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PRESS RELEASE

Positive Biomarker Results in World-First Stem Cell Knee Osteoarthritis Trial

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- **MRI shows HiQCell therapy has potential disease modifying effect by slowing cartilage degradation**
- **Cartilage breakdown marker (CTX-II) stabilises in HiQCell treatment group and increases significantly in placebo group**
- **Inflammation and osteoarthritis biomarker (macrophage inhibitory factor (MIF)) decreases significantly in HiQCell treatment group and increases in placebo group**
- **Discovery that biomarker MIF can be used to accurately measure the anti-inflammatory effects of stem cell treatments**

Regenerative medicine company, Regeneus (ASX: RGS) announced today important findings from the biomarker analysis of its landmark double-blind placebo-controlled clinical study of HiQCell® for knee osteoarthritis. The results demonstrate a molecular basis that explains how HiQCell may slow cartilage degradation.

The study results show two statistically significant findings:

- Treatment with HiQCell stabilised levels of CTX-II in urine, an important cartilage breakdown molecule that increases in patients with osteoarthritis as the disease progresses. Patients that received the placebo showed an increase in CTX-II over the course of the study whereas patients that received the HiQCell treatment showed no increase.
- A second important biomarker of inflammation and osteoarthritis, Macrophage migration inhibitory factor (MIF) increased in the serum of the placebo group and decreased in the treatment group. MIF induces the production of enzymes that degrade cartilage and the reduction of MIF levels in the treatment group is likely to have reduced cartilage degradation via decreased enzyme levels.

Regeneus CEO, Professor Graham Vesey, said: "These biomarker results are important as they provide medical specialists with a molecular basis that explains how HiQCell slows cartilage degradation. CTX-II is well recognised as a key measurement in trials to determine whether a treatment is slowing the progression of osteoarthritis. While MIF is recognised as an important inflammatory marker, to our knowledge this is the first time that it has been demonstrated that you can use MIF to measure the anti-inflammatory effects of cell therapy. Due to the significance of these findings, we have sought patent protection on the use of biomarker measurements, including MIF, for determining when to administer stem cell therapies."

Dr Diana Robinson from Sydney Sportsmed Specialists, who has treated 117 joints across a cohort of 54 HiQCell patients, said: "The lack of disease progression and the biomarker results indicate that HiQCell treatment may have a disease modifying effect. This correlates well with the post-treatment MRI results I

have observed in many of my patients. This means that I can now use the measurement of biomarkers, such as MIF, to monitor HiQCell treatments and importantly to determine when additional injections of stem cell treatments should be administered. I look forward to working with Regeneus on future studies."

Results

The study showed that the HiQCell treatment was safe and clinically feasible. HiQCell treatment was well tolerated by patients and there were no major safety concerns and no joint infections during the course of the study.

Additionally, the study revealed that HiQCell treatment is effective at reducing pain. Both treatment and placebo groups experienced a large and statistically significant decrease in total pain score from baseline. A significant effect in the placebo group was not unexpected, as it is well known that placebo treatment can decrease pain in osteoarthritis trials.

The potential disease modifying effects of HiQCell therapy were investigated using MRI T2 mapping, which revealed that loss of cartilage was slower than expected at the 6 month post-treatment time point. The analysis was performed by Qmetrics Technologies, an independent contract research organisation that specialises in MRI imaging. It was found that both groups exhibited a greater proportion of participants remaining stable than those progressing. Although all participants met the radiographic inclusion criteria the MRI analysis showed that prior to treatment there were significantly more participants with advanced cartilage damage in the treatment group. This would tend to predispose the treatment group toward an accelerated progression of OA, which was not observed.

The study also established a molecular basis for the decreased cartilage degradation observed in the treatment group. Serum cytokine analysis was undertaken at the Australian Proteome Analysis Facility (APAF) at Macquarie University. The analysis indicated that HiQCell treatment reduced inflammation at both 4 and 24 weeks compared to the placebo group. The key cytokine was MIF, which was significantly reduced in the treatment group at 4 weeks and 24 weeks ($p<0.0001$). MIF induces the production of enzymes that degrade cartilage and the reduction of MIF levels in the treatment group is likely to have reduced cartilage degradation via decreased enzyme levels. Cartilage degradation can be measured by quantifying a specific collagen fragment in urine (CTX-II). A 31% increase in urinary CTX II was observed between baseline and 24 weeks in the placebo group ($p=0.04$). The levels of CTX II decreased in the treatment group, which was unexpected given the MRI analysis indicated the group contained significantly more participants with advanced cartilage damage at baseline. The decreased MIF and concurrent reduction of CTX-II correlates well with the Qmetrics T2 mapping MRI results for the treatment group.

Regeneus intends to submit peer-reviewed papers for publication on these results.

About the Study

The Osteoarthritis Stem Cell Advanced Research Study (OSCARS) was a randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of Regeneus' autologous in-clinic cell therapy HiQCell® for the treatment of human knee osteoarthritis. The study was a world-first and is registered with the Australian New Zealand Clinical Trials Registry.

The 20 participants in the treatment group received the HiQCell procedure, which involved harvesting a small amount of adipose tissue using a mini-liposuction procedure, isolation of the regenerative cells from the adipose tissue, and injection of these cells into the patient's arthritic knee. The cells are a mixture of adipose-derived stem cells, stromal vascular fraction cells and adipocytes. The 20 participants in the surgical placebo group underwent the liposuction but received an intra-articular injection of saline rather than their cells.

Patients aged >40 years were eligible to enter the study if they had knee osteoarthritis, graded as Osteoarthritis Research Society International (OARSI) grade 1 or 2 joint space narrowing in either medial or lateral compartments and / or osteophyte grade 2 or 3 in the medial or lateral compartment.

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To enable an assessment of cartilage degradation MRI T2 mapping was performed at baseline and 24 weeks post-treatment. This type of MRI imaging indicates areas of increased or decreased water content, which generally correlate with cartilage damage. In addition, serum and urine samples were collected at baseline, 4 weeks and 24 weeks post-treatment to enable the analysis of biomarkers related to inflammation and cartilage degradation.

Each patient received an injection into one knee. The patients and the treating medical staff were not aware of which patients were receiving HiQCell treatment and which patients were receiving the placebo control.

About HiQCell

HiQCell is a proprietary cell therapy which is prepared from a small amount of the patient's own adipose (fat) tissue. Adipose tissue is readily available and contains a rich source of regenerative cells, including mesenchymal stem cells, which work to reduce inflammation and also promote regeneration and repair of tissue. HiQCell is prepared in-clinic by a skilled technician under the supervision of the treating medical practitioner.

About Regeneus

Regeneus is a Sydney-based regenerative medicine company that develops and commercialises proprietary technologies for the preparation of point-of-care and off-the-shelf cell therapies using adipose (fat)-derived regenerative cells for the treatment of musculoskeletal and other inflammatory conditions in humans and animals.

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