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MSB.AX - Mesoblast Ltd to Provide Update on Randomized Controlled Trial of Remestemcel-L on Patients with ARDS due to COVID-19

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PRESENTATION

Operator

Hello, and welcome to the Mesoblast update on COVID-19 ARDS trial. An announcement and presentation has been lodged with the ASX and also available at the home and investor pages at www.mesoblast.com. (Operator Instructions) As a reminder, this conference call is being recorded.

Before we begin, let me remind you that during today's conference call, the company will be making forward-looking statements that represents the company's intentions, expectations or beliefs concerning future events. These forward-looking statements are qualified by important factors set forth in today's announcement and the company's filings with the SEC, which could cause actual results to differ materially from those such forward-looking statements.

In addition, any forward-looking statements represent the company's views only as of the date of this webcast and should not be relied upon as representing the company's views of any subsequent date. The company specifically disclaims any obligations to update such statements.

With that, I would now like to turn the call over to Dr. Silviu Itescu, Chief Executive of Mesoblast. Please go ahead.

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Thank you, operator. And thank you for joining us on this call today. We wanted to update everybody on the COVID-19 ARDS trial. We've currently enrolled 223 patients. And we wanted to update on the third interim analysis performed by the Data Safety Monitoring Board on the trial's first 180 patients.

The trial was powered to achieve the primary endpoint of a 43% reduction in mortality at 30 days for treatment with remestemcel on top of maximal care in a trial of size 300 patients. This projected mortality reduction overall was based on pilot data observed during the initial stages of pandemic early in March, when control mortality rates were exceedingly high and prior to the new evolving treatment regimens that have reduced disease mortality in ventilated patients.

On the third interim analysis of the trial's first 180 patients, the DSMB reported no safety concerns, but noted that the trial is not likely to meet the 30-day mortality reduction endpoint, if the trial were to continue to 300 patient enrollment.

The DSMB recommended the trial stop, complete and follow the currently enrolled 223 patients through to the end of the study, at least 60 days of follow-up, where we will be unblinding the data and evaluating overall survival and a whole range of secondary endpoints, including days alive off mechanical ventilation; days in intensive care; duration of hospitalization; end organ damage, particularly involving the heart, the neurological systems and pulmonary damage. And additional measures of evidence of biomarkers, such as circulating cytokines and inflammatory markers will be evaluated.

None of these key secondary endpoints were, of course, included in the interim analysis by the DSMB. And therefore, the trial will evaluate all these endpoints through 60 days of follow-up in all the 223 enrolled patients.

The data will be evaluated in great detail by Mesoblast and our strategic partner, Novartis, together. In order to evaluate what meaningful clinical outcomes can be attained that can guide our plans for the development of the program for remestemcel, both in ongoing COVID application as well as in non-COVID acute respiratory distress syndrome, which is a very large unmet need and around which the strategic partnership was built.

It's important to note that during the course of the trial, as the pandemic evolved, numerous changes in the treatment regimens for COVID-19 patients occurred, including regimens both prior to and while on mechanical ventilation that may have had an effect on the mortality endpoint in this trial.

In particular, patients who have been currently included in trials have a very different management of their lung disease. Prior to ventilator support, they're provided with many experimental therapies, including dexamethasone, and in particular, repurposed immunomodulatory agents that on their own have not demonstrated any effectiveness, but by the time patients are put on ventilators, the duration of inpatient stay, the access to various medications means that the type of patients that are in the -- in -- on ventilators in our trial are very, very different from those patients that were originally enrolled and that reflected the interim data, the pilot data earlier in the pandemic.

All of these changes have materially altered the natural course of ventilated patients with COVID-19 and reduced mortality rates during the trial compared to the early stages of the pandemic.

Nonetheless, we are very keen to take the study to its completion unblinded, and evaluate the potential therapeutic benefits of remestemcel in the overall population and in various subsets.

So I think with that, I'll open the line to anybody who might have some questions. Thank you.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from Louise Chen from Cantor.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

So I had a few. First question I have for you is, what are your thoughts on how close you got to that 43% reduction in mortality? And then what type of reduction in mortality do you think the FDA needs to see for emergency use authorization? And do you see a path forward here?

And last question I had for you is just, can you comment on the age of your patient population? Did that change as the treatment paradigms change for COVID-19?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Thank you very much, Louise. So first of all, we know from the DSMB that interim 1 and interim 2 both demonstrated differences in mortality that favored the remestemcel-treated patients. We also know that by the time interim 3 was done, those differences have narrowed somewhat.

And the conclusion was that to achieve the very high bar of 43% reduction in overall mortality by the completion of the trial would have required more than the 300 patients that we had planned for.

In terms of -- I think the question you've asked is about age. I think age, other demographics and the way patients are treated today compared to how they were treated at the beginning of the trial, have changed quite substantially. Within -- in the first half of our enrollment, patients had a mean age of less than 50. The second half of the trial resulted in patients with mean age of more than 60 and approaching 70.

And so I think it's very important to understand that the evolving pandemic, and particularly, those patients who end up on ventilators across the U.S. are those patients who are becoming older and older. In particular, these are patients who are treated a lot longer prior to being put on ventilators with various experimental agents, particularly agents that have already been approved for other diseases and are being tried to reduce inflammation.

And the longer these patients are being off of various experimental agents and precluded from getting on ventilators, the longer, of course, it takes for them to have access to our potential experimental therapy in our trial. And so the type of patients that we were seeing now for patients who were very refractory to other immunomodulatory agents presumably had partial reduction in their general inflammation, potentially had transition towards a fibrotic state. And those patients are inherently very difficult to treat. And they're different, very different from the early stage patients and completely different from the younger patients that we were seeing and that we had shown very rapid resolution of symptoms early in the pandemic.

I think you were also asking about the regulatory pathway, I think, is that correct, Louise?

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

Yes. If there's a path forward? And what the FDA needs to see?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Yes. So I think it's going to be very much dependent on our ability to evaluate subset analyses and biomarker data when we fully unblinded data at the 60-day endpoint. The FDA is desperately looking for agents that can provide both survival benefits, but also important improvements in outcomes. And those outcomes include reduction in ICU stay; reduction in -- of time on ventilators; reduction of time in hospital; improvement in pulmonary function, cardiovascular function, neurological function.

All of those parameters we will look at. And I remain very confident that we will see signals in -- across all patients in some areas and in certain subsets, specific signals such as potentially survival benefits. We'll have to wait, and we'll see. But I think if we see any of those, there's the potential for faster pathways towards regulatory approval, including the type of EUA options that are available to various drug makers.

Operator

Your next question comes from Tanushree Jain from Bell Potter Securities.

Tanushree Jain - *Bell Potter Securities Limited, Research Division - Healthcare and Biotech Analyst*

Just a couple from me. In terms of the non-COVID ARDS indication, I think you mentioned that you and Novartis are going to officially analyze this data and then determine path forward for COVID and non-COVID. So I guess in terms of non-COVID, what particular secondary endpoints do you think is going to be really vital or I guess transferable from one -- the COVID-19 indication to non-COVID indication for you both to make that decision to move forward with it?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Well, thanks, Tanu. I think what's important is to look for commonalities. Commonalities in terms of mechanism of action and those relate to the degree of inflammation. As I just mentioned earlier, I think we have to be careful the type of patients that are enrolled are sufficiently inflamed and have early enough in their disease stage that both the cells are able to respond, the cells are able to have an effect and the patient is not so far advanced that is not irretrievable.

And as we just learnt in our heart failure program that we announced several days ago, the ideal patient population in heart failure, for example, is Class II, advanced Class II on their way to Class III, but not so far advanced that they've lost so much muscle mass that they're not irretrievable.

So I think in ARDS, it's the same story. And in fact, there are protocols that are being developed, particularly in COVID-19 patients, where the ARDS definition, the severity of pulmonary dysfunction in ARDS may not actually require the patient to be ventilated.

Maybe -- the patient may be receiving nasal flow. And so that already is a change in treatment paradigm. And so if we, for example, learn the patients on the cusp or just before they get ventilated are very highly inflamed that are more appropriate patients to be targeting with that S cells, that may be an ideal patient population, both in the COVID scenario and also in the non-COVID respiratory distress syndrome patients.

But I think there's a wealth of information in this study, and we will learn whether age; whether degree of biomarker activation, including inflammatory cytokines like IL-6, IL-8, TNF, all of which are elevated in COVID disease as well as in non-COVID ARDS.

If they've been impacted and to what extent and how durable that impact might be will be very important teaching in terms of identifying patients at risk and patients who might be more likely to respond in the non-COVID scenario to S cells.

Certainly ARDS, all caused ARDS, influenza related, bacteria related is a major area of focus for both Novartis and Mesoblast. That is the focus of the partnership. And all of the learnings we're going to have from the COVID study will be applied to the larger, broader non-COVID ARDS programs.

Tanushree Jain - *Bell Potter Securities Limited, Research Division - Healthcare and Biotech Analyst*

All right. And just one more question. Just in terms of the COVID opportunity from here, assuming the secondary analysis does give you really meaningful insight into either subset or the right patient population or certain biomarkers, et cetera? Would you say then the likely path forward would be running another confirmatory trial with those learnings?

And if that's the case, then I guess, just given that a lot of vaccines, et cetera, are coming out in the market and another trial might take time to read out, I guess, strategically, then would it make sense to continue to pursue COVID? Or would you rather focus your efforts on non-COVID ARDS?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

I think that we have to wait to see the results fully when they become unblinded. But I think that the opportunities for Mesoblast in the COVID space will remain very, very important. The sweet spot really for the technology is what we need to identify. We believe that it's likely to be in that transitional phase from a patient who's got pneumonia and is deteriorating but before they've received other therapeutics.

In other words, that the cells ought to be used first or second line in order to be effective as long as we identify that there's a signal of sufficient inflammation to warrant effect. So I think that that's the target population we'd like to focus on. But of course, it's going to be dependent on the results that we unblind.

Far more important to do that than to wait until a patient has been tried on many things and is end-stage and is irretrievable on ventilation.

With respect to whether vaccines will make a difference or not in this patient population? Of course, we're all hoping that the reduction in transmission rates are going to have a major impact on the incidence of infection, and therefore, the incidence of severe complications.

Nonetheless, what we're talking about is even if we have 70%, 80% reduction in transmission rates, the hospitals are going to continue to be full of COVID pneumonia, and those patients will require treatment in order to reduce the inflammatory process either pre- or post-acute ventilation. So that opportunity will remain even with successful vaccines.

In addition to that, there is no doubt that the larger commercial opportunity is non-COVID respiratory distress syndrome caused by influenza despite the fact that there are vaccines. There are more than 60,000, 70,000 people a year in the U.S. who die of the influenza ARDS every year.

The effectiveness of flu vaccines is only about 50% annually. And so there is an ongoing large need for an immunomodulatory treatment of those patients with ARDS. And of course, there's bacterial-related ARDS due to either pneumococcus or gram-negative sepsis, very, very large unmet need.

And those are the areas that we, together with our partner, Novartis, is going to be focusing on, that formed the primary objective of the strategic alliance. And I think the data, as they become available, will inform us as to what is the right strategy, what's the right patient population, et cetera.

Operator

Your next question comes from Kennen MacKay from RBC Capital Markets.

Kennen B. MacKay - *RBC Capital Markets, Research Division - MD & Co-Head of US Biotechnology Research*

Two questions. First, it seems like there are maybe 2 variables at play here. The patient population is getting more severe and refractory as the pandemic is progressing, and that's resulting in remestemcel-L beginning to underperform expectations. And also maybe that the control arm is sort of outperforming as supportive care knowledge is growing and these patients are having access to advancing experimental agents as the pandemic progresses, and they're receiving the cytokine directed and steroidal and immunomodulatory agents that you were discussing.

I guess thinking about those 2, which is -- has been sort of the primary driver of this utility finding? And thinking about the path forward, the developmental path forward, how would you think about refining that?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

No, I think you're absolutely right. I think there are both elements are at play, which makes performing a randomized controlled trial, which has to have a consistent methodology to its recruitment strategy, so difficult to perform in the middle of a pandemic, which has got an evolving treatment paradigm, right?

Clearly, it's very difficult. And what we are seeing is that the patients who are progressively ending up on ventilators, and therefore, refer into our trial, are 10 to 15 years older today than they were 4, 5 months ago. That's a big difference. Now what we do know also about age is that these patients are the most difficult to treat using anything, including dexamethasone, of course.

And so we're finding more and more of a patient population that not only is refractory due to age, but also because, by definition, these patients have been in the hospital longer whilst they've been tried on various experimental protocols. In fact, these days, especially as our program was part of an NIH network, the patients referred into our trial formed part of a much larger network of clinical trials where patients were being randomized to various arms of repurposed immunomodulatory drugs, including anti-IL-6 agents, JAK inhibitors, convalescent plasma and antibodies targeting the virus.

So when you've been on all of those agents and perhaps even sequentially more than one, then you're right, there are 2 convergencies. One is duration of disease and duration of refractory disease and reduction of certain inflammatory pathways that otherwise could have been amenable to our treatment.

And secondly, a selection for all the more sick and more refractory patients because the younger ones have responded better to a variety of other agents. So it is a very difficult trial to conclude and what it taught us is that we need to go earlier in the stage of the disease, just like we saw in heart failure, where we evaluated that therapy in Class III and in Class II patients, both of whom had advanced disease.

And clearly, we saw a major survival benefit in those patients in Class I, 2 years or so before they progressed to Class III. So that taught us that the earlier stage of a disease process where inflammation is present and where there's tissue to be protected is the critical space for our technology to do what it needs to do. And I think it's exactly the same scenario in the COVID-19 lung disease.

We need to identify exactly where the sweet spot is, and we will do that when we unblind this trial.

Kennen B. MacKay - *RBC Capital Markets, Research Division - MD & Co-Head of US Biotechnology Research*

And so -- one final question, if I may. It seems like there is sort of another variable at play here, just to make things even more complicated. And that's just relating to, I guess, the patient population that you use to think about powering another trial.

Just thinking about this the median trial that was used to power this is it possible that now China is one of the best hospitals in the world, and that initial data generated in that hospital had one of the best survival rates in the world and maybe wasn't representative of how those patients would have performed at other centers? And just thinking about that, how do we, I guess, go about interpreting the data out of this trial...

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

No, no. Can I -- let me sort of take you back there. No, that's not the case. The group at Mount Sinai at the time in March was -- the intensive care was overwhelmed with patients, absolutely overwhelmed.

And the patients that we treated were no different than the majority of the patients that they were treating at the -- in intensive care at that point in time.

The mortality rate in the Mount Sinai ICUs and from the main hospital and its affiliate was of the order of 80%. And that was both based on the internal dossiers at the Mount Sinai Hospital as well as what was published subsequently in the literature.

What has happened -- and is that -- there's been a significant learnings and improvements, both in ICU care and also pre-ICU care. And so there has been a dramatic reduction in overall mortality of COVID-19 patients in ICU on ventilators and before they ever get to ventilators. And that's really about routine management of these patients.

That is universally seen right across the U.S. On top of that, I think that is the complexity of therapeutics, yes.

Operator

Your next question comes from Jeff Cohen from Ladenburg Thalmann.

Jeffrey Scott Cohen - *Ladenburg Thalmann & Co. Inc., Research Division - MD of Equity Research*

Silviu, I wondered if you could expand upon a little bit how this may develop some learnings and how do you think about IBD and remestemcel in that indication going forward?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

That is a great question. Really, really good question. So I think there are a lot of parallels between IBD, inflammatory bowel disease, and inflammatory lung disease. And let me explain what I mean by that. We have been looking at inflammatory bowel disease, Crohn's, in particular, using the remestemcel cells both intravenously.

And very recently, in a new study of direct delivery into the colon in Crohn's colitis and ulcerative colitis. And the patients that are now being studied in the colitis study are those that have failed just 1 anti-TNF agent. The reason for that is that in earlier studies with intravenous use of remestemcel, we found very exciting data in patients who had failed just 1 anti-TNF agent, but more difficulty in treating patients with who have failed multiple biologic agents.

And that has to do, again, with exactly the same that's being seen now in the inflammatory lung disease scenario that patients who continue to fail multiple agents have severe refractory disease not amenable to other therapies. And again, the signals that we've seen are clearly in the patients who failed a single biologic early refracted to an anti-TNF, but not so far advanced that they failed other agents.

So therefore, we believe that our therapy in IBD should be in that first-line after failure of an anti-TNF in the same way that in graft-versus-host disease, ideally, we believe that our cells should be used as first-line after patients are refractory to steroids, and they have severe disease.

But not as salvage therapy after many drugs have failed, even though in GVHD in children, we were able to risk patients after many drugs have failed, but that's not where the ideal patient population lies.

In terms of inflammatory bowel disease and, in particular, colitis, we're very excited by the ability to deliver the cells locally to the colitic mucosa under direct visual observation so that the surgeon can actually see the inflamed patches, can locally inject the remestemcel. And what we're looking to achieve is remission within the first 4 weeks.

The major unmet needs really in inflammatory bowel disease is early remission. And particularly with colitis, the inability to achieve remission and the majority actually of immunomodulatory oral agents do not achieve remission and perhaps at best achieve responses -- late responses. But the inability to achieve early remission results in a high risk of the patient requiring surgery. And surgery in colitis, of course, is total colectomy, which is a devastating problem for young people.

That's what we're trying to fix. We're addressing these patients right now. And that trial is going on a Cleveland Clinic. I'm happy to discuss in greater detail that trial. But we're very excited, and we're seeing some pretty exciting initial preliminary data.

Jeffrey Scott Cohen - *Ladenburg Thalmann & Co. Inc., Research Division - MD of Equity Research*

Is it harder to find those patients earlier that are refractory in the case of IBD that have not already spent months or years on other products or failing other products, I should say?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Well, no. It depends on the referral centers, but Cleveland Clinic is a major referral center for inflammatory colitis, inflammatory bowel disease.

And I think the protocol is clear that the protocol requires 6 months of an anti-TNF. And then progression of a patient who is either not responded or has had a response and then had a flare. And so it's really quite a strict protocol.

We're not recruiting patients who've gone cycled through one and another and another biologic. We're clearly looking for patients in a relatively early stage disease, having failed or not responded to a single biologic. So it's not hard to recruit those patients. They just need to have a very clear referral structure.

Jeffrey Scott Cohen - *Ladenburg Thalmann & Co. Inc., Research Division - MD of Equity Research*

Okay. After one -- earlier patients after one failure is what you're saying?

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

That's right. That's right.

Operator

That brings us to the end of today's call. I will now hand back to Dr. Itescu for closing remarks.

Silviu Itescu - *Mesoblast Limited - Founder, CEO, MD, Chairman of Scientific Advisory Board & Executive Director*

Well, thank you, everybody, for coming on to this call. We remain committed to the patient population with this devastating condition, COVID-19 lung disease. We will look forward to unblinding the trial at its conclusion at the 60-day time point, evaluating all the key secondary endpoints. And we will share those with communities at large as we start to plan for further studies in both COVID and non-COVID respiratory distress syndrome. Thank you very much.