ASTRAZENECA UK LIMITED

Moderator: Colleen Proctor
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Colleen Proctor: Good evening, everybody. Welcome. It's a pleasure to be here with you tonight. We're really excited to talk to you about our respiratory portfolio.

I want to start by introducing myself. I'm Colleen Proctor with AstraZeneca investor relations. And I want to introduce the panel of people that we have with us tonight.

We have James Ward-Lilley, who is the head of our respiratory, inflammation and autoimmunity from a commercial perspective. Bing Yao who is the head of MedImmune RIA iMED for the large molecules. We have Maarten Kraan, who is the head of our RIA small molecules iMED. Bill Mezzanotte, who is the head of RIA from a late stage development perspective. And last, but certainly not least, is Chuck Bramlage, who is the president and CEO of Pearl Therapeutics.

So we're going to do a quick Q&A – or we're going to do a quick presentation for you, where we'll talk about the – a summary of the portfolio, and then Bing Yao is going to get into some of the details about what we've presented at ATS. And then we're going to have a Q&A session, where we bring the panel up front.

So I'm going to turn it over to James Ward-Lilley.

James Ward-Lilley: Thanks, Colleen.

Thank you all. It's great to see you all here today, and it's great to be at the ATS. I think the ATS is a very important time and really a milestone for the respiratory, autoimmune and information portfolio and franchise at AstraZeneca. And it marks a milestone in terms of progression of our pipeline which we're excited about.

There's been a lot of discussion here over the last few days about increasing focus in targeted therapies, better understanding of personalized health care, and that applies in all segments, in mild, moderate and severe disease.

And that's where we believe with AstraZeneca we have the opportunity to reestablish an industry leadership position in COPD, and asthma and IPF, and apply that understanding, and perhaps a unique understanding in terms of personalization of medicine, in all of our therapeutic approaches.

And before I get into the details of our plan, as I said, RIA really has four legs of our plan. First, it's existing portfolio. As you know very well, Symbicort and Pulmicort are on the market today and doing extremely well.

Secondly, we're excited about the new inhaled elements of our portfolio, brought to us through the acquisition of the Pearl Therapeutics company, and that's bringing us a series of new opportunities in combination therapy.

Thirdly, our biologics portfolio, and that's primarily going to be the focus of today's session, and in particular we're going to focus on benralizumab, tralokinumab, and also talk briefly about the TSLP, where there's been an interesting new paper presented today in the New England Journal of Medicine.

And then, finally, the fourth leg of our strategy is the autoimmune portfolio. That's not going to be the focus, because you know we've recently made some press releases and announced good progress in

the R.A. sector of mavrilimumab and also in the – in the SLE segment with sifalimumab.

The focus, as I said, is on respiratory leadership. And I think you know I'd simplify this in terms of why do we think we can be leaders.

First of all, it's about having the right molecules, and we believe we do have the right molecules, whether it's with budesonide and formoterol, which we believe in terms of their efficacy and safety profiles are the ideal molecules in the market today.

But also we've got great molecules for the future as well, and we'll turn to that in a moment.

Secondly, it's that right combinations. And we've said being able to formulate these products and put them into a combination, whether it's dual combinations or triple combinations, we see a very exciting bright future.

And then, finally, it's the right devices. And, again, we have today a series of devices, both the Turbohaler and DPI and also the MDI. And, again, that's an important point of differentiation, particularly when it comes to our LABA/LAMA franchise which will be the first and only MDI formulation coming into the market in the first instance.

So when we talk about respiratory franchise you know we're excited for those – for those reasons, and we see a real opportunity for this franchise to contribute significantly to AstraZeneca's growth. We've identified you know we've identified three core therapeutic areas, oncology, cardiovascular metabolism, and respiratory and autoimmune, and the data we're starting to see now I think will give you increasing confidence that we have the real ability to deliver on the pipeline progress and the targets that we set out a couple of weeks ago in our updated guidance.

And in spite the many years of therapy, the market remains one where there are high levels of unmet medical need, partly driven by low

diagnosis and treatment, partly driven by lack of adherence and effective management, partly driven by the severity of the disease.

And you can clearly see here in this chart, this is the G-7 markets only, that around 11 million patients remain poorly controlled in the asthma segment and around 8 million patients remain poorly controlled in the – in the more severe segments in COPD.

In total, there are about 3.5 million patients who remain severe in asthma and COPD, despite good compliance. So in spite of having compliance therapy, you see 1.7 million patients in the severe setting still needing to use and have to use additional therapies, and 1.8 million in severe setting, despite good compliance, with COPD.

So there remains a significant opportunity.

Again, across our portfolio in mild, moderate and severe, and, again, we're going to focus on severe asthma and mild to moderate, sorry, moderate-severe COPD. And I'll update the presentation in a moment.

As I said before, we're excited and we believe we can be an industry leader through our unique inhaled therapies, with Symbicort a differentiated inhaled range and developing new devices and innovative products offering helping patients who adhere to their products more effectively.

Secondly, a series of innovative targeted therapies, and, again, we believe with our portfolio and our research and discovery efforts we have an ability to have a unique insight in terms of choosing and identifying, targeting, the right patients at the right stage, and apply a portfolio approach in delivering solutions for those patients.

And then, finally, our goal is not just treatment for symptoms, but, fundamentally, we are working with the profession clinicians and scientists, looking at disease transformation. How can we fundamentally change the progression of this disease or stop the development of this disease, because we believe it's not just

symptomatic treatment that's going to be of value, and that is going to be a future value to patients and also, of course, to payers.

And before we turn to the biologics data, which, of course, is very exciting, and much of it has been presented here at ATS, I do just want to spend a moment stressing why we see there is continued further opportunity with our inhaled portfolio.

We have a strong franchise, around $4.5 billion worth of sales, continuing to grow, with Symbicort and Pulmicort, and we believe there's continued strong growth potential in both the U.S., in the emerging markets and in Japan, and with China in particular.

And with Symbicort, with a combination of formoterol and budesonide, the speed of the onset, the SMART dosing regimen allows us to further think about innovating with that product, looking now, as we are with the SIGMA program, which is a PRN program, which we're about to start recruiting in the – in the next couple of months, moving into an even earlier setting, the step 2 setting within asthma.

If we go to COPD, as you know we're about to move forward and we are moving forward very well with the recruitment of the LABA/LAMA Phase III program. We've completed enrollment in there. We expect to close the program before the end of this year, and we should be submitting on target by the middle of next year.

We also said in our quarter 1 update we've made great progress with our triple therapy. There's been a lot of data here at this – at this meeting about the potential use of triple therapy, particularly in the more severe setting in – in – in COPD where exacerbation is an important challenge.

So we see that the unique position of Symbicort continuing in asthma developing that but also Symbicort short-term or medium-term with exacerbating patients in COPD, a clear positioning for the LABA/LAMA, a clear positioning for LABA/ICS and then further a clear positioning for the more severe patients with the triple therapy.

And again, it's this unique portfolio approach in the inhaled setting, which we think really gives the opportunity for AstraZeneca to show leadership.

I think one last moment on this slide, I'd stress the potential further combinations we see and again, this is the opportunity we have with unique dose conformity and ability to put the combinations of drugs together whether it's existing drugs or existing drugs with novels or novel/ novels on the – on the Pearl platform, doubles or triples or even more than that. And we have also said we're moving forward with the triple program in asthma.

So that's been our inhaled portfolio. Clearly we're very excited about the progress we are making in the pipeline.

We have three assets today in Phase III as you can see on this slide. We've started our program and recruiting in asthma with benralizumab.

We have PT003, the LABA/LAMA as I said. I gave you the – the details of that a moment ago.

And we also have PT001. That's the LAMA program, which comes out of the LABA/LAMA program and effectively is a further Phase III asset.

We look forward to giving you the details announcing in the near future, tralokinumab's first entry and first patient recruited in dose. As you said, we've – we've – we have made the commitment and are starting that program with – so tralokinumab will be moving into the asthma. That will be a four asset in Phase III.

And then of course, we also have announced we'll be starting the program for benralizumab in COPD so we can expect to see that also moving into Phase III in the very near future.

As I said before, we're accelerating the program with the triple. The triple is now in Phase II. As you can see, PT010, that program is moving extremely well.

We hadn't dosed with and hadn't formulated with the ICS, budesonide last year. That program Phase I started in Q4, completed earlier in Q1. We're now in Phase II and we expect to be entering in Q3 by the middle of next – sorry, into Phase III by the middle of next year.

So very significant acceleration in our pipeline, very significant acceleration in breadth of portfolio pipeline progress in the inhaled portfolio, and also in the biologics.

And I'll hand over to Bing now to go over the details, the data on benralizumab, tralokinumab and on the TSLP.

Bing.

Bing Yao: Thank you, James.

This is a real pleasure to be here to discuss the promising data we shared at ATS. It's good to see so many familiar faces to talk to you again.

As James showed you, we believe that we have one of the most comprehensive portfolios in the respiratory disease areas. But more importantly, why you would then personalize the healthcare approach targeting distinct patient subsets, those therapies have the potential – have the potential to transform disease management from what is step therapy to our personalized healthcare.

I hear very often in this meeting precision therapy – precision therapy. It underscores the importance of targeted therapy, targeting the right drug to the right patient population.

So I'm going to highlight three new molecular entities for you today. We'll start with benralizumab.

Benralizumab is currently in Phase III development for a subset of severe uncontrolled asthma. We have diagnostics targeting eosinophilic asthma.

Eosinophilic asthma represents nearly half of the total severe uncontrolled asthmatics. And we just found that eosinophil cell counts are associated with the disease severity. The higher you have eosinophil in peripheral blood, the more severe the disease, the more likely the patient is to experience exacerbation.

Now I want to call attention to your left. That's how benralizumab works. For those of you online, that's slide number 11.

Benralizumab has a direct impact on eosinophils. It does so by binding to the interleukin-5 receptor on the surface and leads to depletion of this targeted cell.

The efficacy of benralizumab is enhanced. It's engineered to remove the sugar residues from the FC region.

Now on slide number 12, based on the profile from several clinical studies, we believe that benralizumab has the potential to be best in disease of severe uncontrolled asthma. It has a unique MOA. It is a first and only anti-IL-5 receptor currently in clinical study.

This molecule can potently deplete eosinophils, peripheral but also depleted eosinophils from the airway mucosa and sputum.

In terms of efficacy, we shared that at ATS here. Benralizumab not only reduced the exacerbation but also improved lung function as measured as by FEV1. It also improved asthma control, ACQ-6.

This is where we are differentiated from our competitor’s molecule, which achieved exacerbation reduction in secondaries. Dosing, we’re the only one – was the only one testing eight week dosing. This is given by sub-Q and one injection.

Now I'd like to bring a little bit more details of the data. This is on slide number 13.

First of all, looking at the pharmacodynamic impact of benralizumab, looking at eosinophil depletion. All three doses, two, 20 and 100, depleted eosinophils to a very low level, very fast after single dose – after first dose.

And also the depletion was maintained. If you look at the 20 milligram and 100 milligram, those are the purple line and – and the yellow line.

The last dose was given in week 40. It gradually returned to normal after the last dose, in particular with a lower dose. Therefore the depletion is potent but also reversible.

Now looking at the primary endpoints with a reduction of exacerbation, so this is based on index prediction of the eosinophilic – eosinophilic asthma versus non-eosinophilic asthma.

I want to call attention to the yellow bar here. 100 milligram would be used to cut asthma exacerbation by 41 percent in the eosinophilic asthma patient population.

In a non-eosinophilic patient population, that's on our right, 22 percent reduction.

Because of the MOA, which deplete eosinophils, we pre-specified subgroups for analysis and in particular, pre-specified analysis based on the baseline eosinophil cell levels, 200, 300 and 400.

If you look in the middle, the 300, 20 milligram dose and 100 milligram dose reduced exacerbation by 57 percent and 43 percent.

As the baseline eosinophil gets higher, 400. Now we see very – very, very large reduction. Now it goes to 57 to 70 percent reduction of the exacerbation.

Looking forward you know in our phase III development going to use a straight-forward test, which is a peripheral blood, or a simple blood test. Now we're looking at that non-functioning improvement that's on slide number 16. You can see all three doses improved lung-function. That's measured by FEV1. Appears to be a trend, for example, once baseline eosinophil is higher there's more improvement with benralizumab. It was a significant and a markedly improvement of lung-function.

We'll also look at ACQ-6. So this is asthma control on slide number 17. We saw composite questionnaire comprising symptoms and activity and limitation. If you have a decrease of 0.5 that is minimally, clinically important differences. And ACQ-6 is used to predict the severity of a 1.5 means they have severe disease. This is a pre-specified analysis. On your right, that's patients with a baseline eosinophil of over 300. You see minimal differences, improvement of asthma control with a 20-milligram and 100 milligram dose in the patients with elevated eosinophil levels.

Data is promising and encouraging. We're currently now in phase III development for severe uncontrolled asthma. Phase III is ongoing and it's on track to complete by the first quarter of 2016. There are two clinical studies. In terms of patient population, it's very similar to our Phase llb clinical study, severe and controlled patient population on ICS and LABA.

In terms of patient population we pre-specified a cutoff for eosinophils but also testing a range to see which populations will best respond to our therapy. Primary endpoint and secondary endpoints remains to be the same, as in our Phase llb clinical study. Benralizumab, moving on to slide number 19, has also been tested in COPD. So this is where we are doing new science. Traditionally people think COPD is mediated by neutrophils, but increasing evidence and also our own work suggested up to one third of the COPD patients have elevated eosinophils in their peripheral blood.

And importantly, the elevated eosinophils appear to associate with the increased acute exacerbation of COPD. Now we have this potent molecule that has depleted eosinophils so we tested benralizumab in the subset of COPD patient population in a Phase lla of the study.

Now slide number 20 summarized the results from our Phase lla clinical study. Similar to the benralizumab in asthma, we found that benralizumab can deplete the targeted cells in those patient populations. Same dosing regimen.

In terms of efficacy, we saw markedly improvement in terms of lung function FEV1. For the primary importance of the exacerbation reduction is a critical defined population which is primary endpoint in the exacerbation reduction. However, we did see a trend toward reduction of exacerbation in patients with elevated eosinophils.

In this patient population, we'll also see improvement in the health-related quality-of-life improvement and also symptom scores improvement. Dosing very similar to benralizumab we test Q8W dosing regimen, getting into a little bit more details of the data.

Then slide number 21, on the left shows you that exacerbation reduction all comers there's no differences between placebo and the treated group.

On your right side, now if you look at the patients pre-specified with more than 200 cells or 300 cells, now you see a trend toward a reduction in the COPD exacerbation.

Looking at lung function improvement, that's FEV1, slide number 22, this is the protocol-defined population. It's consistent with the COPD patients. If you observe them for one year, you will see the lung function decline. So that's that gray line you saw there. Benralizumab-treated patients now having improvement in terms of FEV1. That main improvement is about 130 mLs.

But two points I want to make here. One is it happened real fast. After the very first visit at week four; and secondly, the improvements sustained. The last dose was given Week 48. Now that the improvement at 56 week goes to 68 week and even week 80. Sustained improvement of lung function. But what's more impressive here is now we have pre-specified analysis, looking at patients with elevated eosinophils. More than 200 or 300 here on the gray bar are the patients treated with a placebo.

Benralizumab to the patients, out of 200. That's basically – baseline, you see a figure of over 200. Now you saw over 200 mL differences. With 300, that's over – that's also over 200 mLs. I want to see this – this is the first – actually, the first biologic demonstrating improvement in terms of lung functioning COPD patients and also the first biologic tested in the eosinophilic COPD patient population. And over the half of the patients here are actually on triple therapies. So that's why it makes that data quite impressive and meaningful.

If you look at same population, patient with elevated eosinophils, on health-related quality of life. That's as measured by St. George Respiratory Questionnaire. You have a total score over 200 or 300, or see your improvement. Improvement of four points would be clinically meaningful. That's over that. And particularly, if you look at symptoms scores so that – of 10 points improvement in terms of symptom scores. When you put all of this together, I think data – this will be encouraging.

And also, along with our proof-of-concept study in asthma, we are taking this molecule into Phase lll – Phase lll is planned to start for the third quarter of this year. There'll be two pivotal studies. There will be moderate and severe COPD patient population similar to the ones in our Phase lla clinical study. So clearly, we are going to be testing this compound in patients with elevated eosinophils. We'll pre-specify a cutoff, but also we're testing a range to determine what patient population would better respond to our therapy.

Primary and secondary, the same as the Phase lla clinical study. So moving on from benralizumab to a second new molecular entity tralokinumab. We also share the data in this conference. Tralokinumab is for severe and uncontrolled asthma. It has potential for different patient subset. Benralizumab for the eosinophilic asthma, this one has the potential for TH2 asthma.

The target if you look in IL-13, if you look at your left into interleukin 13 is a central mediator of asthma involved in the many aspects of the disease pathogenesis. Mucus hyposecretion factor A, including induced constriction and also functional fibrosis, induced fibrosis.

It is a highly elevated target. There are downstream markets identified which can be used to predict the response to anti IL-13 pathways. Also, I mention that we also have a Phase ll study in IPF that is ongoing.

So going to phase lll – phase llb study a few years back we had the hypothesis anti IL-13 would have enhanced efficacy in only a subset of patient population where the anti IL-13 pathway is active.

Therefore, we spent our research efforts to identify the downstream biomarkers that can predict the response. So here are some of the recent experiments. Looking at the genes, the highly up-regulated anti IL-13, so identified periostin that others did, but also a novel marker DPP4 as induced anti IL-13. We incorporated those into our Phase llb data analysis pre-specified.

Looking at the primary endpoint, asthma exacerbation reduction, in this trial, we enrolled all comers, but it was specific several sub-groups based on the clinical phenotype, as well as the biomarker.

I want to draw attention to the right side. If you look at the intent to treat population, we have a small reduction of asthma exacerbation, 7 percent; not significant. But in the pre-specified sub-groups, in particular I want to draw attention to the 12 percent of reversibility.

Now, we saw a trend toward reduction, 30 percent, 34 percent reduction in terms of asthma exacerbation.

Also, there are enhanced reduction in other subgroups, including periostin high, DPP4 high, and also the patients who are not on oral corticosteroids. We further analyzed those groups, particularly combined some of the biomarkers. This is on the slide number 29.

If you look at the blue bar on your left. So these are the patients who are reversible, but not on oral corticosteroids. I want to mention that. These are the populations very similar to the population of lebrikizumab tested in this Phase ll clinical study.

Now, even without the biomarker, we saw 44 percent reduction in asthma exacerbation. Biomarkers like periostin, enhanced the efficacy about 67 percent reduction, with a caveat of the small – smaller sample size with the DPP-4, 57 percent of the reduction of the exacerbation.

Looking at the FEV1, in this patient population, I'm showing you here on the left, so there's a net of placebo 12 percent improvement of FEV1 in a reversible population and patients on oral corticosteroids. I'd like to mention that even in all comers, we saw significant improvement with FEV1 by tralokinumab Q2W double dosing.

Periostin further enhanced the improvement in the lung function, now 14.7 percent.

Now when you look at the other secondaries, these are asthma control and quality of life. I mentioned earlier, for asthma control, this is measured by ACQ-6, a decrease of 0.5 point is minimally important differences. We saw even in the reversible population, without a biomarker, was a point – decrease of 0.55. And periostin further enhanced it.

In terms of quality of life, an increase of 0.5 points is minimally important differences. And in this population tralokinumab improved

the quality of life. I also want to mention that this is where we are different from competitors. We saw the improvement in those control measures ACQ-6 and the quality of life.

So put it together, we believe that our phase llb is very informative. We identify biomarkers can potentially use to predict a response. We identified a patient subgroup, a subgroup have improvement across a range of asthma controls: asthma exacerbation, lung function, asthma control, and quality of life.

We believe we can take this population, we can take tralokinumab into Phase lll in this defined population. And Phase lll will confirm that benefit of tralokinumab therapy in the population.

So we expect Phase lll to start in the third quarter of this year. The population, as mentioned, is a learning from our Phase llb clinical study to be reversal populations, patients not on oral corticosteroids and stratified by biomarkers.

Primary endpoint and secondary endpoint will be the same as our Phase llb clinical studies. For those patients who are on maintenance oral corticosteroids, we'll do a separate sparing study to see whether tralokinumab will be able to taper steroid use in those patient populations and bring benefit to those patients.

The third entity is the anti TSLP or MEDI9929 / AMG157. We're pretty excited about this molecule. This is in collaboration with Amgen. The target is a new cytocine called TSLP. Now, this is on slide number 34. TSLP is an upstream cytocine directly produced by epitheliums induced by viruses and allergens.

If you look at the pathway on your left, TSLP activates multiple pathways. So it is upstream it activates multiple pathways, therefore this molecule, TSLP could have the potential for broader population or higher efficacy potentially for disease modification. So our partner Amgen and their colleagues completed a phase lb study that's allergen challenger study data very strong.

I'm really happy to share with you this news that just came out today. The paper describing anti-TSLP was just published today by the New England Journal of Medicine. Along with the paper there's an editorial highlighting the significance of this finding. This is the first – first anti-TSLP human study and also the first one to elucidate the functions in humans of this new cytocine.

The conclusion is that treatment with AMG-157, this anti-TSLP antibody, reduced allergen-induced bronchial constriction and indexes of airway inflammation. I like the quote from the editorial. It says, "The recent possibility that TSLP could be a master switch between epitheliums and the inflammatory cascade."

This molecule now, we are in development of this molecule. It's currently in phase llb clinical study in severe patients. We have patient enrolled, we're actively recruiting the patients.

So with that, I would like to bring back to what I stated at the beginning. We have a strong, robust portfolio. We're using personalized health care approach, targeting distinct patient population. So these therapies have the potential to transform disease management. I do hope that you appreciate the breadth of our portfolio and share the excitement as we are about our molecules.

So, with that, I would like to thank you for your attention and I would like to hand it back to Colleen.

Colleen Proctor: So as we get ready to take the questions from the audience and from the phone, I just want to caveat that tonight, we have our respiratory, scientific, and commercial folks here, and we'd like to try to keep the questions focused on that, and we would not like to take questions around the Pfizer situation.

So, I'll start by saying if you have a question, please state your name, the company that you work for, and then ask your question. And if

you're on the phone, please press star, one if you want to ask a question.

Seamus?

Oh, and wait for the microphone if you're in the room.

Seamus Fernandez: Thanks, Seamus Fernandez from Leerink Partners. So, maybe question for Bing. You know you have on this slide up here the overlapping potential groups here. Again, looks like a Venn diagram of some kind. But, can you – you know in terms of the overlap of TH2 disease, eosinophilic disease, it seems like there's considerable overlap. You also saw in the abstract for anti-TSLP an impact on eosinophils as well, so obviously these are all intrinsically linked. Just wondering how you are working to carve up these different therapies to really get to a more personalized treatment regimen, and how important it is to have all of these targets to be able to do that?

Bing Yao: Yes sure. That whole area, we are working on now to understand the patient overlap and patient subsets for each of our therapies. So, what I can tell you is for benralizumab so clearly, the MOA for eosinophilic asthma. It depends on the cut-off, this would be 50 percent of the total uncontrolled severe asthma. And because we have multiple trials in the samples we're on, we're in a unique position to have this asset. We were able to characterize, for example, the overlap of the patient population, particularly periostin high and eosinophilic high and low, using biomarkers you can divide the population into four.

So there are, as you stated, there are overlaps between eosinophilic asthma and the TH2 driven but what I can tell you is that benralizumab has the potential to target 50 percent of the severe asthma. Combine the two, for example, benralizumab and tralokinumab, now we can expand that to 70 percent of patients, approximately. But because with TSLP, could also targeting other pathways you saw in the diagram remain to be confirmed, such as our 17 pathway and mast cell got

potential for broader population. So, with that and others, we have the potential to cover the entire spectrum of the severe asthma space.

James Ward-Lilley: I think we really are in a unique position in terms of discovery assets, the development assets we have in terms of really understanding which patients are going to most appropriately respond. What's the right sequence in terms of treatments and therapy and staging a therapy, what is the appropriate cut-off and trade-off cut-off for example, between eosinophil, TH2, non-TH2, and we do see with benralizumab as Bing has said, likely to focus on the higher eosinophil group.

At the moment, we believe you know periostin and potentially DPP4 could be important for tralokinumab and TSLP is very exciting. It could have a broad range of efficacy, particularly in TH2, but also potentially in non-TH2. So, we are able to specify, and I think that has huge value: both for the clinician, the patient, but also for the payer in demonstrating the most appropriate value proposition in the increasingly challenging budget environment.

Next question.

Colleen Proctor: You guys are too easy.

Seamus Fernandez: I can just hold on to the microphone, I guess.

So, I guess there's another question. In one of the COPD sessions you know one of the physicians actually stood up and said, "you know we really need to get away from the utilization of steroids in the treatment of COPD." Can you guys comment on that? Because you're making a pretty strong statement with PTO1O, and I'm just wondering what is the focus there? Do you really believe that budesonide is differentiated from the other steroids? Because it would seem like that's really the only vehicle that would get us you know sort of away from that – that developing mentality.

Bill Mezzanotti: Thanks for that question. So, absolutely, there's a lot of question about the benefit risk of inhaled steroids in COPD versus asthma, and the different studies and different meta-analysis have shown increased incidence of pneumonia in the population. There was a poster from a meta-analysis of six budesonide studies shown yesterday. Actually, I think maybe that same session, I'm not so sure. Showing no increase.

So, we believe that in the near term, inhaled steroids absolutely are going to have a role in the controlled exacerbations in COPD, and that the benefit risk overall with inhaled steroids, it's still positive, and that for budesonide, absolutely is positive because the rate – if – well in some analyses you've seen slight increases, and in some analyses you've seen none, so we believe that we – we have a greater benefit on exacerbation than risk on pneumonia.

Colleen Proctor: So, let's take a question from the phone next, so we'll go to Alexandra Hauber.

Alexandra Hauber: Oh hello. Good evening. I have two questions.

On stuff which hasn't been talked about actually. The last slide, slide 36 does actually show brodalumab but I'm not quite sure where it would fit in. I thought it probably more in the TH2-driven diseases, but – but maybe we're still waiting for the phase to be resolved, but just roughly, if you could explain where in the disease paradigm that agent sits.

And the second question, since we have Chuck from Pearl here, I just want a question on the triple combination. Based on the technology on the draft dispersion in the microparticles, is it just as simple to have – to disperse three molecules as it is two molecules, or is there any sort of complexity to that which you know which you may want to explain?

Thank you.

Bing Yao: OK. Yes, I can take that first question on brodalumab. So, the brodalumab currently is in development for severe asthma, is in phase

llb development that was led by our partner Amgen. If you look at the MOA, the brodalumab is blocking IL-17 family of cytokines that include IL- 25, IL-17. IL-25 could potentially be involved in the TH2. IL-17 could be involved in neutrophil migration into the lung.

So, in terms of where we want to position the brodalumab in here is going to be really depending on the Phase llb results which are going to come out.

Chuck Bramlage: All right, I'll answer. This is Chuck Bramlage. I'll answer the question about the triple. We're very excited at Pearl to contribute to AZ's future by developing this triple. We will present data, we hope, at ERS that will show the data of what we did last – at the end of last year.

The term that you ask and the question – was it simple? I can tell you, in the industry, it is not simple to put three drugs together in the same canister. But, lucky with us, with this technology, we've been able to formulate very quickly. And the whole key to Pearl is the formulation process and what we have here.

So, we've been able to do what many companies have not in putting these products together. And many of the other companies in the industry outside of AZ who stepped up and acquired us all came asking and wanting our triple formulation technology. And we know that they have issues at doing that. We know that there's issues with two compounds in the same formulation.

So, what we see with the Pearl technology is a very consistent dosing, where the first dose is just like 120th dose. And the FDA and regulatory bodies will really like to see this CMC data that goes into the application. Very constant dosing. And you do not see that with powders and you do not see it with the old historical MDIs. What you do see is, with Pearl technology, you're going to see that.

So, again, it opens up all kinds of opportunities. Previous comment about having a LAMA with – with a – LABA as we're doing now, and

ICS with a LAMA, which we're looking at, as well. We've already formulated. So, we've got all kind of combinations. And these guys are going to give us some new compounds to put in combinations. So, it's – it's very exciting for us to have the investor – the investment coming from AZ to make this happen.

Our team has constantly been driving. We're going to deliver everything that we set on time. Our combination product is going to be delivered. You know we finished everything on time. We'll finish the – you'll see data in the first quarter of next year. And the triple, we will start next year.

So, the only thing we're doing right now – the work on the triple – is working on what is the budesonide dosing. We've done all the other dosing in phase two – very comprehensive. We need to do the work on budesonide – we've done it – and we're doing it in trials right now. And that's where the phase two is.

So, the term "simple" I want to challenge a little bit. But we are able to do this, and we're very excited then to have this technology reach patients, because we've got a good marketing arm in AZ. So, very excited about this.

James Ward-Lilley: … I think. And we are able to move quickly. We've demonstrated that. That's why I made the point earlier. We have not formulated and co-formulated with budesonide last year. And we did in the second half of last year, and that allowed us to move quickly in phase one and complete phase one. It's this consistency and predictability which is being replicated in phase one, and now being replicated in phase two, which is by far from simple. But that's giving us a great deal of confidence with putting together known molecules. We know their activity and their profiles. We know with the Pearl technology we have predictability and dosing and dose confirmation and – and delivery, which gives us confidence in terms of both the phase three program, but also, importantly, from a regulatory process. And we know that is a

challenge for many regulatory authorities in demonstrating that dosing and dosing consistency.

And that's why, I think you know we are particularly pleased with the balance of our portfolio. We have a series of novel innovative, what we believe is the best potential to be best in class, novel therapies, and/or even first in class approaches, like the TSLP. And we are the first product to show with benralizumab and COPD, phase llb efficacy across a range of – range of parameters. But also, we've got a portfolio where we've got a balanced risk based on a strong technology platform with known assets which are potentially moving into very big classes for the future in the shape of the LABA/LAMA, and also the LABA/LAMA/ICS, both in – both in asthma, and also in COPD.

That's why I came back and I wanted to reinforce that message on – it's a combination in our strategy of firstly molecules – great molecules. Secondly, great combinations. And especially giving us the combinations of the Pearl platform. And then finally, device technology and device differentiation and just reiterate.

You know the Pearl technology will allow us to be the first meter-dose inhaler, which we know is important for a number of patients, and obviously, for physicians in providing choices. And that ranges between 25 percent and 35 percent typically of patients being treated on that formulation.

Alexandra Hauber: I'm sorry. I'm not – I'm not sure that everyone's still on.

I – I just – first, apologies for using the term "simple." Maybe I should have more – what – I guess what I'm really after is that I – I do understand the importance of the dose uniformity of dose – homogeneous dosing. But once you have shown that you can do this with two molecules – because once the stuff is burnt into microparticles – that's a derisk for triple. Because, I mean, once you can disperse two, then there's no reason why you couldn't disperse three, unless you tell me there is a reason you can't. Because there is anything

specific about the budesonide molecule in terms of you know let's say the specific properties or anything.

So, the – the question is, is it – is it correct to assume that if you can do it with two, you can probably also do it with three…

Chuck Bramlage: Correct.

Alexandra Hauber: … to study?

Chuck Bramlage: Correct. Yes, we can, and we already have. And you'll see the data, but we have no problem at all with the formulation. And we're moving forward.

James Ward-Lilley: And we're also interested Alexandra in looking at beyond three.

Alexandra Hauber: OK. Thank you very much.

Alex To: Alex To from Cross Current Research. In this conference, we started to see some data that demonstrates in more severe patients – you know COPD patients, that you can use LAMA/LABA that's no worse than ICS or equivalent in the patients who are not really experiencing recent exacerbations. And am I correct to assume, in the very severe end of the spectrum – the patients who have a lot of exacerbations – the future life has to be a triple? Or the ICS/ LABA is at the end of this usage?

Bill Mezzanotte: So, I think in the – if you think about you know a lot of the – the quadrants they showed you in a lot of those presentations this week – he's talking about that upper quadrant – a very severe, who are exacerbating, as well. And so, I think those people need both maximal bronchial dilation and control of exacerbations. And that's – so, that – that's a path that generally will lead to triple, we believe.

James Ward-Lilley: And I – I'd add, though – I mean, we believe – and I showed you my slide earlier on in terms of the grids. We do see a very significant opportunity for the more symptomatic patients – the milder – moderate

symptomatic patients for the LABA/LAMA. And that's why we're excited to move forward with the MDI formulation of the LABA/LAMA with – with Pearl.

We do also see, before we reach fixed combinations of – of the triple therapy, there will be a role to add in an ICS, or for LABA/ICS. And, of course, we believe we have a very good one of those. And then ultimately, of course, maybe for the triple therapy providing fixed dose convenience for those patients who are continuing to have demonstrations of exacerbation.

But we are, as I said, covering the whole range of portfolio in terms of symptoms, and also those patients who have got more frequent exacerbations where you've added in the ICS.

Male: So you also have a MABA program on. Where does that fit in, and can you give us an update on that?

Maarten Kraan: Yes, our MABA program has always been seen as a platform to handle co-formulations and actually get control of the – of the broncodilator part of it, and in that context, it's currently treated.

So the MABA will always benefit from combinations to triples to quadriples.

And then, in that context, we looked at the opportunity at this moment, put it in Pearl platform, to simply take it from there onwards, as a basis for further co-formulations, which brings me also back to the question you had on – you have to realize severe COPD is at this moment mainly addressed by bronchodilation, which is symptomatic control from day to day, very relevant for if you're breathlessness.

But the ICS component, as we all know in steroid has a peraformity of reactions, some of which are understood, some are not understood. And underneath, going deeper in what we should, we saw in our pipeline, there is tremendous effort, and I think benralizumab and COPD is actually the first announcement we really want to start

attacking the disease modification arm of COPD. And in that way, you can, you can just, besides signs of symptoms control, also strive to attack preservation of lung and in that way simply either prevent progression or maybe even, in the far future, bend the curve backwards.

That's where the MABA fits in, mainly as a platform for those compounds as far as they will be inhaled.

James Ward-Lilley: I'd also say, I think, purely pragmatic you know we had a DPI, sorry, an MDI formulation with the – with the Pearl platform. And we have the potential with a DPI obviously with MABA. So it gives us another option for us to be equivalent to a LABA/LAMA DPI, so we'll have both the opportunities to deliver both types of formulation, with the MABA on its own or, as Maarten said, with a backbone platform for other combinations.

Colleen Proctor: Sara?

Sarah Potter: I'm Sarah Potter from Bank of America.

And I notice on your slide that the triple isn't scheduled to launch until 2020. I wondered if you could run through kind of what takes four years or so from a trial design perspective, and how we should think about a trial design for a triple, given none of your combinations are currently approved, so, from an FDA perspective.

Chuck Bramlage: OK. First off, we have – like you mentioned, we have to look at budesonide, we have to create the dose on budesonide, what does that look like, first.

We have a series of meetings with all the regulatory bodies, so this is a questionable thing for every company that's going to try this, right? I mean, so we're trying to find out does this combination alone compare with this one, compared to this one, and then what does the triple look like?

So we are effectively showing that with our LABA/LAMA against the singles, we will have to do with budesonide and then we're looking budesonide in – that is a Pearl Symbicort, which we've already developed, so we have to show that combination and what that looks like, and then the triple.

If you take a look, and we – right now we believe 2020 is a great time for us to get that approved. We're trying to work ways to push that into 2019.

Colin Reisner, I would like him to say some things. Colin is our chief medical officer. He's sitting right here in the front. If we could get him a microphone, I'd like for him to comment on this as well.

But there are, again, looking at shortcuts or things that we're trying to do with the regulatory bodies to bring this to patients faster. We're trying to do that.

We know that in the other companies that are competing with us, the real issue is the formulation. That's not a problem with us.

So our issue is doing the data as quick as we can, the trials that the regulatory groups want. And, frankly, we've had several meetings with them already, and they're trying to help us find a way to make this work.

But, Colin, take the floor.

Colin Reisner: Thank you,

Just by way of background, we'd just began our first clinical trial in November of 2008. And by December of 2012, we had had our Phase ll meeting with FDA, EMA and Health Canada. We've completed 10 clinical studies in over a thousand patients to fully characterize the dose selection for glycopyrronium, formoterol and the combination of the two.

We went from a company that was essentially a Phase ll company in December of 2012 to our Phase lll program, which we began end May, beginning June of last year.

There were two large pivotal studies. One is PINNACLE 1 and PINNACLE 2. As well as an extension study, PINNACLE 3.

The two pivotal studies enrolled over 3,100 patients. We completed enrollment last week. And the extension study has also completed its enrollment.

So, as Chuck had mentioned, those timelines that we have put down, we believe are realistic, but maybe somewhat conservative, and we would plan to do – to see what we can do to improve on those.

Thank you.

Sarah Potter: And just as a – just as a follow up to Bing, would you – would you run through again the inclusion criteria that you mentioned for the Phase lll benralizumab and tralokinumab programs? I think you mentioned high eosinophils for benralizumab, and is that specific inclusion criteria, or are you all comers and then just subtyping?

Bing Yao: I can comment on that first, then Bill can comment on that too.

So it's going to be, the major population for Phase lll clearly is going to be the eosinophilic patient population. We've specified a cutoff that's based on our Phase llb data, but we'll have now the ability to test a range of eosinophils for given subgroups….

Sarah Potter: …. the trial?

Bill Mezzinotte: We're investigating a range of patients with the eosinophils.

But we do – as Bing said, we'll have an analysis looking at different cuts to find the prespecified analysis.

Colleen Proctor: I'm going to go next to the phone, to Steve Scala.

Steve Scala: Thank you, Colleen.

Two questions on this. First, what are the dose limiting toxicities of the anti TSLP mechanism? And, secondly, what do you see as the specific weaknesses in comparative products, such as the marketed LABA/LAMAs and the triples that are in development that AstraZeneca is improving upon?

Thank you.

Bing Yao: So, Steve, I just wanted to make sure I understand your question is talking about dose-limiting toxicity of TSLP?

We – so far, we have seen in preclinical and the clinical studies, was we have not observed any significant toxicity. The Phase llb – have acceptable profile analysis is going to be a clinical study. I'm not aware of any tox finding in preclinical studies.

I have a project leader here, so, Janet, do you have anything to add to that?

Janet: No, that's correct.

Colleen Proctor: Steve, can you repeat your second question?

Chuck Bramlage: I've got it. So, the question on the second one is about LABA/LAMAs, and what is AZ looking at in terms of the competitive disadvantages or the things that we would provide that the other competitors don't?

I think the number one thing without a doubt is the MDI, the fact that we're going to provide a different device. I don't know how many COPD patients you know but I have one close in my family who was having a hard time with a dry powder device, and I happen to know this person. I said, "you're going to have to get something else. You need a certain inspiratory flow to get the drug out." And once that patient was switched to an MDI device, had no problem. Again, the device

was activated and they could take the drug. So, I think that's number one.

Number two, maybe it's number one, is the fact that we're going to be dosed twice a day. And I – again, if you look at COPD patients, they have problems breathing in the morning and evening, in particular, and if you take a look at our dose curve, they're going to have the 12 hour dose curve and then a second dose curve applied. Compare that to someone on a 24 hour product, they're going to have declines in the second half of the day, and that's where I think our benefit will be. Take also the fact that when that happens, someone on the managed care side, these patients are going to start taking a once a day medicine twice, and you're going to see managed care or governments getting very upset about that.

So, I think from those two elements are the two biggest things that we offer to our patients with our LABA/LAMA.

James Ward-Lilley: I'd like to build on the triples. I think the question was also related to the triples, and I think first and foremost, as we've seen in a number of the competitors, this is a complex area, and I go back to the reply we gave to Alexandra, we have great confidence in the consistency and reliability of the Pearl platform, but it is far from simple. Making sure you're getting dual combination therapy data, demonstrated to regulator authorities is not straightforward, as we've seen, and we have great confidence in the way in which we can demonstrate those conformity and delivery with the Pearl platform, both for the LABA/LAMA and also for the triple, and that's a key to thinking about what we think about is our probability to success at this potentially very significant portfolio.

The second one is budesonide. You know I think it is important. I come back to Bill's point. You know the profile of budesonide, we believe, very well explored and very well researched, is somewhat different from other steroids, and that's you know documented and labeled as well. So, I don't think we should underestimate that we

have confidence in the MDI, we have confidence in the twice daily. We have confidence in the combination consistency, and also, as I said right at the beginning, the fundamentals of the right molecules in the first place.

Maarten Kraan: And to give some – because the scientist likes to speak out as well. To give the detail on the triple, especially controlling your local drug-to-drug interactions within your formulation is a significant task. And because of the Pearl especially keep them apart, that's something where I think apart from the complexity of co-formulation, actually find the dose that also is, I think, a major upside where – where the pill formulation allows us simply not to worry about local drug-to-drug interaction in your formulation and stability over time.

Colleen Proctor: Yes.

Thank you. Seamus?

Seamus Fernandez: Thanks. Seamus Fernandez, Leerink Partners.

So, I guess a couple of questions for Bing. Again, can you walk us through the story for tralokinumab in IPF a little bit more, particularly in the context of some of the data that we saw for the oral agents and your interest or the prospect of seeing an IL-13 actually potentially combined with the – with those options. And then separately, maybe you can speak a little bit more broadly. I tried to ask this question once before, I think on the first quarter conference call, but got not a complete answer, so I'm going to ask it again.

The opportunities to basically see the mechanisms that we are looking at in respiratory expand into other areas, as we've seen the TNFs expand into multiple other disease areas, atopic dermatitis you know other areas. Where do you see the other opportunities for this portfolio, outside of respiratory?

Bing Yao: So, I'm going to answer your first question first, and to hand to Bill to answer and then we'll come back to your second question. In terms of

IL-13 for IPF, so we have – we and also we collaborated, extensively, with our investigators to build a scientific rationale for IL-13 and IPF, so that's a lot of data, build on that. We're having a major mechanism for IL-13 in the – in fibrosis, in the induction of the fibroblast proliferation and fibrosis.

We have clinical models, tested the – our compound in these models, demonstrating efficacy in pre-clinical models. More importantly, in patients, if we just go to IPF patients and look at biomarkers, we found subsets of patients have elevated IL-13. So in peripheral blood. And also other blood markers such as periostin. So that really have a scientific rationale for integrating into IPF with anti- IL-13 mechanism.

So, we started our phase two of the study I believe last year, and the trial currently is actively recruiting, it's on-going. So – so Bill, you want to add about the oral?

Bill Mezzanotte: Yes, I just – first of all, the informal practicing pulmonologist, it is exciting that they had some positive data finally. And IPF, it's a very miserable disease. And so – and actually the lead authors on the one paper are former colleagues of mine, so it's exciting. But still you know 75 percent of the patients did progress or die, and so it's not like we – we've obliterated these or gotten rid of all the unmet need there.

I think there are two agents that have shown some efficacy. They both have substantial side effects. I think they'll be hard to challenge to combine together, because of the – the G.I. toxicity, but maybe you know we'll see. But I think an additional therapy will still be needed to really bend that curve.

Bing Yao: So going back to your second question, are we pursuing other opportunities with the current respiratory molecules? We did not get a chance to talk about other portfolio inflammation or autoimmunity. While our strategy for – for those information is to understand the shared pathway, go into one indication, you expand, you give a really good example of anti-TNF because to our area expanding to all of the

indications you know PSA, AS, and UC, et cetera, is how they build the franchise.

So that – that's you know for respiratory, that's been no different. For example, in the case of benralizumab, you can imagine we have antibodies of eosinophils. Maybe disease, using the eosinophils plays a major role. Here we can pursue that. That's exactly what we did with COPD. And also we have – we have other investigators approached us for investigators sponsored study. So we are actively evaluating other opportunities for benralizumab as a part of the life cycle plan.

For tralokinumab, you – you mentioned we did, for example, IPF. These are extension of this mechanism that's based on science, based on our own understanding of the disease. I understand that dobilimumab had a – had data published for dermatitis and that's an illustration of the TH-2 pathway.

So we are also evaluating our molecule for other indications. So where the IL-13 pathway is active.

So those are active evaluation. When we start the trial, we'll be announcing those.

Maarten Kraan: Seamus, can I give a more philosophical perspective as well because I've been in the middle – I was in the middle of the – the Remicade franchise, both on the academic and the industry side when we actually went through the journey and – and found out in – in some diseases completely unexpected, there was an overlap.

But as you know if you know the story, there were also other diseases where we tested it and where we didn't find the overlap.

So – so like Bing said, we – we – we, of course, will look at the opportunity and always try to follow the – the biology and not put too much focus on the core area. But on the other hand, we learned from – from all the journeys in the other disease that it's not that easy and

there are some examples where the drug actually works in the hands of clinicians and as a company, you can't reproduce it in a controlled trial simply because of the complexity of the disease or the symptoms complex, which aggregated as a disease.

So there always will be, I think – the opportunity's there, it's flagged but to pursue it is – is not as easy as sometimes it's thought, and you go backwards.

Colleen Proctor: Any other last questions?

Seamus Fernandez: Can I just ask one last one?

It's – it's a little bit of a – it's a little bit of a surprise question but we learned yesterday at an FDA presentation that there has been drug apparently filed for breakthrough designation in lupus.

Is it your drug?

James Ward-Lilley: I guess you – you – we would be saying – we'd be disclosing if we had a significant breakthrough status at this stage so you know we're progressing with a Phase – Phase II data analysis of sifalimumab and we're progressing with a Phase II program with anifrolumab as well.

Seamus Fernandez: Thank you.

James Ward-Lilley: Very good.

We're done, I guess, unless there's any last – last questions. I'll just wrap up and – and summarize.

You know as I said in my – my introductory comments, respiratory autoimmune is one of the chosen areas for focus, one of three key areas for establishing Astra Zeneca's return to – to growth embedded with scientific leadership and I think you can see why.

We have a very strong existing portfolio and we're investing further to differentiate what we believe is strong brands in Pulmicort and in Symbicort.

We have a very strong inhaled future franchise and hope we've demonstrated that in the confidence with the LABA/LAMA and also with the triple.

And we've got emerging, very exciting data with our biologics portfolio, which is now moving forward towards Phase – Phase lll for tralokinumab, in Phase lll for benralizumab in – in asthma and moving towards Phase lll with – with COPD.

And in addition to that you know we're also seeing with the New England Journal a very exciting new data for a potential first-in-class with a very novel mode of action with TSLP. Obviously there's a long way to go there in terms of further data and analysis. But with that range of portfolio and in particular that understanding of the multiple biologics pathways, we think we've got a very good opportunity to truly lead and make a difference to patients' lives, help clinicians and also demonstrate real value to – to payers.

And with that, I'd like to close the session today.

Thanks, Colleen. Thank you all for attending. Thanks for listening on the line.

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