Drugs (2025) 85:1073–1077
https://doi.org/10.1007/s40265-025-02203-y

ADISINSIGHT REPORT

Fitusiran: First Approval

Arnold Lee[1]

Accepted: 2 June 2025 / Published online: 28 June 2025

Abstract
Haemophilia A and B are inherited bleeding disorders caused by mutations in clotting factors. Small interfering RNA therapies may be utilised to restore coagulation by preventing the synthesis of antithrombin. Fitusiran (QFITLIA™) is a small interfering RNA therapy that targets antithrombin, which is being developed by Sanofi for the prophylactic management of haemophilia A and B with or without inhibitors. Fitusiran has the potential to be administered less frequently than other prophylactic treatments for haemophilia. This article summarizes the milestones in the development of fitusiran leading to this first approval for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients aged 12 years and older with haemophilia A or B with or without factor VIII or IX inhibitors.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.29176136

Fitusiran (QFITLIA™): Key Points

A small interfering RNA is being developed by Sanofi for the management of haemophilia A and B

Received its first approval on 28 Mar 2025 in the USA

Approved for use for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients aged 12 years and older with haemophilia A or B with or without factor VIII or IX inhibitors

1 Introduction

Haemophilia A and B are inherited bleeding disorders that occur due to mutations in clotting factor VIII (haemophilia A) or IX (haemophilia B) [1]. Prophylactic therapies aim to reduce the frequency of bleeds, which includes replacement of factors with clotting factor concentrates (CFC) or by the administration of bypassing agents (BPA), such as activated prothrombin complex or recombinant factor VIIa (fVIIa). However, neutralising antibodies raised against CFC can limit their efficacy, and the usefulness of BPA is limited by their short half-lives, requiring frequent infusions [1].

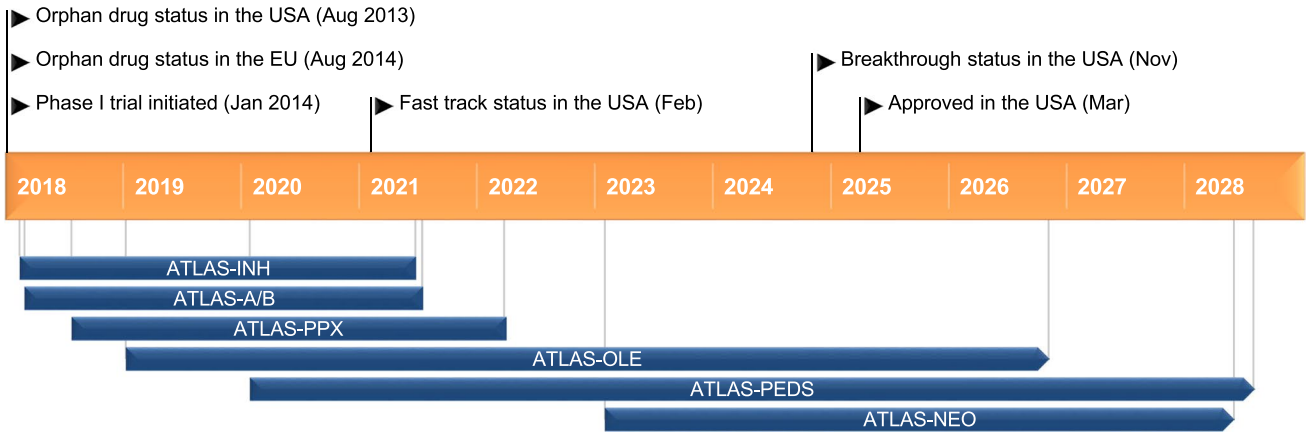
RNA interference has been investigated as a prophylactic treatment for haemophilia [1, 2]. As antithrombin is a key inhibitor of thrombin generation, it has been identified as a possible target; a reduction in antithrombin activity increases thrombin generation to restore coagulation [1, 2]. Small interfering RNA therapies incorporate synthetic double-stranded RNA to target messenger RNA, thereby inhibiting the expression of the target gene, such as the gene coding for antithrombin (*SERPINC1*) [1].

Fitusiran (QFITLIA™) is a small interfering RNA directed against antithrombin being developed by Genzyme Corporation, which received its first approval in March 2025 in the USA for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients aged 12 years and older with haemophilia A or B with or without factor VIII or IX inhibitors [3]. In comparison with other prophylactic therapies, prophylaxis with fitusiran can reduce the frequency of administration (6–12 subcutaneous administrations per year) [3].

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

✉ Arnold Lee
dru@adis.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand



Key milestones and phase III trials in the development of fitusiran for the management of haemophilia A or B

The recommended starting dosage of fitusiran is 50 mg administered subcutaneously once every 2 months, with modifications to dose (10, 20 or 50 mg) and/or frequency (once monthly or once every 2 months) based on antithrombin activity (target activity 15–35%) [4]. Consult local prescribing information for further details regarding dosage modification and recommended on-demand treatments for breakthrough bleeds. Monitor antithrombin activity using an FDA-cleared test during treatment and prior to initiating treatment [4].

Fitusiran carries a boxed warning for thrombotic events and acute and recurrent gallbladder disease [4]. Serious thrombotic events have occurred in patients with risk factors for thromboembolism. Interrupting fitusiran in patients with a thrombotic event is recommended. Acute and recurrent gallbladder disease, including cholelithiasis and cholecystitis have occurred in fitusiran recipients. Recommendations include monitoring patients for signs and symptoms of acute and recurrent gallbladder disease, considering discontinuation of fitusiran if gallbladder disease occurs and considering alternative therapies for patients who have a history of symptomatic gallbladder disease [4].

1.1 Company Agreements

In January 2014, Genzyme Corporation (Sanofi Genzyme) and Alnylam Pharmaceuticals formed an alliance to develop RNA interference treatments for rare genetic diseases [5]. Subsequently, in November 2016, Genzyme and Alnylam agreed to co-develop and co-commercialise fitusiran globally [5]. Although the alliance was concluded in April 2019, existing agreements regarding fitusiran were unaffected [6].

2 Scientific Summary

2.1 Pharmacodynamics

In an animal model of factor X-deficiency, fitusiran reduced antithrombin activity to 17% [7]. Fitusiran-treated mice in comparison with control mice had shorter lag time (3.3 vs 7.0 min), higher endogenous thrombin potential (904 vs 149 nM × min), higher peak thrombin (36 vs 14 nM) and increased haemostatic activity (8 vs 2 clots per 30 min) [7].

In people with haemophilia A or B who received fitusiran at the recommended dosage, the mean antithrombin activity was 24% [4]. Simulations indicated that steady state antithrombin activity was reached within 23 weeks of initiating fitusiran or following dosage modification. Persistent antithrombin activity (> 60% activity) is estimated to occur approximately 6 months after discontinuing fitusiran [4].

2.2 Pharmacokinetics

The pharmacodynamic effects of fitusiran are primarily influenced by its liver pharmacokinetics, rather than its plasma pharmacokinetics [4]. The fitusiran dosage regimen (10, 20 or 50 mg administered once monthly or every 2 months) aims to maintain plasma antithrombin activity levels of 15–35%. In people with haemophilia A or B receiving fitusiran at the recommended dosage, the plasma exposure increases in a dose-proportional manner and no accumulation is expected to occur with repeat dosing. At steady state, the mean maximum plasma concentration with a 20 mg or 50 mg dose is 34.4 ng/mL and 84.1 ng/mL, and the mean area under the plasma-time curve is 491 and 1290 ng · h/mL. The mean time to peak plasma concentration for the respective doses is 2.88 and 3.78 h and apparent volume of distribution is 431 and 570 L. Fitusiran is 96.6% bound to plasma proteins [4].

Features and properties of fitusiran

Alternative names	QFITLIA™, ALN-AT3, ALN-AT3SC, SAR-439774
Class	Amides, amino sugars, antihaemorrhagics, drug conjugates, small interfering RNA
Mechanism of action	Antithrombin III expression inhibitors, RNA interference
Route of administration	Subcutaneous injection
Pharmacodynamics	In an animal model, fitusiran ↓ antithrombin activity, ↓ lag time, ↑ endogenous thrombin potential, ↑ peak thrombin, ↑ haemostatic activity; in people with haemophilia A or B, mean antithrombin activity was 24%, steady state antithrombin activity was reached within 23 weeks, persistent antithrombin activity ≈ 6 months after discontinuation
Pharmacokinetics	Plasma exposure is dose proportional, no accumulation with repeat dosing; C_{max} (with 20 or 50 mg dose) 34.4 and 84.1 ng/mL; AUC 491 and 1290 ng · h/mL; T_{max} 2.88 and 3.78 h; V_D/F 431 and 570 L; 96.6% protein bound; $t_{½}$ 5.57 and 7.98 h; CL/F 41.9 and 50.8 L/h; 14.6% recovery of a 50 mg dose in the urine
Most frequent adverse reactions	Viral infection, nasopharyngitis, bacterial infection, hepatic injury, arthralgia, prothrombin fragment 1.2 increased, injection site reaction, headache, cough
ATC codes	
WHO ATC code	B02B-X12 (fitusiran)
EphMRA ATC code	B2G (systemic haemostatics)

The mean elimination half-life of fitusiran is 5.57 h with a 20 mg dose and 7.98 h with a 50 mg dose. The apparent clearance of the respective doses is 41.9 and 50.8 L/h [4]. Fitusiran is metabolised by endo and exonucleases into short lengths of oligonucleotides and is not a substrate for CYP450 enzymes or transporters. 14.6% of a 50 mg dose was recovered unchanged in the urine over 24 h [4].

2.3 Therapeutic Trials

The mean annualised bleeding rate (ABR) during the efficacy period was significantly ($p < 0.0001$) lower in 38 participants who received fitusiran prophylaxis (1.7 bleeds per year) than in 19 participants who received on-demand BPA (18.1 bleeds per year) during the ATLAS-INH (NCT03417102) pivotal phase III trial (primary endpoint) [8]. In this global open-label study, eligible participants included men, boys and young adults aged ≥ 12 years with severe haemophilia A or B and inhibitory antibodies to factor VIII or IX (subsequently referred to as inhibitors). Additionally, participants had ≥ 6 bleeding episodes requiring BPA ≤ 6 months prior to screening. Participants were randomised to receive prophylactic fitusiran 80 mg once monthly (not a recommended dose [4]) plus BPA for breakthrough bleeding, or continued to receive on-demand treatment with BPA. Efficacy was measured during days 29–246, following an onset period (days 1–28). The mean ABR of secondary endpoints were significantly ($p < 0.0001$) lower in fitusiran prophylaxis recipients versus recipients of on-demand BPA, including all treated bleeds (2.0 vs 18.8 bleeds per year), treated spontaneous bleeds (0.9 vs 15.7 bleeds per year) and treated joint bleeds (1.3 vs 13.8 bleeds per year) [8].

The mean ABR during the efficacy period was significantly ($p < 0.0001$) lower in 79 recipients of fitusiran prophylaxis (4.4 bleeds per year) than in 40 recipients of on-demand CFC (33.2 bleeds per year) during the ATLAS-A/B pivotal phase III trial (primary endpoint) [9]. During this global open-label trial, participants were males aged ≥ 12 years with severe haemophilia A or B without inhibitors and were not receiving prophylactic treatment. Participants were also required to have ≥ 6 bleeding events requiring on-demand treatment with CFC ≤ 6 months prior to screening. Participants were randomised to receive prophylaxis with fitusiran 80 mg once monthly plus CFC for breakthrough bleeding, or continued to receive on-demand CFC. The efficacy was evaluated during the efficacy period during days 29–246. The mean ABR of secondary endpoints, including treated bleeding events (3.1 vs 31.0 bleeds per year), treated spontaneous bleeds (1.8 vs 22.0 bleeds per year) and treated joint bleeds (2.3 vs 23.4 bleeds per year) were significantly ($p < 0.0001$) lower in fitusiran prophylaxis recipients than in recipients of on-demand CFC [9].

The estimated mean ABR was 6.4 bleeds per year across all 227 participants in an interim analysis of the ATLAS-OLE pivotal phase III trial (secondary endpoint, the primary endpoint was safety); the estimated mean ABR in 78 participants with inhibitors was 3.9 bleeds per year and in 149 participants without inhibitors was 7.4 bleeds per year [10]. In this global, open-label, long-term extension trial, participants from the pivotal ATLAS-INH and ATLAS-A/B trials, in addition to participants from the ATLAS-PPX phase III trial (discussed below) were eligible to be rolled over into ATLAS-OLE. Participants initially received subcutaneous doses of fitusiran 80 mg once monthly, which was revised to 50 mg once every 2 months and adjusted to 20, 50 or 80

Key clinical trials of fitusiran (sponsored by Genzyme, a Sanofi company, or Sanofi)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Fitusiran, bypassing agents	PwH A or B	III	Completed	Global	ATLAS-INH, NCT03417102
Fitusiran, factor concentrates	PwH A or B	III	Completed	Global	ATLAS-A/B, NCT03417245
Fitusiran	PwH A or B	III	Ongoing	Global	ATLAS-OLE, NCT03754790
Fitusiran, bypassing agents, factor concentrates	PwH A or B	III	Completed	Global	ATLAS-PPX, NCT03549871
Fitusiran	PwH A or B	III	Ongoing	Global	ATLAS-PEDS, NCT03974113
Fitusiran, bypassing agents, factor concentrates	PwH A or B	III	Ongoing	Global	ATLAS-NEO, NCT05662319

PwH people with haemophilia

mg doses once every 2 months based on the antithrombin activity of each participant [10].

The estimated mean ABR of treated bleeds was significantly ($p = 0.0008$) lower in 65 participants who switched to fitusiran prophylaxis (2.9 bleeds per year) from BPA or CFC prophylaxis (7.5 bleeds per year) during the ATLAS-PPX phase III trial (primary endpoint) [11]. In this global, open-label trial, participants were male and aged ≥ 12 years with severe haemophilia A or B and were receiving prophylaxis with BPA (with inhibitors and ≥ 2 bleeds in the past 6 months) or CFC (without inhibitors and ≥ 1 bleed in the past 12 months) prior to switching to fitusiran prophylaxis. Most participants received fitusiran 80 mg once monthly and two participants received fitusiran 50 mg once every 2 months. The ABR of spontaneous bleeds (2.2 vs 5.0 bleeds per year) and joint bleeds (2.6 vs 5.3 bleeds per year) were significantly ($p \leq 0.0242$) lower with fitusiran prophylaxis than with BPA or CFC prophylaxis [11].

2.4 Adverse Reactions

The most commonly reported (incidence ≥ 5%) adverse reactions with fitusiran dosed to individual antithrombin measurements in 286 trial participants with haemophilia A or B were viral infection (incidence 29%), nasopharyngitis (26%), bacterial infection (11%), hepatic injury (8%), arthralgia (8%), prothrombin fragment 1.2 increased (7%), injection site reaction (6%), headache (5%) and cough (5%) [4]. Serious adverse reactions were reported in 4 (1.4%) participants, including two participants who had serious reactions of cholecystitis. Fitusiran was permanently discontinued in 4 (1.4%) participants, which were attributed to liver injury, post-operative deep vein thrombosis, cerebral infarction and pruritus [4].

In a pooled safety population of 335 trial participants, serious thrombotic events were reported in 2.6% of participants (incidence rate 2.3 events per 100 person-years) who received a fixed fitusiran dose of 80 mg once monthly (not a recommended dose), which included a fatal event of cerebral venous sinus thrombosis. In participants who received fitusiran on an antithrombin-based dose regimen, the incidence rate was 0.8 events per 100 person-years [4].

The incidence of gallbladder events in 270 participants who received a fixed dose of fitusiran (e.g., 80 mg once monthly) was 17% and 4% of participants underwent cholecystectomy [4]. In 286 participants who received fitusiran on an antithrombin-based dose regimen, 3.8% of participants experienced a gallbladder event and 0.3% underwent cholecystectomy [4].

2.5 Companion Diagnostic

The INNOVANCE® Antithrombin assay by Siemens Healthineers has been cleared by the FDA as a companion diagnostic for fitusiran [3].

2.6 Ongoing Clinical Trials

There are four ongoing clinical trials investigating fitusiran for the management of haemophilia. Three trials are included in the ATLAS program and are not recruiting participants: the ATLAS-OLE (NCT03754790) phase III open-label extension trial, the ATLAS-PEDS (NCT03974113) phase III trial to determine an appropriate dosage of fitusiran in people aged 1–12 years and the ATLAS-NEO (NCT05662319) phase III trial to study the effects of switching from standard of care to fitusiran. The NCT06145373 phase I trial is currently recruiting participants to explore the safety and tolerability of switching from emicizumab to fitusiran prophylaxis.

3 Current Status

Fitusiran received its first approval on 28 Mar 2025 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients (aged 12 or older) with haemophilia A or B with or without factor VIII or IX inhibitors in the USA [3].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-025-02203-y.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Arnold Lee is a contracted employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Boyce S, Rangarajan S. RNAi for the treatment of people with hemophilia: current evidence and patient selection. J Blood Med. 2023;14:317–27.
2. Young G, Lenting PJ, Croteau SE, et al. Antithrombin-lowering in hemophilia: a closer look at fitusiran. Res Pract Thromb Haemost. 2023;7(4):1–13.
3. Sanofi. Qfitlia approved as the first therapy in the US to treat hemophilia A or B with or without inhibitors [media release]. 28 Mar 2025. https://www.globenewswire.com/news-release/2025/03/28/3051637/0/en/Press-Release-Qfitlia-approved-as-the-first-therapy-in-the-US-to-treat-hemophilia-A-or-B-with-or-without-inhibitors.html.
4. Genzyme Corporation. QFITLIA (fitusiran) injection, for subcutaneous use. 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219019s000lbl.pdf. Accessed 1 Apr 2025.
5. Sanofi Genzyme. Sanofi Genzyme and Alnylam initiate ATLAS phase 3 program with investigational RNAi therapeutic fitusiran in patients with hemophilia A and B with or without Inhibitors [media release]. 7 Jul 2017. http://www.sanofigenzyme.com.
6. Sanofi. Sanofi and Alnylam conclude research and option phase of 2014 rare disease alliance [media release]. 8 Apr 2019. http://www.sanofi.com.
7. Verhenne S, McCluskey G, Maynadié H, et al. Fitusiran reduces bleeding in factor X-deficient mice. Blood. 2024;144(2):227–36.
8. Young G, Srivastava A, Kavakli K, et al. Efficacy and safety of fitusiran prophylaxis in people with haemophilia A or haemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial. Lancet. 2023;401(10386):1427–37.
9. Srivastava A, Rangarajan S, Kavakli K, et al. Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023;10(5):e322–32.
10. Young G, Kavakli K, Klamroth R, et al. Safety and efficacy of a fitusiran antithrombin-based dose regimen in people with hemophilia A or B: the ATLAS-OLE study. Blood. 2025. https://doi.org/10.1182/blood.2024027008.
11. Kenet G, Nolan B, Zulfikar B, et al. Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024;143(22):2256–69.