Segment 3: Rebalancing Agents – Current Evidence and Clinical Integration

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Rebalancing Agents in Hemophilia: Overview

Drug	Indication	Dosing	Safety / Dosing Context
Marstacimab	FDA-approved for HA/HB without inhibitors	SC once weekly Flat dosing (age ≥ 12 y), 150 mg weekly after 300 mg load No routine laboratory monitoring	One DVT reported in open-label extension trial
Concizumab	FDA-approved for HA/HB ± inhibitors	SC once daily Weight-based dosing Concizumab level monitoring required	Non-fatal thrombotic events in Explorer trials led to a revised dosing approach based on concizumab drug levels
Fitusiran	FDA-approved for HA/HB ± inhibitors	SC every other month (starting at 50 mg Q2M) AT-level–driven dose adjustment AT activity testing required	Thrombotic events on fixed 80 mg QM dose led to revised regimen targeting AT activity 15-35%

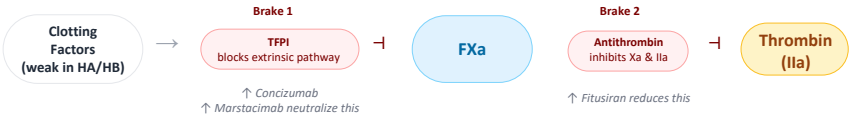
FDA, US Food and Drug Administration; HA, hemophilia A; HB, hemophilia B; SC, subcutaneous.

1. Hympavzi (marstacimab-hncq) US Prescribing Information. Pfizer; 2024 2. Alhemo (concizumab-mtci) US Prescribing Information. Novo Nordisk; 2025. 3. Qfitlia (fitusiran) US Prescribing Information. Sanofi; 2025. 4. Matino D, et al. *Blood*. 2025. doi:10.1182/blood.2024027468. 5. Chowdary P, et al. Concizumab. *The Lancet Haematology*. 2024;11(12):e891-e904.

Rebalancing Agents in Hemophilia: Mechanisms

Restoring hemostatic balance by reducing natural anticoagulant tone — independent of FVIII/FIX

How Rebalancing Works — The "Release the Brake" Concept



Marstacimab
Monoclonal antibody · Anti-TFPI

Target: TFPI

Mechanism

Blocks TFPI-mediated inhibition of the extrinsic tenase complex (TF-FVIIa-FXa). Shares mechanism with concizumab

Concizumab
Monoclonal antibody · Anti-TFPI

Target: TFPI

Mechanism

Binds and inhibits TFPI, relieving its suppression of the TF-FVIIa (extrinsic) pathway. Enables sufficient Xa generation to drive thrombin production even without FVIII or FIX.

Fitusiran
siRNA (GalNAc-conjugated) · Anti-AT

Target: Antithrombin

Mechanism

RNA interference reduces hepatic antithrombin (AT) synthesis. Lower AT levels decrease inhibition of Factors Xa and IIa (thrombin), amplifying the thrombin burst needed to restore hemostatic balance.

AT, antithrombin; HA, hemophilia A; HB, hemophilia B; mAb, monoclonal antibody; SC, subcutaneous; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor; TF, tissue factor; ⊣, inhibition

Young G, et al. *HemaSphere*. 2023;7(6):e911

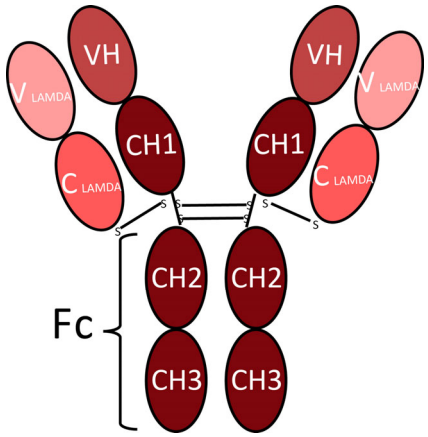
Marstacimab

Anti-TFPI monoclonal antibody

Indicated for HA and HB without inhibitors

No lab surveillance required. Dosing 300 mg loading dose then 150 mg weekly

BASIS clinical trial series demonstrated superiority to on-demand and noninferiority to routine prophylaxis



One thrombotic event reported

HA, hemophilia A; HB, hemophilia B.

1. Matino D, et al. *Blood*. 2026;147(9):920-931. 2. Hympavzi (marstacimab-hncq) US Prescribing Information. Pfizer; 2024. 3. Marstacimab. Medchemexpress. https://www.medchemexpress.com/marstacimab.html

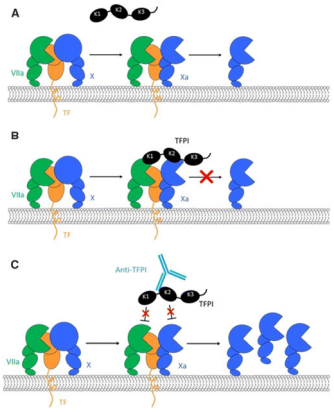
Concizumab

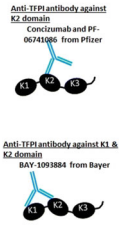
IgG anti-TFPI antibody

SC therapy; indicated for 12 years and older with HA and HB, with and without inhibitors

Lab surveillance required. Dosing is daily. ELISA test level check at 4-8 weeks targeting level of 200 to 4000 ng/mL

EXPLORER clinical trial series demonstrate efficacy in both populations





Multiple non-fatal thrombotic events led to risk mitigation plan with dose adjustments

ELISA, enzyme-linked immunosorbent assay; HA, hemophilia A; HB, hemophilia B; SC, subcutaneous.

1. Chowdary P. *Drugs*. 2018;78(9):881-890. 2. Alhemo (concizumab-mtci) US Prescribing Information. Novo Nordisk; 2025. 3. Seremetis SV, et al. *Blood*. 2020;136:40.

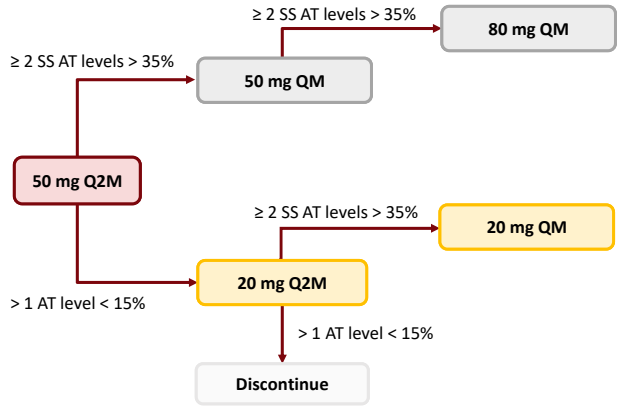
Fitusiran

Small interfering RNA targeting antithrombin (AT) → degradation of mRNA

FDA-approved for HA and HB with and without inhibitors

Lab surveillance required. Dose 50 mg Q2M then adjust to target AT 15-35%

ATLAS clinical trial series demonstrated efficacy vs on-demand factor or bypassing agents



Mitigation dosing plan developed following thrombotic events

AT, antithrombin; FDA, US Food and Drug Administration; HA, hemophilia A; HB, hemophilia B; mRNA, messenger RNA; Q2M, every 2 months.

1. Lu D, et al. *Drug Discov Ther*. 2025;19(2):131-132. 2. Qfitlia (fitusiran) US Prescribing Information. Sanofi; 2025.

Key Takeaways

Three subcutaneous rebalancing agents are now approved for hemophilia A and B: fitusiran (anti-AT siRNA), concizumab (anti-TFPI), and marstacimab (anti-TFPI), expanding non-IV prophylaxis options for patients with various clinical profiles. Each agent has a distinct monitoring approach.

When initiating a rebalancing agent, review breakthrough bleed prescriptions. Reduced doses and lower frequency of clotting factor concentrates or bypassing agents are recommended with fitusiran; specific guidance with other rebalancing agents is evolving.

Shared decision-making guides agent selection: weigh dosing frequency, monitoring burden, and patient preferences; rebalancing agents offer particular value to those seeking independence from IV therapy.

AT, antithrombin; IV, intravenous; Q2M, every 2 months; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor.

1. Qfitlia (fitusiran) US Prescribing Information. Sanofi; 2025. 2. Alhemo (concizumab-mtci) US Prescribing Information. Novo Nordisk; 2025. 3. Matsushita T, et al. *N Engl J Med*. 2023;389(9):783-794.
4. Hympavzi (marstacimab-hncq) US Prescribing Information. Pfizer; 2024. 5. Matino D, et al. *Blood*. 2026;147(9):920-931.