pharma plc

R&D Webinar Clinical Update: Oncology & COVID-19

5 June 2020

Duncan Peyton:

[Slide 1]

Good afternoon and welcome to 4D pharma's research and development update.

My name is Duncan Peyton, I am the Chief Executive of 4D pharma and today I am pleased to be joined by Professor Axel Glasmacher, who is Chairperson of 4D pharma, and Dr. Alex Stevenson, who is the Chief Scientific Officer of 4D pharma

After the presentation we will be taking questions from our covering analysts so we are very pleased to be joined by Gbola Amusa, Head of Healthcare Research at Chardan. We are also pleased to be joined by Olga Smolentseva, Healthcare Equity Analyst at Bryan, Garnier & Co., and finally Edward Thomason, who is an Equity Research Analyst, Life Science at N+1 Singer.

[Slide 2]

[Slide 3]

So today the focus of the presentation will be on our oncology and COVID-19 programmes, but for those who may not be familiar with 4D pharma I will give a brief introduction. At 4D our focus is the development of Live Biotherapeutics – essentially, we use bacteria that originate in our guts as a drug. Specifically, using our proprietary MicroRx® platform we are able to understand and exploit specific properties of single strains of bacteria.

So in much the same way as a traditional pharma company exploits a small molecule, we understand what the bacteria is doing, focusing on how they modulate our immune system, and how they can impact diseases such as cancer.

In addition, because these bacteria originated from our gut and have evolved with us, they have an excellent safety profile, which is not only good for patients, but also significantly de-risks the development process.

To that end, 4D is the world leader in this space. We are a fully integrated company, meaning it is our research, so we have the largest intellectual property portfolio in the space with over 900 granted patents. We have our own development and production facility, so we understand how to manufacture these products and this is a fully GMP-certified facility. And finally, we have been able to conduct a number of clinical trials, two of which we will talk about today: one on oncology and one addressing the COVID-19 crisis.

This builds on our concepts and our thesis that our Live Biotherapeutics have the potential to deliver safe and efficacious drugs in the near term.

[Slide 4]

On that point, Axel and Alex will talk you through the oncology programme. It is worth noting that these patients are unfortunately very ill, they have very few treatment options and are highly refractory. But to date we are seeing a strong safety profile and encouraging signals.

This is the first time that positive data has been presented in oncology with a Live Biotherapeutic. This only goes to strengthen and provide further validation of our technology, but also a potential new therapy for patients with limited options.

We will also take time to update you on the progress of our trial in COVID-19. This was a trial which was approved by the regulators within four weeks of our first conversation. The guys will update you on the progress made towards opening sites and dosing our first patients.

Alex I will hand over to you.

[Slide 5]

Dr. Alex Stevenson:

Thank you very much Duncan, so we will move on now to talk about the immuno-oncology programme.

[Slide 6]

The lead candidate we have in immuno-oncology is MRx0518, a single-strain Live Biotherapeutic from the Enterococcus genus. As we have reported before, we have demonstrated efficacy in vivo, we understand the mechanism of action of the bacteria and we also have a number of ongoing clinical studies with MRx0518, so we are going to explore those studies in a bit more detail now with particular focus on the clinical study.

[Slide 7]

In terms of the initial pre-clinical efficacy that got us excited about MRx0518, this slide summarises three different syngeneic mouse models of cancer – breast cancer, kidney cancer and lung cancer – where we have investigated MRx0518 alongside positive controls of checkpoint inhibitors. And this breadth of activity across the different tumour types got us interested in studying further the mechanism of action, and on the next slide we can see some more details about that work.

[Slide 8]

What we found when we looked at the tumours of mice that were treated with MRx0518 compared to untreated animals in breast cancer and in kidney cancer models, we found that there was an increase in natural killer cells, T cells and cytotoxic cells. These are cell types that are associated both with improved response in cancer but also an improved clinical outcome with the use of the checkpoint inhibitors.

Not only did we further characterise MRx0518 in terms of its induction of a strong innate immune response and also its ability to generate a strong adaptive response, we also were able to identify the effector molecule within the bacteria which was responsible for that stimulatory activity, namely the flagellin protein, and that work was described in a publication last year (Lauté-Caly et al., Scientific Reports 2018).

[Slide 9]

So now we will move on to talk about the current study. This is a combination study of MRx0518 with Keytruda® and it was our pre-clinical work that led us to want to investigate this particular type of patient, who have advanced metastatic cancer, either non-small-cell lung cancer, renal cell carcinoma, urothelial carcinoma or melanoma.

And, importantly, these patients have previously derived clinical benefits from an immune checkpoint inhibitor but then subsequently progressed, so these patients would be categorised as having secondary resistance to checkpoint therapies.

In terms of the study design, there is Part A which was in 12 patients, and this is primarily the safety phase of the study where the patients received MRx0518 twice a day for three weeks and a single cycle of Keytruda®.

Importantly, these patients, once they have completed Part A, are eligible to stay on treatment for up to two years or until progression of their cancer, and that allows us to collect long term data from those patients.

Part B is the larger part of the study where we are looking at up to 30 additional patients of each of the four tumour types, and is more focused on the efficacy outcomes.

[Slide 10]

So in terms of the patients themselves, as I said previously, these patients have to have secondary resistance to immune checkpoint therapies, and I just want to spend a little bit of time talking about how that secondary resistance is defined in the inclusion criteria of the study.

Patients must have previously received at least two doses of an anti-PD-1 or anti-PD-L1 immune checkpoint inhibitor, and progression must have been recorded within twelve weeks of the last dose of that prior immune checkpoint inhibitor.

Very importantly, progression must have been confirmed by two radiological scans at least four weeks apart, and the reason that is so important is because if that is not done there is the possibly that you might be looking at a patient who actually has pseudoprogression, where the tumours actually enlarge due to the effects of the immune checkpoint inhibitor and increased immune infiltration, before reducing in size, so it is very important to use these inclusion criteria to avoid the confounding effects of pseudoprogression in this type of study.

These patients also have no appropriate therapeutic options remaining that were known to provide clinical benefit, otherwise they could not be included in the study, and given these inclusion criteria the expected response rate to an anti-PD-1 therapy on its own would be extremely low, potentially between 0% and 10%.

Dr. Alex Stevenson continued:

[Slide 11]

We recently reported initial results from the twelve subjects of Part A of the study treated with the combination of MRx0518 and Keytruda®. Five subjects remain on treatment and I will tell you more about those subjects in due course, and seven subjects have been withdrawn from treatment either due to radiological progression or progression-related adverse events.

I am pleased to say that the Safety Review Committee for the study evaluated the data from Part A and determined that it was safe to proceed with Part B, which has been open now for a few weeks. Part B will recruit up to an additional 30 patients per tumour type, and we are adding four additional investigational sites in order to achieve our recruitment targets.

Whilst we will submit the full data from Part A for peer-reviewed publication, and potentially presentation at a medical conference, I am pleased to be able to provide you with an update on these patients today.

[Slide 12]

What we see here is a swimmer plot which describes the status of the patients. One thing to note is the dotted line at nine weeks – this is the first planned radiological assessment of the patients. Those patients that remain on study after completion of Part A, every nine weeks of treatment they will be routinely scanned to determine whether they have progressive disease, stable disease or some form of response to the therapy.

Looking at the patients who remain on study, we have one patient with a partial response in metastatic renal cell carcinoma, one patient with a partial response in non-small-cell lung cancer and both of those responses are durable and I will go on to describe those patients in a bit more detail in due course.

We also have a long-term stable disease in renal cell carcinoma, which is out now to well over six months, and we have two shorter-term stable disease patients also with renal cell carcinoma.

So those are the five patients that remain on study. Of the seven who have been withdrawn from the study, two of those patients did make it through to the first planned assessment at nine weeks and they were defined as having progressive disease by the radiological assessment. Three patients had to withdraw from the study due to progression-related serious adverse events (SAEs) prior to the planned radiological assessment at nine weeks, so they were withdrawn from treatment but they did have a subsequent radiological assessment which we can report on. And finally two patients had to withdraw from treatment very early on due to progression-related SAEs and had no radiological assessments.

I think the two real take-home messages from this slide are the durability of the responses that we are seeing and the fact that we are seeing responses and stable disease in this very hard to treat patient group. Also, I think some of these early withdrawals just reflect the reality that what we are dealing with here are patients with advanced cancer and advanced disease.

[Slide 13]

Moving on to the next slide, we can see the waterfall plot which describes in more detail the radiological assessment of those patients that were evaluable, i.e. those patients that did have a radiological assessment either at the nine-week planned restaging point or prior to that; so that is ten patients, two were withdrawn without any form of radiological assessment. You can see that of those ten patients we have an overall response rate of 20%, two out of ten, and a disease control rate at that first radiological scan – either a complete response, partial response or stable disease - of 50%, which we believe is very encouraging at this stage of the study.

I would also point out that, of the patients who were radiologically assessed, we see that progression was actually defined in non-target tumours, rather than the tumours that were being evaluated at the time.

[Slide 14]

So I would like to now move on to talk in a bit more detail about two of the patients who have been on the study for longest and have exhibited partial responses.

The first of these is a renal cell carcinoma patient, a 70-year-old male, diagnosed with Stage IV metastatic clear cell renal carcinoma back in 2016. You can see the previous lines of therapy on the slides. The patient's best response to prior anti-PD-1 immune checkpoint inhibitor was stable disease and this was discontinued after 44 weeks due to confirmed progressive disease.

This patient has now been on the combination of MRx0518 and pembrolizumab for 58 weeks and is continuing to have this long-term partial response which is now out to 32 weeks. The response that we have seen in this patient actually includes the complete absence of one of the two original target lesions, and as I stated no serious adverse events.

[Slide 15]

The next patient that I want to give you an update on is a patient with metastatic non-small-cell lung carcinoma; this is a 62-year-old female diagnosed with Stage IV metastatic non-small-cell carcinoma with an EGFR [epidermal growth factor] mutation four years ago.

The EGFR mutation is relevant because patients with this mutation are thought to be less likely to respond to checkpoint inhibitors so that is an interesting result we have obtained here. This patient has had seven prior lines of therapy if you include the whole brain radiation and again the best response to a previous PD-1 inhibitor was stable disease. This patient has now been on study for 49 weeks and is continuing with a partial response for 31 weeks, and again with no serious adverse events.

[Slide 16]

Moving on to talk about the preliminary responses as a summary, as you can see the current clinical benefit that we are able to describe is three out of the twelve patients which is 25%, and just as a reminder clinical benefit is either a CR [complete response] or a PR [partial response] or stable disease for six months or more. You can see that we also have two patients with stable disease of less than six months. I would like to note that one of those patients, at their first restaging scan actually demonstrated a 24% reduction in tumour volume, so we are keen to re-evaluate at the next restaging scan whether that trend continues. So as of today, the clinical benefit rate is 25% but we will be reporting more fully on that when the patients have had sufficient time for that response to be fully evaluated.

If we were to look purely at the seven patients who had a restaging scan following three cycles of therapy, the clinical benefit rate would be 43%, so we are going to keep a close eye on how the figures develop over the next few months.

[Slide 17]

I would now like to hand over to Axel who will give us some further information and conclusions on the work that we have seen today.

Prof. Axel Glasmacher:

Thank you very much Alex.

It is a pleasure to present you with the conclusions. This study addresses a population of patients who are highly refractory to immune checkpoint inhibitors and have a high unmet medical need and no standard treatment options. The probability that they would respond to another treatment with an immune checkpoint inhibitor is very low.

What we have seen is a strong favourable safety profile for MRx0518 with no specific safety signals. We have not seen any drug-related severe adverse events, and we have also not seen treatment-related drug discontinuation in both tumour type cohorts. It is important also to note that this combination did not result in an increase of immune-related adverse events as typically seen with immune checkpoint inhibitors.

We demonstrated a clear signal of therapeutic clinical benefit in metastatic renal cell carcinoma – one partial response, three stable disease. Alex has spoken to the dynamic of these responses – these are ongoing responses so there is a chance they may improve with continued treatment in five [renal cell carcinoma and non-small cell lung cancer] patients in total. We have seen one PR out of three patients with non-small-cell lung cancer, and it is of note that this response was in a patient with an EGFR mutation which is usually associated with lesser likelihood to respond to immune checkpoint inhibitors.

For patients it is most important that the duration of response lasts for a long period. It is more important to have a long-term stable disease than a short-term partial response, because the quality of life and the prognosis is driven by the control of the disease, the ability to arrest the growth of the tumour, so therefore we are glad to see these long responses, PR durations of 31 and 32 weeks, and stable disease durations between 12 and 44 months. All patients who have shown stable disease or PR are still on treatment and the responses are ongoing.

You have seen in Alex's presentation that we could demonstrate activity in animal models. Now we have confirmed this in patients and we would state that these results demonstrate proof of concept for the synergy between a single strain Live Biotherapeutic and an immune checkpoint inhibitor in patients with advanced renal cell carcinoma who have exhausted other therapeutic options. It might be a bit too early to call that in lung cancer but of course the early data in a few patients is promising and we will continue to evaluate that space and recruit patients with non-small lung cancer.

The next slide please.

Prof. Axel Glasmacher continued:

[Slide 18]

If we now look at the broader picture, where do we go now with MRx0518, the first option of course is to explore expedited regulatory approval pathways that are based on the proof of concept clinical data.

Immune checkpoint inhibitors have brought significant progress to patients with kidney or lung cancer. They are now the standard of care in first line treatment. In consequence, however, those patients whose tumours do not respond any more to these agents are in urgent need of new therapeutic options. The approval pathway to offer a new treatment in the last line setting is something quite established, especially with the FDA.

We also show here a description of the respective market. Both tumours are reasonably frequent, non-small-cell lung cancer of course even more frequent. ICIs [immune checkpoint inhibitors] are first-line treatment and we believe there is a sizable proportion of these populations that would be addressed by this combination therapy.

We expect that the incidence of these tumour populations will increase, both driven through the demographics as well as through the increased use of immune checkpoint inhibitors in these indications.

Furthermore, we are starting to explore MRx0518 in alternative tumour types, alternative combinations and settings in the treatment pathway.

With that I give it back to Alex for the presentation of the COVID-19 study.

[Slide 19]

Dr. Alex Stevenson:

Thank you very much Axel for that presentation.

The next area we want to talk to you about today is our work in COVID-19. Obviously this is a very recent development for us, but I think it really illustrates the ability of our platform to characterise a mode of action and also to apply that relevantly to new indications.

[Slide 20]

So I will start with a slide which just describes the disease in a bit more detail. It is a disease of three stages: there is the early infection, there is the second stage which is the pulmonary phase where the respiratory infection develops, and then the third stage is this hyperinflammatory phase associated with a cytokine storm which is common to a number of respiratory infections. What we are trying to do with MRx-4 [MRx-4DP0004] is to interrupt the progression of Stage II of the disease. I will talk about the study in due course but essentially we are trying to reduce the development of symptoms in patients who are at the pulmonary stage of the infection.

Two aspects of MRx-4 which are important to identify here is that obviously we can demonstrate its immunomodulatory capacity, its ability as an anti-inflammatory, but it is also important to state that it can do that without compromising, we believe, the immune system's ability to fight a viral infection, which is very important. Just using an immunosuppressant with a very non-specific action can obviously lead to a situation where the viral infection would actually be able to run more out of control, so we think both aspects are very important.

[Slide 21]

And on the next slide we talk a bit about the evidence that we have in pre-clinical models with MRx-4DP0004, which is what led us to match that to the observed immune response which is being reported in COVID-19 patients.

Over the next few slides I will pick out some of those features in more detail, but obviously the reduction of pro-inflammatory cytokines in lung tissue is important, as is the reduction of neutrophilia in the lung and also the ability to address inflammation systemically in addition to in the lungs, and all of these are important features regarding COVID-19.

Dr. Alex Stevenson continued:

[Slide 22]

In terms of the model that we used in order to generate the data, as many of you will be familiar MRx-4DP0004 is currently in clinical development for asthma and we used a pre-clinical model of steroid resistant severe neutrophilic asthma. This model is relevant because the sensitisation of the animals skews the inflammatory phenotype towards neutrophilic Th2-low response which is what is seen in COVID-19. And over the next few slides I am going to describe some of the data that we generated in this model which we believe is relevant to COVID-19, but also just to point out that we are able to use this model both prophylactically, dosing the animals prior to sensitisation with the disease, and therapeutically, post-sensitisation of the animals. Anti-IL-17 antibody is used as a positive control in this model because it blocks the neutrophilic aspect of the model.

[Slide 23]

So moving on now to look at some of that data in a little more detail. Obviously one of the aspects behind the mortality of COVID-19 is the hyperinflammatory response and cytokine storm syndrome caused by uncontrolled activation of the immune system, so it is important to be able to demonstrate reduction of some key proinflammatory cytokines actually in the lung tissue, and that is what we demonstrate on this slide. MRx-4DP0004 in the model was able to reduce IL-1α and IL-1α, and also reduce the production of chemokine CXCL2, which is a neutrophil trafficking signal. This is data published a couple of years ago now in relation to the asthma programme [Raftis et al., Scientific Reports 2018].

[Slide 24]

Moving on to the next slide, I mentioned previously that whilst it is important to be able to regulate the excessive activation of the innate immune system, it is also important not to suppress the immune response to the virus. What we see here is evidence that actually, in terms of those adaptive immune cells [CD4+ and CD8+ T cells], you can see that MRx-4DP0004 treatment is comparable to untreated mice so is not leading to an overall reduction in those cell types.

We also show activation of [CD4+ CD44+] memory T cells which are important in maintaining the anti-viral response, so we think this is an important feature of MRx-4DP0004.

[Slide 25]

Moving on now to look at the lung cell infiltrate in the animals and the effect that MRx-4DP0004 has, particularly on neutrophils. You can see with both prophylactic dosing and therapeutic dosing a strong reduction of BALF [bronchoalveolar lavage fluid] neutrophils in the mouse model of severe asthma in both settings. You will also note that the anti-IL-17 monoclonal antibody positive control, also produces a strong signal here, as expected.

[Slide 26]

If we now move on to consider what that immune cell infiltration means in terms of the total inflammatory score in the lung, and also the lung histopathology. This is important for COVID-19 patients because the neutrophilia and the immune infiltration is associated with damage to the lung. We can see that in respect to the total inflammatory score, MRx-4DP0004 is actually able to reduce this in relation to the animals that have had the disease induced in them, whereas the positive control anti-IL-17 monoclonal antibody does not have that effect.

You can see also in the lung histopathology figure on this slide, the mice that were treated with MRx-4DP0004 and sensitised with HDM [house dust mite antigen] actually have lung tissue which looks very similar to untreated animals, whereas the anti-IL-17 treated animals exhibit significant infiltration and damage in terms of the lung histopathology.

[Slide 27]

Finally, in respect of the pre-clinical data that we used, although MRx-4DP0004 is in development for asthma and now COVID-19, we have also investigated MRx-4DP0004 in relation to other inflammatory diseases. We have shown that it is effective in pre-clinical animal models of both multiple sclerosis, shown on the left here, and rheumatoid arthritis, shown on the right.

So, although in COVID-19 the primary battleground is in the lung, the systemic inflammation is also an important aspect and one which we hope that MRx-4DP0004 may be able to address.

Dr. Alex Stevenson continued:

[Slide 28]

So now moving on to give you a brief update on the clinical study. The clinical study is being conducted in up to 90 patients with COVID-19, these patients are hospitalised patients but they are not in ITU [intensive care unit] so these are patients that are coming in and being admitted to hospital prior to reaching that hyperinflammatory phase. We are looking at a 2:1 randomisation of MRx-4DP0004 versus placebo, and dosing for up to 14 days.

The primary endpoint that we are using is around change in mean clinical status score based on the WHO Ordinal Scale for Clinical Improvement in COVID-19. We are also looking at secondary endpoints that are clinical in relation to requirement and duration for ventilation, time to discharge, mortality, and obviously safety and tolerability.

We previously reported that we had MHRA [Medicines and Healthcare products Regulatory Agency] approval of the clinical trial application. Since then we have recently received Research Ethics Committee and HRA [Health Research Authority] approval, which are necessary to actually commence studies in the UK, and clinical site selection and now initiations are underway. We are expecting to be able to report the first patient dosing this month in June.

We are targeting preliminary data from this study in Q4 of this year.

This is a Phase II study, it is a pilot study, and we are hoping that the data that we generate will enable us to discuss fast-track engagement in respect to potentially accelerated approval and/or informing the design and the endpoints of the subsequent pivotal study.

[Slide 29]

So that concludes the data that I wanted to talk about in relation to COVID-19, if we move on to the next slide I would just like to summarise what I think the data that we have described today actually means in both immuno-oncology and COVID-19, the key take-home messages.

[Slide 30]

As Axel and myself described, I think we have demonstrated clinical proof of concept in metastatic clear cell renal cell carcinoma with MRx-0518 in combination with pembrolizumab [Keytruda®] and we are very hopeful that we are able to expand that into additional tumour types, we already have that signal in non-small-cell lung cancer.

But, very importantly, we think this also validates our single-strain Live Biotherapeutic approach, the first time anyone has seen this sort of validation of our approach in a clinical setting, and obviously we are encouraged by the very good safety profile that we have demonstrated so far in these patients.

In terms of COVID-19, I really think that our understanding of the mechanism of MRx-4DP0004, our focus on functionality across our entire platform, was key to being able to identify MRx-4DP0004 as a rational agent to address COVID-19, and that ability to match up rationally the mode of action with the features of the disease enabled us to put together a regulatory application which was in such a form that it was able to be approved very quickly, from idea through to actually getting MHRA for approval for the CTA [Clinical Trial Authorisation] only took around four weeks.

With that I will hand over to Duncan to provide the conclusions today.

[Slide 31]

Duncan Peyton:

Thanks Alex.

So, in summary, we have heard a lot about Live Biotherapeutics, and while Live Biotherapeutics may be a novel class of medicine, novel does not mean that they are not present day. We do not have the issues of delivery or manufacturing that have proved problematic and delayed development of other new therapeutic classes. We are in the clinic now, I think we have just heard some really good evidence of our products showing clear, durable signals of clinical benefit and no safety signals, and that really builds the evidence of the potential of 4D's Live Biotherapeutics to become safe and effective therapeutics.

And in the field of Live Biotherapeutics we are the world leader. We have the largest clinical pipeline. We have multiple near-term shots on goal. We address big issues – you have heard about the oncology programme, you have heard how we are dealing with and looking at hyperinflammation associated with COVID-19. But we are also pushing the boundaries into neurodegeneration.

We have developed a large and strong IP [intellectual property] portfolio and this is a metric of our internal research and the power of the proprietary MicroRx® platform.

Importantly, we also understand how to get these drugs into the hands of clinicians. I think that was demonstrated by the speed at which the COVID-19 project took shape.

And more importantly, we do it safely. We have now seen favourable safety profiles repeatedly with our products, and this has to be good for the patients and the sector as a whole.

So thank you very much for listening, and we will now turn to questions from the analysts, starting with Edward.

[Slide 32]

Edward Thomason:

Afternoon everybody and thank you for having me today. So, a couple of questions. I will lead with one first and follow up with some afterwards.

We obviously saw today there is a quite credible, long duration of this response starting to develop. Can you just talk through the wider implications that might have in the ultimate setting for MRx0518, particularly alongside obviously its excellent safety profile, so could this have implications? Could it be used in earlier lines of therapies, or in wider combinations with other targeted therapies?

Dr. Alex Stevenson:

Thanks Edward, I will pick that up. Yes, so I think we are very encouraged by the long duration response that we are seeing. Obviously, it is highly relevant as Axel was saying, for the patient group that we are investigating right now in terms of these patients with advanced metastatic cancer. As Axel said, being able to even show a long-term stable disease is preferable in those patients to a short term, partial response.

Now whilst this is where we started the story with MRx0518, obviously we have ideas and intentions to investigate MRx0518 in other settings. There is no reason to suppose that we would not be able to see similar activities in other patient groups and that is certainly our intention going forward. This is the patient group with obviously a higher unmet need, which is a good place to start when you are developing a new cancer product. But as we develop more confidence in the signals we are seeing, that then gives us the ability to put the drug into different settings.

Edward Thomason:

Thanks, that was clear.

I guess with a 25% clinical benefit rate arguably you could apply for fast track or breakthrough designation. When do you think you would have sufficient data to apply for those pathways, is it something simultaneously with Part B of the study, or maybe at the end of the Part B programme?

Duncan Peyton:

Axel, is this something you would like to answer?

Prof. Axel Glasmacher:

Yes Duncan, I am happy to answer. Thank you for the question. I think the FDA wants a larger population of patients treated. So I would expect that we need to show around 100 patients or so, in each indication where we would go for an accelerated approval. Therefore, this would be the next step after Part B.

Edward Thomason:

OK. Just one question on the COVID-19 play. So, theoretically, with the anti-inflammatory response that has been seen pre-clinically, does this offer open up the question of maybe expanding MRx-4DP0004 into other infectious diseases that are associated with a hyperinflammation response, for instance influenza?

Dr. Alex Stevenson:

Thanks for the question. Yes, absolutely. Obviously we understand a lot about the mode of action of MRx-4DP0004, and that is why we put it into COVID-19. But you are absolutely right, the features of the disease around hyperinflammation are also features of other diseases, other infections and respiratory diseases. So yes, there is definitely potential there.

Prof. Axel Glasmacher:

Especially influenza, because that is a huge reason for mobility and motility in influenza, the hyperinflammation.

Duncan Peyton:

OK, if we could just turn to Olga Smolentseva, do you have any questions for the team?

Olga Smolentseva:

Hi guys, sure. And congratulations on the ongoing progress. First question on MRx0518. Looking at the patients' background and their treatment history, did anything in particular stand out that could suggest a correlation with clinical response, such as type of previous therapy, PD-L1 status, etc.?

Dr. Alex Stevenson:

In terms of their previous therapies obviously we talked about two of the subjects in more detail today. Other than the commonality obviously that they have progressed and have secondary resistance to prior PD-1 therapy. There is nothing that we can really say I think, in terms of the therapies they have received previously that would lead us to believe that one group would be more likely to respond than another.

In terms of other biomarkers, at present we have an incomplete dataset there, we are collecting information that may allow us to further define the likelihood of response, but that is something we will be reporting on in due course.

Olga Smolentseva:

Thanks, and I will be looking forward to that. On the COVID-19 study, what kind of time to response have you seen with MRx-4DP0004 in pre-clinical models, and how could that be translated into the acute clinical setting?

Dr. Alex Stevenson:

Yes, thanks for that question, it is a very good question. It is something we considered early on in the development programme. In terms of the pre-clinical data we have, it is based primarily around the severe asthma model that I showed you. And really, the way that model works, in the therapeutic setting, there is ten days from beginning of dosing to actually harvesting tissues and assessing the animals on study. So that, from a pure clinical perspective, that is the data we have got.

However, we know, and it is important to stress, that we are not seeking with our products to affect colonisation of the gut in order to see an effect. We know that the bacteria as soon as they are in the presence of immune cells are able to start that process of effecting differentiation or impacting the immune system, so our assessment is that within two to three days we should start to see effects in terms of the immune system, and that is obviously something which is important in something like COVID-19 where you have hospitalised patients. Though we are dosing for 14 days here so we are hoping to be able to show a change in the progression of the patients over that period of time.

Olga Smolentseva:

Thanks, that is clear. And would you have any specific inclusion criteria in the clinical study in regard to stability of COVID-19 symptoms?

Dr. Alex Stevenson:

Yes, again, very good question. So these patients are all hospitalised, and we are using the WHO Ordinal Scale to define those patients that are essentially at that point before they have severe disease. These patients typically will require oxygen but not intubation, they will not be in the ITU, but they will have disease characteristics which will mean we should be able to follow the progression or otherwise of the disease.

Olga Smolentseva:

Thank you for your answers.

Duncan Peyton:

Ok Olga, thanks for that. And Gbola turning to you, do you have questions for the team?

Gbola Amusa:

Yes indeed and thanks and congrats on the progress, on two different fronts. I wanted to start with a broad question on MRx0518, obviously you are seeing good safety so far which is what might be expected. Could you talk about how steps forward might differ for your programme relative to other products being investigated in late stage cancers, given that the profile on safety might be particularly robust? For example, is it your traditional design or might we see something different due to enhanced safety?

And then I have a COVID-19 question after that.

Duncan Peyton:

Axel, do you want to take the first question?

Prof. Axel Glasmacher:

Yes, and maybe then Alex has something to add. So, I think if we can show what we expect, that the safety is just as good in larger cohorts, and Duncan and Alex have talked about why these products are so safe. It will remain a discussion with the FDA, and other regulatory authorities, whether or not this can influence our development programme. I think it would be, at least from my perspective, premature to speculate on that. But in general, obviously it is much easier if you do not have specific safety problems to focus on.

Dr. Alex Stevenson:

So just to add to that and I think those are points well made. I think, obviously with a number of cancer therapies there are concerns around safety profiles which may limit, to some extent, their ability to address certain opportunities. Now, as Axel said, we only have limited data but what we have seen from a safety perspective is very encouraging and clearly, particularly in these patients with advanced cancer, having a treatment has a favourable safety profile is highly desirable, particularly if it enables longer-term administration and longer-term benefit to be derived. So, those are the principles that we are working to.

Prof. Axel Glasmacher:

If I may add to that, obviously what you want to see in a combination partner, enlarging your question a little bit, you want to see synergistic activity and you do not want to see that the burden for the patient, either by administration or by safety problems from either drug, is increased. So this is why we are focused very much on this data and this is why we believe there is a potential for combination therapy especially in earlier lines with this good safety profile.

Gbola Amusa:

Got it. And on COVID-19 and MRx-4DP0004, unfortunately COVID-19 is not a rare disease and to the extent you show a success in the fourth quarter you have a good problem of having to scale up dramatically for production. So can you talk about steps towards commercial readiness, I know it is very early, but would you seek stimulus from the UK Government somehow, do you plan to seek an outside party for help? How do you make sure that you can get an ROI [return on investment]?

Duncan Peyton:

Thanks Gbola. I think in terms of the product itself, it has been through the development process, we have a fairly sizeable facility over in Europe with significant capacity. But I think going forward, in terms of how it develops and how we take it forward, we will wait and see what the signals are.

But from a process and development point of view, we are more than comfortable with what we can do. If we needed to scale it up and go to a bigger production facility, we have already worked with some of the largest CDMOs [contract development and manufacturing organisations] in terms of the microbiome space as well, there is the potential to do that.

But as we are at the minute, the facility that we have in Spain is more than capable of developing enough product for all of our clinical programmes including the COVID-19 project.

Gbola Amusa:

Thank you.

Duncan Peyton:

I think we have time for one more question.

Edward Thomason:

I have another question, it is Edward here, if you do not mind?

Duncan Peyton:

Perfect.

Edward Thomason:

You do talk about the platform and the other programmes earlier in the presentation, but I just wondered if you could spend a bit of time providing an update on Blautix® and the other immuno-oncology candidates, and then just a bit of commentary as well on the strategy for the autoimmune platform, I saw that was referenced as well earlier.

Duncan Peyton:

As you know we are expecting data out of the IBS programme [Blautix] later in the year and we will be reporting on that as and when that comes out.

In terms of the platform itself, there are a number of developments, including in the autoimmune space which we have ongoing, but the focus has been on the oncology programme and the COVID-19 programme at the minute.

As we move forward, we will progress our discussions that we have with potential partners in the autoimmune space and also with the platform. I think, if you look at the deal that we did with Merck [Merck & Co.] in vaccines I think that is a good idea of what people are going to look for in terms of how they use our platform going forward

Edward Thomason:

OK, thank you.

Duncan Peyton:

OK. I would just like to thank Gbola, Edward and Olga for joining us today and listening to our presentation and that concludes our presentation for today.

Thank you.

[Ends]