

## **GSK**

### **Meet the Respiratory Management**

**Friday, 2 September 2016**

#### **Eric Dube, Senior Vice President and Head, Global Respiratory Franchise, GSK:**

We also have a number of folks joining today by phone and by webcast, so for those of you good morning/good afternoon and thank you for your time for joining us today.

My name is Eric Dube and I am the Head of the Global Respiratory Franchise at GSK, where I have been in the role for about a year and a half.

I have been with GSK for about 16 years, most of which of the time I have been in our two largest markets, the US and Japan. My most recent job, before this one, was in Japan where I led our Respiratory business, launching a number of our new medicines. Within the US Pharma business I held a number of positions within Medical, Market Access, as well as Commercial, where I led our Oncology business and Commercial Operations and Strategy team.

#### **Respiratory commercial perspectives**

I would like to walk you through today what we see is a very exciting time for Respiratory and for GSK's position within that market. As many of you know, this weekend is the start of the European Respiratory Society meeting, where, of course, it will be a very busy and exciting time. What I would like to share with you is why we think GSK is poised to continue to be the leader within this market and why we think that this market, the Respiratory area, is a very attractive one now and into the future.

#### **Respiratory commercial landscape**

First, let me start a bit with what we think is going on in the market place, with the trends. These are the trends that we have looked at to evaluate how we need to make choices now and into the future. As many of you know, Respiratory is a key pillar for GSK and we have a 45 year heritage in leadership and innovation within this market. By looking at where we see the opportunities and the unmet needs we believe that we will be able to continue with that scientific and that commercial leadership.

First, with many of the disease insights and scientific innovation, we now are able to deliver on the promise of the right medicine for the right patient, and you will hear much more from Dr Neil Barnes, the Head of our Global Medical Organisation within Respiratory, about what we are seeing there.

We also are seeing, based on a lot of the innovation and the size of this market, that there are new competitors that have entered into the Respiratory space, This has increased the payor pressures and the pricing pressures within the area and it means that we need to think innovatively, in terms of the types of data, the types of evidence that we develop, to be able to support and demonstrate the value to payors of our portfolio.

One of the ways that we will be doing this is looking at the integration of a medicine and technology, particularly digital technology, to be able to measure and demonstrate and deliver that value to payors and to patients.

We see also that while the focus of GSK's heritage has been dominated by asthma and COPD that there is quite a bit of opportunity and area of innovation beyond these two diseases, and Dave Allen, the Head of our Respiratory R&D organisation, will be speaking a bit about that as well.

I would like to focus our attention on where we see the areas of unmet need by these diseases, first within asthma.

Asthma is a disease that afflicts 250 million patients worldwide and of those patients that are treated about 40% of these patients still have symptoms that interrupt their lives and cause quite a bit of anxiety and fear in these patients' lives. The real unmet need is to be able to deliver the right inhaled corticosteroid therapy or combination therapy to be able to help these patients gain control of their symptoms, and we believe that a lot of this has to do with not just getting on the right medicine, but also ensuring good adherence as well, so Dr Barnes will speak a bit about that.

There has been a lot of attention within the severe asthma space and with the recent launch of *Nucala*, an IL5 monoclonal antibody, we see that this is an area that we will be able to deliver on an unmet need of decreasing the risk of exacerbations or asthma attacks that these patients all too often suffer from.

Turning our attention to COPD there really are two major unmet needs. The first is to reduce the symptoms that these patients experience, symptoms of breathlessness that lead to a reduced activity level for these patients. The second area and unmet need is to reduce the risk of exacerbations that often lead to hospitalisations or permanent lung function decline, and so we are absolutely focused on ensuring that we can help physicians understand the right patient type, based on these two needs.

But we also see that there has been a belief that COPD is an inevitable decline of the condition and of the health condition, and what we see is that for the first time there is

evidence to suggest, from the SUMMIT study, that you can slow the rate of decline for lung function, and that is something also that we are particularly focusing on from here on out.

I am going to leave lung function, lung fibrosis and acute lung injury for Dave to speak about.

### **Respiratory portfolio in transition – new portfolio provides platform for continued market leadership**

If we take a step back and look at the size of the Respiratory market, here we look at the global value of the Respiratory market, it is about £24 billion. GSK has about a 30% share of that market and we have predominantly played within the ICS/LABA segment, mostly within asthma, as well as the steroid or inhaled corticosteroid segment.

With the recent launches of *Anoro*, of *Relvar/Breo*, our ICS/LABA, *Incruse*, which is our LAMA, *Arnuity*, which is our new inhaled corticosteroid, and most recently with *Nucala*, we now will be positioned to be able to compete in over 80% of this market, based on what we currently see are the segments or the different classes of medications, and we also are looking at additional launches of our Closed Triple, the ICS/LABA/LAMA, in the next year or so, as well as additional indications for our anti-IL5 monoclonal antibody, COPD as one example. So we believe that we will be well positioned to offer a number of different treatments for the majority of patients worldwide.

### **GSK offers a broad portfolio across the spectrum of COPD and asthma treatment**

If we look at how our portfolio, our current portfolio of *Elliпта* and *Nucala*, maps against the spectrum of COPD and asthma, I can tell you that we have the broadest portfolio of offerings against these two diseases and the severity that patients face. We know that for asthma and COPD not all patients are the same and so we want to make sure that we offer the treatment choice for physicians. However, when we look at where the areas of opportunity are, much of what we are trying to do is to make the right choices and understanding where the market will go, where the unmet need is and where the scientific evidence is pointing us, for example in COPD our focus is much more on *Anoro* as well as open triple of *Relvar/Breo* plus *Incruse*.

But the strength of our portfolio is not just in the breadth of our offerings, we actually have focused on developing this inhaled portfolio by selecting new molecules, this is the only portfolio of the inhaled medicines where every molecule is novel and was selected to be able to be developed as the best-in-class within each of those. In addition, we have *Nucala* that is very recently launched, we believe that we will be able to continue to drive good innovation within treating severe asthma.

But, importantly, all of the inhaled medicines are on the same platform, the *Ellipta* platform, which offers once-a-day medications for these patients to ensure that their treatment does not get in the way of living their normal lives, and also it is in the *Ellipta* device. This device was designed with patient experience and patient insights in mind, to make sure that it is intuitive, easy to use and reduces the rate of errors that, all too often, patients have when they take other inhaled medications.

### **GSK well positioned to address the key unmet needs in asthma**

I would like to focus on asthma and COPD specifically to see where our priorities are and where we believe the opportunities will be, moving into the future.

This, you can see, is the spectrum of the disease and, as you know, most of the use of the medications and the value within this market has been in the ICS/LABA segment. The ICS/LABA segment continues to grow in the mid-to-high single digits over the last couple of years. We believe that this will continue and with the launch of *Relvar/Breo* we believe that we are offering a great option for patients and that it cements our leadership position now and into the future within asthma.

However, we see the largest area of growth in the severe asthma or the biologic space, where we have recently launched *Nucala* and I will speak a bit more about that when we turn to our recent performance, so we are well positioned where the majority of the opportunity is within asthma.

### **GSK expects to maintain leadership in COPD segments**

Now, turning our attention to COPD, I would like to first start, again, with those two areas of unmet need, reducing symptoms and reducing risk. So if we look at reducing symptoms, what we see by the emerging evidence consistently is that patients are better off on two bronchodilators than one, and so we believe that there will be a continued shift, as we are seeing now in the marketplace, away from LAMA therapy to one of LAMA/LABA or dual bronchodilation, and in fact this second segment, this bottom segment, is where we are well positioned with *Anoro* to compete now and into the future.

For those patients that are at higher risk of exacerbations, where the aim is to reduce that risk, we are focusing and believe that in the future there will be a migration towards triple therapy. Right now, about 25% to 30% of patients globally are on open triple and with the offering of Closed Triple in the future we will be able to offer a compelling option for these patients to be able to be treated effectively for their symptoms and their risk. In fact, we announced that our file in the US for Closed Triple was accelerated by about 18 months, where we will be filing by the end of this year.

So into the future we see that where the majority of the patients will be treated they will have two very effective medications on the same platform, once a day, which is unique amongst the competitors.

### **Respiratory portfolio performance**

Now, I would like to step back and say how is our strategy performing? This is the performance over the last six quarters of our Global Respiratory business and you can see, first, that the contribution of sales from that new portfolio has grown steadily over the last six quarters, moving from 4%, now above 15%, and we expect that we will continue to grow across all of the regions.

When we look at that in the context of *Seretide/Advair* sales we see that for the first time in the second quarter of this year we have been able to more than make up for the decline of *Seretide*, in that quarter. We continue to be confident in our commitment to be able to return this Respiratory business to growth this year and our focus is to ensure that we continue the success of this new portfolio.

### **Significant momentum in the US respiratory portfolio**

I would like to now spend a little bit of time focusing on the performance of these launches. Here you will see the performance in our US organisation, where we have seen an acceleration in the uptake of *Breo* as well as our bronchodilators, *Anoro* and *Incruse*, and much of this was enabled by additional market access wins early this year. But I can tell you, having worked in the US organisation, that just because you have market access wins does not mean that the sales will come. You have to have very strong execution and commercial acumen, and I can tell you that the US team, the primary care team led by Deborah Waterhouse, I believe are firing on all cylinders with regard to execution, and you can see here with *Breo* that we have seen an acceleration in the uptake of new patients on *Breo*. So it is the market access wins, very strong sales and marketing execution and, what has turned out to be, a very successful direct-to-consumer campaign for *Breo*.

When we look at the bronchodilator space, let me remind you that the bronchodilator space, in terms of a major opportunity, is a new one for GSK, we have not competed within this segment, which has been dominated by LAMA monotherapy. What we now see is that we have 30% of new-to-brand patients on one of the GSK bronchodilators, either *Anoro* or *Incruse*, and we continue to see improvements there. What you see with regard to the acceleration, or that bolus of uptake, was a managed care win, where we shifted patients away from another monotherapy onto either *Anoro* or *Incruse*, now we expect that we will see a more steady type of growth within the US market.

## ***Relvar* performance continues to exceed recent launch analogues, *Anoro* European launches underway**

But the success of our new products are not just limited to the US. If we see here the performance within Europe, we see that *Relvar* is exceeding some of the recent launch analogues of other inhaled medicines within those markets

In Japan, where I had the privilege to launch *Relvar*, we launched within a month of another inhaled corticosteroid/LABA combination. In the first twelve months of the launch in Japan physicians are only able to prescribe for two weeks, which is a bit of a challenge, which limits the uptake of a new medication. However, after 12 months physicians are able to prescribe for 30 days. Just like those market access wins in the US, this does not guarantee success, it really requires focus and strong execution, and what you can see here is that within Japan we saw an acceleration of the uptake of *Relvar*, we see that nearly a quarter to a third of physicians now are saying that *Relvar* is their go-to ICS/LABA for asthma. In fact in the last month, where we have exceeded over 20% of total prescription share within the ICS/LABA market, we now have more new patients going on to *Relvar* than we do *Adoair* and this is with only the asthma indication, the COPD indication we expect in the next six months, so we expect continued growth within the European and the Japan market.

Now, it is a slightly different story when we look at *Anoro*, which, again, is a new segment of the market for GSK. In Europe we are not first to launch our LAMA/LABA and so it has been a little bit slower going, because we also did not have the component, the monotherapies, in the market to convert, which we see has been part of the acceleration of some of the competitors in this space.

Our goal with *Anoro*, as you saw on the previous slide, is to ensure that we are the leader within that space and the way that we are focusing on it is to establish *Anoro* as the best-in-class bronchodilator. We have already reported a head-to-head study of our LAMA therapy, umeclidinium or *Incruse*, head-to-head versus the standard-of-care LAMA therapy, showing superiority. We also have a head-to-head study of *Anoro* that will report out comparing ourselves to another LAMA/LABA. Also, we have seen in the UK, very recently, where the *Anoro* was the second to launch earlier this year and we have surpassed the two other LAMA/LABAs. Now we are the leading LAMA/LABA within the UK, despite not having a base of business to convert and being second to market.

So we believe that we have a very strong portfolio and we hear anecdotally that when physicians use one of our medicines they understand the efficacy and the ease of use of the *Ellipta* profile, we believe that it will enable growth across this portfolio.

## **Nucala performance - US**

Then, I would like to now turn our attention to our most recent launch, *Nucala*, for severe eosinophilic asthma. Here you see some of the statistics from our US launch performance, where we see an acceleration of our sales performance. We have over 4,500 patients to date, in the last nine months, who have been treated with *Nucala* and the market access has been very favourable. We see nearly two thirds of patients in the US who are eligible for *Nucala* are able to do so without restrictions. For the other third it requires a bit of additional steps to ensure that they are appropriate patients. We expect that this will accelerate because in January we will be granted our J code, which gives physicians much more confidence that they will be reimbursed when they inject a patient with *Nucala*. We will have additional data that will be reporting out later this year from the MUSCA study. That is a study looking at additional benefits beyond the risk of exacerbation, where patients are able to demonstrate an improvement in their quality of life and lung function.

What we are hearing anecdotally across these markets is very consistent and positive, where after, perhaps, the first injection patients are coming back and saying that this is a medicine that makes a difference and we have heard many times that patients say that this is a life-changing medicine for them, they feel the difference and so we believe that and we will continue to study the effects and the efficacy beyond just the risk reduction for these patients.

I have shared with you the performance of the US because we have externally reported data for the US, but I can share with you that consistently across all of the markets in which we have launched *Nucala* the uptake has been as good or better, as well as the anecdotal feedback we hear from physicians and patients is very consistent. So we are quite encouraged that we will be able to demonstrate and build a strong basis for *Nucala* as we expect competitors to come in the next couple of years.

### **Expect 2020 total respiratory sales to be at or above sales in 2015, whether or not there is US generic competition to *Advair***

I would like to end my presentation with just a bit of a view towards the future. This is a slide that you will have seen from the Capital Markets Day presentation, and our focus on being able to shift our focus away from what has been dominated by *Seretide*. In fact last year over 90% of our revenue was comprised of four medicines within Respiratory, particularly *Seretide*. I can tell you that we are well on our way to rebalancing this portfolio, focusing on a rapid uptake of our new products. We expect in 2020 that our sales will be at or above the 2015 revenue figure and balanced across the nine medicines that you see here, the next of which will be Closed Triple, that, again, we will be accelerating the launch in the US and are very excited about the size of that opportunity, but most importantly to be

able to continue to demonstrate the scientific innovation and being able to deliver on what we see is a very high unmet need globally for patients with respiratory disease.

On that note, I would like to introduce Dr Neil Barnes, the Head of our Global Medical Organisation for Respiratory.

## **Respiratory clinical perspectives**

### **Professor Neil Barnes, Respiratory Global Franchise Medical Head, GSK:**

Thanks very much.

Good afternoon, my name is Neil Barnes, I am the Medical Head of the Global Respiratory Franchise at GSK, but until just under three years ago I was Professor of Respiratory Medicine at Barts and the London, so just next door to here, although my main clinical bases were at the Royal London Hospital in Whitechapel and three stops down the Central Line at the London Chest Hospital in Bethnal Green.

What I am going to do is move on from what Eric has talked about, to talk about the clinical/medical perspective.

### **Asthma management – GINA guidelines**

These are the Global Asthma Guidelines, the GINA Guidelines, and these are very well-established and have a very good evidence base to them. About 90% of asthmatics are at Steps 1, 2, 3 or 4, that is, they are requiring inhaled steroids or combination therapy.

### **Asthma management – GINA guidelines: Major unmet need**

The evidence from clinical trials and where clinical practice has been extremely effective is that if you can get patients to take the medicines that are available now, in terms of preventing unscheduled care, emergency courses of steroids, hospitalisations, you can do very well with this 90% of patients.

Interestingly, even though you can prevent them having this unscheduled care many of them remain symptomatic, which gives a space, particularly for the triple, of adding a long-acting antimuscarinic.

### **Making asthma treatment effective**

So the challenge for this group of patients is doing the basics well and we believe, and the GINA guidelines say very similar things, that the four things you have to do, get the diagnosis right, that is particularly important for choosing the right patients for *Nucala*, as I will talk about in a minute. You have to get the treatment right and, as Eric has said, with our

portfolio of medicines we can offer that to clinicians. You need to address adherence and compliance issues, and this is probably the major barrier in this group of individuals to good asthma control. And you need to get the inhaler technique right.

### **Get inhaler technique right**

So one of the great advantages of our new portfolio is the *Elliпта*, because we know that in clinical practice about half the patients who are prescribed a metered-dose inhaler, which is still worldwide the commonest delivery device for an inhaled medication, cannot take the medicine effectively, even with repeated instruction.

Now, what we have focused on is what we call “critical errors”, when patients take an inhaler if they take it wrongly they don’t get drug into their lung which is actually going to have a therapeutic effect, and we have a series of studies in asthma and COPD comparing the *Elliпта* with other delivery devices.

So here there is a study comparing the *Elliпта*, in orange, with the *Diskus* or *Accuhaler*, metered-dose inhaler, and the Turbuhaler, and consistently the *Elliпта* has extremely low error rates, much lower than the other delivery devices. We know, from other data, that if patients make errors they are more likely to have poorly controlled asthma. So we view this common platform, with a very easy to use inhaler with low error rates, as extremely important and dealing with one of those four pillars of making asthma treatment effective.

### **Connected inhaler system: integrated sensor model**

Now, as I said earlier, the other big barrier to good asthma control is poor adherence. As a clinician it is extremely difficult to judge whether a patient has taken their treatment or not, because if you ask them they almost always say ‘Yes, I have taken it,’ but when you actually get prescription records or you measure this objectively it is usually less than 50% adherence. So we think that a major innovation for the future is going to be chipping inhalers to allow clinicians to understand patients’ adherence, to be able to improve their consultations and actually address adherence problems, to understand the barriers to adherence, and this will form part of a digital ecosystem which allows feedback to provider organisations, hospitals, feedback to patients, which will be, we think, a major breakthrough in putting adherence and the patient at the centre of management of asthma and of COPD.

### **Asthma management**

Now, even if you treat patients extremely well you are left with about 10% of patients who even with ideal treatment are left symptomatic, with recurrent exacerbations requiring courses of oral steroids and about a third of them end up on continuous oral steroids, with all

of their side effects. I know this very well, because I ran the Severe Asthma Clinic at the London Chest Hospital for over 20 years.

### **Asthma management: delivery + new treatments**

These patients have the worst of all worlds; they have poorly controlled asthma and particularly the ones who have continuous oral steroids have all the side effects of the medication. So what we need for these patients is better delivery of care, plus new treatments and mepolizumab, or *Nucala*, is a clear breakthrough for a high percentage of these severe asthma patients, and I was lucky enough to take part – not as a patient, but as an investigator – in the studies of *Nucala*.

### ***Nucala* pivotal studies**

So this shows two of the pivotal studies.

The MENSA study took patients who were on high dose combination therapy and despite that were having exacerbations requiring steroids, and with the addition of mepolizumab, or *Nucala*, there was a 50% reduction in the exacerbations that these individuals had and a reduction in hospital admissions.

The SIRIUS study looked at the worst of the worst, these are patients who despite high dose combination therapy and oral corticosteroids have continuing symptoms and exacerbations, and here there was a 50% reduction in the dose of oral steroids that these patients needed to take. Despite the fact that they reduce their oral steroids they had less exacerbations and symptom improvement.

### **MENSA study: *Nucala* improves QoL**

This shows the symptom improvement in the MENSA study, this is a measurement called the St George's Respiratory Questionnaire and because it was developed south of the river it is upside down, so going down is actually getting better. Compared with placebo the marketed dose of *Nucala* led to about a seven-point difference in the SGRQ, which very comfortably exceeds the minimally clinically important difference, and having treated patients in the trials with mepolizumab, or *Nucala*, what Eric said is absolutely right, these patients, many of them, actually it transforms their life, they feel so much better and they lose the necessity to take oral steroids.

### **COPD management – GOLD guidelines**

Now, I am going to switch now to COPD and the big contrast between asthma and COPD, in terms of treatment, is that whereas in asthma we have very well-established guidelines and a tremendous level of agreement about what the correct way to treat patients

is, it is different in COPD. This is the GOLD Guidelines for COPD and recommending the treatment options. You can see, at every point, it is and/or, and when you get to alternative choices at the D patients it is write down every drug you have ever thought of for COPD and put an 'and' or an 'or' between it, so this is confusing for specialists, it is a nightmare for generalists.

### **Potential COPD treatment paradigm: reducing complexity**

But we believe that the evidence is moving towards a much simpler way of looking at COPD, because we think that, as Eric has said, in the future to reduce symptoms patients will either go straight to a LABA/LAMA, a dual bronchodilator, or they will go to a single bronchodilator and then very rapidly move on to a dual bronchodilator.

The main aim of these medicines is to reduce symptoms, but we also know, from recent studies, that they reduce the risk of exacerbations, so in reducing symptoms you also reduce risk, and then the major clinical question becomes 'Which patients, in addition to this, need an inhaled corticosteroid to further reduce their risk?', so we think that this is a much simpler way in which clinicians will be able to look at treatment choices in COPD.

### **Real world studies have shown that most COPD patients remain breathless when using only one long acting bronchodilator**

Why do we think that the march will be towards many more patients being on dual bronchodilators? This is data from the US looking at patients who are on a single bronchodilator, usually tiotropium, and the majority of them remain breathless. The mMRC is a measure of shortness of breath and a score of 2 means that you can't walk at a normal pace without stopping and getting short of breath, so the majority of patients need further treatment.

### **Comparative studies of *Anoro* versus tiotropium**

Now, one of the great advantages of the dual bronchodilators - and here is data with *Anoro* - is that it gives a clinician greater certainty that they are going to get a good response. So in the crimson/purple colour is the improvement in lung function with *Anoro* and it is very reproducible, just over 200mls, whereas tiotropium produces bronchodilation, but it is less and it is variable, so that certainty of response is really helpful for clinicians.

### **Trough FEV<sub>1</sub> at day 85 – PP population**

As Eric said, we think that we have the best-in-class dual bronchodilator and this is supported by the fact that when we look at one of the important components of this, umecclidinium, or *Incruse*, the improvement in lung function is significantly greater than that with tiotropium.

## **Blood eosinophil count is associated with exacerbation frequency and predicts ICS response: post-hoc analysis**

Now, moving on to the role of inhaled steroids, as I am sure you are aware, this has been a matter of discussion and debate, and the problem for clinicians is you can't tell if a patient has responded to a bronchodilator, you can ask them questions, 'Are you less breathless? Can you walk further?'. When it comes to reducing risk it is very difficult to tell if you have reduced the risk of exacerbations. If you give somebody aspirin to treat their ischemic heart disease it is very difficult to know whether you have prevented a heart attack or whether they wouldn't have had one anyway, so having a biomarker, having something that gives you more surety about response, is very helpful.

So this is data from our pivotal studies of *Relvar/Breo* and it looks at the blood eosinophil count, on the x-axis, and, on the y-axis, the rate of exacerbations. The dotted line is vilanterol, this is the bronchodilator, and as you increase the eosinophil count so the risk of exacerbations is increased, so it is a bit of a marker of risk of exacerbation, but when you add the inhaled steroid, which is the green line, *Relvar/Breo*, you get this reduction in exacerbations and the higher the blood eosinophil count the greater the exacerbation risk reduction. So we think that if this is confirmed in the IMPACT study, which reads out next year, this will be a very useful and simple biomarker for clinicians to use. The majority of patients in this have a blood eosinophil count which is considered to be within the normal range, so when we look across studies it is about 60% or 70% of patients.

## **Potential COPD treatment paradigm: reducing complexity**

So what we think in the future is that the backbone of treatment, in terms of symptom reduction, will be the dual bronchodilator to which in these high risk patients, particularly those who have a higher blood eosinophil count, we will add the inhaled steroid, and that potentially in the future we may also be able to identify those patients before they have problems to be able to use the treatment as, what you might call, primary prevention.

## **COPD Salford Lung Study with *Relvar/Breo***

Now, at the ERS over the next few days one of the studies that we will be presenting is the Salford Lung Study and this is a completely innovative study which has the benefits of a randomised controlled trial, but it is performed in routine clinical practice, in primary care, in general practice in Salford. So patients were randomised either to *Relvar* or to standard of care, and standard of care for most patients was either an ICS/LABA or triple therapy. It was a huge undertaking, over 2,800 patients were randomised, 80 general practices and more than 3,000 individuals trained in good research practice.

## **What has the healthcare community asked for?**

The traditional randomised controlled trial obviously has enormous strengths and merits, in that you take a very tightly defined population and you study them intensively, but it doesn't always tell you what happens when you take that medicine out into real-life practice, which is what I, as a clinician, and healthcare systems want to know about, because there you are looking at the drug in normal routine clinical practice and in a broad population.

### **COPD Salford Lung Study with *Relvar/Breo***

The results of the Salford Lung Study showed that in comparison with the routine care there was an 8% reduction in exacerbations of COPD and an improvement in quality of life. Putting that 8% in context, that translated in a number needed to treat of seven, so for every seven patients you treated with *Relvar* compared with their standard of care you reduced by one exacerbation, and in terms of numbers needed to treat that is a very, very good number needed to treat.

This study has produced a huge amount of data which we are analysing and will give us an enormous amount of information about how to better treat COPD in general.

### **Late phase inhaled COPD portfolio**

Now, this shows the results of our studies looking at the addition of *Incruse*, or umeclidinium, to a range of different ICS/LABAs, *Relvar*, *Seretide/Advair*, and in terms of the improvement in lung function you have a very clinically important improvement in FEV<sub>1</sub> of 120mls.

### **FULFIL study design**

But we have recently completed the FULFIL study, which is a comparison of budesonide/formoterol, Symbicort, with our triple therapy of FF, umeclidinium and vilanterol, and the primary outcome measure in this study was the improvement in FEV<sub>1</sub>.

### **FULFIL efficacy data**

The improvement in FEV<sub>1</sub> was 171mls, so contrast that with the 120mls I showed you before, we had a significant improvement in quality of life and although the exacerbation rate was low in this study there was a reduction in the exacerbation rate. So this improvement in FEV<sub>1</sub> of 171mls, compared with 120mls that we saw in the previous slide I showed you, really indicates the power and value of that triple combination.

### **FULFIL safety data**

In terms of adverse events, these were very similar to those spotted in other studies, with a pneumonia incidence which was similar to previous studies.

## **Journey to personalised medicine**

So what we believe is that we are on a journey towards personalised medicine, and we are moving towards that because we have two things, we have that portfolio, that range of different medicines we can offer, and an increasing understanding clinically of how to identify the right patient for the right medicine, both in asthma, with a drug like *Nucala*, and with the use of inhaled corticosteroids and triple therapy in COPD.

I will now hand over to Dave Allen and, personally, I am really excited in the data he has, because, as a clinician, I know that we need new medicines for many of these lung diseases and Dave is going to talk to us about those. Thanks.

## **Respiratory R&D**

**Dave Allen, Senior Vice President and Head, Respiratory R&D, GSK:** Thanks, Neil.

Good afternoon everybody. My name is Dave Allen, I head up the R&D Group in Respiratory, that means my guys are basically responsible for everything from picking the targets that we work on, from the emergent biology, right through to getting the regulatory approvals in all the major markets, so if it goes well I will take the credit, if it all goes horribly wrong it is their fault!

Before that, I actually led the Discovery organisation, so it is my guys that came up with vilanterol, UMEC and everything else, so really great to see these coming through into the market now.

## **COPD R&D strategy**

I have some new stuff to tell you about, I am under strict instructions not to go on forever, so I have limited the content of this really to a bit of an update from where Patrick left it at R&D Day last November, where he covered the complete Respiratory portfolio, so just to stress no attempt to try and cover everything.

I have used this format for consistency. From an R&D perspective we are really finishing off our once a day inhaled portfolio, so you will see that we filed *Relvar/Breo* in Japan at the beginning of the year, hopefully we will get the approval there towards the end of this year. I think Eric mentioned that following discussion with the FDA we have managed to advance the filing of the Closed Triple product, which is very exciting, to later this year. The plan is we will submit Closed Triple in Europe and the US right at the back end of this year. We will see the MABA data within about the next month or six weeks, so that is the dose ranging data.

If we look at the targeted biologics we have the mepolizumab Phase III data scheduled for next year. Those studies are fully recruited, both the pivotal Phase IIIs are fully recruited, so we expect to see that data and we will talk about that next year.

Infection-driven exacerbations - one of the things in COPD that is well-known now and is better understood is the fact that lung infections in COPD patients give rise to these serious exacerbations. That seems to be due to some deficiency in the immune system that actually occurs in COPD as part of one of the features of the disease. We have two approaches where we are looking to modify the immune response to infection and help COPD patients prevent these exacerbations. Very different from the immunosuppressive approach with steroids or the bronchodilator approaches with LABAs and LAMAs.

Both the same mechanisms, PI3K $\delta$  and the CXCR2, which is the danirixin, appear in that final box, which is preserving lung function. Because of the way these mechanisms work there is a reasonable biological hypothesis that they may also prevent lung destruction that occurs in COPD, but we will talk about that because we are progressing that slightly separately.

#### **GSK2269557: Inhaled PI3K $\delta$ inhibitor**

Very quickly to tell you a little bit of an update on our PI3K $\delta$  inhibitor, so PI3K $\delta$  is on the signalling pathway. I think at R&D Day Patrick showed everybody that this inhibitor, our PI3K $\delta$  inhibitor, will rectify a deficit of these inflammatory cells, these neutrophils, that occurs in COPD. If you look at the little panel on the top right the neutrophils should be tracking up the screen to the IL8 gradient, which is how they target to the lung physiologically, when they get there they should be fighting infection and then being cleared. In COPD they don't target accurately, so they don't clear the infection and actually they reside in the lung too long, which then adds to the COPD symptoms. With a PI3, with our molecule, we can rectify that tracking, which clearly is going to be important.

This pathway actually is overexpressed in a rare disease, APDS, and hence gives us some genetic association with this pathway being important, because these patients with this rare disease suffer a sort of recurrent bacterial infection that is very similar to COPD infections. They have it very severely, it shortens their life.

We have previously shown with our inhaled molecule that we engage the target at inhaled doses that we can give. We have shown that we reduce markers of inflammation, IL6 and IL8, which, again, is consistent with the pathway.

We have just had our first look at some interim Phase II data where we use some high resolution CT imaging to look at the lungs of patients actually who have exacerbations

while we are imaging them. So the patients report with their exacerbations, we do some high resolution lung imaging, and there is a little panel, bottom right, which actually is from an enabling study using a bronchodilator, ipratropium. What you see, when you look at the small vessels, which are the critical ones, is you get an increase in airway volume, both with ipratropium, which is expected because it is a bronchodilator, but we also get it with our PI3K $\delta$  inhibitor. This is very encouraging, because by opening up these airways you should help the lung clear infections, improve gas exchange, help the patients feel better and recover from their exacerbation.

So generally here we have an emerging picture of consistent pharmacology, biology and clinical results which are encouraging.

### **Danirixin (GSK1325756): oral CXCR2 antagonist**

The second molecule that fits into this sort of category is danirixin. This was talked a little bit about at the Q2 results. It's an oral CXCR2 antagonist. This blocks the receptor on neutrophils and stops them migrating in such numbers into the lungs which is due in part to this effect I've told you about in COPD.

On the left is a panel showing the E-RS score, this is the symptomatic score in some patients with COPD. A very small number, less than 100 patients, a Phase II study but we enriched these patients to be highly symptomatic and all of them have this feature of mucus hypersecretion. So the feeling is you will appreciate in COPD a lot of patients get mucus, they cough, they splutter, they can't breathe because of this very viscous mucus that clogs up their lungs.

Seeing this sort of symptomatic benefit in this population of a couple of points which is what the E-RS is showing us is very encouraging and consistent with the biology of this.

The panel on the right just shows you that we have analysed the data now for all the patients that we have. There is also a trend in this population to reduce exacerbations. Again, with these sorts of numbers, we are not going to see anything more than a trend, but if you put the symptomatic benefit together with the exacerbation benefit – right at the bottom of the slide – there we also saw trends in efficacy on the CAT (COPD Assessment Test). We saw improvements in lung function by way of vital capacity which is consistent with opening up airways and in fact some blood markers of matrix turnover. Again a consistent picture of biology adding to something which feels like it's getting some of the underlying drivers of COPD and so it is quite different to the approaches currently on the market

## **Asthma R&D strategy**

If I quickly turn to asthma, the same sort of idea, our once a day inhaled portfolio we are finishing off with some paediatric studies with *Relvar/Breo*. We have filed our steroid - *Arnuit* - in Japan. We have also started a Closed Triple programme which both Eric and Neil have mentioned which I will just talk about very quickly in a minute.

In the targeted biologics, I am not going to say any more about *Nucala*, it's been covered elsewhere. Sirukumab, which is the anti-IL6 antibody we are progressing for rheumatoid arthritis with J&J, we are just about to start the Phase IIa study. This will be in eosinophilic low asthmatics, so the complementary population to *Nucala* which could be quite interesting. We have in-licensed the IL-33 receptor mAb which I'll tell you very briefly about and our anti-TSLP domain antibody, that's a fragment of a mAb that we're looking at giving it inhaled is progressing.

If we then turn to the other, our anti-IL-5, our anti-IL-5/13 and our approaches to immunomodulation are all progressing. The TLR7 programme will start an asthma allergen challenge study looking at duration of effect in orders of weeks. This will be intermittent dosing of our TLR7 and then looking at an allergen challenge some weeks later to see if we have moderated the immune response in asthma and we can pick that up with an allergen challenge, so that will be very interesting. That's the beginning of something that feels very different in asthma.

## **Asthma population**

Just thinking quickly about the Closed Triple proposition in asthma., If you think about the asthma population which is what I have represented by the blue circle, Neil has talked about the unmet need in the more severe population, the so-called GINA 4/5s which is in the sort of purple colour that represents somewhere between 20% and 30% of asthmatics. All of the biologics that everybody is talking about fit into that little green or orange boxes at the bottom which are the severe asthmatics that have routine exacerbations and where there is very high unmet need.

But if we go back to that purple box which is a large population of severe asthmatics, the vast majority of them don't have asthma exacerbations. Yet somewhere between 50% and 60% of them have uncontrolled asthma and are still symptomatic and are moderating their lives around their asthma rather than having their asthma controlled. And it is in this population that we think the triple combination will be most effective.

## **Closed Triple for asthma**

Now, I say triple combination. The addition of umeclidinium to *Breo* gives us the triple. Our intent is not to progress umeclidinium as a standalone in asthma. I think from all of the things that Neil said, the one important thing we believe from a patient perspective is that asthmatic patients should take their inhaled steroids and I for one don't want to be putting a new drug on to the market which doesn't contain the inhaled steroid. So we will only progress UMEC as part of a Closed Triple product in asthma to ensure that asthmatics get the combined treatment they need and don't start dipping from one inhaler to the other which is a potential if you have multiple inhalers.

We dose-ranged umeclidinium in asthma – quite a nice design, actually. We dose-ranged it in some patients with this so-called asthma COPD overlap syndrome. These are unfortunate patients that have both diseases. They fare very poorly actually as you might expect, but you can separate them on their primary diagnosis so, were they first asthmatic, or were they first diagnosed as COPD patients.

If you analyse the data of the UMEC dose-ranging which is in the table, you can see that we confirmed first of all in this population 62.5µg is the effective dose in the COPD patients and in fact it is also the effective dose in the asthma patients. We expect that the dose of UMEC in severe asthma will be the 62.5µg. We may put a second dose into the Phase III just to confirm that, but we think there we have a good rationale now and high confidence that the triple product will deliver the lung function benefits and help with the asthma control that these patients need.

## **Diverse asthma biologic pipeline continues to develop**

The IL-33 fits very nicely into this table of targeted biologicals. I will talk in a second about its mechanism of action, but you can see that with *Nucala* targeting the high eosinophilic group, the anti-IL-6 targeting more of the sort of neutrophilic phenotype with elevated IL-6 pathway. There are some asthmatics that actually have the whole pathway up-regulated and are obviously great targets for blocking that pathway with sirukumab and then we have the long-acting anti-TSLP, etc.

## **Anti-IL33r mAb for severe asthma**

If we look very quickly at the anti-IL33 receptor, a mAb, why are we excited about this? IL-33 itself is what's called an alarmin. It is released on damage to epithelium; that can be from virus, it can be from allergen, it can be from excessive coughing, anything that damages the lining of the lung. It is released and then it kicks off a whole host of immune responses and it's this breadth of immune responses that's very attractive.

Obviously it's early days and we are going to have to sort out all of this. The temptation in the severe asthma area is to simplify everything to one cell type; it's eosinophils, it's neutrophils, it's something else. This one looks quite interesting and we will work out the same way as we did with mepolizumab exactly who the responsive population are, which biomarkers we should be using, how we fit it in with the other biologics. We don't know the answer yet but we think we know how we're going to do it.

### **Beyond asthma and COPD**

Finally, just to talk a little bit about some of the other areas that get a bit less news at the moment and remind everybody that in our eosinophilic disorders we have the Churg-Strauss, the EGPA Phase III results for mepolizumab will read out. Rare disease, vasculitic disease, we will see that data later this year.

I have a little bit of data to show you of mepolizumab in nasal polyposis which is quite interesting and we are going to start the study in hypereosinophilic syndrome. This is a very rare disease, but these were the original patients that got mepolizumab. We have had patients with HES on compassionate use now for up to 12 years, so we are going to do a Phase III programme, do the dose-ranging and get it properly approved.

Our Phase IIa study is underway in acute lung injury. I am not going to show you anything on that today, but we are recruiting very well in that area. We can talk about that if anybody is interested and I will show you some PET imaging from an idiopathic pulmonary fibrosis enabling study because we have a new molecule progressing in this area.

### **Mepolizumab, severe nasal polyposis**

Here's the nasal polyposis data. These subjects, nasal polyps if people are aware of them, are these polyps that grow in the sinuses. They grow very large, they occlude the sinus so patients have difficulty breathing, their sense of smell and importantly their sense of taste is affected. They can be removed surgically. Unfortunately in more severe patients you need routine surgery because they simply re-grow again because the underlying driver of the polyps isn't rectified by the surgery. They are benign, but they affect patients' quality of life quite substantially.

All of the subjects we used in this small study had already had surgery, so these were recurrent polyps in these patients and you can see in the panel that we had a good response with fewer patients now needing surgery than on placebo. You can see in the table on the bottom left that we got a reduction in size of the nasal polyps in many patients. When you looked at all the people who had had surgery or on the waiting list for surgery or withdrawn from the study due to lack of efficacy, we had a very clear differentiation between

mepolizumab and standard of care. So we think we have pretty compelling data there for mepolizumab in severe nasal polyposis.

We are just meeting with the regulators to agree the Phase III programmes for that.

### **GSK3008348 inhaled $\alpha\beta6$ inhibitor**

Very interesting this  $\alpha\beta6$  inhibitor for idiopathic pulmonary fibrosis, so many of you will be aware IPF is a fibrotic lung disease of unknown origin. It tends to onset at a mean age of 70. A poor prognosis; mean survival following diagnosis is about three years so it's on a par with lung cancer for mean survival following diagnosis.

At the moment, the approach we are taking to this is to try and halt, not slow but actually halt, the development of the fibrosis once this is diagnosed. Really the only way you can really halt fibrosis is to block TGF $\beta$  which drives the fibrotic response in the lungs and any other organs for that matter. Unfortunately people have tried many times to block TGF $\beta$  and basically your body falls apart. It's important for homeostasis, so crude attempts to block TGF $\beta$  are a non-starter.

However, local production of TGF $\beta$  is driven by expression of this integrin,  $\alpha\beta6$ , so our hypothesis is that by blocking that integrin we can stop local production of TGF $\beta$ , so we will only block it where the integrin is expressed. Clearly the important thing is to show that the integrin is expressed in the lung of IPF patients. This we have done using a bespoke PET ligand, so the PET ligand is taken up by cells that express this receptor and the lighter the colour, the more of the PET ligand has been taken up.

What you can see with the image on the left which is marked 'HVT' and is a healthy volunteer lung and you can see the dark colours are good news for that person – very little PET image, very little integrin expression, consequently very little fibrosis, just a normal lung.

If you look at the IPF patient on the right, and especially when you look at the left-hand lung, you can see it is absolutely covered in yellow and white, high amounts of integrin, high amounts of fibrosis in that patient. So the PET ligand is helpful to confirm our hypothesis. We are also going to use it to dose range our small molecule drug, 348 because we can pre-incubate with our drug, give them the PET ligand, if there is any receptor still left we need a higher dose of our drug.

This will be really important because one of the difficulties with IPF is the studies are long, the progression of the disease is slow so it takes a long time to see the response. So being able to do precise dose-ranging from single dose studies is really important and we think gives us a good advantage in this area to bring forward some very bespoke medicines.

## **Digital ecosystem: real-time full patient experience**

The final slide I wanted to finish with was an R&D take on this digital ecosystem and down the left here you can see all the different things that we are aware of that you can measure and everybody is talking about measuring these and how important it is.

I just wanted to spend one minute talking about the orange boxes on the right because there is where from an R&D perspective I am really excited. If when you are developing a medicine you really want to understand your patient, the medicine and how that medicine interacts with your patient you need to integrate all of the measures that are listed down the left in real time and in the same patient. Because in a way, if you think about the questions that we want to ask, first of all, did the patient take the medicine? Really hard to interpret efficacy in medicines that a patient hasn't taken, so did the patient take the medicine – we will get that from the adherence monitor.

Did their markers of disease improve? Once we know they take it, did all the biomarkers that build our hypothesis change? We can get that along with the need for rescue medicine, everything else.

Did the patient feel better? One of the needs in respiratory now is to have medicines that genuinely help patients feel better. Very few patients I suspect have gone to Neil and said 'I feel so much better now my FEV1 has improved by 120ml', so we need patient-centric outcomes. Having electronic diaries for patients to enter the data in real time, we can mine the free text, we don't need to guide them, we don't need to wonder whether they've filled it in later in the week.

Similarly, was there something else impacting the patient's health? If you think about bronchodilators, things like *Anoro* and say does it affect physical activity, you need to know if the person's arthritis was bad that week they probably didn't do a lot of walking. There is no point interpreting a lung measurement if it's somebody's knee that's stopping them walking so the more that we can collect this data and mine it, the more we can start to find out about our medicine and the impact on the patient.

Ultimately quite honestly the thing we are trying to find out here is, are we giving the right medicines to the right patients, where is the unmet need and are our new medicines starting to meet that.

That's me done! Thank you.

## Question and Answer Session

**Eric Dube:** Okay, so thank you very much and now we will take questions from you in the room as well as on the phone and the webcast. We have some mics around the room to capture and if you could state your name and your institution, that would be very helpful.

**Graham Parry (Bank of America Merrill Lynch):** A few commercial questions just to kick off. It would be useful if you could give us an update on your penetration now into Medicare Part D and commercial plans for *Breo*, *Incruse*, *Anoro* and in particular where you sit on those big formularies, ESI, CVSs, where you are retaining exclusives and perhaps how that's looking into next year because obviously there is some contracting going on already.

Secondly, what are your thoughts on a post-*Advair* generic world and the risk of mandatory switching by payors back to generic *Advair* and exclusion of *Breo*? We are starting to see a lot more aggressive exclusion behaviour by payors as well.

And then thirdly, to what extent do you think you can use Salford Lung in a real world setting, so can you actually market this if it's not on the label, so how can it really benefit your interaction with a physician?

**Eric Dube:** Okay, thank you very much, Graham. In terms of the penetration in the major health plans, including the Government plans, we have broad access for our new portfolio. Looking into next year while I can't comment on what we think those contracts are, many of the contracts that we have are multi-year so we fully expect that we will be able to maintain the type of access that has allowed us to drive the uptake of *Breo* as well as *Anoro*.

Now, the uncertainty for all of us is when will we see a generic for *Advair* and we don't know what that looks like and certainly that will drive some type of disruption within the marketplace.

We believe that with the contracting that we have and the competitive pricing that we have for *Breo* that we will be well positioned to maintain that. Oftentimes we see that payors in the US will look to keep a branded product on their formularies. Our goal is to ensure that we have enough experience with *Breo* for physicians and for health plans to see that that is the right option to be able to offer for their members.

We think that SLS could be part of that, it's the entire package and I think with regard to the real world evidence that we will be able to see with Salford Lung as well as the

integration of some of the digital evidence, so you might see a lot of the integration of this medicine and digital actually be enabled by partnership with health plans and payors and that is certainly part of what we are exploring for the US in the next few years as well.

I hope that answers all of your questions, Graham.

**Michael Leuchten (UBS):** A commercial question on *Nucala*. Your CEO elaborated a little bit on how long it takes from a prescription of *Nucala* to actually getting the drug administered into the patient and I think he said about six weeks. Now if two-thirds of your patient base in the US does not have restrictions in terms of access, effectively what are those steps that delays getting those patients on to a product?

And a question for Professor Barnes on SLS. If you look at the design of the study, I presume the patients in the active arm were given some training on the new device, so when you look at a real life study like the Salford Lung Study, how do you adjust for the fact that administration training was recent in one arm when it wasn't in the other?

**Eric Dube:** Okay, why don't I take the question, thank you Michael, first on *Nucala*. We have seen that we have continued to improve the access. Up to now, two-thirds of patients that are eligible based on the label now have access and can be reimbursed.

There are several steps that are required for a biologic to be used within the office, so some of that is setting that process up within the accounter within the health practice. They also need to make sure that they can get that quickly from the specialty pharmacy and the specialty pharmacy, between that and the office needs to ensure with the payer that this is a patient that is aligned with the label, so it does take a bit of time. We've seen that six weeks continue to reduce and again we believe that we will continue to see that reduce through some of the work in ensuring that we have the right patients identified in the office and the right paperwork that the physician can fill out. With a J code that we expect next year, particularly for those patients on Medicare/Medicaid, that they will be able to get that process done much quicker.

For us, our strategy is to ensure that first physicians know exactly who the right patients are. That certainly will speed the process and we've seen that happen in the last few months.

Neil, I'll turn it over to you for SLS.

**Neil Barnes:** The advantage of the SLS study is it is done in real life clinical practice, and although guidelines always say you should teach the patient how to use their

inhaler, we know that that doesn't happen for large numbers of patients. So I don't think there is any evidence that the reason there is a difference is because of training with the *Ellipta* versus the other inhalers.

Even if there was better training, we know from numerous studies that that training about inhalers wears off within six weeks. So if you train somebody, you see them six weeks later, they have forgotten everything that you have told them, so that cannot be the reason for the difference in the results in the study.

What we believe is that it is an amalgamation of lots of things, the medicine, the simplicity of the inhaler, the once-a-day. There is no one thing; it's all of those attributes together. Sir James Black who got the Nobel Prize for Pharmaceutical Medicine used to call it 'pharmacological resultant', the effect you see is the results of many different things added together and that's what we think we are seeing in Salford.

**Andrew Baum (Citi):** If I was to play devil's advocate for a second, if I was the PBM, how seriously am I going to take data from any real world study done in another country, especially the UK, let alone the issues associated with, or the inability to use it for any marketing purposes currently in the US?

Secondly, from a physician point of view the idea of digital medicine is highly appealing but most, and perhaps Professor Barnes might agree, most primary care physicians struggle to use spirometry, let alone more sophisticated devices, so how do you shift the physician framework on to the brave new world?

And then obviously you have the issue of generic *Advair*, so if you could tell me whether I am being overly negative that would be helpful, and then separately the market for severe asthma is obviously becoming more competitive. *Nucala* hasn't shown an FEV1 benefit, it's driven by exacerbations and there are other agents which look like they may have both; how do you expect *Nucala* to thrive and survive as the competitive framework becomes more challenging?

**Eric Dube:** Thank you, Andrew. Let me first give my view on the use of the real world evidence within the US.

Our primary focus in delivering that type of evidence is to ensure that we can demonstrate the value to payors, so we are not looking for SLS right now in a commercial framework to be able to promote to physicians in the US. It's really to support what we see and what we believe is the difference with *Relvar*.

Now certainly that is not an easy road ahead but we believe that it does contribute to the additional evidence and how we may work with health systems and payors in the US on their evidence to be able to demonstrate, because as you know, many of these payors have very sophisticated and integrated databases where they can look at this type of information. We want to ensure that we can continue, not just with SLS, but to provoke the right questions that we can ask and answer with US payors as well, but I would like for Neil to cover that as well as his view on digital medicine.

**Neil Barnes:** If I can start with SLS, if you look at routine clinical trials, 70% of the participants in COPD trials are men. In the US and in Western Europe, the split between men and women is 50-50; that's exactly what we have in Salford, so Salford is much more relevant for the patients who are actually being treated.

Now when you say Salford, people think 'Oh, that's different', but when you take it down to an individual patient and you say 'This patient is 70, they have heart disease and rheumatoid arthritis, they have COPD, they have two exacerbations a year', clinicians relate to that, so they may not relate to Salford but they relate to the description of the patients who took part in Salford and there is huge interest in the medical community around this effectiveness because they want to know how the drugs are working in real practice.

The GP thing is interesting because I absolutely agree with you, GPs don't look at FEV1, but GPs in the UK and in many other countries are highly, highly computerised. In fact, general practice was computerised far before hospitals and they use data.

As a clinician, if I am confronted with a patient with poorly controlled asthma, after I've sorted out whether I got the diagnosis right, the next thing I want to know is are they taking their medicine and the ability of a clinician to decide whether a patient is taking their medicine or not is about as good as chance, your ability to predict from the questions you ask. To be able to say that this person is poorly controlled because they have bad asthma or because they are not taking their treatment is hugely valuable and there are a number of studies where people have had that information and it transforms the quality of care of patients.

This runs beyond asthma and COPD. Congestive heart disease, diabetes is all around adherence and what we are hearing is that healthcare systems are interested in that because it's one thing that can change the outcome in these chronic diseases.

As regards *Nucala* and the FEV1, it's all down to patient choice. There is no head-to-head comparison of these different anti-IL-5s, but when you compare *Nucala* where it has the similar entry criteria to the other studies, you do see an FEV1 benefit and the MUSCA study is looking at that very specifically. I think that was your last question, wasn't it? [Yes]

**Eric Dube:** Thank you, Andrew. I am going to suggest that we go to a question that we received from the webcast and this is from Franc, and apologies if I mispronounce your name, Gregori from Trinity Delta.

Neil, I am going to ask you to answer this one and it is; I am surprised at the magnitude of the difference between *Ellipta* and Turbuhaler as shown on Slide 21. I can understand the difference with an MDI, but the technique of using Turbuhaler is relatively simple, so what is or are the causes?

**Neil Barnes:** Yes, the main error that patients made with the Turbuhaler is they didn't turn it until it clicks. You have to turn it until it clicks otherwise it doesn't load the dose into the chamber and that was the main error. In fact, that's in keeping with other studies which have been done outside the pharmaceutical industry by independent people and they found similar error rates with the Turbuhaler.

**Kerry Holford (Exane BNP Paribas):** A couple of questions for Professor Barnes please.

You talked a bit about the COPD treatment guidelines being highly complex and how the GSK view would position the different types of drugs. Do you know whether those guidelines will be updated any time soon officially, the GOLD guidelines and do you expect them to follow the internal view here at Glaxo?

And then really for me where does that leave *Breo* and the ICS-containing products in the line of treatment? What proportion of patients with COPD are taking ICS today that perhaps shouldn't be and should instead be taking dual bronchodilators?

And then secondly on the FULFIL data just quickly, you touched on the incidence of pneumonia which I know is an important side effect to watch for in these patients. It was slightly higher on the triple; is that something to watch, to be aware of, something of concern here versus Symbicort? Thank you.

**Neil Barnes:** Obviously we don't know what the GOLD Committee is going to say. They usually meet at the ATS and the RS and then they update in January, so that would be when we would anticipate an update.

Guidelines by their very nature are conservative, they tend to be a little bit conservative which I think is absolutely right. I've sat on lots of guidelines and you want good evidence before you make a change, but from our understanding of the way people are

thinking and the way the evidence is going, because these are evidence-based guidelines, this seems to be the direction of travel. Whether it will reach that point next year or the year after, it's the clear direction of travel.

Your second point about *Breo* - there are within COPD patients who have a component of asthma, who have had asthma when they were a child or have asthma-like features and for them both the asthma and the COPD guidelines say they should be on an inhaled steroid, so they should be on a drug like *Breo*. But for what you might call the pure COPD patients, even if you treat them with a drug like *Relvar/Breo*, they remain short of breath which is why we think that that migration will be towards triple or dual therapy.

As regards pneumonia, this is obviously clinically a very important question. We have done more analysis and more to understand what the risk factors for pneumonia are and we have only had the FULFIL data for a very limited period of time, but I can absolutely assure you that we will be delving into that to understand those patients in whom actually inhaled steroid is not the appropriate treatment. We are not afraid of that because we have the portfolio of medicines that whatever a clinician feels is the right treatment, we can offer them that.

**Eric Dube:** Thank you, Kerry.

**Keyur Parekh (Goldman Sachs):** I have three questions, please, the first one a very broad one. If you can just help us understand how the three of you or your organisations work together? Professor Barnes, when does your organisation step into to the work that Dave's organisation is doing? Eric, when do you step in from a commercial perspective, just to help us think about from an R&D lab, the commercialisation, how the process works at GSK? That's one.

Secondly, Professor Barnes, as a clinician, given the data from the SUMMIT study, can you help us understand why you would ever want to use *Breo* over generic *Advair*?

And thirdly, Eric from your perspective, ICS/LABA in the US, should we think of that as minus 10% pricing, 17, 18, 19 minus 5% minus 20%? Thank you.

**Eric Dube:** Thank you, Keyur for your questions. Dave, why don't I ask you to comment on how we work together, how your teams get input and work with us in Medical and Commercial?

**Dave Allen:** Yes, sure. I'll keep it brief because this is one of those things you could talk for hours on, but essentially from an R&D perspective we are left to select the

areas that we work on, the diseases we work on, the targets we work on from an unmet need perspective, so there is no commercial guidance over where we put our effort.

The reason is we don't believe we can use the science that's out there, our own science in a way that is sort of bent to fit a commercial niche, so we start from where we think the unmet need is.

We go right through the first couple of clinical studies, but as we start to get a measure of what a medicine looks like, the sort of response we're getting, where it's looking, who is reacting well to it, then we engage Eric's team and part of Eric's team is specifically assigned to R&D to help us then ask those tougher questions. They start to challenge us with the commercial landscape 'There's these competitors, there's this other product coming through', they give us that internal challenge which is similar to the one that you will be offering us as it comes to the market; how are you going to position this, what are you going to use it instead of, what's the value proposition for payors? That comes in round about Phase II in quite a serious way and all of the big investment decisions for Phase IIb, Phase III, the commitment to file and then the commitment to launch is a joint R&D/Commercial decision. It goes to a joint Board which is equally represented with both.

Beyond that then, once we get the drug approved in all the major markets, it becomes a franchise asset, Neil's team will take on all of the evidence generation, all the medical activities but R&D execute on the clinical studies simply because we have the infrastructure for doing clinical work.

**Eric Dube:** Thank you, Dave. Just to add to that from my perspective, we have very clear processes and governance steps as Dave has mentioned, but I think the important thing is we speak on a very regular basis just to know how quickly things change within the respiratory market, whether it's evidence that we have, evidence from our competitors or insights that we learn from payors or physicians. It's about that very regular discussion that our teams have so that when we do make those decisions around evidence that is required or interpretation of trends, our decisions are very, very aligned and that requires almost a daily, a weekly discussion amongst all of us.

Why don't we turn, unless Neil you have anything to add on that one, to SUMMIT?

**Neil Barnes:** I would agree with everything that has been said but also myself and others who have joined from their clinical background have struggled with diseases like asthma and COPD all our professional lives and we are fascinated by the opportunities that arise from the new medicines that Dave and his team are developing. We want those to succeed, so we can provide the clinical context of the patients you might wish

to study, the endpoints you might wish to look at, so it's a really good dialogue and we've had a fantastic interaction over what's happening with danirixin.

**Eric Dube:** And why do you think a physician would choose *Breo* over *Advair* generic with the context of the SUMMIT results?

**Neil Barnes:** I don't think it's the SUMMIT results, it's the SLS results. The SLS, a lot of the patients, I think it was something like 80% of them, were on *Seretide* in the comparator limb and you saw better results with *Relvar*, so that to me, it's that mixture of attributes of the drug, the delivery device, the once daily that provides the benefit that as a clinician I'm interested in.

**Eric Dube:** And your final question around where we think the ICS/LABA market in the US will go from a pricing standpoint. I certainly can't speak to that in any detail. I think we've seen continued pressures from not just what we would expect in terms of impending generics but actually from a very competitive environment. We believe that we've been able to be very effective in ensuring the right access and we will continue to do that.

We don't know what the pricing will be but we have ensured that the approach we take will be more per year and we will have a good base in '17 to be able to promote but from there, we have to continue to see how the market evolves.

**Richard Parkes (Deutsche Bank):** A first question just on the FULFIL study, we know that adding a LABA and a LAMA together you get a significant improvement in lung function and a reduction in exacerbations, so not playing down the FULFIL data, but it didn't seem like a big surprise that you saw a benefit there.

Intellectually it seems like the question to me is more about the contribution of the corticosteroid and that contribution and given the regulators' usual requirement in terms of contribution of components, how much of that intellectual debate is relevant from a regulatory perspective and what do you expect in terms of labelling about how you advise physicians about where to use that triple combination?

That's the first question and the second question was just back to Keyur's question on pricing. Are there any comments you can make about Europe, because obviously in Europe you have had a lot of price pressure but you have been maintaining volume. When do we get to a point where prices really can't go any lower in Europe?

**Neil Barnes:** I'll answer part of that and I'll ask Elaine Jones who is the Medicine Development Lead to answer the regulatory bit because like Clint Eastwood, I know my limitations and my limitation is I don't know enough about regulatory.

I agree with you, you would have expected when you added a LAMA to get an improvement in lung function, so that's expected but what I think was not what we expected was the magnitude of that difference and that's due to the whole combination, the attributes of the FF, the vilanterol and the umeclidinium. So yes, we expected that improvement. We didn't I think expect as large an improvement as that.

I agree the question as well, as I said earlier, is who needs the inhaled steroid? That isn't answered by FULFIL; that wasn't the question it was asking, but we have other data that I have shown you that helps us with that and the IMPACT study which will report next year is our comparison of Anoro, Relvar/Breo and triple and that will be the study that really helps define the group with inhaled steroids.

I am going to ask Elaine about the regulatory.

**Elaine Jones:** Sure, yes. Elaine Jones, I'm the Medicines Development Leader for closed triple for COPD.

The FULFIL study actually is for the European filing and we did have discussions with the European Agency obviously. They did talk about the comparison to the individual components but they also accepted comparison to a standard of care and obviously Symbicort is a widely used ICS/LABA, so we decided to go ahead and choose that.

**Eric Dube:** And Richard, with regard to your pricing question for Europe, yes we have seen continued pressures based on the availability of generics within the ICS/LABA class as well as other competitors that have entered in the last few years.

I'm not quite sure that I can say where we think it's going to go. What I can tell you is one of the approaches and the questions that we need to ensure, how do we ensure that we continue to deliver growth through that volume and also how do we think differently about the development and generation of evidence to be able to answer questions to demonstrate the value.

Looking at studies such as the Salford Lung Study where we have with COPD, next year we will have with the Salford Lung Study for asthma with *Relvar*, these are the things that we are seeing interest from payors within the UK as well as beyond. These are the things that we need to think differently as well as to be able to measure that with digital or with the data that may have access to in their countries, but I am not quite sure that I would be able to say anything specific about where pricing will go to.

I think this will be our last question, thank you.

**Marietta Miemietz (Primavenue):** Just a few questions on the closed triple, please. Following on a bit from Kerry's commercial question, the 30% of COPD patients who are currently on open triple, is that actually true for all geographic regions or is that mainly US and can you tell us a little bit about who those patients are? Is that basically the whole GOLD D population or is that a lot of frequent exacerbators who basically aren't appropriately categorised in the current GOLD guidelines and is there actually any chance that we could get a high penetration of triples once the closed triple is available?

And then I just wanted to clarify on the US approval pathway in COPD. Are you actually confident that the FULFIL data are good enough to get a full approval in the US now and what is it that you saw that finally convinced you to file now as opposed to 2018? Should we expect a conditional approval initially? Given that IMPACT as well as the comparison study versus the open triple are becoming available at roughly the time that you would expect the FDA to make a decision under the normal pathway, do you expect a delay because they would want to look at that data?

And then I just wanted to quickly ask about timelines for the closed triple in asthma and whether you think you could still be first or what the marketing implications would be of not being first for your *Advair* and *Breo* franchise? Thank you.

**Eric Dube:** Thank you, Marietta. Let me take a few of the questions around the triple patients and then I will ask Elaine to talk a little bit about the FDA pathway.

Yes, globally we see about 30% of patients on open triple. It does vary market by market, so we see broadly in Europe and in the US it's about 30%. What we see here in the UK is it's closer to 50% and in fact that's what we saw in the Salford Lung Study, but there are other markets such as Japan where I was where it's lower, closer to 10-15% and so there is geographic variability. A lot of that has to do with how the physicians initiate therapy, whether they initiate predominantly with ICS/LABA or with LAMA and what they think about the disease broadly.

I would say that in terms of who these patients are, we have looked at this and there is no easy answer, so what Neil said around the complexity within COPD, we certainly see that with the pathway towards triple. What we see is that most patients throughout the progression of their disease will get on to triple. In fact, we've seen some studies that suggest that over seven years, nearly 100% of patients ultimately will go on to triple.

The real question will be how do they get there and that's right now based on the complexity of the guidelines, the GOLD guidelines that Dr Barnes mentioned. There is no clear pathway and so I would say there are a variety of different patient types that go on to open triple. A lot of them are GOLD D and certainly Neil, you can provide any additional comments on that.

Our view is that is the large opportunity because again many of these patients do suffer with symptoms and with further exacerbations, so we do believe the patients will step up, there is an opportunity, but we need to make sure that we get these patients on to closed triple first and we will continue to evaluate whether we see that there is still more opportunity. Certainly on a patient basis, there is an opportunity for them to progress to closed triple as soon as a physician sees that they still suffer from symptoms.

Neil, anything you would like to add?

**Neil Barnes:** Yes, I absolutely agree with you. There are these different treatment patterns in different countries and that's pretty much like it was when I first did respiratory medicine with asthma because at that stage the evidence was not strong enough to say 'This is the right way to go'. Now, wherever you go in the world you will find the same treatment guidelines and I think that's what we are moving to with COPD. Once the evidence is strong enough, doctors move. If you get tuberculosis, it doesn't matter where you are treated, it will be the same. If you have a heart attack, you are going to be treated the same way because the evidence is strong enough and when we get that evidence strong enough in COPD, the same will happen. Doctors move when the evidence is strong enough.

**Eric Dube:** And Elaine for the questions on FDA.

**Elaine Jones:** Sure, yes. The evidence for the European filing is the FULFIL data. That has the Symbicort strength that's just approved in Europe, that's not the US strength of Symbicort.

The US evidence comes from the open triple studies that Neil presented, so that's the regulatory pathway that is allowing us to file early or to file this year.

We've had discussions with the FDA as we had with the European agencies and obviously the data will be considered by the agency and they will take their action based on the data, but they have indicated that we should go ahead and file.

**Eric Dube:** Okay, and the last question related to closed triple asthma. Dave, would you like to take that?

**Dave Allen:** Yes, sure. Just one additional thought on the closed triple COPD question that you asked and that is that if you look at the global data there is also about 12% to 18% of patients who go straight to closed triple on diagnosis because they are just turning up late. By the time their disease is at a stage they are seeking medical intervention, they go straight to triple so I would echo Neil's point which is it's great when you write all this stuff out on diagrams and you see progression and one therapy being added in the real world, you treat each patient individually, which is frankly the way it should be.

Closed triple asthma, we are good to start the Phase III programme. We have done the dose-ranging, we should get the Phase III programme run by middle of '19, we should be filing towards the end of '19.

**Eric Dube:** Marietta, just on the final part of your question, our aim is to be first. Our aim is to be first with closed triple and as I mentioned our aim is to ensure that we can demonstrate why our portfolio and our medicines and the molecules are best within its class.

We do believe that that will be the timeline that we are aiming for in the development of closed triple asthma as well.

And with that I would like to say thank you very much for your time today. For those of you that are in the room, we will be taking additional questions outside in the reception area and for all of you on the phone and on the webcast, thank you very much, that concludes our session.

- Ends -