GSK Q2 2018 Results and R&D Update

Wednesday, 25 July 2018

Part 2

Emma Walmsley: Innovation is the first of our three priorities of the company, but, most importantly, it really is the driver of the other two. If we innovate successfully we will perform and we do become a more trusted contributor to society for the impacts we have on people's lives, so it is absolutely core to setting GSK on the pathway to success.

Last year I stood in front of you and said we needed to do a better a better job of, first of all, prioritising innovation, our pipeline and R&D, but we really need to do a better job of focusing on fewer assets with bigger potential. We need to focus on improving our development capability, speed things up, get sharper at decision-making, and really sort out the alignment with the Commercial organisation.

We had already made some reasonably quick no-regrets decisions on some of the portfolio to stop things, or, indeed, divest some things.

We hired Luke Miels, who has a long track record of partnering effectively with R&D, and not least with this guy right here, and that's already had a big impact in terms of bringing the Commercial voice in earlier, but by far the most important appointment that I have made in terms of the impact on innovation is, of course, that of our new Chief Scientific Officer.

His job is to transform our pipeline, and to reignite GSK's reputation as an innovator. That is going to take some time, but I can assure you, he is already having a very meaningful impact in just six months, so I am delighted to introduce our new Chief Scientific Officer, Dr Hal Barron, thank you.

A new approach to R&D at GSK

Dr Hal Barron

Thank you, Emma, and good afternoon. Thank you everyone here for taking time out of your busy schedules to come and hear about the new R&D approach, and hello to everybody back at the ranch, as we say, at GSK House and other places, and good morning to the folks in Upper Providence, and other places in the United States.

Today, really is the first, I think, hopefully of quite a few R&D updates. Our goal is to be much more transparent and to give you some insights as to how the portfolio is progressing over the next every six months or so.

I will spend about an hour giving you an overview of how we are thinking about focusing our efforts in R&D, and then we will have an hour for Q&A.

What we are going to focus, really, on three areas: Science, which I will go into; Technology; and Culture, and we will spend about 20 minutes on each.

I thought I would give a little background about the company, the history, because I think it is really important as you think about an organisation that you are coming into new, like myself, to spend time getting to know the people in the organisation, and I spent about 100 days spending time with folks.

I had about 40 or 50 of these meetings with about 20 or 25 people, and listening to what they thought was going well, what they were proud of the company about, what they thought we should do more of, and areas that they thought we could do a better at, and I think, actually, after a while the themes became very consistent, and that was the backbone of the strategy, to a large extent.

GSK has a strong presence and history of leadership in four major areas

It is very clear when you talk to people and look at the history of GSK that there are four areas that GSK has had a real leadership position in, and a very inspiring nature.

The first is leadership in Respiratory, and you have heard a lot about this, but it is important to go back to 1969 when *Ventolin* was approved for asthma, and over the ensuing almost 50 years a number of significant advances, LAMA/LABA, the first anti-IL5, *Nucala*, and most recently, *Trelegy,* the closed triple inhaler with data from the Impact Study really suggesting that there is a big impact of that new medicine launched recently.

Vaccines – it is a group that is different than Pharma in many respects, but what is so inspiring to me about GSK and Vaccines, which is the largest and most important Vaccines group in the world, is that we talk in Pharma about – we used to talk about improving outcomes and at some point we were able to say we are actually increasing survival, and occasionally now we are even talking about cures in certain places.

Vaccines prevent disease. That is really quite inspiring. It is very hard to do this with medicines, if not impossible.

Therefore, in Vaccines, as I said, the number one Vaccines player, and what we have is two million of doses of vaccines given every day, 13 different vaccines in the pipeline, and *Shingrix*, as you have heard a lot about.

We are the leaders in Global Health. This is a very important component to the company's culture. We have one of the most outstanding pipelines in Global Health. We care deeply about patients, not just those that have insurance, but those around the globe, and we have done, I think, an amazing job at ensuring those patients have access to outstanding medicines, and it is very inspiring to me and it was very inspiring to the group that that's part of the culture.

I think HIV/AIDS, the therapies that have been developed is a very personal thing for me. About this time 29 years ago, 1989, I finished medical school and I started on the wards in San Francisco General Hospital at a time when the AIDS epidemic was just becoming an epidemic, and my first day on the wards, my first day as a doctor I was in the County Hospital. My attending was the Head of Infectious Disease, Meryl Sandi, and I would say at that time probably one in every three, every four admissions I would see was a patient with AIDS, usually a cachectic male, who had kaposi sarcoma all over their body, and usually a shortness of breath, having most likely pneumocystis pneumonia.

It was sad, but we both knew – the patient and I knew that this was most likely their last admission. They would usually die on the services. Maybe they would make it out after being on a ventilator for a while, but they would probably die at the next admission.

To think that what you heard today, , about the data from GSK is that now we are talking about one pill, two drugs, complete virus suppression. These patients are living a normal lifespan, and we are talking about compliance and safety, which is just, to me, is so inspiring what the industry can do when we get our act together.

I think I was quoted yesterday for saying I loved big Pharma. This is what I love about it. When we get together and do something great you change medicine, so very inspiring to me and I want to see more of that.

Driving our growth outlook beyond 2020

You have seen this slide. I think I am going to skip most of it.

Those areas are our growth today. They are growing nicely. They will be growing, these four areas, nicely for a few more years. The question, though, is what is coming next? What do we have?

These are 19 different assets that could launch during the ’21 to ’26 timeframe. Of course, not all of them will. I am going to talk about a few of them today, but this portfolio is changing. As Emma said, we are going to be seeing the introduction of a new oncology medicine, BCMA, at the end of ’20, and if you look at the potential launches in 2021 to 2026, we have a lot of different molecules, much more heavily oriented towards biologics, a lot more oncology, a lot more immunology, and we need to think about how to frame up those years, and how do we decide where to resource, what is our strategy going to be?

High performing business reinvent themselves

I like this article. This was from Paul Nunes and Tim Breene from the *Harvard Business Review*, and it’s entitled, “Reinvent Your Business Before It’s Too Late”, and I thought I would just read this little paragraph because it, I think, summarised to me exactly how to think about this.

> “Sooner or later all businesses, even the most successful, run out of room to grow. Faced with this unpleasant reality, they are compelled to reinvent themselves periodically. The ability to pull off this difficult feat – to jump from the maturity stage of one business to the growth stage of the next - is what separates high performers from those whose time at the top is all too brief.”

This is an ideal time to be thinking about reinventing R&D because we are doing well, and it is not a time when we are falling off our S curve, we are growing, and we need to be thinking about where does the future hold possibilities.

The key thing in thinking about how you reinvent yourself is what questions are you trying to tackle? What are the key questions that you think you want your strategy to solve, and what are the levers you have?

We spent some time thinking about this and we evolved to two questions that we think the industry and GSK in particular needs to focus on.

The first is the probability of success of a medicine entering the clinic is about 10%. Despite all these brilliant scientists working all of the time thinking they have the ideal target, when it gets to the clinic nine out of ten never make it through, and this is really, really a very challenging concept in this industry. It is very high risk, and if we can go from 10% to 20%, that is a pretty big deal. You can do twice as many programmes, the programmes cost half as much to develop, however you want to think about it.

The second piece and it relates back to what I said about HIV, we need really innovative medicines, ones that are going to be very transformative, ones that don’t stop after their first indication, sometimes have a broad lifecycle. Ones that help the most

number of patients, and when they help them they help them in a fundamental way, not just symptom relief, but get at the fundamental biology and disease-modifying components.

Science X Technology X Culture

Those are the two questions, and the three levers we thought we would have access to is science. How do you find and focus on the best science, the science that you think is going to take us forward?

What is the technology that you think you can leverage, because technology is a great driver of innovation, not just in the health sciences, but in all fields. Betting on the right technology can unmask lots of signals in the science data that you couldn't see otherwise.

And culture. Culture is really important, and we put this science x technology x culture to imply that it is not just the average of the three. It is not like it would be nice to do two.

If you have the wrong culture it is zero x two things. If you have missed the technologies you are really not going to win. It is really science x technology x culture, and so that is what we will talk about for an hour.

Science

The industry needs more innovative medicines. That might be intuitive. How do you find those?

Drugs that modulate the immune system have had profound effects on patients with many different diseases

One way we decided was to look back. Where have the innovative medicines been? Look forward from the literature, where does the science seem like it is going? Then, look inward, what does GSK do well?

When we look backwards, and we tried to be focused because there are lots of different conclusions you could draw, ours was that looking backwards, drugs that have modulated the immune system, starting with steroids back 70 years ago, have had pretty profound effects. They had lots of toxicities in the steroid era, and that led to a more targeted era where we see now antibodies developed to inhibit B cells like rituximab and *Benlysta* and apolizumab, or antibodies that block cytokines, like TNF with *Humira*, and *Remicade* and *Enbrel*, or antibodies that block IL6, IL 5 like *Nucala,* IL4, IL13, etc. There are a lot of really disease-modifying therapies that have had really pretty significant benefit, and they have had lifecycles beyond their first indication.

Rituximab is such a good example that starts out as a lymphoma drug and evolves to RA, and then studies in ankylosing spondylitis and ankylosing vasculitis, and ultimately in multiple sclerosis, and this is why, because fundamentally the immune system is involved in lots of different diseases, and now we are seeing the immune system clearly having a role in oncology.

Immuno-oncology is a relatively recent field, but we are seeing antibodies to PD-1 and PDL-1 that are having really pronounced effects, and we are seeing T cells being engineered and reintroduced to patients, modulating the immune system in a very different way, having pretty profound effects like the CAR T, the genotype CAR T therapies that we are seeing, and we think there's a lot of opportunity for immunology to advance our understanding of cancer, treat patients more effectively, and get to the places where we are talking about cures.

Scientific understanding of the role the immune system plays in disease is expanding.

However, moving forward, it is very clear that if you look at the literature, we are seeing more and more immune modulators being explored in diseases that hadn't been thought of as inflammatory.

We are seeing IL-1-β looking like it works in cardiovascular disease. We are seeing NLRP3 as a target for the inflammasome, as a metabolic sensor.

We are seeing complement as being potentially involved in Alzheimer's. Microglia playing an important role in nerves generation. Neuroinflammation and pain, something we will talk about briefly in a few minutes, and even getting back to the can we leverage our understanding of immunology to make the Vaccines group even more effective, we are looking at immunomodulators that could be adjuvants for vaccines, enabling the immune system to be more effective in mounting its response.

Even in ageing there is evidence to suggest that as we age the inflammation is causing some of the problems.

That is forward – we heard backwards, that's forward – what do we do?

Broad portfolio with strong focus in immunology

This is to some a reasonably striking figure. We have 43 molecules in the clinic, 27 of which are actually immunomodulators.

It is sometimes hard to tell if something is exactly the only mechanism is immunomodulation, but the vast majority of the 27 are pure immunomodulators, and some of them have dual actions.

In addition, as I said, the 13 projects in the Vaccines' portfolio, which are also, to some extent immunomodulators, and I will talk about seven or eight of these over the next hour.

GSK'165 (aGM-CSF): potential for a disease modifying effect in rheumatoid arthritis (RA) with a unique impact on pain

The first one that I would like to talk about that I think is a pretty fascinating molecule, is it is GSK'165. It is an antibody to GM-CSF, and it's being developed for rheumatoid arthritis.

It is important to remember we talk about all these amazing drugs for rheumatoid arthritis that have had a big impact on these patients, but the disease remains very significant, with about 50% of patients who will remain symptomatic after a year of just TNF inhibitor therapy, and, of course IL6, and JAK inhibitor molecules have been developed and they are adding value, but almost half of the patients will still experience significant pain, 25% of whom actually transfer their therapy to something new because of the pain.

This cytokine that we are blocking has some effects in inducing proliferation of granulocytes and macrophages.

It is one of the first cytokines that was identified in the synovial fluid of patients with RA, and the pre-clinical data is pretty compelling. I won't go into it, because we have clinical data.

This is a fully humanised antibody. There is nothing terribly fancy about that part, but we have gone through the development and recently looked at the 2b data and it will be presented at the ACR, hopefully, or some congress meeting soon, and I think what you will find is that the data are very compelling. There is a significant treatment effect. There is a reasonably rapid onset of symptoms, and what's particularly interesting is these scores that people use to assess the severity of rheumatoid arthritis often have a pain component and an inflammatory marker component like CRP, and what this molecule seems to have is a much greater effect on reducing pain than we think other cytokine inhibitors do, other therapies, and we think this could be a very unique feature, and in fact, I won't get into it unless there are questions in the Q&A here, but we think we understand some of the biology behind that that has to do with CCL17 and the up-regulation of certain receptors that might be driving some of this pain phenomenon.

GSK's expertise in immunology will enable success in immuno-oncology

Moving onto immuno-oncology.

In immuno-oncology we have a very interesting late-stage project, BCMA, but we have nine other projects that are in the clinic, or about to get in the clinic, and we have divided them into therapies that are cellular, like NY-ESO, which I will talk about, a T-cell therapy against the NY-ESO protein that's expressed in certain cancers, as well as some programmes in the epigenetic modulation area where they modulate the chromatin structure to alter transcriptional profiles, and immuno-modulators that can be both antibodies that agonise to stimulate T cells to be more aggressive at doing their job that they are supposed to do, which is eradicating tumours, as well as antibodies that block the inhibitor receptors to allow the T cells to be more effective at getting in the tumour and destroying it, as well as some other molecules that are involved in immunomodulation through pathways such as PI3kβ, STING, etc., and the TLR4.

GSK'916: First-in-class anti-BCMA ADC agent for treatment of multiple myeloma

Let me tell you a little bit about BCMA. It is the most advanced compound. We have pretty striking data, and it is a very unique antibody.

Multiple myeloma is a plasma cell dyscrasia, it is a cancer base of the plasma cell, and this is a very important disease, affecting almost 500,000 people, and over 100,000 people are dying from it.

The treatments have become better, but it is still reasonably clear that if you get this you are going to have a very, very rocky course, and almost will surely die from it.

BCMA is a protein expressed on plasma cells and signals the plasma cells to continue to live, and so this antibody we have is actually quite unique. It has four different modes of action.

First of all, it is an antibody. It blocks BCMA, the protein, from doing the signalling – that's terrific.

It is also, interestingly, and we have quite a few molecules in our portfolio that we have engineered to do different things. This one is so-called afucosylated. It is not made with any fucose, so you don't have any fucosylation of the antibody, and this enhances something called ADCC, and what that is is antibody-dependent cytotoxicity, so the FC portion of the antibody, the bottom part, if you will, binds the NK cells, and that T-cell antibody can actually destroy tumours, and by having this afucosylation you get much more activity.

A third piece that makes this a very effective therapy is that there's conjugated to the antibody, linked to the antibody is a toxin called MMAF, a very potent chemotherapeutic toxin. It's so potent that it can't be given systemically because it would be too toxic, but if you

could link it to an antibody and have the antibody deliver just to the cell that you are trying to kill, in this case, using BCMA to get it right into the plasma cell, you can have some very potent effects.

In addition, and I won't get into this, there is an additional component, this immunogenic cell death that if there are questions we can get into later.

GSK'916 anti-BCMA ADC: robust single agent activity in heavily pre-treated/refractory patients

This really unique molecule has been in the clinic, and you have probably seen thesedata, but I want to put it in context.

In very heavily pre-treated patients you can see on the left that there is an overall response rate of 60% - very impressive for this really severe group of patients, and when you compare that to Amgen's Kyrpolis (IV), which was studied in third line, not as severe population, a refractory population, you see that it is over twice as effective in terms of response rate, and when you look at progression-free survival, again, over double the progression-free survival, and that is true even of Darzalex, which is a monotherapy, a drug being developed by Janssen, and they are fourth line, not quite a refractory population again. Only 29% response rate with a progression-free survival of 3.7 months.

Therefore, we think, when we are trying to do apples to apples, and, again, these are even more severe – 40% actually had received Darzalex, that we are seeing overall, as I said, 60% response rate, 43% in the prior Dara exposed patients, with a 7.9 month overall median progression-free survival, and 6.8 in the Dara group.

We are seeing that we haven't even reached the overall, median overall survival, so we will have that data at some point to be able to compare as well, but we think this is going to be a very active molecule, and the key thing with this molecule, once you see activity, once you see, going back to the one in ten works, this is the one, and when you see this kind of data you want to jump on this, you want to move as quickly as possible.

When I got here we really took a deep dive with Axel and his teams, saying, "how could we really jump start? How could we move as aggressively as possible?" I won't go into all these different combination trials and moving in from fourth line, to third line, to second line, to frontline, and the enabling studies and the combinations with novel reagents like PD-1 to see if we can bring out additional synergy that was in that fourth bucket, but all of these different studies are going to allow us to move from a population that is reasonably large – 36,000 patients, to a much larger population, and more importantly, be able to help more patients because the earlier in the disease you treat, the more likely you are to have a meaningful effect.

We can go through these later if you want, but a lot of exciting trials and we are moving them aggressively forward.

Early stage oncology portfolio with near term data read outs

We don't have time to go through all the oncology assets, but these potential medicines are very unique and already demonstrating single agent monotherapy activity.

We have an agonist antibody to ICOS. Again, agonist antibodies are very unique. These are ones that bind and stimulate the receptor.

ICOS we think is something that when stimulated makes those T cells particularly aggressive, more active, and they are better suited to shrink a tumour.

This is an example of a 64-year-old male who had head and neck cancer where you can see the yellow is not part of the MR, it is to highlight the differences in the tumour size, and you can see a pretty dramatic reduction in tumour size.

The first in-human trials on-going across several tumour types, and we are seeing, as I said, clinical activity observed both as a monotherapy and PD-1 combinations with pembro, so trying to, again, identify the ideal combinations.

Similar with OX40, we are having a dose escalation with both a monotherapy and PD-1 combinations, and we have seen again clinical activity.

This is a 66-year old female with a liposarcoma, and you can see the tumour shrinking, and we have a very interesting, based on some really interesting pre-clinical data, TLR4/OX40 combination, which might be particularly exciting.

PRMT5 inhibitor, first-in-class, potential for broad application. Again, we have responses, and a BET inhibitor, an oral epigenetic-targeted drug, which is being developed for a broad range of tumours and clear activity in that midline carcinoma where the BET mutation is known to be driving, but also other activities being seen, particularly in the HER positive breast cancer.

Therefore, a long list of other immunomodulators in the clinics that we are excited about. These are some of these that might potentially have data read-outs soon, and that ultimately might end up becoming medicines.

Science

I will move on from that. We will have plenty of time in the Q&A to go into more detail if you should have questions on that, but I wanted to talk about the problem that I think I probably have the most passion around is how do we get this one in ten up from one in ten that succeed to some higher number – maybe, ideally, two in ten?

“Genetically validated” targets have a higher probability of success

One of the drivers for this is that GSK has been a leader in understanding how genetically validated targets contribute to the probability of success – a paper that was written on the right here by Matt Nelson and our group at GSK inR&D.

I went back and looked at the literature, and found that genetically validated targets, on average, have about twice the likelihood of becoming medicines, and this is a big deal – going from 10 to 20% would go from being average to best in class. It would go from whatever it costs to develop a drug - $2.5billion, or whatever the most recent number is, to $1.25 billion, or say it a different way again, you could do twice as many.

To show you how this works I thought it would be fun to take a few minutes, maybe ten minutes and explain how this genetic stuff works.

There is something called a GWAS, which is a Genetic, Genome-Wide – so the entire Genome-Wide Association Studies.

What we do is we take patients who have a disease, let’s say in this example, diabetes, and a control group, people who don’t have diabetes, and we do a test on their geno. We go through every gene, essentially – I am oversimplifying a little bit, and we see all the different variations that might occur.

They are all going to be probably reasonably randomly distributed for disease and non-disease, but occasionally you will see one that’s really enriched in either the patients or the controls, and you have a good suspicion that this is involved in driving the disease, the underlying biology, and these are GWAS hits, if you will, genetically validated targets, and when we advance those we get medicines against those targets that have twice the likelihood of succeeding.

An example of this, just to put it into perspective, and you probably know this one, but back in 2006 Helen Hobbs and her group presented in the *New England Journal* about it, essentially a GWAS finding that there are people, not very common, but some people who have a genetic mutation where they don’t have almost any PCSK9, a protein that we make and she asked ‘So what’s different about these people?’ and it turns out they have a very, very low risk of having cardiovascular disease. So if you imagine not having this, that we could pharmacologically try to mimic that, we can make antibodies with that protein, take the antibody away and we can mimic the genetic condition.

If we did that one might imagine that you would reduce the risk of cardiovascular disease and in fact that’s what people did, made an antibody, 11 years later from lots of stuff that we do in drug development, you see it works. It doesn’t always work this nicely but this

is a common theme, that when you have a genetically validated target you spend much less time and you have a higher probability of success.

We think that there is a lot more of these out there and we want to pursue those because those are much better than the targets we think that are generated from understanding pre-clinical models where there is a lot of similarity with humans but there are a lot of differences and I think those differences could be misleading us and causing in part this attrition.

PheWAS can enable discovery of novel genetic associations

Now complementing that and something that's only recently been able to be done because we haven't had the datasets that has been large enough, but it's something called a PheWAS and like a GWAS, a PheWAS is a phenotype-wide association study.

Now what that means is we take all the different phenotypes, like diabetes or cardiovascular disease or osteoporosis or osteoarthritis or neurodegeneration, any kind of disease and we ask 'If you have a gene of interest, let's say PCSK9, besides reducing the risk of cardiovascular disease, does it do anything else and why is this useful?'

So Erik Ingelsson and folks looked at this and what they found was that they looked to see does it reduce Alzheimer's because that would be nice to know, you could put your molecule on development for Alzheimer's if it reduced it or does it reduce something else. It turned out the one thing they could find was that it reduced the risk of ischemic stroke, so from this you can predict that if you did a study to prevent the risk of ischemic stroke, you are probably going to have a successful trial.

So this PheWAS allows you to think about how to do second and third indications and in addition you can imagine that it doesn't just show what it prevents, but you could imagine it might tell you what safety problem you might experience. It might have worsened ischemic stroke in which case you would predict that the side effect of the drug would be that and sometimes the side effects might be so significant that you decide not to even develop the drug, so that's part of why it increases the probability of success because you have so much more information about what the likely effects of these drugs might be; so faster, more likely to work, you can understand the life cycle better and you can understand toxicity through this GWAS and PheWAS. Hopefully that makes sense.

A new approach to drug discovery is needed to make this a reality

We have been leaders in this. We first started with the collaboration called Open Targets back in 2015. We subsequently moved in the UK with the UK Biobank which is 500,000 people where they are deeply in phenotype, they are imaged frequently, they have

blood work done, they are followed serially, one of probably the most important genomic databases that exists and the question is where could we have taken that next.

A new approach to drug discovery is needed to make this a reality

I think you have read the press today so I am very excited to say that the next place we go is to a collaboration with 23andMe, so we are going to have access to a large number of genotyped patients. And this is really probably one of the most significant milestones I think for us as a company and we have decided to commemorate this partnership with 23andMe with something really very special.

We didn't share this with you yet, but today right after my talk, actually, we are actually bringing in a rock star, a very famous person who is going to entertain us. He is a household name, he is going to sign autographs. Any guesses? Richard Scheller?

A new approach to drug discovery is needed to make this a reality

You're right! Richard Scheller – the guy next to Bruno Mars is coming here today. Richard is here in the front row and he will be here to answer questions. I am going to take you through a little bit of what the 23andMe opportunity represents and Richard will be here for questions and he is going to do a little routine later, too!

23andMe database metrics: massive engaged database

23andMe has a dataset of over five million people and I'm not going to give the most updated number, but it's growing fast. Richard shared with me the number of new customers that just came on Amazon Prime Day, it's pretty just shocking. What's interesting about the database is not just its size, because it's over five million and all of these people of course are genotyped like we saw on the GWAS slide but 80% have committed to provide their data for research and importantly, to be re-contacted. There is over 1.5 billion survey questions answered, so you can think about the wealth of information and they provide data on what diseases they have, whether they have diabetes, what medications they take. Richard was telling me one earlier; if they get a mosquito bite, is it actually an intense experience or is it mild and that can tell you something even about their immune system. There is an enormous amount of information collected that we can link to their genotypes and we think this could be combined with open targets and with the UK Biobank, a very, very effective resource.

Leucine rich-repeat kinase 2 (LRRK2): a genetically validated target for Parkinson's Disease

And we have nominated the first target. I want to walk you through this because it's not only an example of the way we might be about to help Parkinson's patients but it's a form first of what we can do over the next years.

And as you know, Parkinson's is the second most prevalent neurodegenerative disease and it's driven by certain genetic drivers and one of them is called LRRK2, a leucine rich-repeat kinase 2. These patients have a mutation, one of their base pairs is abnormal leading to a unique amino-acid sequence that has an active LRRK2 kinase and we can make small molecules to turn that down and that should in theory work. If the overactive kinase is causing the disease and we can turn it down, one might imagine it would work.

And if it does work, it's possible that that pathway is involved even in the wild-types, just like PCSK9 doesn't just work for the patients who have more PCSK9 than normal. It can work on a spectrum of patients and that's what the trials point out and we would have to see if it worked in LRRK2 kinase patients, maybe it would work more broadly. And what's also interesting about genetics, not to get too far ahead of it, is that we know who these patients are before they are symptomatic so there is an opportunity to think about should a drug be safe and effective, can you start moving it more proximally, could you start thinking about prevention, a very exciting component of the genetic validated targets.

LRRK2 inhibitor programme: 23andMe's advantage to expedite clinical trial recruitment

Now let me walk you through not just the target discovery component of this, but what is really I think very exciting and sometimes missed as to what value 23andMe brings to a collaboration like this.

There are a million patients in the United States with Parkinson's and 135,000 people with the LRRK2 carrier and about 10,000 people, 10-15,000 people who have LRRK2 and Parkinson's, so you can think about it as being 1%, 1.5% of people with Parkinson's actually have the LRRK2 mutation. It's not a common cause of Parkinson's, it's just when you have that mutation you are much more likely to get it.

In 23andMe there are 10,000 re-contactable individuals with Parkinson's, 3,000 re-contactable LRRK2 carriers who don't have Parkinson's and more than 250 patients with Parkinson's and the LRRK2 mutation. Now if we were to think about trying to do a study in LRRK2+ patients, we would have to screen 100 patients to find one, maybe two patients with the LRRK2 mutation and if you think about operationally how long it would take to do

that trial, you might conclude it's not even feasible but if you did do it, it certainly would take a long time and be very, very expensive.

We can, once we have the molecule, actually just go right to these patients and identify immediately a large number of people who could in theory be interested in participating in this trial and do a trial twice as fast, three times, four times, it's not even clear exactly how much faster but a lot faster, a lot cheaper and give us the confidence should we see a signal in safety and efficacy to move aggressively as I just described.

So really a very different way of doing drug development; a validated target, a much faster approach, help for patients who are in 23andMe and others and really potentially have a new era in how drugs are both discovered but also developed. I am frankly very excited about this example, but I am also excited about what this example is going to lead to in the future in terms of how we do all of this work.

23andMe and GSK exclusive collaboration

I have sort of gone through this; the collaboration offers scale, size, diversity, sustainability for advancing therapeutic programmes. The questionnaires I should mention, although they are very rich, we have an additional opportunity to go back to patients and ask some questions we want to target for those, so that's a very unique feature of this dataset and this collaboration. As I said, custom surveys and rapid recruitment of trials and it improves target selection, higher probability of success, safer and more effective as I showed you with the PheWAS, it allows more efficient and effective identification for recruitment.

One of the things that you might think about is we know where these patients live. Instead of setting up clinical trial sites where we might want to, we actually can look at where they live and say 'Hey, we are going to put up a clinical trial site so you don't have to travel very far', so we can make it even more convenient for the patients. And that's what I mean by empowering the patients.

Technology has been a driver of innovation in many industries, especially science and medicine.

I am going to move to technology. Technology has been a big driver in every industry. That's for sure. The challenge has been, how do you find the right technology, which ones do you bet on, but when you find the right one and bet on it and take it to the state of the art, sometimes beyond, you can see things that other people just can't see. You can identify signals in data that just others looking at similar datasets without that technology just don't see, or you might have access to a way of making a therapy that allows you to do

things other people couldn't do, so pushing technology to the bleeding edge has been a hallmark of success in innovation in all industries, particularly ours.

Functional genomics: the power of gene editing to unravel biology at scale

Reverse genetics (think PheWAS) is the process of going from genotype to phenotype

Now I want to take five minutes and try to explain this, because the human genetics is phenomenally fascinating. This is going to take that to the next level and that's called functional genomics.

Now GWAS, PheWAS, the 23andMe collaboration is really exciting. It's about structural genetics. We are looking at base pairs and how the As and Cs and Ts and Gs differ but it doesn't really tell you about function. You might guess that if the base pair epidemiology results in a protein in a gene, that that's probably the gene but most of the differences aren't in genes. You have to figure out what they're doing. They might be next to a gene, they might be in-between three or four genes and you are not exactly sure what they do, so there is an area of science and technology called functional genomics that allows you essentially with either TALEN or CRISPR to functionally toggle through the genome and do gene by gene assessments as to what happens to a cell when you take down or up a protein.

Now a cell can't tell you 'Up, I'm fine, I'm fine, I'm fine, now I have Parkinson's, I'm fine, I'm fine, I'm fine', but it can tell you how it looks or what transcripts are made during each of the genetic manipulations and that surrogate which we call an endophenotype, that intermediate that we think is reflective, say for instance with Parkinson's you might get alpha-synuclein which is a hallmark of the neuron in patients with Parkinson's, when you toggle through the genome if knocking out one gene causes that alpha-synuclein you might think that gene might be involved in causing Parkinson's in patients.

And not only can just do that gene by gene, but we can imagine taking a cell from a patient who has a disease and then taking each gene and knocking it out to see if you can reverse the phenotype of that patient. So you might have Parkinson's with the mutation that I just described, the G2019S, and gene by gene by gene seeing if I knock it out, can I normalise that cell. That's called a modifier screen. You can even do this with large datasets and 23andMe are starting to get to the size where you can do these gene modifiers but you can do it in cell culture as well.

And one sort of corollary to that is you can take Gene A and maybe you don't see much of an effect when you knock out Gene A and you can take Gene B and maybe you don't see much of an effect, but sometimes when you take out Gene A and Gene B, the cell is no longer viable or it has some other phenotype of interest and this is called synthetic

lethal if the cell dies or synthetic interaction, a synergy. And this allows some very interesting things because a lot of times, particularly in immuno-oncology, we are searching for what is the ideal combination. We might see drug A doesn't have much activity as a single agent and drug B doesn't have much single agent activity, maybe none, but the combination might be very powerful.

And if you think about the different numbers of combinations, we have ten but what if everybody else has another ten and there are maybe hundreds of these and hundreds of different cancers, the combinations in theory if you start adding them up, there are more combinations almost than there are patients with cancer. So we need to think about more thoughtfully identify the combinations that are going to work in patients and this synthetic lethal-like screen can be used to really help us figure out which are the ideal combinations and we have a couple of combination studies ongoing, particularly TLR4 and OX-40 where we see this synthetic interaction that might be very powerful.

But when you think about it, Gene A times Gene B, there are 20,000 genes times 20,000 genes, some are essential but essentially you get 200 million combinations and that's in one cell type.

Functional genomics (the power of gene editing) combined with machine learning will be very powerful

So if you think about hundreds of cell types and a whole bunch of other assays you might want to run, the data gets enormous, so we have the patient data for ~five million patients, we have this functional genomic data, it's definitely overwhelming for any human to think about how to deal with this, but we now have the second technology which I want to introduce which is the use of machine learning with deep learning, neural networks, lots of different analytic tools that allow all of this data to get understood, the relationships between the genes, the underlying semantic representation, the sort of language of the cell. Once you can figure out this new language, you can start deconstructing the patterns that cause disease and the number of targets could be substantial. Again, they would be hidden in this data if we didn't really do human genetics, functional genomics and machine learning and marry them and push them to state of the art. We think we are going to see tonnes and tonnes of very interesting signals that could ultimately result in genetically validated targets, not just in the cell but we can then go back and take those findings and test and see 'Is that true in humans?' by these datasets that we are collaborating with the organisations on.

Human genetics and functional genomics

Science and technology together to drive better R&D success

I love this quote; 'Artificial Intelligence is the new electricity and is changing industry after industry'. This is from Andrew Ng at Stanford and I think while it can potentially change R&D and pharma in lots of different ways, this is one of the most exciting.

We can probably turn medicine and science from really a biology and a clinically-oriented field and really push it towards being a data-driven, almost a data science, if you will for higher quality targets, faster development and better success rates.

Cell and Gene Therapy is a potentially disruptive technology that has the potential to transform medicine

The third technology that I wanted to highlight today and one that I think reflects both the potential for being very disruptive to our industry, analogous in some respects to what antibodies were to small molecules, a new technology that allows you to target things that you couldn't have targeted before and have effects that you hadn't been able to see with other sort of modalities is cell therapy. We talked a little bit about CAR-Ts. Our approach has been to use T-cells and use genetic editing to introduce a new T-cell receptor that would have higher affinity and be more specific to the cancer and I will give you an example of that in a second.

I am not going to go into all of the specific manufacturing components of this which are quite complex and actually very expensive, but we have actually made a lot of advances and think we can do this a lot better than lots, maybe everyone and if you have a question, Tony Wood will be addressing that.

GSK '794: NY-ESO-1 – a potential first to market TCR-T autologous cell therapy for solid tumours

This is our first programme. It's called NY-ESO because the T-cell receptor that's genetically introduced has a recognition site for a protein fragment that's presented on a tumour cell and it is in fact presented classically on sarcoma cells but it's also present on a lot of different types of cells; myeloma, lung cancer, non-small lung cancer and a few other ones.

And we have affinity-enhanced these so that they recognise the NY-ESO significantly more potently than our own T-cells, so we are making them super T-cells. They recognise it almost picomolar versus ten micromolar. Ten micromolars are very weak binding and picomolars are very tight binding and we think that as well as growing them up in different ways. When we reintroduce the cells we take them from the patients, re-engineering, grow

them back up, sending them back to the patients and they can have a very profound anti-tumour effect.

GSK '794 NY-ESO-1c259 TCR-T is transformational in improving ORR and mOS in synovial sarcoma

What we have seen with this collaboration with Adaptimmune who did the programme, that when we give these cells back to patients after they have been engineered, we are seeing clearly dramatic effects.

Now you might think 'Okay, this is sarcoma, wait until we get the lung cancer data or something else and we will be very excited when we see responses, if we see responses in lung cancer', but I think the important thing to see here is that CAR-T therapy, the other cell therapy that has been so exciting to the world because there have been cures in lots of liquid tumours, this is the first example of a cell therapy for solid tumours.

The CAR-Ts don't seem to be working in solid tumours and this is probably an example of why we think this could be a very disruptive technology and if we start seeing responses in other tumours, there is no reason to think that this might not happen with other targets and we have five targets with Adaptimmune, four others, and maybe a wealth of other targets emerge should this therapy become as impactful as we think it could be with this data being an example.

And when you look at the response rates, I show them over here, when you look at overall survival and you compare it, these are cross-trial comparisons, but when you compare it to what's existing, this looks very, very active.

Expanding the power of our strategy through Business Development

So the last thing I want to talk about before we get to the culture part is that all of the portfolio can be always augmented through external innovation. Only a very small fraction of the biology and the innovation that occurs in the life sciences are going to come from work in GSK. There is a wealth of opportunities both in academia and other industry partners to do business development and Kevin, who was introduced earlier, comes with a wealth of experience and is going to really be forming business development strategies which will be an important part of our growth of the pipeline and it will be focussed on immunology, focussed on genetically validated targets, focussed on finding platforms and technologies that augment what I just described and also importantly to free up resources sometimes we will have maybe targets, medicines, potential medicines that are better off in other companies, as was mentioned earlier and we can use those to free up resources, to generate opportunities that we could apply other places but also importantly to make sure these medicines get to patients in an effective way.

Culture matters. A lot!

I want to end with culture. Someone sent me a little quote last night. What did it say? Something like 'Culture eats strategy for breakfast', something like that and the point is that culture is really an important part of making this work and in some respects it is as exciting and as challenging as it is to deliver, to execute on the science and technology. Having a culture of innovation is incredibly important, one that I am really excited about focussing on.

Culture change will drive solutions to problems that need to be fixed

We have divided this into five different areas really following the science, and by that I really mean, and I want to highlight this piece, is that sometimes, particularly with genetically validated targets, but also in immunology, we need to make sure when the science speaks and says 'Look, I am a target and I am supposed to go into neurodegeneration', that we don't say 'Ah, that's too bad, we are a company that focuses only on these three areas and we will force you to look like you work in one of those'.

So what I mean by follow the science is to do so in research as you are discovering targets and trying to figure out what diseases in a therapeutically agnostic way. Follow the science. If it tells you to go into an area, don't force it to try to work where it's not supposed to. And we have to make sure that when we do that we are not taking molecules into diseases where there is not very much unmet medical need, that is not commercially viable, but we need to make sure we are not pushing it into places where the science tells us it won't work.

Probably the most exciting area for me in culture is ensuring we have the culture where we are incentivising smart risk and by that I mean making people feel appreciated for making courageous decisions and taking risks and not fearing failure and I will talk about that in a second.

The third is something that I have basically grown up in the biotech culture of having single people identified to make decisions, people who have the context needed and the skill set needed and the courage, really to make the right decision and not simply take a vote, not simply to see what everybody can live with, because consensus will get everybody happy, there will be nobody who disagrees, or at least disagrees violently, but it's rarely the best answer. I think it's part of a culture that drives innovation, this feeling that you can be bold and be courageous and be rewarded for taking smart decisions, even when they're wrong.

Focus, focus, focus. We are not going to be successful if we don't identify those projects most likely to work and fund them aggressively at the expense of the ones that probably won't work or clearly won't work. Sounds simple, doesn't always happen.

And lastly, a bit clichéd but really it takes outstanding people in this environment with the right tools and resources to really drive innovation and we are going to demand that we have these outstanding people and we are going to make sure we develop them and do everything we can to retain them because outstanding talent attracts outstanding talent.

Smart risk-taking

I am going to quickly go through this grid. I've shown this grid, I don't know, 30 times when giving talks. It's easy to show, a little harder to operationalise but you will get the concept.

I divide decisions that people make into either good or bad decisions and then either right or wrong, in other words is there a good outcome or a bad outcome and then of course you get a 2x2 grid with four different options.

A good decision that was right, we don't have to talk about that, everybody gets happy about that, those we celebrate. A bad decision that was wrong, that's not good. At best that's a learning opportunity; you have to make sure you have the right people in the right roles.

The two boxes that you can't get wrong for an innovative culture are what you do with a bad decision that had a good outcome, that's called lucky. Do not reward lucky, because what you are doing is you are telling people that we only care about the outcome and if you just reward luck, I can guarantee you over the long-term, that's not going to work. Luck is not a good strategy. You laugh, but people reward luck all the time.

Now even more challenging sometimes is what if you make a really good decision that's wrong, that has a bad outcome? We need to celebrate that as much otherwise we are going to teach people only make those decisions that work. So what do you do? You incentivise a very conservative nature and over time that is not going to be terribly innovative. In fact, I would argue that over the long-term that's going to destroy a company, so you need to make sure that you put incentives and reward people when they make good decisions even when they're wrong.

If you think about it, if we came up with this great strategy that was going to double the probability of success and I told you my first three failed, I would say 'Well, 80% failure rate the first three, that's not inconsistent with a 20% success rate, zero out of three'. You have to celebrate that if that's a good decision and not say 'Ooh, I wonder if we got it

wrong?' You don't have enough data. This is probably still a good decision, but a lot of people are rewarded zero out of three, you know people in my job, zero out of some number you are not going to be in your job very long. What you really have to ask yourself is, is this a good decision?

Focus: prioritisation is critical

Focus. I love focus, I think this is critical and I love these two quotes. David Packard who founded Hewlett-Packard spent a lot of time in the Bay area advising companies and he said this to all of them; 'More organizations die of indigestion than starvation.' You might even think that this is intuitive but, again, these companies believed not only that that wasn't true but they believed the opposite – that they would likely die of starvation. They eat too much and they have too many projects and that is why they died, because none of them were adequately resourced. One of things that I heard over and over again when I met with the folks in R&D was that, despite spending a lot of money, we did not have many team saying 'I'm adequately resourced'. We didn't get rid of the least likely to work, to fund aggressively the ones that are most likely to work.

I like how Steve Jobs said it: 'I'm as proud of many of the things we haven't done as of the things that we have done. Innovation is saying 'no' to a thousand things' and, supposedly in Apple, there is a little sign that says, 'Simplify, simplify, simplify' – with the last two simplifies crossed out. This is the kind of culture that I would love to have at GSK in R&D in particular, so that we can really incentivise people to focus.

Refocusing to reinvest

We have been focusing. As I said, when you saw the numbers earlier, R&D is spend is down, and that is not surprising. We have made 65 decisions to terminate partner or divest programmes since April 2017. Forty-two programmes were in the clinical phase and the remainder were preclinical. There were more than 400 FTs freed up, to be able to work on programmes, as I said, with BCMA and GM-CSF and other programmes we want to push aggressively to do this. We will be continuously looking at the portfolio, to find opportunities, to see things that are working and aggressively move them forward, and find things that are less likely to work and removing them.

This is the pipeline. There are a lot of upcoming milestones that will inform our progress. Again, my commitment to you is that, every six months or so, we will be very transparent about what decisions we have made, what progress we have made, and what things haven't worked for efficacy, safety or whatever and are being removed. Sometimes we can tell you right away, or sometimes we have to wait for the data to mature and be

presented in a meeting, but we will be much more transparent about this so that you can actually see if this strategy of bringing value is measured by the kind of assets that you see in the pipeline.

New R&D approach will support development of current clinical portfolio

The new approach will go from an organisation which we believe was spread quite thinly across many different programmes. It will go from a consensus driven decision-making organisation and an organisation where R&D and Commercial were a bit silo-ed and where we had limited business development activity, to an organisation where we aggressively back the best potential medicines, while removing those that do not look promising. We will create a culture of accountability, where smart risk-taking and courageous decisions are made by individuals. That is not to say that we won't have teams, but teams will have leaders who are accountable for making a decision. And those decisions will be rewarded when they are smart risks.

We will have robust governance models with scientific peer review and commercial input. Emma mentioned Luke and I - one of the fun things about my job is that I get to work very closely with Luke - and we have reorganised the Portfolio Investment Board. We have really terrific analytics that help us make good decisions, from Kate Priestman's group. Together, we are seeing how to optimise the portfolio because that is how you help the most number of patients and provide shareholder value.

Of course, you have heard that we will be investing significantly in Business Development, to further optimise the portfolio, where and what depending on data read-outs.

Again, the strategy, with science and the two areas that we talked about, seeking to understand how the immune system is causing dysfunction, has been, is currently and likely will be in the future a very important area of science where we think we can identify some important targets that will have broad implications for a large number of diseases. We will also use human genetics to really redefine how we identify targets and pursue them. I have talked about all the advances there.

We will really leverage technology. The three bets we are making, and we might have some more – these might not be the right ones but, right now, we think this is really clear, that functional genomics, machine learning and this focus on cells as medicines, are clearly technologies that we want to push to the bleeding edge or beyond. Of course, we want to create this culture that I have just described, so that we have higher quality targets with higher success rates, where we benefit more patients and have more medicines out there.

Faster development: I think the LRRK example will not be unique, and more life-cycle options through lots of different strategies that I have just talked about, so that we ultimately have very, very transformative therapies. Perhaps some of the diseases that we start tackling will be like what HIV is today.

Thank you. We will go to questions and answers.

Question & Answer Session

This is a very distinguished crowd. Rather than introduce everybody – I think you can see their names – I will take the questions and then dish them out because most likely there is somebody who is much smarter than I am. Andrew?

Andrew Baum (Citi): When I look at two recent R&D turnarounds – Merck US, and AstraZeneca – the one thing they had in common was speed, but also the depth of the upgrades in the leaders in their organisations. On the Commercial side, Emma has highlighted the replacement of the top 200 leaders, I think, and what percentage she has done.

My question to you is, how many of your key appointments or reports inside GSK since you joined have been replaced? Could you give us a sense of how many of the replacements have come from internal versus external? That is my first question.

My second question is on the extent to which, rather than waiting for the discovery of new targets and drugs and bringing them into the clinic – which is great, and I understand where you are going with that – where do you have drugs right now which are promising, mechanistically, but are actually sitting in the wrong indication and which are commercially unattractive? I guess what I am thinking about is the potential for repurposing your CXCR2, your kinase inhibitor, and so on. Are those potential targets for repurposing in other indications? Should we expect to see that in the near future?

Hal Barron: The first question is about the team. I think 50% of the people on my leadership team are new as of the last nine months. That number might be too high or it might be too low, but that is the number. The vast majority, and I am trying to look around – I think some of them were internal. Many – the Head of Regulatory hasn't joined yet, but she is from BI, Tony is from Pfizer. We have Kevin who obviously is brand new. Who else I am forgetting? Kate is from within but had been in her job for about nine months

as the Chief Medical Officer. I wouldn't say that this is a brand new team, but it is about as new a team as I have had in a long time. That is just a fact. At least 15% of the officers – the Vice Presidents and above in R&D – are new. I don't actually have the breakdown of how many of them are from outside or within. That number might evolve as we see areas where we need to invest more heavily and get more talent from the outside. I know that Axel can comment on this, because we are really aggressively looking for additional talent in Oncology, to rebuild an organisation which will be incredibly important. Some of the talent left in 2014, when we had the agreement with Novartis, and I can hand over to Axel to comment on this in a moment. I think we have a pretty new team and a very talented on.

Axel, would you like to comment on how many new folk are in Oncology?

Axel Hoos: We are in the middle of hiring new talent to the organisation. This was a natural need after the Novartis transaction. We lost a great deal of talent, particularly in development, and also on the commercial side, just to be clear about that. We are committed to rebuilding this. Some talent has come on board already from other prestigious pharma organisations, so we are again attracting from larger players, but we are not where we need to be yet. There is much more to be done, but I see the trend going in the right direction.

Hal Barron: Your second question was about repurposing. I was trying to get across two things about the value of human genetics. One of them is that – and I think you are right – sometimes we may have taken molecules and pushed them towards a disease because of where they were therapeutically discovered. Had we perhaps had a disease-agnostic approach, even further complemented by human genetics, that might not have been the first indication. I hope in the future we don't call that 'repurposing', but the first purpose.

There are examples of that. You mentioned CXCR2, which is being developed in pulmonary disease, but there are data suggesting that it might be active in preclinical models in oncology. I know that Axel and his team are looking at this carefully in terms of some preclinical models.

Another good example might be RIP1, where it has been developed in psoriasis, RA and inflammatory bowel disease, but we are realising that there might be opportunities outside in neuro – an area we were not so interested in. However, that has been changed and we have a small molecule that we are now aggressively trying to move forward, that penetrates into the brain: this requires a new molecule, but we have that. John or others can talk about that, but that hopefully will be able to be developed, I think as an example of repurposing, which is what you are talking about. I think there will be more of that.

Benlysta is a little bit like that. We are doing a combination with rituxan for lupus. I wouldn't call it 'repurposing' it, but I might have imagined that that should have been a lifecycle opportunity that we did before now, earlier on. Being more aggressive about where the molecules should go, and being quick to decide that, and also aggressively moving them forward when we see activity, will be a hallmark of the new development in the organisation.

Richard Scheller: The 23andMe database can also be very useful, particularly for PheWAS studies, because we have 1.5 billion datapoints on hundreds of different diseases, so we look at snps in the gene and we see what diseases associate with that gene. Hopefully, we will take a look at the GSK molecules in development and in the pipeline and see whether we can generate some ideas for either repurposing or just broadening indications.

John Lepore: We see some other really good examples on the marketed assay, which is *Nucala IL5,* where that team did a very nice job to expand the potential value by looking at other indications, including EGPA, nasal polyposis and, most importantly, COPD as well. The thinking is there but we just need to embed it more, and now we have a great tool with 23andMe.

Hal Barron: We have just seen an example, although I will not tell you which one it is, where a PheWAS identified a disease we are not in, which looks very promising. This was just two days ago, or perhaps yesterday. That looked like a real opportunity perhaps to move up the development timelines so that could be even a first approval. We are definitely thinking along those lines.

Next question – I am sorry that I don't know everybody's names yet.

Richard Parkes (Deutsche Bank): I have a question on R&D productivity, and one product-specific question.

You noted that you were quoted saying that you loved large cap pharma in that article last night, but it feels as though a great deal of the innovation at the moment is coming from smaller companies. It also feels as though large cap pharma has lost some of its leverage, given that many of the opportunities are very concentrated in terms of patient populations, so that you don't need the deep pockets of pharma, either from development spend or sales and marketing infrastructure. That seems to be leading to companies having to pay very high prices to access some of the next generation technology. I just wonder, do you agree with that statement, or do you think that large cap pharma brings something else into collaborations that will still give them that leverage? Do you feel that you have been

given enough in terms of business development budget to continue to access enough external innovation to be competitive?

That is the first question and I have a follow-up on a product.

Hal Barron: Let me answer the first question, and others can chime in if they have thoughts on this. Having spent time in a small company, and time at what was a small company and became bigger, - the reason I said I liked the idea of big pharma is because I think there is an enormous of value that a small, innovative biotech company can get out of a collaboration. I think the 23andMe/GSK collaboration is a perfect example of where both groups will win enormously and, most importantly, the patients will benefit from that.

Yes, Richard could build fermenters and make antibodies and do all of that stuff, or we could really triple down on doing human genetics well. If you have to be a biotech, and do all of the stuff that distracts from what you are really good at, and why people wanted to work with you, you will be distracted. Now, you can make a phone call and have a collaboration, and have someone allow you now to start seeing opportunities in small molecules, which perhaps 23andMe would have passed on because you can't do everything, or other targets that were just beyond the scope of something they could think about – big pharma can bring a great deal to that opportunity of turning targets into medicines.

I don't think they all have enough money. They have enough money to do some of the things they want to do, but when they are successful they will need to grow. The opportunities that we can have, by working with these really innovative people, can allow us to become more innovative too.

One comment on talent. It is very important to have outstanding internal talent, as we do, but I am really excited to get to work with people like Richard and his team. I know a few of the team members and they are outstanding. The idea of having a collaboration with a biotech – when you have the collaboration ideally formed – I am not saying that it is as though they are a part of GSK, but it is analogous to that, in which we will all be a big team, doing human genetics. I would like to see us do more of the innovative deals with small biotechs, which could really benefit from what we bring, and we could benefit from what they bring. I think you will be seeing more of those.

Richard Parkes: There is the BCMA programme, which you have obviously highlighted for accelerated investment and moving into earlier lines of therapy. We are seeing very impressive response rates in the refractory setting but the other notable thing about that clinical data was the ocular toxicity. I was just wondering, as that data is evolving,

how confident you are that you are not seeing any cumulative toxicity in that setting that might become more important as you move into earlier lines of therapy with patients on the drug for much longer periods of time.

Hal Barron: Axel, would you like to take that question directly?

Axel Hoos: It is an important observation. This is a unique type of toxicity. What we have seen so far is that it is mostly low grade and very well manageable with simple measures such as steroid eye drops and potential dose modifications for individual patients. We are managing the toxicity well and it becomes a matter of education of the treating physician and the patient, as the agent is given to more and more patients.

As you go into earlier lines of therapy, you are right – toxicity is more important in earlier lines. Nevertheless, those patients are used to receiving three- or four-drug regimens with more severe toxicities than the mild ocular toxicities that are the characteristic for the BCMA agent. We believe, ultimately, that if we manage this well, it should not be a problem. This is a view shared by many of the treating doctors in the first trial, and that is what market research tells us. We are pretty confident that we can manage this.

There is one other titbit here that is important. When you look at how toxicities with other drugs could enhance the toxicity with our drug, when you start combining them, which we are just beginning to do, we don't see synergistic toxicities so far. There is mechanistically no reason to believe that the MMAF, which is the conjugate to the antibody – when that goes into the eye or into the cornea, it is a diffusion mechanism. It is not driven by BCMA and there is no BCMA in the eye, and it disappears: it is washed out again relatively quickly.

We don't see any other drug that is being used in myeloma at the moment, which actually would enhance that kind of mechanism. So far, we are okay, but the proof of course is always in the data. We will do the trials: several of those begin this year and then more advanced studies next year, where we will be able to answer this definitively.

Ben Yeoh (RBC Asset Management): I have a question on the culture piece. In large organisations, particularly, we have seen that it is very difficult to do cultural change. I was wondering what are the metrics that you are looking at, which might be showing you that the cultural change is on track, and whether there are any early signs of what you are doing having some traction.

A sub-part to that is, how do you incentivise people to say 'no'? It is almost a mindset thing, and it is quite a difficult thing to get right in the process. We hear about it

somewhat, and we see organisations that do it well, but turning an organisation to think about that is quite a challenge.

Hal Barron: That is a terrific question. First of all, on this backing up. We, I – we all believe strongly that we need metrics to figure out how we are doing, so that if we are not doing as well as we would like to, we can figure out what is missing. The metric, specifically on culture – and it is hard to imagine how we could tackle it all – one simple way is that we have HR surveys to see how engaged people are. How well do we think we are doing at decision-making? How fast are we at moving things forward? There are a number of different questions. We have been benchmarking for different reasons, but we have been benchmarking this over the last couple of years, and those who know more can comment. I would expect that we could look at those questions and pull out, prospectively, those that we think will reflect the cultural change and use them, to some extent, at a very level but as a metric.

The second one is just asking people to do these things, I don't think personally is going to work. I think you actually have to ensure that you have things in place that make it easy to do that, in fact that incentivise you to do that. For example, if we have a metric called "Put eight targets into Phase 1 next year", we will have at least, probably, eight targets in Phase 1.

Now that is a progression-seeking culture rather than one that is necessarily going to be incentivised to kill things that don't deserve to move forward. When we set goals, I think we need to be mindful of goals that incentivise what we want. For example, and I don't mean that we should do this for every goal, but certain goals should say 'at the end of Phase 2' - I will make this part up - 'we should take no more than three weeks to assess the quality of the data, its impact and whether we want to move forward.

Now, that might be really easy because it's negative, or it might be really hard because it's grey, or it may be really easy because it's super-positive, but incentivising to do things quickly rather than incentivising to make it go to Phase 3 - because if we incentivise to make it go to Phase 3, we are not telling people to look carefully at the data; do whatever you think is right. There is a subtle bias towards wanting to progress things, so I think it comes in measurable from the surveys, but also creating goals that will incentivise that. Also, doing a lot of talking with employees and seeing how it's going. I'm sure we will come up with other metrics that we think are useful in assessing this.

I don't know if others on the panel have thoughts that they want to add, if people who know more about this than me want to chime in.

Michael Ota (UBS): This is a question for Hal. Thank you for outlining the gestalt of where you want to take the business in terms of decision-making and culture, but can you outline an example so far where you have applied that framework decision versus outcome and it has actually resulted in, we are going to kick disaster out.

What I didn't see in your presentation and your slides that this was the wrong way to think about it and we're actually going to reprioritise, or is it just too early to talk about that now?

Then a follow-up question, I was just wondering if Richard was going to add on to partnering large Pharma versus biotech, whether you had any additional thoughts on that?

Hal Barron: I have to be careful. I think that we have had a couple of programmes that we have reviewed, that I think we will be stopping as an example of courageous difficult decisions. Some we partner. You've heard about the many partnered assets. We are in the midst of doing this, or it's a tiny bit early but not that early. I think you will be hearing about it very soon, programmes that we think from a data-driven perspective don't fit, from a value perspective don't fit, so that we can do more. I think there have probably been two examples in the other direction where there were some debate as to how aggressively we should pursue it and BCMA was the one that I said, looking down the portfolio with the Investment Committee, and said 'let's go!'. The teams are excited.

aGM-CSF itself is another example of 'let's be aggressive'. The other few that I can't really comment on right now, but you will be hearing about, where we will be stopping stuff. John, you have been involved in this for a year, you probably have some examples that you think are good examples of what he is asking for?

John Lepore: I think they are embedded in the 65 you referred to in the slide where clearly we had to make stop decisions taking into account all the information. Some of them were very far along, some of them we have extracted the value, the tapinarof example, the Orchard divestitures.

I would say it's a cultural element too for really getting all the teams thinking how they articulate the value and understand that in it's a portfolio context and we have these discussions. I think we are making significant progress on that. I wanted to tie it back to the last question about how to incentivise people to be comfortable with 'no', and one of the incentives is that when your project is 'yes', it's going to be adequately resourced and it's something Hal talked about before, so I think over time people will get comfortable, 'okay, I don't have to push my thing forward all the time, and I'll have confidence when my thing is

going forward that it will be adequately resourced to win'. So it's a cultural change, and I think it's progressing.

Hal Barron: Richard, do you want to comment on that?

Richard Scheller: 23andMe, we weren't necessarily looking for a partner at this point in time, but as Hal and I often talk to each other, after his move to GSK we continued to talk. As we talked, it just became clear that GSK could bring this, 23andMe could bring that, back and forth, back and forth, such that the collaboration made so much sense for both parties that it was just clear that this was the way for us at the time to proceed. I think Hal gave the example, and we're very good at 23andMe at making antibodies. A number of people from my previous life have moved to 23andMe, and we're terrific at that. We find probably more targets that are small molecule targets or other more innovative modalities that GSK works on, that we just didn't have the wherewithal to pursue at the time. By working closely with GSK, we can potentially start some of those projects.

Manufacturing antibodies, for goodness sakes! Of course 23andM3 has no ability to manufacture antibodies; of course you can outsource that to China, to Lonza, to other places, but it made sense to work with a partner that has those manufacturing capabilities.

I don't want to line up all the pluses and minuses for you here, but just to reiterate, we weren't looking for a partner, but as we discussed it, it just made so much sense that that was clearly the way to go.

Keyur Parekh (Goldman Sachs): Two big picture questions for you. The first one is on genetics and 23andMe. We have seen some of the other people in the industry, including your ex-employers who make investments in formation medicine,

Flat Iron, Hal,. You guys have had this collaboration with Biobank for the last three years, and it is unclear what benefits those have actually driven.

Can you help us think about what is it that we should be looking at externally as to have you made the right decision by going down this road? What are going to be your benchmarks, and what are you going to do differently to make this collaboration successful? That is question No. 1 - and I'll wait for Question No. 2 later on.

Hal Barron: I think it's a great point. As I said, for culture, metrics is important. For the science and technology, these metrics are going to be equally important.

I think there are lots of ways to look at this. I think that the timing is just ideal for a collaboration like this, and we are seeing this - Richard, you should comment on this. There

is a non-linear scale phenomena to the size of the database and its ability to identify targets. There have been many studies where they do the GWAS and there are not hits, and then it's 25,000 people and you say 'that's weird, it seems fairly genetic because of your feasibility studies, and yet no GWAS hits', and then you do 50,000, no hits, but by the time you get to 100,000 patients, you go from 0 and all of a sudden you have 30 hits. It comes down to the sample size and the power. I think that now we are actually taking advantage of the scale, and I think what we are going to see, but again Richard should comment, that when we've gone to 500,000 with UK Biobank a lot of things came out, but five million, I think we are going to be able to see a lot of things that we couldn't, including gene-gene interactions, which I personally believe there is going to be a lot of nuggets there, and you just have no power for gene-gene interactions, gene-modifier which is the way Richard said it.

That size times, again, the technology, functional genomics, the ability to tile through the genome - and maybe Tony can talk about this - with TALEN or gene by gene in the CRISPR A or CRISPR I up-down, the protein, it is just going to give us an enormous swathe of information that frankly, even three years ago, we would’nt have known what to do with had we had it. But again, with machine learning, I think we are just going to be able to put this whole thing together in a way that allows us to see things we just couldn't see three or four years ago. But the question is, okay, you said that already, how are we going to know? I think it's about the targets we enter into the clinic, the pipeline and the value and the quality of the targets and the stories that end up getting told about the value. LRRK 2 is a great example. What's the next one, how do we do this? I think we should be looking for more of those targets entering into the clinic eventually as a metric. If it is not coming in any faster than it was, where all of this isn't translating into the kind of value that I have described, then I would say it's failing. On the other hand, if it is, I think that's a good sign that we are onto something really important.

Tony, do you want to talk about functional genomics? Would that just be a sense or two on how you see this field building up?

Tony Wood: Yes, let me just add a point about our early experiences, both with TALEN, which you can think about is the precision editor, and has been working with the Altius Institute to really understand what is required to get that precision right, and more importantly as well, to have that analytical cycle so that you know you have achieved what you want to achieve. We have early experience through the Open Targets collaboration, doing large scale synthetic lethal screening that Hal mention with CRISPR. I think one of the things that I'm really excited about here is we can bring insights from both the precision world and the large scale world, and I think we are now at a point where we can begin to

properly industrialise those approaches and fundamentally change the early shape of our portfolio so that we can have larger numbers of targets interrogated in this way and make better decisions as we narrow down, and then focus our resources.

Hal Barron: One other metric that we have talked about internally that I forgot to mention is the quality of the collaborations that we have form. If the world see this as compelling, some of the best and brightest in these areas are going want to work with us, they are going to see the value too. If everyone says 'no, I don't know if it's ready, I don't think that's going to work', that could again be a metric, so I think you should judge us on the kind of collaborations and how Business Development is able to augment the strategy, are you impressed or not? I think we are going to put a high bar, but I think that will be another way of evaluating us.

Richard Scheller: Just a final comment, I think that Hal hit on it. It's really scale and with the over five million customers - and I'm not supposed to say this, but Emma did - soon to be ten million, so I guess we have to deliver on that, we have been able to see associations that other people haven't been able to find. There have been many, many attempts to find the genetic basis, there are components of the genetic basis for depression in Europeans, that have all failed. But with 200,000 people in our database with depression, we were able to publish the first associations, and it's all because of scale.

This was with another pharmaceutical company, but all of those studies going forward will be done with GSK.

Keyur Parekh: My second question was some of us had the experience of listening to some of your predecessors talk three years back about a lot of targets. As you spoke about a bunch of things, the similar question, about half of those were highlighted in 2015 as well, and a bunch of those were meant to be filed or have proof of concept between 2018 and 2020, and they seem to have pushed out by at least two to three years, including ICOSs, OX40, really interesting targets.

Without doing the history you mentioned, just help us think what has gone wrong in the last couple of years. Again, as you change your organisation culturally, what will you do to prevent that from happening again?

Hal Barron: Let me throw out two ideas, and may be see if Axel, having lived it, wants to throw in a third.

First of all, I think you are right. The timelines have slipped. I think if you look back at why things are taking longer than they should, this so-called white space, at least one diagnosis is reasonably straightforward to make. It is not the teams and it is not even the

execution; it's the governance. From the time data was available to the time the governance body actually made a decision sometimes was, frankly shockingly long. I think that was in part driven by a lack of clarity in who's actually accountable for things. Teams get confused and that is why I felt so strongly about ensuring, particularly at the Portfolio Investment Board, that when we see data, we can move because we understand who is making decisions and move.

I think that's one component. I have seen a couple of examples where we fix that by having these accountable, and we would see that and the next day we would say 'go'. I don't think that that was common before, including - and this is the second piece - doing things where you are really not being democratic, meaning there are 10 molecules and we're going to give all of the money to two, and not any to the other eight. In the past, I think there was more of a sense of being more equitable, and I think that's not the best way of doing it, and so I think part of it was driven by the lack of the best in analytics to be able to figure out which of the two we really want to back, having an interface between R&D and Commercial to be resolute about which ones to back. Frankly, if I was to say what's the biggest change in the last six months, I think we have that going well. I think we have analytics, I think we have the R&D/Commercial interface, I think we see data, we move. Frankly, we have moved, in my experience, shockingly fast. In fact, the single accountable decision-making, we made a commitment to three months from the idea when we said let's maybe do a deal with 23andMe. I think we said three months, right? Everyone said 'that seems impossible', you even said you were dealing with a smaller company - maybe I shouldn't have said that! Sometimes it takes a long time, and we said 'we're going to do it'. In fact, I think even our own teams were shocked, 'wow, I think we can do this', and it was driven by clear accountability. I really do think that is a serious part of what we're changing and I think it's taking hold.

The specific assets - sometimes things are delayed because of data, sometimes studies are less feasible, but I do think that's the significant driver.

Axel, since two or three of the molecules were named, do you have other thoughts as to what might have slowed us down in the past?

Axel Hoos: There are, of course, several root causes for things in culture which is at the heart of it, as we have already identified. There are two things that I have personally experienced. One is governance, and the way governance runs. We had several delays in some of our oncology molecules because of governance. I am not going into the depth of what happened, but that is just at the heart of some of the issues. Then another is setting realistic expectations. We are equally responsible in terms of expectations from the

company side, but also from the analysts side because we are being pushed sometimes to deliver something faster than is reasonable because otherwise it's not competitive.

The best example is in the agonist antibody space. After PD-1 success, everybody expected that the next checkpoint antibody would be equally successful, like PD-1. If it isn't, it's not interesting. We are now dealing with a different biology, ICOS, OX40, which have a completely different biology. You cannot expect a PD-1-like effect. We have seen OX40 discontinuations because they did not deliver a PD-1-like effect, and it doesn't account for the biology or the ability to deliver clinical benefit at all.

If you see some changes in timelines, in part they come from reactivity to what has happened in this space, and in part, they come from us internally adjusting our own expectations. But in principle, we have been moving quite quickly on a variety of things. If you think about it, the Oncology portfolio is entirely home-grown, with few exceptions like the Adaptimmune deal which was an early adoption of a technology that the rest of the industry did not pay attention to, CAR-T, CD19, CAR-Ts were attractive in cell therapy. TCRTs were not yet of interest, even though those are the entry points for solid tumour therapy. Now we have access to that by making an investment of double-digit millions as compared to an acquisition of double-digit billions, to get access to a CD19 CAR-T, which is much smaller in terms of commercial value.

It all depends on how you look at things, but I am pretty convinced that with new leadership, with new governance, we can actually accelerate things even faster, and the BCMA story is probably a good example of that.

Hal Barron: Let me just make a commitment, because I think it's a great opportunity to highlight what I was trying to get across in terms of transparency. I don't think you should have to wait a few years to ask that question. I think we will be doing these frequently enough that when things change, I'll say 'nothing went wrong, we just had the wrong date', or, 'here's why it's delayed, it turns out it's more complicated because of the dosing, or because of the biomarkers', or whatever it is, and just be transparent about it. You may think we are doing a bad job, or you may think we are doing a great job, but it will be transparent, and I think that's what we are hoping to do by having more frequent interactions with you like this, where we can show you 'look, here's what we showed you last time, here's what's moved, here's why', and get input.

Steve Scala (Cowen): Thank you. I have a couple of questions. First is a follow-up to the last question. Can you compare and contrast at a practicable level the use

of genomics within GSK to that of Roche, and what are the advantages and disadvantages of each approach? For instance, Roche argues that they have scale as well, which was one of the advantages you just cited.

Secondly, this is a longer looking question, but when he was head of SmithKlineBeecham Research in the early 1990s, George Poste made a then pioneering investment in HGSI to specifically harness genomics to - and now I'm reading in a 1995 note - 'develop new therapeutics, diagnostics in gene therapy vaccines. Thirty years later the world has made huge advances, and GSK really hasn't, in this regard. What conclusions should we draw from this, if any – is the answer all culture, or is there something else at work? Thank you.

Hal Barron: Let me take the second one first, and you would think that between me and Richard we should probably be able to answer the first one, but I'm not going to.

Richard Scheller: I'm not allowed to!

Hal Barron: Yes. I think it's really interesting, and I did know about George's comments, and I think they are phenomenally interesting, and I've thought a lot about it. I think he was ahead of his time, and I think the answer is that – and this was not intuitive at the time, because we weren't sure how frequent these polymorphic variants were going to be in the population - and Richard, you can probably comment on this more - that if it turns out that common variants, things that occur in 20, 30% of us, really explain the disease, you're going to see it with a relatively small sample size. If it turns out that the rarer variants or very rare variants are your clues, you're just not going to see it until you get to scale, and I think what was, some people in retrospect were saying, I told you it was going to be rare, but the conventional wisdom at the time, if you go back to the literature, was, it was going to be the common variants that were going to explain the answer, and that's not true, it's not the common variants.

There are some examples, but in the vast majority of targets, genetically identified, genomically identified targets, I think are coming from the more rare variants, and sometimes very rare, and I think that's what explains why it's taken so long. I don't actually think that it was culture, there's a bit of technology that was needed to get more variants, I mean, you measure 70,000 snps or whatever, but you can impute 25 million now, there's a whole bunch of much more sophisticated things you can do, there are way more data sets, there is deep phenotyping with UK Biobank that's very complementary, you have machine learning, functional genomics, I just think that that wasn't available when George was very

prophetically predicting this would matter, but I think the most likely explanation was the common variants didn't explain the disease.

Richard Scheller: I'm old enough to have been around when that statement was made, I'm a little older than Hal, and what was happening then was that the set of human genes were being defined, and that's what people were doing when they were sequencing the human genome, and sequencing cDNAs: they were saying, oh, here's a new gene.

What we've been able to do over the intervening 30 years, and what is so exciting about human genetics today, is we've known all the genes now for a decade, 15 years, there are 21,137 plus or minus, but we are able now to know from human genetics what they do, what diseases they are involved in, and that's new, that's today, that's the last few years.

So I would say what George was commenting about was something totally different – what are the genes? Today we are excited about understanding what they do, and what diseases they're involved in. So it's really a statement comparing apples to oranges, in my opinion.

Sam Fazeli (Bloomberg Intelligence): Two questions, I think is the limit: one is, if you look at the idea of looking at immunity or immunology, or whichever way you want to go, that can take you into basically every possible disease area, which is I think what you have highlighted; should we expect that there be a therapeutic focus emerging out of this, based on the success of the molecules that come through over one year, two years, three years, or will it continue to be, whatever is successful we will pursue it, be it neurologic, be it bone fracture, whatever it is that immunology touches? That's question one.

Question two is with regard to AI: I come from a company that has been working with AI forever, as long as it has existed, in whatever form – where do you expect, where do you actually see a real impact in the next few months, year or two years? Is it in chemistry, is it in automation of reactions and choosing the best reactions and much more – where is it, and where do you expect to see a meaningful impact in the R&D process?

Hal Barron: Let me try and take that – Tony, maybe you can think about beyond what I'm going to say about target discovery where you see GSK has a lot of effort in some of the medicinal chemistry stuff that Tony can talk about.

I think the therapeutically agnostic component of the strategy is in research, and as the target matures and we get more confident that it's both likely to work, likely to be safe, likely to hit a significant unmet medical need, likely to be commercially viable, or whatever,

we're advocating for moving it forward - it might fit nicely into a therapeutic area that we already have expertise in, that's represented here, or it might not.

I just want to tell one quick story about a drug that I was privileged to work on – great that Richard's here – which was a discovery in the research labs by Napoleone Ferrara, who discovered VEGF, and it became clear that protein was involved in the angiogenesis in tumours, and we made an antibody to that to try to be a cancer drug, but data from humans showed that VEGF was over-expressed in the eyes of patients with diabetic macular oedema and diabetic retinopathy, and there were changes in the eyes that were angiogenic, so it was very likely to be involved.

We didn't have any knowledge of ophthalmology, we had no history of ophthalmology, we had nothing, and people said to me many times, how did you guys decide, strategically, to become the number one ophthalmology company? That's not how it worked: we were focused on the science and we let it drive us, and we saw a huge unmet medical need, and very compelling biology.

When you think about it that way, it requires a lot of being nimble, we have to get clinicians, scientists, to know how to translate research findings and focus them when things start moving over here and here. We definitely need to be partnering with commercials so that when we get these assets that can be commercialised well – and Luke and I have talked about this – they rely on big unmet medical needs, where the treatment effects are big and the safety profile is robust.

So the focus part, because it's a really broad research, the way to focus is use these really high bar criteria, and say, look, if it isn't really going to be an innovative therapy, and it's outside of what we know, why would we do that? We might have an out-licensing programme, because somebody else might find that attractive, but we're going to have a high bar, but follow the science.

Just quickly on AI, and then Tony jump in: I personally think that AI can do lots of things, to me the question is not what AI could do, it's what is the most important problem for AI to solve, because if it solves the problem, it's really not the big problem facing us, it's interesting, it's kind of cool science, but it's not the fundamental problem that we need solving.

I believe the fundamental problem is getting better targets, and that's why to me leveraging human genetics, functional genomics, this massive data set, to find the best targets, is something machine learning is really ideally suited to do: massively, highly dimensional data sets; but machine learning is effective in a lot of different areas where that

is the case and we're doing a lot of stuff in medicinal chemistry, and there are lots of other places where there might be shorter wins, but I'm not so sure that that alone will be necessary to drive the kind of change that we're talking about.

Tony, do you want to –

Tony Wood: We're getting into medicinal chemistry, which is my background, so there's a danger I'll go into a lot of detail. I think it is in that area about predictive science, it fundamentally allows us to be more efficient, it allows us to design with other criteria in mind, but as Hal indicated, the nature of the data that we are going to be able to generate in functional genomics and the sorts of questions that we can ask there, they're going to be much more impactful; the rest is about efficiency and about predictive design, as I've said, and it's about ensuring that we have the right data types.

That science isn't new: I was playing around with neural networks in the early 1990s in chemistry, so what you have to bear in mind is that it will help us make better decisions, but if the process that we then follow with that is another rate-determining one like synthesis, where again, we can apply the same techniques, what we're doing is simply becoming more efficient; fundamentally for me it is about transforming through making better choices on, targets in the first instance.

Then of course the opportunity from functional genomic ideas, to go back to Richard, and ask him to help us find qualification within human data sets through 23andMe, creates a virtuous circle of high-scale testing, and then validation hopefully in the real world in the disease state.

Graham Parry (Bank of America Merrill Lynch): First question, on BCMA, and your second line studies, could you run through the rationale for not including Darzalex combination in there – you've referred to it as being in combination with standard of care, but arguably Darzalex is now standard of care there; and do you think not having that in the arm could actually hamper recruitment?

Secondly, on slide 43, you ran through a lot of potential data readouts between now and 2020, I was interested in particular in the number of proof of concept readouts that you still have coming: of those, could you highlight any where you feel you might have a faster market strategy, or where you can go straight to pivotal trials without necessarily having to do further clarification and phase 2 trials?

Hal Barron: Axel, do you want to take the BCMA Darzalex question?

Axel Hoos: It's actually a mixed bag: we do have Darza combinations, in the second line strategy there is one, and there's one that does not contain Darza, and the reason we have done that is simply based on the evolution of the space: the multiple myeloma space is moving very quickly, Darzalex combinations are moving up from later lines to earlier lines, and it's different combinations, so you have pomalidomide as a combination partner in the later line, you have lenalidomide in second line right now, in all likelihood lenalidomide would end up in first line; if a patient receives it in first line, you're unlikely to give it again in second line, you will seek out that combination that uses something else.

We are accounting largely for the dynamics in the space, with the strategy that we are currently running, but there is no way around Darzalex, so we will certainly have Darzalex combinations, meaning working BCMA versus Darzalex combinations, we will have that in every line of the strategy. Darzalex/pomalidomide/dexamethasone versus BCMA/pomalidomide/dexamethasone is a second line component of the strategy. Darzalex is in there.

There is one other important thing to be said: this space is fast-moving, yes, but it also hasn't delivered yet these massively transformational effects for patients that we have been hoping for, and have seen in non-small cell lung cancer, for example, with in some ways curative therapies, with immune-modulators. What we are looking for is to actually drive this a little bit more aggressively, and take a little bit more risk, but also then potentially transform the treatment landscape.

We are doing that in a three-step approach: fast to market with monotherapy, that's something you are familiar with, Darzalex did the same; the second line strategy to bring the standard of care combinations in the mix, that's basically what I just said; and then a third step, which goes into first line, will include some standard of care, but will also include some combinations with novel agents, immune-modulators, eventually our own, or those of partners, to completely transform the treatment landscape. The three steps together could maximise the value of what BCMA can deliver to patients, and what it can then also do for GSK.

Hal Barron: Thank you. let me go to your second question – what number is the slide, 43. How come that says 43? 44? They're numbered funny. [*Identifies correct slide*] I'm going to give you a few minutes to prepare, I'm going to give two – we didn't practise this question, but it's a great question – I'm going to pick two, guys, if you don't like my two you can push back.

I think the heart of your question is essentially, where do you see in Phase 1 the potential for data where you go, wow! I think there are not many diseases where you can do that - the two places I think you can do that is cancer, and frankly, any of the cancer things can go from being not so wow to wow pretty quickly, but the one I want to pick out is NY-ESO, and I'll explain why, so maybe you can get ready.

The other one – and this is a little bit out there – is I want to say something about HBV ASO, because what's really interesting sometimes about doing drug development and virology, and you know well, when your endpoint is measured in log reduction of something, you can see things pretty quickly, right? The reason oncology is kind of cool is because you're getting a volume reduction, which is really pretty interesting, sometimes you can get things like MDR and surrogates of tumour clearance, but the antisense programme with our collaborators has the potential – you can argue how likely it is, but one could imagine that things could come out of that, that would make you say, wow! The NY-ESO, you would say, don't you have data? I think if we see data in lung cancer for instance, where the drug works in lung cancer, again these are very high bars but that's where you say wow! Okay, it's a solid tumour sarcoma, okay I think I know what to do there, but if you have responses in the second tumour type, particularly lung, and there's also studies in myeloma and there's combination stuff – you didn't ask how likely is that – but those are two where that could happen. Maybe you want to briefly tell us what that study's about and how that's working, the HPV.

John Lepore: These are antisense oligos, it's a partnership with Ionis. We have two different ones: one's a direct targeting antisense, the other is a prodrug that allows a lower dose, so it's administered to the liver in a lower dose and gets converted to the active agent. We are looking for evidence of suppression of viral antigens over time, and that is, as you've said, a surrogate marker potential for a cure. The idea is that this will be a treatment not just for the nuclear site analogues that are used in most patients that suppress viral replication, but also to reduce the production of the antigen in the liver which is thought to be the most oncogenic activity. It's a pretty big opportunity worldwide, for sure, but it's also a reasonable opportunity in the US, and Luke can come in on that if he'd like. The study is designed to get a high confidence in the ability to have a good rate of functional cure from that, and we have an option decision next year based on the data.

Hal Barron: Do you agree with NY-ESOs having that potential, and if so could you expand on that?

Axel Hoos: NY-ESO is somewhat of a unique case because it has multiple potential effects on our strategy. The first one is it's the anchor asset, in the clinic at least,

for our cell and gene therapy effort in oncology, and our focus here is on solid tumours. Number one, we want to expand what has already been done with CD19 CAR-Ts in liquid tumours into the much larger unmet need in solid tumours. TCRs allow you to access targets that are inside the cell, not just on the surface of the cell; as such they get you much more opportunity to go into solid tumours, they are already in the first generation of engineering clinically active, as you have seen. The CAR-Ts took three generations of engineering before they were really clinically useful.

Having said that, the way we run the programme is we focus on small indication for entry, that sarcoma, expand into larger indications, which is multiple myeloma, non-small cell lung caner. In myeloma we already have data; in lung cancer we are just gearing up towards that. Then we go into the space of combinations, so there is a PD-1 combo study running in myeloma, there is a PD-1 combo study planned for small cell lung cancer, which is obvious as it's very dominant there. Then there is another aspect of this which is very different to any other modality you can use to treat disease, and that is you can re-engineer cells. That means if putting the T-cell receptor into the cell is not enough, and we are already seeing clinical activity that's quite profound, with that single step, you can engineer the cell further. If you would have a small molecule and you don't get the effect you want, you need to make a new one. Here we take the same cell that they already made genetic change, you add another change. Let's say we put a cytokine gene into the cell, we knock out PD1, we do whatever makes biologic sense, and you can enhance the potential of the medicine.

Cell and gene therapy is really something where we have a lot more opportunities and NY-ESO is our anchor. We get in with that, we will expand to other targets, we will bring in other molecules as we go along and, more importantly, we mature the platform and it goes back to Tony's shop. The platform we approach differently than other pharmas have done. We spend a little bit more time getting manufacturing ready for getting these products to patients, so you don't have the scalability problems that you get when you put a product into patients quick, but you're not yet caught up with CMC, so we're not having that problem. We're not as fast as we would like to be, but we will be commercially ready with a commercial manufacturing process at the time when our pivotal trial starts. That is critical, that is completely the opposite from anything else that you have seen in the industry so far.

Emmanuel Papadakis (Barclays): Hal, you spent a lot of time on the discovery piece of the R&D equation. To what extent should we think that will translate into an uptick on the discovery part of the R&D budget? I guess a bigger question is to what

extent do you avoid unnecessary duplication of a huge amount of genomic work going on in the academic realm of the scientific world? Then a follow-up on NY-ESO Hal, you seem to express some ambiguous confidence about the ability to target solid tumours earlier. Maybe Axel just answered it, but I was going to ask you to elaborate on that a bit, your degree of confidence that it will translate, and if so, why have you not been more aggressive to accelerate the clinical development programme more broadly, because it's felt a little bit slow?

Hal Barron: We'll ask Richard to comment on the academic overlap. I'm not sure how much this will impact the research component, the discovery component of the budget. Probably the way I'm thinking about this is that a lot of this effort we will be able to fund this through things we won't be doing. I think we're going to have a bigger impact in the development side when things start working, but it's early days and it will be data driven.

If I led you to believe I didn't think it [NYESO] was likely to work in solid tumours, that's wrong. It does work in solid tumours, we have sarcoma. What I said was we don't have data outside of that solid tumour, and I'm extremely pessimistic that CAR-Ts will work in solid tumours, so maybe that got confused. I don't think CAR-Ts, at least in their current format, are likely to work in solid tumours. That's why I was so excited about the opportunity for T-cells in solid tumours, and it works in sarcoma, which is a solid tumour. I think there will be a significant inflection if we can find a second –

Emmanuel Papadakis: It was more the question of translation from sarcoma to other solid tumours, it seemed to me.

Hal Barron: I didn't mean to be pessimistic at all, it's just broad data, and it will be wonderful. Should it work? Yes, it should. If it doesn't, one could imagine we need to develop better diagnostics to identify where NY-ESO is over-expressed, and we're working on that. That isn't a straightforward problem, as you might expect. And then finding out which tumour types have the most people with over-expressed antigen to identify them so you can enrol them in trials. I'm optimistic that we'll be able to find other tumours, solid tumours, NY-ESO works, particularly when you think about how to re-engineer the cells, and the second and third generations really get this down. It's a bit of a longer view to be excited about a disruptive technology. This is not something that we're done and let's move on. This is going to be a complicated but potentially very disruptive concept.

Axel Hoos: I add one more data, just to make it easier to follow. Synovial sarcoma is a sub-type of sarcoma, that's the data you just saw on the slide. That's where we had the first, what we believe, transformational response rate of about 50%. This year at ASCO, when the programme was still with Adaptimmune, they reported on a different

histology, still within sarcoma, called myxoid/round cell liposarcoma, the same response rate, basically, like we saw in synovial sarcoma, so that's a different type of tumour. It's in the same realm of sarcoma but different histology, so if you can go from sarcoma 1 to sarcoma 2, maybe we can also go to other solid tumours. It makes sense, so we are pushing towards that. Your point is well taken, we still have to deliver the data.

Richard Scheller: With respect to overlap between 23andMe and the academic community, and other large genetic programmes, there is some overlap but as Hal mentioned, largely in the more frequent, the more abundant snps. Since our database is so much larger than any other database, we're able to see less common snps that other folk aren't powered to see. Perhaps the greatest telling thing about our data compared to the academic world is we have hundreds of requests to collaborate with academia. We've published over 100 papers, most of which are in collaboration with academia, so the academics are actually dying to work with us because of mostly the size of our database, but also the great variety of phenotypic information that we have. We will continue those academic collaborations where it makes competitive sense to do so.

Hal Barron: I want to add one more point and then we'll go to the last question. I'm very excited about the complementarity of some of the other efforts we have ongoing, in particular the UK Biobank. While it doesn't have the same size that I mentioned earlier, it's so deeply phenotyped, it's so rich, that I think the two together are way bigger than the sum of the parts, and we will hopefully be able to show that.

One last question.

Jo Walton (Credit Suisse): I'm going to go back to this slide that you have here. You've told us a lot about how you're re-engineering the early stage of research and some of the failings and what you're going to do to deal with it. If I look at the comments that the AdCom documents for *Nucala* were yesterday, they showed some failings, or at least they perceived some failings in your clinical trial design. Maybe you could comment on that. But I'm more interested in your proof of concept studies here. You have six due in the first half of next year, six in the second half, five or six anyway. Do you think we should look for an industry standard success rate there? You must have looked through these programmes, and with your fresh eyes, do you think they are correctly powered to give you the decision points that you need to move quickly? Or were they half-arsed studies that are going to give you something where you have to redo them? I think that's what Graham was getting at. I think we all understand you're going to have fantastic science in 2021/2022, but some of us investors want to see real progress in the shorter term, and your analysis of how

good those programmes are and what sort of success rate and progression rate we should look for from that would be very helpful.

Hal Barron: That's a great question! It was hard and you made it even harder. I'll give you my very transparent answer. Some of the studies here, if they have a huge treatment effect, will emerge. The current way of designing some of these trials was that some of them didn't have as much robust power as needed to see a signal. The danger in that is two-fold. One is that you can be fooled by a trend which isn't real and you advance them. That's a worse problem to have than deciding that the trend is probably negative and discarding an agent that might have been active. I say that because I think very bayeseian, the prior for a molecule entering the clinic working is only 10%, so I don't have a very high probability. If it doesn't look like it worked in Phase 2, it's not like it had a 90% chance if we're giving it 10. When it looks worse than expected, it's important to kill it.

Moving forward, we need to make sure that we power the Phase 2 studies to be able to see whether it works so we don't advance things into Phase 2B, and certainly in Phase 3 when we don't have the confidence that we know we should have. Some of these are powered but there are definitely ones that I'm worried that the approach had been to be a little bit too democratic and give enough money to all of them and to make them go forward without powering the ones we're most excited about. It's a little of both, but there's no doubt there are some that are probably under-powered. Again, I don't think that was a lack of insight in how to design trials. I think it was going back to this have we really thought carefully about how to really aggressively pick the right targets and fund those really well, at the expense of a couple of others that might be zero, rather than everybody getting 80% of what they need, because that can be lost. I wouldn't be surprised if some of these might be under-powered.

John, I don't know if you want to add anything to that.

John Lepore: It's just a corollary to your last comment, which is I think we can reassure you very strongly that we're not going to progress them just to progress them. It's an obvious statement, but we're going to look at them with a very critical eye, and the order of magnitude of change indicated by the studies are going to have to be consistent with what we think could be a commercially important and clinically important effect. If they're not good enough we're not going to go forward with them, and the ones that we are confident, we're going to put more and more resource behind. I think you'll see that as a significant change in the way of working.

Hal Barron: But I do think a metric going forward is that our Phase 2 proof of concepts were designed to ensure we have clarity in the right decision moving forward, and

that that's going to require that they are adequately powered and have more money associated with the studies to do that, at the expense of other programmes that we just don't think are as valuable. That's the kind of smart risk-taking and courageous decision that is fundamental to making that happen. I appreciate that wraps up a lot of what we're trying to do and say with the culture piece, as a way of optimising development.

I know we've run out of time, and we have an opportunity to get together socially after this, so thank you very much for your time. It was fun for us and we enjoyed hearing your questions.

[*Concluded*]