

GlaxoSmithKline

Investor update: RSV older adults and maternal vaccine candidates

Data Presented at ID Week 2020

Thursday, 22 October 2020

Sarah Elton-Farr (Head of Global Investor Relations): Good morning and good afternoon.

Thank you for joining us to discuss the data presented at ID week on our RSV vaccine candidate for older adults and maternal immunisation. You can access the slides we are going to use for this presentation on the Investor section of GSK's website, under 'Speeches and Presentations'.

Cautionary statement regarding forward-looking statements

I would ask you to please review our cautionary statement on page 2. Also please note that as we are in closed period and have Q3 results next week, we will not be answering any questions on the performance of the business.

Now I will hand over to Dr Hal Barron, Chief Scientific Officer and President of R&D at GSK.

Agenda

Hal Barron: Thank you Sarah, and thank you everyone for joining this call to talk through the encouraging data on RSV we presented at ID week. Joining me on the call we have Dr Emmanuel Hanon, who leads our Vaccines R&D organisation; and we also have Roger Connor, the President of GSK Vaccines, who will frame up the evolving landscape within RSV vaccines and how we think our candidate vaccine fits within this. With that, I will make a few introductory comments and then turn it over to Emmanuel.

At Q3 I spoke to you about three new vaccine candidates starting Phase 3 studies. Two of them are for RSV. The first is for older adults, which is a very large and growing population: in the US alone there are an estimated 70 million people aged 60 and above.

The second RSV vaccine is for pregnant women, to help pass protective antibodies to new-born infants, which in the United States represents approximately four million women per year, and globally more than 130 million women per year.

You will see from the data that we share with you today, that these vaccine candidates are well-tolerated and have demonstrated a strong immune response, giving us confidence in the data and our decision to advance these programmes into pivotal studies.

Science x Technology x Culture

As we have outlined in the past at GSK our approach to R&D is based on the multiplier effect of science x technology x culture. We define this as strengthening our R&D pipeline by focusing on science related to the immune system, the use of human genetics and the application of advanced technology, such as vaccines, functional genomics, machine learning and cell therapy.

Our focus on immunology is resulting in a world class Infectious Diseases portfolio

As you can see on slide 5, our focus on immunology and these advanced technologies has resulted in our world class infectious disease portfolio, which includes 27 therapies in development, of which 18 are vaccines. This accounts for around a half of our entire pipeline. The medicines and vaccines we are developing will treat or prevent HIV, COVID, urinary tract infections, hepatitis B and many other infectious diseases. This pipeline complements our existing marketed portfolio of more than 20 infectious disease therapies, that together delivered almost \$17 billion in revenue for GSK in 2019.

I mentioned this when I showed the slide of our Q2 results, but I think it's worth repeating, that analogous to the declared war on cancer, which has resulted in a marked increase in investment by the Pharma/Biotech sector on discovering and developing important medicines for cancer patients, we are optimistic that the world's experience with COVID may lead to an increased focus on the importance and value of developing new medicines and vaccines to treat and prevent infectious diseases.

RSV vaccine opportunity: high unmet need

With that set-up, let me tell you why we are excited about the potential for our RSV vaccine candidates. RSV is a very common respiratory virus. This infection causes acute bronchiolitis, which can lead to respiratory distress and hospitalisation and even death, and it is a leading cause of hospitalisation in infants under the age of one. In addition, RSV is an important pathogen in the elderly and in high-risk adults. Although paediatricians are keenly aware that RSV may cause serious illness in their patients, most internists are less familiar with the morbidity and even mortality associated with the virus in patients over 60. Given the lack of treatment options, this lack of awareness is understandable. In older adults, the infection can lead to pneumonia, which can lead to hospitalisation. It was observed that the

one-year mortality following RSV infection in such a population may be as high as 25% for these unfortunate people.

In older adults, RSV is estimated to cause 177,000 hospitalisations and as many as 14,000 deaths per year in the US alone. Given the significant unmet medical need and the high burden on healthcare systems, we are excited that we have two RSV vaccine candidates about to enter Phase 3 development.

With that, now let me hand over the discussion to Dr Emmanuel Hanon.

Vaccines R&D approach

Dr Emmanuel Hanon
Senior Vice President and Head of R&D, GSK Vaccines

Thank you and welcome everybody. My name is Emmanuel Hanon. Most of the people call me Manu. I am responsible for the vaccine R&D pipeline in GSK.

Before getting into the specifics of our RSV candidate vaccine and the data that was presented at ID Week, I would first like to talk a little about the vaccine R&D strategy.

Our R&D approach for vaccines

At GSK we are looking for the multiplier effect between science x technology x culture, to design and deliver ground-breaking vaccines with for example the strategic lifecycle management of the *Shingrix* vaccine as well as our meningitis franchise, with the key new product assets in our RSV franchise or with a deeper desire to enter new fields of vaccinology, specifically therapeutic vaccines and vaccines that target antimicrobial resistance.

We do this by leveraging our portfolio of technology platforms, which is literally the toolbox with the goal of addressing unmet need and improving vaccine efficacy, making manufacturing simpler and faster and speeding up development timelines. This approach is underpinned by a special mindset and culture where we take smart risks, we ensure a single point of accountability for key decisions and we attract and retain the best talent, leveraging our presence in key geographic locations.

Vaccines innovation approach built on platform technologies

I believe that one of our key competitive advantages at GSK is the strength and breadth of our technology platforms – the toolbox I was mentioning earlier. Over the last 20 years, we have been investing strategically to deliver this rich portfolio. We are the leading

company in adjuvant technology and we have a strong position in adenoviral vectors as well as in bioconjugation.

We are also investing heavily in mRNA with our SAM platform, self-amplifying mRNA and with our recent CureVac partnership. Both of these platforms are highly complementary.

All this means that we can uniquely select the right platform or the right combination of platforms, to deliver high efficacy vaccines, that we can develop at pace and manufacture efficiently.

GSK Vaccines Pipeline

Slide 10 shows the GSK vaccines pipeline. It is colour coded; new products actually in blue, strategic lifecycle management in orange and global health access in green. We have added a special category in grey for our three COVID-19 collaborations, that are at a clinical phase.

When looking at this pipeline, you can see the broad application of our adjuvant technology impacting all areas from lifecycle management to discovery and our pipeline is making good progress.

In August we started the Phase 3 of our pentavalent meningitis vaccine which combines *Bexsero*, the market-leading meningitis B vaccine with *Menveo*, our vaccine for the ACWY meningitis strain.

We have also started the Phase 1/2 study for our staph vaccine which is a great example of platform combinations. The AS01 adjuvant and the bioconjugation platform have been combined to deliver a unique formulation.

For COVID-19, we now have pre-clinical stage collaboration level reaching a pandemic adjuvant, which we believe has the potential to deliver strong and long-lasting immunity, which is really important for the at-risk population. With this collaboration we hope to provide an effective solution at scale. We have announced we will manufacture billions of doses of the adjuvant in 2021.

The pre-clinical data for these assets we have in-house so far are excellent and clinical data will be available soon.

Finally, and this will be the focus of the rest of my presentation, yesterday we reported positive clinical trial results for two major assets: the RSV maternal and RSV older adult vaccines, which are now progressing through stage gate and will move to Phase 3.

GSK approach to RSV vaccines

Let me now cover our approach to RSV vaccines.

For 50 years, scientists have been trying to develop an RSV vaccine, but so far without success.

Pre F protein structure gives greater chance of success

It is only recently that science has progressed enough for us to have precise information about the identity of the antigen that should be considered to develop a successful vaccine. We know now the best antigen is likely to be the RSV fusion or F protein, and that it needs to have the right conformation to induce the sufficient quality and quantity of protective immunity.

On the left of the slide 12, you can see a three-dimensional representation of the post-fusion conformation of the F protein. When used as a vaccine antigen, the F protein in its post-fusion conformation only triggers a moderate increase in neutralising antibody, a maximum of threefold.

We believe that the reason for this is that it does not display the most potent neutralising epitopes, which are displayed on the pre-F conformation of the proteins showed in red and orange on the right-hand of the slide.

If a pre-fusion conformation of the antigen is used in the vaccine it has been shown by DNIH actually first, that it can boost neutralising antibody by up to 15x, and this is exactly the antigen that GSK activated.

It is really important to highlight that the response induced by a vaccine approach is polyclonal and this is essential to get high-level protection against the virus, and potentially reduce the risk of escaped mutant viruses. Both these factors may mean vaccination may have advantages over monoclonal approaches.

RSV vaccine candidates

The development of a portfolio of RSV vaccines is a major area of focus for us at GSK Vaccines.

The maternal vaccine is based on the pre-fusion antigen used alone. It is designed to protect babies during the first six months of life, during which 50% of hospitalisation takes place.

The vaccine is given during the third trimester of pregnancy with the goal of protecting the baby from birth through a passive polyclonal immunisation. In addition, the vaccine might also offer protection for the mother.

The paediatric vaccine aims to expand protection beyond six months up to two years, by raising active immunities against RSV, using an adeno vector and therefore addressing the remaining medical burden associated with RSV in children.

For the older adult vaccine we are leveraging our adjuvant platform ASO1, in the same way as we did for the *Shingrix* vaccine we know that the older adults are less responsive to vaccination due to an age-related decline in immunity, specifically, T-cell response. This is why we have combined the pre-F antigen with the ASO1 adjuvant, to create a vaccine designed specifically for that older age group.

All three vaccines have been designated fast track by the FDA. The paediatric vaccine is in Phase 2, and some data will be presented next week. The maternal and the older adult vaccines are on track to start Phase 3 in the coming months, and this is why the next part of the presentation will focus on these two assets.

Key data on immunogenicity and tolerability for Maternal Vaccine Candidate (RSVPreF3) administered to non-pregnant women

Study designed to evaluate multiple doses in non-pregnant women

Now let me take you through the key data from the Phase 1/2 trial of the maternal vaccine candidate analysing immunogenicity and tolerability.

We enrolled 500 non-pregnant women who were divided into four groups. One group is placebo, and three groups received the vaccine at different doses, 30, 60 and 120µg. Now, before going into the details of the results, let me give you a very important context. As you know, last year, Novavax shared disappointing Phase 3 results for their maternal vaccine, and it did not meet the primary endpoints. Despite this, an important learning was made for the world field. The data showed that with a vaccine able to boost neutralising antibodies by three-fold, the efficacy was between 40-50% depending on the severity of the endpoint used for sick children.

This data gave an important indication of the level of immunogenicity needed that may confer protection.

One dose is highly immunogenic and persistent at all dose levels

On Slide 16, for all maternal vaccine, we were actually impressed by the response observed. Up to a 14-fold increase in RSV neutralising antibody using the 120µg dose, clearly this is well above the three-fold impact delivered by the Novavax candidates.

In addition, the response was neutralising against RSV-A sub-types, and a similar response was obtained for the RSV-B sub-type. We also observed strong persistence of

this response, after three months there was still a six-fold increase above baseline natural immunity.

All doses well tolerated

In terms of safety, the vaccine was well-tolerated at all doses with the most frequent adverse events being pain at injection site and headache. There were no vaccine-related safety concerns. So we are very confident in our candidate vaccine and Phase 3 is expected to start within a few weeks, with the first major result anticipated in the second half of 2022.

Key data on immunogenicity and tolerability for Older Adults Vaccine Candidate

Let me now go through the key data on immunogenicity and tolerability of the older adult vaccine candidate.

Study designed to evaluate antigen and adjuvant vaccine doses in target population

On Slide 19, you can see that the trials enrolled more than 1,000 subjects. Part A involved young adults exposed to placebo or various doses of antigen, 30, 60 and 120µg. This was needed to assess the safety of the vaccine, but importantly to also develop a benchmark. Young adults do not develop severe RSV disease, and so the immune response can be used as a relevant benchmark to compare with the immune response of older adults.

I will come back to this.

Part B of the trial exposed older adults to either placebo or one of three different dose levels of antigen. This was combined with two different dose levels of adjuvant. Please note that ASO1_B is the adjuvant used in *Shingrix*, and ASO1_E is the lower dose version of the same adjuvant optimised for tolerability.

Today, I am reporting data one month after the first dose. Data following the second dose and any subsequent analysis will be shared in due course.

Results in older adults showed strong induction of antibody and T-cell response

On Slide 20, I am showing you both the antibody response on the left and the T-cell response on the right.

If we look at the antibody response first, it is worth noting that after the allergy season, people who have had RSV disease generally have around a four-fold increase in antibodies. So we set the barrier in our clinical trial with a six-fold increase as a minimum target. You can see that the results are very clear. Using 120µg of antigen, we get from 8-9.9-fold increase in neutralising antibody.

For the T-cell response, because of the work on adjuvants and vaccines like *Shingrix* that we have done over the last 20 years, we have acquired a lot of experience in assessing T-cell immunity. The graph on the right represents the distribution of the T-cell response in each group before and after vaccination. Please note, these are median, upper quartile and lower quartile distribution. This graph shows that statistically significant impact of the AS01 formulations on the distribution of T-cell response in vaccinated individuals. Both doses of AS01 were statistically superior to the non-adjuvanted formulation, which actually is in line with our expectations in this population.

When assessing the overall data, including tolerability, we concluded that combining the AS01-E formulation with the 120µg of our Pre-F antigen is the optimal formulation for the older adults vaccine.

Compelling neutralising antibody response and T-cell restoration

Now the next critical question is; is that immune response sufficient to give incremental efficacy and efficacy for older adults? To answer this question, it is important to look at the benchmark we measured in young adults. This is on slide 21.

For the antibody response, on the left of the slide 21 it is pretty clear that vaccination stimulates the immune response in older adults to reach a similar level of neutralising antibodies as young adults.

On the right-hand side of the graph, looking at the T-cell response, I want to draw your attention to the fact that the pre-existing T-cell level in older adults before vaccination is much lower than the one you can observe in young adults prior to vaccination. Actually this might explain the increased susceptibility of older adults to severe infection.

Now following vaccination, the level of T-cells in older adults is well above the pre-existing level in young adults and is approaching the post-vaccination response of the same young adult population.

I think this is pretty exciting data to see after only one dose.

Well tolerated in older adults

From a safety perspective, the first dose was well tolerated across the different doses. The most frequent adverse events were pain at the injection site, fatigue and headache, with a trend for the slightly higher rate using the AS01_B-adjuvant, the higher dose of adjuvanted formulation.

There were no vaccine-related safety concerns and so combining all the data, we are very confident in our vaccine and we are having discussions now with regulators and are on

track to start Phase 3 within a few months. The first major results should be available during the second half of 2022.

I will now hand over to Roger Connor.

RSV opportunity

Roger Connor
President, GSK Vaccines

Thank you, Manu and hello everyone. I have to say, we are really excited about the opportunity for our RSV vaccines, given the severe unmet need in both older adults and babies and the very encouraging data that we have generated on our candidates.

We have been working hard to accelerate the progression of these programmes and believe that they really have significant potential. In particular, I am excited about our older adults asset because of the scale of the opportunity and the encouraging data that we are seeing on immune response from the vaccine formulations containing our proven adjuvant technology platform, AS01, the same platform used in our *Shingrix* vaccine.

We are also very encouraged by the Phase 1/2 results and look forward to seeing how these assets are going to perform in their pivotal studies.

RSV older adults represents major opportunity

On slide 24, we wanted to summarise the overall older adults opportunity. As Hal mentioned earlier, RSV creates significant and widespread health burden in older adults. We have the opportunity here to introduce a vaccine to help protect 70 million older adults in the US alone and hundreds of millions more around the world from a common, burdensome respiratory virus that can lead to pneumonia and other complications.

I think a really important point is that two thirds of older adults in the US receive vaccines regularly to prevent 'flu and pneumococcal disease, so this is a population of health-conscious individuals and we have a particular expertise here, with tremendous consumer insights having successfully launched *Shingrix* in this older adult population. But we shouldn't forget, GSK has a 'flu franchise that has had a strong track record of successful execution and expansion in recent years and there are a number of similarities between 'flu and RSV from an epidemiological perspective.

The bottom line, an older adults vaccine for RSV represents a meaningful commercial opportunity with multi-billion dollar potential and we believe we have the opportunity to deliver a potentially first in class and best in class differentiated asset.

Now this belief is based on the knowledge we have about our adjuvant systems where it's delivered unprecedented efficacy in *Shingrix* for the same target population, so we are very excited to invest in the Phase 3 programme and we are on track with our plans to start early next year.

Maternal vaccination offers potential for broad protection from birth to 6 months

If I move to the maternal vaccine shown on slide 25, the burden of RSV is also really significant in infants and we believe the best way to protect them up to the age of six months, is through vaccination.

The opportunity here is the annual birth cohort, which is about four million in the US and millions of babies more around the world. A key point here is that children are almost guaranteed to get RSV by the age of two. It is the leading cause of hospitalisation in infants less than one year of age. The burden is most pronounced in the youngest of infants where half of hospitalisations occur in the first three months of life.

Our maternal vaccine candidate is designed for routine administration during the third trimester of pregnancy, to protect the infant by transferring maternal antibodies to protect from birth through the first six months of life.

Another benefit is that the mother may also be protected, which is good for her and potentially reduces the risk of transmission from mother to baby.

At GSK, we also have an existing portfolio of vaccines that are recommended for pregnant women, with our pertussis and flu vaccines. We estimate about half of mums-to-be in the US receive those recommended vaccines already, so there's a partially filled market in place and an opportunity to expand the market size.

Manu also highlighted that our RSV vaccines induce a polyclonal antibody response, which we believe could help address escaped mutant viruses, which is a benefit of our approach to preventing RSV infections, and by helping to protect infants from birth, this programme also really complements our paediatric RSV programme, designed for routine administration to help protect babies through to age two.

Our RSV assets offer a compelling opportunity for GSK

In summary, as we move to slide 26, we are pleased to share these data sets for two of our RSV candidate vaccines with you today and look forward to initiating our Phase 3 studies, with initial data expected for both of these large-scale programmes in the second half of 2022.

The study timings are best estimates and are dependent on how RSV infections circulate during pandemic lockdowns, but we will continue to keep you updated on the progress.

I want to finish by reminding you of the three key points I think we are making today.

First, I think the opportunity is clear. There are currently no vaccines for RSV and there is a significant market potential, in particular for older adults, but also to protect babies and children.

Second, at GSK we have the chance to introduce a first-in-class and potentially best-in-class older adults vaccine with our candidate, which includes our ASO1 adjuvant system to boost the immune response. We view that as a potential multi-billion dollar opportunity.

We are also competitive with our maternal vaccine, with the added advantage that we could add this to our existing portfolio of maternal vaccines for flu and pertussis.

Third, the data we shared are compelling for both our older adults and maternal vaccine candidates and with other data we have in-house, supports our decision to move to Phase 3 studies.

Finally, remember that if you add in our paediatric vaccines, we are the only company to be developing a vaccine to treat all of the at-risk populations for RSV.

To deliver our RSV portfolio we will continue to invest in our global manufacturing network that today already distributes almost two million doses per day, expanding capacity to deliver the potential for these priority assets.

With that, the team here are ready to take your questions, and I will hand back over to the operator to start the Q&A. Thanks very much.

Question & Answer Session

Geoffrey Porges (SVB Leerink): Thank you very much and I appreciate all the data and congratulations on the broad programme. A few questions, if I may.

First, what sort of efficacy do you believe is required in the different populations for approval of a vaccine against RSV and could you disclose your specific endpoints, primary and secondary, for the two Phase 3s that you have disclosed?

Secondly, could you just give us a little bit more information about what you know about the consistency of the immune responses across different genotypes or subgroups of

RSV, specifically the NA1, ON1, BA genotypes and it is a virus that has different forms circulating from year to year?

And then lastly, given the importance of the Pre-F3 protein structure, why not consider an mRNA vaccine in this situation, given the success that they appear to be having in COVID? Thank you.

Roger Connor: Thanks very much for the question. We are not going to disclose detail on our Phase 3 programme today, but maybe, Manu, you could take those questions in all three?

Emmanuel Hanon: Yes, so as Roger said, indeed I am sure you realise we have active discussions with the regulators to agree on the final design of our Phase 3, so I don't want to disclose exactly the level of efficacy but obviously we are targeting a high level of efficacy. We have definitely accumulated a lot of data that allows us to really target a high level of efficacy.

To your question related to different viruses circulating, yes, RSV is an RNA virus so it's a virus that can slightly evolve and this is the reason why it is so critical to target that virus with what we call a polyclonal response, so a response that targets multiple neutralising epitopes on the antibody side, but at the same time for the older adults using an adjuvant to boost T-cell immunity, we all know that T-cell immunity can be also highly cross-reactive, so this is definitely the strategy that we are pursuing and this is why we are favouring a polyclonal approach in terms of induction of immunity in the pregnant woman for the babies as well as older adults.

In terms of mRNA, you are totally right in saying that this is definitely a disruptive technology that can accelerate the very initial phase of progression into clinical development. Now, once you have reached a Phase 1 clinical development plan, your timings are really dependant on the design of the Phase 3 and the season that needs to be rolled out with the attack rate, so the technological advantage is less important here.

But I want to acknowledge, the mRNA technology is a very important technology and this is why GSK is heavily investing into that platform using actually two platforms, the self amplification messenger RNA platform, as well as the messenger RNA platform from CureVac.

I want to remind you that we are in reach of starting the Phase 3 while those that consider using mRNA against RSV are just starting.

Roger Connor: Thanks, Manu. Next question, please.

Jo Walton (Credit Suisse): Hello. I wonder if you could just tell us a bit more about your degree of confidence in carrying to six months in terms of efficacy on the maternal side and if you were to let's say give birth in April and you are in the Northern Hemisphere so you have the summer, it's really only months, say, seven to 12 that you are going to experience the RSV. Are you confident that you will have your paediatric vaccine in place for that timepoint?

And I just wonder if you could explain a little bit more again why you think a vaccine approach is better than a mAb approach in the maternal space.

Roger Connor: Maybe I'll start with the comparison to MABs and, Manu, you can take the six months question as well.

I think there are a number of factors to think about. First of all, vaccines have been a proven method of protection at scale as well as at start. From a maternal immunisation, GSK knows and understands maternal immunisation and this is a well-established method that utilises that natural transmission of antibodies to the baby, so I think making sure that we make the most of the already understood methods of transmission where we use it for 'flu and pertussis are very, very important.

I think Manu mentioned it as well. A vaccine does potentially protect the mother as well and that can help in terms of reduced transmission, and this is important between transmission potentially of RSV from mother to the child as well. Although Manu just mentioned it, I think this polyclonal point is important.

We know that this antigen has been designed in this way to ensure that we get that polyclonal protection and that has the potential to reduce this risk of those escape mutant viruses which does give us that potential for benefit over monoclonal, so I thought I would point that out.

Manu, on the duration of protection.

Emmanuel Hanon: Yes, so it is very clear that we will definitely measure in our Phase 3 efficacy duration of six months, so the data needs to be generated, but when we are looking at the fold increase we have combined up to 14-fold increase with the selective dosage, we think, actually, we have pretty good margin versus the previous minimalistic benchmark that was reported in the previous year.

I am not going to repeat the comparison between monoclonal and polyclonal, but I think this is really important.

Finally, I also want to insist on the notion that if we, in terms of positioning, are going to do the combination of maternal and paediatric vaccine that would really ensure the

protection up to two years, because, actually, there is still 50% of the medical need that needs to be addressed after six months, and this is actually the proposal we have with the paediatric vaccine and an active immunisation.

Roger Connor: Thanks, Manu.

Jo Walton: Can I please just clarify your manufacturing capacity comment? In fact two of them. I believe you said was it that you could make a billion doses of the adjuvant from a COVID perspective? Then, could you clarify what sort of capacity you would have for RSV, given that, presumably, if you are getting data in 2021 and 2022 you could need this in a relative short timeframe?

Roger Connor: Yes, a great question. I think it is, just to clarify, one billion doses of our adjuvant available manufactured in 2021, so that is of the ASO3 adjuvant, and then for the capacity to support RSV, I won't give you the specific capacity number, but we are investing to support the significant ambition that we have for the vaccines.

Tim Anderson (Wolfe Research): Hi, I have two questions, please. I am wondering how your trial powering and timing takes into account COVID dynamics? You note on Slide 26 that the timelines for readout depends on RSV infection circulation rates during the pandemic, so are you benchmarking against past infection rates that would not have been influenced by COVID, or has there been an adjustment made based on the best guess of what the impact of COVID could be?

Then, the second question, with both vaccines, you say "initial data expected in the second half of 2022", that seems to suggest maybe that there will be some final data available at some later point, and I am wondering if regulatory filings can be done on that initial data, or is it going to be based on some later data. If it is the latter, what is that later data and what will be the filing timeline for the vaccines?

Roger Connor: Tim, thank you. Manu, maybe if you take both of those.

Emmanuel Hanon: Yes, thanks. It is very true that nowadays COVID-19, and it is a well-known phenomenon when there is a pandemic actually it occupies the space, and the attack rate of other viruses can go down, and it is actually what is today being monitored in the field, so first of all, this is something we are actively monitoring very, very closely to understand what is going to be the evolution.

The second point is that, yes, obviously, both for the maternal and the older adult trials, we have been working on assumptions adapted to the current knowledge we have on

what could become the attack rate in the future, taking into consideration COVID-19, so, clearly, that has been taken into consideration.

Thirdly, when we speak about initial data for the second half of 2022, this is definitely in the context of leveraging this data for a regulatory move. It is not an additional set of data of interest, but we will see you two years later with the rest of the data – no, that is not that.

Roger Connor: Post that datapoint, we will be assuming positive outcome and move through registration regulatory process.

Emmanuel Hanon: Exactly.

Andrew Baum (Citi): Thank you, three questions, please. Firstly, could you talk to how you perceive the benefit of cellular immunity, both for your COVID vaccine but also for your RSV elderly vaccine? My recollection is that even adjuvated protein subunit vaccines don't elicit effective CD8 responses. Is that the concern here?

Second, on manufacturing in relation to the RSV vaccine, how have you changed your mindset in terms of scale-up given your experience with *Shingrix* where obviously demand significantly exceeds capacity? I am just trying to gage and put some context around the earlier comments.

And then finally in relation to your COVID-19 vaccine, could you clarify whether this will be a one shot or two shot vaccine? Many thanks.

Roger Connor: Thanks, Andrew. Manu, why don't you take the first T-cell question?

Emmanuel Hanon: Yes. As I explained during the presentation, because of the let's say unprecedented investment we have been doing in adjuvant platforms over the last 20 years, we have acquired a lot of knowledge on the way we measure T-cell immunity.

What does it mean, a specific increase? I can definitely relate to we actually made exactly the same learning for *Shingrix*. With *Shingrix* we were measuring 15 years ago antibody response and T-cell immunity, and realised that with the adjuvant we were able to actually impact the T-cell immunity and we went directly into Phase 3, as you know, translating into very high levels of efficacy. T-cell immunity in most of the viral infections plays a really important role.

You are totally right mentioning CD4, CD8 T-cells. Going back to *Shingrix*, the *Shingrix* vaccine does not induce any CD8 T-cells, it actually mainly impacts the CD4 T-cell component and it is exactly the same that we observed for the RSV older adults vaccine.

Finally on the T-cell response, I would again point out the observation that we have consistently made between respiratory viruses where in older adults, both for influenza and now for RSV, you can see that the T-cell immunity is significantly lower than what you observe in young adults. That is actually what we think really, that with the use of adjuvant and with the ability to restore the T-cell immunity to levels that are comparable to young adults, we are able, like for *Shingrix* actually, to get again an efficient response able to control the virus in combination.

Andrew Baum: You are just talking about CD4, right? You are not seeing any effect on CD8, correct?

Emmanuel Hanon: Yes.

Roger Connor: I'll take the next question, Manu, which is on the manufacturing scale-up. Because of the significant opportunity we are seeing, we are already working on that manufacturing scale-up plan and will be investing to support the asset.

One thing to understand is that this is a subunit vaccine which is a platform manufacturing process for us, so we are not starting from scratch as well, so we are able to scale up what we already have, but as I mentioned, we are going to be investing behind this asset because we believe it is a significant opportunity for us.

On the COVID vaccine, our belief is that our partnership for this is most likely to be a two dose vaccine. The data will obviously show that but our working assumption is that it would be two dose. Obviously the AS03 plays a very important role in these vaccines from a dose sparing perspective in terms of reducing that dose and hopefully the data will show the impact that it has both on the at-risk populations, but then hopefully as well on duration of protection as well, but our starting assumption is two dose.

Thanks, Andrew. Maybe we could move on to the next question.

James Gordon (JP Morgan): Hello, thanks for taking the questions – James Gordon from JP Morgan. Two questions please.

Firstly, can you contrast the RSV vaccine for maternal and the older adults population products to the respective Pfizer and J&J products, any important differences there?

And the second question on the older adults product. Ultimately if it is successful, would that be something that you could try and administer alongside *Shingrix* and would you

then have to develop a different combo because presumably you can't give two adjuvanted products at the same time, so you would have to phase it out or could you ultimately come up with some sort of combo product?

Roger Connor: Manu, do you want to start with the comparison with Pfizer and J&J?

Emmanuel Hanon: Pfizer has developed an antigen that is categorised in the same place as the GSK antigen. It is a prefusion conformation antigen. Pfizer has been recently communicating on their maternal vaccine. They also have an older adults vaccine, presumably using the same antigen but there is less information available on that so I cannot say more.

J&J is following a completely different strategy. They use a adenovirus vector vaccine to immunise individuals against RSV, so it's a very different technology. We have not done systematic comparisons between what they do and what we are doing. What I can say is that we are pretty confident in the results that we have obtained, on the consistency, the quality and the quantity of both antibodies and T-cell immunity.

Whether we could combine the vaccine with *Shingrix*, that's possible. This needs to be potentially included in future life cycle management opportunities, but I cannot comment more at this stage.

Roger Connor: I think one thing that having *Shingrix* on the market gives us is that obviously a very strong understanding of the older adult vaccination market, the channels associated with those. I think it's too soon to tell whether co-administration with *Shingrix* would be appropriate for RSV. As Manu mentioned that is something that we could look at, but we do think one of the differentiating factors here for GSK's RSV older adult vaccine is not just the adjuvant but also our knowledge of that older adult space as well,

The other point I would make when comparing the GSK maternal RSV to competitor activity is this point on portfolio should not be missed. Our maternal understanding is very high, we know this space, we have trusted vaccines in this space as well, and we know again the populations through which we would administer, so I think that's a significant benefit for GSK's portfolio here to add benefit to both vaccines that we're talking about.

Laura Sutcliffe (UBS): I was just wondering if you could share your thoughts on the timeline and maybe probability of success for your vaccine in older infants – do you think it's more challenging than the maternal and older adults? Thank you.

Emmanuel Hanon: On the success of the paediatric vaccine. First of all, this is one of the most challenging areas as 50 years ago active immunisation in children unfortunately led to, let's say, a completely opposite outcome of what you want to do with a vaccine, so we need to progress extremely carefully.

The vaccine that GSK has been developing is now being accessed in RSV seronegative children, which is the ultimate target population. I think we are among the first doing that, and we will soon actually collect internally the data out of this investigation.

The probability of success of that asset remains at this stage low, but I want to say at the same time that all the pre-clinical investigations, including challenge trials, that we will do in a calf model, which is actually extremely close to the human situation, gave us extremely positive results, which give us hope that we can not only protect the first six months of life of these children with polyclonal passive immunisation, but we can expand beyond two years with this active immunisation.

Louise Pearson (Redburn): I have a question for Manu, and apologies if I missed it. Just on the adjuvant, could you just elaborate on the difference between the B and E formulations, what is it that makes E potentially more tolerable than B, and if these changes might sacrifice some of the adjuvant effects that were so powerful with *Shingrix*?

Emmanuel Hanon: AS01_B is the adjuvant that is used for *Shingrix*, AS01_E is a lower dose of adjuvant, it's actually a 50% dosage of adjuvant, it's actually the same adjuvant that we have been using in other programmes. It is definitely optimised in terms of tolerability, without actually losing the impact that it can have both on antibody response as well as in T-cell immunity, but it's clear that AS01 is slightly more powerful. We actually get already a lot of the T-cell benefits by using the AS01_E adjuvant, but at the end it's exactly the same composition, it's simply half the strength, and I think it's important to mention that as we have already exposed 20 million people with AS01_B so we are pretty comfortable on the safety database of this adjuvant.

Graham Parry (Bank of America): First question, on the older adults vaccine: will you generate any data on reduction in hospitalisation or mortality prior to the outcome of the Phase 2 data in 2022, is there any chance of getting any of that data out of the Phase 2? Similarly, in terms of duration of response, timing of boosters, etc., do you think you will have that ahead of the Phase 3 data, or is that going to require longer-term follow-up post the 2H '22 readout for the older adults?

Then, on the paediatric vaccine, can you just help us understand your thought process on timing from move to Phase 3 for that, what the hurdle is to move Phase 3? You are in Phase 1/2 in seronegative infants at the moment. Is that going to be sufficient data for a pivotal trial?

The rationale, if you could explain it there, so using AAV and the not pre-fusion design that you are using in the other vaccines? Thank you.

Roger Connor: Manu, are you okay to take this?

Emmanuel Hanon: Yes, so, again, I am not going to disclose the Phase 3 protocol, but it is very clear that we are going to target the impact of the vaccine on the low at risk that we track infection RSV, so we are not going to go after the mild symptoms of RSV, we are going to go after the severe symptoms, and there is obviously primary endpoint and secondary endpoint that will collect the kind of severities such as hospitalisation as you just mentioned.

We believe it is really important as the cost effectiveness assessment of the vaccine, and it is absolutely this kind of data.

I hope I captured all of the question. There was a second question around the paediatric vaccine and the reason why we selected this one instead of using the pre-F.

One of the findings that we made in actually 20 years of research in that specific field is that to actively immunise children against RSV to beyond the protection controlled by the mother, you absolutely need to prime T-cells. There were different approaches that were possible and we found, actually, that the one that was the most effective in that specific age group and that specific population was with using an adenovirus vector that is able not only to induce T-cell response as well as antibody response, and so the question was what was going to be the next step? As I see it, we will collect internally really important data either by the end of this year or early next year, and this definitely will be a critical readout conditioning the next steps for the asset.

Roger Connor: Yes, and Graham, I think your middle question was on the duration of response of the older adults, is that right?

Graham Parry: Yes, exactly. When will you know duration of response and timing of boosters?

Emmanuel Hanon: On that, basically, we need to keep all the options open with that vaccine, so, obviously, our pivotal Phase 3 efficacy is going to assess the efficacy, the safety and the duration of protection.

At the same time, we will also do the same on the immune response with obviously a vaccination, and so on, but, we are speaking here again about the Phase 3 protocol design, and so on, so we don't want to provide more information at this stage, but we will come back to you as soon as we can.

Roger Connor: Graham, thank you. Maybe one last question.

Seamus Fernandez (Guggenheim Securities): Thanks very much for the question. Just a couple of questions on the market opportunity and the level of efficacy that you believe needs to be demonstrated in the adult-type population? We have seen in the adult population the utilisation risk parameters that tend not to make for very successful market opportunity, so I am just wondering what the regulators, more so, the government regulators like the ACIP are likely to be looking for in an adult vaccine to achieve the \$1 to 2 billion market opportunity that you are talking about?

Then, as a follow-up question, with regards to your CoV-2 strategy, you have collaborated on a CoV-2 vaccine with your adjuvant, but also have the antibody effort alongside Vir. Why not have a similar type of dual approach? It just seems like with a monoclonal antibody, especially one that targets the conserved epitope, you could actually have a more targeted coverage of a paediatric patient population and potentially be easier for governments to reimburse, so just trying to get a better sense of that. Thanks.

Emmanuel Hanon: For the first question - you would have to remind me the second question - so for the first question, very clear, but again I'm not going to disclose to you the level of efficacy we are targeting, but it's definitely in the upper quartile that we are targeting. It's very clear also that we are going to monitor the impact of the vaccine on the severe symptoms and consequence of the infection, such as hospitalisation and possibly death, but in a Phase 3 of this design it's unlikely we would be able to show a difference in deaths, but potentially post-marketing commitment might allow us to generate that.

We obviously also evaluate the efficacy of the vaccine for all the population that is at risk of developing severe infection. Taking the example of COPD patients, or people treated with immunosuppressive drugs, I want to remind everybody that *Shingrix*, we just got the approval in Europe for its use in immune-compromised patients because again, thanks to the adjuvant and the impact on T-cell immunity, it has the ability really to confer a high level of protection, even in these people that have a fragile immune response.

Roger Connor: I just want to clarify, your last question was why are you only going after vaccines and not after a mAb also for RSV, is that correct?

Seamus Fernandez: Yes, you chose a certain strategy with CoV-2, which is a bit broader, maybe it's just we were going after hospitalised patients with Vir more so than prevention, but it does seem like a prevention strategy can perhaps offer a more obvious economic return to the governments that are going to be likely paying for it significantly around the globe, so it's just more a question of that choice.

Emmanuel Hanon: First of all, I want to remind everybody, GSK strategy actually is both. We have a vaccine strategy for prevention, and to vaccinate the mass population, but there is also a monoclonal antibody that is being actually in Phase 3 today, in partnership with the Vir company, and that specific monoclonal antibody is being accessed in therapeutic settings, and I think, but maybe Hal can complete, potentially some prophylactic setting also.

Roger Connor: I think your question, Seamus, is about RSV though, isn't it?
[Confirmed]

I think this is choice, and it's really around where we think we can make the biggest difference. I won't go back through what we believe the differentiating factors are versus mAbs, but again, in maternal where we have the strength and this knowledge and an established method of delivery, we really believe in it. A key point is that vaccination through maternal protects the baby from day zero, from the moment of birth there is protection, we think that's not fully understood yet, and that could actually be an important differentiator as well.

Hal, is there anything you want to add on that particular question?

Hal Barron: I'll just maybe add a couple of things very quickly, I know we're out of time, but I think the difference to some extent reflects the fact that there are a lot of unknowns with COVID. The first point is that we're already starting to see evidence of resistance, and one of the things that made the Vir antibody so unique was that it was found from reverse translation of the B cells from patients who were infected with the SARS CoV-1, and by identifying antibodies that would be both protective of that and COVID-19, we believed, and pre-clinical data supports this, that the antibody would be binding an epitope that was highly conserved. I think when you have the situation where there's fitness advantages from different mutations, the polyclonal spot response may be enough but we are already seeing resistance, so we're excited about the Vir antibody from that perspective. As you said, the other big difference is treatment of infected patients is a real opportunity for patients who were an antibody candidate, a unique thing from Vir, so those are the two rationales for doing that work.

Roger Connor: Seamus, thank you for the questions. I think we are over time, folks. I know that there are more questions – if you can email those in through the IR team, we will make sure that we get back to you. We hope you have enjoyed this session and you have a sense of our enthusiasm and excitement for this, we think, potentially very important set of vaccines.

Enjoy the rest of your day. Take care, and thanks very much.

[Ends]