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Fitusiran: The first approved siRNA therapy for hemophilia *via* reducing plasma antithrombin levels

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SUMMARY: Hemophilia is a coagulation disorder caused by deficiencies in clotting factors and is primarily classified into hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency). Current treatment relies predominantly on replacement therapy, where patients receive clotting factor concentrates either episodically or prophylactically to achieve hemostasis or mitigate bleeding risks. Despite its efficacy, this approach presents limitations, including suboptimal treatment accessibility due to high costs, reduced patient compliance from frequent intravenous administration, and therapeutic failure in patients developing plasma inhibitors. These challenges underscore the need for novel therapeutics addressing unmet clinical demands. On March 28, 2025, the US Food and Drug Administration (FDA) approved fitusiran, a small interfering RNA (siRNA) therapeutic for hemophilia. This first-in-class agent demonstrates pan-hemophilia efficacy by targeting antithrombin to enhance thrombin activity, irrespective of factor VIII/IX deficiency status or plasma inhibitor presence. By pioneering a mechanism of antithrombin suppression, enabling sustained therapeutic action, and facilitating precision monitoring protocols, fitusiran has the potential to redefine hemophilia treatment paradigms.

Keywords: fitusiran, siRNA, replacement therapy, hemophilia, clotting factors

Hemophilia is a genetic bleeding disorder primarily caused by deficiencies in clotting factors, leading to impaired blood coagulation. Based on the specific clotting factor deficiency, it is mainly classified into hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency), accounting for 80-85% and 15-20% of cases, respectively (*1*). The disease follows an X-chromosome-linked recessive inheritance pattern, predominantly affecting males, while females are typically carriers. Globally, the estimated prevalence of hemophilia A is 17.1 per 100,000 males (with severe cases at 6.0 per 100,000 males), and hemophilia B has a prevalence of 3.8 per 100,000 males (*2*).

Current treatment for hemophilia relies on replacement therapy, where patients receive clotting factor concentrates either on-demand or prophylactically to control or prevent bleeding (*3*). While effective, replacement therapy has limitations, including high costs limiting accessibility, poor patient compliance due to frequent intravenous infusions, and treatment failure in cases where plasma inhibitors (neutralizing antibodies) develop (*3*). These challenges highlight the need for novel therapies to address unmet clinical needs.

On March 28, 2025, the US FDA approved fitusiran, the first small interfering RNA (siRNA) therapy for hemophilia (*4*). Administered via subcutaneous injection, fitusiran delivers siRNA targeting the *SERPINC1* gene in liver cells to suppress antithrombin synthesis (*5*). By reducing plasma antithrombin levels, fitusiran enhances thrombin activity to restore hemostasis, regardless of whether patients have a factor VIII (type A) or IX (type B) deficiency or plasma inhibitors. A key advantage is the reduced frequency of dosing compared to traditional clotting factor replacement. The initial dose is 50 mg every two months, with adjustments based on the INNOVANCE antithrombin assay, a companion diagnostic that monitors antithrombin activity to maintain levels within a target range (15-35%), balancing prevention of bleeding and the risk of thrombosis (*6*).

The approval was based on positive results from randomized controlled Phase III clinical trials, including **ATLAS-INH**, **ATLAS A/B**, and **ATLAS-OLE**. The **ATLAS-INH** trial involved 57 adult and pediatric males (age ≥ 12 years) with hemophilia A or B and neutralizing antibodies against factor VIII or factor IX (*6*). Patients in the treatment group received prophylactic fitusiran at a fixed monthly dose of 80 mg, while the control group received on-demand bypassing agents (BPAs) for bleeding events over 9 months (*6*). The **ATLAS A/B** trial involved 120 adult and pediatric

males (age ≥ 12 years) with hemophilia A or B without inhibitory antibodies (*6*). The treatment group received prophylactic fitusiran at a fixed monthly dose of 80 mg, while the control group received on-demand clotting factor concentrates over 9 months (*6*). Due to increased risks of severe thrombotic events, gallbladder disorders, and hepatotoxicity associated with the fixed monthly dose of 80 mg in these trials, the **ATLAS-OLE** study was conducted with a modified dosing regimen (*6*). This study included patients from ATLAS-INH, ATLAS A/B, and a crossover study (ATLAS-PPX) involving patients previously receiving clotting factor concentrates or BPAs. An antithrombin activity-guided dosing strategy (targeting antithrombin activity of 15% to 35%) for fitusiran prophylaxis was adopted for a total of 223 patients who underwent a 6-month dose adjustment period and a 7-month primary efficacy observation period. Results indicated an overall median annualized bleeding rate (ABR) of 3.7 (1.9 for inhibitor-positive patients and 3.8 for inhibitor-negative patients) (*6*). Compared to control group data from ATLAS-INH, the antithrombin-guided dosing strategy significantly reduced ABR in the treatment group (5.1 *vs*. 19.1), indicating that fitusiran prophylaxis is superior to on-demand BPAs in patients with inhibitors (*6*). Similarly, compared to ATLAS A/B control data, the treatment group had a significant reduction in the ABR (9.0 *vs*. 31.4), demonstrating fitusiran's superiority over on-demand clotting factor concentrates in patients without inhibitors (*6*). In terms of safety, fitusiran carries potential risks of thrombotic events, gallbladder disorders, and hepatotoxicity (*6*). Other common adverse reactions included viral infections, common cold symptoms (nasopharyngitis), and bacterial infections (*6*).

Capitalizing on its innovative mechanism of antithrombin suppression, sustained pharmacological activity, and precision monitoring framework, fitusiran has the potential to redefine therapeutic paradigms for hemophilia. Nevertheless, comprehensive validation of its real-world efficacy and safety necessitates further longitudinal clinical evaluation across diverse patient populations.

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