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

M Ahuja[1], M Duiker[1], C Gravance[1], D Navuru[1], R Krishnan[1], D Skerrett[1], O Cumming[2], P Bloom[3]

[1]Paradigm Biopharmaceuticals Ltd., Melbourne, Australia, [2]Novatrials Kotara Australia, [3]Sportsmed Biologic, Box Hill, Australia

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.

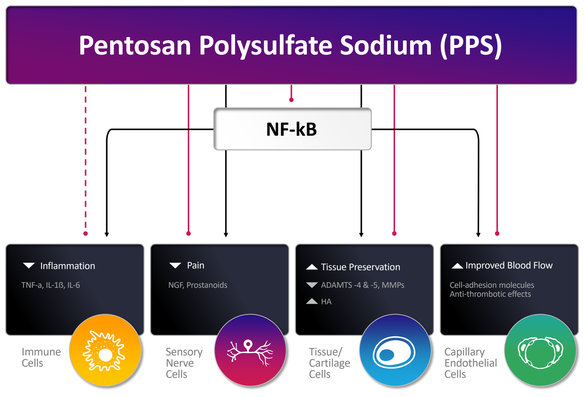
Preclinical and clinical evidence suggests that PPS may treat the pain and arthropathy in osteoarthritis[4, 5, 6, 7], filling a significant unmet medical need for a safe and effective therapy.

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

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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

1. Woolf, Pfleger. Bull World Health Organ. 2003;81:646–656.
2. Nencini, Ivanusic.Front Physiol [Internet]. 2016;7:157. doi:10.3389/ fphys.2016.00157.
3. Bove SE, et al. Brain Res Rev [Internet]. 2009;60:187–201. doi:10.1016/j.brainresrev.2008.12.012.
4. Wijekoon et al. Res Vet Sci. 2019;122:179.
5. Read et al. J Small Anim Prac. 1996;37:108-114
6. Ghosh et al. Curr Ther Res Clin Exp. 2005;66:552
7. Kumagai et al. BMC Clin Pharmacol. 2010;10:7
8. Sunaga T, et al. J Vet Med Sci. 2012;74:707–711.
9. Bwalya EC, et al. PLOS ONE. 2017;12(5):e0177144,
10. Stapledon CJM, et al. PLoS One. 2019 Sep 26;14(9):e0222602.
11. Troeberg L, et al. Biochem J. 2012;443(1):307-15.
12. Kutlar A, et al. Am J Hematol. 2012;87:536–539.

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

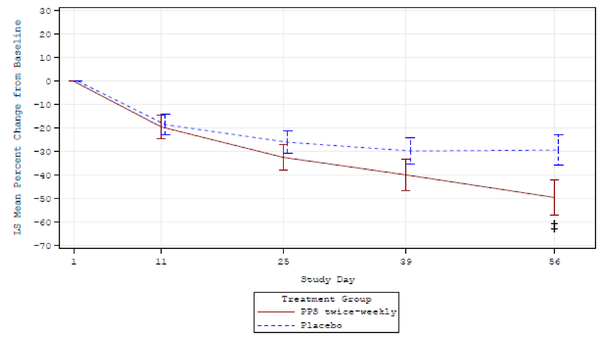
Clinical Assessments

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

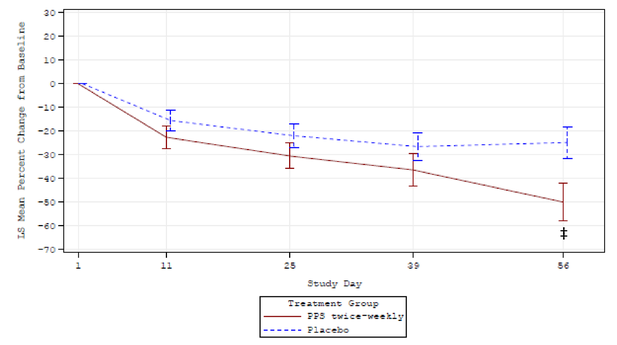
Treatment with PPS was well tolerated with no serious AEs and no AEs of special interest in any subjects. The most common AE was injection site reactions which were mild to moderate in severity.

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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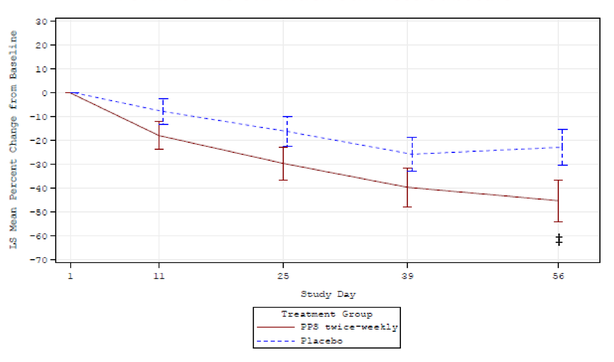
‡ p = 0.017

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