

## **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 19<sup>th</sup> 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 neutrophilic 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 $\delta$  inhibitor targets neutrophil-mediated lung damage in COPD**

The first of these is our inhaled PI3K $\delta$ . I want to take a moment just to tell you why I think PI3K $\delta$  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* -