REVIEW ARTICLE

Revolutionizing Treatment Strategies through Inhibition of Tissue Factor Pathway Inhibitor: A Promising Therapeutic Approach for Hemophilia Management

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Abstract

Hemophilia, an X-linked genetic bleeding disorder, is caused by the deficiency of coagulation factors VIII (hemophilia A) or IX (hemophilia B). Regular replacement therapy with the missing clotting factor is an effective standard-of-care treatment. However, it comes with a significant fallout of frequent intravenous dosing with poor compliance, the risk of inhibitor development, and a substantial treatment burden. Research has progressed from missing clotting factors and factor VIII mimetics to the most recent rebalancing therapy that suppresses tissue factor pathway inhibitor (TFPI). Thrombin generation is restricted by TFPI, which inhibits the tissue factor-mediated activation of factor VII. This promising therapeutic approach rebalances hemostasis by inhibiting TFPI, a critical regulator of the extrinsic coagulation pathway, thereby increasing thrombin generation. Novel monoclonal antibodies (concizumab and marstacimab) enhance thrombin generation by blocking TFPI to restore hemostasis. Clinical trials have demonstrated good clinical efficacy and safety of these anti-TFPI, besides their convenient subcutaneous administration using pen devices. These innovative therapies have the potential to enhance the quality of life (QoL) of people with hemophilia. This review provides a comprehensive overview of the clinical development, therapeutic potential, challenges, and prospects of anti-TFPI in the management of hemophilia.

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Introduction to Hemophilia

Hemophilia A (HA) and hemophilia B (HB) are X-linked genetic bleeding disorders associated with the absence or deficiency of coagulation proteins, factor VIII (FVIII) and factor IX (FIX), respectively. Hemophilia occurs at an estimated rate of 1 in 10,000 live births. HA is the predominant type, comprising 80–85% of all hemophilia cases, with a prevalence of approximately 1 in 5,000 live male births, while HB is less common, affecting about 1 in 30,000 live male births.[1,2] According to the World Federation of Hemophilia's 2023 Annual Report, out of 218,804 individuals diagnosed with hemophilia worldwide, 1,79,703 had HA, and 37,385 had HB.[3] Hemophilia is classified based on FVIII/FIX plasma levels into three severity categories: severe (<0.01 IU/mL or <1%), moderate (0.01–0.05 IU/mL or 1–5%), and mild (>0.05–0.40 IU/mL or >5–40%).[4]

In hemophilia, bleeding episodes most commonly affect the joints (hemarthrosis), as well as the muscles and soft tissues. While patients with mild or moderate hemophilia experience these events following trivial trauma, those with severe hemophilia frequently experience spontaneous bleeding events. Delayed treatment and recurrent hemarthrosis can lead to progressive arthropathy, resulting in joint dysfunction, chronic pain, and a diminished quality of life (QoL).[5] The HAEMOcare study, an international epidemiological assessment, evaluated the burden of hemophilia in developing countries using the EuroQol Five-Dimension Questionnaire. Findings indicated that nearly 70% of adults with severe hemophilia experienced issues related to pain, discomfort, and mobility.[6] Additionally, the high cost of treatment and the limited use of immune tolerance induction in people with hemophilia (PwH) in India present significant challenges in managing inhibitor development.[7]

Highlights and Limitations of Modern Hemophilia Treatment

Conventionally, hemophilia is treated by administering standard half-life (SHL) factor concentrates, either on demand (during a bleeding episode) or as regular replacement (prophylaxis). Prophylactic therapy involves regular intravenous (IV) factor infusion in patients with severe hemophilia, two (for HB) or three times (for HA) a week, aiming to convert the bleeding phenotype to moderate hemophilia (trough factor levels >1%). Factor (FVIII or FIX) replacement therapy has been the cornerstone of hemophilia treatment for the past 50 years.[8]

The International Society on Thrombosis and Haemostasis defines prophylaxis with varying goals depending on the patient's age and underlying circumstances.[9,10] Table 1 summarizes the types of prophylaxis. Primary or early secondary prophylaxis results in a normal life span and near-normal joint health.[11]

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Barriers to Effective Hemophilia Management Standard Half-life Factor Products

Of the several barriers to early treatment of hemophilia, the most important is the lack of awareness and knowledge of warning symptoms of bleeding and the significance of early management among PwH.[12] Identifying and removing these obstacles can improve treatment outcomes, including better compliance rates, the prevention of joint damage, and a better QoL.[12]

The administration of SHL factor concentrates has limitations, such as the need for regular IV infusions, difficulty with venous access, treatment ineffectiveness due to the development of inhibitory antibodies,[13] the risk of intracranial bleeding, progression of joint disease, poor implementation of prophylactic regimens, patient compliance, drug costs, and modest treatment goals, all of which negatively impact QoL.[12,13] Other challenges to hemophilia care include a significant financial burden due to high treatment costs, absenteeism from work, disruption in education, disability, restricted access to healthcare centers, the lack of genetic counseling and psychosocial support, loss to follow-up, and social stigma associated with the disease.[14] Some of these challenges were addressed in the past decade by the introduction of extended half-life (EHL) factor concentrates and factor mimetics.

Advantages of Extended Half-life Concentrates over Standard Half-life

Recombinant factor VIII (rFVIII) and factor IX (rFIX) products with EHL promise optimal prophylaxis by lowering dosing frequency, improving compliance, and enhancing QoL without compromising safety and efficacy. Products with EHL may increase trough levels without increasing the frequency of infusions or make it easier to sustain trough levels while lowering the frequency of infusions.[15]

Factor-mimetic and Rebalancing Therapies

Factor-mimetic and rebalancing therapies signify a substantial transformation in the treatment approach for hemophilia, especially for patients with inhibitors who exhibit a poor response to conventional factor replacement therapy.[16] These innovative agents seek to restore hemostasis by emulating the function of coagulation factors or rebalancing the coagulation system to mitigate the bleeding propensity in PwH.[16]

Factor-mimetic Therapies

Factor-mimetic therapies, such as emicizumab, are designed to replicate the function of activated factor VIII (FVIIIa).[16] Emicizumab, a bispecific monoclonal antibody, connects activated factor IX (FIXa) and factor X (FX), promoting the generation of factor Xa and thereby restoring coagulation even in the absence of FVIII.[16] The HAVEN 1–4 clinical trials demonstrated the effectiveness of emicizumab in significantly reducing annualized bleeding rates (ABRs) in patients with or without FVIII inhibitors.[17,18]

Other FVIII-mimetic agents under development include Mim8[19] and BS-027125,[20,21] both of which can potentially improve the landscape of HA treatment. These next-generation bispecific antibodies have mechanisms of action similar to emicizumab and promote thrombin generation. Table 2 provides a comparison between Mim8 and emicizumab.[22–24] In recent communication, the innovator reported positive results on Mim8 in the FRONTIER 2 clinical trial. Mim8 appears to have a safe and well-tolerated profile. The trial reported no deaths or thromboembolic events.[25] The ineffectiveness of FVIII mimetics in patients with HB represents an unmet need in hemophilia care due to fewer options (recombinant factor VIIa) for patients with HB with inhibitors.

Rebalancing Therapies

Rebalancing therapies adopt a different approach by targeting natural anticoagulants in the coagulation cascade to enhance clot formation. Such therapies in the advanced stages of clinical development include anti-tissue factor pathway inhibitor and anti-antithrombin agents.[16] Because of their novel mechanism of action aiming to enhance thrombin generation, these therapies could be effective for patients with HA and HB as well as other rare bleeding disorders.

Anti-tissue factor pathway inhibitors such as concizumab, marstacimab, and befovacimab are designed to block TFPI activity, thereby promoting thrombin generation and compensating for the deficient thrombin burst seen in PwH.[16] Clinical trials, particularly with concizumab and marstacimab, have shown promising results. However, concerns regarding thrombotic events have led to the temporary suspension of and adjustments in some of the trials (refer to Section "Pivotal Clinical Trials of Anti-tissue Factor Pathway Inhibitors").

Another rebalancing agent, fitusiran, an siRNA-based therapy drug,[26] reduces antithrombin (AT) expression and consequently enhances thrombin generation.[16] Fitusiran has shown potential in early trials, although safety concerns, including thrombotic complications, have led to protocol adjustments.[27,28]

Table 1: Definitions of the prophylaxis[9,10]

Prophylaxis	*Definition*
Primary prophylaxis	Prophylaxis is started in the early childhood, if there is no known joint disease, before the second clinically evident joint bleed and before the child reaches the age of 3 years
Secondary prophylaxis	Prophylaxis is started after two or more joints bleed but before the onset of the joint disease, as confirmed by a physical examination and/or imaging investigation
Tertiary prophylaxis	Prophylaxis refers to starting treatment at any age after the onset of the joint disease

Table 2: Comparison between Mim8 and emicizumab

Mim8 vs emicizumab[22–24]
Mim8 binds to FIXa and FX on the activated platelet membrane, demonstrating minimal interaction with FIXa and FX in circulation. This ensures that hemostasis occurs where and when it is needed. Mim8 has been optimized to enhance the proteolytic activity of FIXa by >20,000-fold, whereas it binds to a distinct site of the EGF1 domain
The anti-FX epitope of Mim8 binds at the interface of the serine protease domain and EGF2 domain, whereas emicizumab SIA binds at the isolated EGF2 domain
Mim8 stimulates peak thrombin generation at much lower plasma concentrations than emicizumab SIA
Mim8 is delivered as a uniform, low SC injection volume of 0.8 mL for all patients, irrespective of dose or dose frequency, whereas emicizumab has a variable administration volume, with some exceeding 1 mL depending on weight and dosing frequency

EGF, epidermal growth factor; FIXa, coagulation factor IXa; FX, coagulation factor X; SIA, sequence-identical analog

Factor-mimetic and rebalancing therapies, despite offering substantial advantages—including reduced treatment burden and improved prophylaxis remain challenging. Long-term safety and efficacy, particularly in perioperative and trauma settings, require further investigation.[16]

Anti-tissue Factor Pathway Inhibitors

An anti-TFPI therapy for hemophilia was proposed in 1991,[13] after showing promising results in reducing bleeding times and restoring thrombin generation in animal models.[29,30] TFPI (Kunitz-type serine protease inhibitor) regulates tissue factor (TF)-induced coagulation. It functions through FXa-dependent feedback inhibition of the FVIIa-TF complex, thereby controlling thrombin generation and preventing excessive clot formation.[31,32] TFPI, which consists of three Kunitz domains (K1, K2, and K3), inhibits extrinsic tenase (TF-FVIIa) and early prothrombinase complexes, essential for balanced hemostasis.[33–38]

Mechanism of Action

By blocking TF-activated FVIIa and FXa, TFPI counteracts the effects of early coagulation phases.[5]

Tissue factor pathway inhibitor exerts its activity through its Kunitz domains, with each domain playing a distinct role. The first domain inhibits the TF-FVIIa complex, while the second targets FXa. The third domain, which binds exclusively to lipoproteins and heparins, has no known inhibitory function. In addition to FXa inhibition, the C-terminal region facilitates the interaction of TFPI and FXa with the phospholipid surface. *In vitro* studies have shown that TFPI molecules lacking the C-terminal region exhibit reduced anti-Xa and anticoagulant activity. The inhibitory activities of TFPI can contribute to the significant decrease in thrombin production, which can explain excessive bleeding in PwH. Additionally, TFPI blocks FXa-activated FVa and platelet FVa, inhibiting thrombin generation and clot formation.[39] Therefore, TFPI inhibition can be an important target for managing bleeding disorders, employed by novel agents such as concizumab.[40]

Anti-tissue Factor Pathway Inhibitor Antibodies

Several monoclonal antibodies targeting TFPI are under clinical investigation. Table 3 summarizes the current and pipeline molecules of the anti-TFPI therapy.

Concizumab

Concizumab (mAb-2021) is a humanized monoclonal IgG4 antibody designed to target the K2 domain of TFPI, a key regulator of FXa and the FVIIa-TF complex.[41]

Preclinical Studies of Concizumab

Concizumab neutralizes the inhibition of FXa generation by TFPI in purified systems and cell-based assays. In a modified prothrombin assay using normal plasma, concizumab demonstrated a dose-dependent reduction in clotting time and effectively restored thrombin generation in FVIII-depleted plasma. In whole blood samples rendered hemophilic, concizumab reduced clotting time and increased thrombus formation to normal levels in a dose-dependent manner.[42] In a rabbit hemophilia model, concizumab significantly reduced cuticle bleeding when administered before or within 5 minutes of the onset of bleeding. However, it was ineffective when given 15 or 30 minutes after bleeding induction. The antibody demonstrated a dose-dependent reduction in blood loss and maintained efficacy after subcutaneous (SC) administration.[42]

Pivotal Clinical Trials of Tissue Factor Pathway Inhibitors

Concizumab

Explorer 1

The initial phase 1 clinical trial included both patients with severe HA and HB, as well as healthy volunteers. This randomized, double-blind, multicenter, placebo-controlled, single-dose, dose-escalation study was conducted to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of concizumab.[43]

Participants were randomized into different dose cohorts to receive a single dose of concizumab or placebo. The study began with healthy volunteers, and concizumab was administered to PwH upon reaching predefined safety thresholds. The trial included IV and SC administrations, with escalating doses of concizumab ranging from 0.5 to 9,000 µg/kg. The primary and secondary endpoints focused on evaluating safety and PK/PD parameters, respectively.[43]

Among the 52 participants (28 healthy volunteers and 24 individuals with hemophilia), no serious adverse events (SAEs) were reported. Treatment-related adverse events (TRAEs) included one case of superficial thrombophlebitis in a healthy volunteer from the 1,000 µg/kg SC cohort, along with injection site reactions in several participants, comprising one moderate reaction and 65 mild reactions. Patients receiving concizumab reported mild adverse events (AEs), such as trace protein in the urine (those receiving the 250 µg/kg dose) and abdominal pain (those receiving the 9,000 µg/kg dose). Elevated troponin T levels and fibrinogen reduction were observed in some PwH receiving higher doses (1,000 or 3,000 µg/kg SC) without any clinical significance.[43]

Concizumab remained detectable in plasma for up to 43 days postdosing. Plasma concentration profiles exhibited nonlinear PK, characterized by rapid clearance at lower doses and slower clearance at higher concentrations. Both IV and SC administration led to dose-dependent increases in $AUC_{0-\infty}$ and Cmax in healthy volunteers and PwH. The PK profiles were comparable between the two groups, aligning with target-mediated drug disposition (TMDD), where concizumab's interaction with TFPI influenced its distribution and elimination.[43]

No antidrug antibodies were detected. A dose-dependent procoagulant response was observed, evidenced by increased D-dimer and prothrombin fragment 1 + 2 levels, particularly in healthy volunteers after IV administration.[43]

Explorer 3

The phase 1b/2 study included 24 male patients with HA without inhibitors and a documented FVIII activity level of ≤2%. Building on the findings of Explorer 1, this double-blind, multicenter, multiple-dose-escalation study evaluated the safety and efficacy of concizumab, which was administered subcutaneously over a 42-day period.[44] Patients were randomly assigned in equal proportions to one of three concizumab dose groups (0.25, 0.5, and 0.8 mg/kg every fourth day). To facilitate the rapid attainment of a steady-state plasma concentration, the first two doses were administered on consecutive days, followed by dosing every fourth day.

Concizumab showed a dose-dependent decrease in free-total TFPI levels and increased thrombin generation. In the higher-dose cohorts, thrombin generation parameters reached normal ranges, demonstrating a more substantial procoagulant effect. No SAEs or antidrug antibodies were observed. A trend toward lower bleeding rates at higher concizumab exposure levels was noted.[44]

Explorer 4 and 5

Following the positive safety and PD results from Explorer 1 and 3, Explorer 4 (in patients with HA or HB with inhibitors) and 5 (in patients with HA) (phase 2 proof-of-concept) studies were designed to explore the

Table 3: Current and pipeline molecules of anti-TFPI antibodies [13,43–60]

Antibody	*Description*	*Status*
Current molecules		
Concizumab (mAb-2021)	Humanized monoclonal IgG4 antibody targeting the K2 domain of TFPI	• Explorer 1 (phase 1) reported no serious AEs, and PK profiles and dose-dependent reduction in TFPI in healthy volunteers and patients with hemophilia were similar, with the highest-dose cohort demonstrating sustained low TFPI levels for up to 2 weeks • Explorer 3 (phase 1b/2) showed a dose-dependent decrease in free-total TFPI levels and increased thrombin generation • Explorer 4 and 5 reported that ABRs were lower. No differences were noted in PK/PD among hemophilia subtypes. No severe AEs, drug withdrawal, or thromboembolic events were reported • Explorer 7 (phase 3) concluded that in patients with HA or HB with inhibitors, ABRs reduced with concizumab prophylaxis compared with no prophylaxis • Explorer 8 reported that the estimated mean ABR ratio for treated spontaneous and traumatic bleeding episodes during prophylaxis vs no prophylaxis was 0.14 (95% CI 0.07–0.29; $p < 0.0001$) and 0.21 (0.10–0.45; $p < 0.0001$) for patients with HA and HB, respectively. • Explorer 10 is ongoing
Marstacimab	An investigational human IgG1 monoclonal antibody that targets the K2 domain of TFPI	• Phase 1 trial concluded that single doses were safe, supporting the progression to multiple-dose trials in patients with hemophilia • Phase 1b/2 marstacimab was safe and well tolerated and effectively reduced bleeding rates, confirming its ability to target TFPI • In the phase 2 study, weekly SC marstacimab was well tolerated and maintained efficacy for up to 365 days • Phase 3 is ongoing • BASIS KIDS study is ongoing
Befovacimab	A fully human IgG2 monoclonal antibody engineered to bind with both the K1 and K2 domains of the TFPI	• Phase 1 study results showed dose-dependent effects on TFPI-related parameters and PK consistent with TMDD. The PK and PD responses were similar in patients with HA and HB, regardless of the presence of inhibitors, and safety concerns were observed in neither single-dose nor multidose settings • The sponsor terminated the phase 2 study because of the lack of correlation between befovacimab dose, TFPI inhibition, safety or efficacy outcomes, and the unpredictable nature of thrombosis risk
Pipeline molecules		
MG1113	A human monoclonal antibody of TFPI that is being developed for prophylaxis in patients with HA with or without inhibitors against factor VII	Under phase 1b study to assess the safety, tolerability, PK, and PD of MG1113 in patients with hemophilia
BAX-499	An oligonucleotide aptamer against TFPI	Study was terminated: In phase 1 dose-escalation study, a higher incidence of bleeding events in the cohort receiving the maximum dose (72 mg subcutaneously) led to the early termination of the study
KN057	NA	Phase 2 study is ongoing

ABR, annualized bleeding rate; AE, adverse event; CI, confidence interval; HA, hemophilia A; HB, hemophilia B; Ig, immunoglobulin; mAb, monoclonal antibody; NA, not available; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; TMDD, target-mediated drug disposition

prophylactic efficacy of concizumab along with its safety and immunogenicity in patients with severe HA and HB, with or without inhibitors. In these trials, concizumab was administered SC daily, beginning at a dose of 0.15 mg/kg. If patients experienced three or more spontaneous bleeding episodes within 12 weeks of treatment, the dose was escalated to 0.25 mg/kg. Patients continued their usual FVIII or recombinant FVIIa (rFVIIa) treatments for breakthrough bleeding episodes.[45]

The estimated ABRs were lower in patients with HA and HB with inhibitors compared to those with HA without inhibitors: 3.0 [95% confidence interval (CI), 1.7–5.3] and 5.9 (95% CI, 4.2–8.5) vs 7.0 (95% CI, 4.6–10.7), respectively. The expected PK/PD outcomes were achieved, with no significant differences observed among hemophilia subtypes in terms of concizumab exposure, free TFPI levels, thrombin generation, prothrombin fragment 1 + 2, and D-dimer levels. No SAEs, drug withdrawal, or thromboembolic events were reported during the treatment. However, three patients reported positive antidrug antibody tests (very low to medium titer) in each trial without any clinical effects.[45]

Explorer 7

This phase 3 randomized trial assessed concizumab in 133 patients with HA or HB with inhibitors. Patients were assigned to receive either no prophylaxis for 24 weeks (group I; $n = 19$), concizumab for 32 weeks (group II; $n = 33$), or concizumab for 24 weeks (groups III and IV; $n = 81$). The primary endpoints were treated spontaneous and traumatic bleeding episodes. Secondary endpoints included patient-reported outcomes, adverse events, PK, and PD.

The mean ABR was 11.8 episodes in group I and 1.7 episodes in group II (rate

ratio, 0.14; $p < 0.001$). The median ABR for concizumab-treated groups (II, III, and IV) was 0. No thromboembolic events were observed. Concizumab levels remained stable. The study showed that concizumab reduced ABRs compared to no prophylaxis.[46]

Explorer 8 and Explorer 10

Explorer 8 (NCT04082429) was a multicenter, randomized, phase 3 clinical trial that included 148 male patients aged ≥12 years with HA and HB without inhibitors. Patients were randomly assigned to receive concizumab prophylaxis or no prophylaxis, with some assigned to nonrandomized arms based on prior treatment. Concizumab prophylaxis included a 1.0 mg/kg loading dose at day 1 followed by 0.20 mg/kg daily starting on day 2.

The mean ABR rate ratio for spontaneous and traumatic bleeding episodes during prophylaxis vs no prophylaxis was 0.14 (95% CI, 0.07–0.29; $p < 0.0001$) for HA and 0.21 (95% CI, 0.10–0.45; $p < 0.0001$) for HB. Common adverse events included COVID-19 (13%), increased fibrin D-dimers (8%), and upper respiratory tract infection (7%). One fatal adverse event, possibly related to treatment (intra-abdominal hemorrhage in a hypertensive HA patient), was reported.[47]

Explorer 10 (NCT05135559) is an open-label, phase 3 study evaluating concizumab prophylaxis in 90 male children <12 years with HA or HB, with or without inhibitors. The primary objective is to assess treated bleeding episodes over 32 weeks. The study is expected to be completed by 2029.[48]

Marstacimab

Marstacimab is an investigational human immunoglobulin G1 (IgG1) monoclonal antibody that targets the K2 domain of TFPI. By inhibiting the action of TFPI on FXa, marstacimab enhances hemostasis through the extrinsic coagulation pathway, potentially offering a therapeutic approach for patients with bleeding disorders such as hemophilia by promoting clot formation.[5]

Phase 1

Forty-one healthy male volunteers (18–55 years) were randomized to six different cohorts: cohort I [30 mg SC (n = 4) and placebo (n = 1)], cohort II [100 mg SC (n = 6) and placebo (n = 2)], cohort III [300 mg SC (n = 6) and placebo (n = 2)], cohort IV [150 mg IV (n = 6) and placebo (n = 2)], cohort V [440 mg IV (n = 6) and placebo (n = 2)], and cohort VIII [300 mg SC (n = 4) in Japanese patients]. Following the termination of dose escalation, cohorts VI and VII were not enrolled. The results showed that all doses were safe and well tolerated, with mild-to-moderate TRAEs, no SAEs, and no infusion or injection site reactions. The PK data indicated that plasma exposures increased greater than proportionally with SC and IV doses, while the PD data demonstrated effects on total TFPI and coagulation markers.[49]

Phase 1b/2

A phase 1b/2 study evaluated marstacimab in participants with HA or HB, with or without inhibitors, for over 3 months. Participants were divided into four cohorts and received escalating weekly doses based on their inhibitor status (without inhibitors: 300 mg, 300 mg loading dose followed by 150 mg or 450 mg; with inhibitors: 300 mg).[50]

Of the 26 participants, 24 completed the study, and TRAEs occurred in 80.8% of participants. The ABR significantly reduced compared with an external on-demand control group ($p < 0.0001$) and baseline ($p < 0.0001$) across all dose cohorts. Marstacimab exposure increased in a dose-dependent manner, and by day 57, steady-state concentrations were reached. The PD biomarker changes (fibrinogen, prothrombin fragment 1 + 2, and D-dimer) were consistent across all cohorts.[50]

Phase 2

A phase 2 study investigated the long-term safety, tolerability, and efficacy of marstacimab for weekly prophylaxis in patients with severe HA and HB, with or without inhibitors. Two dosing regimens were used: once-weekly 300 mg or a 300 mg loading dose followed by 150 mg weekly for up to 365 days.[5]

Of the 20 participants enrolled, 18 completed the study. Treatment-emergent AEs were observed in 70% of participants, including injection site reactions, hematomas, and hemarthrosis, but no treatment-related SAEs or thrombotic events were reported. The mean and median ABRs ranged from 0 to 3.6 and 0 to 2.5 episodes per year, respectively, demonstrating efficacy comparable to that of the shorter-term parent study. Importantly, no antidrug antibodies were detected.[5]

Phase 3

This is an ongoing, open-label, interventional extension study to evaluate marstacimab prophylaxis (NCT05145127) in participants with severe HA (coagulation factor activity <1%) with or without inhibitors or in those with moderately severe-to-severe HB (coagulation factor activity ≤2%) with or without inhibitors (n = 145). The primary outcome measures (for up to 7 years) include the number and severity of AEs, SAEs, thrombotic events, thrombotic microangiopathy, disseminated intravascular coagulation (DIC)/consumption coagulopathy (CC), injection site reaction, the incidence of clinically significant persistent neutralizing antibody (NAb) against marstacimab, changes in vital signs from baseline, significant laboratory value abnormalities, and severe hypersensitivity and anaphylactic reactions. The study is expected to be completed by 2030.[51]

Another phase 3 (NCT03938792), open-label, multicenter, crossover prevention study on marstacimab (300 mg SC loading dose followed by 150 mg SC once weekly; 6-month observation period) with 186 adolescent and adult (12–74 years) participants with severe HA or moderately severe-to-severe HB with or without inhibitors is ongoing. The primary outcome measures include ABR, the incidence and severity of thrombotic events, antidrug antibody, persistent NAb, injection site reaction, laboratory value abnormalities, AEs and SAEs, DIC/ CC, and thrombotic angiopathy. The study is expected to be completed by June 2025.[52]

BASIS KIDS Study

This is an ongoing, open-label, single-group, interventional, multicenter phase 3 study (NCT05611801) performed on 100 pediatric (<18 years of age, males) participants with severe HA (coagulation factor activity <1%) with or without inhibitors or participants with moderately severe-to-severe HB (coagulation factor activity = 2%) with or without inhibitors, comparing 12 months of historical standard treatment to marstacimab prophylaxis. The primary outcome measures include ABR, AEs and SAEs, thrombotic events, thrombotic microangiopathy, DIC/CC events, injection site reaction, and immunogenicity against marstacimab. The study is expected to be completed by 2028.[53]

Befovacimab

Befovacimab (formerly BAY1093884) is a human IgG2 monoclonal antibody designed to bind to the K1 and K2 domains of TFPI.[54,55] Preclinical studies in mice and nonhuman primates showed a procoagulant effect, reducing blood loss without causing thrombosis. Pharmacokinetic studies revealed bioavailability and TMDD when administered subcutaneously in various *in vivo* models.[55]

Phase 1

The first-in-human study evaluated befovacimab in a multicenter, open-label trial involving patients with severe HA or HB, with or without inhibitors.[13] The study assessed safety, PK, and PD after a single IV dose (0.3 and 1 mg/kg) and a single SC dose (1, 3, and 6 mg/kg). The results showed dose-dependent effects on TFPI-related parameters

and PK consistent with TMDD. The PK and PD responses were similar in patients with HA or HB, regardless of the presence of inhibitors, and no safety concerns were observed in single-dose or multidose settings.[13]

Phase 2

The phase II study (NCT03597022) was a nonrandomized, open-label, sequential-assignment, dose-escalating, multiple-dose trial to evaluate the safety of befovacimab in patients with HA or HB, with or without inhibitors, across three dose cohorts (100, 225, and 400 mg).[56] A total of 24 patients, 8 in each dose cohort, participated in the study. Befovacimab showed clear PD effects, with dose-dependent protection against bleeding. The preliminary efficacy data showed that the 225-mg dose cohort significantly reduced bleeding rates compared with prestudy levels. In comparison, no reduction was observed in the 100-mg dose cohort.

Three participants developed thromboses within the central nervous system. Two thromboses were reported in the intermediate-dose cohort (225 mg) (one venous, one arterial), and one arterial event was observed in the high-dose cohort (400 mg). None of these participants experienced a bleeding event or received additional hemostatic agents at the time of thrombosis. No signs of hemolysis, platelet consumption, or other abnormalities were noted in the monitored laboratory parameters. Due to the lack of correlation between the befovacimab dose, TFPI inhibition, safety or efficacy outcomes, and the unpredictable nature of thrombosis risk, the sponsor terminated the study.[56]

Anti-tissue Factor Pathway Inhibitor Antibodies in the Pipeline

MG1113 is a human monoclonal antibody of TFPI that is being developed for prophylaxis in PwH with or without inhibitors against FVIII products, which have previously been used to treat HA.[57] It is being investigated in a phase 1 single-dose escalation study (NCT03855696) in healthy subjects and PwH, but the results have not yet been published. A phase 1b study is being conducted to assess the safety, tolerability, PK, and PD of MG1113 in PwH.[58]

BAX-499 (previously ARC19499, Shire), an oligonucleotide aptamer against TFPI, demonstrated strong and specific inhibition of TFPI in preclinical *in vitro* and *in vivo* experiments, restoring thrombin production and clot formation.[59] Then, in a phase 1 dose-escalation study, the procoagulant activity of BAX-499 was assessed in PwH with and without inhibitors (NCT01191372). Unfortunately, a higher incidence of bleeding events in the cohort receiving the maximum dose (72 mg SC) led to the early termination of the study. These side effects were linked to decreased thrombin production because of elevated plasma TFPI levels.[59]

Another open, multicenter, dose-escalation, nonrandomized, phase 2 study is ongoing to evaluate the safety, tolerability, PK, and PD of multiple SC doses of KN057 (NCT05421429; Suzhou Alphamab Co., Ltd.) in 24 adult subjects (male, 18–70 years) with HA or HB, with or without inhibitors. The primary outcome measures include the frequency and severity of TRAEs, withdrawals due to TRAEs, abnormal laboratory findings, changes in electrocardiogram, and injection site reactions. The study is still recruiting participants and is expected to be completed in 2024.[60]

Advantages, Challenges, and Opportunities for Anti-tissue Factor Pathway Inhibitor Therapies

While treating PwH, anti-TFPI therapies offer both opportunities and challenges. A reduction in the treatment burden associated with frequent IV infusions is a major advantage.[61] Current recombinant FVIII and FIX therapy necessitates numerous weekly administrations, but prolonged half-life variants reduce the frequency to one or two infusions weekly. Subcutaneous administration, exemplified by anti-TFPI therapy, streamlines drug delivery and is highly appreciated by patients.[11] Nongeneration of antidrug antibodies, a lesser risk of thrombotic events, and unique mechanisms of action are other advantages of anti-TFPI therapies. Additionally, these medicines may enhance hemostatic control by stabilizing the coagulation capacity, granting patients greater autonomy in daily activities.[11] The SC injection for drug delivery through pen devices has the potential to enhance compliance and subsequently improve long-term outcomes, including target joints and QoL.[62]

A few challenges persist, especially regarding TMDD, potentially requiring more frequent injections. TFPI, secreted by platelets and endothelial cells at sites of injury, inactivates the TF complex, with elevated levels of TFPI in hemophilic joints.[11] Elevated D-dimers are frequently observed, but their clinical significance remains debatable. Inhibition of the plasma TFPI pool appears to be a promising strategy for preventing bleeding; however, the therapeutic window and optimal coagulation control balance remain to be established.[11]

Concizumab is being evaluated for other treatment potential. An *in vitro* study determined the utility of concizumab in improving hemostasis in patients with Glanzmann thrombasthenia (GT) (n = 5–9). Concizumab enhanced thrombin generation [the lag time was significantly longer (+85%; $p < 0.0001$ in patients with GT than in controls)], decreased the rotational thromboelastometry clotting time, improved thrombus formation under flow, and reduced clot lysis, demonstrating prophylactic potential in patients with GT.[63]

Anti-TFPI therapies may have other potential applications due to their ability to modulate coagulation and bleeding disorders. Surgical bleeding,[64] trauma-induced coagulopathy, sepsis-induced coagulopathy,[65] anticoagulant reversal,[66] chronic bleeding disorders,[67] and liver disease-related coagulopathy[68] are other potential areas where anti-TFPI therapies can show promising results.

Anti-TFPI therapies may be beneficial in controlling bleeding during or after surgery in patients with coagulopathies or in surgeries that pose a high risk of bleeding. Major injuries can cause dysfunctional blood coagulation, resulting in fatal hemorrhages. Anti-TFPI therapies could be considered to enhance coagulation stability in bleeding trauma patients.

One study reported increased levels of TFPI in patients with acute promyelocytic leukemia, highlighting the potential of anti-TFPI therapies in managing hemorrhagic events.[64] In septic patients, coagulopathy often leads to DIC, wherein excessive bleeding and clotting occur simultaneously.[65] Patients on oral anticoagulation for conditions such as atrial fibrillation or venous thromboembolism may occasionally need to stop or reverse anticoagulation quickly, particularly in cases of major bleeding or surgery.[66] Apart from hemophilia, other bleeding disorders such as von Willebrand disease or GT, involving defective platelet function or clotting factor deficiencies,[67] might benefit from anti-TFPI approaches to better regulate coagulation. Patients with advanced liver disease often experience significant coagulation problems of either bleeding or thrombosis.[68] Anti-TFPI therapies could potentially stabilize clotting abnormalities in these patients.

Conclusion

The inhibition of TFPI is a promising advancement in the treatment of hemophilia, providing potential advantages over

conventional factor replacement therapies and existing nonfactor (emicizumab) therapy. Unlike FVIII mimetics, these agents can also be used for patients with HB with or without inhibitors. The anti-TFPI, such as concizumab and marstacimab, can minimize bleeding episodes by restoring hemostasis and enhancing thrombin generation and improve patient compliance, outcomes, and QoL, particularly for those with inhibitors, while simplifying SC administration *via* pen devices. Although early clinical trials have demonstrated efficacy and reduced treatment burdens, challenges remain, such as the need for long-term data. Further research and clinical development are imperative to optimize these therapies and guarantee their effective integration into hemophilia management, thereby providing patients with a more accessible and efficient treatment option.

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