Evercore ISI 2017 Biopharma Catalyst/Deep Dive Conference - Glaxo Smith Kline

November 30, 2017
10:15 AM ET

Umer Raffatt: We have the management team from ViiV business at Glaxo Smith Kline here to talk about HIV in as much detail as you'd like. I know there's a bunch of people on the webcast too that were very interested. So thanks for joining us, really looking forward to this discussion. Maybe just to kick things off, perhaps some brief opening comments as well as introduce yourselves and we'll dig right into it.

David Redfern: Thanks, Umer, and thanks for the opportunity to be here. It's a great pleasure. I'm David Redfern. I have two hats actually. I'm the Chairman of ViiV Healthcare, and have been pretty much since its creation in 2010/2011, and I'm also the Chief Strategy Officer of GSK. I'm joined by Deborah who is the CEO of ViiV and Dr. Kim Smith who is Head of Clinical Development at ViiV and really the architect behind driving the pipeline forward. I would say we're very pleased with the progress. Tremendous momentum in the business including this year. Obviously that's driven principally off dolutegravir. We're up to about 34,000 scripts a week here in the US now and very pleased with the momentum. Of course, the competitive intensity increases next year with our friends at Gilead potentially launching another integrase, and I'm sure we're going to talk about that. But we have our dual therapy regimens that Kim has been a big part of and we're very pleased with the first of those with Juluca, dolutegravir/rilpivirine, was approved last week. And I think that is a milestone. Indeed, the FDA press release said that's an important milestone for HIV patients to introduce the first and we've got a whole program behind that. So I'm sure we're going to get into more detail around all of that, but we're in a good place.

Umer Raffatt: That's fantastic. So maybe since you mentioned Juluca, maybe just to kick things off from there, your -- so for those of you in the room, this is the first dual approved, this is dolutegravir plus rilpivirine. Very curious to get your thoughts on who you think is the right eligible patient for Juluca. Where would you like to target it?

David Redfern: Deborah, why don't you take that?

Deborah Waterhouse: So the patient that we're targeting is pretty much in line with the clinical studies, so the SWORD data that we published as the pivotal study that got us the registration. So Juluca is for experienced patients that are virologically suppressed. And patients who are going to be on their HIV meds for a long period of time and who are looking to reduce the number of medicines that they take on a daily basis. So we've got a very clear profile of the patient that we're looking at and it's very much in line with the profile of the patient in the SWORD data.

Umer Raffatt: Got it. So generally speaking, the positioning versus TIVICAY and TRIUMEQ would be this is on the more experienced side, those are on the more naive side?

Deborah Waterhouse: So TRIUMEQ is licensed for both naive and experienced patients. TIVICAY is actually the same, so we have very broad labels. But as we look at HIV patients who are now in the main infected between the ages of 15 and 23 and will actually live until they are 70 and 80 with the virus, you need a very clear pathway of medicines that you can take throughout your life, which are not just efficacious and suppress their virus, but actually offer you long term safety and obviously have limited drug interactions. So for us, this two-drug regimen opportunity is another way in which experienced patients to begin with can kind of add an option to their lifetime of treatment.

Kim Smith: Just to add to that a little bit, when we talk about experienced patients for Juluca, we're talking about patients who are currently on therapy and suppressed. They may be on 4 drugs, they may be on 3 drugs, but the goal of switching to a Juluca regimen would be to limit the exposure to drugs that they may not need to maintain suppression. So our philosophy being that we want patients to be on the least amount of drug that they need in order to maintain virus suppression. And so the FDA press release on this actually was somewhat remarkable to us in that this was a real surprising level of endorsement from the FDA. They often are fairly benign in their comments, but they actually did talk about this as being a milestone and a way of reducing toxicities and adverse events for patients and that's exactly the way we see it.

Umer Raffatt: Excellent. So maybe digging into your upcoming data from the Gemini studies, there's so much investor interest in it, both from a GSK perspective as well as from a Gilead perspective. So this would be for the dual of dolutegravir plus 3TC alone, just those two. So maybe just to kick things off, when should we expect the data? Where do we stand? And I'll start to dig into the trial a little bit more.

Kim Smith: So first half of 2018 is when we'll see the data, that will be the 48-week data.

Umer Raffatt: Got it. And how important is the 96-week data for this, especially as you think about regulatory filing? Do you need 96-week data for filing?

Kim Smith: So we'll file with 48-week data in the United States and so the 96-week data will not factor in, that will be another year later. So the 48-week data we'll see in the first half of 2018 and that will be the basis of the filing.

Umer Raffatt: Got it. And I should know this -- was Juluca based on SWORD studies filed on 48-week data as well?

Kim Smith: Yes, it was.

David Redfern: Mainly all of our pivotal studies are being 48-weeks and then you run forward another year. That's pretty standard.

Umer Raffatt: Okay, got it. Then based on prior experience, how do you think about emergence of one-off cases of possible resistance mutation in the week 48 to 96 period versus in the first-year period? How does that usually shake out?

Kim Smith: So usually if there are individuals with virologic failure, they would happen early on, within that first 48-week period. The later individuals who would have a snapshot failure

or a failure, are usually people that go off the medications or lost to follow-up or something like that. It's usually not a virologic failure, it's a nonadherence or a change in their lifestyle and their need to move off of the regimen. And so if there are virologic failures, you would typically want to see that in the first 48 weeks.

Umer Raffatt: Got it. Which takes me to my next point which is one of the questions that comes up in conversations with sort of clinicians as well as your competitor also, has been that in real world setting where people often miss doses, how should we think about the emergence of resistance profile, especially when you're in a two-drug regimen and not -- so it's dolu plus one nuke, not dolu plus two nukes. So how do you think about that in a real world adherence setting?

Kim Smith: Sure. Well I think at first it's important to recognize that with our two-drug regimen, we are basically attacking two targets. So the integrase and the reverse transcriptase. With a three-drug regimen, we're attacking two targets, it's just that the reverse transcriptase is being attacked with two drugs as opposed to one. And so is there a greater likelihood of resistance in a two-drug regimen versus a three-drug regimen? Well that's exactly what the studies will determine for us. We don't believe that there will be on the basis of the fact that dolutegravir has a very high barrier to resistance and that it has been very effective in the studies thus far of two-drug regimens. And there are other examples of two-drug regimens using boosted protease inhibitors plus 3TC where there was no difference in the emergence of resistance. And so with protease inhibitors also being recognized as having a high barrier to resistance. And so there was a lot of attention around the case that happened in the ACG5353 study. I was very involved in that study and I can tell you that that's a unique case in a number of reasons because that case, that individual really had not just a missed dose or two, this person had really remarkably chaotic adherence pattern. And that study was designed as an unusually deep dive study in that we allowed the ability to go back and look at timepoints well earlier to try to see if there was any chance we could find resistance. And what we did find was actually a mixture mutation that actually is likely to have little to no consequence to dolutegravir at all. So although it got a lot of attention, in reality I think the impact is really much less to the patient than one might think.

David Redfern: So for us, this brings out the sort of big picture. Because obviously what everyone is trying to figure out is ultimately what is the potential of dual regimens. And I think it's worth saying, if you go back 5 years, there would have been tremendous skepticism from the community, from physicians, from regulators, from patients around the use of dual therapies particularly here in the US. Triple regimens, 3.5 regimens, very, very strongly established. But I think since then, doctors and patients have seen the power of dolutegravir. We have now over 500,000 patients globally on dolutegravir. We've built up a tremendous amount of real world evidence that has obviously accompanied the very broad range of pivotal clinical trials. We have 5 superiority studies. So that really led to the possibility that it's worth exploring given the power and efficacy of dolutegravir, but also the very high resistance barrier of dual therapies. Because a lot of, most HIV patients are newly diagnosed in their late teens, early 20s, so they live potentially multiple, multiple decades now. And I think the skepticism was high to begin with. We did the studies conservatively. We started in the easiest patients, those virally suppressed which is what dolutegravir/rilpivirine is. Obviously had a fantastic result in that. That's been endorsed in the guidelines, endorsed by the FDA, as Kim says.

I think we've moved the skepticism a long way and a really long way. But the question about resistance and so forth is still out here. I think what is absolutely pivotal will be the Gemini dolutegravir/rilpivirine studies that read out as we just said, in the first half of

next year. Because they are being studied in naive patients and at a wide variation of viral loads, up to 500 copies/L. And I think those are patients who the virus is replicating in, and if we can show very strong efficacy, but also no resistance in those more difficult virally replicating patients, then I think we will go a very long way to slaying the resistance question. And obviously that will be added to with real data over time. So we're not declaring absolute victory on this, but we've come a long way. There is real momentum in the community as the guidelines have borne out, and we feel in a good place. But more data to generate.

Umer Raffatt: So maybe that's a nice segue into the trial itself, the Gemini studies. And the way it was worded on including criteria for this trial was it was supposed to enroll patients with under 100,000 copies/mL and as evidence developed in some of these other investigator sponsored studies, like one of the ones you mentioned, it would have been expanded to patients with up to 500,000 copies/mL. So when was that change made? Was the initial enrollment only under 100,000 and you guys -- I just wanted to understand that dynamic.

Kim Smith: That's exactly right. Originally we wanted to get more assurance in the efficacy above 100,000 and we got that from the 5353 study, the FDA got that from the 5353 study. And so early on, actually we had enrolled roughly, of the 1,400 patients that enrolled in the study overall, we had enrolled roughly 300 before we got the okay to expand to individuals above 100,000. And so of those 1,400 patients enrolled, 21% of those individuals are above 100,000. Which is pretty typical actually of Phase III studies of naive patients nowadays. If you look for example at the bictegravir Phase III studies, they had 16% and 19% and they had no caps on the viral load. So we actually enrolled very well in the high viral load groups and so will certainly be a good indicator of how effective we can be. Also importantly, 5353, even though it was a pilot study, a third of the individuals in that study had viral loads above 100,000 and there was no difference in the primary outcome between the individuals who were above 100,000 and those who were below. So that again was very reassuring to us, and very reassuring to the field.

Umer Raffatt: Got it. Kim, from your experience, what percentage of patients in real world are above 500,000?

Kim Smith: From our dolutegravir Phase III program, there was roughly 6% of the population was above 500,000, so not very large. And those were done in the 2010 to 2012 period was when they were enrolled. And so nowadays, because we're treating people earlier even than we did then, if anything, that number has shrunk. And those also were global studies. And so if we focused just on the United States, that number is probably even smaller than 6%.

Umer Raffatt: Got it. Just to close the loop on this dolu plus 3TC, you mentioned several times the ACTG5353 study. There were also other investigator sponsored studies of the same dual regimen, including LAMIDOL, there was the ASPIRE trial, as well as PADDLE. Can you just refresh for us what we know coming out of those studies? Did a resistance to integrase emerge in any of those?

Kim Smith: So no, in none of those others. So the only case it has occurred was a case that was in 5353. And as I mentioned, that was pretty unique situation. And so the PADDLE study was really the beginning of dolutegravir 3TC. It was a very small pilot study over 20 patients. We did, because we were pursuing this in really a very responsible and sort of step wise fashion, we limited that enrollment. We did this in collaboration with an investigator in Argentina and limited it up to individuals with baseline viral loads of 100,000. It was remarkable that really nearly the entire population was undetectable by

week 4. And so it was impressive to us and impressive to everyone, and that really triggered the excitement to go into the next one which was 5353 and treat the naive patients and expand the entry criteria up to 500,000. So those are the naive studies. The LAMIDOL study and the ASPIRE study were switch studies. And so those studies basically looked at individuals similar to what we did with SWORD, but they took individuals who were basically on different treatments and switched them to a D3 regimen. And they were able to maintain suppression in those individuals and there have been no individuals who have -- one, there have been very few failures at all, and when they did fail it was clearly due to nonadherence. And there's been absolutely no evidence of resistance in those individuals that have counted.

Umer Raffatt: Got it. And just to be clear, Kim, and this is my lack of understanding, LAMIDOL has not been presented, to my knowledge. Has it?

Kim Smith: No, it has been presented. This past year.

Umer Raffatt: Okay, great. Now taking this and moving one step forward, maybe this is a question for all of you. So by 2021, a lot of nukes will be unencumbered. So in theory, you could take this dual regimen of dolu plus 3TC and potentially add a nuke of your choice as well which may not be Abacavir at that point. So my question is, is that something of consideration for you? Or is that something you're not considering at all? A dual regimen effectively.

David Redfern: Well no, I think our whole emphasis is to get to dual regimens without nukes. But maybe you want to comment.

Deborah Waterhouse: So I think if you look at our pipeline, we start with dolutegravir/rilpivirine. We then move into dolutegravir/3TC. We hope that the Gemini data, then the switch study, Tango, that we're looking to start, will actually really convince the external world that two-drug regimens are a very appropriate part of the treatment armamentarium. We then move into long acting two-drug regimens. So we've got cabotegravir plus rilpivirine as kind of the first product that we will bring to market which we hope will end up as an 8 weekly injectable, because we are absolutely committed to the approach of our 2DR pipeline. And then we have a pipeline further on than that with other assets within it. So we don't see ourselves moving back to three-drug regimen. We have TRIUMEQ which is an excellent three-drug regimen, so if that's necessary, then that's an option that physicians can use. We've also chosen to have TIVICAY, so dolutegravir as a standalone is TIVICAY. We know that Gilead have said they're just going to have their bictegravir integrate in a sort of single tablet regimen. So again, the flexibility is there with three drugs with TRIUMEQ, single drug with TIVICAY and then two drugs with our pipeline of two drugs. So you've pretty much got every option you could want within our portfolio. And then of course we've got the attachment inhibitor which is our kind of salvage medicine that we're bringing to market, again, late 2019, so strong data there and another option in our portfolio. All we do is HIV, that's our commitment and we're very much focused to bringing the best patients, treatment for patients at a global level.

Kim Smith: We're committed to being innovative. There's nothing innovative about sticking with three-drug regimens. What dolutegravir, because of its potency and its high barrier to resistance allows us to do, is look at how effective two-drug regimens can be. And obviously Juluca has been the first step in demonstrating that it can be very effective. I think that it's important to recognize that we are doing this in response to the demand in the community. And so this is a demand from providers. Many of these pilot studies that you mentioned, were investigators who came to us and said, dolutegravir can be the core

agent of a two-drug regimen, let's do some studies to verify that. And so they came to us really, I can't tell you how many of them came to us with a desire to do these studies. Again, in that we took a cautious approach, step by step, but the more we've done, the more convinced that we have been by how effective it can be. And patients are demanding this because again, patients are concerned about taking medicines, as David pointed out, for 30 or 40 years. They want to have the least amount of medicines that they need to keep their viruses suppressed. And so that is what we are offering to them.

Umer Raffatt: Taking this discussion forward now, as we think of the future, one of the questions that's come up quite a bit, and perhaps more so among Gilead investors than even GSK investors I would argue, has been is GSK, as one of the two big players in the HIV market, is GSK going to disrupt the pricing in HIV? And the idea is along the lines of how a standalone integrase inhibitor like Dolutegravir or Bictegravir or Stribild, they all cost about just under $20,000, a standalone integrase inhibitor. And as a result of that, if it's -- and on the flip side, an integrase inhibitor combo pill with two generic nukes or with two brand new nukes, what have you, is something like $30,000 to $33,000. So when a GSK version of dolu plus 3TC comes in, will the price be low 20s? And if that's the case, it's a meaningful step down from where for example TRIUMEQ is priced for example. So curious to get your thoughts there. That certainly didn't happen with the dual on Juluca.

David Redfern: Yeah, well you won't be surprised we're not going to get into pricing of D3 which is kind of 6, 9 months away at least and probably depends on the data as well I think. But why don't Deborah, you talk about the general dynamics in the market? Because I think there is some very specific things around HIV dynamics from a payor perspective here in the US. And it's very different US to Europe actually I think, that's a different scenario. It's relatively stable because there's been real innovation and I think we've all got to appoint a pay point, a pricing point that society and the payors think is reasonable value. So that is why it is relatively stable for SDR. One tablet a day to live a normal life span. Why don't you comment more specifically?

Deborah Waterhouse: There's two kinds of things in the pricing area that it would be good to comment on. So first of all, the question comes up, will generics come in and disrupt the market in the US? The answer is, US is a very innovative focused market. You've got very strong patient advocates and you've actually got quite a litigious society I guess all around. So as a result, the thought of people stepping back from the most innovative guideline recommended medicines today that are available, to a tenofovir based regimen or an efavirenz based regimen which might offer a generic in the US, I don't think that's going to happen. I think people are going to move forward and demand the best medicines for their lifetime that they want to suppress their virus. So if you then go to, okay, so what impact could the duals have? We priced rilpivirine and dolutegravir at the sum of the parts as you know. In the US, in my experience having worked here for the last kind of number of years, the system is relatively kind of opaque in the commercial payor space where if you have a cheaper WAC price it doesn't actually deliver you volume. In Europe it's different. So in Europe, you will find that price drives volume. But in the US that's not always the case. For us we will price very sensibly as we always do. We're not going to discuss dolutegravir 3TC today, but at the moment, a lower WAC does not in the US, in multiple therapy areas, deliver you volume. It's about payor access at a macro level. For us, it's about where we are in Medicaid and Ryan White as well, because the government pays for 60% of HIV patient treatment in the US. And then it's about what the access looks like and what physicians want to prescribe for those patients.

David Redfern: But just to finish, Europe is very different. It's much -- STRs, single tablet regimens, is

much less established. Much more pill splitting. So the individual pill is being prescribed separately. And therefore, (inaudible) of course is a complex market, it trends much more to the sum of the parts of the individual components.

Umer Raffatt: Perhaps let's drill down. There's 3 things that you guys just brought up. US pricing dynamic is stable currently, one. Ryan White --

David Redfern: Relatively stable.

Umer Raffatt: Relatively stable. 60% of US prescriptions paid for by the government, 2, in HIV. And 3, the Europe dynamic which is different. How does each of those 3 dynamics evolve when a truly generic Atripla is in the market? And granted that's not an integrase inhibitor, but how do you think -- because that is a meaningful volume single tablet regimen. How do you think that evolves?

Deborah Waterhouse: In the US?

Umer Raffatt: Yeah. So like the stable dynamic, the Ryan White element, as well as Europe.

Deborah Waterhouse: So I think that in the US, patients believe that they are entitled to the best possible treatment and physicians believe that they should prescribe the best possible treatment for the patient that's in front of them. And the market has moved on from Atripla as you can see by the numbers of prescriptions today and the erosion or Atripla over time as people have moved into Stribild, Genvoya, TRIUMEQ, whatever they've moved onto. So I don't see a situation in the US where people would move back.

David Redfern: It's not in the guideline, so you'd be prescribing outside the guidelines.

Deborah Waterhouse: Yes. It doesn't seem like it's --

Umer Raffatt: So moving an integrase inhibitor patient back to non-nuke, that's not in guidelines. And what about -- but incidence population is not meaningful, correct? It's really about the prevalent population in this market?

Deborah Waterhouse: So I think in this market the characteristic is that physicians, and you are a physician, so actually maybe we can ask you to comment, that physicians will prescribe what is best for the patient in front of them regardless of whether they are a Ryan White, Medicaid, or commercial insured patient. And that is the way that this market place operates and that's the way physicians operate. And I don't see them stepping back to older regimens that aren't guideline recommended.

Kim Smith: 100% agree. And there is an incident market in there. There [are] 40,000 new cases in the United States every year. The biggest market are individuals that are already on treatment. They could be a switch market, but certainly there is an incidence market. But the notion that individuals would start on Atripla nowadays is pretty much unacceptable. I mean there's an obvious aggressive advocacy community in the United States and the acceptability of going back to older regimens that have been proven inferior in clinical trials. And so we went head to head versus Atripla with dolutegravir with TRIUMEQ and we showed ourselves to be superior. This is the first time ever that that was accomplished, but that has basically pushed Atripla off of the guideline recommendation. And so it is, it's not likely that things would move in a direction to bring those generics to being the primary things that would be prescribed to patients.

Umer Raffatt: Kim, if I may, one of the points investors, as they debate the HIV dynamic going forward, one of the points investors bring up is, and I'm paraphrasing what investors say, is that HIV guidelines are effectively written by Gilead and ViiV. How do you respond to that?

Kim Smith: Wouldn't that be nice?

David Redfern: I wish.

Kim Smith: You know, they're written -- to the degree that they are written with our influence is because of the trials that we do. So the guidelines are data driven. And so the fact that dolutegravir/rilpivirine made it into the guidelines is because we had a very large, fully powered study that was effective at demonstrating that dolutegravir/rilpivirine is effective in the environment that we placed it in the trial. And so when studies are demonstrating that, particularly in our earlier studies where we demonstrated, as David said, superiority over and over, yes it did influence the guidelines tremendously. Because studies showing superiority in HIV treatment actually are not common anymore. A lot of the regimens are quite similar to each other. So dolutegravir really set a new bar of efficacy that everyone is now trying to meet. And so to the degree we've influenced it, is because we've done tremendous amount of important clinical trial work.

Umer Raffatt: Got it. And would you guys generally agree, based on all the clinicians you guys talk to, including yourself, that HIV docs really follow the guidelines?

Kim Smith: HIV docs do follow the guidelines. They pay close attention to the guidelines. And certainly they aren't going outside -- so the guidelines give you a broad range of preferred regimens. They are all integrase inhibitors now, but they give you choices. And so basically people make a choice among the preferred regimens based upon what they think is best for the patient that's in front of them. They are also driven by the data that's presented. And so we do a good job of taking our data out into the field so people not only look at the guidelines, but they see the data and understand what is the basis of the guidelines. So I do think HIV providers do pay attention very closely to the guidelines.

Umer Raffatt: Got it. And just to close the loop on this broader topic on price --

David Redfern: Way more than respiratory, but that's a whole other story.

Umer Raffatt: We'll save that for another day. Just to close the loop on the broader pricing topic, so if integrase inhibitors clearly have been gaining volumes, non-nukes losing in volumes broadly speaking and that trend may likely continue. With that said, do you expect any change in gross to net? Perhaps this is one for you, Deborah. Do you expect change in gross to net when a generic Atripla is out there in the market?

Deborah Waterhouse: I think we are always under pressure from a price perspective and we respond accordingly market by market. In Europe, the price pressure is different and more aggressive than in the US and we respond market by market. In the US we believe there is some price pressure, but in HIV it still remains a therapy area where the individual choice that a physician makes has to be matched with the requirements of the patient. So having just been managing respiratory in the US for the last few years, you could as a payor choose to put one (inaudible) against another and say I'm only going to have one, pharmaceutical companies, how much discount will you give me? HIV is very different. There isn't that leverage of we will have one integrase inhibitor or we will have one backbone. Because one patient has got to suppress a virus for now 50, 55 years. And

what you need to do is protect that patient along his or her journey to make sure that they have the least number of resistance mutations and the maximum number of feature options so they get to the end of their life in a natural rather than HIV-driven way. So I do think the commercial payor and overall payor environment in HIV is very different and therefore I think there will be pressure. But in the US, I think it's going to be moderately stable. In Europe it's different because there is a willingness to go back to old therapies to split and then we need to decide how we work in partnership with governments across Europe and the rest of the world to do the best thing for patients.

David Redfern: What I would add Umer, is I think actually the biggest determinant on gross to net is not what's going on in the commercial space which as Deborah says, is pretty stable. It's actually just the overall mix of the channel, of the business through the channels here in the US. Because clearly, there's a very big difference in the discounting between the commercial side and Part D is pretty consistent with that. Medicaid, and then even below Medicaid, you have ADAP, Ryan Whites and so forth. And as patients move around in those channels, if Medicaid was to become bigger, that would obviously impact it. And one of the things we saw actually with Obama Care, whatever you think of Obama Care, one of the benefits definitely was in HIV. We did see some trade up from ADAP into Medicaid and it looks like nothing is happening to Obama Care right now, with the Affordable Care Act, but if you saw that reversed, you'd probably see that trade back down again at the margin. So I don't think we see a lot of gross to net change in the short term, but it's really around the channel mix which we obviously can't tightly control.

Umer Raffatt: Got it. And just a quick plug, speaking of respiratory, we're hosting Mylan later this afternoon to discuss their Advair program. So speaking of other --

David Redfern: Which has been the case for the last 9 years. When is Advair going to go generic. So they will know.

Umer Raffatt: Just briefly touching on competition, I want to come back to some of your long acting programs and your potential cure regimens as well. But speaking of competition, it seems to me as also a Merck analyst that Merck is allocating significant resources in HIV. And when I look at their portfolio, they start to scream out as probably the third emerging competitor post 2020 timeframe. And I notice they now have at least two if not three nukes in the clinic, a potential integrase inhibitor and then their lead right now is a non-nuke. A question for the panel I guess, how do you think about Merck's positioning in this market? How would that impact or not impact? And could that disrupt the pricing dynamic? Because I've seen Hep-C pricing dynamic change so fast, so I always wonder, when there's a third entrant, how does that change or not change?

Deborah Waterhouse: I'll make a macro comment and then I'll had to Kim. So for me, I am very positive about there being a number of players in the HIV space. I think if a single company were to dominant HIV, that would be a sad thing for patients actually. Because what you want is a dynamic market where innovation thrives and we offer at a global level the opportunity for people living with HIV to live a long and full life. So I'm happy for the generic companies to be involved, I'm very happy for Merck and Janssen and Gilead. I think that's a very good outcome for patients. So I'm delighted to see Merck actually stepping back into the HIV space. I think they've got some good products in their portfolio. And as we partnered with Janssen on rilpivirine, we're always open to conversations with all companies about partnership opportunities as well as kind of being competitors at the same time. So I think this is a market where we all need to just focus on what's best for the patient and Merck having a strong pipeline is really good for patients. Now what's in that pipeline, obviously they've got a number of assets, particularly the long acting EFDA

which has got quite a lot of external commentary. They've got nukes, they've got a number of different programs and we hope that those programs thrive and do well.

Kim Smith: Yeah, I think we'll see where they go. What we've seen so far with doravirine is that as you know it was compared to efavirenz and it showed itself to be non-inferior to efavirenz, so we've just talked about the fact that Atripla is sort of on the downswing. So when you're comparing yourself to something that's the downswing, it makes it hard, and you aren't even differentiated from that very significantly, it makes it sort of hard to have a big impact on the market. So what will EFDA do in the future, it's still quite early, is a big question. I think there's a lot of interest in the field in long acting which is obviously we are leading in that area. I mean we are in Phase III with cabotegravir and rilpivirine. This is something that is definitely a demand from patients. This is something that patients are asking for. And so we'll see if they are able to contribute an additional long acting agent in the future.

David Redfern: It's some way off though I think, isn't it?

Kim Smith: Quite a ways off, yes. It's very early.

Umer Raffatt: Are you aware of an integrase inhibitor in the clinic for Merck as well?

Kim Smith: Other than raltegravir? No, I'm not.

David Redfern: But it's not impossible. They tend to be quite quiet.

Umer Raffatt: Got it. So speaking of, actually before long acting, is there a question from the audience before we keep proceeding? All right, so let's jump into the long actings then. So specifically, cabotegravir/rilpivirine, it's a program I track, but I'll acknowledge not as closely as perhaps like your Gemini studies or the SWORD studies. So is there two different regiments in the clinic, like a monthly and a quarterly? Can you just catch us up on them as well as what the development track is?

Kim Smith: There are two different regimens that are in the clinic. So there is a monthly and then a two monthly. When we did our Phase II program, we looked at both every 4 weeks and every 8 weeks. And we initially made the decision to move forward with the every 4 week for Phase III because it was very successful in Phase II. But the every 8 week was very successful in Phase II as well. And so then as we saw more data and got out to 96 weeks in the Phase II Study, we were just really knocked over by how great both the every 4 week and the every 8 week did. And so we initiated our Phase III program with an every 4 week and then we have now followed it up with every 8 week. So what we intend is that we will file initially with every 4 week and follow that shortly after with every 8 week dosing, assuming that the studies are successful.

David Redfern: They read out, they're fully recruited, they read out at the backend of next year, at the end of 2018.

Umer Raffatt: So this is going to be the monthly?

Kim Smith: The monthly reads out at the end of next year. The every 8 week has just started enrollment and so we expect that enrollment to finish --

Umer Raffatt: So you'll basically introduce two products in the market?

Kim Smith: Well we would start out with every 4 and then supplement, so you'd basically just expand the label to include every 8-week dosing.

Umer Raffatt: Two quick follow-ups on that. One is, and maybe this is a very basic question for Kim, but can nukes not be converted into long acting?

Kim Smith: There's a lot of investigation and looking at sort of older nukes and see which ones possibly could be. But for the most part, they haven't been successful at being able to convert them into medications that can be dosed as much as every month or every two months. Now EFDA is different and so it says that it is possible. But the older nukes that are out there haven't been able to be successful in converting to that in that way.

Umer Raffatt: Got it. And then perhaps one for you, Deborah. I noticed in antipsychotics market, there was a, despite the market just completely genericizing Invega, Invega Sustenna, Risperdal concept, they've gained really meaningful sales at least, but despite being fairly premium products on price, even premium to the oral branded price as well as -- so A, they were premium and yet they got to a meaningful amount of sales for J&J. So my question to you is, do you think that 5% to 10% penetration is a good proxy for penetration to think about how long actings could do in HIV? And do you think of these as a premium to where the regimens are priced right now on oral basis?

Deborah Waterhouse: So in terms of how we see the HIV market evolving over the next 3 or 4 years, I think you will be able to have quite a personalized approach to treatment, not just based on your resistance profile, but based upon your personal preference. So what do I mean by that? So if you talk to physicians about long acting, they are very enthusiastic about it, but they are concerned with the impact of the shot on the patient. So it's an 8 weekly or 4 weekly shot, not so sure that patients will like that, therefore I'm not sure how significant this medicine will be. If you go out to patients who were in the study, or more broadly the openness and the pull for a 4 and particularly an 8-weekly injection, is significant. Because people want to forget that they are HIV positive and every day, at the exact same time, either with or without meal, you have to take your medication. And you cannot miss one day. It has a massive impact psychologically and physically on the life of a patient. So I think how we should look at HIV moving forward is that it will be tailored to the patient and actually there will be a group of patients, which is quite significant in number, who will absolutely want that long acting once every 8 weeks shot. There will be a group who will want two-drug regimen, and will want an oral very day. There will be a group who will be more appropriate for three drugs or whatever, whatever. So I think I wouldn't use the analogs that you've just used, I would actually look into the marketplace as this is a very patient orientated therapy area, and look at the pull from patients. Back to your original point about we co-create this market almost with the advocacy groups and the patients to see what the demand is, I would look at it from a demand perspective. And I think the demand is going to outstrip what's currently being anticipated by physicians and the external world.

Kim Smith: Yeah, I agree with that 100%. To give a personal anecdote, I actually joined the industry only about 4 years ago and I had been taking care of many patients with HIV. And so when I made the decisions to leave my practice, I had to have this conversation with many patients. And it was sad. Some of them I had taken care of for 20 years. So there were tears, theirs and mine, about me leaving until I told them that I was going to work on a long acting medication. Then they were like, okay, you can go. So there is a tremendous amount of excitement enthusiasm among patients about the idea of a long acting. HIV disease is still tremendously stigmatized. And so as Deborah points out, the psychological impact of sort of the daily reminder is what patients talk to us about all the

time. They don't -- even though it's wonderful that we've gotten down to one pill a day, that's a tremendous accomplishment, just the fact that they have to do that very day, it reminds them that they are living with a very stigmatized disease.

Deborah Waterhouse: And that medication sits in your bathroom cupboard and if you share a house with friends or however you live your life, that shot will never be in your bathroom cupboard. You will not be in any way identifiable through the medicine that you take every day at the same time either with or without food. So that is where that demand is coming from.

Umer Raffatt: Just my last one, and we're up on time as well, cure. Where do we stand? Is there a realistic chance at a cure, something that looks particularly interesting?

David Redfern: So very briefly, lots of exciting science working very hard at it. We have two research groups, we have a great collaboration with the University of North Carolina looking at all different things. Probably more functional care, so taking a course of medicine and then suppressing the virus to a level that maybe it's still in your body, but it's not medically significant. So definitely a big effort towards it, but I think bottom line, quite a long way off.

Umer Raffatt: Is there any data you look forward to over the next 12 months?

David Redfern: No,

Umer Raffatt: Okay. For you or competitors?

David Redfern: On cure?

Umer Raffatt: On cure.

David Redfern: Not that I'm aware of I'm afraid, but we're working hard. Ask us in 5 years.

Umer Raffatt: Sounds great. Okay, good to know. Thank you very much. Thanks again for joining us, this was super helpful. Thank you again.