Part 2

Vaccines R&D

Dr Moncef Slaoui

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

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

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

Shingrix

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

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

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

Existing zoster vaccine

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

Shingrix candidate vaccine developed to differentiate

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

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

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

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

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

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

Shingrix – Efficacy against shingles

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

Existing vaccine – Efficacy against shingles

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

Shingrix – immune response across age segments

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

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

Existing vaccine – Immune response across age segments

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

Shingrix – Efficacy against PHN

PHN: post herpetic neuralgia, a severe complication of zoster

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

Existing vaccine – Efficacy against PHN

PHN: post herpetic neuralgia, a severe complication of zoster

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

Shingrix – Duration of protection against shingles

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

Existing vaccine – Duration of protection against shingles

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

Immune response persistency is a good predictor of duration of efficacy

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

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

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

Shingrix: a potentially significant advance in vaccination to prevent shingles

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

Shingrix: a potentially significant advance in vaccination to prevent shingles

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

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

Meningococcal meningitis

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

Meningococcal disease: evolving and unpredictable epidemiology – requires combination vaccine

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

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

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

Most advanced meningitis vaccines portfolio including candidate pentavalent

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

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

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

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

Bexsero: multi-component antigen composition adds value, differentiation

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

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

Bexsero: multi-component antigen composition adds value, differentiation

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

Competing vaccine for MenB

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

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

Sustained MenB transmission in Quebec region

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

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

Sustained MenB transmission in Quebec region

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

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

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

MenABCWY Phase III starts in 2017

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

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

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

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

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

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

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

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

Respiratory syncytial virus (RSV)

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

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

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

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

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

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

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

Candidate paediatric RSV vaccine, a novel approach

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

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

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

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

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

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

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

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

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

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

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

Novel candidate RSV maternal vaccine approach

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

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

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

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

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

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

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

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

Novel candidate RSV maternal vaccine approach

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

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

Group B Streptococcus (GBS)

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

Maternal immunisation for GBS

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

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

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

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

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

Maternal immunisation for GBS

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

GBS maternal immunisation expanded programme

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

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

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

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

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

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

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

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

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

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

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

A new vaccine concept

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

Testing hypothesis for a COPD vaccine

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

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

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

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

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

Data and planned filings support positive growth outlook

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

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

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

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

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

That is the end of my presentation.

Introducing the Vaccines panel

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

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

I will be happy to take your questions now.

Question & Answer Session

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Moncef Slaoui: Thank, Alain.

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

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

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

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

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

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

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

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

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

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

[*Break*]