PREVIOUS STEMSMART™ MSC THERAPY SUPPORTS CLINICAL DEVELOPMENT IN RENAL TRANSPLANTATION

StemSmart™ MSC and Renal Transplantation

- StemSmart™ MSC therapy shows promising results in two early studies in renal transplantation.
- Both studies support further clinical development and the potential of StemSmart™ MSC in both preventing and treating graft failure and rejection.
- A case series of 10 adult patients with **treatment-refractory acute renal rejection** (Appendix 1) following renal transplantation were treated with StemSmart™ MSC on compassionate grounds, as a salvage and adjunctive therapy. These **patients were facing the loss of their donor kidney.**
- Importantly, positive clinical outcomes from the use of StemSmart™ MSC therapy were observed.
- **8 out of 10 patients retained their kidney following the StemSmart™ MSC infusion.**
- A second study was undertaken in 12 adults **undergoing deceased-donor renal transplantation** (Appendix 2), to assess if StemSmart™ MSC therapy was safe and could be tolerated, to potentially alleviate ischaemia-reperfusion injury of transplantation.
- Ischaemia-reperfusion injury occurs when blood circulation is re-established to the kidney during the transplantation procedure and can result in delayed functioning of the kidney and an increased risk of graft rejection and loss. It is particularly relevant in deceased-donor kidney transplantation.
- The study demonstrated that StemSmart™ **MSC infusion was well tolerated and safe in patients undergoing renal transplantation, with no infusion related toxicities** (Appendix 2). Although the study was not designed to determine efficacy, results were encouraging for an **improvement in delayed graft function immediately post transplantation and kidney graft function was excellent at 3 months and 12 months.**

NeuroScientific Biopharmaceuticals Ltd (**ASX:NSB**) or (**the Company**) continues its review of historical studies, data, findings and publications following the acquisition of Isopogen WA Ltd (**Isopogen WA**).

Dr Marian Sturm, Chief Scientific Advisor of NSB, said:

"Resolution of acute rejection in the majority of the small group of patients facing loss of their kidney was fantastic. The anti-inflammatory and immunomodulatory properties of StemSmart™ MSC brought the inflammatory cell invasion of their kidney under control and resulted in a stabilisation of renal function.

Additionally, the safety and tolerability of administration of StemSmart™ MSC at the time of kidney transplantation was demonstrated in the second study. The study demonstrated that using StemSmart™ MSC therapy early in the transplantation process has the potential to mitigate the kidney damage associated with the transplant procedure and would be a major advancement for deceased-donor renal transplantation."

StemSmart Key Addressable Markets (ASX Ann: 27 June 2025)

- **Crohn's Disease:** Global market US$13.8 billion by 2026.
- **Kidney Transplant:** Global market for organ transplant immuno-suppressants, increasing to US$7.2 billion by 2030 (majority for renal).
- **Lung Disorders:** Global market US$33 billion by 2034; and
- **GvHD:** Global market increasing to US$5.31 billion in 2032.

Kidney transplantation is the best treatment for end-stage renal disease. However, despite improvements in tissue-type matching and developments with immunosuppressive agents, clinical outcome is compromised by acute graft rejection and poor long-term graft function.

The procedure of renal transplantation involves the re-establishment of blood circulation to the transplanted kidney. The re-establishment of blood circulation can cause injury to the kidney, known as "ischaemia-reperfusion injury", and occurs particularly where the donor kidney may have been subjected to a prolonged cold storage/transport time such as for deceased donation. With ischaemia-reperfusion injury, there is a broad inflammatory cell invasion of the kidney, with associated inflammatory cytokine release and platelet activation, contributing to vascular occlusion and cell death can ultimately occur. Ischaemia-reperfusion injury can result in delayed graft function, graft dysfunction, increased immunogenicity of the graft with increased risk of rejection and activation of injury pathways leading to fibrosis and ultimately premature graft loss.

Mesenchymal stromal cells have anti-inflammatory and immune-modulatory actions and can play a role both in bringing acute renal rejection under control and also potentially mitigating some of the risks associated with ischaemia-reperfusion injury of the transplantation procedure.

Following the successful clinical outcomes with StemSmart™ MSC in other immune-inflammatory disorders, the MSC were provided on compassionate grounds to 10 patients with biopsy proven, treatment refractory, acute renal rejection. These patients were losing their kidney grafts. Patients received intravenous infusion of StemSmart™ MSC weekly for 4 weeks and underwent renal biopsy at 3 and 12 months to evaluate histological changes in rejection and fibrosis. For 8 of 10 patients, rejection resolved and there was reduction in, or clearance of, T-cells and inflammatory cells evidenced on biopsy and a stabilisation of renal function. For the other 2 patients, one responded then deteriorated with renal complications at 3 months while the other had extensive fibrosis prior to treatment and was unsalvageable. For those patients with high level class II antibodies against their donor kidney, there was a fall or clearance of the donor specific antibodies. Infusions were well tolerated with no infusion-related toxicities and no subsequent toxicities attributed to MSC infusions noted. A further 6 patients have also received StemSmart™ MSC for biopsy proven, treatment refractory, acute renal rejection on compassionate grounds and will form part of a total cohort of patients for publication.

Further to the compassionate treatment of acute renal rejection, the second study was undertaken to assess if StemSmart™ MSC therapy could alleviate ischaemia-reperfusion injury of renal transplantation, improving graft functioning and reducing the risk of graft rejection and loss. Twelve adults undergoing deceased-donor renal transplantation received intravenous infusions of StemSmart™ MSC within 12 hours of reperfusion of the deceased donor kidney and at 7 days post reperfusion. Although the study was not designed to determine efficacy, results were encouraging with no post operation dialysis required for 10 patients and the remaining 2 patients requiring only one or two dialysis procedures. Kidney graft function was excellent at 3 and 12 months.

Although these studies only involve small numbers of patients, they support further clinical development and the potential of StemSmart™ MSC in both preventing and treating graft failure and rejection and improving outcomes in renal transplantation.

This announcement is authorised by the board of NeuroScientific Biopharmaceuticals Ltd.

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Forward Looking Statements

This announcement may contain certain "forward-looking statements". Forward looking statements can generally be identified by the use of forward-looking words such as, "expect", "should", "could", "may", "predict", "plan", "will", "believe", "forecast", "estimate", "target" and other similar expressions. Indications of, and guidance on, future earnings and financial position and performance are also forward-looking statements. Forward-looking statements, opinions and estimates provided in this presentation are based on assumptions and contingencies which are subject to change without notice, as are statements about market and industry trends, which are based on interpretations of current market conditions. Forward-looking statements including projections, guidance on future earnings and estimates are provided as a general guide only and should not be relied upon as an indication or guarantee of future performance.

There can be no assurance that the Acquisition will be completed or that plans of the directors and management of the Company will proceed as currently expected or will ultimately be successful. You are strongly cautioned not to place undue reliance on forward looking statements, including in respect of the financial or operating outlook for the Company. Except as required by law or any relevant listing rules of the ASX, the Company assumes no obligation to provide any additional or updated information or to update any forward looking statements, whether as a result of new information, future events or results, or otherwise. Nothing in this announcement will, under any circumstances (including by reason of this announcement remaining available and not being superseded or replaced by any other presentation or publication with respect to the Company, or the subject matter of this announcement), create an implication that there has been no change in the affairs of the Company since the date of this announcement.

Appendix 1

Study	Compassionate use of mesenchymal stromal cells in refractory renal allograft rejection
Condition	Treatment-refractory, acute renal rejection following allogeneic kidney transplantation
Drug	Human, allogeneic, bone-marrow derived, mesenchymal stromal cells (MSC) for infusion
GMP Compliance of Unapproved Biologic Drug	Manufacture in TGA licenced facility (Licence No: 44165/ MI-25112004-LI-000212-1)
Study Registration	N/A- Compassionate (Special Access Scheme)
Study Type	Interventional
Phase	Case series
Design	Treatment, real-life experience
Intervention	MSC infusion (2 x 10^6 cells/kg recipient weight) infused intravenously weekly for 4 weeks.
Primary Outcome Measure	Resolution of acute rejection Stabilisation of renal function Safety
Primary Measure Description	Renal biopsy at 3 months for evaluation of histological change in rejection/fibrosis Renal function by estimation of glomerular filtration rate/ blood creatinine levels
Secondary Outcome Measure	Fall/clearance of kidney donor specific antibodies
Secondary Measure Descriptions	Measurement of kidney donor specific antibodies in blood by Luminex SAB
Actual Enrolment	10 subjects
Subject Evaluation	10 subjects with biopsy confirmed refractory graft rejection: median age 44 years (29-67 years), 7 males
Recruitment period	2012-2015
Statistical method	Descriptive methods indicating survival of kidney and restoration of renal function
Primary Outcome Result	8/10 patients retained their kidney. T-cell numbers and inflammatory cell reduction after MSC treatment was confirmed on biopsy. Renal function stabilised for 8/10 patients. Of the 2/10 patients who did not retain their kidney,1 responded then deteriorated with renal complications at 3 months post MSC, while the other patient had extensive fibrosis prior to MSC treatment and was unsalvageable. Infusions were well tolerated with no acute infusion-related toxicities and no subsequent toxicities attributable to MSC infusions noted.
Secondary Outcome Results	For patients with high level class II donor specific antibodies (4/10), there was a fall or clearance in antibodies without plasma exchange.
Publication/Presentations	Ashley Irish, Raja Sinniah, Suda Swaminathan, Anne Warger, Samantha Fidler, Marian Sturm, Richard Herrmann. Allogeneic, bone marrow derived, mesenchymal stromal cells as adjunctive therapy for refractory renal allograft rejection. Immunology & Cell Biology 91, 2013. Marian Sturm. MSC therapy for immunomodulation. 9th Australian Society for Stem Cell Research Annual Scientific Meeting 2016. Marian Sturm. Stem cell therapy. Renal Society of Australasia, 2015.

Appendix 2

Clinical Trial	Mesenchymal Stromal Cells (MSC) for the amelioration of ischaemia-reperfusion injury after deceased donor renal transplantation, a phase 1 pilot study.
Condition	Kidney failure- adult, deceased-kidney transplant recipients
Drug	Human, allogeneic, bone-marrow derived, mesenchymal stromal cells (MSC) for infusion
GMP Compliance of Unapproved Biologic Drug	Manufacture in TGA licenced facility (Licence No: 44165/ MI-25112004-LI-000212-1)
Trial Registration	ACTRN12615000678594
Study Type	Interventional
Phase	Phase I
Design	Open-label, non-randomised, intervention, preventative
Intervention	MSC infusion (2 x 10^6 cells/kg recipient weight) infused intravenously at reperfusion of deceased donor kidney and at 7 days post reperfusion
Primary Outcome Measure	1. Safety and tolerability 2. Graft function 3. Renal allograft rejection episodes to 1 year post transplantation
Primary Measure Description	1. Clinical monitoring, infusion reactions 2. Estimated by glomerular filtration rate 3. Proven by renal biopsy
Secondary Outcome Measure	Immunogenicity against third party donor kidney
Secondary Measure Descriptions	Measurement donor specific antibodies by Luminex SAB
Actual Enrolment	12 adult subjects
Subject Evaluation	12 deceased-kidney recipients: median age 45 years (33-57 years), 7 males.
Recruitment period	Oct 2014 -Feb 2017
Statistical method	Comparative analysis with deceased-donor control (114 patients)
Primary Outcome Result	1. MSC were administered in theatre and on the ward without complication. Treatment was well tolerated. No infectious complications (viral or bacterial). 2. Only two patients had delayed graft function; one requiring 2 x dialysis and the other a single dialysis. Compared to donor controls, there was a trend to better initial graft function at 1 and 3 months with MSC treatment. Kidney function at 3 and 12 months was excellent in all 12 subjects. 3. 2/12 patients were treated for rejection within 6 months of transplant (one patient on steroid-free regimen, single rejection episode and resumed steroids; other patient was non-compliant, stopped all immunosuppression and deceased). 4. No early safety signals of allogenicity, graft injury or over-immunosuppression were observed.
Secondary Outcome Results	Serial HLA monitoring detected a weak de novo donor specific antibody against donor kidney for one patient at 12 months but without any evidence of antibody mediated rejection. No donor specific antibodies were detected against MSC donors
Publication/Presentations	A Irish, S Swaminathan, S Fidler, L'Dorsogna, R Sinniah, M Sturm. A phase I study of MSC and ischaemia reperfusion injury in deceased renal transplant. Nephrology 22, Suppl. 3, pp29, 2017. Marian Sturm. Mesenchymal stromal cell therapy for immunomodulation; clinical trials in WA. 9th ASSCR Annual Scientific Meeting Dec 2016, Margaret River WA.