ViiV Healthcare Investor and Analyst Update

Tuesday, 24 July 2018

Jeff McLaughlin: Good morning and good afternoon, everyone. Thank you for joining us to discuss the results of the GEMINI 1 and GEMINI 2 studies that were presented today at the International Aids Conference in Amsterdam. You should have received our press release and slides that accompany today's call are located on the investor section of GSK website. As you follow along with the slides we will call out the number, moving on to Slide 2 now.

Cautionary Statement Regarding Forward Looking Statements.

Please refer to this slide for the presentation of our cautionary statement. Moving on to slide 3.

Viv Healthcare Investor and Analyst Update

Our speakers today include Chief of Strategy and Chairman in ViiV Healthcare, David Redfern, the Chief Executive Officer of ViiV Healthcare, Deborah Waterhouse, and the Chief Scientific and Medical Office of ViiV Healthcare, Dr John Pottage. Following our presentation, we will open the call to questions and answers where we will also be joined by Dr Kim Smith, Head of Global Research and Medical Strategy. Kim is the senior author of the GEMINI studies and until quite recently was a practicing physician treating people living with HIV. We request that you ask only a maximum of two questions so that everyone has a chance to participate and with that I will hand the call over to David.

David Redfern: Thanks Jeff, and good afternoon and good morning everyone. The main purpose of this call is to take you through the details of the GEMINI results that were presented at the International Aids Conference here in Amsterdam this morning. These Phase 3 readouts of the investigational two-drug regime, of dolutegravir plus the lamivudine in the HIV-naive patient setting are very important to our overall HIV strategy, and we think for the treatment for HIV patients going forward.

I will hand you over to Deborah and John in a moment but all I wanted to say by way of introduction is that we are enormously proud of the outstanding clinical work that has been achieved by ViiV in recent years, and are pleased to be able to continue to innovate around

an outstanding molecule like dolutegravir which has now enabled us to achieve this whole concept of achieving compelling clinical outcomes with fewer drugs.

Whilst there remains a significant unmet medical need in HIV across the both developed and developing world, we at ViiV Healthcare will continue to be 100% focused on HIV and 100% dedicated to continuing to invest in innovation in this space, be it in two-drug regimes, long-acting formulations, the attachment inhibitor, anti-body approaches or our discovery research efforts into finding a cure.

Before I hand you over to Deborah and John I would like to point out that we would like to keep this discussion today focused only on the data that was presented here today at IAC. We will not be commenting on business performance or commercial trends as we are less than 24 hours away from presenting our Q2 financial results and there will be plenty of opportunity tomorrow to discuss those. With that I will hand you over to Deborah.

Deborah Waterhouse: Thank you, David. I am going to start on Slide 5.

ViiV Healthcare is pleased to engage with the broader HIV scientific community here at the International Aids Conference 2018. We are proud of our ambitious mission to leave no person living with HIV behind. HIV is a unique therapy area. Of the 37 million people living with HIV globally, the vast majority continue to live in resource-poor settings where we focus our efforts on ensuring access.

Within a generation, innovative treatments have transformed the quality of life to the point that a person diagnosed at 20 years old today can expect to have the same life expectancy as a person who does not have HIV. Moving to slide 6.

Our strategic focus needs to shift from quantity of life to quality of life. All medicines bring side effects and HIV medicines are no different and when I meet HCPs and patients the message is loud and clear. Ideally, we would love a cure, and actually we are working on that, but in the absence of a cure we would like fewer medicines and fewer side effects and this informs our two-drug regimen strategy. From *Juluca* for virally supressed patients looking to take fewer medicines, to dolutegravir plus 3TC for naïve patients, which John is going to talk more about shortly, to cabotegravir, a potential long-acting injection which brings the promise of being able to supress the virus without the daily reminder of taking pills. Moving to slide 7.

We believe the potential of two drug regimens is significant. As I said before, a person diagnosed with HIV at 20 is likely to live to, let's say, 75, and if that's the case they will take around 60,000 doses of medication for HIV. A highly efficacious and well-tolerated 2DR regimen could reduce that by 20,000 doses: less medicine, less toxicity, fewer drug-drug

interactions. With that, I will hand to John, to walk through the GEMINI data presented today, and move to Slide 8.

The GEMINI 1 & 2 studies

Introduction

John Pottage: Thank you, Deborah. I am now on Slide 9. I would like to acknowledge the excellent presentation of these data this afternoon by Dr Pedro Cahn, who is the lead author of the study. I will share some of the slides for this presentation.

Historically three-drug regimens became the standard of care due to the sequential availability of drugs being added together as they were approved. As the drugs have improved over the last decade, it has become clear there was a strong possibility that two drugs could be sufficient for the long-term treatment of patients, and that raises the question we always ask --- If HIV appeared today, and we had all the medicines available to choose for treatment, what would be the best combination and how many drugs would be needed?

We believe the answer to that is a two-drug regimen, and this is because of the exceptional potency, the safety and the high resistance barrier of dolutegravir. We would view it as making an optimal core agent for this two-drug regimen.

In order to show that, we have evaluated the two-drug regimen of dolutegravir and 3TC versus the three-drug regimen of dolutegravir plus tenofovir and FTC, or Truvada, for the treatment of patients with HIV-1 infection who are naïve to anti-retroviral therapy through 48 weeks.

GEMINI-1 and -2 Phase III Study Design

Moving over to slide 10, the GEMINI Phase III programme consists of two identically-designed studies which are termed GEMINI-1 and GEMINI-2. They were randomised double-blind parallel-group non-inferiority studies. The study was done across the globe, producing a diverse, real world study population. The patients were randomised to either receive the two-drug regimen or the three-drug regimen in a 1:1 fashion. The primary endpoint was at 48 weeks, and measured patients who had undetectable HIV-1 RNA, that is, less than 50 copies per millilitre, by an ITT-E snapshot analysis.

I'll present the data from both the studies, pooled together.

Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

Moving on to slide 11, the patient demographics are listed here. The baseline characteristics were comparable across both treatment groups, the median age was 32, it should be noted that approximately 10% of the patients were older than 50, in fact, the oldest patient was 72.

The GEMINI studies are global and diverse: the gender, race, ethnicity show real world representation of the people affected by HIV across the globe. The median viral load at entry was approximately 25,000 copies, and it should be noted that the inclusion criteria limited patients to a screening viral load of less than 500,000 copies. I'd like to call attention, though, to the fact that 20% of the patients in the study had a viral load greater than 100,000 copies. The median CD4 count at baseline was approximately 430 cells.

Pooled Snapshot Outcomes at Week 48: ITT-E and Per Protocol Populations

Moving on to slide 12, turning to the results themselves, and you can see from this slide that the results are very compelling, reinforcing our confidence in this treatment option for patients. We achieved the primary endpoint of non-inferiority, the pooled analyses support non-inferiority of the two-drug regimen versus the three-drug regimen, at Week 48. 91% of the patients on the two-drug regimen and 93% of the patients on a three-drug regimen were undetectable for less than 50 copies per millilitre of HIV RNA. Today, when you really look at clinical trials being performed, you need to have numbers greater than 90% efficacy rate in order to be considered in the optimal range. We see that we have it with both regimens here.

The Per Protocol analysis is also shown and demonstrates non-inferiority. Note the lower number of patients in the Per Protocol population: this is because those patients who had protocol violations are eliminated from the analysis.

Snapshot Analysis by Visit: Pooled ITT-E Population

Moving over to slide 13, this is the same data but it's presented in a different way.

You will first notice the typical brisk response to therapy between the two and the three-drug regimen, with most patients becoming undetectable by Weeks 8 to 12 – this is quite typical of treatment with integrase inhibitors, and importantly you see the similarity between the two and the three-drug regimens. You will also see the two lines are almost on top of each other, which indicates the similarity of efficacy again between the two and the three-drug regimens. Additionally, the chart on the right shows the CD4 cell recovery rate, and that it is similar between the two regimens: both arms had an approximate 220 cell increase at 48 weeks.

Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis

Moving on to slide 14, on this slide I would like to show you three things, and the first thing I would like to look at is on the far left: the efficacy across the two and three-drug regimens was the same, regardless of low or high viral load. In the next graph, showing the CD4 sub-analysis, the response rate with a baseline CD4 count greater than 200 was the same between the two regimens. In those patients who had a baseline less than 200 cells, 79% of the patients receiving the two-drug regimen were undetectable versus 93% of those receiving the three-drug regimen. This lower response rate is due to the number of patients in the two-drug regime group who discontinued for reasons not related to their treatment. Examples of this, for being withdrawn from the study, would be going to jail, or developing opportunistic infections such as tuberculosis, or Chagas disease.

The chart on the right side shows a pre-planned TRDF analysis: this stands for therapy-related discontinuation equals failure. This analysis accounts for patients who have withdrawn from the study for either treatment failure or treatment-related adverse events. As you can see, the differences between the two regimens across all CD4 counts, as well as all viral loads, are essentially the same.

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

Moving on to Slide 15, in this slide we show the low rate, less than 1%, of virologic withdrawals through Week 48. Importantly, there were no treatment-emergent integrase mutations or major nucleoside mutations and none of these were observed among participants who met the confirmed virologic withdrawal criteria which is defined on the slide.

The overall data regarding emergence of resistance seen thus far for two drug regimens is similar to that for three drug regimens. Clinical trials remain the best predictors of the barrier to resistance of a regimen, and the 48-week outcome is one of the best indicators of subsequent resistance in the real world. Of course, going forward, we will continue to generate additional data, including a comprehensive schedule of real world studies, once the medicine has been approved.

Adverse Events: pooled ITT-E Population

The safety results are consistent with the product labelling – moving on to Slide 16. Drug-related adverse events are less frequent in the patients on the two-drug regimen compared with the three-drug regimen. The percentage of patients withdrawing due to adverse events was approximately 2% across both study arms, and the most common greater than 1% drug-related adverse events across the study was headache.

It should be noted that the study will continue for two more years and we will get a better idea of the differences between the two regimens as the study moves along.

Conclusions

Moving on to Slide 17, in conclusion, the GEMINI studies have demonstrated non-inferior virologic efficacy for the two-drug regimen versus the three-drug regimen at Week 48, which is the primary endpoint.

Both the two and three-drug regimens were associated with low rates of confirmed virologic withdrawals through Week 48, and most importantly, there were no treatment-emergent integrase or nucleoside mutations observed among any of the patients who met CVW criteria.

The overall safety and tolerability profile at Week 48 was comparable between the two regimens and these data support dolutegravir and 3TC as an effective option for the treatment of HIV-1 infections.

Some may raise the question that GEMINI studies are not 'real world' *per se*, and they may not reflect the reality of patients who lead complex or non-adherent lives – I would like to address that. First, the patients were spread out across the world, and their disease characteristics were quite diverse. There were patients who were non-adherent in this study, but despite that, none of the participants who did experience a confirmed virologic withdrawal criteria developed treatment-emergent mutations. We believe this is a good test of how a two-drug regimen will perform.

In terms of next steps, ViiV Healthcare will now plan for regulatory submissions in the United States and Europe for the two-drug combination of dolutegravir and lamivudine in a fixed-dose combination pill later this year.

Highly innovative pipeline

Moving on to Slide 18, I would like to end the presentation with a quick summary of our pipeline. Our two-drug strategy is primarily focused on dolutegravir and 3TC, and then the long-acting cabotegravir.

Important studies ongoing that are planned to start are the TANGO and the SALSA studies which look at dolutegravir and 3TC as a switch option in suppressed patients.

Still to come in 2018, we have data read-outs of the ATLAS and FLAIR studies for cabotegravir and rilpivirine long-acting injectables. These are the Phase III pivotal studies for that combination.

We are also developing drugs including the attachment inhibitor, fostemsavir, for people with limited treatment options, and this emphasises again how we leave no patient behind.

We have other exciting projects coming through the discovery group, including long-acting formulations and medicines with new mechanisms of actions. This clearly supports our commitment to HIV and our continued growth in the business powered by a broad and innovative pipeline.

With that, I'll turn it back to David.

David Redfern: Thanks, John. That concludes our presentation, so operator we would now like to open up for any questions.

Question & Answer Session

Kerry Holford (BNP Paribas): A few questions, please. Firstly, you have shown us a lot of data today, the majority of which is pooled data. Can you just confirm that you also saw statistical non-inferiority for the two-drug regimen in both the individual GEMINI studies?

Secondly, on adverse events, can you say anything in particular on sleep disturbance? I know that has been something that has been seen in certain dolutegravir studies in the past. Anything of note in GEMINI?

And then you also referenced the fact that these studies continue for a further two years. I am wondering whether you might highlight any of these adverse events on the list that you might expect to be more or less evident in the two arms as you move forward in the next couple of years.

Then lastly, I wonder if you could provide more broader updates on the market share position in the USA for dolutegravir in light of the Gilead Biktarvy launch? I wonder if you could comment on the NBRx market share. Thank you.

David Redfern: Thanks, Kerry. On your third question around the market share, I am going to pass on that today but I assure you, you will have plenty of opportunity to discuss that in our Q2 results tomorrow, so we will keep that back for then.

On the individual studies, Pedro Cahn did show the data on that for both of those studies, and today I can confirm that both were very similar, both met statistical non-inferiority, but for the sake of simplicity in this presentation we pooled them but the separate studies we will make available. I am going to ask Dr Kim Smith who is Head of Clinical Development and

also, as Jeff said, the senior author of the study, to talk a little bit about the adverse events and what we saw in each of the arms.

Dr Kimberley Smith: If you go back to slide 16, you would basically see the list of the adverse events that were reported through Week 48, and you can see specifically it asks about insomnia. As you can see in the middle there the rate of insomnia is listed as roughly 4% which is pretty comparable to what we have seen in our other Phase III studies. As you can see here, obviously dolutegravir is included in both arms and so not a surprise that we see similar rates of insomnia in both arms.

The other adverse events that you see here really there were no surprises. These are all obviously very common things, most of them not related to the drugs. I would note that the main difference when we stop the drug related adverse events was mostly GI adverse events being more commonly in the three-drug arm compared to the two-drug arm.

Michael Leuchten(UBS): Two questions please. One, just reading across from the SWORD data at 100 weeks, it appears you had six patients in that trial that had confirmed virological withdrawal at 100 weeks that I think is more than it was at 48. I just wondered how you would frame that as we go into the extension data for the GEMINI trial?

The second question, on the patients with low CD4 count, is there any reason why that particular group would have a lower success rate in the snapshot analysis when you include patients that you would exclude in the TRDF analysis. That is the one chart that stood out in presentation, thank you.

David Redfern: Thank you Michael. Thank you for mentioning the SWORD 100-week data that we also announced and published this morning as well. I am going to ask Kim who is close to obviously SWORD as well as GEMINI to comment on both of those.

Kim Smith: We were actually quite happy to see the persistent durability of the dolutegravir plus rilpivirine combination in the SWORD study after Week 100 with 89% of folks continuing to have undetectable viral loads. As you mentioned, there were a few more confirmed virologic withdrawals at Week 100 compared to Week 48 which is pretty typical. We often see patients that drift out of the study or have challenges with adherence over a longer period of time. I think you mentioned six, there were actually eight, confirmed virologic withdrawals in the study which again we think is a relatively low rate given that there are almost 1000 patients now who have been treated with dolutegravir / rilpivirine, and half of those now for two years.

With regard to your second question about the individuals who had the lower snapshot response in the seat in the less than 200 CD4, it is important to note that individuals that come into a trial with a CD4 cell count that is less than 200 are more advanced so they have a more advanced disease, they actually qualify as having definitively reached AIDS criteria, and so those individuals have more going on in their lives, they are more vulnerable to opportunistic infections, they have other challenges, and so the individuals that discontinued the study were discontinued for reasons that were not related to drug treatment.

There was only one confirmed virologic withdrawal in that group. It is also notable that that group is only roughly 50 patients in one arm and 60 in the other so it's a small group and since it is such a small group relatively to the other group, you see one or two patients actually make the big difference in the percentage. And so, when you think about the things people left the study for, things like tuberculosis and Chagas disease, those are things you see in patients with more advanced disease and so this is not a surprise. It ends up being that you just unfortunately ended up having more in the D3 arm as opposed to in the three-drug arm but again this is not a surprise, and so when you look at the analysis that only looks at individuals who discontinued as a result of treatment related issues, you can see that that difference in the two arms goes away.

John Pottage: Could I just add a comment coming back to the SWORD study, I think it is common and it emphasizes how happy we are with this data. When you look at typical switch studies, I would over time, and we get up to 96 weeks, if you look at some of the Genvoya switch studies, roughly 2% of the patients have virologic failures at that timepoint, so this is really on par with what one would expect at 100 weeks or 96 weeks.

Laura Sutcliffe (Berenberg): Just one question please. Do you expect the clinical use pattern for the dolutegravir/lamivudine regimen specifically to be materially different in the US versus ex-US? For context, I think you have said before some countries in Europe already have a meaningful proportion of patients on a two-drug regimen, although I am not totally clear whether that means they are taking integrase inhibitors or not. Thank you.

Deborah Waterhouse: If we think overall how our portfolio is going play out over the next few years, obviously we have had *Tivicay* and *Triumeq,* we have added *Juluca* to the portfolio, but as I think you know, *Juluca* is a smaller opportunity. We are then adding in dolutegravir 3TC which will be our largest medicine in our portfolio and actually we are hoping we will have a broad label, and will be used broadly, both in the US and Europe. We are not expecting any difference between the populations that that medicine will be used in. Then we have, obviously, cabotegravir/rilpivirine, a smaller population of people who really

struggle to take a tablet every day, because it just reminds them that they are living with HIV. Overall, we have a very clear offering for each patient type, and it's pretty similar across the US and Europe, to be honest with you.

The overall perspective that we have is that when we bring that full portfolio to market, and we obviously add on fostemsavir which is for the highly treatment experienced patient, we will end up with more share than we have today. Exactly how that plays out remains to be seen, because the cabotegravir/rilpivirine data is still to read out, but I guess the key messages would be no difference between Europe and US. We believe D3 will be the biggest medicine in our pipeline that we will bring to market in the next few years, but that overall, we will have a bigger share of the HIV market because we have this very personalised approach to the patient population that is out there.

David Redfern: Thanks, Deborah. All I would add is what John said at the beginning: the GEMINI studies were global studies, we recruited from right around the world - that includes the US, it includes Europe, it includes Asia and Latin America – so these are global studies with patients coming from everywhere, and I think global buy-in, and HIV is a specialist area is very guideline-driven and the guidelines tend to be quite consistent around the world.

It is true in Europe today there are already some 2DR regimes effectively being used through separate tills, so the take-up and the appetite for it in places like Italy - some of that may be fiscally-driven – is already there, but I agree with Deborah, we think this will be a global proposition.

Thanks Laura. Next question, please.

Louise Pearson (Redburn): Hi, thanks for taking my question. You alluded on the call to the fact that you are continuing to collect data on drug resistance, I was just wondering if you are in a position to confirm that there have been no subsequent cases of drug resistance in either of the arms in GEMINI since the 48-week data cut-off has been made? Thank you.

David Redfern: I think we can confirm that, Louise, but I'm going to look at Kim to definitively confirm it.

Kim Smith: That is correct. I would mention that this is late-breaking data, so most of the patients are not that far beyond Week 48, but no, we do not have any cases of resistance that have been identified.

John Pottage: And a key time coming forward will be the 96-week readout, which will occur next year.

David Redfern: Thanks, John.

Graham Parry (Bank of America Merrill Lynch): Thanks for taking my question. Just going back to the less than 200 CD4 cell count group, what might explain the difference between the regimens on the number of patients that you were losing in these arms, given that the randomisation criteria were well matched across the arms?

Secondly, any physician reaction or reception to the data that you could pass on at this stage, and how you might rebut physician scepticism or concern over the resistance development that you did see in a poorly compliant patient at CROI last year. There was one patient, I think, who developed integrase-resistant mutations, and some of the feedback we've had from physicians is, this is a better-controlled study, where patients are more compliant, and they worry about non-compliant patients more.

Then just thirdly, how much of the volume, do you think, of this drug will be cannibalisation of your existing dolutegravir franchise versus gains from other franchises and from competitors? Thank you.

David Redfern: Thanks Graham. I'll get Kim and John to comment on CD4 again, and also the physician feedback.

All I would say is, for sure, HCP engagement here in Amsterdam around this study has been enormous. Individual physicians will clearly make up their own minds on the data, but the level of interest, the level of engagement that we at ViiV and the study investigators have had, Pedro Cahn in particular - we think there were 600/700 physicians around in the presentation this morning - has been enormous, so there is no doubt there is great interest in the data. Kim and John, maybe you can comment on some of the anecdotal feedback you're getting, recognising it was only published at ten o'clock this morning.

Kim Smith: Just to address the less than 200 CD4 group that received dolutegravir/3TC again, we were very specific in the presentation to lay out all of the details of the individuals who were snapshot virologic failures. As I mentioned, there was only one confirmed virologic failure, so that would be the only one that would be considered a treatment-related failure. The rest of the failures were for things that had nothing to do with the fact of what regimen they were on. For example, I mentioned an individual with tuberculosis, an individual with Chagas disease, which is a parasitic infection you see in South America. There were a couple of protocol violations, there were two individuals who were lost to follow-up

during the trial. One individual left the study because he elected to go on hepatitis C treatment, even though his viral load was undetectable at the time that he left the study. Those sort of things, again, are fairly random, and it just is somewhat, as I said, a little unfortunate that they ended up being more in the D3 arm.

Again, I think it's important when you look at the numbers you see that this was the smallest group, less than 9% of the population, so when you have a small group, you see a few of these types of drop-outs that can make it appear that there is a big difference between the arms when in reality, we didn't see any virologic difference between the arms at all.

John Pottage: Just to add the anecdotal reactions to it, I think as clinicians have looked at it and we have had advisory boards but also talk here, I think that people do understand what happened in the study. As Kim explained, the small sample size, and part of it is a little bit of luck of the draw as the patients pan out, and with the load number it really magnifies that difference.

I think that is the importance of doing the other analysis, where you really eliminate that, and you don't see any difference there. I don't detect any big push-back from that at the meeting. Certainly, during Pedro's presentation, during the Q&A, no-one asked any questions about it, so I think the explanation stands for itself.

David Redfern: Thanks, John. Deborah, do you want to comment on how you see the market evolving with dolutegravir/lamivudine?

Deborah Waterhouse: Yes, sure. The way we think about the portfolio of medicines that we have in our hands today and those that we will launch in the future, is that dolutegravir is at the core of many of those medicines, or cabotegravir which is the sister of dolutegravir. Now, if we think about where we started which is *Juluca,* 50% of *Juluca's* business is coming from our own portfolio, 50% is coming from our competitors, so that just shows us that there will be some cannibalisation as we introduce new medicines.

The way we are looking at it at the moment is that we will have a portfolio of medicines that will allow us to meet the individual needs of patients, regardless of whether you want *Tivicay* plus something that's outside our portfolio, whether you want a triple, whether you want a NRTI-sparing regimen which is what *Juluca* is, whether you will want dolutegravir 3TC, a long-acting with cabotegravir / rilpivirine or fostemsavir. So, there will be some cannibalisation within the portfolio, exactly how that looks at the moment is in part a work in progress because we haven't seen the data yet for cabotegravir/rilpivirine, so we are trying to map out where each medicine will get its business from. Some of it will be from our portfolio, some of it will be from our competitors. What we are relatively confident about is that overall,

our share of the HIV market will increase over the period of time that we are launching all of these new medicines.

David Redfern: Thanks, Deborah.

Keyur Parekh (Goldman Sachs): Two questions, please. The first one is, just as we go out to longer term data, can you highlight some of the areas where you might see fewer adverse events for the two-drug regimen compared to the three-drug regimen? For example, looking at Slide 16, it doesn't look like there's a specific area where the two-drug regimen might have less tolerability issues.

Secondly, I believe there were two deaths on the dolutegravir arm, and you were saying they weren't related to the drug, but I am wondering if you have incremental details around those deaths and why they weren't adjudicated to be linked to dolutegravir. Thank you.

David Redfern: Thank, Keyur. I will pass that to Kim, because safety issues over the long term and adverse events will be critical.

Kim Smith: I think there are a couple of points to make. One, we actually started to see again more drug-related adverse events already, even in the first year with just a 6% difference, which is favouring dolutegravir/3TC.

In addition, specifically around some of the areas where we might see a difference are toxicities that are associated with tenofovir, and so we already in this study saw that there were four individuals who discontinued on the three-drug arm due to renal abnormalities and only one on the two-drug regimen. In addition to that, we looked at renal and bone biomarkers, and in each case, we saw statistically significant differences between the two-drug arm and the three-drug arm in both serum and urine renal markers as well as all of the markers of bone turnover. Again, we know that tenofovir is associated with some of these side effects and so this is not surprising that you would see this, but I guess it is somewhat surprising that you see it already in just one year. So, when we are watching individuals over three years, we expect to see those differences continue.

David Redfern: Just on that point – Kim, sorry to interrupt – it is worth saying, Keyur, that the bone and renal data of 48 weeks was presented today by Pedro, so we can make that data available. We haven't shown it in our more simplified form, but we can certainly give you that.

Kim Smith: With regard to the two deaths, both of those happened to be on the two-drug arm. One of them was a cardiac arrest that was associated with substance use,

and the second one was a Burkitt's lymphoma, so neither one of those would be related at all to the treatment.

David Redfern: Thanks, Keyur.

Steve Scala (Cowen): A couple of questions. First, I understand the benefit of taking two drugs versus three, but curious as to what percent of patients would need to switch to a doublet because they can't tolerate a triplet. Secondly, were there any cases of neural tube defects seen in the trial? Thank you.

John Pottage: I will start with the neural tube defects. No, was the answer to your question of that being seen in the trial.

Just to comment on the neural tube defects, certainly we take any safety signal quite seriously at ViiV but the findings from the Botswana cohort which you are referring to, are really preliminary and interim findings. At present there is really no current evidence for a causal relationship between dolutegravir and neural tube defects. The pre-clinical studies have not shown a signal and there have been no other clusters that have been reported around the world. Right now, we are really conducting a full assessment of the signal and acting though with an abundance of caution, we fully informed the HIV treatment community and have been working with regulators, public health authorities, governmental organisations and academicians around the world to make sure everyone has the most up-to-date information. Certainly, there is a lot of discussion on that at this meeting and I think this is obviously a developing topic but as I said these are all preliminary findings and so it is always important to be cautious with that.

I will turn it back to Kim or Deborah.

Deborah Waterhouse: For your other question Steve, we have studied dolutegravir plus 3TC in the GEMINI study which is a naïve population and TORCH and SALSA will study in the switch population, so we think that dolutegravir/3TC - and we have this feedback from physicians and patients - is a very appealing regimen for those patients that want to take less medication. We have seen with *Juluca* that actually whilst physicians are positive about *Juluca*, it is often the patients that had the initial conversation with their physician, asking about this new opportunity to reduce the number of medicines particularly those that are ageing and have other things happening in their life, other co-morbidities such as diabetes, cardiovascular issues which we know happen earlier and more commonly in people who are living with HIV.

At a macro level, we are hoping that dolutegravir/3TC will have a very broad label both for naïve patients and for switch patients. Your specific question was about switch. I think part of it will be driven by a desire to move people from older to newer regimens, part will be the desire to reduce the number of medicines that a patient takes, and a large part of it - and this is the same with cabotegravir will actually be driven by patient demand which in all the research we have done, actually we have seen a very, very positive reaction to this opportunity.

Kim, is there anything that you would add?

Kim Smith: No I think you have said a lot, the one thing that I would just add is we have fully enrolled the TANGO study, and we enrolled it in record time. Just to describe for people, the TANGO study is taking individuals that are supressed on a TAF-based regimen and randomising them to stay on that versus switch to dolutegravir plus 3TC in the fixed dose tablet. The enthusiasm for this study really overwhelmed us and it enrolled super-fast, so we think that there is a tremendous desire from both clinicians and patients to be able to use fewer medicines as long as they don't have to give anything up from a virologic standpoint.

Trang Huynh (Credit Suisse): I have three if I may. Firstly, can you comment on if there were any trends of adverse events or treatment-related discontinuations across the different age groups? Secondly, with equivalent efficacy between the two-drug regime versus the three-drug regime, how much cheaper will it be for the payer of the two-drug regime? Finally, just following up on Steve's question, have you conducted any research on what proportion of treatment-naïve patients would use a two-drug regimen versus a three-drug regimen?

David Redfern: Thank you, Trang. I will get Kim to comment a bit more across the age groups, although I am not sure we have that data at this point. We will as we get into further sub-cuts with the analysis.

On pricing, it is obviously too early to talk about pricing at this point ahead of the regulatory file and regulatory process, but all I would say is that you would expect that two-drug regimes to be cheaper than three drug regimes. I think we have said before, certainly in the United States, pricing is a component but what really matters is the value proposition to the patient and the clinical data, and we think we have a very compelling clinical story here, but there will also be benefits to society from two-drug regimes being cheaper, but, Kim, do you want to talk about adverse events and what data we have.

Kim Smith: Right now, we don't have those cuts of adverse events by different sub-groups of age, gender and so on. We will have that data as we have mentioned before, this is really late breaking data and so we will have that to present at subsequent conferences.

Deborah Waterhouse: In terms of percentage, I don't want to go into specifics, but I will just give you a broad perspective. I think what you will see as you have seen the data today, we hope that you will see compelling naïve data and compelling switch data with dolutegravir/3TC, and this does give physicians the opportunity to embrace a new treatment paradigm which is that you can keep the virus suppressed from a switch and a naïve perspective with two drugs rather than three. We know that in Europe particularly and in Latin America and a few other places, there has been a very strong push for this particularly as 3TC is a generic, so they have the opportunity of having a very impressive medicine at the same time as having a price point which is less than three drug regimens.

There is a piece around strong clinical data that has to be the first thing that physicians use but then you have obviously got the opportunity of something which is cost effective as well. I think we are going to see strong uptake in Europe and Latin America based on efficacy and price. I think in the US it will be first and foremost efficacy and we are expecting a strong performance for this medicine in both naïve and switch in the US as well.

Andrew Baum (Citi): A couple of questions. I hear your excitement about the GEMINI dataset. I expect what your sales reps would like to hear even more perhaps is the excitement of the external KOLs endorsing the two-drug regimen. With that in mind, can you remind us what the official policy has been historically for using external medical experts as part of your marketing strategy, and how that may change given your new Chief Legal Counsel that has recently been appointed. Then second, in terms of providing reassurance on the emergence to resistance, when will you be in a position to share the 96-week data with physicians? Thank you.

David Redfern: Thank you, Andrew, I will get Deborah to comment on our specific medical engagement policies although I will tell you, as you know, they are absolutely the same as GSK overall. Deborah, can you explain how they relate in HIV?

Deborah Waterhouse: Yes, in scientific engagement we can pay healthcare professionals to partner with us, so if you are just talking about broad scientific topics such as ageing, resistance and evolving treatment approaches, actually we already pay healthcare professionals to partner with us because we know that they have the breadth and depth of knowledge which then complements our own internal staff.

When it comes to promotion, we do not pay healthcare professionals, PE/KEs, whoever, to speak on our behalf. We believe that we know our medicines best, and we have a very strong group of global medical directors and also local medical teams that actually communicate about our medicines, similar events where you gather a number of people together and go through data.

In terms of our commercial model, we know it is different to our competitors. It doesn't mean that that puts us at a disadvantage because we've managed to successfully launch *Tivicay, Triumeq*, *Juluca*, and we hope dolutegravir / 3TC on that basis. Obviously, I am not party to any future changes.

David Redfern: What I would add, Andrew, at ViiV, particularly in the last two years, we have invested very heavily in the medical function on the medical advisory side as Deborah said, with global medical directors and very senior physicians. We have actually been very successful in recruiting some really senior, well-regarded people across the globe. Kim Smith is an example of that, who before she joined ViiV was a very eminent physician up in Atlanta. The reason they are coming to ViiV is because they see real innovation happening here. Obviously the two-drug regime is part of that, but there is a whole research programme around long-acting formulations which a lot of physicians are very interested in, and then our research efforts around different types of ALDs and so forth. And clearly, the dedicated nature. In a speciality area like ViiV, having a world-leading medical capability is critical and I think we have built that.

John, the timing of the 96-week data?

John Pottage: The 96-week data will come for evaluation in the second quarter of 2019, and then subsequent to that, we will go for the nearest medical meeting to present that, so I would assume it would be the International Aids Conference in Mexico City next year.

David Redfern: Thanks, John, thanks, Andrew. Next question.

Richard Parkes (Deutsche Bank): Thanks for taking my questions. Just going back to the SWORD data that has been presented, I think of those virologic failures, there were three cases of treatment-emergent resistance, two of which occurred after 48 weeks. I wondered if you could help us put in context that resistance incidence versus what you are seeing with three-drug dolutegravir regimens. I didn't see any cases reported in the prescribing information.

Then I just wondered if you could discuss what the clinical implications of resistance developments are for those unfortunate patients where it does occur.

The second question, I just wondered if you could discuss what percentage of patients don't tolerate current three-drug integrase-based regimens, either from clinical trials or in the real world, and how that is likely to evolve with increased use of TAF-based backbones.

David Redfern: Thanks, Richard. Not surprisingly, we have a pretty detailed understanding of those three patients who became resistance in the SWORD 100 data, so Kim can comment on those.

Kim Smith: Out of the eight confirmed virologic withdrawal criteria patients, there were three individuals who developed some NNRTI mutations. I say, it is specifically in NNRTI mutations, and there were no individuals who developed integrase mutations, and that is a key point that I will get to in just a moment. But to be specific about those three cases, the first one was an individual who had a mixture at a particular site, and that didn't confer any significant resistance to rilpivirine, so there was presence of one mutation, but that individual actually continued on dolutegravir/rilpivirine, and by the time they reached their withdrawal visit, they were back to undetectable on that regimen.

The same thing is true for the second case, different mutation, a mixture at a different code on, and again, no significant fold change to rilpivirine, and that individual suppressed down to 55 copies, so almost undetectable, before they withdrew from the study.

The third case is actually quite interesting. This is an individual who had virologic failure at Week 100, so after being on the study for two years. At the time of resistance, this patient had multiple NNRTI mutations, so when we went back and did DNA sampling of their baseline, that individual had several of those mutations at the time that they entered the study, so it is quite remarkable that that individual maintained viral suppression for 100 weeks on a regimen of dolutegravir/rilpivirine, despite the fact that rilpivirine was quite compromised from the beginning. We actually think that this is really a very impressive durability and impressive data here that you are only seeing one individual who has developed significant rilpivirine resistance in again nearly 1000 patients with two years of data.

I think the important point, the question you asked about what is the impact, this is really important. Because these individuals had no integrase resistance mutation, they still have a wide range of options, so those individuals are still eligible to receive an integrase based fixed-dose tablet like *Triumeq*, for example. So, they have not limited their options substantially. We think that this is really important information for the field, that they understand that yes, there were a couple of individuals who had failure but they did not compromise their future treatment options.

David Redfern: And the percent of patients that are resistant to NRTIs or other backbones?

Kim Smith: Yes, that's difficult to answer, to pinpoint a specific percentage. What we recognise is that when individuals fail most of the older regimens, the first thing they lose is often the nucleoside, and so for some individuals, they may have the 184V mutation. Those individuals for example would still have activity of dolutegravir plus rilpivirine. It is difficult to quantify exactly what percentage, but we know that there are a number of individuals that are out there, fewer of them of course when they fail on an integrase-based regimen.

David Redfern: I think we have time for just one more question, please.

Marietta Miemietz (Primavenue): I wanted to ask you very general questions at this stage. One is in terms of the study lasting another two years and additional data becoming available to compare the regimens. Are there any key points of differentiation that you feel could emerge above and beyond the convenience of lower adverse events, or do you actually mainly see the additional adverse event data as cementing the role of two-drug regimens over time?

On the treatment emerging adverse events that led to discontinuations, specifically when it comes to infections, can you just explain how the call is being made that these infections are really 100% treatment-unrelated. If you wanted to play devil's advocate I was wondering if you could actually argue that if there is slightly lower efficacy then maybe you could have a higher risk of developing something like TE than you do on the three-drug regimen, so to try and understand that.

Then in terms of the real-world treatment issues, is Hepatitis C treatment going remain a contraindication going forward and also is there currently situation where people come off drugs just because they go to jail, and can you talk a little bit through the dynamics of that what proportion of patients on your overall franchise are affected by that and what treatments they then go onto after jail. I am just very, very surprised that going to jail would be a reason for dropping out of the study.

Finally, I was just wondering, very high level, if you can talk a little bit more about your efforts on the cures in terms of timelines, your definition of cure, would that be functional cure with long treatment-free intervals or do you actually think a full cure is realistic.

What is your confidence on being first-to-market? Would you consider in-licensing? Thank you very much.

David Redfern: Thank you very much, Marietta. We will try and be reasonably brief on all of that. I think on the follow-up, clearly the efficacy is already very high so most of the interest in the follow-up in going to be less around the efficacy and more around the adverse events, but Kim can comment.

Kim Smith: That was a mouthful, so I want to address the question specifically around whether or not the adverse events that were infections were related to treatment. In the case of the tuberculosis and the Chagas disease, these are typically diseases that individuals actually have already in their system before they start, so they actually exited the study fairly early and didn't have a chance to have the treatment failure because they basically had to come off in order to pursue treatment of those opportunistic infections. We are quite confident that they were not related to the treatment itself.

With regards to the question about the person in incarceration. This person is actually not off the study, he is still on the study. He was incarcerated for a period of time and had to change medicines during that period, but came out of being incarcerated and went back on the dolutegravir plus 3TC regimen and remains suppressed on that regimen now.

The one question about hepatitis C, the only limitation that we have is that for the first year in the study individuals, if they need to have hepatitis C treatment in the first year, we recommended that they not enter the study, just because although there is no drug interactions that would preclude individuals from getting treatment of hepatitis C during the first year, often you can see individuals have significant increases in their liver function test and complications of hepatitis C treatment that might make them need to leave the study, and so we don't like for that to happen in the first year, but beyond the first year individuals can remain in the study and receive hepatitis C treatment.

David Redfern: John, are you going to tell us when you are going to cure HIV?

John Pottage: I think it will be quite a bit, years in the future so I am not optimistic for something in the next 10 to 20 years.

David Redfern: We do have a good research effort though.

John Pottage: We do, and we have a very good collaboration with the University of North Carolina regarding cure research, and so I think when you think about it, I think it is probably best to think about it in a step-wise fashion. If we can cause what maybe better called a remission so that someone is treated and then they do not need to be on medicine for two, three or five years and then maybe they come back with it, it is similar to what you think about with cancer chemotherapy. But for the most part this is a long slog going through really understanding the basic virology, the basic immunology, but I think it is

something that gets great attention from us so we are fired up for that to get to that point, but I believe it will be a long way off.

David Redfern: Thank you John, and we appreciate everyone's time and interest and all of your questions. We hope you found this session, and particularly the data useful, and some of you no doubt we will talk to tomorrow on our Q2 results. With that thank you very much and good afternoon.