asx announcement

mesoblast
the regenerative medicine company

DURABLE RESPONSES AND SUSTAINED LOW DISEASE ACTIVITY OVER NINE MONTHS AFTER A SINGLE DOSE OF MESOBLAST CELL THERAPY IN RHEUMATOID ARTHRITIS PATIENTS RESISTANT TO ANTI-TNF AGENTS

Key points:

- A single intravenous infusion of Mesoblast's allogeneic "off-the-shelf" Mesenchymal Precursor Cells (MPCs) resulted in durable responses through nine months (39 weeks) in a 48-patient placebo-controlled, randomized Phase 2 trial in rheumatoid arthritis (RA) patients resistant to anti-Tumor Necrosis Factor (TNF) agents
- The safety profile over 39 weeks was comparable among the placebo and both MPC treatment groups, with no cell-related serious adverse events
- Both MPC doses outperformed placebo at week 39 in each of ACR20/50/70 responses, as well as by median ACR-N analysis
- Continuous variables ACR-N, HAQ-DI and DAS-28 were used in line with the FDA Guidance For Industry Rheumatoid Arthritis: Developing Drug Products For Treatment, May 2013, and identified the 2 million MPC/kg dose as the most effective over 39 weeks
- The 2 million MPC/kg dose showed the earliest and most sustained treatment benefit
- The RA population resistant to anti-TNF agents constitutes about one-third of patients treated with these agents, is the fastest growing branded market segment within the $19 billion global RA biologics market, and is set to grow further as multiple anti-TNF biosimilars become available; the goal of therapy in these patients is to achieve early and sustained low disease activity which correlates with prevention of structural joint damage in RA
- Given the serious nature of anti-TNF resistant RA, MPC-300-IV is well-positioned to be developed as a regenerative advanced therapy to target this major unmet medical need

New York; USA; and Melbourne, Australia; February 16, 2017: Mesoblast Limited (ASX:MSB; Nasdaq:MESO) today announced 39-week data from its Phase 2 trial in patients with rheumatoid arthritis (RA) resistant to anti-Tumor Necrosis Factor (TNF) agents. The results showed that a single intravenous infusion of the Company's proprietary allogeneic cell therapy product candidate, MPC-300-IV, was well tolerated and demonstrated a durable improvement in clinical symptoms, physical function, and disease activity relative to placebo over this period of follow-up.

Mesoblast Chief Executive Silviu Itescu commented: “The nine-month outcomes generated from this study are highly encouraging. The early and durable effects seen from a single infusion of 2 million MPC/kg support the potential of our allogeneic cell therapy to be positioned as an early treatment option for patients resistant to anti-TNF agents.”

Major advances in the treatment of RA using biologic agents have resulted in a $19 billion global market in 2016, the majority of which is due to use of anti-TNF agents. The RA population resistant to anti-TNF agents, which constitutes about one-third of patients treated with anti-TNF agents, is the fastest growing branded market segment within the global RA biologics market, and is set to grow further as multiple anti-TNF biosimilars become available.

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Mesoblast's Phase 2 trial recruited a total of 48 patients with active RA who were on a stable regimen of methotrexate and had an inadequate prior clinical response to at least one anti-TNF agent. Of the 48 patients, 30 (63%) had previously received 1-2 biologic agents. Patients were randomized to a single intravenous infusion of 1 million MPCs/kg (1M/kg, n=16), 2 million MPCs/kg (2M/kg, n=16) or placebo (n=16). The study was comprised of a 12 week primary study period, and a total study duration of 52 weeks.

The primary objective of the study was to evaluate safety and tolerability of a single intravenous MPC infusion in these biologic refractory RA patients through a 12 week primary endpoint. Additional objectives were to evaluate clinical efficacy at the 12 week endpoint and to assess the durability of effects and safety profile through the full 52 week study.

Pre-specified efficacy endpoints included the following: American College of Rheumatology (ACR) composite clinical response, which is an endpoint used in RA clinical trials to measure improvement in signs and symptoms of the disease in terms of 20%, 50% or 70% improvement from baseline; ACR-N which measures the mean or median magnitude of benefit using an ACR composite for a typical patient; the health assessment questionnaire-disability index (HAQ-DI), a standardized measure of functional status; and the DAS28 composite measurement of disease activity; no adjustment for multiplicity was performed as these efficacy endpoints were exploratory and the trial was not powered for efficacy.

Additionally, continuous variables ACR-N, HAQ-DI and DAS-28 were evaluated in a pre-specified manner since the use of endpoints sensitive to change provide better discriminatory power for dose-response assessment, in line with the FDA Guidance For Industry Rheumatoid Arthritis: Developing Drug Products For Treatment, May 2013.

Analyses were performed for the whole study population and for the pre-specified exploratory subgroups based on whether the subjects had previously received 1-2 biologic agents or more than 2 biologic agents.

Key results over nine months are shown in detail in the tables below, and were:

- A single intravenous MPC infusion of either 1 million or 2 million MPC/kg resulted in durable responses through nine months (39 weeks) in the 48-patient placebo-controlled, randomized Phase 2 trial in patients who have failed one or more TNF inhibitors
- The safety profile over 39 weeks was comparable among the placebo and both MPC treatment groups, with no cell-related serious adverse events
- Both MPC doses outperformed placebo at week 39 in each of ACR20/50/70 responses
- Both MPC doses outperformed placebo at week 39 in the proportion of patients who achieved the target of low disease activity (DAS-28$\leq$3.2); disease remission (DAS 28 <2.6) was seen at similar levels across all groups
- Use of continuous variables ACR-N, HAQ-DI and DAS-28, in line with FDA guidance for dose-finding Phase 2 trials of new RA therapies, identified the 2 million MPC/kg dose as the most effective over 39 weeks
- While both MPC doses achieved higher median ACR-N scores compared with placebo at 39 weeks, the 2 million MPC/kg dose achieved the maximal ACR-N score earlier, at 12 weeks
- Over the entire 39 weeks, the 2 million MPC/kg MPC group had a significantly greater ACR-N Area Under the Curve (AUC) than placebo, indicating a more robust durable effect with the higher treatment dose

- At 39 weeks, there was a dose-dependent treatment effect on mean change from baseline in function (HAQ-DI) and disease activity score (DAS-28), with the 2 million MPC/kg dose showing the greatest effect
- MPC treatment effects for all parameters were greatest in patients who had failed 1-2 biologic agents

Summary of Key Efficacy Responses at Three and Nine Months for All Subjects:

	Week 12			Week 39		
	Placebo	**1M/kg**	**2M/kg**	**Placebo**	**1M/kg**	**2M/kg**
	N=16	N=16	N=16	N=16	N=16	N=16
ACR20	50%	47%	53%#	36%	69%	57%
ACR50	19%	27%	40%#	14%	31%	21%
ACR70	0%	20%	27%*	0%	23%	21%
ACR-N median	20%	11%	28%	9%	27%	27%
ACR-N mean Area Under Curve (AUC)	204.7	602.6	1476.3*	1952.4	3033.4	8326.4*
HAQ-DI <-0.22	38%	53%	93%*	46%	75%	64%
HAQ-DI (LS mean change from baseline)	-0.2	-0.3	-0.5*#	-0.1	-0.5	-0.5*
DAS28-CRP (LS mean change from baseline)	-1.4	-1.3	-2.0	-1.8	-1.9	-2.4
DAS28-CRP $\leq$3.2	19%	27%	36%	29%	54%	50%

* p<0.05 with p-values vs. placebo from Fisher's exact test for frequencies, from ANCOVA model using treatment as factor and baseline value as covariate for mean change, from one-way ANOVA on ranks for median ACR-N, and from t-test on log-transformed geometric mean for ACR-N AUC.
# week 12 results have been updated following access to additional patient visit data.

Summary of Key Efficacy Responses at Three and Nine Months for Subgroup with Prior Use of 1-2 Biologics:

	Week 12			Week 39		
	Placebo	**1M/kg**	**2M/kg**	**Placebo**	**1M/kg**	**2M/kg**
	N=9	N=10	N=11	N=9	N=10	N=11
ACR20	33%	60%	55%	22%	67%	60%
ACR50	11%	30%	55%	0%	33%	30%
ACR70	0%	20%	36%	0%	22%	30%
ACR-N median	13%	28%	50%	6%	43%	48%*
ACR-N mean Area Under Curve (AUC)	-393.0	1629.8	1713.8	-1567.0	7786.6*	10102.9*
HAQ-DI <-0.22	33%	60%	91%*	44%	67%	70%
HAQ-DI (LS mean change from baseline)	-0.1	-0.4	-0.6#	-0.1	-0.4	-0.6*
DAS28-CRP (LS mean change from baseline)	-1.1	-1.8	-2.4	-1.8	-2.0	-2.8
DAS28-CRP $\leq$3.2	22%	30%	40%	33%	56%	67%

*p<0.05 with p-values vs. placebo from Fisher's exact test for frequencies, from ANCOVA model using treatment as factor and baseline value as covariate for mean change, from one-way ANOVA on ranks for median ACR-N, and from t-test on log-transformed geometric mean for ACR-N AUC.
#week 12 results have been updated following access to additional patient visit data.

About Rheumatoid Arthritis
RA is a chronic autoimmune disease of unknown etiology, affecting approximately one percent of the global population. The disease is attributed to chronic inflammation affecting the synovial membrane of multiple joints, which eventually leads to cartilage and bone destruction. The health-related quality of life in patients with RA is significantly impaired by pain, fatigue, and decline in musculoskeletal function. RA is associated with an increased risk of cardiovascular disease and mortality.

Standard criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) are used to assess the effectiveness of RA treatments. The ACR20/50/70 response is a composite measure based on achieving 20%/50%/70% improvement in tender joint counts (TJC) or swollen joint counts (SJC) plus improvement in three of the following:

- Patient global assessment
- Physician global assessment
- Patient pain assessment
- Physical function/disability questionnaire (HAQ-DI)
- Acute phase reactant (sedimentation rate or high-sensitivity C-reactive protein)

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The patient and physician global assessments and pain assessment are measured using a visual analogue scale on a scale of 0-100. The ACR-N provides a single number that characterizes the percentage of improvement or deterioration from baseline that a patient has experienced in analogy to ACR20, ACR50, and ACR70 responses. The ACR-N is defined operationally as the lowest of 3 values (the percent change in the SJC, the percent change in the TJC, and the median of the other 5 measures in the ACR core data set). The ACR-N can be used to measure improvement at specific time points in a landmark analysis and expressed as the mean or median ACR-N achieved, or to compare the area under the curve (AUC) by patient over time. This approach may substantially increase the power to detect small differences between treatment arms.

The HAQ-DI assesses physical function in performing a variety of activities of daily living and yields a score ranging from 0-3 (lower is better). A reduction in the HAQ-DI score of -0.22 is the minimal clinically important difference. The DAS28 is another validated RA disease activity index based on a 28 joint count. The derived DAS28 scores are comprised of tender joint count; swollen joint count; acute phase reactant (hsCRP or ESR) and the subject's global assessment of disease but do not include measures of pain or physical function. High disease activity is defined as DAS28 score >5.1; moderate disease activity is defined as DAS28 scores between 5.1-3.2; low disease activity and remission are defined as DAS28 scores of $\leq$3.2 and <2.6, respectively.

In line with the FDA Guidance For Industry Rheumatoid Arthritis: Developing Drug Products For Treatment, May 2013, for dose-ranging studies the use of endpoints sensitive to change provide better discriminatory power for dose-response assessment. A clinical endpoint such as the ACR20 response criteria may not be optimal for this purpose, because it is a dichotomous endpoint, and using the proportion of responders in a small group of patients could be unreliable. Continuous variables such as DAS28, HAQ-DI, and ACR-N may be more sensitive to change and provide a more suitable alternative to ACR responder index. For continuous variables where changes from baseline are reported, the Least Squares of the Mean (ANCOVA) is utilized in order to adjust for baseline differences between groups.

About Mesoblast's Product Candidate MPC-300-IV and Potential Mechanisms of Action
Mesoblast's Tier 1 product candidate, MPC-300-IV, comprises 1-2 million immunoselected and culture-expanded STRO-1 positive cells/kilogram which are intravenously delivered. These cells express receptors for various pro-inflammatory cytokines, including TNF-alpha, interleukin-6, or interleukin-17, and are triggered by these cytokines to release potent immunomodulatory factors.

Mesenchymal lineage precursors and stem cells have been shown to be capable of targeting mechanistic pathways that are central to the process of progressive RA in humans, including by inhibiting the joint synovial fibroblast pro-inflammatory factor NF-kappaB that is implicated in synovial proliferation, inflammation, and joint destruction, and by polarizing pro-inflammatory monocytes and T cells to anti-inflammatory states. Notably, STRO-1 positive MPCs have been shown to be at least 10-fold more potent inhibitors of T-cell activation and proliferation than conventional plastic-adherent mesenchymal lineage cells.[1]

As reported on February 13, 2016, in the current version of *Stem Cell Research & Therapy,* published results in a sheep model of early RA showed that Mesoblast's MPCs administered intravenously significantly ameliorated inflammatory arthritis, providing important mechanistic and translational support for the improved clinical outcomes seen in this ongoing Phase 2 trial in patients resistant to anti-TNF agents.[2]

About Mesoblast
Mesoblast Limited (ASX:MSB; Nasdaq:MESO) is a global leader in developing innovative cell-based medicines. 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, 'off-the-shelf' cell product candidates target advanced stages of diseases with high, unmet medical needs including cardiovascular diseases, immune-mediated and inflammatory disorders, orthopedic disorders, and oncologic/hematologic conditions.

[1] Nasef et al. Int. Jnl. Lab. Hem. (2009) 31, 9.
[2] NCT01851070. Additional information available at: https://clinicaltrials.gov/show/NCT01851070

Conference Call and Webcast Details
Mesoblast will hold a conference call beginning at 9:00 am Australian Eastern Summer Time on Thursday February 16, 2017 / 5:00 pm Eastern Standard Time on Wednesday February 15, 2017.

The live webcast can be accessed via:
http://webcasting.boardroom.media/broadcast/589d209414b64de6232ccb86

To access the call, please dial:

Australia Toll Free	1 800 558 698
Australia Alternate	1 800 809 971
United States	1 855 881 1339
United Kingdom	0800 051 8245
Japan	0053 116 1281
Singapore	800 101 2785
Hong Kong	800 966 806
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The conference identification code is 957783.

Forward-Looking Statements
This press release includes forward-looking statements that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. Forward-looking statements should not be read as a guarantee of future performance or results, and actual results may differ from the results anticipated in these forward-looking statements, and the differences may be material and adverse. You should read this press release together with our risk factors, in our most recently filed reports with the SEC or on our website. Uncertainties and risks that may cause Mesoblast's actual results, performance or achievements to be materially different from those which may be expressed or implied by such statements, and accordingly, you should not place undue reliance on these forward-looking statements. We do not undertake any obligations to publicly update or revise any forward-looking statements, whether as a result of new information, future developments or otherwise.

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