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Paradigm's Presentations at the OARSI 2023 World Congress on Osteoarthritis

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 provide the presentations that were delivered at the Osteoarthritis Research Society International (**OARSI**) 2023 World Congress. The international conference was held in Denver, Colorado from 17–20 March 2023, with the Clinical Trial Symposium presented during the evening on March 16.

Paradigm conducted three presentations during the OARSI World Congress:

1. Clinic Trial Symposium (**CTS**): Dr. Donna Skerrett, Paradigm's Chief Medical Officer, was invited to present the technology, mechanism of action, and clinical translation potential for Paradigm's ongoing global OA program.
2. Poster Presentation of Day 56 PARA_OA_008 data: Dr. Mukesh Ahuja, Paradigm's Global Clinical Head of OA, presented a poster detailing the clinical trial design and Day 56 top-line data from the PARA_OA_008 clinical trial exploring the disease modifying potential of injectable pentosan polysulfate sodium (**iPPS/Zilosul®**) in patients with knee osteoarthritis (**OA**).
3. Sponsored Theatre Presentation: Paradigm's Chief Scientific Officer Dr. Ravi Krishnan and Dr. Mukesh Ahuja conducted an oral presentation which covered Paradigm's global OA program, including the Day 56 top-line data from the PARA_OA_008 clinical trial and 8-week data from the canine study of naturally occurring OA.

The poster presented during the OARSI World Congress is available at the end of this release. The CTS and Sponsored presentations can be viewed via the Paradigm website: https://paradigmbiopharma.com/performance-progress/#announcements .

Paradigm's Managing Director, Mr Paul Rennie commented from the OARSI conference "*The OARSI conference was an excellent forum for Paradigm to annunciate its significant progress in the clinical development of iPPS for the treatment of OA. Paradigm's preclinical and clinical data was a standout as it presented significant clinical improvements (reduction in pain and improvement in joint stiffness), synovial, serum and urine OA disease biomarkers, joint structural changes, and durability of effectiveness. I would like to congratulate the entire clinical development team, led by Dr Skerrett and head of OA, Dr Mukesh Ahuja and the entire R&D team led by Dr Ravi Krishnan. Paradigm had many visitors to our conference stand, and they all congratulated us on the speed of development and the quality of the data*"**.**

Six-month Follow-up (Day 168) Data Release

The 6-month data from the PARA_OA_008 phase 2 clinical trial exploring the disease modifying properties of iPPS, will provide further data on the duration of effect of iPPS on

WOMAC pain and function compared to placebo. In addition, this study aims to provide insights into the changes to the joint structure by MRI of iPPS-treated subjects compared to placebo. The secondary and exploratory endpoints at the 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 confirms it expects to release these data by the end of March 2023. Data from this study will be prepared for peer-review and publication with the Company providing an update once timing can be confirmed.

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.

Authorised for release by the Paradigm Board of Directors.

To learn more please visit: www.paradigmbiopharma.com

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An Exploratory, Phase 2 Clinical Trial in Knee Osteoarthritis Subjects Suggests Therapeutic Effects of Pentosan Polysulfate Sodium on Synovial Fluid Biomarkers of Pain, Inflammation and Chondroprotection

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Background

Osteoarthritis

Osteoarthritis (OA) is a multifactorial and disabling disease, leading to chronic pain, disability, and a decreased quality of life (QoL). Pain is a primary symptom of knee OA. Pain associated with bone pathology, including OA, results in substantial burden, in terms of QoL and health care costs. The prevalence of these conditions is high; OA affects 10% of men and 18% of women older than 60 years of age (worldwide estimate), and up to 30% of postmenopausal women in the US[1, 2]. Even with current standard of care therapies, QoL in most patients with OA is significantly impaired by severe, often intractable, pain[3]. Currently approved drug treatments for OA are only palliative and do not slow or reverse disease progression. The search for a disease-modifying osteoarthritis drug (DMOAD) is a continuing goal. Recent research for a DMOAD has focused on biomarkers of pain and cartilage degeneration.

Injectable pentosan polysulfate sodium (iPPS, Zilosul™-Paradigm Biopharmaceuticals Ltd, Australia) is an investigational drug with disease modifying potential for OA treatment. PPS targets inflammation via inhibition of the transcription factor NF-κB, pain through the inhibition of NGF expression in osteocytes, and tissue preservation by inhibiting the cartilage-degrading enzymes (Figure 1).

PPS in Osteoarthritis

Pentosan polysulfate sodium (PPS) is a semi-synthetic xylose-based polysaccharide (hemicellulose) that is derived from beechwood and is highly sulphated during its manufacturing process. Due to the added sulfated moieties, PPS structurally mimics glycosaminoglycans.

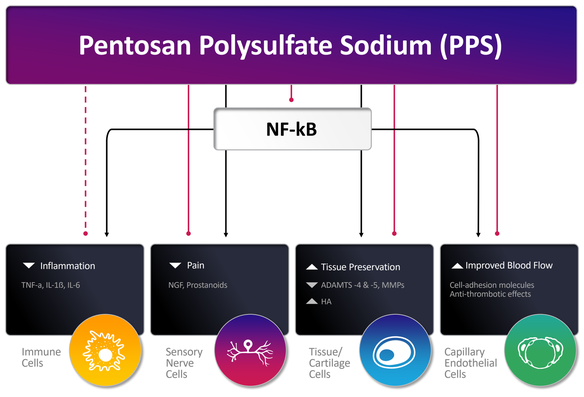
Preclinical and clinical evidence suggests that PPS may treat the pain and arthropathy in osteoarthritis[4, 5, 6, 7], filling a significant unmet medical need for a safe and effective therapy.

PPS Mechanisms of Action in Osteoarthritis

The key mechanisms of action of PPS that are relevant in OA are mediated through inhibition of NF-kB (Figure 1) resulting in:

- Directly binding to the transcription factor, NF-kB, in the cytoplasm inhibiting its activation and therefore translocation into the nucleus. The inhibition of nuclear translocation of NF-kB results in the reduction of gene expression of pro-inflammatory mediators including inflammatory cytokines, IL-1β , IL-6 and TNF-α[8 ,9].
- Reduced expression of the pain mediator nerve growth factor in osteocytes from degenerating joint[10].
- Inhibition of cartilage-degrading enzymes known to play a key role in progression of OA[11].
- Mild antithrombotic activity, which acts to improve blood flow in subchondral bone[12].

Figure 1. PPS Mode of Action in Patients with OA



Acknowledgements

This study is funded by Paradigm Biopharmaceuticals Ltd. MA, MD, CG, DN, RK, and DS are employees of Paradigm Biopharmaceuticals Ltd.

Study Design

Objective

Investigate changes in synovial fluid (SF) biomarkers in subjects with knee OA pain treated with PPS compared with placebo-treated subjects.

Key Eligibility Criteria

- Subjects ≥ 18 years of age.
- Radiographic diagnosis of knee OA with Kellgren-Lawrence (K-L) Grade 2, 3, or 4.
- OA pain for ≥6 months and unresponsive to conservative therapy.

Treatment and Follow-up

Subjects received injectable PPS (iPPS) 2.0 mg/kg ideal body weight (IBW) twice-weekly for 6 weeks, 2.0 mg/kg IBW PPS once-weekly + placebo once weekly, or placebo-twice weekly for 6 weeks. Following the 6-week treatment period subjects are being evaluated in a 46-week follow-up period.

Assessments

Synovial Fluid Biomarker Assessments

- Cartilage oligomeric matrix protein (COMP).
- A disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5).
- c-terminal telopeptide (CTX)–II
- Type II collagen (C2C).
- Nerve growth factor (NGF).
- Interleukin (IL) -1β.
- Aggrecan amino acids alanine, arginine, glycine, and serine (ARGS).
- Tumour necrosis factor alpha (TNF-α).
- Tissue inhibitor matrix metalloproteinase 1 (TIMP-1).
- IL-6.

Clinical Assessments

Western Ontario and McMaster Universities Osteoarthritis (WOMAC®) Numeric Rating Scale (NRS) 3.1 Index

- Pain
- Function
- Stiffness

Safety Assessments

- Adverse events
- Laboratory values

Analyses

Analysis of SF biomarkers was quantitated using verified enzyme-linked immunosorbent assay (ELISA) kits and where samples were lavaged correction factors were imputed.

The percentage change from baseline to Day 56 were compared between treatment groups using a mixed model for repeated measures (MMRM) analysis. The MMRM model included factors for treatment group (PPS once-weekly, PPS twice-weekly, placebo), randomization stratification factor (K-L grades 2, 3, 4), age as a continuous variable, treatment-by-time interaction, baseline value of the biomarker, and baseline-by-time interaction.

References

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Results

Study Subjects

Baseline Characteristics

- Of the 61 subjects treated within the study, 49 (80%) had K-L grades 3 - 4 (moderate/severe) OA.
- Mean baseline WOMAC NRS 3.1 overall scores for iPPS once-weekly, twice-weekly, and placebo were 7.08, 6.43, and 6.75 respectively.

Randomization

- 20, 19 and 22 subjects were randomized to iPPS once-weekly, twice-weekly, and placebo, respectively.
- 17, 15 and 21 subjects randomized to iPPS once-weekly, twice-weekly, and placebo, respectively completed study treatment.

Study Results

Synovial Fluid Biomarker Assessments

The SF biomarkers at Day 56 showed favorable changes from baseline in subjects treated with iPPS compared to placebo. Biomarkers of COMP, NGF, ARGS, TNF-α, and IL-6 were reduced, while TIMP-1 increased in subjects treated with iPPS compared to placebo (Table 1). Adjusted percent change in synovial fluid biomarkers with favorable changes from baseline are provided in Table 2.

The SF biomarkers of ADAMTS-5, CTX-II, C2C, and IL-1β had insufficient numbers of results above the lower limit of quantification (LLQ), therefore the data for these biomarker data could not be reliably interpreted.

Table 1. Summary of Synovial Fluid Biomarkers with Favorable Changes in iPPS-treated Subjects at Day 56

Biomarker	iPPS Compared to Placebo	Biomarker Function
TNF-α	Reduced	Pro-inflammatory cytokine
IL-6	Reduced	Pro-inflammatory cytokine
NGF	Reduced	Pain mediator
COMP	Reduced	By-product of cartilage degradation
ARGS	Reduced	By-product of cartilage degradation
TIMP-1	Increased	Endogenous inhibitor of cartilage degradation

ARGS = aggrecan amino acids alanine, arginine, glycine, and serine; COMP = Cartilage oligomeric matrix protein IL-6 = interleukin – 6; NGF = nerve growth factor; TIMP-1 = Tissue inhibitor matrix metalloproteinase 1; TNFα = tumor necrosis factor alpha.

Table 2. Adjusted Percent Change in Synovial Fluid Biomarkers with Favorable Changes from Baseline

Biomarker	Statistics	PPS once-weekly N=17	PPS twice-weekly N=15	PPS pooled N=32	Placebo N=22
COMP (µg/mL)					
	LS mean change from baseline	-25.56	9.47	-4.67	26.17
	(95% CI)	(-67.31, 16.19)	(-25.53, 44.47)	(-33.04, 23.70)	(-3.14, 55.49)
	LS mean difference[1]	-51.73	-16.70	-31.42	
	(95% CI)	(-100.62, -2.84)	(-60.97, 27.57)	(-70.42, 7.57)	
NGF (pg/mL)					
	LS mean change from baseline	5.33	51.12	35.10	60.33
	(95% CI)	(-72.58, 83.24)	(-5.70, 107.94)	(-10.29, 80.50)	(13.24, 107.43)
	LS mean difference[1]	-55.01	-9.21	-26.47	
	(95% CI)	(-141.70, 31.68)	(-81.23, 62.81)	(-88.31, 35.36)	
ARGS (ng/mL)					
	LS mean change from baseline	25.16	23.02	23.82	79.96
	(95% CI)	(-32.54, 82.85)	(-23.12, 69.16)	(-13.69, 61.33)	(40.82, 119.10)
	LS mean difference[1]	-54.81	-56.94	-56.15	
	(95% CI)	(-123.44, 13.83)	(-115.88, 1.99)	(-108.32, -3.98)	
TNFα (pg/mL)					
	LS mean change from baseline	65.01	184.71	142.44	245.46
	(95% CI)	(-119.63, 249.65)	(44.57, 324.86)	(26.00, 258.87)	(125.81, 365.11)
	LS mean difference[1]	-180.45	-60.75	-100.97	
	(95% CI)	(-398.98, 38.09)	(-238.57, 117.06)	(-262.74, 60.79)	
IL-6 (pg/mL)					
	LS mean change from baseline	-9.29	97.86	56.00	72.38
	(95% CI)	(-119.35, 100.78)	(7.46, 188.25)	(-19.39, 131.40)	(-3.59, 148.34)
	LS mean difference[1]	-81.66	25.48	-17.32	
	(95% CI)	(-211.33, 48.00)	(-89.36, 140.32)	(-121.32, 86.68)	
TIMP-1 (µg/mL)					
	LS mean change from baseline	32.49	4.97	14.31	4.83
	(95% CI)	(-19.07, 84.04)	(-33.09, 43.03)	(-17.41, 46.04)	(-27.42, 37.08)
	LS mean difference[1]	27.66	0.14	9.29	
	(95% CI)	(-32.26, 87.58)	(-48.11, 48.40)	(-34.27, 52.85)	

ARGS = aggrecan amino acids alanine, arginine, glycine, and serine; Comp = Cartilage oligomeric matrix protein; CI = confidence interval; IL-6 = interleukin – 6; LS = least square; NGF = nerve growth factor; TIMP-1 = Tissue inhibitor matrix metalloproteinase 1; TNFα = tumor necrosis factor alpha.
[1] PPS - Placebo

Study Results

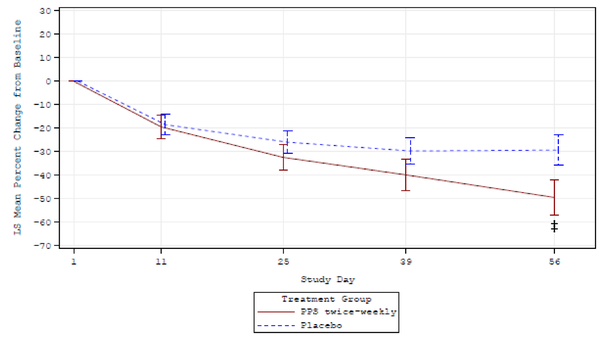
Clinical Assessments

Significant improvement in WOMAC NRS 3.1 Index Pain Subscale scores were observed over time in subjects treated with iPPS twice-weekly. At Day 56, the LS mean percentage change from baseline WOMAC NRS 3.1 Index Pain score was 49.5% and 29.7% (Figure 2), in participants treated with iPPS twice-weekly (mean baseline score was 6.37) and placebo (mean baseline score was 6.69), respectively (p=0.050). The LS mean percentage change from baseline WOMAC NRS 3.1 Index Function Subscale score at Day 56 was 50.0% and 24.9% (Figure 3), in participants treated with iPPS twice-weekly (mean baseline score was 6.43) and placebo (mean baseline score was 6.71), respectively (p=0.017). The LS mean percentage change from baseline WOMAC NRS 3.1 Index Stiffness Subscale score at Day 56 was 45.2% and 23.2% (Figure 4), in participants treated with iPPS twice-weekly (mean baseline score was 6.43) and placebo (mean baseline score was 6.71), respectively (p=0.058). At Day 56, significant changes in pain and function were not apparent in the once-weekly iPPS group compared to placebo.

Safety

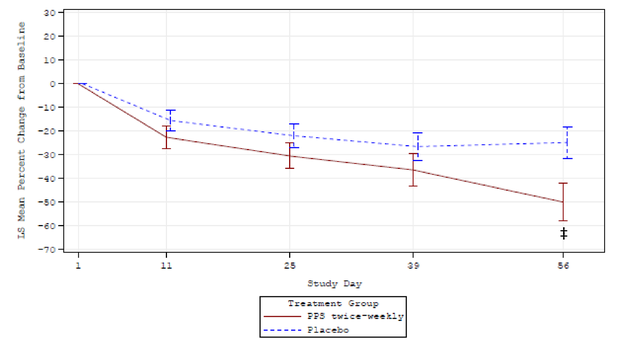
Treatment with PPS was well tolerated with no serious AEs and no AEs of special interest in any subjects. The most common AE was injection site reactions which were mild to moderate in severity.

Figure 2. Percentage Change from Baseline in WOMAC NRS 3.1 Index Pain Subscale



LS = least square; WOMAC = Western Ontario and McMaster Universities ; NRS = Numeric Rating Scale; PPS = pentosan polysulfate sodium
Error bars are standard error.
‡ p = 0.050

Figure 3. Percentage Change from Baseline in WOMAC NRS 3.1 Index Function Subscale



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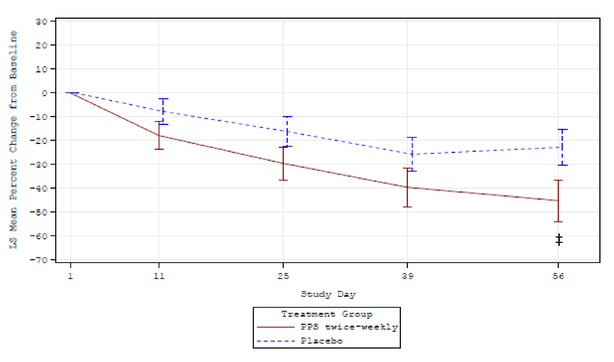
Error bars are standard error.
‡ p = 0.017

Figure 4. Mean Percentage Change from Baseline in WOMAC NRS 3.1 Index Stiffness Subscale



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Error bars are standard error.
‡ p = 0.058