Luke Miels: Thanks Alisa, and good afternoon and thanks for joining this GSK investor and analyst conference call to discuss the data that was presented yesterday at ASH for GSK ‘916. I’m Luke Miels, President of Global Pharmaceuticals and I am pleased to be joined today by Axel Hoos, Senior Vice President of Oncology R&D and also Dr Paul Richardson from the Dana Farber Cancer Institute.

Before we start, I would like to note that this is my first meeting with the investment community since joining GSK in September and I am very pleased actually that my first call is to discuss an innovative asset which I think allowing for its stage in development has quite striking efficacy.

Also I would like to remind those who have not already called up the slides that the presentation that we will be speaking from today is available on the Investor section of GSK.com and as we go through the presentation, we’ll list the slide numbers or titles so that you can keep track.

Cautionary statement regarding forward-looking statements

Before we go any further I will direct you to please read the cautionary statement regarding the forward-looking statements on Slide 2.

Agenda

Moving now to Slide 3 entitled ‘Agenda’, the objective of today’s call is to review the exciting new data of GSK ‘916, the Phase 1 clinical trials on anti-BCMA antibody drug conjugate or ADC for the treatment of multiple myeloma and although it’s early days, we are excited about the potential of this ADC to provide a new treatment option for patients.

As a general comment going forwards, I think it’s fair to say you should expect to see GSK engage with you, the investor community, around key data for our assets in our priority areas on a more regular basis, both myself and Hal Barron and other members of the team and our objective being to keep you informed and answer your questions about the pipeline in an ongoing manner.

So turning to today’s agenda, I will provide a few quick thoughts on the multiple myeloma market and how we are thinking about the opportunity, then Axel will talk more about GSK ‘916 and how it fits into our broader oncology pipeline and then we’ll turn to Dr Paul Richardson who will provide all the data from the ASH late stage presentation. For
those of you who don’t know him, Dr Richardson is a renowned medical oncologist from the Dana Farber Cancer Institute and a clinical investigator who has personal experience with GSK ‘916.

We expect the prepared remarks to last around 20 to 25 minutes and then we will welcome any questions you may have on GSK ‘916. Again, the focus of the investor call is on the data presented yesterday at ASH more broadly and also the opportunity that this product specifically represents.

**Developing the pipeline in Pharma**

**Development capital focus on 2 core and 2 potential therapy areas**

Moving to the next slide, and that’s entitled ‘Developing the pipeline in Pharma’, when Emma presented the GSK long-term priorities back in July, accelerating innovation was highlighted and the top priority there really is to strengthen the Pharma pipeline. This is a clear focus of ours, and as Hal Barron comes on board in January, he and I will be working very closely together again to assess the ability of our assets within the portfolio to deliver both scientific and commercial value, and we will work together to ensure that the future GSK products will both meet the significant unmet medical need and help patients, and create value for our shareholders.

From the slide in front of you, you can expect a continued focus on R&D spend and capital allocation in terms of Respiratory and HIV, Infectious Diseases, where we have established leadership positions but also we are very interested in investing in immunoinflammation and oncology and I think it’s fair to say that we have a very interesting early stage pipeline in these two areas.

**Multiple Myeloma (MM): An incurable hematologic malignancy with high unmet medical need, despite new treatments**

This is Slide 5. I would like to provide the context on the disease of multiple myeloma. As many of you know, it’s the second most common haem malignancy after non-Hodgkin’s. It’s around 15% of cases. If we look globally the numbers that we have are around 125,000 people of which more than 50% of these patients are found in the US, EU5 and Japan. These numbers technically make it an orphan disease and GSK ‘916 now has actually received orphan drug designation by the FDA and the EMA in addition to breakthrough and PRIME.

On the right-hand side of the slide, while new treatments have certainly allowed for an increase in the survival of multiple myeloma patients over the last decade, the five-year survival of patients remains under 50% based on the most recent ten-year data and although
we do expect and hope that more patients will survive with the extended use of newer, targeted therapies, there is a significant unmet need that remains.

**Market growth creates opportunity for innovation**

If we go to the next slide in terms of the market itself, in a value sense the market is large and growing. It is expected to double to more than $12 billion in 2016, around £9 billion, to $28 billion, around £22 billion, in 2022. As you would probably expect, the US is the biggest contributor representing 65% of market value and the key drivers of this growth are the increasing incidence which is growing by around 2% a year driven by an ageing population, and then secondly the arrival of innovative and marked adoption of new treatment options which has allowed patients to be treated for longer durations and multiple treatment lines, and then finally the combination therapy which is quite common and driving higher response rates and higher levels of durability.

**Fragmented treatment paradigm**

**Opportunity for new entrants**

If we go to Slide 7, which talks about the fragmentation in the market and I think in the interests of time I will stop here, but I think the key point here is that the graphics show the minimising of the treatment of patients has the potential to cycle through and is really an indication of the lack of a firm, set treatment paradigm but I think also very compellingly it shows that this area is highly receptive to innovation and very, very dynamic which is what attracts us.

With that point and with that background I will now pass over to Axel who will provide an overview of GSK ‘916 and then he will hand over to Dr Richardson.

**Axel Hoos:** Okay, thank you, Luke.

**Oncology R&D**

I wanted to just say a few words about the GSK Oncology R&D strategy and our pipeline before we go to the ‘916 agent itself.

So on Slide No. 8, we have laid out the scientific focus for the new Oncology R&D effort after the Novartis transaction, so we are about two and a half years out from the Novartis transaction where we sold our marketed Oncology products to Novartis. We retained the R&D pipeline which was basically all the Discovery work at the time, and that has now been expanded and has matured and focuses on three particular areas of science
that are laid out here. Immuno-oncology, cancer epigenetics and cell and gene therapy, and the cell and gene therapy piece is, as you know, in large part also immunotherapy.

Our aim here is to look for innovative medicines that are transformational so they are really moving the needle for patients either alone or in combination regimens and if that is your objective, I think BCMA as our first agent in the new pipeline is meeting those criteria.

**Innovative & Emerging oncology pipeline**

**BCMA is the lead asset**

Now if you go to the next slide, No. 9, this is a pipeline snapshot where you can appreciate the innovation that we actually have created in the three focus areas.

Beginning with immuno-oncology, BCMA is our lead asset here and I will speak about the mechanism of action in a minute, and then we have a set of clinical assets that are all in one particular category where GSK has placed a bet which is the category of checkpoint agonists.

As you know, the PD-1 wave was quite attractive in immuno-oncology, has provided a lot of patient benefit but hasn’t solve all of our problems yet and this is an antagonistic antibody, so is CTLA-4, the first two generations of bio. The third generation we believe has to offer something different, and agonist antibodies are targeting well conserved and well understood biologic receptors. We just have to find how they work in the clinic, how we can best make an antibody or a targeting agent that can leverage that biology, so we are in Phase I with an ICOS agonist, the OX40 agonist and also the TLR4 agonist. We will combine then with each other, but we will also combine them with other modalities to leverage that biology.

Beyond that we have other modalities that we use to target immuno-oncology targets. That includes novel small molecules for the tumour marker environment, ImmTacs which is a partnership with Immunocore for bi-specific antibodies that can connect T cells and cancer cells and bi-specific antibodies of different formats, so that rounds out a well-balanced, innovative pipeline in immuno-oncology.

And then if we go cancer epigenetics there are currently three agents in the clinic and they are named here, the BET inhibitor, the PRMT5, PI3K beta, they are the tip of the iceberg, if you want, of a well-built nine-year old discovery effort in epigenetics where GSK has a leadership in the industry.

And then at the bottom in red you see the Cell and Gene Therapy effort which is young. We only opened our Cell and Gene Therapy Unit a year ago even though the platform effort, the CMC, effort to manipulate cells and introduce new genes in the cells is
older. That part exists for about five years and as you know GSK has marketed a product in the rare disease space already last year and we are now moving big into oncology. The first programme, the NY-ESO-1 TCR-T, is partnered with Adaptimmune. We opted in on that programme earlier this year. It is our first clinical programme. It has breakthrough designation and PRIME designation from the FDA, and it is being followed by other TCR-T programmes and by CAR-Ts which are in-house projects.

**First-in-class anti-BCMA agent with multiple modes of action**

If I go now from the pipeline to the lead asset of BCMA, this is now Slide No. 10. This is a first-in-class antibody drug conjugate that has a four-fold mechanism of action. So first it is an antibody, an IgG1 antibody that binds BCMA. That is afucosylated so that means it enhances the antibody dependent cellular cytotoxicity and it is conjugated to MMAF which is a spindle cell poison that can very effectively kill cancer cells.

So the four-point mechanism of action offers a lot of versatility for this molecule, so you have ADC and ADCC more standard features of an antibody. We have of course the BCMA receptor signalling inhibition and the immunogenic cell feature which we believe is an attribute of the MMAF conjugate. When the antibody gets internalised into the cell it blows up the cell from the inside and the cell releases antigens that induces an immune response which makes it attractive to combine BCMA ADC with potential immunomodulatory agents in myeloma. So this is part of what we will do as we expand the programme now that we have the first phase of data.

Another few things that are worth pointing out, a key attribute of this antibody drug conjugate is that it doesn’t require pre-medication for infusion reactions which is commonly the case with other antibodies, it’s easy to administer, so we give a one-hour infusion every three weeks which is much shorter and easier for the patient than other antibodies used in multiple myeloma, and the new mechanism of action lends itself nicely to combination therapy.

With that, I will give the word to Dr Paul Richardson who will tell us about the recent results.

**Paul Richardson:** Thank you so much, Axel and thank you, Luke for your earlier introduction. It is a pleasure to be on the call following Suzanne’s beautiful presentation yesterday afternoon at the meeting.
As Luke mentioned I am a co-investigator with Suzanne on the project and we have been involved in the application of ‘916 in the myeloma space pre-clinically as well as clinically.

What I hope to do today after Axel's lovely introduction to the antibody which I think tells us an awful lot about why it’s so promising, is to walk you through the clinical information that we have so far.

**DREAMM-1: study design**

**Driving Excellence in Approaches to Multiple Myeloma**

On Slide 11 what we sought to do here is summarise the DREAMM-1 study design. I like the title of the study, it’s actually very nice and in any event the bottom line here is to share with you the schema of what’s happened.

Essentially this was a Phase I trial and in the dose-finding stage we were very encouraged to see really no dose limiting toxicity observed, although a selected dose was chosen at 3.4mg/kg and that basically was taken forward into the expansion phase.

Now in Cohort 1 of the expansion phase, that’s the cohort that Suzanne presented yesterday, that’s all myeloma. It is worth mentioning Cohort 2 below it, at 3.4mg/kg it is ongoing but that’s in diffused large B cell lymphoma. The presentation at ASH last year in San Diego that Adam Cohen and I co-investigated on the study was obviously about the dose-finding phase, so what I am going to focus on today in the interests of time is the 35 patients that Suzanne presented yesterday afternoon.

**DREAMM-1 Part 2: Demographics and baseline characteristics**

If we move to Slide 12, you will see here that in Part 2 it’s just worth sharing with you some of the demographics and baseline characteristics of the patients to give you a context in which to interpret the information.

First and foremost, the median age was typical for an early phase study population in myeloma. I would point out, though, that the oldest patient we’ve treated is 75 years of age, and it’s an even sex distribution. Probably what is important to note is the number of lines of prior therapy and that’s actually obviously very informative. And if you look at that, 57% of the patients had had five or more prior lines, 90% of the patients had been previously transplanted.

And then if we start to break down previous exposures, I think that’s very helpful. What you can see is that all the patients had had immunomodulatory treatment and that of course is very typical. IMiD is an absolute backbone of our therapy now in myeloma and has
obviously contributed enormously to the success of novel therapy platforms in the disease. But as you can see, almost all the patients have had prior lenalidomide, and in fact two-thirds had had pom and even a third had had thalidomide, so this is an important observation in the trial database because this is a highly IMiD exposed and refractory population.

If you actually look at the number who are actually refractory to immunomodulatory therapy, it’s almost all of them.

Now if you drop down into the proteasome inhibitor exposed patients, again these data are very informative. All of the patients had a previous proteasome inhibitor, and of course the vast majority have had bortezomib, but I think what is important to note here is that a significant number, 80% of the patients in fact, had had second-line therapy with carfilzomib and of course refractoriness to proteasome inhibition was documented in almost all the patients.

Critically in the most recent set of approvals underpinned by daratumumab, I think what has been very compelling to us and extremely helpful, actually, therapeutically has been that a number of the patients had been previously exposed to daratumumab and in fact of 14 patients, that’s 40% of the cohort, 13 of them were refractory, so just to give you that context.

If you then look at what we call a classically triple refractory population, you can see here that those who were refractory to both IMiD and PI, or I should say double refractory is probably the better term here, that’s 90% of the patients, 31 of the 35. But I think this is the interesting part; if you look at those patients who were refractory to both IMiD, PI and to prior daratumumab, it jumps to 34% of the cohort, which is a very informative group of patients to look at.

Then finally I would like to touch a little bit on the high risk. This obviously is an evolving space in myeloma but it identifies a particularly poor prognosis group, and it’s an area of unmet medical need. If you look here, you will see that approximately 30% of the patients met high-risk characteristics and that’s defined by genetic abnormalities, including 4:14 translocation, deletion which is particularly ominous and at the same time 14:16 and 14:20 translocation or nonhieridiploidy or gain of 1q. Now all of those pertain of course to a bad outcome.

**Transformational efficacy in multiple myeloma: ORR**

If we move to Slide 13, and I think this is the really nice part of the analysis and as I say was beautifully presented by Suzanne yesterday, you can see that with this waterfall plot we have an overall response rate of 60% which for a monotherapy, as Axel so nicely
presented, with a convenient infusion schedule of once every three weeks with minimal pre-
medication required, to see this kind of activity in such a refractory population is very
compelling.

In the box that we have presented to the side of the slide you can see the refractory
populations and how they performed. If you look at the classical double refractories, it’s 58%
recognising of course that they could have enriched carfilzomib as well, so technically it’s a
little bit more than the classical double refractory, it’s the triple refractory to be more precise.

Then if you start to move into those patients who have had prior daratumumab, the
response rate is 43%. You may have heard in the jargon there is now triple refractory, quad
refractory and penta refractory. I think it’s fair to say that patients who have had prior dara
can be considered to be penta refractory equivalent. Patients who have had prior pom and
carfilzomib can be considered in the quad refractory group, so based on all of that and just to
frame this for you, this is the kind of response rate in this kind of group of patients that’s so
compelling.

If you look here, 60% overall response rate and then if you drill down to the dara
refractory patients, it’s 43% and I think that to me is the really between the eyes observation
from the response of analysis.

DREAMM-1 Part 2: Response characteristics

Now obviously responses matter if they last, and that takes us to the next slide which
is 14, which gives you in a very nice graphic way the response characteristics.

This is a busy slide but it’s basically a swimmer’s plot that I would argue are GPS.
What I mean by GPS is that it has the doses, it shows you what happened to the responses
and it shows you what happened to our dosing because this is an important point.

Essentially we saw early responses after one to two doses, the majority are durable
but what is critical is that we obviously do dose reduce, you see that, that’s a very important
part of managing the side effect profile, but what’s really exciting is that dose reduction does
not lead to loss of responsiveness which is critical.

And I think Axel’s very nice introduction to how the antibody works may explain that,
too, because this effect that I think is so interesting to me personally anyway is what we
alluded to which is this immunogenic effect and what we would call immunogenic cell death
that may be part of this sort of effect because it’s so interesting, and I agree with you, Axel,
very provocative.

So anyway, to look at this swimmer’s plot you can see durable responses even when
we dose reduce and we see high quality of responses, and again in this population what
particularly grabs us are VGPRs and CRs, and as you can see, that's well represented here and points in our view to a very promising signal.

**DREAMM-1 Part 2: Efficacy – progression-free survival and duration of response**

But of course, the final sort of analysis of durability comes down to PFS and DOR, and on Slide 15 we seek to show you that. As you can see, of the total number of patients on intent-to-treat, remember, this is not a selected population in that regard, this is an ITT population, you can see that in terms of progression-free survival we have a median of 7.9 months which in this population to me is remarkable, and the durability of response obviously reflects that as well.

**Manageable safety profile - summary**

Now what about the safety? Let’s move to Slide 16 to address that, and in the interests of time I am going to move through this relatively quickly. But suffice to say the important toxicities that we identified in the initial dose-finding phase of the trial included thrombocytopenia, and of course this corneal effect which requires careful work with an ophthalmologist as part of the study.

In our own experience, the data in aggregate are very reflective. There are all grade corneal events, 63%, but the vast majority are Grade 1 and 2. There is 9% Grade 3 only and importantly, dose discontinuation for corneal effects did not occur.

In my own experience from my patients in the trial, this was manageable with steroid eye drops and we had a really good relationship with our ophthalmologist at the Deaconess Center. There are diabetologists by expertise in fact, but they also help us with GVHD management of the eye, and so consequently they were an excellent resource.

I will share with you, though, this was generally very manageable and we had genuine concerns about this to start with, but as my team got more and more comfortable with managing the ocular side effects, this has become substantially less of a concern to us certainly as a team.

In terms of the thrombocytopenia, certainly in our cohort of patients we didn’t see significant bleeding at any time and this was a manageable side effect. It’s important to note that also in myeloma, we are quite comfortable with managing the haematologic side effects.

What about infusion-related reactions? A couple of quick points there; relatively low incidence - 23%. They did occur at first dose without premedication, but very importantly they didn’t recur which I think is a key message.
My summary point would be that as a clinician in this space in such a highly refractory population, to be seeing a response rate as robust as this with the quality of response and the durability of response that’s so promising as well as manageable side effects, we really are very encouraged by this early but very promising experience to date with ‘916.

Thank you.

**Axel Hoos:** Paul, thank you very much.

**GSK ‘916 single agent has transformational efficacy**

I am taking the words back to give you a little bit more granularity around the profile for BCMA, so one word, and this is now on Slide 17, about the single agent effect that we have observed. As you know, myeloma in early lines of therapy is often treated with combinations, but there are several drug combinations which are quite efficacious. If you look at where every drug starts at the end of this space is with monotherapy, and we have seen here a very high single agent response with one antibody in this disease, an antibody that is potentially acceptable to all patients.

Relative to the two other agents, for which we have monotherapy data which are on the market, which are Kyprolis and Darzalex, it is about a doubling of the response rate in every single agent. The same is true for the durability. As Dr Richardson said, the response is only as good as it lasts, and we have seen here a median PFS of around eight months, compared to nearly four months for the other two agents that are on the market. We believe we are doubling response rate, we are doubling durability. These are good signals to enter into a larger programme for BCMA.

That larger programme looks as follows, and is depicted on slide 18.

**GSK ‘916: expected next steps**

Our next steps are the regulatory interactions, of course, that we will have with the FDA and EMA to reach the market as fast as possible. We have breakthrough designation from the FDA, we have PRIME designation from the EMA, and we have orphan drug designation. These are the cornerstones for the regulatory interaction.
We will then segment the clinical development programme into three major areas in myeloma, and another area outside of myeloma. It begins with monotherapy, with the data you have seen is only in monotherapy so far. We will start a pivotal Phase 2 study in the last line of treatment, which is the Darzalex refractory population next year, as early as we can open the trial, and expect the pivotal data read-out one year later. This is a small, single arm study, that can deliver response rate data relatively quickly, and then by 2020 we expect to be able to launch the product, following a more conventional development path with a monotherapy.

In parallel to that, we will also start next year combinations with standard of care and early alliance, so the lenalidomides, the pomalidomides of the world, to make BCMA acceptable to patients in early alliance. We expect those drugs to start next year, and provide data read-outs for decisions of pivotal trial start by latest 2020.

In parallel to that, here is the third tier of the approach, we will also start Phase 1/2 trials with novel-novel combinations, and that goes back to the mechanism of action. With an immunotherapeutic component to the molecule, we believe that the immune response induced by BCMA could possibly be modulated by immune checkpoint modulators, and that would make for very attractive novel-novel combinations, then we will test in several areas in multiple myeloma, several different lines, and several different combinations, as the programme unfolds. We expect to start that next year, and will have critical data read-outs again by 2020, when decisions are due for starting the pivotal programme.

Then, as a separate project, we know that BCMA is also expressed in Non-Hodgkin’s lymphoma. Some patients with DLBCL have 20% level of BCMA expression, so we have an ongoing cohort in the first-in-human trial that investigates that. If we see similar effects there as we have seen in myeloma we will expand that programme and also seek a registrational trial in that setting.

All of that will be accompanied by regular interactions with regulators, and the breakthrough designation that we receive from FDA recently is now a really good starting point to discuss accelerated approval and move this programme forwards as fast as possible.
With that, I think we are at the end of the presentation.

**Luke Miels:** Thanks, Axel. Before we go to Q&A I will just grab slide 19, because we do get asked from time-to-time by investors about the relationship with Novartis in respect to the oncology pipeline.

**Right of first negotiation for GSK oncology assets**

You can see slide 19, the key components here – I will just pick a few of them out.

Novartis does have right of first negotiation, and you can see the trigger there, but the second bullet point is probably the most important one on this slide, which is Novartis does not have an opt-in or a call option in relation to the GSK oncology pipeline.

Naturally, our obligation is to negotiate in good faith, and GSK would only enter into a transaction if it believes that transaction will be in the best interests of our shareholders.

Finally, I think the last two points are pretty clear there. The ROFN does not oblige GSK to sell or to partner with Novartis, right of first negotiation is not an obligation to consummate a transaction with Novartis, and under the ROFN we are able to continue to develop and commercialise assets on our own. You can see the timeframe there; it expires September 2027.

Let me now in the formal presentation, and I think you can go straight to questions.

**Question & Answer Session**

**James Gordon (JP Morgan):** Two questions, please, one clinical and one regulatory. The clinical question was just how important is BCMA expression in determining response to BCMA therapy? I know Celgene has some pretty strong data, and maybe stronger ORR even in a more heavily pre-treated population, but I think they have selected for BCMA expression therefore, so could that be part of the
difference? I note you have chosen BCMA positive only for the DLBCL in cohort 2. That was the clinical question.

Then regulatory, the slide suggested that it was 2020-plus for first filing and launch, and that is doing a pivotal first, but then if you do have breakthrough therapy designation is there any possibility of an even earlier filing, and when would you have clarity with the FDA on that? Have you already had the chance to discuss that with them?

Luke Miels: Thanks, James. Dr Richardson, if you would like to take the first question, please, and Axel, if you would cover the second?

Paul Richardson: Absolutely. In terms of BCMA expression, a great question. I will say it is very interesting because the Celgene programme is adjusting now to not require minimum BCMA expression threshold to enter into the CAR-T programmes, and are looking at over 50% and under 50%. Certainly, we see responses in both groups. In our trial, with '916, it wasn't required, and I think that is very important. BCMA is a complex entity, and the issue here in myeloma is obviously we think it is incredibly important, and we also think it is relatively ubiquitous, so therefore, looking at this BCMA expression, from our point of view with the '916 trial, one of its strengths is that we have not required that, we have been able to just go straight in and see activity. I worry a little bit that the BCMA expression idea takes us in a slightly wrong direction, and it may be an artefactual thing in some respects. I say that very carefully, but my point is I don't think just BCMA expression on the cell surface tells you the whole story of how patients' particular BCMA vulnerability may be. Certainly, these data would support that.

Axel Hoos: Thank you, Paul. I will answer the second question on breakthrough designation. As you know, breakthrough designation was instituted by the FDA to help accelerate promising drugs to reach a patient faster. We have received breakthrough designations very recently. We have initiated a dialogue with the FDA and we will ask them the question how fast we can proceed to make this available to patients as fast as possible? To your point, is it conceivable that we could file before 2020? It is conceivable, but it will depend on the interactions with the agency, and we are not far enough along yet to be able to provide a specific
answer. The filing, or the launch year that I gave you, 2020, seems a very safe bet. It could be earlier if the FDA allows it.

**James Gordon:** Thank you.

**Graham Parry (Bank of America Merrill Lynch):** Thanks for taking my questions. The first one is on the Phase 2 pivotal programme and I guess a simple question: why isn’t it more aggressive given the strong efficacy, clean safety you see? Why not accelerate further up the treatment paradigm into earlier lines of therapy straight into pivotal combo trials? Doing it the way you are doing it, is there a risk you become superseded by specifics, given that they were expecting Phase 1 data on those fairly soon as well?

Secondly, where do you see the ultimate positioning of the drug? Your combo with standard of care include Darzalex combos, or do you think you can replace Darzalex with a backbone over time, and where do you see this relative to CAR-T in the more advanced settings?

Thirdly, on the novel combinations, are those internal or external combinations, and have you got any deals or any further in negotiation combination trials? Thank you.

**Luke Miels:** Thanks, Graham. On the third question I would just answer that by saying we don’t comment at this stage. I think we are very interested in combinations, and there are a lot of discussions going, but we will probably keep them to ourselves at this point. Axel, did you want to answer questions one and two, and I will also add, this is clearly an area of focus for Hal when he arrives in January. Over to you, Axel.

**Axel Hoos:** Thank you. In terms of acceleration of the programme, what we have laid out here is a very solid approach, and it is not a slow timeline. Could it be faster? Sure, it can always be faster, if you are willing to take significantly more risk. If you think about it, if we start combination trials next year, and we only have monotherapy data so far, we believe the agent, based on its mechanism of action, lends itself nicely for combinations. We have a lot of preclinical data that supports that, but of course, we have to prove that in the clinic, so we need a dose for combination, and from that dose then accelerate into an expansion of the
programme. It is conceivable that we would have data that enabled pivotal trials in 2019 instead of 2020, but it will be less data, and the call to end the pivotal trials will be a larger call. We will keep you posted as this programme unfolds, and I can tell you, the interest in the treating community to work on BCMA ADC is very high.

Right after the presentation yesterday, many of the most senior people in the field have expressed interest to participate in this programme, particularly for the combination. I am expecting this will enrol fast, and we will get answers, and we will get these answers as quickly as possible and then drive those pivotal programmes.

**Paul Richardson:** I would echo that excellent analysis from Axel. I would say one thing, just speaking from a clinical perspective, there is a wonderful old saying “Less haste, more speed”, because let’s not forget what happened with pembrolizumab – and their very rapid advancement of that into early phase disease, with results that were obviously very surprising and disappointing. I think this more cautious – it is not cautious, it is solid, and it is appropriately timetabled to be successful, in my view.

**Luke Miels:** Thank you. I would just add, in terms of antibody we have an excellent analogue in the form of daratumumab. I think also we want to further understand the CAR-T environment, but our intent is naturally to move this as quickly and as intelligently as possible. Thanks Graham.

**Andrew Baum (Citi):** Thanks. Three questions, please. Firstly, what data do you have on the impact of BCMA inhibition on ICOS expression?

Second, what are your thoughts on minimal residual disease, and the extent to which the FDA may allow expedited or accelerated approval, thinking about endpoints that relate to your development plan?

Finally, the median age of your population I saw was 60; it strikes me as somewhat the lower end of some of the historic trials. When you look at the safety profile that you saw during the trial, particularly the upper-end of the age band specified, do you see more toxicity in the older patients?
Luke Miels: Thanks, Andrew. Axel if you just want to answer number one on ICOS and then Dr Richardson, and Axel, if you want to answer question two and three, please?

Axel Hoos: Of course. For ICOS expression, Andrew, we don’t have data that we can publicly share yet on the ICOS expression in multiple myeloma. This is part of the biomarker plan for this programme, and as you are probably alluding to the ICOS agonist that is in our pipeline, that would be a natural candidate for potential combination, and the biology here matters, so we will investigate this and then have an answer for you, but it is slightly too early to answer this now.

Paul Richardson: If I may for the MRD question, I think that is an excellent question. I would only say this, that the FDA have made it very clear that they consider that MRD an appropriate surrogate, but the key endpoints in this particular accelerated approval pathway of response durability and response progression free survival will remain obviously key endpoints as far as they are concerned. MRD would probably still fall into the exploratory category, but the fact that it is likely to be very favourable is, of course, a positive.

Again, I would just focus on the response rate of 60%, but very importantly, the 43% in the daratumumab exposed population.

In the same context, the very good question about older patients. I would say one thing that in Phase 1 we typically obviously, this is a Phase 1 study, and therefore, this is a very typical Phase 1 age group. Median age in most Phase 1s is around 60, so this is not different in that regard.

Having said that, the oldest patient was 75, and certainly from my own perspective I would argue that I don’t anticipate this to be less well-tolerated in the elderly in any meaningful way. Obviously, the ocular toxicity doesn’t appear also, necessarily, to be age dependent, that is not something that we would expect.


Steve Scala (Cowen): Thank you. I have two questions: why are you confident that these results will be replicated in a larger trial, particularly given that the confidence intervals are quite wide in this particular trial?
Secondly, why would a physician want to place the anti-drug conjugate ahead of CAR-T when there is a chance for antigen loss relapse disease? Thank you.

**Luke Miels:** Thanks, Steve. Axel, do you want to take the first one, but again, Dr Richardson, feel free to contribute, and then the second question from Steve for Dr Richardson?

**Axel Hoos:** Yes. I will take the first one on the robustness of the data. This is a decent sized Phase 1 dataset, with 35 patients treated at the same dose, with a response rate that is, in my mind, yes there is a confidence interval, but it is likely going to be stable. We have made that experience when we have the first 15 patients in the same trial, we reported a 67% response rate, that was last year. Now we have 35 patients and we have 60%. It is within the same confidence interval, and if I refer back to other products in this disease, daratumumab had a 30% response rate when they reported data at about the stage that we are at, and they got labelled at 30%, so it did no longer change over time. I think we can anticipate that this is likely going to be stable, and then, of course, as we move this into earlier lines of therapy, and combine it, we need to see the synergy with other agents, and what is important here, and it comes back to the notion of MRD, is the depth of the response, and then, of course the durability and the median PFS. An agent that is so potent by itself and lends itself for combinability, we think we have something that could rival Darzalex for sure, and, potentially, in some places, replace it.

As you know, the treatment landscape with myeloma is more or less fluid now, where some new agents, like Darzalex, are being used in different lines, and if a patient gets it early, he may not get it again later, or vice versa. It will be somewhat fluid, as we bring in a new agent like this, efficacy is king – if we have strong efficacy we will enter the space. We can push some things aside, but they will likely have to coexist.

**Paul Richardson:** I would echo that. As a myeloma clinician I can tell you it is never a zero-sum gain; it is always we need every tool that we have in the toolbox, that’s for sure.

I agree with Axel that what is impressive to me in a Phase 1 setting is when you see CR and VGPR to the degree that we did in such a refractory population; that is a strong signal clinically to us that this is a very promising strategy. I would also
say to you that, in terms of the larger experience and where will this belong, obviously, it is highly convenient, it is a three-weekly infusion. The infusion reaction signal is minimal, and it is a one hour or so of infusion time. This is very practical, and especially as we move into the combination spaces this will be good.

In no way to diminish the incredible results that were presented yesterday from the team in the Bluebird group, with Celgene being the obvious powerhouse behind the development of that CAR-T platform, however, it is important to recognise that this is not an easy technology to deploy broadly, and, in contrast, something like ‘916 is, or certainly we hope it to be, so that is the way I would look at this. I would say sure, there is plenty of scope for CAR-T, but is it going to take care of everyone out in the community, or are we going to be able to be delivering CAR-T therapy in community settings in the Mid-West? I’m really not sure about that yet. I think we have to be realistic and say “We need all”. I personally think there is plenty of space for both.

Axel Hoos: If I may, I answered the antigen loss question – before I forget about that. The possibility of course that some myeloma cells will no longer express the BCMA at some point in the therapeutic cycle that exists – I can’t predict exactly how that will play. Take the CD-19 example, for the CAR-Ts we know some patients do relapse because their antigen disappears. Could that happen here for a modality that solely relies on the expression of BCMA? You could expect something similar, so that would certainly apply to the CAR-Ts. There is something different about this mechanism, because of the four-pronged MoA; once you blow up the cell, there is a lot of antigen that is going to be released from the cell that goes way beyond BCMA. It engenders broad immune responses, you will have cross-priming for the immune system, and then you then end up having a much more versatile mechanism to keep a response, even if it is not BCMA driven any more. The initial driver is to show BCMA, but what comes after that is a bit more versatile.

Paul Richardson: I completely agree, Axel, that is very well put, and when we combine ‘916 with IMiDs, I think this will be very exciting. As I say, that is why I think the timeline and the fastidiousness of the development approach is very wise, because my own prediction is this could be a very potent platform. As I say, tolerability is very important, and this approach is very appropriate, given what we have already learnt in the IO space, that some of the toxicology can really matter.

Steve McGarry (HSBC): Thanks; just a quick one. If you are looking at potentially filing and launching this product in 2020, we are already nearly in 2018, and one of the things we have seen with J&J with Darzalex is scrambling around to get enough manufacturing capacity, so what manufacturing capacity do you have in place today? What do you have planned by the time you might have launched, and how does that cover both the antibody portion and the toxin portion?

Luke Miels: Axel, do you want to cover that, and I can add a comment at the end?

Axel Hoos: A good question. We are acutely aware that this is a short timeline to launch, within about two years. We are feverishly working on making manufacturing capacity available, but start, of course, with supplying a fairly rapidly moving clinical programme, but then actually launching the drug globally, so expect that we will be prepared for that. We are not prepared for that today. We are prepared for the clinical programme today; we are not prepared for launch today, but in the next two years, the plan is in place for reaching that level of preparedness.

Luke Miels: Thanks, Axel. That last bit is exactly what I was going to say. I think that is something no-one has seen in the last couple of months – it is something that we have looked at very intensively once this full data picture became apparent, and beyond manufacturing of the structure, we are also looking at putting a team in place that can properly assess this opportunity and develop a clinical plan that is going to get this to patients very quickly.

Tim Anderson (Sanford C Bernstein): Thank you; a few questions. Can you just give us the number of patients in the US, Europe, Japan, who are fourth line?

Second question is on commercialisation, I am wondering how you are leaning, and I am wondering in terms of going it alone versus seeking a partner, can you say? I am guessing it flexes with whether you can file early versus possibly waiting until 2020.
Just to clarify, in manufacturing, if I heard you right, you said you are not prepared to launch today? I just wanted to understand that in the context of possibly filing early. I would imagine in this current dataset it is in the realm of possibilities. You could file in the first half ’18; it gets fast cycle time approval, your launch approval by the end of the year – are you saying you wouldn’t be able to manufacture to launch in that timeframe?

Luke Miels: Thanks, Tim. The last question, Axel, you take. I will just answer the fourth line. I am quoting Kantar Health here, Tim – it is a 2017 estimate. My fourth line is around 1,800 in EU five, 4,400 in the US, and Japan is just under 1,000, so G7 in total is just over 7,000 patients, however, I think our ambition for this product is not limited to fourth line.

In terms of your question in terms of partnership, no comment at this stage. I think the key metric is we will do what creates the most value in the mid to long term for GSK shareholders. What is also very interesting, I have observed since joining the company is the level of interest from people in the field, just within my own personal network contacting me, interested about joining the company because of this programme. Christine Roth has just joined us from Novartis is a good example of that, but we are having very good conversations with people in the three most dominant companies in this area. Axel, do you just want to cover the manufacturing capacity one?

Axel Hoos: Yes. This is, of course, a question that touches on a subject that is in flux; we are working on this. What I said earlier is we will be ready for 2020. I have no doubt on that. If we need to launch in 2019, the projections we have made are that we could be ready by the middle of 2019, and that might just fit together, if we would file in ’18, and expect at least a six-month window that you need before you can launch, we must just get there, but as I said, this is in flux, and we are working to accelerate this as much as possible.

Tim Anderson: Thank you.

Luke Miels: One of the benefits of Emma’s presentation in terms of game changes, which is to really focus on a collection of assets, and also to just make more decisive choices earlier. I have certainly seen a shift in the last couple of months there – this is clearly one of the highest priorities that we have. Thanks, Tim.
Kerry Holford: Hi, I have two questions, please? First just on the corneal events; I wonder if you can just detail a little more around the mechanism behind that issue? 9% of those events were grade three, I wonder if you can just detail how that manifested itself, what did it involve, how those patients with grade three were treated, and were those issues reversible? I think you said they were, but just clarify.

Then secondly, on the patient population for the next pivotal study, you mentioned that 40% of patients in DREAMM 1 had been pre-treated with daratumumab. Given that drug is now standard of care, effectively, in the second-line, should we anticipate a higher percentage of dara failures enrolled into that next pivotal study? I am looking at the comparison with the Celgene data published at ASH, where that proportion was much higher – I think around 70%.

Then, just quickly to clarify, I think you were asked earlier, but I missed the answer, whether you would study '916 in combination with daratumumab? Thank you.

Luke Miels: Thank you, Kerry. Axel, do you want to cover the question in relation to warhead and tox, and then, maybe Dr Richardson, if you could expand on your clinical experience and also answer the third question, and Axel, you can pivot to that in the fourth, the final component; I think it is probably one for you, Axel. Thanks.

Axel Hoos: Very good. For corneal events, the mechanism of action, as much as we understand it, is quite consistent with other experiences that have been made with similar antibody-drug conjugates. Just to be clear, the conjugate itself comes from Seattle Genetics. Seattle Genetics have a pretty good experience across multiple ADCs with MMAF, and they have consistently seen corneal events with the same characteristics as we are seeing them, mostly low-grade, manageable with steroid eye drops and, potentially, dose reduction and not precluding the patient to receive further therapy. That is a very consistent theme.

The mechanism that Seattle Genetics seems to understand for this drug, similar to what we have come up with, is that the antibody with the poison, even though there is no expression of BCMA in the eye or on the cornea, somehow in
small quantities finds its way into the cornea. The exact reason, whatever drives the affinity is not clear to us, and you can treat this very well, just through lubrication, just sterile eye drops or steroids, which reduce the level of inflammation in the eye, and therefore it is harder for the drug to get in. That is mechanism.

In terms of clinical manifestation, I will let Dr Richardson speak to that.

**Paul Richardson:** Excellent; that was very helpful as a prelim to the manifestations. Essentially, in our cohort of patients the complaint is sometimes of some minimal irritation, sometimes of some blurring, but again, these are mild to moderate symptoms. We did not have any of our patients encounter grade three toxicity as categorised in the trial.

Dose reduction is critical; that clearly makes a difference, and I agree absolutely with Axel that the management is pretty straightforward – we have used eye lubricants, we use the steroid drops, although we are going to be exploring whether or not that is particularly necessary, and third of all, the simple use of an eye ointment such as an erythromycin ophthalmic ointment can sometimes be very beneficial. It is worth noting that the erythromycin ointment has some anti-inflammatory effects as well, and allows better irrigation of the eye from relaxation of lacrimal muscles. There are a number of tricks of the trade as it were that we use to help manage this and make it a relatively straightforward issue.

**Luke Miels:** The development programme in combo with daratumumab, thanks, Axel?

**Axel Hoos:** It is absolutely right, the rate of daratumumab failure was about 40% in this trial. The reason for that is very simple, the trial started in 2014, we had a very careful dose escalation as you have seen. We have been a little bit disturbed by the Novartis transaction, to be fair, but the programme picked up speed again in the last year. The key thing is that there were not enough daratumumab treated patients around when this study started. We didn’t preclude them from entering, they were just less such patients. For the CAR-T programme, which were enrolled more recently, there were more daratumumab failures around, so that is one explanation for the distribution.

As it comes to the next study, the next study will be last line of therapies for daratumumab failures only, so that means patients need to have received the
proteasome inhibitor, and IMiD and have to have failed daratumumab, and then they are truly last line of therapy and would be qualified for the next trial.

**Luke Miels:** Thanks, Axel. We are getting very short of time. Seamus Fernandez sent in his question which I think we have answered around ADC. Maybe one final question, from Michael Leuchten, can we just have one, please, and then we will close the call?

**Michael Leuchten (UBS):** Thank you. Just a quick one. The 11 patients where you didn’t see a response, did you see any commonality across those 11 patients?

**Paul Richardson:** That is an excellent question and we are looking at that in a little more detail. Again, an important point here is that, if you look at those who progress, and you look at the waterfall plot which gives you the best clue, what is quite interesting to me is the majority of the patients have relatively modest increases in their paraprotein and only one seems to particularly be more aggressive, but we are looking at that to better understand who those might be.

Again, the response characteristics are very broad, the resistance characteristics we shall see, but as combination strategies come forward obviously we are very hopeful that those who, unfortunately didn’t benefit from the ‘916 that proportion will diminish.

**Luke Miels:** Thanks, Michael.

Now we will conclude the call on GSK ‘916. Clearly, you can sense our excitement and interest in this asset. I start by thanking Dr Richardson for his generous time, and also Axel, and thank you to all who have asked questions, it is very much appreciated. For everyone that dialled in, we thank you for your interest in the company and in GSK ‘916. Have a good afternoon, and thanks again.

*Call concluded*