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MANAGEMENT DISCUSSION SECTION

James Daniel Gordon
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Good morning. I'm James Gordon, JPMorgan Pharma and Biotech Analyst. And this morning, I've got the pleasure of introducing the GSK presentation. So, you're going to hear from GSK President of R&D, Patrick Vallance, and we're going to have breakout in the Borgia Room which is just behind us. So, thanks for coming and over to you, Patrick.

Patrick J. T. Vallance
President-R&D, GlaxoSmithKline Plc

Thanks and good morning, everybody. It's not very often that you leave London and fly in to San Francisco and the weather is worse, but it certainly happened this time. I'm Patrick Vallance. I head R&D at GSK, and it's a pleasure to give you an update on the company and some of the things you might expect in the pipeline over this year and next year.

So, let me just start with a little bit about R&D. We're very focused in the discovery organization around our discovery performance unit structure where we bring together chemists, biologists, clinicians, scientists, drug metabolism and kinetic experts to really focus deeply on areas that we want to pursue, and I'll give you an example from one of those during the presentation as to how that really drives focus and scientific depth. Those, of course, are supported by a big platform infrastructure to allow us to industrialize the output and to provide scientific technologies across the DPUs.

About 65% of the NMEs in the pipeline have come from the DPUs, and the DPUs, of course, continue to be at the forefront of scientific publications important to be a part of the scientific community but also important for talent recruitment and access to other scientists. Our focus is very much on innovation, very much on medicines that can make a transformational difference coming out of the DPUs, and about 80% of the pipeline in vaccines and pharmaceuticals has the potential not only to be first-in-class but to be something that's truly important for patient need. Underpinning that are a series of expertises, technical platforms, capabilities, some of which are listed here, which provide a competitive advantage both in vaccines and pharmaceuticals.

We're very focused on external collaboration. We have major collaborations across leading academia, important public-private partnerships particularly now in the area of data analytics and data access, and of course, multiple links with biotechs. And it means that in our pipeline, about 60% of the products come from homegrown R&D, and about 40% are partnered or in-licensed.

We continue to focus on improving the efficiency with which we operate. We're focused on better trial design, better use of data analytics to drive trial outcomes and faster study times. And you can see a 20% reduction that we've had over the past couple of years in terms of study execution times. And we've also focused on R&D organization down to two major hubs in order to drive investments in technologies and to create environments where we can get greater interdisciplinary access between the scientists. The balance between discovery and development is about 60% spend on development and 40% on discovery.

So, let me just go through some of the medicines that have come out in the last couple of few years in order to look at the performance of those. So, we've said that from the 11 new products, 10 of which are approved and launched, one, Shingrix, still to come, is in the regulatory process at the moment. We said we'd achieve £6 billion sales by 2020. It's very clear that's going to be more and can come as early as 2018.

So, to give you an example and these are obviously medicines from HIV, from respiratory, amongst the vaccines as well, what we see is that in Q3, the sales from these medicines was £1.2 billion, so that annualizes obviously at £4.8 billion. We'll have Q4 results in due course. That's 25% of pharmaceutical sales from these new products in Q3. So, good progress and growth from the new products launched and four important files currently under regulatory consideration: closed triple, which I'll say more about for COPD; the Shingrix vaccine, we're extremely excited about the efficacy that that's showing; Benlysta subcut; and sirukumab, the anti-IL-6 for arthritis. Five Phase III studies were commenced in 2016 in HIV, respiratory, and importantly, daprodustat, our prolyl hydroxylase inhibitor for renal anemia, and a number of Phase II studies, some of which I'll talk about in terms of data expectation over the next year or two.

So, let me start with HIV. When we look at the focus areas that we have, these are the six across the organization. Vaccines, I'm not going to talk much about. The reason is we are excited about the growth in vaccines. We're excited about the margin improvement. We have got good growth across the vaccines organization coming from the Meningitis portfolio and are excited about the potential for Shingrix with the efficacy that we've seen. But there was a vaccines day at the end of November, which covered all of that, so I'm not going to cover that today. We have two areas, which are mature in terms of established pipeline, late-stage delivery, and early-stage progress, and that's HIV and respiratory. And we have three others, which are emerging in terms of the pipeline: immuno-inflammation, oncology, which I'll touch on, and rare diseases where I'll speak specifically about our developments in cell-based therapies.

So, in HIV, the very important bedrock of the HIV business is dolutegravir, a molecule that came from a very early chemistry collaboration between us and Shionogi in the mid-2000 that was rapidly progressed to candidate selection and taken into the clinic. And the properties of dolutegravir have stood the test of time and actually, are extremely important in terms of the foundation for the therapies going forward. It has very rapid and potent antiviral activity, something that we saw early in development, in fact, very early, as soon as we went into the clinic.

Importantly, it has a high barrier to resistance because of its binding site and binding mechanisms. So, there's an inherently high barrier to developing resistance. It has a long half-life and is low dose. It's now being out there in the world treating hundreds of thousands of patients and remains very well tolerated in terms of its profile. And importantly and I think this is increasingly important with an aging population in HIV, it has very little in the way of

drug-drug interactions. That drug-drug interaction point is key because, of course, this population is increasingly getting comorbidities and using other medicines. So, an important profile of the drug but one thing that I'd like to just highlight is it's not just its inherent profile but the breadth and depth of the clinical trial data which support it.

On the right-hand side of the slide, you can see the unprecedented and unmatched clinical trial results against competitors with a range of superiority outcomes against the competition. That's important because it not only defines the profile of the medicine but of course, that sort of confidence in terms of its position is important for prescribers.

So, a very impressive I think outcome in terms of dolutegravir, and I want to just talk a little bit about the move to a new paradigm of potentially two-drug treatment in HIV. Why is this important? I think it's an absolutely well-understood basic pharmacological medical principle that you don't use more drugs than you need to use. You use the number of drugs you need to use. There is no such thing as a drug that doesn't come with some sort of liability. If you can move from three to two, you have a potential advantage. And we've gone for a two-drug regimen. The first readout was for the dolutegravir + rilpivirine studies, two studies, both of which met a non-inferiority endpoint that will be presented in detail in due course. And they support filing of this approach to scale back the number of medicines you need in the maintenance treatment of HIV.

So, when we look at our HIV landscape, dolutegravir-based regimens remain the absolute bedrock, Tivicay and Triumeq continue to grow and get market share. The two-drug regimens are emerging. The first readout with dolutegravir and rilpivirine met its endpoint, as I discussed, and that will lead to filing in 2017.

Not only oral but long-acting becomes important. And this paradigm shift, which is really being spearheaded by our infectious diseases organization to take cabotegravir, a long-acting injectable integrase inhibitor, is I think going to be important. We've got a combination of cabotegravir and rilpivirine long-acting monthly treatment and every other month for PrEP for Prophylaxis. And the treatment paradigm from the IIb study, very effective in terms of viral suppression, up actually to 96 weeks. So, we can see here again a two-drug regimen that works out for a long period.

And increasingly, actually, we're getting the feedback on the way in which patients see this as an important development to have intermittent injectable. For some patients, this is important. It allows them to forget the fact that every single day they have to take a tablet for HIV to move to intermittent injections. For prophylaxis, we believe that the two monthly injection provides a really important step to provide a secure coverage over a longer period.

In addition to the medicines coming through cabotegravir, we have a number of new antiretrovirals coming in, which we do think is important for those patients who remain either at the end-of-treatment options or have other needs. And the attachment inhibitor, which got breakthrough designation, is one of those coming through. And we have the possibility of three different options for a maturation inhibitor in the clinic to choose from in order to take the maturation inhibitor forward. And we also have established a relationship with University of North Carolina to establish a new entity called Qura, really focused on a number of approaches to try and to look for that elusive possibility of really eliminating the HIV virus. So, good progress I think on HIV and a pipeline which is very grounded in innovation, both in terms of the medicines and in terms of new approaches to long-acting intermittent treatment and dual therapies.

Let me move to Respiratory. Very pleased that Respiratory portfolio is growing, 8% growth for Q3, 2% year-to-date, an impressive now pickup of this portfolio, and I want to focus on one particular point from it, and this is the inhaled pipeline. The Ellipta device, which allows us to put multiple medicines into a single device, is important

because it provides a certain simplicity in terms of usability for patients. That's important for healthcare systems. It is important for patients because it means you can swap treatments without having to swap devices, may sound trivial, actually rather important when you think about the way in which these are used.

The Ellipta device is now the home for all of these medicines coming through. In September, something like 100,000 patients prescribed in Ellipta device each week, and the total volume of Ellipta prescriptions is now over 40% of the total Advair volume of prescriptions. We've got good growth with Breo up to 18%. This is obviously Q3 September results with the Q4 due to come. But 18% NBRx for Breo, good growth on Anoro, and Incruse bumped, which was due in part with other competitors coming of formularies and in part, the approval of the open triple, and now steady growth with Anoro up to 20% NBRx. So, we've got good growth on the duals, and we're moving very fast towards closed triple.

So, closed triple is filed in the U.S. and the EU. We expect a 10-month review time in the U.S., so expecting a decision this year. We have data from closed triple in the European study, which is closed triple against Symbicort , so the European dose of Symbicort. And there, we were very pleased with what we saw. This was presented at the European Respiratory Society in September, FEV1 gain of over 170 mLs, quality-of-life gain. And actually, in that study, even though it wasn't design to show this, a reduction in exacerbations which reached over 40% in those patients who were on the drug for 48 weeks. So, an impressive initial results, we expect further results in the IMPACT study, focusing on this question of exacerbation reductions in the second half of this year.

We've also started a Phase III for asthma closed triple. Triple therapy is in the guidelines for asthma. It's rather underutilized at the moment, but it's clear there are some patients who are poorly controlled who need it, and we've started the study looking at that group with closed triple for asthma.

The other big area for us is in biologics in asthma and the anti-IL5 Nucala got off to a very good start, was launched very soon after approval, and continues to exceed expectations. Now launched in 16 countries, in September, something approaching 6,000 patients were on Nucala. It continues to outperform in terms of the feedback we're getting from patients. There is significant demand and there is very good payer access in the UK. The studies themselves continue to actually come out positive, and you know when you've got a medicine where you keep seeing these positive results. This is really telling you something important because in the study, safety and efficacy, we know we are seeing reduction in hospitalizations and ER visits in patients receiving Nucala.

The MUSCA study is positive, will be reported in full in March. And we're expecting Phase III data in COPD later this year. In terms of other diseases this might be used for, there are a range of them listed down in the bottom here, all of which are generating positive data. And I just want to show you one data slide for eosinophilic granulomatosis, vasculitis with very significant lung involvement previously known as Churg-Strauss syndrome, a difficult disease to treat, and I think what you'll see is the results from mepolizumab, again reinforce the importance of this medicine. So these are the co-primaries and secondary endpoints. You can see a pretty dramatic effect on remission, remission at 36 weeks and 48 weeks, 32% in mepo, 3% in placebo. Secondary endpoints, reduction in oral corticosteroids used and remission, and reduced time to first relapse in this disease with a hazard ratio of 0.32. So, continued performance from this medicine, which we think has quite significant use across the respiratory space.

In terms of our approach in respiratory and asthma, we are very focused on now going after the other severe asthmatic population, so the non-eosinophilic driven asthmatics, the neutrophilic asthmatics, and we have an anti-IL3 receptor there, which we're going to take forward for those indications. We may also progress the IL6, and we are looking at an extended pharmacology six monthly version of mepo.

In COPD, our focus is on disease modification with an inhaled medicine PI3Kδ, mepolizumab and danirixin, an oral medicine. And we're expanding beyond COPD and asthma and building on our respiratory expertise in pulmonary fibrosis and acute lung injury.

One data slide, oral danirixin, CXCR2 antagonist, now in Phase IIb studies. This mechanism is established, however, all of the medicines to-date cause systemic neutropenia, which makes them unusable. The mechanism of binding for danirixin means we don't get the systemic neutropenia. We do see an improvement in quality of life and a reduction in exacerbations. This is in IIb. It has the potential, if the studies continue to carry on as they have done, to be a well-tolerated, simple oral medicine to reduce exacerbations in COPD.

Inhaled PI3Kδ, an important medicine, PI3Kδ, we know is causal in lung disease. We know there are patients with activating mutations who develop very advanced COPD or bronchiectasis-like syndromes. We know it's activated in common COPD. This slide shows a CT scan where green means the airways have actually improved in terms of their wall thickness and diameter. Red means they've got worse. Inhaled PI3Kδ and I do think it's important if it's inhaled because the systemic effects probably make this not sensible as a systemic agent. We see an improvement, which means that the patients are getting fewer exacerbations. This again is entering IIb and has the potential for disease modification.

Let me say a word about immuno-inflammation, which is a core underpinning strength in GSK and one that not only underpins modulation of inflammatory diseases but also underpin some of our approaches in oncology, but I'll pick out three things here, Benlysta, ant -GM-CSF where we'll see some results this year, and RIP1 kinase. We have a broad pipeline where you're going to see many results over the next few years, but those are the three I want to concentrate on today.

Benlysta remains the only medicine approved to treat SLE in the last 50 years, and it's important to note that despite many other medicines that have come along, this is the only one that continues to get positive results in Phase III. Just got another positive result, fourth consecutive study, and on this time, we've seen a reduction or an improvement in the time to first severe flare. So, we've got improvement in time to flare, which I think is an improvement endpoint. We've filed for subcutaneous Benlysta now which we think will be an important continued development of this medicine which continues to grow at about 25% per year.

What we have also got in train is a number of other studies looking at subgroups in SLE, and there is some investigator reports coming out which are absolutely intriguing in terms of the possibility that using Benlysta in combination with a single dose of an anti-CD20 to reduce B cells may lead to very, very profound disease resetting or very long-term remission. And we're studying that to see whether that is born out in the clinical trials but a tantalizing prospect. The real-world studies for Benlysta actually show performance in the real world which is impressive and actually is encouraging. So, about 80% of patients show an improvement in the real-world studies on Benlysta.

Anti GM-CSF, anti-macrophage. Macrophages are absolutely instrumental in driving disease progression in inflamed joints and rheumatoid arthritis. This drug has very rapid onset. In the slide, in the colors, you see doses, but more importantly, you see times. It starts within four weeks and maintains its effect over the six and eight-week period. It's got through its first futility analysis which was a high futility bar in Phase IIb, and you'll expect to see results this year in terms of the first readout from that IIb study.

One point that I want to just emphasize on this slide is we're also looking at hand osteoarthritis. Hand osteoarthritis is a very under recognized syndrome in terms of treatment. It's common, it's got a quite strong

genetic basis, and it affects a large proportion, particularly women in the population. There are no treatments currently and no real surgical options. We'll get readouts on this drug in hand osteoarthritis later this year.

And finally, in immuno-inflammation, I just want to highlight the RIP1 kinase, which we believe is a potential whole new class of medicine, oral medicine for anti-inflammatory. It's involved in TNF signaling, importantly, not all TNF signaling. So, it's important in some of the key damaging effects of TNF signaling, and it's also important in non-TNF pathways leading to apoptosis, necroptosis, and increased cytokine production.

We've been working on this in the DPU for seven or so years. We have a real-world leadership position in it. We have a very clean molecule. The plot on the right simply shows the kinase plot. It only hits one kinase. That's RIP1 kinase. This medicine is now in trials for three indications: psoriasis, rheumatoid arthritis, and ulcerative colitis, but has the potential to go broader. And many of you will know this has also been looked at in people wondering whether this could be important in neuroinflammation. So, we're excited about potentially what we think is a new oral medicine and a new class of medicine for inflammation.

I'm not going to say much about oncology other than we have nine things in the clinic. You can see here lots of readouts in 2018, heavily focused in two areas: immuno-oncology and epigenetics. We will see some readouts on the BET inhibitor, which is working in a rare tumor, NUT midline carcinoma. We'll see some of the readouts for common tumors. And we will begin to see readouts in 2018 around OX40, our first-in-class ICOS agonist. And we have ongoing results with some of the cell therapies. So, expect to see a lot on oncology over the next two years from GSK.

One of the recent readouts was the anti-BCMA. I'm not going to go through the details. It was reported recently at the ASH meeting. I know BCMA is super exciting in terms of CAR-T. This is an antibody drug conjugate showing very clear effects in terms of the initial results in resistant patients. Our cell therapy programs continue both in cancer and in rare diseases. We have an option, and I'm not going to talk about it from TIGET for thalassemia, and the results on the right show the transfusion dependency before and after treatment, blue before, orange after. And you can see a dramatic decrease in a very resistant beta thalassemia population.

So, our cell therapy pipeline both in cancer and rare diseases, we got the first product approved, ADA-SCID, two more on the way with MLD and WAS, and beta thalassemia an opt-in decision to make shortly around that.

If I can end to say what we have over the next two years and in 2017, a number of significant approvals, we have important clinical readouts between 20 and 30 key assets. We're going to need to choose and back the winners very carefully. We have key developments in respiratory, HIV, but also in immuno-inflammation and oncology, and we have a number of starts in both 2018 and files in 2018.

So, a lot of activity with the early to mid-stage pipeline now maturing and I think reaching a stage where you can see some potentially very important groundbreaking medicines in terms of the impact they could have. Thank you very much.