Steven Pipe, MD:

Hello, and welcome to this CME presentation entitled Hemophilia Clinical Research Highlights from ISTH 2025. I'm Dr. Steven Pipe from the University of Michigan, and this year's ISTH was an excellent meeting in Washington D.C., and I'll be presenting some of the influential clinical research abstracts that are relevant to novel therapeutics for hemophilia. These are my faculty disclosures, and this program is supported by an independent medical education grant from Sanofi.

So first, let me level set for all of you participating so that we can understand the clinical context for the research that I'm highlighting today. So hemophilia is a rare bleeding disorder that impairs the blood clotting process. Individuals may experience prolonged bleeding after injuries or with surgery, and in the severest forms, heavy bleeding can occur even after minor trauma or spontaneously without any injury. Serious complications may result from bleeding into the joints, particularly repeatedly over the lifespan, as well as bleeding into muscles, the brain and other internal organs. And so, the standard of care is regular prophylactic therapy to prevent bleeding. And the two major types are hemophilia A, which is caused by a deficiency of clotting Factor VIII, or hemophilia B, which is caused by a deficiency of clotting Factor IX.

Now, this background I'm going to share is going to help you understand some of the unique mechanisms of action of novel therapeutics that I'm going to discuss. So hemostasis depends on a balanced coagulation system of the procoagulants and the natural anticoagulants. So on the procoagulant side, we have Factor VIII, Factor IX, as well as some of the other clotting factors. And then, balanced against that are the natural anticoagulants, antithrombin, tissue factor pathway inhibitor and proteins C and S. And if these are in proper balance, we have all of the ability to generate thrombin when we need it, and then the natural anticoagulants are able to contain so that thrombin generation doesn't become excessive, and then we form just the optimal amount of thrombin to convert fibrinogen into fibrin and then get a stable clot.

So in this view of hemostasis, thrombin is the key enzyme in interconnected and overlapping cellular and proteolytic events that maintain hemostasis. So first, during the initiation phase of coagulation, a small amount of thrombin is formed on the tissue factor-bearing cells. Thrombin is then available to activate other coagulation factors to amplify the procoagulant signal and to activate platelets, and these newly activated procoagulants and the activated platelet surface drive Factor X activation, and then a burst of thrombin generation occurs that will ultimately lead to efficient conversion of soluble fibrinogen to insoluble and cross-linked fibrin that yields a stable clot.

Now, the deficiency of the procoagulant Factor IX or its cofactor, Factor VIII, in hemophilia impairs the amplification phase, and this leads to a reduced thrombin burst and an inability to form an efficient fibrin clot. Now, we can see this in vitro using a plasma thrombin generation assay. After initiating the coagulation process, control plasma quickly generates a burst of thrombin until it's consumed or inactivated in the assay, whereas in plasma from a patient with severe hemophilia, you see the markedly delayed and impaired peak thrombin generation. The thrombin generation correlates with plasma [inaudible 00:03:59] levels, as well as bleeding risk in people with hemophilia.

Now, on the left, you can see control plasma in blue, and then sequentially, a person with severe hemophilia, less than 1% Factor VIII, with a very blunted thrombin generation. Next, a person with moderate hemophilia with a Factor VIII level of 2.7%, and then a person with mild hemophilia at a Factor VIII level of 10%, where you see increasing levels of thrombin generation. Now, if you then look at a pool of persons with severe, moderate and mild bleeding phenotype hemophilia, you can see a clear correlation of their clinical bleeding phenotype and their thrombin generation parameters.

Now, replacing or mimicking the action of the procoagulants can increase thrombin generation in persons with hemophilia. The two strategies that we use, replacing Factor VIII or Factor IX or using a Factor VIII mimetic, which is a bispecific antibody called emicizumab, what we are doing is we are enhancing thrombin generation. So on the left, you see the impaired thrombin generation with severe Factor VIII deficiency in green. However, following Factor VIII concentrate infusion, thrombin generation is restored similar to the healthy control. On the right, we see the effect of the Factor VIIIa mimetic, emicizumab, and in this assay, emicizumab also modulates thrombin generation into a range that's similar to mild hemophilia.

Now, if we look at the benefits and risks of these strategies, let's start with factor replacement therapy first. It replaces what's missing. This is easy to talk to patients about; it's something that they can understand. We retain the natural regulation of the infused Factor VIII or Factor IX, there's a wide therapeutic window, and we've gained experience over multiple decades of efficacy of factor replacement in almost any clinical scenario, as well as we have the availability of laboratory monitoring when we're replacing those factors. The risks are that the peaks and troughs of infused Factor VIII and Factor IX really do not mimic normal physiology, and so there are real consequences of non-adherence to the prophylactic regimen, because then your levels will drop below critical thresholds and then bleeding is at risk, and this strategy overall, over the long-term, has not completely abrogated adverse joint outcomes for patients.

There's a real therapeutic burden in maintaining prophylaxis with factor replacement, because it's IV access, and because of the relatively short half-life of these agents, you have to do frequent IV infusions. And then, of course, there's an annual cost of that replacement therapy. And the most important adverse events that we've seen with factor replacement therapy, particularly with factor replacement, are inhibitors, which happen in about a third or more of patients who receive this, and depending on how these patients are receiving these factors in different clinical contexts, we have seen thromboembolism with factor replacement therapy.

Now, for what I'm going to be presenting today, it's important to distinguish between the different subtypes of Factor VIII replacement therapy. There are really three classes of Factor VIII therapies. The legacy factor therapies are now called the standard half-life agents. Essentially, we're almost exclusively using recombinant Factor VIII molecules, different bioengineered forms, but they all have a very similar half-life. There are some modifications, such as adding PEG conjugates or Fc fusion to Factor VIII, and both of these strategies will extend the half-life of Factor VIII. However, the half-life extension is only about 30% or so beyond the standard half-life of agents, and the reason for that is that the clearance of these molecules is still dependent on their interaction with von Willebrand factors. So since these Factor VIIIs get infused, they bind to von Willebrand factor; they're really limited to the plasma half-life of the von Willebrand factor itself.

So there is now a new, what you could call, an ultra-extended half-life agent. This is efanesoctocog alfa. It's been approved in the US just over the past couple of years. It's really in a class of its own due to its clear differentiation from the standard half-life and the extended half-life Factor VIII therapies. It has a unique conjugation system, such that it is divorced from von Willebrand factor. So it's stabilized through a fusion to an Fc-fused fragment of von Willebrand factor, as well as it has these additional polypeptides, called extend residues, which buffer it from clearance receptors. And overall, this produces a high sustained Factor VIII activity that's in the normal to near-normal range for most of the week after a single IV infusion. In fact, levels are still at about 15%, so in the mild hemophilia range, at the end of a one-week dosing regimen. And so, this produces a high efficacy with a once-weekly dosing

regimen and has been shown to be superior in bleed protection compared to previous prophylactic Factor VIII therapies. So we'll talk more about some abstracts related to this molecule coming up.

Now, if we're thinking about why we still need additional innovation in hemophilia, it's because we still have some unmet needs. Breakthrough bleeds and joint deterioration still occur with factor replacement therapy. Patients are really looking to achieve zero bleeds, particularly joint bleeds, over the long term. I mentioned the treatment burden; they're looking for easier and less frequent administrations. We'd like to avoid the development of inhibitors or be able to offer a prophylactic option for people who have developed inhibitors, particularly to Factor VIII. They're looking for an improved quality of life; we want new therapies to allow persons with hemophilia to live active lives that are really similar to non-hemophilic individuals. And then, we want to also improve access to treatment, particularly on a global scale, so that everyone has access to prophylactic therapy.

So the non-factor therapies really have changed the hemophilia treatment landscape, and these therapies are not Factor VIII or Factor IX replacement, but they target the hemostatic system in different ways, and they're all aiming to correct the hemostatic defect without replacing the missing Factor VIII or Factor IX protein. Now, the first one that's approved is only effective for patients with hemophilia A; this is emicizumab, and it's a substitution therapy for hemophilia A. It's a bispecific antibody, binds Factor IXa and Factor X, and it functions as a mimic of the activated Factor VIII. It allows for Factor VIII avoidance, so because this looks nothing like Factor VIII, it's a very effective strategy for patients who have inhibitors to Factor VIII. And it will not induce Factor VIII inhibitors, and so even using emicizumab in very young infants, we can avoid the immunologic response to Factor VIII. It's demonstrated superior bleed protection to traditional Factor VIII prophylaxis, it's had a positive effect on health-related quality of life, and really has allowed for unparalleled health equity advance for persons with hem A with inhibitors because it's an effective prophylactic agent for those who have developed inhibitors.

As far as risks, it doesn't treat acute bleeding events; it's a prophylactic therapy only, so you still have to rely on Factor VIII replacement for breakthrough bleeds or for surgery or bypassing agents if you have an inhibitor. There is a ceiling effect for its efficacy, so it doesn't provide sufficient hemostasis for all traumatic injuries or for all surgical interventions. It reduces the therapeutic burden because it can be given subcutaneously, because it has great bioavailability, because it's a monoclonal antibody, and it has a really long half-life, it produces steady-state levels, and so dosing regimens are typically once a week, once every two weeks or once every four weeks. We do lose some of the natural coagulation regulation, but it's not clear if that has any clinical implications. There have been adverse events. TMA events and thromboembolism were observed early on; these were primarily driven by using high doses and sustained administration of a particular bypassing agent, activated prothrombin complex concentrates, and so there's a need for risk mitigation when you are doing replacement therapy to make sure that you use the recommended doses of those agents.

So what we've reviewed so far is that hemophilia therapies are all trying to restore an adequate thrombin burst to treat bleeding or to provide prophylaxis. Now, the standard therapeutics have been factor replacement therapy with Factor VIII or Factor IX concentrates or emicizumab for hemophilia A. However, thrombin generation can also be increased by reducing the function or the levels of the natural anticoagulants of coagulation, so these include tissue factor pathway inhibitor, antithrombin and activated protein C. Now, we have newly approved monoclonal antibodies that target TFPI, these are concizumab and marstacimab, as well as a small interfering RNA therapeutic, called fitusiran, which knocks down antithrombin levels. Still under clinical development are novel therapeutics that target activated protein C.

Now, if we look at a summary of these emerging non-factor therapies, they all share some key similarities that may improve the overall management of people with hemophilia. Again, they're only used for prophylaxis, so you still require concomitant use of other hemostatic agents for breakthrough bleeds or surgeries. Because they're targeting the natural anticoagulant pathways, they're effective in hemophilia A or B, and they may be used in people with and without inhibitors. So this may increase the number of treatment options that are available for people with hem A and B with and without inhibitors. There are no peaks and troughs between doses for these therapeutic agents; however they modulate the hemostatic benefit for the patient, it's steady-state and it's the same degree of hemostatic protection 24 hours a day, seven days a week, 365 days a year. These therapies can all be given subcutaneously, and in general, they require a reduced frequency of administration compared to factor replacement therapies and the bypassing agents.

So, finally, let's discuss the potential of gene therapy for hemophilia, because there were some abstracts in this area as well. So gene therapy presents the opportunity for a single treatment event that can lead to long-term correction of the deficient clotting factors. Now, what's depicted in the graphic at the bottom is the measurable factor levels achieved first with factor replacement therapy on the left, and because of the relatively short half-life of these proteins, you see the repeating peaks and trough factor levels in the plasma, and then above, you see the corresponding modulation of the hemostatic effect. Now, the extended half-life therapies reduce the frequency of the infusions, but the hemostatic effect is the same. The non-factor therapies really change the paradigm, whereby there's no measurable factor level, since we're not replacing the missing factor, yet they offer a prolonged steady-state modulation of hemostasis that's sufficient to prevent breakthrough bleeding. Now, however, to date, these have not been able to sustain hemostasis in the non-hemophilic range.

So gene therapy offers the potential, by endogenous expression of Factor VIII or Factor IX from the liver, to produce prolonged steady-state and measurable factor levels, even into the non-hemophilic range over the long term. And the experience to date, particularly with hemophilia B gene therapy, is that stable, steady-state factor levels of Factor IX have been achieved over the long term, whereas there have been observations of a gradual decline of Factor VIII levels over the years with the hemophilia A gene therapies investigated.

So how do we do this? We use an adeno-associated virus-based liver-directed gene transfer. This is a one-time infusion. The AAV particles get taken up on the surface of the hepatocyte, they get taken up by endosomes, they escape the endosomes, they then deliver the payload, which is the transgene, the Factor VIII or the Factor IX, into the nucleus. And there, the transgene mainly persists in an episomal form, it forms circles and concatemers of multiple trans genes together, and then interacts with the transcription and translation machinery so that the cell starts to synthesize Factor VIII or Factor IX, and then it follows the normal secretion pathway into the plasma. And then, over days to weeks, you end up with steady-state levels of production of Factor VIII or Factor IX. We're going to talk about primarily one marketed Factor IX therapy, etranacogene dezaparvovec, but also mention a couple of the other gene therapies as well.

So the beneficial clinical outcomes that have been observed with AAV gene transfer are that we see durable Factor IX activity at therapeutic levels, reduced bleeding rates compared with prior replacement therapy, reduced factor concentrate usage, because these patients stopped having the need for routine prophylaxis, and an overall acceptable safety profile. There are some challenges. First of all, at least for now, this is only offered to adults aged 18 or older. And for many of these therapies, AAV antibodies that can pre-exist because of natural exposure to AAV in the community, if you've generated antibodies, these can neutralize the effect of the gene therapy, so many of the gene therapies that are offered

preclude eligibility to receive these therapies. With regards to durability, this is predominantly a non-integrating effect within the hepatocyte, and so the effect could be lost upon cell division, so we really don't know what the long-term efficacy is over multiple decades.

From a safety perspective, there is a manageable hepatotoxicity. We intervene in patients with a course of corticosteroids to manage this. But long-term risks on liver safety are an unknown, at least over multiple decades. And then, with regards to immunogenicity, even if you didn't have antibodies before you received AAV gene therapy, afterwards, everyone has high antibodies, and so this makes re-dosing with current technology really not possible. Ideally, we'd like to do this gene therapy as early in life as possible, because that would reduce the likelihood of already having pre-existing immunity against AAV, and as well, we would save these younger men from progressing to chronic joint damage by getting their definitive therapy early in life. And actually, the first adolescent trials have just started with one of the approved Factor IX therapies.

Okay, so with all that background, let's jump into the ISTH abstracts and see what new information was shared this year. So we'll start with the efanesoctocog alfa. This has been evaluated as part of a clinical trial system called XTEND, and what this particular abstract was providing additional information on was the long-term extension study of children who are under age 12 years who participated in the XTEND-Kids phase three trial and are now continuing on this therapy. They all continually receive efanesoctocog alfa for breakthrough bleeds if they have any over the course of their prophylaxis, and so this allowed them to also look at the efficacy of efanesoctocog alfa for managing and treating bleeds in children.

So what we see is that in this group of patients, there were 61 total bleeding events that were evaluated; the majority of these were into joints, about 44%. The overall breakthrough bleed rate, measured by an annualized bleeding rate, was very low, it was 0.67 bleeds per year. But what this abstract showed is that when patients needed to have a bleeding event treated, a single injection of efanesoctocog resolved nearly 89% of the bleeds, and most of those bleeds were rated as having an excellent or good response, and patients maintained the low ABR through the extended follow-up. So this is not surprising, given the characteristics of the pharmacokinetics of this molecule, and it is something we can share with patients to show them that both their prophylactic therapy and their breakthrough bleed management can be quite effective with this agent.

In addition, they also looked at the perioperative hemostatic control in adolescents and adults who had surgery in the long-term extension, and this included looking at both orthopedic surgeries as well as non-orthopedic surgeries. Patients received 50 units per kilo preoperatively, and then 30 to 50 units per kilo as needed every two to three days postoperatively, and thromboembolic prophylaxis was permitted if the clinicians chose to. And what was observed in this trial is that efanesoctocog alfa actually provided excellent and good hemostatic control in 93% to 100% of the cases, with really low overall product consumption and minimal complications. And if we see that even for the orthopedic surgeries, there was a median of only five infusions that were needed over a 14-day period, and then for non-orthopedic surgeries, the median number of injections was only three. If we look at the time when the patients were able to resume just their routine prophylaxis, it was about 15 days coming out of the orthopedic surgeries and nine days after the non-orthopedic surgeries.

We're next going to look at an abstract that was presented on the prospective evaluation of perioperative hemostasis protocol in patients on emicizumab. Now, what they did in this study, patients had to be initiated on emicizumab for at least four weeks before they underwent a major surgical procedure. They had patients aged between two to 60. There were 39 patients who had 40 surgeries, and they included 15 patients who had inhibitors. Predominantly, this was orthopedic procedures, at about 75%. If we look at the overall surgical hemostasis was rated as excellent, and over 90% of the

surgeries with a very high rating for wound healing. And breakthrough bleeds did occur, but these were mostly minor, and they occurred after stopping the additional replacement therapy, and for the orthopedic procedures, this mostly occurred during the rehab phase. So overall, there were no thrombotic complications observed, and none of the clinicians chose to use thrombo prophylaxis for these procedures.

Now, there is a database in Europe that collects a number of different parameters from the clinics distributed over the EU, and they reported on the thrombosis rates that are reported amongst patients with inherited bleeding disorders, and this data was collected from 2008 through 2023, and they're analyzing thrombotic events that were at least associated with previously receiving factor concentrates and bispecific antibodies. So they had 204 thrombotic events that occurred within 30 days of those product uses, and then they were able to calculate the rate of thrombosis.

It did vary by the different product classes, you see them listed here, with plasma-derived Factor VIII/VWF concentrates, standard half-life Factor VIII, extended half-life Factor VIII, bypassing agents, like FEIBA and NovoSeven, and then prophylaxis with the bispecific antibody emicizumab. And overall, the rates can then be calculated in a rate per 1000 person-years. Now, the reason this is important is it provides really a baseline for when new therapies come into the clinic, and since these are the most widely used therapies, when we have new therapies that are starting to be used by clinicians, having this knowledge of the background thrombosis rate will help us analyze as thrombotic events may or may not be reported with these new agents.

Now, there are second-generation by specific antibodies being developed. Mim8 is one of them, still under clinical development. And one of the questions is, what are the advantages of these agents? Well, these strategies are trying to improve on the properties of emicizumab, and one strategy is to alter the affinities of the bispecific antibody to increase the potency of the molecule. With a higher potency, maybe better bleed control, maybe some advantages in the formulation administration for the patient. So Mim8 is one of them; it has about a 15-fold higher potency compared to emicizumab. And so, one of the questions was, how would patients switch over from their first-generation emicizumab to a second-generation agent, like Mim8? So they assessed the safety of switching to Mim8 in patients with hemophilia A with and without inhibitors previously treated with emicizumab.

So it was an open-label 26-week phase 3b trial, which enrolled 61 individuals. This was a direct switch, so whenever they were due for their next dose, Mim8 was initiated instead of emicizumab. And what was observed is that this was well-tolerated with this direct switch strategy; there were no thromboembolic events, and no neutralizing antibodies, anti-drug antibodies, were observed with this transition. So I think this will give confidence. If this moves forward to clinical approval in the future, clinicians will be armed with this information and know how to switch patients, if that would be useful for them.

So this is one of the approved rebalancing agents, this is concizumab, which is an anti-TFPI monoclonal antibody. And this is looking at ABR outcomes, so annualized bleeding rate, in the phase three Explorer8 trial of concizumab prophylaxis. So this study had a primary endpoint for phase three, and then patients were invited to continue to an open-label extension, where they remained on daily subcutaneous dosing with concizumab. And what they did in this abstract is they looked at the protection from bleeding for individuals who had target joints at baseline before they switched to concizumab prophylaxis or those who had no target joints. This is looking at patients who came into this trial who were previously not on any prophylaxis, so were on-demand, and so you can see why the mean ABRs were so high when they were in the on-demand arm. But after the switch to concizumab, you see a marked reduction, a 77%

reduction in target joint bleeding in those who had target joints at baseline and a 99% reduction in bleeding in those without target joints at baseline.

And the open-label extension here is really showing that concizumab significantly reduced the ABR versus on-demand, with sustained efficacy over 56 weeks, regardless of the presence of target joints. So what this table is showing is the initial 32-week cutoff of phase three, and then as patients rolled over in the open-label extension, this data cutoff was at 56 weeks, just showing that the ABRs remained quite low after switching. And this is true for all of the types of bleeds that were measured, so all treated and untreated, spontaneous and traumatic bleeding episodes.

Marstacimab is the other approved anti-TFPI monoclonal antibody, and this was evaluated initially in their phase three trial, which was called the BASIS trial, and patients, again, were invited to continue to evaluate long-term efficacy in an open-label extension. This enrolled patients with severe hemophilia A or B without inhibitors, and patients were on either the standard dose of 150 milligrams, which is administered weekly, which is the primary fixed-dose strategy. A few patients were on 300 milligrams if needed for bleed control. And what the open-label extension long-term efficacy is showing is that marstacimab shows sustained reduction in bleeding over 30 months and supports its continued long-term use.

And actually, what I thought was interesting from this study is that coming out of the original data cut from the phase three trial, where the mean ABRs were a little bit higher than maybe people had seen in other clinical trials, this was probably driven by the geographies and the status of the patients who were enrolled into the trial, but at least in the open-label extension, these ABRs are significantly lower even than what was observed in the primary analysis, maybe suggesting that there's continued improvement in the joint status for these patients as they have a bleed protection from this prophylactic intervention.

So the last rebalancing agent that has just recently been approved is fitusiran. So fitusiran knocks down antithrombin levels through an siRNA interference strategy. Now, this program has been going on for close to 10 years, and in the original strategy, it was a fixed dosing regimen of 80 milligrams administered monthly, and the mean antithrombin levels in the clinical trial patients were roughly around 11% to 12% antithrombin levels, and they achieved very good efficacy with that degree of knockdown. However, there were a handful of thrombotic events that were thought to be related to the severity of the antithrombin knockdown, and there was a correlation with the amount of time that patients spent with antithrombin levels less than 10%.

So they came back in an open-label extension study with a revised strategy of not fixed dosing anymore, but an antithrombin level-targeted dosing regimen. Patients were started at a dose of 50 milligrams every other month, and then antithrombin levels were measured. If their levels were above 35%, this was thought to reduce the efficacy, and so they could be escalated to 50 milligrams monthly, or if they reached a level that was less than 15%, we were trying to optimize the safety outcome, and so patients could have their dosing reduced to 20 milligrams every two months. And then, there was a further analysis of the AT levels, again, targeting this range between 15% to 35%, and they could either go to 20 milligrams monthly if needed, or if they persisted with antithrombin levels less than 15%, they would be discontinued.

Now, ultimately, this was approved just in the last few months, and with the approval, the FDA actually encouraged one more dosing regimen at 10 milligrams, and this is likely to allow even more patients to maintain continued prophylaxis with fitusiran. So what was presented in this abstract was using a population pharmacokinetic/pharmacodynamic model, taking about 1,000 hypothetical patients and looking at what they knew from the clinical trial data, what would this AT-targeted dosing regimen look like as it rolls out for, say, 1,000 patients. And what they observed in this modeling is that antithrombin

levels would be effectively maintained in that target range of 15% to 35% with either zero or not more than one dose adjustment in the majority of patients. So this confirms that the modeling and the treatment design that went into the approval really looks to be quite consistent, and it also means that a minimal number of assays would be needed to establish patients on this therapy.

Now, one of the other abstracts that was presented, again, informed from the clinical trials and then modeling that out over a number of patients, what would the levels that would be expected to be achieved with the AT dosing regimen, what would that mean for bleed control? So what this showed, again, looking at 553 person-years of observation time from the clinical trials, the median antithrombin levels would be about 23% using the AT dosing regimen as compared to 11.5% on the original dosing regimen. But if we look at the range, from 15% to 35%, or those patients who would be closer to the 10% level, we see that the lower AT levels were associated with lower ABRs. So this supports that individualized dosing may make sense in managing patients on fitusiran, and that patients who are at the higher bounds, close to the 35% level, may not have as good bleed control as those who are down closer to the 15% level. And so, there may be some implications for how patients are managed with this newly approved therapy.

So for the last section, we're going to just look at some of the gene therapy abstracts. So first, we have four-year outcomes with the etranacogene dezaparvovec for hemophilia B. This is a single-arm four-year follow-up study in 54 males, 52 of whom expressed the highly active form of Factor IX, which we call Factor IX Padua, and then were able to discontinue regular prophylaxis. And what this abstract shows is that the gene therapy achieved sustained Factor IX expression, there was a 90% annualized bleed rate reduction, near complete elimination of Factor IX prophylaxis, and overall, it remains well-tolerated.

Another Factor IX AAV therapy, which is not moving forward in marketing, but did go through an FDA review, they now presented the six-year follow-up in patients who received this therapy. The follow-up enrolled 14 of 15 original participants in this long-term outcome data collection, and what they were able to collect is the Factor IX activity levels, as well as the safety data and bleed protection over that time. And what this abstract is showing is that the Factor IX expression was maintained in the mild hemophilia range, and you can see by year six, mean Factor IX was about 26%, median was 22%, with very effective bleed control, with median ABRs of zero. No patients resumed Factor IX prophylaxis over this timeframe.

The last one is a five-year musculoskeletal outcome of the only approved hemophilia A gene therapy, which is valoctocogene roxaparvovec, and in this one, they are assessing the long-term musculoskeletal health of patients who received this therapy, analyzed by some physical exam evaluations, patient-reported outcomes, as well as musculoskeletal ultrasound. But in addition, these patients had annual biomarker evaluations for inflammation, cartilage and bone metabolism outcomes. And what's on the table over here, you can see a significant drop in almost all of these biomarkers, and overall, this suggests that there's reduced inflammation and really important signs of reduced joint and bone remodeling as a consequence of their joint disease, and it suggests that gene therapy really is having an impact at the biological level of musculoskeletal health.

So let's do a summary here to take home some clinical pearls from what we've studied today. So first, for efanesoctocog alfa, during major surgery, this ultra-long half-life Factor VIII therapy provides reliable perioperative hemostasis with low product consumption and minimal transfusion needs, and it offers effective single-injection bleed resolution in children with severe hem A, able to maintain a low ABR and high response rates for breakthrough bleeding over time. With respect to emicizumab, when this is combined with short-term Factor VIII or VIIa, it allows for effective perioperative hemostasis for major surgeries; breakthrough bleeds were rare, with no thrombotic complications observed. From EUHASS

Safety Surveillance, covering a number of approved various products, this outcome from this study provides baseline thrombosis rates for Factor VIII products and the bypassing agents, and really serves as a reference for evaluating thrombotic risk when newer rebalancing agents, like fitusiran or concizumab and marstacimab, are rolled out into the clinical realm.

Mim8, a second-generation higher potency bispecific antibody, can be safely initiated immediately after emicizumab, without a washout and without a loading dose, and really offers a flexible transition for patients who are on prophylaxis with one and switching over to the other. From concizumab, this is a once-daily subcutaneous prophy regimen, but it significantly reduces the ABR compared to on-demand treatment, regardless of baseline target joint status, and really makes it broadly applicable across patient subgroups. The other TFPI-inhibiting agent, marstacimab, again, in an open-label extension study, provides sustained long-term bleeding control in hem A and B without inhibitors with a favorable safety profile over this extended follow-up period. And for fitusiran, an antithrombin-based dosing regimen, maintains steady-state AT levels within the target range of 15% to 35% AT knockdown and requires minimal dose adjustments. However, lower levels are strongly associated with lower ABR, and support may be a personalized prophylaxis based on AT monitoring.

And then, finally, from the gene therapy abstracts, etranacogene, which is the gene therapy for hemophilia B, offers durable Factor IX Padua expression, with a 90% ABR reduction sustained over four years, with reduced prophylaxis needs and no new safety concerns. Another gene therapy for hemophilia, fidanacogene, maintains mild-range Factor IX levels for up to six years, with minimal bleeding, no patients who've had to resume prophylaxis, and no treatment-related serious adverse events. And then, finally, valoctocogene, which is a gene therapy for hemophilia A, maintains stable musculoskeletal health and improves inflammatory biomarkers over five years, and really supports long-term joint protection occurring in these patients who receive this therapy for severe hemophilia A.

So thanks for the opportunity to share with you today, and hopefully you have gained some new insights on what's going on with these novel therapeutics for hemophilia. Thank you.