CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219019
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Reviewer Name	Sarah K. Brant, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	March 19, 2025
Subject	Evaluation of Need for a REMS
Established Name	Fitusiran
Trade Name	Qfitlia
Name of Applicant	Genzyme Corporation
Therapeutic Class	Antithrombin-directed small interfering ribonucleic acid (siRNA)
Formulation	Solution for subcutaneous injection (50 mg/0.5 mL single-dose pre-filled pen and 20 mg/0.2 mL single-dose vial)
Dosing Regimen	Starting dose: 50 mg subcutaneously once every 2 months. Dose adjusted to maintain antithrombin activity between 15-35%.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Qfitlia (Fitusiran) is necessary to ensure the benefits outweigh its risks. Genzyme Corporation submitted a new drug application (NDA) 219019 for fitusiran with the proposed indication of 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. This application is under review in the Division of Nonmalignant Hematology (DNH). During the course of the review, the Agency revised the indication to the following: 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. The Applicant did not submit a REMS with this application but proposed voluntary risk management activities to address the risks of thrombotic events and transaminase elevations.

The benefits of treatment with fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and hemophilia B with and without inhibitors were demonstrated in two pivotal, Phase 3 studies. There was statistically significant reduction in the estimated annualized bleeding rate in the fitusiran treatment group compared with the on-demand active control in both studies.

Based on the safety and efficacy information available, DRM has determined that a REMS is not needed to ensure the benefits of fitusiran outweigh its risks. The risks associated with fitusiran include serious thrombotic events, hepatotoxicity, and acute and recurrent gallbladder disease. Adverse events associated with fitusiran occurred at lower rates with antithrombin-based dosing (AT-DR) of fitusiran compared with the original fixed dose of fitusiran 80 mg monthly. The change to the dosing strategy appears to mitigate these risks. Similar to other approved treatment for hemophilia, the review team recommends the risk of thrombotic events be communicated in a Boxed Warning and Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide. To mitigate the risk of serious thrombotic events, the importance of antithrombin (AT) level monitoring with an FDA-cleared AT activity assay will be described in Section 2: Dosage and Administration and Section 5: Warnings and Precautions.

The review team recommends the risk of hepatotoxicity be communicated in Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide. The risk of hepatotoxicity is also labeled for the adeno-associated virus (AAV) vector-based gene therapies used for treatment of hemophilia, and prescribers of fitusiran are expected to be familiar with monitoring of liver tests necessary for these gene therapies. The review team recommends the risk of acute and recurrent gallbladder disease be communicated in a Boxed Warning and Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide. Although this risk has not been observed for other hemophilia treatments, inclusion of a Boxed Warning is expected to increase prescriber awareness of this risk, and patients are expected to seek prompt treatment if experiencing the severe symptoms of acute gallbladder disease and to be closely managed by a multidisciplinary team that can facilitate treatment should gallbladder disease occur.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Qfitlia (fitusiran) is necessary to ensure the benefits outweigh its risks. Genzyme Corporation (hereafter referred to as the Applicant) submitted a new drug application (NDA) 219019 for fitusiran with the proposed indication of 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.[1] This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant did not submit a REMS with this application but proposed voluntary risk management activities to address the risks of thrombotic events and transaminase elevations.

2. Background

2.1. Product Information

Qfitlia (fitusiran), a new molecular entity[a], is an antithrombin-directed small interfering ribonucleic acid (siRNA) proposed 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.[1] During the course of the review, the Agency revised the indication to the following: 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] Fitusiran is a double-stranded siRNA-GalNAc conjugate that uses RNA interference to target degradation of antithrombin (AT) messenger RNA (mRNA).[3] Degradation of AT mRNA results in reduction of plasma AT levels. AT functions as a naturally occurring anticoagulant and inhibits the effects of the procoagulant thrombin. Therefore, reduced levels of AT decrease bleeding and help restore hemostasis in patients with hemophilia.[3]

Fitusiran is proposed to be supplied as a solution for injection as both a 50 mg/0.5 mL pre-filled pen and a 20 mg/0.2 mL single-use vial.[2] The recommended starting dose of fitusiran is 50 mg injected subcutaneously once every 2 months.[2] The dose should then be adjusted to maintain AT activity between 15-35% with doses ranging from 10 mg every 2 months up to a maximum of 50 mg monthly.[2] AT activity levels should be measured prior to fitusiran initiation; at Weeks 4, 12, 20, and 24; and annually thereafter. If the dose is modified, AT activity measurements should be restarted.[2] Clotting factor concentrates (CFC) and bypassing agents (BPA) prophylaxis should be discontinued after the first 7 days of fitusiran treatment. The dosing and frequency of CFCs or BPAs for breakthrough bleeding episodes should be reduced to minimize the risk of thrombotic events.[2]

Fitusiran may be self-administered by the patient or caregiver after the healthcare provider provides training on preparation and administration.[2] As fitusiran is to be given as routine prophylaxis to prevent or reduce the frequency of bleeding episodes, fitusiran is likely to be administered primarily

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

in an outpatient setting and is proposed for chronic use.[b] Fitusiran is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219019 relevant to this review:

- 08/12/2013: Orphan drug designation granted for fitusiran for the treatment of hemophilia B.
- 08/16/2013: Orphan drug designation granted for fitusiran for treatment of hemophilia A.
- 12/23/2020: Fast track designation granted for fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in people with hemophilia A or B with and without factor VIII or factor IX inhibitors.
- 12/06/2023: Breakthrough therapy designation granted for fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patient with hemophilia B with factor IX inhibitors.
- 09/18/2023: Applicant was informed at a Type C meeting for IND 125632 that the Agency had insufficient information to determine whether a REMS would be necessary for fitusiran and that the Agency would determine the need for a REMS during the review of the application. Applicant was advised to request a meeting with the Center for Devices and Radiological Health (CDRH) regarding laboratory monitoring of AT levels to appropriately dose-adjust fitusiran.[4]
- 03/19/2024: Applicant met with the Agency at a pre-NDA Type B meeting for IND 125632. Applicant discussed plan to submit a companion diagnostic AT assay to CDRH around the time that the NDA is submitted for fitusiran. CDER and CDRH agreed that an FDA-approved AT assay would be necessary for fitusiran.[5]
- 03/28/2024: NDA 219019 submission 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 received.[1]
- 09/17/2024: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that safety signals for hepatocellular and hepatobiliary injury had been identified for fitusiran and further Agency analyses were in progress. The impact on labeling and need for a REMS would be determined after completion of these analyses.[6]
- 12/19/2024: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant the Agency continues to evaluate the

[b] [b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

safety signals of hepatoxicity, cholecystitis/cholelithiasis, and thrombosis, and the potential need for a Boxed Warning for these signals.[7]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hemophilia is an X-linked recessive bleeding disorder characterized by a deficiency in either coagulation factor VIII, known as hemophilia A, or factor IX, known as hemophilia B.[8] Hemophilia predominantly affects males, with a male to female ratio of approximately 32:1. Most people with hemophilia are diagnosed before 2 years of age.[9] The estimated prevalence of hemophilia in the United States is approximately 13.4-19.4 cases per 100,000 males, with hemophilia A accounting for 80-85% of cases.[8,10,c]

Disease severity is classified based on the level of circulating clotting factor, with mild hemophilia having 5 - <40%, moderate having 1 - 5%, and severe having <1% of normal clotting factor levels.[8] Approximately 60% of individuals with hemophilia A have severe disease.[11] Severe hemophilia is associated with spontaneous bleeding into joints, muscles, or internal organs, which can lead to significant disability or death. Patients with mild hemophilia may only experience abnormal bleeding during surgery or with serious trauma.[8] Bleeding into the joints, or hemarthrosis, is the most common site of bleeding (70-80% of bleeds) and can lead to long-term disability. Intracranial bleeds are the most life-threatening, but occur rarely (<5%).[8,d] Due to the unpredictability of bleeding episodes and disease complications, individuals with hemophilia are at increased risk for mental health issues, such as depression and anxiety.[12]

One of the most serious complications of hemophilia A and B is the development of neutralizing antibodies (also known as inhibitors) to factor replacement. Approximately 30% of patients with hemophilia A and 5-15% of patients hemophilia B will develop inhibitors rendering the factor concentrates ineffective to prevent bleeding events.[13-15] Because bleeding is more difficult to prevent and treat, patients with inhibitors have an increased risk of serious and potentially fatal bleeding episodes.[16]

3.2. Description of Current Treatment Options

Treatment for hemophilia can either be in response to a bleeding event ("on demand" treatment), prophylactic treatment to prevent bleeds, or gene therapy to replace the deficient factor.[17,18] Therapeutic options for prophylaxis include FDA-approved plasma-derived or recombinant standard half-life factor, extended half-life factor, and non-factor replacement such as Hemlibra

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

(emicizumab), Hympavzi (marstacimab-hncq), and Alhemo (concizumab-mtci).[19-22] For patients with a history of high-titer inhibitors, the only hemostatic options currently available are Alhemo and bypassing agents (BPAs) that augment other parts of the coagulation cascade.[8,20]

BPAs include factor eight inhibitor bypassing activity (FEIBA), a plasma derived activated prothrombin complex concentrate (aPCC), and recombinant activated human FVII (rFVIIa) products such as NovoSeven and SevenFACT.[19] FEIBA is the only BPA that is FDA-approved for prophylaxis in patients with hemophilia A with inhibitors and hemophilia B with inhibitors.[23] Treatment burden is high with the use of BPAs that require frequent, high-volume, and extended intravenous infusion. BPAs carry a Boxed Warning describing the risk of thrombotic events as well as warnings and precautions for the risk of hypersensitivity reactions.

Emicizumab, a humanized, monoclonal, bispecific, factor IXa-and factor X-directed antibody, is an FDA-approved non-factor replacement product for routine prophylaxis in adult and pediatric patients with hemophilia A with and without inhibitors.[21] There is a Boxed Warning for emicizumab describing the risk of thrombotic microangiopathy and thrombotic events with concomitant use of aPCC, and recommending to monitor for this risk, and to discontinue aPCC and suspend dosing of emicizumab if symptoms occur.

Notably, during the course of this review, two tissue factor pathway inhibitor antagonists, Hympavzi and Alhemo, were FDA-approved. Hympavzi (marstacimab-hncq) was approved on October 11, 2024, for routine prophylaxis in adult and pediatric patients with hemophilia A without inhibitors and hemophilia B without inhibitors.[22] Alhemo (concizumab-mtci) was approved on December 20, 2024, for routine prophylaxis in adult and pediatric patients with hemophilia A with inhibitors and hemophilia B with inhibitors.[20] Both Hympavi and Alhemo have a warning in labeling for risk of thromboembolic events. While the approval of Hympavzi and Alhemo provide additional options for hemophilia A and B patients with and without inhibitors, there is still an unmet need for safe and effective therapies to prevent or reduce bleeding in patients with hemophilia A and hemophilia B with and without inhibitors.[24]

Adeno-associated virus (AAV) vector-based gene therapies are FDA-approved for treatment of hemophilia, including Roctavian (valoctocogene roxaparvovec-rvox) for treatment of hemophilia A, and Hemgenix (etranacogene dezaparvovec-drlb) and Beqvez (fidanacogene elaparvovec-dzkt) for treatment of hemophilia B. [25-27] Labeling for these AAV vector-based gene therapies includes warnings for hepatotoxicity, infusion reactions, and hepatocellular carcinoma.

4. Benefit Assessment

The benefit of fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and hemophilia B with and without inhibitors was evaluated in two pivotal phase 3 trials, Study EFC14768 (hereafter referred to as ATLAS-INH, National Clinical Trial [NCT] 03417102) and Study EFC14769 (hereafter referred to as ATLAS A/B, NCT03417245).[24,28]

ATLAS-INH was a multicenter, randomized, active-controlled, open-label study which evaluated 57 male subjects (fitusiran group=38, on-demand group=19) aged ≥ 12 years of age with severe hemophilia A or

B with inhibitors, who previously received on-demand treatment with BPAs for bleeding episodes.[28] Subjects were randomized 2:1 to receive fitusiran 80 mg subcutaneously once monthly or BPAs on-demand to treat bleeding episodes for 9 months.[28] Subjects receiving fitusiran could receive on-demand BPAs for treatment of breakthrough bleeding episodes. The study population of ATLAS-INH had a median age of 27 years, were predominantly Asian (68%) and diagnosed with hemophilia A (79%).[28] The baseline demographics were generally well-balanced between study groups.

ATLAS-A/B was a multicenter, randomized, active-controlled, open-label study which evaluated 120 male subjects (fitusiran group=80, on-demand group=40) aged ≥ 12 years of age with severe hemophilia A or B without inhibitors, who previously received on-demand treatment with CFCs for bleeding episodes.[28] Subjects were randomized 2:1 to receive fitusiran 80 mg every month or CFCs on-demand to treat bleeding episodes for 9 months.[28] Subjects receiving fitusiran could receive on-demand CFCs for treatment of breakthrough bleeding episodes. The study population of ATLAS-A/B had a mean age of 31 years, were predominantly Asian (59.2%) and diagnosed with hemophilia A (77.5%).[28] The baseline demographics were generally well-balanced between study groups.

The primary endpoint for both ATLAS-INH and ATLAS-A/B was the annualized bleeding rate (ABR)[e] for treated bleeds during the efficacy period of Months 2 to 9 of treatment.[28] There was a statistically significant reduction in the estimated ABR in the fitusiran treatment group compared with the on-demand active control in both studies.[28] There was a 90.8% reduction in estimated ABR with fitusiran treatment in the ATLAS-INH study and 89.9% reduction in the estimated ABR with fitusiran treatment in the ATLAS-A/B study as outlined in Tables 1 and 2 below.[28]

Table 1. ATLAS-INH Annualized Bleeding Rate During the Efficacy Period[28]

	Fitusiran 80 mg n=38	Bypassing Agent On-Demand n= 19	Rate ratio (95% CI)	P-value
Estimated ABR (95% CI)	1.7 (1.0, 2.7)	18.1 (10.6, 30.8)	0.092 (0.04, 0.19)	<0.0001

Table 2. ATLAS-A/B Annualized Bleeding Rate During the Efficacy Period[28]

	Fitusiran 80 mg n= 80	Bypassing Agent On-Demand n= 40	Rate ratio (95% CI)	P-value
Estimated ABR (95% CI)	3.1 (2.3, 4.3)	31 (21.1, 45.5)	0.101 (0.06, 0.16)	<0.0001

Study LTE15174 (hereafter referred to as ATLAS-OLE, NCT03754790), is an open-label extension study evaluating the long-term efficacy and safety of fitusiran.[28] ATLAS-OLE evaluated 281 subjects with severe hemophilia A or B with or without inhibitors that had either completed one of the phase 3 studies (n=227) or that were enrolled de-novo (n=54).[28] Subjects were treated with dose-adjusted fitusiran

[e] The annualized bleeding rate (ABR) is the number of bleeding episodes that occur in a year. ABR is calculated by dividing the number of bleeding episodes that occurred by the number of months evaluated and multiplying by 12.

(hereafter referred to as AT-DR) with a target AT level of 15-35% for up to 76 months.[28,f] The starting dose of fitusiran after a dosing pause and change to AT-DR was 50 mg every 2 months, and doses were adjusted to a maximum of 50 mg monthly and a minimum of 20 mg every 2 months.[28,g] The fitusiran treatment arm of ATLAS-OLE was compared to the control arms in the pivotal studies (ATLAS-INH and ATLAS-A/B) to evaluate for efficacy.[24] In subjects with inhibitors, the estimated ABR was reduced by 73% with fitusiran compared to BPA on-demand treatment (p=0.006). In subjects without inhibitors, the estimated ABR was reduced by 71% with fitusiran compared to CFC on-demand treatment (p<0.0001).[24] The review team concluded that efficacy of the AT-based dosing regimen was similar to the fitusiran 80 mg monthly regimen.[24]

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on two adequate and well-controlled trials, ATLAS-INH and ATLAS-A/B.[24,h]

5. Risk Assessment & Safe-Use Conditions

The primary safety population for fitusiran consists of all subjects in the clinical development program for fitusiran that received the AT-DR dose regimen.[24] The safety population includes subjects from ATLAS-OLE (N=269), Study LTE14762 (N=18), and Study EFC15110 (N=2).[24] Study LTE14762 was an open-label, long-term extension study in subjects with hemophilia A or B with or without inhibitors who were previously enrolled in a phase 1 study, Study TDR14767.[29] Study EFC15110 was an open-label, switching study in subjects with hemophilia A or B with or without inhibitors, previously on BPA or CFC prophylaxis.[29] Pooled safety assessments of subjects who received at least one dose of fitusiran (N=335) in the clinical development program, whether a fixed or AT-DR dose, provide additional supportive safety data.[24]

The median duration of exposure for subjects in the primary safety population was 96 weeks (range 73 to 118 weeks).[29] There were no deaths in the primary safety population, however there were 2 deaths in supportive safety studies. One death of a subject randomized to fitusiran 80 mg monthly in ATLAS-A/B was due to metastatic adenocarcinoma, and was not considered by the clinical reviewer as related to fitusiran treatment.[24] The other death was in a subject receiving fitusiran 80 mg monthly in Study LTE14762 was considered treatment-related and is described further below in Section 5.1.1, Serious Thrombotic Events.[24]

[f] The dosing regimen of fitusiran was modified for the long-term extension study to target AT levels to mitigate the risk of thrombotic events that were observed with the 80 mg monthly dosing.

[g] There were 180 subjects that rolled over into the long-term extension study from the phase 3 trials. These subjects initially received fitusiran 80 mg monthly with a median duration of fitusiran treatment exposure of 166 days. After the dosing pause and resumption of the study with the AT-DR dosing, there were 213 subjects enrolled that had rolled over from phase 3 studies with a median duration of fitusiran treatment exposure of 767 days.

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Serious adverse events (SAEs)[i] in the primary safety population were reported in 14.3% of subjects receiving fitusiran, however, many were hemorrhagic events that could be attributed to the subject's underlying hemophilia.[24,29,j] Cholecystitis was reported in 2 subjects (0.7%) and was considered to be treatment-related by the review team.[24,29] 5 subjects (1.7%) receiving fitusiran permanently discontinued the study early due to the following adverse events: cerebral infarction, post-operative deep vein thrombosis, hepatocellular carcinoma, livery injury, and pruritis.[29] The most common adverse events (≥5% of subjects receiving fitusiran) were viral infection, nasopharyngitis, bacterial infection, hepatic injury, arthralgia, increased prothrombin fragment, injection site reaction, headache, and cough.[2,29] See Sections 5.1.1, 5.1.2, and 5.1.3 below for further discussion of thrombotic events, acute and recurrent gallbladder disease, and hepatotoxicity, respectively.

5.1. Adverse Events of Special Interest

5.1.1. Serious thrombotic events

In the fitusiran clinical development program, thrombotic events occurred in 7 subjects (2.6%) that had received fitusiran 80 mg monthly, including one fatal event described below, and in 4 subjects (1.4%) that had received the AT-DR dosing of fitusiran.[29] Thrombotic events included deep vein thrombosis, spinal vein thrombosis, cerebral infarction, embolic stroke, thrombosis on papilla of left eye, cerebral venous sinus thrombosis (CVST), right atrial thrombosis, and cerebral artery embolism.[29] In those subjects that experienced thrombotic events while receiving fitusiran AT-DR dosing, two subjects experienced thrombosis post-operatively and one subject experienced an embolic stroke approximately 5 months after the last dose of fitusiran.[29] In the two subjects who experienced thrombosis post-operatively, the bleed management guidelines in the study protocol were not followed.[29]

There was one death that occurred in a 25-year-old subject with hemophilia A who completed phase 1 Study TDR14767 and enrolled in extension Study LTE 14762.[29] The subject received the fixed dose of fitusiran 80 mg monthly.[29] On Day 492 of treatment, the subject presented with severe headache, vomiting, and fever and was diagnosed with a subarachnoid hemorrhage based on computed tomography imaging.[29] The subject was treated with CFC therapy 2 to 3 times daily, and ultimately clinically deteriorated and died.[24] Post-mortem evaluation of the

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

initial imaging revealed a CVST was the cause of the subject's initial symptoms and death.[29] Prior to presentation, the subject had received doses of factor VIII for treatment of hip pain.[24] The clinical reviewer determined that the fatal event was likely related to fitusiran.[24]

Following the fatal event, the Applicant implemented bleed management guidelines across the study protocols and later changed the dosing of fitusiran from a fixed 80 mg monthly dose to AT-DR dosing with a target AT activity of 15-35%.[24] The bleed management guidelines implemented in the studies included recommendations on use of CFCs or BPAs during acute bleeding events or surgical procedures.[29]

The review team recommends the risk of serious thrombotic events be communicated in a Boxed Warning, Section 2: Dosage and Administration, Section 5: Warnings and Precautions, and Section 17: Patient Counseling Information of the Prescribing Information, and be summarized for patients in the Medication Guide.[24] Draft labeling includes the recommendation to follow the bleed management guidelines, to monitor patients for signs or symptoms of thrombotic events, to interrupt fitusiran in patients with a thrombotic event occur and to manage as clinically indicated.[2] Draft labeling also describes risk factors for thrombotic events including persistent AT activity of <15%, the use of the unapproved fixed dose fitusiran 80 mg monthly, presence of indwelling venous catheters, and the post-operative state when bleed management guidelines are not followed.[2]

Draft labeling recommends monitoring AT activity and guidelines for management of breakthrough bleeds.[2] AT activity should be measured prior to fitusiran initiation, at Weeks 4, 12, 20, and 24, and after any dose modification.[2] Fitusiran should be dose-adjusted based on AT activity with a target AT activity of 15-35%. Once the patient's AT activity reaches the target activity of 15-35%, it is recommended to measure AT activity annually.[2] The bleed management guidelines recommend reduced doses and frequency of CFCs and BPAs in patients treated with fitusiran to reduce the risk of thrombotic events.[2] Draft labeling recommends to monitor AT activity using an FDA-cleared human factor Xa based chromogenic activity assay, which will be labeled as a companion diagnostic for fitusiran.[2]

5.1.2. Acute and Recurrent Gallbladder Disease

There were 48 subjects (14%) that experienced acute gallbladder adverse events in the fitusiran clinical development program including cholecystitis (acute and chronic), biliary colic, cholestasis, cholangitis, gallbladder enlargement, and cholelithiasis.[24] Twelve subjects (25%) who experienced cholecystitis/cholelithiasis events required cholecystectomy (CCY).[24] Eleven subjects (92%) did not interrupt fitusiran treatment prior to CCY and were able to resume fitusiran treatment after recovery.[24] One subject experienced cholangitis and pancreatitis caused by gallstone disease more than a year after CCY.[24] Acute gallbladder adverse events were more common with fitusiran 80 mg monthly compared with AT-DR dosing (N=40 [14.8%], N=11 [3.8%], respectively).[24] Two episodes of cholecystitis in subjects receiving AT-DR dosing were SAEs.[29]

DNH consulted the Division of Hepatology and Nutrition (DHN) Drug-Induced Liver Injury (DILI) Team to evaluate cases of potential hepatotoxicity and whether fitusiran may be contributing. During their review, the DILI team identified the above cases of acute gallbladder disease to further evaluate. The DILI team concluded that there was substantial risk of indirect DILI via gallbladder complications associated with fitusiran.[30] As gallstones and gallbladder disease are rare in patients with hemophilia, the rate of gallbladder complications in the clinical development program for fitusiran was very high, indicating a strong association between fitusiran and gallbladder adverse events.[30] Due to the indolent nature of gallstone formation and potential delay in gallbladder disease recognition, the DILI team could not stablish a dose response relationship for this risk.[30] Although the 12 subjects requiring CCY recovered well, the bleeding risk and need for specialized care are increased in a patient with hemophilia.[30]

The review team and the DILI team recommend the risk of acute and recurrent gallbladder disease be communicated in a Boxed Warning and Section 5: Warnings and Precautions and Section 17: Patient Counseling Information of the Prescribing Information and be summarized for patients in the Medication Guide.[2] Draft labeling recommends prescribers monitor patients for signs and symptoms of acute gallbladder disease and consider alternative treatments for hemophilia in patients with history of symptomatic gallbladder disease.[2] If gallbladder disease is suspected, appropriate imaging and clinical follow-up are indicated.[2] Prescribers should interrupt or discontinue fitusiran if acute or recurrent gallbladder disease occurs[2].

5.1.3. Hepatotoxicity

In those subjects who received fitusiran 80 mg monthly across the clinical development program for fitusiran, alanine transaminase (ALT) elevations >3 times the upper limit of normal (ULN) occurred in 13 (32%) of subjects and aspartate transaminase (AST) elevations >3 times the ULN occurred in 5 (12%) of subjects compared to no events in the on-demand control groups.[24] Elevations of ALT and AST of >3 times the ULN were less common with AT-DR fitusiran dosing (3.4% and 2.6%, respectively) compared to the fixed 80 mg monthly dose.[29]

DNH consulted the DHN DILI Team to evaluate cases of potential hepatotoxicity and whether fitusiran may be contributing to these laboratory findings. The DILI team identified five subjects with at least probable DILI due to fitusiran, of which all but one were administered fitusiran 80 mg monthly. The pattern of injury tended to be hepatocellular, and the latency of injury onset from drug initiation was a median of 42 days. There was one subject that met Hy's law criteria from the subjects who received fitusiran 80 mg monthly dosing.[24] The subject was a 20-year-old male with hemophilia A receiving fitusiran 80 mg monthly. On Day 42 of treatment, the subject's ALT increased to 4-5 times the ULN and then improved with fitusiran interruption. On Day 198, the subject met Hy's law criteria with a total bilirubin of greater than 2 times the ULN and ALT of 7 times the ULN.[24] Fitusiran was discontinued and the subject's liver tests improved.[24] This subject's liver injury was determined by the DILI team to be highly likely due to fitusiran.[30] The DILI team concluded that the evidence for idiosyncratic DILI was substantial, and there was a clear increase in liver enzymes and bilirubin associated with fitusiran compared to the on-

demand therapy.[30] Although there appears to be a dose response for risk of DILI, selection bias could also contribute because those who tolerated fitusiran 80 mg were more likely to roll-over into the study using ATDR dosing.[30]

The review team and the DILI team recommend the risk of hepatotoxicity be communicated in Section 5: Warnings and Precautions and Section 17: Patient Counseling Information of the Prescribing Information and be summarized for patients in the Medication Guide.[2,30] Draft labeling recommends prescribers obtain baseline liver function tests in all patients initiating fitusiran and monitor liver function tests monthly for at least 6 months.[2] If new or worsening liver dysfunction is observed, prescribers should perform appropriate diagnostic evaluations, initiate medical management as appropriate, and monitor laboratory parameters until normalization to baseline.[2] If ALT or AST elevations occur >5 times the ULN, prescribers should interrupt fitusiran treatment and allow liver tests to return to baseline before continuing fitusiran treatment.[2] If ALT or AST elevations >5 times the ULN reoccur or the patient experiences jaundice thought to be from hepatotoxicity with other causes of liver test elevation ruled out, prescribers should permanently discontinue fitusiran.[2]

6. Expected Postmarket Use

Fitusiran is proposed 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. It is proposed as a single-dose pre-filled pen and single-dose vial for subcutaneous injection. Fitusiran will likely be prescribed and self-administered in the outpatient setting. Most hemophilia patients manage their disease through one of the 141 Hemophilia Treatment Centers which are federally funded facilities that provide comprehensive multidisciplinary care that can include hematologists with hemophilia expertise, nurse coordinators, physical and occupational therapists, counselors, social workers, and other healthcare professionals.[17]

The most likely prescribers of fitusiran will be hematologists who specialize in hemophilia treatment and have experience with managing the risks associated with anti-hemophilic therapies. Hematologists are expected to have experience with treatments requiring dose adjustments based on laboratory monitoring such as heparin sodium and Alhemo (concizumab-mtci) and should, therefore, be comfortable using laboratory test results to dose-adjust fitusiran.[20,31] In addition, patients with hemophilia are often knowledgeable about their disease, are able to identify treatment-emergent adverse events such as thrombosis, gastrointestinal discomfort, or jaundice, and communicate concerns to their healthcare providers.

7. Risk Management Activities Proposed by the Applicant

Drafting labeling includes the Prescribing Information, Instructions for Use, and a Medication Guide.[2] The Applicant proposed the following risk management activities beyond routine pharmacovigilance and labeling:

- **Voluntary Distribution of Educational Material**: the Applicant proposed to voluntarily distribute an educational material, the Healthcare Provider Guide, "to reinforce the key safety messages/instructions associated with fitusiran and its potential risks of thrombotic events, and transaminase elevations."[1] The Applicant's target audience for this guide is prescribers of fitusiran and any healthcare providers responsible for the management of patients with hemophilia.[1]

Reviewer Comments: *We do not object to voluntary educational activities proposed by the Applicant; however, we defer to the Office of Prescription Drug Promotion and the Division of Pharmacovigilance for their review and input on this activity.*

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of fitusiran on the basis of the efficacy and safety information currently available.[24]

Congenital hemophilia A and B with and without inhibitors are bleeding disorders predominantly affecting males and characterized by bleeding events which may include life-threatening spontaneous or traumatic bleeds. Bleeding into the joints is the most common site of bleeding and can lead to long-term disability. Treatment for hemophilia can either be provided on demand in response to a bleeding event with CFCs or BPAs or with prophylactic treatment with either CFCs, BPAs, Hemlibra, Hympavzi, or Alhemo. Treatment options also include AAV vector-based gene therapies for hemophilia A and B. For patients with inhibitors, the only hemostatic options currently available are Alhemo and BPAs. While the approval of Hympavzi and Alhemo provide additional options for hemophilia A and B patients with and without inhibitors, there is still an unmet need for safe and effective therapies to prevent or reduce bleeding in patients with hemophilia A and hemophilia B with and without inhibitors.

The benefits of treatment with fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and hemophilia B with and without inhibitors were demonstrated in two pivotal, phase 3 studies, ATLAS-INH and ATLAS-A/B. There was statistically significant reduction in the estimated ABR during the efficacy period in the fitusiran treatment group compared with the on-demand active control in both studies. Although the AT-based dosing regimen proposed in draft labeling is a lower dose than was studied in ATLAS-INH and ATLAS-A/B, the review team concluded that the efficacy of fitusiran was maintained with the AT-based dosing in the long term extension study, ATLAS-OLE.

Fitusiran is associated with increased risk of serious thrombotic events, hepatotoxicity, and acute and recurrent gallbladder disease. The AT-DR dosing of fitusiran proposed in labeling was associated with reduced rates thrombotic events, hepatotoxicity, and acute gallbladder disease when compared with the fixed 80 mg monthly dose and the change to the dosing strategy including AT monitoring appears to mitigate these risks. Given the hemostatic balance between bleeding and clotting in treatment of hemophilia, thrombotic events are a risk of treatment observed across several therapies to treat the disease including bypassing agents (aPCC and rFVIIa), Hemlibra, and Alhemo.[20,21,32,33] The anticipated prescribing population for fitusiran will likely be hematologists who specialize in hemophilia treatment

and have experience with managing the risks associated with anti-hemophilic therapies, and the care of patients with hemophilia A and B with and without inhibitors. The risk of serious thrombotic events will be communicated in a Boxed Warning and Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide.[2] AT levels should be monitored with the FDA-cleared AT activity assay to ensure accuracy of AT measurements, as recommended in Section 2: Dosage and Administration, and Section 5: Warnings and Precautions.[2]

Adeno-associated virus vector-based gene therapies including Hemgenix, Roctavian, and Beqvez have been associated with risk of hepatotoxicity requiring monitoring of transaminases for varying durations ranging from 3 to 6 months after administration.[25-27] Hematologists managing patients with hemophilia should be familiar with monitoring liver tests associated with AAV gene therapies and the management of hepatotoxicity should liver test elevations occur. The risk of hepatotoxicity will be communicated in a Boxed Warning and Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide.[2]

Acute gallbladder disease is not a commonly observed disease state in patients with hemophilia and patients with hemophilia are at increased risk of bleeding events should they require CCY.[30] However, patients with hemophilia are expected to be knowledgeable about their disease and able identify symptoms indicative of acute gallbladder disease including sudden, severe abdominal pain, nausea and vomiting, or fever, and seek medical attention for these symptoms.[34] Additionally, these patients are likely managed by a multidisciplinary team at a Hemophilia Treatment Center that can promptly direct the patient to appropriate treatment for acute gallbladder disease.[17] The risk of acute and recurrent gallbladder disease will be communicated in a Boxed Warning and Section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide.[2] Inclusion of a Boxed Warning for this risk is expected to increase prescriber awareness of the importance of monitoring patients for symptoms of gallbladder disease and to consider alternative treatments in patients with history of symptomatic gallbladder disease.

Based on the data available, the seriousness of the disease, the prescribing community's likely familiarity with the risks, and the expectation for patients to be closely managed by a multidisciplinary hemophilia-specialized healthcare team, this reviewer has concluded that a REMS is not necessary to ensure the benefits outweigh the risks of fitusiran.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks of fitusiran. The serious thrombotic event risk associated with fitusiran use is similar to other products used for prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophlia, and the hepatotoxicity risk is similar to the AAV vector-based gene therapies used in treatment of hemophilia. The likely prescribers of fitusiran are expected to be familiar with and able to appropriately monitor for these risks. While the risk of acute and recurrent gallbladder disease has not been observed for other hemophilia treatments, inclusion of a Boxed Warning is expected to increase prescriber awareness of this risk, and patients are expected to seek prompt treatment if experiencing

severe symptoms of acute gallbladder disease, and to be closely managed by a multidisciplinary team that can facilitate treatment should gallbladder disease occur.

At the time of this review, labeling negotiations with the Applicant were ongoing. Please notify DRM is new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Genzyme Corporation. Qfitlia (fitusiran). NDA 219019. Original Submission (Orig-1). March 28, 2024.
2. Genzyme Corporation. Qfitlia (fitusiran). NDA 219019. Draft Prescribing Information, Agency edits as of March 19, 2025.
3. Genzyme Corporation. Qfitlia (fitusiran). NDA 219019. Module 2.5 - Clinical Overview. March 28, 2024.
4. Thompson M. Type C Meeting Minutes for Fitusiran. IND 125632. October 12, 2023.
5. Farrell AT. Pre-NDA Type B Meeting Minutes for Fitusiran. IND 125632. April 9, 2024.
6. Diamond C. Food and Drug Administration. Division of Nonmalignant Hematology. Midcycle Communication for fitusiran, NDA 219019. October 10, 2024.
7. Diamond C. Food and Drug Administration. Division of Nonmalignant Hematology. Late-cycle meeting minutes for fitusiran, NDA 219019. January 16, 2025.
8. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158. https://doi.org/10.1111/hae.14046.
9. Data and Statistics on Hemophilia (Centers for Disease Control and Prevention). Available at:. https://www.cdc.gov/hemophilia/data-research/index.html. Accessed June 5, 2024.
10. Schieve LA, Byams VR, Dupervil B, et al. Evaluation of CDC's Hemophilia Surveillance Program — Universal Data Collection (1998–2011) and Community Counts (2011–2019), United States . MMWR Surveill Summ 2020;69(No. SS-5):1–18.
11. Hemophilia A. Rare Disease Database (National Organization for Rare Disorders). Available at:. https://rarediseases.org/rare-diseases/hemophilia-a/. Accessed June 5, 2024.
12. Strachan S. Hemophilia and mental health. Hemophilia News Today. December 13, 2023. Accessed at: hemophilianewstoday.com
13. Male C, Andersson NG, Rafowicz A, et al. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. *Haematologica.* 2021;106(1):123-129.
14. Jardim LL, Santana MP, Chaves DG, van der Bom J, Rezende SM. Risk factors for antibody formation in children with hemophilia: methodological aspects and clinical characteristics of the HEMFIL cohort study. *Blood coagulation and fibrinolysis.* 2021;32(7):443-450.
15. National Bleeding Disorders Foundation. MASAC Document 243 - Recommendation on SIPPET (Survey of Inhibitors in Plasma-Product-Exposed Toddlers): Results and Recommendations for Treatment Products for Previously Untreated Patients with Hemophilia A. In. *Medical and Scientific Advisory Council (MASAC) Documents*June 28, 2016.

16. National Bleeding Disorders Foundation. MASAC Document 274 - Recommendation on Administration of Inhibitor Bypassing Agents in the Home for Patients with Hemophilia and Inhibitors. In. *Medical and Scientific Advisory Council (MASAC) Documents*September 08, 2022.
17. Hoots WK and Shapiro AD. Hemophilia A and B: Routine management including prophylaxis. In: Leung LLK and Tirnauer JS, eds. *UpToDate*. Waltham, MA: UpToDate; 2024.
18. Hoots WK and Lewandowska M. Gene therapy and other investigational approaches for hemophilia. In: Shapiro AD and Tirnauer JS, eds. *UpToDate*. Waltham, MA: UpToDate; 2023.
19. National Bleeding Disorders Foundation. MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors. In. *Medical and Scientific Advisory Council (MASAC) Documents*April 27, 2022.
20. Alhemo (concizumab-mtci). Prescribing Information. Novo Nordisk Inc. Plainsboro, NJ 08536. Issued December 2024; accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761315s000lbl.pdf. Accessed January 31, 2025.
21. Genentech Inc. Hemlibra (emicizumab-kxwh) Prescribing Information. *South San Francisco, CA.* 01/2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761083s018lbl.pdf.
22. Hympavzi (marstacimab-hncq). Prescribing Information. Pfizer Inc. New York, NY 10001. Issued October 2024; accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761369s000lbl.pdf. Accessed November 15, 2024.
23. Taketa Pharmaceuticals USA Inc. FEIBA (anti-inhibitor coagulant complex) Prescribing Information. *Lexington, MA.* 03/2024. https://www.fda.gov/media/78852/download?attachment.
24. Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Integrated Review: Fitusiran, NDA 219019 DRAFT as of February 13, 2025.
25. Roctavian (valoctocogene roxaparvovec-rvox). Prescribing Information. BioMarin Pharmaceutical Inc. Novato, CA 94949. Issued June 2023; accessed at: https://www.fda.gov/media/169937/download?attachment. Accessed February 19, 2025.
26. Hemgenix (etranacogene dezaparvovec-drlb). Prescribing Information. uniQure, Inc. Lexington, MA 02421. Issued November 2022; accessed at: https://www.fda.gov/media/163467/download?attachment. Accessed February 19, 2025.
27. Beqvez (fidanacogene elaparvovec-dzkt). Prescribing Information. Pfizer, Inc. New York, NY 10001. Issued April 2024; accessed at: https://www.fda.gov/media/178140/download?attachment. Accessed February 19, 2025.
28. Genzyme Corporation. Qfitlia (fitusiran). NDA 219019. Module 2.7.3 - Summary of Clinical Efficacy. March 28, 2024.
29. Genzyme Corporation. Qfitlia (fitusiran). NDA 219019. Module 2.7.4 - Summary of Clinical Safety. March 28, 2024.
30. Hemmat S. Division of Hepatology and Nutrition. Draft consultative review on potential hepatoxocity safety signals for fitusiran. March 14, 2025.
31. Heparin sodium injection. Prescribing Information. Fresenius Kabi; 12/2019. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=cb1c1e7a-c9ca-4a07-8833-e45ce436d287&type=pdf. Accessed January 31, 2025.
32. FEIBA (anti-inhibitor coagulant complex). Prescribing Information. Takeda Pharmaceuticals, Inc. Lexington, MA 02421. Issued March 2024; accessed at: https://www.fda.gov/media/78852/download?attachment. Accessed February 19, 2025.

33. NovoSeven RT (Coagulation Factor VIIa [Recombinant]). Prescribing Information. Novo Nordisk Inc. Plainsboro, NJ 08536. Issued July 2020; accessed at: http://www.novo-pi.com/novosevenrt.pdf. Accessed February 19, 2025.
34. Clinic M. Cholecystitis. Available at:. 2024; https://www.mayoclinic.org/diseases-conditions/cholecystitis/symptoms-causes/syc-20364867. Accessed February 19, 2025.

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LAURA A ZENDEL
03/19/2025 12:18:13 PM