GlaxoSmithKline

GSK'165: anti-GM-CSF antibody

A novel mechanism with potentially differentiated impact on pain in the treatment of

Rheumatoid Arthritis

Tuesday, 23 October 2018

Sarah Elton-Farr (VP, Head of Investor Relations): Good morning, good afternoon and good evening everyone. Thank you for joining us to discuss the data presented yesterday at ACR on GSK'165, our anti-GM-CSF antibody. You can access the slides we are going to use for this presentation on the Investor section of GSK's website.

Cautionary statement regarding forward-looking statements

Before we begin, please refer to Slide 2 of our presentation for our cautionary statement. Please also note that as we are in closed period and have Q3 results next week we will not be answering any questions on the performance of the business.

I will now hand over to Dr Hal Barron, our Chief Scientific Officer to start the presentation. Hal.

Dr Hal Barron (Chief Scientific Officer): Thank you, Sarah, and thank you everyone for joining this call to talk through what we believe are very encouraging data that were presented yesterday at the ACR on GSK'165, our anti-GM-CSF antibody.

Agenda

Joining us on the call today we have Dr Roy Fleischmann joining us who will take you through the data. Roy is a Clinical Professor of Medicine at the University of Texas Southwestern Medical Center and Co-Medical Director of the Metroplex Clinical Research Center in Dallas. He is a private practice rheumatologist and has decades of experience in the field of treating RA patients.

We also have Luke Miels on the call who will frame up the evolving landscape within RA and how we are thinking about anti-GM-CSF and how it could fit in in the various treatment paradigms, and then also importantly we have Mark Layton who is our Internal Development Lead for GSK who will join us for the Q&A session to answer any questions you may have on this potential medicine.

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I spoke to you at Q2 about the new approach we are taking here at GSK and how we want to be more transparent about the progress we're making and GSK'165 is one of those assets that we believe can become a medicine and play an important role for patients with RA and we wanted to have this call with you today to help you understand why we think this is the case.

Rheumatoid Arthritis (RA): a chronic and debilitating inflammatory disease

I won't spend too much time on the background, you are probably all familiar with this. RA is an important and prevalent autoimmune disease affecting approximately 1% of the world's population above 18, about 25 million people. You know that the incidence is higher in women than men and in addition to the significant disability there is of course increased mortality, largely due to the accelerated risk of cardiovascular disease.

Recent progress with new treatment options, but unmet need remains

There has been recent progress with new treatment options but there is a significant unmet medical need. The new therapies introduced, including biologics, we know has improved the treatment paradigm for RA patients, reducing symptoms and signs of the disease and reducing the progression of structural damage to joints in a subset of patients but what is important here is even with the multiple targeted therapies, only approximately 30% of patients achieve remission.

Almost half of RA patients continue to report pain on a daily basis and this drives a lot of patients to switch therapies and we are learning a lot more about what is driving this pain and the role that a GM-CSF or an antibody to GM-CSF might be playing, and more on this in a minute.

But based on the epidemiology and the unmet need, we think there is an opportunity for new therapies which provide better efficacy, particularly in patients who are failing the TNF inhibitors.

GSK'165 (aGM-CSF): potential for a disease modifying effect in rheumatoid arthritis (RA) with a unique impact on pain

So our asset, GSK'165 is, as you know, a fully humanised antibody targeting anti-granulocyte macrophage colony-stimulating factor which is a proinflammatory cytokine that induces differentiation and proliferation of granulocytes and macrophages. It was one of the first cytokines detected in the human synovial fluid from inflamed joints of patients with the disease and we have, as you know, and we are going to advance this through clinical testing and have data presented today.

We believe that at the end of the programme the administration will likely be weekly via a subcutaneous injection with either an autoinjector or a prefilled syringe and we believe, as I said, the Phase 2 data in RA that was just presented is encouraging and we have begun planning studies that we think will enable us to advance the medicine.

We of course need to have discussions with regulators which are upcoming that will help us understand their feelings about this programme and we will learn whether we will need another Phase 2b study or whether we can employ an adaptive Phase 2b/3 design, but that of course still remains to be determined, but hopefully we will have clarity on that soon. And we do hope that given what I hope you'll see and appreciate is a significant impact on pain that we are looking for other additional indications beyond RA where pain is actually driving a lot of the pathology and symptoms in this patient population.

Strong rationale for moving forward

Before moving over to Roy, I wanted to go through a couple of components of the Phase 2 data in some detail to explain to you why our view is that this is a promising asset and why we have decided to advance the molecule, so let me just summarise in a few minutes.

The first reason we believe this is really encouraging data is based on the preclinical package and I'm not someone who drives a lot of my thinking behind preclinical data, but I think this package is actually very compelling. There is a wealth of preclinical data in multiple animal models that is all uniformly compelling, including many models that look specifically at pain control which strongly implicate a role for GM-CSF and inhibiting it.

There's recent data, as recent as March of this year from *JCI*, the *Journal of Clinical Investigation*, suggesting that while TNF is required for initiation of both GM-CSF-driven inflammatory pain and joint disease, it is actually not required for the maintenance of either pain or disease once established. This might be an important piece of information as we think about the patients who become refractory to TNF and other agents.

Also we are learning a lot about how GM-CSF is probably inducing its effect. We know GM-CSF upregulates CCL17, the cytokine that's produced in human monocytes and macrophages and we know that cytokine is required for GM-CSF dependent arthritic pain and disease. And this might explain why we are seeing the benefit in pain if CCL17 is emerging in the literature as an important cytokine for the development of both neuropathic and inflammatory pain, so that's the preclinical side.

From the clinical side, I think it's important to note that not only do we have data from the antibody to the ligand but mavrilimumab is an antibody against the alpha chain of the

GM-CSF receptor and that's been studied reasonably extensively as well and data from those clinical trials have demonstrated that there is a rapid improvement in pain oftentimes seen it's been one week of treatment in patients as well as marked improvement in other clinical meaningful endpoints at 12 and 24 weeks. This again from a prior probability perspective gives us more confidence that our own data are positive.

As we look, and as I said we will go into this in great detail with Roy in a second, there is now data from our Phase 2 study and we have seen that this data has demonstrated a lot of different findings that we want to make sure that you are aware of.

The data we've seen at Week 12 in the ACR20 and the DAS 28 are robust and compare favourably to other RA assets and I have to say these are more traditionally used endpoints and the two that I've put more weight on in interpreting this study. In addition the DAS 28 at Week 24 when measured as a continuous variable was actually statistically significant.

There are clearly other endpoints that we measured; Swollen Joint Count where there was over a 7.5 point reduction and a p-value of 0.001, the Tender Joint Count, almost a 9.0 point reduction with a p-value of 0.003, Simple Disease Activity Index, the SDAI, almost a 17 point reduction with a p-value of 0.001, the CDAI - and again, Dr Fleischmann will talk about this - which really measures the clinical disease activity, very impressively reduced by 17 and with a p-value of 0.001, so many endpoints with highly statistically significant and clinically meaningful effects.

Now I do need to point out that while many of the endpoints measured, as I just described in this study, did achieve statistical significance, the one that did not meet statistical significance unfortunately was the stated primary endpoint of the study, the DAS 28 (CRP), less than 2.6 at Week 24.

This endpoint is the induction of remission, it's an incredibly high hurdle and frankly an unusual endpoint to be used in a Phase 2 study, especially in a study where in the 180mg arm there was only 37 patients. But despite this unusual endpoint and the under-powering, we did see a more than five-fold increase in the number of patients achieving this endpoint, 16% versus 3% in the placebo but again the p-value was only 0.13, a trend not achieving statistical significance.

A couple of other points before we get into more detail that give me and the company confidence in this data is that in addition to the primary endpoint being less traditional, it was further confounded by another non-standard design element whereby patients on the placebo could switch to active of therapy at Week 12 if their EULAR response rate moderate or good, wasn't achieved.

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This resulted in 70% of the placebo patients switching to the 180mg dose after Week 12, and again the primary endpoint was measured at Week 24.

And finally it's clear that the decision to move forward after Week 5 with every other week dosing we believe could have significantly limited our ability to see the medicine treatment effect and there is thus the potential that a q-week dosing might have resulted in greater efficacy. Of course we don't know that but from our modelling efforts we believe that that's certainly distinctly possible.

What's important here I think is to focus on the totality of the data, our prior probability of success from the preclinical models, the substantial improvements that we've seen in clinically relevant endpoints, the opportunity to further improve on this with weekly dosing potentially and maybe most importantly the significant unmet need of patients with RA, particularly as it relates to their pain. So we think that moving forward with subsequent studies is a smart risk to take. It's not without some risk but we believe for all the reasons I've just highlighted that this makes a lot of sense and we are excited to do so.

With that as an introduction, I would like to hand it over to Dr Fleischmann to take you through in much more detail the Phase 2 data. Dr Fleischmann.

Key data demonstrating efficacy of GSK'165 aGM-CSF from the BAROQUE Phase 2 study
Presented at ACR 22 October 2018
Dr Roy Fleischmann

Thank you. GSK has asked me to look at this study almost independently because I did not take part in this study design, I didn't take part in conducting this study and to use my experience which as Hal said is decades and I actually made a joke and said 'Probably centuries' of drug development. I have been involved in the development of every drug for rheumatoid arthritis since methotrexate and to evaluate it.

I think that this is a very interesting study. It did have some very unusual quirks and that's where I would start.

Phase 2 study design

A randomised, multicentre, double-blind, parallel group, placebo controlled study with novel features to support a 52 week study

It's a Phase 2a study and a Phase 2a study is always a proof of concept study in my mind and you may pick a primary endpoint and the primary endpoint may be positive, it may be negative, in some ways it's almost immaterial. I think that what Hal said is correct, it's the

totality of the evidence that you see in the Phase 2a which actually tells you whether or not the molecule can be effective or not. *[Correction, this was a Phase 2b study].*

In this study, they enrolled 222 patients and it was the usual type of patients, adult patients with active rheumatoid arthritis. The companies always say moderate to severe but actually when you look at the demographics which you will in a moment, my guess is that 99% of these patients had very high disease activity.

They had to meet rheumatoid arthritis by the ACR 2010 criteria, they had to be a methotrexate incomplete responder and because they had to have a Swollen and Tender Joint Count greater than four out of 28, that's the reason why they had so much high disease activity.

And the other part of this study that was I think very good in the design was a CRP that was higher than the upper limit of normal, so we knew that these patients had active RA.

What was unusual, I don't think was the escape at Week 12, we do that, that's ethical; if a patient doesn't respond by Week 12 and they were with any group, you escape. The question is where they escape to but you should not continue them in the study so I don't think that that is a change.

What was unusual to me when I first looked at the data was that the Week 12 was change from baseline in DAS 28 (CRP) and the Week 24 which was the primary endpoint was a DAS 28 (CRP) less than 2.6 and I don't think that these are perfect endpoints in a study of this type. This is a placebo controlled study and in a placebo controlled study the endpoint should be an ACR 20 either at Week 12 or Week 24. And if you look at the speed of response it should be at Week 12. If you look to see whether or not the drug has a response, you look at Week 24. And then all the other secondary endpoints that they had I think were reasonable and you would look at it.

The other problem with the study was something I think we are going to address a little bit later and this is actually the dosing, so this is dose ranging and this is also dose spacing and it's the problem of modelling in a study versus what you really see, so those are the comments I would have on Slide 9 and then let's go to Slide 10.

Baseline patient demographic characteristics

Typical, established RA MTX-IR population; well balanced across treatment groups

In Slide 10 what we saw was the population that you would expect and that would be patients who are methotrexate IR who have still very active disease. Their average age was what we see in the usual studies, predominantly female. The rheumatoid arthritis diagnosis,

and this is diagnosis so symptoms are actually even longer, was something like six, seven years, so this is established RA.

What we think is that with this type of molecule, the way that it works, it would actually work much better if it was earlier, so I'm actually taking a look at this population and thinking 'This is the most difficult population to use it in and I would expect to use it earlier', so we'll see what the results were but we'll see.

Many of the patients were ACPA positive or rheumatoid factor positive. There's a little bit of difference in the groups in the Phase 2a, that's not that important. The methotrexate dose was reasonable, it was over 15mg a week, closer to 16mg, many of the patients were on corticosteroids which is what we see on a dose of corticosteroids that we usually see in a study, so this looks like the usual population that we have.

Baseline RA disease characteristics

Well balanced but with high DAS 28 (CRP) and HAQ-DI

When you take a look at baseline disease characteristics, clearly these patients had high disease activity. As Hal correctly pointed out, swollen joints and tender joints are important and these were high. The DAS 28, the SDAI and the CDAI were high in all the groups. The Patient Reported Outcomes, the pain, the Patient Global Assessment, the Physician's Global Assessment were all high, HAQ which is function was high. These are all accurate disease characteristics. This is Slide 11 and I actually think I made a mistake and I said a '2a' and I meant 2b.

Rationale for weekly dosing going forward

Let's take a look at Slide 12, because Slide 12 is very interesting. What you can see is you can see the dose response that was seen, so this is what was seen and you can see that the 180mg dose reached a level of about 3000 ng/mL. It was predicted to be effective as I understand at 2000. So that was fine at Week 4 it was there. The 135mg was there but the lower doses, the 90mg and the 45mg and the 22.5mg were below, so these are below what was predicted and this is after weekly dosing.

And then when you switch at Week 4 to every other week dosing, all seven levels dropped, so you see residual effects when you get to endpoint and I think that that's very key in understanding whether this is a positive study or a negative study or 'boy, this is an interesting study' and I would have to say it's interesting. So the drug levels were not where they should have been.

Patient disposition on randomised treatment

70% of placebo patients switched to GSK'165 180mg dose at Wk12 early escape point

If we take a look at Slide 13 which is the patient disposition on randomised treatment, you can see there were about 37 patients in each group which I think in my experience is actually adequate in a Phase 2 study to be able to see the dose response.

When you take a look at what happened to the placebo group, they basically disappeared which is because they didn't respond, they didn't have a EULAR response which is like an ACR 20 at Week 12 they were taken out which is ethical. And at low dose there was also more attrition as the doses were lowered but when you look at the 180mg dose which is close to the effective dose, then patients tended to stay in the protocol.

Significantly higher response rates at Week 12 with GSK'165 versus placebo

ACR 20 at Week 12

And then what was very interesting was Slide 14; this is not the primary endpoint. The primary endpoint is DAS 28 2.6 at Week 24, that was what the company selected. I would have selected the ACR 20 at Week 12 and that's what Week 14 shows and there are two very interesting things.

GSK, for whatever reason, picked really good sites because the placebo response rate is only 11% and what we have seen with all the studies - and I'm involved in studies of JAKs - and all the other mechanisms, especially in placebo, response rates of 30%, 40%, close to 50% and I do think that it is related to the sites. I think they probably picked very good sites that knew how to do studies.

What was surprising was even though the level of the drug was below what we think it should have been and even though there was a dose response, the ACR 20 is consistently significantly better than placebo for all of the doses.

It looks like the 90mg and the 180mg is actually quite reasonable. The 135mg, the ACR 20 was a little bit low. We do see these quirks when we do a Phase 2 study. I said that 37 patients is enough but you can imagine if two or three patients have an ACR 19 it could drive the percentage, so it's something that GSK does have to look at going forward, but I think that these are reasonable results.

What the ACR 20 will tell you is does the drug work or not. That's all it says; it doesn't say how well it works – does it work or not and actually, even with the low levels using this definition, the drug works. So in my mind this is a positive study, although if I was

writing it up I would have to write it up as a failed study because the primary endpoint failed. That's with the totality of the evidence.

Rapid onset of action during weekly dosing phase

Clinical Response: DAS 28 (CRP) and DAS 28 (CRP) <2.6

And then if you look at Slide 15 you see the rapidity of the response and the rapidity of the response is really pretty good. This is within Week 1, Week 2, Week 4 you are seeing a change in the DAS 28 (CRP). That's a valid endpoint, a change in the DAS 28 (CRP) is valid and you see it pretty quickly.

At ACR which is where I'm at, where I've been presenting all week, JAK inhibitors are the talk of the town. They are really very, very good. They also reduce the DAS 28 (CRP) quickly and this doesn't look that different than a JAK. I'm not going to say that this is as effective as a JAK and you don't have the same type of studies, but it does work quickly.

And then even though the levels of drug drop off after Week 4, whatever the response is, it's kind of maintained, which I think is kind of interesting as well. The response may not be terrific, so it changes CRP of -2 for the highest dose at Week 24, may not be the most I've ever seen with any drug. I do know that the level is low and I know that it has been maintained which I think is interesting.

You see on the top of this Slide 15 that the primary endpoint did fail which I am not going to discuss further.

Rapid and substantial improvement in joint counts

Swollen Joint Count (SJC) 66 & Tender Joint Count (TJC) 68

You do see changes in Tender and Swollen Joint Counts as you would expect and it does appear to be dose-related.

Rapid and substantial improvement in pain, CRP reduced but not suppressed

On Slide 17 you see a rapid and substantial improvement in pain and I think that that's important because the GM-CSF is actually involved in the pain pathways. So for those of you who know this area, and I imagine most of you do, you'll know that some of the JAKs, particularly baricitinib, but we're also being able to see with upadacitinib and probably going back and looking at tofacitinib, the pain response is better than DMARDs and baricitinib may have a special improvement because of its effect on IL-6. This is an anti-GM-CSF and there is a different pathway for pain.

Marked clinical response on Clinical Disease Activity Index (CDAI)

The patient is interested in swelling. They are not interested in DAS, they're not interested in CDAI, they are not interested in any of that. They are interested in pain, fatigue, 'Can I function?' and that's what it is; pain, fatigue, 'Can I function?' Those are the three things they tell me when I see them, so this change in pain, even a lower dose, is actually very encouraging to me that this is a mechanism that should be pursued.

The change in the CRP is also interesting, it's not that dramatic. So it's not that dramatic, maybe because of the dosing but if you take a look at the JAK inhibitors which we would all say, or after the data that I presented this week, the data that was presented this week, JAK inhibitors are probably better than biologics. It should be used before a biologic; they don't affect CRP either to a great extent, so that one inflammatory marker really doesn't concern me that much.

Totality of data supports further studies

Benefits across multiple endpoints, notably in pain and swollen and tender joint counts

If we take a look the improvements in this Slide 19, so the change in the DAS 28 (CRP), I think it's reasonable. It's not great but it's reasonable. The change in the CDAI is quite impressive. How it compares to other drugs in a head-to-head trial, who knows, but it would probably be fairly similar we think. You would have to get them in a head-to-head but it is impressive.

The change in pain is impressive, the change in the HAQ is certainly better than the minimally clinically important difference, so it meets that mark, the Patient's Global Assessment is greater than the minimally clinically important difference, Swollen Joint Count decreases, Tender Joint Count decreases even with the lower level of drug level. So this is to me positive even though it failed the primary endpoint. It's the totality of the evidence.

If you take a look at the ACR responders at Week 12 the ACR20, the ACR50, the ACR70 is not unreasonable looking at the placebo and still remembering that the drug levels are low.

So in my mind clearly the drug works, they hit the ACR 20, that's not the issue. If the drug works, that's fine but safety becomes a very important part.

Overall AE profile unremarkable; majority were of mild or moderate intensity

I am going to say that I do understand that the drug levels were a little bit low so seeing great safety, maybe it's because the drug levels are a little bit low and the reason why I say that is because they have seen great safety. So I want to couch my remark

understanding that as they do further trials, if they go to weekly dosing and the drug levels are then higher, then safety may change.

It's something I think the company has to look for but this is a molecule that we had great concerns about safety particularly with respect to the lung and other areas, and you don't see an awful lot here.

You see adverse events, we see that in every trial and it was compared to the placebo, and actually in pre-rescue the adverse events were almost the same in placebo as they were in some of the drug groups.

Serious adverse events, there were a few but not many. I don't really look at treatment related because the investigator could be wrong, like they were with the placebo group, where there were two and they were on placebo.

Withdrawal due to AEs, I think is important, and there are only a few, but, again, you also take a look at treatment exposure years, it is not a lot, because it's a few patients for a short period of time. And in pre-rescue/post-rescue there was really no difference. There were no deaths, there were no malignancies, no venous thrombotic emboli, but this is a very small database. So it is encouraging that there were none, but I don't know if that's really true.

With that, that's my take on the clinical programme. I do think that the company should pursue it, and should really take a look what the real dose is, with the correct endpoint and see what they really have, because this is not a negative study to me.

Thank you.

RA market and commercial opportunity

Luke Miels, President, Global Pharmaceuticals

Evolving treatment paradigm provides opportunity for new mechanisms of action

Thanks, Dr Fleischmann, and as you can imagine, we have spent quite a bit of time looking both at the profile, and the totality of the data, but also at the marketplace. And when we look at the treatment landscape in RA right now, we see a market, which I think it's fair to say, is in a degree of flux driven by the penetration

of novel mechanisms of action, continued patient need, and I think over time we should expect, with the introduction of biosimilars.

RA market growth to be driven by new mechanisms

The majority of patients in first line are still, of course, on TNF, but about half of these will be switched before two years of treatment, and with cycling, as you know, less common within a class, these are the factors that we think are going to create an opportunity for novel mechanisms, and with the profile that we expect for GSK'165.

This is an opportunity largely in second line-plus. Although first line use, of course, when you look at the marketplace is increasing. Our focus is very much on second line-plus, and this is a population which should increase with biosimilars and new mechanisms that are driving earlier treatment of the disease.

This should translate into what we believe is the material opportunity for a mechanism like '165, as described by Hal and Dr Fleischmann, and with that, I will now hand over to Hal.

Strong rationale for moving forward

Hal Barron: Thanks, Luke. I hope this was helpful to hear from us and from Dr Fleischmann, an independent clinician, about how we all see the data and why we are encouraged by what we have seen and why we think it makes sense that it is helpful to move forward with subsequent trials.

We believe, as I've said earlier, that we think this is a smart risk. We believe the data, particularly, the CDAI at week 12, where you can see the benefit is really on clinically meaningful endpoints, particularly pain, and as I mentioned, evolving biology on neuropathic inflammatory pain and why we might be able to make an impact on an enormous number of patients who continue to have pain and debilitating symptoms, despite all available therapies.

With that, let me turn it over to the operator, and she can open it up for subsequent questions. I will moderate that and identify who should be on point to answer the questions from all of you.

Thank you for your time.

Question & Answer Session

James Gordon (JP Morgan): Hello. Thanks a lot for taking the questions. I have three questions, please.

The first question - I appreciate that you need to discuss the data with regulators, but depending on whether you need to do another Phase 2 first, or whether you can go straight to Phase 3, can you talk about what the potential development timelines are under the two different scenarios, so by when might the product be able to come to market?

The second question – if I heard correctly that JAKs may be better than biologics, my question is if we think the efficacy maybe looks better in something like tofacitinib with an ACR 20, efficacy looks comparable at 12 weeks, but ACR 50, even on a 12-week data, it looks like the JAKs might be more effective, and if the JAKs are oral, then where does this product potentially fit in the sequence? Is the way to think about that patients would use an anti-TNF, and then they try a few JAKs, and this fits pretty far down the chain of products that could be used?

Then, the third question, which is with the other indications that you mentioned, do you need to successfully develop the product for RA first, approve it, or might you do some other indications in parallel? Thanks.

Hal Barron: Okay, Mark, would you mind taking those and I will add anything that's additional comments, but why don't you start with those three questions?

Mark Layton: Sure, and, James, thanks for the questions.

On the timelines, I really can't comment on that definitively. We have a meeting planned with the FDA later this year. We are discussing development options. We will be discussing these data, and as you alluded to, there are a number of ways we may take this, and so I think it is a little premature.

If you come back to us early in the New Year, then we can talk more definitively about timelines.

In terms of where this fits in clinically, for me, it is the marked clinical response at three months in the data that we see, and the promise that optimising the dose

regime might enhance that further. Therefore, we may well see a different clinical response that might be appropriate for different patients, and we need to get on and profile this at weekly dosing and see what the clinical response really looks like, but I think there is promise in the data we see.

In terms of other indications, yes, we are interested in other indications. We are particularly interested in the first place in ankylosing spondylitis, but also others, because the macrophage is at the heart of a number of immune-mediated diseases, and there is potential in other indications as well, but rheumatoid arthritis is our core indication. Ankylosing spondylitis we are working up at the moment, and then we are also at a drawing-board stage with further indications.

James Gordon: Thank you.

Hal Barron: Let me just add one comment to that that it is very hard to draw any conclusions from cross-trial comparisons. There are so many ways that can lead to spurious conclusions, but I would encourage all of you to look very carefully at a placebo-corrected baseline change in CDAI at week 12, because we believe that really reflects the clinically appropriate endpoints for a drug like this that we think is really impacting pain, and see how you think that compares to all the other available biologics and targeted therapies that gave us confidence that, particularly with the incremental dosing, as described, that we have an opportunity here to help patients.

Let's take the next question.

Emmanuel Papadakis (Barclays): Thanks very much for taking the question.

I would actually love to hear Dr Fleischmann's answer to the same question, as in, it's early, but based on this data set, where could you envisage, or which patients could you envisage using this option?

Then, a question perhaps for you, Hal. It seems like this would be particularly suited to patients where there is pain as a particularly strong aspect of the disease. Is there a biomarker that you could develop in tandem, or, indeed, that you are

developing that could help identify or physicians could identify the most suitable patients for this option?

Then, maybe a last one, if I could take it, for Luke? Biosimilars are coming. They are obviously going to have a very big impact in Europe. They are already. Is referenced pricing to a biosimilar something you are concerned about for additional biologics coming to market in the future? Thanks very much.

Hal Barron: Thanks, Emmanuel.   Dr Fleischmann, do you want to take the first one?

Dr Fleischmann: So that's where it would be positioned?

Emmanuel Papadakis: Yes, exactly.

Dr Fleischmann: Right, so thinking about your last question, clearly, there are patients – you have 97,000 biosimilars, and, clearly, in a patient who doesn't respond to the bio or original, or several of them, this drug could conceivably work in that salvaged patient, and you might think that that's a small part of the market. It isn't. It is probably 20% of patients, maybe 30%.

If you really think about the per cent of patients who achieve remission, and I don't use DAS28 (CRP) remission. That's like saying that a small, little Kia is a car and a Rolls Royce is a car. They are both cars, but I would rather have one than the other, and I would rather have a CDAI remission. There's a bulk of patients who we treat, but really have not reached target, so that's the obvious.

The other, though, is this is an intriguing mechanism because of the way it works, and I made the point before that this actually might work much better than some of the agents we have now in earlier disease, and it depends upon the clinical development programme that GSK comes up with and how clever they are, and whether or not they are able to really find this niche, but it may work really well early.

Then, the other one that you brought up, which is a little unique is we do have patients in whom we can get inflammation under control. We have shown that in the baricitinib programme. We have shown that in the upadacitinib programme. I could go back and do the tofacitinib programme – all the programmes we did where patients have a normal CRP, a normal ESR, I really can't detect any tender joints, and yet they are not under control because of the pain.

This is pretty simple, because it's a DAS scale. I don't need a biomarker. All I need is to give the patients a drug on the DAS scale and I can tell whether or not they are doing well.

Therefore, there may be really specific situations. Patients who have failed everything, rescued; patients who are early – this really may be advantageous in terms of really bringing disease under control, and maybe even being able to stop therapy because you have such long effect, who knows; and then the patients with pain.

Then I would be looking at the other calculations and seeing how well this really does work, versus the comparators we have. I think we become transformational with JAKs this week, with the data we have presented this week. I think it is transformational. A year ago I never would have said that we have used JAK before a TNF in most patients.

This is a totally new mechanism for us, and if GSK is lucky and if it can develop a good programme and a smart programme, who knows where this would be, but I think that's really pie in the sky.

I do think that late patients, patients with pain, and early patients would be the targets for me.

Hal Barron: Thank you. Let me take a stab at biomarker, and then turn it over to Mark.

I think it's a terrific question, Emmanuel! I think there is patients' covariant that can be like biomarkers, as we have just stated, that patients with a more aggressive pain course might be particularly amenable, but we are also looking at – and I alluded to this - exploring the biology behind what GM-CSF does and what blocking it, therefore, might do, and looking at cytokines like CCL17, given that, as I said, the emerging data is really suggesting it might play an important role in pain and GM-CSF is known to induce the transcription and translation of that protein in many different cell types, including cells that we think are directly involved in pain, such as neurons.

Therefore, that is something that is premature to talk about to a larger degree, but certainly something that we have on-going efforts on.

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Mark, do you want to add anything to that, or other biomarkers that you think are important to highlight?

Mark Layton: Yes, thanks, Hal. I agree with that. We also have a poster at this Congress reporting CCL17 as a potential biomarker, so we have a big interest in biomarkers.

For me, and I guess perhaps with a clinician's background, and as Roy mentioned briefly in his previous answer, it's the clinical aspect, so we could, as Roy said, just take a simple VAS, ask the patient, get them to write it down. But we are also interested in other ways of assessing pain, and particularly whether there's a neuropathic element to that.   So at the moment we are investigating various other ways of assessing and classifying pain from more of a clinical phenotype approach to that.

Hal Barron: Luke, do you want to take the third question around biosimilars?

Luke Miels: Sure, yes.

Emmanuel, a very fair question, and as you can imagine, it's something we have spent quite a bit of time thinking about.

Firstly, the bulk of the opportunity, as you can imagine, is in the US, but your question was on Europe. If you look at the EULAR guidelines, our expectation is that as the prices of TNFs are reduced, then you are going to see more patients being progressed off methotrexate onto a biologic. As you know, there are a series of barriers that are erected to ensure patients' appropriateness, as described by particular patients within Europe, so I think those barriers to entry are reduced and you are getting more patients coming in at the start there.

We also, during the period of '165, of course, you will see JAKs beginning to lose patents, so that's another thing we have looked at, but in all of our cases, and in Europe more so, we have positioned this at second line-plus, and when you look at dimensions such as pain in areas such as Germany, which do place value on patient-relevant outcomes, we think we can find ways to position this agent and get reimbursement, and ultimately through this protocol, which is going to be detracted, we are going to create some value.

Emmanuel Papadakis: Thank you very much.

Jo Walton (Credit Suisse): Thank you, a few questions, please.

Just looking at the data on slide 13, there do seem to be a lot of people dropping out, not only just in the placebo arm, and I understand that if they didn't get a good response they could drop out, but in the second-highest dose arm, for example, as well, there was a very high drop-out rate. Is that because patients weren't happy and wanted to go somewhere else? It doesn't give me a sense of great patient satisfaction with this study, so I would be intrigued on that.

Secondly, just looking at the dose, if you are going to go from bi-weekly to weekly, do we effectively think of you doubling the dose, because it's effectively the same dose given weekly, and do you have any sense of what the highest dose that you could safely give would be?

A third question would be whether you have any continuing interest in osteoarthritis? Looking at the GSK website, it does say that this molecule is in development for osteoarthritis, but that hasn't been mentioned today.

Finally, I wonder if the doctor could give us his view? If you were sitting there, and GSK asked you, "Doctor, what would be your advice for a Phase 3 study?" roughly how many people would you like to see in that study, what would the endpoint be, and would you like to see the patients taken in, specifically having failed, let's say, two TNFs, so they are particularly hard patients to treat to come into that study, or would you just accept anybody potentially new to RA?

Hal Barron: Okay, Jo, thank you for those questions. Mark, do you mind talking about the drop-outs, the bi-weekly, and then coming on osteo, and then turn it over to Dr Fleischmann to give his thoughts on the Phase 3 design question.

Mark Layton: The dropout question – what we have, I think, in that group that you called out there specifically is more similar to what you would typically see the views of this type. You have to take into account that these were later drop-outs and at a time when the fortnightly dosing had led to the reduced serum concentrations, and that perhaps might be related, but they are not as striking as in

the placebo group and the lowest dose there, where the EULAR moderate-to-good criteria forced people to switch.

That's the dropouts.

In terms of the weekly dosing, we've again a poster at this congress, which has actually been able to build quite a robust PK simulation, and because we did have the weekly dosing in the study, then that allows us to build a robust model.

That model predicts that we will be looking at a dose of around 150mg, and that will provide us the necessary exposure to block GM-CSF, and produce a therapeutic dose that we predict, and obviously we will be taking that approach to dosing to regulators, as I mentioned, later this year.

Osteoarthritis, we did a study in hand osteoarthritis. We saw a pain signal, but we didn't see a large pain signal, and we didn't see any effect on inflammation on MR. Therefore, for the moment we are not progressing hand osteoarthritis. We are focusing on rheumatoid arthritis, and I talked about other indications earlier as well.

The first of the new indications that we are looking at progressing will be ankylosing spondylitis.

Dr Fleischmann: I will answer your question direct, but I do want to add a couple of things to Mark's.

First of all, the 135mg group. I made a comment that with 37 patients in a group you should be able to see a response in a Phase 2 study. What I should have also said is it is dangerous, and the reason why it's dangerous is because when you have 37 patients, it could be just a few patients could change your numbers dramatically, and you don't know why these patients dropped out, so it could have been for lack of efficacy. They could have been forced out if they just didn't meet the criteria. They could have had an AE. They could have been bored. You don't know, but it is very difficult.

I want to go back to the Lilly baricitinib programme, just to bring you up-to-date, and make the point. If you know that programme, you know that they picked their doses based on Phase 2, and they did one phase to one variable Phase 2b study. I think it was a little bit larger than this, but not much, and in that study they found a placebo really didn't respond, so 1mg had a response; 2mg failed; 4mg had

a response, and 8mg was equivalent to the 4mg. Therefore, they decided to go into Phase 3 with two doses, and the doses they picked was 2mg because it failed in the Phase 2, and 4mg because it plateaued.

They showed me that data as they were developing the Phase 3, and I said, "you have to be careful of that 2mg dose because the 1mg did have a numerical effect." They said, "no, no, no, it is just a quirk, it is just a quirk." So in the United States they have 2mg because it worked in Phase 3, and they don't have 4mg because 2 mg worked as well as 4mg.

Therefore, you have to think about that, and I certainly would actually do another Phase 2, where we would have more patients in a group, so to have more confidence of what this would be. That is one.

That was one point you talked about was the Phase 2.

OA. OA is very difficult. We've done a number of OA trials, and I would like to tell you that our success rate is 0%, and with a number of different molecules, other than incense, because with incense you can actually tell a pain change pretty quickly, but I think it is actually almost the metrics that we use. The fact that this failed, we have seen this fail, we have seen IL-1s fail, we have seen very few, if any, drugs really work in osteoarthritis, but I think it may be the metrics.

Let me go back to what you asked me, which is what would I design in Phase 3? In Phase 3 I would have to know what a repeat Phase 2 would show, and then I would think about where I would go.

I would not go for a double TNF failure, a double biologically marked failure, or a biological and inject failure if I were GSK. I wouldn't do it. There's a market, and you could sell a drug, but if that's the only market to go into, I think I could take my resources better elsewhere.

I would go for the gold. I would go for 'I have the drug that's going to work at least as well as everything else, and at least as safe as everything else, but I am actually going for one that actually is better', and better in terms of safety is really good, better in terms of efficacy would be better, better in terms of safety and efficacy would be better yet.

I think that they have a chance for better efficacy, in some ways, particularly the patient-reported outcomes, which is very important to patients, and they may have a chance for better safety just from what I am seeing, but I would wait to see the Phase 2 before I decide where I would go, and in Phase 2, I would actually do the same population.

Jo Walton: I am not sure that I understand, is the pain mechanism, or the actual pain that you experience in your joint if you have hand osteoarthritis, is the pain mechanism fundamentally different from the pain in RA? I am just surprised that it works in one type of pain, but not another type of pain, but I may not understand it.

Could you also just say, then, you would recommend, would you, a head-to-head with one of the standards of care for the Phase 3 to show that's it's better?

Dr Fleischmann: I don't know that I know the answer to that first question, because it is pretty easy to get a change in pain in the RA studies. We use a WOMAC for the OA studies, and I think the diseases are different.

I don't understand why we can't show it in one, but we can show it in the other. That's a really, really good question, and that's why I think it is the metric.

I might think in a Phase 2, because I was actually thinking about that as you asked the question, how I design it. I would take the GM-CSF, I would use the doses that I think I would do, and I would use an active comparator. The active comparator would also use the placebo. You need the placebo to make sure the active comparator is really showing what it should show, and if you use the active comparator, then you could actually begin sitting back and saying, "this is a difference in CDAI response". That's what I would do, but they haven't asked me yet.

Mark Layton: I would just like to clarify one thing. The hand OA poster that we are showing at this Congress is not completely negative. It does actually show an effect on pain in osteoarthritis. It is a relatively small effect, and we don't think it supports indication in hand OA per se, and it also isn't backed up by any evidence of improvement in inflammation, so that's why we have decided not to progress that at the moment, but there is a small pain signal, and that might actually

be relevant to the pain effect that we see in rheumatoid arthritis, and also in other indications.

Dr Fleischmann: What was the placebo? I have one major point. In osteoarthritis trials, the reason why many of these drugs fails is because the placebo is positive in 60% of patients. What was the placebo effect?

Mark Layton: We will just have to check on that. We will come back to that in a minute.

Dr Fleischmann: Okay, that's usual.

Luke Miels: The other challenge with osteo hand arthritis is the comparative courses over-the-counter pain medicine, so from a pricing point of view it can be more of a challenge, independent of any efficacy signal we may or may not have seen.

Dr Fleischmann: Right, so I am coming to the conclusion that the osteoarthritis trials that we are doing now, that it would actually be well to have an active comparator such as an NSAID in a trial, but these are difficult trials to design.

I think that if we could figure out how to really do the design and we found an effective drug, clearly, this is the market. We have NSAIDs, which are dangerous drugs. We have opioids, which are dangerous drugs. We don't have a lot else in osteoarthritis, and as Mark was talking about, we don't have any disease-modifying osteoarthritis drugs, but we are pursuing it right now.

Mark Layton: Yes, so in answer to your direct question, the placebo effect was 1.3 in NRS points versus 1.7 on active.

Hal Barron: Okay, I think we will move on. I know we only have a couple of minutes left, and I would like to see if we can get one last question in. Can we hear one last one, before we finish?

Laura Sutcliffe (Berenberg): Hello. I have just one question, please. It has been mentioned a couple of times over the course of the call that ACR 20 might have been a more appropriate endpoint to look at in this trial. We get a hint of what that could look like, I think, on slide 19. With the obvious caveat that this wasn't your pre-specified primary endpoint, does what you can see at the moment on the

ACR 20 measure feel like it is compelling efficacy-wise, or could be compelling efficacy-wise, especially in the light of the fact that the response rate and the placebo arm was unusually low? Thank you.

Mark Layton: Hello, yes, thanks for the question. I will take it, and then Roy might want to comment as well.

When I look at these data, and keep in mind that even at week 12 there has been four to six weeks of lower exposure than we expect, but even with that caveat we actually see a large delta, so the placebo effect we had an 11% response on placebo, and 51% on the highest dose. And that's quite a large delta as it is, which we would then expect to be greater still, and, indeed, that's what the model predicts that we've got a poster on today at ACR.

Therefore, I think as it stands, even with the under-exposure we have quite a large delta in ACR 20, and we would expect that to increase some more, and that's predicted by the model that we post today.

I am expecting that Roy will have a comment to add to that as well.

Dr Fleischmann: Thank you, I do. I disagree. I fully disagree. The ACR 20 tells you whether it works or not, and it does. The question is, what other evidence do you have that the drug is effective, and you actually have a lot. So the change in the CDAI, the degree of the change in the CDAI, the degree of the change in the tender and swollen joints, the mean change in the HAQ, all of these are very, very important endpoints in terms of depth of response.

The ACR 20 tells you it works. These others actually are telling you that you are getting a response that's clinically meaningful for the patient. Therefore, the fact that you have an ACR 20, fine, but it is these others that actually make me think it is worthwhile to spend money on this drug. If these were not there I would say don't do it, but these are important.

Mark Layton: Thanks, Roy, that's a really great point. I was responding directly to the question of the ACR and the predictions, but I agree entirely with you that it's the CDAI and the clinically driven scores which are our source of excitement in this potential medicine.

Hal Barron: Okay, I think we probably need to wrap it up, but I just want to thank the other panellists, and particularly Dr Fleischmann for taking time out of his very, very busy schedule to review our data and provide independent thoughts, and also to Mark and Luke, as well to all of you, the analysts, that took the time to join us. Hopefully, this was a good use of your time, and hopefully helped you understand a little bit better why we find the data encouraging, and feel like it is a smart risk to pursue this for RA, and hopefully other indications, as things progress.

Thank you very much, and I look forward to speaking with you again soon.

[*Concluded*]