

GLAXOSMITHKLINE
INNOVATIVE PIPELINE

Tuesday, 3 November 2015

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Sir Andrew Witty (CEO): Welcome everybody to this R&D Investor Update from GSK here in New York. I would like to also say welcome to everybody who is watching this on the live webcast investors media around the world. I would particularly like to say a warm welcome to all of the GSK employees, particularly those in R&D and especially those who are working on the projects, which we are going to describe to you during the rest of the morning. I hope they take the great chance just to sit back and reflect on the work that they have done so diligently over the last five, 10, 15 years to get the company to where we are on this portfolio.

What we plan to do during the morning or so is to take you through a reasonably large number of projects in the six focused areas of research at GSK. You will hear really from just two presenters after me, Moncef and Patrick, but, as you may have noticed, we do have a number of GSK personnel in the front row or two here. These are all of the Discovery and Development leaders of all the various programmes which you are going to hear about today. While they are not going to present to you, they are certainly here for you to interact with, certainly in the coffee session, of course, but also if there are questions which Moncef or Patrick feel are better answered by the various individual leaders, you will be hearing from them in that context as well. So just so you understand that is how you are going to, hopefully, get to dive into some of the detail.

Cautionary statement regarding forward-looking statements.

Now before I go into the session and the rest of the session, I draw your attention to the slide in terms of the various warnings and safe harbours.

Innovation is critical to maximising the potential of GSK in the current environment

Moving to the real focus of what we want to talk about, I just want to make a few introductory comments, very straightforwardly, orientating us within the overall context of the Group. The company has been going through a very significant amount of change over the last few years in the face of some quite tough challenges, particularly in 2014, and particularly in the era of moving through *Advair*. Clearly, over the last year or two, we have had to start to deal with price competition on *Advair* at a significant level and more generic competition around the world for us.

That has, clearly, been a driver of some of the headwind for us but the reshaping of the Group has been (a) to try to ameliorate that pressure as much as possible in the short

run but, much more importantly, to set the company up for long-term, sustainable growth as we move through that pressure and whether or not there is a generic over the next few years. We need to make sure we have a company which is vibrant and in growth post-*Advair*.

We believe that the three businesses that comprise GSK really represent three individual platforms for that growth. The transaction with Novartis really was about delivering scale in Consumer and an opportunity to transform the margin structure of that business, alongside maintenance of a very competitive growth rate. Over the next five years, we believe we can build something very special there. The Vaccine integration, similarly, gave us a very significant opportunity to broaden out our therapeutic coverage and achieve a significant quantum of synergy in the short run. You have begun to see how the transaction in Q3 has begun to really change the momentum of those two businesses.

What we are focused on here today then is really the Pharmaceutical and the Vaccine R&D portfolio in the sense of the R&D organisations really being the drivers of growth for the Pharma business specifically and, of course, for the Vaccine business alongside the transaction that we did. So we see innovation being pivotal to drive forward this part of the company. I am more than on the record to describe my anxiety about the ongoing price environment that we face around the world.

The challenges in the markets generally are common but we are beginning to see, over the last two years, much more precise risk in the US as not just legislation but also market change, partly stimulated by the Affordable Care Act, starts to change buyer behaviour, payor behaviour and consumer behaviour in the US. We can't take price increases for granted for ever and we need a business which can withstand those sorts of shifts.

Our belief is that the way to withstand that is to have a business which, of course, tries to expose itself to the price opportunity that exists, but also makes sure it's exposed to the volume drivers which exist both in the developed and in the emerging markets, which is why we are focused on that part of the business.

It is also important that the products that we develop are as robust as possible to achieve the maximum price benefit they can and that is all about differentiation. I am very pleased that in the portfolio you are going to see today, up to 80% of the molecules that we are going to describe to you we think could be first in class. That is important but we also believe that they are going to be differentiated from competition either at the molecular level, the claim level, the trial design or the delivery system level, so various ways we are looking to build into our products that kind of differentiation. We believe that having a scaled

Consumer Healthcare business, global leadership in Vaccines and an R&D business driving the future growth of Pharma, particularly as the *Advair* drag starts to recede over the next three or four years represents a very long-term opportunity of growth for the company, a very sustained opportunity of growth.

R&D strategy: reliable fill & flow with greater novelty & improved return on investment

If we look at what we have done in R&D over the last several years, you see this in your slide pack, this just summarises some of the changes that we have made in the business. First of all, you can see the process of accelerating the number of programmes. You all know we implemented with Patrick and Moncef a new discovery approach back in 2008, the DPUs. We said at the time it would take seven or eight years before you would really see much of an impact from that, because discovery is a long cycle business, you are now seeing a very substantial amount of product coming forward from that portfolio of research teams. We are very keen to allow those teams to do their work, have their chance to succeed or fail, but we don't let them fail forever and about two-thirds of the teams we began are still operative, the rest have been recycled and renewed with new ideas, it is exactly the kind of vibrant challenge that we wanted to build into the business. Of the work you are going to see presented today about a third was discovered by Discovery Performance Units inside GSK and about two thirds are worked on by those Discovery Performance Units, obviously in collaboration with outsiders.

I have already described the potential novelty of this portfolio, it is worth noting you are going to hear a lot about large molecules, you are going to hear a lot more about biological molecules, monoclonals, an area where the company hasn't necessarily been the leader, at the beginning of that science field, it is an area where we have invested significantly over the last several years to develop, we think, some interesting products, obviously *Nucala* where we are already in receipt of the positive opinion in Europe, anticipate FDA action imminently, *Nucala* is really one of the most exciting near-term opportunities for us in that particular area.

A lot of what you are going to see today was discovered inside GSK, there is an easy rhetoric to talk about how big companies don't discover anything, actually that couldn't be further from the truth, big companies, scientists inside big companies, discover enormous amount of product and GSK is no exception, but equally it is wrong to say that big companies only discover things internally, we have a very active collaborative research culture in the organisation and actually the split is about 60:40 in terms of where the products come from, and in terms of how we think about our discovery versus development focus about 60:40, and over the last seven or eight years we have been very focused on

taking fixed cost out of our organisation to allow us to develop our products going forward, so to move fixed cost to project cost has been a priority. That is why, over the last five years, nobody else has developed or filed or gained registration approval by FDA for more products than GSK, so we have been able to deliver a very substantial amount of product, while we have been able to control our R&D cost, because we have been taking out fixed cost and dedicating the resources to flexibility project cost. We will continue to do that.

Earlier this year we made the decision to close our research facilities in North Carolina, that releases a very significant amount of fixed cost, it has allowed us to spend more on projects, without overall increasing our expenditure. The Novartis transaction gave us a chance to unwire some of our fixed development cost which had built up around Oncology and some of the platforms, similarly giving us more flexibility.

As we look forward, we have, over the last few weeks, gone through a process where we have made a variety of decisions to stop investing in some of the products which are already on the market, where we believe there is not much utility in doing more work which generates more information in 2020 or 2022. The consequence of that prioritisation decision is we have created an envelope within our forward R&D spend over the next three years to accommodate the bolus of products that we are now seeing. So we think at least for the next two or three years we can absorb the likely cost of all of the progressions you are going to hear about today without a material change in the R&D budget, because we have made the choice to prioritise our investment in this portfolio.

New product contribution increasing as generic exposure reduces

As we think then about what does the next 10 years look like, you see the various phases of assets coming through, the group which came through, up through the end of 2014, that obviously includes the Oncology products that were then sold at the end of 2014 to Novartis, the batch which we have talked about generating at least £6 billion by 2020, the products we have launched last year plus *Nucala* and *Shingrix*, and then the next batch which, essentially, flow through from everything you are going to hear today; a very substantial amount of product we expect to be able to drive through the organisation.

Importantly, the drag on the company's Pharmaceutical business really diminishes as we run through that cycle.

New product growth more than offsets Advair decline

So over the last seven or eight years, of course, our Pharmaceutical business hasn't grown very much during that period, mostly because it has been burning off an enormous amount of genericisation assets in particularly the US. It is often why predicting or

understanding what the exact margin of this business is so complex, because it is easy to underestimate how much profit was skewed into that North American older business, but that business has gone now, the *Advair* price is moving through, there may or may not be a generic in the future.

Assets profiled at R&D day by planned filing dates

As we look through all of that portfolio you can see that the balance of growth delivery from the new products on a sustainable basis looks very different from the balance of drag that you would expect from the older products dropping out. Really for the first time since the creation of GSK the pipeline will have the opportunity to essentially be the contributor to growth, rather than the neutraliser of the drag before it contributes to growth, and that is a big shift and I think it is going to be a very notable point over the next five to ten years.

It is worth noting that after *Advair*, if indeed there is a generic *Advair*, the next material patent expiration for any asset within any of the forward forecasts that is imputed on this slide does not occur until after 2025, so you have an extremely long period of very calm water in terms of intellectual property protection. That is going to be very different picture to the picture we have been dealing with for the last decade and is a consequence of the focus we have made on innovative medicines and vaccines which we believe will give us sustainable growth going forward.

Just to reflect back to last week in terms of the Q3 results and really a proof point if I can put it that way, this just puts that schematic that I've just shown you into actual delivery over the last quarter and the last three quarters in fact, you can see the accelerating contribution.

New product growth more than offsets Advair decline

This is growth year-on-year, this isn't the absolute sales delivered by these new products in Q3 was £591 million, the year-on-year growth was £412. You can see that the drag, the year-on-year drag from *Advair* was £182 – bear in mind most of that was price because we are actually holding pretty big chunks of our volumes – most of it is price. That's the drag that we are having to deal with, but you can see that already the new products are significantly moving ahead of the drag and we would like to see that trend continue. We think it can continue at a pretty material pace as we go forward.

Assets profiled at R&D day by planned filing date

In terms of what you are going to see and how these products lay out over the time periods going forward, this is essentially hopefully a reasonably helpful sort of segmentation of when we think the filing dates are likely to come.

You can see here a summary of all the key assets and we all know not all of these assets will make it. This is the drug development business. There is inevitably an attrition rate, but this is our anticipation. Some things may go quicker, some things may go slower, there may be failures along the way but we think this is a pretty good estimate and of course we are not describing to you absolutely everything in the pipeline today in any case. It's simply a focus on the major projects.

I just want to make one point here. You will see that the first column says 2014 to 2017. I am well aware we are in 2015. The reason why it says 2014 to 2017 is because *Nucala* is on there and as you know, *Nucala* is still a filed asset rather than an approved asset and given its potential very substantial scale of opportunity for the company, that's why I've used the slide that way, so I think that's pretty straightforward.

Focus on delivering innovative and sustainable presence in 6 key areas

In terms of how that portfolio is essentially represented in how we focus in the company, we are focussed in R&D on essentially six areas - HIV/Infectious Disease, Respiratory, Vaccines, Oncology, Immuno-inflammation and Rare Disease.

These are the six focus areas of GSK. We are focussed within those six areas on innovative science. We focus on discovery ourselves, where necessary in collaboration with academia or other companies.

We believe that that focus on innovation will deliver a sustainable growth capability for the company. It's important to recognise that when we think about business development partnerships we have seen over the 15 years or so of the life of the company that the greatest value added transactions we can do are early stage, often academic rather than biotech, often platform rather than molecule. That doesn't mean to say that there aren't great molecules to buy in or partner with and it doesn't mean to say there aren't great late stage molecules to partner or buy in.

But generally speaking, the evidence that we've seen through our own actions over the last 15 years and looking at the rest of the industry is that it's better to focus on the earlier collaborations than the late and that's where our focus of partnering is.

Right now we have about 1,500 partners like that. We believe that's very important. Of course you don't necessarily see the outcome of that partnership in the next quarter or the next year but it absolutely drives the future value creation.

Great examples of that would be the adjuvant technologies, the cell and gene therapy technologies, those are examples of extraordinary early partnerships. The epigenetic collaborations we have with academia are unsurpassed by anybody else in the world and that's how we think about R&D. It's focussed, it's all about innovation and it's all about delivering a sustainable growth for the company, not just for the next year but over the next ten or 15 years.

Focus for today: Innovation to deliver products of value

During the rest of the day you are going to be led through these various programmes by Patrick and Moncef, the heads of our Pharmaceutical and Vaccines R&D businesses, two people who have been involved really from the start of the new way of doing R&D at GSK from 2008. They have been all over every decision that we have ever taken inside this portfolio.

The projects which have been killed have been killed because they have approved them and the projects that have been green-lighted have been green-lighted because they have approved them.

In the case of Moncef, his name is on some of the patents. You are not going to meet a researcher who has got more credibility around understanding the science, particularly in the vaccines field and in the case of Patrick you have one of the most accomplished academic physicians in British medicine. Again, you are going to go a long way before you find somebody who is better qualified to think about how medicines can be developed to change people's lives.

I have been incredibly privileged to have these two men on my team over the last seven or eight years and I am extremely proud of the work that everybody who works for them across all of our R&D organisations has done to move the company's R&D portfolio so far forward.

It gives me great pleasure now to ask Patrick to come up to begin the rest of the presentation and to start the day in full. Thank you very much. Patrick.

Part 1

HIV, Infectious Diseases, Respiratory & PHI

Patrick Vallance

President, Pharmaceuticals R&D

Thanks very much, Andrew. Good morning everybody.

GSK R&D: what is important to us

I am Patrick Vallance, I head the R&D part of Pharmaceuticals and what I would like to talk about is the medicines, but before I do that I just want to say a little bit about R&D and specifically to say the things that really matter to me in terms of R&D.

Innovative science absolutely underpins how we make the medicines I am going to talk about. Patient need absolutely underpins why we choose to make the medicines against the diseases we do and quality in terms of how we work and how we end up with a quality product.

Now in each of these areas, of course, the ultimate proof is the medicines themselves that come out, but there are some benchmarks which allow us to see where we are. So in Innovative science, Andrew has already alluded to the fact that the medicines we made and how they are performing but also in terms of the percentage of potential first-in-class. Publications are a surrogate for how well-connected we are, how well-respected we are in the academic community. Not only do we publish a lot but actually we publish in the very highest quality journals, highest citations, 35 publications annually in the very top journals.

In terms of patient need you are going to see a focus today around quality of life measures. You are going to see a focus on how we look at preventative and curative medicines and we at all stages have significant patient input into how we think. How do we look at that externally? Well we have got breakthrough designations, priority review and we expect many more of these.

Quality: Andrew has already alluded to the fact we have had more approvals than any other company. The number isn't what matters, the fact is that actually we have more first-cycle approvals and we have had nothing but first-cycle approvals since 2012. That is a marker of quality; you don't get that just by doing things fast, although you will see we actually do, do things fast in terms of development organisation.

There is an emphasis in molecule quality which you are going to see running through a lot of what I say, because fundamentally the quality of the molecule determines a lot of what comes next.

Throughout all of this, partnership is of critical importance. Partnership with regulators, and you will see an example of a partnership around the qualified biomarker for COPD, partnership with other big companies, which is increasingly important in areas where combinations become the norm. Partnerships with biotech at very different – many stages of what we do in partnerships with academia, including new models of how we actually take academic ideas through to medicines.

I will just pick out one thing before I move on and that is the partnership with the European Bioinformatics Institute, Sanger Centre and now with the Altius Institute in Seattle – this is around harnessing the rapidly daily advances in genetic information which give a real different insight into how you pick targets for medicines. This is a complex process that needs the sort of power in these places of real academic expertise of bioinformatics.

Recruiting and developing the best scientists

The other thing of course that matters enormously is people and you are going to meet some of the world-class leaders that we have at GSK this morning. Whether they come from academia, such as Paul-Peter Tak, who came from the Amsterdam Medical Centre and heads our Immuno-inflammation unit, Lon Cardon, who is not here today, but was Professor of Genetics at Oxford and heads all of the genetic information, including the collaborations I have just mentioned, his team has recruited extensively from the very top genetics labs. Whether it is people like John Lepore from Harvard and Penn into GSK, or Chris Carpenter, who is Associate Professor at Harvard, and from Biotech people like Edith Hessel, Zhi Hong, who heads Immuno-inflammation, John Bertin, who has done an amazing job in innate immunity, and of course from big companies. And we have people here today such as Sven Kili, who came from Genzyme, who is heading our gene therapy approach, we have others such as Carolyn Buser from Merck and, importantly, we have Axel Hoos, who came from BMS and was the person who developed ipilimumab, so you will see some of these people today.

Career development is crucially important for us and actually at all stages – I will just highlight one programme and that is the programme we have for chemists, where we have 50 chemists in training doing PhDs whilst being part of GSK. I think the 19th one was awarded last week, but the fellowship schemes go throughout GSK with individuals being allowed to focus on science. Probably the best example is some of the most senior successful drug discoverers who are actually able to get on with discovering drugs rather

than just rise up the organisation by being managers of more and more people. So pathways for career development and science – incredibly important to us.

Finally, all scientists need challenge. They need challenge from external group and our external advisory group, my research advisory Board, Chaired by Joe Goldstein – two Nobel prize winners, Joe Goldstein and Jim Rothman, four others, amongst whom others are tipped for Nobel prize – Carolyn Bertozzi from Stanford, Hal Deitz, Peter Ratcliffe from Oxford and Tom Jessell from Columbia, challenging high level input from really world-class scientists and this pervades throughout the organisation.

One final thing to say about our external advice. We have recently formulated an immunology network to really try and bring in immunology challenge throughout the organisation because it is such a key theme through many of the medicines I am going to talk about and the latest example is actually bringing in six external academic investigators to have labs based inside GSK, not only to challenge, but of course to stimulate and give new ways of thinking, a so-called immunology catalyst.

I am going to move off the general though and talk about the medicines in particular and I am going to start with HIV and Infectious Diseases.

HIV/Infectious Diseases

Infectious disease burden continues to grow and present public health challenges

There are four areas that we are working on: HIV with ViiV of course; HBV, HCV and acute complicated infectious diseases.

Let me start with HIV: this isn't a problem that's gone away. Nearly 40 million people are living with HIV and actually 1.2 million in the US and, of those 1.2 million, only about 30% are adequately virally suppressed. It's a huge unmet need – a need to deal with issues of resistance, adherence to therapy, to addressing long-term toxicities of medicines by reducing the burden of therapies and, of course, ultimately to look for things like remission and cure.

HBV – a major worldwide problem, despite vaccination. About 240 million people with chronic hepatitis B can't be cured and there's an urgent need to look for things that cause remission or cure. HCV, of course – there are cures, and here I will just focus on one thing when I get to it, which is the way of thinking about the single administration cure for HCV.

Acute, complicated infectious diseases – there is little doubt there is a major problem to address. Look at the problem of rising antimicrobial resistance and the threat that that poses across the world – huge problems to address.

How do we do this? There are three areas we cover: I will focus on remission and cure, I will focus on prevention and I will focus on innovative treatment regimens, and I will focus on long-acting treatments.

Dolutegravir set to be at the heart of future treatment regimens

I'm going to start with HIV and I'll start with dolutegravir – a great success story for GSK and ViiV. I want to draw your attention first to the bit of paper in the top left-hand side of this slide. This bit of paper was a note on which one of our chemists, Brian Johns, in 2005, sitting down with his counterpart from Shionogi, drew some structures of a molecule that he thought they might want to make, and some approaches to chemistry – in this case, trying to look at how they can make a third ring in the molecule close. That was a pivotal step in what then became dolutegravir: this collaboration with Shionogi was a very early-stage collaboration along the lines that Andrew has spoken to.

The second really key step in the development of dolutegravir was a decision made by Zhi Hong, who is here today, which was to take three integrase inhibitors into the clinic simultaneously and choose the best molecule in the clinic – and that best molecule was dolutegravir. As you know, the efficacy is good in terms of rapid and sustained viral load drop. The resistance profile is actually very good and important in terms of the properties of the molecule itself and how it binds, the favourable PK profile and the drug is well tolerated – and you know it is launched and is doing very well.

Not only is it launched, but it's in combination in *Triumeq* and there are now nine ongoing studies backing dolutegravir at the moment – looking at switch, looking at TB infected populations, looking at women, and looking at other ways of using the medicine. But the two I want to focus on today are the idea that dolutegravir becomes at the very heart of future treatment regimens, and look at dual therapy – an idea which is gaining ground.

There are two trials, one with rilpivirine and one with 3TC, and you can see the launch date there.

Why do we think this could be a good way to go forward? I want to show you some data not from us but from an investigator-sponsored study which was presented last week at the European AIDS conference.

PADDLE (Pilot Antiretroviral Design with Dolutegravir and LamivudinE): investigator sponsored study design

This is a small study of a dual therapy, with dolutegravir and lamivudine, looking at patients with a viral load – so naive patients to treatment with a viral load between 5,000 and 100,000 and a two-tablet treatment to see whether this two-tablet approach can work. Small – as I say, it is two cohorts.

There's a couple of things I want you to notice, though, and really only two that are really important here. So, first of all, the baseline viral load – you can see that some people were actually higher than 100,000 but the key thing is that week eight suppression below 50, week 24, suppression. It tells you it's fast and it tells you it's durable. This is the sort of reason to believe that the ongoing studies with dual therapy can lead to a change in treatment paradigm.

Cabotegravir

I mentioned that, when we took dolutegravir into the clinic, one of three integrase inhibitors at the same time, there was another molecule that went in at the same time and that was cabotegravir. Cabotegravir had some particular properties, one of which was an extremely long half-life. That half-life can be extended further by a particular nanoformulation.

On the left-hand side here is a pharmacokinetic analysis of cabotegravir, so you are looking at the concentration of drug against time. Normally, when you look at these graphs, you are looking at hours along the bottom but you are looking at weeks here. Following a single, intramuscular injection, this formulation of cabotegravir leads to drug levels in the blood which were between the two dotted lines – and the two dotted lines are the therapeutic index: you don't want to go below it and you don't want to go above it. What you can see is that we can reach a dose of drug which has sustained levels in the blood for many, many, many weeks. So this raises the possibility of a new paradigm of HIV treatment, where you are looking at intermittent injections, perhaps every two or three months, rather than daily treatment.

We know that cabotegravir works and so in the middle panel what you are seeing is the percentage of patients with viral load drop below detectable. You can see in three lines there the cabotegravir and, in the purple-y line, the comparator. You can see very rapid viral load drop and very sustained effect. So this drug works. On the right, you see the possibility in prevention, pre-exposure prevention, and this is an animal model, rectal challenge in a non-human primate. It is pretty self-evident: if the drug is given, there is 100% protection; if the drug isn't given, there is 100% infection. So here is a possibility of long-acting treatment with the possibility of better adherence, potentially turning into a resistance advantage

because you don't miss doses, and potentially enhancing the possibility of improved quality of life for some people.

Cabotegravir long-acting clinical studies

Where are we in this programme? In prevention, two Phase III studies, one in women, one in men, both in partnership and that partnership will be announced shortly with the MIH. These studies, HIV prevention ongoing due to start, HIV treatment - what about the treatment? Here we need to know that we have got an effect of the long-acting drug: LATTE 2 is the read-out for that, followed by the Phase III start.

In HIV prevention, we expect the drug perhaps to be given every two or three months. In HIV treatment, the question is can you do it every one month or every two months and, of course, you need a partner and the partner compound here is rilpivirine from Janssen, which can also be formulated long-acting. It is not quite as long-acting as cabotegravir, so that will probably determine the overall dosing interval.

LATTE 2 - cabotegravir LA + rilpivirine LA for treatment of HIV

What I want to share with you this morning are the headline results from LATTE 2 to show you what effect this has. These are hot off the press, more work to be done analysing them but I would like to share with you the results. This is a IIb study examining long-acting cabotegravir in combination with long-acting rilpivirine.

People were initially treated with oral therapy and then either kept on oral or given four-weekly injection or every eight weeks. Through the entire study, the 32 weeks, what you can see is on the eight-week injection, there was a 95% success, four-week injection 94% and with oral 91%, so very clear proof of principle that this can be done, a very clear path now to the Phase III study. As you would expect, there were some injection site reactions and some withdrawals but you can see rather low numbers in terms of withdrawal. So cabotegravir LA in combination with rilpivirine LA looks like a way forward in terms of Phase III for a new paradigm for treatment for long-acting medicines.

Next wave cabotegravir long-acting combinations

Just to stick with cabotegravir for a minute, I said there were some properties of the molecule itself which were important, and there is the way in which we can formulate it in nanocrystals, allowing us to give it every two or three months. This then, we believe, becomes an anchor for other long-term treatments, other intermittent treatments. The one that we are excited about now beyond rilpivirine is broadly neutralising antibodies, and many of you will know this is a very hot area in the HIV field: the idea that antibodies from patients with broadly neutralising potential can be turned into drugs. You can see how this could

work for prevention but also, of course, once you have a partner like cabotegravir, there is a possibility you can use this for treatment as well.

The other thing that I am pleased to be able to tell you is that we have an agreement being put together with the NIH which should be announced later this week on taking cabotegravir together with a broadly neutralising antibody into the clinic to test this concept that this provides a new way of looking for intermittent treatments for HIV. That will be in the clinic next year and we start to get results from these sorts of studies very quickly.

GSK & Regulus combination offers potential for a single administration treatment for HCV

Just sticking with this notion of long-acting medicines and this way of formulating them, I want to move from HIV to HCV. If you look at the bottom graph here, take the middle graph, this is an NS5B inhibitor that we have, so an HCV pan-genotype inhibitor NS5B. This is following oral dosing, you can see a drop in the HCV RNA with 30mg and 60mg, lasting for many days following two oral doses. So this is a long-acting oral.

If you now look at the right-hand graph, this is the prolonged PK in animals when we make it in the same nanocrystallisation as we have for cabotegravir. In fact, in the orange line is cabotegravir pharmacokinetics, and in the blue line is the HCV medicine, so you can see many weeks pharmacokinetics following a single dose in the animals. That raises the possibility of a single dose treatment for HCV and at the top half, of course we need a partner molecule again and here it is the Regulus molecule, which is an oligo against the micro RNA miR-122, which inhibits HCV viral replication, again pan-genotype, and their medicine works for many weeks as well. So the possibility here of combining these two leading to the concept you go to the doctor, you get diagnosed, actually you have one treatment there and it's done. We don't know yet as we go into the clinic next year, it is going to go in with the Regulus compound plus, initially, oral 175 and then we'll move to long-acting and long-acting, and we'll get the results from that over the course of the next year.

GSK & Isis collaboration targeting next generation of HBV medicines: functional cure

To move from HCV now to HBV, the problem, as I said, is that HBV remains prevalent, it remains devastating and it is very difficult to eradicate. One of the reasons it is difficult to eradicate is that the viral antigens themselves cause immune suppression. It is important, therefore, to get rid of those antigens in order to allow the immune system to clear it and the approach here, really pioneered through Zhi Hong again, was to go with an antisense approach with our partners in this Isis Pharmaceuticals to say 'Could we knock down the antigens and therefore restore the innate immune system in order to try and clear

the virus?’ What you can see here is the experiment in animals showing both HBV surface antigen and e antigen decrease in an animal model with the treatments and we know it works, the concept works, it has been into Phase I, it will go into Phase II early next year and we expect to start seeing results on that fairly quickly, again we will know quite quickly whether this works – this has the potential to cause long-lasting remission and potentially even lead to cure of patients with chronic HBV infection.

Infectious Diseases strategy: from innovative treatment regimens to the pursuit of care

So have talked about HIV, HCV and HBV, and the other major need is around this whole area of acute complicated infectious diseases and particularly antibiotics, and you will be well aware of the urgent need for new antibiotics and particularly antibiotics that can really tackle these major resistance problems that are emerging.

First in a new class of antibacterials: gepotidacin (GSK2140944) – a topoisomerase inhibitor

I am pleased to say that we have a new class of antibiotic in late stage development, gepotidacin, this is a topoisomerase inhibitor. At the bottom of the slide, on the right, is the crystal structure published in one of the *Nature* journals, showing where the topoisomerase class bind compared to quinolones.

Why are we excited? Well, this is now been into over 400 people, we know it has got the tolerability profile which is acceptable and we know it has effects, and the effects it has have a potential to really go after some important areas. Yes, it works in MRSA, that is not such a big area anymore, the really key thing is gram-negative infections and in fact there have been no new class of antibiotic for gram-negative infection for well over 20 years. It hits E.coli and it hits drug resistance gonococcus, two major areas of unmet need. In fact, the E.coli is very interesting, it has two topoisomerases, 2 and 4, both of which get hit by gepotidacin, and you can imagine if you hit two critical enzymes with the same sort of potency it is very difficult to get resistance against that, because the bug has to get resistance simultaneously to both and that doesn’t happen. So we believe there is a very good innate barrier to resistance in this medicine and this will go forward in trials in both of those areas and, in fact, in gonococcus we have already got some results showing that this is working.

The one other area, clearly not a major area to be used in at the moment, but something important for the future, is in plague and in the top graph what you are seeing there is the animal model and, of course, you can get these medicines potentially approved on the basis of the animal data, the graph shows the plague results and it is, again, one of those ones you don’t need a statistician for, if you are treated with the drug there is 100%

survival, if you are not treated with the drug – this is non-human primate model – there is 100% death. So an important new antibiotic to add to the armamentarium.

Infectious Diseases strategy: from innovative regimens to treatment and pursuit of care

Let me just summarise this, in HIV dolutegravir, we believe, is at the heart of future regimens, cabotegravir opens up a totally new concept of intermittent treatment in partnership with others, there are new medicines coming on behind this, in terms of maturation inhibitor, VEGF and others, some of which have got potential for long-acting potential as well and, of course, there is the partnership I mentioned with broadly neutralising antibodies. HCV and HBV, I have given you a glimpse to just two medicines there and I have told you about the antibiotic. I haven't told you about the single shot or single tablet treatment for plasmodium vivax which is in Phase III, and I will mention the other molecule here, danirixin, when I come to a later stage.

The final thing I want to talk about in here is just to say in remission and cure we have started what we think is a very important new venture together with the University of North Carolina, Qura, looking at ways of combining medicines, some of our own and some others, to start to look for this holy grail of how you can actually cure HIV.

Respiratory

Let me move now onto the second powerhouse area, which is Respiratory.

Respiratory diseases: still significant unmet need

In Respiratory the areas that we focus are asthma, COPD and now increasingly lung fibrosis and acute lung injury.

Asthma hasn't gone away, it is increasing in prevalence across the world. We do think that the GOLD standard treatments, the inhaled treatments that we have got available do provide most of the need for mild and moderate asthmatics, except the one thing they now want is remission. But the area where there remains very major unmet need is in severe asthma, this is a smaller population, maybe 5% to 10% of all the asthmatics, they occupy about 60% of the total healthcare utilisation and for these individuals this is a very devastating disease. Let me give you some examples.

Patients with severe asthma will have been to the hospital ER room 50% of them in the past year. 50% of them will have had an oral corticosteroid burst in the last year. 30% of them will have been admitted to hospital in the last year. 20% of them will have had a day off work or school in the past two weeks. 25% of them – and this is an astonishing statistic –

25% of them will have had a near-death experience. This is a very different group and where the major unmet need is.

In COPD, major cause of mortality and morbidity, predicted to be the third cause of death by 2030, the third leading cause of death, an absolute need for biomarkers and I have already alluded to the fibrinogen biomarker that has now been qualified by the FDA, but also an absolute need to look at the underlying causes of disease driving progression of lung damage.

And in lung fibrosis and acute lung injury, first of all the mortality and morbidity is extremely high in these conditions. The number of medicines coming through actually is not that great and the ways in which these are evaluated doesn't really allow them to progress and I will come back to that at the very end.

Asthma R&D strategy: from secondary prevention to primary disease modification

But let me start with asthma. Severe asthma, the cell types that we really worry about, the eosinophil, the neutrophil and the dendritic cell of course for the remission part.

If you take severe asthma, about 30% of patients are driven by eosinophilic asthma, 30% neutrophilic, about 20% overlap between neutrophilic and eosinophilic and then 20% with a paucicellular approach. What we want to do, we want to go against these targets with biologics, with extended duration biologics. We want to go for remission-inducing therapies where we can and where we go for inhaled we want it to be once a day.

Nucala (mepolizumab) demonstrates significant reduction in exacerbations

I am going to start though with the eosinophilic asthma and start with *Nucala*. *Nucala* has, as Andrew said, a positive opinion from the EU. It's PDUFA date for the FDA is tomorrow. I show you the results here; cumulative exacerbations in this severe asthmatic group on placebo and in this case, placebo means standard of care, so these people are already on multiple therapies against mepolizumab IV or subcutaneous and you can see about a 50% reduction in exacerbations.

Straightforward patient selection; patients who've got severe asthma with exacerbations raise the eosinophil levels, very easy to do clinically. A 50%-plus reduction in exacerbations, a slightly higher reduction in the visits to the emergency room and hospitalisations, just over 60%.

An improvement in health status as assessed by the St George's Respiratory Questionnaire. This is really important. The quality of life measures for these things are important, a seven point reduction. Four points is the minimal clinical importance, seven is actually not really seen with these sorts of medicines and don't forget, most of the things for

which this scale have been used are against placebo, not against people taking existing maximum standard of care.

Dosing every four weeks, no weight adjustment and well tolerated. It might be worth just sort of putting this into context of what else is coming along and what else is out there.

Nucala will be first in class with a strong profile

Xolair of course is out there with use adjusted by weight and so on for the administration. *Nucala*, we are in the last stages hopefully of getting this approved and what I want to do is just outline to you some of the things that we think are important in terms of the properties of molecules in this biological class for severe asthma.

The first is we do believe subcutaneous is important and we believe that monthly intervals are important. It's clearly important you need to have efficacy in the right patient group. They need to be the patients who are resistant for some of the other medicines that can already be taken or have failed rather on some of those medicines and still have exacerbations.

We think it's important there's a very low injection site reaction. Of course it's also true that you don't want to see things like angioedema. We think it's important that the patient selection biomarker needs to be straightforward. It needs to be something like eosinophils which can be measured clinically and of course we don't yet know what the output is in some of the other medicines. We have our own experiences with IL-13 and as you know there are some failed trials in IL-13 and in the IL-4R we will wait and see how the data look at the end.

One of the things that we do think is important though is that eosinophils drive this disease and we think it's rather important that the medicine decreases the eosinophils and of course in some of these other mechanisms there is actually an increase in eosinophils in some patients, so we are very confident that there is a good profile there for *Nucala*.

Nucala has potential in other indications

Let me just talk about *Nucala* in other indications. Actually it has got potential in virtually every eosinophilic-driven disease, so where eosinophils drive disease there is clearly indication expansion.

So we are looking in eosinophilic COPD and we expect our trial to read out in 2017. We are looking in eosinophilic granulomatosis or Churg-Strauss disease where we already have data to show this works. That study will read out in 2017.

Hypereosinophilic syndrome, we have had discussions with the FDA on the correct endpoints. We've already got data that we know this drug has an effect in that syndrome, that trial reads out in 2018.

Nasal polyposis and chronic rhinosinusitis, again we've got data showing it works in these eosinophilic-driven patients and we are also entering a study in atopic dermatitis, so we see potential for quite considerable expansion beyond severe asthma.

Two novel biologicals

Targeted approaches for uncontrolled asthma patients

I want to move now from the eosinophil to the neutrophil and here I want to talk first about a molecule partnered with Janssen which you will hear more about later on and this is sirukumab, an IL-6 monoclonal antibody.

We believe this has the potential to target the neutrophilic and the neutrophilic eosinophilic overlap group in severe asthma. You will see at the bottom the IL-6 levels are up in these groups and that actually lung function is decreased in this group as you would expect.

Critically important, there is a genetic association, a strong genetic association of this pathway with asthma. We will start studies in 2016 of IL-6 antibody sirukumab in asthma. We expect read-outs in 2017 on the clinical effects.

The second area is again a sort of validated target this time because TSLP monoclonals have been used systemically and already effects have been seen in mild to moderate asthma and there are studies ongoing in severe asthma. We are taking a rather different approach, which is to go for an inhaled antibody fragment, a domain antibody. Why do we do that? We think it is important, actually, that this is an epithelial target, that we can target the epithelium by inhalation and actually get a better risk benefit profile by doing so.

We know that inhaled domain antibodies can work and the bottom part of the slide isn't a mistake, it is a different target I am talking about – I just want to show you that this can actually work. This is an inhaled domain antibody in healthy volunteers with an endotoxin challenge; this happens to be a TNFR1 domain antibody and in the red you can see the effects on lung neutrophils and cytokines of inhaling a domain antibody.

So we are going from an inhaled approach with TSLP dAb and that will be in the clinic in 2016.

Let me just try and summarise for you the biologics pipeline.

***Nucala* is at forefront of a diverse asthma biologic pipeline**

We talked about *Nucala*, sirukumab into the clinic next year, tackling that other population of neutrophilics and eosinophilic neutrophil overlap. We have also got a long acting IL-5, so we have engineered the antibody to be extremely long acting. The reason for this is that we think ultimately this may move to the concept of being able to give an injection twice a year and the rest of it managed with one puff once a day inhalation from inhalation therapy. Anti-TSLP dAb; I have talked about that – it goes into the clinic next year and behind this we also have a long acting, so again a six monthly potential anti-IL-5/13 bispecific.

I want to move to the last bit of asthma, where I have talked about remission. Remission of course is the major aim for many people with asthma: “How can I stop having the asthma that I have got?”

GSK2245035 intranasal TLR7 agonist

TLR7 is actually quite a well-established target. Many people have gone after this as a way of inducing allergen independent immune modulation and potentially leading to long term remission.

The issues with TLR7 have been target engagement, tolerability and durability and with the molecule we have got we believe we have addressed all three of those. So what is the evidence we have got target engagement? Top-right here you can see the effects of intra-nasal TLR7 on IP-10, a marker of interferon alpha production in this case and you can see this increasing substantially following intranasal administration.

In the bottom this is a study looking at nasal symptom scoring and we are giving the drug into the nose because that is where the allergen goes first and we are looking at this as a surrogate effect. What you can see is a decrease in nasal symptom score with the intranasal TLR7. The magnitude of effect that you are looking at here is roughly the same as you see with an intranasal corticosteroid.

The fact it works is perhaps neither here nor there because you expect it to; the fact, if you look at the right-hand side down at the bottom, three weeks post the last dose it is still working is what matters. This is the durability point. And we know the medicine is well-tolerated given the intranasal formulation. So we are actually rather confident here that there is a route now to go into asthma looking at intranasal TLR7 with a molecule which has the properties that you would want.

Asthma R&D strategy:

Let me try and summarise this. Targeting the eosinophil, the neutrophil, the dendritic cell with targeted biologicals, extended duration – I haven't mentioned the inhaled products

which you know about, which Andrew has talked about the growth in that we have launched recently and the potential for remission.

Let me move to COPD.

COPD R&D strategy:

So COPD again we are targeting particular cellular drivers of disease – the eosinophil, neutrophil and epithelial cell in this case, with the epithelium we think being particular important. The eosinophil I have talked about; we are targeting eosinophilic COPD with mepolizumab. I do want to come back to the two major aims: reduce infection driver exacerbations, preserve lung function. This isn't a reversible disease, we need to try and stop it.

I will first of all tell you where we are on inhaled daily treatment, because we do believe here inhalation treatment has become the mainstay and will remain that mainstay of treatment for the foreseeable future.

Closed Triple: once daily triple therapy in established *Ellipta* inhaler

So where are we on closed triple, the idea of having three existing mechanisms – steroids, LABA, LAMA altogether in one device, one puff once a day?

On the right-hand side you can see the effects of UMEC, the anticholinergic add-on to ICS LABA, whether that is *Advair* or *Breo*, and you can see you get about another 120mls of FEV1 advantage; that is very; significant, very clinically important, so there is no doubt that three therapies bring benefit.

We filed the open triple with the FDA. The closed triple, so all of this in one device, ongoing studies – we expect to file in the EU in 2016 and in the US in 2018 because there needs to be an exacerbation claim there in 2018 with the closed triple. So good progress on moving to this once a day inhaled triple therapy.

I want to come back, though and talk about neutrophilic mediated disease.

So the neutrophil is a key driver of lung damage and, indeed, the recurrent exacerbations and I am going to show you two programmes trying to target neutrophilic mediated lung damage in COPD.

GSK2269557, inhaled PI3K δ inhibitor targets neutrophil-mediated lung damage in COPD

The first of these is our inhaled PI3K δ . I want to take a moment just to tell you why I think PI3K δ is important in lung disease.

At the top right-hand side of this slide, you will see a family tree and the individuals marked in black have a particular mutation in PI3K-delta. This is an activating mutation, and they have a syndrome called Activation of PI3K-delta Syndrome, so the disease is caused by over-activity of PI3K-delta. It manifests itself as recurrent infections in the lung. They get a picture of both bronchiectasis and COPD-like changes in the lung, which you can see in the CT scan, and they die at a very early age. So there is no doubt that PI3K-delta activation causes lung disease. There is also no doubt that in COPD we see increased activity of PI3K-delta, so we have some evidence in common COPD that this is a problem.

I just want to illustrate for you what we think the mechanism is and why we are excited about this. In the bottom here [*on slide*] is a study looking at neutrophil migration in response to gradient of IL8 in patients with COPD and healthy volunteers. What happens is neutrophils move towards the IL8 gradient in a rather purposeful, linear fashion, and that is shown in the green circles. In the patients with COPD, the neutrophils do not move in a purposeful way: they move around randomly, presumably spewing out toxic substances including free radicals and this lack of directionality we think is important. This is corrected with a PI3K-delta inhibitor.

So, PI3K-delta is important in human disease and the genetics have absolutely showed that. It's increased in activity in COPD. We think the neutrophil directionality is important. We are in the clinic with this molecule. We know it engages the target and we know it decreases inflammatory cytokines in patients on top of standard therapy – so this is on top of therapy again. And we have preliminary evidence that actually the neutrophil gene signature looks as though it is corrected towards a normal phenotype. So we are excited about this and expect to get more read-outs over the course of 2016, with a plan to start the IIB studies either at the end of 2016 or the beginning of 2017.

Danirixin (GSK1325756): an oral CXCR2 antagonist

The second is danirixin, and danirixin is a well-known target, actually, CXCR2, and this has been studied by others as well. CXCR2 prevents neutrophil migration and so, again, we are trying to stop the neutrophil getting into the lung where it can cause the damage.

This is, again, in this case, a sort of validated target in a way, because others have actually produced CXCR2 antagonists and shown that you improve some effects in both bronchiectasis and in COPD actually. So there isn't much doubt that, if you can do this, you're going to have some effect. The problem is that the compounds that have been produced all cause systemic neutropenia: you lower the neutrophils in the blood and therefore you expose the patients to infections elsewhere.

We have a molecule which engages the target, does what we want in the lung, but does not cause systemic neutropenia. We think we understand the reasons for that in terms of the way the molecule works – I'm not going to go into details on that. But, therefore, we've overcome the problem of this class.

Just to show you that this does have an effect, on the right-hand side, you can see the results from an ongoing study. This is a symptom score in patients with COPD and it is a real-time data capture using one of the digital approaches we are now using in our studies, where we can see real-time data evolution. What you can see is the two groups, in blue danirixin and in red/orange, placebo, and you can see clear separations of the curve. This separation on this score – two points is about equivalent to four points on the St George's respiratory questionnaire I mentioned earlier. So this is a significant separation, a clinically important separation of these curves.

So, a molecule which goes after an established target, doesn't cause a neutropenia, evidence of efficacy in the clinic and we expect the Phase IIB studies to start in 2016. We will have more clinical read-outs on this study in 2016.

I alluded to it earlier under infectious diseases and you can see why this could also prevent lung damage and certain acute infections. We have ongoing studies there in influenza.

OPD R&D strategy: pipeline

Let me draw that together for you. I have talked about targeting COPD with biologics, with *Nucala*; infection-driven exacerbations that we're tackling through neutrophils; preserving lung function and, of course, the once-daily, one-puff inhaled therapies which we think form the bedrock of how these things are going to be treated.

Drivers of our long-term leadership in asthma and COPD

I don't think there's any doubt that, in the respiratory space, GSK has been a major player for a long time, with excellence in inhaler and delivery technologies and now understanding how to develop a biological in this difficult area; understanding of targets; patient phenotypes, and expertise in both the design and delivery of trials. Why do I show you that? It is because we have two new areas that we are going into, where we intend to apply exactly that knowledge to those areas.

Respiratory R&D beyond asthma and COPD

The first is in idiopathic pulmonary fibrosis. This whole area has been plagued by a lack of proper clinical trials. I mean, we rely on things like a six-minute walk as an endpoint, which can't be sensible. We have spent a long time, under the leadership of Richard

Marshall – a real world leader in pulmonary fibrosis – developing technologies for imaging, to know how we can see that the drug has actually got to the right part of the lung and that it has an effect. We have a great molecule with the alpha-v-beta6, which is a super target for this, which will go into the clinic shortly but, more importantly than that, we've developed the underlying principles of how we do trials in this area with the right read-outs. The second area which I have alluded to which is inhaled dAbs, this time for acute lung injury, and the molecule I talked about earlier on, the TNFR1dAb, is in clinic for acute lung injury. We can talk more about that in questions if people are interested.

PHI and oxygen sensing

Daprodustat (GSK 1278863) low dose PHI for treatment of anaemia of CKD: new Phase IIb data

I want to end this now by talking about a different form of oxygen problem and that is oxygen sensing. Oxygen sensing is clearly important across the body, it is clearly important for every cell and what is also clear is that one particular molecule, prolyl hydroxylase, is a key oxygen sensor. What happens is that prolyl hydroxylase senses oxygen, a whole lot of physiological changes happen as a result of that sensing. If you live at the top of a mountain, this is how you sense where you are, this is how the body adapts and begins to make changes.

One of the changes that happens if you inhibit prolyl hydroxylase is that you start to make more red blood cells. The first indication for a prolyl hydroxylase inhibitor is for certain types of resistant anaemia particularly in renal failure. At the moment, anaemia renal failure is treated by erythropoietin given by injection, which is both difficult in terms of the injection but also carries with it an increased liability for cardiovascular risk.

The idea with the prolyl hydroxylase inhibitor is go in with an oral medicine, easy to titrate, without the cardiovascular risk, hopefully, and there is good reason to think this does not have cardiovascular risk, which is more to do with the level of EPO than the increase in haemoglobin, and provides a really important alternative. The Phase IIa data have been published last week, the IIb data I am showing you for the first time here, so this is a glimpse of the IIb data. They show the haemoglobin rise with our prolyl hydroxylase inhibitor versus erythropoietin. In the orange line is the increase with the oral medicine, in the blue line is the injectable. You can see the very smooth curve of increase in haemoglobin with the oral. This is important, to titrate this up and you can do this very easily with the oral medicine.

So it increases haemoglobin, we know it is durable from the Phase IIb study, we know it is as good as erythropoietin in terms of what it can do, it lasts for at least six months, we see minimal elevations in EPO so we are not getting a big increase in erythropoietin, we

do not see an increase in VEGF and we see no blood pressure increases. The overall safety profile looks consistent with the chronic kidney disease population.

Daprodustat: success factors for development

I just wanted to outline what we think is important when we look at this class of medicine, because there are obviously others with these molecules as well. The first is we have a large experience of safety and efficacy for over six-months treatment, we have over 650 patients. We do think, and the FDA certainly agree with this, that an active comparator for the cardiovascular safety studies is going to be essential; the FDA have been very clear about that; it needs to be compared to erythropoietin.

We think the low dose is important. We have a medicine here which is effective for most patients below 5mg, between 1-5mg. Safety is going to be paramount and very low dose treatment we think is going to be very important. It is a once-a-day medicine which is convenient, it can also be given three times a week in dialysis patients and that will be part of our Phase III programme.

The Phase III design is a single cardiovascular outcomes trial, again we think that is important. We don't believe you can answer the cardiovascular risks here by doing multiple studies and trying to do meta-analysis. We know the flaws of meta-analysis, so we think the single study is going to be important and two other things which we have learned through experience.

We had molecules before that inhibited collagen-4-hydroxylase. I can tell you that you don't want to do that: that causes a cardiac problem in animals and we think that is an important thing to completely avoid, and we know that you want to avoid molecules that have liver risk in terms of their profile - hepatotoxicity! These are some of the things we think are important in terms of the profile of the medicine and we are happy with the molecule that we have really taken the time to pick the right molecule.

Daprodustat - indication expansion to maximise value of HIF-activating mechanism

It is not just for anaemia. It is very clear that this mechanism is quite a profound mechanism across the body. Ulceration in animal models can be improved by putting the molecule on topically, and we have a study ongoing with diabetic foot ulcer. The notion of hypoxia drives the growth of the tissues into the ulcer.

Muscle injury. We have recent data here which I show of muscle injury through repetitive use, extreme activity, and what we find is that the prolyl hydroxylase inhibitor prevents the leakage of creatine kinase, that is in the bottom right-hand, which the marker of muscle damage compared to placebo. We believe there are many other indications

including general fitness in the elderly, which is something that we may look at at some point. So with prolyl hydroxylase inhibitor, we believe we have a very good molecule with a lot of experience in clinic so far and the Phase III design, which we think is an important one and one that the FDA have advised is the correct design.

Introducing our experts

Let me now end by bringing all this together and introducing our experts. I have alluded to some of them as I have gone along and you can ask questions which, if I feel appropriate, I can field to them: Zhi Hong, who heads our Infectious Diseases unit, is absolutely instrumental in both dolutegravir and cabotegravir, and now leading the hepatitis work; John Pottage, who is the Chief Scientific and Medical Officer for ViiV, who was prior to that Head of Development in our Infectious Diseases organisation; Steve Pasco who came from Novartis, who heads the Physician Group in the Respiratory Unit and has had a lot of experience in both the experimental medicine and late stage development of Respiratory medicines, Edith Hessel is really the brainchild behind the PI3K delta project, amongst others. Dave Allen, who has been involved in virtually every Respiratory medicine at GSK and really spearheaded much of the inhaled therapy that is now marketed. John Lepore, who I have mentioned, who heads the Cardiovascular Metabolic Unit and has been the leader of the prolyl hydroxylase programme, and Ruchira Glaser, who is a key physician in his unit.

So I will stop now and I think we have exactly 30 minutes for questions before we get on to the next session, so I will open this up now for questions.

Question & Answer Session

James Gordon (JPMorgan): A couple of questions on HIV. For cabotegravir, for the treatment firstly, does cabotegravir need to show superiority to dolutegravir or otherwise once there is generic dolutegravir do you think that that is just going to get used instead? Is the convenience advantage going to be enough? *[Agreed]* An allied question, which would be on prevention, do you need to be superior to Truvada or is the same efficacy sufficient with the convenience advantage? Then, just a third one, what is the size of the needle as well? What is the size of the needle for which cabotegravir would be delivered?

Patrick Vallance: Let me deal with the question of superiority, so I think the point about cabotegravir is that by giving a long-acting medicine – first of all, by the way,

there is quite a strong patient preference in many groups to have that long-acting treatment. The second is that actually one of the things that, I guess, none of us do is remember to take our tablets every single day and that loss of tablet taking does have the potential to allow resistance to emerge at some point to treatment, so that is a potential advantage, and we know therefore that you have got, if you like, an adherence to therapy which is understood.

It doesn't have to be better than, in terms of the ultimate effect, although actually maybe it will be better than some other things for the reasons I have alluded to, that you end up with actually the total coverage, rather than missing treatments – we don't know that yet and that will come out in the clinical trials. I don't think at a virological level this is going to be better as a molecule and, as I already said, we picked dolutegravir for a reason, from the first lot.

Your second question?

James Gordon: The second question was similar, but on prevention –

Patrick Vallance: Yes, and Truvada. Yes, I mean, again, it comes down to this question of what happens when you miss a tablet, and we know people miss tablets and we think that everything suggests that for prevention, being able to give something, let's say, four times a year, is much better than having to take it every single day, and I think in the real world – I don't know this yet, but I think in the real world that is where we are going to see quite a substantial advantage, it is where, if you tightly control everything and you say 'I am going to make sure you take your tablets every day,' I don't think necessarily this is better, but that isn't what happens, and so I think in the real word we are going to see substantial benefits.

In terms of the tolerability of the injection, actually this is pretty well tolerated, I mean it said on the slide 93% of people got some injection pain – well, if you asked people 'Did you get pain from a needle?', you get the answer 'Yes,' but actually this is rather well accepted.

I don't know, John, whether you want to add anything to that?

John Pottage: The size of the needle is a 25 gauge for that and just to re-emphasise again it is a matter of choice, so when we look about the parenteral or injectable regimen versus an oral regimen, I think we are just offering opportunities for all the patients to pick and choose what is the best way forward.

Nicolas Guyon-Gellin ... (Morgan Stanley): Three questions, please, two big picture ones first about R&D and the third one is about cabotegravir.

To start with, regarding the R&D budget, I think you mentioned there was no need to increase the R&D budget in the next two to three years, but I would have thought that given the new business mix, with much more Vaccines and OTC, there were also opportunities for savings, so if you can elaborate on that? Second, you mentioned three very important criteria, innovative science, patient's need and quality, you did not mention returns in that slide, so, again, how shall we think about returns? Finally, on cabotegravir, could you help us quantify the prevention opportunity? Thank you.

Patrick Vallance: So let me deal with the second one first of all. I think when you meet unmet patient need you get significant returns, if you do it with a high quality molecule, so I think there is no doubt you make medicines against important diseases – and I have illustrated some of them today and they are big diseases, they are big problems across the world – you get returns. I think that is how you focus on returns and, of course, we publish our data on IRR and we will do so again next year, so no questions on that.

In terms of the R&D budget, clearly, as Andrew has said, we have actually undergone some quite substantial reduction in headcount, we have done restructuring to end up with the right sites, with the right footprint, and that has freed up money to put into projects and I think that we have got a budget which allows us to deliver what we have described here, we have got a budget which allows us to drive these things forward fast. I will remind you that we took BRAF from powder on the bench to approval in under five years, we took dolutegravir from powder on the bench to approval in six years, we have done the same with actually *Anoro* for inhaled. So I think we have got a budget which is designed to allow us to deliver what we have got there, I don't think we are in the stage where we are going to need an uplift unless all of this turns out to work that I am going to talk about today and I don't expect that all of it is going to work and I don't see opportunities for reducing that. I think that would be a way of actually diminishing the chance of getting the returns that we've got from these medicines.

And the final point to say is we every year, and this year particularly knowing the excitement that we've got in the pipeline, really go through a process of prioritisation and stopping things and one of the key things in R&D is knowing what to stop and making sure that you don't spend money where you don't need to.

Cabotegravir, I think that cabotegravir has the potential to be paradigm-shifting in HIV treatment and we'll see how that evolves. In prophylaxis you can see its potential; in treatment, I think it depends what proportion of patients decide that they don't want to remember every single day that they've got to take a tablet because they've got HIV and

what proportion would rather have that intermittently and we already know from surveys that's rather high.

Jeff Holford (Jefferies): On HIV that's obviously a huge opportunity. I wonder if you can just tell us firstly a little bit more about the nano formulation that goes with that, just how proprietary that is for GSK and just your view around the competitive landscape and how many other companies might be going down that route in the future.

Second, on HCV, that's indicating around about a 20-22 entry to the market based on the filing time you have up there. Just give us your thoughts a bit more on the size of the market and the durability of that opportunity in that timeframe and then just lastly on the triple therapy you talked about uniqueness around clinical trials and how that's going to drive your thinking internally. Just tell us what you are thinking about, what the key label claims need to be for that product to drive the best up-take of the product. Thank you.

Patrick Vallance: Okay, so I think what we've done with the long-acting is understand the principles by which you can select the molecules that have long-acting potential and I'm not going to tell you those principles now. There is know-how within GSK and as I said, we've got other molecules coming on behind which we think fulfil this type of criteria.

The nano crystallisation we think has a chance to be applied quite widely across these medicines. I am not going to say other people won't find a way of making long-acting preparations, I'm sure they will but this work didn't start yesterday. This started in 2008 and I think it will take others a while to get to the same position and as you probably know, there is no other molecule out there that has the same duration that we are talking about here with cabotegravir, so we remain confident we have a good position there.

The HCV question is an important one and frankly it depends on what we see next year. So if next year this combination of 175 and the Regulus compound shows that you can really eliminate the virus, we are going to go very fast and I don't know what the filing date will be on that. We obviously need to go fast if that's positive and we won't know until next year.

It's very clear that the HCV burden in the world is not going to be wiped out quickly and then your third question about triple therapy, it's worth reflecting that currently about 30% or more patients end up on triple therapy. This isn't a new concept. This is actually what doctors are currently doing and in fact many doctors start patients almost immediately on triple therapy, so I don't think we are entering a world where people wonder whether you

should use triple therapy. We are more entering a world where they say 'How can I get to triple therapy with the right quality of product with a once a day treatment and how easily can I do that?'

And the trials we've got are claims around lung function, as I said which is the European endpoint and also exacerbation claims for the US at the ongoing trial so we expect to come up with a profile which will allow ready easily usable triple for the right patient group in a market which actually is already using triple.

Question Steve Scala (Cowen and Company): Three questions. First AstraZeneca claims that antibodies for severe asthma can be as large a class as TNF inhibitors in terms of sales potential. I am just wondering if you agree and if so, how do you get to numbers that large?

Secondly, what is your competitive intelligence on the Mylan *Advair* generic that apparently will be filed by the end of the year?

And then thirdly, I continue to be fascinated by the fact that no other company has followed your DPU strategy. To what do you attribute that fact and I might be overstepping my bounds, but in addition to your view, may we ask for the opinion of Judy Lewent? Thank you.

Patrick Vallance: Okay, well I am sure Judy – we will pick up with Judy at the coffee break and she would be happy to talk to you.

Let me deal with the first question. I absolutely believe that the biologics in asthma are a big deal and I think I've made that clear as to why I think it's a big deal. I think there is a patient population which is desperately in need of treatments which cause very substantial effect sizes, I think biologics provide that opportunity, I think that's why we are so pleased with the profile that we have on *Nucala* and I think the 6-10% or the 5-10% of asthmatics with severe asthma, it's actually a very large population across the world so I think there is a very substantial opportunity there.

I think Andrew has been clear on the *Advair* generics entry position over many years, actually. No change or anything to add to that actually, but you know, who knows when it comes and we will see whether and when it comes.

DPU model: well actually the DPU model is really pretty straightforward. It is about saying "Have you got leaders in the organisation that you trust to try and get on and make medicines in interdisciplinary groups?" I think if you look at what many companies have done they have pretty much gone down that sort of road one way or another; not fully, not

always calling it a “DPU model”. I don’t think it is as unusual now as it was when we first introduced it and it is based on a pretty simple idea, which is you need the disciplines inter-related. They need to be able to talk to each other on a daily basis, you need a leader who can lead that. It is rather like the biotech model in that respect and you need to give people time to pursue their areas. Perhaps the best example that you are going to see today is the unit that John Bertin leads, which has been absolutely relentlessly focussed on innate immunity and pattern recognition receptors for the last six or seven years and has become world-leading. You will see other examples in epigenetics, you will see examples in some of the respiratory spaces as I have already discussed.

So I think the DPU model actually is just a fundamental way in which science is done these days and it is enshrined in our organisation and the DPU models; others have tried to make variations on the theme. You need big platforms behind it as well.

I do need to take one question, actually, from the webcast, so I have got one question here on the Phase III trial for the prolyl hydroxylase inhibitor: can we give an idea of the likely size, length of the Phase III cardiovascular outcome study that we plan?

Well, we plan an outcome study against erythropoietin, as I have already alluded to, looking for a non-inferiority with obviously the upside of picking up a superiority claim against that. John, I don’t know whether you want to comment on timelines or size of that study?

John Lepore: Sure, maybe just a few brief additions to that. The studies will start in 2016, they will be one each, large cardiovascular outcome study in pre-dialysis subjects and dialysis subjects. Large means in the range of 3,000 to 4,500 subjects. Those are subject to end of Phase II review and with the exception that in Japan we will do a separate programme that is smaller because a cardiovascular outcome study is not required.

Graham Parry (Bank of America Merrill Lynch): A couple on cabotegravir to start with. What sort of per cent of patients do you think will be more amenable to injection? So have you done a characterisation yet of which patients in the HIV market do you think this product would be able to apply to?

Edurant that you are combining it with has psychiatric adverse event issues; it is one of the reasons why *Tivicay* gained share in the market, so how are you dealing with that in the clinical trials and should we be looking at the Q4 weekly, given the injection site reaction, as the most likely injection frequency?

Then a question on TLR7, given that works on the Th2 pathway, could that also be a candidate for atopic dermatitis?

Then finally one big picture question: just what do you think is the message you really want the investment community to walk away from this meeting with? You are laying out a lot of assets here, is it just a shots on goal argument, which we have seen from GSK in the past and arguably failed fairly spectacularly, or is it that you are now a high quality science organisation the quality of what is coming through is better, therefore you can expect a higher probability to market? Thank you.

Patrick Vallance: Let me deal with the last one of those first. I think it is pretty clear actually that this is not a shots on goal strategy. This is about focusing in some key areas, it is also about focusing on key approaches and I have indicated for example in asthma the two areas are on the cellular approaches to severe asthma and on remission, it is not a wide-spread, across all different could it increase FEV1 a little bit type approaches? I think that is very clear from the medicines we have profiled.

I also want to remind you of the statistics on the high quality files and the fact that we have got first cycle approvals and the quality of molecules which I have alluded to. I think it is pretty clear that the combination of innovative science coupled with quality molecules does increase the likelihood and success of these and we are talking about these molecules today that we think have higher probability of success, even when we are talking about some of those that are much earlier. So shots on goals, absolutely not; I don't agree with it. I think you have got to make choices, you have got to go with these choices and you have got to back those choices.

I think the moment we see a sniff of efficacy success, and this to some extent answers a question which I can see on the screen here, we go very fast and focused with that molecule to the end and that is why I gave you the statistics around some of the things we did with BRAF/MEK and that is why when we look at some of the file data we put in there, I don't know where they are going to be – some of those can definitely be accelerated when we start to see the data we need to see.

In terms of the cabotegravir, clearly the reason for doing the IIb study is to come up with a final decision on dosing interval. I presented the results; it is early days. We are analysing those in full and we will come up with the dosing interval once we have had a chance to look at that fully.

The patient population – I may ask John to comment again on this in a minute, but we have definitely got a significant number of patients who have expressed an interest for having intermittent therapy. We think this is going to be quite a big growth area, and the atopic dermatitis was in relation to which? I am sorry, I slight missed – the TLR7. No we are absolutely focusing at the moment on the inhaled nasal route for that, and that is very clearly

around the nose being the first point that you get these antigens. It is about getting it to where you see the antigens and actually it is about making sure that you time the administration at the right time when you've got maximum antigen exposure. So we are focusing on the intra-nasal approach.

John, do you want to comment on patients?

John Pottage: A quick comment. I think, when we think about taking care of patients, for HIV it is now a lifetime of treatment and so we do think about producing choices or different options for patients. I think that does revolve all round taking all oral regimens, or all parenteral regimens. I think as we develop the data, and I think an important thing to keep in mind with the cabotegravir programme is that we are looking at that as a maintenance regimen for someone who is fully suppressed, switch on to a two-drug regimen. And so that again is kind of the dogma therapy which revolves around three drugs and so we do have to do the work, and what we've shown in the LATTE study, and then in the LATTE-2 study results, is that the two-drug regimen is quite effective and so it gives us encouragement, going forward. But I think, as the data develops, you'll see a sizeable number of patients and they go from oral regimens to parenteral regimens, back and forth, and so I think that these are still early days, while that's being sorted out. Thank you.

Graham Parry: There was a question about the fact that the adjuvant combination that you are combining with it has an AE adverse event profile, and psychiatric AEs.

John Pottage: Yes, we're still digging through the data on that.

Keyur Parekh (Goldman Sachs): I have multiple questions – apologies in advance.

The first one: can you just help us understand, of the £2.5 billion in Pharma R&D spend at GSK, or roundabout, how is it split across the various of the six therapeutic areas that you have spoken about?

Secondly, Andrew, you mentioned multiple times, that you have gone through a period of significant changes, taking the fixed cost base and making it more variable. We could have got this completely wrong but our analysis shows that Glaxo has more R&D sites than Roche for a budget that is 50% lower than Roche. Your Annual Report – your spend on facilities and central support functions is now about 15% of total R&D, up from 11% in 2012. What are we missing there?

Then the second set of questions. GSK have had – you have clearly outlined a lot of interesting, early stage assets. GSK have also had some spectacular failures and outcome studies in the last three years. What have you learned from those failures? Was it about study designs? Was it about patient populations? Or was it about the quality of the molecule itself?

And then thirdly, a lot of the assets that you are highlighting in early stage today appear to be in asset classes where there is significant competition – be it severe asthma, be it the oral product for CKD. Given your views on pricing more generally going forward, and that these opportunities aren't going to come to market until 2020 at the earliest, can you just help us think about how you rationalise doing such large studies for those projects? Thank you.

Patrick Vallance: Okay, so let me deal with the R&D funding. We are roughly 60% spend on late-stage development and 40% on early. We are split across areas in terms of the opportunity we see, so we are very much driven by the opportunity that we see in the science there and, of course, the late-stage funding for area depends on which projects are there – so it may be more in one area one year than another, depending on a Phase III study.

We clearly have major investments across the areas we are talking about today and I'm not going to go into a further breakdown of exactly how that comes out, not least because it will change, year on year.

The fixed asset base: we are reducing to two sites, so that is one of the decisions that we announced. We are a long way through that. We've closed the major site in North Carolina and we're reducing many of the satellite sites and coming down to a substantially reduced, fixed infrastructure cost, which also allows us to then invest, of course, in equipment and other things on those sites. So I think we have dealt actually with a very clear, historic issue of sites.

We also closed a major site in the UK about seven years ago, to try to rationalise our site base. So we've come down very substantially on the cost base and believe that, by the time we've got to this two major site model, we are in exactly the right place in terms of the fixed costs. And so our substantial fixed costs of the past have now been reduced and we've got more to put into projects.

In terms of outcome studies, yes, we have learned from outcome studies. I think we've learned a number of things. First of all, I think we've been actually rather effective at running the studies. Of course, you can't predict the results of some of these things sometimes. We absolutely have introduced new designs which include interim analyses,

utility analyses and ability to get early read-outs, and I gave you an example for a smaller study here in respiratory with a real in-stream data analysis. We think we've got actually a rather sophisticated way of looking at outcome studies.

The outcome study – the key thing is to get to a go/no-go decision during the study and we've had examples where we've managed to achieve that as well. Some of the outcome studies, as you say, have failed. Others, for example SUMMIT which missed its primary endpoint, contained within it an awful lot of incredibly useful information which the scientific community are picking up on: reduction in exacerbations, the ability to show that the safety signals are rather reassuring and in fact the decrease in the decline of lung function in patients on the treatment there. So I think they are a mixed bag with some of the outcome studies. We have a way of looking at designs for the future, incorporated into the prolyl hydroxylase study that John was just talking about.

Then you talk about volume pricing and severe competition. I don't think, for the reasons I have said, I am in any way concerned about where something like *Nucala* goes. There is a massive unmet need, there is a massive need for the patient population and the fact that there are others coming along behind, I have illustrated some of the things I think are important to think about in terms of the competition there.

In terms of prolyl hydroxylase inhibitors, yes, there are two others that are coming up behind it. It is not such a highly competitive space to be in with two others and I have given you some reasons why I think we have a molecule there that are important. I'll come back to the question of failure. I don't think the failures we have had are molecule quality failures. There is no doubt where we have had failures, there are issues around targets and that is why there is such a big investment we have put in target sciences.

Florent Cespedes (Société Générale): I have three quick questions on Respiratory please. First, on the triple combo, could you be a little more specific and tell us what you really need to show in terms of exacerbations: are they severe exacerbations, mild to moderate, total exacerbations? Also what is the comparator? Second question, could you say a few words on the MABA approach: is it more a back-up and not a top priority? The last question is on *Nucala*: could you remind us of the threshold of eosinophil level needed to be eligible for this treatment and could you share with us your discussions with the payers, because it seems that the eligible population may be pretty broad. Is there any risk that, at the beginning, you may be limited to a higher level due to the potential costs?

Patrick Vallance: I shall deal with the last one first. On *Nucala* our studies were an entry of 150 eosinophils and above at the time of diagnosis or 300 historic. When

we finalise labelling discussions, you will see what the ultimate patient population is but that is the trials. Others have gone with much higher eosinophils in the medicines they are trying to develop.

MABA is progressing and provides a route for a different mechanism, and that is still ongoing within GSK and triple therapy, we expect to see a decrease in exacerbations. Clearly, with a reduction in exacerbations, people then do look at the more severe versus the less severe. We are looking at all of those as endpoints but the overall endpoint is exacerbations. I think it is worth noting that open triple is filed already with the FDA, which I think tells you some of the things they are interested in when looking at these.

I think we are done and we shall take a 15-minute break now. Thank you very much for your attention.

- *Break* -

Part 2

Vaccines R&D

Dr Moncef Slaoui

Okay, morning everybody, I am Moncef Slaoui, I am Chairman of GlaxoSmithKline's Vaccine organisation and I am really delighted to be here today and tell you about a select sample of clinical stage programmes in our pipeline for the Vaccine R&D.

R&D programmes to deliver near-term growth with significant future opportunities and novel immunisation platforms

My presentation will be in the three parts, in the first part I will tell you where our R&D organisation is focused between now and 2018, in particular on two programmes, our shingles vaccines, *Shingrix*, and our meningitis vaccines portfolio. These two programmes each will account for about a third of our expected growth between now and 2020, the last third will be accounted for by our existing products portfolio and its active lifecycle management. I will not be telling you about those programmes for a matter of time, but I will, of course, be very happy to address any questions you may have about them. In the second part of the presentation I will be telling you about two vaccine programmes that are currently in the clinic, but will be the focus of our late-stage development activities in R&D between 2018 and 2022, and these are vaccines against respiratory syncytial virus Group B streptococcal disease. Finally, in the third part of the presentation, I will tell you about the new concept of vaccine that impacts the evolution of established chronic disease that has been enabled by our decades long investment in cutting edge technology for platform immunisation in namely adjuvants.

Shingrix

So I am going to start with *Shingrix*, our shingles vaccine.

Shingles is an unavoidable disease, 90% of use in this room harbour in our nervous system the varicella or chicken pox virus, this virus reactivates regularly and when we are young and fit we control its reactivation before clinical disease appears. However, as we age or when we are immunocompromised, such as a cancer patient undergoing chemotherapy or HIV patients, the virus reactivates and causes shingles disease and also, in a number of cases, its severe complication post-herpetic neuralgia, which, as you probably know, is one of the leading causes of suicide in the elderly population. So a very frequent, very unavoidable risk that comes with ageing or immuno-compromission.

Some numbers – the risk of shingles starts to significantly increase as of the age of 50 and if you are lucky enough to live to the age of 85 your cumulative risk is 50%, one out of two people living to the age of 85 would have experienced an episode of shingles.

Existing zoster vaccine

There is a vaccine against shingles and I am going to show you on the next slide the published characteristic of this vaccine. It is a live attenuated form of the varicella or chicken pox virus, it is a one-dose vaccine. It has an efficacy, as you can see on the slide, of about 50% across the four decades where individuals are at risk for this disease, between the age of 50 and above 80. It has been approved by the FDA and other agencies for use for the prevention of shingles in individuals aged 50 and above, however, it has been recommended for use by the Advisory Committee for Immunisation Practices in the US only in those individuals aged 60 or above, because of its overall performance, the efficacy of this vaccine decreases with the age of vaccination, meaning with the increasing risk of shingles and also its efficacy decreases over time, after immunisation. Because it is a live virus it is contraindicated in immunocompromised individuals. We estimate that about a quarter of the target population for this vaccine has been immunised and it has a healthy sales figure associated with it.

Shingrix candidate vaccine developed to differentiate

For the past decade we have been developing our shingles vaccine with the conceptual limitation of a live attenuated virus vaccine in mind. That is the reason we decided to use a recombinant approach, using the major glycoprotein of this virus, glycoprotein E, and also we knew that we needed to induce a very strong cell-mediated immune response, because that is the part of the immune system for which senescence is the more impactful. And we used a novel adjuvant, that we call adjuvant system 1, which combines two immune-simulants with a liposome formulation that we knew induces a very effective and long-lasting cell-mediated immune response against the antigens we associated with it.

We have completed the Phase III development programme for this vaccine, at least for its elderly population indication, we just announced last week the outcome of the second Phase III trial conducted in population 70 years and older and we had announced a year ago the data from our first Phase III trials conducted in populations of 50 years and above.

I am going to share with you, on this slide, what we believe to be the characteristics of this vaccine, based on the data that we have, and we firmly believe that this data is very strong, but, of course, this vaccine, as you can see on the slide, will only be filed for approval

across the world in the second half of 2016 and therefore these are not yet approved characteristics or indications for the vaccine.

This vaccine is a two-dose vaccine that is given two to six months apart. It has I believe exceptional efficacy against shingles, between 90% and 97% whether you are 50 years old or 80 years old. The persistence of its protection is absolutely flat over the four years' follow-up in our Phase III trials. It should not be contraindicated in the immunocompromised population because it's not a live attenuated virus but actually we have an ongoing Phase III trial in the immunocompromised population which will read out in 2017 and we should be seeking an indication in this population by 2018.

We believe that on the basis of this data, this vaccine should not only be approved by regulators for use in the 50 years old and above, but also recommended by organisations such as the ACIP for immunisation in the 50 and above and we expect this vaccine to be a significant contributor to the growth of our Vaccines organisation, not only through 2020 by which time it will, as we said, contribute about a third of our growth in the sale line, but well beyond that.

Shingrix – Efficacy against shingles

I am going to share with you now some of the data that supports these characteristics as I have just described them to you. On this slide you can see data that actually comes from the two Phase III trials, depending on the age bracket that shows efficacy against shingles whether you are 50, 60 to 70 or above 70 years old and you can see I believe very, very high efficacy against shingles.

Existing vaccine – Efficacy against shingles

For your reference, these are data with the existing zoster vaccine protection against shingles. Clearly these are not the outcome of a head-to-head comparative trial but I think it's important for the audience to know what is the published data with the existing vaccine.

Shingrix – immune response across age segments

I told you that the induction of cell-mediated immuno response was a very important element for protection against shingles. These data here show the induction of cell-mediated immunity with our *Shingrix* vaccine and you can see in grey the pre-immunisation level there is a little bit of immune response because we all harbour this virus already. In blue is the response induced with the vaccine antigen without the AS01 adjuvant and in orange is a very significant induction of T-cell response when the AS01 adjuvant is added to the vaccine antigen. So very high T-cell response, but also you can see that across the age

brackets this response remains the same, consistent with the fact that the protection remains the same across the age brackets.

Existing vaccine – Immune response across age segments

Again, for your reference, not from a head-to-head trial. These are the published data with the existing vaccine that shows you in grey the pre-immunisation levels of T-cell response in vaccinees and in orange the post-immunisation with the existing zoster vaccine and you can see that the delta between the pre-immunisation and post-immunisation disappears as the age bracket increases in line with the decreasing efficacy of this vaccine with increasing age.

Shingrix – Efficacy against PHN

PHN: post herpetic neuralgia, a severe complication of zoster

Post herpetic neuralgia is a very important complication of this disease and shown here on the slide again is the efficacy against post herpetic neuralgia. You can see very high efficacy in the 90% across the age brackets.

Existing vaccine – Efficacy against PHN

PHN: post herpetic neuralgia, a severe complication of zoster

And for your reference, the published efficacy with the existing vaccine.

Shingrix – Duration of protection against shingles

For a disease where the risk carries through and increases from the age of 50 through to the age of 70, 80, 90 persistence of protection is very important. These are data showing you the persistence of protection with *Shingrix* against shingles. Similar data with PHN and you can see that it's very high, unwavering protection over the four years and of course we are continuing to follow up this population for further persistence of protection.

Existing vaccine – Duration of protection against shingles

And again for your reference, not from a head-to-head trial but from published data is the persistence of protection with the existing zoster vaccine.

Immune response persistency is a good predictor of duration of efficacy

That persistence of protection with our vaccine will be very long-lasting and is supported by data in the next slide. I showed you data showing a correlation between cell-mediated immunity and protection. These data from a Phase II study for which we now have six years of follow-up tests the T-cell response against varicella virus in our vaccinees over a period of six years.

In red is the T-cell response level they had pre-immunisation, so it's the baseline and in blue is the response after immunisation. This is a log scale and you can see that over a period of six years the T-cell response remains significantly higher than the baseline. We have used three mathematical models to project how long will the persistence of the blue line remain above the red line and it's at least 15 to 20 years. Of course we will further document this as time passes.

We believe that on the basis of these data, this vaccine efficacy will be highly sustained over time, highly effective and therefore should support really extensive recommendation by the various recommending bodies across the world once it is approved by regulators.

Shingrix: a potentially significant advance in vaccination to prevent shingles

We are conducting and planning more studies to support the profile of this vaccine. In particular, we're conducting studies for co-administration with existing elderly vaccines, concomitant administration. We're also conducting head-to-head trials comparing the reactogenicity of this vaccine with that of other elderly vaccines such as Pneumovax or Prevnar. We are conducting, importantly, studies – or planning, sorry – studies in Zostavax immunised individuals that are re-immunised with our vaccine, in order to, or with the intent to afford them much higher efficacy and much longer-lasting efficacy.

Shingrix: a potentially significant advance in vaccination to prevent shingles

I told you also that we have an ongoing Phase III trial in the immunocompromised and you can see on the slide that it will be reading out in 2017 and we will be filing for this indication in 2018. So, a very important programme in our portfolio – I think an exceptional vaccine for the elderly, that will support significant opportunities for growth for this business. Our manufacturing capacity is in line with our ambition for this vaccine.

A second point about this vaccine is about the adjuvant formulation, AS01. We believe that this is a breakthrough in vaccinology: all elderly vaccines have moderate efficacy, whether it is flu, or pneumovax or others, and it's having an adjuvant formulation like AS1 that will allow us, or will enable the feasibility of a number of elderly vaccines. I will be describing to you one of those, but there are more to come.

Meningococcal meningitis

Let me now move to the second key focus of our R&D organisation in the near term, which is our meningococcal meningitis vaccines portfolio.

Meningococcal disease: evolving and unpredictable epidemiology – requires combination vaccine

Invasive meningococcal disease is a very significant disease with high mortality and morbidity rates. It is a disease that impacts the overall population but however has two peaks associated with the fact of how these bacteria are transmitted. It has a peak in the paediatric population and a second peak in the adolescent population. Five serogroups out of the 12 of mycelium meningitis bacteria are relevant to human disease: they are called serogroup A, B, C, Y and W.

The relative incidence of these serogroups in a particular geographic location varies over time in an unpredictable way. You can see the doughnuts on the slide: for instance, in the late eighties, serogroup Y was almost non-existent in the US but it became prevalent by the mid-2000s, and is on its way out – so again, it becomes much less prevalent today. If I showed you the same data for a European country or an Asian country, it would be very different. So this unpredictable association of strains, if you wish, is both unpredictable on a time basis as well as on a geographic basis.

The other characteristic of this disease is that there are outbreaks that are also unpredictable and I am sure that many of you are aware of the two outbreaks that happened in the US in 2014, in major colleges. Because of that, the most effective approach to tackling this important pathogen, is universal mass vaccination against all five serogroups of mycelium meningitis.

Most advanced meningitis vaccines portfolio including candidate pentavalent

We believe that GSK has the broadest and most advanced product portfolio of vaccines to respond to this important public health issue. Indeed, we have *Menveo*, a tetravalent combination vaccine, addressing serogroups A, C, Y and W: it was approved in 2010, as you can see on the slide. It is approved actually for paediatric as well as adolescents' use across Europe, the US and a number of other countries. It has been recommended by the Advisory Committee for Immunisation Practices in the US for immunisation in adolescents at the age of 11, and then a booster dose at 16 or 17. It is a robust vaccine.

We also more recently had the approval of our meningitis B vaccine, *Bexsero*. It's a vaccine that is recommended – sorry, approved – in Europe and a number of other countries for use as of the age of two months, through to adulthood. It is approved in the US more recently for adolescent use, as a two-dose vaccine. It has been recommended by the ACIP, with a category B recommendation, which means a permissive recommendation. It is now approved in 38 countries, as you can see.

Finally, we have well-advanced Phase II trials for a pentavalent combination of these two approved vaccines: an ABCYW combination, for which I will be describing to you how

we position it and how our Phase III plans are. But, before that, I'd like to share with you more information about *Bexsero*, our meningitis B vaccine.

Bexsero: multi-component antigen composition adds value, differentiation

The feasibility of a Men-B vaccine has eluded the community for decades, because Men-B, capsular polysaccharide, resembles a structure in the brain, so that is the reason why we couldn't use a polysaccharide conjugate to make this vaccine. For decades, we have tried to discover protein antigens on the surface of the bacteria under the capsule that could be the target of protective antibodies. We have discovered and patented a number of these.

We have elected to include four of these antigens proteins in our vaccines. Why? Because we know that *Neisseria* bacteria mutate their proteins to escape immunity, but also importantly modulate the level of expression of their protein on the surface to escape immunity.

Bexsero: multi-component antigen composition adds value, differentiation

I am going to share with you key data, immunogenicity data with this vaccine that have supported this approval recently for the adolescent population in the US and you can see in orange the per cent response rate in the population pre-immunisation everybody has encountered some day *Neisseria* bacteria without getting sick, and in black is the post-1 response and in grey the post-2 response and two key message here: very fast onset. The overwhelming majority of individuals are already seroconverted after one dose. This is important for outbreak control and number two by a second dose 100% are seroprotected and therefore this was approved as a two dose vaccine.

Competing vaccine for MenB

For your reference, and again, these are not out of a head-to-head comparative trial, these are the data with the other existing approved meningitis vaccine. Two important points: this vaccine contains two forms of one protein antigens because of the genetic variation and you can see from the data that this vaccine requires three immunisations for the overall population to seroconvert and that is the reason why it has been approved as a three dose vaccine.

Now importantly, because the incidence of MenB is unpredictable, it was impractical to run a Phase III trial where the outcome was clinical efficacy, so these two vaccines have actually been approved in the absence of demonstration of clinical efficacy.

Sustained MenB transmission in Quebec region

I am going to share with you new data today that I believe show that *Bexsero* is the only meningitis B vaccine with effectiveness data in real-life use. These data come from a Canadian province that is part of Quebec.

In the slide now what you see are the numerical cases of meningitis B in Quebec province in Canada over the past five years. You can see that there is an ongoing low endemicity of MenB cases as is usually the case when an outbreak happens.

Sustained MenB transmission in Quebec region

When *Bexsero* vaccine was approved in Canada a particular province of Quebec, Saguenay Lac, has decided to introduce universal mass vaccination in its population aged two months through to 20 years. 55,000 people were immunised between March and May of 2014 and remarkably, as you can see in the slide in orange, the cases stopped. Within a year of that two cases appeared and very interestingly these two cases are imported cases of individuals who were living in other provinces and migrated to the province. This is demonstrating that MenB is still circulating there, but there is protection. I believe these data support a very high effectiveness of this vaccine.

The other important thing with *Bexsero* is that it is the only vaccine approved for paediatric use. In fact it is the only vaccine approved outside of the US and the UK has decided and started to implement as of the month of September, universal mass vaccination of its paediatric population, all its birth cohort – 700,000 a year, with *Bexsero*. Embedded in that programme is again an effectiveness study of this vaccine in the paediatric population. That study will read out in 2019 and will inform our decision to fight for this indication in the US and also, importantly, as happened with meningitis C in the 1990s, should inform other countries' decisions for implementation of universal mass vaccination in their paediatric population.

I believe important data that supports the effectiveness of *Bexsero* and I believe these data show how strong a vaccine it is.

MenABCWY Phase III starts in 2017

Moving onto our pentavalent combination ABCWY. As I told you we are well-advanced in our Phase II study. On the left-hand side of the slide you can see the seroprotection level induced in the adolescent population with this vaccine, the vaccine is with the pentavalent combination, responding to all five serogroups.

We have elected to focus the development of this vaccine for now on the adolescent population in the US and we have elected to position this vaccine in a way that will simplify

and potentially enhance adherence to this immunisation against all five serogroups of meningitis.

Let me take you through the immunisation schedule as it exists today in the top part of this slide to explain how we plan to position this vaccine. Currently, adolescents at the age of 11 receive the tetravalent vaccine, ACWY at the age of 11 – about 80/85% of adolescents are immunised in the US.

Then, as recommended, by the age of 16 or 17 they should receive a second dose of this vaccine, which they do, but now only 20 to 30% receive the dose. Low adherence to the second dose and with the category B permissive recommendation at that same age, adolescents 16 to 17 should receive either two or three doses of MenB vaccine, depending on which meningitis B vaccine they elect to take.

We have elected to position our pentavalent combination as the booster dose at the age of 16/17 for adolescents that were immunised at the age of 11 with the ACWY, as you can see in the bottom part of the slide. That same dose will serve as the first immunisation dose for meningitis B vaccination that should be then followed with one dose of *Bexsero*. With this strategy, we believe we can eliminate one or two injections, one or two visits to the paediatrician and we can, therefore, simplify the immunisation schedule and potentially enhance adherence for this vaccine.

In conclusion, I believe these data really support that GSK has the broadest and most advanced Vaccine portfolio against this important disease that can afford protection against all five serotypes either with *Bexsero* and *Menveo*, or with the pentavalent combination in development. *Bexsero* is approved ex-US in the paediatric population and data to come from the effectiveness study embedded in the UK universal mass vaccination programme should inform our decision to file in 2019.

Our capacity to manufacture *Bexsero* and *Menveo* again is in line with our ambition for this vaccine that, as I told you, should support about a third of our growth to 2020 and well beyond.

Respiratory syncytial virus (RSV)

I shall move now to the second part of my presentation and tell you about vaccines against two diseases, starting with respiratory syncytial virus. This is a respiratory virus highly infectious that really impacts either the infant population or the elderly. In infants, it induces pneumonia and bronchiolitis and is associated with the development of severe asthma, and it accounts for a large number of hospitalisations of infants across the western

world. In the elderly, about 30,000 deaths are associated with RSV disease in US and in Europe, so a significant disease burden.

The glycoprotein F vaccine that I shall be talking to you about in five minutes will be associated with our S1 adjuvant that made all the difference for the *Shingrix* vaccine in the elderly but these two will be put together for an elderly RSV vaccine is obviously in the work but I am not going to tell you about it today.

Period of most severe RSV cases for young infants occurs from birth to 12 months

I am going to focus my presentation on our paediatric vaccine development. This slide shows the incidence of RSV-associated hospitalisation in the paediatric population in the US per age bracket in months between zero and 24 months. Two important points here. One is that there is a very large number of hospitalisations annually and, therefore, a high cost to the health system. The second point is that 50% of the disease burden happens in the first three to five months of life; the other 50% in the remaining 18 months when you look at the first two years. That is a challenge for vaccine development because the immune system is still immature immediately after birth and inducing a strong immuno-response very quickly will be challenging.

Our answer to that challenge is to develop two vaccines. The first vaccine will be given to third trimester pregnant women when the baby's embryogenesis is completed. This vaccine should be aimed at increasing antibody titers that neutralise the virus. There is evidence to show that mothers with high antibody titers at the time of delivery have children with a lower risk of RSV hospitalisation than mothers who have lower antibody titers at the time of delivery.

These antibodies transfer from the mother to the baby through the placenta and they will live in the baby for the first three to four months of their life, and should afford protection against that first severe peak of disease. During that period, we plan to give them a second vaccine which would be an active immunisation vaccine that should induce protection for the rest of their childhood and, potentially, for the rest of their life.

Candidate paediatric RSV vaccine, a novel approach

I am going to start by describing to you the active immunisation vaccine in the paediatric population and then move to the maternal vaccine.

Development of an RSV vaccine for paediatric has been defined by the dramatic outcome of a Phase III trial conducted in the late 1960s with an RSV vaccine candidate. Babies were immunised and then the RSV season came and the vaccine group in that trial

had more hospitalisation and more deaths than the placebo group. The vaccine had induced exacerbation of disease.

Since then, 40 years ago, no single RSV vaccine has been able to reach in its development the infant population around two months of age who are sero-negative to RSV. Why? Because vaccines have to demonstrate not only that they are protective against RSV disease, but also that they do not induce exacerbation.

There is a leading hypothesis to explain what happened in that 1960s trial, which is that that particular vaccine had induced the wrong type of inflammation and T-cell response against RSV antigen, and that inflammation when the virus came in not only wiped out the virus but, unfortunately, also the lung tissues.

The challenge with a paediatric RSV vaccine is to find a strategy to immunise against RSV antigens that induce the right kind of T-cell response and the right kind of inflammation that will clear the virus from the lung without clearing the lung tissue. We believe that we have a new platform immunisation technology in the form of a replication-defective chimpanzee adenovirus vector that we acquired from a biotech company called Okairios in 2013 that is able to induce that type of T-cell response, in fact this vector has been, in clinical trials in neonates with a malaria vaccine candidate and shown to be safe and able to induce the right T-cell responses. It is also the vaccine vector that we use in our Ebola vaccine, that, as you know, is in Phase III trials in a few thousand individuals.

We have completed a number of pre-clinical studies using animal models for both protection against RSV infection and disease, but also that assess the capacity to reduce exacerbations, and in both models this vaccine is highly effective in protection and absolutely not inducing exacerbation.

We have completed Phase I trials with this vaccine in adults and we are, as you can see on the slide, embarking a lengthy, highly regulated, step-wise development process into populations that are first seropositive for RSV and then seronegative for RSV, decreasing in age, that will go between now and 2020 to get us to infants that are seronegative, and we expect to achieve clinical proof of concept in a large Phase IIb study by 2021, which would then inform, I think, a Phase III trial.

The big point here is that demonstration of efficacy is quite simple, demonstration of lack of exacerbation is the very important endpoint.

We believe that this is the most credible vaccine in the industry against RSV, this is a very high risk programme, but this is also a very high reward programme. I believe that the vaccine against RSV will undoubtedly be a vaccine universally recommended across the

globe for immunisation in infants, because of the incidence and importance and severity of the disease.

Novel candidate RSV maternal vaccine approach

While we are developing this vaccine we are also in parallel developing a maternal vaccine, I told you that there is data that supports that boosting the antibody response in a mother can afford protection in the first few months of the life of the baby, and for that we cannot use this recombinant virus, probably not a good idea to put a virus into a pregnant mother. We elect to use a recombinant glycoprotein and, like others, we are targeting the major glycoprotein on the surface of this virus, called glycoprotein F. Unlike others, and this is the major differentiator, we have been successful in expressing a form of this glycoprotein that is different than its most common form. Everybody is expressing – including ourselves in the past – what is called the Post-Fusion form of glycoprotein F, we have been successful and we have proprietary protection around it in expressing what is called the Pre-Fusion form of glycoprotein F.

Why is this important? That is the histogram that you show there, the Pre-Fusion, the new form that we have, of this glycoprotein is able to absorb about 80% of the neutralising antibodies that exist in a human serum of an individual who was infected with RSV. In other words, they induce or they're recognised by antibodies naturally induced, they look like what is on the virus.

You can see there in orange that the Post-Fusion form of the glycoprotein F is much, much less effective in absorbing such naturally occurring antibodies.

Stabilised Pre-F generated high titers by Day 7 and potent boost of PCA without adjuvant

We have taken this glycoprotein in clinical trials in man and this is the data from these trials, you can see what is important here is to see the increase in neutralising antibodies from pre-immunisation, which is in blue, to 7 or 14 days or 30 days sorry, post-immunisation, which is in purple or green, and you can see that there is a very fast increase when 60mcg of plain antigen, no adjuvant, no aluminium, nothing, just plain antigen, a significant increase in neutralising antibodies, and what is called their PCA, those are synergies like antibodies, synergies is the approved monoclonal antibody for treatment of pre-term infants with severe RSV disease, and you can see that this vaccine also induces a very high increase in the amount of synergies like antibodies. This data supports that this vaccine should be protective against RSV infection by neutralising the virus.

Stabilised Pre-F generated high titers by Day 7 and potent boost of PCA without adjuvant

For your reference, this is recently published data from another company's vaccine that also uses the F-glycoprotein, but this time the Post-Fusion version of the glycoprotein, and you can see that when the plain glycoprotein is used there is very limited boost in the neutralising antibody responses, there is a requirement for use of an adjuvant in the form of aluminium and the requirement for use of a higher dose.

So we believe that we have qualitatively the best form of glycoprotein, highly effective in inducing neutralising antibodies against RSV in the absence of any adjuvant used, which we believe is important in third trimester pregnant women.

Novel candidate RSV maternal vaccine approach

We have completed our Phase I studies, we have ongoing Phase II studies in non-pregnant women with dose-ranging, we will then move into pregnant women to confirm our dose ranging, and then progress into a Phase III trial starting in 2019.

We are aggressively accelerating this programme to make available this vaccine to pregnant mothers, in the short term. We believe this is a very important and high quality programme. I wouldn't be surprised if things look like *Shingrix* when the data come up at the end.

Group B Streptococcus (GBS)

The second vaccine that I would like to tell you about which is the focus of our R&D organisation between 2018 and 2022 is a vaccine against Group B streptococci. These are bacteria that colonise our gastrointestinal tract without making us sick. In women from time to time they move from the GI tract to the genital tract and colonise the birth canal when a woman is pregnant and delivering the babies, a baby can acquire this bacterial infection during birth in the birth canal.

Maternal immunisation for GBS

This causes severe disease with very high mortality and morbidity in the form of sepsis, pneumonia, meningitis, very, very severe disease.

There has been sold over the past decade prophylactic antibiotic treatment but about half of the cases of GBS are resistant to antibiotic prophylaxis either because of antibiotic resistance or for reasons we don't really understand.

About one in 2,500 births in the US experience GBS disease, a very important disease.

That antibodies are protective in the mother, are protective for the infant and here you have to protect the infant at the time of birth so you cannot immunise the baby of course, you need to immunise the mother.

That antibodies in the mother can be protective is shown on this slide. These are collaborative data with a group in South Africa where we have studied mass cohort of women all infected in their genital tract with GBS at the time of birth so their babies have been exposed to GBS.

Maternal immunisation for GBS

In black are the babies born to mothers that had GBS who contracted GBS as a baby. In orange are babies born to mothers who had GBS and the baby did not contract GBS and they are ranked on the basis of the level of bactericidal antibodies against GBS polysaccharide, surface polysaccharide and you can see that the babies in orange are all above a certain level of antibodies, no baby in black is in that area. That means that if your mother had antibody titers above that threshold, you will be protected and if your mother had less than that threshold they had a 50% more or less chance of getting infected. Very strong data to support that a vaccine that induces levels of antibodies ahead of that threshold will be protective.

GBS maternal immunisation expanded programme

We have a vaccine in advanced Phase II development. It's a trivalent vaccine with three serotypes of GBS. These three serotypes cover about 70% of the circulating GBS serotypes. It's a conjugated polysaccharide vaccine, a technology that we master very well. It has completed significant Phase II studies in pregnant women, about 700 pregnant women immunised and you can see in the histograms pre-immunisation and then a huge booster in the antibody response post-immunisation in pregnant women in orange and then importantly in this particular data, you can see in green the antibodies in the babies from the immunised mothers and how about 50% of the antibodies are transferred to the babies and then they last for about three months or so which is the window of time during which GBS disease can occur in the neonates. Strong data to support that this vaccine will be effective.

The challenge with the GBS vaccine is the same as with Men B. This is a very impractical programme on which to run a clinical outcome efficacy trial because of the low incidence of this disease and the clinical treatment of the disease in the context, in the setting of a clinical trial.

We believe that as for meningitis B vaccine, the use of a surrogate marker of protection could support approval and the data I showed you in the previous slides support

that. If we are able to identify the threshold of antibodies protected against each one of the serotypes of GBS we should be able to file this vaccine.

We are discussing with the regulatory agencies how to set up assays, how to validate them and how to use a collection of samples, matched, control cohorts that we uniquely have access to to validate this threshold of antibodies. These discussions and set-ups will take us through 2016 and early 2017 and we have elected during this period of time before we reach an agreement with the agencies to enhance the composition of our vaccine from a trivalent vaccine to a five valent vaccine, five serotypes which would then cover about 95% of the circulating strains.

So again I think an important programme in the pipeline that's well advanced. Key dates – 2017 at which time the development of this vaccine could become quite straightforward in the form of an immunogenicity study in pregnant mothers.

With RSV and GBS we have two vaccines that can be the cornerstone of a new portfolio of vaccines for a new segment in the population for vaccination which is the segment of pregnant women.

Maternal immunisation validated strategy to prevent diseases that afflict very young infants

That immunisation of pregnant women can be protective for their infants has now been demonstrated in a field efficacy trial of a flu vaccine given to pregnant women in South Africa and looking at the outcome in their babies for protection against influenza. And you can see on the slide here, that that trial has demonstrated about 50 per cent efficacy against flu, which is comparable to the efficacy of this vaccine in the adult population.

GSK has in its portfolio not only our RSV and GBS vaccines, which I have just described to you, targeting this potentially very important population, but also we have in our portfolio two vaccines against the other two important diseases in the very early days of life, which are influenza disease, for which we have *Fluarix* and *FluLaval* quadrivalent formulations, and also pertussis, for which we have *Boostrix*, the adult form of our DTP vaccine. So we believe that we have a very broad portfolio of vaccines potentially against a very broad new segment in the population, that is equivalent in size, obviously, to that of the paediatric population, with at least equivalent health awareness.

I believe it is a portfolio that should support the development of our vaccine business over the very long run.

A new vaccine concept

Briefly now, in the last part of the presentation, I would like to share with you a new concept of a vaccine against chronic disease, and the chronic disease is chronic obstructive pulmonary disease, or COPD.

Testing hypothesis for a COPD vaccine

As Patrick was telling you earlier, COPD is driven – this disease and lung injury, irreversible lung injury – is driven by exacerbation episodes, often associated with an infectious pathogen in the lung.

Data from us and others have documented that two bacterial infections particularly, with nontypeable haemophilus influenza and moraxella catarrhalis – that is the name of the two bacteria – are associated with anywhere between 30 and 50 per cent of episodes of exacerbation in COPD patients. Actually, some data from Japan in the early 2000s have also shown that prophylactic treatment of COPD patients with erythromycin induced significant reduction in COPD exacerbation episodes – probably an outcome of the antibacterial as well as the anti-inflammatory properties of the macrolide.

Based on that hypothesis, we have embarked on discovering a number of protein antigen on the surface of both anti-HI (nontypeable haemophilus influenza) or moraxella catarrhalis. We have discovered three antigens on anti-HI, validated them in preclinical models, and we have formulated the three antigens in the AS01 adjuvant – our proprietary adjuvant for the elderly. As you know, COPD is an elderly disease in a frail population.

And, as you can see on the slide, we have completed Phase I studies and Phase II studies in elderly population, healthy, and we are conducting a proof of concept study in about 140 COPD patients, GOLD stage II and III, which will be reading out in 2017. If the data from this study are positive, we will add an antigen that we have identified on the surface of moraxella catarrhalis, the second bacteria that causes exacerbations, and we will embark on a Phase III trial.

Just as a reference, if this vaccine is 75 per cent efficacious against nontypeable haemophilus and moraxella catarrhalis, it will have an impact that is equivalent to that of the standard of care today in the treatment of COPD exacerbations, which is ICS/LABA combinations. So, I believe it is a quite novel and important new concept for immunisation against a chronic disease where infectious pathogens can accelerate the progression of the chronic disease. The availability of the AS01 adjuvant for us is, I think, very important in allowing us to induce a very strong immune response in frail populations.

Data and planned filings support positive growth outlook

So, in conclusion, I would like to share with you the key events that are coming over the next decades. You can see, in blue, the programme that I have described to you and how they will be filed over the next 10 years but also, importantly, in orange, there are those programmes that I have not described to you but I would like to point out to you, which are our life-cycle management programmes.

The way we look at life-cycle management is in three different ways. We either look at life-cycle management as a geographic expansion, taking some of our vaccine and expanding their approval in a number of countries – and you can see, for instance, that our measles/mumps/rubella vaccine is undergoing five Phase III trials for filing in the US in 2017 and later on in Japan. We also have life-cycle management as acquiring a new indication for an existing vaccine and that, as an example, would be our recent - not yet public, so this is news – Phase III data with our flu vaccine, quadrivalent, in the paediatric, six-month old population, where we successfully completed the Phase III trial and will be filing for this indication in 2016 here in the US.

And then the third type of life-cycle management has to do with the process – manufacturing – of the vaccine, either improving the formulation as with our liquid formulation for rotavirus or, not shown here, improvement in manufacturing reliability, cost of goods capacity, which are very active. About one-third of the R&D budget is allocated to these three types of life-cycle management. So, important in a vaccine business where patent cliffs don't exist and, as I told you, the active lifecycle management and the growth of our existing products should account for about a third of our expected growth between now and 2020.

R&D programmes to deliver near-term growth with significant future opportunities and novel immunisation platforms

In conclusion, I hope I have convinced you that in our vaccine R&D pipeline, and this is just a sample of the clinical stage programme, we have programmes in the near term, this will strongly support our committed growth between now and 2020 and then open for us opportunities for very significant sustainable growth, either through accessing new segments in the population for immunisation in the form of pregnant women or new concepts of vaccine in the form of vaccine against chronic diseases.

That is the end of my presentation.

Introducing the Vaccines panel

Let me introduce the panel that will support me in addressing your questions, starting with Dr Emmanuel Hanon, who is the Head of R&D for GSK Vaccines, Alain Brex, who is the leader of our shingles vaccine, *Shingrix*, Rip Ballou, who is the leader of our new US

R&D Centre that we have announced in May – I take this opportunity to remind you that many of our lifecycle management programmes as well as the new vaccine programmes are really focused on a first approval in the US, something that we committed to as a means to further accelerate the growth of our business in this very important market, and finally, Dr Giovanni Della Cioppa, who is the head of our Siena base in Italy, R&D Centre for Vaccines, focused on bacterial vaccines.

I will be happy to take your questions now.

Question & Answer Session

Steve Scala (Cowen and Company): Thank you; so I think you have 16 vaccines in development and you have covered four or five; apologies if I missed it, but what is the status of the *Staph*, the new *Pseudomonas* and Hep C vaccines?

Secondly, what accounts for zoster vaccine's decreasing efficacy as one ages? Is it insufficient dose, the lack of an adjuvant or something else? It seems to me that Merck should do a double-dose study; do you think that would be a risk to your franchise?

Then lastly my memory is a bit foggy, but my recollection is that GSK was the only company not to get a pandemic vaccine approved in the US a few years ago and my recollection again is that it was because of the existence of the adjuvant. You are making a big bet on adjuvants, can you refresh our memory on why it didn't go well last time and why it will go better this time? Thank you.

Moncef Slaoui: Yes, thanks. So the two first programmes you said was *Pseudomonas* and Hep C or was there a third one? I didn't hear – *Staph*. Yes. So *Pseudomonas* vaccine, addressing your first question, is in a proof-of-concept Phase II study, quite a significant study, that had – it is a partnership with our partner, Valneva. This Phase II trial will be reading out in the middle of 2016 and, based on the data, we will of course make the appropriate decisions for development. This can be an important vaccine as it is, but it can also be a vaccine that will benefit from our AS1 adjuvant, given its intended use for prevention of complicated *Pseudomonas* infection in the ICU.

Our Hep C vaccine has been inherited from our acquisition of the Okairos biotech company. It is using the replication-defective adenovirus. It has shown efficacy actually in primates. It is in a Phase II proof-of-concept study with an efficacy endpoint in a high risk population for Hep C acquisition with the NIH and again, the data should be coming during 2016 and define our further development plan with this vaccine and for *Staph* we are very

excited actually for this programme. It is also one of the programmes that came from the integration of the Novartis legacy organisation and pipeline. We have really exciting antigens as well as a highly innovative approach that we believe can make something very important out of these vaccines. Actually, one of the most exciting early development programmes we have in the pipeline.

Regarding your question on zoster vaccine, I am not going to advise Merck on what they should do with their vaccine, but varicella is known to be an incredibly sensitive virus, for those of us who have been working in this field for decades and it is actually unknown whether it is the replicating part of this virus that immunises or the non-replicating defective particles that are present in the virus that are immunising, but I will leave it to the owner of that vaccine to decide how best to improve it, including improve its presentation as you know it is a frozen vaccine today.

Regarding the pandemic, it is very important to know that there are very many different adjuvants. Adjuvant is not one, it is a generic name to describe modalities that are able to enhance the immune response. There are adjuvants with very, very well-established safety profile, such as our AS4 adjuvants using *Cervarix* vaccine that as you know is highly used outside of the US. There are also adjuvants like AS1 that are used in five week old babies as in our *Mosquirix* vaccine, recently approved by the European agency or, of course, in our *Shingrix* vaccine. And there are adjuvants like our adjuvant called AS3, which is an oil in water immersion, totally different from AS4 and AS1 that has been used in our pandemic flu vaccine. You know that this particular adjuvant, through a mechanism that we don't understand and that we are supporting others to try to understand, may be - may be - not established associated with an impact on narcolepsy. That is the main reason why it has not been [commercialised] in the US however it is stockpiled.

Andrew Baum (Citi): I have three or perhaps four questions all on *Zostavax* please. I would be interested in your thoughts on why *Zostavax* isn't a larger revenue product, whether it is supply chain, whether it is the waning efficacy, in light of the potential opportunity for *Shingrix*? Secondly, in terms of timing for ACIP recommendation, at what point would you approach ACIP and when would you expect the recommendation given your filing strategy? Thirdly, could you contrast the cold chain with *Zostavax* and storage compared to *Shingrix*: you briefly highlighted it but that would be interesting? Finally, just going back to the US concerns on the adjuvant, which obviously is likely to have the higher acceptance, the higher selling point, we have not seen a significant commercial return with a novel adjuvant-containing product given there seems to be the US's legacy concerns with

that, and that was one factor with *Cervarix*. Is that still there or is it in the process of change, and what can you do to change the level of concern from both the physicians and potentially the regulator as well? Thank you.

Moncef Slaoui: Thanks, Andrew. What can be done for *Zostavax* to improve? Again, I have to say I'll refer to Merck to look into that but, suffice it to say, we also have a live varicella vaccine for paediatric use. This is a very sensitive virus to produce, a lot of it comes as dead virus and some of it comes as replicating virus. It is not really understood which part of these two is important and it is a very unstable virus that needs to be stored, at least that is how the *Zostavax* formulation exists.

If I look at it from a patient or subject perspective, if I have a disease that is an unavoidable risk, there is nothing I can do, I cannot change my diet, wear a mask or something. We have this virus in us. The most important thing I will be thinking about is certainty of protection by far, miles away, and I believe that if I have something that gives me 90% or 97% protection, that is what I am going for.

In my book, 50% is usually what happens when I toss a coin and then I don't know which face is going to come out. I think that is the most important challenge and I believe that *Shingrix* is an exceptional vaccine for its efficacy. I also believe it is exceptional from a safety standpoint and this is on your fourth point.

When you look at the safety data, long-term safety in the population vaccinated with *Shingrix* versus that vaccinated with saline, it is very important for everybody to understand that, the control group in our Phase III group is saline, it is not another vaccine. Therefore, when you compare to control, you have to keep that in mind. The safety of this vaccine is numerically fewer cases of adverse events in the vaccinees than in the control population. I am very comforted by that, it is very important.

Clearly, the safety of a new intervention, whatever it is, will be unravelling as larger and larger numbers of recipients of that intervention accumulate. The very same adjuvant formulation AS1 has been in thousands of newborn babies as a malaria vaccine in a population where health is fragile in sub-Saharan Africa, again with a very good safety profile. We feel confident that this vaccine adjuvant is very safe and I would like to correct your perception that *Cervarix* performance in the US was related to the adjuvant formulation. Actually, it was related to two things: our decision to make this vaccine a non-STD vaccine but, rather, a cancer vaccine and deciding as we were developing not to include HPV types against genital warts but, rather, only against the cancer-inducing types. As you know, the efficacy of the vaccine against cancer-inducing types is very high, very good and high persistence and induced after two doses.

The second reason why we have not been very successful in the US with this vaccine, or successful at all in the US with this vaccine is because we were late. I believe that if we had been first, it would have been very difficult to displace a cancer vaccine with a genital wart vaccine. That is how things unfolded but I just wanted to correct the perception that the adjuvant formulation has anything to do with the performance of that vaccine.

Finally, thirdly, the *Shingrix* vaccine storage is 4 degrees like other vaccines, normal cold chain, and on the ACIP recommendation I am going to ask Alain to comment more, but we have, we are setting up our plans and a series of studies of which, for instance, the mathematical modelling around the T-cell response for projected long-term efficacy as well as the potential pharmacoeconomics associated with the 97% protective vaccine, as an important driver of arguments that will be presented to the ACIP.

Alain, would you like to build up more on that and the timing for that?

Alain Brex: So regarding ACIP we are, as we speak, already actively engaging with them. Regarding the date of the ACIP meeting to discuss the recommendation for *Shingrix* at this stage we cannot give any firm or precise date, because, as you said, as you know, we have indicated that we will file during the second half of 2016, so that will depend when exactly during 2016 we will file.

For your information, there are three ACIP regular meetings per year, which are fixed, that is February, June and October.

And then just a comment on the cold chain, so as indicated by Moncef, indeed we will be fridge versus frozen for Zostavax, we will also be, in terms of shelf life, the shelf life we target is 24 to 36 months for the shelf life versus 18 to 24 months for the existing vaccine.

Moncef Slaoui: Thank, Alain.

Nicol (Morgan Stanley): Three questions, please. The first one is about the pentavalent meningitis vaccine, what are the main technical hurdles when trying to combine the five strains? Number two, on the RSV vaccine, forgive my naïve question, but just to clarify, do you need to succeed in both the maternal and infant population to make it a commercial viable project? Finally, how do your new vaccines candidates fit within your affordable medicine and volume strategy? I mean, do you plan to have any health economics data for all of them to try and support them? Thank you.

Moncef Slaoui: Thank you. The most significant technical hurdle a men A, B, C, Y, W formulation may reside with the meningitis A component in this vaccine, which is known to be susceptible in a liquid formulation, but that is something that we are actively

working on. Other than that, what is really important to know is that these are two approved vaccines – I would like to highlight what that means. The requirements for approval of a combination vaccine of approved vaccines is very different than the requirements for a recommendation of combining an approved vaccine and a non-approved vaccine, it sounds obvious, but I am pointing to what could happen with competitors, given that *Nimenrix* vaccine, for instance, is a vaccine we have developed against A, C, Y, W, is not approved in the US yet.

As to your RSV question, there is actually no association necessarily between the two vaccines. I believe that the paediatric vaccines against RSV will be universally recommended and I believe that a maternal vaccine would be actually also, certainly, recommended, given that in the US and in the UK, flu and pertussis immunisation in third trimester pregnant women are recommended, despite the fact that they are not specifically indicated, but they are not contraindicated in that population.

So I expect both vaccines to be very important and standalone vaccines. Clearly, as we develop these vaccines, if the two are to be given in succession, in the mother and then into the infant, it will be important to show that the maternal immunisation does not impact the baby's capacity to respond to the new vaccine, which is another reason why using the chimpanzee adenovirus vector completely different than the glycoprotein F is a major plus.

As to our volume strategy for vaccines, it has always been our strategy, in fact our strategy in the recent past is – and you could see it on how our pipeline is unfolding – is to very significantly increase our presence and success rate and market share in the US, without impacting our volumes ex-US, which has a significant accelerating effect on both our top line and bottom line, and that will continue for all of these vaccines.

Graham Parry (Bank of America Merrill Lynch): Just two commercial questions. Firstly, on Zostavax, how many doses of the existing zoster vaccine do you estimate are shipped into the market compared to your expected 25 to 30 million capacity for your own vaccine, and how should we think about pricing of that, given that you have, what appears to be, a pretty superior vaccine? Secondly, on *Bexsero*, again if you are looking at pricing this for a two treatment course, rather than three, should we be thinking about this as being parity to your competitor per course or per dose?

Moncef Slaoui: I am going to first remind you that this is an R&D Day and suggest that you talk to our Commercial colleagues in the room during the lunch time or the breaks, but let me just say that our ambitions are very high for *Shingrix* and we will position it

in a way that should allow us to be by far the leading shingles vaccine, first because it's the most effective and efficacious vaccine and I will leave your *Bexsero* question to the break.

Okay, I think we're done – thank you very much. [*Applause*] Okay – sorry, a 15-minute break.

[*Break*]

Part 3

Immuno-Inflammation, Oncology & Rare Diseases

Patrick Vallance

Immuno-Inflammation

Okay, thanks very much. I spoke about areas that are sort of major areas for GSK, established areas; I am now going to move into some areas in which we think we have got very strong emergent pipelines that I want to talk about. The first of these is immuno-inflammation.

Immuno-Inflammation areas of focus

There are four areas I am going to cover: rheumatoid arthritis, which of course remains a major problem with an ageing population and remains a problem actually where most patients remain active with their disease, there is still active disease, patients cycle through multiple therapies, there is very significant need for more durable therapies and particularly for remission and early treatment.

The second area is actually osteoarthritis which I am going to touch on which, of course, traditionally we thought of as a disease of wear and tear and has been managed accordingly, but it is very clear that there are quite significant immune drivers of the disease and actually there are opportunities to start thinking about immune modulation in some subsets of patients with osteoarthritis with potentially a big impact.

The third is SLE, where we already have a medicine, *Benlysta*, and I will update on where we are on that and how we intend to further the management of this important and actually rather debilitating disease, but the fourth thing to just focus on here is actually something like 6% of the population have some sort of immune mediated inflammatory disorder, so if you add together all the smaller indications from all the other diseases, some of which are not that small, like Crohn's, ulcerative colitis and psoriasis, but some are smaller such as Sjögren's syndrome, systemic sclerosis, myasthenia gravis; actually it is a rather big population and of course many of the medicines I am going to talk about have potential to work across these and one of the strategies, of course, is to expand from initial indication into the new ones.

Immuno-inflammation R&D strategy:

The cell types involved here of course are many and I am just going to just highlight a few things that we think are particularly important. The macrophage, which I am going to talk

about, as a key target, the stromal cell, which is often ignored as a target in immune-mediated disease, but is increasingly recognised as being of importance. Of course T and B cells as well I'll cover.

What are we trying to do? We are trying to get to early intervention, trying to get to disease remission and trying to target resistant disease as the key features of where we are going.

I want to start with a medicine which has actions across multiple cell types in fact and across multiple mechanisms of inflammation and that is the anti-IL-6 that we are developing in partnership with Janssen.

Sirukumab: rheumatoid arthritis

The IL-6 class, as you know, is the fastest growing of the biologics and one of the reasons I think is the rather effective monotherapy data for the anti-IL-6 class. You will also know of course this is one of several IL-6s that is in development and I just want to spend a few moments talking about why we think there is a position here which is quite important. The first thing to note is that sirukumab targets the cytokine, not the receptor and that has certain properties which we think are important.

I will just show you the data on the right-hand side. So we have got the ACR20 and the ACR50 data, so the 20% improvement, the 50% improvement in the Phase II data and you can see there clear effects, TNF-like effects in terms of the response.

In the bottom, monotherapy, and this is quite important new data from a Japanese monotherapy study and much of the data is going to be presented shortly at meetings, but you can see very clear responses, ACR20, 50 and 70, but there are two points I want you to take away from this. First dose – this is actually rather lower in dose than the other IL-6s and secondly dosing interval. Because of targeting the cytokine we think that, and you can see here, either monthly or two-weekly, but you can see the efficacy at monthly dosing and if you take an analogy with a TNF space, actually monthly dosing became a rather important feature of where people gravitated in terms of which medicine they wanted to use.

So low frequency, subcutaneous dosing. Clear efficacy demonstrated in Phase II. Phase III data emerging, over 3,000 patients studied to date. We have Phase III read-outs later this year in resistant patients who failed other therapies and head-to-head data, reading out against Humira and we expect to be filing this medicine in 2016.

We are also looking at, of course, additional indications and two that are starting are in giant cell arthritis and in inflammation of the blood vessels which causes both muscle problems and vascular problems and I have already spoken to you about the Phase II start

in asthma. So we believe that in the IL-6 class sirukumab has certain features which mean that this is actually going to gain a significant part of the market and it is going to be positioned in a way which we think has a uniqueness which will be important.

Clinical improvement in RA is consistently associated with decreased macrophage infiltration

The next area that I want to touch on is macrophages and macrophages are key drivers of tissue destruction in rheumatoid arthritis and, indeed, in other disease as well. You see macrophage infiltration in the tissue and macrophage effector mechanisms to cause tissue destruction. In fact, if you look at the existing medicines there is a rather close correlation between their effect and their ability to stop macrophages infiltration into the tissue, so there is no doubt that there is an important cellular target and we are targeting it through GM-CSF, which is involved in virtually every part of macrophage from production through to infiltration in the tissues and, in fact, behaviour in the tissues as well.

GSK3196165 – aGM-CSF, targets key effector cells in RA

So the antibody against GM-CSF – I'll show you the Phase II data and on the Phase II data there on the right, what you will see is a dose response in patients with rheumatoid arthritis – the EULAR good to moderate response is roughly the same as the ACR20, or you can conceptualise it like that, so very, very significant responses here.

But here I want you to focus on two things: one, this is very rapid, so if you look at the response at the 1 and 1.5, even the 0.3, you can see that at week four you are at the maximal response, so very rapid onset of action which we believe is important, durability and, actually, progression of that durability following stopping the medicine. So we have got a medicine which works quickly, is effective and actually has a long duration of action and this is exactly what you want if you want to go in earlier rheumatoid arthritis and position this for remission and that is exactly what we intend to do. We intend to start the Phase III once we have the read-out of the ongoing IIb and we expect to see the initial data on the IIb in 2016 and plan to do an early remission study in the Phase III.

So anti-GM-CSF for rheumatoid arthritis we think is important.

GSK3196165: Potential for disease modification & analgesic activity in hand osteoarthritis (HOA)

But I want to move away from rheumatoid just for a minute and talk about osteoarthritis, and I have alluded to the fact that osteoarthritis as a macrophage and inflammatory disorder is important and here there are data which we think are pretty important in terms of where GM-CSF could get positioned.

So there is no doubt that an anti-GM0-CSF works in animal models of osteoarthritis, but the important thing is it also affects pain, so if you look at the bottom-right you will see in an animal model anti-GM-CSF decreasing pain in the model, and that is not due only to the effects on the joint. If you look at the upper panel, in fact what this is saying is that GM-CSF receptor is expressed on afferent nerves so there is a neurological effect as well as a tissue destruction effect.

Okay, so far so good, so how do you develop such a medicine in osteoarthritis? That is where we think hand OA is a particularly important area to go. One of the problems dogging osteoarthritis field has been if you try and do a trial in osteoarthritis in the knee or the hip it is confounded by weight, it is confounded by how much you walk, how much activity you choose to do and many, many other things. Hand OA, which is about 10% of the OA population, is a much more homogenous disease. It is actually a much more genetically driven disease as well and we believe presents a unique opportunity to do a study in osteoarthritis and we will be starting a Phase II study with our anti-GM-CSF in 2016, looking specifically at hand OA.

GSK2982772: RIP1 kinase inhibitor in the clinic

I come back now to rheumatoid arthritis, but go much earlier in the pipeline and I want to talk about a particular molecule that we think has the potential to be very significant in this space, and that is the RIP1 kinase inhibitor.

So I have already spoken about the fact that we have had a unit working on innate immunity and pattern recognition receptors, the way that cells sense danger and so on for many years, led by John Bertin, who is here, and the molecule which we are excited about is the RIP1 kinase inhibitor. This is, to quote from the review in *Nature Reviews* "A key regulator of inflammation, apoptosis and necroptosis, RIP1 is positioned at a strategic crossroads of multiple signalling nodes in the innate immune response". So a very key target to go after. A potential new class of oral therapeutic.

We have world-leading internal team. I think if you ask anyone in the field they know that the team here is really doing work that is at the very cutting-edge and this brings the potential, and this is important, of anti-TNF-like efficacy, but with something really rather important on top of that, which is this effect on both apoptosis and necroptosis, so cell death, so the potential of efficacy with preservation of cell viability.

Why are we excited about this, even though at the moment it is at Phase 1? Well the first is the molecule itself; you can see in the middle panel here the kinome plot, so this is a plot of all the other things that the molecule might hit that would be an off-target effect. The red dot is RIP1 kinase, the green dot is all the things it doesn't hit and this, to our knowledge,

is the most selective ATP competitive kinase inhibitor to advance into man; highly, highly selective.

The second point is we are in the clinic, we are up to doses that we know engage the target and we are up to doses that we know, if you take the cells, prevent the stimulation of MIP-1 alpha in response to TNF alpha, so you have got evidence of efficacy in terms of where we are, so definitely hit the target, got a nice molecule and got the potential to go into multiple areas where you have not only inflammation, but you have cell death driving the inflammation.

Let me just take that a little bit further and tell you how we propose to take this forward, because it gives you an illustration particularly of how we are approaching immunoinflammatory disorders under the leadership of Paul-Peter Tak.

GSK2982772: studies in three indications to start in 2016

Here are three experiments. The first is a genetic experiment at the top, in a sharpin knockout mouse, which has very severe skin necrosis and this is completely prevented if you knockout RIP1 kinase. So no doubt that RIP1 kinase is causal in causing this skin necrosis.

The middle panel is an animal model when the animals are actually given TNF, which is a very, very difficult model to prevent shock in, and what we are doing is preventing the effects of TNF in this shock model and the third is human samples from Crohn's disease, showing that actually the RIP1 inhibitor blocks TNF production. So there is a very large body of preclinical and human tissue data showing the effects of this inhibition.

So we are going to go next year into parallel early experimental medicine studies, rheumatoid arthritis, ulcerative colitis and psoriasis. We will pick early from these and we will go very fast from that point through to file when we know exactly what direction to take this in, but we think a potential important rather pluripotent inhibitor with a broad profile and, potentially, a rather clean safety profile in terms of off-target effects and other problems.

***Benlysta* (belimumab)**

I am going to move from arthritis to SLE, where *Benlysta* of course is already a marketed product. *Benlysta* is currently intravenous. We have got the subcutaneous preparation – I am showing you here the new data on the Phase III readout for the subcutaneous preparation, which we think is a big step forward in terms of what patients want.

So these are, on the right-hand side, the proportion of patients with the SLE responder index response, and you can see in the orange bar the *Benlysta* subcut treated group and in the grey bar the control group. I just want to be very clear about what we are

looking at here: it is called “placebo”, but actually it is complete standard of care, and this is on top of standard of care, so this is actually what you do on top of standard of care.

Just to put that into context, when *Benlysta* was approved it was the first medicine for 50 years; if you look at the number of other people who have tried in SLE, there have been three other failures in Phase III from other compounds in SLE, so the fact this has hit again on a third pivotal study is not chance, it is actually a rather important observation.

The second is that in the new study we have got clear evidence of improvement in time to first severe flare, so we are reducing flares in the patients and flares, as you know, are the way in which this disease progresses and end-organ damage occurs. There is a trend for reduction in corticosteroids seen again for the third time, which we need to evaluate further, so subcutaneous, weekly medicine, there are nine ongoing studies in subgroups, in subgroups of patients and looking at other endpoints but also in other conditions.

So transplant rejection, ANCA-vasculitis, myasthenia gravis, idiopathic membranous glomerulonephropathy and, in that last one, we already know this produces significant effects in terms of reducing proteinuria, for example, from the kidney.

I think *Benlysta* with the subcut has the potential not only now to move into a different population, in terms of more people wanting to use this, but also in terms of different diseases that we are looking at and we will be filing for this very shortly, either at the end of this year or the beginning of 2016.

Translating clinical experience into a new hypothesis:

Phase II experimental study to start 2016

Now one of the things that happens in this area, as in oncology, is once medicines are out there, of course physicians start using them and once they start using them you find out things and I just want to share with you one thing that has been found out by a physician using this, which I think is important and something that we are going to be exploring next year in a study.

So there is a case report: severe, refractory Sjögren’s syndrome, parotid B-cell lymphoma and vasculitis. This patient had failed several immunosuppressants; actually had failed both rituximab and *Benlysta* alone, but had a very dramatic response when the two things were given.

Now why might that be? When you deplete B-cells with an anti-CD-20, the B-cells then repopulate the bone marrow. Those B-cells repopulating the bone marrow do so in the presence of high BLyS levels and they become autoimmune B-cells again.

If you suppress BlyS with *Benlysta* so it can't signal, the hypothesis is you repopulate with non-autoimmune B-cells, hence leading to both a bigger effect, but also a durable and, potentially, a very profound re-setting of the immune system.

There are other sort of anecdotes out there like this; we will be exploring this, obviously – and this is experimental, but we will be exploring this in a clinical study starting in 2016.

Early Immuno-Inflammation clinical phase pipeline with multiple first in class assets

So the late phase I have described and I have given you a glimpse of early clinical phase projects with RIP1 kinase and I want to end this section with four first in class antibodies, all in the clinic, all of which, we believe have the potential to be important across a number of autoimmune conditions.

Four “first in class” antibodies in the clinic: GSK2618960

The first is the anti-IL-7R antibody. So IL-7 is an important cytokine driving pathogenic T-cell survival. It also does something which is rather important which is to drive the formation of ectopic lymphoid tissue and this ectopic lymphoid tissue seems to be very important in disease maintenance and disease progression.

So if you are looking in the salivary glands or, indeed, the parotid glands of patients with Sjögren's syndrome, and Sjögren's syndrome is a destruction of those glands leading to quite significant problems and actually quite a significant population – there is something like between two and four million patients suffering from this in the US and about half a million in the UK, something like that. So if you look in these tissues what you see is ectopic lymphoid tissue in the glands with IL-7 receptor. You don't see that in the controls and you see an increase in IL-7 positive cells in the tissue.

In animal models IL-7 drives the disease, so a very good rationale for why this is a target to go after in Sjögren's syndrome and probably in other areas where you see this ectopic lymphoid tissue as well. This is in Phase I and will be going into Phase II in 2016.

Four “first in class antibodies in the clinic: GSK3050002

The next is an anti-CCL20. This is a single receptor preventing the CCR6+ T-cells, so preventing inflammatory T-cells from entering into tissues and I just want to show you this because I think it illustrates again an experimental approach which is important.

In order to test whether this antibody does do what we hope it does, we used a blister model. This blister model creates an inflammatory blister on the skin of volunteers and into that blister CCR6+ T-cells migrate. The antibody, as you can see in this experiment, actually

decreases the migration of CCR6+ cells. Why is that important? That is actually quite a tough test, so you are giving a systemic antibody, you are creating a very profound local inflammation and you are seeing a decrease of cellular migration. So we believe this has the potential to work in a number of conditions; it will start in psoriatic arthropathy and we plan to start the Phase II in 2016, so we are pretty excited about where this one goes as well.

Four “first in class” antibodies in the clinic: GSK2831781

Probably the antibody which we are most excited about at the moment is actually an anti-LAG3 cell depleting antibody. So this depletes LAG3 cells, so depletes the recently activated pathogenic T-cells. This has the potential therefore for really inducing disease remission. I am sure this doesn't project terribly well, but actually, what this is showing on the right-hand side is a study in non-human primates, pre-dose are the red dots are showing LAG3 positive cells, post-dose the LAG3 positive cells are all removed, so it definitely does what it is supposed to do in terms of depleting those cells.

At the bottom is the skin erythema response to a tuberculin antigen challenge; two doses in blue and red and what you can see, and you don't really need to be a statistician to see this, is that when the drug is given on the right it is completely abolished. So a rather profound effect in this model.

This will go into psoriasis first of all, but we expect to move very rapidly into inflammatory bowel disease and believe there is a potential for quite significant disease modification.

Four “first in class” antibodies in the clinic: GSK2330811

The final one I want to highlight is anti-OSM, and this comes back to my point about stromal cells. So OSM is important for both fibroblasts and also some of the vascular cells and androgenises occurring in some of the lesions and here we are looking at the OSM expression in a skin biopsy of patients with systemic sclerosis. Systemic sclerosis is a disease with an incidence of somewhere between 10 and 15 per 100,000. It affects women more than men. It causes profound tightening of the skin and actually does the same in organs as well and those people affected with this in the organs actually have a very poor prognosis in fact and obviously have very miserable lives.

OSM is highly expressed in the skin biopsy and the anti-OSM will go into – it is in Phase I at the moment – will go into trials in systemic sclerosis and you can see how the positioning of these is very much driven by the underlying mechanisms.

Four “first in class” antibodies in the clinic

So four first-in-class antibodies, all either in Phase I or Phase II and data reading out over the next couple of years on these.

Immuno-Inflammation R&D strategy

Let me just try and pull the immuno-inflammatory section together so we have got a number of important targeted biologics which I have spoken to, we have got the strategy to target resistant disease and I think you will see in some of the Phase III designs a rather ambitious approach to go early and target remission and enduring remission with some of these agents.

The one other medicine mentioned on here that I will come onto in the next section is the BET inhibitor, which is an epigenetic approach in immuno-inflammation where we have a very significant activity, but I am going to talk about that in cancer first.

Immuno-inflammation we believe is somewhere that is a growth area for GSK and where we have a number of really quite promising medicines coming through the clinic.

Oncology

Let me move now, though, to oncology.

Oncology R&D strategy

Oncology is an area in which we are very clear about the three things that we are going to focus on. We are going to focus on the cancer stem cell, the cell that actually formulates the reproduction of the cancer, we are going to focus on areas of immuno-oncology, the ability of the body to fight the cancer and damp it down and cancer epigenetics, the process by which we might actually revert cancer cells to a non-cancerous phenotype. Those three areas, of course, are independent scientifically but are also overlapping in terms of how they might interact.

What are we aiming for? Reprogramming cancer cells, combination therapy with first-in-class and actually stimulating anti-tumour immunity. I am going to start with epigenetics.

GSK Epigenetics: an early commitment with a pipeline now at the forefront of industry

What is epigenetics? Epigenetics is the way in which DNA in a cell is allowed to be expressed or not expressed, and it is obvious there has to be such a mechanism because you have got the same DNA in every cell in your body and you don't express the same genes in your eye and the way you do in your skin.

So epigenetics is the way this is controlled and it is now clear there are ways to interfere with this. This is important for cancer because reversing some of this can potentially reverse the phenotype.

Where are we in the field? I think we have a world-class team. We have been working in this field for seven years or more, both in immuno-inflammation and oncology with some substantial publications and you can see from the list of collaborators, both academic and biotech, that our group is really seen as at the very forefront of this.

I am going to talk about two medicines.

GSK525762: potential first in class BET inhibitor

The first is the BET inhibitor. So at the top is the structure of the protein with the inhibitor in there which was published in *Nature*. What is BET? BET is a family of proteins that actually allow gene expression to be manipulated and in some of those genes there are oncogenes as well so you can either increase or decrease the expression of the gene profile.

The area that most directly links this to human disease is a very rare tumour called NUT midline carcinoma, and in NUT midline carcinoma what happens is there is a chromosomal translocation that leads to a fusion protein which ultimately activates through the BET pathway. This means that is a causal mechanism in human cancer. This disease is rapidly lethal, affects young people and it is rapidly progressive and doesn't respond well to treatment. So this is where a BET inhibitor really should work.

If you look, though, this pathway is potentially active in lots of tumours and is a target in lots of tumour types, so at the bottom here is a measure of cell inhibition of growth, so this is about reducing the growth rate of cells and it is important to recognise that epigenetics isn't the same as just killing cells, it is actually about reverting them to a more benign phenotype and reducing growth.

So this is the growth inhibition, the IC50, so the dotted line is one micromole and across the different colours are different tumour types. On the left-hand side it is mainly solid tumours, I think it is pancreas first and then we have breast and then we have lung cancer; right in the middle there is a tiny little few bars there which are actually the NUT midline carcinoma and then on the right-hand side is haematological malignancy.

So you can see effect across a wide range of cancers. Let's look at the data in NUT midline carcinoma.

GSK525762: early evidence of potential clinical benefit

This is a prototypic disease where they should work and of course this is a paradigm which was worked out in the past in cancer with things like Glivec going down to this approach to really targeting to the key areas. So on the right-hand side here is a CT scan of a patient with NUT midline carcinoma; very resistant to treatment, very rapidly progressive, universally lethal. The lesions are outlined with the arrows. Following treatment with the BET inhibitor we see a 90% reduction in tumour volume at 16 weeks.

We have now treated seven patients; one too late – I think much too late. The six patients who were treated in the time when it did seem possible do something within the dose which is, we believe, the effective dose, we have seen responses, so we are very confident that we are seeing responses in NUT midline carcinoma.

We are also in tumour studies across both solid and haematological malignancies and we expect data to read out over the next couple of years on this.

Our filing strategy is going to entirely depend on what we see and you can already see that we can see responses in NUT midline carcinoma.

GSK525762: potential to treat and reset disease in rheumatoid arthritis

I said I would mention this again in relation to immuno-inflammation and I just want to show you one slide in relation to the BET inhibitor and we have a whole programme behind this of more or less selective BET inhibitors for different indications, but here is the data for rheumatoid arthritis. So in a rat collagen-induced arthritis model, top right-hand, you can see the clinical score increasing following the initiation of the insult in the rat and in the line right on the bottom, in other words, complete protection, is what happens with treatment with the BET inhibitor.

At the bottom human RA stromal cells, again the stromal cell which I have stressed is an important cell, looking at gene expression profiles in response to a BET inhibitor – I am not going to take you through all of that, but I can tell you what it says – is you can see a pattern of gene expression change which is a reversion to a more normal gene expression profile in the stromal cell.

So we have got a lot of excitement in the immuno-inflammation space as well and we are going to be entering the clinic in 2016 with the BET inhibitor and we have other follow-on molecules.

GSK2879552 LSD1 inhibitor: Early signal of efficacy in SCLC

Let me come back to cancer and epigenetics and tell you about the second molecule I want to talk about, which is the lysine demethylase inhibitor. The easiest way to think about this is to look at the picture in the middle. The untreated cells, and this is a mouse

leukaemia cell-line, look horrible. They look like malignant blast cells, they will reproduce rapidly and they are exactly the type of picture that you don't want to see. Treatment with the LSD inhibitor reverts the phenotype, so on the right-hand side you can see what they have done is differentiate into normal cells. They look like normal cells now, so it is this process of changing a cancerous type blast phenotype to a differentiated phenotype which is important.

Where are we in the clinical study? We are in two studies: one in acute myeloid leukaemia and the second in small cell lung cancer and I just want to show you the data from the small cell lung cancer study which is on the right hand side. These are patients who have failed lots of treatment, they have been resistant to treatment, they have got progressive disease which is often where one would start in these sorts of things with cancer and I want to show you one thing in particular – so the patient at the bottom had resistant lung cancer, had failed multiple treatment and now had a prognosis probably of three months and has now been stable on the LSD1 inhibitor for 540 days plus.

You can see some others above that marked stable disease where we are seeing longer stability than you would expect.

So we are seeing the sorts of effects you would expect where you would start to turn this into a more benign phenotype and of course this will mean different endpoints to think about for epigenetic medicines as well.

Behind these programmes we have seven other programmes, some of which are getting close to the clinic and one other in the clinic which is EZH2 and Chris Carpenter can speak to that in Q&A if people are interested, so excited about the potential about epigenetics.

Immuno-Oncology: NY-ESO T-Cell Therapy

I want to move now to immuno-oncology and to start with a cell based therapy. Cell based therapies will come up as a theme in some of the other areas I talk about. This is a partnership collaboration with Adaptimmune and it is about engineered T-cells with an increased affinity T-cell receptor which can then target the tumour and kill the tumour. So the target is NY-ESO, the cells are engineered to have a high affinity T-cell receptor. In the top you can see the CT scan, what happens when you give these engineered T-cells back? So the baseline scan shows the tumour – in this case a sarcoma, the second one shows the inflammation you get when the tumour is hit with the T-cells and then you get a complete response. Then in the bottom panel here you see the response in sarcoma so far – 12 patients treated – the orange line indicates something that would be seen as a complete or partial response and you can see significant responses in sarcoma.

Why am I stressing this sarcoma results? It is because the Holy Grail actually of the cell-based therapies is to go from haematological to solid tumours and I think you can see here some encouraging results in terms of the solid tumour profile.

So this is in trials now for both solid tumours and haematological malignancies, multiple tumours actually and the filing strategy will obviously, again, be dependent on the data we see, but the sarcoma data certainly look very encouraging.

Immuno-Oncology: GSK3174998 OX40 agonist mAb

Let's move on now to from cell therapies to checkpoint inhibitors and I am just going to highlight two. This work has been led by Axel Hoos, who I have already said was instrumental in the development of ipilimumab. So the first one to talk about is the OX-40. OX-40 agonist antibodies are in the clinic. Actually there are now four around; we are one of four. Dual mechanisms: enhancing effector T-cells and also affecting suppressor T-Regs, so this is important as a way of controlling the tumour. I will just show you some results from the animal model.

This is a colon cancer model and the first thing to say in this model you can see the PD-1 on its own not terribly effective – the OX-40 on its own not terribly effective, but the combination hugely effective. So what does that tell us? It tells us that combination checkpoint modulators have the potential to be rather profound in their effect and have the potential to broaden the responder population. As you will know, one of the interesting things in the whole immuno-oncology space is some people respond terribly well and some people don't and the question is how can you broaden that population? Here is a real opportunity to think about that.

The second below is the combination with TLR-4 and we have a TLR-4 agonist which we can take into the clinic next year and we hope to be in combinations the year after. Again, little effect of OX-40 on its own, some effect the TLR-4 on its own, but very striking effects in combination. So we do believe this field of immuno-oncology will move to combinations and we actually believe that this will be immuno-oncology to immuno-oncology combinations more than immuno-oncology to targeted therapy combinations, where we think there are other sorts of risks emerging.

So the OX-40 is in the clinic and you may have noted that today we have announced a collaboration with Merck to do a combination study with their PD-1 and our OX-40. We are excited about the OX-40 and we are also excited about the ICOS.

Immuno-Oncology: GSK3359609 first-in-class ICOS agonist antibody

Now ICOS is a really interesting antibody. We actually got this through a collaboration with a French group, INSERM, and I want to tell you why we are excited about it. If you look at the middle column here, this is the ICOS T-cells in ipilimumab treated patients, the cell count. Ipilimumab responders in blue and non-responders in red. So what you can see is high CD-4 ICOS T-cell is a marker of response.

If you go to the bottom bit in the middle, you have overall survival, so this is cut a different way now, CD-4 ICOS greater than four overall survival very good, CD-4 ICOS less than four overall survival not good.

So it starts to tell you this is a biomarker. So the interesting thing is this biomarker now becomes the target, so on the right-hand side you will see what happens with the antibody, T-cell activation *in vitro* very effective, T-cell proliferation *in vitro* very effective. So we believe this has the potential to be a rather universal mechanism across cancers. Importantly the patient selection biomarker is, in a sense, embedded in the programme and that has been a big stumbling block in the field – how do you select responders?

It enhances T-cells associated with survival and we believe there are multiple places one might think about using this, both in refractory patients and, of course, in combinations.

So we are excited about the ICOS – that goes into the clinic early next year and, as you are well aware, these things can move very quickly once they are in the clinic.

Cancer Stem Cells: tarextumab (anti-Notch 2/3)

Let me end the oncology section with one last bit of data and this is in the cancer stem cell space with our partnership with OncoMed. So this is a Notch 2/3 antibody, targeting cancer stem cells and the data shown here in pancreatic cancer and you will be aware that pancreatic cancer is one of the most difficult of all cancers to treat and the same format, below the orange line, is a response. These are in patients – it is a Phase 1 study data I am showing you here, but it is a combination with the standard of care plus the Notch 2/3 and you can see a response rate which is higher than has been seen previously. It is currently in Phase II, so that is in both pancreatic cancer and small cell lung cancer and we expect to get read-outs in 2016. Again, what is the filing strategy? It is totally data dependent and will go as fast or otherwise as we need to, depending on the data that we see.

Oncology R&D strategy

So if I try to pull together where we are in the cancer field at the moment; we believe we have got an industry leading position with epigenetics which we are very excited about and we are beginning to see the real outcome of this in the clinic. In immuno-oncology we

have both got cell based approaches, but also checkpoint inhibitors and modulators in the clinic now and cancer stem cells we are beginning to see responses.

Oncology – Pipeline snapshot

These things are not unrelated, as I say. The potential of linking epigenetic medicines to immuno-oncology I think is an important one that we are exploring and you can see the aims that we are trying to have there in terms of the impact on the cancer. Our entire activity in oncology is focused in these areas and you can see quite a profound pipeline emerging, both across epigenetics in blue and indeed in both cell based and other approaches in immuno-oncology. I am not going to go through the whole thing.

Assets profiled at R&D day by planned filing date

Let me try and draw all of this together and then end with some work on some rare diseases. So I think Graham asked “What is the takeaway message from some of the stuff that I am showing?” I am absolutely showing you, both in the first section of this that there are a number of things that we know work.

There are a number of things that we are going to progress rapidly and there are a number of things that are near-term in terms of their file dates. These are the outline of the things we have covered today and, of course, there are other things as well that we are not speaking about, but you can see the progress near-term, mid-term and, indeed, long term sustainability.

Rare Diseases

What I want to do, though, is to talk about rare diseases now for the last bit. I am going to cover just two areas that we think are particularly exciting in the pipeline. The first is amyloidosis.

Amyloidosis: a complex protein deposition disease process with ~50% mortality at 3 years

Amyloidosis is a disease of protein deposition with abnormally folded proteins. There are a number of causes of amyloidosis. It can be caused by an immune response from monoclonal production of light chains, it can be caused by either a genetic or acquired over production of so-called TTR, transthyretin protein and it can be caused by long term chronic inflammation. This is actually less common now in developed countries, the AA amyloid. The point is that the amyloid gets deposited in tissues, in nerves, in kidney, in heart and liver and, of course, is substantial destruction – it actually has a prognosis which is worse than cancer in many cases.

Two fundamental approaches to treatment: prevent amyloid formation and remove amyloid deposits

We are taking two main approaches. The first, in partnership again with Isis Pharmaceuticals, is an antisense approach, switch off the protein production. So this is an oligonucleotide to switch off the TTR production, decrease the levels of TTR and therefore try and prevent the accumulation of the amyloid.

The second, which I think is a really very different approach and one pioneered through an academic collaboration through our very unique collaboration model called DPAC, that I am happy to say more about, which is with a key academic, who has got a very, I think, important hypothesis and that is that amyloid gets coated in something called serum amyloid P and that serum amyloid P stops the amyloid from being phagocytosed and taken out of the tissues.

So the approach we are taking is to target the serum amyloid P, make that visible to macrophage so they can now take the amyloid out. In order to do that, because there is loads of serum amyloid P in the circulation, you need to wash the serum amyloid P out of the circulation and then give the antibody and that is the approach we are taking: small molecule, take the serum amyloid P out of the circulation, antibody, on to the tissue now to allow phagocytosis.

GSK29908728 RNA targeted transthyretin (TTR) knockdown

Let me just show you results from two of these. Here is the knockdown, the TTR approach. So on the left-hand side is the early phase data showing a dose dependent knockdown of TTR, so we are stopping the protein that forms the amyloid. On the right-hand side is the new data which is the knockdown in the open label extension study of the ongoing Phase III and you can see we get about a nearly 80% reduction in TTR with a maximum reduction of about 92.

This is in pivotal studies for familiar amyloid polyneuropathy and is starting in the cardiomyopathy and we have got a single agent for both diseases.

CPHPC + Anti-SAP mAb for systemic amyloidosis

Results from the serum amyloid P approach – well the scan again is one of those again where you don't need the statistician to show you. This is the scan of amyloid in the liver before treatment and 42 days after. What is the consequence of that?

Liver volume decreases, so it has gone from 36 to 29, back into the normal range, liver stiffness decreases, so we are increasing the normal constituency of the liver and you can see the percentage of tracer in the liver decreases.

What is more we are seeing end organ function improve in terms of liver function. This was published in the *New England Journal* this summer. This is proof of concept of being able to remove amyloid from tissue which we think is a really rather important observation and one with potentially very big implications and this is in studies at the moment and we are going to look at what the filing strategy is for this medicine.

Amyloidosis: a comprehensive R&D approach

Two approaches. Stop the protein being made, take the amyloid out and, of course, those are complementary and we have others, including oral SAP depleters and an anti-fibril approach which I am not going to talk about.

GSK2696273 for adenosine deaminase severe combined immunodeficiency: 100% survival at median 7 year follow up

I come now to the final section, which is on cell and gene therapy. Maybe this story of ADA SCID, which is a very rare disease, and I have already talked to you about cell and gene therapies, which is an area that we are growing in in terms of our investment in platform capabilities. ADA SCID is a very rare disease, so this is not going to move the needle for GSK in terms of an income, however, it is a way to really get into an area that we think is going to be fundamentally important; it is a platform and it is clearly important for the children who have this disease.

This disease is fatal, unless children can have a sibling matched bone marrow transplant, which most don't end up with. It causes life-threatening infections.

The treatment, and this is in collaboration with Telethon and San Raffaele Hospital in Milan, is to take the cells out of the bone marrow, re-insert the normal gene, under a promoter, put the cells back, the cells repopulate the bone marrow, so it is a single, one time treatment and you can see here increased T-cell count. Just for reference, because you may not be able to read it at the back, these are years – that is seven or eight years following a single treatment and that is the reduction in infections over seven or eight years.

This has been filed with the European Agency; it is going to be filed in the US in 2017. This looks like a very profound treatment for this disease.

Gene therapy works in different monogenic diseases

We have a pipeline behind this of this cell and gene therapy based approach – we have got the world first *ex vivo* autologous cell therapy file. We have a filing strategy agreed for two more: those are the two on the right, Wiskott-Aldrich Syndrome and metachromatic leukodystrophy, a beta thalassemia study is starting, which we have an option on and we are building a platform in cell and gene therapy both for the oncology indications, which I have

talked a little bit about, and the rare diseases indications and we believe it has got potential utility beyond that.

I want to end – there is the pipeline in the middle that we are working on and, by the way, in the three ongoing studies, which is ADA SCID, MLD and Wiskott-Aldrich, we have 100% survival of patients so far in these three studies, but I want to end by just showing you some data from metachromatic leukodystrophy.

Cell Gene Therapy clinical effect in MLD

This is a brain disease. I don't think any of us thought that a cell therapy in the bone marrow would work in a brain disease. These patients have rapid loss of motor function. So what you are looking at here is the results from patients and their siblings and in this disease the siblings tend to run the same course, so if your sibling lost motor function at 40 months, you are probably going to lose motor function at 40 months.

In the grey zone is the normal development of motor function in normal children. In the orange dots are the motor function in the siblings, showing the ages at which they lost motor function.

In the coloured dots and lines are the children treated with gene therapy, showing a remarkable preservation of motor function. This tells you the impact that you can actually do something about brain disease as well with this approach of cell therapy.

I am going to end on what I think is a sort of striking glimpse of where this can go and introduce the panel.

Introducing our experts

Paul-Peter Tak I have mentioned; he joined us from Amsterdam Medical Centre – I think has a very, very deep clinical and scientific expertise and I think a very important way of looking at experimental medicine.

Ravi Rao, who joined us from Roche and he is leading the IL-6 programme, John Bertin, who leads the Pattern Recognition and Innate Immunity Unit, Chris Carpenter, who leads the Epigenetics Unit and Axel Hoos, who I have mentioned, who was from BMS, did ipilimumab, Duncan Richards, who has really spearheaded much of the amyloidosis work and Sven Kili, who has joined us from Genzyme to head the Cell and Gene Therapy area.

Assets profiled at R&D day by planned filing date

So I will end at that point there and move onto Q&As. The way we are going to run this is I would like the questions to be related to this section to start off with and then we will open it up to more general on any of the areas we have discussed today.

Question & Answer Session

Steve Scala (Cowen and Company): Two questions: you showed us a number of oncology assets, and there are many others in development, just to clarify, which of those, if any, did Novartis have access to but not take during the business swaps? And if they didn't take them, then why didn't they take them?

Patrick Vallance: It is a simple one to answer; they didn't take them because they weren't offered.

Steve Scala: Okay.

Patrick Vallance: And very clearly they took the marketed products. There was one pipeline product, AKT, which was part of the deal; they had access to nothing else that was in the pipeline.

We are discussing with them, at the moment, some of the other ones, but not these.

Steve Scala: Okay. The second question is five of the ten major Pharma companies either have a PD-1 or PD-L1 or were licensed one, obviously GSK does not, is this because – and I have three options – first, GSK, simply didn't appreciate the importance of the target early enough, second, GSK realised the importance but simply didn't find a good molecular target or, third, that GSK thinks the target is overrated?

Patrick Vallance: Well, definitely not the latter. I think the target is an important target, an important medicine and I have already alluded to the fact I think this is going to be important in combination.

We actually did have a PD-1, it was a fusion protein, I think it was a mistake, in terms of the molecule we went after and we didn't get to where we needed to be, and we made a very clear decision that we were not going to be chasing the pack, we were going to jump to the next generation of what we saw as combination medicines, rather than come in with the, sort of, sixth, seventh, whatever it might be, PD-1.

Andrew Baum (Citi): Two technical questions and one strategic. So, first of all, for Axel, perhaps you could contrast your ICOS molecule with that of Jounce specifically in the relative agonistic and Treg depleting properties of the two molecules? My perception is theirs is more agonistic than yours, but please correct me if I am wrong. Second, on Epigenetics, I think it was Chris was the Team Leader there, there have been a number of interesting publications in animal data showing some pretty profound CNS disturbances with

these quite promiscuous agents. I know there are a number of clinical trials, but interesting in what you are seeing or what you could expect?

Then, finally, the strategic question is this, I like, I suspect, many other investors scratch our heads a little bit about the future of GSK Oncology, firstly because, obviously, you have divested your in-market and that does send a message to research, it is a little bit like allowing me to research but not communicate in print, and then, second, the strategic deal with Novartis, which effectively sells your birth right on your portfolio and prevents any kind of JV, at least that is my understanding, makes it difficult to imagine how you are going to maintain key talent within the organisation, especially when you are not based in sunny California. So to what extent is that a preoccupation for you and what can you do to address that?

Patrick Vallance: Let me answer that, first of all, and then I will let the key talent answer the other two things and you will see how good they are.

So the Novartis deal gives them the right to be shown what we have before file and the right to make an offer on that to develop it commercially. We have no obligation to accept that offer and, in fact, we can progress ourselves, if we choose to. What we cannot do is then partner with somebody else at worse terms than we were offered, should Novartis have chosen to put an offer in.

So I think the deal actually gives us a lot of freedom to develop our pipeline and I think the other thing that has happened as a result of it is actually we have put all of our investment – all of it – in the areas we are talking about. We are no longer doing combination studies, catch-up studies with targeted agents, everything is on this and actually the Discovery organisation is exactly the same type, slightly bigger actually than it was initially. So I think it gives us a lot of freedom to actually go in the way we want to and the deal with Merck, to some extent, shows that we are able to work with others in the clinical development space.

Now I will ask Axel to talk about the ICOS.

Axel Hoos: The ICOS antibody is possibly the first-in-class antibody in this area and in terms of differentiation it is a little bit hard to say, because we don't have a side-by-side comparison here. But the one thing I can tell you is that our ICOS antibody was engineered not to deplete cells, it does not deplete either T-regs or effector cells, it aims for an agonistic approach to boost the effector cells and actually conveying clinical benefit.

So what Patrick has shown you here is that the ipilimumab data, from which this emerged as a biomarker, suggests that patients have a better outcome, survival or

response, if they express ICOS on their T-cells. If you now agonise those T-cells they will continue to divide and you will increase the size of the army of cells, that is ultimately conveying the clinical benefit.

So our intent here is to really maximise the effect, either in PD-1 unresponsive patients or CTLA-4 unresponsive patients, or as a follow-on therapy to those treatments, because one thing we know for sure, ICOS upregulation occurs as a consequence of T-cell activation and that could happen either through CTLA-4 pre-treatment or PD-1 pre-treatment; the number of patients that have been pre-treated now is constantly increasing, so these are large populations and there are other ways of activating T-cells.

So we expect that ICOS can make a significant contribution and when it comes to this question about 'Do we need a PD-1 or do we not need a PD-1?', we believe we actually don't need a PD-1 in order to have a successful strategy. We believe that you can either latch on to PD-1s that are on the market and there are two very successful PD-1s already out there, which is BMS's and Merck's product. We have a combination programme that will start with Merck on OX40, there will be other things coming down the pipe that I cannot yet talk about, and we believe that it is quite possible that any of these checkpoint modulators could become another backbone strategy or another backbone medicine, if you want. So when we developed ipilimumab nobody had fully appreciated how big PD-1 would become afterwards. Now we are at PD-1 and I don't think we fully appreciate yet how big the next generation will be, so our focus is on the third generation with leading molecules, so ICOS and OX40 both could possibly be, depending on how we develop them, backbone strategies.

Patrick Vallance: Thanks, Axel. Okay, and then, Chris, I mean actually there is a related question as well, which has come up to the one Andrew asked, which is from Simon Baker in London on the fact that lapatinib did cross the blood brain barrier and side effect profiles, so it is really about the side effects. Maybe I will just make a general comment before you open.

I think four years ago, Andrew, the real question was can you interfere with epigenetics in this way at all without having all sorts of scattergun effects across the body? I think in a way that has been answered, you can, and I think this is a sort of coordinate response.

So I think the first fundamental safety question which we were really concerned about has been answered, which is why we are happy to go into immuno-inflammation, and the second thing is we have spent time over the past few years developing a safety organisation expertise and pre-clinical expertise in really understanding how to think about side effects profile, but, Chris, I will leave you to answer the question.

Chris Carpenter: Sure, so we are certainly aware of the data you describe on learning effects, on learning and memory in mouse models and we have not seen anything that raises our concerns in our human studies. But, that said, we have enrolled 50 to 60 patients in our two studies, so it is early, it doesn't rule it out, but often pre-clinical data doesn't translate into the clinic, but it is something we will pay particular attention to going forward. We have had patients on study for 20-plus weeks and still haven't seen anything that raises our concern.

As far as whether it crosses the blood brain barrier, we don't think it does, we haven't done a definitive study to prove that it doesn't, but we don't think so.

Patrick Vallance: Thank you.

Graham Parry (Bank of America Merrill Lynch): Three questions. Firstly, what do you need to see in the clinical data, the Phase II data, for the Adaptimmune collaboration on NY-E so as to pull the trigger on actually licensing in that fully? Are you waiting for solid tumours data there, so just the pivots for that decision, and could we see a decision next year on that? Secondly, could you clarify the eight tumours for the OX40 as a mono, which patients are you looking specifically at, PD-L1, CTLA-4 failures there – and I think you answered part of my question there – you do see this as a potential future backbone? Then, thirdly, could you run through the differentiation of your amyloidosis portfolio versus Sanofi and Alnylam, given you are running a little behind, about 12 months behind, but I do see you have announced you are moving into Phase III in cardiomyopathy as well today? Thanks.

Patrick Vallance: Okay, so let me answer the last one first, which is I don't think anyone else has got the molecule that clears amyloid from tissue in the way I have just shown you. I think that is a unique approach to amyloidosis with profound implications.

I think in terms of the knockdown, as you know, we are neck and neck with Alnylam. You can view them being ahead with two molecules, if you take some of the endpoints you are looking at, you can view the ISIS as being ahead if you take the more substantial endpoints; I think we are neck and neck and I think this will play out. I think there is an advantage in having a single molecule that deals with both the neuropathy and the cardiomyopathy, and we will see where we get to with the trial results on that.

In terms of the OX40, the plan there – and I think this is an approach which Axel is going to pursue – which is we go into multiple tumour types, look for responses and actually then change the trial design, depending on what we see. So it is not that we are going in to

lots of tumours in complete parallel designs, it is more of an approach to see where to be guided.

The Phase II NY-E, so I am sure you don't expect me to stand up here and tell you when we are going to opt in on that; you have seen the data.

Graham Parry: *[Inaudible comment]*

Patrick Vallance: We have an option on it, we can take the option when we have seen the data that we think is right for us to own it and take it forward in our own hands, and we have a very, very good partnership with Adaptimmune on this, with other programmes behind that that we are excited about.

Richard Parkes (Deutsche Bank): I have three questions as well. Firstly –

Patrick Vallance: You always do, there are always three; I mean that is great.

Richard Parks: Firstly, again on Oncology and it is more related to capital allocation in R&D, I am just wondering how you take into account now with the Oncology programmes that you don't have the opportunity later on down the line to leverage that through your own commercialisation infrastructure, do you set different hurdles for taking programmes forward versus other therapeutic areas? Then, secondly, on the Adaptimmune technology, what are you seeing in terms of the safety profile there, are you seeing any indications of anything like cytokine-release syndrome, the problems that have hampered other programmes? Then, finally – and I know this is a little bit related to commercialisation – on the IL-6 antibody, can you remind us what the deal with Janssen is, what the terms are in terms of the commercialisation there and do you think that antibody is sufficiently differentiated for you to invest in building out your own Rheumatology capability?

Patrick Vallance: Okay. So on the first one, I hope I have been clear and if not I am going to be clear now that the approach in Oncology is to go for those areas which we think are profoundly disruptive, in terms of what may happen in cancers. We are not pursuing any of the other things, we are not pursuing targeted therapies, we are not pursuing other approaches; we are putting all of our investment in those areas and we have a high hurdle, which is we expect to see really profound effects, like the type I have shown you in the NUT midline carcinoma, like the type we expect to see with the molecules that are going in OX40 and ICOS, and, yes, in that sense we have a very high hurdle, but we expect that the choices we have made will actually jump that hurdle.

That cleaning up of the pipeline, which was part of what we were able to do with the Novartis deal, is important actually, it means all of our activities can be put on the key things.

The Adaptimmune signal, I think I showed you a bit on the CT scan, you give a T-cell therapy with an engineered T-cell receptor, you get an inflammatory response and so you do see that, you see it on the CT scan, that was at Day 2, I think, and so you do see that in patients. It is manageable and you have seen that patients are in the trial and those trials are ongoing, so I think that is a manageable side effect, but it is obviously one of the risks and obviously the risk of the approach is that you get T-cell responses against tissues and you need to watch out for that.

The deal with Janssen is around us commercialising in the US and then commercialising elsewhere; it is the Americas, actually broader than the US.

The IL-6 differentiation, I really tried to pinpoint – I don't think there is going to be massive differentiation in overall efficacy in the IL-6 class. I do think though things like 'What is the dosing interval, monthly?' 'What is the dose? What is the safety profile? How do you give this?' become really rather important, 'How many other indications can you show that you can use this in?' and I have given some indications as to why I think there is a rather competitive position.

Florent Cespedes (Société Générale): Three quick questions. A follow-up on OX40. Andrew flagged at the beginning of the year that there is a leading portfolio in OX40, so I am happy to see a slide on this topic today, but as you are not the only company in this field could you please put things into perspective and give us how and why you believe that your approach is better or is differentiated versus the competitors? The second question, a follow-up on sirukumab, do you believe that if you are not the best-in-class, as you are not the first-in-class, maybe it could be outside RA, the main potential for this product? The last one, a quick one on the –

Patrick Vallance: Sorry, what was it? It could be outside, what did you say?

Florent Cespedes: Outside RA, the potential? The last one, a quick one, the 165 the anti-GM-CSF, what could be the best comparator for the Phase III? Thank you.

Patrick Vallance: Okay. So the OX40, I think we have got a very nice, human OX40, a very nice molecule in the clinic and I think probably the best way to explain this is why have Merck announced they are doing the PD-1 with our OX40? Okay, so we think we have got a nice molecule and a nice opportunity there.

Sirukumab, again, I have tried to indicate and if you take the analogy with the TNF space, it was things like dosing interval, dose and side effect profile that became important. We do think though that the use of sirukumab in RA, how we position it, is important and how we look at other indications is important, and I will ask Paul-Peter to say a word about that in just a minute and also to speak to the GM-CSF comparator.

Paul-Peter Tak: So, I think it is good to remind everybody that if you look at the success of the TNF blockers and rituximab, for example, that about 50% of the sales come from RA, in other words 50% come from other indications. So, we have a strong rationale here to go into all the IL-6 dependent diseases, so starting with the ?arthritis, where we are going to dose the first patients within the next few weeks or so, you heard about asthma, we are going to make decisions about other IL-6 dependent diseases over the next few weeks/two months, so we will have a very aggressive approach here. We do believe it will be the best-in-class, but in any case we will seek an indication in other non-RA indications as well.

With regard to anti-GM-CSF, we are going to develop this in a very different way compared to other biologicals, so we are aiming for early disease, even in patients who have not seen conventional disease modifying anti-rheumatic drugs, so we aim for induction of remission and we have reason to believe that this medicine will be more effective than the TNF blockers in early disease, and the ultimate goal is actually to induce biological free remission over time.

So, having said that, it is quite logical, I think, that TNF blockers will be the comparator in the Phase III clinical trial in early RA.

Patrick Vallance: Thank you. I have two questions here from London, both actually about assets that we haven't mentioned, one asking specifically about some and some saying how should you interpret the ones that aren't mentioned? Maybe I will deal with that in one go.

So the asset asked about was retosiban, which is an oxytocin antagonist for pre-term labour, the reason we didn't mention that is actually that is a semi-validated target, in that there is a peptide that works against it. It is in a Phase III study, it will readout and we will see what the study shows. We are excited about the mechanism; we are excited about the data that we have seen so far.

The second was 776 for geographic atrophy, so this is an anti-a-beta antibody, the same as the Biogen type molecule being used or being studied in dementia. We have gone

for a rather different approach, which is to look for the amyloid deposits in the eye, in some ways geographic atrophy is thought of as Alzheimer's of the eye. That is an ongoing study where we are going to really try and see whether you can see an effect of this mechanism in that Alzheimer like disease and we will get a readout on that over the course of the next year or so, and then we will decide which way, if any way, to take that.

The medicines we have chosen I have chosen for a very specific reason, which is we have got some ones near-term which we are very excited about, we have got ones where we have data that we think really shows these are on-track to work and therefore we are going to fast-track them, and those are the ones which we think provide both near, mid and longer term sustainability. Not to say that some of the others in the pipeline – and every company has other things in the pipeline that can be wildcards that suddenly take you by surprise.

Jeff Holford (Jefferies): A couple of questions around the Immuno-Oncology and just thoughts around development there. You briefly mentioned an IO kinase combination risk, I wonder if you could talk a little bit more about that, are you referring to some sort of tolerability or is it –

Patrick Vallance: Sorry, what?

Jeff Holford: I think in your presentation you referred to an IO kinase combination risk, you sort of mentioned about how you were thinking of IO to IO, not IO to kinase –

Patrick Vallance: Yes, I think it is IO-to-IO. That is why the OX40/PD-1 or the OX40/TLR type response, rather than going for an Immuno-Oncology plus a targeted therapy approach, where a) we haven't got any of those medicines at the moment of our own, but b) I think there is a bit of toxicity that has started appearing around that.

Jeff Holford: I just wondered if it was specific toxicities you wanted to point us to, that you –

Patrick Vallance: No, I think that is for others. I mean it is other companies and they have published recently on it.

Jeff Holford: Okay, and then the second question is with obviously a lot of the ancillary or secondary IO assets you have, like OX40 and there are clearly others coming down the pipeline, when you are thinking about developing those first of all with some sort of PD-1 or PD-L1 combination product are you always thinking about going with a commercial partner like Merck or potentially you might think about where you want to have

more rights and flexibility, potentially buying products on the market and doing trials that way? Then, if you do choose a commercial partner, can you just tell us about some of the key things that you think about on whom to choose, or is it just someone that doesn't have that particular combination asset? Thank you.

Patrick Vallance: I think one of the advantages in a funny way of not having a full Oncology pipeline is we don't have to partner our molecules with our own molecules, we can actually go with whoever we want to go to and I think that is important, that freedom to be able to actually look for where is best.

Why have we gone with Merck for the PD-1? We think it is a really good PD-1 and we think it is a really good combination to go for, and that is the sort of thing we are going to look for. It doesn't mean you end up with a single product, I mean clearly we are testing our OX40, they are testing their PD-1 with an OX40 and how that ultimately transfers into a commercialisation position is obviously a completely different question.

We won't go out and buy a PD-1, I mean, for the reasons I have said.

Is it possible we would buy another Immuno-Oncology asset if we thought it was a good partner for the ones we have got or another Epigenetics medicine where we have got partnerships and collaborations with biotech? Yes, we will do that, where it is appropriate to do so.

Naresh Chouhan (Liberum): A few big picture questions, please. Obviously, there has been much said about the high profile historical failings of risky assets, where I think you have said that the targets were perhaps not that well characterised, and all of the assets discussed today seem to be more well-known targets but in more competitive areas, so can you talk a bit about how the risk profile may have changed over the last few years in R&D?

The second question, a lot of the pipeline you have shown obviously is a number of years away, you have got *Advair* generics on the way, losmapimod has just fallen over, pricing is obviously getting a lot worse for assets where differentiation is limited. How do you see that mid-term gap being bridged and do you envisage a lot more external innovation being bought in?

Then, finally, a question on the return on investment and, obviously, you showed us what you believe your return on investment to be, a couple of years ago. In that time darapladib and losmapimod have fallen over and *Breo* and *Anoro* are doing, perhaps, less

well than we all expected, so would you expect that return on investment to fall dramatically when you restate it next year? Thanks.

Patrick Vallance: Maybe I will take that one first and say we will be publishing the IRR next year, as we said we would, and, no, I don't, and I think if you look at the value that is created from the Oncology pipeline you will see that there have been some very startling successes as well, in terms of the income.

The risk profile is a very interesting one, I don't think, if you look at the targets I have talked about and some of the things that we have talked about, we have gone for targets which are me-too targets at all. I mean we have talked about a lot of things which are very novel and yet are more validated, and I think that is the key question, how you use both the genetic and, increasingly, the immunological knowledge about human biology to get the validation in where we are going, and you will see that across all of the pipeline, that is why I spoke to things where we have got results. So take Oncology as an example, the BET inhibitor clearly works, a highly novel target, highly important in terms of the potential it has; the same around some of the Immuno-Oncology.

So I think, as a company and I think this may be across industry, you will see more innovation early stage, you will see more things in the clinic, there will be weeding out in the clinic, no question about that, there will be fewer things going to late stage that you don't understand whether you have got an efficacy signal, and that is certainly the approach we are taking.

Your question about external innovation, we are not planning to go out on a shopping spree of late-stage assets. Our experience is that that is not a good way to end up with high quality molecules.

It is worth remembering that the growth from the products that have already been launched, that Andrew spoke to, they are things that came out of R&D recently and actually they are growing, and so there is a growth coming from those and you can see the next wave of things behind them, some very imminent including in Vaccines, but also *Nucala* and other things which we think have got significant growth potential. So I don't think there is this big gap and I think the worst thing to do is go out and go on a shopping spree and end up with things you later regret.

Now there may be some things we want to look at, there always are, and we will look at them and we will take them on a case-by-case basis.

I am happy to open this up to other areas, if people want to, from anything that has [been] covered today and I am sure Moncef can speak to Vaccines, if there are further Vaccines questions.

Question: I wanted to follow up with a general question for you as well, which is just someone has mentioned about, you know, being located in sunny California, you can also be located in a biotech company and have much more leverage to your ideas and successes as a scientist and a researcher. So can you just tell us a little bit more about how the researchers and scientists in R&D are rewarded for long-term successes within the company? Thank you.

Patrick Vallance: Yes, so we introduced a system a few years ago, which I actually think we need to update and modify now, which is about giving reward, particularly in discovery, and the process is that at the time that a medicine gets to the stage for full late-stage development we make an award, which can be up to £10 million, which the scientists don't see that day, they a little proportion of it that day. They see the whole lot at the time it reaches approval, very clearly to give a more biotech like reward, but one which is tied to our mission, which is to make a medicine, not to make an exit, and that is why we have done it in that way. Those are beginning to pay out, they can be anywhere between £1 million and £10 million, they are divided between a limited number of people and it is about driving quality and about driving medicines through to the end of the process.

As I say, I think the system needs a bit of a tweak at the moment, it is something we are looking at, at the moment, but I think it is a good system to reward people for innovation.

Andrew Baum (Citi): : Just one further follow-up, given the repositioning of GSK as an Immunology company, which is effectively what you are saying in some of the disciplines, at least in Immuno-Inflammation and in Oncology and, indeed, in Respiratory, to what extent do you need to build out the competencies that you have internally inside the company, because I think, as Andrew pointed out, antibody engineering is a not necessarily core compared to Genentech, or MedImmune or Biogen, or so on? So in everything from basic science, to discovery, to engineering, to clinical trials, how much work is there to be done to bring in external people in order to become competitive in this segment, given the intense competition that you are facing?

Patrick Vallance: Yes, so I think, first of all, just to speak to the Respiratory point, I think you can see we have actually got first in that, in terms of the IR5 class and the

subsequent classes, so I think the ability to take these things through, do the clinical studies and position them is absolutely there.

I think we have recruited, in Paul-Peter and others, some very significant clinical and basic scientists in the Immuno-Inflammation field and, in Axel, in the Immuno-Oncology field. So I think we are building a really rather substantial skillset there and we are joining it up, and I think that is the key point, I think it is what you are alluding to. Actually Immunology and Immuno-Inflammation is a theme that runs across a lot of these areas and I referred, right at the beginning, to the Immunology network we have put in place and the Immunology catalyst, where we are bringing in scientists into GSK with their own laboratories to work with inside GSK.

I think the question of engineering of antibodies is an important one and we have recently undertaken a restructuring of our Biopharmaceutical organisation and, of course, we have got various partnerships in play around that. It is an area where we need to be absolutely at the cutting edge of it and I think we are part way through, I think, a transformation there.

Alan Sebulsky (Adage Capital): I have two questions. One is on the BET domain inhibitor. It appears there has been a lot of toxicity with other companies' molecules in the space, so can you talk a little bit about the toxicity and safety profile of your molecule? Secondly, in terms of Novartis and the option to negotiate for the Oncology assets, in the case where you want to do a collaboration with someone who has an asset potentially to combine with one of your assets, how is that taken into account in thinking about the consideration of a collaboration if Novartis is an alternative?

Patrick Vallance: As far as the BET inhibitor, we partially addressed the side-effect profile of that. We went very cautiously in terms of how we thought about the side-effect profile and have gone very carefully in the clinical studies, and we are actually very satisfied with what we are seeing. It is much better tolerated than we expected. In the immunoinflammation space, we are confident enough to go into immunoinflammation with it and also have various approaches for targeting BET inhibitors and for looking at BET inhibitors that aren't as broad as the one that we have in cancer, so there are several approaches around that.

In terms of the partnership, again, I'll come back to the fact that we have just announced the Merck partnership - it is pretty straightforward actually. The option that Novartis have is that, before we file the medicine, so if we file our OX40, we must show it to

Novartis and given them an option of putting an offer on it, which they may or may not do, and we may or may not accept, and I think it gives us a lot of freedom.

I have some questions here from London as well. Can we co-formulate cabotegravir and rilpivirine in a single LA injection at the same injection frequency in HIV treatment? That is a tricky one and I am going to get John to comment on that, because I am not sure that is ultimately what you need to do anyway.

John Pottage: You cannot coformulate them together, so they both have to be given as separate and, obviously, when we look at the dosing scheme, they both have to be given at the same time. What we are looking at in the treatment is giving it once either every four weeks, or once every eight weeks; both will be given together but as two separate injections.

Patrick Vallance: And, clearly, that is going to be the case when we get onto things like broadly neutralising antibodies: you are not going to have a single coformulation of these things.

The second question from London is on the PHI - the prolyl hydroxylase inhibitor - with respect to coadministration of CIP2C8 inhibitors. John, do you want to address that? The question is: is this a meaningful issue?

John Lepore: The primary route of metabolism is indeed through CIP2C8, and that means in the studies we will need to exclude strong inducers or inhibitors. Many of you will know that is a very limited number of molecules that are very rarely used in the CKD population, so it is not a clinically significant issue.

Patrick Vallance: That is our view on that. Graham?

Graham Parry (Bank of America): I have a couple of follow-ups on Respiratory and then a big picture question. On *Nucala*, you hinted about label discussions there. In the FDA Advisory Committee meeting, one of the options they talked about was not having a eosinophil cut-off on the label at all and just describing the relationship. Is that still an option that is on the cards, or has that been removed from the option set?

Patrick Vallance: I think we need to wait and see what the label says, the discussions are ongoing.

Graham Parry: Okay. On *Tivicay* and *Triumeq*, just your thoughts on the non-boosted integration of Gilead that they just recently moved into Phase III. They have an

in-house head-to-head versus dolutegravir, which I assume must have shown some non-inferiority but they are thinking about moving that forward?

Patrick Vallance: Sorry, which compound?

Graham Parry: That's Gilead's non-boosted integrase inhibitor that they just moved to Phase III.

Patrick Vallance: What is the question?

Graham Parry: Just your thoughts on competitive threats from that?

Patrick Vallance: Well, I can't comment on data that they may or may not have seen. What I will reiterate is why we think that we have a huge programme of activity around dolutegravir with lots of data showing how good this medicine is in terms of its efficacy, tolerability and use in different populations, and we are pretty confident about the position of dolutegravir.

Graham: Okay, and the last big picture question which is a little similar to my earlier question as well. What do you think is the key differentiator of R&D at GSK? So if you are looking from the outside and somebody wanted to invest a dollar in GSK's R&D versus Roche, Novartis, Bristol, what would you say to that investor is your key selling point?

Patrick Vallance: I am going to say something which I think is important in relation to this, which is that two or three years ago, we said we would deliver six approvals in one year and we delivered six approvals in one year of big medicines, some of which are now with Novartis. I think the key in R&D is to make choices and when you say you have something that you think is going to make it like these, stick with it and get it through. I think it is that delivery through from an innovative science base which becomes important, not hyping things and hoping for the best, so I think delivery is the answer to that.

I think there is time for one more question only, I'm afraid, then we have to stop.

James Gordon (JPMorgan): : We haven't had an R&D day for quite some time and you have given us a lot more disclosure today, so does this mark a change that we are going to see a lot more disclosure in R&D? Every quarter, are we going to get a big pipeline presentation, lots of detail on the early pipeline? Also what has now made you change your disclosure policy? You have had much less disclosure than some of your peers on assets that are further out or earlier stage assets: what has prompted the change at this time as well?

Patrick Vallance: We think we have a lot of things to talk about. We've talked about them, I am hoping to do this virtually every week because I've got virtually nothing else to do than do this! Yes, we are going to talk about these things and you've heard about some of the early stage pipeline that we are excited about as well as some of the near-terms, and I think you can tell that this isn't the last time we'll do something like this.

I would like to thank everybody in the audience. I would like to thank the audience on the webcast and those of you who have brought questions through from that. Thank you very much. There is now an opportunity to mix with all of these guys from the panel and pick up any other information from them that is relevant to what you need to know. Thank you very much for your attention.

- *Ends* -