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4D Pharma Plc (DDDD.GB)

Investor Meeting - Key Opinion Leader

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MANAGEMENT DISCUSSION SECTION

Operator: Ladies and gentlemen, thank you for standing by. I am Jason, your chorus call operator. Welcome and thank you for joining the 4D Pharma conference call. Throughout today's recorded presentation, all participants will be in a listen-only mode. The presentation will be followed by a question-and-answer session. [Operator Instructions]

I would now like to turn the conference over to Duncan Peyton. Please go ahead.

Duncan Peyton

Chief Executive Officer & Executive Director, 4D Pharma Plc

Thank you, operator. Good morning and good afternoon, everyone. Thank you for joining us today to discuss the results from Part A of the Phase 1/2 trial of MRx-4DP0004, which for ease of reference we'll refer to as MRx-4, for the treatment of asthma and to discuss the current asthma treatment landscape. You can access our previous topline results press release for MRx-4 as well as the slides that we'll reviewing here today by going to the Newsroom section of our website at www.4Dpharmaplc.com. As you may recall, we previously announced top line results in mid-December, and we're pleased to be sharing with you today additional details of those results as well as discussion of the asthma treatment landscape.

With me today are Dr. Alex Stevenson, our Chief Scientific Officer, and Professor Chris Brightling of the National Institute for Health Research, a senior investigator and clinical professor in respiratory medicine at the University of Leicester and principal investigator of the Mrx-4 Phase 1/2 trial. Before we begin, I'd like to remind you that we'll be making forward looking statements, details of which are highlighted here relating to 4D Pharma's live biotherapeutic products regarding regulatory approval times, the market and commercial opportunity, the potential for our live biotherapeutics to treat disease, the need for additional safety and efficacy data to support regulatory approval, and their impact on a broad range of diseases. Actual results may differ materially. Additionally, these statements are subject to certain risks and uncertainties which are discussed under the Risk Factors section and elsewhere in our annual report. Any forward-looking statements made on today's call represent our views as of today only. We may update these statements in the future, but we disclaim any obligation to do so.

So moving on. before we listen to Chris talk about the asthma space and the progress, we ust want to remind you guys why we're here. First, we want to give clinicians more tools to treat serious disease effectively, whether it be cancer, Parkinson's or, as we discussed today, asthma. And we also want to do that safely, and we can do this by leveraging the power of the microbiome to bring a new class of safe and effective therapeutics to market.

So moving on and looking at the progress that we've made towards this goal, we do this in much the same as any other pharma company. We look for functionality and mechanism of action. Just instead of using a small molecule or a protein, we use a single strain of bacteria and we have a proprietary platform, MicroRx, that allows us to do this. The understanding MicroRx gives us is how these single strains of bacteria work, or to put it another way, exert a therapeutic effect. And MicroRx really showed us the possibilities of treating systemic disease. For example, we can manipulate the immune system and are able to target diseases such as asthma. But it's also opened up the possibilities in oncology and neurodegeneration. So the research and output from MicroRx give us confidence that single strands can act like drugs systemically and the development of the microbiome is not simply constrained to diseases of the gut or defined by essentially ecological competition.

But what really demonstrates the use of single strain as therapeutics is two things. Firstly, we've been able to translate this research into a robust pipeline of Live Biotherapeutics drugs, three of which are already well into the clinic generating data, including MRx0518 for immuno-oncology, in IBS we look to move Blautix towards Phase 3 building on the real potential from the Phase 2 we completed last year, and the focus of today's call MRx4 for the treatment of asthma. And secondly, as evidence to the direction we've taken the establishment of collaborations with leading pharma partners to progress our pipeline of Live Biotherapeutics and expand the possibilities of the MicroRx platform to turn the microbiome into new directions.

I also talked about giving clinicians the tools, we placed a lot of emphasis on ensuring we can translate our discoveries through development to viable commercial products. This has included an investment in our in-house commercial scale cGMP manufacturing facility, which gives us the ability to deliver and give to clinicians stable products reliably.

And finally, I talked about leveraging in the microbiome. We do this through our amazing research team who through their focus, understanding and following through on the science, really understand and lead the field and because of that, we built up a strong and wide IP portfolio.

So just moving on and from the above, you can see from all our programs, including MRx-4, these were all discovered, developed and manufactured in-house. And in fact, 4D Pharma is a Live Biotherapeutic one-stop shop. And here I'll try and give you a broad overview of the process and how we go about it.

So we start with our extensive strain library isolated from microbiome samples from healthy human donors. Then using our proprietary platform to identify the single strains based on their functionality and mechanism of action that can act on pathways of interest and impact the target disease. And what that meant for us, maybe we were looking for strains with a particular immunomodulatory effect, and I will talk to this later.

From there, we passed the live biotherapeutic to our development manufacturing team to ensure we can produce stable, well-defined product, which is not as easy as it sounds. And to clarify, each strain is different. They have a unique profile, not only do they have different mechanisms they also have different manufacturing conditions. And at that point is then ready for the patient, and patients simply take one or two capsules depending on the strain, and with MRx4 it was two capsules twice a day. And this is what every patient and clinicians wanted. It's really easy to do. And think about that, and I just want to flag, we do not need any antibiotic pretreatment or bowel prep. We're not looking to repopulate the gut. We're looking to exert a defined therapeutic effect like any other drug. And finally, if you remember, one of the cornerstones that 4D Pharma has developed drugs that are not only effective but safe. And I'm proud to say that we've dosed now over 500 patients. We've seen a really strong safety profile and MRx4 is no different in this respect.

So at 4D Pharma, we continue to focus on progressing our pipeline, but today we will focus on the progress we've made on asthma, and we're pleased to be sharing the additional results from Part A of our asthma trial with you today. But first, to talk about the current asthma treatment landscape, I'm pleased to hand over to Professor Chris Brightling of the National Institute for Health Research, a senior investigator and clinical professor in respiratory medicine at the University of Leicester, and also the principal investigator of the MRx-4 Phase 1/2 trial. So Chris, over to you.

Professor Chris Brightling

Thanks very much. Thanks for that kind introduction and welcome everybody to this meeting. I am really pleased to be joining this meeting because I am excited about the opportunity that's ahead of us with this intervention, and I am really excited about the clinical trial data and you'll see a little bit more about that shortly. So my main role is seeing patients. So I specialize in asthma and we lead the regional asthma service, particularly for those with more severe disease and covering a population of about 3 million. And what I do outside of that role as looking after patients is I am also on the Scientific Committee for the Global Initiative for Asthma, so that's the world asthma guidelines. And I'm on the American and European Thoracic Society asthma guidelines as well as the UK, so the British Thoracic Society guidelines. And then I coordinate the whole guideline portfolio for the European Respiratory Society through my role in the Science Council lead. So I have sort of a broad view in terms of the clinical and the research perspective in terms of what is asthma and what do we need to do next.

So we're going to the next slide, please. So I really want to just frame this in terms of what is the overall scale or burden of disease. So let's look at the world-wide asthma prevalence. So we know that the global burden of asthma is currently affecting around about 300 million individuals worldwide, and this will increase up to a round about 400 to 450 million people by 2025. If we just advance the slide, then it should actually show that on the slide. Thanks very much. And that really shows us that the prevalence in industrialized countries is around about 5% to 10% in the adult population and around about 10% to 15% in those who were affected in childhood. And in those patients, around about 1 in 10 have what we consider to then be severe disease. So this is a really common problem. So those with severe disease is still affecting around about 1% of the population.

We then think about what asthma actually is. If we then go on to the slide just called out Airway Disease Domains. So I think about asthma is divided up into what the patient presents with, so they present with abnormal symptoms, so they have cough, breathlessness and wheeze, and then they also have episodes where they have worsening, so asthma attacks, also known as exacerbations. So I consider that as being the clinical expression of asthma. So that's in the top right. We then know that people with asthma have abnormal lung function. And this changes over time. So we then call that variable airflow obstruction. And then underpinning this, we have abnormalities that occur in terms of inflammation in the airway, which can be partly driven by allergy, it can be also impacted by the environment, including pathogens and changes in the microbiome in the airway, so you end up with quite a mixed and heterogeneous inflammatory process. And that over a chronic period of time can then also lead into changes in the airway wall structure, which is what we mean when we talk about remodeling. So the three domains; clinical expression, physiology and pathology.

But the patients that I see in clinic don't come in and tell me that they're worried about their variable airflow obstruction and nor do they tell me about what type of inflammation they've got, although I worry about that, measure that and then think about response in those terms. I also think about it in terms of what's more patient centered, and that's clearly what the patients are worried about. So the kind of ways that we then measure what's important to the patient is we then have standardized ways of measuring symptoms, and we do this using tools where we can measure asthma control.

And the standard tool that we use is the Asthma Control Questionnaire which then gives us an index of control by collecting standard information around those symptoms. We could also measure the quality of life which we also call the health status, again with standardized tools such as the Asthma Quality of Life Questionnaire. One of the things that happens when patients start to lose control, they also need to then go to their blue inhaler, so their reliever. So that's a short acting bronchodilator, the beta agonist. So actually understanding how often they use their SABA is a very good index of actually how well their asthma is controlled. These things change over relatively short-time scale. They can be within a day or between days or between weeks. So the other measure that's really important is the measure where we can then think about their asthma attacks or exacerbations. So these are really the outcomes that we focus on when we're then thinking about regulatory studies, but also the things that patients are actually most interested in.

If we then move a little bit into what is the treatment landscape and how do we then manage patients. I'm going to show you a slide from the GINA guidelines, you remember I said this is a global initiative for asthma and these are the GINA guidelines. And the GINA guideline start with a cycle of management. So if you could go to the next slide. Thank you. And these are things that you perhaps would imagine are intuitive. So we first of all, we have an assessment, so we need to confirm the diagnosis of the typical symptoms, to gather evidence about their obstruction. What else is affecting our patient? What are the other co-morbidities? Are they already on treatment? And if so, how are they taking those? What are the patient's goals? So in what ways do they want to be able to do things now that they can't do at the moment because they're impacted by their asthma? You can start them on treatment and then adjust. And then you obviously need to have clear education around their inhaler usage. Then there's a constant review of the symptoms, exacerbation, side effects, long term effects, ensuring the patients should be satisfied with what you do. And that's all done on the framework of a stepwise treatment paradigms. If we then go on to the next slide.

Again, this is the GINA guidelines, and it's going to show the treatment steps that we currently recommend for patients with asthma. You'll then see the treatment steps, so they're numbered from 1 through to 5. And what we have is I won't go through each step in detail, but essentially you start in the lower steps with low dose inhaled corticosteroids. You then go up to medium dose. And then there's some other additional controllers, such as long-acting beta-agonists, LABA. And then you get to the more severe end where patients are not adequately controlled in spite of high dose therapy, including inhaled corticosteroids and other inhaler therapy and some small molecule therapies such as anti-leukotrienes. And it's in this advanced stage where you then really have to make sure that you are then considering specialist input and thinking about how we can then measure different types of asthma so the different phenotypes of asthma. So if you then just click on. So then for step five, you refer for phenotypic assessment. So, what do I mean by that?

So, if we are going to the next slide please and if we think about how we phenotype patients, then at the moment we're really looking for patterns that link with allergy and link with the eosinophillic inflammation. So, this is a particular white blood cell that goes up in asthma and allergy. So, we are then looking for those features, we are then looking for those eosinophils in blood tests. We look at a breath molecule which also looks at activation in asthma cells called exhaled nitric oxide or FeNO. We can look at the eosinophils in sputum samples. We can measure allergens and we can also then measure the degree of allergy in the individual and their treatment needs, so do they need to be on systemic steroids. And we do these things largely because our current treatments that we, have treat these aspects of the disease. But what we don't have is we don't have treatments that can actually then be successful in those who are non-eosinophilic so patients who don't have this typical pattern in asthma but represents up to half the patients that we see with moderate-to-severe asthma. So, if we go into my last side, then what we know is unmet in terms of mechanisms, so I'll start with that in the bottom right hand corner, is that we do have good treatments for patients who have this what we call type two immune-mediated disease, which is largely eosinophillic. But even in that population, there are patients where they still have ongoing symptoms, ongoing exacerbations.

but instead recruited patients with partly controlled asthma that were treated with inhaled corticosteroids with or without LABA.

So in terms of the baseline characteristics of these patients UHFUXLWHGLQWR3DUW$ you can see that their symptoms aW entry into the study, as defined by the clinically validated ACQ-6 score, were relatively mild &d related to this the lung function in terms of forced H[SLUDWRU\ volume and the ratio of FEV1 WR forced vital capacity, ZUH normal at baseline. So because we're looking at patients with relatively mild symptoms, we might expect that for many of the secondary endpoints, it will be difficult to see an effect or an improvement from the starting point, particularly in the size of this part Acohort, which ZV not powered for statistical significance. So to illustrate this, if we look at the secondary endpoints related to the lung function, we can actually see that FEV1, 3()DQG FEV1/FVC ratio remained within normal range throughout the course of the study.

So moving on to safety$ mentioned earlier, we're incredibly pleased with the safety profile RI MRx-4 that has been demonstrated in Part A. The treatment with MRx-4 was associated with less frequent adverse events WKDQ placebo, and no serious or severe DGYHUVH events were reported. Most common adverse events were mild to moderate, with only one occurrence of treatment related adverse events in each category. 6XFFK Part A RIWKH study successfully met its primary endpoint.

So, moving onto a key secondary endpoint ACQ-6, as you heard from Chris, is a clinically validated tool that's used to measure asthma control and the effect of treatment on asthma control, and it's frequently used in clinical trials. The primary endpoint of Part B of the study will be the proportion of patients with reduction in ACQ-6 compared to baseline versus placebo. ACQ-6 ZDs measured at a number of time points in Part A of the study, enabling changes from baseline to be measured, and we saw some very encouraging data. While 3DUW$ was not intended to be powered for VWDWLVWLFDO significance at time points a significantly greater proportion of 05[treated patients showed a reduction in $&4 as compared with placebo &d at the end of treatment, 83.3% of MRx-4 treated patients improved their ACQ6 score, compared to 56.3% on placebo, giving a placebo adjusted improvement rate of 27%. This is obviously very encouraging for moving into Part B.

Still on ACQ6, a reduction of 0.5 or more is considered clinically meaningful. So the data from Part A was also analyzed in this way looking at the proportion of patients in each treatment arm ZKR showed an improvement in ACQ6 from baseline of at least 0.5. And here we saw 50% of MRx-4 treated patients showed a clinically meaningful reduction in ACQ6 at the end of treatment, compared with 37.5% for placebo, giving a placebo adjusted response rate of 12.5%. 1RZ OWKRXJK ZH know power for statistical significance, this is also a very encouraging trend, particularly when the relatively mild baseline symptoms of the patients are taken into consideration &d to give some context and without attempting to draw any direct comparisons between different studies DQGEHWZHHQ very different patient populations Eut as a guide to why we're so encouraged by this data, the ODEHO tezepelumab a recently approved biologic for asthma Vhows a placebo adjusted ACQ6 response rate of 9%, and this is something we will continue to record in Part B of this study, looking ahead to late stage development.

So, as Chris mentioned and as stated in the 2021 update of the GINA report, reducing the need for short acting beta agonists or SABA rescue medication is an important goal for future asthma treatments and a measure of success of any new treatment. This is because while SABA bronchodilator use provides short term relief of symptoms, it can lead patients to mistakenly believe that their asthma is under control without having any impact on the underlying inflammatory cause of their condition. So over-reliance on SABA has been repeatedly shown to increase the risk of asthma attacks, hospitalizations and even early mortality. So, in Part A of the study, we measured the proportion of patients who reduced their total weekly use of SABA from baseline at four different time points. At each time point, a greater proportion of patients on MRx4 showed a reduction in their reliance on SABA rescue medication.

And importantly, you can see that this increase is maintained over the dosing period in the MRx-4DP0004 treatment group while actually declining in the placebo group, which could be an important signal that we're actually having an effect here. This is very, very encouraging, as it could be seen as a good surrogate for the extent to which the patients believe their asthma is under control, with positive implications for long-term outcomes and healthcare resource utilization. But it also indicates improved quality of life, where patients can lead a more normal day to day life and where they're less anxious about remembering their rescue inhaler. As Professor Brightling described this as an important outcome for those real world asthma sufferers.

Another validated and widely used tool that Chris mentioned that's used in clinical development is the asthma quality of life questionnaire or AQLQ. This is comprised of a broad range of questions that assess the impact of asthma on a patient's quality of life and also the effect of the treatment on this. It's measured on a 7-point scale and an increase in AQLQ of 0.5 or more is considered clinically meaningful. In Part A, the proportion of AQLQ responders, that is patients showing a change in AQLQ score of 0.5 or more from baseline, increased at each of the measured time points. AQLQ was not recorded at day 15. At the end of the dosing period, 50% of patient's on MRx4 were AQLQ responders, compared to 31.3% on placebo. And this gives a placebo adjusted response rate of 18.7%, a very promising result. Again, just for context, tezepelumab achieved a placebo adjusted AQLQ response rate of 6% in pivotal studies. Again, only for comparison we don't want to draw any conclusions, but it's certainly a positive trend that we'll continue to monitor and we hope will be continuing in Part B.

Again, as Chris mentioned, when it comes to pivotal studies the gold standard primary endpoint for approval of asthma therapeutics is the annualized rate of asthma exacerbations. This is what really matters to patients and compared to Part A of our study being reported here pivotal studies are typically carried out in more symptomatic patient groups with inclusion criteria relating to the numbers of historical exacerbations, which is not the case in our study. They're also grown over a longer period, and therefore we expect to see more exacerbation events than in our 12-week Part A. Nevertheless, it's interesting to note that one exacerbation was recorded in the MRx-4 treatment group compared to two in the placebo. Albeit in a small sample size of relatively mild patients and over a relatively short duration, this is an encouraging trend. And we're making some adjustments to Part B which we expect will help to increase the strength of this signal, and this will be another important factor to monitor as we move forward in development.

So you can see, based on the results discussed today on the commentary from Professor Brightling, we feel that we have a promising, potentially disruptive therapeutic option for patients with persistent or poorly controlled asthma. The unmet need continues to be substantial with a large addressable market, and MRx-4 is potentially uniquely positioned to address many of the current gaps and issues with asthma treatment options. In particular, we feel that the prospects for a safe, easily administered oral therapy are the potential to treat a wide range of asthma patients is very attractive. And now for concluding remarks, I will hand back over Duncan.

Duncan Peyton

Chief Executive Officer & Executive Director, 4D Pharma Plc

Thanks, Alex, and thank you, Chris, for giving us a greater view of the asthma landscape and the patient needs. To summarize, we feel we have, you know, potentially really unique [indiscernible] here by being able to understand, identify the immunomodulatory reaction and show that we have yet another drug with a clean, safety and attractive product profile. Not only do we build on the long-term value of 4D Pharma [indiscernible] platform, we believe this drug [indiscernible] has the potential to improve long-term treatment and control in a wide range of asthma patients. The results of [indiscernible] are hugely encouraging and informative with positive trends with achieving the primary endpoint and seeing the positive trends in multiple [indiscernible] points of efficacy that are the focus of Part B this is another great step forward for 4D Pharma and our asthma program.

We look forward to progress the study into Part B, where we'll be enrolling 90 patients and assessing clinical activity while also collecting biomarker data to inform a potentially targeted clinical strategy and we'd be taking the findings from part A to help inform Part B, potentially enrolling slightly more symptomatic patients and consider the inclusion of additional biomarkers as we plan ahead for this development.

With that, we'll open a call for questions. Operator?

QUESTION AND ANSWER SECTION

Operator: Ladies and gentlemen, at this time we'll begin the question-and-answer session. [Operator Instructions] Our first question comes from Keay Nakae from Chardon. Please go ahead.

Q

Yes, thank you, can you can hear me, okay?

A

Yeah, it's fine, Keay.

Q

Great. So first question for Dr. Breitling when we think about the placebo responses using either [indiscernible] or the quality of life how noisy are these, using these validated instruments and is that how might we think about that noise if you will as you move into a more symptomatic patient population?

A

So there is -- this great question, thanks for that and we know from particularly from the pivotal phase three trials of biologics that the placebo effect in that setting is -- does usually go beyond jobs. So we tend to get a sort of a placebo response in the region of about 30% to 50% to the noise of the instrument seems to be very good in terms of the repeatability of those tests outside of the setting with the clinical trial.

So I think they're very robust to the uses of importance and then the magnitude of the placebo that seems to be larger in biologic trials than it is with small molecules and inhalers. So I think it's definitely something that can be used to the outcome and it absolutely does match with patient -- patient centered medicine, that is actually what patients are complaining or setting actually having that is an important part of your outcome measures is really key.

Q

Okay, great. And then just back to Duncan, what else can you highlight in Part B, beyond the degree of symptoms that could further reduce the heterogeneity Degree of symptoms that should further reduce the heterogeneity just to use that kind an umbrella term of the patient population.

Q

Adrian, do you want take this?

A

Yeah, yeah, sure. So – so in one respect, we don't really want to reduce the heterogeneity of the patients in terms of their biological background, if you like, it is important, I think, to consider becoming a slightly more symptomatic patient group than – than was in Part A. Clearly Part A was primary end point focused on safety. These are patients who are currently treated with ICS with or without [indiscernible] (00:34:05). So it's very important to establish that safety in these patients. And going into patients about slightly more symptomatic might enhance our ability to see more around the signals that we've already talked about today. And the other thing that we're thinking about is whether it's possible to also predict perhaps the likelihood of exacerbations that patients that might be heading towards in Part B. So we'll update more as we formulate those plans later this year. But that's certainly the basic principles of our thinking.

Q

And then just a final question, what – what about the – the use of concomitant meds? How do you control or what's allowed? What's not allowed?

A

Well, in terms of this – this current study, you know, these are partly controlled asthma patients and as you've seen from Chris's presentation around the different genes. Perhaps, these are patients who are already on inhaled or topical steroids and with or without long-acting beta agonists. And it's those type of patients who're partly controlled before they get to be truly severe and who require biologics that we're going to be interested in.

Q

Okay, thank you.

Operator: Our next question comes from Michael Higgins from Ladenburg Thalmann. Please go ahead.

Q

Thanks, operator. Thanks, guys, for taking the questions. Really interesting data, congrats on having a lead here in asthma with Live Biotherapeutic. Couple of questions on the Part B. Did you make any changes in the enrollment, such that you can get a -- you can try to express a difference in the asthma exacerbations, the gold standard as you mentioned, there's obviously some important endpoint that you've captured will capture again

here. But just curious about that. And as a second part of this, I guess you talk about the number of sites in Part A and Part B, the timings for enrollment in Part B quick?

A

Yeah, sure. So in terms of these exacerbations, nothing is final yet, but, you know, there are ways we could consider looking at that. So, you know, [indiscernible] (00:36:27) that's commonly used in trials in order to closely. And then there are clinical tools can be used that may help to predict the likelihood of patients progressing towards exacerbations, which, you know, the two could be used to help refine the population for later-stage development.

In terms of the number of sensors and, you know, start times, I think we've said that we'll be starting up, but we're trying to start the study this year. The number of sensors is yet to be fully determined, but you know, we have both UK and US sensors active in Part A, who are keen to progress rapidly, so they market further as we get closer to the actual start the study.

Q

Just a follow up when the alert started that the Part B, would you Just a follow-up, when might be next start of that part B, would you think it would be ready?

A

It's still not absolutely clear yet, but we've be hoping sort of midway through this year would position to be to be starting up.

Q

Okay. And then question for Dr. [indiscernible] (00:37:40). Any reason to believe MRx-4DP0004 is affective in mild asthmatic would be greater in moderate to severe patients? Looking for little for additional comments on your in your comment there. Thanks.

A

You know think there's opportunity here for it to be really very broad, through the proposed mechanism of action in the way that it's immunomodulatory could be additive in the more severe population. And then there would be more leads to improvements in exacerbations as being sort of the key points in that group have much higher treatment requirements. But as you then go into the more mild moderate population where exacerbations are less frequent than their day-to-day symptoms are really all they worry about. And the signals that we're seeing in the ACQ-6 s then you could then early data that you've just seen, this is really quite striking. And if that was borne out in immunology studies and showing a big impact on easy care, then you could then imagine that that could actually be beneficial across the whole spectrum of severity. And that clearly would be a much larger population of patients to say to them, do you think you know, it's interesting?

Q

I think, it's interesting. And then just one more follow up that they could for either of you. Did you detect a change from the baseline in the number of – it's in the fields or neutrophils in the blood or sputum. Thanks.

A

[indiscernible] (00:39:15)

A

Yeah. Sure. I mean, because of the size of [indiscernible] (00:39:18) and actually some of those analysis is still ongoing. But no analysis is still ongoing. But this is sample, not really sufficient to annualize trends there. Some individual patient data that we're investigating, but we're looking to Part B, with a large group of patients where we have more consistent sampling. Our sampling was impacted little bit by COVID and the ability to collect samples. So in Part B, we're hoping that we're going to get larger populations of patients and more samples to make that analysis. And that's certainly one of the – as Duncan said, one of the key outcomes are looking for Part B.

Q

Appreciate it, guys, and congrats. I'll jump back in the queue. Thanks.

Operator: The next question comes from Franz [indiscernible] from Oppenheimer. Please go ahead.

Q

Hi. Thanks for taking the questions. Just a couple here. Can you just help us understand maybe how subjective or objective the diagnosis and categorization of the severity of asthma is? Is it quite obvious when someone has mild, moderate versus severe?

A

Chris, do you want to have a go at this one.

A

Yeah, I was going to jump in there. It's a question that actually generates a huge amount of debate amongst those who look up to patients with asthma, so the definition of asthma and why people have – and how it's so when someone has asthma or not is quite – that's quite clear. So, it's based on symptoms and then changes in their physiology that we had measured with lung function testing. So severity is more complex and we have a lot of available therapies. So because of that, what we do is, we think about ongoing symptoms and disease control with background therapy taken into account. So we then include the need for high dose and either the need for very high dose therapy such as biologics and oral corticosteroids in order to control and oral corticosteroids in

order to control that disease or that they need high dose inhaled corticosteroids steroids and they're still poorly controlled. And that's how we define severe asthma, which doesn't really apply in some countries that don't have the same level of medications available. So if you're in a country where you only have inhalers in a few numbers of people and clearly if you die of asthma, you've got severe asthma and it wouldn't fit the definition [indiscernible] (00:41:50). So there's absolute clarity around the definition of yes, no for asthma, and there's clarity around the definitions that we use in our clinical settings within industrialized countries that have access to therapies. But it becomes more confusing when you don't have access to therapy around what you cause of it. That's all. Does that help?

Q

Okay. Yeah. No, that's helpful. And obviously it's a great debate and to make it even, I guess, more harder here. How many, if you were to quantify the amount of patients you see that you would consider severe, did I hear well that of those first of all, what is that percentage, a rough estimate of what you would see that severe. And of those, did I hear that about 50% are [Technical Difficulty] (00:42:41) right now?

A

So the number that are severe is around about 10% of the overall asthma population. There are some theories that suggest that may be as low as 5% and some are over 10%, but it's around about 10%. The proportion that are controlled is beginning to get better because of biological therapies. But one of the big challenges of biological therapies is around access. So there's very variable access because of the high – because of its high cost to where you have very good access to biological therapies, [indiscernible] 00:43:24 is better controlled, but even in that setting, you could imagine and I guess this is some distance down for the program, I'm sure the – shortfall beyond on thinking that it's quite yet, but because if they're successful in these planned studies, then you could also imagine getting studies where you actually try and see if you can add this in two patients who are on biologics and then try and withdraw biologics, where they might not actually need them, if you can modulate that to do so, that's of the future to think about, but I'm just trying to put that out there that actually this might be very broad and even if you have control with that, control necessitates high cost therapies in specialist centers, wouldn't it be fantastic if you had a biotherapeutic who could replace that.

Q

Now, that's very interesting, thank you for that, and then I was just wondering, obviously this pandemic seems to be lingering, never ending. I don't know if we'll ever get over it with these variants, but, in asthma, obviously respiratory disease, any color you want to give on, maybe, obviously, there's the population is huge with asthma, but any issues that you've seen with enrollment of these trials just because of the ...

A

Yeah, so in actual fact, in the early days, there was obviously a lot of caution about senses say no for us not asking patients going to centers for full clinical studies. Actually, as things settle down a bit, recruitment wasn't too much of an issue for us, and I don't know if Chris would like to comment, but I'm not actually sure about how much of a compounding factor [indiscernible] 00:45:05 actually is in respect of COVID. So Chris, you won't make any comments?

A

So the pandemic, certainly in the first 18 months, completely crushed being able to do clinical trials of the [indiscernible] in an effective way. So actually, delivery of so many trials such as this has really been absolutely fantastic that it's been done. Being able to run trials now is now really opening up, just becoming much easier and Omicron definitely is for the lower variants. I think that would be lesser impact. The relationship between COVID-19 and asthma will actually do a really good slide deck as part of the [indiscernible] so you can actually access that online by just going on to the [indiscernible] website. And in essence, the messaging is very much they take regular treatment, which you would imagine, I would say. But what's reassuring is that the – there isn't a very large signal suggesting that people with asthma have a particularly adverse response to COVID, but that the only group that really seems to be affected [indiscernible] very severe disease and particularly those who are not [indiscernible] treatment or needing or corticosteroids close to the time of infection. But otherwise COVID doesn't have that much of an impact on asthma and ability to do trials is now opening up.

Q

Okay. Great. That's it from me. Thanks for the questions and congrats.

A

The next question we have was sent to us through e-mail it is, how should we think about this data in the context of your MicroRx platform? How does this validate things?

A

Shall I take that?

A

Yeah. Sure.

A

So I think in terms of validating the platform, it's another program of the MicroRx platform on top of the oncology [indiscernible] that we've got. So it really validates not only the platform and that's the value of the platform, but also it's another good point in terms of budget and the approach that we're taking in terms of the single stress. And behind that as well, it's – if you think about the microbiome, you think about how microbiome develop, this is really another example of using microbiome therapy for systemic disease and not just a disease which is related to the gut, for example, such as [indiscernible] . With asthma, with oncology, it demonstrates that the microbiome can move to treat systemic disease. I think it's also good that we can validate the platform further. And helps us think about the approach and also opens up other ideas that we've got around immunomodulatory diseases, [indiscernible] .

A

I think – I mean that's absolutely right. I think from the perspective of microbiome therapeutics as a whole. And more evidence that single strains that ministered to the gut can have an impact on systemic disease, I think is an important step forward, not just for us at 4D, but actually for the whole field of microbiome therapeutics.

A

Okay, next question?

Operator: The next question is a follow-up from Michael Higgins from Ladenburg Thalmann. Please go ahead.

Q

Thanks again, guys, for the follow-ups. If there's time here, I'll poke in – with a few more. Any differences in the fecal microbiota, we believe that was one of the items that was assessed in the trial? Thanks.

A

Yeah, Michael, that was still under investigation, one of the exploratory endpoints where we haven't. But certainly something... Yeah.

Q

Okay. As a follow-up to that, when might we see further details from Part A? Any plans to present at conferences this spring, this summer? Thanks.

A

We were hoping to be presenting on the [indiscernible] at upcoming conference and we'll be able to update on that [indiscernible]

Q

Okay. I didn't hear comments on the market opportunity in neutrophilic and eosinophilic asthma. For me, I think it's a big driver for the value of the asset. Any thoughts or comments on having that ability to affect the neutrophilic driven asthma? Thanks.

A

I think as Chris was saying, in terms of the TH2 approach [Technical Difficulty] (00:49:47) build a targeted drug, there are solutions, biologic solutions those are quite in that. In terms of the other on the immune system,

neutrophilic element, which is obviously present in a number of asthma patients, there's really nothing out there right now, which has been shown to be able to be used [indiscernible] the patient. We're actually because of the mode of action the MRx4 have and because we've seen the effect both on neutrophils and the eosinophils, we're quite keen at this stage the key things open in terms of the patient population that we might actually see the effects in and to gather that data, particularly in Part B of the study. So we're not sort of narrowing in too far. Yeah, I think the unique thing about MRx4 is that it's able to impact both of those both arms of the immune system.

Q

That's great. Thanks. And then outside of MRx-4DP0004 here with slide 18, any updates for us on the timing for [indiscernible] data there? Thanks.

A

We looked at the market as and when we got all that – we collect all the data together, today we're focused on asthma.

Q

Appreciate it. Thanks for the follow-up guys. Thanks.

A

No problem.

Operator: The next question comes from Ravi Kiran from Merck. Please go ahead.

Q

Hi there. Ravi Kiran from Merck KGaA.

Q

Hi, there. Ravi Kiran from Merck KGaA. Excellent overview Duncan and the team, and thanks for that. And asthma is an exciting new area to show the effects of the microbiome. So, really looking forward to the outcome of this. My question is essentially that triple combination therapies are gaining ground in asthma. So how do you propose that we do clinical trials in this space with every new triple combination? Do we have to go back to the clinic to prove the effect of the microbiome, especially because the exact mechanism of action of how the microbiome actually does the effect is largely unknown, so any thoughts on that? Thank you.

A

I'll let John address the comment about the microbiome [indiscernible] , and I will ask Chris about the triple combinations.

A

Yeah. Sure obviously, our approach Ravi is to try and turn the microbiome effects into being unknown. So, in terms of MRx4, we've got very clear evidence, which we've published in preclinical models showing how MRx4 was actually able to reduce activation levels of dendritic cells and things that actually trigger the immune responses and the damaging immune responses that occur in asthma. So, we look at MRx4 very much as a biologic drug. We're not trying to alter the microbiome per se in terms of the network of microorganisms. So we're routing something in which has a very specific biological effect, which we can measure intestinal tissue. So that's the first thing to say, these are drugs [indiscernible] drug is not per se microbiome intervention. Maybe I can hand over to Chris to give some commentary on how triplet medications and you know how drug development can be taken forward in asthma.

A

Yeah, thanks for that. So whatever are you going to position? This is going to need to be on top of standard of care. So you're absolutely right. Probably the triple combination is really taking hold and so should because we know that ICS slab is very effective in a reasonable proportion of patients who are uncontrolled, there is a benefit from adding in [indiscernible] . But even in that population, there's still a substantial amount need because in that population, all the patients who have severe disease should be able to test whether those benefits over and above the patients who are on triple therapy. And there are still challenges around adherence to inhaler therapy and inhaler therapy versus being able to take an oral medicine. So those are patient preferences involved and mentality to adhere health treatment. So I think even though there's been successive in triple therapies and I very much welcome them in my clinic, I also know that there's a position both in terms of those who are still uncontrolled on triple, as well as an opportunity in those with mild-to-moderate disease before you're thinking about continually adding in inhaled treatments where the disease might be better controlled with alternatives.

Q

Thank you.

Operator: Ladies and gentlemen, the conference is now concluded, and you may disconnect your telephone. Thank you for joining and have a pleasant day. Goodbye.