CelGro® study results open up new US market access strategy

- **US 510(k) pilot animal study results indicate CelGro® facilitates superior nerve regeneration when compared to the market leading nerve repair device,** restoring the sciatic nerve to its pre-injured state with no adverse reactions;
- **Pilot study provides critical insights into CelGro®'s mode of action in nerve regeneration** and underpins the consistent restoration of arm and hand function to paralysed upper limbs observed in patients treated in the CelGro® nerve clinical trial;
- **Breakthrough results position CelGro® as the potential market** leader in nerve regeneration and restoration of voluntary muscle control in patients with tetraplegia or paralysed upper limbs;
- **In light of these results, strategic evaluation of medical device US regulatory pathways underway** to identify opportunity for expedited approval of CelGro® and route to the highest reimbursement value;
- **Further CelGro® nerve clinical trial data from all patients at 12 months post treatment on track for release in Q2 2021.**

Perth, Australia; 28 April 2021: Regenerative medicine company Orthocell Limited (ASX:OCC, "Orthocell" or the "Company") is pleased to announce positive results from the US 510(k) animal pilot study, indicating that CelGro® faciliates superior nerve regeneration when compared to the market leading nerve repair device - restoring the sciatic nerve to a pre-injured state. As a result of this breakthrough nerve regeneration data, and in light of the previously released interim human clinical data, the Company is evaluating the medical device US regulatory pathways to identify opportunities for expedited approval of CelGro® and the ideal route to the highest reimbursement value.

Orthocell Managing Director Paul Anderson, said: "*CelGro® has shown to be the superior product for nerve regeneration when compared to the market leading alternative. We are excited by the opportunity to provide patients access to this life changing treatment. Importantly, this evaluation of regulatory and reimbursement pathways position the Company towards a more attractive reimbursement value increasing the market opportunity.*"

US 510(k) pilot study results

Orthocell has completed the pilot stage of its 510(k) animal study titled "Evaluation of collagen nerve wraps used in peripheral nerve repair in a rat sciatic nerve injury model" which was designed to provide evidence of safety and efficacy of CelGro® in peripheral nerve repair, to meet the requirements of the US 510(k) regulatory pathway. The pilot study involved augmenting the repair of severed sciatic nerves in four rats in two separate study groups (CelGro® and an FDA approved nerve repair device) with outcome measures focused on the facilitation of nerve regeneration recorded at four weeks post treatment.

The independent principal investigator, Dr Zoran Pletikosa at the University of Western Sydney, responsible for reconstructive surgery on all animals reported the following post-operative results and handling characteristics:

CelGro®:

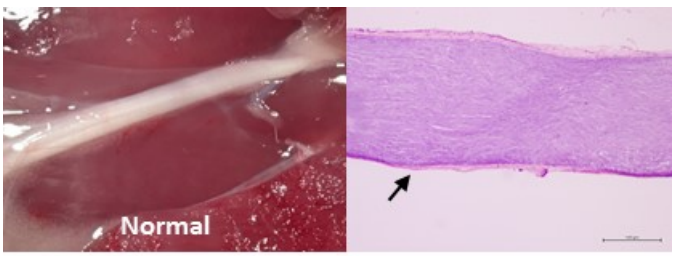
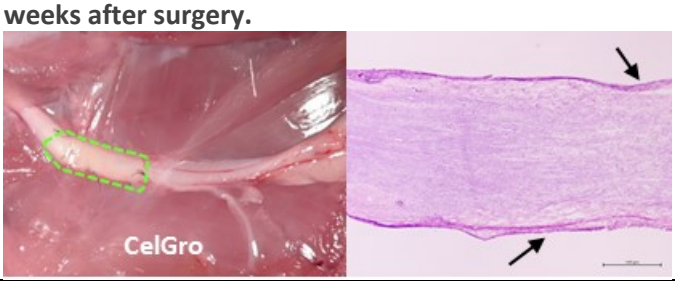
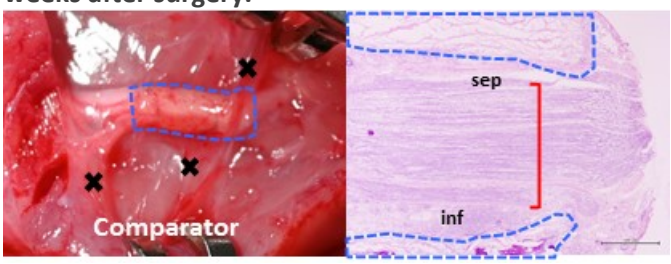
- Nerve repaired with CelGro® exhibited no inflammation, scar tissue formation or fibro-adhesions. CelGro® integrated into the host epineurium (outer layer of connective tissue of the nerve: Figure 2), was

remodelled into natural tissue, and at 4 weeks post treatment, resembled the native sciatic nerve in appearance;

- CelGro® had better handling properties in surgery. It was easier to cut to size, manipulate and position when wrapping around the injured nerve, and hydrated immediately upon contact with tissue fluid (no pre-soaking required). It was easier to suture to the epineurium.

Comparator nerve repair device:

- The FDA approved comparator was thicker and not easy to cut to the required size, rubbery in texture, required 15-30 minutes pre-soaking to hydrate and remained difficult to manipulate once hydrated. The comparator product was also hard to suture adding significant operative time to the surgery;
- Nerves repaired with the FDA-approved comparator device showed significant inflammation with foreign body reactive giant cells, excessive fibro-adhesions to the surrounding soft tissue. The comparator also caused fibro-encapsulation and separation of the epineurium to the nerve fibres. The bulky and protruding nature of the device and the severe inflammatory reaction caused entrapment and compression of the nerve inside the device. At 4 weeks post-treatment the sciatic nerve had not yet returned to its pre-injured state.

Figure 1: Normal rat nerve anatomy and histology. 	Nerve fibres are surrounded with a protective outer layer of connective tissue called the epineurium (black arrow).
Figure 2: Severed nerve repaired with CelGro at 4 weeks after surgery. 	Macroscopic appearance of repaired sciatic nerve resembles pre-injured state. Histology shows integration of CelGro (green dashes) into the regenerated epineurium (black arrow), nerve fibres resemble normal architecture.
Figure 3: Severed nerve repaired with comparator at 4 weeks after surgery. 	Macroscopic appearance of repaired sciatic nerve showed adhesion to the surrounding soft tissue and muscle (black cross) with signs of traumatic neuroma formation. Histology shows that the comparator device (blue dashes) exhibited significant inflammation (inf) with fibro-encapsulation, entrapment (red bracket) and separation of epineurium to nerve (sep).

Significance of CelGro® nerve repair study results

The 510(k) animal study results suggest that restoration of the damaged nerve to its pre-injured state can translate to faster and more predictable return of upper arm and hand function. The previously released interim human clinical data, in patients with tetraplegia or paralysed upper limbs showed that nerve repair using CelGro® resulted in more rapid and consistent outcomes. Improvements in muscle power at 12 months were comparable to repair outcomes sometimes achieved at 24 months either with direct suturing or with the use of the comparator device tested in this 510(k) study.

In light of these study results and the previously released interim human clinical data, Orthocell believes that CelGro® represents a breakthrough in nerve regeneration and is an important development in nerve repair surgery to return function to paralysed upper limbs. CelGro's® superior ability to integrate into nerve tissue with optimal resorption profile and no adverse reactions, provides the ideal conditions for nerve regeneration. These properties, combined with CelGro's excellent handling characteristics will empower surgeons, and ultimately improve the lives of more patients suffering from complex spinal cord or traumatic nerve injuries.

Study data compels review of US regulatory and market access pathway

The Company is on track to announce further clinical data from its CelGro® nerve regeneration human clinical study in Q2 2021, which focuses on the return of arm and hand function of all trial participants, measured at 12 months post treatment. This data will guide the Company's approach with FDA and US payers (Medicare, Medicaid, private payers and the Veteran's Administration) to determine whether an expedited regulatory approval, pursuant to a "De Novo" or "Pre-Market Approval", is possible and what this will mean for reimbursement value for the product.

The currently planned 510(k) pathway for CelGro® is underpinned by an assessment of substantial equivalence to a predicate product (i.e a currently approved and marketed device such as that tested in the 510(k) animal study). The 510(k) pathway also essentially caps the potential reimbursement value paid by private insurers, regardless of any additional patient or economic benefits delivered by use of the new nerve repair device.

On the other hand, De Novo, Pre-Market Approval pathways and expedited programs allow for increased interaction with the FDA and provide the opportunity for the Company to gain a stand-alone approval for a novel nerve repair device, based on the unique clinical benefit delivered by that device. These pathways also allow the Company to leverage the evidence generated in the studies to support FDA approval and maximise the value ultimately paid by US payers for the new product, rather than referencing the existing price for currently marketed products. This would potentially allow Orthocell to reap the benefit of the significant patient and economic advantages generated by using CelGro® in nerve repair applications, and take a larger, more profitable share of the nerve repair market.

Orthocell continues to assess the approval pathways available for CelGro® and following finalization of the CelGro® nerve regeneration human clinical study in Q2 2021, will engage with FDA to determine whether an expedited regulatory approval is possible and what this will mean for reimbursement value for the product.

About CelGro®

CelGro® is manufactured by Orthocell at its Good Manufacturing Practices (GMP)-licensed facility in WA, using the Company's proprietary SMRT™ manufacturing technology, developed in conjunction with Professor Minghao Zheng and the University of Western Australia.

CelGro® facilitates tensionless repair of peripheral nerves and is of significant clinical interest to the surgical community (eg. Orthopaedics and neurosurgery) due to its potential to improve the efficacy and efficiency of surgical procedures. Tensionless repair helps to reduce surgery time and the risk of additional trauma to soft tissue through the use of sutures.

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About Orthocell Limited

Orthocell is focused on regenerating mobility for patients by developing innovative products for the repair of a variety of bone and soft tissue injuries. Orthocell's portfolio of products include CelGro®, a collagen medical device which facilitates tissue repair and healing in a variety of orthopaedic, reconstructive, and surgical applications. CelGro has received regulatory approval in the EU, Australia and the US for bone and soft tissue regeneration in dental procedures. The Company is investigating other clinical used for CelGro™ in peripheral nerve and tendon repair. The Company's other major products are personalised cell therapies Autologous Tenocyte Implantation (Ortho-ATI®) and Autologous Chondrocyte Implantation (Ortho-ACI®), which aim to regenerate damaged tendon and cartilage tissue. Orthocell is moving forward with clinical studies for Ortho-ATI® designed to assist in the US (FDA) approval process.

For more information on Orthocell, please visit www.orthocell.com.au or follow us on Twitter **@Orthocellltd** and LinkedIn www.linkedin.com/company/orthocell-ltd