ASX RELEASE 18 October 2023

iPPS increases cartilage thickness at 6 months in participants with knee osteoarthritis compared to cartilage loss in placebo group

Webinar

Paradigm Senior Management will be hosting a webinar at 11:00 AM (AEDT) to discuss new quantitative MRI 6-month data analysis from the PARA_OA_008 phase 2 clinical trial.

When: Oct 18, 2023 11:00 AM Canberra, Melbourne, Sydney (AEDT) time

Topic: Paradigm Biopharma's PARA_OA_008 Day 168 MRI Results Webinar

Register for this webinar via:

https://us02web.zoom.us/webinar/register/WN_a1INIMLMRz67s_yScRJTIQ

After registering, you will receive a confirmation email containing information about how to join the webinar.

Osteoarthritis (OA) leads to significant structural changes to the entire joint. Bone remodelling, adverse inflammation of the synovium, and cartilage loss are all structural changes in knee OA. In the natural course of the disease, it is expected that a person with moderate to severe knee OA will lose approximately -40 µm (-0.04 mm) of cartilage thickness in the central medial femur per year on MRI (1).

KEY HIGHLIGHTS

- iPPS demonstrates preservation of cartilage in knee OA participants in a phase 2 study.
- A 6-week twice weekly course of subcutaneous iPPS was shown to increase cartilage thickness and volume and reduce bone marrow lesions and synovitis on MRI follow-up at 6 months.
- Participants who received iPPS had an average improvement of cartilage thickness in the central medial femur of the knee of 60 µm (0.06 mm) at 6 months. This is compared to placebo who lost an average -20 µm (-0.02 mm) of cartilage thickness.
- The twice weekly 2 mg/kg dose for 6 weeks outperformed the once weekly via MRI assessment and is consistent with the optimal clinical dose for knee OA.
- The results indicating a treatment effect on OA beyond the relief of symptoms supports iPPS as a blockbuster opportunity.

- These data are expected to be key with partnering and regulatory discussions (TGA Provisional Approval and US FDA).

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 very exciting new analysis from the phase 2 PARA_OA_008 clinical trial. demonstrating that a single 6-week treatment of injectable pentosan polysulfate sodium (**iPPS)** treatment at 2mg/kg twice weekly results in:

A) An increase in overall cartilage thickness, across all compartments of the knee, of 0.17mm (p=0.05) compared to overall decrease of -0.09mm in placebo;

B) An increase if overall cartilage volume by 1.9% (p=0.07) compared to a decrease of -1.58% in the placebo group;

C) Resolution or decrease in of bone marrow lesions (BML) volume by 17% in the iPPS group, whereas placebo subjects saw a 2% increase in BML and;

D) Reduced area and intensity by 1% of synovitis in the iPPS group compared to an increase 0f 4% in synovitis intensity in placebo.

E) As previously reported (ASX release 10 October 2023) symptomatic improvements of pain and function out to 12 months.

The above results support that iPPS both treats the symptoms of OA and preserves and/or regenerates joint tissues. This is significant from a commercial perspective because the disease modifying effects of iPPS observed in the PARA_OA_008 phase 2 clinical trial are expected to support a greater reimbursement compared to that which would be expected for a therapeutic that only treat the symptoms of OA**.**

In the phase 2 clinical trial, subjects treated with iPPS (2 mg/kg twice weekly) had an average increase of 60 µm of cartilage thickness (0.06 mm) in the central medial femur whereas the placebo group lost an average 20 µm of cartilage (-0.02mm) in the same region. Based on extensive literature research, this phase 2 randomised controlled trial appears to be a world first showing:

- A decline in disease biomarkers compared to placebo at Day 56 and Day 168;
- Durable pain and function improvements over placebo out to Day 365, and now;
- Increased cartilage thickness and increased cartilage volume at Day 168, while placebo showed a reduction in both cartilage thickness and volume.

Next Steps

- Paradigm has identified the optimal dose for achieving durable responses in pain, function and patient global impression of change (PGIC). Furthermore, this dose results in structural preservation of cartilage, and reduction in BML and synovitis.
- Paradigm is progressing with the TGA Provisional Approval application which would expedite the pathway to marketing approval in Australia.

- The Company is also moving forward with the 2 mg/kg twice weekly optimal iPPS dose for registration programs for the improvement of pain and function in knee OA.
- These data are expected to further support with partnering discussions.

Paradigm's Managing Director, Mr Paul Rennie commented *"The treatment of osteoarthritis has not progressed for many years, with available therapies mostly treating the symptoms of the disease for a short period. There is a high unmet need for a new OA therapy to slow OA progression in tandem with symptomatic improvement of pain reduction and functional improvement. In this placebo-controlled clinical trial, Paradigm's iPPS has now demonstrated that it not only has a durable and beneficial effect on pain, function, and the patient's impression of improvement out to 12 months, but we are also seeing it is improving the underlying disease as early as 6 months following a single 6-week treatment course. We look forward to presenting the PARA_OA_008 data package to global regulatory agencies including the TGA and FDA."*

"What I find most compelling about these data, is that all participants entered the clinical study with active structural degeneration already occurring and yet iPPS has been able to reverse disease progression. Paradigm aims to reach agreement with the US FDA on what data would be necessary to confirm these results in our larger phase 3 program to include disease modifying data on our label at registration. If this is unachievable within our current timelines and budget, the Company or our partner may undertake subsequent additional studies (post marketing clinical studies) to achieve a disease modifying label once iPPS is registered on the market."

Top-line results

Osteoarthritis background

Osteoarthritis (OA) is a chronic progressive disease, over time leading to the destruction of all joint tissues. The hallmark of OA is cartilage loss (2). As osteoarthritis progresses, the medial side of the knee tends to lose cartilage more rapidly compared to the lateral side.

Overall Average Change from Baseline

All Compartments/Regions	**iPPS-Twice-weekly N=15**	**Placebo N=22**
	Day 168	**Day 168**
Overall cartilage thickness (mm)	0.17 (P= 0.05)	-0.09
Overall cartilage volume (mm^3)	191.51 (P= 0.07)	-86.81
BML overall (mm^2l)	-86.26	120.65
Synovitis overall (mm^2l)	-5086.13	-2707.38

Table 1: Adjusted Change from Baseline (absolute) least squares mean (LSM) results for overall cartilage thickness, cartilage volume, BML and synovitis size and intensity following twice weekly iPPS compared to placebo in PARA_OA_008 at Day 168.

In the above table (Table 1) iPPS treatment was shown to increase overall cartilage thickness and volume whilst also reducing overall bone marrow lesions and synovitis on MRI follow up at 6 months from a 6-week treatment course of subcutaneous iPPS. The data presented below will focus on cartilage thickness (mm) and volume (%) in the medial compartment and overall BML and Synovitis percentage changes from baseline. All MRI data including the lateral compartments are shown in the Appendix.

The crucial role of cartilage

Cartilage loss is generally considered to be the most important structural disease feature of OA (Figure 1). Numerous studies have shown cartilage loss to be predictive of knee replacement surgery for OA.

There has been substantial published research on MRI cartilage measurements showing as osteoarthritis progresses, the medial side of the knee tends to lose cartilage more rapidly than the lateral side (3,4). A reduction of this loss, or an increase in cartilage thickness, may therefore delay time to total knee replacement (**TKR**) in an osteoarthritic knee. Cartilage serves as a cushion and provides smooth, low-friction movement in the knee joint. When cartilage degenerates, it can lead to bone-on-bone contact, resulting in severe pain. Any improvement in cartilage health can help alleviate pain, improve joint functionality, and improve the quality of life for people with knee osteoarthritis.

In knees with an OA disease severity of 2–4 on the Kellgren and Lawrence (KL) grading scale (such as for the PARA_OA_008 participant cohort and who would already be experiencing cartilage loss), natural OA progression would be expected to result in an estimated continued annual loss in cartilage thickness of around 40 µm (0.04 mm) (1) and an annual loss in cartilage volume of around -4% (6) at the central medial femur.

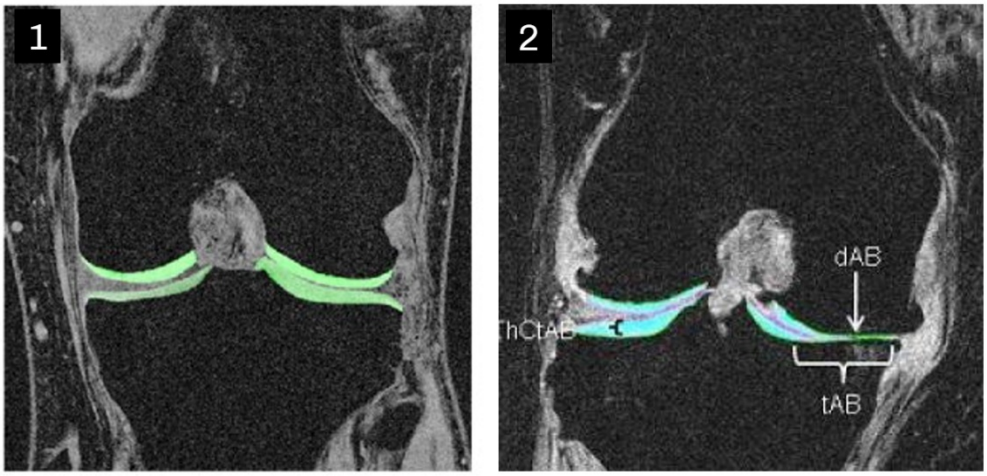


Figure 1. Composite image showing example front-facing (coronal) knee MRIs with highlighted cartilage layers. Image 1 shows a healthy knee and image 2 shows an osteoarthritic knee with preserved cartilage thickness on the lateral side and severe damage to the medial side, indicated by dAB and tAB labels. Images from Hinterwimmer S. et al. Knee Surg Sports Traumatol Arthrosc. 2014, and Reichenbach S. et al. Ann Rheum Dis. 2010 (7,8).

Increase in cartilage thickness with iPPS

- The twice weekly iPPS arm consistently demonstrated an improvement in cartilage thickness from baseline to 6 months was reported in all medial knee regions following iPPS treatment (Figures 2 and 3).
- The placebo arm demonstrated a loss in cartilage thickness in all medial regions at 6 months consistent with the natural progression of OA.
- iPPS increased the cartilage thickness in the central medial femur by 60 µm (0.06 mm) compared to a reduction of 20 µm (-0.02 mm) in the placebo group consistent with the naturally occurring cartilage loss rate in knee OA progression (-40 µm or 0.04 mm per year).

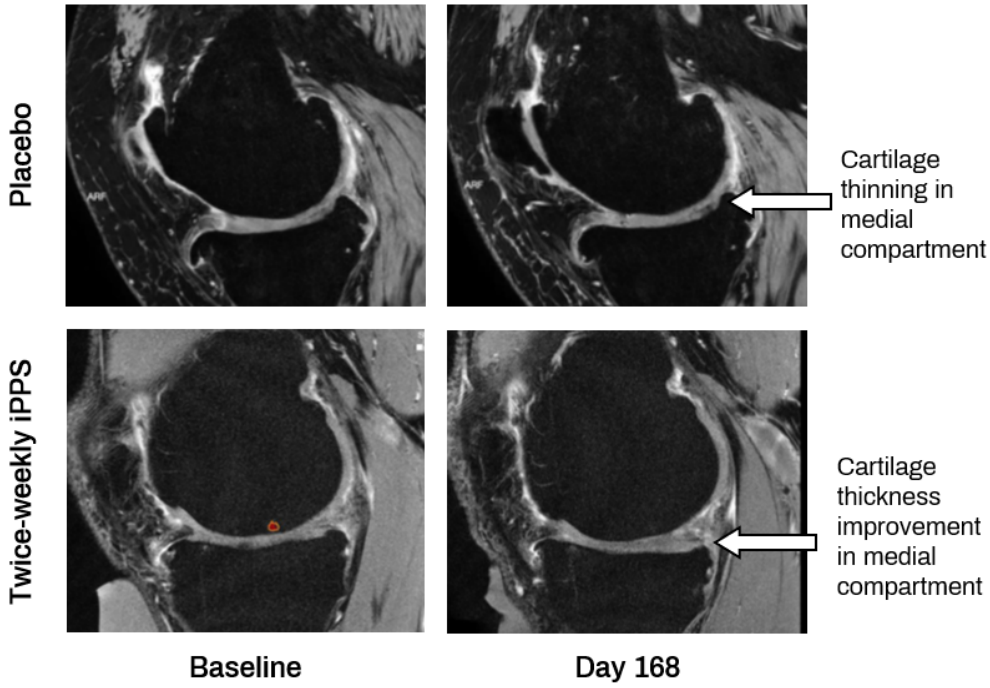


Figure 2. Representative side-on (sagittal) MRI images from PARA_OA_008 of the knee at baseline (left panels) and at Day 168 (right panels) from a participant receiving placebo (top panels) and a participant receiving twice weekly iPPS (bottom panels) demonstrating changes in cartilage thickness in the medial compartments. In the twice weekly iPPS baseline image, there is a small bone marrow lesion in the subchondral bone (bone that is directly under cartilage) of the femur (circled in red), that is resolved at Day 168.

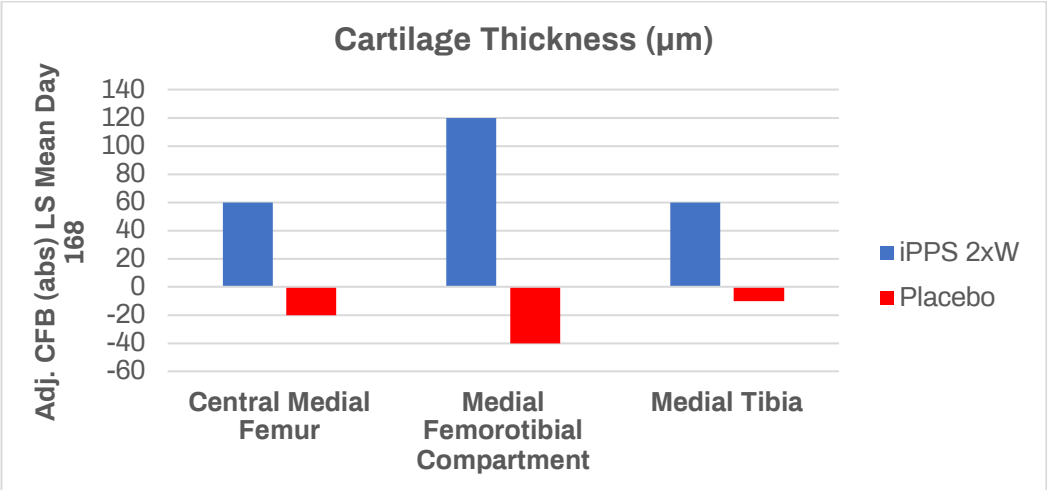


Figure 3: Cartilage thickness (µm). Absolute adjusted change from baseline (CFB). Least squares mean results by medial region in the knee. iPPS 2xW is iPPS twice weekly.

Increase in cartilage volume with iPPS

- At 6 months, subjects receiving twice weekly iPPS showed an average increase in cartilage volume of 3.8% in the central medial femur compared to baseline, whereas the placebo arm showed a loss of cartilage volume of -2.2% (Figure 4).
- This data again demonstrates iPPS is reversing the breakdown of cartilage at 6 months. This is in contrast to placebo which is showing further cartilage volume loss from baseline consistent with the natural progression of the disease (4% reduction in cartilage volume per year).

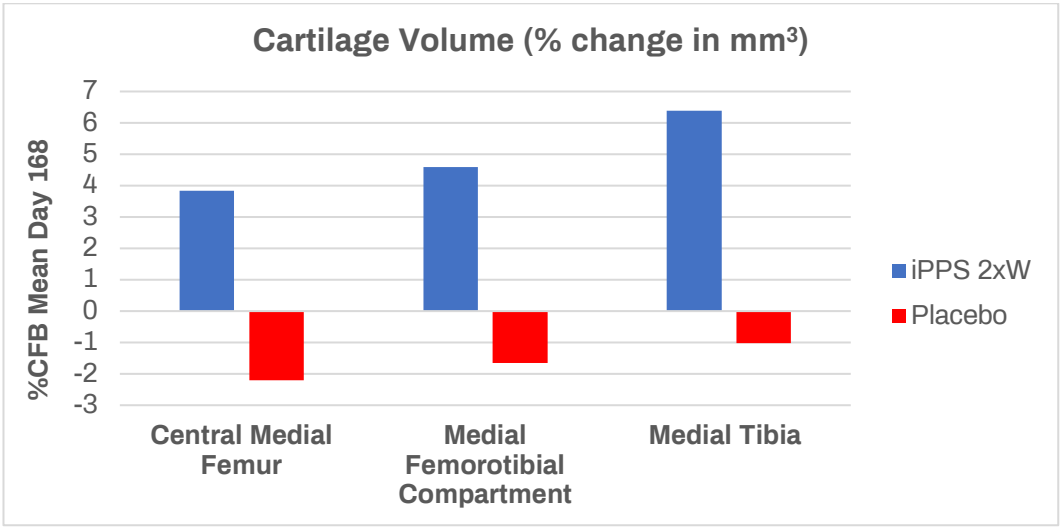


Figure 4: Average percentage (%) change from baseline (CFB) in cartilage volume (mm^3) by medial region in the knee. iPPS 2xW is iPPS twice weekly.

Reduced bone marrow lesions (BML) with iPPS treatment

Subchondral ("below the cartilage") BMLs are a common finding on MRI, in OA. Loss of the normal weight bearing function of articular cartilage along with shifting contact points

associated with joint laxity can cause joint overloading and is believed to result in microtrauma which expresses as a BML (Figure 5).

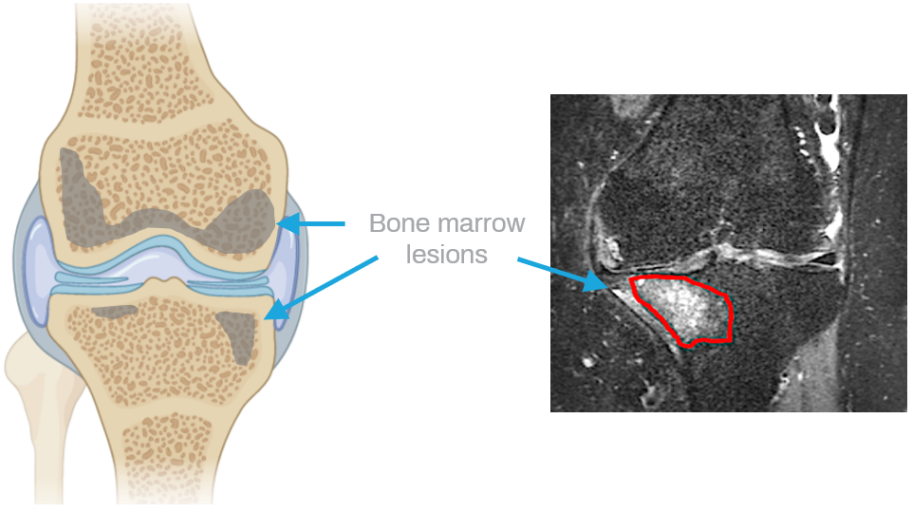


Figure 5. Schematic of a knee joint showing representative locations of bone marrow lesions alongside a representative MRI demonstrating a bone marrow lesion in the medial tibia (circled in red). Figure created with an image from BioRender.com. MRI image, Paradigm PARA_005 clinical trial.

Like cartilage loss, BMLs have been shown to be highly predictive of knee replacement (9–11). This means that the loss of the cushioning cartilage layer in a major weight-bearing joint such as the knee can change how weight is distributed. These incessant gradual forces on a joint where bone is moving on bone can result in cartilage breakdown and bone remodelling to cope with the changing stresses.

- Overall bone marrow lesion volume in the knee was reduced by 17.6% on average in the iPPS twice weekly group, compared to a 2% increase in the placebo group (Figure 6).

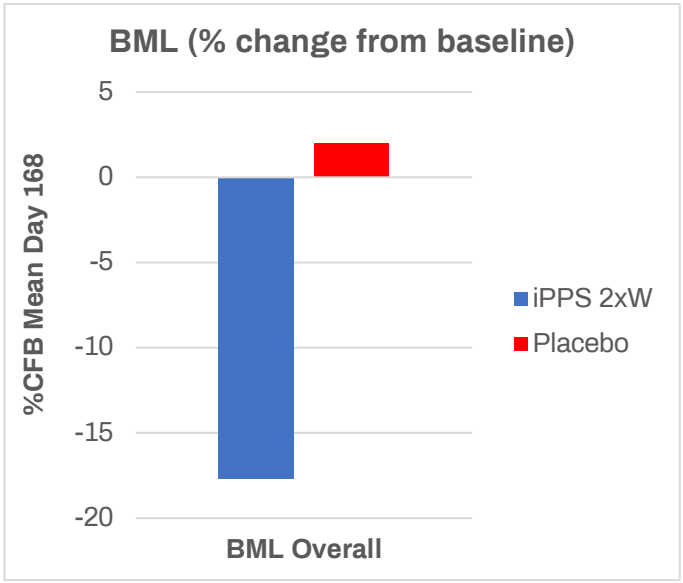


Figure 6: Average percentage (%) change from baseline (CFB) in overall bone marrow lesions. iPPS 2xW is iPPS twice weekly.

Reduced synovitis (joint inflammation) with iPPS

OA-associated synovitis is defined as an inflammation of the synovial membrane, the thin layer of tissue that lines the joints (Figure 7). In OA, the synovial membrane can become inflamed and thickened as the body's immune system responds to joint degeneration. This inflammation can cause increased production of synovial fluid, which is a lubricating fluid that normally helps the joint move smoothly. The excess synovial fluid can lead to joint swelling and can be associated with increased pain and stiffness in the affected joint.

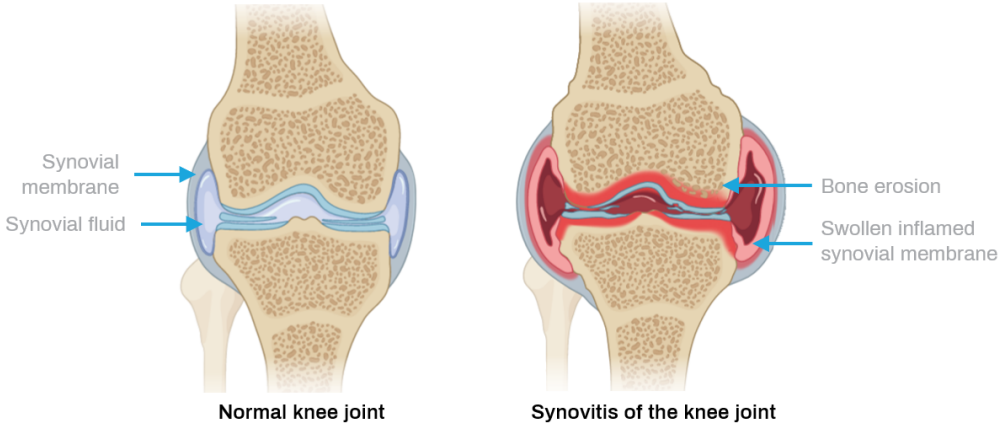


Figure 7. Schematic of a normal knee joint and an inflamed knee joint with synovitis. Figure created with images from BioRender.com.

- At 6 months in this phase 2 clinical trial, synovitis increased from baseline in the placebo arm (4.6%) compared to a slight decrease (-1%) in the twice weekly iPPS arm (Figure 8).
- The observed reduction in the biomarkers of inflammation reported at Day 56 (ASX release 4 October 2023) such as TNF-alpha and IL-6, are consistent with the reduction in synovitis as demonstrated via quantitative MRI analysis at Day 168.

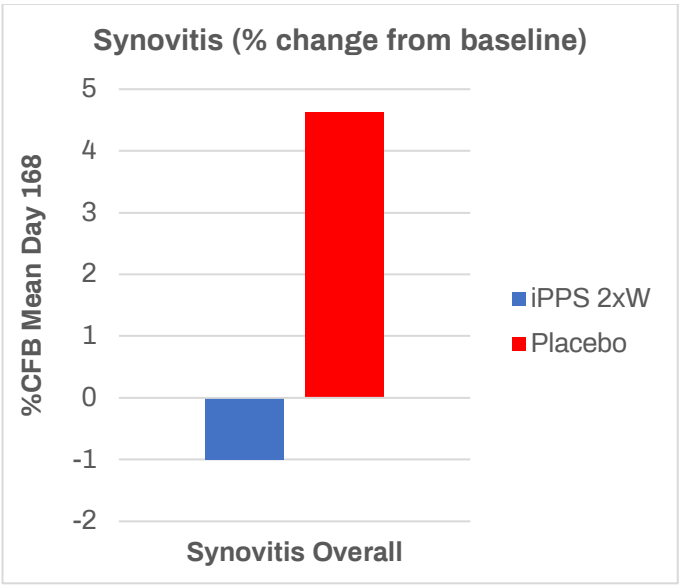


Figure 8: Percentage change from baseline in overall synovitis as measured by MRI in participants treated with twice weekly iPPS (iPPS 2xW) versus placebo.

About Paradigm Biopharmaceuticals Ltd.

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 iPPS, 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.

-ENDS-

APPENDIX

Summary of studied OA biomarkers

The PARA_OA_008 trial investigating participants with knee OA who had received a 6-week course of either iPPS treatment versus placebo was unique in both the breadth of biomarkers assessed at 6 months, as well as the duration of clinical effect out to 6 and then 12 months (Figure 9). The results from the broad range of structural and molecular biomarkers studied in combination with the clinical results builds a convincing picture of iPPS effects on OA disease progression.

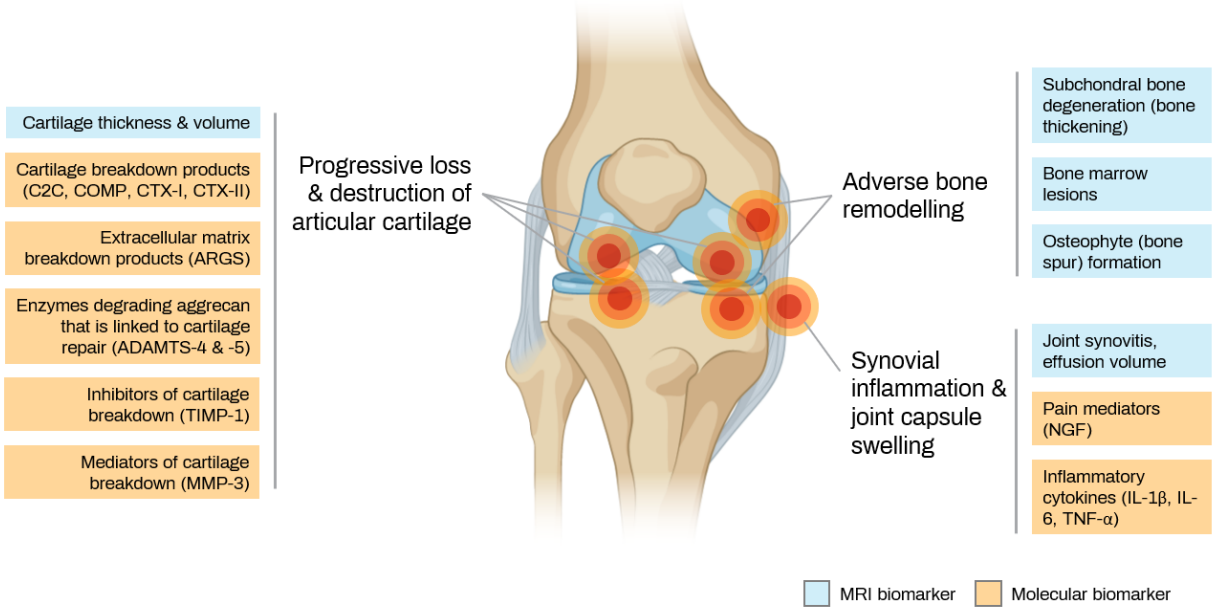


Figure 9. Schematic of osteoarthritis biomarkers investigated in PARA_OA_008. These biomarkers are measures of osteoarthritis, a disease of the whole joint, as such, disease pathophysiology locations are indicative. Figure created with images from BioRender.com.

Semi-quantitative versus quantitative MRI analyses

Semi-quantitative and quantitative analyses in the context of MRI (Magnetic Resonance Imaging) refer to different approaches for evaluating and measuring various aspects of the images produced by MRI machines. A breakdown of the differences include:

Semi-quantitative analysis:

- Semi-quantitative analysis involves a subjective assessment of MRI images. Based on visual criteria, a score is assigned to each region.
- This approach relies on broad visual interpretation, comparisons, and subjective judgment by radiologists or researchers.
- It is often used to evaluate features like lesion size, shape, location, and other qualitative aspects of the image.
- Semi-quantitative analysis is useful to establish a preliminary understanding of the MRI changes over time.

Quantitative analysis:

- Quantitative analysis, on the other hand, aims to provide precise numerical measurements and data from MRI images.
- It involves the use of specific software tools and algorithms to extract numerical values related to parameters of interest, such as tissue volumes, or signal intensities.

- Quantitative analysis is more objective and less reliant on human interpretation, making it suitable for research, clinical trials, and cases where exact measurements are required.

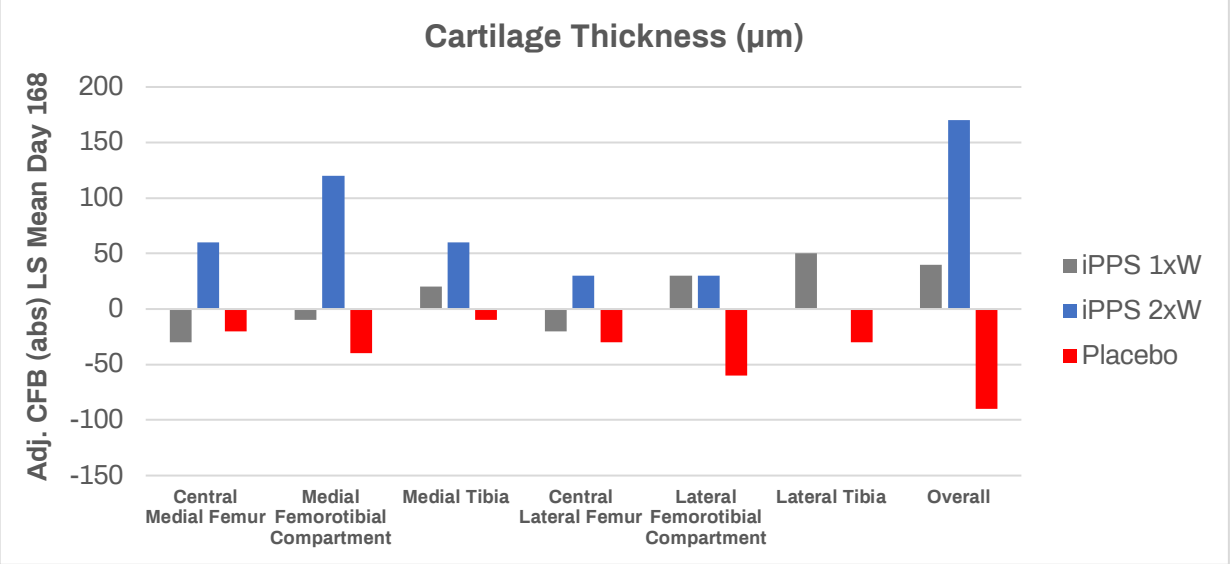
Full Quantitative MRI Data Set

Cartilage thickness

Cartilage Thickness (mm) Adj. CFB (abs.) LSM results.

Compartments/Regions	iPPS-Once N=19	iPPS-Twice N=15	Placebo N=22
	Day 168	Day 168	Day 168
Overall Thickness (mm)	0.04	0.17 (P= 0.054)	-0.09
Central Medial Femur Thickness (mm)	-0.03	0.06	-0.02
Medial Femorotibial Compartment Thickness (mm)	-0.01	0.12	-0.04
Medial Tibia Thickness (mm)	0.02	0.06	-0.01
Central Lateral Femur Thickness (mm)	-0.02	0.03	-0.03
Lateral Femorotibial Compartment Thickness (mm)	0.03	0.03	-0.06
Lateral Tibia Thickness (mm)	0.05	0.00	-0.03

Overall cartilage thickness is calculated as the sum of the medial and lateral compartments, i.e. Medial Femorotibial Compartment + Lateral Femorotibial Compartment.



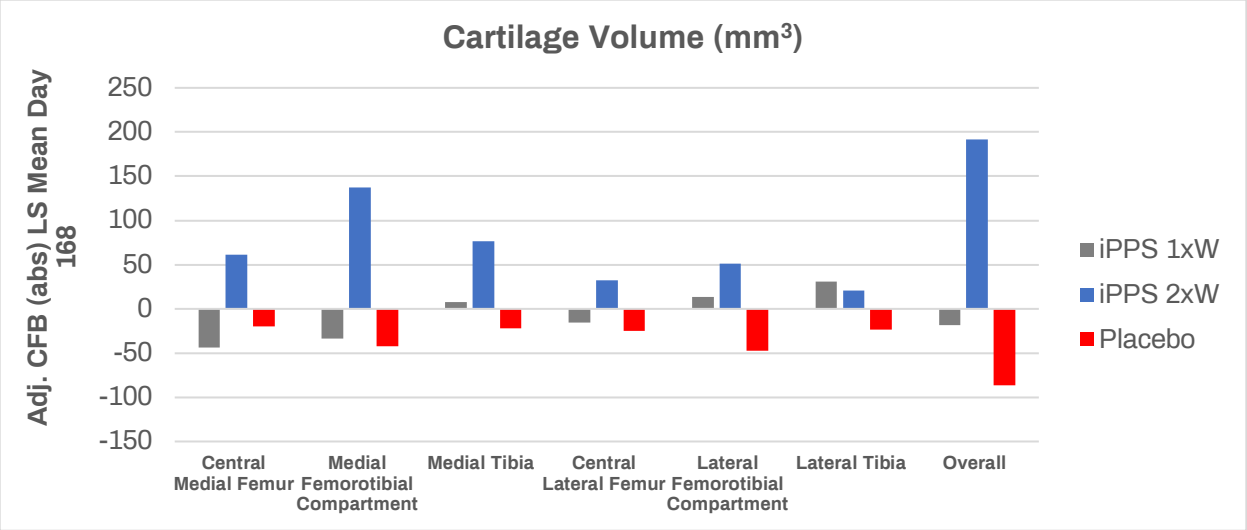
Cartilage volume

Cartilage Volume (mm^3) Adj. CFB (abs.) LSM results.

Compartments/Regions	iPPS-Once N=19	iPPS-Twice N=15	Placebo N=22
	Day 168	Day 168	Day 168
Overall Volume (mm^3)	-18.67	191.51	-86.81

		(**P=** 0.073)	
Central Medial Femur Volume (mm^3)	-43.56	61.11	-20.01
Medial Femorotibial Compartment Volume (mm^3)	-33.68	137.32	-42.36
Medial Tibia Volume (mm^3)	7.78	76.66	-22.20
Central Lateral Femur Volume (mm^3)	-15.85	32.43	-24.86
Lateral Femorotibial Compartment Volume (mm^3)	13.24	51.45	-47.29
Lateral Tibia Volume (mm^3)	30.78	20.81	-23.46

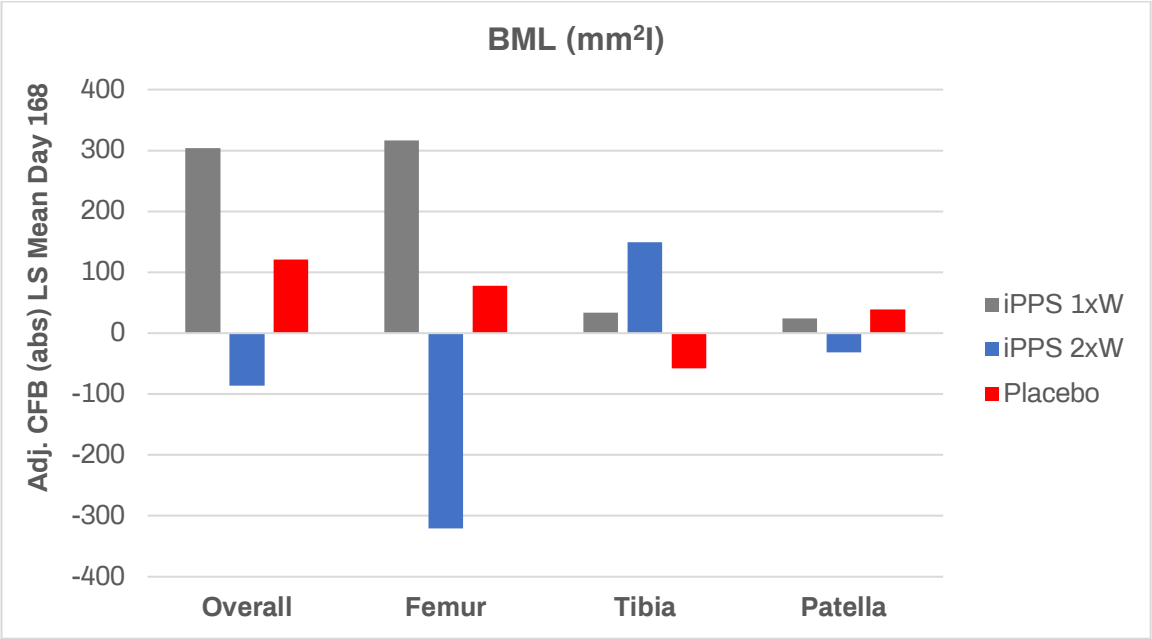
Overall cartilage volume is calculated as the sum of the medial and lateral compartments, i.e. Medial Femorotibial Compartment + Lateral Femorotibial Compartment.



Bone marrow lesions

BML (mm^2I) Adj. CFB (abs.) LSM results.

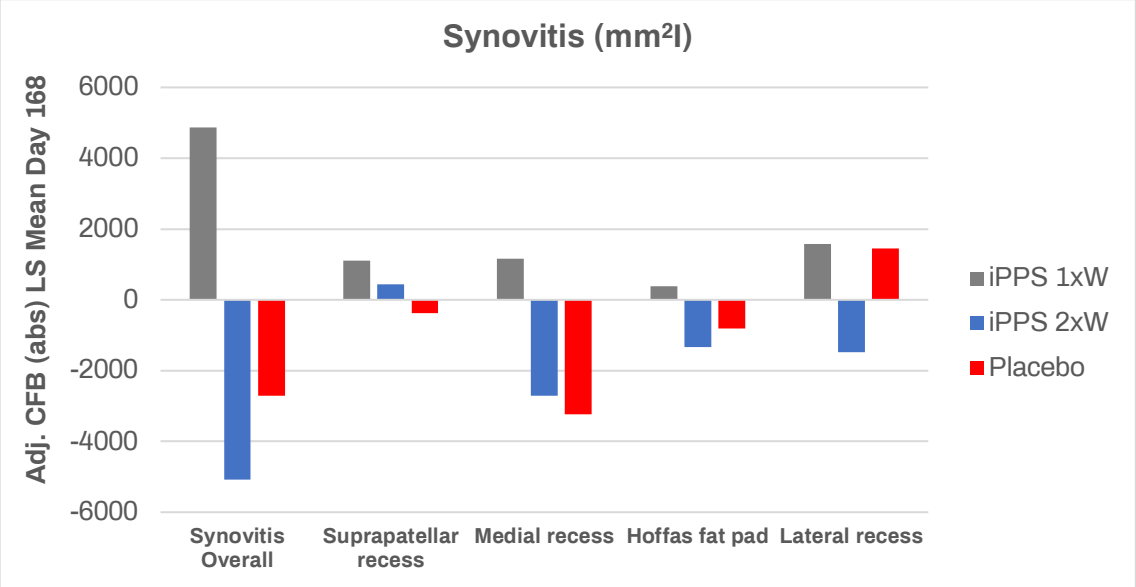
Compartments/Regions	**iPPS-Once N=19**	**iPPS-Twice N=15**	**Placebo N=22**
	Day 168	**Day 168**	**Day 168**
BML Overall	303.73	-86.26	120.65
Region: Femur	316.95	-320.63	77.71
Region: Tibia	34.12	149.17	-57.47
Region: Patella	24.17	-31.14	39.31



Synovitis (inflammation)

Synovitis (mm²l) Adj. CFB (abs.) LSM results.

Compartments/Regions	iPPS-Once N=19	iPPS-Twice N=15	Placebo N=22
	Day 168	Day 168	Day 168
Synovitis Overall	4873.47	-5086.13	-2707.38
Region: Suprapatellar recess	1115.35	436.01	-367.38
Region: Medial recess	1161.82	-2702.41	-3232.04
Region: Hoffas fat pad	387.92	-1337.67	-806.95
Region: Lateral recess	1579.10	-1470.93	1450.95



Previously reported Day 168 molecular biomarker analysis

The structural changes demonstrated via MRI are consistent with data previously reported (4 April 2023). These data showed reductions in molecular biomarkers of cartilage degradation from baseline to Day 168 in iPPS-treated subjects compared to placebo.

Molecular Biomarker	Day 168 iPPS v placebo
C2C (Se)	Reduced (p=0.024)
CTX II (U)	Reduced
COMP (SF)	Reduced
COMP (Se)	Reduced
ARGS (SF)	Reduced (p=0.024)
ARGS (Se)	Reduced

Molecular biomarkers of cartilage degradation reduced following iPPS treatment compared to placebo at Day 168. ARGS = Aggrecan amino acids alanine, arginine, glycine, and serine; C2C = collagen type-II C-terminal cleavage neoepitope; COMP = cartilage oligomeric matrix protein; CTX II = C-terminal crosslinked telopeptide type II collagen; Se = serum; SF = synovial fluid; U = urine.

The biomarkers C2C, CTX II, COMP, and ARGS are known to be associated with cartilage degradation (12,13). PARA_OA_008 results demonstrated reduced biomarker levels in the synovial fluid following iPPS treatment. These changes are consistent with the structural changes of improvement in cartilage thickness and volume seen with MRI.

PARA_OA_008 clinical trial design

PARA_OA_008 is a phase 2 exploratory study conducted at two sites in Australia. It explored changes in synovial fluid biomarkers with pentosan polysulfate sodium (iPPS) treatment compared with placebo in participants with knee osteoarthritis pain.

Sixty-one (61) eligible participants were enrolled and randomly assigned to a study intervention. Participants were administered twice weekly subcutaneous (SC) injections of iPPS calculated for ideal body weight (IBW):

- iPPS twice weekly: 2.0 mg/kg IBW PPS twice weekly for 6 weeks, (N = 19).
- iPPS once weekly: 2.0 mg/kg IBW PPS once weekly + placebo once weekly for 6 weeks, (N = 20).
- Placebo: placebo twice weekly for 6 weeks, (N = 22).

The primary objective of the study is to evaluate the effect of iPPS on synovial fluid biomarkers associated with pain and OA disease progression in participants with knee OA pain.

The Primary Endpoint was change from baseline at Day 56 in one or more synovial fluid biomarkers of inflammation, pain, and joint degradation, including but not limited to cartilage oligomeric matrix protein (COMP), c-terminal telopeptide II (CTX-II), nerve growth factor (NGF), interleukin-1β (IL-1β), tumour necrosis factor alpha (TNFα), IL-6, a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5), aggrecan

ARGS fragment, tissue inhibitor matrix metalloproteinase 1 (TIMP-1), CTX-I, and type II collagen (C2C).

Secondary Objectives included evaluating clinical outcomes, determining the correlation between synovial fluid biomarkers and clinical outcomes, determining the correlation between biomarkers in synovial fluid and biomarkers in serum and urine, and evaluating the effect of iPPS on serum and urine biomarkers associated with inflammation and OA disease progression in participants with knee OA pain.

Participants in the study were asked to provide baseline pain scores using the self-assessed WOMAC Osteoarthritis Index. After patients had initiated treatment, their pain scores were measured at predetermined timepoints from Day 11 out to Day 365 (12 months), with Day 56 the first predetermined timepoint for WOMAC assessment after the completion of treatment (Day 39).

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Approved for release by the Paradigm Board of Directors.

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PARADIGM

BIOPHARMA

PARA_OA_008 PHASE 2 TRIAL TOP-LINE RESULTS
DAY 168 QUANTITATIVE MRI DATA ANALYSIS

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Executive Summary

PARA_OA_008

Key Highlights – Structural improvements at Day 168

- iPPS shows improvement in joint structures at Day 168 vs placebo in a randomised, double-blind, placebo-controlled phase 2 clinical study (PARA_OA_008):
  - Improved cartilage volume and thickness.
  - Reduced bone marrow lesion size and volume.
  - Reduced Synovitis intensity.
- MRI data consistent with WOMAC pain and function improvements at Day 168.
- Consistent with the durability and significant pain and function improvements reported at Day 365.
- **High unmet need for new OA therapies to slow** OA progression in tandem with symptomatic improvement (pain reduction and functional improvement).
- Enhances data package for discussions with key regulatory agencies and attractiveness of iPPS to potential partners.

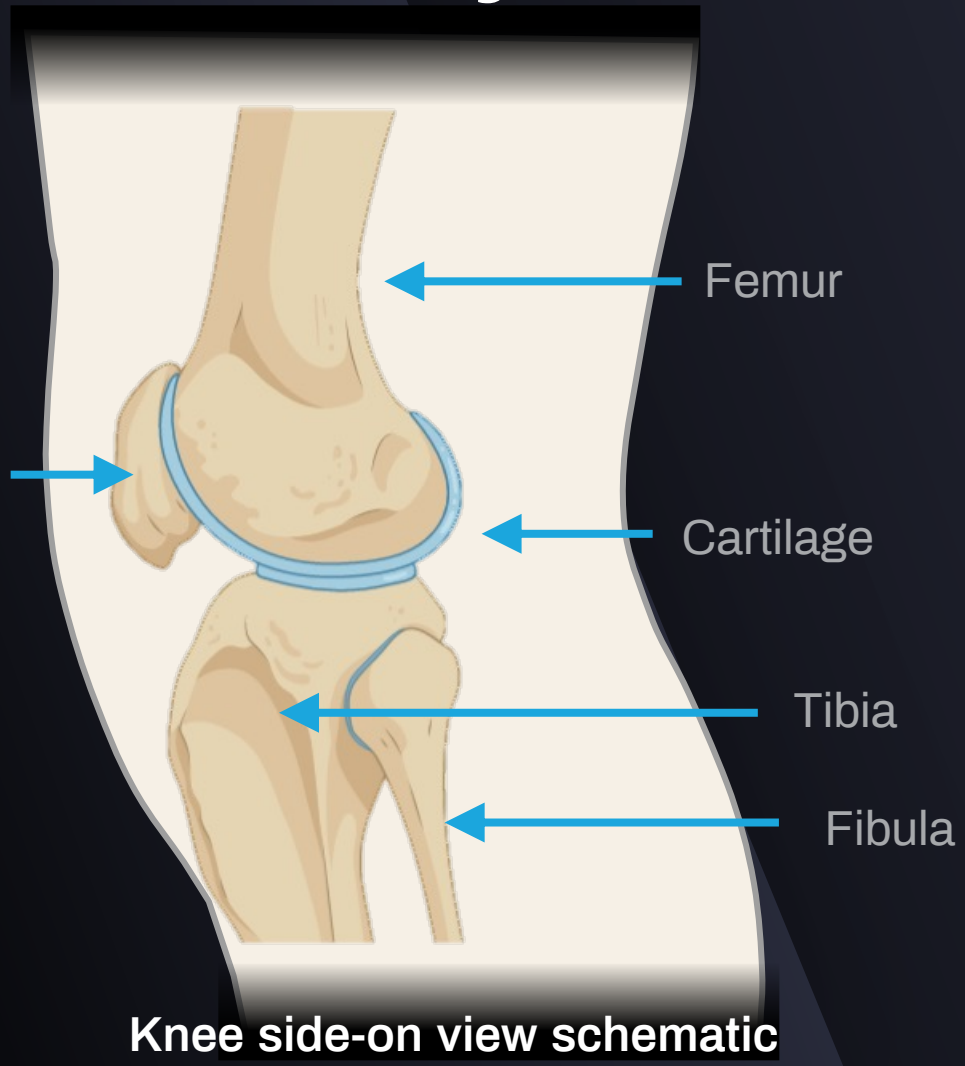
Near-term News flow

Upcoming Catalysts

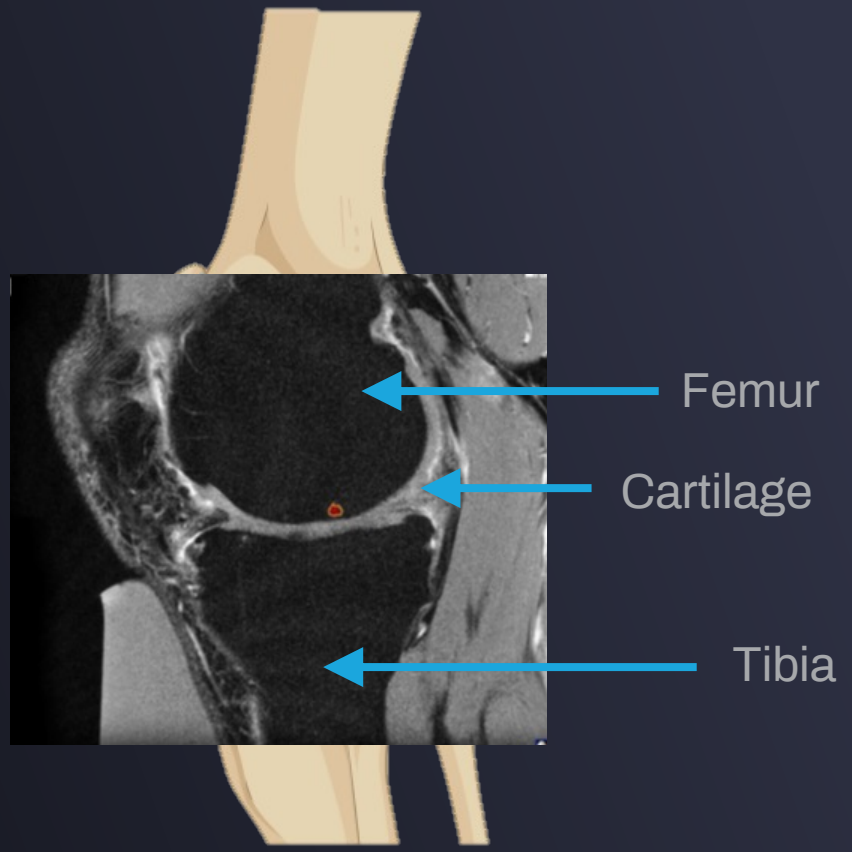
Near-term news flow

- ✓ PARA_OA_008 clinical trial – 12-month clinical outcome data.
- ✓ PARA_OA_008 clinical trial – 6-month quantitative MRI data.
- DMOAD pathway – discussion with regulatory agencies (FDA, EMA) Q1 CY2024.
- TGA Provisional Approval – Update on application timeline Q4 CY2023
- MPS VI phase 2 clinical trials – top-line data Q4 CY2023.
- PARA_OA_002 Dose Selection followed by phase 3 progression – Q1 CY2024.
- The MPS I and PARA_OA_008 – clinical data sets are currently being prepared for peer review. Publication likely in CY2024.
- Paradigm is currently in active discussion with potential regional partners for its phase 2 asset in mucopolysaccharidosis (MPS) and phase 3 asset in OA.

Knee anatomy | Cross-sectional images from a side-on view



Knee side-on view schematic



Knee side-on view MRI

Figure created with images from BioRender.com

Knee compartments | As seen via MRI with a front-on view

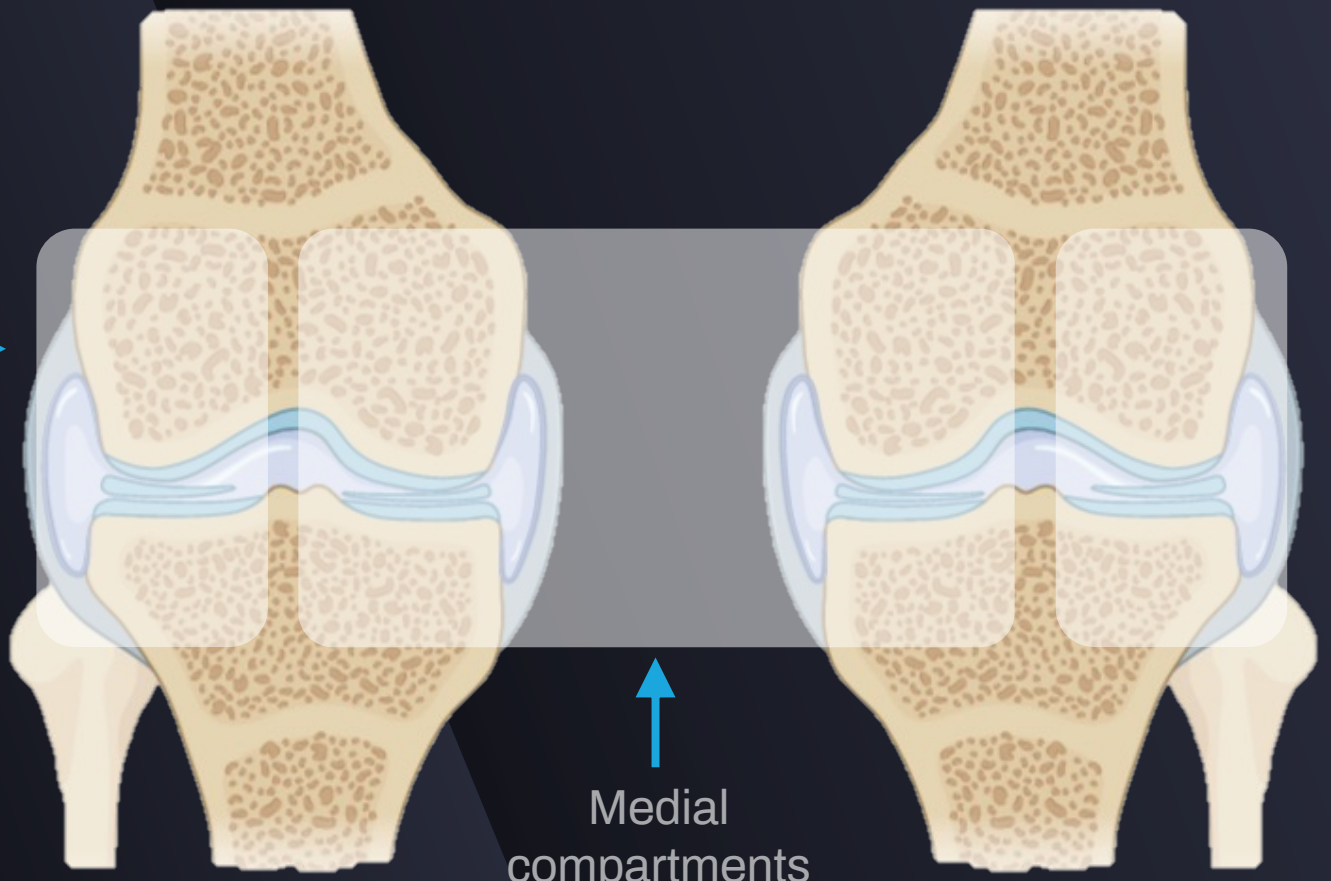


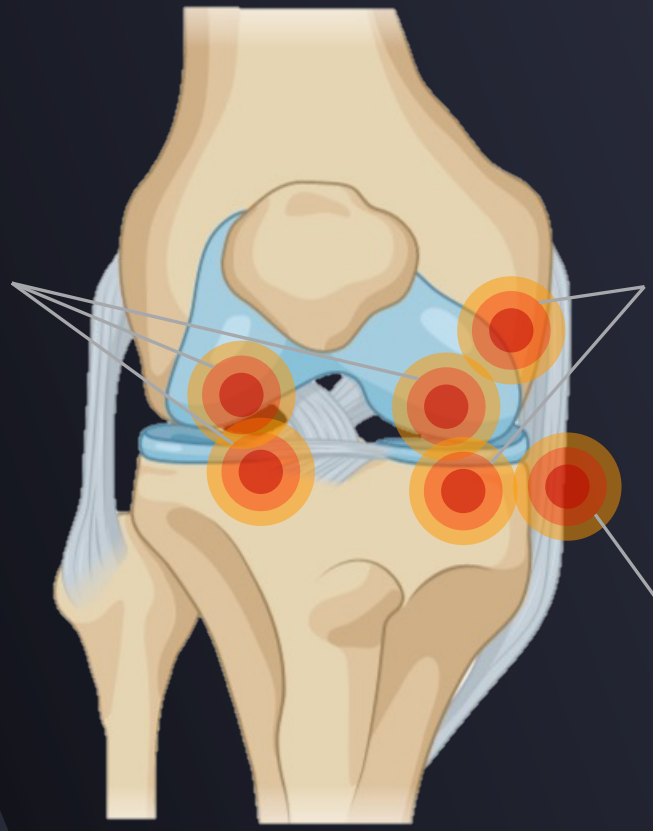
Figure created with images from BioRender.com

PARADIGM

Biomarkers of osteoarthritis | A disease of the whole joint

Progressive loss & destruction of articular cartilage

- Cartilage thickness & volume
- Cartilage breakdown products (C2C, COMP, CTX-I, CTX-II)
- Extracellular matrix breakdown products (ARGS)
- Enzymes degrading aggrecan that is linked to cartilage repair (ADAMTS-4 & -5)
- Inhibitors of cartilage breakdown (TIMP-1)
- Mediators of cartilage breakdown (MMP-3)



Adverse bone remodelling

- Subchondral bone degeneration (bone thickening)
- Bone marrow lesions
- Osteophyte (bone spur) formation

Synovial inflammation & joint capsule swelling

- Joint synovitis, effusion volume
- Pain mediators (NGF)
- Inflammatory cytokines (IL-1β, IL-6, TNF-α)

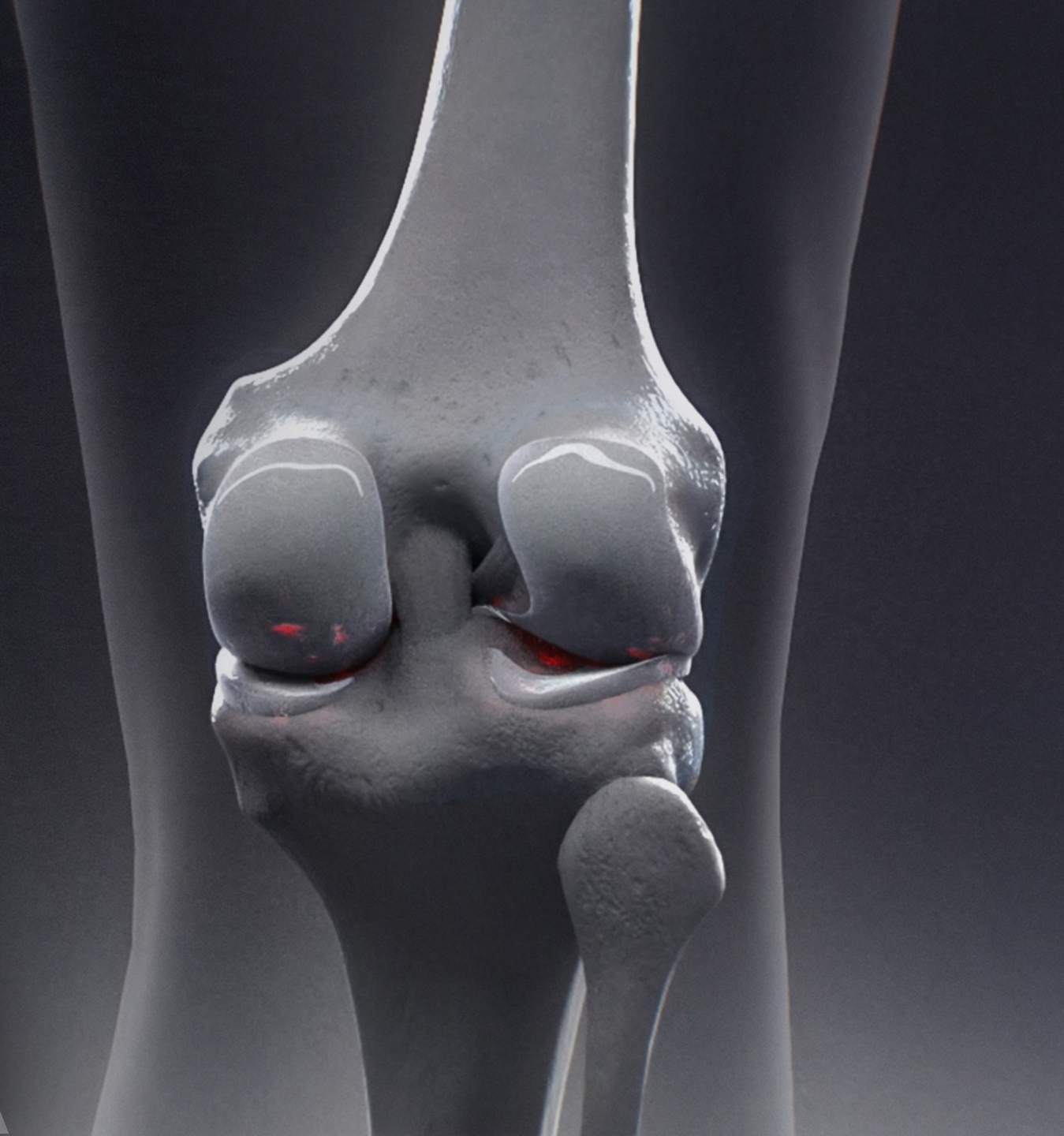
MRI biomarker Molecular biomarker

Figure created with images from BioRender.com

PARADIGM

PARA_OA_008

OA



Top-Line Results

PARA_OA_008

Top-Line Results – Day 168 Quantitative MRI

- MRI quantitative analysis data demonstrates that a six-week iPPS treatment course can alter osteoarthritis (OA) disease progression compared to placebo in a study of 61 participants with knee OA by:
  - Increase in cartilage volume and thickness most notably in the medial compartment where the highest proportion (72%) of knee OA occurs.
  - Reduction in bone marrow lesions.
  - Reduction in inflammation (synovitis).
- As osteoarthritis progresses, the medial side of the knee tends to lose cartilage more rapidly than the lateral side.

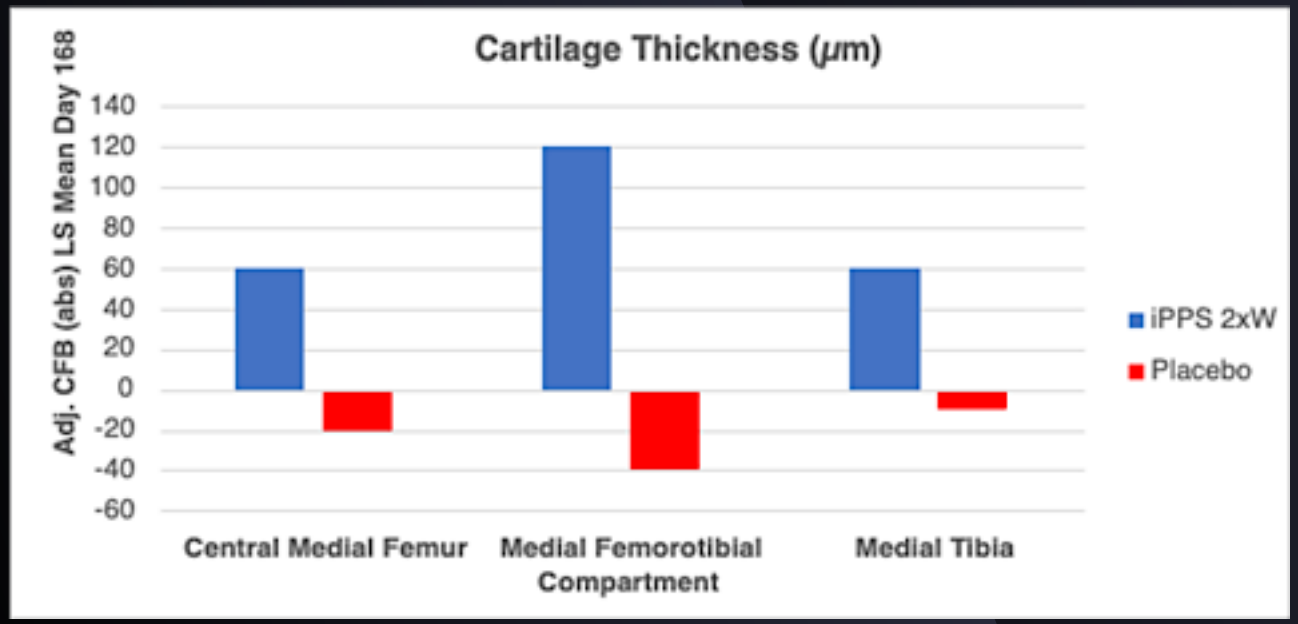
Cartilage Thickness & Volume

PARA_OA_008

Day 168 Top-Line Results – Cartilage Thickness and Volume

- Considered the most important feature of OA disease.
- Predictive of knee replacement surgery in OA sufferers.
- As knee osteoarthritis progresses, the medial side of the knee tends to lose cartilage more rapidly than the lateral side.
- The reduction of cartilage loss (cartilage preservation), may therefore delay time to total knee replacement (TKR) in an osteoarthritic knee.
- In the natural progression of OA, knees with Kellgren Lawrence (KL) grades of 2-4 (PARA_OA_008 subject cohort) would be expected to have an annual loss in cartilage thickness of around 50µm and loss in cartilage volume of around -4% at the central medial femur.

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results

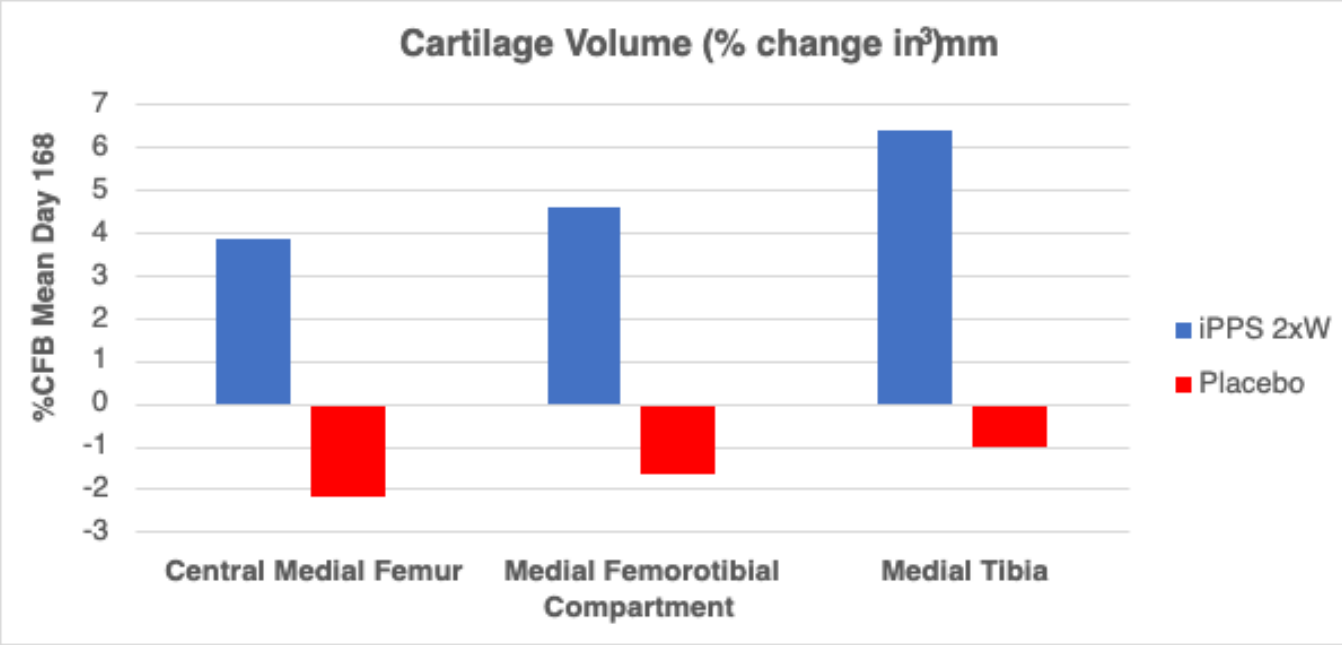


Cartilage Thickness (μm) Adj. CFB (abs.) LSM results by medial region in the knee

Changes in Cartilage Thickness from baseline

- Twice weekly iPPS arm, demonstrated a consistent pattern across regions of cartilage thickening over 6 months
- Placebo showed a loss in cartilage thickness in all medial compartments at 6 months.
- iPPS increased the cartilage thickness in the central medial femur by 60μm (0.06mm) compared to a reduction of -20μm (-0.02mm) in the placebo group at 6 months.
- Placebo consistent with the naturally occurring cartilage loss rate in knee OA progression (-40μm or 0.04mm per year).

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results



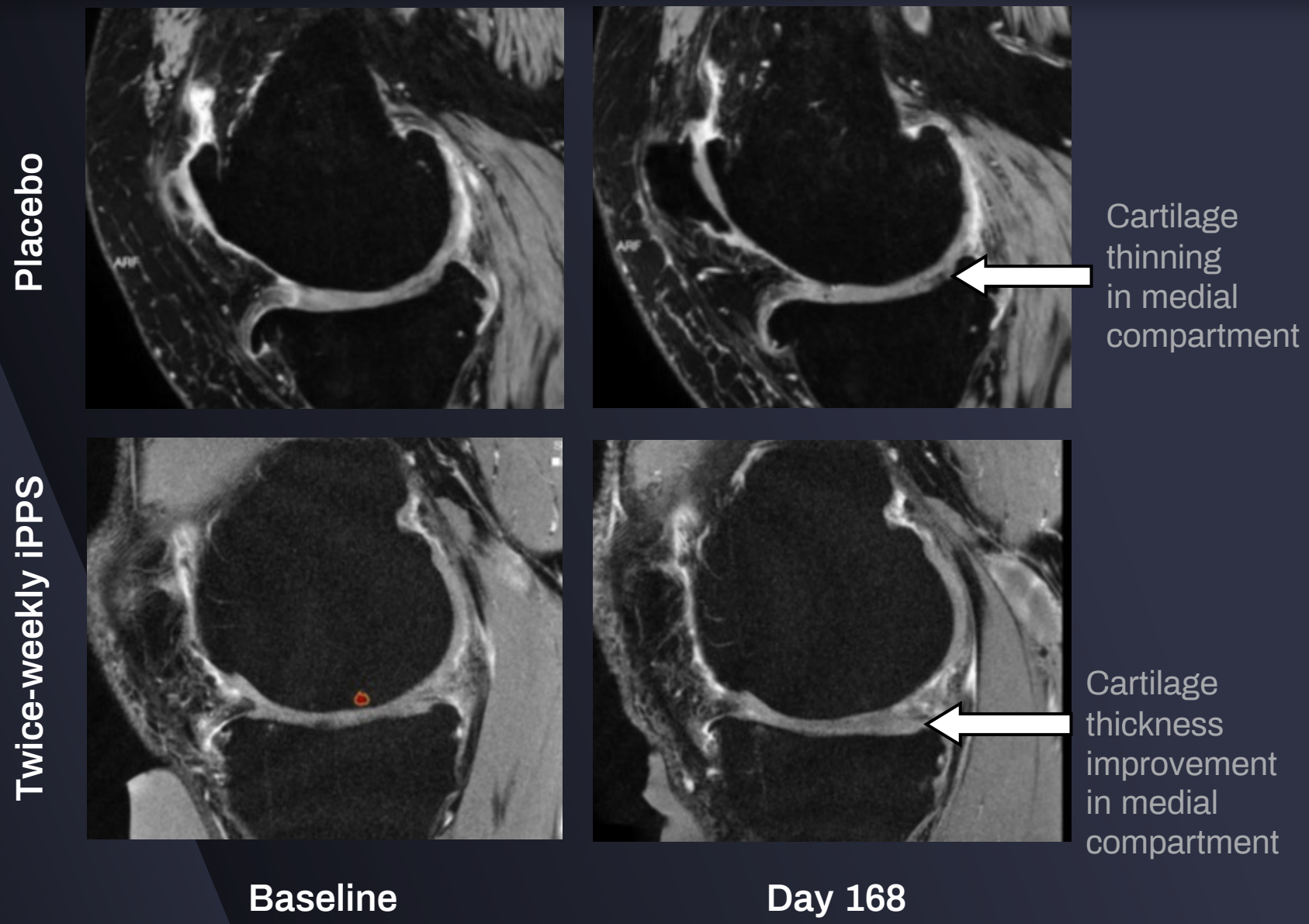
Average percentage (%) change from baseline (CFB) in cartilage thickness (mm) by medial region in the knee.

Changes in Cartilage Volume from baseline

- iPPS showed an average increase in cartilage volume of 4.6%, in the medial femorotibial compartment compared to baseline, whereas the placebo arm showed a loss of cartilage volume of -1.7%.
- iPPS is reversing the breakdown of cartilage at 6 months, compared to placebo which is showing further cartilage volume loss from baseline consistent with the natural progression of the disease (4% reduction in cartilage volume per year).

Cartilage thickness

PARA_OA_008 representative images



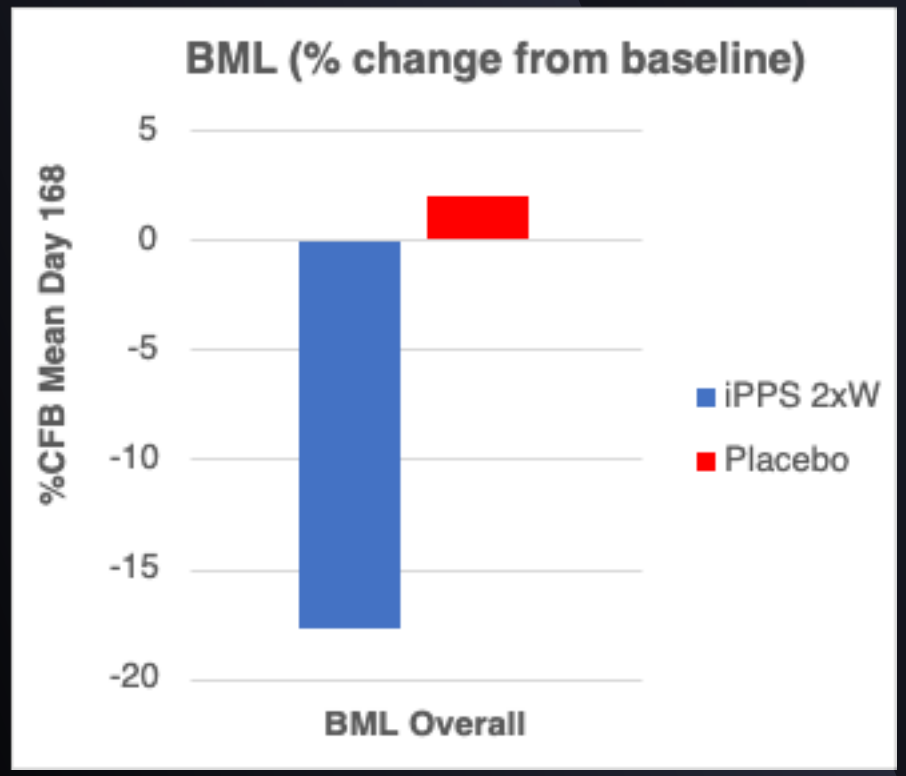
Bone Marrow Lesion

PARA_OA_008

Day 168 Top-Line Results – Bone Marrow Lesion (BML) Volume

- BML's appear as increased signal intensity within the bone marrow.
- Subchondral BML's are a common in knee OA and believed to be related to microtrauma resulting from overloading caused by loss of the normal weight bearing function of articular cartilage
- Increasing presence of BML are predictive of increased cartilage loss and like cartilage loss, BML's have been shown to be predictive of knee replacement.

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results



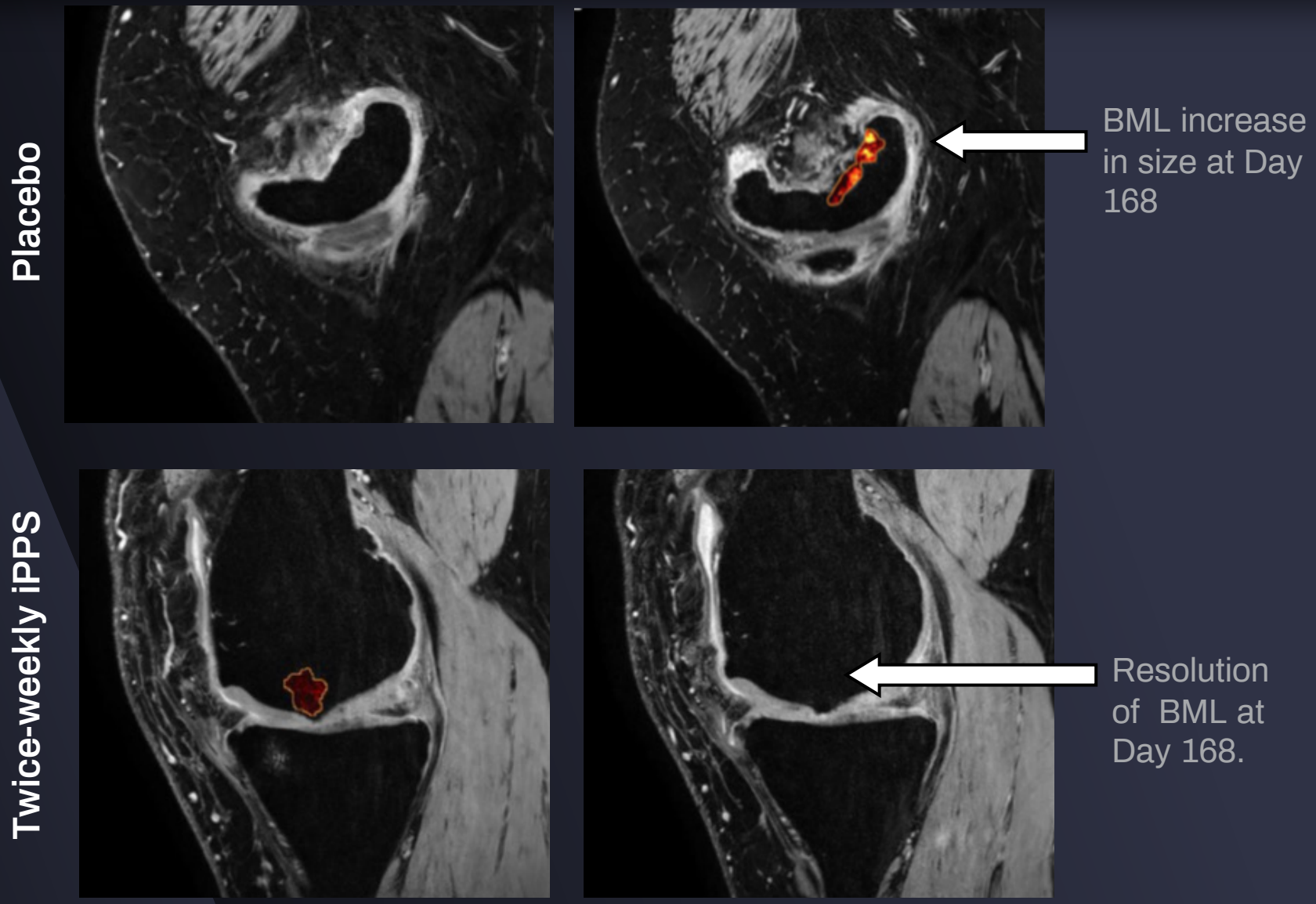
Average percentage (%) change from baseline (CFB) in overall bone marrow lesions

Changes in bone marrow lesions from baseline

- Overall BML volume in the knee was reduced on average by 17.6% in the iPPS twice weekly, compared to a 2% increase in the placebo group.
- The reduction in BMLs is consistent with reduced inflammation and cartilage preservation.

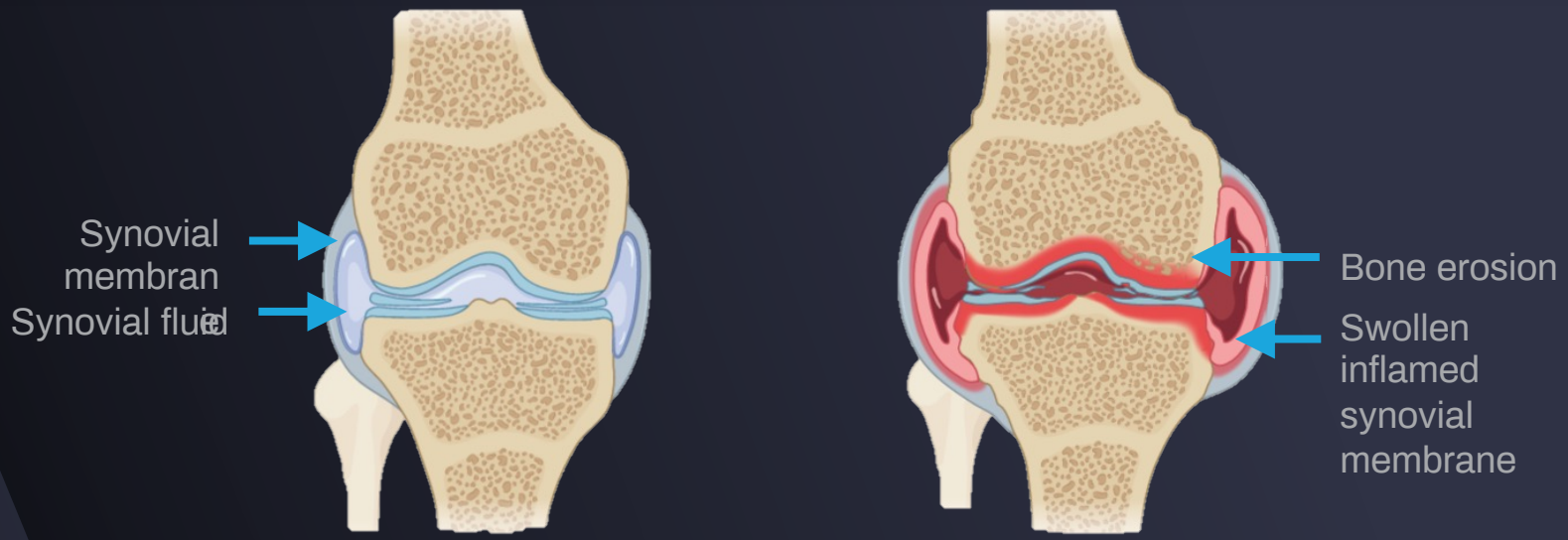
Bone marrow lesions

PARA_OA_008 representative images



Synovitis

Synovial joint inflammation

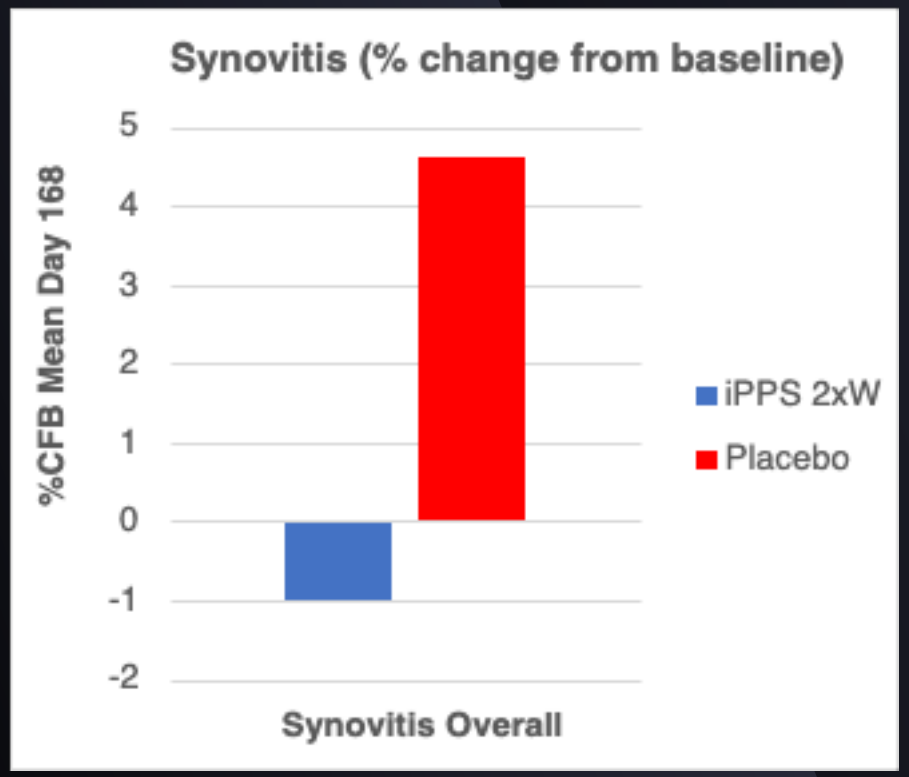


Normal knee joint **Synovitis of the knee joint**

- In OA, the synovial membrane can become inflamed and thickened in response to joint degeneration.
- Inflammation causes increased synovial fluid production.
- Excess synovial fluid can lead to joint swelling and can be associated with increased pain and stiffness.

Figure created with images from BioRender.com

PARA_OA_008 | Top-Line Day 168 Quantitative MRI Results



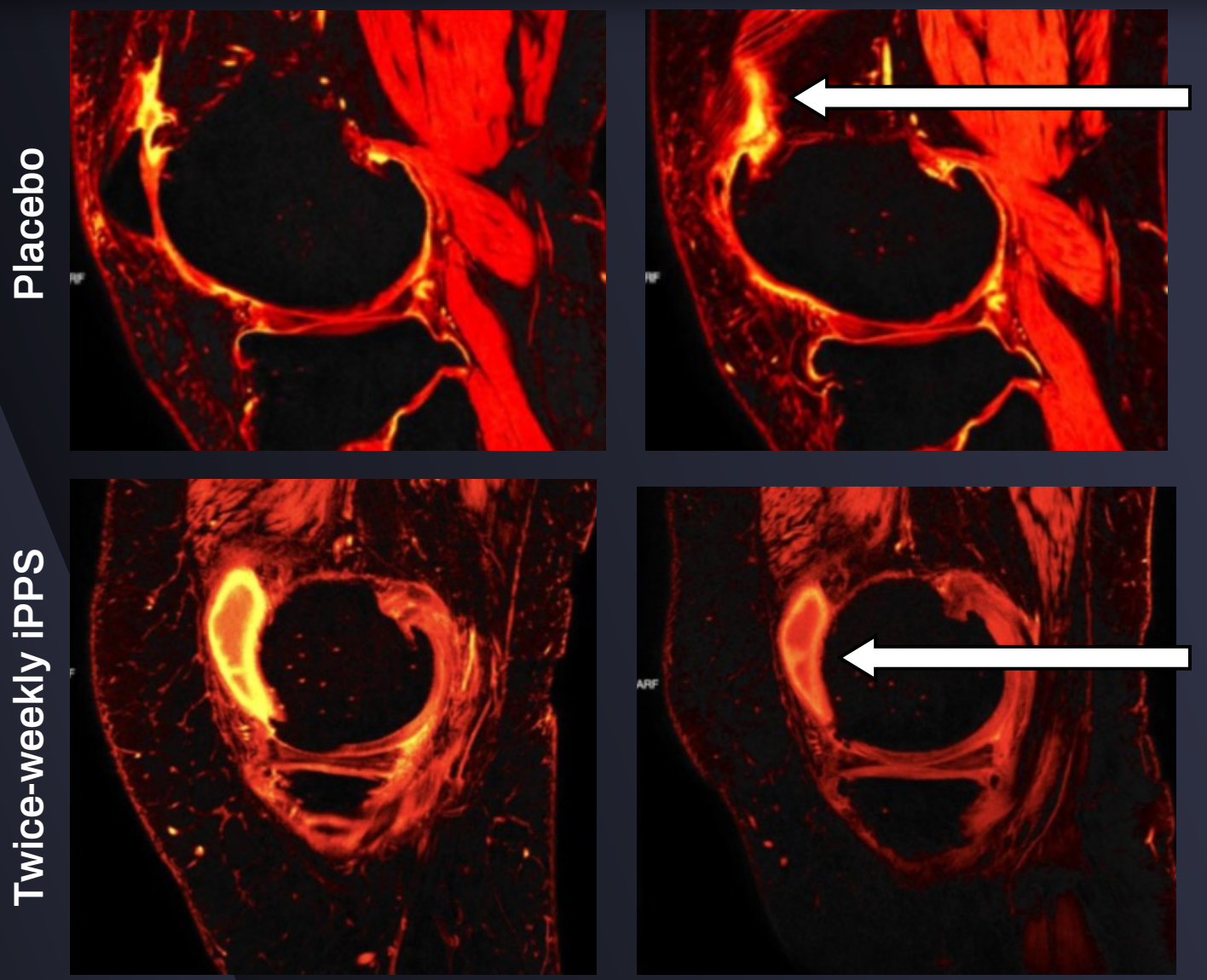
Average (SD) percentage (%) change from baseline (CFB) in overall knee joint synovitis.

Changes in synovitis from baseline

- At Day 168 in this phase 2 clinical trial synovitis increased from baseline in the placebo arm (4.6%) compared to a slight decrease (-1%) in the twice weekly iPPS arm.
- MRI images analysed from baseline and at 6 months following iPPS twice weekly versus placebo demonstrate an overall reduction in the intensity of synovitis.

Synovitis

PARA_OA_008 representative images



Optimal Dose

OA Program

iPPS optimal dose 2 mg/kg twice-weekly

- A lot of clinical experience with 2 mg/kg twice-weekly:
  - PARA_005, 121 participants total.
  - PARA_OA_008, 61 participants total.
  - TGA Special Access Scheme (SAS), >600 patients.
- Regulatory authorities requested identifying the minimal effective dose.
- Included a dose finding arm in the two-stage global placebo-controlled, randomised, adaptive PARA_OA_002 phase 3 trial.
- Program to proceed with dose of 2 mg/kg iPPS twice weekly for further development based on the above clinical experience and dose finding results.

PARA_OA_008 | Summary of phase 2 randomised controlled clinical trial

iPPS demonstrated efficacy on both objective and subjective measures compared to placebo

OBJECTIVE DATA MEASURES	Reported
Improvement in synovial fluid biomarkers associated with OA disease progression	Day 56 & 168
Improvement in structural changes in the knee determined by MRI	Day 168

SUBJECTIVE DATA MEASURES	Reported
Significant improvement in mean change from baseline in WOMAC pain, function, and overall scores.	Day 56, 168 & 365
Significant improvement in Patient Global Impression of Change (PGIC)	Day 365

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