NeuroScientific
BIOPHARMACEUTICALS
ASX:NSB

ASX ANNOUNCEMENT
19 JUNE 2025

PREVIOUS STEMSMART STUDIES DEMONSTRATE CLINICAL RESPONSE IN SEVERE GVHD

StemSmart™ and Graft Versus Host Disease (GVHD)

- Positive and life-saving clinical results of StemSmart™ MSC therapy for adults and children with **severe and life-threatening steroid-refractory GVHD**, supports the use of StemSmart™ MSC therapy in this clinical indication[2,3].

- The graft versus host disease (GvHD) treatment market was valued at USD$2.55billion in 2023 and is expected to grow to USD$5.31billion in 2032[5].

- A Phase I clinical trial in adults with **steroid-refractory GVHD[2]**, and a series of children treated on compassionate grounds for **steroid-refractory GVHD[3]** found the majority of adults and children responded to StemSmart™ with a complete or partial resolution of symptoms and improved survival.

- Indications from the Phase I clinical trial in the management of both **steroid-refractory acute GVHD** and **steroid-refractory chronic GVHD** in adults, suggest StemSmart™ is well tolerated and safe, with no infusion related toxicities[2].

- **10** children were treated on compassionate grounds for **steroid-refractory GVHD** (6 acute and 4 chronic GVHD). **All children survived out to 12 months post-transplant**, an improvement on anticipated mortality. Three of the chronic GVHD patients were alive at more than 6 years post treatment[3].

NeuroScientific Biopharmaceuticals Ltd (**ASX:NSB**) or (**the Company**) continues to progress its proposed acquisition (**Acquisition**) of the StemSmart™ patented Stem Cell technology (**StemSmart**) from Isopogen WA Ltd (**Isopogen WA**). As part of the Acquisition, NSB continue to review historical studies, findings and publications. Patients both locally and interstate have already received StemSmart™ MSC therapy on compassionate grounds, for a variety of serious and life-threatening clinical conditions, with multiple strong positive clinical responses[1].

Dr Marian Sturm, Chief Technical Officer, said: *"The significant clinical responses in these studies demonstrate the potential for life changing outcomes with StemSmart™ MSC therapy. Those patients who develop steroid-refractory GVHD are no longer responding to treatment, and with no other treatment options available, face a high rate of mortality.*

For children, because of the seriousness of their GVHD and their bleak chance of survival, StemSmart™ MSC therapy has been accessed on compassionate grounds, and with good clinical outcomes. StemSmart™ MSC works by interacting with a patient's immune system to attenuate the immunological and inflammatory responses in severe GVHD. In an inflammatory environment, MSC respond by releasing an array of factors that inhibit and suppress the immune cells driving GVHD, induce immune tolerance and reduce inflammation.

Treatment with StemSmart™ MSC has reduced suffering and improved lives for those with steroid refractory GVHD."

On 16 April 2025, the Company reported that a Phase 2 trial of 18 patients with refractory Crohn's disease who received StemSmart™ MSC therapy demonstrated promising results, with the majority of patients experiencing clinical improvement and many clinical remission[1]. The development of StemSmart™ MSC in 2006-2007 however, was driven by the desperate need of patients who had undergone an allogeneic (donor) bone marrow transplant for blood cancers (i.e. leukemia).

Graft versus host disease (GVHD) is a common and severe complication of allogeneic bone marrow transplant and is a result of immune cells from the transplanted marrow recognising the recipient patient's body as foreign and attacking healthy tissue. GVHD manifests as both acute and chronic; acute occurs soon after the transplant and commonly affects the skin, gastrointestinal tract and liver, while chronic occurs later and is more insidious, affecting the lungs, eyes and mouth.

With advances to transplant practises in Australia and New Zealand, the incidence of acute GVHD has fallen from occurring in up to 64% of transplants to now occurring in about 30% of cases. Of these, a significant proportion (25-30%) do not respond or become refractory to standard corticosteroid treatment. Unfortunately, steroid-refractory acute GVHD has a high mortality and morbidity, with survival less than 20% at 200 days post-transplant. Chronic GVHD develops in up to 50% of recipients, with infection being the leading cause of non-relapse death. With steroid-refractory chronic GVHD, long term survival is diminished (30-50% at 5 years) and disabling morbidity is common.

In a clinical trial of adults with steroid-refractory GVHD[2] and for a series of children treated on compassionate grounds for steroid-refractory GVHD[3], the majority of both adult and child patients have responded to StemSmart™ MSC treatment, with a complete or partial resolution of symptoms and improved survival. These patients had no other therapy options available. The treatment was well tolerated with no serious adverse events related to MSC infusion or long term related adverse events noted. StemSmart™ MSC therapy appears to be effective and safe.

The Phase I clinical trial of 19 adult patients (12 acute GVHD and 7 chronic GVHD) was conducted to evaluate safety of the treatment in the management of both steroid-refractory acute and also chronic GVHD[2]. For the steroid refractory acute patients, 11 patients responded to StemSmart™ MSC therapy, with 58% having a complete response and 33% a partial response. The actuarial 3-year survival for these patients was significantly improved at 55% as compared to the expected survival of 15-20%. Clinical responses were also seen in 58% patients with chronic GVHD, with a complete response occurring in 29% and a partial response in 29%. StemSmart™ MSC was well tolerated and safe, with no infusion related toxicities.

1. ASX Announcement 16 April 2025.
2. Annexure 1.
3. Annexure 3.
4. Annexure 3.
5. https://www.globenewswire.com/news-release/2024/11/07/2976830/28124/en/Graft-Versus-Host-Disease-GvHD-Treatment-Industry-Forecast-Report-2024-2032-Global-Market-Size-Forecast-to-Double-with-Emerging-Markets-Offering-Substantial-Growth-Potential.html

Similarly, of the 10 children treated on compassionate grounds for steroid refractory GVHD (6 acute and 4 chronic GVHD)[3], with the exception of one child, all children showed a response to StemSmart™ MSC therapy with an improvement in symptoms, particularly of the skin and gut. The child who failed to respond to StemSmart™ MSC therapy only received a single infusion before all clinical intervention was declined. Of the 5 evaluable patients with acute GVHD, 3 had a complete response and 2 patients a partial response. All children survived out to 12 months post-transplant, which was an improvement on anticipated mortality. All 4 patients with chronic GVHD responded to treatment with one patient having a complete response. Three of the chronic GVHD patients were alive at more than 6 years post treatment.

Following the successful outcomes for patients with steroid-refractory acute GVHD, another study was undertaken in patients with newly diagnosed and non-refractory acute GVHD[4]. No benefit from StemSmart™ MSC treatment was observed in patients with newly diagnosed and non-refractory acute GVHD. Differences between the patient groups, treatments and inflammatory status are considered responsible for the lack of efficacy observed in new-onset GVHD as compared to steroid-refractory GVHD.

In summary, although the numbers are small, the positive and life-saving clinical results of StemSmart™ MSC therapy for adults and children with severe and life-threatening steroid-refractory GVHD supports the use of StemSmart™ MSC therapy in this clinical indication, given the poor outlook of these patients. As a consequence, StemSmart™ MSC therapy has continued to be requested on compassionate grounds for patients with steroid-refractory GVHD.

StemSmart Key Addressable Markets[1]

- **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[5]

The Acquisition of Isopogen remains subject to a number of conditions precedent, including each of the shareholders of Isopogen WA signing a separate share sale agreement with the Company[1].

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

-ENDS-

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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.

Annexure 1

Clinical Trial	A phase I study to evaluate the potential of mesenchymal stromal cells to treat steroid refractory graft versus host disease (both acute and chronic) after bone marrow transplantation
Condition	Acute and chronic steroid-refractory graft versus host disease following allogeneic bone marrow transplant
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	ANZCTR12610000068066
Study Type	Interventional
Phase	Phase 1
Design	Treatment, non-randomised, single-group assignment, open-label
Intervention	Initial intervention of MSC infusion (2×10^6 cells/kg recipient weight) infused intravenously twice weekly for 4 weeks, subsequently adjusted to two infusions at weekly intervals.
Primary Outcome Measure	To evaluate safety of infusions of MSC in the management of steroid-refractory acute GVHD (grades 2-4) and chronic GVHD of extensive degree
Primary Measure Description	Clinical observation and measurement of vital signs post infusion for adverse reactions. Monitored for adverse events at regular on-going follow-up.
Secondary Outcome Measure	Best response and overall survival post MSC infusion
Secondary Measure Descriptions	Monitoring of clinical symptoms of GVHD. For acute GVHD, complete response was loss of all symptoms and signs of GVHD, partial response was at least an improvement of one grade or more. For chronic GVHD, complete response was as for acute GVHD and partial response was an improvement in the NIH consensus score of at least one.
Actual Enrolment	19 adult subjects 12 subjects with steroid refractory acute GVHD (grades II-IV), aged 21-68 year; 8 males. 7 subjects with steroid refractory chronic GVHD (NIH consensus score $\geq$2), aged 31-53; 5 males
Recruitment period	September 2007- April 2010
Completion Date	2011
Subject Evaluation	19 subjects 12 subjects with acute GVHD 7 subjects with chronic GVHD
Statistical method	Descriptive methods indicating the overall experience of patients. Survival, described as time from first MSC infusion. Kaplan-Meier method to estimate survival times. The non-parametric log-rank test to examine for differences in survival between groups and to examine trends in survival patterns.
Primary Outcome Result	Infusions (109) were well tolerated with no acute infusion-related toxicities and no subsequent toxicities attributable to MSC infusions noted.
Secondary Outcome Results	The overall response rate for acute GVHD was complete response in 7/12 patients (58%), partial response in 4/12 (33%) patients and no response in 1 patient. Of the patients with chronic GVHD, a complete response was observed in 2/7 (29%) patients, a partial response in 2/7 (29%) and no response in 3 patients (43%). The actuarial 3year survival for patients with acute GVHD was 55%, compared to the expected survival of 15-20%. The median survival of patients with chronic GVHD was 8 months.

	Complete response to MSC therapy was a statistically significant predictor of survival for acute GVHD patients (X^2 = 11.3, p= 0.0008) but not for chronic GVHD (X^2 = 2.79, p= 0.100)
Publication	Richard Herrmann, Kathryn Shaw, Marian Sturm, Paul Cannel, Julian Cooney, Duncan Purtill, Matthew Wright. Mesenchymal stromal cell therapy for steroid-refractory acute and chronic graft versus host disease, a phase I study. Int J Haem 95 (2), 182-188, Feb 2012.

Annexure 2

Clinical Study	Compassionate use of mesenchymal stromal cells in refractory graft versus host disease after bone marrow transplantation
Condition	Acute and chronic steroid-refractory graft versus host disease following allogeneic bone marrow transplant
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	N/A- Compassionate
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 2 or 4 weeks, as indicated.
Primary Outcome Measure	The management of steroid-refractory acute GVHD (grades 2-4) and chronic GVHD of extensive degree, and safety
Primary Measure Description	Monitoring of clinical symptoms of acute and chronic GVHD Clinical observation and measurement of vital signs post infusion for adverse reactions. Monitored for adverse events at regular on-going follow-up.
Secondary Outcome Measure	Overall survival
Secondary Measure Descriptions	Assessment of survival
Actual Enrolment	10 paediatric subjects 6 children with steroid-refractory acute GVHD (grades II-IV), aged 1.8-18 year; 5 male 4 children with steroid-refractory chronic GVHD (grades II-III), aged 5-8 years; 3 male
Treatment period	April 2013- June 2018
Completion Date	2020
Subject Evaluation	9 subjects 5 subjects with acute GVHD 4 subjects with chronic GVHD
Statistical method	Descriptive methods indicating the overall experience of patients. Survival, described as time from first MSC infusion.
Primary Outcome Result	All children showed a response to treatment, with the exception of 1 child where clinical interventions were declined after a single infusion. For 5 acute GVHD patients, 3 had a complete response by day 28; 2 had a partial response. Additional treatment was given to those with only a partial response or who had flares of GVHD. All 4 patients with chronic GVHD responded to treatment, with one child having a complete response.

	Infusions were well tolerated with no acute infusion-related toxicities and no subsequent toxicities attributable to MSC infusions noted.
Secondary Outcome Results	Acute GVHD: All children survived out to 12 months post-transplant. 3 patients deceased at $\geq$ 1 year due to poor graft function and infection, disease relapse and viral infection. Two patients maintained their response for >2years (> 31 months, >5 years). Chronic GVHD: 1 patient deceased at 3 years due to pulmonary failure Remaining 3 children were alive > 6 years post-transplant but with ongoing chronic GVHD. In total, 5 of the 10 children remained living (50%) and achieved long term survival of at least 2 - 6.6 years post MSC treatment.
Publication	Shanti Ramachandran: Compassionate use of Mesenchymal Stromal Cells in refractory graft-versus-host disease. Oral presentation at Annual Scientific Meeting of Australia and New Zealand Children Haematology-Oncology Group (ANZCHOG) 2016.

Annexure 3

Clinical Trial	A phase II trial of standard of care treatment versus mesenchymal stromal cells therapy together with standard of care treatment for the treatment of de novo acute graft versus host disease following allogeneic bone marrow transplantation
Condition	Newly diagnosed untreated, acute graft versus host disease (grades 2-4) following allogeneic bone marrow 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)
Trial Registration	NCT01589549
Study Type	Interventional
Phase	Phase 2
Design	Randomised (1:1), parallel assignment, open-label, treatment Recruitment target 66 participants (33 in each arm)
Intervention	One arm will be randomised to receive MSC therapy in addition to corticosteroid therapy. • Active comparator: corticosteroid therapy • Intervention: Mesenchymal stromal cell therapy; (2 x 10^6 cells/kg recipient weight) infused intravenously on day 1 and day 8.
Primary Outcome Measure	Overall survival at 12 months post randomisation
Primary Measure Description	Assessment of survival
Secondary Outcome Measure	• Acute GVHD response at day 28 • Progression-free survival at 12 months • Safety (infusion reactions & major infections)
Secondary Measure Descriptions	Monitoring of clinical symptoms of acute GVHD Monitoring of progression-free survival Clinical observation and monitoring for adverse events post-infusion and at regular on-going follow-up.
Actual Enrolment	30 adult subjects Control: 15 MSC: 15
Recruitment Period	May 2012-April 2017
Completion Date	April 2018
Subject Evaluation	28 subjects Control: 13, median age 55 years (22-64 years) MSC: 15, median age 47 years (20-64 years)

Statistical method	SPSS software and Graphpad Prism
Primary Outcome Result	No difference in survival at 12 months post-randomisation- 53% MSC arm (8 surviving) and 77% control arm (10 surviving) Time to death similar in both arms- MSC: 93 days (range 28-210 days); control: 86 days (range 46-295 days). Causes of death were similar in both groups.
Secondary Outcome Results	• Day 28 acute GVHD overall response: -67% for MSC arm (complete response (CR) 47%, partial response (PR) 20% -100% for control arm (CR 62%, PR38%) • Salvage therapy was added for 6 patients (40%) MSC and 2 patients (15%) in the control arm • Safety: no significant infusion reactions with MSC; no difference in infections
Outcome Summary	Early results do not support the use of MSC in addition to corticosteroids at first diagnosis of acute GVHD. Study, which was planned to recruit 66 patients, was terminated early on grounds of futility. Challenges of study: • Recruitment was slower than anticipated due to a decreasing incidence of grade II-IV acute GVHD at our centre (43% in 2012-14 vs 30% in 2015-2016) • 12-month overall survival endpoint is vulnerable to variations in treatment factors outside MSC therapy • Both GVHD response rate and survival in control arm were higher than anticipated, for reasons that are not clear from patient information • Inflammatory status of recipient may affect efficacy of MSC therapy. All patients had received corticosteroids for up to 72 hours prior to MSC therapy. We postulate that steroid pre-treatment may have inhibited MSC activity.
Publication	Early cessation of a randomised study in acute graft versus host disease: upfront mesenchymal stromal cells with corticosteroids versus corticosteroids alone. Duncan Purtill, Melita Cirillo, Janice Fogarty, Dino Tan, Julian Cooney, Matthew Wright, Paul Cannell, Richard Herrmann, Marian Sturm. Bone Marrow Transplantation (2020) 55:2199-2201 https://doi.org/10.1038/s41409-020-0955-9