INVESTOR BRIEFING

October 2009

With Silviu Itescu, Executive Director, Mesoblast Limited

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 United States for spine fusion applications and a Phase 2 trial in Melbourne for the prevention of knee osteoarthritis. The company intends to launch its first product for the treatment of non-union bone fractures in Australia in 2010.

Mesoblast owns 38.4% of US-based associate company, Angioblast Systems, which is applying the same adult stem cell technology for the treatment of heart disease, with three Phase 2 trials underway in the US. It is also conducting a Phase 2 trial for expansion of cells using MPCs in bone marrow transplantation procedures.

Topic: New Clinical Program for Intervertebral Disc Repair & Program Update

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Spinal Treatment

The CEO Transcript: Mesoblast is currently applying its adult stem cell technology in the repair of non-healing bone fractures, in the prevention of knee osteoarthritis and in spine fusion. It recently released some positive preclinical data in the repair of damaged intervertebral discs. Can you explain this new potential application and how it fits into the Mesoblast portfolio of products under development?

Silviu: It is part of our global spinal franchise, because we are developing quite a product selection for the spine, which is the fastest growing segment in the orthopaedic industry. The primary problem in the spine is intervertebral disc disease, which is the number one cause of low back pain and can result in severe disability and incapacitation. There are as many as four million people in the United States alone, on an annual basis, who have severe low back pain requiring some type of therapy.

The CEO Transcript: What type of therapies are currently available for this type of disc damage in the spine?

Silviu: Analgesia, bed rest and ultimately steroid injections into the disc space. About 50% of patients who need a steroid injection will fail to report a benefit so it is that segment that we think will be appropriate for our disc repair product. That could be as many as two and a half million patients a year. For that group of patients, there is nothing that works, and it is a segment of that group that goes on to be a candidate for either an artificial disc replacement or a spinal fusion procedure. Both of those are major surgical operations. If you can develop a non-invasive treatment to reduce pain, retard cartilage degradation and disc degeneration, you really have a major market opportunity.

The CEO Transcript: So what you are looking to do potentially is to work further up the line with an earlier stage treatment?

Silviu: Yes. That earlier stage disease accounts for maybe 10 times as many patients as for the spinal fusion endpoint. That's always been our number one strategy, and for which there are no competitors. What we've accomplished, and we announced to the market in September, was a very successful result in a randomised controlled study of 36 sheep where we demonstrated that a single low-dose injection of our allogeneic cells into severely damaged intervertebral disc, resulted in dramatic reversal of the degenerative process, regrowth of disc cartilage and sustained normalisation of disc pathology, anatomy and function.

The CEO Transcript: Over what period did this occur and what type of model was used?

Silviu: Over six months, so effectively it was permanent. The model that we used was injection into healthy discs in sheep of an enzyme that destroys the anatomy of the disc. You can see that on X-ray and on MRI. The disc looks like chronic arthritis of the disc in humans. That's what you see normally in people who subsequently have to undergo spinal fusion.

Therefore, after three months of destruction we then tested either a single injection of our cells or a control carrier scaffold of Hyaluronic Acid on its own. We then followed the animals up for another six months.

Only the discs that were injected with our cells, in fact with a very low dose of our cells, a dose about 10-fold lower than the dose we're currently using for our spinal fusion clinical trials, were found to have become completely normalised and indistinguishable from healthy non-degenerated discs.

The CEO Transcript: Were there any effects seen in the placebo Hyaluronic Acid group?

Silviu: No effects. So in the placebo model six months later, the discs looked as horrible and destroyed as they were at baseline.

The CEO Transcript: Does the spine of the sheep compare reasonably well to the spine of a human?

Silviu: Absolutely. The spine of a sheep is the standard model for which we tested our spinal fusion product for bone repair, and the standard model for which many of the other spinal fusion products, like BMP2, were tested in. It's a model for which artificial discs have been tested in.

The CEO Transcript: How does this change your commercialisation plans for spinal treatment products, including the spinal fusion applications that are currently in Phase 2 trials?

Silviu: There are two aspects to this. Number one is the size of this market. Conservatively we estimate potential revenue generation from the intervertebral disc repair product alone, assuming that we get the results that we think we will in the clinic, to be in excess of $2 billion per year. It's a huge market opportunity for us, based on fairly conservative penetration rates and conservative pricing strategies.

The second advantage of this potential market is that the timelines, in terms of primary endpoints of Phase 2 and pivotal trials, are significantly shorter than for our spinal fusion trials. If we can demonstrate significant improvement over a six-month period as an endpoint then that becomes a much faster path to product registration and revenues than for our spinal fusion products.

The CEO Transcript: What is the primary endpoint period for pivotal spinal fusion trials?

Silviu: Between 12 and 24 months. That's because there's an alternative treatment. The alternative in spinal fusion is autograft, bone from the hip. The FDA (US Food and Drug Administration) expects you to demonstrate sustained equivalence to the gold standard. In intervertebral disc repair, we're talking about a patient population where there is no alternative therapy.

The CEO Transcript: Are there any other groups that have trialled some type of therapies for regenerating damaged spinal discs?

Silviu: To our knowledge there's nobody else out there that has these kinds of data. We are in the process of submitting an Investigational New Drug submission to the FDA, and we expect to commence a Phase 2 trial next year. As a result of the capital that we raised back in March, we have sufficient funds earmarked to complete the proposed Phase 2 trial for intervertebral disc repair.

The CEO Transcript: How large will that trial be and how long do you expect it will take to complete?

Silviu: We're aiming to do a 48-patient trial with a six-month endpoint. If everything goes to plan, we hope we can complete it by the end of 2010.

The CEO Transcript: In that Phase 2 trial, how many doses will you be trialling?

Silviu: We would test two doses versus a placebo, in much the same way as we've just done the sheep study.

The CEO Transcript: And then you'd look to move into pivotal trials in 2011?

Silviu: Yes.

The CEO Transcript: What are the risks involved with the intervertebral disc repair procedures you're proposing?

Silviu: I think the risks are pretty minimal, no greater than having a steroid injection into your back for severe back pain. There is no major surgery involved, it would be performed under a local anaesthetic as a same-day procedure. We have not seen any adverse events related to the cells in our sheep trials.

The CEO Transcript: Does intervertebral disc repair now become more of a focus within your spinal repair programs?

Silviu: This becomes a top priority and I think you'll see it gradually overtake our spinal fusion programs in terms of importance. It just demonstrates again, why you've got to be flexible and have multiple simultaneous programs, and be open to good preclinical results and be able to slot those into your overall lists of priorities.

The CEO Transcript: How do you expect to commercialise a product like this? Will you look to partner it out?

Silviu: This is very different from our spinal fusion products in that the spinal fusion products will require major surgery. For the fusion products there's an existing sales and marketing industry that we would need to use as our distribution partners because of the associated hardware and surgical requirements. For intervertebral disc repair, we're talking about a simple percutaneous injection under a local anaesthetic and under X-ray guidance.

The CEO Transcript: As a day procedure?

Silviu: Absolutely. It's not clear exactly who would be our principal distributor. It may be an established spinal industry player, or it may be a biologics company, or perhaps we could even build our own sales force. I think it's the type of product that could lend itself to any one of a number of different sales and marketing and distribution strategies.

The CEO Transcript: Will you continue with your spinal fusion trials?

Silviu: Yes. There's clearly still major existing markets in spinal fusion. There's 500,000 patients per year or more, in the US who undergo spinal fusion surgery. And we're in the midst of two Phase 2 trials; one for lumbar minimal invasive spinal fusion, and one for cervical minimal invasive spinal fusion where our cells get implanted in between the two vertebras where the disc used to be. The objective is to create a bony bridge between the vertebra above and below to eliminate pain and instability of the joint.

The CEO Transcript: So essentially, you're immobilising that part of the spine?

Silviu: That's right. The abnormal movement of that part of the spine is what causes the pain. So once you've taken it out of action the pain is relieved. It's a pretty crude procedure, but at the end of the day when you've lost your disc cartilage, it's one that does work. This is an existing market opportunity for us, and we're going through our Phase 2 trials. Those trials are recruiting well. Through 2010, we're anticipating having at least interim results from both the lumbar and the cervical spine fusion to allow us to make some strategic decisions around which of those areas we would move forward with a pivotal trial.

Knee Osteoarthritis

The CEO Transcript: In January this year, you received ethics approval to commence a Phase 2 trial in Melbourne, applying the Mesoblast adult stem cells to prevent knee osteoarthritis. Can you explain this market and how you intend to commercialise your technology for this indication?

Silviu: Knee osteoarthritis is a very large market opportunity; probably the largest of all of our orthopaedic opportunities. It starts from early arthritis of the knee after sporting injury and trauma, to end stage arthritis where you have lost most of your cartilage lining the joint, in people who are older or overweight and have had a long history of knee pain. The number of patients with this disease is as high as 10 million in the US. It is a huge market opportunity. The objective is to have an injectable product into the knee joint to improve cartilage in the knee joint. You want to delay or remove the need for a knee replacement. The question is how best to tackle it, and whether we do that on our own or with a partner. That type of pivotal trial is going to be quite large. It becomes an obvious indication for a partnering opportunity with a major pharmaceutical company.

There is another opportunity for us, which is starting much earlier on with patients who have post-traumatic knee injury, where there's a small focal lesion of cartilage loss and where our cells could be used to be locally implanted by arthroscopy and repair that focal defect. That's termed an osteochondral defect repair. That's an area that we think the type of pivotal trials are going to be much smaller in size, more aligned to a device-like program, where we could manage our own program independently of the necessity for a partner.

The CEO Transcript: How is the Phase 2 knee osteoarthritis trial progressing?

Silviu: The objective there is to treat early after post-traumatic knee injury, where the incidence of osteoarthritis is as high as 50% at as early as 12 months. We're trying to see by MRI (Magnetic Resonance Imaging) whether we're able to retard the disease. We're making good progress with recruitment, and we hope to report on interim results early next year.

The CEO Transcript: Can you measure accurately how effective your treatment is?

Silviu: MRI is a reasonable measure of disease progression. But remember, the primary objective of this study initially is to demonstrate safety of an intra-articular injection. We certainly hope to also show effectiveness in this trial, but to definitively show improvement we will need larger patient numbers.

Non-union Long Bone Fracture Repair

The CEO Transcript: Mesoblast is looking to introduce a product into the Australian market next year for the treatment of non-union long bone fractures. Can you explain the rationale of introducing this product into the Australian market given its small market size, and how it is that you can start commercialising this product so quickly?

Silviu: Because of the success of our pilot trial, many patients have approached us directly as well as many orthopaedic surgeons around Australia who have a list full of patients with non-unions. It's really a service that we'd like to provide given that the technology appears to work, and these patients have no alternatives.

We're hopeful to have approval from the TGA (Therapeutic Goods Administration) for our manufacturing process quite imminently. Under the Special Access Scheme, hopefully it would allow us to be able to provide that treatment to patients with non-unions broadly around Australia.

The CEO Transcript: What happens to patients if they can't have their bone fractures repaired?

Silviu: Well the alternative, in many cases, is amputation.

The CEO Transcript: Why can't this be done through insertion of metal pins?

Silviu: These are patients who failed pin placement, which is the standard therapy for this type of fracture. So patients who have non-union are those who have undergone standard surgery with pin placement, and often even autografts, and have failed those therapies. We represent really the last possible treatment stage.

The CEO Transcript: Would Mesoblast receive revenue from this early product?

Silviu: Yes.

The CEO Transcript: Are there any other benefits of having this technology out in the marketplace for that initial application?

Silviu: In addition to early revenues, it provides us with clinical data that can be used for follow-on approvals for other applications.

The CEO Transcript: Do you think that you would potentially be in a position to be treating patients in 2010 with that product in Australia?

Silviu: Yes.

Partnering

The CEO Transcript: In partnering your programs, do you think that you will choose one commercialisation partner for all applications, or will you split up the applications with several marketing partners?

Silviu: We are still open either way. It would make a lot of sense to work with one large pharmaceutical partner who has an interest broadly around orthopaedic and cardiovascular products. But I think it is also realistic, too, to imagine very different types of companies for our spinal programs and for our arthritis programs.

The CEO Transcript: Are those partners looking for Phase 2 data before they sign a deal?

Silviu: Yes, in general, they want to see Phase 2 results and proof that we're able to move into Phase 3/Pivotal registration trials relatively smoothly. In some of the spine areas, it is possible that the Phase 3 trials might be relatively inexpensive to conduct. On the back of strong Phase 2 results, we may be in a position with our spinal products to go through to complete Phase 3 trials on our own, and more important for us, to retain a significant component of the final market opportunity.

The CEO Transcript: Thank you for your time.

Silviu: A pleasure.

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

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