PARADIGM BIOPHARMACEUTICALS LIMITED

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PARADIGM PHASE 2B TRIAL MEETS KEY SECONDARY ENDPOINTS IN OSTEOARTHRITIS OF THE KNEE

KEY HIGHLIGHTS

PHASE 2B CLINICAL TRIAL SUBJECTS RECEIVING INJECTABLE PENTOSAN POLYSULFATE SODIUM WERE SHOWN TO HAVE:

- **IMPROVED KNEE FUNCTION FOR 6 MONTHS,**
- **DURABLE PAIN REDUCTION FOR 6 MONTHS, AND**
- **REDUCED BONE MARROW LESION (BML) GRADE, VOLUME AND AREA AT DAY 53.**
- **BML REDUCTION SIGNALS POSSIBLE REGRESSION OF DISEASE**
- **PARADIGM SUCCESSFULLY MEETS ITS PRIMARY ENDPOINT AND SECONDARY ENDPOINTS OF ITS PHASE 2B TRIAL IN OSTEOARTHRITIS OF THE KNEE.**

SUMMARY OF RESULTS

- **Improved Knee Function** (Activities of Daily Living) to Day 165:
  - The key functional secondary end-point of Activities of Daily Living (ADL) showed improved physical function to Day 165 in subjects treated with injectable pentosan polysulfate sodium (iPPS) compared to placebo. See Charts 1A and 1C.
  - The mean % change of ADL of iPPS (39.6%) versus placebo (26.6%) was statistically significant (p=0.0061). See Charts 1B and 1D.
- **Pain Reduction for 6 Months** (KOOS pain score to Day 165):
  - The mean change in KOOS pain score demonstrated a clinically effective outcome at Day 165. This means the pain reducing effects of iPPS are durable over a 6 month period. See Charts 2A and 2B.
  - At Day 165 the proportion of subjects receiving iPPS with a greater than 50% reduction in KOOS pain score is clinically meaningful and statistically significant (p=0.0469) over placebo. See Chart 3A.
- **Objective MRI Data** – Total Population (PPP) at Day 53:
  - The objective data end-point measuring Bone Marrow Edema Lesion (BML) Grade by MRI demonstrated that the number of subjects receiving iPPS treatment had a clinically meaningful reduction in the Grade of their BML compared to placebo. The iPPS group's reduction was also statistically significant over placebo (P=0.03).

  - iPPS treatment also reduced BML Volume compared to placebo. iPPS:(-)34.2% vs placebo: (-) 3.6%. See Chart 4A.
  - iPPS treatment reduced BML Area by (-)25.3% in contrast to a (+)11.9% increase in the placebo group. See Chart 4B.

- **Objective MRI Data** – PPP NRS 4-6 Stratum at Day 53:
  - iPPS treatment reduced BML Volume by (-)37.3% in contrast to an increase of (+)28.5% in the placebo. See Chart 5A.
  - iPPS treatment reduced BML Area by (-)15.6% in contrast to an increase of (+)15.2%, in the placebo group. See Chart 5B.
- These objective MRI data, of large reductions in BML Grade, Volume and Area, signals potential of disease regression of osteoarthritis in subjects treated with iPPS.
- These objective MRI data also support the subjective data of the clinically meaningful and significant outcomes of reduced pain, improved Patient Global Impression of Change (PGIC, p=0.0062) and Activities of Daily Living (ADL) in subjects treated with iPPS.
- Compared with BMLs that stay the same, enlarging BMLs are strongly associated with increased cartilage loss, pain, joint destruction and increased risk of joint replacement.

THE DETAILS

Paradigm Biopharmaceuticals Ltd (ASX: PAR) is pleased to announce the positive secondary end-points of improved knee function (Activities of Daily Living or ADL) and pain reduction to 6 months (reduction in KOOS pain score from baseline to Day 165). Additionally, Paradigm is pleased to report the secondary end-point objective data of reduction in BML Grade, Size and Volume in the iPPS groups as measured on MRI. Reduction of BML Grade, Size and Volume on MRI highlights the potential of iPPS to slow the progression of the disease.

These objective data corroborate previously reported Top-Line-Data that iPPS is safe and clinically effective (as measured by >KOOS 10, percentage of subjects with >50% reduction in pain) and statistically significant improvement of Patient Global Impression of Change (PGIC).

THE SECONDARY ENDPOINTS EXPLAINED

Knee Function – Improvements in Activities of Daily Living (ADL)

The activities of daily living (ADL), which measures physical function of daily life, is one of five subscales of the Knee Injury Osteoarthritis Outcome Score (KOOS), which assesses physical function outcomes related to daily life. ADL includes 17 different items, such as ascending/descending, standing, going shopping, putting on/taking off socks etc, which patients score the degree of difficulty (None, Mild, Moderate, Severe, Extreme). A normalised score (100 indicating no symptoms and 0 indicating extreme symptoms) is determined in subjects during the course of treatment and post-treatment.

Subjects treated with iPPS have demonstrated greater improvement in ADL scores from baseline compared to placebo, as demonstrated in Chart 1A (total population) and Chart 1C (NRS 4-6 stratum), with higher mean % change from baseline in ADL scores during the course of treatment from Day 0 to 165. The mean % change from baseline during Day 11 to Day 165 is 39.6% (iPPS) versus 26.6% (placebo) is statistically significant (p=0.0061) for the total

population (Chart 1B). Statistically significant differences in the improvement in mean % change from baseline of ADL scores during Day 11 to Day 165 were also demonstrated for the NRS 4-6 stratum in the iPPS group compared to the placebo group (Chart 1D): 37.7% vs 15.4% (p=0.00014).

Therefore, these data suggest that iPPS improves physical function as assessed by the ADL in subjects and these changes are concomitant with the observed clinically meaningful and statistically significant improvement in the Patient Global Impression of Change (PGIC) and reduction in knee pain as previously reported.

Pain Reduction – Mean change in KOOS pain score (from baseline) at Day 165

The mean change in KOOS pain score from baseline at Day 165 is greater than KOOS 10 (a clinically meaningful benchmark for pain reduction - OARSI) for both the total PPP population and the NRS 4-6 stratum. In addition, the proportion of subjects with a greater than 50% reduction in KOOS pain score from Baseline (NRS 4-6) at day 165 was 35.1% vs 15.4% (p=0.0469). **This result demonstrates iPPS achieves a clinically meaningful, statistically significant and durable pain reduction to Day 165.**

Objective MRI Results – MRI analysis shows Regression of Bone Marrow Edema Lesions (BML)

MRI studies have provided evidence that there is a relationship between subchondral bone marrow lesion changes and pain, which is related to both the prevalence and the fluctuation in size of bone marrow edema lesions (BML).

The MRI analyses performed in Paradigm's Phase 2B clinical trial were aimed to provide an objective data measurement of iPPS effects on BML Grade, Size and Volume to support the subjective analysis of the clinical outcomes of pain and function. Therefore, the demonstration of a change in the physical measurement of BML Grade, Size and Volume of the bone marrow edema lesion would further characterise the therapeutic effect of iPPS in association with clinical outcomes of pain and function.

The BML data were not normally (statistically) distributed, therefore the median (interquartile range) of the % change in volume and maximal area and change in grade of BMLs from baseline to Day 53 were compared between the iPPS and control groups using the Mann-Whitney U test.

At day 53 compared to baseline, there was a strong trend for the iPPS group having greater reduction in total BML Volume [-34.2% vs. -3.6%] and total BML maximal area [-25.3% vs. +11.9%] compared with the placebo group (Charts 4A and 4B). Effects of iPPS were noted in the medial compartment of the knee for BML volume [-37.0% vs. +2.2%] and BML area compared with the placebo group [-22.9% vs. +6.8%]. The data from the NRS 4-6 stratum (Charts 5A and 5B) showed that the iPPS group had a greater reduction in BML volume -37.3% vs. +28.5%, and total BML area -15.6% vs. +15.2%, compared with the placebo group. This represents a net reduction in the iPPS group compared to the placebo group of 65.8% for BML volume and 30.8% for BML area, respectively. The magnitude of the effects mediated by iPPS observed in the NRS 4-6 stratum for reduction of BML volume and area are supportive of the KOOS pain reduction.

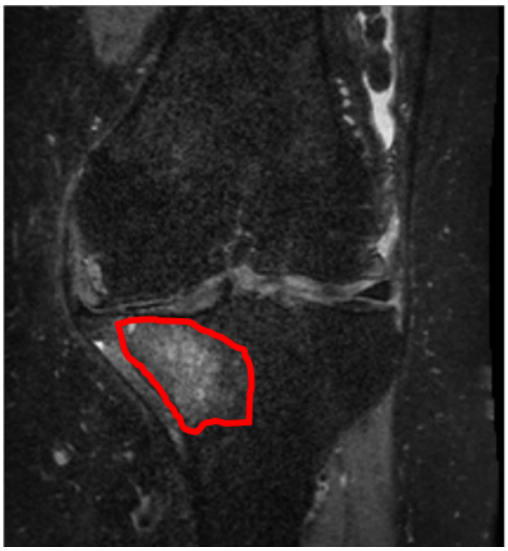
BMLs were graded for the assessment of progression or regression of BML from baseline to day 53. BML were graded as 0-3 for each site: grade 0 = none; grade 1 = <33% of region; grade 2 = 33% - 66% of region; grade 3 = >66% of region. The progression (i.e. Day 53 grade –

baseline grade ≥1) and regression (i.e. Day 53 grade – baseline grade ≤ -1) of BMLs from baseline to Day 53 were compared between the iPPS and control groups using chi square test. iPPS group was more likely to have BML regression compared with the placebo group in the medial compartment (50.0% vs. 27.3%, p=0.03), and total knee (51.9% vs. 37.7%). This is a clinically important finding given that the medial compartment is subject to greater loading and the prevalence of knee osteoarthritis in the medial compartment is 4-times of the prevalence in the lateral compartment.

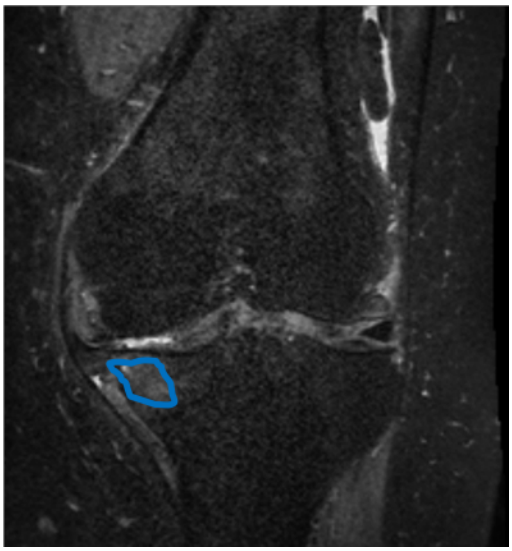
The implication of the objective MRI data is that it confirms the efficacy of iPPS therapy demonstrating structural effects on the BML by reduction of BML size (determined by reduction in BML grading, area and volume). These effects on the BML are likely to translate to halting disease progression and promoting regression of disease and the facilitation of pain reduction and improvement in physical function. The MRI data further validate the safety profile of iPPS, unlike the anti-NGF agents (e.g. Tanezumab), which result in the reported adverse effects, such as rapidly progressing OA and osteonecrosis. BML that persist and enlarge are strongly associated with cartilage loss and are a harbinger for total knee replacement, therefore the reduction in Bone Marrow Lesion size and grade by iPPS therapy may 'stave-off' the need for total knee replacement.

Regression of Bone Marrow Edema Lesions (BML)

Subchondral bone marrow lesions (BMLs), as shown in the MRI below are an important feature in OA and appear as region(s) of increased signal intensity within the bone marrow and are a promising target for therapy. The image below shows a Grade 3 BML at baseline in the medial tibia (left image) and regression of the BML to Grade 2 (right image) at follow up at Day 53.



Grade 3 medial tibial BML before treatment



Grade 2 medial tibial BML after treatment

What is the clinical significance of Bone Marrow Edema Lesions (BML)?

- "Increase in bone marrow lesions are associated with cartilage loss. The prevalence and severity of BMLs are associated with less tibial cartilage volume and greater

cartilage loss over 2 years. Moreover, severity of BMLs was positively associated with risk of knee joint replacement over 4 years."[1].

- "Lesions of the bone marrow are unlikely to resolve and often get larger over time. Compared with BMLs that stay the same, enlarging BMLs are strongly associated with more cartilage loss"[2].
- Patients with BME and OA have an increased risk of total knee replacement as opposed to OA and no marrow edema. Subjects who had BME of any pattern type were 8.95 times as likely to progress rapidly to TKA (knee replacement) when compared with subjects with no BME (p=0.016)[3].
- A review of recent and past literature suggests that chronic bone marrow edema (BME) or bone marrow lesions are definitely linked to pain, the progression of cartilage damage, and the acceleration of joint degeneration[4].
- BMLs are strongly correlated with pain. **"**Our results confirm that severity of pain is correlated with BML size, and furthermore, demonstrate that increases and decreases in the amount of pain reflect growth or reduction in BML size, respectively"[5].

Paul Rennie, Paradigm Biopharmaceuticals CEO, said "we are pleased with the positive Activities of Daily Living data and the positive objective MRI data being reported today. Additionally, the KOOS pain reduction to day 165 demonstrates the potential of iPPS to be a long-lasting and efficacious pain treatment in subjects with OA. Traditionally, in OA sufferers, bone marrow lesions remain the same size or get larger over time. Here, we see iPPS producing a net 65% reduction in BML Volume in the NRS 4-6 strata, which is impressive, especially considering the MRI images were taken just two weeks after the last injection of iPPS, which is a very short time period after cessation of the drug.

At such an early time-point of Day 53 we were looking for early MRI signals to demonstrate the trend in remission of BMLs. To have such a magnitude of difference on the total knee volume and area and statistically significant difference for the medial compartment of the knee is an amazing result and something that the medical, scientific and pharmaceutical fraternity will appreciate the importance of."

Mr Rennie further added "When we look at all the results from the complete Phase 2b trial, we are seeing an accumulation of positive results of iPPS over placebo in every single component of the trial and outstanding results for the NRS 4-6 pain stratum, which in our view shows iPPS is safe and effective. Obviously, the very positive effect that iPPS is having on the NRS 4-6 stratum further confirms this group will be our target patient group for our upcoming pivotal phase 3 clinical trial. To have a large and rich data set of both subjective pain and function scores along with the objective MRI data showing the potential OA disease remission effect of iPPS is indeed powerful and very valuable in the eyes of partnering pharmaceutical companies. Osteoarthritis is the major cause of disability and impaired quality of life of people in the over 50 years of age. Paradigm's clinical trial has confirmed iPPS reduces pain, improves both joint function and structure in subjects with OA".

[1]Tanamas S et al 2010 "Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study" Rheumatology.

[2]J. Hunter et al, Increase in Bone Marrow Lesions Associated with Cartilage Loss Arthritis & Rheumatology, May 2006

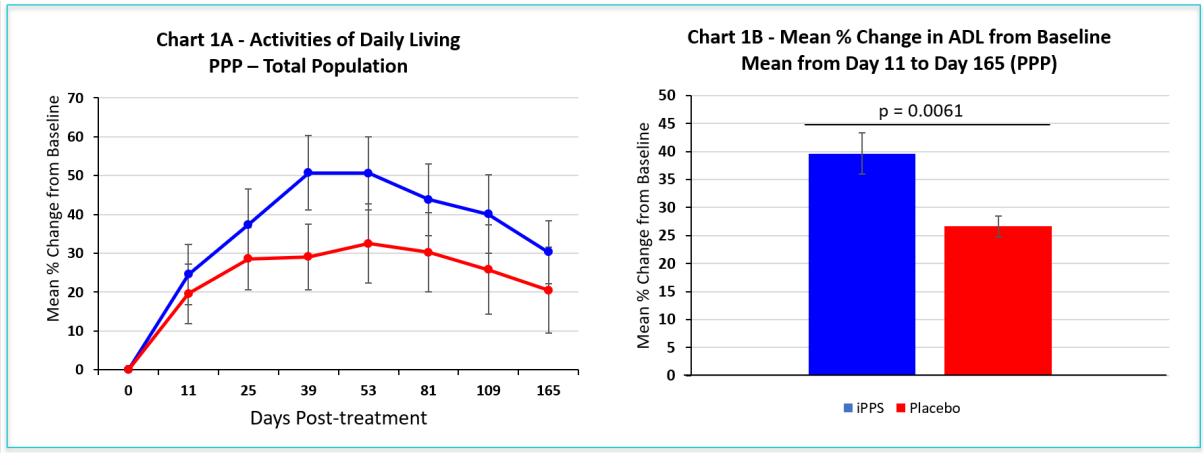
[3]Courtney Scher, Nelson et al, Bone marrow edema in the knee in osteoarthrosis and association with total knee arthroplasty within a three-year follow-up, Skeletal Radiol (2008)

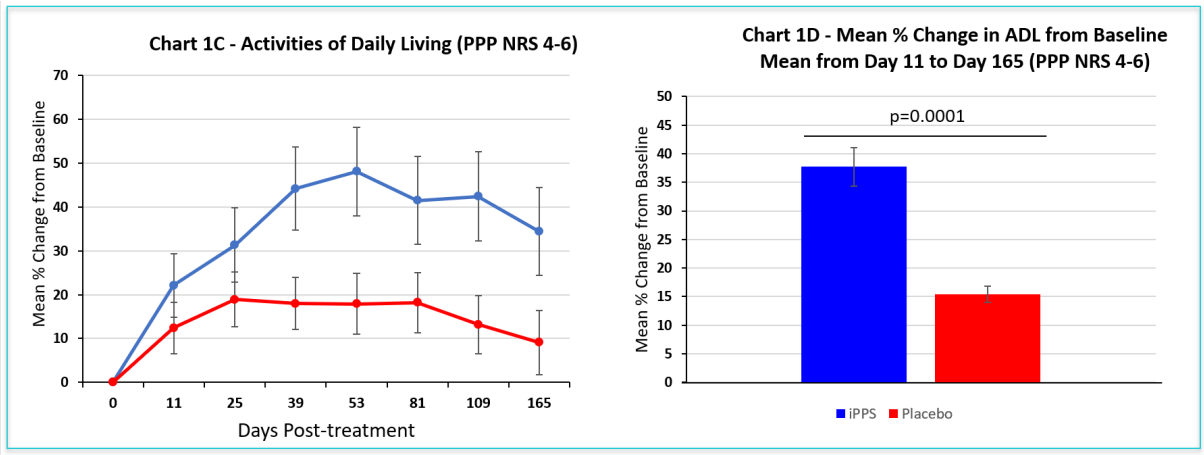
[4] Sharkey PF et al, Subchondral bone marrow lesions associated with knee osteoarthritis, Department of Orthopaedic Surgery Thomas Jefferson University Hospital, 2012.

[5] d'Agostino C, Romeo P, Lavanga V, Pisani S, Sansone V. Effectiveness of extracorporeal shock wave therapy in bone marrow edema syndrome of the hip. Rheumatol Int 2014; 34: 1513–1518. [PubMed]

THE CHARTS

Chart 1A, B, C, D: iPPS shows improvement in Activities of Daily Living compared to Placebo.





- The KOOS activities of daily living (ADL) subscale is one of the five dimensions of the KOOS Scale (equivalent to that of function in the WOMAC Osteoarthritis Index). It includes 17 different items, which patients score the degree of difficulty experienced in the last week on a scale of 0-4 (None, Mild, Moderate, Severe, Extreme). The items include, ascending/descending, standing, going shopping, putting on/taking off socks etc.
- **Improvements in ADL are consistent with iPPS treatment whereas the placebo shows a plateauing and then reduction of ADL.**
- iPPS treatment is statistically significant compared to placebo for the total population and NRS 4-6 stratum.

Chart 2A, B - Mean change in KOOS pain score (from baseline) at Day 165 for both the PPP Total Population and the PPP NRS 4-6 stratum

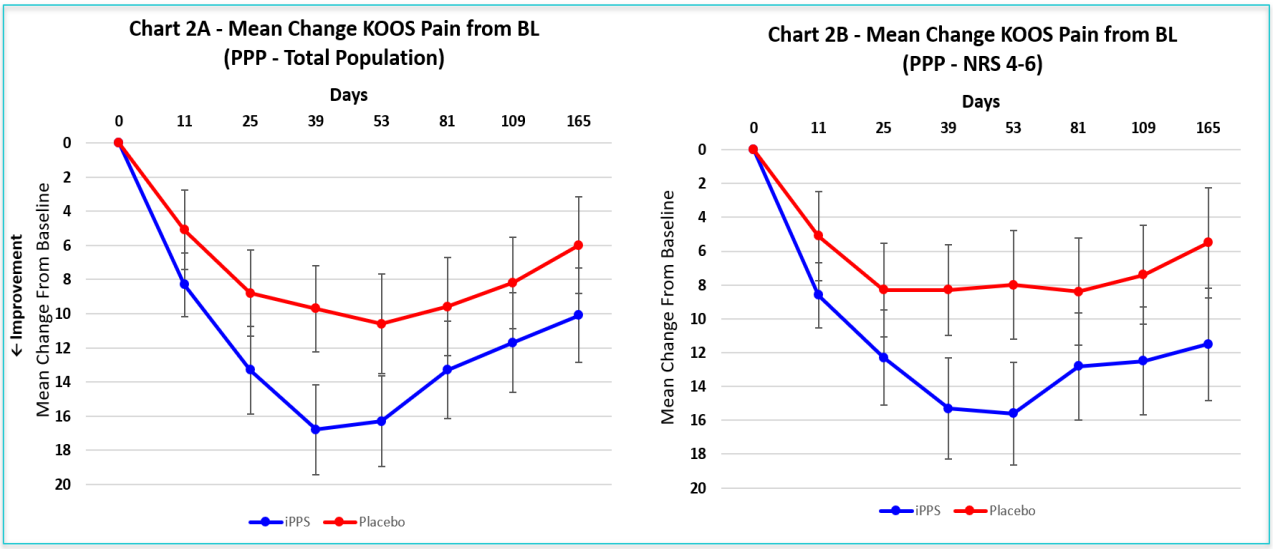


Chart 3A - The proportion of subjects with at least greater than 50% reduction in KOOS pain score from Baseline (NRS 4-6)

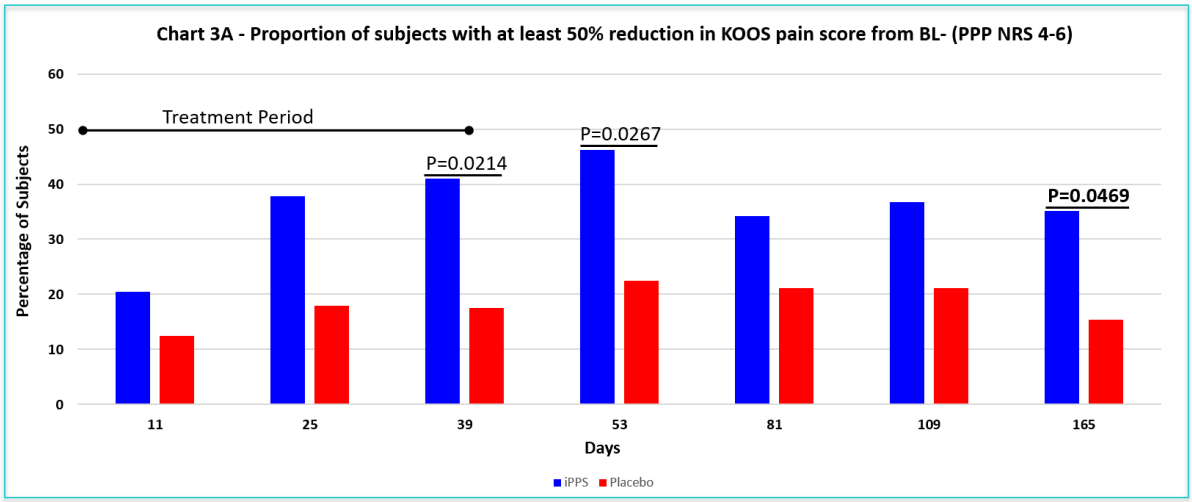
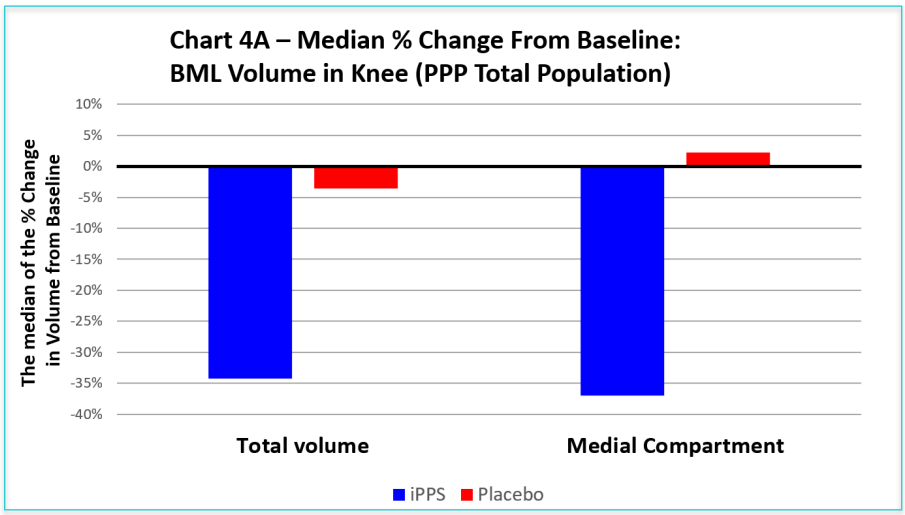
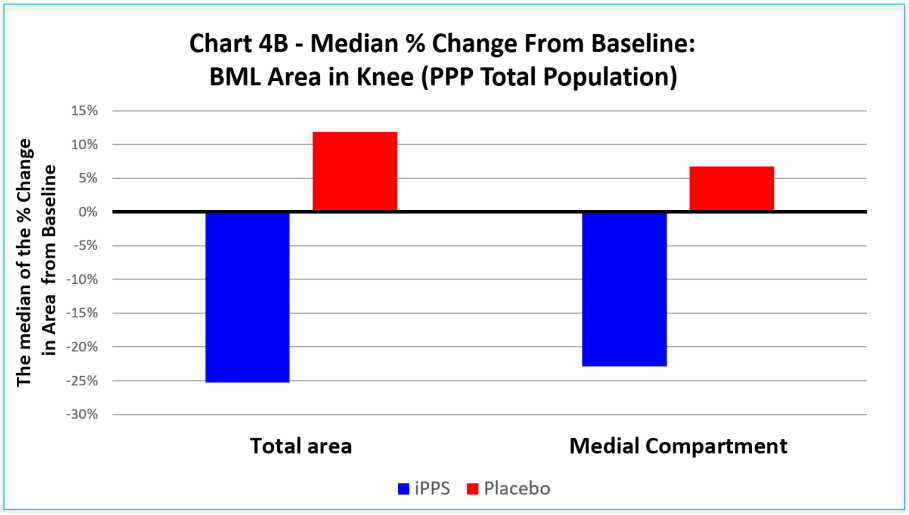


Chart 4A, B: Clinically Meaningful Reduction in Bone Marrow Edema Lesions determined by MRI analysis of lesion Volume and Area iPPS treatment versus Placebo (PPP Total Population)



- **BML Volume in Knee (3D analysis)** median % change from baseline to Day 53

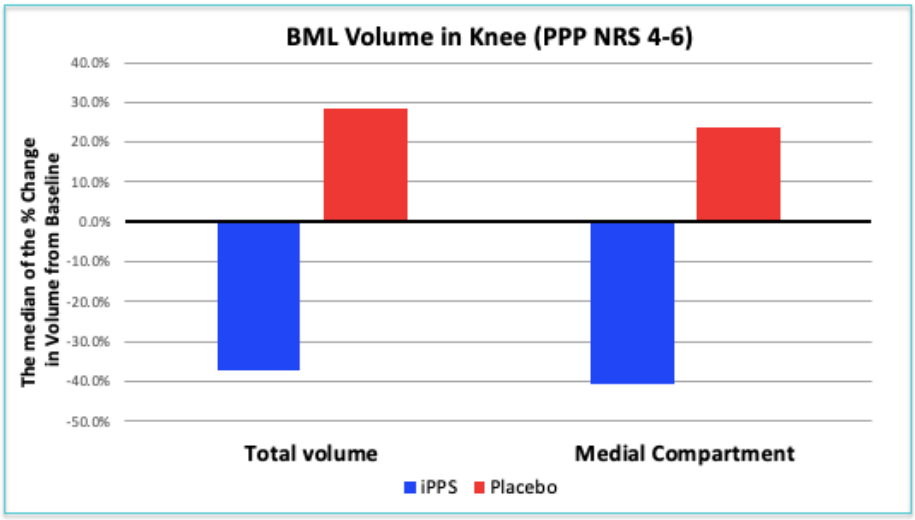
  In Total Knee the median % change [interquartile range] from baseline to day 53 is: iPPS (-)34.2% [-65.3 – (+)55.5] vs Placebo (-)3.6% [-41.2 – (+)91.8] and for the Medial Compartment: PPS (-)37% [-65.8% – (+)60.5] vs Placebo (+)2.2% [-37.1 – (+)81] , **iPPS demonstrated a strong trend of efficacy from baseline to day 53**



- **BML Area in Knee (2D analysis)** median % change from baseline to Day 53

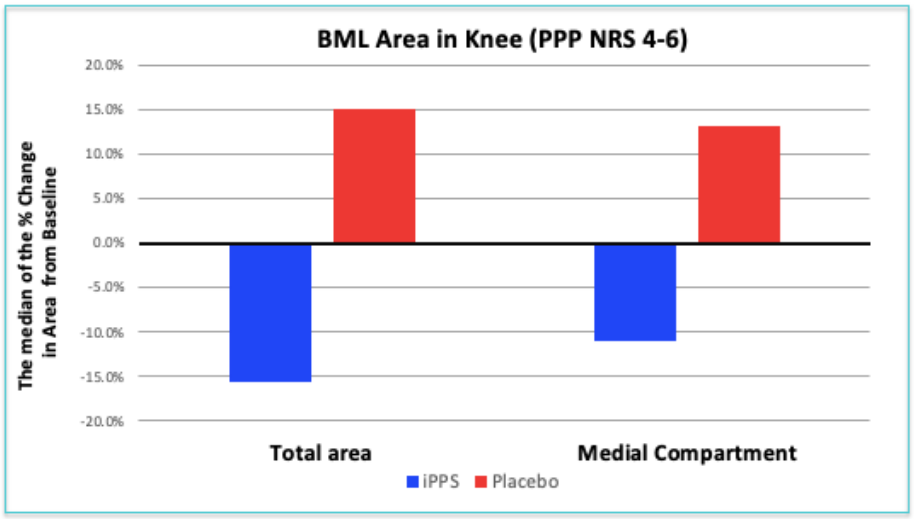
In Total Knee the median % change [interquartile range] from baseline to Day 53 is: iPPS (-)25.3% [-61.8 – (+)49.8] vs Placebo (+)11.9% [-33.2 – (+)59.2] and for the Medial Compartment: PPS (-)22.9% [-66.7% – (+)61.4] vs Placebo (+)6.8% [-35 – (+)50.1], **iPPS demonstrated a strong trend of efficacy from baseline to Day 53**

Chart 5A, B: Clinically Meaningful Reduction in Bone Marrow Edema Lesions determined by MRI analysis of lesion Volume and Area in iPPS treatment versus Placebo (PPP NRS 4-6)



- **BML Volume in Knee (3D analysis)** median % change from baseline to Day 53

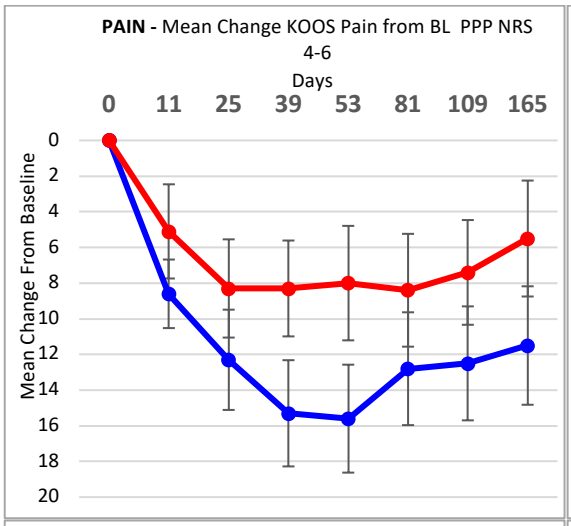
  In Total Knee the median % change [interquartile range] from baseline to day 53 is: iPPS (-)37.3% [-63.2 – (+)60.5] vs Placebo (+28.5% [-45.9 – (+)102] and for the Medial Compartment: PPS (-)40.6% [-64.8% – (+)94.6] vs Placebo (+)23.6% [-43.1 – (+)119], **iPPS demonstrated a strong trend of efficacy from baseline to day 53**

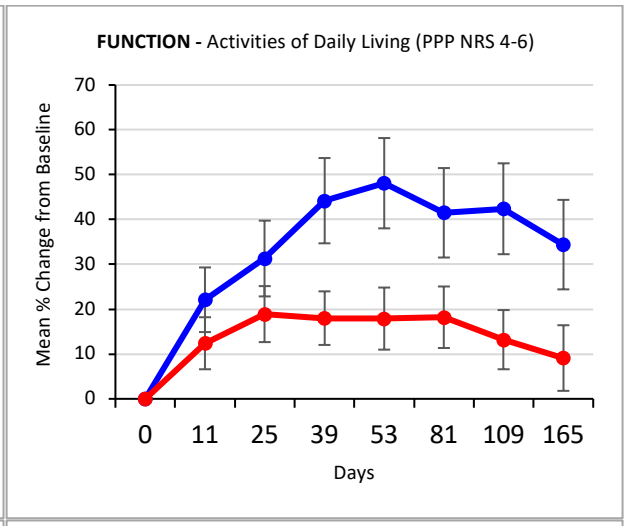


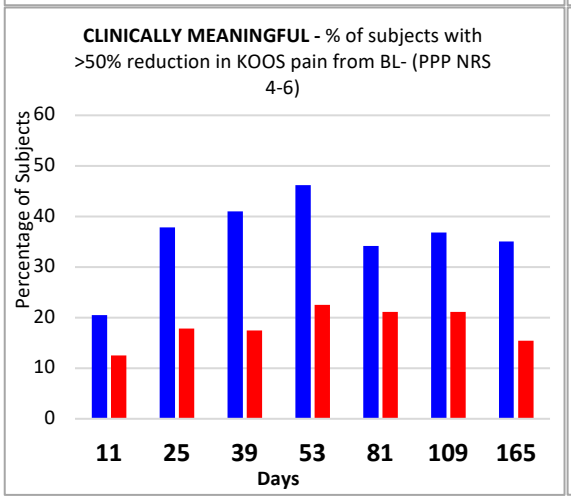
- **BML Area in Knee (2D analysis)** median % change from baseline to Day 53

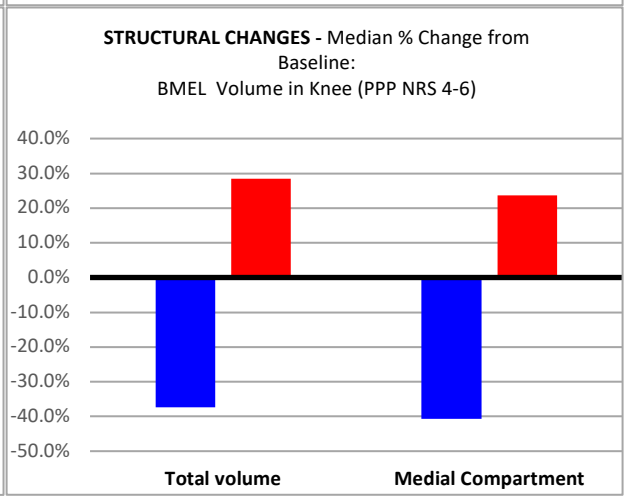
In Total Knee the median % change [interquartile range] from baseline to Day 53 is: iPPS (-)15.6% [-56.4 – (+)55.3] vs Placebo (+)15.2% [-21.8 – (+)61.3] and for the Medial Compartment: PPS (-)10.9% [-65.4% – (+)57.3] vs Placebo (+)13.2% [-35 – (+)55.5], **iPPS demonstrated a strong trend of efficacy from baseline to Day 53**

SUMMARY OF THE NRS:4-6 STRATUM – TARGET POPULATION FOR PHASE 3









THE OSTEOARTHRITIS MARKET

OA also remains the most common form of joint disease globally. In the US alone, it affects over 30 million adults, while in Australia, arthritis affects around 3 million people. In both countries, the condition is a leading cause of pain and disability among the elderly and a cause of life-years lost due to disability.[6]

The demand for a new effective treatment is significantly amplified by the opioid epidemic throughout the United States ("US"). Every day, more than 115 people in the US die after overdosing on opioids.[7] The misuse of and addiction to opioids is a serious national crisis that affects public health as well as social and economic welfare. The Centers for Disease Control and Prevention estimates that the total "economic burden" of prescription opioid misuse

[6] https://www.cdc.gov/arthritis/basics/osteoarthritis.htm
[7] CDC/NCHS, National Vital Statistics System, Mortality. CDC Wonder, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://wonder.cdc.gov.

alone in the United States is $78.5 billion a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.[8]

THE FILING OF INVESTIGATIONAL NEW DRUG (IND) WITH THE US FDA AND FAST TRACK

Paradigm believes iPPS has the potential to receive Fast Track designation from the US Food and Drug Administration (FDA), which is greatly concerned about the opioid epidemic. In particular, the previous FDA Commissioner Scott Gottlieb was recently quoted as saying "The opioid epidemic continues to take an emotional, physical and financial toll on Americans. The U.S. Food and Drug Administration is committed to taking every possible step to address the many facets of this complex public health crisis"[9] and furthermore "Our goal is to support more rational prescribing practices, ***as well as identify and encourage development of new treatment options that don't have the addictive features of opioids***."[5]

Fast-Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Filling an unmet medical need is defined by the FDA as providing a therapy where none exists or providing a therapy which may be potentially better than an available therapy.

Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some advantage over available therapy, such as avoiding serious side effects of an available therapy or an ability to address emerging or anticipated public health need.[10]

Paradigm's iPPS is neither an opioid nor a steroid and most importantly is non-addictive, thus has the potential to positively impact the opioid epidemic and treat OA pain.

ABOUT PARADIGM BIOPHARMACEUTICALS LTD

Paradigm Biopharmaceuticals Limited (ASX: PAR) is an ASX-listed biotechnology company focused on repurposing Pentosan Polysulfate Sodium (iPPS), an FDA approved drug that has a long track record of safely treating inflammation over 60 years.

On 18 December 2018 the Company announced the successful results from their phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with osteoarthritis and concurrent bone marrow edema lesions (n=112). There is a global trend for safe and effective non-opioid and non-steroid pain relief for chronic disease such as osteoarthritis which presents a huge market opportunity for Paradigm's iPPS treatment.

The Company is aiming to achieve Fast-Track designation and begin a phase 3 trial in the US in CY2019, both these initiatives are expected to attract significant big pharma interest.

Paradigm recently executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders. A key unmet medical need in this class of inherited disease is the lack of treatment of joint pain and dysfunction akin to osteoarthritis, hence the applicability of iPPS in treating these rare joint diseases. MPS is classified as an Orphan Indication/Designation in the US/EU and

[8] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm
[9] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm
[10] https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm

provides Paradigm the opportunity to serve a US$1.4bn p.a. market that is in desperate need of new cost-effective treatments.

In parallel to its clinical programs, Paradigm is pursuing a Provisional Approval for iPPS for OA pain via the Australian Therapeutic Goods Administration (TGA), in addition to treating retired elite sportspeople and past NFL players via a US Expanded Access (Compassionate Use) program.

In July 2017 the Company commenced a phase 2a clinical trial to treat people recently infected with the Ross River virus. The results of this trial are also expected to be released in Q2/Q3CY2019.

The Company continues to execute on its drug repurposing strategy. The key benefits of this strategy are lower costs, accelerated development timelines and higher success rates than the standard clinical development timeline.

To learn more please visit: www.paradigmbiopharma.com

For more information, please contact

CORPORATE ENQUIRES

Paul Rennie
Director & CEO
Paradigm Biopharmaceuticals Ltd
E: info@paradigmbiopharma.com