

POSITIVE TRIAL RESULTS OF MESOBLAST CELL THERAPY IN PATIENTS WITH DIABETES AND ADVANCED CHRONIC KIDNEY DISEASE

New York; USA; and Melbourne, Australia; 9 June 2015: Mesoblast Limited (ASX:MSB; USOTC: MBLTY) today announced that results from the Company's Phase 2 trial in patients with diabetic nephropathy showed that a single infusion of its intravenously delivered allogeneic mesenchymal precursor cell (MPC) product candidate MPC-300-IV was safe, reduced damaging inflammation, and preserved or improved renal function over at least 24 weeks.

The results were presented at the late-breaking scientific sessions of the 75th annual meeting of the American Diabetes Association (ADA) currently being held in Boston. The ADA annual meeting brings together approximately 14,000 participants, including clinicians and researchers from 124 countries.

The trial's lead investigator, Associate Professor David Packham, Department of Medicine, University of Melbourne, and Director of the Melbourne Renal Research Group, stated that: "The results show that Mesoblast's allogeneic cell therapy was safe and may be particularly useful in patients with moderate to severe diabetic nephropathy, a disease which, despite all existing therapies, continues to have a high rate of progression to dialysis or transplantation, and to portend a high risk of death from cardiovascular disease."

Diabetic nephropathy affects 40-50% of patients with type 2 diabetes and accounts for about 40% of all patients with end-stage renal disease (kidney failure). It is thought to be caused by ongoing monocyte inflammation and endothelial dysfunction (abnormal blood vessels) in the kidneys. Mesoblast's bone marrow-derived MPCs are potent modulators of monocyte inflammation, and have been shown in preclinical studies to reduce monocyte infiltration in diabetic kidneys and to reverse endothelial dysfunction. Consequently, Mesoblast is developing MPC-300-IV for intravenous delivery in the treatment of diabetic nephropathy.

MPC-300-IV was evaluated in a double-blind, randomized, placebo-controlled, dose-escalating Phase 2 trial of 30 patients with type 2 diabetes and moderate to severe renal impairment, stage 3b-4 chronic kidney disease (CKD), who were already on a stable regimen of the standard of care therapy for diabetic nephropathy (renin-angiotensin system inhibition with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers). Patients received a single infusion of 150 million MPCs, 300 million MPCs, or saline control.

The objectives of the trial were to evaluate safety and to explore potential efficacy signals of MPC treatment on renal function. The pre-specified primary efficacy endpoint was to evaluate effects of MPC treatment relative to placebo on renal functional decline at 12 weeks, as defined by change in glomerular filtration rate (GFR) measured both by direct isotope scan and by serum-creatinine based estimation, and then for an additional 48 weeks of follow-up. Pre-specified secondary analyses included GFR differences between treatment and placebo groups with baseline $GFR > 30 \text{ ml/min}/1.73\text{m}^2$ (stage 3b CKD, accounting for 60% of enrolled patients), and treatment-related effects on the monocyte-derived cytokine interleukin-6 (IL-6), a major inflammatory marker associated with renal failure progression and adverse cardiovascular outcomes.

The primary efficacy endpoint of decline or change in GFR was in line with the 2012 joint workshop held by the United States Food and Drug Administration and the National Kidney Foundation which recommended that time to 30%-40% decline in GFR is an acceptable primary endpoint for evaluating potential benefits of new therapies for this patient population (*Levey et al. GFR decline as an endpoint in clinical trials for CKD. American Journal of Kidney Disease 2014; 64(6):821-835*). This joint workshop recognized the significant unmet medical need and urgency to make new therapies accessible to patients who may benefit from them. This revised endpoint could make new treatments available earlier to patients with chronic renal failure by reducing trial size and duration, compared with the previously accepted composite endpoint of time to first occurrence of doubling of serum creatinine (equivalent to a 57% reduction in GFR), renal replacement or death.

Key findings at 12 and 24 weeks in the MPC-300-IV trial were:

- Safety profile for MPC treatment was similar to placebo, with no treatment-related infusion or other events.
- Efficacy testing showed that MPC-treated subjects had improved renal function relative to placebo, as defined by preservation or improvement in GFR at both 12 and 24 weeks; these effects were seen even though this trial was not powered to show statistical significance of treatment.
- While all three groups had similar mean GFR at baseline, 34.6, 35.7 and 34.6 ml/min/1.73m², at 12 weeks the placebo group showed a decline in measured GFR of 4.0 ml/min/1.73m² and 3.9 ml/min/1.73m² relative to the groups receiving a single infusion of either 150M MPC or 300M MPC, respectively; the difference in creatinine-based estimated GFR decline between placebo and the 150M group reached significance (p=0.05).
- By isotope-measured GFR, in patients with GFR>30 ml/min/1.73m² at baseline the placebo group showed a GFR decline at 12 weeks of 6.2 ml/min/1.73m² relative to the pooled MPC-treated patients (p=0.07).
- By creatinine-based estimated GFR, the placebo group with GFR>30 ml/min/1.73m² at baseline showed a GFR decline at 12 weeks of 4.5 ml/min/1.73m² and at 24 weeks of 4.6 ml/min/1.73m² relative to the pooled MPC-treated patients (p=0.04 and p=0.13, respectively).
- There was a correlation between increased baseline IL-6 levels and improvement at 12 weeks in both serum creatinine and GFR ($r=0.57$, $p=0.008$) in MPC-treated patients.
- MPC treatment was associated with a dose-dependent inhibition of IL-6 increase over 12 weeks; serum IL-6 levels increased by 2.5 pg/dl at 12 weeks in the placebo group compared to a reduction of 0.2 pg/dl in the 300M MPC group (p=0.01).

Key study conclusions were:

- The safety profile and the potential efficacy signals of allogeneic MPC therapy for prevention or reversal of renal functional decline in diabetic nephropathy supports advancing the clinical program in patients with the highest medical need, e.g. rapid progression towards dialysis or renal transplantation, defined as an annual GFR decline of >5ml/min/1.73m², and high risk of cardiovascular events.
- Positive response to MPC therapy may be enhanced by the presence of viable, but at-risk, renal tissue and an aberrant pro-inflammatory milieu in the kidney.
- Baseline GFR>30 ml/min/1.73 m² and high interleukin-6 (IL-6) levels may be biomarkers that predict efficacy with MPC treatment.

- Reduction in IL-6 levels suggests that the mechanism of action by MPCs may involve reduction of pro-inflammatory M1 monocyte cytokines in the diabetic kidney.
- MPC therapy may have applications in diverse renal conditions where inflammation plays a central role.

Mesoblast Chief Executive Silviu Itescu said: "We are very encouraged by the safety profile and the sustained efficacy signal that we have seen over 24 weeks after a single intravenous infusion of our allogeneic cell-based therapy in patients with diabetes and advanced chronic kidney disease. The growing burden of diabetic nephropathy and its impact on healthcare make this an important disease target for Mesoblast and our technology. We will specifically evaluate whether MPC-300-IV can alter the natural course of the disease in patients with rapid progression towards dialysis or renal transplantation, and will focus on early access regulatory pathways for developing this product."

Diabetic Nephropathy

Diabetic nephropathy is the single leading cause of end-stage kidney disease, accounting for nearly half of all end-stage kidney disease cases in the United States and over 40% of new patients entering dialysis treatment. There were almost 2 million cases of advanced diabetic nephropathy in 2013. With the current diabetes population exceeding 20 million, over 6 million new patients are expected to develop diabetic nephropathy in the United States alone. Staging of CKD is based on absolute levels of GFR, and GFR decline is on the path of progression to kidney failure (stage 5, GFR<15ml/min/1.73m²). The current standard of care (renin-angiotensin system inhibition with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers) only slows the rate of progression to kidney failure by 16-25%, leaving a large residual risk for end-stage kidney disease. For patients with end-stage kidney disease, the only treatment option is renal replacement (dialysis or kidney transplantation) which incurs high medical costs and substantial disruptions to a normal lifestyle. Due to a severe shortage of kidneys, in 2012 approximately 92,000 persons in the United States died while on the transplant list. For those on dialysis, the mortality rate is high with an approximately 40% fatality rate within two years.

Mesoblast Limited

Mesoblast Limited (ASX: MSB; USOTC: MBLTY) is a global leader in regenerative medicine. The Company has leveraged its proprietary technology platform, which is based on specialized cells known as mesenchymal lineage adult stem cells, to establish a broad portfolio of late stage product candidates. Mesoblast's allogeneic or 'off-the-shelf' cell product candidates target significantly advanced stages of diseases where there are highly unmet medical needs, including cardiovascular conditions, orthopedic disorders, immunologic/inflammatory disorders and oncology/hematology conditions. The lead therapeutic product candidates under investigation include MPC-150-IM for chronic congestive heart failure; MPC-06-ID for chronic discogenic low back pain, MSC-100-IV for acute graft versus host disease, and MPC-300-IV for biologic refractory rheumatoid arthritis, and diabetic nephropathy.

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