

**GLAXOSMITHKLINE
INVESTOR SCIENCE EVENT**

**GETTING AHEAD OF RESPIRATORY SYNCYTIAL
VIRUS DISEASE IN OLDER ADULTS
19-23 October 2022, Washington DC**

Friday, 21 October 2022

Jeff McLaughlin: Good afternoon and good morning, welcome to GSK's Investor Science Event, 'Getting Ahead of RSV Disease in Older Adults'. I am Jeff McLaughlin from the IR team and your moderator for today's call. We are here today for an update from the IDWeek 2022 Conference, on GSK's vaccine portfolio, of which the highlight is the pivotal Phase III data, on our vaccine candidate for the prevention of RSV in older adults. As usual, the presentation materials are available on GSK.com and were sent to our distribution list earlier today. Please also note that the data presented on today's call are available on the IDWeek website and have been submitted for publication in a peer review scientific journal.

Cautionary statement regarding forward-looking statements

Moving to slide 2, I want to remind you all of the usual cautionary statement regarding forward-looking statements.

Speakers

We are joined today by Dr Tony Wood, Chief Scientific Officer; Dr Phil Dormitzer, Global Head of Vaccines R&D; Roger Connor, President of Vaccines and Global Health, and Luke Miels, Chief Commercial Officer. We are also delighted to welcome Dr Michael Ison, Professor of Medicine and Surgery at Northwestern Medicine. Dr Ison is a lead investigator for the 006 Phase III trial in GSK's RSV vaccine candidate in older adults, and presented the detailed results of this important study yesterday at the IDWeek conference.

Why we're here - Agenda

Slide 4 shows our agenda for today's call, which we anticipate will last around 75 minutes. We shall try to ensure that we take as many other questions as possible in the Q&A session and, in that spirit, we would ask that you limit yourself to one question. You can always jump back in the queue if you have additional questions. As a reminder, questions can be asked via telephone by using *1.

Before I hand over to today's presenters, I would like to remind you that the call is being recorded and that a replay and transcript will be available after the event. With that, I shall now hand over to Tony.

Innovation leadership in vaccines

Dr Tony Wood (Chief Scientific Officer): Thank you, Jeff, and hello everyone. It is a pleasure to be here with you on today's call. Please turn to slide 6.

A new biopharma company

This is my first Investor Science event as Chief Scientific Officer of GSK and it is the company's first event of this type since the demerger of Haleon in July. Therefore, I hope you will forgive me for setting out a quick reminder that GSK is a global biopharma company with the ambition and purpose to unite science, technology and talent to get ahead of disease together.

Our R&D efforts remain focused on the science of the immune system, human genetics and advance technologies, with an emphasis on developing novel specialty medicines and vaccines.

Innovation in vaccines

As Roger will discuss later, GSK has a long, proud history of developing innovation in vaccines stretching back many decades. The ground-breaking data presented at IDWeek continue this tradition of innovation and excellence. The pivotal Phase III data on our novel RSV vaccine candidate in older adults demonstrates, we believe, a best-in-class profile.

It is important to recognize the significance of these data, as the industry has been trying unsuccessfully to develop an effective vaccine for more than 60 years. This represents the first clear demonstration to reduce the risk from this serious disease.

In addition to pivotal data, you will hear tomorrow the results of the key study in which our RSV vaccine candidate was co-administered with an influenza vaccine in older adults. It is important in this population to be able to safely co-administer vaccines for 'flu and RSV. There are clear attractions in doing so when addressing two of the most serious respiratory pathogens in terms of disease burden.

I would also like to highlight the latest data on our herpes zoster vaccine *Shingrix*. This is, again, completely ground-breaking. It shows that the duration of protection against shingles can extend to 10 years. With efficacy approaching 90% at this timepoint, this is

tremendous news for people affected by shingles and its devastating effect. It also sets a new Gold Standard which we believe will be incredibly difficult to match.

RSV data: the highlight of strong year of RSV vaccines R&D delivery

There is no doubt that the pivotal results are a key highlight for our Vaccines R&D organisation in 2022. However, I do want to draw your attention to the strong progress GSK is making elsewhere in strengthening its vaccines and pipeline capabilities. It has accomplished several important regulatory approvals and an advanced number of novel vaccines, including our mRNA candidates for influenza and COVID, and a therapeutic vaccine candidate against herpes simplex. We also expect the late stage read-out from our pentavalent meningococcal vaccine candidate before the end of the year.

Last but not least, we recently added to our platform capabilities as well as our pneumococcal pipeline through the acquisition of Affinivax. The novel disruptive MAPS technology we acquired will allow us to pursue higher valency vaccines than is possible with conventional conjugation technology. This, in turn, enables us to investigate vaccine candidates with broader serotype coverage, which may significantly improve the potential for pneumococcal and other bacterial vaccines.

RSV program leveraged unique vaccines R&D capability

Looking more broadly at the successful execution of our RSV program in older adults, I truly believe this is a testimony to the unique capabilities we possess within GSK and the synergies from our focus on vaccines and specialty medicines. No other biopharma company replicates our dedicated approach towards the science of the immune system for the prevention and treatment of disease, our leadership in infectious diseases, our one capital allocation approach and one Development organisation and our incredible suite of platform technologies.

As a consequence - and Phil will expand on this point - we are able to select the right candidates and the right technologies, leveraging our expertise in adjuvants for older adults from our *Shingrix* heritage. Having the right candidate alone is not enough in a competitive environment of course, and here our excellence in clinical trial design and execution meant we were not just the first company to recruit patients into our Phase III study, but also our team accurately modelled RSV prevalence and anticipated infection rates which informed our recruitment strategy, the design and execution of the clinical trial program for the positive results observed during this interim analysis.

I am exceptionally proud of what our Vaccines R&D organisation has achieved in the battle against this serious viral pathogen and would now like to hand over to Phil to provide more details on how we designed and executed this program.

Phil, over to you.

Prevention of RSV in older adults

Dr Phil Dormitzer (Senior VP and Global Head, Vaccines R&D): Thank you, Tony, a pleasure to be on today's call. Please turn to Slide 11

Significant unmet medical need and disease burden

RSV is a very common contagious virus that causes respiratory disease. It scores the highest value in remaining unmet medical needs in infectious diseases. The risk of exposure, RSV is universal, we experience repeated infections through life. In developed countries RSV is associated with about 420,000 hospitalizations, 29,000 deaths per year and half of those arise in those 65 and older in the United States.

Older adults and those with underlying health conditions such as cardiovascular disease, respiratory disease and diabetes are at particularly high risk for severe disease. The consequence of this is a substantial clinical and economic burden on which Roger Connor will speak later.

The last and critical point is that natural immunity wanes which is behind the re-infections that occur throughout life.

Designing a potentially effective RSV vaccine for older adults

GSK is fortunate to have the broadest suite of vaccine platform technologies available and this allows us to select the right approach to develop the best vaccine for each pathogen, either virus or bacterium.

Now there are three key platform technologies among the large number that we have at our disposal. The first is subunits with or without adjuvant. Our adjuvant portfolio is a particular area of strength for GSK. Among the adjuvants, AS01, the adjuvant used in *Shingrix*, is being applied in a number of our pipeline assets. AS01 induces a more robust immune response. We believe it compensates for the waning of immunity with age and potentially allows increased efficacy.

A second key platform is mRNA where we are pursuing both advances in our collaboration with CureVac and our increasing internal mRNA capabilities.

Most recently, as Tony referred to, is our MAPS technology, MAPS standing for Multiple Antigen Presentation System, which is particularly useful for bacteria with key carbohydrate antigens. The MAPS technology allows for a more high multivalent approach for complex pathogens that have multiple serotypes.

Now in the case of RSV, we selected a protein with adjuvant approach particularly to deliver high efficacy in older adults in the presence of immunosenescence.

RSV candidate vaccine for older adults

How did we at GSK go about designing an effective vaccine after 60 years or more of unsuccessful attempts by the industry? Well, the vaccine candidate was intended to overcome the challenges of protecting against RSV in vulnerable older adults. It combines the RSV pre-fusion F3 surface antigen with a proven AS01 adjuvant.

Key to this was a scientific breakthrough from NIH when the pre-fusion structure of RSV was determined and enabled us to engineer the protein to stabilize it in the pre-fusion conformation, and we learned that much of the frustration of the previous 60 years was from the fact that the protein switched to an ineffective post-fusion form. Knowing the structure, it could be stabilized in the pre-fusion form which is much more effective at eliciting neutralizing antibodies.

The inclusion of AS01 has also proved to be a very effective adjuvant for another vaccine for older adults. This approach is unique and a combination has delivered exceptional efficacy.

Comprehensive clinical program targeted to adults at greatest risk

This slide sets out the accelerated clinical program for RSV vaccine candidates in older adults at greatest risk. Candidates entered the clinic in January 2019 and started a Phase III program in February 2021 and reported positive headline results for the pivotal 006 study in June 2022. This is a little over three years and, during that time, over 29,000 participants were involved in the study. This pace is remarkable and speaks to the excellence in clinical trial design and execution that Tony referred to. This is especially impressive, given that the pivotal trials took place against the backdrop of the COVID-19 pandemic.

There are three Phase III clinical studies, including the regulatory package. The pivotal 006 efficacy study, from which positive headline results were announced for a pre-specified interim analysis, will continue to examine the benefits of annual re-vaccination over three seasons and the additional re-vaccination will also look at the consequence of the single immunization as observed over multiple seasons.

The 004 study primarily examines safety, reactogenicity and immunogenicity. The 007 study examines whether the RSV vaccine candidate can be safely co-administered with a quadrivalent influenza vaccine. Those results will be presented tomorrow at IDWeek and this is particularly relevant when you consider the typical seasonal overlap of RSV and influenza viruses, and the practical consideration of administering vaccines against both these illnesses in the Fall.

The pivotal 006 study is obviously the main study of this call and it is my pleasure to hand over to our guest speaker, Dr Ison, principal investigator of the 006 study, to discuss the results in detail.

AReSVI-006 phase III results and potential impact

Dr Michael Ison (Professor of Medicine and Surgery, Northwestern medicine): Thank you, Phil. It is a great honor to share some of these results with you today, as I did yesterday, in a standing-room only room.

Methods: ongoing, phase 3, randomized, observer blind, placebo-controlled, multi-country study (NCT04886596)

Starting with slide 16, which shows you the clinical trial design of this study, the study was designed to enroll about 25,000 individuals. It would be randomized in a 1:1 fashion, to receive a single dose of the RSVPreF3 OA vaccine and follow them up over the following flu season. Blood was drawn at Day 31 to assess immunologic response. The study is ongoing into the subsequent two RSV seasons. This year, patients will be randomized again, to receive either a booster dose of the vaccine or placebo, to really assess the need for secondary boosting in subsequent seasons.

The primary endpoint of this study was vaccine efficacy of a single dose of the vaccine, in preventing RSV lower respiratory tract disease, in adults greater than 68 years of age, during the first RSV season. The criteria for success was to have a lower limit of the two-sided confidence interval for vaccine efficacy, greater than 20%.

In addition to the primary endpoint, there were a number of other secondary endpoints, including the vaccine efficacy against severe respiratory RSV, lower respiratory tract disease, RSV specific ARI – that is, acute respiratory illness. Then these primary and secondary endpoints in certain subgroups, including the protection against both RSV-A and RSV-B, protection in various age cohorts, protection in those patients with various baseline comorbidity and frailty status, as well as key safety and reactogenicity endpoints.

Results: demographic characteristics were similar between groups

Moving on to slide 17, this is a graphical representation of the enrolled patient population. To orientate you, the blue is the patients who received vaccines; grey is the population who received placebo. As you can see across all measures, the populations were well-balanced across the treatment and placebo groups. We had relatively low proportions of patients – 8.2% in both arms – that were greater than 80 and a relatively small percentage of patients, 1.5%, who were frail on enrolment.

Results: The primary endpoint (vaccine efficacy against RSV-LRTD) was demonstrated

On the next slide, slide 18, you can see the results of our current estimate for our primary endpoint, RSV-lower respiratory tract disease. The vaccine efficacy is estimated to be 82.6% overall, with seven cases of RSVPreF3 infection in the vaccine arm and 40 cases of greater infection in the placebo arm.

Results: A single dose of RSVPreF3 OA is highly efficacious against the full spectrum of RSV disease, from RSV-ARI to severe RSV-LRTD

Going on to slide 19, you can see our other key secondary endpoints. There was significant protection against RSV acute respiratory infection, with an estimate of 71.7%, as well as significant protection against severe RSV lower respiratory tract disease, with estimated vaccine efficacy of 94.1%.

Results: Consistently high VE was observed regardless of RSV subtype

Moving on to slide 20, this is where we look at the vaccine efficacy for both. On the top half, for RSV lower respiratory tract disease, and in the bottom half, for RSV-ARI between those patients who have greater infections with RSV-A or B.

As you can see, vaccine efficacy is consistent across the two subtypes for both of these primary and secondary endpoints.

Results: High VE against RSV-LRTD was seen across different age groups

This is where we look at the vaccine efficacy across age groups. Again, you can see excellent vaccine efficacy against RSV lower respiratory tract disease across the two larger age groups that we enrolled in the study.

In the population greater than 80, we had very few cases of break-through RSV in a relatively small population, and so we need to collect further data over subsequent years, to understand the true vaccine efficacy in these populations.

Results: Robust immune response to RSV-A and RSV-B regardless of age

On Slide 22, we have some important immunologic information that helps us feel comfortable that protection should be preserved in this older age population. A sub-set of patients had immunologic testing, looking for neutralizing antibodies. In blue, is at time of enrolment, green is in those patients, 31 days after their vaccine.

As you can see, you had excellent development of novel or increased boosting of neutralizing antibodies across all age groups, for both RSV-A and RSV-B.

Results: High VE against RSV-LRTD was observed in participants with pre-existing comorbidities and in pre-frail and fit participants

Moving on to slide 23, this is where we look at the estimated vaccine efficacy by comorbidity and frailty status. Again, we maintained excellent vaccine efficacy, particularly in those patients with one or more co-morbid conditions as well as excellent vaccine efficacy in those patients that were fit or pre-frail.

Much as with the older age population, those that were frail, represented a very small population and too few cases of greater infection to have a reliable estimate of vaccine efficacy. We will continue to follow these patients over subsequent years, which will better refine our information with regard to vaccine efficacy in this smaller subset.

Results: High VE against RSV-LRTD was observed over the median follow-up period of 6.7 months, supporting efficacy over the course of an RSV season

Moving on to slide 24, this is a critical set of curves that look at the protection of the vaccine over time. This seems to be maintained throughout the entire study period that we are reporting on. Today which is about 10 months of follow-up, for those patients who had the vaccine, low levels of greater infection are persistent throughout the entire study, suggesting protection over at least the first season.

Results: RSVPreF3 OA was well tolerated, and most solicited AEs were mild or moderate and resolved within the 4-day solicitation period (mean duration: 1-2 days)

Moving on to slide 25, this was our data on adverse events, and SAEs. On the top half, this is the adverse event profile of our safety subset of patients. As you can see, the expected effects of the vaccine was local pain at the injection site. Fatigue, headache and myalgias did occur, as the most common adverse events. These tended to be transient, and as you can tell from the color-coding, almost all of these events were either Grade 1 or Grade 2, so relatively mild.

Likewise, looking at other safety signals, there were no imbalances observed between the vaccine and placebo groups. In overall rates of SAEs, vaccine-related SAEs

were markers of immune-mediated disease or enhancement of greater infection with the vaccine.

Conclusions

To conclude, on slide 26, our vaccine in this study met the primary endpoint that we had designed in the protocol.

A single dose of RSVPreF3 OA vaccine, is highly efficacious in preventing RSV-acute respiratory infection, RSV-lower respiratory tract disease, and severe RS-lower respiratory tract disease, in adults greater than 60 years of age, over one RSV season.

Vaccine efficacy remained similar across both subtypes of RSV, RSV-A and B, and was consistently high in patients 60-69 and 70-79, in pre-frail adults and in those with comorbidities.

RSVPreF3 OA vaccine was well tolerated and had an acceptable safety profile.

The study is ongoing and will follow participants to evaluate both an annual need for revaccination and long-term protection over multiple RSV season.

Thanks for the opportunity to present, and I'll turn it back over to you, Phil.

What do these important data mean when addressing the burden of RSV disease? What do they mean for physicians and for older adults

Phi Dormitzer: Thank you, Dr Ison. If I may I'd like to ask you a few questions. First, and on the next slide, what do these important data mean when addressing the burden of RSV disease? In particular, what do they mean for physicians and for older adults?

Michael Ison: I think I'll focus on the older adults, because that is who our focus really needs to be on. Every single year, we see patients that get admitted to the hospital and suffer through RSV and some of them are dying. The ability to reduce the burden of disease at a level we are seeing in this study, and a relatively high rate of protection, really has the potential to markedly improve the quality and quantity of life for older adults. I think that, hopefully, this will represent a significant advance for the field, and a great opportunity to reduce morbidity and mortality in this at-risk population.

How did study investigators determine degree of severity of lower respiratory tract disease?

Phil Dormitzer: That's great! How did the study investigators determined the degree of severity of lower respiratory tract disease?

Michael Ison: The investigator, when they were seeing these patients, had to categorize patients based on the type of respiratory infection that they had. There were standardized definitions for the definition for severe lower respiratory tract infections. They had to have at least two lower respiratory signs, as well as evidence of severe disease in the clinician's assessment, or they had to be on therapies that would be reflective of severe disease such as supplemental oxygen, CPAP or mechanical ventilation in those patients who had tested positive for RSV by PCR.

Phil Dormitzer: That is helpful in understanding the study. Could you elaborate a little further on the rationale for the clinical study design, specifically with the endpoint focused on adults with comorbidities?

Michael Ison: As you highlighted in the introduction to this, older adults in general have a much higher rate of complications, progressive disease and death as a complication of RSV, even though all of us get RSV throughout our lives.

Among those who are over 60 years of age, those who have underlying comorbidities, particularly cardiovascular or pulmonary disease, diabetes as well as other underlying medical conditions, those who are immuno-compromised and those who are frail have the highest risk of having progressive disease and severe infection. Therefore, it makes sense to design a study that is really targeting the population who will get the greatest benefit from this intervention.

Phil Dormitzer: Thank you very much, Dr Ison, and I would now like to turn it over to Roger Connor.

Roger Connor (President Vaccines & Global Health): Thanks very much, Dr Ison, for a really clear and compelling presentation of the data and let me also add my welcome to everybody on today's call.

A long history of innovation leadership

Tony mentioned earlier on that at GSK we have a really long history of vaccine innovation, and we have built our leadership position over many years, developing and launching novel vaccines to address genuine unmet medical needs. Consequently, we now have the broadest vaccines portfolio in the industry. We supply 25 vaccines across 160 countries, with market-leading positions in multiple key categories that include pediatrics, meningitis and shingles.

We have a deep innovative pipeline of assets and, as Tony outlined earlier, our pivotal RSV data is a key highlight from a strong year of R&D delivery in vaccines. It is this

relentless innovation that really drives our growth and, with the help of more than 15 new product launches, our Vaccines business has grown sales at a 10% compounded annual growth rate since 2000. Over the period between 2021-2026, we expect to deliver a high single digit compound annual growth rate, excluding pandemic sales.

Data at IDWeek 2022 further strengthen GSK's vaccines position

The impressive data you have heard about today from Dr Dormitzer will further strengthen our vaccines business with a potential best-in-class profile. Our older adults RSV vaccine candidate looks set to further enhance our growing portfolio of vaccines to help those populations who, due to age and comorbidities, often face the most severe consequences from vaccine-preventable viruses.

Furthermore, if approved, our RSV older adults vaccine will be joining a family of vaccines portfolio that is already built around excellent efficacy. Just as a reminder, 90% of our portfolio by sales has an efficacy level of above 90%. That is an incredibly high bar that will protect us from potential disruption from new technologies.

While *Shingrix* is not the focus of today's call, the duration of protection is unprecedented and will, we believe, help us in our ambition to double sales by 2026. As a reminder, the commercial opportunity for this incredible vaccine is still very substantial, with roughly 100 million adults aged 50 and above in the US remaining unvaccinated against shingles and with our plans to expand our geographic roll-out to more than 35 countries by 2024.

Data offer potential best-in-class profile in the most vulnerable adults

Let me focus now on the market potential for RSV in older adults. It is important to realize that, when we think about who of those adults who are exposed to RSV are at the greatest risk of severe complications, namely hospitalization, death or serious long-term health consequences, the key risk factors are age and comorbidities. The elderly are inherently more susceptible to RSV infection and the risk among older patients is even higher among those with underlying health conditions, including cardiovascular disease, for example, congestive heart failure, or those with respiratory disease or diabetes.

Data from the CDC show that over 90% of adults hospitalized with RSV disease have underlying medical conditions, and around half have at least three conditions. The consequence of RSV infection is a substantial economic and societal burden. The direct medical cost of RSV-related hospitalizations in the US alone is estimated to be up to \$3 billion, and this figure does not take into account the cost of lost productivity or of the long-term health consequences among those discharged from hospital.

For example in a recent study of patients hospitalized with RSV, around 60% of those aged over 75 required home help services or additional care post-discharge.

As you have heard today, our vaccine candidate showed exceptional overall efficacy of well over 90% in the most vulnerable at-risk older adults, mainly in those with severe RSV and those with underlying comorbidities and in 70-79-year-olds.

These are the individuals that result in the greatest impact on healthcare costs and the magnitude and consistency of our results is why we believe our vaccine candidate offers a best-in-class profile in these vulnerable populations.

Given the sheer scale of the unmet need and our potential to positively impact the health and wellbeing of vulnerable adults, we are confident our vaccine represents a significant commercial opportunity for GSK with multi-billion pound *Shingrix*-like annual potential.

I will now hand over to Luke to wrap up our presentation today.

Luke Miels: Thanks, Roger, and I wanted to close now on Slide 34.

RSV OA vaccine candidate represents significant opportunity

Q4 2022: US FDA submission acceptance; EU regulatory submission

I am going to summarize what you've heard today and touch briefly on our plans to maximize the opportunity of this important potential new vaccine. We shared data that showed consistently high efficacy in the individuals who suffer most and have the greatest impact on healthcare cost, the magnitude of this result along with the consistent high efficacy shown across adults aged 70-79 and the A and B strains we think clearly demonstrates a best-in-class profile.

This is just the latest milestone in a long proud history of vaccine innovation for this company. You have heard about the unmet patient need and the health economic burden of RSV disease. This is why this common contagious virus has been in the sights of the industry for decades. You have also heard that our vaccine candidate was uniquely engineered to deliver efficacy in the most vulnerable patients and that is precisely what the data shows.

For these reasons we are convinced that our vaccine candidate represents a multi-billion market opportunity.

Right, that being said, what are the next steps and we will cover this more in Q&A. This quarter we expect to receive FDA acceptance of our regulatory submission and to

complete our filings in the EU and you may have seen just this morning we have announced that we have filed in Japan.

Looking into 2023, we are confident that we are on track for consideration at the critical ACIP meeting in June and we plan to launch in the US soon after, subject of course to FDA approval.

Our confidence level is such that we have already prepared the bulk of material for launch at risk so that we can fully meet the anticipated demand.

I want to reinforce that this is a novel, underdeveloped vaccine category in the older adult setting so it will be focused on appropriately raising awareness employing both our vaccine and long-standing respiratory expertise.

And then looking further ahead we will continue to seek to deepen the competitive profile of our vaccine through critical work on revaccination, multi-season protection, co-administration with other adult vaccinations and also other life cycle innovation initiatives.

In conclusion, this is an incredible potential new vaccine and these are exciting times for GSK Vaccines. With that, I would like to hand back over to Tony to moderate the Q&A session.

Question & Answer Session

Tony Wood: Thanks, Luke. I will moderate the Q&A. Operator, perhaps you could introduce the first question for us, please.

Richard Parkes (BNP Paribas): Thanks for taking my question. I am hoping you will allow me to squeeze in a quick clarification and then a question if that's okay.

The clarification is just can you help me understand the definition of lower respiratory tract disease that is in the back of the pack? It says 'At least two lower respiratory symptom signs for at least 24 hours, including at least one lower respiratory sign'. Could you just help us understand the difference between sign and symptom and that wording suggests there might be some cases where patients had two symptoms but weren't classified as having lower respiratory tract disease, so just a quick clarification there?

Then to the question hopefully for Dr Ison. I wondered if you might be able to help us with anything to help understand the likelihood of durability of protection. Is there anything

we can learn from durability of protection from re-infection, post-infection in the real world and what do we know about how RSV strains evolve over time and accumulate changes in the F3 surface protein that might predict how often patients need a revaccination?

Thanks very much.

Tony Wood: Thank you, Richard. Let me just repeat both of your questions, first the clarification and then on durability, and Dr Ison, if you don't mind I will go to you to answer both of those.

First of all, there is a request for clarification of signs and symptoms and then a broad question with many facets to it, Richard, on the nature of durability. Dr Ison, over to you.

Michael Ison: Yes, the first thing is clarification of what a sign and a symptom is. A symptom is something that a patient reports, a sign is something that usually the clinical team is assessing for, so that may be respiratory rate, it may be oxygen levels, or things like that. That is the differentiation between a sign and symptom, in the keenest definition.

All of these have some degree of subjectivity: there is the patient's perception and the clinician's perception. Signs are relatively firm but, again, there is sometimes some subjectivity to interpretation: is it low oxygen because they have underlying lung disease, or is this something new, based on the infection that they have? Usually, the clinician is taking other information and context. If the patient is known to them and they had normal pulse/ox before but now it is lower, that would be a reasonable sign for a lower respiratory tract infection. Again, while there is some degree of subjectivity that is different from person to person, the way that this definition is designed and has been used across a range of respiratory and viral infection is a relatively standard definition that is generally agreed upon.

Getting to the question, about re-vaccination and the need for that. It is the question I was asked the most yesterday, and the question everyone wants to have answered, that is why we have the study design as it is. We are going to need to see what the data in subsequent seasons show, and from the data that comes from second randomization, where some people have a second season dose and some don't, to see if that changes the vaccine efficacy. I think this is the data that we need to really make that decision about whether or not we need to vaccinate on an annual basis or on a broader range.

Getting to the second part of that question, which is how much does RSV change over time, there are a couple of things that typically occur with RSV. There is this cyclic change in prevalent RSV every year. Textbooks say that it alternates, for one year RSV-A and then RSV-B in the second year. We have just completed a study with 10 years' worth of

data in Northwestern for all of the patients admitted to the hospital there, and found that, over the 10 years, we saw a cycle that was A, a hybrid season with both, and then a subsequent season with three, so it was an every three-year cycle instead of the classic every two-year cycle. That is part of the driver. We know that patients have waning immunity after infection: they have an antibody level that recedes over time, naturally, and this is part of the reason why it is thought that there is re-emergence of infection in previously exposed patients.

There is change in the fusion protein over time and that change currently is relatively low and so probably will not require the same degree of updating as we see with influenza vaccine. That being said, like everything, we will have to wait and see. Once we introduce a vaccine in a broad segment of the population does this drive further change in the virus? Again, in time, future studies will inform the need for updating of the vaccine and changing the frequency of re-dosing.

Tony Wood: Thank you, Dr Ison, for that comprehensive answer.

Evan Wang (Guggenheim Securities): Thank you for taking my question. Following on with the topic of durability, when do you expect to see essential data that will answer that question? Is that likely to be before the June 2023 ACIP?

Similar to that, in terms of whether we have seen durability across two or three seasons, are there any experiences, internally or externally, that will support the timeframe that will see potential waning or protection? Thank you.

Tony Wood: Thank you, Evan. Those are two questions again, that I will repeat. Phil, if you wouldn't mind, I would like you to start on answering those. The first question was related to the collection of durability data and, in particular, in the context of what we might know in time for the June 2023 ACIP.

The second one was about the dynamics of the immunological response and what we might conclude from that as regards longer-term vaccine efficacy. Could you start, please?

Phil Dormitzer: Sure. Although the timing will be tight to get this for the second season before the ACIP, it is a goal and it could be possible. It is tight, but the team has shown what they can do, so that is what we intend to do.

We do have data on the greater durability of the immune response than we do at this point on the duration of efficacy. What we see from the 004 study is that we do not go back down to baseline at the end of 12 months. Exactly what that will translate to in terms of

efficacy, we will have to determine by the study, because we do not have a clear immunological code of protection. We are hopeful that there could be something but we really have to see what the data tell us.

Tony Wood: Thank you, Phil. I suggest we move on to another question now, please.

Michael Leuchten (UBS): I want to go back to your commentary about best-in-class profile. The ACIP working group contrasted and compared your agent with the competitor one and I guess their conclusion is perhaps less clear on which one is better. I wonder what datapoint you would point to where you think you are clearly differentiated, both in terms of efficacy and tolerability? I notice that the infection site reactions seem to be a little higher for you than perhaps for the competitor.

Tony Wood: Thank you, Michael, so a question relating to differentiation in the context of the ACIP discussion yesterday. I might start answering that question by going to Phil.

Phil Dormitzer: First, it is challenging to compare directly the numbers that come from different studies, so there are limitations to what we have. What I can say about the GSK vaccine profile is that it really does show not only very high efficacy but a great consistency across the sub-groups, whether it be different levels of disease severity, RSV A and B, or those with and without comorbidities. That gives us high confidence in the exceptional profile that we believe to be best-in-class.

An important comment on the reactogenicity is, first, that it is predominantly mild to moderate and transient. Certainly, compared to the consequences of RSV disease, a reactogenicity that is mild-to-moderate is a small price to pay for what is really exceptional efficacy.

The other point I would make is that we need to make a very clear distinction between reactogenicity, which is expected after many immunizations and is commonly found after immunization, and safety. What we have is some mild to moderate reactogenicity and the safety profile is excellent.

Tony Wood: Thanks, Phil, and perhaps, Luke, if you don't mind, I might go to you to ask for any thoughts on how the profile that Phil has described might work through to your commercial thinking?

Luke Miels: I shall try to keep this practical but, hopefully, in a scientifically fluent way. Based on what we know today, I would rather have our dataset than theirs. Phil

has made the point around the consistent, tightly-bound nature, the robust activity in high groups like 70-79 years and in groups with comorbidities. Again, operationally, when you look at those side-effects and at the percentages, it can be misleading but, if you break it down as was done on slide 25, these are very small and manageable rates based on our experience with *Shingrix*.

The other element that is intriguing is that COVID has upregulated individuals' understanding, both of physicians and patients, of the consequences of respiratory infections in people with comorbidities, such as heart failure, diabetes, etc. This group is primed to be more aware and more sensitive, and our market research is very clear that these people will be naturally biased to efficacy, because of their concerns around underlying disease, and our market research is very clear that this profile is compelling. Therefore, net-net, these are all elements which support the statement of a best-in-class profile.

Tony Wood: Thank you, Luke.

Phil Dormitzer: I would like to make one additional point. At the ACIP some of the co-administration data, there was a presentation at IDWeek that ideally covers these data. The non-inferior influenza vaccine responses in co-administration with the RSV vaccines presented at the ACIP, it could also be a very important factor given the likelihood that it will be desirable to have a schedule by which you might give both vaccines at one visit rather than requiring two visits, one for RSV immunization and one for influenza.

Luke Miels: Phil, I would also add that, if you contrast it with what some of the other vaccines such as Prevnar have in terms of retail utilization, our expectation is that around two-thirds to three-quarters of shots given will be given in a retail setting. Prevnar is about 7%, Fluzone is about half, *Shingrix*, as you know very well, is 55-60%, so these considerations are material in that setting.

Tony Wood: Thank you both for a very informative dialogue in answering that question. Shall we move on to the next question?

Graham Parry (Bank of America): Thanks for taking the questions and thanks for doing the call today as well. I just want to follow up on the ACIP Working Group commentary, your points you made to some of the questions they raised.

They seemed to bracket the vaccine primary efficacy endpoint of 83% within the range of a 67-86% from Pfizer as well. They didn't sort of break out their 86% as being in line with your 94% more severe disease, so do you think that's how the market will view the efficacy broadly, so less differentiation than perhaps previously thought?

But also at ACIP they suggested they would like to see data on the same endpoint basis just given the difference in the vaccine endpoint, so is that an analysis that can be performed, so can you actually go through your existing data in order to generate that, so could we see a same endpoint at an ACIP meeting next year for example?

And then they also criticized the low recruitment into older cohorts of both yours and Pfizer's vaccine. Obviously you have the statistically significant data in the 70-79 but neither of you has enough events in the over eighties where the hospitalization rate is significantly higher, so could you actually need more data there and could it be a sort of staggered age recommendation across narrower age cohorts to start off with, and then expand over time as you get additional age cohort data? Thanks for that.

Tony Wood: Okay, Graham, thank you. Again, quite a lot there. Let's return to both components of it. In your first question you are re-asking the question with regard to endpoints and in particular highlighting the ACIP Working Group table that made comparisons against both. Perhaps this time, Phil, I might ask you to comment on that and perhaps in the context of the broader dataset.

And then we will return to the question on recruitment, or low recruitment in the 80-year old. I will come back to that after we have heard an answer on the endpoint comparison, so Phil, why don't you start on the endpoints and I will make sure we return to the 80-plus category and perhaps for that, Dr Ison, I will come to you first.

Michael Ison: I think that one of the challenges is the older age population is hard to recruit into studies overall. I have been working on studies of prevention and treatment of respiratory viruses where the older age population consistently is the population that has the highest risk of complications, but it's the hardest to enroll in studies and particularly the ones you really want to enroll are those that are frail, have underlying comorbidities and are significantly older. These are the people that can't get out of their home or nursing home very easily and it's hard for them to become involved in clinical trials.

Part of the reason why I am making this point is, not only is it hard to actually enroll, I think that both regulators and groups like ACIP recognize that it is challenging to study those populations and given other markers of protection in other populations, particularly with safety which would be expected from the data presented across each group that they would allow this to be used in those older adults while additional data is being collected.

That I think is going to be the way to think about this to understand some of the challenges. For the comparative issues I'll turn over to Phil to finish up.

Phil Dormitzer: Sure. There were a couple of questions asked on the comparative issue. One is can we expect that we are all going to have the same case definition in the latter part study and there is no standard definition for either the lower respiratory tract disease or for the variants, and of course we have to prespecify what our definition is, so while we all have our definitions approved by FDA, we can't in the study change the definition because then we would have to lose the ability to compare the second season to the first season.

As an alternative to that, we have to look at the overall pattern that we see. One result I believe I could highlight is not just the very high efficacy that we see in the more severe disease, but the fact that even with acute respiratory illness, which includes relatively mild illness and upper respiratory illness as well as lower respiratory illness and which has conventionally been thought of as relatively difficult to protect against, we also see very strong efficacy.

I think that the degree of strong efficacy that we see across different categories of illness suggests that this is not just a matter of specific acute definition, that we have seen a very broad pattern of very strong efficacy from the GSK vaccine.

Tony Wood: Thank you, Phil. Let's move on to another question, please.

Peter Welford (Jefferies): Thank you for taking my question. If I could go back to the safety comment and the point that was made by Luke, I wonder if, when you talk about what you saw with the reactogenicity, could you put what you see in the RSV trial in context for us versus what you see with for example, Fluzone, *Shingrix* and some of the other vaccines? That is just to help us understand where it lies when we think about what we are seeing in this study.

Do we have any data yet on actually preventing hospitalizations, CPAP use, supplemental oxygen? I guess those would be hard endpoints, if you like, that could go to payers as well, to convince them that this vaccine actually is also preventing those costly potential endpoints for the elderly. Thank you.

Tony Wood: Thank you. Phil, I will ask you to comment on the reactogenicity question, particularly in the context of the experience with other commonly used adult vaccines first. Then we will move on and perhaps Dr Ison could comment on the question regarding CPAP or hospitalization data, and what we are learning there.

Phil, please: reactogenicity, relative to other well-established adult vaccines.

Phil Dormitzer: Although precise class comparisons are challenging, because of differences in the way that reactogenicity is studied, what we can say with confidence is that the reactogenicity that we see with this vaccine is well within the range of reactogenicity that we see with commonly used vaccines for diseases in older adults. I think we are confident that we are in a range where this should not have an impact on uptake: this is the sort of reactogenicity that people are used to experiencing after immunization.

Michael Ison: With regard to the second question about whether there is a hard endpoint, these are data that are in the process of being collected, and have been collected in the first season. These will be looked at as we move forward. I do not personally have the specific details of that in front of me at this moment but, clearly, it is something that is being collected.

One of the challenges again – thankfully, particularly in the vaccine population – is that the rates of greater infections is very low and so it will likely take data over multiple seasons to get a firm estimate of the impact on hospitalizations, supplemental oxygen, and CPAP and those kinds of things over time.

Emmanuel Papadakis (Deutsche Bank): Thank you for taking my question. This is just a follow-up on efficacy and consistency by subgroup. You have referenced several times, and it did cover most of the key subgroups, except for the over-80s, which was a relatively significant subgroup in your study of over 2000 patients. The efficacy dropped to 34%, whereas it seemed in fact to be better in the competitor study for Pfizer. Do you have any perspectives on why that might be the case.

Just a follow-up to the question that was asked earlier about any implications from that potential recommendation? Do you expect still to be recommended for that subgroup of patients, based on the data you have? Thank you.

Tony Wood: Thank you for that question. Given the time, I will not repeat it. Perhaps, Dr Ison, you could take this first.

Michael Ison: As I highlighted, while there were 1000 patients aged over 80, that is still a fraction of the other populations where we had about 12,000 to 15,000 enrolled in those aged populations. It is still a relatively small population and the number of greater respiratory infections was relatively low in both arms. Really, it will take more data over more seasons to refine the estimate. While we were able to generate a number, the reality is that the reliability of that, because of the small numbers, is quite challenging. I suspect that, over the next year or two, we will have a much more refined endpoint. From my

personal perspective, I will have to wait and see what ACIP does but, again, I think that with safety, and particularly looking at the totality of information, where again, pointing to the neutralizing antibody levels where they are consistent across all age groups, that will probably give them the comfort to authorize it in all age groups over 60.

Tony Wood: Thank you. Before closing out on the call today, Phil, perhaps I might give you an opportunity to make any additional comments that you would like to on this final point.

Phil Dormitzer: Thank you. I agree completely with Dr Ison. When you have such small numbers of registry cases in both this and the placebo group, those numbers are not statistically meaningful at that point, to get an actual rate. Where you do get essential numbers is in the number of people who are offered immunogenicity testing, and there we see consistent levels of immunogenicity between those in their 60s, 70s and 80s, which gives us some confidence. We will have to see what the data show, when we accumulate more breakthrough cases over 80, but the immunogenicity results are very encouraging, and we see consistent immune responses across the age groups.

Tony Wood: Thanks, Phil. I'm aware there are some additional questions, so don't we run for an extra 15 minutes to cover those.

Jo Walton (Credit Suisse): Thank you. My question is about expected penetration. I think we all understand the flu vaccine market and still the latest data suggests only 67% of people over 65 get vaccinated. How well known is RSV and what sort of level of penetration of the market do you think that you could get to over the next few years? Would it be right for us to think that it would be better if there were two of you, each with an annual vaccination, to drive that level of education?

Tony Wood: Thank you, Jo, a great question on penetration into the market. Luke, that will be one for you, please.

Luke Miels: You're right, Jo. We model 67-68% for flu. I think it's interesting because COVID has changed things somewhat in terms of bringing adults who historically may not have presented for an annual vaccine. That is the positive side. I think that physicians are aware of the impact of RSV infections, particularly in compromised individuals or individuals – we have strong data there, so I think these are all favorable elements. I think the market research, when we have groups who have been educated and then we've tested

their motivation to be vaccinated, their willingness actually goes up significantly with a profound change of people who obviously have complicated health conditions.

I think the fact that it's retail-dominated, as mentioned earlier, will be helpful because they have a different intensive structure and more structured workflows, so doctor's offices. The negative element or the drag on that would be, as you rightly say, the lack of awareness. I think this is difficult to quantify. In some cases, vaccine fatigue, and the fact is, yes, with *Shingrix*, Prevnar, Fluzone, COVID-19, etc., the adult schedule is getting more complex.

In the next five or six years, I don't think we'll see the type of penetration we have achieved with flu. That being said, I can imagine that this class continues to grow over the next 15-20 years. I think it is beneficial for two companies that have a heritage in innovation and a heritage in terms of building markets and informing patients in place, so I think that's definitely a positive element, and on top of this, the Inflation Reduction Act, removing between what would have been between a \$30-\$50 co-pay in individuals of 65 and above, will be a positive element and help with penetration in those groups.

I can't give you an exact percentage of course, but it will be lower than flu.

Tony Wood: Thank, Luke. Apparently we have four questions left, and I'm trying to move us through those promptly. If you can be as concise as possible, it will help me with that ambition; that would be fantastic, thank!

James Ridley (Morgan Stanley): Thank you for taking my question. Just a quick one on durability. How important is the adjuvant in durability of protection, and from what you are seeing from the immune responses so far, are they behaving as you would expect or in line with *Shingrix*. That could give you a clue on durability across the distance and age groups.

Tony Wood: Thank you, James. I'll be equally as quick about this. Phil, for you please, a question on durability and the role that the adjuvant plays in that.

Phil Dormitzer: I would say that we are hopeful that the adjuvant will provide durability. On this one, we can say that we have looked for durability over the course of a single RSV season, and we will collect data on the durability over multiple seasons, or after three seasons.

Although, of course, with the continuous *Shingrix* data, we would love it if we saw something like that for RSV, but the biology of those viruses is so different that I don't think we can predict one on the basis of the other.

Kerry Holford (Berenberg): Any comments that you are able to make on pricing. When you think about pricing of vaccines, when you don't know how much of the population will need to be immunized by it, should we be thinking about *Shingrix*-type pricing for the course here because you will have had a similar debate, no doubt, when you launched *Shingrix* on measurability. Any comments on that, please.

Luke Miels: Let's assume it's an annual based vaccine. I think if you look at the flu zone price of around \$60, and the *Shingrix* price of around \$170, and you draw a midpoint between those two, the price will be on the righthand side of that side. I don't want to speculate how far or how little on the right side of that midpoint. Obviously if a multi-year potency is demonstrated, then we would revisit that assumption.

Steven Scala (Cowen): Thank you so much. GSK has articulated why its vaccine is superior to the competition but Dr Ison, what do you see as most important factors physicians will consider when choosing between the available RSV vaccines and will these factors tell you to argue for the GSK vaccine if the Pfizer vaccine is what is stocked in your clinic? Thank you.

Tony Wood: Thank you for helping me with my job, Steven, that one is for you, Dr Ison.

Michael Ison: Yes, no problem. I think you bring up a very valid point. We at least here in the United States work generally in systems. Those systems have system-wide decisions that are made as far as which vaccines are stocked. Where I work we have one flu vaccine and even though there is a whole range of available vaccines, any provider within the system can advocate for one vaccine or another.

The other advantage that we have is with the majority of people accessing vaccines through pharmacies. If our system doesn't have the vaccine that I think is most effective, I can send people to a pharmacy and recommend that, so for an individual provider usually you unfortunately have to follow the formulary in your system and how they make those decisions are very complex, a balance between cost effectiveness as well as the overall efficacy of the vaccine. But again there are alternatives if you feel very strongly of advocating within your system or sending them to a commercial pharmacy.

Tony Wood: Thank you. Let's move to what I believe is the last question now.

Emily Field (Barclays): Hi, thank you for taking my question. I just had a follow-up to the penetration question. I was wondering how much you think that ultimate penetration rate would be informed by durability, i.e. durability lasts more than a season or even if seasonal vaccinations require that the efficacy remains as tight as it is, why couldn't that penetration rate be higher or is it simply a matter of where we're at?

Tony Wood: Thank you, Emily. A question on penetration in the context of durability, Luke.

Luke Miels: Sure. Thanks, Tony, thanks, Emily. Yes, the sweet spot is probably a three-year durability which would take time to establish of course. Again we are very intrigued by the presence of the adjuvant and any potential influence that could have. I think one to two years is less impactful but yes, if we did get two or three-plus years then I think you could potentially see flu levels of penetration over a ten-year timeframe. It really just depends on how effective we are. I think the efficacy is quite interesting when you break it down, if you look at the 60 to 64 high-risk population and then you add in the 65-plus it's 80 million people in the US, so a sizeable group and our market research shows these people are very engaged in their health, so it could be higher if the frequency is lower.

Tony Wood: Emily, Luke, thank you. I believe that brings us to a conclusion today. Thank you, everyone for an engaging session and that's that done.

[Ends]