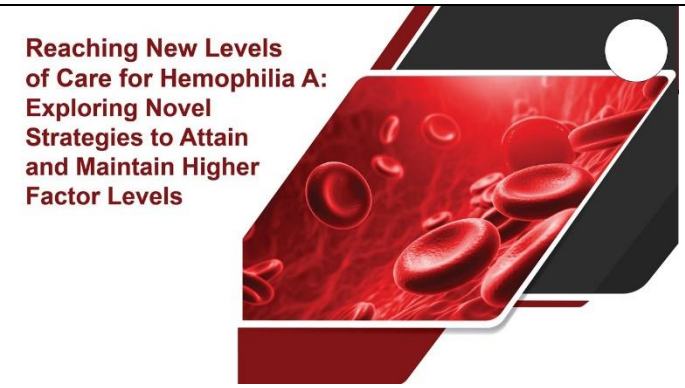
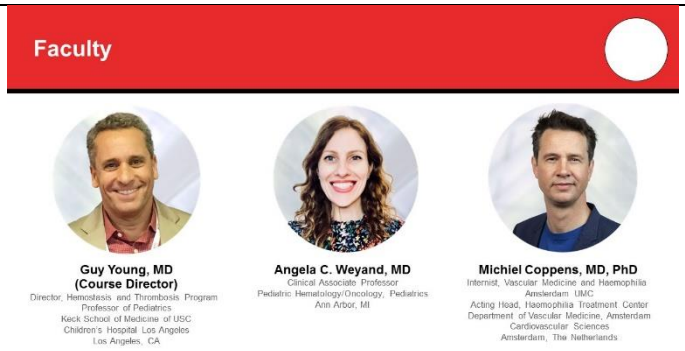
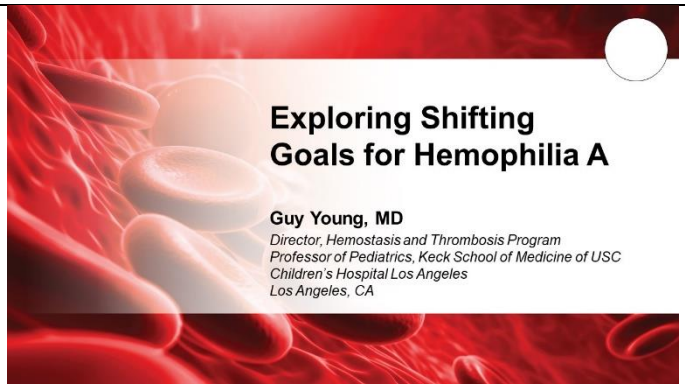
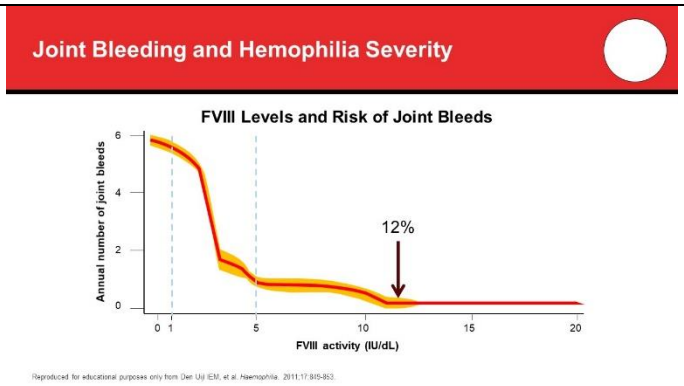
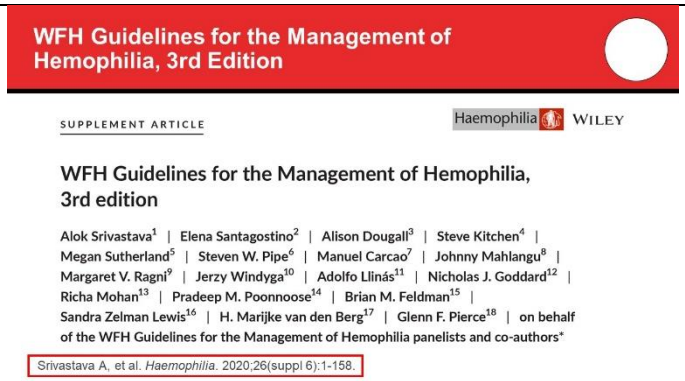
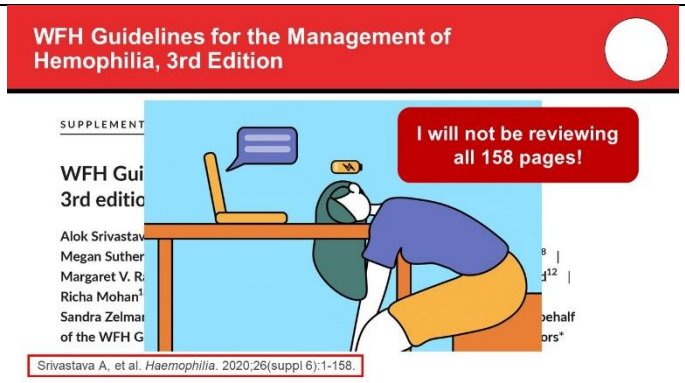
1.		*[Guy Young, MD]* Hello, everyone, my name is Guy Young, and we have a great program for you called "Reaching New Levels of Care for Hemophilia A: Exploring Novel Strategies to Attain and Maintain Higher Factor Levels."
2.		The subtitle for this section is called "Achieving Freedom From Bleeding: Exploring the Evolving Evidence on New and Emerging Treatment Strategies to Maintain Higher FVIII Levels."
3.		I am from the Children's Hospital Los Angeles and the director of the Hemostasis and Thrombosis Center there. We have Angela Weyand, MD, who's a Clinical Associate Professor at the University of Michigan in Ann Arbor, Michigan, and Michiel Coppens, MD, PhD, who is an internist, vascular medicine specialist, and hemophilia specialist at the University of Amsterdam.
4.		I will open this discussion, or open this program, by exploring shifting goals for hemophilia A.

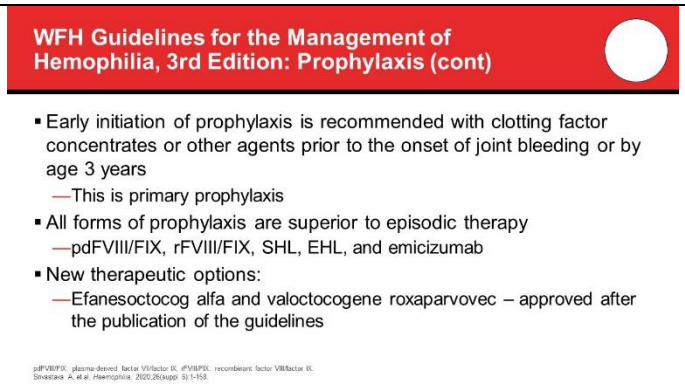
5.	**Prophylaxis With FVIII Replacement in Hemophilia A** ▪ Factor prophylaxis entails the scheduled infusion of FVIII replacement therapy to prevent bleeding episodes and their associated complications ▪ Primary prophylaxis — Initiation of factor prior to any joint bleeding (or after 1-2 joint bleeds before any obvious joint disease) ▪ Secondary prophylaxis — Initiation of factor replacement after the onset of joint disease to prevent further bleeding **The original goal of prophylaxis was to maintain factor levels >1%-2%**	Prophylaxis with factor VIII replacement. This has been our mainstay now for several decades, in fact. In Europe, going back probably 50 years or even perhaps a bit more. And factor prophylaxis entails the scheduled infusion of factor VIII replacement therapy to prevent bleeding episodes and their associated complications. It's loosely defined—there are some different definitions—but essentially primary prophylaxis really means the initiation of factor prior to any joint bleeding, which is what would be preferable, or after 1 to 2 joint bleeds, but before any obvious joint disease. Secondary prophylaxis would be the initiation of factor replacement after the onset of joint disease to prevent further bleeding and, ultimately, hopefully improve quality of life long term. Now, the original goal of prophylaxis was to maintain factor levels above 1%. This came from data from the 60s and 70s, particularly from Sweden, but also from the Netherlands, where this goal was able to substantially improve patients' quality of life over episodic treatment. This really was the standard for many decades, well into the 90s and the 2000s.
6.	**SHL vs EHL (First-Generation) FVIII** SHL FVIII Replacement Therapy / EHL FVIII Replacement Therapy Type: Traditional FVIII / FVIII attached to Fc, albumin, or PEG (single chain FVIII) Half-life: Standard (12 hours) / Extended 1.5x, approximately 18 hours Dosage frequency: Typically administered 3 times weekly (sometimes every other day) / Given twice weekly or every 4-5 days (more often to maintain higher trough levels) Trough levels: Maintained at approximately 1%-2% / Approximately 5% (variable) EHL: extended half-life; PEG: polyethylene glycol; SHL: standard half-life	We have different factor VIII options at this point. We have the standard half-life factor VIII, and we have the extended half-life, which I characterize here as first-generation extended half-life. You're going to be hearing about a molecule that's quite a bit different than what the extended half-life factors are able to do, called efanesoctocog alfa, a bit later, so, until we have a term for that newer category, if you will, that's why I labeled this as the first-generation

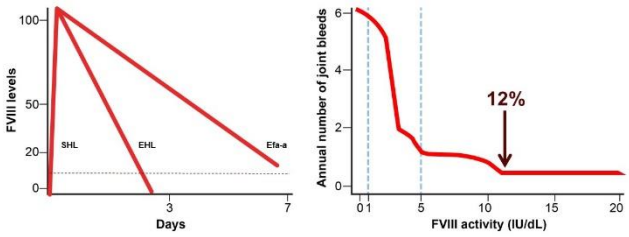
		extended half-life, something that's not a typical term that we use at this time. If you look at the 2 of them in this table, the mechanism of action for the extended half-life factor VIII is either factor VIII Fc fusion or polyethylene glycol (PEG). The half-life extension of the extended half-life products is about 1.5 fold, so, going from 12 hours to 18 hours. We've not been able to achieve a longer half-life with these, which we're calling first-generation extended half-life products. And again, you'll hear about a newer molecule that can do better than that a bit later. The dosage frequency for these extended half-life factor VIII therapies is typically every 3 to 5 days or twice a week. That's according to the prescribing information for the 4 drugs in this category that are currently available. And that's better than the factor VIII replacement therapy with standard half-life, which is typically 3 times a week or every other day. The trough levels with the standard half-life factor VIII, as I mentioned, they're typically 1% to 2%. I mean, unless you're dosing every day, you're not going to be able to achieve a trough much better than that. The extended half-life factor VIIIs—there's some variability. Some of them are down, also around 1% to 2%, but with less frequent dosing. Others were able to get up to the 3% to 5% range. It's quite variable between the products and between the studies, depending on whether they were trying to minimize infusions or whether they were trying to keep factor VIII levels a bit higher.

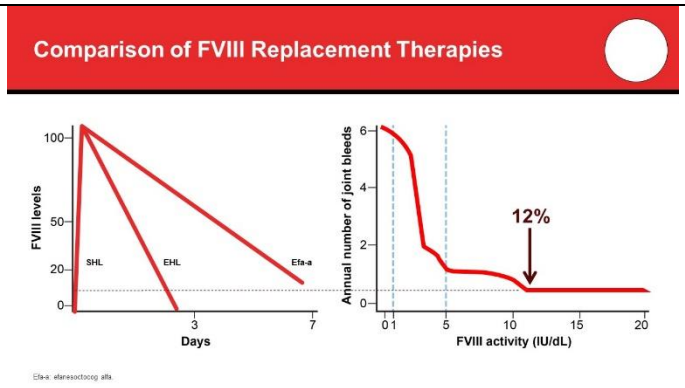
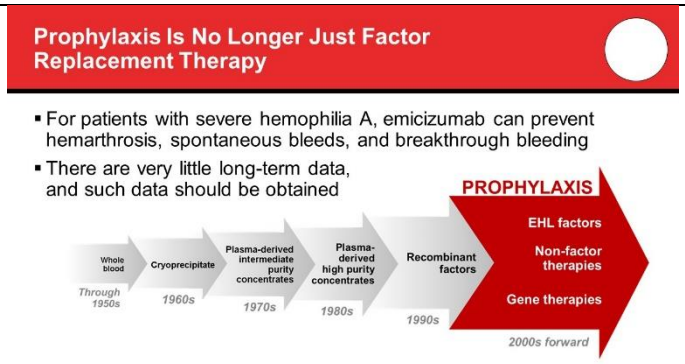
7.	 Reproduced for educational purposes only from Den Uijl IEM, et al. Haemophilia. 2011;17:849-853.	This is a quite famous slide that we've seen in many meetings, and this is from the Netherlands, and it's a natural history study. Basically, looking at patients with all levels of hemophilia A—mild, moderate, and severe—and looking at the number of joint bleeds relative to the factor VIII level at baseline. You can see some inflection points. For example, below 3%, you see a sharp rise in the number of annual bleeds that are expected. A smaller inflection point at 5%, going from 5% to 3%. Then, the line is fairly flat between about 5% and 10%, but another small inflection point once you get above 10%. And above 12%, you see that the line is flat and pretty much at zero joint bleeds. So, our understanding from this is, first of all, that your baseline factor VIII level definitely dictates and relates to the number of joint bleeds you can expect to have, but also that once you get above 12% (some people say about 15%), that the number of joint bleeds is expected to be very, very low and, in fact, close to zero. NOTE: 1. Clinical severity of hemophilia A…Den Uijl IE, et al. 2011, p850, col 2, Fig 2. ➢ Above 5 IU dL^{-1} factor VIII, age at diagnosis, onset of treatment, and joint bleeding kept increasing steadily, whereas the number of joint bleeds decreased to approximately zero in patients with more than 12 IU dL^{-1} factor VIII

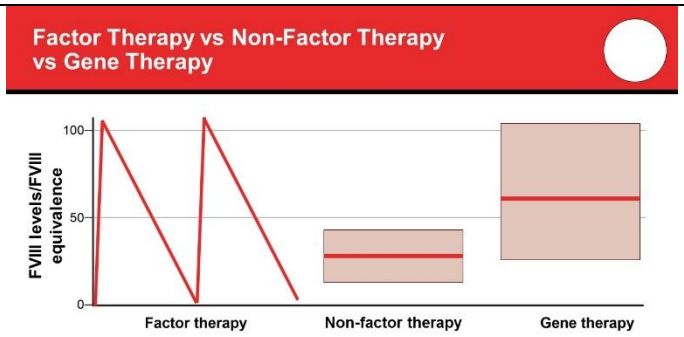
		2. NHF MASAC Document 179: A goal of maintaining trough levels of factor VIII or factor IX higher than 1% between doses is suggested
8.		This is the World Federation of Hemophilia (WFH) guidelines published in 2020. You see some of the overall authors on this. There are multiple chapters. In fact, if you see on the bottom, there are 158 pages of this article or these guidelines, and the good news for you, and even better news for me, is I'm not reviewing all 158 pages.
9.		That would be pretty challenging to follow on a Zoom webinar. So, I will pick out some highlights.

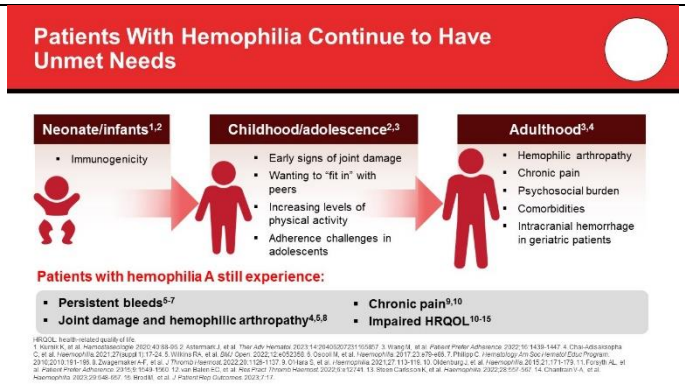
10.	**WFH Guidelines for the Management of Hemophilia, 3rd Edition: Prophylaxis** ▪ All patients with severe hemophilia A and B should be receiving prophylaxis that is sufficient to prevent bleeds at all times ▪ In countries with less access to factor, WFH recommends prophylaxis to those patients as well though with less intensive regimens ▪ When prophylaxis is not available, on-demand treatment must be available for early bleed treatment WFH. World Federation of Hemophilia. Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6):1-158.	Some of the highlights regarding, for example, the chapter on prophylaxis say that all patients with severe hemophilia A and B should be receiving prophylaxis that is sufficient to prevent bleeds at all times. That's a pretty strong statement, but I think that's ultimately the goal of prophylaxis: to prevent bleeds at all times. In countries with less access to factor—because in WFH, of course, the W is world, so we're serving the whole world with these guidelines—they recommend prophylaxis for those patients as well, though potentially with less intensive regimens to handle to lessen the cost. And when prophylaxis is not available (and notice, it says all patients should be on prophylaxis, but we know that in some countries it's not available), at the very least, they should have on-demand treatment available for early bleed treatment.

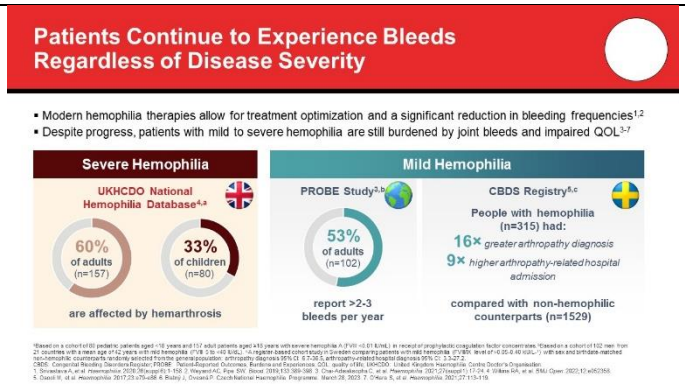
11.		Furthermore, early initiation of prophylaxis is recommended with clotting factor concentrates or other agents prior to the onset of joint bleeding or by age 3 years. In other words, nobody should start prophylaxis after the age of 3 years. In fact, in severe hemophilia and most cases of moderate hemophilia that are low enough, joint bleeding is going to become apparent well below this marker of 3 years, typically around 1 or 1.5 years. And this is what's considered primary prophylaxis. And then, finally, all forms of prophylaxis are considered superior to episodic therapy. In other words, if there's a country where plasma-derived factor VIII or factor IX or what is available, that is fine and that works fine. If it's a standard half-life recombinant factor VIII or IX, that is fine. If you have extended half-life products and if you have emicizumab, you know, even better. But the point here is that any type of prophylaxis is better than no prophylaxis. Now, there are new therapeutic options that have become available since those guidelines were published. And mind you, when guidelines are published in 2020, it means that those have been probably written and worked on mostly in 2018 and 2019, so they're a little bit older than 2020. Most recently, efanesoctocog alfa and valoctocogene roxaparvovec, one being a sort of newer generation of factor VIII replacement therapy and the other being a gene therapy. These were approved after the publication of the guidelines, and so those guidelines obviously don't discuss those whatsoever.

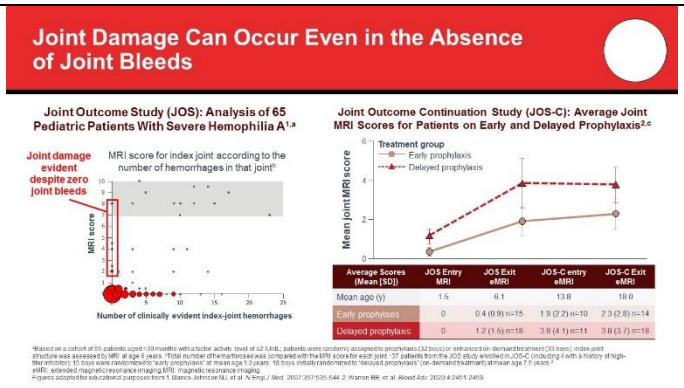
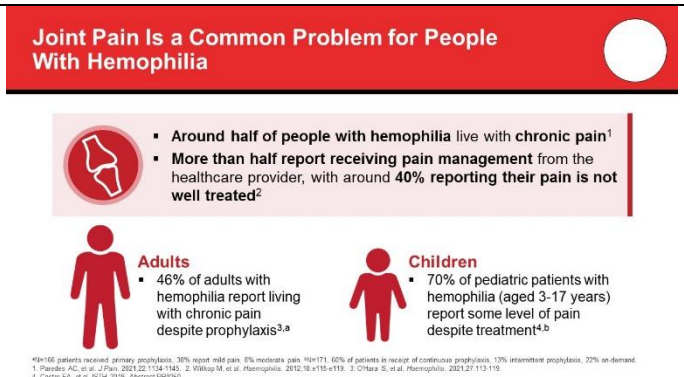
12.	**WFH Guidelines for the Management of Hemophilia, 3rd Edition: Prophylaxis (cont)** **We can do better** ▪ It is recognized that troughs of 1%-3% are insufficient to prevent joint disease ▪ Gradual onset of joint disease over the years ▪ Trough levels should be aimed for 3%-5% —EHL allow us to reach this range ▪ Emicizumab allows for better bleed control Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6):1-158.	But the guidelines do say, "We can do better." It's recognized that troughs of 1% to 3% are insufficient to prevent joint disease. And again, that's taken directly from the guidelines. And that there's a gradual onset of joint disease over the years. And so the 2020 WFH guidelines say that trough levels should be aimed for 3% to 5% and that extended half-life products allow us to reach this range. And again, as you'll see later with efanesoctocog alfa, we have a newer factor that can achieve substantially higher trough levels. And then it also says that emicizumab allows for better bleed control. And again, this is based on the fact that these guidelines were published before efanesoctocog alfa was available. And that the HAVEN 3 study, which was the study that compared emicizumab with standard half-life or extended half-life factor VIII, did demonstrate that emicizumab had better control. So, that's where that statement is coming from in those 2020 guidelines.
13.	**Comparison of FVIII Replacement Therapies**  Efa-a: efanesoctocog alfa	We compare factor VIII replacement therapies. Standard half-life factor VIII, we have peaks, and then we have troughs, with extended half-life factor VIII we can get a little bit further in terms of troughs by getting a better level out to 3 days. And then with efanesoctocog alfa, as you'll see a bit later in more detail, trough levels are closer to 15% to 20%, as opposed to 1% to 3%.

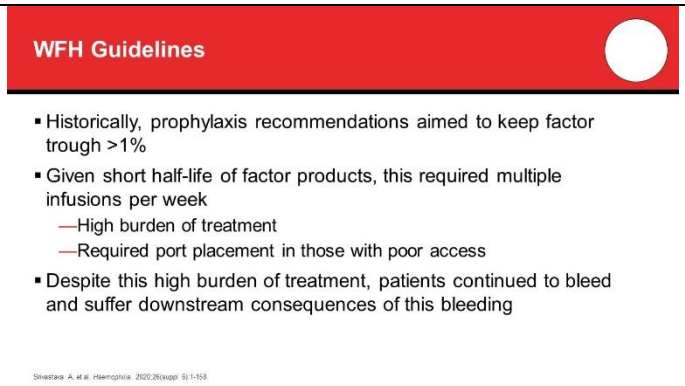
14.		If I take the figure I showed earlier from the Dutch study, and I just lay it here, and then I just draw a line across from about 10%, as you can see there, 10% to 12%. What you'll notice is that with efanesoctocog alfa, you can be above that marker the entire dosing interval, with the dosing interval being once every 7 days.
15.		The other part of the WFH guidelines, and I'm coming back to that now, is that prophylaxis is no longer just factor replacement therapy. And it says for patients with severe hemophilia A, emicizumab can prevent hemarthrosis, spontaneous bleeds, and breakthrough bleeding. And it does say there are very little long-term data, and such data should be obtained. And so again, these guidelines were written and close to finalized in 2019, at which time emicizumab was available in most countries only for maybe about a year, and in many countries wasn't quite yet available. So, those data are being collected. As you know, there are long-term studies and real-world studies, and you can find those on emicizumab throughout the literature. Here we are with the timeline from the 50s through the 2000s. And going forward, we're now in an era where we have extended half-life factors, including the newer one, or the one that's probably not exactly in that category, efanesoctocog alfa; nonfactor therapies; and gene therapies, all of which are available, at least in some parts of the world.

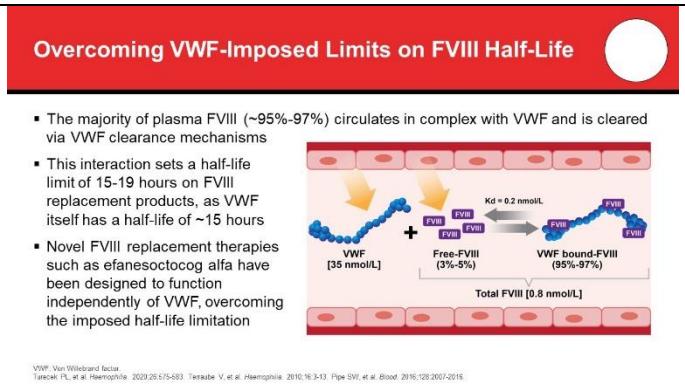
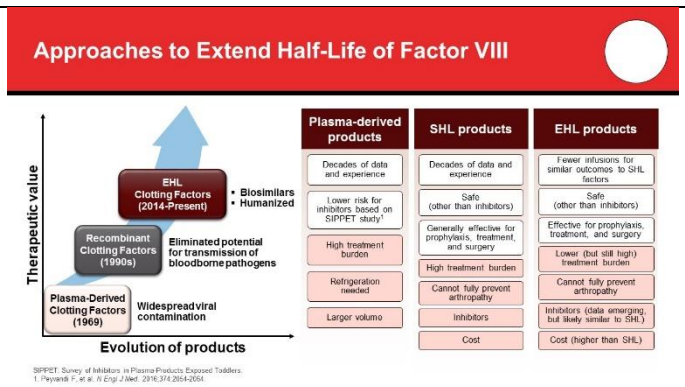
16.		Another way to look at this is factor therapy. You have these sharp peaks and troughs, either standard half-life or extended half-life factor VIII. Nonfactor therapy—and the Y axis, by the way, is factor VIII equivalence, which I know some people don't like that term, but we don't have a better one, where the non-factor therapies, at least currently with emicizumab, seem to put us somewhere around 10% to maybe 30%. Most people agree it's probably around 15%, that's where I kind of drew that line. Maybe it's a little bit higher than that on this graph, but probably around 15% to 20%. But we have new nonfactor therapies that are being developed, and the hope is that they can put patients into really the normal range in terms of hemostatic factor VIII equivalents, but that remains to be seen. Gene therapies are available now as well, and we have 1 in hemophilia A. We seem to have quite a broad range of levels in the patients; however, we do have patients that are in the normal range at least for some period of time, and you'll hear more about the gene therapies later, and the details of the factor levels.

17.		With that, we're going to transition over to Dr. Weyand. She's going to really dive into more detail about increasing the target factor VIII goals, getting, in other words, factor VIII levels higher than what we have traditionally achieved and higher than what the WFH guidelines suggest. And she's going to look at the rationale, the evidence, the challenges, and the opportunities. So, Dr. Weyand, please go ahead and take us through this next section. *[Angela Weyand, MD]* Thank you, Dr. Young. My name is Dr. Angela Weyand, and I'm going to be speaking about "Increasing Target FVIII Goals: Rationale, Evidence, Challenges, and Opportunities."
18.		We know that despite the incredible advancements that we've made in the last decade in treating our patients with hemophilia, they do continue to have unmet needs, and these vary. When the patient is young, we know that our neonates and infants deal with their first exposure to factor VIII therapies and the immunogenicity of these therapies and the development of inhibitors. As they start to grow older and get into childhood, we do start to see early signs of joint damage. We know that they start to become more aware of their disease and that this causes them to feel different than their friends and peers—they would like to fit in with their friends and peers. They're also having increasing levels of activity, and as they enter into adolescence, they often can have adherence challenges. Further on in their lifespan, we know that the bleeding that they've had earlier in their lives

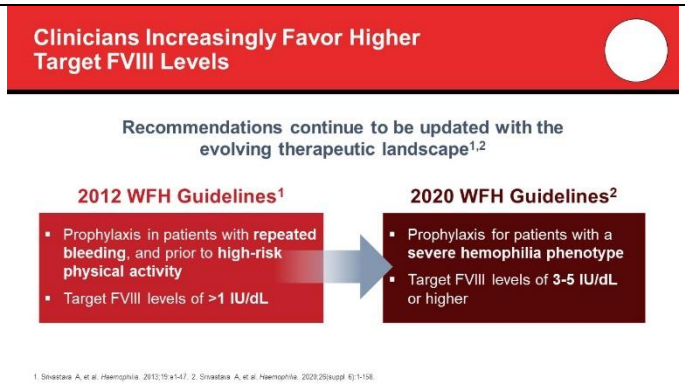
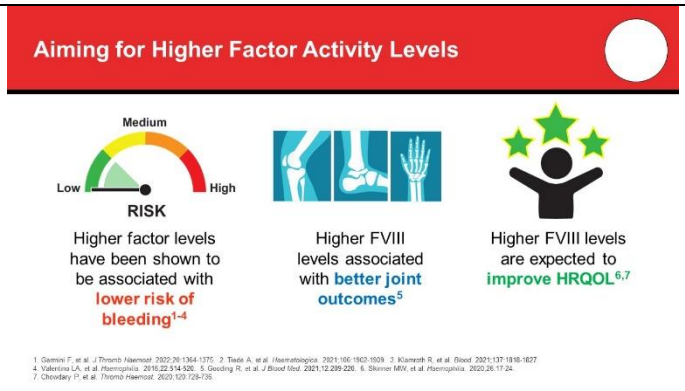
		and hemarthrosis can lead to hemophilic arthropathy. This arthropathy often is accompanied by chronic pain. There's significant psychosocial burden as well as the complications of having additional comorbidities to deal with. And so despite the advances we've made and the incredible treatments that we have available, we know that patients with hemophilia A still experience persistent bleeds, joint damage and arthropathy, chronic pain, and really impaired overall health-related quality of life.
19.		And we know that patients with hemophilia continue to experience bleeds, and this is regardless of their disease severity. We have optimized treatment in our patients using modern hemophilia therapies, and this has allowed us to achieve great significant reduction in bleeding frequencies. But despite this progress, there is still a burden of joint bleeds and impaired quality of life. So these are data from the severe hemophilia patients in the UK showing that over half of adult patients are affected by hemarthrosis, and a third of children. And as I mentioned, this is regardless of disease severity, so looking at patients with mild hemophilia, over half of these patients report more than 2 to 3 bleeds per year, so way more than we would think optimal. And that patients with hemophilia are much more likely to have an arthropathy diagnosis and arthropathy-related hospital admissions.

20.		In addition to bleeds that are clinically evident, we also know that joint damage is occurring even in those who have not been aware of a clinically evident bleed. These are data from the Joint Outcome Study, an analysis of 65 pediatric patients with severe hemophilia A, and as you can see, even in those patients with zero clinically evident joint bleeds, they do still have abnormal joint MRI scores indicating joint damage despite no history or knowledge of any joint bleeds. And this occurs in patients on prophylaxis with worsening joint MRI scores over time, although a little bit better scores than those who have early initiation of prophylaxis, but still worsening over time, and even worse in those with any delay in start of prophylaxis.
21.		We know that not only are joint bleeding and joint damage, as indicated by the joint MRI score, common in patients, but joint pain is a common problem for patients with hemophilia as well. And this is likely secondary to that joint damage and joint bleeding that are occurring. Around half of people with hemophilia live with chronic pain, and more than half of people with hemophilia report receiving pain management, although a really significant proportion of those patients actually report that their pain is not well treated. So, 46% of adults with hemophilia report living with chronic pain, and 70% of pediatric patients report some level of pain despite treatment. So, clearly we're failing to give our patients the comparable quality of life to those without hemophilia.

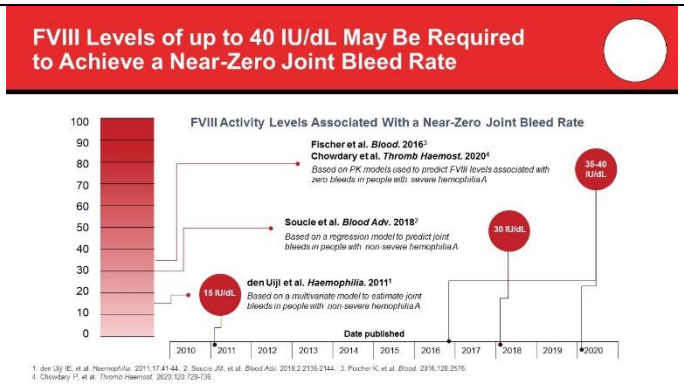
22.		The WFH guidelines historically have recommended that we initiate prophylaxis in patients with severe hemophilia and aim to keep factor trough levels greater than 1%. I think this was largely a number that was arrived at because we have seen that there is a difference in bleeding between moderate and severe patients. But also due to the short half-life of factor products, even just this low goal of keeping factor trough levels greater than 1% requires multiple infusions per week. So, a really significant treatment burden and in patients, especially pediatric patients who might have poor access, this often requires port placement, which comes with a whole other host of problems. And despite this high burden of treatment, infusing multiple times a week just to keep factor levels greater than 1%, we have a lot of data that show that patients continue to bleed and suffer all of the downstream consequences of that bleeding.

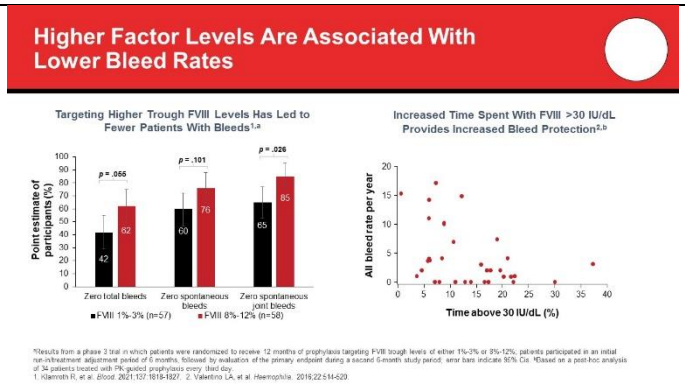
23.		Unfortunately, we've really been challenged by the inability, historically, to significantly extend the half-life of factor VIII products, and we've subsequently learned that this is due to von Willebrand factor (VWF)-imposed limits on factor VIII half-life. So, the majority of plasma factor VIII circulates in complex with VWF and, therefore, is cleared via VWF clearance mechanisms. Because the VWF itself has a half-life of around 15 hours, this interaction and the fact that infused factor VIII products are cleared with VWF, the half-life of these products has been limited to 15 to 19 hours. But now we have products that are trying to take this into account, the first of which was efanesoctocog alfa, which was designed specifically to function independently of VWF in order to overcome this imposed half-life limitation. NOTE: Endogenous VWF stabilizes and protects factor VIII from degradation and clearance, but it also subjects factor VIII to a half-life ceiling of approximately 15 to 19 hours
24.		Over time, as I mentioned, we have been really challenged trying to extend the half-life of factor VIII in order to decrease the treatment burden on our patients and also provide them with improved hemostatic protection. So, we first started with plasma-derived products. The positives around plasma-derived products, we know, are that we've had decades of experience and data from using them. We know there's a slightly decreased risk of inhibitors based on the SIPPET data, but they do carry quite a high treatment

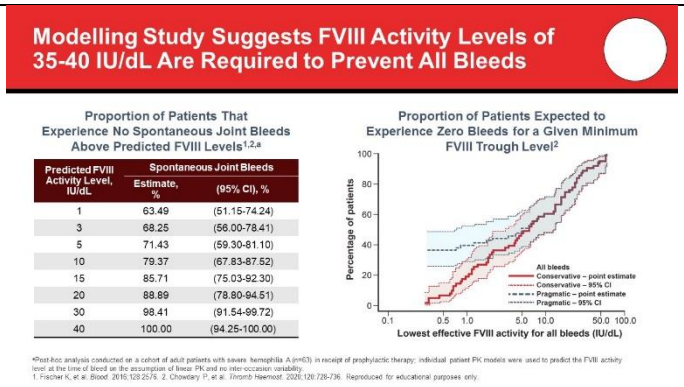
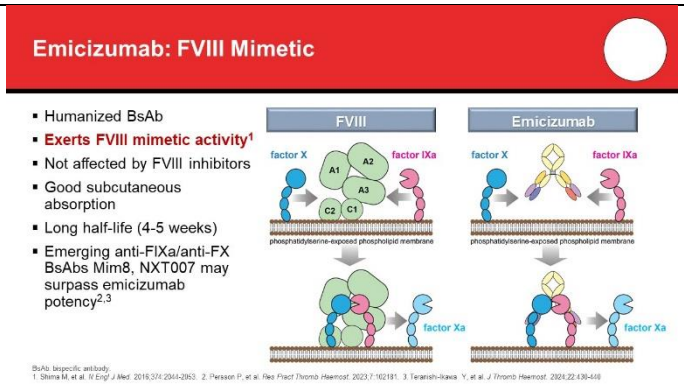
		burden and require a larger volume and refrigeration, which can make it challenging for patients. Next, we had standard half-life recombinant products, which again we have decades now of data and experience using. They're relatively safe, especially because they don't have the concerns of viral transmission, but they do have obviously the risk of inhibitors. They're generally effective, but again, still carry quite a high treatment burden and are a little more costly than plasma-derived products. And then the extended half-life products, which again were limited by that VWF-factor VIII interaction in terms of their half-lives. So, although we call them extended half-life products, they're not all that extended in comparison to standard half-life. Sometimes we are able to give fewer infusions, although many providers would keep the number of infusions per week the same and just aim for slightly higher trough levels. They are safe other than the risk of inhibitors and are quite effective for prophylaxis treatment and surgery, but still, even given slightly decreased treatment burden, they still confer a substantial treatment burden with multiple intravenous (IV) infusions per week. We know that patients continue to have bleeding, and they also carry a high cost as well as that risk of inhibitors.

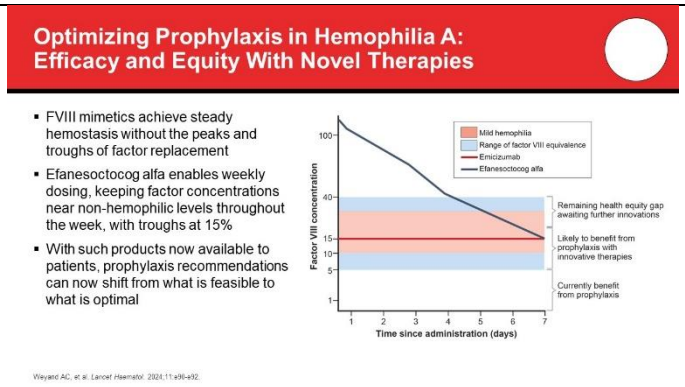
25.		As we continue to make progress in our products that are available to treat factor VIII deficiency of hemophilia A, clinicians and organizations are increasingly favoring higher target factor VIII levels, and recommendations are being updated, especially with the evolving therapeutic landscape. So, the 2012 WFH guidelines for the treatment of hemophilia recommend prophylaxis in patients with repeated bleeding and prior to high-risk physical activity. And those were targeting, again, those factor VIII levels of greater than 1%. So, the trough level would be around that, just above 1%. These were updated in 2020 to recommend prophylaxis for patients with a severe hemophilia phenotype, and rather than just keeping levels above 1%, they suggest targeting factor VIII levels of 3% to 5%, or even higher. And I think that as we have better products, we are better able to achieve these higher goals.
26.		Aiming for higher factor activity levels: why should we do this? We know that higher factor levels have been shown to be associated with a lower risk of bleeding, which is obviously what we want for our patients. We know that higher factor VIII levels are associated with better joint outcomes, and we expect that higher factor VIII levels should improve health-related quality of life due to the fact that patients will have less bleeding and better joint outcomes.

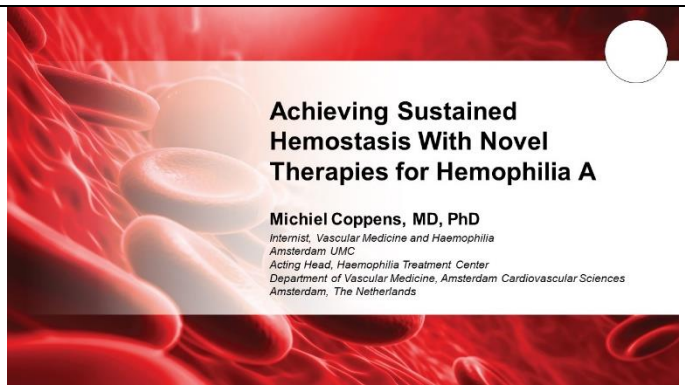
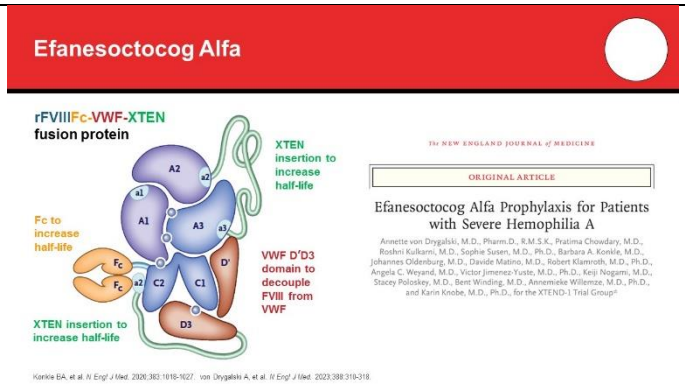
27.		So, thinking about this, I think it's time to really question whether we should be thinking about a new therapeutic goal for hemophilia A. We know that when factor levels are normal, patients should not have spontaneous bleeding, their joint function should be preserved, and they should have an increasing ability to enjoy an active life similar to patients without hemophilia. An updated treatment model is outlined in this figure that has been co-developed by not only hemophilia providers, but patient advocates and health economists. And really, the model aims that people with hemophilia can progress toward attainment of a "functional cure" by achieving specific milestones in a stepwise fashion. So, before, when we didn't have great products, just surviving was sometimes the goal. But as we improve our treatments of hemophilia, we really need to be aiming for health equity and normalized hemostasis—not just better, but actually normal—in order for our patients to live lives similar to the lives that are led by patients without hemophilia.

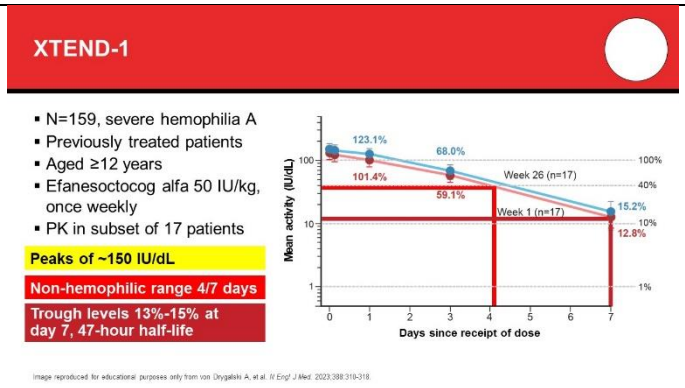
28.		We know that this will likely require much higher factor VIII levels than we have historically targeted. We have lots of data now showing that actually, factor VIII levels of up to 40% may be required to achieve near-zero joint bleeding. Some of these data started to be published back in 2011. There was a multivariate model that was created to estimate joint bleeds in people with non-severe hemophilia A, and this is obviously a somewhat different population than our severe hemophilia patients who are receiving prophylaxis, but that 15% is much higher than what we had historically been aiming for. Another publication in 2018 used a regression model, again, to predict joint bleeds in people with non-severe hemophilia A and found that probably levels of 30% were needed in order to achieve a near-zero joint bleed rate. Another study used a pharmacokinetics (PK) model to predict factor VIII levels associated with zero bleeds, actually, this time in patients with severe hemophilia A. And that study found that levels between 35% and 40% were likely required in order to achieve zero joint bleeds. NOTE: Additional notes • A survey administered to 1,587 Dutch hemophilia patients included data from 119 patients with moderate hemophilia and 314 patients with mild hemophilia. According to estimates based on self-reported joint bleed data, patients with factor levels of less than 5% had the highest risk of joint bleeds. A

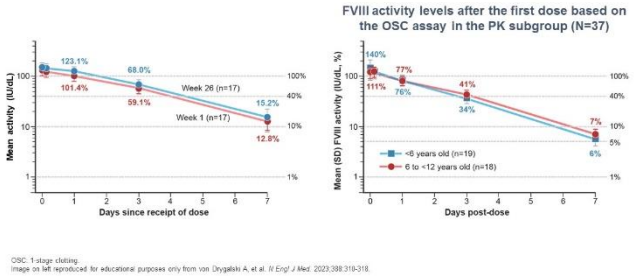
		level of protection corresponding to no expected joint bleeds was achieved only in patients with a factor level of 15% and higher[1] • According to a regression model based on data collected from 4,771 male patients with nonsevere hemophilia A or B, 1.4 joint bleeds per year were predicted for hemophilia A patients with a factor activity level of 15%. The predicted number of bleeds reached zero for all age groups at a factor activity level of 30%[2]
29.		We do know that these higher factor levels are associated with lower bleeding rates. This figure on the left demonstrates bleeding in patients who had been randomized. This was a phase 3 study where patients were randomized either to factor VIII trough levels between 1% and 3% or factor VIII trough levels between 8% and 12%. And so, in the black is the lower trough level goal, and the red is the higher trough level goal. And as you can see, the higher trough level goal of 8% to 12% resulted in much higher proportions of patients with zero total bleeds, zero spontaneous bleeds, and zero spontaneous joint bleeds. Of note, it was seen in that study that it was challenging for patients to achieve this higher trough level goal between 8% and 12% because this was prior to efanesoctocog alfa and other options that have allowed us to raise those trough levels. And so these patients, to achieve these 8% to 12% levels, did require very frequent infusions, which was a high burden of treatment. And then here on the right shows that the increased amount of

		time that patients spend above factor VIII levels greater than 30% really provides increased bleed protection, showing that it's not just about where our troughs are, but kind of the total area under the curve and the total amount of time during the week spent at higher levels.
30.		This is that modeling study, looking at what factor VIII levels are required to prevent all bleeds, which did find that factor levels between 35% and 40% were where zero bleeds really would be expected to occur, highlighting that in an optimal situation, that may be what we should be aiming for.
31.		We do have newer treatments that are available to us now that should allow us to provide greater hemostatic protection for our patients, one of which is emicizumab, a factor VIII mimetic, that is approved for hemophilia A, both with and without inhibitors. It does exert factor VIII mimetic activity. So, it's not factor VIII specifically and, therefore, is not affected by factor VIII inhibitors. It has good subcutaneous absorption and quite a long half-life, which really contributes to a significantly decreased treatment burden for patients who are able to dose weekly, every 2 weeks, or every month with a subcutaneous administration, which allows really great access to hemostatic protection for our patients who have poor IV access. In addition to emicizumab, there are multiple emerging bispecific factor VIII mimetic therapies, including Mim8 and NXT007. It is thought that these 2 molecules may actually surpass emicizumab potency and provide

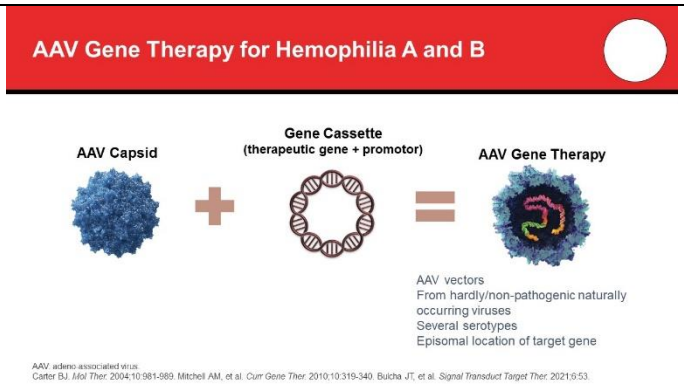
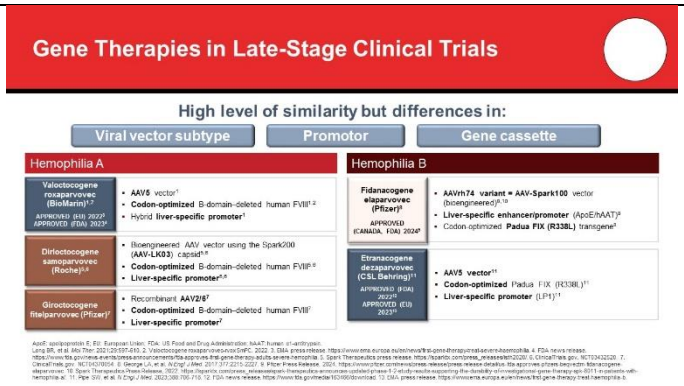
		higher levels of protection, again with that same subcutaneous administration and longer half-life, allowing less frequent treatments.
32.		So, as we have these new therapies available to us, like emicizumab and efanesoctocog alfa, we really need to be thinking about who is receiving prophylaxis, who is benefiting from these great strides that we are making in the treatment of hemophilia, and who we may be leaving behind. We know that factor VIII mimetics achieve steady hemostasis without the peaks and troughs of factor therapy. It's a little bit controversial what exactly factor VIII equivalence emicizumab provides, but definitely it's much higher than that 1% that we've been aiming for with our troughs previously. We know that efanesoctocog alfa enables weekly dosing and keeps factor concentrations near the nonhemophilic levels for over half the week, with troughs landing around 15%. And as these therapies are now available, we need to consider the fact that we're only really recommending prophylaxis in patients with severe hemophilia and typically moderate hemophilia, or those with a severe hemophilia phenotype. But really, now that we're able to achieve these near-normal hemostatic equivalencies, we need to think about if some of our patients with mild hemophilia may be left behind in our current treatment paradigm and whether or not these patients may also benefit from some of the newer therapies available.

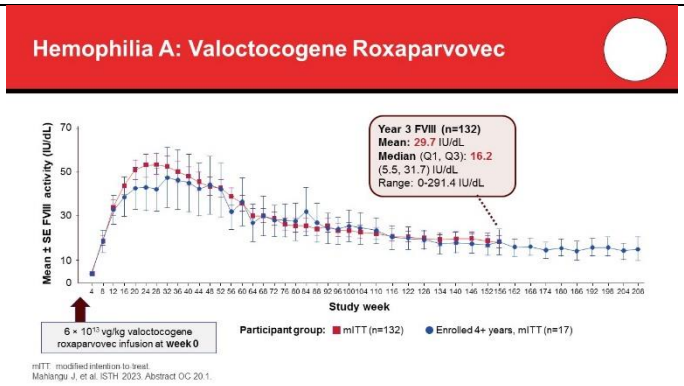
33.		So, with that, thank you, and I'm happy to hand over the floor to my colleague, Dr. Coppens. Thank you! *[Michiel Coppens, MD, PhD]* Thank you, Dr. Weyand. And now moving to my part, and, well, I guess as a hemophilia treater in recent years, I can't help to be absolutely amazed and thrilled about the huge amount of new molecules and new therapeutic approaches that are hitting research and are about to or have already hit the market. And I guess this is really a fascinating and spectacular time to be a hemophilia doctor. I think I'm confident that our patients are benefiting from those new therapies as well, but we are not [fully] there yet.
34.		So, in the first section of this presentation, I will actually move to raising the bar in factor VIII, not by factor VIII mimetics, as Dr. Weyand just finished off with, but really moving the bar higher with real factor VIII. So, let's start there.
35.		The first molecule that's been already alluded to is efanesoctocog alfa. And I think Dr. Weyand discussed why. Well, the intrinsic problem technologically with increasing the elimination half-life in factor VIII is VWF. Factor VIII is locked with VWF and, therefore, the clearance of VWF determines to a large extent the clearance of factor VIII molecules. And that's where efanesoctocog alfa really comes to the theater with something new and spectacular because basically, it has this molecule that became completely independent

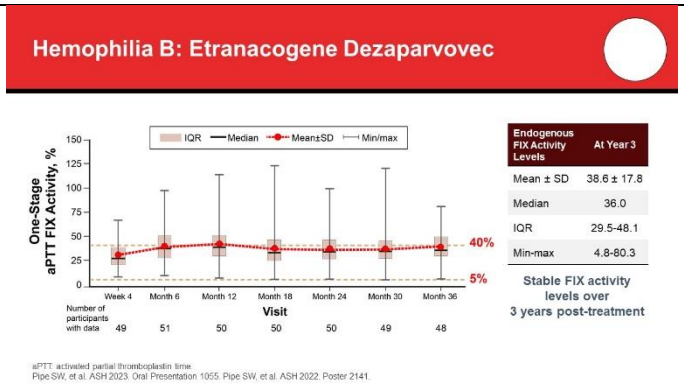
		of the binding to VWF. And then coupled with another, well, molecular modifications, it comes up with something that we can maybe call second-generation-extended half-life, extending the half-life well beyond what we have come to know from the extended half-life products that are available right now.
36.		Efanesoctocog alfa is an improved factor VIII replacement therapy with 3 main enhancements to increase half-life and reduce administration frequency. The addition of the VWF D'D3 domain prevents binding and decouples the recombinant factor from endogenous VWF clearance. Two XTEN polypeptides provide steric shielding to increase half-life in addition to a dimeric Fc domain.
37.		So, let's now dig into the results. Efanesoctocog alfa was evaluated in adults in the XTEND-1 trial, and that trial included 159 patients, all with severe hemophilia A. They needed to be previously treated patients of at least 12 years or older, and they were dosed with efanesoctocog alfa 50 IU/kg once weekly. In a subset of 17 patients, there was extensive PK done, and that's essentially the graph that you're seeing on the right, so this, in terms of factor VIII level, is more or less what you can expect from efanesoctocog alfa. So, there are a couple of things to point out. First of all, we're going beyond 100% in peak levels. We are going to 150%, which is still within the reference range or the normal values of the general population, but it is the very top of that reference range. And to some extent, people may be asking whether or not that 50% over 100% may well infer some thrombosis risk at the highest levels. However, more

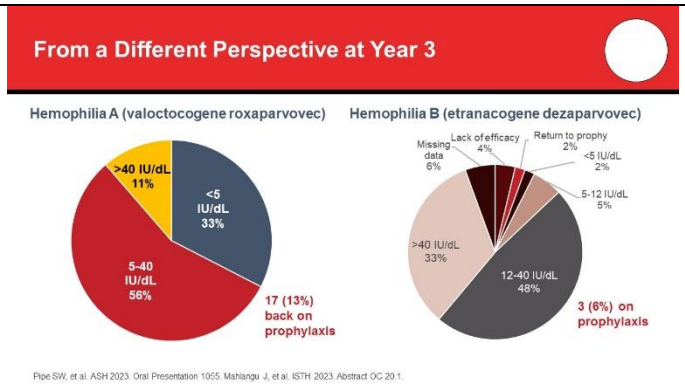
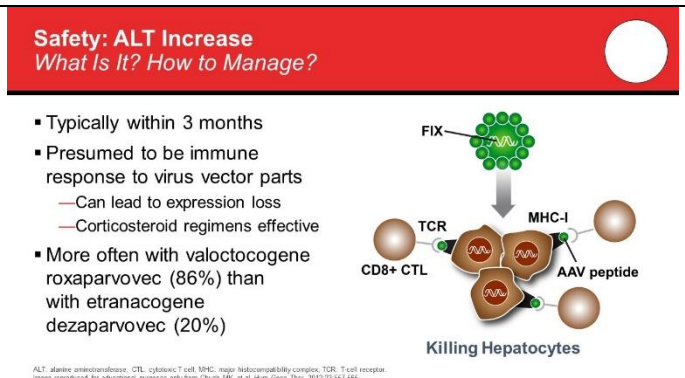
		importantly, or more spectacularly, I'd almost say, if you dose this 4 out of 7 [days], that's actually the majority of time, the patient has a factor VIII level of 40% or over. So, that's really in the nonhemophilic range. With the once-weekly IV injections, you are out of the hemophilic range in 4 out of 7 days. And then finally, what does this mean at a trough level? One week after dosing, the achieved trough levels are 13% to 15% at day 7. And all in all, that means that the half-life of efanesoctocog alfa has really shifted toward 47 hours, and that's something that's completely new in the hemophilia A arena.
38.	**XTEND-1 vs XTEND-Kids**  OSC: 1-stage clotting. Image on left reproduced for educational purposes only from von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318.	Comparing this with children, in general, children clear factor products faster than adults. So, there was an XTEND-Kids study as well, and basically in these 2 PK graphs, you can see the differences. And indeed it is true that in children, efanesoctocog alfa has cleared somewhat faster than in adults, but still come up with a trough level of 6% to 7% in total. And this is just after the first dose in that particular study. When you go to steady state, when you have weekly injections, this number actually rises to about 10%, which is still slightly lower than in adults, but it does raise the trough level bar to about 10%. NOTE: Fischer: Effective protection with once-weekly efanesoctocog alfa in children: Secondary analyses of pharmacokinetics and bleeds from the XTEND-Kids trial

39.	**Efficacy and Safety XTEND-1** **ABRs** Group A (N=133) Endpoint: Prestudy Prophylaxis / Efanesoctocog Alfa Prophylaxis Intrapatient ABR comparison No. of patients evaluated: 78 / 78 Median (IQR): 1.06 (0-3.74) / 0 (0-1.04) Mean ABR (95% CI), model based: 2.96 (2.00-4.37) / 0.69 (0.43-1.11) Rate ratio vs prestudy prophylaxis (95% CI): – / 0.23 (0.13-0.42) *p* value for superiority: – / *p* < .001 ABR, annualized bleeding rate; IQR, interquartile range. von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318. **Safety** 15% antidrug antibodies ▪ 7% pre-existing ▪ 3% during study No effect on FVIII PK	So, what can you expect when you raise factor VIII to this level? These are the results from the XTEND-1 study, the adult study. And there was a before and after comparison to the prestudy prophylaxis in 78 patients. What you can see is that the annualized bleeding rate goes down from about 3 in a model-based annualized bleeding rate in the prestudy prophylaxis, to well below 1. And that is almost 70% to 80% bleed reduction. And yes, that is statistically significant. On the safety end, of course, we see reported that 15% had antidrug antibodies. Interesting. And I really have to ask the authors at some point. They say, well, 7% had preexisting antidrug antibodies, so, in fact, before exposure to efanesoctocog alfa, and 3 developed such antidrug antibodies during the study. But it was also well claimed in the study that these antidrug antibodies had no effect on factor VIII PK. So, I think there is still much to be answered whether or not these are really antidrug antibodies and what the prevalence and clinical impact of such antibodies could be once we start using this molecule on a daily basis.
40.		Moving to, I'd almost say, the "science fiction" part of this presentation, or at least the most tantalizing part. It's been buzzed about for years already, and it's something that is always referred to as the potential cure of hemophilia A and B. Moving to gene therapy.

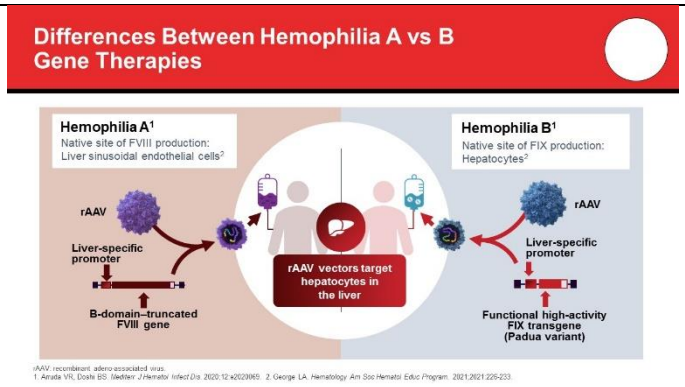
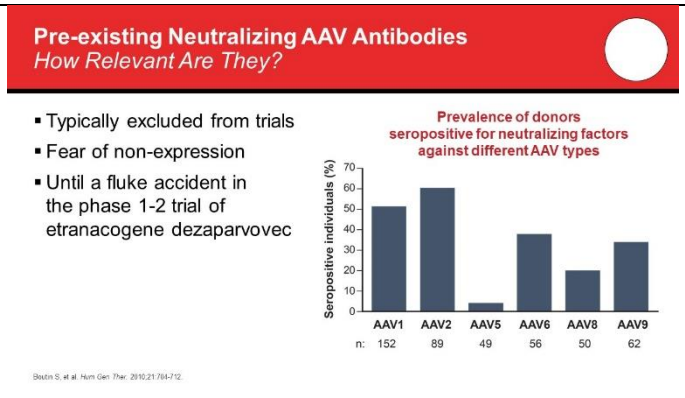
41.		Well, first of all, what is gene therapy? Well, the 2 gene therapies that are approved in hemophilia are adeno-associated virus (AAV) gene therapies. And this is essentially what the gene therapy looks like. The gene therapy uses the outside (the capsid) of the AAV. It does so to move into the cell without actually destroying it, and it has specificity to move into specific tissues. The goal of the gene therapy is to bring the gene cassette into the liver. And the gene cassette, of course, contains the therapeutic gene, but also, quite importantly, it contains a promoter, and in this case, a liver-specific promoter. And why do we use AAV vectors? Well, essentially, they are hardly or almost even not pathogenic, the natural variants. So, basically, if you contract one, you will probably not get symptoms, and if at all, maybe runny nose, nothing more. There are several serotypes, and what it actually does, it doesn't incorporate into the chromosomes, but it actually places the DNA episomally in the nucleus.
42.		Where are we right now with gene therapies? I think it's probably best to say that there is not 1 gene therapy. There is a high level of similarities between the gene therapies, but there are different viral vector subtypes that are being used. You can use different kinds of promotors with more or high specificity or efficacy. And finally, there is also something to choose from in the gene cassette. So, even if we're looking at only a few components, the total combinations you can achieve are huge. Essentially, there is no single gene therapy. There are only products that will each need to undergo clinical evaluation. So in hemophilia A, we right now have 1

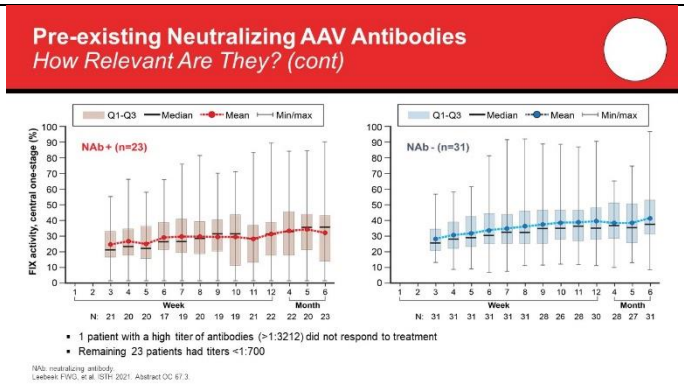
		thus-far approved gene therapy. That's valoctocogene roxaparvovec, which uses an AAV vector. And the other 2 are the gene therapies that are now in a phase 3 clinical evaluation program. But we have not seen the results of that yet, so I will not be dealing with those in the remainder of my presentation. In hemophilia B, there are now 2 gene therapies: fidanacogene elaparvovec (it's approved now as of 2024). It's also an AAV gene therapy, and it uses the Padua gene, which is a highly effective factor IX gene. And the other one that has been approved is etranacogene dezaparvovec, also AAV5, also using the factor IX Padua gene in the gene cassette.
43.		Moving now to the results in hemophilia A: valoctocogene roxaparvovec. This is now the 3- to 4-year follow-up slide figure of the phase 3 study. And what you can appreciate here: notice on the Y axis, you see the factor VIII activity, but the error bars you're seeing here are standard errors of the mean, so they are not standard deviation. So, the actual spread of factor VIII levels is much higher than the error bars you're seeing right here. But in this, 133 patients have been dosed and completed the 3- year follow-up. The mean factor VIII level is about 13%, and the median is 16%, showing you that it's sort of skewed. But there is still quite a range for patients who have actually lost expression to almost still 300%. And we talked about thrombosis risk with efanesoctocog alfa just now, but patients who are going into the 300 range and staying there for years are probably at increased thrombosis risk. There are many epidemiologic studies

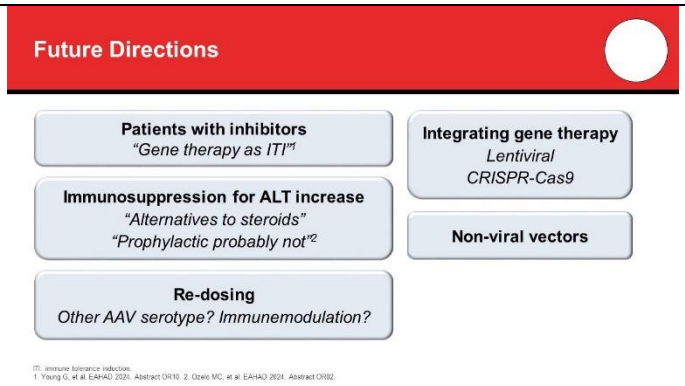
		from the thrombosis field actually showing there is an increased thrombosis risk in obtaining those levels. What you can also clearly see in the figure is the peak in effect somewhere around that 6-month mark, and then the level goes down. And the discussion is really in the tail part. Is this something that goes down and will eventually go to zero in all patients, or is there a subset of patients in whom the expression stays stable over years, and maybe many, many years? The answer is still out.
44.		Then switching to hemophilia B, there is sort of a different picture we're seeing here. This is the etranacogene dezaparvovec study. Also here what you're seeing is the 3-year follow-up. Have a look at the error bars in factor IX. Also considerable spread, although the spread is smaller than it was in the hemophilia A study; the mean and median levels are much closer to each other and both around the 40% mark. And the most striking difference is the stability of the expression. What you can see by this graph that, over a 3- year period, there doesn't seem to be a peak, and most importantly, the levels don't seem to come down after that 3-year period. So, with this one particularly, there's much hope that this expression can be years, perhaps many years, and even some are speculating that it could be for the rest of a person's life, although the answer is obviously out with not so many years of follow-up in yet.

45.		So, let's switch perspective. What can you expect 3 years after gene therapy? Moving from the left first, the hemophilia A field. I think it's important. We said gene therapy has the potential to bring patients into normality. Well, I think a reality check is that 3 years after gene therapy, only 11% of patients are still over 40%; the large bulk is between 5% and 40%. And I've seen some numbers that suggest that a group of these patients is at the lower end of this range. And about 33%—1 in 3 patients—is now below 5%. And according to the last update, 17 patients, which is 13%, have had to go back on prophylaxis after those 3 years. Moving to hemophilia B. Again, a different picture. Here is one-third of patients being in the normality range, over 40%, about half of the cohort, somewhere between 12% and 40%. And there were 2 patients who didn't achieve initial expression, and then a third patient during the course of the study lost expression and went back on prophylaxis. The total number of patients back on prophylaxis is 3 patients, and 6% of the cohort.
46.		Of course, there are what we call “the known unknowns,” this stuff we really are not sure about and is practically very important for patients while considering this therapy. First of all is alanine transaminase (ALT) increase. And the questions really are what is it, and how should we manage it? Typically, those ALT increases start within the first 3 months after gene therapy. And after a very elegantly followed-up case in one of the first landmark hemophilia B gene therapy studies, there was a strong presumption that these ALT increases

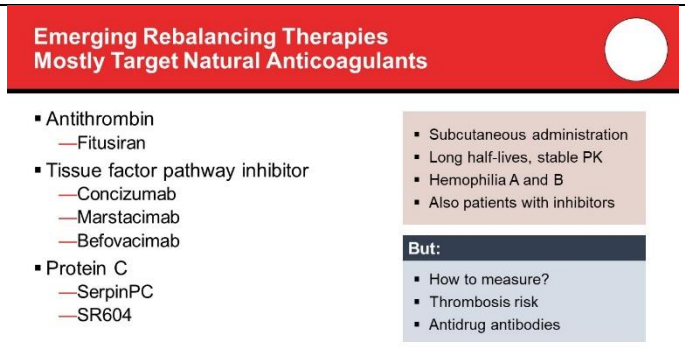
		must be an immune response to probably virus vector parts, essentially, on the right side [of the slide]. And that more or less coincides also with that 12-week range, where antigen-presenting cells actually, well, offer parts of that viral vector to our immune system, leading to selective destruction of the transfected cells. So, the fear was always that it can lead to selective destruction of transfected cells and, therefore, loss of expression. But in that first study, it was shown that corticosteroid regimens are actually effective at normalizing the ALT, and, if you do that fast enough, you are probably able to prevent the loss of expression. So, from that first case, all subsequent hemophilia gene therapy trials more or less have very stringent follow-up, weekly follow-up in the first 12 weeks after gene therapy, looking out for those ALT increases and corticosteroid regimens to be installed immediately when the ALT levels go up. And in hindsight, I think the results show that it works; there are hardly any patients who lose expression after an ALT increase, although the cost of therapy is quite high, and also quite high dosages of corticosteroids. Within the hemophilia A trial, the median duration of corticosteroid use was 6 months. So, it's realistic to expect side effects there. Something strange that we to this day do not really understand is that this ALT increase with valoctocogene roxaparvovec is much more prevalent, 86%, compared with etranacogene dezaparvovec, which is only 20%. And bear in mind, those gene therapies use the same AAV5 viral vector. So, if this is really a response to the viral vector,

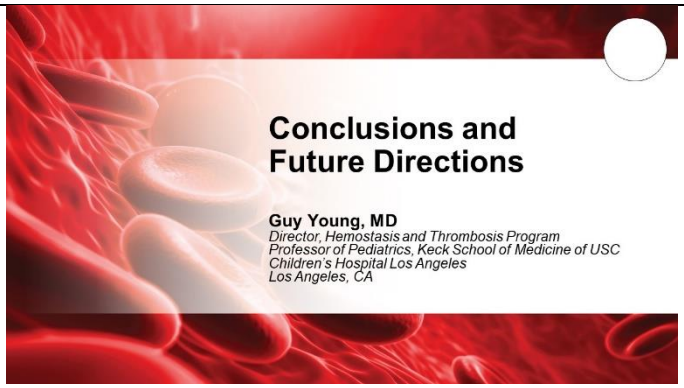
		why are we seeing such a big difference between the 2 therapies?
47.		Well, the running hypothesis is probably that it could have to do with the site or the target cells of gene therapy. Gene therapies target hepatocytes, and basically the DNA enters the hepatocyte and uses the hepatocyte protein–manufacturing mechanisms to produce factor VIII or factor IX. And in hemophilia B, well, essentially that's reproducing nature because hepatocytes are the natural site of factor IX production. So, you're in fact transfecting to the normal, natural site of production. But although factor VIII does come from the liver, it does not come from hepatocytes. It actually comes from the liver sinusoidal endothelial cells. And now in gene therapy, we are actually targeting hepatocytes. So could it be that targeting non-natural tissue leads to other sorts of problems down the line? Could that be the explanation for the difference we're seeing in ALT increase? Can that be the explanation for the different curves we see over time with factor VIII levels going down, but the factor IX levels remaining stable? I think it's the best-sounding hypothesis, but we are far, far from proving that yet, so that will definitely be something to look at in the future.
48.		Another thing that's important is preexisting neutralizing antibodies. Well, if you have been in contact with a natural variant of a specific AAV, then you will have AAV antibodies. And the fear has always been if you treat a patient with gene therapy, before the liver is actually transfected, before the hepatocytes become infected by the gene therapy and the DNA is delivered, these gene

		therapy particles would already be cleared.
49.		Typically, those patients were excluded from trials. There was a fear of non-expression until a funny fluke accident in the phase 1/2 trial of etranacogene dezaparvovec occurred. In that trial, only 10 patients participated. All those patients needed to be AAV5 antibody negative, but during the trial they actually switched to a better AAV5 assay. And then it turned out that 3 of the patients already had antibodies and were dosed nonetheless. And, in fact, the 1 with the highest antibody titer also had the highest expression. And in a sort of bold move in the phase 3 study, they completely removed the exclusion criterion of preexisting neutralizing antibodies.
50.		In the next slide you will see what the difference was between the patients with antibodies on the left side and patients without antibodies on the right side. And almost ideally, about 40% of the cohort actually had preexisting neutralizing antibodies. And what you can see here is that the expression is really in the same ballpark in the patients with and the patients without the neutralizing antibodies. However, titer may be important. There was 1 patient with an excessively high titer of those antibodies, 1 in 3,212, and that patient did not respond to treatment. And the hypothesis is that he did not respond to treatment due to these antibodies. The remaining 23, the ones in the graph, had titers below 700, so that's now coined as more or less the acceptable number, where you can still dose gene therapy in spite of those antibodies.

51.		Where are we headed next? I think we are really at the stage where we can't call it a cure for hemophilia yet. And there are, well, ongoing developments which may bring it there, but also other interesting parts. One of the fascinating thoughts is to target patients with inhibitors. Maybe a liver that produces factor VIII molecules every minute is maybe the best immune tolerance induction you can ever think about. And, in fact, Dr. Young presented in February 2024 at European Association for Haemophilia and Allied Disorders Congress the first results of the first 2 patients with inhibitors who were dosed in the context of a trial. And that's something that we are very much looking forward to follow-up on. I think we can do better with the immunosuppression for the ALT increase. I think corticosteroids are effective but will cause side effects. And there probably are better immunosuppressants with fewer side effects that should do the same immunological job as corticosteroids. And I think there is a clear push that prophylactic steroids will probably not become standard of care because there is some evidence that if you actually install corticosteroids prophylactically, this will also hamper your initial expression of factor VIII or factor IX. Can we redose, especially in hemophilia A, where there may be a loss of expression, where after 3 years, 13% of patients are back on prophylaxis? Can we do some form of redosing? If another gene therapy is approved that uses another serotype, can you simply use that one? Would you need some form of immunomodulation to be able to dose below antibodies?

		Because as a consequence of dosing hemophilia gene therapy, your antibodies will go up and they will go up dramatically, really into the range of that patient with a titer of 1 in 3,000, making it perhaps unlikely that redosing the same gene therapy will be effective without any action beforehand. Finally, I think we should really also be looking at maybe integrating gene therapy. That's always been the scary part because if you open up the chromosomes, you may open it up at the wrong point. There is always the fear of oncogenesis by doing this. Lentiviral approaches have been suggested in the past, but especially with lentiviral approaches where the integration is more or less random, this is a potentially serious risk. But I think for the future we are looking at CRISPR-Cas mainly, which is not so random. And ultimately, why is integration maybe important? If at some point gene therapy will be carried over to children, pediatrics, maybe trying to cure them at an early age, you will need an integrating form of gene therapy that actually is given over to the daughter cell when the liver proliferates and grows over time. The very final point is that we should also be looking at nonviral vectors. And there have been other disease areas that have now -sort of used nonviral vectors. You can also add some specificity toward the liver, even if you don't use that specificity of AAV viruses, so something also quite interesting to look at.

52.		In the very last minutes, I will take a few minutes to talk about rebalancing therapies. And again, as I said, and as I started with, we are really in a time of marvelous new molecules.
53.		Essentially, rebalancing therapy is targeting natural anticoagulants, and it really is, well, the targets that we have come to know from the thrombosis field more than from the hemophilia field. Fitusiran is a small interfering RNA blocking antithrombin production, so in fact what it does is it creates antithrombin deficiency quite to a severe form—50% to 75% reduction in antithrombin activity. But a severe antithrombin deficiency to counteract hemophilia. Tissue factor pathway inhibitor has been the target of a couple of molecules. Concizumab is entering the clinics in some countries already, and it's really rounding up its evaluation and trials. Marstacimab is in its phase 3 trials—it's somewhat behind—but befovacimab is the one that has been started. But the development has been halted in the past due to the emergence of thrombotic complications in patients in those trials. That's a sign of concern there. Other targets that are also coming from the thrombosis field: creating protein C deficiency or resistance. And there are 2 compounds for that, SerpinPC and in the preclinical stage, SR604. In general, they are subcutaneous, most of them. They really have long half-life, have stable PK, can be used for

		both hemophilia A and hemophilia B, and especially can also be used in patients with inhibitors. I think it's probably relevant to mention hemophilia B with inhibitors, which is really the horrible case to treat for most hemophilia doctors, for which we practically have no alternative treatment. So, this is really the first treatment for those sorts of patients. How do we measure such products? What is the equivalent in terms of factor VIII or factor IX? I told you about thrombosis risk. But not only in befovacimab, but also in concizumab trials, there have been thrombotic episodes. In fitusiran trials, there have also been thrombotic episodes. And in reaction, the trials have made risk-mitigating plans, which make a lot of sense and probably have improved the product. But still, a slight concern about thrombosis revolves around those products. And finally, anti-drug antibodies with any new molecule could be a problem that makes any treatment ineffective.
54.		So, I'm wrapping up here. And finally, for the conclusion and the future directions, I'm happy to hand off to Dr. Young. Thank you very much. *[Guy Young, MD]* Thank you. Very detailed presentation.

55.		I think, in conclusion, I would say that we have more and more options to treat patients. Quite a lot of different options from novel factor therapies. We have factor VIII mimetics, and we will have at least 1 or 2 more of those coming. We'll have the rebalancing agents that you just reviewed for us briefly, and there are obviously several different mechanisms of action there. And then, of course, gene therapy. So, the menu is growing, and the advantage of a growing menu is that we can really offer patients very individualized choices that will fit their lifestyle, that will fit their current hemophilia status, that will fit whichever treatment burden they prefer, or that will fit whatever activity level they want to achieve. And so with more and more options also comes more and more complexity. Understanding laboratory assays, as you mentioned, particularly for rebalancing agents, some of which will require therapeutic drug monitoring, understanding how to manage the gene therapy patients in the long run. What if their factor VIII levels do drop to a certain point, or factor IX for that matter? We don't see quite as much for factor IX. How do we then intervene? What prophylaxis makes the most sense in those scenarios? There's a lot to learn, and there's a lot to understand about these future treatments. And finally, also switching from one treatment to another is going to be complicated when drugs have a long half-life. Emicizumab stays in the blood for 4 months, 6 months, until it's fully out of the blood. If you want to switch a patient from emicizumab to something else, how does that work?

		There are trials that are aimed at addressing that. So, I think that the future for hemophilia is getting better and better, but for us, as the treaters, it's getting more and more complicated. And we have to really keep on top of understanding all of these new agents, their mechanisms of action, the laboratory ramifications, and the issues of switching. But that's what these educational programs are for, to at least give some information to those listening here. And I encourage those of you to continue to ask questions, continue to listen to these educational programs, and, ultimately, you're going to be able to give your patients the best possible treatments and make the best possible decisions.
56.		Thank you, everybody, for listening, and we will sign off at this point. Bye-bye.