Biologics: Targets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Marstacimab for the Treatment of Hemophilia A or B

Johnny Mahlangu

Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

Correspondence: Johnny Mahlangu, Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of Witwatersrand, 7 York Road, Parktown, Johannesburg, South Africa, Tel +27114898413, Email johnny.mahlangu@wits.ac.za

Abstract: Hemophilia A and B, caused by deficiencies of coagulation factors VIII or IX, result in impaired thrombin generation with consequent spontaneous or trauma-related bleeding, particularly hemarthroses. Although prophylactic factor replacement therapy remains the global standard of care for hemophilia, it has significant limitations, including intravenous administration, breakthrough bleeding, inhibitor development, and deteriorating arthropathy despite prophylaxis. Marstacimab, an IgG1 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), represents a novel non-factor approach. Marstacimab restores thrombin generation via the extrinsic pathway, bypassing intrinsic pathway deficiencies and offering prophylactic benefit independent of inhibitor status. Clinical evaluation across Phase 1b/2 and Phase 3 (BASIS) trials and ongoing extension studies has demonstrated robust efficacy. In Phase 3, marstacimab reduced annualized bleed rates by 91.6% compared with episodic treatment and was non-inferior to factor prophylaxis. Bleed control was sustained though zero-bleed outcomes were not uniformly achieved. Pharmacokinetic data support once-weekly fixed dosing independent of body weight, simplifying administration and potentially improving adherence. Across all studies, marstacimab demonstrated a favorable safety profile. Injection site reactions were the most common adverse events, while anti-drug antibodies, including neutralizing types, were transient and without clinical impact. Marstacimab, the first FDA-approved anti-TFPI antibody for prophylaxis in hemophilia A and B without inhibitors, addresses key unmet needs, particularly for hemophilia B patients lacking subcutaneous (SC) prophylaxis options. Its novel mechanism, ease of administration, and sustained efficacy position it as a significant therapeutic advance. Marstacimab's exact role in the hemophilia treatment armamentarium is yet to be established with the availability of coming real-world experience data. The long-term studies remain essential to fully demonstrate its role, especially in populations with inhibitors and in the context of evolving non-factor therapies. This review summarises currently available clinical data and contextualises these in light of other treatments in hemophilia.

Keywords: hemophilia A, hemophilia B, marstacimab, tissue factor pathway inhibitor, TFPI, non-factor therapy, subcutaneous administration, monoclonal antibodies

Introduction

Hemophilia is an X-linked genetic disorder caused by a deficiency or dysfunction of clotting factors VIII or IX, leading to hemophilia A or B. This deficiency impairs thrombin generation, resulting in spontaneous or trauma-related bleeding in tissues such as muscles, mucosa, and joints. Joint bleeding (hemarthroses) is a hallmark of the disease and can initiate a destructive cycle of inflammation and damage, underscoring the need for early and continuous prophylactic treatment.

Prophylactic factor replacement therapy, currently regarded as the global standard of care in managing hemophilia, can prevent this progressive and harmful cascade.[1,2] The administration of factor replacement therapy is impeded by the necessity of intravenous delivery, the occurrence of breakthrough bleeding episodes, the potential for inhibitor development, and restricted access in resource-limited environments.[3,4] The challenges of replacement therapies have led to the development of non-factor therapeutic modalities. Recent therapeutic innovations have encompassed FVIII mimetics,[5,6] anti-thrombin inhibitors (small interfering RNA (siRNA)),[7,8] activated protein C inhibitors (anti-APC),[9] and anti-tissue factor pathway inhibitors (anti-TFPI).[10,11]

Received: 5 May 2025
Accepted: 19 June 2025
Published: 24 June 2025

Concizumab and marstacimab are the two anti–tissue factor pathway inhibitors (anti-TFPIs) that have completed Phase 3 clinical evaluation. Although both agents share an identical mechanism of action—binding to the Kunitz-2 (K2) domain of TFPI—they exhibit distinct pharmacokinetic properties. These include differences in terminal half-life (1.6–8.2 days for concizumab versus 7–10 days for marstacimab) and systemic clearance (0.19 L/day for concizumab versus 0.019 L/day for marstacimab).[10–12] These pharmacokinetic disparities translate into divergent dosing regimens, with concizumab requiring daily subcutaneous administration, in contrast to the once-weekly dosing schedule of marstacimab.

This review evaluates emerging clinical data from marstacimab development studies, placing the findings in the context of the known limitations of factor replacement therapies. Critically analyzing the evidence aims to determine marstacimab's potential role within the current therapeutic landscape for hemophilia A and B.

Marstacimab Mechanism of Action and Pharmacology

Mechanism of Action of Marstacimab

Marstacimab is an IgG1 monoclonal antibody designed to target the tissue factor pathway inhibitor (TFPI), a key regulator of the extrinsic pathway of blood coagulation. The physiologic role of TFPI is to inhibit the formation of the tenase activated Factor FVII-tissue factor ((FVIIa-TF)) and prothrombinase (Factor Xa-Factor Va) complexes.[13,14] By binding to the TFPI via its K2 domain, marstacimab enables the formation of the tenase and prothrombinase complexes, resulting in downstream thrombin generation and consequent clot formation.[15] This mechanism is particularly beneficial in hemophilia, where the intrinsic pathway is impaired by deficiency of FVIII or FIX, and the extrinsic pathway becomes crucial for clot formation.[16] Administered subcutaneously at a fixed dose regardless of weight or age, marstacimab supports consistent thrombin generation and bleeding prevention in hemophilia A and B patients.[17]

Pharmacokinetic Profile of Marstacimab

When administered subcutaneously, marstacimab has a bioavailability of 71%.[11,18] It has a terminal half-life of 7–10 days and 16–18 days when given intravenously and subcutaneously, respectively. Its time to maximum concentration is 23–50 hours and reaches steady concentration by day 57. Marstacimab clearance is low at 0.019/L/hour and nonlinear due to target-mediated drug disposition.[11,19,20]

For bleed prevention, marstacimab is given at a fixed dosing regimen of 150 mg subcutaneously weekly, which is preceded by a single 300 mg loading dose.[18] The dosing is independent of body weight. In a prefilled pen, this dosing approach simplifies dosing, reduces the risk of errors, and enhances patient compliance.[18,21] In the event of recurrent breakthrough bleeds, the prophylaxis dose can be titrated to 300 mg SC weekly.[18] Combining marstacimab with other hemostatic agents does not lead to excessive coagulation.[22–24] Breakthrough bleeding during marstacimab prophylaxis is treated with the lowest dose expected to achieve hemostasis.

Pharmacodynamics

Peak thrombin concentrations did not exhibit any discernible trends based on weight, demonstrating similar median values and overall ranges of peak thrombin measurements across all weight classifications.[25] Generally, the observed peak thrombin values remained within the normative physiological spectrum (90% confidence interval [CI] for pre-dose peak thrombin was 44–176 nM, as established in a phase 1 investigation involving healthy adult subjects),[11] with no indication of pharmacological excess.[22] This observation is presumably attributable to marstacimab concentrations within the E_{max} range of the exposure–response relationship.

Overview of Study Design, Endpoints, and Populations of Clinical Studies

The B7841001 (www.ClinicalTrials.gov) ID NCT02531815 study was a single ascending dose first-in-human Phase 1 study assessing the safety, pharmacokinetic, and pharmacodynamic profiles of PF-06741086 in a cohort of 32 healthy volunteers.[26] The administered dose spectrum ranged from 30 to 440 mg via intravenous administration. The administration of single doses of PF-06741086 across multiple dosing intervals demonstrated safety and tolerability within

a healthy adult male demographic. The safety, pharmacokinetic, and pharmacodynamic data from this study provided a robust rationale for advancing to a multiple-dose investigation in individuals diagnosed with hemophilia.[26]

The B7841003 (www.ClinicalTrials.gov) ID NCT02974855 was a Phase 1b/2, open-label, multiple-dose cohort study executed in participants with hemophilia A or B, both with and without the presence of inhibitors.[11] Participants were allocated to four distinct cohorts, receiving escalating weekly dosages contingent upon their inhibitor status (those without inhibitors received: 300 mg, a singular 300 mg loading dose followed by weekly subsequent 150 mg doses, or 450 mg; those with inhibitors received 300 mg. The endpoints were safety, efficacy, pharmacokinetics, and pharmacodynamics. Among the cohort of 26 participants comprising hemophilia A without inhibitor, n = 16 (61.5%); hemophilia A with inhibitor, n = 7 (26.9%); hemophilia B, n = 3 (11.5%), 24 completed the study. Marstacimab exhibited a dose-dependent exposure, attaining a steady-state concentration by day 57. Modifications in pharmacodynamic biomarkers were noted across all dosage cohorts. Overall, marstacimab demonstrated a favorable safety profile and was well tolerated by participants.[11]

The BASIS trial (NCT03938792) is an ongoing Phase 3, open-label, multinational study assessing marstacimab's safety and efficacy in hemophilia A or B patients, with or without inhibitors. Data from the completed non-inhibitor cohort has been submitted to support marstacimab's marketing authorization for that population.

The key eligibility criteria for the non-inhibitor cohort included hemophilia A or B without inhibitors who were on episodic (minimum of 6 bleeds in the preceding six months) or factor prophylaxis (minimum of 80% compliance with no history or current thromboembolism events or planned surgery. The study consisted of four periods: screening up to 45 days, a six-month lead-in period, a twelve-month active treatment period, and a long-term extension period. A total of 128 participants met eligibility criteria, and 116 have completed the active treatment phase.

Participants who completed the BASIS study were invited to the B7841007 (NCT05145127) study, an ongoing open-label extension. The Phase 1b/2 study results have been published, and the safety and efficacy results of both the BASIS and open-label extension have been presented at various congresses and are included in this analysis.

Safety of Marstacimab from Clinical Trials

Safety Endpoints

Marstacimab's safety has been assessed in multiple studies, including phase 1b/2, phase 3, and long-term extensions, involving 144 participants (Table 1). Safety monitoring covered clinical and laboratory adverse events, including bleeding, hepatic issues, hypersensitivity, hypertension, thromboses, and injection site reactions. Immunogenicity was evaluated via anti-drug and neutralizing antibodies over 5.8–50 patient-years of exposure in the four studies.

Table 1 Key Safety Features of Marstacimab from Clinical Trials

	B7841003 (NCT02974855)[11]	B7841003 (NCT02974855)[17]	B7841005 (NCT03938792)[27]	B7841007 (NCT05145127)[27]
Study phase	Phase 1b/2	Phase 1b/2 Long-term Follow-up	Phase 3 Pivotal study	Phase 3 Long-term extension
Number of participants, n	26	28	116	87
Total exposure, patient-years,	5.8	25.5	11.2	50.0
Adverse events, n	65	112	271	35
Serious adverse events, n	4	7	8	2
Injection site reactions, n	7	10	11	3
Thromboses, n	0	0	0	0
Anti-drug antibodies, n	0	0	23	0
Neutralizing antibodies, n	0	0	6	0

https://doi.org/10.2147/BTT.S500480

Serious Adverse Events

Across the four studies in Table 1, 21 serious adverse events (SAEs) were reported, mostly mild (grade 1 or 2), all resolving without lasting effects. In the Phase 3 BASIS study and its extension, only one SAE—peripheral swelling—was considered related to marstacimab; the rest were unrelated. Of the 12 SAEs reported in various BASIS study phases, nine occurred during marstacimab exposure. Still, just one was treatment-related, and only one participant discontinued due to an unrelated, protocol-mandated surgical SAE.

Injection Site Reactions

Injection site reactions (ISRs) are among the most common side effects associated with marstacimab administration. During the four studies (Table 1), thirty participants experienced one ISR each. The overall frequency of ISRs in the marstacimab program is 11.5%. These were clinically recognised as pain, erythema or pruritus. Most ISRs were mild or moderate in severity, and all resolved and did not recur during the study. The ISRs are typically managed with simple interventions such as changing injection techniques or sites, and they rarely necessitate discontinuation of the drug.

The prevalence of ISRs with marstacimab is consistent with other biologics, where rates can range from 0.5% to 45%, depending on the specific agent and patient population.[28] Moreover, the ISR prevalence in the marstacimab program is comparable to that documented in other subcutaneously administered haemostatic agents.[5–8,29] The ISRs do not appear to compromise the drug's effectiveness or lead to significant adverse outcomes.

Immunogenicity of Marstacimab

The prevalence of anti-drug antibodies (ADA) is 20%, with 23 ADA reported in 116 tested participants in the Phase 3 study.[27] Of these, only six were found to be neutralizing (NAB) in vitro. Their presence was inconsequential from a safety and efficacy perspective, as all NAB-positive participants continued to use marstacimab and did not have a change in their bleeding phenotype. However, the ADA and NAB are typically low-titer and transient, resolving in most participants by the end of the study.

The immunogenicity of marstacimab can be contextualized by comparing it to other monoclonal antibodies, where ADA formation is a common challenge leading to loss of efficacy. Strategies such as epitope analysis and deimmunization are employed to mitigate these risks.[30] In the broader context of antibody-based therapies, the route of administration and the specific target can influence immunogenicity. However, marstacimab's subcutaneous administration is generally associated with a lower risk compared to intravenous routes used in other therapies.[31]

Although marstacimab appears to have a favorable safety and efficacy profile, the potential for immunogenicity remains a critical consideration, as with all monoclonal antibody therapies. The absence of detailed ADA data in the studies suggests that further research may be needed to fully understand the immunogenicity profile of marstacimab. However, the current evidence indicates that any immunogenic response does not significantly compromise its clinical utility in hemophilia treatment.

Marstacimab Thrombogenicity

Thrombin generation assays (TGA) have demonstrated that marstacimab induces pro-coagulant responses, comparable to recombinant coagulation factors, without excessive thrombin generation.[15,32] In all the clinical studies to date, marstacimab exposure has not been associated with thrombosis during the active treatment phase. A catheter-related thrombosis occurred in the study during the observation phase. This observation differentiates it from other anti-TFPIs and rebalancing agents, where this is common.[6–8,10] The exact reason for this absence of thrombosis is poorly understood; however, the generation of thrombin within the physiologic range is the most plausible explanation.[15] The inability of marstacimab to generate supraphysiological levels of thrombin may be related to the unique epitope binding sites on the K2 domain of TFPI. No deaths occurred during the four studies.[23,27]

Marstacimab Long-Term Safety Profile

Long-term extension studies of marstacimab, with treatment durations up to 28 months, have shown no new safety signals and a consistent adverse event profile. Most participants tolerated the drug well, with no clinically significant changes in labs or key biomarkers.[27,32]

Efficacy Profile of Marstacimab

Efficacy Endpoints

The marstacimab clinical program evaluated efficacy using annualised bleed rates (ABR) via a negative binomial regression model. It aimed to demonstrate superiority over episodic treatment and noninferiority to factor prophylaxis, with secondary endpoints covering bleed types, quality of life, and perioperative use.[33,34]

Marstacimab Annualized Bleed Rates in the Phase 1b/2 Study

The Phase 1b/2 study compared the model-based ABR of marstacimab in 4 cohorts relative to the historical controls.[11] The four cohorts comprised 26 participants: 300 mg SC QW non-inhibitor (n = 7) in cohort 1(C1), 300 mg SC LD + 150 mg SC QW non-inhibitor (n = 6) in cohort 2 (C2), 450 mg SC QW non-inhibitor (n = 6) in cohort C3, and 300 mg SC QW inhibitor (n = 7) in cohort 4 (C4).[11]

Compared to the control's mean ABR of 27.6, the mean ABR on marstacimab in cohorts C1-C4 were 4.2, 1,5, 4.2, and 0.7 for cohorts C1, C2, C3, and C4, respectively. The relative reduction in ABR in cohorts C1, C2, C3, and C4 was 85%, 95%, 85%, and 98%, respectively. The phase 1b/2 study reported a significant reduction in ABRs during treatment with marstacimab compared to both an external on-demand control group and pretreatment ABR levels ($p < 0.0001$).[11] This reduction was observed across all dose cohorts, demonstrating the efficacy of marstacimab in reducing bleeding episodes in hemophilia patients. In this study, marstacimab exposure increased dose-relatedly, with a steady-state concentration reached by day 57. This suggests that higher doses of marstacimab may lead to greater reductions in bleeding episodes.[11]

In a long-term follow-up study, marstacimab maintained its efficacy in reducing bleeding episodes over up to 365 days, with mean and median on-study ABRs ranging from 0 to 3.6 and 0 to 2.5 bleeding episodes per participant per year, respectively.[17]

Marstacimab Bleed Rates in the Phase 3 Study

The Phase 3 BASIS study showed that marstacimab significantly reduced the annualized bleeding rate (ABR) by 91.6% in participants previously on episodic treatment, from 38 to 3.2 ($P < 0.0001$), demonstrating clear superiority. In those previously on prophylactic factor treatment, marstacimab reduced the ABR from 7.9 to 5.1, a 35.2% decrease. These findings support marstacimab's superiority over on-demand therapy and non-inferiority to established factor prophylaxis.[27]

Marstacimab maintained low annualized bleeding rates (ABRs) in the open-label extension (OLE) study, with a model-based ABR of 2.9 in participants previously on episodic treatment and 2.3 in those on prior prophylaxis after an average of 7 months. Across successive six-month intervals, marstacimab progressively reduced mean model-estimated ABRs from 5.4 (0–6 months) to 3.6 (7–12 months) and 2.3 during the OLE.[23,27] Subgroup analyses from the BASIS study showed low annualised bleed rates (ABRs) among participants on episodic treatment, with mean ABRs of 2.83 for joint bleeds, 2.44 for spontaneous bleeds, and 2.84 for target joint bleeds. Those previously on factor prophylaxis had slightly higher mean ABRs of 4.13, 3.78, and 2.51, respectively.[27]

Marstacimab Lowered the Mean Model-Estimate by 7–12 months, and the OLE

Impact of Marstacimab on Target Joints

The effect of marstacimab on target joint resolution remains unreported. In contrast, other anti-TFPI therapies like concizumab have shown a significant impact, with up to 86.3% target joint resolution.[7,8,35,36] Knowledge of target joint

resolution is critical in understanding how to target specific molecular pathways in arthritis and may offer further insights and advancements in the treatment of joint-related complications in hemophilia.[37]

Zero Bleed Rates with Marstacimab Prophylaxis

In a Phase 1b/2 study, marstacimab demonstrated a mean and median on-study ABR ranging from 0 to 3.6 and 0 to 2.5 bleeding episodes per participant per year, respectively.[23] This indicates a substantial reduction in bleeding episodes but not a zero-bleed rate. In the Phase 3 BASIS study, 73.3% of participants experienced at least one bleeding event during the active treatment phase, indicating of the need for additional hemostatic agents.[23,27]

Achieving zero bleeds in hemophilia is linked to improved quality of life, reduced joint damage, and better overall health outcomes. This preventive approach enables greater daily activity and alleviates the psychological stress associated with bleeding risk.[1,36,38,39]

The Potential Place of Marstacimab in the Hemophilia Treatment Armamentarium

Marstacimab represents a significant advancement in hemophilia treatment, offering a novel, non-factor approach for patients with hemophilia A or B without inhibitors. It is the first FDA-approved anti-tissue factor pathway inhibitor (TFPI) antibody for non-inhibitor hemophilia prophylaxis. It provides an alternative to traditional factor replacement therapies, particularly benefiting those with hemophilia B, who previously lacked subcutaneous prophylactic options.

Marstacimab introduces a novel mechanism in the prophylactic treatment of hemophilia A and B. Targeting the extrinsic coagulation pathway provides an alternative to conventional factor replacement therapies, aiming to reduce or prevent bleeding episodes. Marstacimab can address several unmet needs of replacement therapies, including the intravenous route of administration, inconsistent hemostatic cover due to peaks and troughs, and high immunogenicity of replacement therapy.[40]

Marstacimab has demonstrated robust efficacy across phase 1, 2, and pivotal phase 3 trials.[11,23,27] The BASIS Phase 3 study reported statistically significant reductions in annualized bleeding rates (ABR) compared to both on-demand and routine prophylaxis regimens. Safety data reveal marstacimab to be generally well tolerated. No thromboembolic events were observed, and common adverse events included mild injection site reactions and transient anti-drug antibodies, which typically resolved.[22,25,27]

Administered subcutaneously once weekly with a fixed dose independent of body weight, marstacimab simplifies treatment logistics and minimizes dosing error.[18] A loading dose is followed by maintenance therapy, maintaining therapeutic concentrations across weight categories without compromising safety.[25] Marstacimab offers a valuable non-factor-based approach, particularly for patients with inhibitors against factor VIII or IX. Its efficacy in reducing bleeding frequency and improving quality of life complements treatments like emicizumab and fitusiran. At the same time, its distinct mechanism and convenient administration provide unique benefits in select patient populations.[19,41]

Marstacimab enriches the hemophilia treatment armamentarium, particularly for severe hemophilia A or B patients without inhibitors. As with all therapies, individualized treatment plans remain essential.[42] While traditional factor replacement retains its foundational role, marstacimab represents a significant step forward. Ongoing studies will clarify its long-term utility, especially in patients with inhibitors.[32,43]

Conclusion

Marstacimab represents a major advance in the prophylactic management of hemophilia A and B, offering the first FDA-approved anti-TFPI antibody for patients without inhibitors. Its subcutaneous administration, fixed-dose regimen, and demonstrated efficacy in reducing annualized bleeding rates address key limitations of traditional factor replacement therapies, including venous access challenges, variable pharmacokinetics, and immunogenicity. Across early- and late-phase clinical trials, marstacimab has shown a favorable safety profile, with no thrombotic events during the active treatment phase and manageable injection site reactions. Although immunogenicity warrants continued surveillance,

current data indicate no clinically meaningful impact on efficacy or safety. While zero bleed rates remain aspirational, marstacimab significantly reduces bleeding frequency. Positioned alongside other rebalancing agents, it expands non-factor therapeutic options and offers value to hemophilia B patients previously underserved by the absence of subcutaneous prophylaxis. Further long-term and real-world data will be critical to defining marstacimab's full therapeutic role, including its utility in inhibitor populations and impact on joint health outcomes.

Disclosure

JM has received research grant/research support from BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, and Vega has been a consultant/scientific board member for BioMarin, CSL Behring, Novo Nordisk, Roche, Takeda, Sanofi, Spark, and Vega; and has received speaker bureau fees from Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. The authors report no other conflicts of interest in this work.

References

1. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1–158. doi:10.1111/hae.14046
2. Mahlangu JN, Blanchette V, Klamroth R. Redefining prophylaxis in the modern era. *Haemophilia*. 2021;27(Suppl 3):21–27. doi:10.1111/hae.14035
3. Mahlangu J. Emicizumab and unmet needs of patients with hemophilia A who are managed with replacement therapies. *Expert Rev Hematol*. 2024;17(10):741–748. doi:10.1080/17474086.2024.2402304
4. Mahlangu JN. Bispecific antibody emicizumab for haemophilia a: a breakthrough for patients with inhibitors. *BioDrugs*. 2018;32(6):561–570. doi:10.1007/s40259-018-0315-0
5. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia a without inhibitors. *N Engl J Med*. 2018;379(9):811–822. doi:10.1056/NEJMoa1803550
6. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia a with inhibitors. *N Engl J Med*. 2017;377(9):809–818. doi:10.1056/NEJMoa1703068
7. 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–e332. doi:10.1016/S2352-3026(23)00037-6
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):1427–1437. doi:10.1016/S0140-6736(23)00284-2
9. Baglin T, Huntington JA, Koch A, Mocanu I, Makhaldiani L. Serpin-PC in persons with severe hemophilia (PwH): updated results from a multicenter multi-part, first-in-human study. *Blood*. 2023;142(Supplement 1):2619. doi:10.1182/blood-2023-179969
10. Matsushita T, Shapiro A, Abraham A, et al. Phase 3 trial of concizumab in hemophilia with inhibitors. *N Engl J Med*. 2023;389(9):783–794. doi:10.1056/NEJMoa2216455
11. Mahlangu JN, Lamas JL, Morales JC, et al. A phase 1b/2 clinical study of marstacimab, targeting human tissue factor pathway inhibitor, in haemophilia. *Br J Haematol*. 2023;200(2):229–239. doi:10.1111/bjh.18420
12. Eichler H, Angchaisuksiri P, Kavakli K, et al. A randomized trial of safety, pharmacokinetics and pharmacodynamics of concizumab in people with hemophilia A. *J Thromb Haemost*. 2018;16(11):2184–2195. doi:10.1111/jth.14272
13. Broze GJ Jr, Girard TJ. Tissue factor pathway inhibitor: structure-function. *Front Biosci*. 2012;17(1):262–280. doi:10.2741/3926
14. Marlu R, Polack B. Gla-domainless factor Xa: molecular bait to bypass a blocked tenase complex. *Haematologica*. 2012;97(8):1165–1172. doi:10.3324/haematol.2011.055699
15. Patel-Hett S, Martin EJ, Mohammed BM, et al. Marstacimab, a tissue factor pathway inhibitor neutralizing antibody, improves coagulation parameters of ex vivo dosed haemophilic blood and plasmas. *Haemophilia*. 2019;25(5):797–806. doi:10.1111/hae.13820
16. Sidonio RF Jr, Hoffman M, Kenet G, Dargaud Y. Thrombin generation and implications for hemophilia therapies: a narrative review. *Res Pract Thromb Haemost*. 2023;7(1):100018. doi:10.1016/j.rpth.2022.100018
17. Mahlangu J, Luis L, Cristobal Morales J, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: Phase II study results. *Br J Haematol*. 2023;200(2):240–248. doi:10.1111/bjh.18495
18. Hympavzi marstacimab package insert P, New York, 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761369s000lbl.pdf. Accessed April 30, 2025.
19. Mahlangu JN. Progress in the development of anti-tissue factor pathway inhibitors for haemophilia management. *Front Med Lausanne*. 2021;8:670526. doi:10.3389/fmed.2021.670526
20. Parng C, Singh P, Pittman DD, et al. Translational pharmacokinetic/pharmacodynamic characterization and target-mediated drug disposition modeling of an anti-tissue factor pathway inhibitor antibody, PF-06741086. *J Pharm Sci*. 2018;107(7):1995–2004. doi:10.1016/j.xphs.2018.03.010
21. Taylor CT, Hwang E, Hinnershitz T, et al. Safety biomarkers in participants with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors receiving prophylactic marstacimab treatment: results from the phase 3 BASIS trial. *Blood*. 2024;144(Supplement 1):1210. doi:10.1182/blood-2024-205843
22. Acharya SS, Matin D, Mahlangu J, et al. Marstacimab, an anti-tissue factor pathway inhibitor, in participants with hemophilia A or B, with and without inhibitors: an integrated analysis of safety. presented at: 65th annual meeting of the American Society of Hematology (ASH), 9–12 December, San Diego, California, USA 2023.
23. Matino D, Acharya S, Palladino A, et al. Efficacy and safety of the anti-tissue factor pathway inhibitor marstacimab in participants with severe hemophilia without inhibitors: results from the phase 3 basis trial. *Blood*. 2023;142(Supplement 1):285. doi:10.1182/blood-2023-181263
24. Pruthi RK, Chen D. The use of bypassing treatment strategies in hemophilia and their effect on laboratory testing. *Semin Thromb Hemost*. 2023;49(6):651–660. doi:10.1055/s-0043-1768660

25. Nayak S, Suzuki A, Ravva P, Raje SV. A fixed (weight-independent) subcutaneous once-weekly dose for marstacimab, an anti-TFPI monoclonal antibody for the prophylactic treatment of hemophilia A and B. *Blood*. 2024;144(Supplement 1):1215. doi:10.1182/blood-2024-199766
26. Cardinal M, Kantaridis C, Zhu T, et al. A first-in-human study of the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06741086, an anti-tissue factor pathway inhibitor mAb, in healthy volunteers. *J Thromb Haemost*. 2018;16(9):1722–1731. doi:10.1111/jth.14207
27. Matino D, Gould T, Teeter J, Taylor CT, McDonald R, Palladino A. Descriptive characterization of bleeding events in participants with severe hemophilia α or B without inhibitors, receiving prophylactic marstacimab treatment. *Blood*. 2024;144(Supplement 1):716. doi:10.1182/blood-2024-205975
28. Kim PJ, Lansang RP, Vender R. A systematic review and meta-analysis of injection site reactions in randomized-controlled trials of biologic injections. *J Cutan Med Surg*. 2023;27(4):358–367. doi:10.1177/12034754231188444
29. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127–2138. doi:10.1182/blood.2019001869
30. Sun RXN, Qian MG, Zhang XB. T and B cell epitope analysis for the immunogenicity evaluation and mitigation of antibody-based therapeutics. *Mabs*. 2024;16(1):Artn2324836. doi:10.1080/19420862.2024.2324836
31. Davda J, Declerck P, Hu-Lieskovan S, et al. Immunogenicity of immunomodulatory, antibody-based, oncology therapeutics. *J ImmunoTherapy Cancer*. 2019;7(1):ARTN105. doi:10.1186/s40425-019-0586-0
32. Acharya S, Matino D, Mahlangu J, et al. Marstacimab, an anti-tissue factor pathway inhibitor, in participants with hemophilia A or B, with and without inhibitors: an integrated analysis of safety. *Blood*. 2023;142(Supplement 1):3980. doi:10.1182/blood-2023-174682
33. Benitez O, Kim HK, Taylor CT, et al. Surgical and medical procedures in participants with hemophilia A or B without inhibitors receiving marstacimab in the basis and open-label extension trials. presented at: 18th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), 4–7 February, Milan, 2025.;
34. Jiménez-Yuste V, Mazar I, Khanji C, et al. Health-related quality of life outcomes for marstacimab in participants with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors: results from the phase 3 basis trial. presented at: 18th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), 4–7 February, Milan, 2025.;
35. Castaman G, Abraham A, Angchaisuksiri P, et al. The effect of concizumab prophylaxis on target joints, resolution and joint bleeds in patients with hemophilia A or B with or without inhibitors in phase 3 clinical trials. *Blood*. 2023;142(Supplement 1):284. doi:10.1182/blood-2023-180790
36. Mahlangu J, Jimenez-Yuste V, Ventriglia G, et al. Long-term outcomes with emicizumab in hemophilia A without inhibitors: results from the HAVEN 3 and 4 studies. *Res Pract Thromb Haemost*. 2024;8(2):102364. doi:10.1016/j.rpth.2024.102364
37. Axelsen MB, Eshed I, Horsley-Petersen K, et al. A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without Adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. *Ann Rheumatic Dis*. 2015;74(5):867–875. doi:10.1136/annrheumdis-2013-204537
38. Mannucci PM, Kessler CM, Germini F, et al. Bleeding events in people with congenital haemophilia A without factor VIII inhibitors receiving prophylactic factor VIII treatment: a systematic literature review. *Haemophilia*. 2023;29(4):954–962. doi:10.1111/hae.14803
39. Hermans C, Pierce GF. Towards achieving a haemophilia-free mind. *Haemophilia*. 2023;29(4):951–953. doi:10.1111/hae.14807
40. Mahlangu J. Emicizumab for the prevention of bleeds in hemophilia A. *Expert Opin Biol Ther*. 2019;19(8):753–761. doi:10.1080/14712598.2019.1626370
41. Olasupo OJ, Le TH, Shonde TB, et al. Direct X-ray detectors based on an eco-friendly semiconducting zero-dimensional organic zinc bromide hybrid. *Acs Energy Lett*. 2024;9(12):5704–5711. doi:10.1021/acsenergylett.4c02662
42. Lopez-Jaime FJ, Montano A, Marco A, Marco P, Fernadez-Bello I, Palomo-Bravo A. Plasma levels of emicizumab and its correlation with global assays: do the patients need individualization? *Haemophilia*. 2023;29:26.
43. Mahlangu J, Lamas J, Morales JM, et al. Treatment with marstacimab for people with severe hemophilia a or b: a plain language summary of the results from a short-term study and a longer-term study. *Future Rare Diseases*. 2023;3(4):1–13. doi:10.2217/frd-2023-0004