Cortical Carcinoma	0/60 (31) 0.4921	1/60 (33) 0.5156	1/60 (31) 0.5000	0/60 (31) NC
	Cortical Adenoma/ Cortical Carcinoma	4/60 (32) 0.8134	4/60 (34) 0.3896	9/60 (34) 0.1319	2/60 (32) 0.6641
	Pheochromocytoma, Benign	2/60 (32) 0.5014	0/60 (33) 0.7615	1/60 (31) 0.4879	1/60 (31) 0.4879
	Pheochromocytoma, Malignant	0/60 (31) 0.4880	1/60 (33) 0.5156	0/60 (30) NC	0/60 (31) NC
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	2/60 (32) 0.5971	1/60 (33) 0.5117	1/60 (31) 0.4879	1/60 (31) 0.4879
	Adenocarcinoma	17/60 (40) 0.6997	14/60 (39) 0.6442	20/60 (40) 0.3271	13/60 (37) 0.6654
	Adenoma	7/60 (34) 0.7200	4/60 (35) 0.7606	7/60 (33) 0.5932	4/60 (33) 0.7265
Gland, Mammary	Adenocarcinoma/Adenoma	24/60 (43) 0.8203	16/60 (40) 0.8890	24/60 (42) 0.5379	16/60 (39) 0.8680
	Fibroadenoma	31/60 (44) 0.3748	37/60 (48) 0.3134	27/60 (42) 0.6481	34/60 (45) 0.3809
	Sarcoma	0/60 (31) 0.4921	1/60 (33) 0.5156	1/60 (31) 0.5000	0/60 (31) NC
Gland, Parathyroid	Adenoma	1/59 (31) 0.7480	0/57 (31) 0.5000	0/60 (30) 0.4918	0/60 (31) 0.5000
Gland, Pituitary	Adenoma, Pars Distalis	35/60 (50) 0.5346	34/60 (50) 0.5000	39/60 (50) 0.2473	31/59 (45) 0.4586
	Adenoma, Pars Intermedia	0/60 (31) 0.2419	0/60 (33) NC	0/60 (30) NC	1/59 (30) 0.4918
	Carcinoma, Pars Distalis	3/60 (33) 0.3601	6/60 (35) 0.2689	4/60 (33) 0.5000	5/59 (33) 0.3542
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia/ Carcinoma, Pars Distalis	38/60 (51) 0.5507	40/60 (52) 0.4776	43/60 (52) 0.2201	36/59 (48) 0.5699

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.03 mg Low (L) P - VC vs. L	0.1 mg Mid (M) P - VC vs. M	0.3 mg High (H) P - VC vs. H
Gland, Thyroid	C-Cell Adenoma	5/60 (33)	3/60 (34)	4/60 (32)	4/60 (33)
		0.4941	0.6626	0.4798	0.5000
	C-Cell Carcinoma	1/60 (31)	0/60 (33)	0/60 (30)	2/60 (31)
		0.1517	0.5156	0.4918	0.5000
	C-Cell Adenoma/ C-Cell Carcinoma	6/60 (33)	3/60 (34)	4/60 (32)	6/60 (33)
		0.2960	0.7770	0.6133	NC
	Follicular Cell Adenoma	0/60 (31)	2/60 (33)	1/60 (31)	3/60 (32)
		0.0835	0.2619	0.5000	0.1249
Hemolymphoreticular Tissue	Histiocytic Sarcoma	1/60 (31)	0/60 (33)	0/60 (30)	1/60 (31)
		0.4360	0.5156	0.4918	NC
	Lymphoma, Malignant	2/60 (32)	1/60 (33)	1/60 (31)	2/60 (31)
		0.3841	0.5117	0.4879	0.6815
Kidney	Nephroblastoma, Malignant	0/60 (31)	0/60 (33)	0/60 (30)	1/60 (32)
		0.2540	NC	NC	0.5079
Liver	Cholangioma	1/60 (31)	0/60 (33)	0/60 (30)	0/60 (31)
		0.7520	0.5156	0.4918	0.5000
	Hepatocellular Adenoma	4/60 (32)	2/60 (34)	0/60 (30)	0/60 (31)
		0.9946	0.6926	0.9355	0.9396
	Hepatocellular Carcinoma	0/60 (31)	1/60 (33)	0/60 (30)	0/60 (31)
		0.4880	0.5156	NC	NC
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	4/60 (32)	3/60 (34)	0/60 (30)	0/60 (31)
		0.9956	0.5347	0.9355	0.9396
Lymph Node, Mesenteric	Hemangioma	0/60 (31)	0/60 (33)	0/60 (30)	1/60 (31)
		0.2480	NC	NC	0.5000
Ovary	Granulosa Cell Tumor, Benign	0/60 (31)	0/60 (33)	0/60 (30)	1/60 (31)
		0.2480	NC	NC	0.5000
	Mixed Sex Cord Stromal Tumor, Benign	0/60 (31)	0/60 (33)	0/60 (30)	2/60 (31)
		0.0600	NC	NC	0.2459
Pancreas	Islet Cell Adenoma	3/60 (32)	0/60 (33)	0/60 (30)	0/60 (31)
		0.9848	0.8864	0.8689	0.8751
	Islet Cell Carcinoma	0/60 (31)	0/60 (33)	0/60 (30)	1/60 (31)
		0.2480	NC	NC	0.5000
	Islet Cell Adenoma/ Islet Cell Carcinoma	3/60 (32)	0/60 (33)	0/60 (30)	1/60 (31)
		0.6693	0.8864	0.8689	0.6815

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	0.03 mg Low (L) P - VC vs. L	0.1 mg Mid (M) P - VC vs. M	0.3 mg High (H) P - VC vs. H
Skin	Basal Cell Tumor, Benign	0/60 (31) 0.2460	0/60 (33) NC	1/60 (31) 0.5000	0/60 (31) NC
	Basal Cell Tumor, Malignant	0/60 (31) 0.2540	0/60 (33) NC	0/60 (30) NC	1/60 (32) 0.5079
	Basal Cell Tumor, Benign/ Basal Cell Tumor, Malignant	0/60 (31) 0.1860	0/60 (33) NC	1/60 (31) 0.5000	1/60 (32) 0.5079
	Papilloma	2/60 (31) 0.5328	0/60 (33) 0.7693	0/60 (30) 0.7459	1/60 (31) 0.5000
Small Intestine, Duodenum	Adenoma	1/60 (31) 0.7520	0/60 (33) 0.5156	0/60 (30) 0.4918	0/60 (31) 0.5000
Subcutis	Fibroma	1/43 (23) 0.1770	2/41 (23) 0.5000	0/41 (21) 0.4773	3/44 (25) 0.3369
	Fibrosarcoma	2/43 (24) 0.4296	1/41 (23) 0.4837	1/41 (22) 0.4667	2/44 (25) 0.3202
	Fibroma/Fibrosarcoma	3/43 (24) 0.1868	3/41 (24) NC	1/41 (22) 0.6620	5/44 (26) 0.3987
	Leiomyosarcoma	0/43 (23) 0.2637	0/41 (23) NC	0/41 (21) NC	1/44 (24) 0.5106
	Lipoma	1/43 (23) 0.4031	0/41 (23) 0.5000	1/41 (22) 0.7444	1/44 (24) 0.2553
Thymus	Thymoma, Benign	0/59 (30) 0.1829	0/60 (33) NC	1/58 (30) 0.5000	1/60 (31) 0.5082
Uterus	Endometrial Stromal Polyp	5/60 (33) 0.3088	2/60 (34) 0.7987	5/60 (32) 0.6133	5/60 (33) NC
	Endometrial Stromal Sarcoma	0/60 (31) 0.2480	0/60 (33) NC	0/60 (30) NC	1/60 (31) 0.5000
	Endometrial Stromal Polyp/ Endometrial Stromal Sarcoma	5/60 (33) 0.2033	2/60 (34) 0.7987	5/60 (32) 0.6133	6/60 (34) 0.5219
	Leiomyoma	1/60 (31) 0.7520	0/60 (33) 0.5156	0/60 (30) 0.4918	0/60 (31) 0.5000
Vagina	Granular Cell Tumor, Benign	0/59 (31) 0.3120	1/60 (33) 0.5156	0/60 (30) NC	1/60 (31) 0.5000

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	Vehicle Control		0.05 mg/kg/week Low		0.15 mg/kg/week Mid		0.5 mg/kg/week High		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13							1	4.00	3	12.00
14 - 27	1	4.00			1	4.00			11	56.00
Accidental Death									1	4.00
Terminal sacrifice	24	96.00	25	100.00	24	96.00	24	96.00	10	40.00
Total	25		25		25		25		25	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High		Vehicle Control vs. Positive Control	
Dose-Response (Likelihood Ratio)	0.0813				0.2390		0.0935		<.0001**	
Homogeneity (Log-Rank)	0.2882				0.3173		0.1531		<.0001**	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level; ** = Significant at 1% level.

Table 3B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	Vehicle Control		0.025 mg/kg/week Low		0.08 mg/kg/week Mid		0.25 mg/kg/week High		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									1	4.00
14 - 27	1	4.00							16	68.00
Terminal sacrifice	24	96.00	25	100.00	25	100.00	25	100.00	8	32.00
Total	25		25		25		25		25	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High		Vehicle Control vs. Positive Control	
Dose-Response (Likelihood Ratio)	0.0959		0.2390		0.2390		0.2390		<.0001**	
Homogeneity (Log-Rank)	0.3916		0.3173		0.3173		0.3173		<.0001**	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level; ** = Significant at 1% level.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle (VC)	Low (L)	Mid (M)	High (H)	Positive (PC)
		0 mg	0.05 mg	0.15 mg	0.5 mg	0 mg
		P - Trend	P - VC vs. L	P - VC vs. M	P - VC vs. H	P - VC vs. PC
Gland, Adrenal	Pheochromocytoma, Benign	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (12)
		NC	NC	NC	NC	0.3333
Gland, Harderian	Adenocarcinoma	0/25 (24)	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (11)
		0.7526	0.5102	NC	NC	NC
	Adenoma	2/25 (24)	2/25 (25)	0/25 (24)	0/25 (24)	1/25 (12)
		0.9823	0.7110	1.0000	1.0000	NC
	Adenocarcinoma/Adenoma	2/25 (24)	3/25 (25)	0/25 (24)	0/25 (24)	1/25 (16)
		0.9858	0.5200	1.0000	1.0000	0.7951
Gland, Thyroid	Follicular Cell Adenoma	0/25 (24)	0/25 (25)	1/25 (24)	0/25 (24)	0/25 (11)
		0.4948	NC	0.5000	NC	NC
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	13/25 (20)
		NC	NC	NC	NC	0.0000 \$
Kidney	Hemangiosarcoma	0/25 (24)	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (11)
		0.7526	0.5102	NC	NC	NC
Liver	Hepatocellular Adenoma	1/25 (24)	3/25 (25)	0/25 (24)	2/25 (24)	0/25 (11)
		0.4302	0.3202	1.0000	0.5000	1.0000
	Hepatocellular Carcinoma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (11)
		NC	NC	NC	NC	0.3143
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	1/25 (24)	3/25 (25)	0/25 (24)	2/25 (24)	1/25 (15)
		0.4302	0.3202	1.0000	0.5000	0.6275
Lung	Bronchioloalveolar Adenoma	4/25 (24)	4/25 (25)	2/25 (24)	3/25 (24)	5/25 (13)
		0.6565	0.6729	0.9059	0.7921	0.1419
	Bronchioloalveolar Carcinoma	1/25 (24)	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (11)
		0.7526	1.0000	0.7653	1.0000	1.0000
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	5/25 (24)	4/25 (25)	3/25 (25)	3/25 (24)	5/25 (16)
		0.7474	0.7892	0.8896	0.8776	0.3512
	Squamous Cell Carcinoma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (11)
		NC	NC	NC	NC	0.3143
Skin	Keratoacanthoma	0/25 (24)	1/25 (25)	0/25 (24)	1/25 (24)	0/25 (11)
		0.3119	0.5102	NC	0.5000	NC
	Papilloma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	7/25 (15)
		NC	NC	NC	NC	0.0004 \$
Small Intestine, Duodenum	Adenocarcinoma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (12)
		NC	NC	NC	NC	0.3333

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice
(Continued)**

Organ name	Tumor name	Vehicle (VC)	Low (L)	Mid (M)	High (H)	Positive (PC)
		0 mg P - Trend	0.05 mg P - VC vs. L	0.15 mg P - VC vs. M	0.5 mg P - VC vs. H	0 mg P - VC vs. PC
Small Intestine, Jejunum	Hemangiosarcoma	0/25 (24)	1/25 (25)	0/24 (23)	0/25 (24)	0/25 (11)
		0.7500	0.5102	NC	NC	NC
Spleen	Hemangiosarcoma	0/25 (24)	1/25 (25)	0/25 (24)	2/25 (24)	0/25 (11)
		0.1055	0.5102	NC	0.2447	NC
Stomach	Adenoma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (11)
		NC	NC	NC	NC	0.3143
	Papilloma	0/25 (24)	0/25 (25)	0/25 (24)	0/25 (24)	12/25 (16)
		NC	NC	NC	NC	0.0000 \$
	Squamous Cell Carcinoma	1/25 (25)	0/25 (25)	0/25 (24)	0/25 (24)	4/25 (15)
		1.0000	1.0000	1.0000	1.0000	0.0564

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle (VC)	Low (L)	Mid (M)	High (H)	Positive (PC)
		0 mg P - Trend	0.025 mg P - VC vs. L	0.08 mg P - VC vs. M	0.25 mg P - VC vs. H	0 mg P - VC vs. PC
Body Cavity, Nasal	Squamous Cell Carcinoma	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	1/24 (9)
		NC	NC	NC	NC	0.2727
Gland, Harderian	Adenocarcinoma	1/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (8)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Adenoma	1/25 (24)	1/25 (25)	0/25 (25)	0/25 (25)	2/25 (9)
		0.9431	0.7653	1.0000	1.0000	0.1738
	Adenocarcinoma/Adenoma	2/25 (25)	1/25 (25)	0/25 (25)	0/25 (25)	2/25 (15)
		0.9858	0.8827	1.0000	1.0000	0.4841
Gland, Salivary, Mandibular	Adenoma	0/25 (24)	1/25 (25)	0/25 (25)	0/25 (25)	0/25 (8)
		0.7576	0.5102	NC	NC	NC
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	16/25 (21)
		NC	NC	NC	NC	0.0000 \$
Lung	Bronchioloalveolar Adenoma	1/25 (24)	1/25 (25)	1/25 (25)	2/25 (25)	3/25 (9)
		0.2664	0.7653	0.7653	0.5156	0.0523
	Bronchioloalveolar Carcinoma	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	2/25 (10)
		NC	NC	NC	NC	0.0802
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	1/25 (25)	1/25 (25)	1/25 (25)	2/25 (25)	5/25 (16)
		0.2592	NC	NC	0.5000	0.0261
Skin	Papilloma	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	3/25 (10)
		NC	NC	NC	NC	0.0201 \$
Small Intestine, Jejunum	Adenoma	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (9)
		NC	NC	NC	NC	0.2727
Spleen	Hemangiosarcoma	0/25 (24)	2/25 (25)	2/25 (25)	0/25 (25)	0/24 (8)
		0.7515	0.2551	0.2551	NC	NC
Stomach	Hemangioma	0/25 (24)	1/25 (25)	0/25 (25)	0/25 (25)	0/25 (8)
		0.7576	0.5102	NC	NC	NC
	Papilloma	0/25 (24)	1/25 (25)	1/25 (25)	0/25 (25)	10/25 (13)
		0.6339	0.5102	0.5102	NC	0.0000 \$
	Squamous Cell Carcinoma	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (25)	2/25 (9)
		NC	NC	NC	NC	0.0682
Thymus	Thymoma, Benign	4/25 (24)	1/25 (25)	1/25 (25)	0/25 (25)	0/25 (8)
		0.9879	0.9777	0.9777	1.0000	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

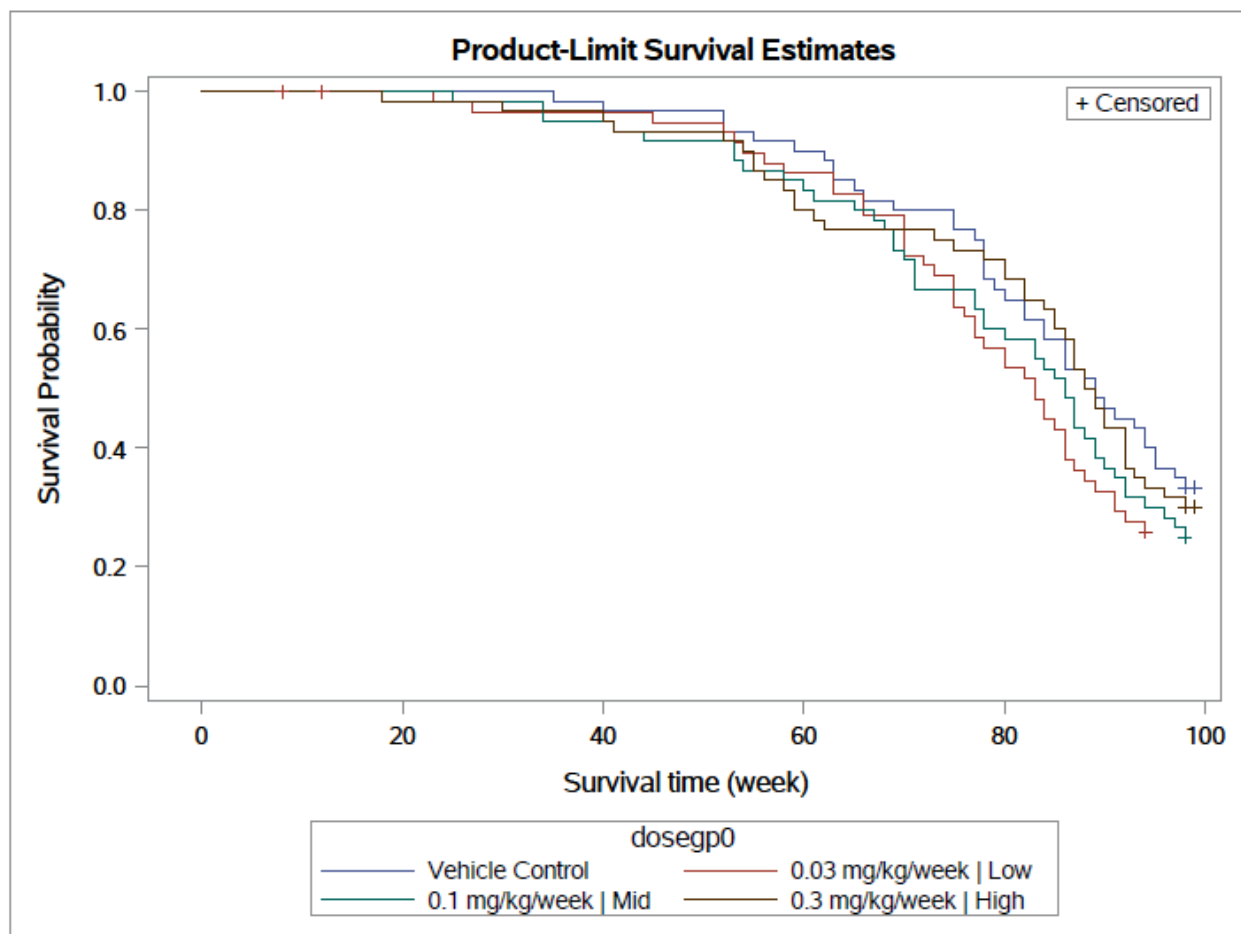
Figure 1A: Kaplan-Meier Survival Functions for Male Rats

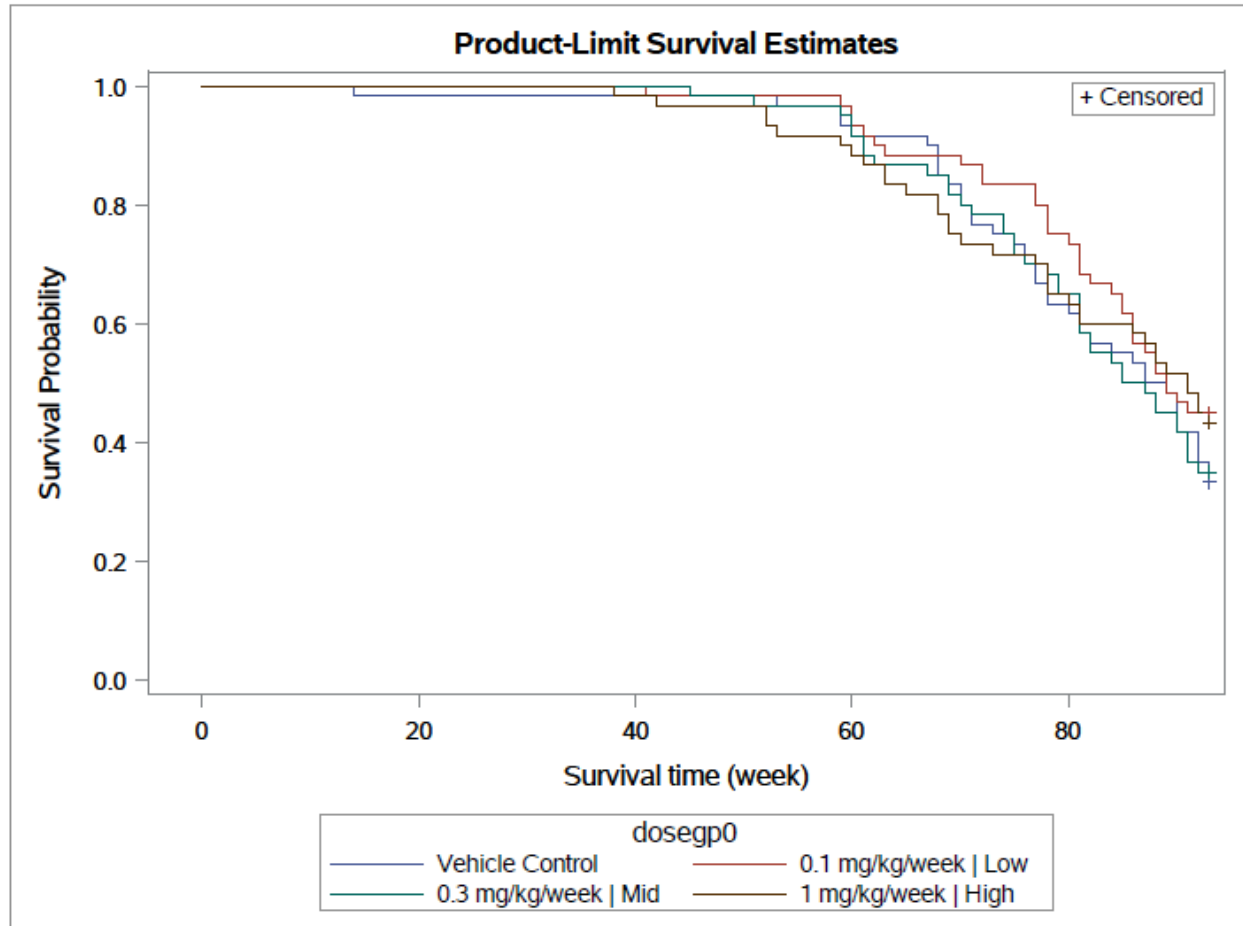
Figure 1B: Kaplan-Meier Survival Functions for Female Rats

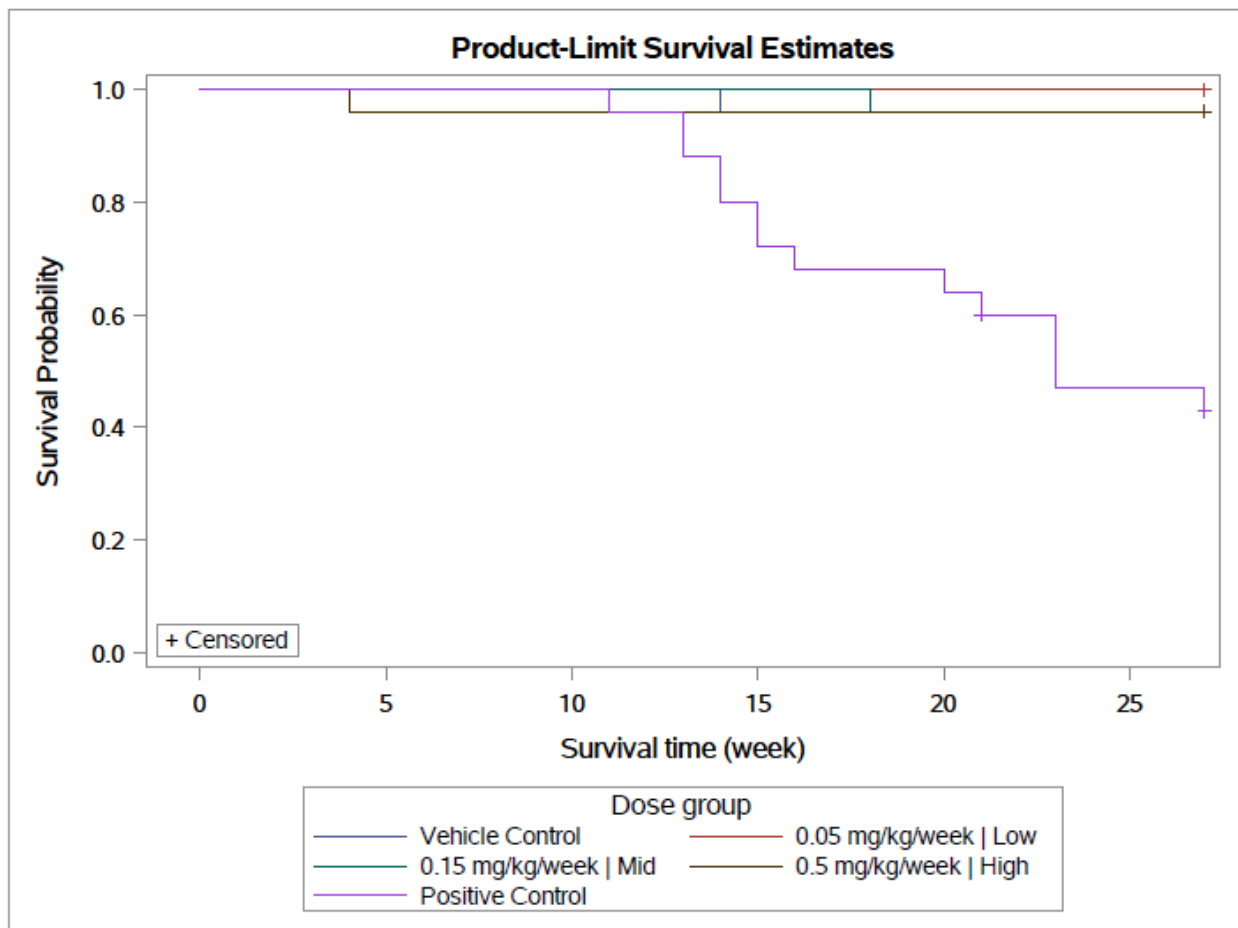
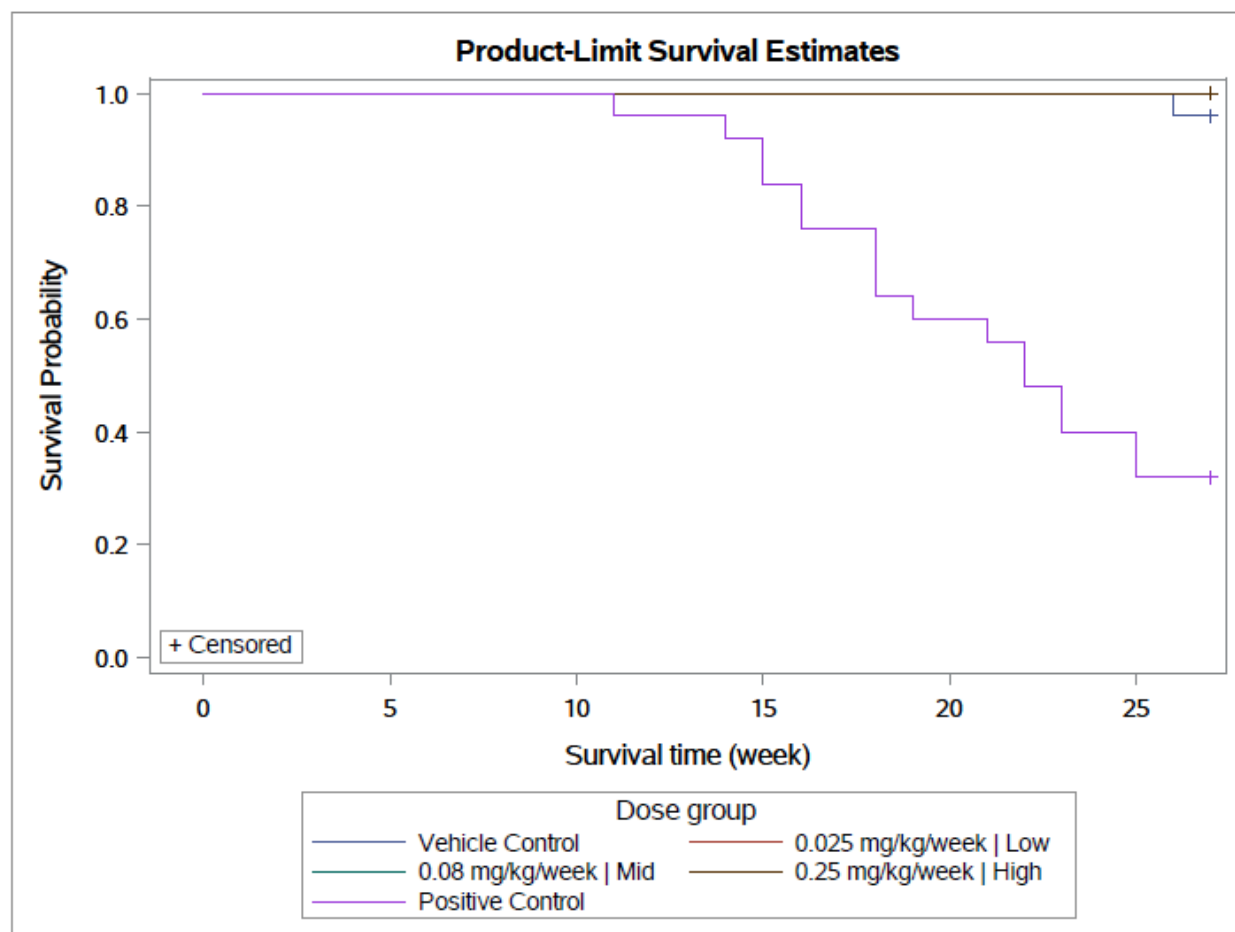
Figure 2A: Kaplan-Meier Survival Functions for Male Mice

Figure 2B: Kaplan-Meier Survival Functions for Female Mice

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