Darrell Baker, SVP, Global Head of Respiratory:

Agenda

Good afternoon and welcome everybody to this call, which is from the ERS at Munich where there has been a lot of very interesting new science, and the primary aim of our call this afternoon is to update on some of that science, and in particular some of the science related to eosinophils, so the presentations that we have for you this afternoon have the theme of eosinophils. I'll do a quick update on the business situation, and then we'll move to the primary purpose of the call, and we have a number of presenters for you. Now the role of eosinophils in asthma really is not controversial, it's well established, and Professor Ian Pavord will review for you some of the evidence to demonstrate the importance of eosinophils in severe asthma, before he hands over to Steve Yancey, who is our Medicine Development Leader for mepolizumab, and the mepolizumab phase III data were presented at this conference and also have been published in the New England Journal and have created a great deal of interest. So that's the role of eosinophils in severe asthma, but also at this conference, very importantly, there has been a lot of discussion about a potential role for circulating eosinophils to help guide patient management in COPD, and Neil Barnes will discuss that potential role and some of the data which we have presented in support of that. Before that though, let me do a brief update on where we now stand in the respiratory portfolio.

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

As you will know I expect, GSK is the global leader in the respiratory market with a 33% share of what is now a 21 billion global market, and the vast bulk of the market currently is inhaled medications. Amongst those inhaled medications obviously GSK has leading products at the moment, notably *Seretide* and *Advair*, but we're in a phase now of introducing a new range of *Ellipta* based inhalers, beginning with *Breo Ellipta*, and then there is Relvar outside of the US and especially in Europe, which has been approved and has launched – I'll give you an update on that. *Anoro Ellipta* similarly, which is in its early launch phase, but you will probably have seen that we have recently announced approval of *Incruse Ellipta*, this is a mono-therapeutic umeclidinium and *Arnuity Ellipta* which is our brand name for mono-therapeutic fluticasone furoate.

In addition to that we have a whole range of products in development of which the next and very important one is mepolizumab, and that's a departure from the inhaled range. Mepolizumab is a biological treatment, and as you can see from this slide biologicals really represent a small share of the market currently, but we've been interested to see a number

of analysts reporting an expectation of a significant growth in this biologicals market as we see new agents introduced, which Mepolizumab will be one. So we see this as a very important area and a source of potential growth in the future.

***Breo Ellipta* / *Relvar Ellipta* launches underway**

Moving on to *Breo Ellipta*, as you can see *Breo Ellipta* now is actually approved in 51 countries around the world, and launched in 19, including importantly the major markets in Europe, in the US, and in Japan. And uniquely, certainly as far as our portfolio in respiratory experience is concerned, we launched in those three regions within three months. We actually expect to launch in a further 19 markets between now and the middle of 2015, and some of those very significant markets. We have secured reimbursement in Australia and we will be launching there before the end of the year, and then also expect to launch in other significant markets including large markets in Europe, like Italy and Spain, and also we are expecting to launch in Brazil almost a year ahead of what would be a normal timeline for that market. The data which I'll show you will be data from the US, and you're looking here at new to brand prescriptions, so these are not the total prescriptions, but this is the share of opportunity which we have achieved with *Breo* in the US, and as you can see that share has been growing progressively as we've secured increased access to that market, especially in Medicare part D, which is very important for the COPD market in the US.

As we have increased the access position we have increased share, and we're especially pleased to see a share now of well over 10% amongst pulmonologists and their prescribing obviously is a very good lead indicator for the future. Now our plan is not at this meeting to update on the access situation, that will be formally updated at the quarter three results, but I thought I'd show you this graph to illustrate the progress that we are making there, and also just to remind, although I'm sure many will have seen the announcement we made in June, that we have now filed *Breo Ellipta* in the US for use in asthma, and then we also announced that we have now completed recruitment of the large Summit study in COPD, which will study *Breo Ellipta* and we expect to see the data for that study next year.

***Anoro Ellipta* launches underway**

Moving on to *Anoro*, it is much earlier in its launch phase, but we have launched in eight markets, again including key markets as you see there, and achieved approval now in 38 markets globally, and we see a similar picture, although much earlier in its launch phase in the US, you can see that again with *Anoro* we've achieved approaching 10% share of the new to brand opportunities for pulmonologists prescribing, and that's translating to a 4% share of new brand prescribing over all. And importantly in the US we have now secured agreement through FDA and OPDP that we can directly claim superiority in terms of lung

function improvement over tiotropium (*Spiriva*), and our representatives in the US have just recently begun detailing with that significant important head to head claim over *Spiriva*.

Upcoming catalysts in our respiratory franchise

A brief update on other really upcoming events in the portfolio, as I've said *Incruse Ellipta* now is approved in the US and Europe and launch is anticipated by the end of this year, and similarly *Arnuity*, the mono-therapeutic FF approved in the US and launch in the US as anticipated in 2015. Similarly, we have announced an expectation that we will file for mepolizumab in severe asthma by the end of this year, and we've also announced the beginning of phase III studies for EGPA, which commenced in February of this year. And also we have commenced a COPD phase III programme which commenced in April, also for mepolizumab.

In severe COPD too, a closed triple therapy. This is our three once daily molecules in a single inhalation, single inhaler once daily approach has begun phase III in July, and we announced that study. That study is known as IMPACT, and the intent is to recruit 10,000 patients into that study and to follow them over 12 months and compare directly *Breo*, *Anoro*, and this triple therapy looking at exacerbation reduction, reduction in the rate of exacerbations over the 12 month period as the primary end point.

I mentioned that we had filed for *Breo Ellipta* in the US, we expect an FDA action in Q2 for this asthma filing, and as we've completed now recruitment for SUMMIT, as I said, we will see that reading out next year. And we also, and covered at this ERS, we expect to complete recruitment in the Salford Lung Study for COPD by the end of this year, but I do remind that the patients in that study, 2,800 patients, will be treated for 12 months, so data will not be next year, and similarly asthma recruitment is progressing well and we gave a significant update on the Salford Lung Studies in our symposium at this congress.

Seretide* comparator study DB2116134: *Anoro Ellipta* vs *Seretide

So that's the business update, let me now move on to really introduce the question of why we feel in COPD that blood eosinophils, circulating blood eosinophil levels are important, and I will do that by talking about using as an example this study, the outcome of which we announced earlier in the year, in March, there is a lot of detail on this slide, but essentially what it is saying is that we in a short term study in COPD, including a range of moderate COPD patients, we put *Seretide*, the 500mcg strength of *Seretide*, which is the European approved strength, against *Anoro* and studied in the short term this group of patients in terms of their lung function improvement.

Anoro Ellipta* significantly improved FEV_1 compared to *Seretide

These are clearly typically COPD patients, but what's really important is that these patients were recruited because they had not had a history of exacerbations, and they had not had an exacerbation in the last 12 months. The aim for these patients is to improve lung function, and we saw in this study, perhaps not surprisingly, that at the end of the study, on day 84, there was a significant improvement in lung function for the dual bronchodilator, compared to a single bronchodilator, together with an inhaled steroid. As you see here on average over the 24 hours an 80ml improvement. We've done two similar studies comparing with the US strength of *Advair*, and other companies have done studies which have compared dual bronchodilators to ICS/LABA in these kind of patients, again without a history of exacerbations. So perhaps this finding is not surprising.

Patient profiles for the new portfolio

We also find that these treatments are well tolerated, there is no significant differences in terms of all of the safety outcomes that we measure, and indeed we would say along with many others, that if you have a COPD patient like the one on the left, whose primary concern is breathlessness, whose not had a history of exacerbations, that we would recommend *Anoro*; a dual bronchodilator for such a patient. The real question is which patients should be managed with inhaled corticosteroid therapies. And in particular how do you manage those patients who do have exacerbations, should they be managed with dual bronchodilators, or should they be managed with a regimen which includes inhaled steroids? And that's been very much the debate here at the ERS over the last few days. Our view is that many patients do require inhaled steroid therapy in their regimen and we recommend *Relvar* or *Breo* for such patients if they're receiving a dual regimen, so we recommend ICS/LABA in those patients, although of course there is the option, again as you see on the slide, that if a patient with ICS/LABA is still experiencing symptoms you can add further bronchodilation, and we recommend that we would add in this case *Incruse*, our mono-therapeutic LAMA compound, so we give triple therapy with two inhalers, which includes the ICS/LABA and the LAMA separately. So this is our approach, and this is obviously one of the reasons why we are interested in triple therapy. And you see here a simple description of the profile of the patient as they may sit in front of a physician in a physician's office. We acknowledge though, that what we really would like is something which is more objective, a biomarker perhaps, which would allow us to inform appropriate selection of patients to get the right medicine to the right patient in a more objective fashion, and that's what we've been looking at in GSK, and I'm now going to hand over to my colleague Neil Barnes, who will

take you through some of the data which we have presented here, which is beginning to shed light on this question and identify possibly such a biomarker.

Professor Neil Barnes, Global Medical Head, Respiratory:

Thank you Darrell, the idea that eosinophils may have a role in COPD, particularly during exacerbations, has been around and intermittently discussed for quite a long time now.

Exacerbations in mild COPD: Eosinophils

So this is a study which is nearly 20 years old, doing bronchoscopy and biopsying from the airways of patients with a variety of different respiratory problems. So over on the left you will see the patients with asthma, and it is no surprise that they have a raised eosinophil count in their airways. But what was surprising, particularly when this study was done, was that individuals with COPD having an exacerbation, having a worsening, also had a raised level of eosinophils compared with those with chronic bronchitis, which is really mild COPD, and controls. Now there have been since then a lot of relatively small academic studies which have supported in some patients a role for eosinophils, and further suggested that making a very simple measurement of a blood eosinophil count, which is widely available in primary and secondary care, had predictive value.

Significant reduction in the annual rate of exacerbations with FF/VI compared with VI alone in COPD

So the team who were looking at *Relvar* took this data from the pivotal trials, this is the trials that demonstrated the value of FF when added to vilanterol in patients with COPD to demonstrate a reduction in exacerbations. So this is data that has now been published for more than a year, and what it demonstrates is that if you add various doses of FF to vilanterol you get a reduction in COPD exacerbations, and with the licensed strength of *Relvar / Breo* 92/22, that's around a 27% reduction in exacerbations. But with this data, in that a blood eosinophil count may be helpful in predicting those who have a better response, they retrospectively analysed the results of this trial, broken down by blood eosinophil count. So the orange bars are the exacerbation rates with vilanterol, and the blue are the treatment with *Relvar*.

Now you can see a number of things from this graph, the first is that as your eosinophil count climbs from 0-2, 2-4, 4-6, and 6 and above, the number of exacerbations in the vilanterol treated group increases. So this suggests that a blood eosinophil count may be a marker of those at increased risk of exacerbations. And secondly, that the reduction in exacerbations is greater in those with a raised eosinophil count. And further and intriguingly there does seem

to be a level of exacerbations of somewhere around 0.8 to 0.9 per year which is difficult to drive individuals below.

So what we thought would be interesting would be to go back into the large database of trials that GSK has in COPD, and see if we could confirm these results.

INSPIRE results

So this is the result of the INSPIRE study. Just to remind you the INSPIRE study was a trial comparing *Seretide* with tiotropium over a one year period in individuals with a history of exacerbations, and the overall results of the trial showed no difference in exacerbations between *Seretide* and tiotropium. But when we break this down by eosinophil levels we find a different result. So on the left are the individuals with the less than 2% eosinophil level, and here tiotropium provides slightly greater reduction in exacerbations than *Seretide*, although that does not reach statistical significance. In contrast those with the eosinophil level of 2% or greater again there is a higher exacerbation risk in that group, when they are treated with tiotropium, and that is significantly reduced with treatment with *Seretide*.

ISOLDE rate of decline of pre bronchodilator FEV_1 blood eosinophils >=2% and <2% in COPD

Now one further result with this retrospective analysis of the previous trials that we're intrigued by is this: This is a study called ISOLDE, which is about 20 years old, which tried to investigate whether if you treated individuals with COPD with an inhaled steroid you could reduce their rate of decline of lung function, because of course one of the hallmarks of COPD is this accelerated decline in lung function.

Treatment effect for FF/VI vs VI alone based on increasing levels of blood eosinophils

On the left are those individuals in the study who had less than 2% eosinophil count, and in the white is the placebo, and in the yellow fluticasone treated group. So there's the small increase in lung function that you see when you treat with an inhaled steroid, but then if you look from the three month time period on the technical term is to look at the hockey stick effect. The slope of the lines is almost identical. In contrast again, on the right, are those with the greater or equal to 2% of blood eosinophil count. Again the white is the placebo group, the yellow have an increase in lung function, again this small increase in lung function when going onto an inhaled steroid, but now the slope of the line is quite different, and the difference is 38mls a year with a very significant p-value, and just to put that into context, that's about the difference between a smoker and a non-smoker. Unfortunately we have no other data set to confirm or refute this finding.

Distribution of COPD patients by a 2% eosinophil cut-point in RCTS (SFC, FP, FF/VI), NHANES

Now just to put this into some context, we have looked here at all the trials in COPD and how often individuals have an eosinophil count of above 2%, and the light blue shows that in the majority of the trials there is a greater than 50%, generally around 60%, but on the extreme right I have highlighted data from NHANES, which is a large American database, very well validated, where they have spirometrically confirmed COPD, and in more than 90% of these individuals a blood eosinophil count. And in that database of the community it is 71%. And what we now know from looking at this data is that the majority of these individuals are within the normal range. So although some of them have an eosinophil count above the normal range, the majority of them are an eosinophil count within the normal range, and we will be planning to look into this further in a variety of different research techniques, because we feel if we can confirm this, this becomes a very simple and useful biomarker that physicians in primary and secondary care can use to guide their treatment decisions.

COPD Conclusions

So we think this higher eosinophil group having a greater reduction in exacerbations when treated with inhaled steroids, and possibly a greater reduction in lung function is important, and the data strengthens the academic studies that have previously suggested that a blood eosinophil count has predictive value in COPD.

So it is now my pleasure to hand over to Professor Ian Pavord, Professor of Respiratory Medicine at the University of Oxford, and he is going to switch back now to looking at the role of the eosinophil in severe and difficult asthma. Ian…

Ian Pavord, Professor of Respiratory Medicine, University of Oxford:

Eosiniophilic airways disease: Focus on Severe Asthma

Thank you Neil, and thank you all for listening. This has been a 20 year journey for me, but it started when I spent some time in Canada with Freddy Hargreave, a man who devoted his life to developing techniques to measure airways disease, and at the time I was in Canada they were developing this technique called induced sputum, as a means of objectively assessing airway inflammation, and it proved to be surprisingly robust, and particularly good at identifying eosinophilic and neutrophilic airway inflammation, and if you look at that cell count in the middle. Those cells with red staining are eosinophils, and the cells with multi load nuclei are neutrophils.

So I must say at the time I wasn't convinced that this technique would have great clinical utility, and 20 years on that remains in some people the prevailing view, and the reason I wasn't convinced was that the paradigm we had for disease at the time for asthma, but eosinophilic airway inflammation as the root cause of the abnormality of airway function, that underlined most of the clinical problems that our patient had. So it seemed to me that it would be better to assess the downstream consequences of airway inflammation than assess it itself. So I was unconvinced at the time, but when I got back to the UK and to Leicester and started measuring airway inflammation in large numbers of patients in a relatively unbiased way, we had a number of surprises.

Sputum eosinophilia in airway disease

The first is shown on this slide and each of these dots is an individual study, and that study's estimate of the prevalence of a sputum eosinophilia in that category of patients. And you will see in asthma that sputum evidence of eosinophilic airway inflammation was only really present in about two thirds of patients. So it was not invariably present in patients who had asthma and symptoms.

The second surprise were conditions that we considered to be very distinct from asthma, such as chronic cough and chronic obstructive pulmonary disease in some patients were associated with sputum evidence of eosinophilic airway inflammation. So the implication is that in categorising patients using our traditional categories we are not in fact identifying distinct pathologies, and particularly that is the case for eosinophilic airway inflammation.

Sputum eosinophils and steroid response

The second clear finding was that when eosinophils were present in sputum the patient responded to steroids, be they inhaled steroids in a patient with asthma, or oral steroids with a patient with COPD. So it was largely irrelevant what the label was, if they had this pathological feature there would be a response to steroids.

Which patient needs more steroids?

And the third unexpected finding was that within patient groups there was really no correlation between symptoms on one hand, and inflammation on the other. So if we look at the patient on the left, this is a patient with a lot of symptoms, with very chaotic airway function as shown by morning and evening peak flows, and large amounts of beta 2 agonist consumption. So very poorly controlled asthma, but if you look at the sputum there are none of those red cells, so there is no eosinophilic airway inflammation. On the other hand the patient on the right has what appears to be well controlled disease, with no day or night time symptoms, very good peak flow, and relatively little beta agonist use but a sputum that is

packed full of eosinophils. So in making an assessment of disease control, when it is not necessarily identifying information. And it seemed to us that inflammation related rather more to the risks of sudden severe attacks of the disease, and you can see the patient on the right, despite having well controlled disease, has in fact nearly died of their asthma on two occasions.

Targeting sputum eosinophilia and severe exacerbations of asthma

So the question was what should be guiding steroid treatment in patients with airways disease. Should we continue to use symptoms, and lung function as our primary means of identifying people who should be treated and titrating that treatment, or should we in fact use objective measures of eosinophilic airway inflammation, and this became a very important clinical question. This study by Ruth Green is the most cited paper in airways disease research of the last ten years, showed very clearly that if you titrate steroids by markers of eosinophilic airway inflammation, induced sputum eosinophils, the patient benefits in terms of exacerbation. So exacerbation frequency was reduced by two thirds.

I think the reason this study had such a big impact is that it taught us three very important things. Firstly, the major read out of better inflammation control is reduced risk of severe exacerbations. Secondly, it is possible to have better inflammation control without impacting on the patient's symptoms or lung function. If you look on the left here you can see that there is no difference in lung function over the 12 months of this study in the patients in red who had inflammation control, and the patients in yellow who didn't.

The third important lesson was that a significant number of patients with severe asthma don't have eosinophilic airway inflammation, and in this population we were able to withdraw steroids without any apparent deterioration in their condition. So at this time we changed the paradigm from the one I showed earlier, to one that looks a bit like this. Symptoms we felt were largely a result of abnormal airway function, whereas exacerbations and attacks were much more closely linked to eosinophilic airway inflammation.

Effect of monoclonal antibody to IL-5 (mepolizumab) on sputum eosinophils and traditional outcomes

At roughly this time when we had this eureka moment, this study came out on the left. The first evaluation of mepolizumab, a monoclonal antibody that blocks IL-5, and therefore targets eosinophils, and if you look at the top panel on the left you will see that this drug really works. This shows the induced sputum eosinophil count prior to and for a month after one injection of mepolizumab, and you'll see in the lighter colour that the induced sputum eosinophil count went down well into the normal range after treatment, so it does what it is

supposed to do. The bottom panel shows that this reduction in eosinophilic airway inflammation was not associated with any improvement in airway function, assessed here as airway responsiveness, which is perhaps the most sensitive test of airway dysfunction in asthma, and if you look on the right a subsequent relatively large clinical trial showed no evidence that two doses of mepolizumab improved lung function.

Mepolizumab in refractory eosinophilic asthma

At the time the scientific community's views were that the eosinophil's role in airways disease was dead, and I remember that being said in pubs at the ERS, but we felt that this didn't preclude a beneficial effect of treatment on exacerbation frequency, and thankfully GSK listened to us, and they made available a small amount of money to do this 60 patient randomised control trial where we investigated placebo versus mepolizumab 750mg intravenously every month, and there were two key features to this trial. One, we knew the patients had eosinophilic airway inflammation, so they had the pathology that the drug inhibits, and secondly, we knew they had the clinical consequences of that pathology; they were having recurrent severe exacerbations.

Effect on airway inflammation and clinical parameters in severe asthma

This first slide showed that mepolizumab did what we expected it to do in that it greatly reduced the blood shown at the top left, and the sputum, the one down, eosinophil counts. We didn't see a lot else in terms of symptoms and lung function, there was a minor improvement in quality of life but no effect on FEV1 asthma symptoms airway responsiveness.

Mepolizumab: Effect on exacerbations in severe asthma

What we did see was a marked 50% reduction in the number of severe asthma exacerbations that occurred over the 12 months of the study, providing strong support for the view that inflammation control leads to reduction in risk of exacerbation.

Corticosteroid sparing effect in severe asthma

And a study that was published at the same time as our study looked at the effects of mepolizumab in patients with severe asthma who required oral steroids to control their disease. Now these drugs cause horrendous side effects, and patients who require them their big ambition is to get off treatment, so this is what we call an oral corticosteroid sparing study, only 20 patients with severe eosinophilic asthma, but showing that four months treatment with the same dosing regimen allowed patients to reduce their prednisolone dose by 84% compared to 44% with placebo, and there was no loss of asthma control, in fact

there was some evidence of improved control in the treated group. So good supportive evidence for a role for this treatment in asthma.

The DREAM study

Now at this point Hector and Steve came on board and the clinical development of this drug has been a dream for me. We next did the DREAM 2b study. There was concern from all of us that the biomarker induced sputum eosinophil count was not going to be applicable in standard clinical practise. So we used more permissive criteria for eosinophilic airway inflammation which I can go into, but one of the criteria was a raised blood eosinophil count. There was also concern about dose ranging, and we looked at three different doses, despite a bitter row between Steve and me, we went down to 75mg, which is ten times lower than the effective dose from the earlier studies, and you'll see on the right that all three doses were effective in reducing exacerbations, and there was no evidence on his outcome of a dose related effect.

The rather complex diagram on the bottom is interesting, and I'm going to talk you through it, but broadly there were only two predictors of exacerbation frequency during this study. The number of exacerbations that the patient had had in the previous year, and you'll see as we move from the green dashed line to the red dashed line, that as your prior exacerbation frequency increases the risks of exacerbations in the future increases.

The other determinant of exacerbation frequency was the peripheral blood eosinophil count, and the higher that was, the higher the risk within all three strata. With mepolizumab, and you can see three lines that look very close together at the bottom, the relationship between prior exacerbation frequency and future frequency was lost entirely, as was the relationship between blood eosinophil count and future exacerbation risk. And if you look where the thick lines cross the dotted lines, you can see that the value is around 0.15 times ten to the six eosinophils per litre of blood. So that seems to be the point at which efficacy began to be. That's roughly equivalent to 2% in the differential cell count.

Is there a role for mepolizumab in eosinophilic COPD?

I'm going to finish here because what's particularly exciting for me is that there are a large number of patients who have a diagnosis of COPD who have eosinophilic airway inflammation, both in the proof of concept study that I showed you first, and in the dream study, characteristics that you might associate with COPD such as the absence of a bronchodilator response, onset of symptoms after the age of 40, fixed airflow obstruction, and a smoking history, these were not in any way associated with a positive response to treatment. In fact if anything patients with a COPD like pattern of disease seemed to do

rather better with treatment that patients with an asthma like pattern of disease. So this is a drug for eosinophilic airways disease, not asthma, not COPD, that's my feeling.

Adverse events and deaths

I show the adverse effects here.

Steve Yancey, Medicine Development Leader, mepolizumab

So thank you Ian, my name is Steve Yancey, I'm the Medicine Development Leader with mepolizumab, and we're very appreciative of Ian's 20 year journey, and I think what we'll show you today really are the highlights from two key phase three trials that were released and presented here at ERS just yesterday, and were simultaneously published in the New England Journal of Medicine. But before I move to those, I would also like to introduce with me today Dr Hector Ortega, he's the Lead Global Physician for mepolizumab. He is also the lead author for one of the trials that were described today, so it was very convenient to have him with us today. So I've mentioned the two trials that were released.

Objectives/design of the Phase III asthma programme

You can see on the screen now they're designated as MEA115588, known as the MENSA trial, and also MEA115575, known as SIRIUS. Now, the objectives of those trials are listed in the blocks, you can read that, but if I were asked to be a bit more definitive around the key objectives I would describe three key objectives in the 5588 trial, MENSA, and that would be firstly to replicate the finding around efficacy of mepolizumab in reducing severe exacerbations. My second objective in that particular trial was also to introduce subcutaneous administration to patients. So this is the first trial where we have looked at both IV dosing, as well as subcutaneous dosing, and we're moving from 75mg intravenous dosing to 100mg subcutaneous dosing. My other third primary objective in this study would be just to further characterise the overall benefits as well as the safety profile of mepolizumab in continuing long term treatment. The second study, the SIRIUS study, or 5575, Ian has already spoken on this. He mentioned a small, 21 subject study looking at sparing of oral corticosteroids. This is a larger study, now stepped up to 165 subjects who were treated for 24 weeks, and in this trial we are trying to examine whether or not 100mg of Mepolizumab given subcutaneously can reduce the dose of oral corticosteroids in a group of patients all of whom require oral corticosteroids. In addition this trial further informs on the overall efficacy and safety of mepolizumab.

Asthma and eosinophilic inflammation

So this is an illustration just reminding you that as Darrell said at the beginning of the meeting, the role of eosinophils in asthma is uncontroversial. The over expression of eosinophils can lead to airway inflammation through the release of preformed toxic granules. They lead to hyperplasia, hyper-reactivity, mucus production, remodelling. Eosinophil production, migration and activation however, is triggered by IL-5, and mepolizumab is a targeted antibody against IL-5, and that by inhibiting the activity of IL-5 on the eosinophil itself, it will reduce the levels of IL-5 circulating in blood, but also in sputum.

MENSA: Design and patient identification

This is a very simply diagram of the MENSA study, this is the exacerbation reduction trial. You can see by the closed blue diamonds, the closed orange squares, and then the black diamonds, it represents the treatment groups of mepolizumab 75 IV as well as 100 subcutaneous, as well as placebo, but the key feature of this trial is really illustrated on the left, and it represents how these subjects were identified for study. All of these subjects were required to be receiving high dose inhaled corticosteroids as well as an additional controller medicine. So the vast majority of these patients are on medicines such as *Seretide* and *Symbicort*. In addition, subjects could or could not be receiving oral corticosteroids, in this trial about 25% of patients are also receiving daily oral corticosteroids. But importantly all subjects had to have a requirement for two or more exacerbations in the prior year, and thirdly we have a very targeted biomarker; blood eosinophils, and as Ian showed in the previous presentation, we use a cut off of 150 cells per micro litre at screening, as well as 300 cells per micro litre as shown in the past 12 months. These three criteria, clinical criteria as well as a blood biomarker, are the predictive criteria for a response to mepolizumab.

Results: Primary Endpoint – Reduction in Exacerbations

What is shown on this slide are the results of the primary end point, and firstly it is always important to note the primary end point was met, and what's illustrated on this particular slide are the cumulative number of exacerbations on the vertical axis, and on the horizontal axis it is representing time or time in the study, and what you can see is the accumulation of exacerbations over time up to week 32, and in the blue and in the orange lines you see the cumulative number of exacerbations for patients who receive mepolizumab, either as IV or subcutaneous administration. A couple of key points to take from this slide; the first is there is a 50% reduction in the exacerbation rate for patients receiving mepolizumab independent of treatment. In one treatment it is a 47% reduction, in the other it is a 53% reduction. But what is evident from this slide is that these effects are comparable, and you may recall when I opened my talk I said I had several key objectives in the MENSA trial, one was to replicate

the response in terms of reduction in terms of serious exacerbations shown on this slide, but also to show that subcutaneous administration can be comparable to IV administration, also demonstrated on this slide.

Secondary Endpoint - Changes in Pre-BD FEV_1

Other physiological end points include measures of lung function, and this is a plot of lung function again, looking at the change of FEV1 over time from screening over to week 32, and the black line represents the response within the placebo group, and the blue and the orange line represent the responses to mepolizumab. And what is shown is that there was an improvement of mepolizumab treatment above the changes in the placebo group. Those changes represent 100ml improvement at the end of the study which was found to be statistically significant at 0.001. But it is also important to understand what's the impact of our medicines on a patient's quality of life.

Secondary Endpoint - Changes in St George's Respiratory Questionnaire

This is illustrating the results of the St. George's respiratory questionnaire, this is the results at the end of the trial, and what's illustrated are the changes in both placebo shown in black, and then the two doses of mepolizumab to the right. A change of four units in this instrument is considered to be clinically meaningful to patients, so even in the placebo group you see that patients improved over time, Hawthornee effect is very common in randomised controlled trials, but importantly when we look at the mepolizumab treatments we see much larger changes, and we compare those changes against the placebo group we see changes of 6.4 units, and also 7 units, which are also both highly statistically significant. Representing that these patients are achieving a large improvement in their overall quality of life, and that it exceeds that seen in the placebo change.

Key Results by Higher Blood Eosinophil Counts (≥500 cells/μL)

As Ian mentioned in his presentation, it is also well understood that there is a direct or a positive association between the level of eosinophils as well as the overall patient severity, and we've been interested in trying to look at the various subgroups of patients within our own studies. This is a particular two panels which are from the supplement in the New England Journal of Medicine. What it is showing is the response to mepolizumab treatment for patients who had incredible high levels of eosinophils, in this instance greater than 500 cells per micro litre. Shown in the left panel are the exacerbation rate or changes per year in this subgroup, and on the right panel we'll move to lung function. But if we focus firstly on the left panel we see that there was a 74% reduction in the exacerbation rate for patients as well

as an 80% reduction in the subcutaneous administration for patients with the highest levels of eosinophils.

Correspondingly there were greater increases in lung function. Shown on the right panel are the pre dose FEV1 as well as the post dose FEV1 changes, and you can see those changes in this subgroup of patients with highest eosinophil levels represent 183 and 132ml changes, and in the post dose changes you see 222ml and 380ml respectively.

Of course all medicines are defined by their benefit to risk profile and it's very important that we fully examine and understand the adverse event profile of our medicines.

Summary of Adverse Events

This is simply providing a top line overview of the adverse event profile of mepolizumab in this 32 week trial. Again, you can see that this is a large trial with nearly 200 patients per arm, but what is evident is that all AEs are similar across treatments, including placebo. SAEs are similar across treatments, including placebo. There was one fatal event that unfortunately occurred in the placebo group, but the overall takeaway message from this slide is that mepolizumab has a favourable safety profile and one that is similar to subjects receiving placebo.

SIRIUS: Design and patient identification

I'm now going to move to the second trial. This is the trial designed to look at the ability of mepolizumab to serve as a steroid sparing agent, an oral steroid sparing agent. I'm not going to spend a lot of time on the overall methodology of the trial, just to highlight that before patients were randomised to treatment there was an optimisation phase in which the lowest effective dose of oral steroids was determined, and in most instances most patients moved down their dose of oral steroids. They were then moved into an induction phase, this was when they would be randomised to either placebo or mepolizumab, and maintained without any changes in their oral steroid dose for four weeks. They then moved into an OCS reduction phase where the dose of oral corticosteroid was titrated according to a pre planned algorithm, and then lastly between weeks 20 and 24 there were no further changes in the reduction of oral corticosteroids, and the two groups were compared with regards to the relative changes of each. I should also mention before moving to the results that these patients like the MENSA trial are also receiving high dose inhaled corticosteroids as well as another controller medicine. So recognising what Ian has told us and reminded us of, that these patients suffer many side effects from both short and long term systemic corticosteroids, so it has been a very intriguing trial to the clinicians attending ERS.

Results: Primary endpoint of OCS reduction

We look at the primary end point, the primary end point was met, and the odds ratio of a patient likely being able to reduce their dose of oral corticosteroid was 2.39 in favour of mepolizumab with p-value of 0.008. So perhaps just to orient you to how these results can be interpreted, if you look at the top bar you can see that a greater proportion of mepolizumab patients shown in the orange were able to reduce their dose of steroids from screening by 90-100%. A 100% reduction would represent going to zero requirement for oral steroids. Likewise there is a greater reduction of between 75-90%. If we look to the bottom of the screen at the category called 'Other', these are the patients who are unable to achieve a reduction in oral corticosteroids between the weeks of 20 and 24 compared to their screening levels, and you can see that there is a much higher proportion of patients in the placebo arm compared with mepolizumab. How does that translate in terms of the overall median dose, or dose reduction of steroids in the study?

Results: Median OCS reduction during the study

This is a plot showing the median OCS change from base line over time, and at the end of the study the median reduction in the dose of oral steroids was 50% in those subjects receiving mepolizumab compared with zero in those subjects receiving placebo.

Changes in Asthma Control Questionnaire

Likewise, it is important that patients maintain a level of asthma control, a study should not have an effect such that by reducing steroids in a placebo arm, for example, you cause a loss of asthma control. In this instance it was a well crafted protocol, and one in which maintained asthma control shown by the placebo group in black, the dotted line represents where their level of asthma control was indicated using the ACQ asthma control instrument, and you can see that over time they remain near that level of unity. In fact they are drifting just below the line which is a point of improvement. But more importantly for patients who received mepolizumab following a 50% reduction in their dose of oral steroids, you see a significant improvement in their ability to maintain asthma control or show improvements in asthma control with a p-value of 0.004.

Reduction in Exacerbations

Likewise, there was a reduction in exacerbations requiring further doses of oral steroids, a 32% reduction in mepolizumab group compared with placebo, and you can see the exacerbation rate per year shown in placebo as 2.2, compared with 1.4 in the mepolizumab arm, with a p-value of 0.042.

Summary of Adverse Events

As I mentioned before, being able to define the benefit risk profile incredibly important through the development of a medicine. Here again we show the adverse event profile for mepolizumab and placebo in a group of 165 subjects treated over 24 weeks. Again, the adverse event profile is favourable for the mepolizumab, with mepolizumab similar to placebo for standard of care.

Conclusions – Asthma

So to summarise, both MENSA and SIRIUS met their primary objectives. Mepolizumab's phase three data demonstrated the potential as an add-on therapy in patients with severe eosinophilic asthma, producing a clinically and statistically significant reduction in the exacerbation rate compared with placebo, and the change I showed you was a 50% reduction. Mepolizumab produced a similar treatment effect in exacerbations, lung function, and quality of life measures, regardless of the route of administration. So the comparable bridge between IV and subcutaneous administration has been established. Mepolizumab was well tolerated with a safety profile similar to that of placebo, and in the standalone large oral corticosteroid sparing trial, mepolizumab in patients with severe eosinophilic asthma demonstrated a potential to reduce oral corticosteroids while maintaining control, and the validity of this OCS reduction approach was supported by the stability of FEV1 and ACQ5 over the course of the study. Likewise the safety profile was similar, as we've seen in previous trials, mepolizumab was well tolerated with a safety profile similar to that of placebo.

At this time I'd like to close and hand back to Darrell who will move us through the programme.

Darrell Baker:

Q&A

Steve, thank you very much. So we are perfectly on time and we now move into the question and answer session, and I want to remind, which I should have done at the beginning of this broadcast, you can ask questions through the webcast, so if you want to ask questions through the webcast please do, we do have one or two of those. We're just organising the questions which are on the line at the moment, so while we're doing that I'll take chairman's prerogative and ask Ian, as somebody who manages a lot of patients with very severe asthma, can you put into context for us what these kind of changes that we've seen to the STRQ in MENSA, the reduction in exacerbations, and particularly reduction in oral corticosteroids, what does that really mean for patients?

Ian Pavord:

I think the reduction in oral steroids was very noteworthy, and Steve said, and I agree, that that had a big impact when it was presented yesterday. We simply don't have an effective oral steroid reduction treatment available to us, none are recommended. Regular oral steroids in particular cause irreparable problems; osteoporosis, diabetes, hypertension, mood changes, and they're very difficult to take. Patients will compromise, they usually take less than they need to completely control their condition and they'll do anything to come off oral steroids, so that's a big impact.

The St. George's is an unfamiliar measure in asthma studies. It was actually a questionnaire that was developed for airways disease in general, but it hasn't been used greatly in asthma, and it was one of the great calls that Steve and Hector made in this clinical trial to go with that, because we were getting reports back that patients were feeling a lot better, and we weren't really picking it up on the asthma questionnaires that we'd used before. Now with a good bronchodilator in COPD or SGRQ will improve above around 4, which is the minimally clinically important difference, so this is a very large effect on SGRQ. I'm not aware of any inhaled drugs that have done better than that for that measure in COPD. So I think the big impact on symptoms and quality of life, and very impactful impact on oral steroid use when we've got nothing.

Darrell Baker:

Ian, thank you. So let's now go to the first question, we'll go to the first caller on the phone, please.

James Gordon, JP Morgan:

Hello, thanks for taking my questions. I had two on mepolizumab and one on Summit, and one general respiratory question. On mepolizumab, one question I had was just about the competitor situation in terms of IL-5. I know that AstraZeneca have suggested that their IL-5, benralizumab, targets the receptor rather than the ligand, and that means it will have a more profound eosinophil depletion and should have better efficacy. Based on the mechanistic data, or the mechanistic concepts and the clinical data, do you think there is an argument that their compound could theoretically be more efficacious? I had a commercial question on mepolizumab which would be about pricing, in that you've got first mover advantage, but this looks like it could be a crowded market, should we think about a big discount to existing biologic respiratory products like *Xolair*? And then one question on SUMMIT was I saw the recruitment has completed, but where are we on the interim, has that happened yet, or is that something that could happen quite soon? And then my final question was just an overall

respiratory question, there was a lot of different moving parts in your respiratory franchise which you highlighted on the slides at the beginning, what is the overall outlook for respiratory for the next few years? It doesn't sound like there's going to be growth in the next couple of years, but where do you think we are in terms of when could there be a return to growth for respiratory?

Darrell Baker:

Okay, James thank you for those questions, I'll comment on some and obviously I will pass on to our experts on others. On pricing of mepolizumab we are not going to be comment on pricing, we haven't actually any decisions on pricing to comment on, but one point I would make there is that actually we are talking about a different population largely to that which is currently treated by *Xolair*, so I might ask Steve to comment on that. So let's deal with the mepolizumab questions first, so beyond the pricing question Steve, this relative to benralizumab and other biologicals which have an effect on IL-5, do you see differences, and perhaps you could comment, because it seems to me if you look at headlines sometimes you miss what's really important, which is that all of these agents have been studied in different populations, which might explain some of the differences in headline events.

Steve Yancey:

Yes, I think James' question is a good one, and it is one that is not clear based on the indirect comparisons that can be made across studies. As you rightly point out, comparing across these various populations can be a tricky business. As we showed in our own slides, if you move up the scale of eosinophils in blood, for example you move into a more severe population, likewise if you have a requirement for two or more exacerbations versus one you're studying a different population. In addition, if you're requiring moderate to high dose steroids that's a different population compared to a population who may be on strictly high dose steroids, but I think looking across the data it's unrealistic to expect that there may be an efficacy advantage based on the depletion of eosinophils that was James' specific question. So looking across the data that had been published, when I look at the cell counts, the geometric mean from the mepolizumab data, I see a mean of around 50-60 cells. We've been reporting our data as a percent reduction from base line which makes that translation a bit more challenging, but our mean cell counts are also in the 50-60 range. So it appears that from a PD effect, which is going to drive an efficacy effect, these medicines appear that they may be similar with regard to their overall ability to reduce eosinophil numbers in both blood and sputum.

I think your other question was around an overlap with *Xolair*, so I can answer that, Darrell, also. It would be based on the data from the mepolizumab programme, so these subjects in these programs represent our target population. When we look within these populations at the percent of subjects who would also be eligible for *Xolair* treatment, and that would be based on their label meaning they have to meet their indication statement as well as fall within the dosing guidelines that are set forth for omalizumab, we see that around 30-33% of patients may also be eligible for omalizumab as they also would be for mepolizumab, and I think if you think of the inverse of that, it's saying that upwards of 70% have no other treatment options. So the anti-IL-5s are stepping into a space where there may be no other alternative treatments for patients.

Darrell Baker:

Great Steve, thank you. I'll just pick up your question on SUMMIT, James. SUMMIT has completed recruitment, there was no formal interim that will be announced in terms of efficacy, we do have a safety monitoring board for the SUMMIT study and they have taken a look to ensure that there is nothing in the data which required us to finish that study early, that has happened, but you won't be seeing a formal interim reported for that. As I've said you will see the final data next year, and then the question of all of these various moving parts, you are right, we are, as I said in my introductory comments, we are introducing the new portfolio globally, rolling out these products as fast as we can. We are very excited by this new portfolio, but at the same time obviously our established products, including *Seretide* and *Advair*, are also encountering significant competition, and you will have heard Andrew I'm sure comment on this in the mid year, significant pricing pressures, especially in the US, and other new competition in terms of ICS/LABA treatments. And at the end of the day we are looking at the net effect of the gains in new business versus the impact on our current business. And that's not something that we're going to be able to make public predictions about. All I can say is that we're very committed in the long term to respiratory and we believe we have in our hands a portfolio of products which are unsurpassed in their classes, and the ability to provide this portfolio, I believe, will be really important for physicians, and also for payers into the future.

Good, can we go to the next caller on the phone, please?

Dani Saurymper, Barclays:

Thank you for taking my question. Apologies if I missed these in the earlier slides, but are you able to quantify just the number of patients with severe eosinophilic asthma globally, or in G7 markets, and then as a relation to that, the proportion of that population which would have an eosinophilic blood count of greater than 150 cells per micro litre, I'm conscious you

gave obviously a subgroup analysis of patients with greater than 500 cells per micro litre and you alluded to different patient populations being looked at by the likes of Astra and Teva, and it is notable for example with benralizumab their inclusion criteria was greater than 400 cells per micro litre, and I'm just trying to sort of understand the cut off points that were chosen from your perspective. There was an article in The Lancet that referenced around benralizumab that actually patients with a sputum eosinophil count less than 3% there is a potentially deleterious effect in terms of exacerbation, so I just wondered if you had seen any evidence of that as well. And then just lastly, you talked about IL-5, I was just curious to understand where you consider the IL-13 agents may fit within this, they seem to be also targeting a similar patient group?

Darrell Baker:

Great, Dani thank you, I'm going to pass that question in terms of numbers of patients, or proportion of severe asthmatic patients and the impact of the eosinophil cut offs on that to Steve, and then perhaps Ian would like to comment too. Steve?

Steve Yancey:

So in terms of addressing the question about blood levels that may predict response and how various sponsors may or may not have taken approach, I can speak for GSK's approach. Our approach has been one of trying to allow the data to lead the way. As Professor Pavord mentioned earlier, and you may want to come back to that, he mentioned the DREAM trial, and he showed a plot which was a model. It's a model of covariates, base line covariates that may or may not predict a response to mepolizumab. So he only mentioned the two covariates that were predictive, and those were blood eosinophils as well as the prior history of exacerbations, but many covariates went into that model. So we tried to examine the data looking at gender, FEV1, past history, reversibility, etc. That constellation of covariates only identified the blood eosinophil count of 150 and 300 that we then moved forward through our program and have demonstrated replication in the MENSA trial. The cuts that may be used by other competitors really come from historical data, we started down that same path looking through the literature, trying to understand where eosinophilia may be defined in both sputum as well as blood. They're not unreasonable approaches, it's just that I would say GSK has taken a data driven approach, and we refer you to the DREAM study. Was there a second question?

Darrell Baker:

I think really what Dani is trying to get to though is of all patients with asthma, how many have very severe asthma, and what proportion of those have these high or relatively high eosinophil levels.

Steve Yancey:

So if you look through the literature, severe, difficult to treat asthma is generally then classified as 5-10% of the overall asthma population. If you look at those patients who have an eosinophilic profile it ranges in the 50-60% space. We believe that those patients who would be eligible for mepolizumab meaning that they also have a background of high dose steroids and two exacerbations, represent about 3% of the overall asthma population, I think.

Darrell Baker:

Ian, would that accord with your experience?

Ian Pavord:

Yes, and I would add that I think you'll find that people have found that have been… because there will be an awareness of the biomarker, and so clinicians will find patients with a raised eosinophil count, and that will prompt questions, and in fact it will be recognised that this person has severe asthma, it's just that they have accepted nothing could be done except oral steroids, and that wasn't an acceptable treatment for them. So I think there will be patients that will be found as awareness of this pathway grows. So I suspect it will be more than that, that's my own view. You asked about benralizumab, and you've obviously seen the online, the paper online in The Lancet Respiratory Medicine in COPD. Yes, there was a suggestion that the patients with low blood eosinophil counts were getting problems with potentially infections, but this wasn't a significant signal. The other main finding, the studies when you got above 300 eosinophils, you were seeing marked efficacy in that subgroup. So I think that more work needs to be done in COPD. We don't really know enough to draw any firm conclusions yet.

Darrell Baker:

Ian, thank you. We go now to a question which is on the webcast, the question is from Kerry Holford from Exane BNP Paribas, and she is asking:

Any thoughts on why in the MENSA study statistically significant reduction in hospitalisation rate was seen with a sub cut formulation, but not with the IV formulation?

Again, I think that's one for you Steve, or perhaps Hector.

Steve Yancey:

I'll take that, thank you Kerry. Really this is a reflection of small numbers. So let's start by reviewing what we've seen in previous trials. I'll even think back to the DREAM trial where we presented an exacerbation rate reduction across three doses. That rate reduction ranged from 39-52%. So you can expect the effect of a medicine to have some variation within a clinical trial. What we showed in that DREAM study was that there was no overall dose response, and when we looked across all the other parameters including exacerbations and ED visits, hospitalisations, so when you see this difference across IV to subcutaneous administration, and recalling those numbers, at least the ED hospitalisation rates I believe were 39 versus 61 or 62%. And it falls within the normal variation that we see, and when you move into smaller numbers, because ED visits and hospitalisations are a subset of serious exacerbations, the overall natural variation that one would see will emerge, but we do not believe this represents a distinct treatment response to mepolizumab, where they're given both IV or subcutaneous, and I think that would also be supported by all the other end points as we look across the MENSA trial, which show very strong comparability, and this is an effect of small numbers.

Darrell Baker:

Steve, thank you. Now we go to the next question which is on the phone.

Richard Parkes, Deutsche Bank:

Hi, thanks for taking my questions and congratulations for impressive data. Just in terms of the population of patients and the eligibility criteria of high eosinophils. I wondered if you had looked at how that overlaps with the eligibility criteria being used to select for response to IL-13 inhibitors, as well as Xolair, just to kind of see if we can define that patient population and the overlap a little bit more. And then secondly, just wondering how much can a single patient eosinophil count vary over time, and I'm just wondering what impact that has on utility of that as a biomarker and how you have managed that in the clinical trials. And then my final question is, there's been a lot of discussion at ERS over the relevance of the WISDOM trial, to use of inhaled corticosteroids in COPD patients. I'm just wondering if we could get your perspective on that, whether it's influenced any of your expectations for the triple therapy, thanks.

Darrell Baker:

Thank you, Richard. So again you can see, Steve, people trying to understand how all of these biologicals fit together, how big are the populations, how they overlap, so your comments on IL-13?

Steve Yancey:

So I heard three different questions, one was the IL-13 question, one was around the durability of the eosinophil biomarker, and the other one was around do we have data that suggests what would be the response for patients receiving omelizumab. I'd like to put the IL-13 question last, and I'm going to ask Dr Ortega to address that. I'll take the first two questions, with regards the overall durability of the eosinophil as a biomarker. We've actually studied this and have a publication in 2014 at ATS, and the lead author is Katz and colleagues, and what we've done is we looked at the predictability of eosinophils over time, meaning whether or not the eosinophil measure is going to be sustained above 150 cells over that 52 week period, and what we've found was that overall 85% of all patients who were above 150 cells at the beginning of the study, remained above 150 cells throughout the duration of the trial. We also learned from that trial that if you look at whether you measured eosinophil at week one, and then again four weeks later, that that really had no additional predictive value in whether or not patients would stay above the 150 cell count. There is some additional advantage, if you begin to move into more longitudinal assessments, meaning if you looked at week eight and 12, this becomes very problematic in the clinic trying to assess whether or not a patient may be eligible for mepolizumab, even having said that, the additional predictive value was quite low. The other question was around what's the comparisons to *Xolair*, well there have been no direct head to head treatment comparisons, so we have to rely on how we can extract this data from the existing clinical studies. So if you look in DREAM and it's in the supplement section of The Lancet, you will see an analysis that was reported by GSK. In that trial we looked at the patients who had both very low IGE levels, meaning they would not be eligible based on IGE levels for *Xolair* treatment, we looked at more moderate IGE levels, that would be the areas targeted for *Xolair* treatment, and actually we looked at the extremely high IGE levels, which are beyond the labelling for omalizumab or *Xolair*, and what we're able to show is that mepolizumab was effective in continuing to produce nearly a 50% reduction in exacerbations across those subgroups, recognising subgroup numbers will vary, so if you go look at that you're not going to see exactly 50%, but the overall clear, consistent response across those IGE levels was maintained. And Hector there was a question about the IL-13.

Hector Ortega, Lead Global Physician, mepolizumab:

IL-13, yes. I think essentially the IL-13 pathway is different than the IL-5 pathway, and one can think about that that can be correlated with different improvements and various end points. We clearly have demonstrated improvements in the reduction of exacerbations, but the data with the anti-IL-13 still is not entirely clear. There have been some improvements in

lung function, but it's only trends in exacerbations. I think one important point, it is very difficult to establish comparisons because partly the population that is recruited in their phenotypic characteristics recruited in some of the ongoing trials is still different, would be a stratification by a unique biomarker for anti-IL-13 studies. And also, having one exacerbation in those trials, it may have a different output in relation to our studies with at least two exacerbations.

Darrell Baker:

Right Hector, thank you. Just to remind that we can take questions through the webcast, and we're really encouraging questions through the webcast, and Richard asked the second question which is about WISDOM. The WISDOM study was presented here at the ERS. I think it is fair to say that it has given rise to quite a bit of controversy. I'll describe a little bit about it and then I'm going to ask Neil to comment on it, and then I'll come back and answer this question about whether it changes our view about the impact study.

So this WISDOM study was actually a very large study, and it's been conducted in COPD patients who are really quite severe. So their average lung function on entering into the study was less than a litre, and these patients were studied on tiotropium, and then they were placed on to *Seretide* if they weren't already on *Seretide* as part of the run in, and then what happened is over a three month period in a very staged fashion, the inhaled corticosteroid element of the treatment was withdrawn, so that for nine months in this study they were managed just on tiotropium and salmeterol. And what the study was looking at was the time to the first moderate to severe exacerbation, so essentially it was asking the question about what is the contribution in these patients that have inhaled corticosteroids of stopping exacerbations. But it is notable that actually 30% of these patients, around about, were not being managed on an inhaled steroid before they came into the study. They were placed on the inhaled steroid as part of the run in process. And these patients were required to have had an exacerbation in the previous year, a severe exacerbation, or and in many cases to be categorised as group D patients that had more than that. So there is a presumption from the 70% of patients who have been maintained on the inhaled steroid that that inhaled steroid was not enough to prevent them having exacerbations, they may not have been responsive to inhaled steroids.

So that was what the study was about, and what we saw in this study was that in terms of the primary end point which was non-inferiority, the tiotropium plus salmeterol was non-inferior to the regimen which also included the inhaled corticosteroid, although there were more exacerbations in that dual bronchodilator group, actually the time to the first exacerbation was longer actually, the time to first exacerbation was longer in the inhaled

steroid containing group. It didn't meet the pre specified non-inferiority criteria. But then other secondary end points were being looked at which included lung function, and quality of life. And there were changes seen there, so there was a deterioration in lung function and quality of life in those patients who had their steroid withdrawn. So that's the headline, which I think many people on the line may have seen reported, but Neil, I'm interested in your comments about this.

Neil Barnes:

Well as Darrell has said, only about 30% of the individuals were not on inhaled steroids before the start of the study, and in fact only 38% were on triple therapy before the start of the study. So the majority of the patients were put up to treatment which their treating doctor had not considered they had needed. So that's one concern we have. A second is that for the first three months of the study all the individuals were on inhaled steroids, and almost half of the exacerbations that they count are when both groups are on inhaled steroids. So we would very much like to see what happens in the nine months when patients have actually stopped, or half of them have stopped inhaled steroids. And lastly, the primary outcome was time to first exacerbation, but what you really want to look at is the rate of exacerbation because we know that it's the more frequent exacerbators which benefit more from inhaled steroids. Now as Darrell said, the lung function actually did statistically (and we would think, clinically) significantly deteriorate in the group who came off inhaled steroids. At the end of the year there were 43ml less. Now that may not seem a huge amount but these patients had a lung function that was less than a litre, so for them that percentage wise is we think significant. And actually the more I've thought about it, indirectly it supports what our analysis of the ISOLDE data, which has shown that when we split by the eosinophils you get a reduction in the rate of decline of the lung function, and that is really confirmed in a way without the eosinophil count obviously in the WISDOM study. So we think, you know, that the headline is not really representative of the subtleties of what is actually a relatively complex design.

Darrell Baker:

Thanks Neil, this is a really interesting study, and it has led to important debate, but like all good studies it has raised as many questions as it has tried to answer, I think. And certainly there has been a whole spectrum of views expressed here at the ERS, about the importance of the study and its implications for how we should manage patients. Now Richard did ask as part of his question has this affected our view about the IMPACT study, and to remind, in the IMPACT study we are studying exacerbation rates, and we're comparing dual bronchodilator with close triple therapy with ICS/ LABA. And we wouldn't have done this study if we didn't

expect that we will see some contribution from the inhaled steroid in the triple over the dual bronchodilator therapy. We were aided in that because by looking at some of the studies we conducted would be short term studies where we looked at the bronchodilator added to *Relvar* or *Breo*, I described one of those at the beginning of this webcast, and that gave us some signals that we thought that we could see changes in exacerbations in a larger, highly powered study which was well conducted. So we don't believe WISDOM really changes the probability of that study succeeding. We will be looking as a secondary, a predefined secondary in that study, at patients with a higher level of circulating eosinophils, and it may well be that we can do some validation of the biomarker which Neil reported earlier as part of that study, and frankly personally I would quite like to see if it's possible, whether analysis in the WISDOM study of circulating eosinophils sheds any further light too. So that's a rather long answer, but it has been a really, really fully discussed study here in ERS. So thanks for that question, Richard.

So let's move on now to the phones for a final question, so the final question caller please.

Terence McManus, Credit Suisse**:**

Yes, good afternoon. Three questions please. Mepolizumab appeared to fail to reach the minimally clinically important difference on the asthma control questionnaire end point in the MENSA study, I was just wondering if you could describe this end point and significance to the asthma community. Second question, could you describe the near 50% decrease in exacerbation rates for the placebo control group in MENSA, and would this indicate that many of the patients within this study population simply need to be better managed with inhaled therapies, and then related to this, could you comment on the opinion in The New England Journal of Medicine editorial that appeared to suggest mepolizumab's utility might be best reserved for patients currently taking oral steroids, thank you.

Darrell Baker:

Okay, so Terence, thank you. Three very direct questions, again we're keeping Steve busy this afternoon, but the ACQ in MENSA, can you first of all describe that end point and then is there any reason why that didn't meet statistical significance. The 50% decrease on placebo which was commented upon in The New England Journal editorial and also that suggestion in the editorial that perhaps mepolizumab should be reserved for patients who are on chronic oral steroids, and I'm also going to ask Ian Pavord for his view on that, too. You go first, Steve.

Steve Yancey:

Okay, thank you for that. So I think I'll tackle first the question around the 50% reduction in the placebo group. So, it's a fairly common observation that there will always be a Hawthorne effect, or nearly always a Hawthorne effect, meaning that patients will improve in a randomised controlled trial, based on observation and the fact that they are being better managed in a trial. Is it surprising that you would see a 50% reduction? Not necessarily in a RCT, we didn't see that same response in DREAM, but you do see it in this trial, but the suggestion from that editorial is that these patients may be well controlled, or just require additional therapies. I think we have to look at the data in its totality. So if we look at, for example, the patients in the placebo group, there is still a mean response of exacerbations of 1.7 in that group. These patients are not well controlled. If we look at the ACQ findings in that group, the placebo group, you will notice that the ACQ5 end point, the mean change from that still remains above 1.5 in that population, suggesting that their asthma control is very low. So I believe overall there is a Hawthorne effect. We do believe that these patients were adherent. Adherence to a medicine is incredibly important. There was a requirement for these patients or subjects as they entered a trial to be documented by their enrolling physician, that they had a requirement for inhaled steroids at high dose, and additional controller for the last 12 months. This was not systematically checked against electronic records, but it was queried by the investigator enrolling the subject. And maybe Ian would want to comment on that in just a moment. I think the other question was around the ACQ finding in MENSA, and again it was statistically significant, but you are correct, it did not cross the MCID. I would comment that the MCIDs are derived in large and broad populations, they're not derived in populations with severe asthma. This MCID may be relevant in this population it may not be, but I think that given the overall reductions in exacerbation, the large improvements in quality of life, the reduction in other more severe exacerbations including ED visits and hospitalisation we did not touch on that data explicitly, you'll see that the overall profile is one that control is overall improved, albeit granted in this particular trial that was not achieved. If you look at the ACQ5 data in the oral steroid sparing trial, it does cross the MCID, and it is statistically significant, I didn't highlight it simply because it is a tertiary end point in that trial and not a predefined secondary.

Darrell Baker:

Good, thank you, and Ian your comments… be interested in your comment, then I'll pass on to Neil, but in particular this question whether the right population is one that is also on oral corticosteroid.

Ian Pavord:

I think the problems associated with frequent rescue courses of oral steroids are underappreciated and there's some work being presented at the ERS looking at GP databases just trying to quantify how much trouble they cause, and it's quite significant. My comment on the adherence, we were pretty secure and serious that the patients were taking their oral steroids because they were required to go through an optimisation phase where reducing the dose led to loss of control of asthma, so I think that gave us considerable confidence that they were adherent, but certainly patients will take less steroids than they need commonly, that's a common compromise that patients take because they're not easy to take. So I think it'll be pitched at step four to five, and there's a real reluctance to go to regular oral steroids, and I wasn't convinced by that aspect of the editorial at all.

Darrell Baker:

Thanks Ian, and Neil you also have managed many of these patients.

Neil Barnes:

Yes, well before I joined GSK I ran for many years a severe and difficult asthma clinic, and recruited patients into these trials, and Ian hinted at this but really there is a rather artificial divide between those who have frequent exacerbations and require steroids, and those who require continuous oral steroids, because some individuals will choose in discussion with their doctor to go onto regular oral steroids to prevent exacerbations, others would rather not be on the oral steroids and have the exacerbations when they take a course of oral steroids. But having recruited into both groups, both patients who required frequent courses of oral steroids and that was reduced, and those who were on continuous oral steroids and either reduced or got rid of their oral steroid burden, were equally grateful. There wasn't any divide between them, they were both groups who were very, very grateful for the response they'd had.

Darrell Baker:

Okay, thanks Neil. Thanks for those questions Terrance, they were actually the last questions that we have, so I'd like to thank you all for joining again for this busy and eventful ERS, and with that I'll close this conference.