Fitusiran in Hemophilia: A Novel Therapeutic Approach Targeting Antithrombin

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Abstract

Fitusiran was FDA approved on March 28, 2025, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A or hemophilia B, with or without factor VIII or IX inhibitors (neutralizing antibodies). This article contains an overview of hemophilia and current treatment and prophylactic strategies, highlighting the key differences between fitusiran and other agents used for prophylaxis. It summarizes antithrombin's role in the coagulation cascade and how fitusiran uses a novel mechanism as a small interfering RNA inhibitor that reduces expression of antithrombin. Pivotal clinical trials that led to its FDA approval are discussed, including dosing regimens, therapeutic drug monitoring, adverse effects, and clinical outcomes. This article provides in-depth information and clinical critique inclusive of and beyond the package insert guidance for advanced practitioners in hematology/oncology.

Hemophilia is an X-linked recessive inherited bleeding disorder caused by clotting factor deficiencies, specifically factor VIII in hemophilia A and factor IX in hemophilia B. These deficiencies can result in spontaneous bleeding and/or increased severity of bleeding following surgery or trauma, potentially leading to arthropathy, end-organ damage, and, in severe circumstances, hemorrhagic shock and death (Centers for Disease Control and Prevention, 2024). Currently, prophylaxis is recommended for patients with severe or moderately severe hemophilia to preserve joint structure and reduce the frequency of bleeding episodes (Manco-Johnson et al., 2007). However, new data are emerging that suggest

minimum factor levels of approximately 15% to 20% (or equivalent hemostatic activity) are needed to completely prevent bleeding and that prophylaxis may also be recommended for patients with mild or moderate hemophilia (Weyand et al., 2024; Négrier et al., 2023; Table 1).

Historically, prophylaxis regimens for severe hemophilia involved intravenous administration of clotting factor concentrates (CFCs) multiple times per week, which can be inconvenient and lead to poor therapy adherence (Thornburg & Duncan, 2017). Extended half-life CFC products have been developed but require frequent intravenous infusions every 4 to 7 days for FVIII products and 7 to 14 days for FIX products. Frequent CFC administration increases the risk for development of autoantibodies (or "inhibitors") that neutralize CFCs and consequently disrupt the intrinsic coagulation cascade. Therefore, recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) were developed as "bypassing agents" (BPAs) to provide hemostatic control through activation of the extrinsic coagulation cascade for patients with inhibitors. However, these products require more frequent administration than CFCs (multiple infusions daily to every other day) and offer suboptimal long-term bleed control (Ljung et al., 2019).

Non-factor prophylaxis therapies offer advantages over CFCs and BPAs for both patients with or without inhibitors, including mitigating concerns for inhibitor development and reducing patient burden through subcutaneous administration every 1 to 60 days (Table 2). Fitusiran (Qfitlia) is the most recent non-factor prophylaxis product approved by the US Food & Drug Administration (FDA) on March 28, 2025, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B with or without inhibitors (U.S. Food and Drug Administration, 2025).

PHARMACOLOGY AND CLINICAL DATA

Fitusiran is the first FDA-approved small interfering RNA (siRNA) product used for prophylaxis in hemophilia. Fitusiran binds and degrades messenger RNA (mRNA), which leads to decreased endogenous antithrombin (AT) expression. AT is a natural anticoagulant that primarily inhibits procoagulant factors FIIa and FXa, but also inhibits factors FIXa, FXIa, and FXIIa to a lesser degree. Therefore, fitusiran-mediated downregulation of antithrombin production helps restore the physiologic balance of hemostasis in patients with hemophilia (Figure 1).

Fitusiran requires therapeutic drug monitoring based on AT levels to reduce the risk of clotting or bleeding. Once fitusiran is initiated, patients may continue their prior CFC or BPA prophylaxis for up to 7 days. This recommendation comes from the first three trials that showed fitusiran's quick effect on reducing antithrombin activity with a mean reduction of up to 77% by day 15 after the initial dose (Young et al., 2023; Srivastava et al., 2023; Kenet et al., 2024). AT activity labs must be monitored using an FDA-approved test. Fitusiran's manufacturer recommends measuring AT activity at weeks 4,

Table 1. Hemophilia Severity Classification

Severity	Factor level	Clinical features	Indication for prophylaxis
Severe	< 1%	Spontaneous bleeding; joint damage	Recommended
Moderately severe	1%–5%	Spontaneous bleeding; joint damage	Recommended
Moderate	1%–5%	Minor trauma or surgery causes severe bleeding; occasional spontaneous bleeding	Not routinely recommended[a]
Mild	5%–40%	Major trauma or surgery causes severe bleeding; rare spontaneous bleeding	Not recommended[a]

Note. Information from Srivastava et al. (2020).
[a]Recommendations are from the most recent guidelines published by the World Federation of Hemophilia in 2020. However, new data are emerging that suggest minimum factor levels of ~15%–20% are needed to completely prevent bleeding and that prophylaxis may also be beneficial for patients with mild or moderate hemophilia (Weyand et al., 2024; Négrier et al., 2023).

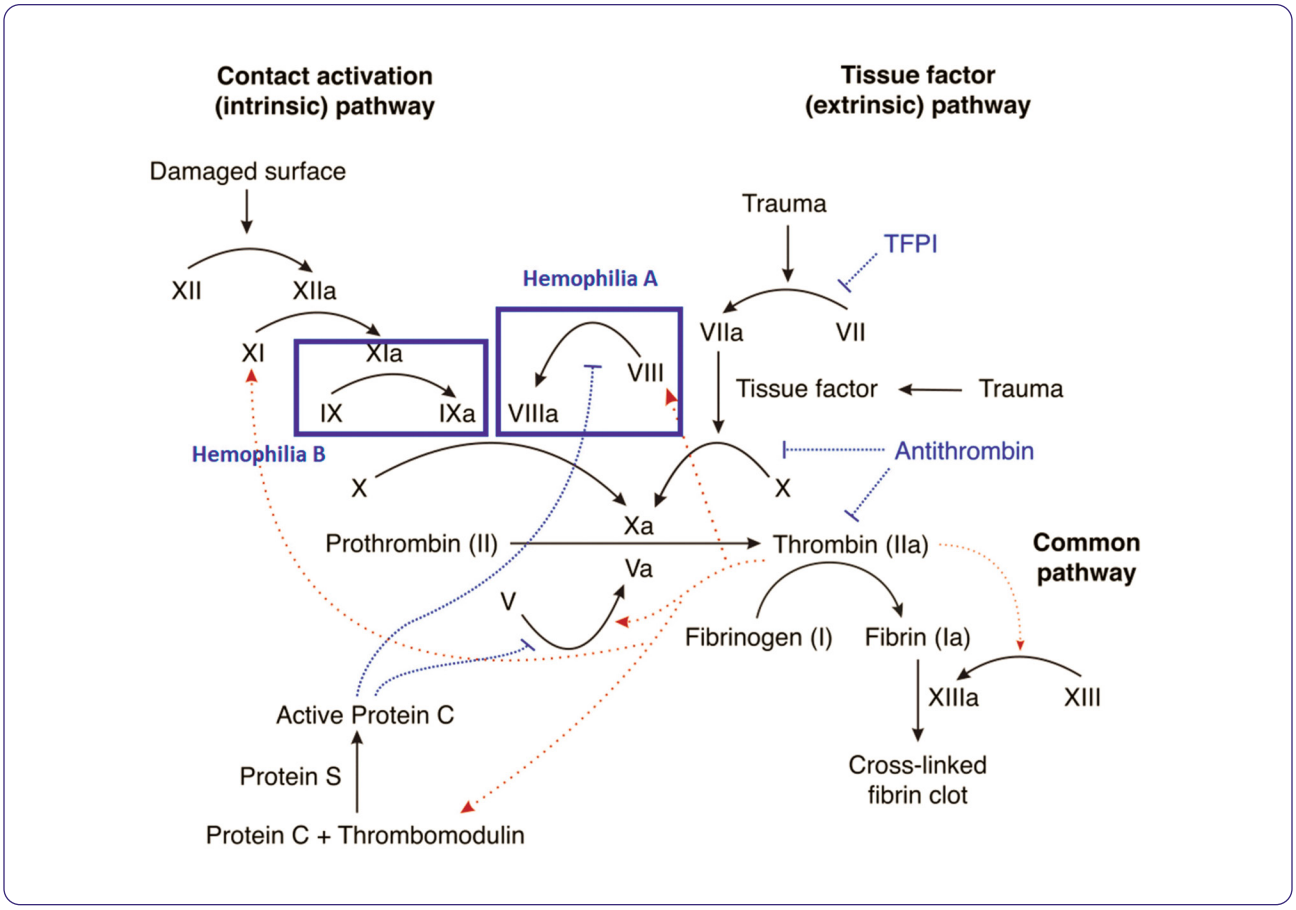

Figure 1. Coagulation cascade. Adapted from Badulescu et al. (2024).

12, 20, and 24 following the starting dose and after dose modification. When AT activity is < 15%, the dose should be decreased to reduce thrombosis risk. When AT activity is > 35%, the dose should be increased to reduce bleeding risk. Once the patient's target dose is determined based on AT activity between 15% and 35%, AT activity is measured annually. Fitusiran's industry-sponsored website contains an interactive dosing tool to determine recommended dose based on AT activity level and current dose (Sanofi, 2025b). Table 3 lists trials with fitusiran.

ADVERSE EFFECTS

Fitusiran carries two black box warnings, the first being thrombotic events. Thrombotic events were reported in 2.6% of patients who received the 80-mg monthly dose, including a fatal event of cerebral venous sinus thrombosis. Notably, this event was initially misdiagnosed as a cerebral bleed and treated with CFC dosing that exceeded current guidelines (National Bleeding Disorders Foundation, 2021). Thrombotic events were reported in 1.4% (n = 4) of patients who received an AT-based dose regimen (AT-DR) that targeted AT activity of 15% to 35%. In these 4 patients, their AT levels were 15.5%, 65.3%, 23.3%, and 24.4%. Their concurrent risk factors included diabetes (n = 2), hypertension (n = 2), hyperlipidemia (n = 2), postoperative status (n = 2), obstructive sleep apnea (n = 1), nephrotic syndrome (n = 1), and morbid obesity (n = 1). Both postoperative patients had noncompliance with blood management guidelines (BMG), with one patient receiving an aPCC dose and another of FVIII exceeding BMG. The only event determined to be due to fitusiran was in the patient who received excess FVIII. Notably, all trials excluded patients at higher thrombosis risk, including baseline AT activity < 60%, antiphospholipid syndrome, factor V Leiden, protein S or

Table 2. Comparison of Non-Factor Hemophilia Agents and Their FDA-Approved Indications

Generic Name	Hemophilia A without inhibitors	Hemophilia B without inhibitors	Hemophilia A with inhibitors	Hemophilia B with inhibitors
Emicizumab-kxwh FDA approval: 11/16/2017	✓	X	✓	X
Marstacimab-hncq[a] FDA approval: 10/11/2024	✓	✓	X	X
Concizumab-mtci FDA approval: 12/20/2024	✓	✓	✓	✓
Fitusiran FDA approval: 3/28/2025	✓	✓	✓	✓

Note. Information from Novo Nordisk Inc. (2025); Pfizer Inc. (2024); Genentech Inc. (2025); Sanofi (2025).
[a]2025 BASIS trial offers preliminary data to support reduced annualized bleeding rates and favorable safety profile in patients with hemophilia A/B with inhibitors (Matino et al., 2025).

C deficiency, prothrombin mutation G20210A, malignancy within 2 years, or history of arterial/venous thromboembolism, atrial fibrillation, valvular disease, myocardial infarction, angina, transient ischemic attack, or stroke. Patients with platelet count ≤ 100,000 and an eGFR ≤ 45 mL/min (using Modification of Diet in Renal Disease; MDRD) were also excluded.

The second black box warning is recurrent gallbladder disease. 17% of patients receiving the fixed dose of 80 mg monthly had a gallbladder event, with 4% requiring cholecystectomy. 3.8% of patients receiving the AT-DR regimen had a gallbladder event, with 0.3% requiring cholecystectomy.

In addition to expected changes in antithrombin levels, there have been increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Hepatotoxicity may be related to fitusiran's mechanism of action, as fitusiran is taken up by the asialoglycoprotein receptor found only on hepatocytes and is cleaved into smaller fragments that bind and silence the mRNA of antithrombin within hepatocytes (National Institute of Diabetes and Digestive and Kidney Diseases, 2025). Serum ALT and AST elevations > 3 × ULN were seen in 24% (n = 10) of patients receiving fitusiran in ATLAS-INH and in 19% (n = 15) of patients receiving fitusiran in ATLAS-A/B. In ATLAS-OLE, which used AT-DR, 3.5% (n = 10) of patients treated with fitusiran had at least one LFT value > 3 × ULN, with a median onset of 89 days after initial dosing. Baseline LFTs should be obtained before initiation, monthly for the first 6 months or after a dose increase, and then as clinically indicated. It is recommended to hold and consider discontinuing fitusiran if LFTs elevate > 5 × ULN. If patients have hepatic impairment (Child-Pugh Class A, B and C), it is not recommended to initiate fitusiran.

Phase I and II trials did not evaluate fitusiran's impact on aPTT (activated partial thromboplastin time), PT (prothrombin time), or INR (international normalized ratio). A study in 2020 using plasma from hemophilia A patients evaluated the impact of reduced AT levels on coagulation assays and found no effect on aPTT, with no therapeutically relevant effect on PT (Wang et al., 2020).

CLINICAL APPLICATION AND FUTURE DIRECTIONS

Fitusiran's every-2-month administration schedule is the least frequent among the non-factor replacement therapies, with other recent approvals requiring daily concizumab (Alhemo), weekly marstacimab (Hympavzi), or every 2 to 4 weeks emicizumab (Hemlibra). Fitusiran is one of only two non-factor replacement therapies, in addition to concizumab, with specific therapeutic drug monitoring. While this monitoring can be inconvenient, some patients prefer having an objective metric of their response to therapy.

If higher doses, more frequent administration, or repeated doses are needed to control a breakthrough bleed, antithrombin replacement may be considered to counteract fitusiran's effect; however, specific antithrombin dosing remains based on clinical judgement (Table 4). In clinical studies, patients with hemophilia A or B with or without inhibitors have undergone both major (n = 60) and

Table 3. Trials With Fitusiran

Trial	Patient population	Intervention	Comparator	Findings	Limitations
ATLAS-INH	Age 12 and older, severe hemophilia A or B with inhibitors	Fitusiran 80 mg SQ monthly	On-demand BPAs	Mean ABR was significantly lower in the fitusiran prophylaxis group (1.7 [95% CI = 1.0–2.7]) than in the on-demand BPAs group (18.1 [95% CI = 10.6–30.8]), corresponding to a 90.8% (95% CI = 80.8–95.6) reduction in ABR in favor of fitusiran prophylaxis ($p < .0001$).	In this study, fitusiran was used for prophylaxis and was compared to non-standard of care of on-demand treatment with BPAs. Standard of care would be prophylactic BPA administration every 1–2 days.
ATLAS-A/B	Age 12 and older, severe hemophilia A or B without inhibitors	Fitusiran 80 mg SQ monthly	On-demand CFCs	Mean ABR was significantly lower in the fitusiran prophylaxis group (3.1 [95% CI = 2.3–4.3]) than in the on-demand CFCs group (31.0 [95% CI = 21.1–45.5]; rate ratio 0.101 [95% CI = 0.064–0.159]; $p < .0001$).	In this study, fitusiran was used for prophylaxis and was compared to non-standard of care of on-demand treatment with CFCs. Standard of care would be prophylactic CFC every 4–14 days, depending on product used.
ATLAS-PPX	Age 12 and older, severe hemophilia A or B with or without inhibitors	Fitusiran 80 mg SQ monthly	Prophylaxis with BPAs or CFCs	Observed median ABRs were 6.5 (IQR, 2.2–19.6)/4.4 (IQR, 2.2–8.7) with BPA/CFC prophylaxis vs. 0.0 (IQR, 0.0–0.0)/0.0 (IQR, 0.0–2.7) with fitusiran respectively. Estimated mean ABRs were reduced with fitusiran by 79.7% ($p = .0021$) and 46.4% ($p = .0598$) vs. BPA/CFC prophylaxis, respectively.	Patients were compared to their historical prophylaxis regimens, which varied widely in intensity and adherence.
ATLAS-OLE	Age 12 and older, severe hemophilia A or B with or without inhibitors who completed ATLAS-INH, A/B, or PPX	Starting dose 50 mg every 2 months and dose adjusted with the AT-DR	Historical patient data from a previous trial	Median observed ABR with AT-DR was 3.7 (IQR, 0.0–7.5). Integrated efficacy analyses demonstrated superiority of AT-DR over on-demand CFCs (CFCs; 71% mean ABR reduction; $p < .0001$), and on-demand BPAs (BPAs; 73% mean ABR reduction; $p = .0006$); improvement over BPA prophylaxis (70% mean ABR reduction); and ABR comparable with that observed with CFC prophylaxis.	Participants were trial completers from previous ATLAS studies; this may represent a healthier and/or more adherent subset of patients. It also excludes those who discontinued during previous trials due to adverse events.

Note. ABR = annualized bleeding rate; AT-DR = antithrombin-based dose regimen; BPA = bypassing agent; CFC = clotting factor concentrate; INH = inhibitor; IQR = interquartile range; OLE = open-label extension; PPX = prophylaxis; SQ = subcutaneous. It is important to note that the mean ABR was significantly lowered with fitusiran prophylaxis compared to on-demand treatment with CFCs (rate ratio 0.101 ($p < .0001$)) or BPAs (90.8% reduction ($p < .0001$)), as well as when compared to prophylaxis with CFCs (46.4% ($p = .0598$)) or BPAs (79.7% reduction ($p = .0021$)). Information from Young et al. (2023); Srivastava et al. (2023); Kenet et al. (2024); Young et al. (2025b).

Table 4. Suggested Factor Product Dosing for Management of Breakthrough Bleeding in Patients Receiving Fitusiran

	Factor VIII	Standard half-life factor IX	Extended half-life factor IX	Activated prothrombin complex concentrate	Activated recombinant factor VII
Recommended dose	10 IU/kg (max: 20 IU/kg)	20 IU/kg (max: 30 IU/kg)	20 IU/kg (max: 30 IU/kg)	30 U/kg (max: 50 U/kg)	≤ 45 µg/kg
Repeat dosing	Should not repeat in < 24 hours	Should not repeat in < 24 hours	Should not repeat in < 5 to 7 days	Should not repeat in < 24 hours	Should not repeat in < 2 hours

Note. It is important to note that activated recombinant factor VII dosing may differ between formulations (eptacog alfa and eptacog beta) based on in vitro findings and has not been studied in vivo to date (Zaheer et al., 2025). While bleeding is a risk, so is thrombosis. Risk mitigation measures have been identified, including pausing the dose when thrombotic events are observed, preventing prolonged AT levels < 10%, and targeting AT activity levels of 15% to 35%. Information from Sanofi (2025).

minor (n = 71) surgical procedures without discontinuing fitusiran. Documentation in clinic notes should clearly identify fitusiran use to inform other clinicians. Hemophilia clinical teams should proactively educate patients and caregivers on fitusiran's unique considerations, including its dosing, monitoring, and potential interactions with other therapies as they are identified. Additionally, targeted education initiatives may be warranted to raise awareness of fitusiran's management strategies, like prior efforts with emicizumab.

Patients can administer fitusiran at home once properly trained. While CFCs and BPAs can be administered at home, they require IV access, which comes with its own risks and inconveniences. Fitusiran is supplied in single-use vials or pre-filled single-use pens. Both formulations can be stored in the refrigerator or at room temperature. If stored in the refrigerator, patients should be counseled to allow the vial or pen to warm up at room temperature for at least 30 minutes to decrease stinging with administration.

In contrast to concizumab and marstacimab, early evidence suggests fitusiran is safe to continue perioperatively, regardless of AT activity level (Pipe et al., 2025). Of note, major and minor surgeries have been performed safely in patients receiving emicizumab also (Kruse-Jarres et al., 2022).

While there are short-term data with fitusiran, results from long-term treatment are lacking regarding the risk of bleeding, thrombosis, and other adverse effects. Currently, the ATLAS-NEO trial is underway to assess long-term safety and efficacy of the AT-DR for fitusiran. The SWITCH study investigating the safety and tolerability of patients with hemophilia A switching from emicizumab to fitusiran prophylaxis is currently ongoing and will be important for establishing guidance on converting between prophylaxis strategies (Young et al., 2025a). Other comparative and converting studies between fitusiran and other non-factor products would be helpful to guide clinical decision-making.

Disclosure

The authors have no conflicts of interest to disclose.

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