GSK

CAB LA for PrEP: Superior Efficacy

Thursday, 9 July 2020

David Redfern (Chairman): Thank you, Philippa, good afternoon everyone, or good morning, if you are listening from the US. Thank you very much for joining us today. My name is David Redfern, I'm the Chairman of ViiV Healthcare and also the Chief Strategy Officer of GSK.

We are delighted to host this investor webcast on our cabotegravir long-acting PrEP data. These data were presented at the AIDS 2020 conference yesterday. The slides we're using today are hosted on the Investor section of GSK.com. It's a presentation where you should see in front of you the first slide of the presentation is entitled 'CAB LA for PrEP: Superior efficacy'.

CAB LA for PrEP: Superior efficacy

Of course, we were all supposed to be in San Francisco in person at AIDS 2020, which is always a very big and important event for us; not surprisingly COVID-19 has meant this has had to move to a virtual setting, but we'd like to pay tribute to the organisers, who have really done an excellent job through this week of ensuring that HIV/AIDS remains prominent in these times, with a great mix of data presentations, symposia and, of course, the all-important global village.

I should just say that we are now in the closed period, and therefore we will not be making any comment today on GSK ViiV HIV performance-related matters, those will be covered in the GSK Q2 results reported at the end of July.

Welcome

In a moment I will introduce Deborah Waterhouse, the Chief Executive of ViiV, to give some context to our CAB PrEP story; then we shall hear from Dr Kimberly Smith. Kim was a distinguished HIV physician based out of Chicago for a significant portion of her career, but now, of course, is the Head of Research and Development for ViiV Healthcare. After that there will hopefully be plenty of time for Q&A.

Suffice to say, we are very excited about the data that was presented just yesterday at the IAS conference. The threshold of superiority is an extremely high bar to reach, and the

reception therefore that we received, both from the HIV community and other stakeholders, has been very encouraging and very positive.

Cautionary Statement regarding Forward-looking Statements

This sets out our cautionary and forward-looking statements, and with that, I am pleased to hand over to Deborah Waterhouse, the CEO of ViiV.

Deborah Waterhouse (CEO): Thank you, David. As you mentioned, the AIDS 2020 conference is in full flight, and it's been an incredible week: the virtual conference is still channelling the spirit of San Francisco, a city that stands as the backdrop to the HIV/AIDS story. It's humbling to think how far we have progressed since the days of the late '80s and early '90s, when doctors in San Francisco were initially perplexed by the procession of men who have sex with men presenting with a new and rapidly-debilitating virus.

Innovation has been incredible, from AZT, discovered by GSK, through to ART, which revolutionised treatment, and the inception of the belief that HIV could be contained and potentially beaten, but there is still an awful lot to do.

To leave no person living with HIV behind

I always start every presentation, whether it's inside the company or outside, with our mission statement. That is 'To leave no person living with HIV behind'. This statement galvanises our employees and presents an open and progressive face to the HIV community which we serve. In the last few months we've had some wonderful FDA approvals, which are real testament to this mission.

We have gained approval for *Tivicay* PD, or *Tivicay* paediatrics, which is a 5mg dispersible tablet for the treatment of children who are living with HIV. Around two million children worldwide have to endure sub-optimal treatment to manage their HIV. This has been going on for a long, long time, and it's great news that they now have access to dolutegravir in a formulation that they can swallow with water and tolerate.

We've also just received approval for *Rukobia*, otherwise known as fostemsavir, and this is a medicine for heavily treatment-experienced adults who are living with HIV. This really is a life-saving medicine for that small number of people who are running out of options.

We now believe that our long-acting injectable CAB, long-acting for PrEP, could transform things again, potentially leading to the prevention of hundreds of thousands, if not millions, of HIV infections.

Helping end the HIV epidemic

However, despite advances in HIV, it remains a significant challenge, 1.7 million new infections occur each year, and that is actually a similar number to the number of AIDS related deaths. Most people living with HIV in resource poor countries are living on less than $1 a day, and so 38 million people are now living with HIV worldwide. This is why we prioritise our partnerships with the WHO and generic partners to enable to access to our medicines wherever you live in the world. We ensure that in those least developed countries our medicines are produced under voluntary licences for people who are living with HIV in these least developed countries.

The HIV Challenge

Even in countries with advanced healthcare systems the picture is complex. Let's take the US for example. In the US, 50% of people living with HIV are not virally suppressed. There are still around 38,000 new infections a year, and this number has remained fairly consistent for the last few years. Those who are becoming infected are predominantly men who have sex with men, many of whom are from challenged populations such as black and Latino communities. These are men who have sex with men who are often in the lower socio-economic bracket, and have limited access to support networks.

Additionally, one in five people who become HIV positive in the US are women. There is encouraging momentum. Activism remains strong, and the President has actually announced ending the HIV epidemic initiative, which is committing significant resources in terms of people, capabilities and finances to ending the HIV epidemic. The onus is to reduce new infections by 75% by 2025, and 90% by 2030, and a big part of this initiative focuses on prevention and PrEP and we hope particularly CAB PrEP has a big role to play.

The PrEP Landscape Worldwide

Let's go a little bit more into PrEP. There are currently 200,000 people taking PrEP as an option in the US. The US Government believes that 1.2 million people would benefit from PrEP if they were at risk of becoming HIV positive, and so the gap is quite significant and creates a compelling opportunity for new innovation such as cabotegravir long-acting for prevention.

In Europe the landscape is mixed. Some countries have encouraged to take a PrEP and some have not. There are an estimated 500,000 men who have sex with men who

could benefit from PrEP. Barriers to update are high and specifically people at risk of HIV expressed dissatisfaction at taking pills every day. Some view it as stigmatising and potentially discriminating.

In Africa the state of HIV is very different. The key population at greatest risk is adolescents, girls and young women, a group that could really benefit from a new PrEP innovation. This is why we are so excited about the potential of CAB long-acting for PrEP. If approved, we believe it could present a new and persuasive option in the PrEP market. It is every two months, and obviously it is a highly efficacious medicine which Kim will talk more about shortly.

The market remains strong and viable, approximately $2 billion per annum in terms of value in the US but with significant room to grow. The market is currently 20% per year, so we see this as a considerable opportunity but actually to talk through the data, I am now going to hand over to Dr Kimberly Smith so, Kim, over to you to tell the story of the data.

Kimberly Smith (Head of R&D): Thank you, Deborah.

From Evolution to Revolution: the 2DR Era

Many of you have seen this slide before. This is our pipeline strategy side, and on the left-hand side of the slide you can see our legacy medications in the current standard of care, including dolutegravir-based three drug regimens – *Tivicay* and *Triumeq*. In the middle of the slide you see our new treatment paradigm, two-drug regimens including the two dolutegravir-based two drug regimens and our long-acting treatment regimens – Cabenuva, which is CAB plus rilpivirine. Cabenuva is approved in Canada and I will talk a little bit more about our plans for the United States in just a few moments.

If you move over the right-hand side of the slide you can see that there is a list of new mechanism of action medications including *Rukobia*, which Deborah just mentioned, which is our attachment inhibitor fostemsavir, which we are happy to say was recently approved in the United States on 2 July, focused on highly treatment experienced individuals and we are extremely excited about this product. As Deborah mentioned, it's a life-saving medication for individuals who have a significant amount of treatment experience and are running out of treatment options.

You can also see that there are several other products in our pipeline, including maturation inhibitor portfolio, a capsid inhibitor and broadly neutralising antibodies.

But today our focus of discussion is prevention and cabotegravir long-acting for prevention.

LONG Acting injectables – Giving a shot for treatment and prevention

As you can see here, we have big plans for long-acting cabotegravir. Our plan is for cabotegravir to be a part of the treatment regimen, long-acting that includes cabotegravir LA and rilpivirine long-acting with both a four-week dosing regimen and an eight-week dosing regimen.

As many of you are aware, we filed for the monthly approval for Cabenuva dosed every month in April 2019. We anticipated approval at the end of last year. Unfortunately we received a complete response letter from the FDA due to some challenges and questions related to manufacturing. We are in the process of resolving those questions and plan to re-file within the coming weeks.

In addition to HIV treatment, our plan is to develop cabotegravir long-acting as a monotherapy for HIV prevention and that's what we are going to spend a lot of time talking about today.

CAB LA: PrEP

Now you might wonder why do you need a long-acting medication for PrEP. The answer is actually quite clear. Despite the fact that Truvada has been approved for HIV prevention since 2012, as Deborah mentioned, we continue to have in the United States 38,000 new infections every year and around the world, many, many thousands of infections and unfortunately oral PrEP alone has not been able to have a significant reduction in the risk of HIV infection.

Some of the challenges that come along with oral PrEP are, as Deborah mentioned, stigma but also many individuals complain about the fact that they need to take a medication every day, they complain about side effects, they complain that it does not fit into their life.

I can tell you in my time taking care of patients, not only HIV infected patients, I also worked in an STD clinic and saw individuals who were at significant risk for HIV but the idea of needing to take a medicine every day, a pill every day to prevent HIV was difficult for some individuals, even though they were at high risk, to wrap their minds around. And so long-acting PrEP has the potential to add a new tool to the very important toolbox for HIV prevention.

Cabotegravir long-acting for prevention (PrEP)

On slide 13 you can see the two trials that make up our Phase 3 programme for development of long-acting cabotegravir for prevention. HPTN083 is a study focussed on men who have sex with men and transgendered women who have sex with men. It's an event-driven study and the primary data for this study is being presented, as you have heard already, at this conference but I want to make note of the fact that actually we anticipated that this study would go on until at least 2022 because it's an event-driven study and so the fact that we delivered this data actually quite early is quite surprising, but really quite thrilling to us.

On the right side of the slide you see HPTN084, nicknamed the LIFE study, Long-acting Injectable For the Epidemic. This is a study that focuses on young women in sub-Saharan Africa. It is also an event-driven study but in comparison to 083 which was designed as a non-inferiority study, the 084 study is designed as a superiority study and will involve 3,200 women and the design is actually quite similar to 083 which I will discuss in just a moment.

The 084 study is dome in collaboration with the NIH, similar to the 083 study, but in addition the Bill and Melinda Gates Foundation is a partner in the 084 study.

HPTN 083 Study Design

This describes the 083 study design. It's a Phase 2b/3 randomised, double-blind, double-dummy study at 43 sites globally. As I mentioned, it focuses on men who have sex with men and transgendered women who have sex with men who are at least aged 18.

These individuals are at high risk for HIV due to risk factors such as condom-less anal receptive intercourse with more than five partners, stimulant drug use, incident rectal or urethral sexually transmitted diseases in the past six months or a SexPro Score of less than 16 in the US.

They are generally in good health, they were not Hepatitis B or Hepatitis C co-infected and they had no contraindication for gluteal injections, had no history of seizures, no gluteal tattoos or skin conditions that could interrupt the gluteal injections.

The planned enrolment was 4,500 individuals. We targeted more than 50% individuals who were under the age of 30. We also targeted more than 10% transgendered women and for the US enrolment our target was to have at least 50% of the population be black or African American men who have sex with men. I can tell you that we reached all of those targets with roughly two-thirds of the population being men under the age of 30,

roughly 12% of the population was transgender women and the US enrolment included 50% black men who have sex with men.

Later on today there will be a presentation by Dr Beatrice Grinsztejn, the co-chair of the 083 Study and she will go into detail about the results for the key population. I will share one slide from that presentation with you a little bit later.

The primary efficacy endpoint was incident HIV infections in step 1 and step 2 and the primary safety endpoint was grade 2 or higher clinical or laboratory adverse events.

HPTN 083 Study Design

This slide shows you the study schema. Individuals are randomised to cabotegravir or tenofovir/FTC but, as I mentioned, this is a double blind, double dummy study. To walk you through this slide, CAB is represented in orange - both the pill and the syringe filled with orange - and tenofovir is represented in the blue. What is in the grey is a placebo, so all individuals in the trial during step 2 received both an injection every eight weeks, half of which were active, half of which were placebo, and a pill every day, again half of which were active and half of which were placebo.

To start from the beginning, step 1: individuals who are randomised to either CAB or TDF took a CAB pill or placebo for the first five weeks, this was the oral lead-in period. Then they moved into step 2, where they received an injection every eight weeks and a pill daily, and for those individuals who were randomised to cabotegravir, anyone who received at least one injection but who went off cabotegravir went into step 3. Therefore, either they completed their full time on step 2, which was three years, and then went on to step 3, or if they interrupted or stopped CAB, they went on to step 3.

Statistical Design: Efficacy

I do want to give you a little bit of understanding of the design of this study and, again, as I mentioned, this was a non-inferiority design. The non-inferiority margin was a quite conservative 1.23. The alternative hypothesis was the CAB was at least 25% better than oral Truvada with a hazard ratio of 0.75.

The target background HIV incidence where the population enrolled in this trial was 4.5%, so this was a very high risk population of individuals. It was anticipated that adherence to tenofovir/FTC based upon TDF plasma levels was 67%. As I mentioned, this was an endpoint-driven study, the plan for the study was that there would be 172 endpoints and there were pre-specified interim analyses that occurred at 25%, 50% and 75% of endpoints.

The O'Brien-Fleming stopping boundaries for interim data analysis were used to determine early stopping metrics.

This study got to the 25% endpoint period and the DSMB made a recommendation to terminate the blinded portion of the study on 14 May 2020 due to crossing pre-specified stopping bound, so again with 25% of the endpoints accrued. This was quite a remarkable event, it is very unusual to stop a non-inferiority study this early.

The DSMB's recommendations in addition to stopping the blinded portion of the study were that the individuals be unblinded and that individuals who were on the Truvada arm would be offered cabotegravir.

HIV incidence: CAB vs TDF/FTC

This slide shows you the primary endpoint results for the study. There were 52 HIV infections in 6,389 patient years of follow-up, which results in roughly 1.4 years median follow-up per individual. The pooled incidence using both arms was 0.81, so in comparison to the 4.5% incidence that was expected for the trial, you can see 0.81 was a significant reduction as you look across both arms.

If you look at the panel on the bar graph on the left-hand side of the slide, you can see the incidence broken down by arm. There were 13 infections which translates to an incidence of 0.41 in the cabotegravir arm, and there were 39 infections which translates to an incidence of 1.22 in the tenofovir/FTC arm. If we move to the right-hand side of the slide, you can see a clear understanding of the statistics here.

The hazard ratio for this comparison is 0.34. In other words, there was a 66% reduction in the likelihood of HIV acquisition comparing cabotegravir to tenofovir/FTC, and you can see the confidence interval is quite far to the left. If I would start you all the way to the right, the non-inferiority margin was 1.23, clearly the confidence interval was well to the left of that. Superiority could have been claimed if the confidence interval was all to the left of 1. Again, as far as the alternative hypothesis which suggested that cabotegravir may be as much as 25% better than Truvada, we surpassed that as well moving to the left of that vertical line. Therefore, as you can see, this was a very definitive superiority finding for this study.

HIV incidence - ITT

What this slide shows you is the incidence over time, and this is the intent-to-treat analysis. You can see in the orange, the cabotegravir, the accrual of events on cabotegravir, and in the blue the accrual of events on TDF/FTC. Again, it is quite clear that

after the first year or so is when you really started to see a very wide difference in the incidence of HIV events between the two arms and, again, as I mentioned, the hazard ratio for this data is 0.34 or a 66% reduction favouring cabotegravir. As you can see the statistical P value for this was very high at 0.0005.

Results: HIV incidence in populations deemed most at risk

As I mentioned, the populations involved in this study were really the populations that were most at risk for HIV. This is young men who have sex with men and in the United States in particular, this is young black men who have sex with men. Also transgendered women are at particular high risk, and so what you see on this slide is the breakdown based upon age, cohort, race and region. I have circled a couple of these whisker plot data points just to emphasise a few points.

You can see in the population on the basis of age the individuals who were less than 30. You see the hazard ratio for cabotegravir was 0.5 and compares to 1.5 for TDF. Again, similar rate, a difference between CAB and TDF as seen in the overall population and, again, this is the largest portion of the population. You see the population that is over 30 is a smaller group and the whisker plot crosses 1 here.

If you move on to the cohort of transgender women versus men who have sex with men, again, the biggest proportion of the population is men who have sex with men and you can see again here findings very similar to the overall population, hazard ratio for CAB being 0.39 versus TDF at 1.14.

For race, looking at black or African American men you can see the CAB hazard ratio at 0.58, the TDF/FTC at 2.1, and this overall hazard ratio difference comparing the two being 0.28, again a very significant difference favouring cabotegravir.

Looking at regions, you can see that roughly half of the population came from the US and you can see that there was clear, statistical significance for the US population as well, and so what is clear from the sub-group analysis is that the populations that were most represented in the trial and absolutely the populations at the greatest risk, showed the same pattern as we saw in the overall population which is a clear, superiority for cabotegravir over TDF/FTC.

Injection Site Reactions

Looking at adverse events, the most common adverse event in the study was injection site reaction. So just to walk you through this slide, which is a little bit complex, the solid bars are cabotegravir, the green are mild, yellow is moderate, and red is severe

injection site reactions, and TDF/FTC are the slashed bars, again with green – mild, yellow – moderate, and red being severe. It is quite clear from this slide that you saw in the beginning of the study actually a very high rate of injection site reaction, but that tended to wane over time, and this is completely consistent with what we saw in our treatment studies for long-acting cabotegravir plus rilpivirine.

What is also noticeable in this graphic is that the individuals who received cabotegravir were more likely to have injection site reactions than the individuals receiving the placebo. The placebo for your information was made of intralipid which basically was made to look similar to the appearance of cabotegravir in order to maintain the double-blind, double dummy design of the study.

There were 47, or 2.2% individuals who were on CAB, who permanently discontinued the injectable product due to injection related adverse events, and the more severe the event the more likely those individuals were to discontinue.

Conclusions

Slide 21 makes the conclusions or overall summary of the study. Investigational CAB LA administered every two months is 66% more effective than daily tenofovir/FTC pills in preventing HIV acquisition, and I want to emphasise that this is actually a very dramatic difference, a very unexpected difference and, as was mentioned earlier, the bar to have this stuff so early was quite high, and so this superior result is really quite remarkable and, as I have said many times, are quite thrilled with these results.

CAB LA was well tolerated, ISRs not surprisingly were more common on cabotegravir than on tenofovir/FTC. The key populations such as black men who have sex with men were well represented in this study and demonstrated high rates of effectiveness for CAB LA consistent with the overall results.

What we do not have available at this moment is data on drug levels or the potential of development of resistance in the incident cases for both arms. Unfortunately, Covid related closures of the labs that manage these particular assays interrupted our ability to get this data in time for the International AIDS Conference presentation. However, we look to have this data soon and certainly we hope it will really help us to understand this data better.

Importantly, HPTN084 in cisgendered women which I described earlier is ongoing and is highly anticipated. Now one important point to know about 084 is that it started roughly a year after 083. It started in Rome roughly a year later, even though from the beginning the plan was to complete both 084 and 083, because 083 had individuals starting in the US we were able to get it approved for regulatory start sooner than 084. We are very

excited about 084. We really look forward to getting that data. Hopefully we will see more information on this study within the next year and we would love to see a result very similar to the result of 083.

Our next steps are that we are already working with the FDA and other regulatory agencies to prepare a file and we anticipate submitting this data in 2021.

Reaction

This slide is just a little bit of our reaction, so you can see we saw this data obviously in the Covid period and so this is me and some of my team members and our celebration because I will tell you, I can't say the word 'thrilled' enough. Many of our team was in tears when we saw this data because we really believe that this is a game-changer. Then when we talk about ending the epidemic, again as I have said earlier, we need more tools and I think that this is really a tremendously powerful tool towards ending the epidemic and so we were extremely excited to see this data and extremely excited to share it with you today.

As you have seen, it has gotten a lot of coverage in the media. I think this is quite a significant move forward for the field.

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

David Redfern: Thanks Kim, thanks Deborah and as you say, we now have a bit of time if anyone wants to ask some questions, so operator, perhaps you could coordinate that? Thank you.

[*Instructions for Q&A given*]

Questions & Answer Session

Tim Anderson (Wolfe Research): Thank you, a couple of questions. The PrEP opportunity thus far has really only been in the US from a commercial perspective because outside the US in places like Europe, generic Truvada is what's used because of the cost differential.

Do you think these new data with cabotegravir could change this dynamic and generate meaningful sales in Europe and other ex-US countries as well?

Then the second question; the data clearly show better efficacy. Some would say this is all driven by the fact that in a clinical trial setting you can force compliance with an injection that has to be given by a care-giver, but by contrast you can't force compliance with oral therapy taken at home with no-one looking over your shoulder, so in a real-world setting, the question is whether there could be an equal compliance problem with cabo because it's not exactly easy to be a care-giver every two-months for an intramuscular injection. Any perspective on that criticism would be helpful.

David Redfern: Great. Thanks, Tim and it's nice to hear from you. Deborah, why don't you talk about the commercial potential? There's clearly strong commercial potential in the US, but your thoughts on Europe and then Kim, we will come to you on how you think this translates in the real world.

Deborah Waterhouse: Yes, so let me give an overview to what I think the potential is. In the US this is a significant area of focus. We know that it's where 85-90% of the global value sits today with Truvada and Descovy and obviously there is a big push from the President and the US Government to actually invest in reducing the number of HIV infections down from 38,000 by 75% by 2025 and 90% by 2030 and they are putting this year alone about $700 million into helping achieve that.

I think a majority of the opportunity sits in the US. We will register this medicine in Europe and there are a few markets where actually they are still looking to bring down their transmission rates, so there could be an opportunity in a smaller, limited number of markets but I think with the Truvada generic across Europe and available therefore at very low generic prices, the opportunity for CAB PrEP is going to be limited in most markets.

We need to dive a bit deeper into Japan where obviously we know that innovation like in the US is rewarded and there may be other opportunities, but it will be on an *ad hoc* market-by-market basis. The majority of the value will sit in the US.

Kimberly Smith: Let me answer the question with regard to the real world versus the clinical trial. Let me first just say in the clinical trial, while you are right to a degree, forcing is maybe a word that I wouldn't use! I would say in a clinical trial we try to motivate individuals to stay in the trial and come for their visits.

I think the key point is that when individuals come for their visits, they get their shot and they're done. There is nothing they need to do in the interim and so we had actually very good retention in the study and that's because these men recognised they were at risk and certainly had a desire not to become HIV infected and so they did show up for their visits.

The challenge with oral prep is it requires individuals to consistently take it every day. So the time in between they may forget, it happens, you can't always necessarily predict your ability to just remember about the time, and that's what we saw actually over time, is that even though individuals started out consistently taking their oral medications, it waned over time; whereas we actually saw a high rate - after 18 months there were more than 80% of individuals that were making it to every one of their visits. So in the real world, we expect that we would have similar motivation to want to avoid HIV infection.

It will be important that we do everything to enable individuals to get access to CAB for PrEP long-acting in their community, so in community-based clinics, even potentially in mobile clinics, just finding ways to make sure you can reach out to individuals, and having a long-acting product enables that – you can't enable directly-observed therapy with daily pills, but enabling directly-observed therapy, either for treatment or potentially for PrEP, becomes possible when you have a long-acting agent. But certainly what having a long-acting agent does is again adds a tool to the toolbox, and then we use all of our public health professionals to take these tools and put them into best use, again, to try to do something towards ending the epidemic – we need more tools, we think this is one of them.

Steve Scala (Cowen): This is a follow-up to the first question, but Truvada will lose its exclusivity in the US in September, so wouldn't the US dynamic be similar to that in Europe - I guess I'm confused as to why it would be different – and do you anticipate patients will have to try generic Truvada first?

Then the second question is, 109, the broadly-neutralising antibody for HIV, has been in Phase 1 since 2018, what are the gating factors to moving this forward? Thank you.

Deborah Waterhouse: About 40% of the Truvada business has already been moved over to Descovy, I'm sure many people on the call know, Truvada and Descovy are priced at exactly the same price point, which is around $2000, so we have already seen willingness of payers to reimburse Descovy following on from its licensure and the DISCOVER study, which showed that it was non-inferior to Truvada, with some side effect benefits, so we've already seen payors willing to pay for something which is non-inferior, with some side effect benefits. They knew, obviously, that Truvada was going generic at the point at which that happened. So we believe that, had we come out with a non-inferior result, then that could have been challenging with payors, but we would have still had some market penetration, because obviously we're offering a different mode of administration.

With superiority data at this level - 66% improvement versus Truvada – we believe that we will be able to secure reimbursement within the US amongst those payors who actually themselves are keen to see - whether you are a government payer or a commercial payor – much lower rates of HIV acquisition, so we believe there is an opportunity in the US despite Truvada going generic. I think the Descovy example is one that shows that this is an area that payors are willing to invest in, even for non-inferiority, let alone superiority.

David Redfern: The only other thing I'd add, Steve, is the point Deborah made: I think there is a real difference between the US and Europe on the political will here – it's very clear in Washington there is a very strong desire to see the incidence of HIV decrease, the incidence of new infections in particular decrease, and that means they're going to put substantial money behind it and we've seen that, as Kim has said, having new tools available at this time I think plays straight into that, the fiscal desire here is an important differentiator.

Kim, do you want to talk briefly about bNAbs and making our early stage long-acting pipeline, which we're quite excited about?

Kimberly Smith: The N6LS bNAb, I think the question was, what's taking so long, to put it in a nutshell. We in-licensed it at the end of last year, so I can't really answer what was going on about the pace of progress while it was at the NIH. I can tell you that we are moving this forward as quickly as we possibly can, we're looking to get into a proof of concept study as soon as possible, ideally that would be by the end of this year – I will say that Covid causes a little bit of challenge, so it may put us off until the beginning of next year, but I can tell you there is nothing about the product that has delayed this from our perspective, it's really just, it's now in our hands, and so we get to drive.

With regard to the rest of our portfolio, as you saw, there are several other targets including capsid and maturation inhibitor, it is our belief that the future of HIV treatment includes primarily, new agents should be long-acting agents, the field has told us that they want long-acting agents, and so we see our pipeline as being primarily long-acting, so we have a capsid inhibitor with the potential for long-acting, as well as a maturation inhibitor can be a long-acting agent, so that is our pipeline for the future, and we're very excited about it.

Laura Sutcliffe (UBS): Thank you for taking my question. I know you said that you'd currently have access to some of the analysis around potential resistance mutations, do you have any sense of any characteristics that the patients who contracted

HIV infections in the cabo arm might have in common? Or is your hunch that it's just down to resistance mutations in the ITT analysis?

Then secondly, monotherapy in patients with integrase inhibitors in patients who have an infection isn't recommended partially because of resistance development, do you have any long-term concerns around the use of integrase inhibitors in the prophylactic setting? Thank you.

Kimberly Smith: Hi Laura, thank you for the question: the first point, around the individuals who acquired HIV on the CAB arm, I think first it's important to recognise while there were thirteen individuals in the ITT analysis, of those thirteen there were eight individuals who did not contract HIV during a period when they were receiving CAB injections. There were five who appeared to be receiving CAB injections, or at least appeared to be regularly, who were infected, so understanding those five individuals is going to be really key. When you look at the fact that there were only five that actually makes that difference versus Truvada even starker, and so understanding whether or not these individuals actually received their injections appropriately or did they have mal-administration which has occurred on rare occasions. All of those things, understanding drug levels is going to be critically important, and so I don't really want to speculate as to what the cases were, I have to see the data, and we just don't have it.

With regards to the second part of the question about whether or not there is a concern about the fact that integrated regimens are in the most popular first-line regimens are we concerned about the possibility of resistance developing to cabotegravir; I think the answer to that is that we expected there should be very few individuals who fail cabotegravir PrEP with resistance because for the most part we expected either CAB is there and you don't get it or it is not there, and you don't select for resistance. That is what we believe to be the case, and we will understand that better when we have the full data set.

In addition to that, what we have observed in the treatment space is that even individuals who have developed some resistance upon failure to cabotegravir actually have maintained sensitivity to dolutegravir and so I think that is really important. It just means there is the potential that individuals could break through with cabotegravir resistance and still have second generation integrated inhibitors but just dolutegravir as a treatment option.

Obviously the same challenge exists for Truvada and Descovy. They are also first-line regimens and so individuals failing PrEP with resistance to those have the potential to challenge first-line therapy, actually arguable even more so than cabotegravir, but that is something that we will learn a lot more about with the full results of this data set.

Andrew Baum (Citigroup): A couple of questions please. The first is to Kim. There is massive under-utilisation of PrEP in the US, especially in the black population, I can see how you can take market share from the existing PrEP users, but it is not obvious how you expand the market, particularly into the black patient population. Could you talk to, together with Deborah, how you may seek to do this, given the particular barriers related to an injectable IM.

Second, I didn't see any data in your presentation, or indeed online, about weight gain, which is obviously a feature associated with TAF. There has been some suggestion that TDF is a suppressive, so I am just interested in the data in weight, particularly because integrates themselves are associated with weight, so was there any increase in weight from baseline with the two drugs disfavouring the cabotegravir arm? Many thanks.

Kimberly Smith: Let me start with the first question about the African American population in the US, which is very close to my heart, and we were determined that this study would represent the population at greatest risk in the United States, which is black African American, and I think the fact that we were as successful as we were in including 50% of the US population was black African American actually is really a great indicator of the fact that actually Black African American can be reached for PrEP if the right efforts are made. I really do think that it is the job of our public health professionals to really reach out to these populations, and a lot was learned during the enrolment of this trial about how you get to these populations.

I also think the trial itself, the fact that actually black African Americans see themselves represented in the trial, that they see that this is data actually about them and not what has been enrolled in previous PrEP trials, which is the older men and often mostly Caucasian men. I think that the makeup of this trial and, again, the learnings of this trial will pick up a long way in starting to figure out how we can penetrate at risk Black African Americans in the US and that is going to be one of those important legacies of this trial.

So to answer the second question about weight gain, in the trial the overall change in weight out to week 105 is that individuals on CAB gained 1.3kg per year, individuals on the TDF/FTC gained 0.31kg per year, so there was overall a difference of 1kg per year. However, one of the notable things that Dr Landovitz, when he presented the data pointed out was that he looked at specifically the first year individuals who were randomised to CAB gained 1.5kg whereas individuals who were on TDF/FTC lost 0.5kg, so gained 1.5kg on CAB, down 0.51 on TDF/FTC.

In the second year the change in weight for CAB was 1.07 and for TDF/FTC was 1.06, so in the second year no difference, and so what you saw in the first year was that weight loss effect of TDF/FTC which we have seen in the treatment space. If you followed the ADVANCE trial or other trials there is something about TDF that is making folks lose weight. I don't know that that is a good thing. I think that is probably something deleterious about the weight loss, particularly in individuals that are treatment naïve and start on therapy weight loss is not something that we would think is good or would be expected.

When we looked at CAB in the HPTN077 study compared to placebo we actually found no difference in weight gain per year. It was basically 1.5kg per year on CAB or on placebo, so CAB in our treatment studies is not going to push you to have huge amounts of weight gain, it has been a relatively small amount of weight gain. This seems to be following a similar pattern.

Dani Saurymper (AXA Investment Managers): I have three quick questions. Deborah, can you talk about the response you mentioned that you expect to refile in the coming weeks. Given the unprecedented Government support, would there be an acceleration in approval time or would you expect a Class 2 review as per normal in these situations in spite of the tremendous data?

Secondly, can you perhaps remind people of the IP around cabotegravir and your likelihood of getting patent term extension given the duration it has taken to develop? In particular as it relates to that, do you have a bit more information on the pipeline as it relates to additional formulations that you are working on for cabotegravir, whether it be self-administered once-monthly, or moving to an every three months dosing regimen?

David Redfern: Thanks for the questions and Deborah will take all three of those.

Deborah Waterhouse: I can probably do all three quite quickly. In terms of the CRL, we are expecting to resubmit in the next couple of weeks, we are expecting to be a Class 2 and we expect approval within six months but we are not expecting anything expedited. This is the CRL that relates to the treatment regimen of Cabenuva which is cabotegravir plus rilpivirine, so it doesn't affect CAB for prevention, so that is the kind of Cabenuva answer.

As far as the patent, we are expecting the cabotegravir patent out until early 2030s for the core patent and we will do what we usually do, which is explore the utility of this medication in children where it often leads to a paediatric exclusivity patent extension, and

then there are some other patents that take us a bit beyond that. I would say early 2030s is the way we should now be thinking about the cabotegravir patent.

Regarding the reformulation, we are reformulating cabotegravir 200 hopefully into a cabotegravir 400, which then allows us to partner it with a lower volume with the maturation inhibitor, with the CAB and other things we have in our pipeline. This gives us the chance to move from an intramuscular to a more convenient patient-oriented administration, so that is how the evolution of our pipeline is going to look.

David Redfern: Thanks, Deborah. One day probably next year, we shall do a much fuller review of the earlier stage pipeline for ViiV and HIV, which may be part of GSK Day, but there are a lot of active programmes, as Kim said, principally around long-acting treatment. Next question please?

Geoffrey Porges (SVP Leerink): Thank you very much and congratulations to Kim and her team on these really impressive data. I have three questions if may. The first is for Deborah: what is your market research suggesting is the proportion of the current US PrEP population that is willing to trade off the burden of daily tablets versus the burden of every two months visits to physicians and the injection site reactions? Then particularly could you talk about how the superiority data influence what you expect that proportion to be?

Secondly, could you share a little bit more, Kim, about any imbalances or numerical differences in laboratory and clinical observations other than the weight gain and injection site reactions?

Lastly, could you talk a little about the profile with your Capsid inhibitor? There were some data for your competitor's Capsid inhibitor at this meeting: could you talk about how your Capsid inhibitor looks and what the next stage and next steps for development look like? Thanks.

Deborah Waterhouse: I can answer the first one quite quickly. The … market we know for treatment with an intramuscular injection, so the amount of people who would be willing to take that, is 15-20%. Because these data have come out 18 months before we were expecting and with superiority not non-inferiority, at the moment I do not have the research to give you a proportion of the market that we think will take this. However, we know that the minimum is 20% because we know that people are willing to do that in the treatment space. We think it will be more than that but we are currently in the middle of the research to discover people's willingness to take it every eight weeks and,

don't forget, it is only six times a year, so every eight weeks a single injection versus the oral, and that work is ongoing at the moment. Kim, over to you on the other questions.

Kimberly Smith: On the imbalance in labs and adverse events, creatinine clearance decreased was more common in Truvada, which again is not surprising. Nasopharyngitis was slightly more common on cabotegravir. Non-fasting blood glucose increase was slightly higher on cabotegravir and pyrexia was higher on cabotegravir. That pyrexia was associated with injections, so we know it was roughly 5% of the time, you saw individuals feeling feverish, basically around the time that they got the injection in roughly 5% of individuals compared to 2.5% on the TDF arm.

And with regard to your question around capsid, our product is still quite early. We anticipate first time in human next year.

David Redfern: I think what I would add there, because we have alluded to there's a lot going on in our early stage pipeline on long-acting treatment and I guess CAB 400 is an important component of that. Nothing is going to be monotherapy and the question is what do we then add to that and there are different options. We have talked about bnAb today, potentially the maturation inhibitor, long-acting and certainly as you mentioned, capsid is another option but as I say, another day we will talk more fully around that whole programme.

Deborah Waterhouse: Yes, and I think how you should think about the portfolio moving forward is obviously we have the oral portfolio underpinned by dolutegravir and then cabotegravir then becomes the underpinning of the long-acting both PrEP and treatment and so for us cabotegravir is a really, really important medicine and you have this kind of sister/brother, the oral in dolutegravir and then the cabotegravir being the long-acting.

It's important to see cabotegravir in the round, not just as a 200, but also as a 400 moving forward as we evolve our portfolio.

Jo Walton (Credit Suisse): Thank you - just two quick ones; firstly to check the timing. You say you are going to file in 2021. Do we assume that you file the day that Cabenuva is approved and then this goes in as an sNDA?

Then my second question is just about patient co-pays in the US. I can understand the pricing from a drug point of view, but here we also have to factor in an additional payment presumably for a healthcare professional to provide this treatment and the patient is going to have to go back to a clinic presumably more frequently than they normally would

because maybe they would go every six months or maybe every year and get repeats, but they've actually got to go in.

On the ground, what would you expect a typical patient to have to pay in terms of a co-payment for this versus what would be a generic pill which will be available, and I appreciate not as effective, but I'm just trying to think of the patient incentive or disincentive to take this medication?

David Redfern: Okay, thanks, Jo. Kim can comment on the filing. It's actually not related to the timing of the Cabenuva treatment filing, but Kim, why don't you explain in a little bit more detail about how we are thinking on timing?

Kimberly Smith: Yes, so I don't want to commit too much regarding the timing because as you see, this is a collaboration with the Division of AIDS in NIH and there are literally sites all over the world and so the timing, I would just say is not as fast as it would be if it were all in our hands.

It will not be an sNDA, it is a completely new indication so it will be a new drug application and so all I can commit is that it will be the first half of 2021 and I can't commit anything more detailed than that.

Deborah Waterhouse: In terms of the plan, there are two parts to it actually in terms of the way we are thinking. You have your commercially insured people who it varies wildly on what your plan looks like in terms of what your out-of-pocket will be, so for some it will be nothing and for others there will be an additional cost through having this as an injection that happens six times a year, so it really does depend upon what plan you are part of.

If I put commercial to one side, actually what the US Government are trying to do through something called Ready, Steady, PrEP which is the underpinning kind of financials and delivery of prevention to the hardest to reach communities is they are trying to ensure that there is no cost to the patient, so actually they are trying to bring any barrier of cost completely out of the way and allow people to access all forms of prevention with no cost to the individual. It will be varied in the payer space and I think it will be at very low cost in the Government paid-for channels.

David Redfern: Very good. Okay, I think we have time for hopefully a couple more questions, so the next question, please.

Damien Conover (Morningstar): Great, thanks for taking the questions. I just have one clarifying question around the compliance rates within the study. In the CAB arm I am assuming compliance was very high, but it wasn't clear to me what the compliance rates were in the other arm. I wasn't sure you could talk about that relative to showing efficacy between the two different drugs versus the two different levels of compliance with taking the drugs. Thank you.

David Redfern: Thanks, Damien. Kim?

Kimberly Smith: Sure, so the data that was presented regarding adherence to tenofovir was based upon a random subset of individuals that were on the tenofovir arm and that was about 370 or so. What was shown with the data was that 87% of individuals had detectable TDF levels, meaning that they were taking the drug some of the time. 75% had levels that were consistent with them taking it daily, so as instructed, taking it daily, so again, as I mentioned in the design of the study the assumption was that compliance would be roughly 67%, so the population ended up being more adherent to tenofovir than was anticipated when the study was designed, which I think makes it even more notable that we were able in this early timepoint to demonstrate such a significant benefit above TDF/FTC.

Peter Walford: I just have a few quick follow-ups if you don't mind: first the 084 study, just to check the first half '21 filing – none of the more info you were waiting for on the 084 study is needed for that, as I guess what concerned me is that the first half filing that you talked about is contingent entirely on the 083 study.

Secondly, then, just with regard to the filing of the mono – I appreciate it's different and not dependent on the combo, as you've outlined, but is it dependent on the FDA at least accepting the answers to your manufacturing questions, and that the issues have been resolved, or do the manufacturing questions in the CRL, are those completely unrelated to the manufacture and distribution of the mono CAB form? Thank you.

David Redfern: Thanks Peter – do you want to talk about the filing, Kim?

Kimberly Smith: With regard to the CRL, what we anticipate is that that would be resolved and the approval for treatment will have occurred before we file for PrEP, so it would just cross-reference to that, so it should not impact the PrEP filing.

With regard to 084, our desire is to file in a way that will allow us to get a broad indication that includes all genders, so it would be ideal if 084 could deliver data that enabled

that in time for us to meet both timelines for that mentioned so a lot of this depends very much on the timing of the delivery of 084 data.

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

James Quigley (Kepler Cheuvreux): Hi, thanks for taking my questions. The first one – apologies if I missed this – on slide 15 you have the injectable CAB taken for three years and then it looks like step 3 switching over to Truvada, is that what the treatment regime will be once approved, a 3-year injection? Apologies if I missed the reason for that.

Secondly, you mentioned 15-20% of the population could be willing to take the injectable - what are the key reasons for the 80-85% not taking the injectable? I'm just trying to work out how you expand that population - again, I appreciate you need to do the work, and are you guys going to point to the fact that it's 66% more effective? I would think that Gilead would point to 98.8% versus 96.4%, so what would be the incentives to increase that penetration? Thanks.

Deborah Waterhouse: Thanks for the question, then I will hand over to Kim for the other half. In terms of market, the 15-20% we know is the number of people in the treatment phase who are willing or would prefer to take an injectable versus a daily oral, because daily orals work really well, we've demonstrated non-inferiority so far between rilpivirine and cabotegravir taken every four weeks – and every eight weeks, actually - and oral, so there's no difference, so it becomes personal choice.

We believe with the 66% improvement in HIV acquisition that that number is going to be a lot larger, what I don't know at the moment is whether it's 40%, whether it's 50%, and that's where the research comes in, but it will be, I think, significantly above the 20% that we have seen for the treatment, so if I were to be taking a guess I'd be thinking more like 40-50% would be quite open and willing to take the injectable versus the oral, and actually, with the data that we have, it could even go higher than that; so I think that's the way I'd think about it, not reference it to the 20% - I guess I see that as my minimum, but I think we can go much beyond that, given the strong data that we have.

Kim, as a practising physician, do you want to give a view on that, is that something that you think is a reasonable way to think about it?

Kimberly Smith: I do, I think that there will be an appeal to not having to take a pill every day, there's just no question about it for individuals with PrEP. Part of the biggest challenge with PrEP today is that while it is, as mentioned, more than 90% effective when

taken, the problem is that it is not consistently taken. So whereas individuals may start out taking their medicine daily, it wanes over time, and that is when they become vulnerable, and I think that both individuals that are in public health as well as individuals that are at risk would really desire a medication that can take that need for daily therapy out of the mix.

Just to come back to your question about the study design, why was Step 2 three years? Mostly, you have to end the study at some point, you can't go on forever, and so three years was the designated time point. Obviously it is different now because the blind proportion of the study is being stopped. Individuals have been unblinded, individuals will soon be offered the opportunity to take cabotegravir if they were on Truvada, and those who were on cabotegravir will be offered the opportunity to continue to take cabotegravir until it is available commercially, and so the design is completely different now.

With regard to your question about will people need to take TDF after they have stopped CAB, again, that was part of the design of the study because individuals who went off CAB for study reasons they are presumed to still be at risk for HIV acquisition. So if you are still at risk for getting HIV you need to be on some sort of PrEP and that is really why you need to have Step 3. In the real world, individuals who go off of CAB, if they go off it because they don't want to take the injections anymore, they don't tolerate it, then yes, if they are still at risk for HIV they would need to go to an alternative type of PrEP, for example, TDF/FTC. If they go off because their risk profile has changed, then there is no need to take follow-up medication.

David Redfern: Very good. Thanks, Kim. That has completed the questions, so really appreciate everyone's time today as we have tried to explain, we are very excited about this data, and above all, what it could potentially mean over time is to reduce the incidence of HIV on a global basis. With that, I thank you and we look forward to discussing a bit more the HIV results at the Q2 presentation later in the month. Have a very good day.

[*Ends*]