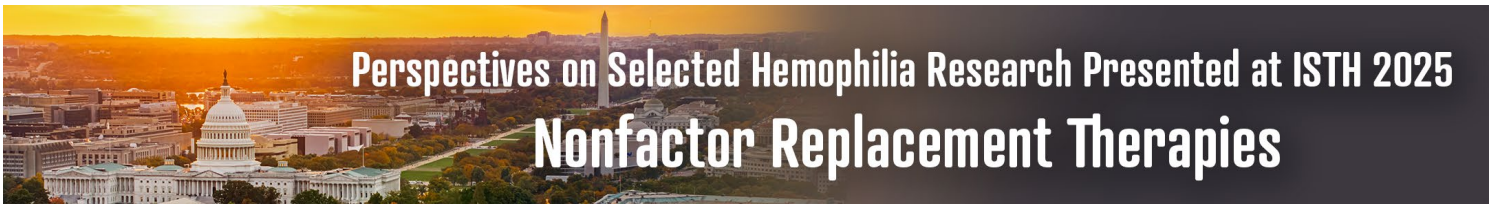

Editor's Note: The is a transcript of a presentation on July 22, 2025. It has been edited and condensed for clarity. To obtain credit for participation CLICK HERE.

REBALANCING AGENTS

INTRODUCTION

Thirty percent of patients with hemophilia A develop inhibitors. Rebalancing agents act through the factor-independent clotting pathway to promote hemostasis and they are designed to overcome some of the limitations with clotting factor concentrates. For instance, those limitations relate to limited availability, diminished efficacy, in patients who develop inhibitors or neutralizing antibodies, and frequent intravenous administration, with potential impacts to patient adherence and convenience. There have been 3 rebalancing agents which received approval in the United States: concizumab, fitusiran and marstacimab.

OC 59.3. Association of antithrombin levels with efficacy of fitusiran prophylaxis in people with hemophilia A or B with and without inhibitors: a predictive modeling approach: Guy Young, et al.

To assess the relationship between antithrombin levels and ABR, an Andersen-Gill model with frailty was employed. ABR stands for annualized bleed rate. The analysis utilized data from patients who received at least 1 dose of fitusiran during the steady-state period of 3 completed phase 3 trials and ongoing phase 3 extension study, the ATLAS-OLE, and a subset of 34 patients from a phase 2 trial. All available data from participants who received both the 80 mg once-monthly original dose regimen and the antithrombin-based dose regimen were included in the analysis. The antithrombin dose regimen targets antithrombin levels between 15% and 35% to balance efficacy and safety.

The key findings were as follows: Data from 254 patients, spanning over 559 patient-years of observation, were included in the analysis. The individual mean antithrombin levels were 11.5% with the ODR and 23.2% with the AT-DR. A monotonic increasing relationship between ABRs and antithrombin levels was confirmed by modeling and simulation at 10% antithrombin levels, the median ABR was low, less than 1, 0.73 to be exact, and then it increased over the 15% antithrombin level and 35% antithrombin level to a mean ABR of almost 5. As these antithrombin levels increased, the median ABR increased and, with that, also the confidence interval.

Now, what are the implications for current patient care? Although it appears advantageous to strive for lower antithrombin levels by drug dose adjustments just to get lesser bleeds, the FDA prescribing information now recommends antithrombin percentages to be capped between 15% and 35%. So, no lower than that due to the potential of thromboembolic complications at very low antithrombin levels. The good news is that antithrombin-based rebalancing agents can be not only used for hemophilia A, but also for hemophilia B. So, for both hemophilias alike.

OC 59.2. Annualized bleeding rates in hemophilia A/B and target joints: Concizumab explorer8 study: Allison Wheeler, et al.

Patients in the phase 3 explorer8 were randomized 1:2 to either on-demand treatment, that was arm 1, or concizumab, arm 2, or assigned to nonrandomized concizumab arms 3 and 4. This was a prospective open-label study. All patients received 1 mg/kg concizumab as a loading dose on day 1, followed by 0.2 mg/kg daily starting from day 2. And then potential dose adjustments followed, between 0.15 and 0.25 mg/kg after 5 to 8 weeks based on concizumab plasma concentration measured after week 4. Target joints were defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-month period and treated spontaneous and traumatic bleeding episodes were assessed at 32 and 56 weeks as cut-offs.

The key results were as follows: 173 patients were screened and there was a 77% reduction in treated spontaneous and traumatic bleeding episodes with concizumab prophylaxis in arm 2 vs the on-demand arm 1 in patients with target joints at baseline. Specifically, the estimated mean ABR, or annualized bleed rate, was 14.9 for on-demand in arm 1 and 3.4 for concizumab prophylaxis in arm 2. Thirty-five-point 1 percent of patients with target joints at baseline and 60% of patients without target joints at baseline in the concizumab prophylaxis arm achieved zero treated spontaneous and traumatic bleeds. And then the mean ABRs remained low at 56 weeks.

What does that mean for clinical practice? In my view, rebalancing using tissue factor pathway inhibitor (TFPI) modulation with concizumab is suitable for hemophilia A and B to reduce or avoid bleeding. Now, since approved for patients with inhibitors, concizumab is very helpful to provide prophylaxis to patients with hemophilia B and inhibitors, which is a real unmet clinical need.

OC 20.1. Long-term efficacy of marstacimab in participants with severe hemophilia A or B without inhibitors: Davide Matino, et al.

This open-label extension study, in short OLE, followed eligible male participants aged 12 to less than 75 years with severe hemophilia A or B without inhibitors who had completed the phase 3 BASIS trial, which showed that marstacimab reduced bleeding episodes compared with previous on-demand and routine prophylaxis factor therapy. Participants entered the OLE continuing their marstacimab dose, either 150 or 300 mg every week, from the end of the BASIS study. Bleeding episodes and marstacimab doses were recorded via electronic diary and the study primarily focused on describing the long-term efficacy of marstacimab.

And here are the key findings. In total, 107 out of 116 patients, 92.2%, and these noninhibitor patients from the BASIS trial, enrolled and were dosed in the OLE, comprising 89 adults and 18 adolescents. That would be 83% adults and 17% adolescents. Participants in the OLE had a median exposure to marstacimab of 18.9 months, so the range was 1.2 to 29.4 months, with a combined median exposure from the BASIS plus the OLE study of 30 months. Across both BASIS and OLE, 27, which is 23.3% of participants, had their dose escalated from 150 mg to 300 mg once weekly.

The annualized bleed rate, again abbreviated by ABR, for treated bleed was as follows: In the BASIS pivotal study, overall, 116 participants, a mean estimated ABR was found and that was 4.52. In the OLE, overall, 107 study participants, the mean estimated ABR was 2.94, and in both studies, the median was lower than that. The annualized bleed rate for total bleeds were expectedly slightly higher for means and median and marstacimab remained generally safe and well tolerated. One participant in the OLE reported a deep vein thrombosis which was non-life-threatening and did not require hospitalization. This participant had multiple risk factors.

The implications for current patient care here are, in my opinion, again rebalancing using TFPI modulation with marstacimab is suitable for hemophilia A and B, so hemophilia-independent, to deliver prophylaxis. The weekly subcutaneous dosing seems very advantageous and, of note, the drug is currently not approved for patients with inhibitors.

Additional trials: In addition, I will now provide a brief overview of 2 additional key posters. The first one is by Chowdhary and the title is "Low incidence of anti-drug antibodies to fitusiran in people with hemophilia A or B with or without inhibitors." And the key finding here was that fitusiran has a low risk of causing immunogenicity. Antidrug antibodies did not impact efficacy or safety.

The second poster was by Shapiro. The title was "Non-joint bleeds in patients with hemophilia A or B with inhibitors." It was the concizumab explorer7 study. And the key finding here was that concizumab had few non-joint bleed reports and annualized bleeding rate treatment.

FACTOR VIII MIMETICS

INTRODUCTION

Factor VIII mimetics function by bridging activated factor IX and factor X, effectively mimicking the cofactor function of factor VIII. Emicizumab is the only approved factor VIII mimetic. Mim8, a factor VIII mimetic bispecific antibody, is in late phase investigation. It causes the replacement of the factor VIII function, allowing for the restoration of thrombin within normal limits, and it delivers improved potency and sustained efficacy across flexible dosing intervals, up to once monthly prophylaxis.

PB0280. Effectiveness of emicizumab in hemophilia A: A fourth interim analysis of the real-world study EMIIL: Johannes Oldenburg, et al.

EMIIL is single-arm, 2-cohort, prospective, multicenter, noninterventional study designed to collect safety and effectiveness data in adults and children with hemophilia A newly treated with emicizumab. Cohort A includes patients without factor VIII inhibitors and cohort B with factor VIII inhibitors. The primary endpoint is the annualized bleed rate of treated bleeds, estimated using a negative binomial regression model.

Key findings are as follows. At data cut-off, 125 patients in cohort A and 7 patients in cohort B were available for evaluation. The majority of patients had factor VIII activity less than 1% and that was a severity at baseline in both cohorts. After a median treatment duration of 918 days for cohort A, the model-based ABR was 0.67, so way below 1. In cohort A, zero treated bleeds were recorded in 44.8% of patients, zero treated spontaneous bleeds in 76%, zero treated joint bleeds in 66.4%, and zero treated target joint bleeds in 95.2%.

All patients in cohort B had zero treated bleeds after a median treatment duration of 378 days. Most patients in cohort A experienced zero treated bleeds across the study period, ranging from about 88% to 94% when recorded in 12-week time windows. Overall, 87 out of 132 safety-evaluable patients reported 313 adverse events; 16.8% were reported as grade ≥3. No new safety concerns emerged.

What does that mean in terms of implications for current patient care? Prophylaxis with emicizumab yields low ABRs long-term, however, joint bleed rates were nonzero. In fact, those joint bleed rates were only 66% for joint bleeds, which truly leaves room for improvement with newer formulations in development.

OC 64.3. Prospective evaluation of a defined replacement protocol for peri-operative hemostasis in patients with severe hemophilia A, with and without inhibitors, on emicizumab prophylaxis undergoing elective major surgeries– final results (EmiSurg Study): Aby Abraham, et al.

This was an investigator-initiated, prospective study focusing on peri-operative hemostasis in patients with severe hemophilia A, with or without inhibitors, aged 2 to 60 years, who had been on emicizumab prophylaxis for at least 4 weeks and required elective major surgery. Patients received additional hemostasis via a defined protocol using standard half-life recombinant factor VIII for those without inhibitors, or recombinant factor VIIa for those with inhibitors. Replacement therapy was generally stopped after 5 days for those without inhibitors and 7 days for those with inhibitors, unless clinically indicated. No thromboprophylaxis was administered and the outcome parameters were as follows: the efficacy of surgical and postoperative hemostasis following ISTH criteria, blood counts, factor VIII levels, rotational thromboelastrometry (ROTEM), thrombin generation, and DVT screening.

The key findings were as follows. Thirty-nine patients, 15 with inhibitors, with a median age of 30.5 years—the range of ages 14 years to 56 years were included—40 procedures were recorded. A variety of surgical procedures were performed, but the majority, 75%, were orthopedic. Three long-standing giant body cavity pseudotumors were analyzed separately as high-risk cases. Hemostatic efficacy for the 37 standard-risk procedures was assessed as excellent in 91.9%. It was assessed as fair in 2 of the 3 high-risk categories and poor in 1. The overall hemostasis at wound healing was assessed as excellent in 97.3% of the standard-risk procedures. It was assessed as fair in 2 and moderate in 1.

Preoperative ROTEM and thrombin generation testing (TGT) were normal or near-normal after recombinant factor VIII or recombinant factor VIIa infusion. Twelve breakthrough bleeds (BTB) occurred in 9 standard-risk procedures. For standard-risk procedures without inhibitors, 2 of 25

procedures had a BTB within 7 days of procedure. For standard-risk procedures with inhibitors, 1 of 15 procedures had a BTB between days 7 to 14 and that was bilateral total knee replacement with extended support, and 2 out of 11, 13.3%, procedures after day +14.
These BTBs neither required additional transfusion support nor affected wound healing and mostly resolved with 1 to 2 doses of factor replacement. Most BTBs occurred either by total knee replacement, there were 3 unilateral and 3 bilateral, or the excision of these large pseudotumors, 2 in the thigh and 1 in the ankle. In all except 2, BTBs occurred after stopping the recombinant factor VIII or recombinant factor VIIa 5 or 7 days postop and then again during physiotherapy and mobilization.

For the 3 high-risk patients who underwent abdomino-pelvic or thoracic giant pseudotumor resections, 2 were without an inhibitor and 1 with an inhibitor, the recombinant factor VIII and recombinant factor VIIa support was electively continued. There were multiple BTBs requiring additional transfusion of blood products; 2 without inhibitors received only packed red cells, while the 1 with inhibitor experienced continued bleeding despite global hemostasis parameters in the normal range, leading to septic complications and death on day 23. There was no thromboembolism or thrombotic microangiopathy.

What are the implications for current patient care? Major surgeries on emicizumab providing continued hemostatic support are definitely feasible, whereby breakthrough bleeding is responsive to treatment with factor VIII or recombinant factor VIIa. To avoid breakthrough bleeding, which mainly started several days after, one may consider an *a priori* factor coverage. That takes a little longer, maybe 10 days or longer, particularly going through physiotherapy and other rehabilitation procedures. There's no need to interrupt emicizumab.

OC 20.4. FRONTIER5 direct switch study: Safety of initiating Mim8 prophylaxis without washout of emicizumab: Johannes Oldenburg, et al.

The study was a single-arm, open-label, 26-week, phase 3b study to evaluate the safety of Mim8 in adults and adolescents with hemophilia A with or without inhibitors. It included males and females aged 12 years and older who were directly switched to Mim8 prophylaxis from emicizumab prophylaxis without a washout period nor an Mim8 loading dose. Mim8 was administered subcutaneously via a pen injector once-every-week, once-every-2-weeks, or once-every-month for 26 weeks, using a weight-based, tiered-dosing approach. No Mim8 loading dose was given. The treatment frequency was determined by patient preference and investigator discussion, which may have differed from their previous emicizumab dosing. The first Mim8 maintenance dose was given on the planned emicizumab dosing day. The primary endpoint was to evaluate the number of treatment-emergent adverse events.

The key findings are as follows. Sixty-one patients were exposed to Mim8 and completed 26 weeks of treatment. The total exposure time was 30.77 patient-years. The patient demographics showed that almost everyone was male and the mean age was 39 years. Ninety point two percent of patients were inhibitor-negative and 93.4% had severe hemophilia.
Previous emicizumab dosing frequency was once weekly for most of the patients, like 50.8%, once every 2 weeks for 37.7%, and once every 4 weeks for 11.5%. A total of 107 treatment-emergent adverse events (TEAEs) were observed in 70.5%, corresponding to 3.48 TEAEs per patient-year of exposure. Most TEAEs were mild in 65.6%, moderate in 23%, and severe in 3.3%.

Four serious TEAEs were reported, none of which were considered to be related to Mim8. These included 1 case of hyperglycemia, 1 pneumothorax, and 2 knee arthroplasties. Twenty-nine point 5 percent of patients reported 24 TEAEs that were possibly or probably related to Mim8. Injection site reactions were reported by 19.7% of patients, occurring in 15 out of 990 total injections—to be precise that was only 1.5% of injections—and were mostly transient and mild. No thromboembolic events, hypersensitivity reactions, or TEAEs leading to permanent discontinuation of Mim8 were observed. There were no neutralizing anti-Mim8 antibodies and steady state levels were achieved by week 16. Emicizumab was eliminated by week 26.

The clinical implication of this study is important since this study shows that a seamless transition from emicizumab prophylaxis to Mim8 is possible that truly allows us to establish fully therapeutic Mim8 levels within a short period of time and also have flexible dosing intervals, similar to emicizumab.

Additional trials: In addition, I will now provide a brief overview of 3 additional key posters. The first one is by Dr. Chrisentery-Singleton. The title is "Factor VIII inhibitor titers in people with hemophilia A on emicizumab prophylaxis in ATHN 7." The key finding here is that factor VIII inhibitor titers remained stable or decreased over a median exposure to emicizumab of 116 weeks.

The second one is by Dr. Mahlangu with the title "Evaluating pen-injector handling and PROs in patients switching from emicizumab to Mim8 in FRONTIER5." The key finding here is that after 26 weeks, most of the 61 patients—these were 84% adults—rated the Mim8 pen-injector as easy to use and 97% preferred it over their previous injection system.

The third one is by Tardy et al. It's called the "PHILEOS (haemoPHILia and ostEporOSis) study: results of a multicentre case-control study." This study demonstrated that persons with severe hemophilia who did not receive prophylaxis were nearly 14 times more likely to experience osteoporosis than healthy controls.

CONCLUSION

The studies presented at ISTH 2025 highlight significant progress in non-factor replacement therapy. Rebalancing agents demonstrate significant advancements and factor VIII mimetics continue to show high effectiveness and favorable long-term safety. Ongoing investigations will further refine treatment approaches ensuring personalized and effective care.

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