INVESTOR BRIEFING

1 September 2009

With Silviu Itescu, Executive Director, Mesoblast Ltd

Background
Mesoblast is a Melbourne-based biotechnology company commercialising a proprietary adult stem cell technology, called Mesenchymal Precursor Cells. It has established proof-of-concept with its technology and is now progressing Phase 2 clinical trials in the US and Australia for orthopaedic applications.

Mesoblast owns 38.4% of United States-based Angioblast Systems Inc., which is trialing the same adult stem cell technology in four Phase 2 trial applications, these being for (1) the treatment of congestive heart failure, (2) treatment of heart muscle following heart attack ,(3) expansion of cells in bone marrow transplantation and (4) use in conjunction with LVAD implants.

Topic: Angioblast Update – Progression of Four Phase 2 Trial Applications

The CEO Transcript: A few months ago, you released some results from the first 20 patients (the first and lowest-dose cohort) in your Phase 2 Heart Failure trial being conducted in the US. There was a 37% mean increase in the treatment group in heart ejection fraction after three months versus a mean 11% decline in heart function in the control group. The results looked stunning. Were you surprised by those results?

Silviu: I was very pleased by those results. I was surprised in the sense that in most of our preclinical large animal studies, this lowest dose was the least effective and we were hoping to get at least a degree of improvement with the higher doses. Therefore, we were very pleasantly surprised to obtain this sort of an effect with the lowest dose to date. The second part of this was that we were very pleased to see a relatively early effect, within three months, even though the primary endpoint (period) is six months.

The CEO Transcript: With some of the higher doses in the preclinical studies, did you generate a similar effect to what you've seen earlier on in this trial?

Silviu: We saw this sort of effect with the higher doses in sheep models of heart failure. So this level of improvement is what we were hoping for, based on our results, but it is a whole level different than any other therapy out there is currently able to generate. The next dose is three times the size, and that cohort is currently well underway. There are three cohorts. The third cohort will be another two-fold higher again. So in total a six-fold increase on the first dose.

The CEO Transcript: In the sheep studies you conducted did you see a dose response and was there a sustained effect?

Silviu: We did (see a dose response). We saw the best results with the highest dose. The sheep studies were taken out to about three months of follow-up, because that's all we had to do. That's pretty much the equivalent to what you would follow-up in human terms for say six or eight months. So from that point of view they were sustained, which is why our primary endpoint in the human trials is six months.

The CEO Transcript: And in the sheep studies, was it just a one off delivery of cells?

Silviu: Yes.

The CEO Transcript: How do the patients receive the cells in this current trial?

Silviu: The patients go into a day procedure in a catheter lab in a major medical centre. The cardiologist will do a standard cardiac catheterisation procedure through the groin, with the patient under a local anaesthetic. Using a special catheter made by Johnson & Johnson, they are able to navigate the catheter into the chamber of the left ventricle. That catheter is able to detect live muscle that is damaged but not dead, so we can differentiate between muscle tissue and scar tissue. The cells are delivered in multiple injections in live, but damaged muscle, and we steer clear of thin scar tissue. The objective is to try to stimulate the live muscle tissue to start dividing and replicating.

The CEO Transcript: Do you know if the cells migrate, or do you give multiple injections as part of the procedure?

Silviu: We conduct about 20 small injections and the cells have an effect locally.

The CEO Transcript: How does this compare to any other therapies that are approved, or in development, in terms of stimulating heart muscle regrowth?

Silviu: There is nothing that's approved that has shown heart muscle can repair or regenerate. There have been a number of failed cell-based technologies that have attempted to do this, the majority of which have used patient's own cells. To our knowledge, Angioblast has the most advanced approach towards improving heart function in this very sick population.

The CEO Transcript: Can you just describe the condition of the patients in this heart failure trial, and was there any physical improvement noticed by the patients following the treatment?

Silviu: These patients are what we would call Class II/III heart failure patients. These are patients who have pretty advanced symptoms of heart failure with shortness of breath, difficulty in walking and difficulty in exercise tolerance, and whose symptoms reflect the loss of heart muscle as measured by a reduced ejection fraction. They're sick patients who over the next couple of years have a significant risk of dying because of continued deterioration in their heart muscle function.

Not only have we seen an improvement in ejection fraction but also we've seen improvements in a number of other very important parameters that are associated with clinical symptoms and progressive risk to mortality.

The CEO Transcript: What about the safety aspect of this therapy? What are the main risks with this therapy? Is the actual procedure for injecting the stem cells a risk for the patient and the technology?

Silviu: The injection procedure itself is always a potential risk because it's a needle-based catheter that's injected into the heart muscle. The good news about using this particular catheter is that it's been trialled in over a thousand patients to date, so it's got a large database of human data. And in the hands of experienced cardiologists, the risk of any mis-events from the needle procedure itself is pretty low. To date, in either Cohort 1 or 2, we have not had any adverse events whatsoever, related either to the catheter procedure or to the cells.

Particularly, with respect to the cells, we are really pleased. We're using universal donor cells from one donor into totally unrelated recipients. A theoretical concern could have been that there might have been an immune response against these cells, and that immune response might have had an adverse impact on these patients. We've had no adverse events whatsoever to these allogeneic or universal donor cells, which is terrific at this point in time.

The CEO Transcript: What's the timeline for this trial in terms of completing the enrolment, completing the follow-up and releasing the results?

Silviu: We anticipate completing total enrolment of 60 patients by the middle of the first quarter of next year. In terms of data analysis and release of data, we certainly expect to release full six-month analysis for each cohort as we move forward. So that will be ongoing release of data to the public. In order to move from one cohort to the next higher dose, we only need 30-day safety. As soon as we have completed 30-day safety of the entire second dose cohort, and have cleared the United States Food and Drug Administration (FDA) requirement to move to the next cohort, we'll be announcing that. And I would hope that that's fairly soon.

Once we have significant six-month data analysed from both first and second cohorts, we may actually be in a position to consider what a large pivotal trial would look like, and what the endpoints may look like.

The CEO Transcript: So it sounds like you've finished dosing the second cohort of patients or you're close to?

Silviu: We're certainly close to it, yes.

The CEO Transcript: After that trial is finished, you'll be considering whether you move forward to Phase 3, whether further Phase 2 trials will be required or whether you can start planning for a Phase 3, is that right?

Silviu: That's right. The issues are around how strong the data are within the 60 patient group, firstly. Secondly, what are the costs of a Phase 3 (trial). And thirdly having a potential partner in place to assist us with those Phase 3 costs, assuming that those costs would probably require a partner rather than our ability to raise capital in a public market.

The CEO Transcript: So it's likely that you will seek a partner to assist you with the Phase 3 trials?

Silviu: I think it's likely, for two reasons. A Phase 3 trial in a cardiovascular indication is large and is expensive. But in addition to that, the ability to sell and market a product in the cardiovascular space requires a specialised sales force capability, and I think that is clearly outside of our expertise. I think the sooner we lock ourselves into a partnership with a company that has cardiovascular expertise, the sooner we would want them to have input into the Phase 3 clinical trial design, and the organisation of that.

The CEO Transcript: So you're hoping, if all goes well, to start a Phase 3 trial next year some time?

Silviu: Yes.

The CEO Transcript: And that would take a couple of years to complete?

Silviu: It would probably take 12 to 18 months to reach the primary endpoint depending on the recruitment. The advantages of our allogeneic cell therapy approach is that it's a very easy clinical trial to recruit. We've been extremely pleased by how rapidly we've been able to recruit the patients to date. Over several months we've recruited the majority of 40 patients in only four centres. So it would be quite easy to scale our program up to about 10 to 15 centres across the United States, all of which have expertise in using this type of catheter technology. And that would allow us to recruit rapidly in a pivotal trial.

The CEO Transcript: If you continue to get this sort of clarity in the results, would that mean that potentially your numbers might not have to be that high for a Phase 3 trial?

Silviu: That's right; we're talking hundreds, not thousands.

The CEO Transcript: Looking at the commercial potential of this therapy, it seems like a widely applicable therapy that may benefit a large number of people?

Silviu: The heart failure market is huge. There are about five million patients in the United States alone with congestive heart failure. We're targeting, at the moment, the sickest 40% of those patients with an ejection fraction of 40% or below. The reason we're targeting that population is because it's known that any further lowering of ejection fraction in that group of patients correlates with relatively rapid progression to death. So if we can have a significant impact in that group of patients, we'll have an approvable product that can justify an appropriate reimbursement, and that could be widely used in as many as 40 per cent of the heart failure population, which really is a spectacular market opportunity.

The CEO Transcript: That's about two million people in the US.

Silviu: Yes. Around two million people in the US. There are 500,000 new cases per year, so that's an additional 200,000 potential patients per year.

The CEO Transcript: Do you have any idea of what a sustained treatment would look like? Would it just be a once-off therapy or would it be an annual therapy for patients?

Silviu: It's very hard at this point to envisage. I think all we can say is all of our modeling and our planning for an US FDA approval process with Phase 3 trials are based on a single injection with a 12 to 24-month sustained primary efficacy. Beyond that, I think it is too early to say.

The CEO Transcript: Do you have any idea of what you could charge for this type of a treatment?

Silviu: Yes, we do. I think the pharmaco-economics would dictate that if we were able to impact on the clinical signs and symptoms of heart failure and improve heart muscle function, the way we're seeing it at the moment, then what you're really impacting on is the current scenario of repeated hospitalisations and potential mortality. We think that on that basis the pharmaco-economic justification of $15,000 per therapeutic dose is easily justified.

The CEO Transcript: Moving on to results from the other trial that you announced in June this year in the bone marrow transplantation, where more positive early data was received in a 30 patient Phase 2 study. In the first five patients the medium time to engraft was 15 days; two weeks faster than without the use of your adult stem cells. Can you just explain this application of using adult stem cells (Mesenchymal Precursor Cells) for bone marrow transplantation?

Silviu: Sure. A very unusual property of our Mesenchymal Precursor Cells is that they seem to secrete some interesting growth factors that stimulates hematopoietic stem cells to grow by up to 40-fold. That has very significant implications for any indications where hematopoietic stem cells might be useful.

Hematopoietic stem cells are very useful for rebuilding bone marrow for bone marrow transplant patients. The real potential benefit would be if we could increase the pool of patients who would receive an allogeneic hematopoietic bone marrow transplant. Because at the moment the only kind of bone marrow transplants that are routinely being done are using your own haematopoietic stem cells, which in a setting of leukaemias and other bone marrow cancers is again a very heterogeneous and a very iffy proposition from one patient to the next.

If we could use a source of allogeneic hematopoietic cells that don't cause graft-versus-host disease - which is a big risk with an allogeneic bone marrow transplant - then there's a very large market opportunity. It turns out that cord blood - the hematopoietic stem cells from cord blood - do not seem to cause graft-versus-host disease, or to a much lesser extent that hematopoietic cells from adults, and so they are preferred use for this kind of an approach. However, the problem is the amount of hematopoietic cells in cord blood is trivial, and so they do not engraft very well.

So in conjunction with clinicians at MD Anderson Cancer Center in Texas, we've initiated a trial under an Orphan Drug Designation where our cells are being used as feeder cells to expand cord blood hematopoietic cells. As I said, the results to date indicate that we can expand them by about 40-fold. That 40-fold expansion, when those cells are implanted in an individual who needs an allogeneic bone marrow transplant, seems to engraft, at a very high frequency, and in half the time approximately than non-expanded cord blood.

The CEO Transcript: Can you quickly describe that bone marrow transplant procedure, when and why it is used?

Silviu: Yes. So in patients who have leukaemias or lymphomas, or other cancers that involve the bone marrow, in order to eradicate the cancer from the bone marrow all together, they need to undergo high-dose chemotherapy and/or radiation therapy. The problem with the level of high-dose chemotherapy needed to completely remove the cancer is that it also destroys all the other elements in the bone marrow. So the only way to try to cure them of their underlying cancer is to kill the healthy bone marrow. The idea is to salvage or save the patient by transplanting healthy bone marrow back. The problem with transplanting a patient's own bone marrow, which might have been harvested earlier, is that it often contains the same leukaemic cells that you were trying to get rid of.

So, ideally, if you can get an allogeneic source of bone marrow cells that could rebuild the patient's bone marrow, you could, on the one hand, kill the cancer and rebuild the bone marrow quickly and get them through that period, within the first couple of weeks, when they are at most risk of infections and death. In the absence of a healthy bone marrow you get infections and you die. So the idea here is to try to expand the options for patients with leukaemias and lymphomas

The CEO Transcript: How will that change the current market?

Silviu: We could expand that market by maybe two to three-fold over the numbers of patients today who are getting allogeneic cells.

The CEO Transcript: What is the timeline for the Phase 2 program currently underway?

Silviu: The exciting thing about this particular clinical trial is that it is under an FDA Orphan Drug Designation. It's a relatively small number of patient population, less than 200,000 per year in the US. But the FDA is looking to encourage companies like ourselves to develop products for this type of patient population. And they're encouraging us by fast tracking the clinical development and approval process. We think, on the back of data within this 30 patient population, we'll be able to go back to the FDA and talk about what a pivotal Phase 3 trial would look like. We anticipate that the size of that sort of trial would be around 100 patients.

The CEO Transcript: So, potentially, next year Angioblast could be in two pivotal trials for two different indications.

Silviu: Yes. And the end point for this Phase 3 trial would be probably around 100 days or so. It would be much shorter than any other indication that we're targeting.

The CEO Transcript: For both of these indications for heart failure and for bone marrow transplant, do you know if two pivotal trials would be required in the US?

Silviu: It's too early to say at this point. Cardiac, potentially (two trials). For bone marrow transplant, probably not. Therefore, this (bone marrow transplant) probably represents the fastest road to market for us. The other part of this is that bone marrow transplant patients all get treated at very specialised centres around the US, and those centres are finite in number. The type of sales force needed to manage these centres would be fairly small. So, potentially, we might be able to build a small, specialised sales force and not necessarily need a partner at all for this program.

The CEO Transcript: So this could potentially be your lead program in terms of getting to market first then?

Silviu: Yes.

The CEO Transcript: Another application you've found for your stem cells is incorporating them with an LVAD implantation procedure. Can you explain how that trial eventuated?

Silviu: We were actually approached by a consortium of surgeons in the US who had obtained a grant from the National Institutes of Health to study a cell type in conjunction with implantation of an LVAD - left ventricular assist device - in patients in Class IV heart failure. Having seen the results we've obtained in our initial Class III heart failure patients (discussed earlier), and the fact that we provide an allogeneic uniform cell product, they approached us to see whether we were interested in providing our technology to be used in that particular trial.

All of these patients get LVADs when they are put on the heart transplant waiting list. The average time they are waiting for a heart transplant is about three months whilst they're on a heart pump. The objective of this trial is to see whether during that three-month period, implantation of our cells into the native, but end-stage heart, might potentially improve the function of that native heart.

We hope that perhaps what we might see is some degree of functional recovery in the native heart. Potentially, if there is recovery, and that recovery is significant, the patient may even come off the transplant waiting list, although that's a very long shot.

The CEO Transcript: Is Thoratec involved with this trial or are you just using a Thoratec device?

Silviu: Well it's the Thoratec device in this trial, and they've certainly collaborated in the trial.

The CEO Transcript: When do you expect that trial to start recruiting?

Silviu: I expect it will start recruiting over the next month. We've got IND (Investigational New Drug) clearance and we've got ethics clearances from a number of sites already. And this 80 patient trial is fully paid for by the National Institutes of Health.

The CEO Transcript: So that trial is due to complete some time in the next year?

Silviu: We hope to complete recruitment within 12 months.

The CEO Transcript: Is there opportunity for some interim data coming out over the next 12 months in that trial?

Silviu: Absolutely. Again, it's a two-dose trial, both 40 patient cohorts where 10 patients are controlled and 30 patients get a particular dose of our cells. I would expect that there would be interim data, at least when the first cohort is completed.

The CEO Transcript: And the fourth application that Angioblast is investigating with the Mesenchymal Precursor Cells is for use in patients who have had a heart attack, to inject the cells into the heart to repair the damaged heart. Is that correct and how is that trial progressing?

Silviu: Well, there's two ways that our cells can be applied to heart attack patients. One is exactly what you just described. So after the heart attack you find those patients – maybe the minority of patients, I would say around 20% of patients who have poor function despite having had all the therapy upfront – and then bring them back and inject them with the same catheter into the damaged heart muscle, several weeks out. That trial is ongoing.

The CEO Transcript: And the other option?

Silviu: A more preferred way of delivering our cells, because of the fact that they are universal in nature and "off-the-shelf", would be to inject them immediately at the time a patient undergoes angioplasty and stent placement. Unlike any other patient-specific cell therapy, our allogeneic cells would be the only type of product that would be available in that immediate, acute coronary setting. From our point of view, it makes a lot more sense to be injecting the cells at the time of an angioplasty and stent placement to prevent the damage that otherwise occurs over the next couple of weeks.

This is a program that we're rapidly moving forwards. We'll be making announcements around the completion of the preclinical data and how we're moving forward with a clinical trial in that area over the next few months.

The CEO Transcript: So you seem to be finding new applications for the stem cells for cardiac purposes. Have you got enough to keep you busy now, or are there more potential applications that you're looking at?

Silviu: I think for the time being Angioblast has a lot on its plate. These are expensive applications and they are important for a company that's moving into the cardiovascular area. It's about risk mitigation and broadly capturing the large market opportunities. But these are big and complex trials, and I think it underscores the need for partnering some, or most of these applications.

The CEO Transcript: And just finally, a $10 million capital raising for Angioblast has just been completed. Where were the majority of those funds raised?

Silviu: The majority of those funds were raised from existing and new institutional shareholders who are familiar with the story and have had an opportunity, over time, to evaluate the technology and how it has progressed. Among them were several Australian institutions. I think it sends a very strong signal of the support for both Angioblast and Mesoblast that the Australian investment community is backing the story up in that way.

The CEO Transcript: What stage of development will those funds take the company to and will further funding be required?

Silviu: The use of the capital is primarily to complete some of these clinical Phase 2 programs and to put the company on a runway to a public liquidity event. It's pretty clear that both the US and the Australian public markets are now open for biotech listings. The US just had its first two IPOs in the last week, and they were both very successful. I think we're going to see a lot more activity over the next few months in the US. Similarly, the Australian public markets are looking very robust. We're hoping that over the next six to nine months there will be the ability to list Angioblast on one or other public markets, with a view to obviously raise significantly more capital for the next level of clinical trial activity.

The CEO Transcript: Can you say anything about the pricing of this capital raising? Was it at a premium to the last time Mesoblast put money into Angioblast?

Silviu: The most recent valuation of Angioblast associated with a capital raising was at a 60% premium to the last time Mesoblast invested, so we expect Mesoblast's investment to continue to increase significantly.

The CEO Transcript: Thank you for your time.

Terms

Autologous adult stem cells – Stem cells derived from patient's own bone marrow
Allogeneic adult stem cells – Stem cells derived from unrelated source
Mesoblast core technology – Mesenchymal precursor stem cells
Hematopoietic stem cells – develop into all types of blood cells

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This is an edited record of interview conducted by The CEO Transcript with Silviu Itescu, Executive Director of Mesoblast, conducted in August 2009.