

Part 3

Immuno-Inflammation, Oncology & Rare Diseases

Patrick Vallance

Immuno-Inflammation

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

Immuno-Inflammation areas of focus

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

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

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

Immuno-inflammation R&D strategy:

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

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

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

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

Sirukumab: rheumatoid arthritis

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

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

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

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

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

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

Clinical improvement in RA is consistently associated with decreased macrophage infiltration

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

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

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

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

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

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

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

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

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

GSK2982772: RIP1 kinase inhibitor in the clinic

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

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

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

Why are we excited about this, even though at the moment it is at Phase 1? Well the first is the molecule itself; you can see in the middle panel here the kinome plot, so this is a plot of all the other things that the molecule might hit that would be an off-target effect. The

red dot is RIP1 kinase, the green dot is all the things it doesn't do and this, to our knowledge, is the most selective ATP competitive kinase inhibitor to advance into man; highly, highly selective.

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

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

GSK2982772: studies in three indications to start in 2016

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

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

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

***Benlysta* (belimumab)**

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

So these are, on the right-hand side, the proportion of patients with the SLE responder index response, and you can see in the orange bar the *Benlysta* subcut treated group and in the grey bar the control group. I just want to be very clear about what we are looking at here: it is called “placebo”, but actually it is complete standard of care, and this is on top of standard of care, so this is actually what you do on top of standard of care.

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

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

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

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

Translating clinical experience into a new hypothesis:

Phase II experimental study to start 2016

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

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

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

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

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

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

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

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

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

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

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

Four “first in class antibodies in the clinic: GSK3050002

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

In order to test whether this antibody does do what we hope it does, we used a blister model. This blister model creates an inflammatory blister on the skin of volunteers and into that blister CCR6+ T-cells migrate. The antibody, as you can see in this experiment, actually decreases the migration of CCR6+ cells. Why is that important? That is actually quite a tough test, so you are giving a systemic antibody, you are creating a very profound local inflammation and you are seeing a decrease of cellular migration. So we believe this has the potential to work in a number of conditions; it will start in psoriatic arthropathy and we plan to start the Phase II in 2016, so we are pretty excited about where this one goes as well.

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

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

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

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

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

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

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

Four “first in class” antibodies in the clinic

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

Immuno-Inflammation R&D strategy

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

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

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

Oncology

Let me move now, though, to oncology.

Oncology R&D strategy

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

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

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

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

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

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

I am going to talk about two medicines.

GSK525762: potential first in class BET inhibitor

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

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

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

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

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

GSK525762: early evidence of potential clinical benefit

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

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

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

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

GSK525762: potential to treat and reset disease in rheumatoid arthritis

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

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

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

GSK2879552 LSD1 inhibitor: Early signal of efficacy in SCLC

Let me come back to cancer and epigenetics and tell you about the second molecule I want to talk about, which is the lysine demethylase inhibitor. The easiest way to think about this is to look at the picture in the middle. The untreated cells, and this is a mouse leukaemia cell-line, look horrible. They look like malignant blast cells, they will reproduce rapidly and they are exactly the type of picture that you don't want to see. Treatment with the LSD inhibitor reverts the phenotype, so on the right-hand side you can see what they have done is differentiate into normal cells. They look like normal cells now, so it is this process of changing a cancerous type blast phenotype to a differentiated phenotype which is important.

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

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

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

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

Immuno-Oncology: NY-ESO T-Cell Therapy

I want to move now to immuno-oncology and to start with a cell based therapy. Cell based therapies will come up as a theme in some of the other areas I talk about. This is a partnership collaboration with Adaptimmune and it is about engineered T-cells with an increased affinity T-cell receptor which can then target the tumour and kill the tumour. So the target is NY-ESO, the cells are engineered to have a high affinity T-cell receptor. In the top you can see the CT scan, what happens when you give these engineered T-cells back?

So the baseline scan shows the tumour – in this case a sarcoma, the second one shows the inflammation you get when the tumour is hit with the T-cells and then you get a complete response. Then in the bottom panel here you see the response in sarcoma so far – 12 patients treated – the orange line indicates something that would be seen as a complete or partial response and you can see significant responses in sarcoma.

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

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

Immuno-Oncology: GSK3174998 OX40 agonist mAb

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

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

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

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

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

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

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

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

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

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

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

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

Oncology R&D strategy

So if I try to pull together where we are in the cancer field at the moment; we believe we have got an industry leading position with epigenetics which we are very excited about and we are beginning to see the real outcome of this in the clinic. In immuno-oncology we have both got cell based approaches, but also checkpoint inhibitors and modulators in the clinic now and cancer stem cells we are beginning to see responses.

Oncology – Pipeline snapshot

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

Assets profiled at R&D day by planned filing date

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

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

Rare Diseases

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

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

Amyloidosis is a disease of protein deposition with abnormally folded proteins. There are a number of causes of amyloidosis. It can be caused by an immune response from monoclonal production of light chains, it can be caused by either a genetic or acquired over production of so-called TTR, transthyretin protein and it can be caused by long term chronic inflammation. This is actually less common now in developed countries, the AA amyloid.

The point is that the amyloid gets deposited in tissues, in nerves, in kidney, in heart and liver and, of course, is substantial destruction – it actually has a prognosis which is worse than cancer in many cases.

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

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

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

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

GSK29908728 RNA targeted transthyretin (TTR) knockdown

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

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

CPHPC + Anti-SAP mAb for systemic amyloidosis

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

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

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

Amyloidosis: a comprehensive R&D approach

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

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

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

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

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

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

Gene therapy works in different monogenic diseases

We have a pipeline behind this of this cell and gene therapy based approach – we have got the world first *ex vivo* autologous cell therapy file. We have a filing strategy agreed

for two more: those are the two on the right, Wiskott-Aldrich Syndrome and metachromatic leukodystrophy, a beta thalassaemia study is starting, which we have an option on and we are building a platform in cell and gene therapy both for the oncology indications, which I have talked a little bit about, and the rare diseases indications and we believe it has got potential utility beyond that.

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

Cell Gene Therapy clinical effect in MLD

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

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

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

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

Introducing our experts

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

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

Assets profiled at R&D day by planned filing date

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

Question & Answer Session

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

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

Steve Scala: Okay.

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

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

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

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

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

Andrew Baum (Citi): Two technical questions and one strategic. So, first of all, for Axel, perhaps you could contrast your ICOS molecule with that of Jounce specifically

in the relative agonistic and Treg depleting properties of the two molecules? My perception is theirs is more agonistic than yours, but please correct me if I am wrong. Second, on Epigenetics, I think it was Chris was the Team Leader there, there have been a number of interesting publications in animal data showing some pretty profound CNS disturbances with these quite promiscuous agents. I know there are a number of clinical trials, but interesting in what you are seeing or what you could expect?

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

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

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

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

Now I will ask Axel to talk about the ICOS.

Axel Hoos: The ICOS antibody is possibly the first-in-class antibody in this area and in terms of differentiation it is a little bit hard to say, because we don't have a side-by-side comparison here. But the one thing I can tell you is that our ICOS antibody was

engineered not to deplete cells, it does not deplete either T-regs or effector cells, it aims for an agonistic approach to boost the effector cells and actually conveying clinical benefit.

So what Patrick has shown you here is that the ipilimumab data, from which this emerged as a biomarker, suggests that patients have a better outcome, survival or response, if they express ICOS on their T-cells. If you now agonise those T-cells they will continue to divide and you will increase the size of the army of cells, that is ultimately conveying the clinical benefit.

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

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

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

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

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

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

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

Patrick Vallance: Thank you.

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

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

I think in terms of the knockdown, as you know, we are neck and neck with Alnylam. You can view them being ahead with two molecules, if you take some of the endpoints you are looking at, you can view the ISIS as being ahead if you take the more substantial endpoints; I think we are neck and neck and I think this will play out. I think there is an

advantage in having a single molecule that deals with both the neuropathy and the cardiomyopathy, and we will see where we get to with the trial results on that.

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

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

Graham Parry: [*Inaudible comment*]

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

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

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

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

Patrick Vallance: Okay. So on the first one, I hope I have been clear and if not I am going to be clear now that the approach in Oncology is to go for those areas which we think are profoundly disruptive, in terms of what may happen in cancers. We are not pursuing any of the other things, we are not pursuing targeted therapies, we are not pursuing

other approaches; we are putting all of our investment in those areas and we have a high hurdle, which is we expect to see really profound effects, like the type I have shown you in the NUT midline carcinoma, like the type we expect to see with the molecules that are going in OX40 and ICOS, and, yes, in that sense we have a very high hurdle, but we expect that the choices we have made will actually jump that hurdle.

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

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

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

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

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

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

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

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

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

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

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

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

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

So the asset asked about was retosiban, which is an oxytocin antagonist for pre-term labour, the reason we didn't mention that is actually that is a semi-validated target, in that there is a peptide that works against it. It is in a Phase III study, it will readout and we will

see what the study shows. We are excited about the mechanism; we are excited about the data that we have seen so far.

The second was 776 for geographic atrophy, so this is an anti-a-beta antibody, the same as the Biogen type molecule being used or being studied in dementia. We have gone for a rather different approach, which is to look for the amyloid deposits in the eye, in some ways geographic atrophy is thought of as Alzheimer's of the eye. That is an ongoing study where we are going to really try and see whether you can see an effect of this mechanism in that Alzheimer like disease and we will get a readout on that over the course of the next year or so, and then we will decide which way, if any way, to take that.

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

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

Patrick Vallance: Sorry, what?

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

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

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

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

Jeff Holford: Okay, and then the second question is with obviously a lot of the ancillary or secondary IO assets you have, like OX40 and there are clearly others coming down the pipeline, when you are thinking about developing those first of all with some sort of PD-1 or PD-L1 combination product are you always thinking about going with a commercial partner like Merck or potentially you might think about where you want to have more rights and flexibility, potentially buying products on the market and doing trials that way? Then, if you do choose a commercial partner, can you just tell us about some of the key things that you think about on whom to choose, or is it just someone that doesn't have that particular combination asset? Thank you.

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

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

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

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

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

The second question, a lot of the pipeline you have shown obviously is a number of years away, you have got *Advair* generics on the way, losmapimod has just fallen over, pricing is obviously getting a lot worse for assets where differentiation is limited. How do you

see that mid-term gap being bridged and do you envisage a lot more external innovation being bought in?

Then, finally, a question on the return on investment and, obviously, you showed us what you believe your return on investment to be, a couple of years ago. In that time darapladib and losmapimod have fallen over and *Breo* and *Anoro* are doing, perhaps, less well than we all expected, so would you expect that return on investment to fall dramatically when you restate it next year? Thanks.

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

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

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

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

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

big gap and I think the worst thing to do is go out and go on a shopping spree and end up with things you later regret.

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

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

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

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

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

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

done to bring in external people in order to become competitive in this segment, given the intense competition that you are facing?

Patrick Vallance: Yes, so I think, first of all, just to speak to the Respiratory point, I think you can see we have actually got first in that, in terms of the IR5 class and the subsequent classes, so I think the ability to take these things through, do the clinical studies and position them is absolutely there.

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

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

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

Patrick Vallance: As far as the BET inhibitor, we partially addressed the side-effect profile of that. We went very cautiously in terms of how we thought about the side-effect profile and have gone very carefully in the clinical studies, and we are actually very satisfied with what we are seeing. It is much better tolerated than we expected. In the immunoinflammation space, we are confident enough to go into immunoinflammation with it and also have various approaches for targeting BET inhibitors and for looking at BET

inhibitors that aren't as broad as the one that we have in cancer, so there are several approaches around that.

In terms of the partnership, again, I'll come back to the fact that we have just announced the Merck partnership - it is pretty straightforward actually. The option that Novartis have is that, before we file the medicine, so if we file our OX40, we must show it to Novartis and given them an option of putting an offer on it, which they may or may not do, and we may or may not accept, and I think it gives us a lot of freedom.

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

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

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

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

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

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

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

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

Graham Parry: Okay. On *Tivicay* and *Triumeq*, just your thoughts on the non-boosted integration of Gilead that they just recently moved into Phase III. They have an in-house head-to-head versus dolutegravir, which I assume must have shown some non-inferiority but they are thinking about moving that forward?

Patrick Vallance: Sorry, which compound?

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

Patrick Vallance: What is the question?

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

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

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

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

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

James Gordon (JPMorgan): : We haven't had an R&D day for quite some time and you have given us a lot more disclosure today, so does this mark a change that we are going to see a lot more disclosure in R&D? Every quarter, are we going to get a big pipeline presentation, lots of detail on the early pipeline? Also what has now made you

change your disclosure policy? You have had much less disclosure than some of your peers on assets that are further out or earlier stage assets: what has prompted the change at this time as well?

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

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

- Ends -