ASX RELEASE

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Paradigm Achieves Primary Endpoint in PARA_OA_008 Synovial Fluid Biomarker Phase 2 Clinical Trial

KEY HIGHLIGHTS

- Primary endpoint relating to synovial fluid biomarkers achieved and positive top-line results reported for the PARA_OA_008 phase 2 clinical trial (n=61).
- Several osteoarthritis (**OA**) biomarkers analysed were observed to favourably change over time in patients treated with injectable PPS (**iPPS**) compared to placebo. These biomarker changes provide insight into iPPS mechanisms of action as well as signals of disease modifying potential.
- iPPS was associated with positive changes for several chondroprotective biomarkers.
- Additionally, iPPS-treated subjects demonstrated statistically significant improvement in WOMAC pain, function, and stiffness scores at day 56 for the twice-weekly group compared to placebo.
- Of the 61 patients, 48 (78%) had KL grades 3-4, indicating moderate to severe OA.
- In a separate canine study, positive interim observations on the effects of iPPS treatment on dogs with naturally occurring OA are also reported.
- Seven of nine dogs treated with iPPS had a clinically meaningful functional improvement in the affected limb as measured by the total pressure index percentage (**TPI**%) at week 8 compared to baseline. This provides supporting evidence on the improvements in clinical outcomes in PARA_OA_008 following iPPS.
- Paradigm will be hosting a webinar to discuss the positive top-line results at 9:30am (AEDT) today, Tuesday 4th October.

Paradigm Biopharmaceuticals Ltd (ASX:PAR) (Paradigm or the Company), a late-stage drug development company focused on delivering new therapies to address unmet medical needs, is pleased to announce that the primary endpoint has been met and additionally significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) pain and function scores were demonstrated for injectable iPPS in the PARA_OA_008 phase 2 clinical trial.

The day 56 data analysed by an independent clinical research organisation, demonstrates synovial fluid biomarker change from baseline for the iPPS treatment group. iPPS impacted multiple biomarkers measured in the synovial fluid. Reductions in nerve growth factor (**NGF**) indicate iPPS mechanisms related to pain reduction. Reductions in TNF-α and IL-6 indicate mechanistic effects on inflammatory pathways. Reductions in COMP and ARGS and an increase in TIMP-1 provide important insights into iPPS mechanisms of action impacting cartilage preservation and potential disease modification. In all cases, the synovial biomarker changes in iPPS-treated subjects at day 56 were favourable compared to placebo controls.

WOMAC data has also been collected from baseline. iPPS treatment showed statistically significant improvements at day 56 in pain, function, stiffness, and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm. The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.

iPPS was well tolerated in this randomised, placebo-controlled study. There were no serious adverse events and no adverse events of special interest in any patient receiving iPPS or placebo. The most common adverse reactions were injection site reactions, all of which were mild in intensity and self-limiting.

Paradigm is also pleased to present preliminary data from nine dogs treated with iPPS in the ongoing canine model of naturally occurring OA. Initial data in this study demonstrates a trend towards functional improvement in osteoarthritic dogs following iPPS treatment as well as a trend towards reductions in cartilage degrading biomarkers locally within the joint (synovial fluid) and systemically (serum).

The Urgent Need for a Disease Modifying OA Drug (DMOAD)

Osteoarthritis is the most prevalent form of arthritis and the risk of developing degenerate OA rises with increasing age. This debilitating disorder severely impacts upon quality of life due to primarily affecting the hands, lower back, neck, and weight-bearing joints such as knees, hips, and feet. A recent 2021 analysis of results from the 2017 Global Burden of Disease Study found that approximately 303.1 million cases of hip and knee OA existed worldwide, accounting for a global cumulative 9.6 million years lived with disability(1). Further underlining the economic burden, an additional comprehensive study estimated that in 2013, total US arthritis-attributable medical expenditures reached almost $US140 billion, which when combined with wage losses, totalled losses of over $US303 billion (2).

Current OA therapies, such as paracetamol, opioids, and nonsteroidal anti-inflammatory drugs (**NSAIDs**), as well as intra-articular medications, such as corticosteroids and hyaluronic acid, are solely focused on symptom management, as there are no established disease modifying therapies (3). Due to patient dissatisfaction with current OA treatments(4), there is a high unmet medical need for new therapies that can effectively reduce pain, improve joint function, and impede OA progression in tandem with symptomatic improvement. A DMOAD is defined as a drug that will “alter the natural history of disease progression by arresting joint structural change and ameliorate symptoms, either by reducing pain or improving physical function”(3).

Market research conducted through a global market intelligence and research organisation (ASX release 8th November 2021) found that payers in the United States would likely accept a price of US$2,000 to US$3,000 per year for iPPS as a therapy to reduce pain and improve function in knee OA.

If approved by the FDA with a disease modifying label, the price per year of therapy in the US could increase to US$6,000 and potentially higher.

PARA_OA_008 Clinical Trial Design

The PARA_OA_008 phase 2 clinical trial is designed to evaluate the treatment effects of iPPS on synovial fluid biomarkers associated with OA-related pain, inflammation, and disease progression in humans. The study also evaluates the effect of iPPS on these

biomarkers in serum and urine and investigates any correlation with synovial fluid biomarkers. In a prior phase 2b clinical trial, Paradigm observed serum and urine changes in biomarkers COMP, ADAMTS-5, and CTX-II, providing promising signals of iPPS mechanisms of action on joint preservation.

In the PARA_OA_008 clinical trial, subjects (n=61) were randomised and received either a subcutaneous injection of 2 mg/kg iPPS twice weekly, iPPS once weekly plus one placebo injection, or two placebo injections for 6 weeks. Patients had moderate to severe arthritis with Kellgren Lawrence (KL) grade 2-4 (where 4 is the maximum indicating severe OA), and baseline WOMAC pain scores of 4.6 to 10. This phase 2 clinical trial is an exploratory study and was not intended to be powered to obtain statistical significance. The aim is to provide novel scientific evidence to test the hypothesis that iPPS acts locally in the knee joint of OA subjects as well as provide data on whether biomarker changes correlate with clinical outcome (WOMAC pain and function assessments). Further evaluation on serum and urine biomarker correlations, and further longer-term clinical outcomes are in progress.

Biomarkers that alter in relation to clinical outcomes could help further clarify the multiple proposed mechanisms of action for iPPS in OA. This contrasts with currently available pharmacological agents which have thus far failed to deliver durable satisfactory patient outcomes of improved pain and/or function and disease modification.

PARA_OA_008 Top-Line Results

The Australian clinical trial operating at two sites in Victoria and NSW aims to gather data on the medium-term structure-modifying and symptom-modifying effects of iPPS on knee OA. Participants have been randomised into three treatment groups according to a 1:1:1 ratio (19 randomised to iPPS twice-weekly, 20 randomised to iPPS once-weekly plus a placebo injection once-weekly, 22 randomised to placebo twice-weekly). Of the 61 patients, 48 (78%) had KL grades 3-4, and the average median baseline WOMAC scores were 6.6 for pain and 6.9 for function.

Synovial Fluid Biomarkers

The primary endpoint for PARA_OA_008 is change from baseline at day 56 (two weeks post final injection) in one or more synovial fluid biomarkers. The analysed biomarkers include inflammatory cytokines (TNF-α, IL-1β, and IL-6); pain mediator NGF, and cartilage degrading markers such as COMP, ARGS and other disease modifying molecular biomarkers.

iPPS has been shown to exert anti-inflammatory activity by blocking the effects of proinflammatory cytokines, such as TNFα and IL-1β, in a cellular model of canine OA(5); inhibiting the expression of NGF, a pain mediator, in differentiated human osteocytes derived from subchondral bone samples obtained during arthroplasty for knee OA(6); and by inhibiting cartilage degrading enzymes known to play a key role in OA disease progression(7). In small clinical studies of 114 and 20 participants respectively, PPS has been shown to reduce pain and improve joint function in patients with knee OA(8,9).

Synovial Biomarker	iPPS compared to Placebo	Biomarker Function
NGF	**Reduced**	Nerve growth factor (**NGF**) is an important mediator of chronic pain and has been demonstrated to be increased in the synovial fluid of patients with OA. NGF production is also increased via upregulation of pro-inflammatory cytokines, such as TNF-α(6,10).
TNF-α	**Reduced**	Tumour necrosis factor alpha (**TNF-α**) is a pro-inflammatory cytokine that is upregulated in the synovial membrane in OA and contributes to cartilage degradation and hyperalgesia. TNF-α has been reported to activate sensory neurons directly via its receptors and initiates inflammatory reactions via production of interleukins. Serum levels of this cytokine have also been demonstrated to negatively correlate with WOMAC scores in OA patients(11).
IL-6	**Reduced**	Interleukin-6 (**IL-6**) is a pro-inflammatory cytokine implicated in the inflammation that contributes to the development and progression of OA. Increased concentrations of IL-6 have been detected in both the synovial fluid and serum of OA patients(12).
COMP	**Reduced**	**COMP** is a structural protein integral to proper articular cartilage function and increasing levels of COMP in serum have been correlated to subsequent radiographic degradation of articular surfaces in the knee(13).
ARGS	**Reduced**	Alanine–Arginine–Glycine–Serine (**ARGS**) is a biomarker used to assess the degradation of aggrecan, a major extracellular matrix (**ECM**) component. Increased ARGS concentrations in the synovial fluid, reflecting cartilage degradation, have been observed in OA patients in several studies(14).
TIMP-1	**Increased**	Tissue inhibitor of MMPs (**TIMP-1**) is a major endogenous inhibitor of cartilage degrading enzymes. TIMP-1 has been demonstrated to be reduced in OA(15).

Table 1: Biomarkers analysed with favourable results

WOMAC Pain and Function

Paradigm is assessing a number of key secondary and exploratory endpoints in the PARA_OA_008 phase 2 clinical trial, including:

- correlation between synovial fluid biomarker changes and clinical outcomes;
- changes in one or more synovial fluid biomarkers from baseline to 6 months;

- changes in WOMAC pain, function, stiffness, and patient global impression of change (**PGIC**) from baseline at designated timepoints; and
- MRI changes in the bone and joint.

Participants in the study were asked to provide baseline pain scores using the WOMAC osteoarthritis index. After patients had initiated treatment, their pain scores are measured at predetermined timepoints from day 11 out to 12 months, with day 56 the predetermined endpoint for WOMAC assessment. In Para_OA_008, the mean percentage change from baseline in WOMAC pain is 50% compared to 30%, p=0.05 for twice weekly iPPS and placebo, respectively. The mean percentage change from baseline in WOMAC function is 50% compared to 25%, p=0.017 for twice weekly iPPS compared to placebo, respectively.

Paradigm's primary endpoints in the current PARA_OA_002 phase 3 trial are improvements in pain and function from baseline at day 56 using the WOMAC osteoarthritis index.

Dr Donna Skerrett, Paradigm's Chief Medical Officer, said: *"We are very encouraged by the synovial fluid biomarker signals we see in this study. The observed changes indicate mechanistic effects through pain, inflammation, and chondroprotective pathways. These changes are consistent with the clinical effects observed in this and prior studies of iPPS in osteoarthritis. Evidence of multimodal effects supports our understanding of the actions of iPPS. These biomarker changes in the joint, following subcutaneous administration of iPPS, demonstrate local effects in the synovial fluid. These are meaningful signals that we will evaluate together with clinical and imaging outcomes in order to demonstrate disease modifying effects and to pursue regulatory authority guidance on a disease modifying pathway."*

Preliminary Analysis of the Ongoing Canine Model of Naturally Occurring OA

Interim analysis of the effects of iPPS treatment on dogs with naturally occurring OA has identified positive trends. This ongoing study consists of 21 client-owned dogs of varying breeds that presented at the U-Vet Werribee Animal Hospital, Victoria, Australia, for lameness assessment. Dogs of both genders with either radiologically and/or clinically defined OA of the knee/stifle (hind limb) or elbow (front limb) are progressively screened and randomised in a 2:1 ratio to either treatment with iPPS or saline (placebo) groups to attain a total of 14 iPPS treated and 7 control dogs.

The canine OA study aims to confirm the *in vivo* mechanism of action of iPPS and to define potential disease modification outcomes. The key data sought from this study are changes from baseline at week 8 and week 26, in:

i) Joint function as measured by percentage body weight distribution (**BWD**%) in the affected limb as measured by the TPI%.

ii) Biomarkers of joint degeneration within the synovial fluid and in serum; and

iii) Structural changes determined by OA clinical scores as assessed by X-ray and MRI.

Early interim observations in nine osteoarthritic dogs who had received subcutaneous iPPS at a dose of 3 mg/kg (human equivalent dose of 1.7 mg/kg) weekly for 6 weeks demonstrated the following:

i) Seven of nine dogs treated with iPPS had a clinically meaningful improvement in the affected limb as measured by TPI% at week 8 compared to baseline.

ii) A mean percentage change (improvement) from baseline in TPI% of 10.08% was observed for the affected hind limb (n=5) and 5.6% for the affected front limb (n=4). A mean increase of 5% in TPI% is considered to be a clinically meaningful improvement (16,17).

iii) Dogs demonstrated a response to iPPS treatment with changes in cartilage degradation biomarkers in the synovial fluid. Aggrecan degradation neoepitope (**ARG**) the canine equivalent of human ARGS, levels were reduced in the synovial joint of 3/4 iPPS-treated dogs. These results support the *in vivo* MoA since iPPS inhibits ADAMTS-5 enzyme, which degrades aggrecan in cartilage to produce ARG (18). Furthermore, it is known that degrading cartilage matrix releases hyaluronic acid (**HA**) into the synovial fluid in OA (19). In this study, 4/4 dogs had reduced levels of HA following iPPS treatment.

iv) Analysis of serum biomarkers demonstrated that 3/6 dogs showed a reduction in serum ARG, and 5/9 dogs had reduced serum HA, supporting the effect of iPPS on these biomarkers observed in the synovial fluid. Additionally, in the serum, it was demonstrated that 7/9 iPPS-treated dogs responded to treatment with reduced levels of C3M (a degradation fragment of type III collagen), 6/9 dogs had lower levels of CTX-I (a degradation fragment of type I collagen), and 4/9 dogs had reduced levels of CTX-II (a degradation product of type II collagen) (20).

Paradigm Chief Scientific Officer, Dr Ravi Krishnan, commented on the study: *"We are encouraged by these preliminary data on the potential of iPPS to improve joint function and reduce the levels of biomarkers of cartilage degeneration in this translationally relevant model of naturally occurring OA. We are continuing with the recruitment of dogs to obtain the complete set of data points to allow comparisons with iPPS treated and placebo-treated dogs to provide supportive evidence for iPPS as a potential treatment to modify the progression of OA and provide long term durability of effect".*

Naturally Occurring Canine OA and Translational Relevance of the Canine OA Model for Evaluating DMOADs

The phenotypic characteristics and heterogeneity of OA are similar in both humans and dogs. Therefore, it is expected that the canine model of OA would provide relevant translational data that parallel the human clinical scenario (21).

Both human and canine OA are progressive degenerative disorders and are influenced by similar risk factors. OA in humans primarily affects the knee, hip, and shoulder joints, and pathological changes closely resemble those observed in the canine stifle (knee), hip, and shoulder joints (21). Because the dog's lifespan is shorter relative to that of humans, all stages of development from birth to adulthood and ageing are represented over a shorter time frame, including disease onset and manifestation. This aspect of the canine model is potentially advantageous in rapidly evaluating DMOAD status of iPPS that otherwise would require a longer assessment period in humans to analyse OA joint structural changes.

Early top-line results indicate that iPPS treatment in osteoarthritic dogs likely demonstrates a functional improvement in BWD% as measured by the TPI%. TPI% is functionally equivalent to BWD%, and since TPI% is not influenced by stride frequency, it was identified to be the most accurate and valuable measurement for veterinarians when evaluating a heterogeneous group of dogs. Improvement in the TPI% scores is defined as a numerical increase in the TPI% value of the affected limb.

In four iPPS-treated dogs, the front limb demonstrated an initial trend towards improved TPI%. A similar positive trend was also observed in the hind limb in five iPPS-treated dogs.

iPPS treatment in osteoarthritic dogs may also demonstrate a reduction in cartilage degradation biomarkers locally within the synovial joint and systemically via serum analysis. Responders are defined as dogs that demonstrated a reduction in the level of a specific biomarker at week 8 when compared to the biomarker level at baseline. At the time of analysis, synovial fluid biomarker data was only available for four out of the nine dogs.

Six-month Follow-up (day 168) Data

The PARA_OA_008 phase 2 clinical trial will continue to monitor trial participants following treatment through the 6-month and out to 12-month timepoints. The 6-month time point for PARA_OA_008 will provide further data on the duration of effect of iPPS on WOMAC pain and function compared to placebo combined with observations on changes to the joint structure by MRI of iPPS treated subjects compared to placebo. The secondary and exploratory endpoints at 6-month timepoint, include:

- changes in one or more synovial fluid biomarkers;
- changes and correlation between synovial fluid, serum, and urine biomarkers and correlation with changes in clinical outcomes;
- changes in WOMAC pain, function, stiffness and quality of life scores;
- MRI changes in the bone and joint; and
- Incidence of treatment-emergent adverse events (**TEAEs**), including serious adverse events (**SAEs**).

Paradigm expects to report on the 6-month data in Q1 CY2023. Data from this study will be prepared for peer-review and publication with the Company providing an update once timing can be confirmed.

Recruitment for the canine OA model remains ongoing in order to complete treatment groups to enable meaningful comparisons to be made. The longer follow-up period at week 26 (equivalent to 3 years in human terms) will allow for collective analyses of pain, function, joint structure, and biomarker levels following iPPS therapy, and will provide informative data to assess the potential of iPPS as a DMOAD. The complete study report examining both week 8 and week 26 responses in the final cohort of dogs will be reported in 1H CY2023.

Paradigm CEO, Marco Polizzi commented: "*Achieving the primary endpoint with consistent significant reductions in pain in iPPS-treated patients compared to placebo is an outstanding milestone for the Company. The top-line results are encouraging at day 56 and we look forward to further data at 6 and 12 months.*

The biomarker changes following iPPS, the statistically significant signals that we are observing in the WOMAC scores along with the safety and tolerability of iPPS in this exploratory study, will be valuable in discussions with regulatory bodies (FDA and TGA) and commercial partners".

Investor Webinar

Paradigm Biopharmaceuticals will hold an investor webinar on Tuesday 4th October 2022 at 9:30am (AEDT) with CEO, Marco Polizzi; Chief Medical Officer, Dr Donna Skerrett; and Chief Scientific Officer, Dr Ravi Krishnan.

The webinar will discuss the positive top-line results from the PARA_OA_008 phase 2 trial and early observations from the canine OA model released to the market.

Please register for the webinar at the following link:
https://us02web.zoom.us/webinar/register/WN_Yf-BLoMjTKODHnnfduX1uA

After registering, you will receive a confirmation email about joining the webinar. Following the webinar, a recording will become available on the Paradigm website.

A copy of the presentation can be viewed on the Paradigm website
https://paradigmbiopharma.com/performance-progress/#presentations

About WOMAC Scores

The Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) is a widely used, proprietary set of standardised questionnaires used by health professionals to evaluate the condition of patients with OA of the knee and hip, and includes pain, stiffness, and physical functioning of the joints. The WOMAC has also been used to assess back pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia. It consists of 24 items divided into 3 sub-scales (22):

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright;
- Stiffness (2 items): after first waking and later in the day;
- Physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) is a late-stage drug development company driven by a purpose to improve patients' health and quality of life by discovering, developing, and delivering pharmaceutical therapies. Paradigm's current focus is developing injectable (subcutaneous) pentosan polysulfate sodium (**iPPS**) for the treatment of diseases where inflammation plays a major pathogenic role, indicating a need for the anti-inflammatory and tissue regenerative properties of PPS, such as in osteoarthritis (phase 3) and mucopolysaccharidosis (phase 2).

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical

trials, regulatory developments and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

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To learn more please visit: www.paradigmbiopharma.com

FOR FURTHER INFORMATION PLEASE CONTACT:

Simon White
Director of Investor Relations
Tel: +61 404 216 467
Paradigm Biopharmaceuticals Ltd
ABN: 94 169 346 963
Level 15, 500 Collins St, Melbourne, VIC, 3000, AUSTRALIA
Email: investorrelations@paradigmbiopharma.com