THE WALL STREET TRANSCRIPT
Connecting Market Leaders with Investors

Mesoblast Limited (NASDAQ:MESO)

SILVIU ITESCU, MBBS, FRACP, is Chief Executive Officer and Managing Director of Mesoblast Limited. Dr. Itescu has served on Mesoblast's board of directors since the company's founding in 2004, was Executive Director from 2007, and became Chief Executive Officer and Managing Director in 2011. Prior to founding Mesoblast in 2004, he established an international reputation as a physician scientist in the fields of stem cell biology, autoimmune diseases, organ transplantation and heart failure. Dr. Itescu has been a faculty member of Columbia University in New York, and the University of Melbourne and Monash University in Australia. In 2013, Dr. Itescu received the inaugural Key Innovator Award from the Vatican's Pontifical Council for Culture for his leadership in translational science and clinical medicine in relation to adult stem cell therapy. In 2011, he was named BioSpectrum Asia Person of the Year. He has consulted for various international pharmaceutical companies, has been an adviser to biotechnology and health care investor groups, and has served on the board of directors of several publicly listed life sciences companies.

SECTOR — GENERAL INVESTING

TWST: Would you explain to us what Mesoblast is?

Dr. Itescu: Mesoblast is a late-stage development company with products derived from mesenchymal lineage cells, with cell therapies focused on targeting inflammatory and immune-mediated diseases. These are conditions for which alternative therapies have been exhausted and are limited. We have identified this unique cell type that is present in all of us that is isolated using monoclonal antibodies. These cells have very unique characteristics that allow them to be expanded to very large numbers under industrial manufacturing conditions. They do not activate the immune system when used from a single donor to treat many thousands of potentially unrelated recipients.

Our commercial manufacturing process allows scalability and batch-to-batch consistency. This translates to reproducibility at high standards of potency, and that meets regulatory compliance. These cells uniquely have the ability to be activated by factors that are present in inflammatory diseases and sites through very precise receptors. When activated, these cells release counter-regulatory factors that switch off the damaging inflammation that is the cornerstone of the diseases that we target. There is a very well-characterized mechanism of action by which these cells work that links the main diseases that we have initially focused on.

We currently have three Phase III assets and, through a licensing partner, have the first approved product using industrially scalable mesenchymal lineage cells in the world. That product is in Japan through our licensee, JCR Pharmaceuticals. A second product will be launched in Europe shortly by our technology licensee, Takeda Pharmaceuticals. We believe that we will have the first industrially manufactured mesenchymal lineage product launched and approved in the U.S. over the coming period.

TWST: I want to break the science down just a little bit. These cells are received from a donor. Where in the body are they being taken from?

Dr. Itescu: We have a very large panel of qualified donors. They are FDA-compliant and come to our facility in Maryland where they undergo a bone marrow donation. It is a very simple outpatient procedure that allows us to extract the cells using monoclonal antibodies. It is a very pure population of the cells that become the starting point of the whole manufacturing process.

Given the scalability of the process and given the proprietary manufacturing capabilities and media components from just a handful of donors, we believe we would have more than enough therapeutic units to create commercial-scale amounts that meet the right requirements to treat diseases as diverse as heart failure, chronic back pain and graft versus host disease as well as rheumatoid arthritis. Accessing the foundational material is actually a very minimal component of the entire manufacturing process.

TWST: These lineage cells you've taken from the donor, part of what you are doing in the manufacturing process is expanding them. Are you doing a lot of other alterations to them? How are they being treated, and are they treated differently depending on the disease they are being prepared to treat?

Dr. Itescu: The manufacturing process is critical. The key ingredients in the culture media, for example, allow us to optimize the cells as they are being expanded to be used for disease A versus disease B versus disease C. So there is a lot of intellectual property and know-how in the manufacturing process that results in the final product being used in patient A with heart failure versus patient B with chronic debilitating back pain. How we measure the qualities of these final products is based

on very precise tests and assays that demonstrate batch-to-batch-to-batch reproducibility for that disease.

TWST: So depending upon what cells you want to expand for what indication, you might tweak them to do one thing versus another?

Dr. Itescu: That is right.

TWST: It is interesting to me that you are saying that they have no immune effect when they are put in someone else's body. And to your understanding, something so biological is not having any off-target effects in studies to date?

Dr. Itescu: Yes. There are two parts to the question you just asked. First of all, they do not induce a T-cell immune response, which is the primary immune response that we are all worried about when putting a foreign graft into a patient. The reason there isn't a T-cell immune response is because our cells lack certain key surface co-stimulatory molecules that are necessary to stimulate the T cells of another individual. That is a unique aspect that underpins our ability to use them allogeneically.

The second question you asked is, why aren't there off-target side effects? Think about small molecules, and the problem with small molecules traditionally has been that the broader target effects, the more likely they are to have off-target side effects. Hence, the pharmaceutical industry has been diligently working for a long period of time to develop small molecules that are very narrow in their specificity. Our cells require activation by the local environment they find themselves in to release their multitude of factors that are relevant to the disease modification.

So if, for example, they find themselves in a healthy tissue, they won't be activated. If they're not activated, they won't release any of their biological molecules, and you'll get no off-target side effects. They will only be activated when placed in the tissue where there is a high degree of inflammation. The response is very specific. The release of counter-inflammatory factors is specific and localized. At sites outside of where the disease occurs, you won't get off-target side effects. The paradigm is exactly the opposite of small molecules.

TWST: You have a couple of partnerships going on right now, one of which is around an actual marketed version of this therapy in Japan. Can you describe that and the income stream that might be expected there?

Dr. Itescu: The first product based on our technology that has been approved globally is being marketed in Japan as it has been licensed to JCR Pharmaceuticals, which is an orphan drugs specialist in Japan. The approval was the first fully approved cell therapy product of any type in Japan. It occurred about two and a half to three years ago after an approval for use in children and adults with steroid-refractory graft versus host disease.

Graft versus host is a disease that is a devastating complication of an allogeneic bone marrow transplant. It occurs in about 50% of people who get an allogeneic bone marrow transplant, and typically, 90%-plus of people who undergo these transplants have had high-dose chemotherapy for their underlying leukemia. So the transplants serve to rebuild their bone marrows after chemotherapy. You can imagine seeking a cure for the underlying leukemia and then getting this devastating complication of graft versus host disease, which has a very high mortality in its most severe forms. It is a terrible complication.

There is nothing that is approved other than steroids in the first instance. Also, 50% of people will fail steroids. After steroids, nothing else is approved anywhere in the world other than our mesenchymal lineage product in Japan. So we've been very pleased that this product was approved.

It has received very good reimbursement. We believe that since the launch of the product, the adoption rates by clinicians approximates about 50% of our expected addressable market. So we are very pleased by the uptake and the way it has performed.

We are aware of no safety issues. It gives us great insight into how we would expect a similar drug to perform once it has launched in the United States. We hope to begin filing with the FDA for the same product shortly. We have been using it now in the United States for several years under an expanded access program, so over 240 children have already received this in the United States.

We have performed a very rigorous Phase III trial that demonstrated similar data to what we had generated in the earlier EAP program. In the Phase III trial, we were able to establish a very significant improvement in overall response rates at day 28 and a very significant association with improvement in survival at three months and at least through to six months. So the results that we have achieved clearly demonstrate that this product, if approved, will be a first-line therapy after steroids have failed. The Japanese experience informs us and gives us great confidence as to how it's going to perform in the U.S.

"In the Phase III trial, we were able to establish a very significant improvement in overall response rates at day 28 and a very significant association with improvement in survival at three months and at least through to six months. So the results that we have achieved clearly demonstrate that this product, if approved, will be a first-line therapy after steroids have failed."

TWST: I know you are going to the FDA, but will you be going to the rest of the world after that?

Dr. Itescu: Yes. We would expect first approval in the U.S. Then, we will use both the data that has been generated in our U.S. Phase III and the expected FDA approval to support an entry point into Europe and, beyond that, into Asia.

TWST: That product is a different formulation than the drug candidate that is in Phase III for chronic heart failure?

Dr. Itescu: Yes, it is a very different and very distinct formulation.

TWST: OK.

Dr. Itescu: All of our products are able to respond to core elements of inflammation in diseases. Through activation by inflammatory signals, they then release counter-inflammatory proteins that switch off the inflammation, but they also release additional factors that are relevant to improving that particular disease. In the case of chronic heart failure, it is now well-established that inflammation is at the core of progressive heart disease and associated with progressive inflammation in the myocardium, particularly driven by so-called tissue macrophages. That level of inflammation may not be as great as that which is in graft versus host disease, but it is a similar driver of the disease state.

New York Heart Association Class III and Class IV heart failure represent the sickest 20% of patients with heart failure. Over the next few years, it is expected that as many as 8 million patients in the U.S. will have heart failure, so it represents a huge unmet medical

need today. By the time you progress beyond Class II into Class III, patients have failed existing therapies, meaning they have failed ACE inhibitors, beta blockers and the like. There really isn't anything else to offer these patients.

Once they get to Class III and beyond, the mortality rate really starts to look very similar to cancer patients with death rates of about 20% over several years. By end-stage heart failure, there is a 50% death rate within 12 months on medical therapy alone. So these are big issues, big problems.

We have formulated a product that is called Revascor to have unique properties that respond to the inflammatory signals in the heart. It releases factors that switch off the damaging inflammation as well as induces normalization of the blood vessels and even induces new blood vessels to grow. The requirement for new blood vessels and normalization of the vasculature is critical in heart failure in order to improve blood flow to damaged heart muscle and reverse the disease process. So the combination of anti-inflammation and improvement of blood vessels are what the formulation of the heart failure product is all about.

The results of our previously completed successful Phase II trial were published in *Circulation Research* several years ago. We have now completed enrollment in 566 patients in a Phase III trial. These patients are now being followed up through the course of this year to collect enough hospitalization events, such as terminal cardiac events including mortality. This is a requirement for transplant or unofficial devices. We will be looking at the primary endpoint of this trial over the next 12 months or so. It is the largest trial of cell therapy in cardiovascular disease. We are very optimistic about how it's going right now.

"We have formulated a product that is called Revascor to have unique properties that respond to the inflammatory signals in the heart. It releases factors that switch off the damaging inflammation as well as induces normalization of the blood vessels and even induces new blood vessels to grow."

TWST: This is in the U.S.?

Dr. Itescu: Yes, in North America, as in the U.S. and Canada.

TWST: When is the earliest that this treatment could reach the market?

Dr. Itescu: We are targeting 2021 or in that time frame.

TWST: And then, would you go to Europe after that?

Dr. Itescu: Yes. In fact, we are in discussions right now with our existing partner in China together with the new additional potential partners as to how to initiate a second global trial that would cover sites in Europe, in China as well as North America as a confirmatory second trial.

TWST: This question is pie in the sky, but I would imagine this, while today has as a specific application it is being tested for, could be used potentially earlier in the heart disease process. Down the line, could this be used as an earlier-stage treatment to maintain heart health?

Dr. Itescu: Well, this is a very specialized and very complex technology, so it is not going to be routinely available for everybody. It is a very state-of-the-art and innovative product.

TWST: Understood.

Dr. Itescu: It is being delivered by catheter into the left ventricles. It requires a fair amount of sophistication and use in tertiary care hospitals. So I would expect that for the foreseeable future, it will be focused on those sickest 20% of patients who need it to prevent progression to recurrent hospitalizations and death. That is, today, the biggest unmet need in this field. Beyond that, we can certainly think about other formulations that could be used more widely, but this current product in this formulation is ideally suited to severe and advanced disease.

TWST: What are patients reporting who have received this therapy to date? What is being reported on their outcomes?

Dr. Itescu: In Phase II, we saw over three years of follow-up, there were no heart-failure related hospitalizations or deaths in patients who received a single injection of our cells compared to anywhere from 30% to 70% hospitalization rates in control patients over that same period of time. That was extremely heartening to see. If we can reproduce that in our current Phase III trial, it would be absolutely a remarkable innovation and improvement in outcomes.

These patients go in and out of the hospital with progressive heart failure. Each time they are in the hospital, they are potentially on death's doorstep with intensive care requirement, severe shortness of breath and fluid overload. Each hospitalization is one step closer to death. If we can make an impact on that natural history of the disease, it will be a very important change in the way patients are being managed.

TWST: During follow-up, I am assuming there might be some imaging involved. Are you actually seeing newer heart tissue being developed? What is being witnessed?

Dr. Itescu: Yes. What we have seen in much earlier preclinical studies, meaning in various large animal models, for example, is that we prevented further loss of heart muscle cells from a particular point in time. We have prevented loss of heart muscle and replacement by scar tissue. This was associated with the increase in local blood vessels and reversal of abnormal blood vessel function. All of that has been shown in published preclinical studies.

It is very hard to prove those kinds of outcomes in human studies, but what we saw in the Phase II trial was that, over a six-month period, the size of the left ventricle started to normalize. It reduced in diameter compared to controls. That is an important signal. Patients were able to walk substantially further over a six-minute walking test relative to controls. So we clearly saw an improvement in the anatomy of the heart and the ability of it to function.

Really though, what the primary endpoints are, as in what the FDA wants to see and what clinicians hold as the bar is, can we keep patients out of the hospital, and can we keep them alive? If we are able to improve blood flow by any measurement and if we're able to improve the anatomy of the heart does not count, unless we are able to keep patients out of the hospital, reduce hospitalizations and improve survival. Those are the key elements.

It is very much along the line of what one expects for a new cancer drug. It is about keeping people alive. We will know when this trial completes. If we have a survival benefit, then this becomes the new standard of care.

TWST: Do you think it will be difficult for patients to get this treatment given what the reimbursement paradigm is?

Dr. Itescu: No, it will be very straightforward. If you demonstrate a reduction in hospitalization, you can calculate the pharmacoeconomic

value to the hospital and to the insurance company of what it means to be kept out of the hospital, so that change is easily quantifiable. If you keep patients alive, that's worth more than any hospitalization. So there are precedents, as in certain devices, as in cardiac rhythm therapy like artificial hearts that are all currently reimbursed in even sicker patient populations. There are well-established precedents of how insurance companies will pay for this type of therapy.

The good news is that because we were able to industrially manufacture and scale the production of these cells, we can produce them at a cost that is commensurate and appropriate for the high volume of patients that will be using the product. So I don't envisage a pricing point that is particularly different than most other cardiovascular advanced therapies. Again, cardiac rhythm therapy is well-established and now used in many patients with severe disease. That is a guide to pricing.

This is very different from recent cell therapy for cancers that have been talked about, as in the CAR-T approaches, whereby those type of cells are very different from ours and have to be used in a given individual autologously — that is, a patient's own cells are used for themselves. The cost of goods of scaling up on that patient cell is so high that it makes for a very, very high pricing point of the product based on the underlying cost-of-goods structure.

We don't have that issue at all because our cells are scalable. They are allogeneic, batched and off-the-shelf. There is an economy of scale, if you like, in terms of what we are doing, which is not applicable to patient-specific therapies. That allows us to price this in the appropriate range based on pharmacoeconomics.

or anti-IL-17 turns off just one of multiple arms of activated immune system. Our cells turn off all of these arms in tandem, and that makes them a very powerful immunomodulatory therapeutic.

We then start to look at which diseases are ideally suited. It is those diseases that are traditionally refractory or resistant to one or more biologic agents, such as graft versus host disease, which became a very obvious initial target because each of these monoclonal-targeted specific pathways have failed to change the natural history of graft versus host disease. This was our first obvious clinical target. We have been successful both in the clinic and now commercially in Japan, and hopefully in the U.S. commercially.

The second disease area involves diseases like TNF refractory, rheumatoid arthritis or Crohn's disease. Those are diseases whereby anti-TNFs have worked well as line agents, but a substantial number of patients, as in 30% to 50%, respond poorly or not at all. Those patients are amenable to our cells as second-line therapy. There are diseases where inflammation is at the core, and there have been no benefits seen with immunologic agents. That includes heart failure and inflammatory back pain.

So with heart failure, anti-TNFs agents have failed miserably. Recently, anti-IL-1 has shown some efficacy in the early post-myocardial-infarction patients but comes at the expense of severe side effects due to severe immunosuppression. We have focused on heart failure as an area that is a large to very large unmet need and with which inflammation is clearly at the core of progression of disease. Again, traditional agents don't seem to make a difference.

"I would expect the commercial distribution of the product will obviously require partnerships. We do not expect to be establishing our own distribution channels. We are in discussions precisely around on how to leverage the existing distribution channels of potential commercial partners on a global or a regional basis in the U.S. and Europe, etc."

TWST: You have already entered into a strategic relationship with Tasly Pharmaceutical for the deployment of this therapy in China, correct?

Dr. Itescu: That is correct.

TWST: The company just released a press release stating that once this agreement was closed, you received a $40 million payment.

Dr. Itescu: Yes, that is right.

TWST: Other than that, for the rest of the world, you are open to talking to others for partnerships?

Dr. Itescu: Yes. That is right. In fact, we are currently having discussions with a number of very prominent cardiovascular-focused companies. I would expect the commercial distribution of the product will obviously require partnerships. We do not expect to be establishing our own distribution channels. We are in discussions precisely around on how to leverage the existing distribution channels of potential commercial partners on a global or a regional basis in the U.S. and Europe, etc.

TWST: You have other indications in your pipeline. How did you decide on what those should be?

Dr. Itescu: It goes back to the underlying mechanism of action. We understand that these cells are very, very powerful immunomodulatory cells, meaning they are activated by a very active immune system and are able to release factors that turn off multiple arms of the immune system. That is very different from each of the monoclonal antibodies currently in use. An anti-TNF or an anti-IL-6

The third area that we are in Phase III is inflammatory back pain, which is the fundamental root cause of the severe pain associated with intervertebral disc degeneration. Here, the anatomy of the disc changes as the disc starts to degenerate. Immune cells come into the disc space and activate the immune cells; that results in severe pain that is very chronic.

As you know, there is a major opioid epidemic today because the vast majority of patients fail to respond to most agents, and many patients move on to chronic opioid usage. In fact, 50% of prescription opioid usage in the U.S. is for patients with chronic severe lower back pain. It is the number-one cause really of the opioid epidemic.

To the extent that we may have a product that gives long-term and durable pain relief as well as functional recovery, we may have a product that fits in well into the current treatment paradigm for patients. Most physicians are looking to dramatically reduce the usage of opioids in this very severe patient population.

TWST: That Phase III is in the United States?

Dr. Itescu: Yes. And that Phase III has completed a 404-patient enrollment that involves a 12-month follow-up of all patients, which is happening this quarter actually. We are very excited about this Phase III program. In an earlier Phase II trial of 100 patients, a single injection of our cells resulted in up to almost 50% of the patients having no pain for at least two years of follow-up, which is quite dramatic.

We are looking to both significantly reduce pain and improve function within the same patients. So we are not looking for a short-term reduction in pain. We are not looking for just pain. We are looking for durable long-term improvement in pain and function that is sustained. That would give us something that is completely unique and standalone in this field between nonsteroidal drugs, epidural steroids and, ultimately, the requirement for surgery.

TWST: Do you have any final thoughts for potential investors in Mesoblast today?

Dr. Itescu: We think 2019 is an extremely important year for us. We expect to be filing imminently with the FDA for our first product approval. We have a Fast Track designation for that product, so we hope to see it as a rolling BLA submission and an accelerated approval pathway.

Beyond that, we have two Phase III trials that are reading out, meaning the heart failure program and the back pain program. Those outcomes will be fundamental to the value creation of this company. As I said, we are in advanced discussions with a number of pharmaceutical partners as we need to put in place our distribution channels in various jurisdictions on the assumption that these Phase III trials will be positive.

TWST: Thank you. (KJL)

SILVIU ITESCU, MBBS, FRACP
CEO & Managing Director
Mesoblast Limited
55 Collins St.
Level 38
Melbourne 3000
Australia
+61-3-9639-6036
www.mesoblast.com
email: info@mesoblast.com