PARADIGM BIOPHARMACEUTICALS LIMITED

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PARADIGM REPORTS VERY ENCOURAGING REAL-WORLD DATA AHEAD OF ITS PHASE 3 OA CLINICAL TRIAL.

KEY HIGHLIGHTS

- Paradigm reports very encouraging real-world data ahead of its phase 3 OA clinical trial using the Phase 3 product and two Phase 3 endpoints.
- Phase 3 clinical trial IND filing will have primary endpoint as (i) reduced WOMAC pain from baseline and (ii) improved Patient Global Impression of Change (PGIC) at as secondary endpoint.
- Paradigm is pleased to report that pain reductions in 34 SAS patients (new data) being treated using the Phase 3 product (Zilosul®) are consistent with prior reports under TGA SAS. The chronic pain response as measured by the WOMAC pain score demonstrated a mean reduction of 44.9%. The acute pain response in the 34 SAS patients demonstrated a mean reduction in baseline NRS pain score as at 3 months (week 12 or Day 81) of 50.1% which is consistent with previous reported reductions using NRS pain score measure. (Refer PAR ASX Announcements 25 Sep. 2018, 28 May 2019)
- The WOMAC pain score which is a composite of 5 pain subgroups demonstrated pain reductions across patients in; night-time pain (75%); sitting (61.3%), standing (48.4%), walking on flat surface (45%) and pain on stairs (reduction 38%). These WOMAC scores compare favourably with analgesic products (see table 4 below).
- The 34 SAS patients showed that the phase 3 PPS formulation was well tolerated and had demonstrated a continued excellent safety profile with no serious adverse events reported.
- These results provide important Real-World Evidence (RWE) and inform us of the anticipated responses in everyday clinical practice and will support Paradigm's Phase 3 clinical trial. Paradigm intends to report on a cohort 100 SAS results by Q3 CY 2020.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) The primary and secondary endpoints for Paradigm's proposed phase 3 trial will be (i) reduced WOMAC pain from baseline and (ii) improved Patient Global Impression of Change (PGIC) at week 8 (Day 53). Paradigm is pleased to report a 45% mean reduction in WOMAC pain subscale of the WOMAC Osteoarthritis index across 34 patients with knee osteoarthritis (OA) using the current phase 3 clinical trial product. Doctors treated their OA patients with injectable pentosan polysulfate (iPPS) (Zilosul®) under the Therapeutic Goods Administration Special Access Scheme (TGA SAS). As previously reported (ASX release 28 May 2019), Paradigm has completed the production of its Phase 3 Clinical trial product (Zilosul®) and from Q3 CY2019 Doctors commenced treating patients with the Phase 3 Clinical Trial product under the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS).

About WOMAC Scores

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)™ is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including 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 subscales[1]:

- 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.

Paradigm's primary endpoint in the forthcoming Phase 3 trial design will be a reduction in pain from baseline using the WOMAC pain scale. **Table 1** below shows the average WOMAC pain reduction (5 items) for 34 patients treated with iPPS under the TGA SAS.

Table 1: Womac Pain Reduction (N = 34).

WOMAC Pain Questionnaire	Mean Baseline value (95% Confidence interval)	Mean Post-treatment value (95% Confidence interval)	Mean Reduction in Pain (percentage) (N=34patients)
1. Pain Walking on flat surface	5.94 (5.23, 6.65)	3.18 (2.46, 3.90)	44.8%
2. Pain Going up/downstairs	7.24 (6.56, 7.92)	4.3 (3.38, 5.22)	37.93%
3. Pain At night	4.97 (3.96, 5.97)	1.68 (0.96, 2.4)	75.11%
4.Pain Sitting/lying	4.15 (3.36, 4.94)	1.59 (0.87, 2.30)	61.39%
5. Pain Standing upright	5.29 (4.61, 5.97)	2.53 (1.78, 3.28)	48.54%
WOMAC Pain Subscale	**27.38 (23.94, 30.81)**	**13.38 (9.97, 16.78)**	**44.93%**

These data are well defined within 95% confidence intervals. This means these data have tight standard deviation around the mean with no overlap of intervals between the baseline results and the post PPS treatment results.

On the 28th of May 2019, Paradigm reported greater than 50% pain reduction across 205 patients with Knee OA. The clinical knee pain outcome measure that was used was NRS pain score 0-10. **Table 2** below displays the 34 patients treated with iPPS (Zilosul®) showed pain reductions consistent with prior reports under TGA SAS.

Table 2. NRS Acute pain

NRS Pain	Mean Baseline value (95% Confidence limits)	Mean Post-treatment value (95% Confidence limits)	Mean Reduction in Pain (percentage) (N=34patients)
Acute	5.11 (4.4, 5.82)	2.74 (1.91, 3.57)	50.07%

Patient Global impression of Change (PGIC) is a self-reported measure that reflects the patient's belief about the overall efficacy of the treatment. Patient's rate their change from No Change (or condition worsened) through to Considerable improvement that has made all the difference. Paradigm's Phase 3 trial will include an improved PGIC at week 8 (Day 53) as an endpoint. Table 3 below shows the PGIC Scores for 34 patients under the TGA SAS.

Table 3: PGIC Score (Subjects with WOMAC scores)

Visit PGIC Scores	WOMAC Subjects (N = 34)
Post-Baseline	
No Change (or condition has got worse)	0
Almost the same, hardly any change at all	2 (5.7%)
A little better, but no noticeable change	2 (5.7%)
Somewhat better, but the change has not made any real difference	0
Moderately better, and a slight but noticeable change	8 (22.9%)
Better and a definite improvement that has made a real and worthwhile difference	13 (37.1%)
A great deal better and a considerable improvement that has made all the difference	9 (25.7%)

85.7% (30 out of 34) of SAS patients had reported Patient global impression of Change (PGIC) of moderately to definite and considerable improvement in their OA condition with iPPS (Zilosul®) treatment.

Comparisons

Currently opioid use has resulted in significant dependency issues (addiction) and non-addictive alternatives are lacking. Paradigm's Zilosul® is a strong candidate to fill a much-needed gap in the treatment options available to clinicians.

Table 4. Comparing iPPS WOMAC pain reduction with Daily Opioids (Opiate **once a day**) for 12 weeks.

	Mean Reduction in WOMAC pain score week 12
Paradigm results iPPS under SAS.	**45%.** The WOMAC pain score reduction of treatment with Zilosul® from baseline to 12 weeks is 45%. This means the pain reduction result is still present 6 weeks after the last Zilosul® injection.
Source:	Paradigm data

	Mean Reduction in WOMAC pain score week 12
Tramadol (Opiate) 300 mg	**46%**
Tramadol (Opiate) 200 mg	**43%**
Source:	*Fishman RL et al Efficacy and safety of 12 weeks of osteoarthritic pain therapy with once-daily tramadol (Tramadol Contramid OAD).2007. J Opioid Manag. 2007 Sep-Oct;3(5):273-80.*

Mr. Paul Rennie, Paradigm's Chief Executive Officer said:
"We are very pleased to see continued real world evidence that Zilosul® reduced Knee OA pain and that the WOMAC pain subscale score showed a reduction of 45%. This reduction in pain from baseline compares with the published WOMAC pain reduction of the opioid analgesic, Tramadol. Of important relevance to us is that when compared to other treatment options available for OA, Zilosul® has a longer lasting effect".

"In clinical trials the Patient global impression of Change (PGIC) scale is used as the "gold standard" of clinically significant change and therefore we were delighted to note that 85.7% of SAS patients had shown moderately to definite and considerable improvement in their OA condition with iPPS (Zilosul®) treatment".

"The number of patients seeking Zilosul® treatment via the TGA SAS is a strong feedback that there is a lack of effective and satisfactory treatment options available for the treatment of OA pain".

"The very well-defined SAS data at 95% confidence intervals is very impressive. This means these data have tight standard deviation around the mean with no overlap of intervals between the baseline results and the post PPS treatment results which is very encouraging given the small sample size (n=34). This gives us great confidence going forward towards a Phase 3 clinical program" (please see table 4 for details).

"The acquisition of real-world evidence concurrent to our FDA IND submission for the Phase 3 OA trial with our newly manufactured Phase 3 trial product provides important ongoing efficacy and safety data."

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[1] https://www.physio-pedia.com/WOMAC_Osteoarthritis_Index
2 Seghal N, Colson J and Smith H; Expert Rev Neurother. 2013;13(11):1201-1220

Details of case study patients and outcomes

The 34 patients [16 males and 18 females, median age of 58 years (range 43 to 74 years)] had been clinically diagnosed with OA and subchondral BMLs. At the onset of PPS treatment patients were symptomatic with OA pain for at least six months and had failed current standard of care, which involved treatment with analgesics, NSAIDs (non-steroidal anti-inflammatory drugs) or corticosteroids.

Patients were administered with two injections of iPPS per week for six weeks. (a total of 12 injections). Patients were followed up at six weeks following the last treatment. During the course of PPS treatment, patients did not receive NSAIDs or corticosteroid treatment.

About injectable PPS

Injectable PPS is not currently registered in Australia, but it is registered in four of the seven major global pharmaceutical markets. In those European markets, injectable PPS is registered as an antithrombotic agent. In Australia, injectable PPS for human use is not currently available for sale. Injectable PPS for human use is only available by inclusion into a Paradigm Sponsored clinical trial or via a treating physician applying for its use in patients via the TGA's SAS - Category B.

To learn more please visit: www.paradigmbiopharma.com

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