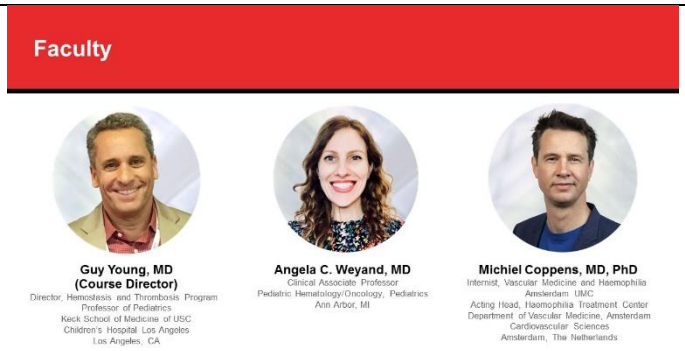
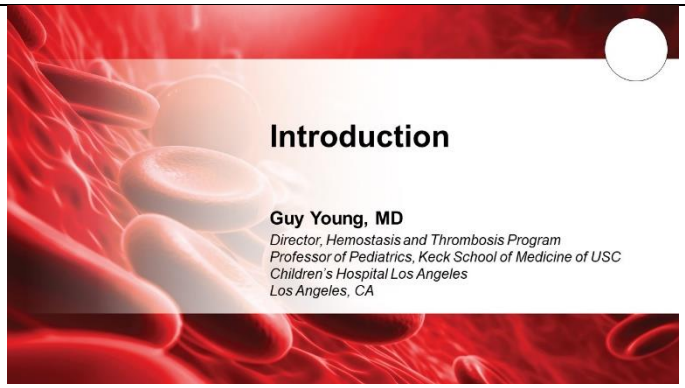
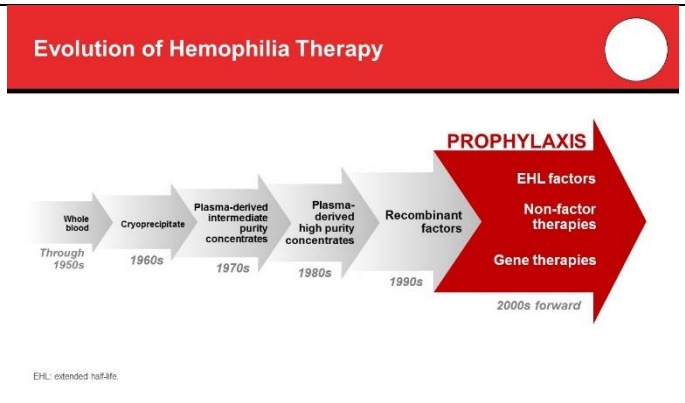
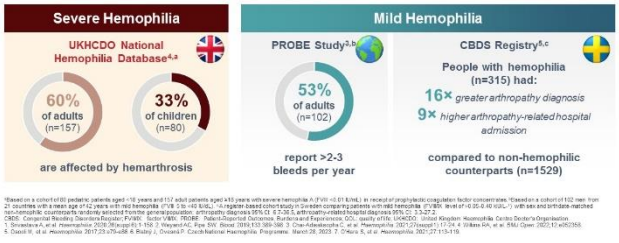
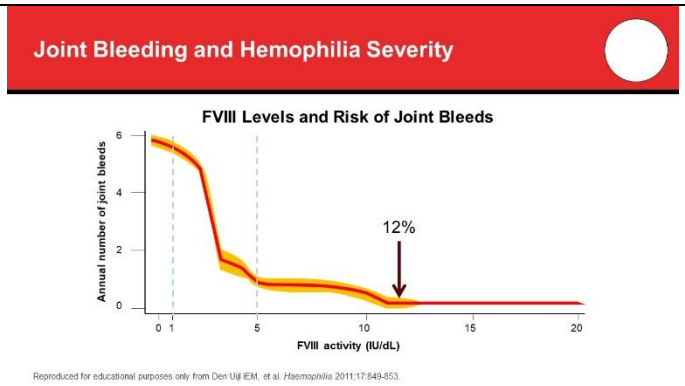
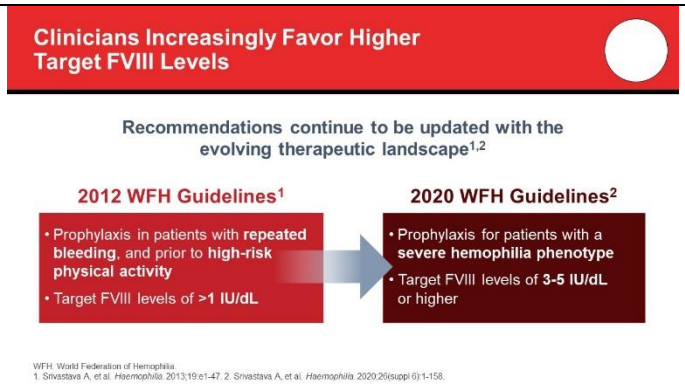
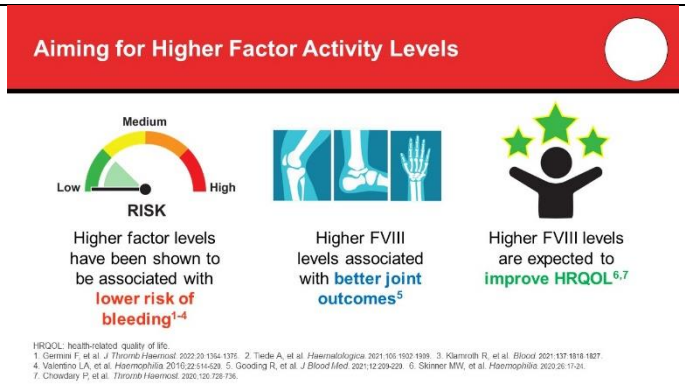
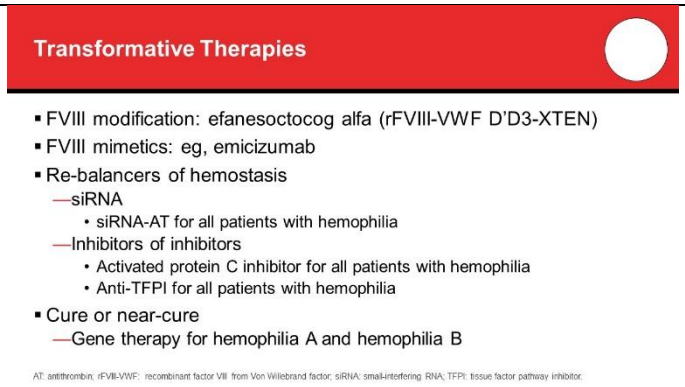
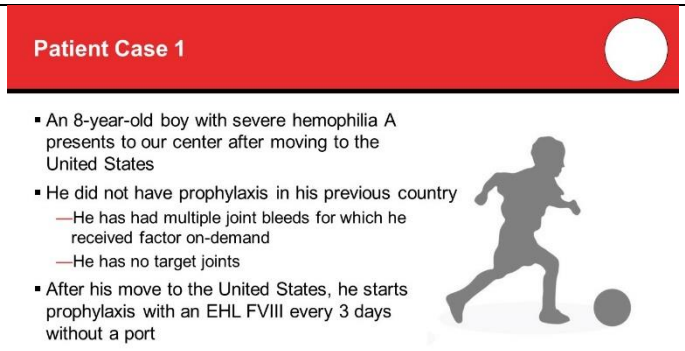
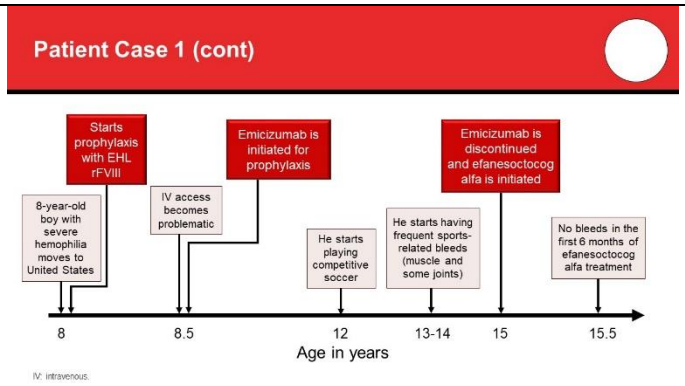
1.		*[Guy Young, MD]* Hello! My name is Guy Young, and I'll introduce the co-panelists in a moment. We are here to discuss a topic on hemophilia A called "Achieving and Sustaining Higher FVIII Levels in Hemophilia A: Exploring Real-World Strategies for Treatment and Monitoring Trough Levels Considering New Treatment Options."
2.		I'm from Children's Hospital Los Angeles, University of Southern California. The co-panelists are Angela Weyand, MD, from the University of Michigan and Michiel Coppens, MD, PhD, from the University of Amsterdam. And we're going to be hearing and discussing a few cases between the 3 of us momentarily.
3.		Let's start with the introduction.
4.		We know there's been an evolution of hemophilia care. I won't read each and every one of these, but those of you who've been around long enough certainly know that we've had quite a revolution in the 2000s, particularly in the last 7 to 8 years, with the introduction of extended half-life factors, non-factor therapies, and gene therapy.

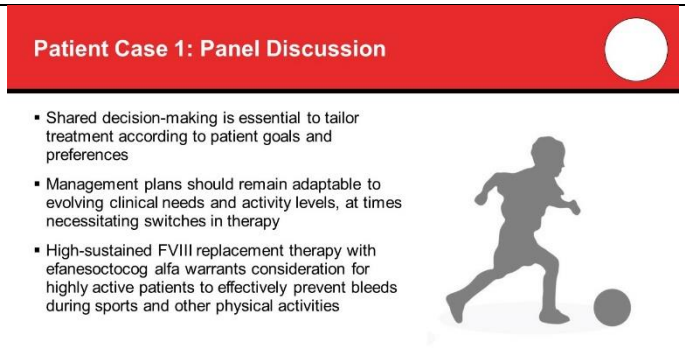
5.	**Challenges With Factor Replacement** ▪ Requires venous access ▪ Time consuming ▪ Factor levels in blood not maintained at steady state ▪ Trough levels of factor not fully protective against bleeding	The challenges with factor replacement, we all know, are that it requires venous access, and it's time consuming. Factor levels in the blood are not maintained at steady state, so we have typically sharp peaks and troughs, and the trough levels are not fully protective against bleeding. And the trough level target has been moving as we've gotten better and better treatment. So, overall with factor replacement therapies that we've had for many decades now, they do impart a high treatment burden and don't ultimately provide us with steady factor protection.
6.	**Patients Continue to Experience Bleeds Regardless of Disease Severity** ▪ Modern hemophilia therapies allow for treatment optimization and a significant reduction in bleeding frequencies[1,2] ▪ Despite progress, patients with mild to severe hemophilia are still burdened by joint bleeds and impaired QOL[3–7] 	As a result, patients continue to experience bleeds regardless of disease severity. There are several publications—you can see some of them on the bottom, including this one from the United Kingdom Haemophilia Centre Doctors' Organisation on severe hemophilia—demonstrating that the large proportion of adults, more than half, are affected by hemarthrosis. And also, a substantial proportion of children are affected by hemarthrosis. And even in patients with mild hemophilia, there are different studies and registries that report that patients can bleed as much as 2 to 3 times a year in the PROBE study. And that patients in the Swedish study have a substantially higher risk of an arthropathy diagnosis compared with nonhemophilic counterparts and a 9 times' higher risk of arthropathy-related hospital admission. So, patients with mild hemophilia can, especially over years, have bleeds, and those bleeds can lead to arthropathy.

7.		This is a fairly famous slide from an excellent study from the Netherlands. The study took a look at the natural history of hemophilia. It took a look at patients with different factor levels and assessed the annual number of joint bleeds. And you can see several inflection points, one at about 3%, where below 3% you get a sharp rise in the number of annual bleeding rates. Another small inflection point at 5%. I think the key message here is that patients with a baseline factor VIII level above 12% seem to have a very low risk of having joint bleeds. So, that's one study that suggests that as you get to higher and higher factor VIII levels, you're less and less likely to have joint bleeds. In fact, getting close to zero joint bleeds. 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

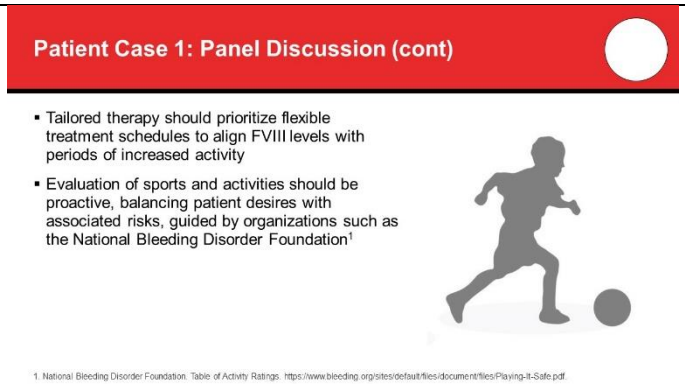
8.		Now, also, the recommendations have evolved. So, there were World Federation of Hemophilia guidelines in 2012, which suggested a target trough of 1%. But the newer guidelines, which are, at this point, about 4 years old from when they were published, have a target factor level of 3% to 5%. And this came before we had the approval of some other new drugs like efanesoctocog alfa and gene therapy. So, I think that this target factor VIII trough level does seem to continue to move to higher and higher levels as we have treatments that can achieve those.
9.		We know aiming for higher factor activity levels is associated with a lower risk of bleeding. I think this is fairly obvious. And as a result, higher factor VIII levels will result in better joint outcomes. And we do know that patients on the very milder end of hemophilia, above 12%, or even, let's say between 15% and 40%, we don't often see joint disease in those patients. And then that will result in higher and improved health-related quality of life.
10.		What have been some of these newer therapies? Well, we have a novel factor VIII molecule. It's been available for about a year in the United States (US) and becoming more commonly available in other countries. It's called efanesoctocog alfa. We have factor VIII mimetics, we have emicizumab, currently the only one. But there may be others, or likely to be others in the future. Then, we have agents that are not yet commercially available in most places, the rebalancing agents, small interfering RNA (siRNA) therapy for knockdown of antithrombin, which could work for all patients with hemophilia. In other words, hemophilia A and B, with and without inhibitors, and also inhibitors of other inhibitors like activated protein C and tissue factor pathway inhibitor. And then we have this cure, or near-cure. We can argue about what we would use to define the word cure

		in hemophilia, or what we would need to define cure in hemophilia. But be that as it may, the gene therapies for hemophilia A and B that are approved in a variety of countries around the world are intended to be a single dose. Well, they can only be given once, but the aim is to give them once and to achieve factor levels, either factor VIII or factor IX, that are in the, at least, what I call "therapeutic range," meaning your number of bleeds is close to zero, you're unlikely to bleed, or perhaps even for the luckier ones, you are in the normal range.
11.		So, with that, I'll stop, and we will now get into our case presentations and panel discussion. So, I'm going to present a case, and then we'll have a discussion between myself and Dr. Angela Weyand and Dr. and Professor Michiel Coppens. And then Michiel will have his own cases to present, and we'll have those discussions after each case.
12.		My case is a child, and we'll hear some adult cases momentarily. It's an 8-year-old boy with severe hemophilia A, and he presented to our center after moving to the US. He had not been able to receive prophylaxis in his previous country, and he did have a history of multiple joint bleeds, and he would receive factor on demand for those. Now, fortunately, he did not have any target joints. And once he moved to the US, we decided to start him on prophylaxis, which is our standard for any child with severe hemophilia. So, he was put on an extended half-life factor VIII every 3 days, and we managed to do that without a port.

13.		Now, here's a bit of a timeline because the case starts when he's 8, but you can see it ends when he's almost 16. So, again, he moved to the US. We started him on the extended half-life factor. Then, intravenous (IV) access really started to become a problem, even within 6 months. So, yes, we tried to do this without a port, but it was quite challenging. At the time, emicizumab was already available in the US, and so we were able to initiate him on emicizumab at that time for prophylaxis. So, fast forward 3 to 4 years later, and he starts playing competitive soccer. He starts having frequent sports-related bleeds, muscle bleeds, and some joint bleeds, although mostly with some muscle bleeds. So, at the age of 15, we had a long discussion with him, and soccer really became an important part of his life. He was joining the high school soccer team, and it just wasn't really acceptable to have the bleeds that he had had while on emicizumab. And again, on emicizumab, his bleeds were only activity- and sports-related. He didn't have any spontaneous bleeds. So, all in all, emicizumab did serve him well for several years. But when we got to this point, we decided that we would discontinue it and start efanesoctocog alfa as it had become available. And so, he started on that. We don't have a long history with that. As you know, it's only been available in the US for about a year, but at least in the first 6 months, continuing his competitive soccer, he has not had any further bleeds. So, I think here we have a case where a patient who's fairly young has switched from one treatment to another and to another. I think what's interesting here is he was on factor, and then he switched to a subcutaneous drug because IV access became a problem. However, the subcutaneous drug, when he became much more active, became a problem for him in the sense that it wasn't as protective of

		bleeding as we had wanted. So, of course, once he was older, IV access became easier. I mean, he was more mature, he was bigger, his veins were easier to access. And also, efanesoctocog alfa was only once a week, as opposed to every 3 days, which was the schedule for his other extended half-life factor VIII he was on before.
14.		So, that's the case that I wanted to discuss, and I know because I've had discussions with Dr. Weyand about this before, about this exact situation. And I'd like to just ask you first, what's been your experience with respect to efanesoctocog alfa now that it's become available, in addition to our other options? *[Angela Weyand, MD]* Yeah, so, you know, as you mentioned, it's been about a year, and I kind of expected that a lot of patients would be interested in it because we participated in the trial and had people who weren't able to enroll in the trial because there weren't open spots. So, we have had similar patients to your patient where, you know, they are just playing higher-level activity. And I think it's always tough with that for me to gauge how higher-level activity it actually is and why some people tend to still kind of do okay on nonfactor versus others. But we've definitely had similar patients who have switched from emicizumab to efanesoctocog alfa for this very reason. And I think it highlights, you know, the importance of this shared decision making because I think in my mind, when emicizumab came out, one of the huge draws in pediatrics was the subcutaneous administration, and I really felt like that was preferred by all patients. But I've also had other patients who end up preferring IV because they're used to it. And they, I don't know, if they get like a little scar, it's less painful. But just, you know, these sorts of conversations about exactly how active are

		you and is this something that you're going to need a nonfactor for or need a factor treatment rather than nonfactor treatment? But also things like administration, because, you know, I think we have our own preconceived notions of what is best, and that's not necessarily always what the patient thinks. *[Guy Young, MD]* Thanks for that. And I think that one of the other points you made is that emicizumab has done well for many patients. You know, not every single one of my, you know, active kids has had to switch, but definitely some have needed to switch because it wasn't protective enough. And I don't know if this boy had, you know, some joint disease that wasn't necessarily visible because he hadn't been on prophylaxis until he was 8 years of age and manifested that way, or something different about his muscles or joints, or something just about the way he plays, maybe he plays a bit more aggressively. And so, Professor Coppens, I believe the Netherlands enjoys a soccer (football) culture as well. Can you tell us, how do you manage young adults who are, you know, in a more aggressive sport? And you have other sports, of course, in the Netherlands as well, when you think about choices for factor VIII prophylaxis? *[Michiel Coppens, MD, PhD]* Well, thank you, Guy. And yeah, absolutely. I am a football (soccer) kind of guy. So, this hemophilia patient who wants to be an active soccer player, that hits home for me, and that's something I would like to accommodate in clinics as much as possible. The discussion we have regularly is this one. I think the majority of severe hemophilia A patients here switched to emicizumab a few years ago. And the continuous discussion that actually keeps coming up is to what

		extent can you do exercise on the activity achieved by emicizumab, and in what circumstances would you need extra boluses, extra peaks for aggressive sports? I think in general in the Netherlands, we see that in pediatrics, most strategies which you do on emicizumab, most kids are able to play sports on emicizumab, but going to adulthood, that's where football soccer becomes much more physical, becomes much more aggressive. Sadly, I have to admit that most adult hemophilia patients at some point abandon soccer. And, well, I guess, personally, if you want a sort of ideal, tailored approach, you may want something like emicizumab, but then factor VIII for aggressive sports activities.
15.		Well, I guess one question back at this efanesoctocog alfa patient of yours. Typically in the Netherlands, 2 times a week you have training, and then 1 time a week you have a soccer game. How do you manage on a once-weekly regimen? Because you're not having the peaks throughout that entire week. *[Guy Young, MD]* That's a very good point. And I think that, you know, we can try to work around the patient's schedule. So, in the US, Sunday typically is the day when kids won't play. So, if he has practice Tuesday, Thursday, and a game Saturday, then the different options would be to dose him on Tuesday and hope that things are good enough on Saturday, or to just allow him to practice on Tuesday. But, you know, let him know, let his coach know that it shouldn't be overly aggressive. He can do, you know, the fitness training and some of the simple drills, and then maybe dose him on Thursday so he can have the more aggressive practice and play on Saturday. But no, you raise a good point, which is that, you know, after about day 4 or 5, the levels are now down closer to 30%,

		20%. And at that point, it's probably not having much more benefit than emicizumab. It's also been brought up, actually, in some of our meetings, to consider—and this would be, of course, off-label use and expensive. But I've also heard patient groups say that we should be dosing efanesoctocog twice a week, so patients are never below 40%. Angela, have you heard that? And what are your thoughts on that? *[Angela Weyand, MD]* Yeah, I definitely have heard that. I think, you know, I think about this because I'm a little bit newer to the space than some people I work with. And I think that when we were targeting greater than 1%, we were targeting that because that was what we could achieve. And now we have these products where we could hypothetically make someone "normal" for the week. And I think the biggest issue in the US, right, is costs, and is someone going to pay for that? Because I personally think, right, of course, we should make people normal. I mean, we do that for other diseases and conditions. If someone comes in with a blood pressure of 220 over 180, we don't say, "Well, we'll get you to 210 over 170, and that'll be great," right? We want them to actually be at a level that is normal and have clinical outcomes that are desired rather than just, "We'll make you a little better than you currently are." *[Guy Young, MD]* Yeah. I think another thing to consider is looking ahead and seeing if there might be other treatments available in the future. Specifically for adult patients, we're going to hear a bit about gene therapy and see what options that gene therapy could achieve. But that would only be for patients 18 years and older. I think the whole point of wanting patients to be as active as possible, you know, in the US, we also have, you know,

		American football or, you know, tackle football, and this is something that we've always said "No" to for patients. And I've, you know, broken some dads' hearts where, you know, that's a sport that's just in the culture of the family. And, you know, for families like mine, where soccer was in the culture, it was just something that bound our, you know, the men in the family, particularly. Not to say women can't play soccer. They can and do it quite well. But, you know, I grew up with *2* brothers and a dad who was a professional soccer player. So, it is really an important part of our upbringing. And so, you know, when it comes to American football, which is a much more violent type of sport, you know, we've always just said "No." And that's been challenging. I hope that one day I'll reach a point where, while understanding the risks associated with tackle football that everyone faces, the risk for a hemophilia patient won't be any higher. And I don't think we're quite there yet, but maybe with, you know, twice-a-week efanesoctocog alfa, it's something that could potentially be possible. So, I'll just ask Professor Coppens if you have any other points to make, and if not, we can move on to our other cases. *[Michiel Coppens, MD, PhD]* Well, I was sort of interested—are there typical sports, would you define sports that you say, well, people can't stay on emicizumab? Because I'm sure there will be problems. Are there types of sports where you say, well, hemophilia patients really can't do this? I think you touched upon that with American football, tackle football. How would you rate soccer? Would you normally do it more, let's say, reactively or proactively switching him to another compound, achieving peaks?

		[Guy Young, MD] That's a good point. I think at this point it's been reactive, but, you know, maybe it should be proactive. And I think that that's a very interesting point you bring up and something that, as I said, the first few patients we switched from emicizumab to efanesoctocog alfa, it's been as a result of emicizumab not being effective. And I think that, you know, the sort of downside is that, you know, we do have a drug that, you know, does probably protect better. And based on the factor VIII levels and what we know emicizumab can do, but rather than subcutaneous injections, let's say every 2 weeks, it's now IV injections every week. So, there's a bit of a treatment burden and cost that comes along with that. But I think, you know, potentially being proactive in somebody who we know is going to be playing at a relatively high level of whatever the sport is. Basketball is another one. I think when you ask about which sports, you know, there is—the National Bleeding Disorders Foundation in the US does have a rating system for, you know, sports and activities. I think most of it is pretty good, although they do put soccer and basketball at a high risk. Not the highest risk, but the high-risk level. And yet I've always thought that those are sports that I would allow patients to play. I think when it comes to one question, you can ask if, "To play the sport, do you have to wear all kinds of equipment all around your body to protect yourself?" And if the answer is "Yes," then, you know, maybe we should be thinking twice. And in the US, those sports would be tackle football, ice hockey, and a sport that's a very American sport called lacrosse. I think, you know, yes, you have to wear shin guards to play soccer, but that's a relatively minor addition to the equipment. So, I think that's kind of where I've drawn the line.

		But anyway, well, thanks for this discussion. I think we treat more and more patients who are getting more and more active. And I think as we have these different options, we really do need to be thinking about it. And thinking about it proactively. I really like the comment that you made, Professor Coppens, about thinking more proactively rather than waiting for bleeds to happen. So, anyway, I think we'll close this case, and we can move on to the next case.
16.	**Patient Case 2** ▪ 52-year-old man, high school physics teacher ▪ Severe hemophilia A, brother also has it ▪ HIV positive, well-controlled by ART ▪ Successfully treated for HCV in 1990s; no chronic liver damage on ultrasound  ART: antiretroviral therapy; HCV: hepatitis C virus.	*[Michiel Coppens, MD, PhD]* Okay. And now for the second case. This is one that I brought along from Amsterdam. And this is a case, a patient, from my outpatient clinic. He's now a 52-year-old man. He is, by profession, a high school physics teacher. So, he's a pretty smart guy. He was born with severe hemophilia A, and, similarly, his brother has it as well. He was one of the patients who became HIV positive. Also hepatitis C through contaminated products, plasma-derived products, in the 1980s, and is well controlled on antiretroviral therapy. His hepatitis C was treated in the 1990s and afterward on ultrasound, no FibroScans at that age yet, no signs of chronic liver damage.
17.	**Patient Case 2 (cont)** ▪ A lifelong episodic/on-demand treatment with SHL FVIII ▪ Never wanted regular prophylaxis —*"3 times a week is just too much"* —*"My bleeds are usually easy managed with 1 or 2 shots of FVIII"* —[Psychological factors must also play a role] ▪ Has serious arthropathy in ankles and knees, clear muscle atrophy in lower extremities —*"Due to being too wild when I was younger. Don't have big joint bleeds anymore."* ▪ Regularly does not show up for outpatient clinic appointment; does not really see the need —*"Experienced enough to manage his disease the way he wants"* SHL: standard half-life.	So, his treatment historically has always been a lifelong cycle of episodic, on-demand treatments with standard half-life factor VIII products. And, you know, we have had many, many discussions through the years in the outpatient clinic, and he never was ready for regular prophylaxis. And the arguments, well, were sort of like, well, "Three times a week is just too much for me." Also, he was quite keen on that. His bleeds are usually quite easily managed with just 1 or maybe sometimes 2 shots of factor VIII. So, the burden of bleeds in my case is not as heavy as in potentially other ones. But I guess, and that's why I'm mentioning it here, I think there's probably a lot of psychological

		factors that must also come into play with his, well, I guess his feeling toward treatment and factor concentrate due to his particular history. As a consequence of lifelong on-demand treatment—because in the Netherlands, of course, prophylaxis and almost primary prophylaxis is considered the standard of care—he has severe arthropathy in ankles and knees, and he has, typically, muscle atrophy in his lower extremities. But still, even if you confront him with that in the outpatient clinic, he says, “Yeah, but that's not now. That was when I had those bleeds when I was too wild, when I was younger. And in recent years, I haven't had any large, big joint bleeds anymore. So, even though I have all the signs of the damage of bleeding, I don't have a bleeding problem right now.” And also, that was something that we regularly see. He regularly also doesn't show up for outpatient clinic appointments. It's not unwilling, but he doesn't see the need. It isn't at the top of his head. He forgot about the appointment, and to some extent, well, he finds, and he has at least some point, that he is experienced enough to manage his bleeds the way he wants to.

18.	**Patient Case 2 (cont)** ▪ 2021 admission for melena and anemia ▪ Gastro-duodenoscopy: Small amounts of older blood in duodenum, no lesions/origin ▪ Started prophylaxis with emicizumab every 2 weeks —Has not had a bleed since —Has been reasonably adherent —Says it changed his life, he can do more now —Yet still has significant joint limitations	So, this all sort of changed in 2021, and then he was admitted for melena and subsequent anemia. He underwent, like all patients with melena do, gastro-duodenoscopy, and they found smaller amounts of older blood in the duodenum, but no clear lesions or indications of where the blood was coming from. That's something that's sometimes called Dieulafoy's lesion, and they have a tendency to sort of rebleed. And maybe, of course, his hemophilia is probably also, well, chipping in on the threshold at which such bleeds may become real clinical bleeds. But this was really the point where he felt, and with the potential of recurrent gastrointestinal bleeds, where he felt, "Well, maybe this is the point where my old strategy is sort of failing." And then at that time, he was maybe the ideal candidate for emicizumab, and he started prophylaxis every 2 weeks. And since then, he has not had a bleed since. He's been reasonably adherent. But that's not nonadherence in itself. This is an active guy. He really tries to prolong the interval slightly. And his motivation for that is not because he doesn't want to self-inject. He says, "I want to reduce costs for society, so I'm sort of stretching it through a 3-week limit." And he says, "Well, 3 is enough, and then I don't get those small joint pains." But he is very clear that this treatment has completely changed his life. He's noticed that his general joint condition has improved. He is now a daily swimmer. He can do lots of stuff on his bike, go more or less where he wants to. In Holland, that's the, well, at least in Amsterdam, that's the preferred mode of transportation, going by bike. And in the past, he really couldn't do swimming and he couldn't do cycling without getting, well, at least a joint bleed once every 2 or 3 times he did so. But still, he has significant joint limitations. And to some extent, he also travels, and sometimes he does have high-risk activities there. And

		there's, well, we sometimes question whether or not the emicizumab would do for those instances as well. So, the point why I brought this case is that sometimes we have patients who are nonadherent. And I think those will be my first questions for my co-panelists here, whether they would recognize this patient in their particular outpatient clinics and how they would deal with them. And in general, when emicizumab came to the market, there was, of course, concern regarding price. And there was a clear statement that patients who are nonadherent to factor VIII therapies may not be your best candidates for emicizumab because they may not also be adherent to that one. And I think this is a typical case where the burden of treatment—switching from IV 3 times a week to subcutaneous prophylactically once every 2 weeks—was such a change in burden of disease that this patient went from a nonadherent patient to a quite adherent patient and is now finally seeing, I think, the benefits of prophylaxis.
19.	**Patient Case 2: Panel Discussion** ▪ Patients may initially benefit from switching to emicizumab from traditional FVIII replacement therapy, but may later encounter adherence challenges as they adapt to their revised treatment schedule ▪ The long half-life of emicizumab may mask immediate consequences of non-adherence, making it challenging to recognize adherence issues solely based on bleeding patterns 	Although, personally, I think there has been a lot of damage already and a lot of bleeds under the bridge, if I may call it that. So wrapping up this case, and as I said, starting with the question I had, what do you think? Is this a typical case from your clinic, and how would you have managed it? *[Angela Weyand, MD]* Yeah, I mean, I think that we definitely, you know, have patients that struggle with adherence. I think that with emicizumab, it's been interesting to see because I think there have been patients who have gone from 3-times-a-week infusions to emicizumab, you know, every 2 weeks or every 4 weeks, and then they start to have trouble with adherence to that, right? And you think, "This is so much better," but I think you just kind of adjust to that as your new normal and then, you know, for whatever reason,

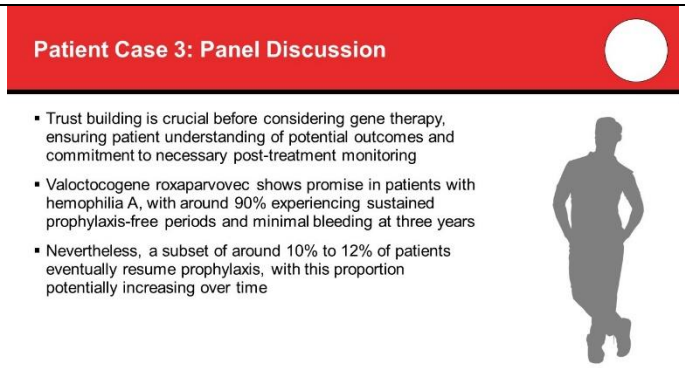
		start to slide into those adherence problems. I also think that we've seen a lot because emicizumab has just such a long half-life, that we have patients who are very nonadherent but somehow do okay despite their non-adherence because it just sticks around so long. And so, I think there isn't necessarily as much of the feedback of—I feel like some of our patients, when they were on factor VIII, you know, if they missed doses, they would bleed pretty quickly after, you know, those missed doses and kind of get that feedback of, "Oh, I need to have my dose on time." And I don't think we've seen that as much in our pediatric patients on emicizumab where, you know, they may, you know, miss doses or be late with doses, but they don't get that immediate, you know, bleeding.
20.	**Patient Case 2: Panel Discussion (cont)** • Adherence issues may arise from various factors beyond mode of administration, including lifestyle considerations, perceived importance of treatment, and forgetfulness • Switching to emicizumab may not resolve all adherence issues, particularly those related to attitudes towards treatment or hemophilia management • The shift to emicizumab may introduce cost and reimbursement considerations that can impact treatment decisions and adherence, varying across countries 	*[Guy Young, MD]* Yeah, I think, you know, the adherence issue is an important one. And the question always is why is somebody not adherent if it's really purely because they can't infuse intravenously, if it's children the parents don't want to port, if it's an adult who can't find their veins very well, you know, they've stuck themselves so many times, or maybe they just, as they get older, have less dexterity, less ability to access the veins. If it really is truly, purely due to the IV nature of factor concentrates, then I think that switching to emicizumab, obviously being subcutaneous, helps the patient. And I think in those cases, adherence typically is quite good. If a patient is not adherent because, you know, they have their lifestyle considerations or they don't think it's that important to do their medication, they don't bleed often, or if it's more of a forgetfulness thing, they just don't consider hemophilia a priority for their medical health. And so, then, switching the patient to emicizumab, you know, sometimes helps at the beginning, but then doesn't help later. I have

		somewhat of a surprising number of patients who are nonadherent with emicizumab, and they either forget to bring their prescriptions or they do it, sort of as they feel like, every month, every 2 months. So, yes, if the issue of adherence is really just the IV infusions, then of course emicizumab will help those patients to adhere. But we know adherence is more complicated than that. And in many cases, the IV access issue is one part, but there are other parts to the non-adherence, in which case those issues need to be addressed, you know, separately. And those are much more challenging to address. You know, the lifestyle issues, the hemophilia is not that important, or, you know, "I've been managing like this my whole life." That kind of attitude often won't result in improved adherence when you switch to emicizumab. And those are patients for whom, you know, we can discuss, perhaps in the next case, you know, gene therapy, because there you don't really have to be adherent to any medication. Although there are some adherence issues with respect to laboratory tests, but that can come up a bit later. *[Michiel Coppens, MD, PhD]* Yeah, thanks very much. And maybe just to finish up this case at a national level, do, at some point, cost and reimbursement come into play? Because in the Netherlands, when emicizumab was evaluated and it finally was approved for reimbursement, there was this sort of feeling that, well, total hemophilia costs in the country can't be more than it is right now. But if you take that perspective, these are the patients who are particularly challenging because on-demand therapy the way he had it—and I think, medically, it's not a good therapy for him—was about the cheapest there is. And by putting him on emicizumab, he suddenly became a

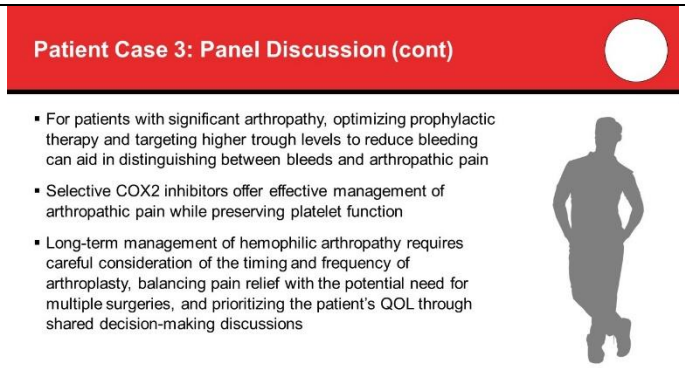
		prophylactic patient with a lot of costs in care. Have such issues been part of the US process in reimbursement? *[Guy Young, MD]* Well, you know, it's interesting, you know, when you think about cost issues; they're so different between different countries. I'll just say simply that in the US, the cost of emicizumab for prophylaxis is not different than the cost for factor VIII for prophylaxis. So, what we switch a patient from doesn't matter, you know, more or less, any brand to factor VIII. I mean, some of the brands have become quite cheap because of the competition. But, you know, when emicizumab was first licensed, the cost to switch was really neutral. Now, of course, if you take an on-demand patient and switch them to prophylaxis, no matter what product, the cost will go up. But we haven't really had that cost issue with emicizumab going from prophylaxis to prophylaxis, because, generally speaking, it's a neutral cost change or no change in cost. *[Michiel Coppens, MD, PhD]* Thank you very much. I think this is a nice wrap-up of case number 2. And let's move on to the third patient.

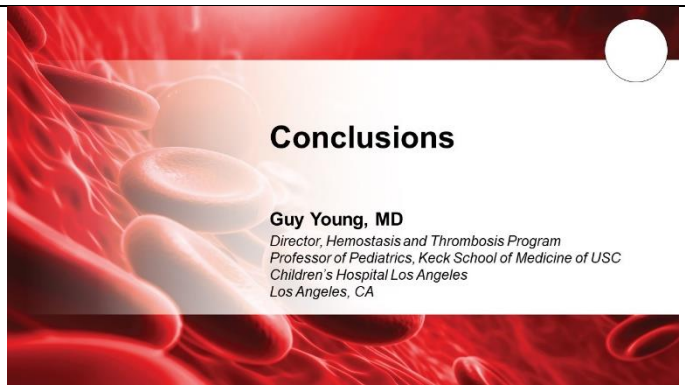
21.		Case number 3 is a 26-year-old man who was born in Bulgaria, and he came to the Netherlands at the age of 19 years old. In Bulgaria, he had a lifelong cycle of on-demand, or, well, often enough, no therapy at all. So, when we first saw him, he had horrible arthropathy in his left knee. It really made a nasty, nasty angle. Basically, you could see he really needed an arthroplasty, even at that age. So, coming to the Netherlands, he started with standard half-life factor VIII prophylaxis, which seemed effective, but he was in chronic pain in his knee. And we were sort of working him up with our orthopedic surgeons to see if we can improve his mobility. But in the end, we felt we were really working toward total knee arthroplasty at some point. But then, he started not showing up at the clinic. And, basically, we can see when patients are not adherent in their prophylaxis because simply they do not order their factor concentrate in time to have a normal, fitting prophylaxis. And when we started calling him, well, it was really hard to get ahold of him, and most times we couldn't. And it was later when his mom, who was a carrier and needed to undergo knee surgery, traumatic knee surgery herself, basically told us, "Well, he sits at home all day on the couch playing video games, and he says he doesn't need prophylaxis anymore because he doesn't do anything else than sit on the couch." And it was sad. And we tried to encourage his mom to please try and send him over because this is probably heading nowhere, I guess. But then 2 years later, he suddenly shows up in the clinic with his stepfather, and they have a real clear plan and basically saying, "Well, I want a knee arthroplasty, and I want gene therapy for my hemophilia A."

22.	**Patient Case 3 (cont)** ▪ Switched to emicizumab —Hard to distinguish *arthropathy pain* from *bleed in arthropathic joint* —Most patients do not want to come in for evaluation —Cost aspects of regular FVIII infusion next to emicizumab prophylaxis ▪ Re-building trust in relationship ▪ Trying to get in better shape/preparing for knee arthroplasty —Working hard in rehabilitation is crucial for good functional results after arthroplasty ▪ How suitable would he be for gene therapy (when/if reimbursed in the Netherlands)?	So, essentially, well, that was a sort of strange first contact. I guess, strange first contact again. And what we've now done, we quite recently switched him to emicizumab. And one of the constant hard parts in having someone on emicizumab with arthropathy is: how does a patient distinguish between arthropathy pain and bleed in an arthropathic joint? Well, you have to realize that most patients with severe hemophilia A do not want to come in for a more proper objective evaluation—whether or not this really is a joint bleed or arthropathic pain. And if they start, well, bolusing breakthrough bleeds, then costs in general, next to already quite-expensive emicizumab prophylaxis, start to rise. And as a treater, well, you get the feeling that you lose control. So, I think the goal right now is to rebuild the trust in the patient relationship. I think, over the past couple of years, it's really partly been damaged. And I think part of him not coming into clinic was sort of that he gave up on treatment and partly on us as a hospital. We are trying to prep him to get in better shape for a knee arthroplasty, and we really are very sure that he should. We want to see some efforts from himself because we really know that the functional result in a knee arthroplasty is really dependent on the work and how well you work in the rehab immediately following the arthroplasty. And, sometimes, we take the preoperative phase as sort of a test case to see if a patient will be doing the rehabs postoperatively. And, of course, that last question, it fell out of the sky for me, more or less. But how suitable would he be for gene therapy when and if that would be reimbursed in the Netherlands? And what would be the steps we should consider before we think he is ready for gene therapy, if we can call it that?

23.		And I guess, [there are] many aspects to discuss in this one. But maybe, I guess, Guy, starting with the latter one, what would you think would be the steps if this were a gene therapy candidate and gene therapy in the Netherlands would be reimbursed? What would be your advice to me on how to counsel this patient, and when would you get the feeling that he knows what he is choosing? *[Guy Young, MD]* Yeah, I think you put it well in your slide, which is trust building. And I think that when it comes to gene therapy, there's no other treatment we have in hemophilia, in which case I think that the trust is so critical. And the reason I say that is because, you know, we need to trust that the patient, post–gene therapy, will follow through in the manner in which it is required, which is with the weekly laboratory testing and the potential for going on steroids. The other part of the trust, though, is for them to understand what are the potential outcomes because we know that while most of the patients have responded, and, you know, the data from the hemophilia gene therapy of valoctocogene roxaparvovec show that at 3 years, about 90% of the patients have remained off of prophylaxis, most of them not bleeding and obviously not needing to do any infusions. But at the same time, that means about 10% to 12% have returned to prophylaxis. And that number does seem to be increasing year after year. There are a few more who end up needing to go back on prophylaxis. So, the other part of the trust is that we need to make sure they understand all the possible outcomes so that, you know, they don't have, I guess, what we call buyer's remorse later, where they say to you, well, “If I knew this wasn't going to work,” or “If I knew I had to go back on prophylaxis, I wouldn't have done it.” So I

		think, yes, it's a situation where we really need to explain in great detail and make sure that the patient understands, you know, what are the possible outcomes, what's required after the gene therapy, the fact that most patients in the trial did need to go on steroids, and those have their own side effects. So in a patient like this, I think I would probably take many months to counsel them, talk to them, get to know them, understand them, and then for them to also get to know me—that's obviously part of the trust-building relationship—before I proceed with gene therapy. As opposed to a patient who, you know, was a model patient, who maybe I've known for 10 or 15 years, where I think we already have that type of relationship. But having said all of that, I think really any patient who's an adult who potentially would be eligible for gene therapy, should have the opportunity to have that discussion. And if they really want the gene therapy, and they meet all the other criteria, then they should have the opportunity to receive it. But we need to make sure that they know all those things I mentioned earlier in terms of outcomes and follow-up. *[Michiel Coppens, MD, PhD]* Yeah, I guess it has some ideal aspects, in the sense that if it really works, it brings up the factor activity to a level—well, even the nonhemophilic level. But again, I think we have seen some diminishing of the effect over time, especially in the hemophilia A registered gene therapy right now.

24.		If we take another look at the other aspect of this case. Well, it's hard for me on a daily basis with some patients who already have pronounced arthropathy, how do you manage patients who report or have a lot of bleeds in joints that we know have significant arthropathy, do not really want to come in, just want to inject factor VIII and be done with it as they have done in the past? And at some point, you're having prophylaxis with factor VIII and emicizumab more or less next to each other. And then there comes, of course, the cost point where, well, this can't go on perpetually. So, how do you work with such patients with serious arthropathy, where the distinguishment between bleeds and arthropathic pain is next to impossible? *[Guy Young, MD]* Yeah, those are really challenging cases. I think first is, you know, maximizing the prophylaxis to the extent possible and whatever that option would be, which is either, you know, a standard or extended half-life factor VIII or efanesoctocog alfa, as we've discussed in another case, or emicizumab. I think they all could work for trying to maximize the prophylaxis. And I think it's really just having that conversation and doing what we need to, or doing what we can to convince a patient to really be diligent about their prophylaxis. And perhaps aiming for even somewhat higher trough levels, whether that's with an extended half-life factor VIII or efanesoctocog alfa. I think that's all we can do, you know, sort of medically to address the hemophilia, to try to minimize bleeding, or to feel comfortable that when pains come up, that it's probably not a bleed. Then the other side is managing the arthropathy itself. You know, we do use anti-inflammatory drugs, you know, ones that don't affect platelet function, so the ones

		that are COX-2 or selective COX-2 inhibitors. We seem to like meloxicam; it does seem to work quite well. We have, in the past, used celecoxib, although we find that meloxicam seems to work better for patients, at least that's what they tell us. And then, I mean, long term, he probably is going to need a knee arthroplasty. And for a young man like this, I guess the balance is, you know, how soon do you do it to relieve him of the pain that he's having secondary to it, versus, how many knee arthroplasties might he need if you do one when he's 30 years old? How long will they last? And that's a discussion to have with orthopedic surgeons. I understand that technology, of course, like in hemophilia, also keeps improving for these prosthetics. And perhaps, historically, we thought, well, they last 10 or 15 years. I mean, maybe they can last longer, but it is a fine balance. And I think, thinking about the patient's quality of life, we have to take that into consideration and then make a shared decision like we do with everything else. *[Michiel Coppens, MD, PhD]* Well, thank you very much, and this is quite helpful because tomorrow I will actually have a video consultation with him to discuss some of these aspects. So, thank you for your opinion there. And I think this is actually a nice wrap-up of our cases, and this case in particular.
25.		*[Guy Young, MD]* So, that wraps up our 3 cases. You saw a pediatric case, an older adult case, and a young adult case. These are all real cases. These are all real situations that come up in our practice on a routine basis.

26.	**Conclusions** ▪ The growing range of treatment options for hemophilia A has increased the complexity of treatment selection, but also presents an opportunity for more personalized therapy tailored to patients' disease status, lifestyle, adherence, and treatment goals ▪ Tailoring therapy to patients' unique needs and preferences necessitates a collaborative, shared decision-making approach, wherein the benefits and drawbacks of each treatment option are thoroughly understood and applied to individual patient circumstances	And I think as we have more and more options in hemophilia A from standard half-life factor VIIIs, extended half-life factor VIIIs, now efanesoctocog alfa, emicizumab gene therapy, and coming in the not-too-distant future will be additional options as well, some of which have really new mechanisms of action. I think it's going to become much more complicated to decide which patient should receive what treatment, but this also allows us the opportunity to really individualize things. And you saw 3 very, very different cases. And I think the opportunity to provide each patient with a tailored, individualized type of therapy based on their current disease status, based on their activities, their goals for life, based on even their adherence and their sort of mental approach to their hemophilia will hopefully allow us to pick the best treatment for each patient. And, you know, subject to their availability in all the different countries in the world, hopefully we will have those options. And again, allowing us to really tailor things based on patients' desires and for us to make decisions together does require a shared decision-making approach, understanding the pros and cons of each treatment and how they'd be applied to each patient. So, thank you. And hopefully there was something for you to learn from all those cases.