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This report has been written to provide qualified Wholesale, Sophisticated and Institutional Investors with detailed information about Paradigm Biopharmaceuticals Limited (ASX.PAR).

This Report may provide information and our analyst insights, on Paradigm Biopharmaceuticals Limited to wholesale & institutional investors.

You should make your investment decision based on all available information.

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# A Deep Dive into Paradigm's OA Program & Partnering Prospects

## RISK CATEGORY

RISK	HIGH
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## BRIEF COMPANY VIEW

Paradigm Biopharmaceuticals Limited (PAR) listed on the ASX in August 2015. Paradigm focuses on repurposing pentosan polysulfate sodium (PPS) for new orthopaedic and rare disease applications. Paradigm addresses conditions that start with and are sustained by inflammation. The Company's lead clinical indications involve treating disease/injury that results in bone marrow edema lesions (BML), including Osteoarthritis, acute joint injury and rare joint diseases (mucopolysaccharidoses - MPS). Paradigm's pipeline includes treatments for cardiovascular disease, respiratory illnesses and atopic dermatitis.

## CORPORATE SNAPSHOT (15/05/2019)

ASX CODE	PAR.ASX
SHARE PRICE	A\$1.50
12 MONTH HIGH/LOW	A\$2.20/A\$0.45
SHARES ON ISSUE	~192m
OPTIONS ON ISSUE	6.35m
20 DAY AVERAGE DAILY VOLUME	~857,000
MARKET CAPITALISATION	~A\$288m
CASH – MAY 2019	~A\$82m, no debt

## 12 MONTH SHARE PRICE CHART



Paradigm Biopharmaceuticals Ltd ('Paradigm' or 'PAR') recently announced positive secondary end-point and MRI data from its placebo controlled, randomised, multi-centred OA/BMEL clinical trial (n=112) osteoarthritis (OA) Phase 2b clinical trial. This data follows the late December 2018 release of the positive top-line results. Together these results demonstrate, over multiple measures, that the drug – injectable pentosan polysulfate sodium (iPPS), is safe, clinically effective, and statistically significant over placebo.

**On the back of the recent release of the positive Phase 2b secondary end-point data, Paradigm successfully raised ~\$78m via an oversubscribed institutional placement and underwritten entitlement offer, demonstrating strong market support for the company.**

**Now, with Pfizer/Eli Lilly's lead compound, Tanezumab, likely falling over due to serious adverse events in their most recent Phase 3 OA clinical trial, we believe iPPS is the front-runner in regard to being the next gold standard for the treatment of OA pain.**

**The commercial drivers for a Pharma deal for Paradigm's OA program are significant:**

- the Opioid Epidemic continues to ravage the US (and the western world) with the US experiencing, for the first time in 50 years, a declining average life expectancy due to opioid related deaths;
- OA affects over 31 million people in the US and a total of 308.9 million people worldwide and despite this there has been no advancement for years in OA pain treatments that can cater for this number of people, let alone a treatment that is non-addictive and non-opioid/non-steroidal;
- The most advanced drugs/treatments in development, the anti-NGF class of molecules, have serious documented safety issues. In clinical trials iPPS has been shown to be comparable in effect to these treatments but much safer; and
- Other investigational/potential OA treatments are expensive and non-mass market e.g. cell based or Platelet-Rich Plasma (PRP) treatments.

## Positive Phase 2b results, onwards to Phase 3 and Partnering

The announcement of the results of Paradigm's Phase 2b OA/BMEL clinical trial showed that iPPS was an effective, durable (>6 months) treatment for knee OA pain and was safe. This coupled with the reported on 183 TGA Special Access Scheme patients (>500 patients treated in total) provides a large body of in-human data pointing to iPPS being an effective and safe treatment for OA pain.

Paradigm will now be advancing its OA program in parallel to executing a partnership with a pharma company. Next operational steps in the OA program involve:

- Discussions with FDA re Phase 3 trial design and trial commencement,
- Seeking Fast-Track designation.

**We see a potential partnership occurring in two ways:**

- **Regional partnership/co-development with an Asian pharma company** purely for Asia rights (ex-China) – est total deal range \$100-400m, with historical OA transactions ranging from US\$300-591m, with the average being US\$424m total deal size (upfronts and milestones).
- **Licensing/co-development with a global pharma for US, EU rights** – est deal range \$700m - \$1 bn+, but we believe that will likely require further positive feedback from the US FDA before eventuating (i.e. US IND for Phase 3 trial, Fast Track designation and/or Phase 3 trial commencement).

A Regional or Global Pharma deal would be largely unexpected by the market and depending on metrics could have a dramatically positive effect on the share price.

We maintain our view that the iPPS OA pain program is a highly valuable asset and a strong cash balance (>\$82m) will only enhance potential transaction metrics as Paradigm can run the pivotal Phase 3 trial itself. **Using a probability weighted DCF model of future iPPS sales from OA and MPS treatments getting to market in the US only – OA via a pharma partner model and Paradigm taking the MPS treatment to market itself - we arrive at a risked valuation of A\$843m (which equates to \$4.29 per share on a fully diluted basis).**

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## Company Overview

Paradigm Biopharmaceuticals Limited listed on the ASX in August 2015 and is focused on repurposing pentosan polysulfate sodium (PPS) for new orthopaedic and rare disease applications. PPS was developed in Germany in 1949 and has established anti-inflammatory and anti-thrombotic properties. It has been in use for approximately 70 years and as such its safety profile has been firmly established.

The Company addresses conditions that start with and are sustained by inflammation. Lead clinical indications involve treating osteoarthritis (and associated pain and injuries that result in bone marrow edema lesion, BML), rare joint diseases (mucopolysaccharidoses, MPS) and viral arthritis (Ross River and Chikungunya virus).

Given the pitfalls, time and costs involved in new drug (De Novo) development, repurposing existing registered drugs has become more popular over recent times. From 2007-09, 30-40% of drugs or biologics that were approved or launched for the first time in the US were either drugs repurposed for new indications, reformulations or new combinations of existing drugs.<sup>1</sup>

Paradigm's aim is to develop and commercialise an ethical, safe and effective Pharmaceutical Agent (PA) for the treatment of musculoskeletal disorders in humans with degenerative disease driven by injury, aging or genetic predisposition.

Paradigm's core business revolves around the repurposing of iPPS for a number of newly targeted indications.

## Top Selling Repurposed Drugs

Often people question how successful a repurposed drug can be and whether big Pharma are interested in repurposed drugs. The below chart highlights some of the most successful repurposed drugs of recent times<sup>2</sup>.

BRAND NAME	ORIGINAL INDICATION	NEW INDICATION	PHARMA COMPANY	PEAK ANNUAL SALES
SPRAVATO	Anaesthetic (Ketamine)	Treatment Resistant Depression	Janssen/J&J	Approved March 2019
REVLIMID	Structural Analogue of THALOMID (below)	Multiple Myeloma	Celgene	\$9.7B (2018)
TECFIDERA	Psoriasis	Multiple Sclerosis	Biogen/IDEC	\$4.0B (2017)
VIAGRA	Angina	Erectile Dysfunction	Pfizer	\$2.05B (2008)
GEMZAR	Anti-viral	Various Cancers	Lilly	\$1.72B (2008)
RITUXAN	Various Cancers	Rheumatoid Arthritis	Biogen & Roche	\$7.1B (2015)
EVISTA	Osteoporosis	Invasive Breast Cancer	Lilly	\$1.07B (2011)
PROSCAR	Hypertension	BPH	Merck	\$741.4M (2005)
THALOMID	Anti-Nausea	Leprosy Multiple Myeloma	Celgene Celgene	\$535.2M (2008)
REVATIO	Angina/ED	PA Hypertension	Pfizer	\$525.0M (2008)
PROPECIA	Hypertension	Male Pattern Baldness	Merck	\$429.1M (2008)
ELMIRON (PPS)	DVT	Interstitial cystitis	Janssen/J&J	US\$280m (2015)

Of particular relevance is the recent approval of Spravato (J&J) which is S-antimomer for well-known anaesthetic Ketamine – this is similar to repurposing, but not via the 505(b)(2) pathway. Spravato was approved by the FDA on just a single positive placebo-controlled trial (there were a number of earlier trials that did not prove efficacy). In the committee review that discussed the approval of Spravato, **the FDA highlighted the un-met need for new depression drugs, that no new depression drug has been approved for 30 years, the side effects of existing depression drugs and willingness of patients to try new treatments.**

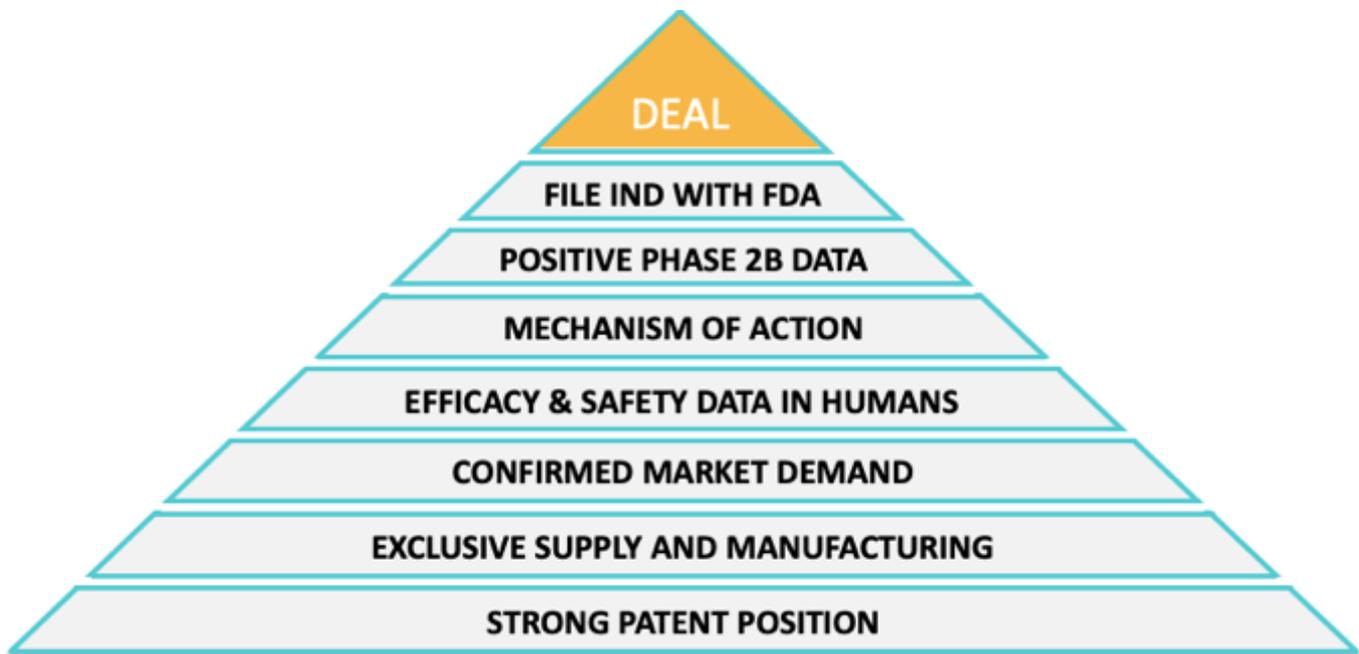
<sup>1</sup> Luther MA. Systems pharmacology and drug repositioning- an integrated approach to metabolic diseases. *Journal of Translational Medicine*. 2012;10(Suppl2):A18. doi:10.1186/1479-5876-10-S2-A18.

<sup>2</sup> Therapeutic Drug Repurposing, Repositioning and Rescue By Dr Stephen Naylor, David M. Kauppi and Judge M. Schonfeld, 2015

## Building blocks are in place for a Pharma deal

Pharmaceutical Companies will look to In-license, Partner, Co-develop or buy outright a clinical program from drug developer if it:

- a) **Makes commercial sense to them** i.e. they can buy the program for a price that they know will return their desired ROI/ROE i.e. they know they will make money from the program; and
- b) **Ticks all the necessary boxes** that are the essential building blocks for getting a drug successfully to market – categorised below as the 'Foundations of a Pharma Transaction'.



Paradigm has systematically completed all the necessary steps that a Pharma company would require to enter into a transaction, namely:

1. **Strong Patent and IP Position** – Paradigm has an extensive family of Use Patents that protect the indication. The minimum patent protection is 2030 and beyond with recent pending patents pushing protection to 2035-2040.
2. **Exclusive Supply and Manufacturing Confirmed** – 20-year exclusive supply agreement with the only FDA approved supplier of PPS, Bene pharmaChem GmbH. Bene has been producing PPS for over 70 years and have extensive knowledge in the manufacturing of PPS and also have capacity to increase production. Bene supply J&J under a similar exclusive supply arrangement as Paradigm i.e. only for the indication of interstitial cystitis (IC) and in oral tablet version. Interestingly J&J's drug, Elmiron, has been off-patent since 2012 but no company has been able to bring a generic version of Elmiron to market and J&J's Elmiron sales have grown steadily to around US\$250m pa. This shows us that human grade PPS is indeed complex and difficult to manufacture, and this is another level of protection for Paradigm.
3. **Confirmed Market Demand** - Osteoarthritis is the most common form of arthritis, affecting over 31 million people in the United States, with over 36 million outpatient visits and 750,000 hospitalisations per year. Current treatments, NSAIDs and opioids are ineffective and dangerous. Paradigm has a real opportunity to be the gold standard treatment for OA, after NSAIDs and before cell based/surgical treatments. This is truly a block-buster potential market.
4. **Efficacy and Safety of iPPS has been proven in Humans** - 183 TGA Special Access Scheme patients (500+ treated thus far), the successful Ghosh et al trial and the Kumagia et al trial provides a large body of in-human data pointing to iPPS being an effective and safe treatment for OA pain.

**It is well established that iPPS is safe and well tolerated in patients – 70 years safe use, >100m injections for DVT and >550 OA patients treated via TGA SAS and PAR clinical trials;**

5. **Mechanism of Action (MOA)** – iPPS has been shown to have anti-inflammatory effects, blocking TNF-alpha and IL-1 and inhibiting ADAMTS-4, ADAMTS-5a and MMP-3b thus preventing cartilage degradation in OA. Furthermore, Paradigm has flagged the release of a study and manuscript that shows iPPS MOA in regard to pain reduction in relation to human Nerve Growth Factor (NGF), something that we believe will be of great interest to the large Pharma (Pfizer, Teva etc) developing their own anti-NGF pain drugs, which have been plagued with safety issues.
6. **Positive Phase 2b Placebo controlled data** – Paradigm demonstrated clinical efficacy in six different ways as detailed in their recent clinical trial and achieved their primary end-point of a mean change from baseline greater than 10 on KOOS scale. Important Secondary End-Points of Patient Global Impression of Change (PGIC), MRI Grade Reduction, Improvements in Activities of Daily Living (ADL) and Mean Pain Reduction to 6 months to showed statistically and clinically meaningful results.
7. **File Investigative New Drug Application (IND) with the FDA and commence pivotal Phase 3** OA trial in the US. Filing of IND and commencing the pivotal Phase 3 clinical trial is not required to execute a Pharma transaction but will often enhance transaction metrics when dealing with a US Pharma company.

**The most likely stage that a pharma company will transact with a drug development company is from completion of successful Phase 2b results onwards – the stage that Paradigm is currently at.** Regional or specialty/junior pharma companies generally will not require the filing of IND, especially if it does not relate to their particular geographic region. Furthermore, regional or specialty/junior pharma companies typically act quicker than large pharma to secure licensing transactions with biotech companies otherwise they will not be able to compete with the large pharma companies - this bodes well for Paradigm.

This is a reasonable course of action for Paradigm to pursue, to build value ahead of a large pharma transaction for the prime US territory.

A Regional or Global Pharma deal would be largely unexpected by the market and depending on metrics could have a dramatically positive effect on the share price.

## What is Osteoarthritis?

Osteoarthritis isn't just a disease that affects older adults; it's the most common form of arthritis, affecting more than 3 million Americans.<sup>3</sup> Anyone who injures or overuses their joints, including athletes, military members, and people who work physically demanding jobs, may be more susceptible to developing this disease as they age, as detailed above. OA is a chronic condition that can affect any joint, but it occurs most often in:

- Knees
- Hips
- Lower back and neck
- Small joints of the fingers and the bases of the thumb and big toe

In normal joints, cartilage covers the end of each bone. Cartilage provides a smooth, gliding surface for joint motion and acts as a cushion between the bones. In OA, the cartilage breaks down, causing pain, swelling and problems moving the joint. As OA worsens over time, bones may break down and develop growths called spurs. Bits of bone or cartilage may chip off and float around in the joint. This can cause inflammation and further damage the cartilage. In the final stages of OA, the cartilage wears away and bone rubs against bone, leading to joint damage and more pain. When OA becomes severe, other than treating symptoms with pain medications, the only option for treatment becomes joint replacement.

<sup>3</sup> <https://www.cdc.gov/arthritis/basics/osteoarthritis.htm>

# The Addressable OA Market

- Currently over 31 million Americans have OA and that number is expected to grow in the coming years driven by aging, obesity and increasingly sports injuries<sup>4</sup>
- The osteoarthritis market is forecast to grow at a CAGR of 8.1% as the global population ages<sup>5</sup>
- The lifetime risk of developing symptomatic knee osteoarthritis is 45%
- **There are 14 million individuals in the U.S. who have symptomatic knee osteoarthritis**
- More than half of all individuals with diagnosed symptomatic knee osteoarthritis (OA) have had sufficient progression of OA that would make them eligible for knee replacement<sup>6</sup>
  - **More than 7 million individuals with moderate to severe osteoarthritis – Paradigm’s target market**
- Since the 1990’s the average age at diagnosis of OA has fallen from age 72 to 56
- OA affects 14% of adults aged 25 and older and 34% of those aged 65 and older
- Accounts for >\$185B in annual U.S. healthcare expenditures
- **Approximately 40% of Medicare patients with OA are prescribed opioids** and 2015 Part D spending for these drugs exceeded \$4 billion<sup>7 8</sup>

## Addressable US Market

Number of people with osteoarthritis in USA	30,800,000
Number of people with knee osteoarthritis in USA	14,000,000
<b>Approximate number of people with moderate to severe knee osteoarthritis in USA</b>	<b>7,000,000</b>

### US Market Opportunity

Addressable market in the United States, based on a treatment cost of US\$2,000 – US\$3,000 is  
**US\$14bn – US\$21bn**

### Global Market Opportunity

The US typically accounts for 50% of the global pharmaceutical sales market, utilising this assumption the global market opportunity for iPPS based on a treatment cost of US\$2,000 – US\$3,000 is **US\$28bn – US\$42bn**

<sup>4</sup> Cisternas MG, Murthy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative Methods for Defining Osteoarthritis and the Impact on Estimating Prevalence in a US Population-Based Survey. Arthritis Care Res (Hoboken). 2016 May;68(5):574-80.

<sup>5</sup> <https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf>

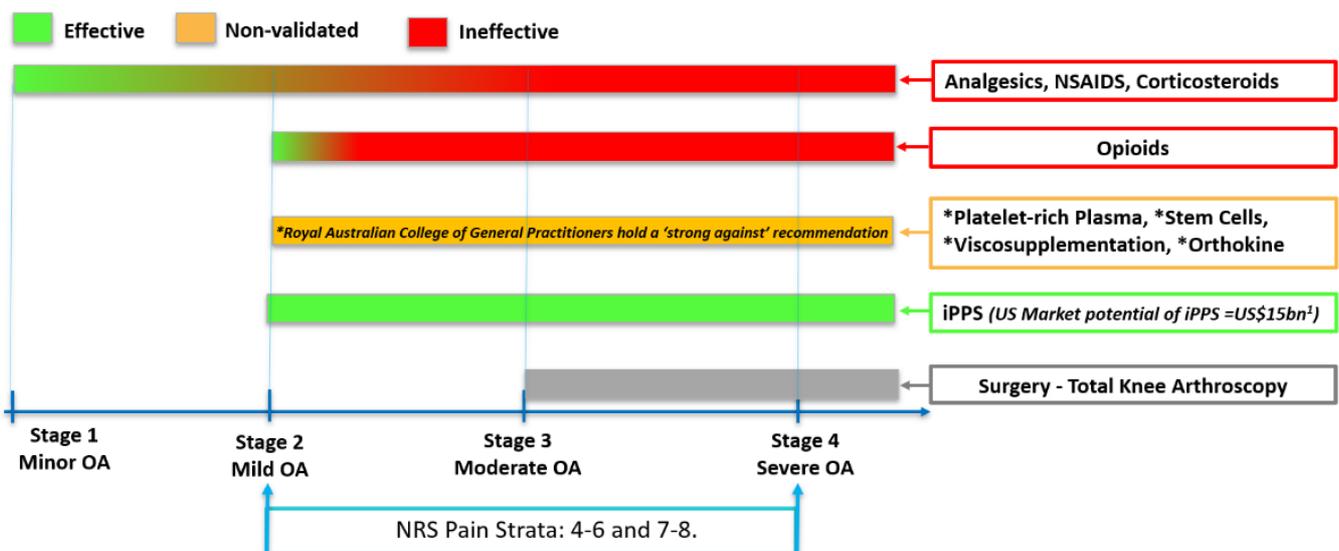
<sup>6</sup> <https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf>

<sup>7</sup> Wright EA, Katz JN, Abrams S, Solomon DH, Losina E. Trends in prescription of opioids from 2003-2009 in persons with knee osteoarthritis. Arthritis Care Res (Hoboken). 2014;66(10):1489-95.

<sup>8</sup> Williams AR, Bisaga A. From AIDS to opioids – how to combat an epidemic. N Engl J Med 2016;375(9):813-815

# There are no effective treatments for moderate to severe OA – iPPS poised to be a new treatment

Below is diagram of the various treatments that are currently available for the treatment of OA. When a patient presents to their physician with the initial symptoms of OA, once diagnosed, they will generally be prescribed analgesics or a NSAID and/or advised to lose weight. This is called first line therapy. Analgesics are considered to have minimal effect on OA pain that is classified as mild/moderate or stronger. NSAIDs, whilst considered effective in the short term, are contra-indicated for long term use due to serious documented gastrointestinal and cardiovascular side effects.



Once a physician is satisfied that the OA pain is not being managed effectively by analgesics/NSAIDs they will look to corticosteroids as the second line of therapy. Corticosteroids, whilst effective anti-inflammatories are once again contra-indicated for long term/repeat use.

**Post corticosteroid treatment a physician has limited treatment options for a patient suffering from OA pain. They can:**

1. Prescribe a strong analgesic to relieve the pain e.g. opioids. Opioid treatment is an effective short term, limited use pain management treatment, generally prescribed post-surgery and not designed as a long-term pain management treatment. It is due to this mis-prescription or over-prescription and the very addictive nature of opioids that the world is currently in the grip of a devastating opioid epidemic.
2. Depending on the individual physician they may recommend a stem-cell, platelet-rich plasma, viscosupplementation or orthokine treatment. These treatments are:
  - a. **Largely exploratory**, are still in trial stage and likely 5+ years away and results vary wildly amongst individuals who have been treated;
  - b. **Invasive** as they require surgery to produce the cell treatment;
  - c. Not without safety issues, either from the surgery itself (complications, infection etc) or from the stem cell treatment itself (tumors); and
  - d. **Expensive** – stem cell treatments generally cost ~A\$10,000 thereby effectively ruling them out for the vast majority of worldwide OA sufferers. Furthermore, mass production of ‘off the shelf’ cell treatments has its own set of regulatory hurdles due lack on conformity across the cell products – i.e. stem cell products are not homogenous.
3. Advise that total joint replacement is required. This is the last line of treatment to cure serious, chronic joint pain that is impacting severely on quality of life. Joint replacement, despite the advancement of modern medicine, is still considered undesirable by many patients.

We consulted with various medical professionals who have experience with iPPS treatment in both the SAS and

clinical trial setting and they support our view that because iPPS appears to work on the vast majority of OA patients who have been treated with it (under the SAS/Phase 2b trial) it offers real hope of being a true second line therapy for the mild/moderate+ OA sufferers. This means iPPS could effectively slot in after analgesics and NSAIDs, which have been found to not reduce pain, being administered alongside or after corticosteroids.

Given the cost and safety advantages over the cell-based therapies and the obvious advantages over opioids, iPPS could effectively provide a long-awaited treatment for what is an incredibly large component of the OA market. This would serve a double benefit of taking people off opioids and prolonging the time before they would need to receive a joint replacement – two factors that would have a major positive impact on global health systems and individuals' lives.

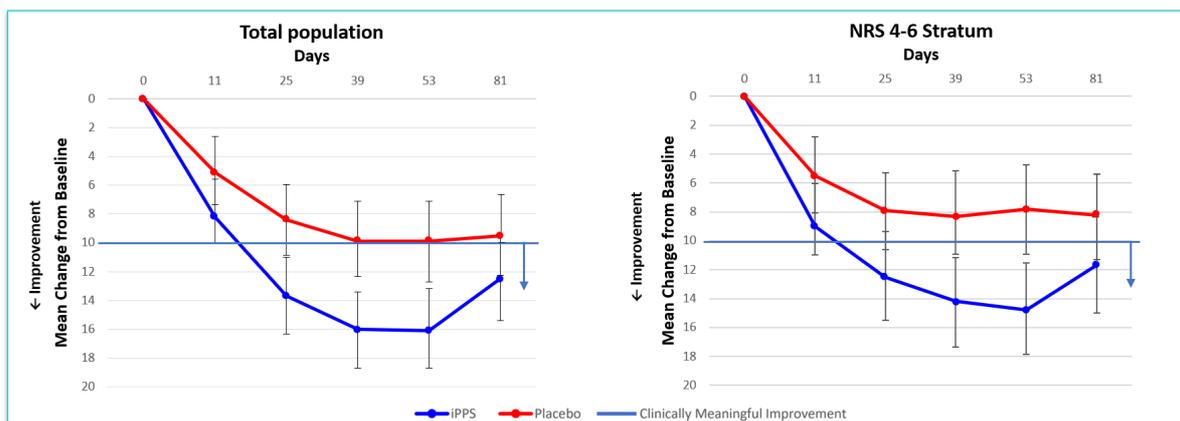
Importantly, General Practitioners (GPs) and clinic nurses would be able to treat this mild/moderate+ group of OA sufferers – something they cannot really do at present, because there is no effective treatment. We note that doctors had patients they treated under the SAS program drive more than 3 hours each visit, twice a week for six weeks to receive their iPPS treatment – something truly indicative of not only the drug working but also the desire of the individual to receive treatment in an environment where there are no other effective treatments. We, and the treating SAS doctors we spoke to, do not see the 12-injection dosing regimen to be an issue in terms of patients seeking treatment. Furthermore, due to the well documented safety of iPPS, over time Paradigm would likely seek to have iPPS in an auto-injector, similar to current insulin pens, thereby permanently solving this perceived issue.

When we dig a bit deeper, it becomes apparent to us that due to timing and massive deficiencies in treatments in the OA market that iPPS has a very good chance of being the go to 'Second Line Treatment' for OA, after analgesics and NSAIDs, but could be a 'First Line Treatment' for stage 2 OA and beyond. Given the US/Australian numbers of OA sufferers, even treating just a portion of these patients easily presents itself as a multi-billion-dollar opportunity.

## Phase 2b – Osteoarthritis Clinical Trial Results

On the 18<sup>th</sup> December 2018 Paradigm announced it met the primary outcome of its phase 2b randomised double-blind placebo-controlled multi-centre clinical trial (n=112). The primary outcome of the trial was to evaluate the effects of injectable pentosan polysulfate sodium (iPPS) on knee pain in subjects with knee osteoarthritis and subchondral bone marrow edema lesions (BMELs) as assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale.

The key outcome from the trial is that clinically meaningful and statistically significant results between iPPS and Placebo were demonstrated across the total subject population and highly clinically meaningful and highly statistically significant results were demonstrated in the NRS pain = 4-6 stratum. In addition, iPPS continues to be safe, well tolerated and very importantly, clinical meaningful as demonstrated by the higher number of subjects with >50% reduction in pain from baseline.



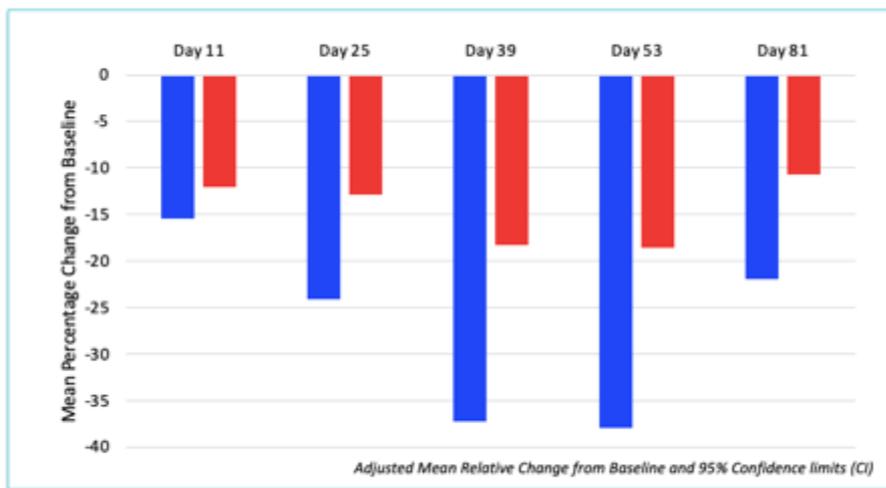
- In the **Total Population and NRS 4-6 Stratum** Paradigm demonstrated a statistically significant mean change in KOOS Pain from Baseline versus Placebo at day 39 and day 53.

- A mean change in KOOS Pain from Baseline greater than 10 is considered clinically meaningful this was achieved the Total Population and NRS 4-6 Stratum from day 25 onward.

In the NRS Pain = 4-6 strata 46.2% of subjects receiving iPPS showed a greater than 50% reduction in pain from baseline compared to 22.5% of subjects receiving Placebo under KOOS pain subscale. This is highly statistically significant at  $p=0.026$  and highly clinically meaningful i.e. subjects received a pain reduction of 50% or more.

The reporting of these top-line results was done in the same fashion as Big Pharma companies report their OA/Pain clinical trials, namely (i) mean change from baseline in KOOS Pain, (ii) Patient Global Impression of Change (PGIC) of OA and (iii) percentage of patients with  $\geq 50\%$  reduction in pain from baseline. Together these results demonstrate that the drug, iPPS, was clinically effective and statistically significant over placebo.

Mean Percentage Change in NRS Pain from Baseline – NRS:4-6 Stratum



- Day 39 PPS (Blue) vs Placebo (Red)  $p=0.028$
- Day 53 PPS (Blue) vs Placebo (Red)  $p=0.039$

In regard to secondary endpoints, to date, in comparisons with placebo, statistical differences were achieved in NRS pain score (day 39 and 53,  $p=0.0062$ ), and proportions of subjects with 50% reductions in timepoints other than day 53.

It is generally considered that a 30% reduction in pain corresponds with a “much improved” or “very much improved” response from patients on a global impression of change, or 2 points on a 0 to 11 pain intensity numerical rating scale for example from 6/10 down to 4/10” 1. While a 30% reduction in pain is significant and is described by participants reporting a much improved or very much improved reduction in pain, Paradigm used the more stringent measure of a 50% reduction in pain. A 50% reduction in pain represents a highly clinically meaningful effect, resulting in a significant shift in ‘intensity of pain’ i.e. from persistent moderate pain to mild/minor pain.

## Secondary Endpoints Data Release – April 2019

On the 15<sup>th</sup> April, Paradigm announced 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 reported the secondary end-point objective data of reduction in BML Grade, Size and Volume in the iPPS groups as measured on MRI.

**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).**

A summary of the positive secondary end-points reported is as follows:

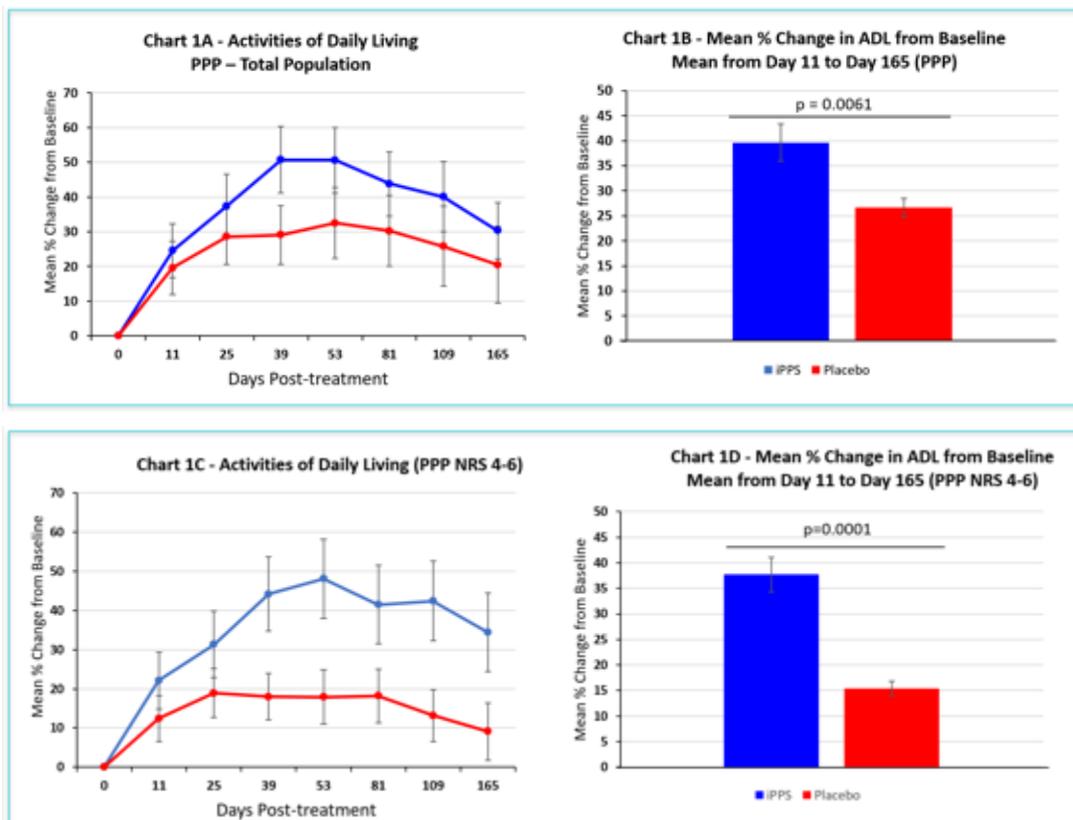
- Improved knee function (Activities of Daily Living or ADL) showed improved physical function to Day 165 in subjects treated with injectable pentosan polysulfate sodium (iPPS) compared to placebo. The mean % change of ADL of iPPS (39.6%) versus placebo (26.6%) was statistically significant ( $p=0.0061$ ).

- Pain reduction to 6 months (reduction in KOOS pain score from baseline 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.
- 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; and
- Objective data of reduction in BML Grade, Size and Volume in the iPPS groups as measured on MRI. 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 ( $P=0.03$ ).

**Importantly, a reduction of BML Grade, Size and Volume on MRI highlights the potential of iPPS to slow the progression of the disease.**

**Improved Knee Function (Activities of Daily Living) to Day 165:**

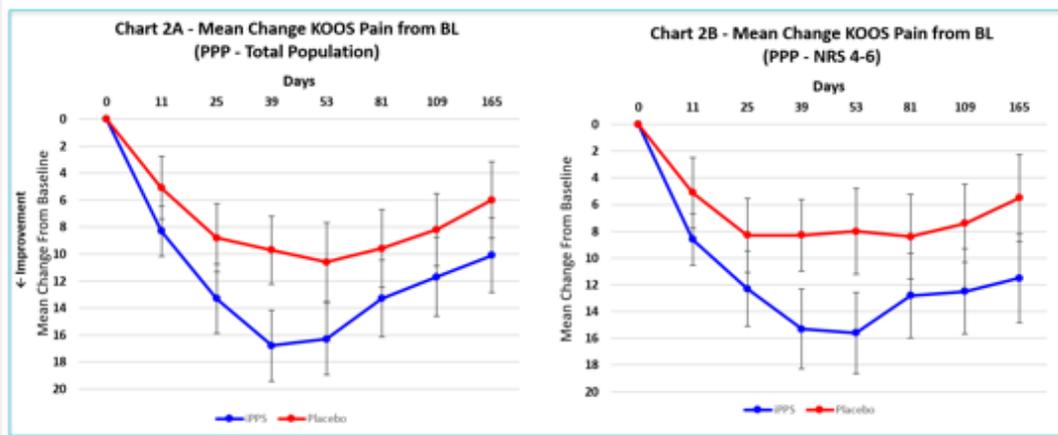
- The key functional secondary end-point of Activities of Daily Living (ADL) showed improved physical function to Day 165 in subjects treated with injectable pentosan polysulfate sodium (iPPS) compared to placebo. See Charts 1A and 1C.
- The mean % change of ADL of iPPS (39.6%) versus placebo (26.6%) was statistically significant ( $p=0.0061$ ). See Charts 1B and 1D.



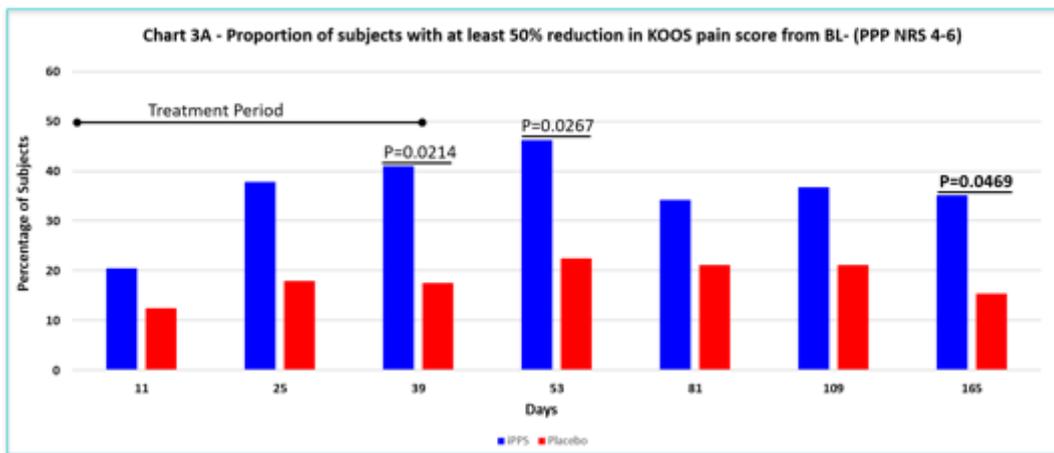
These data suggest that iPPS improves physical function as assessed by the ADL in subjects and these changes are concomitant with the observed clinically meaningful and statistically significant improvement in the Patient Global Impression of Change (PGIC) and reduction in knee pain as previously reported.

**Pain Reduction 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.



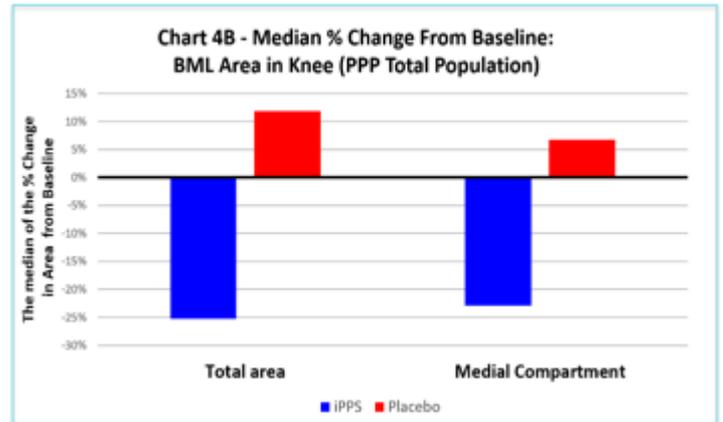
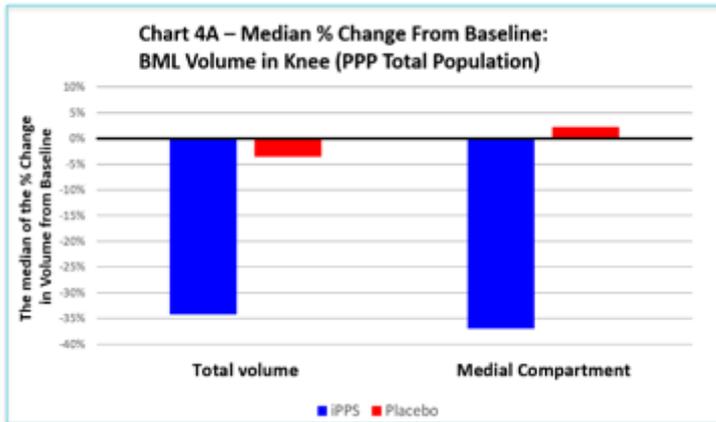
- At Day 165 the proportion of subjects receiving iPPS with a greater than 50% reduction in KOOS pain score is clinically meaningful and statistically significant ( $p=0.0469$ ) over placebo. See Chart 3A.



These results demonstrate iPPS achieves a clinically meaningful, statistically significant and durable pain reduction to Day 165.

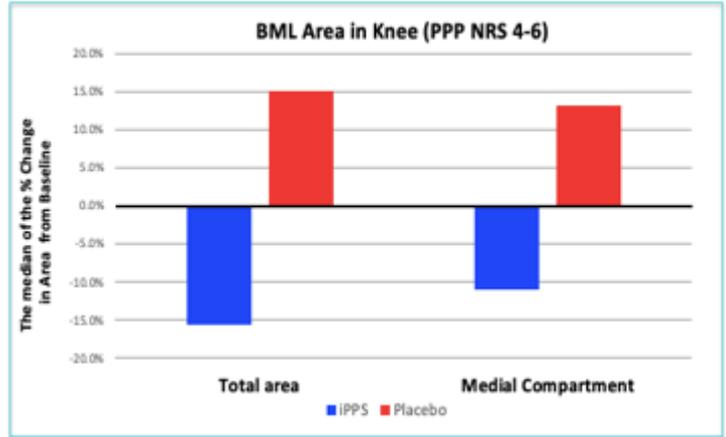
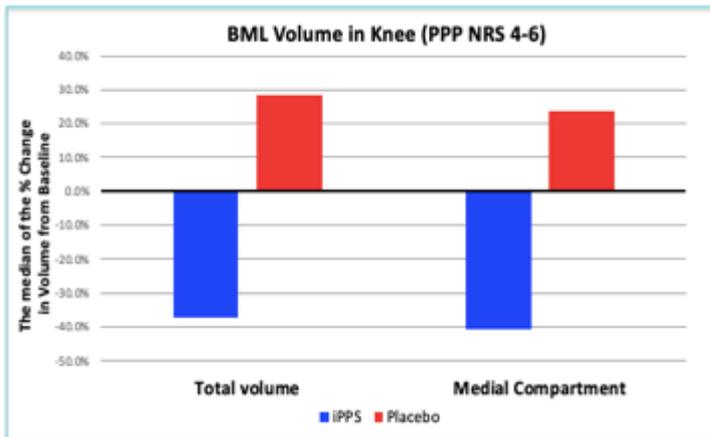
**Objective MRI Data – Total Population (PPP) at Day 53:**

- 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 below.
- iPPS treatment reduced BML Area by (-)15.6% in contrast to an increase of (+)15.2%, in the placebo group. See Chart below.



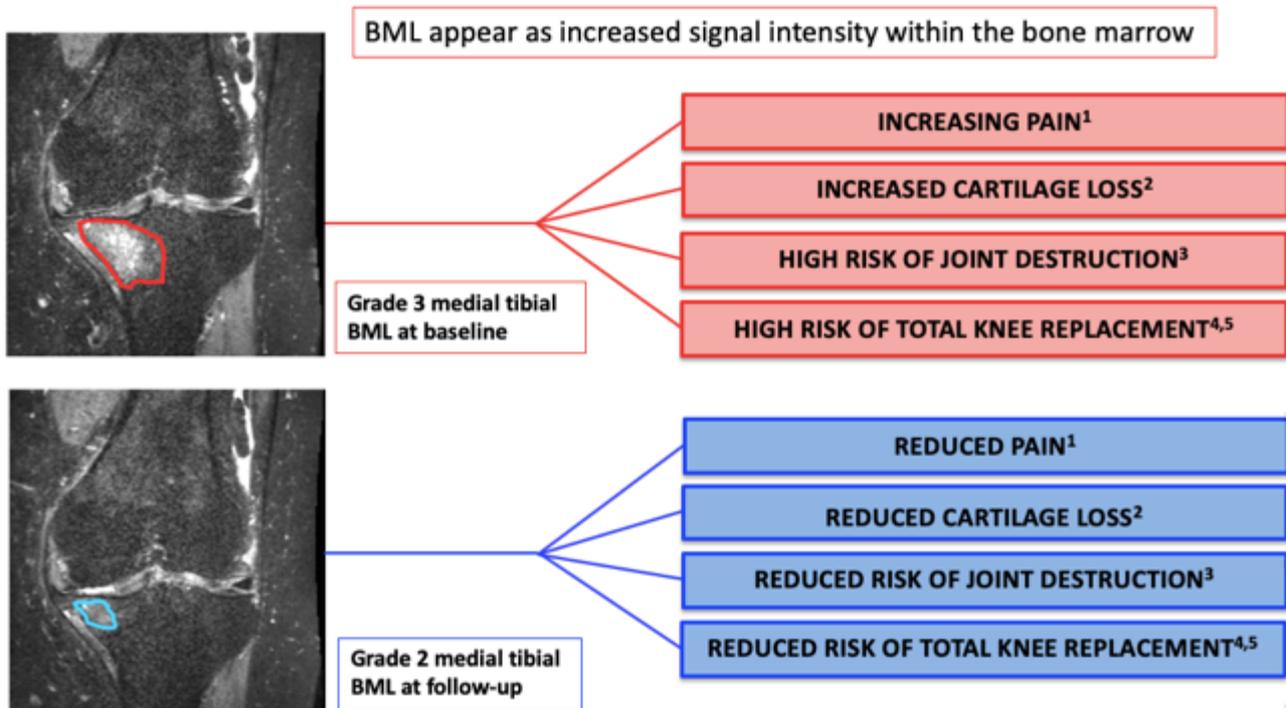
These objective MRI data, of large reductions in BML Grade, Volume and Area, signals potential of disease regression of osteoarthritis in subjects treated with iPPS.

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.

**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 (top image) and regression of the BML to Grade 2 (bottom image) at follow up at Day 53.



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

1. “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.”<sup>9</sup>
2. “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”<sup>10</sup>.
3. 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)<sup>11</sup>.
4. 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<sup>12</sup>.
5. 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”<sup>13</sup>.

**By iPPS achieving a regression in BML, according the scientific literature, there is strong evidence to show iPPS is treating the root causes of the OA pain, cartilage degradation and joint degeneration.**

<sup>9</sup>Tanamas S et al 2010 “Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study” Rheumatology.

<sup>10</sup>J. Hunter et al, Increase in Bone Marrow Lesions Associated with Cartilage Loss Arthritis & Rheumatology, May 2006

<sup>11</sup>Courtney Scher, Nelson et al, Bone marrow edema in the knee in osteoarthritis and association with total knee arthroplasty within a three-year follow-up, Skeletal Radiol (2008)

<sup>12</sup> Sharkey PF et al, Subchondral bone marrow lesions associated with knee osteoarthritis, Department of Orthopaedic Surgery Thomas Jefferson University Hospital, 2012.

<sup>13</sup> 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]

To highlight the strength of the complete Phase 2b results:

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.”

Due to robust nature of the data, we share Paradigm’s view that they are likely to achieve peer reviewed publication and/or presentation at a preeminent global orthopaedic conference.

Lastly, as far as Phase 2b trials go, this trial was designed, recruited, completed and reported on in record time. We put this down to a number of factors, namely a very experienced management and clinical trial team, but secondly the high rate of recruitment – once again a very strong indication of the OA sufferers desire to receive treatment – a clear unmet need.

## Confidence in a Successful Phase 3 OA Trial

Paradigm have been able analyse the phase 2b data to define the ideal patient population (NRS pain 4-6) for their upcoming pivotal Phase 3 clinical trial that will likely return the strong efficacy results that we saw in this strata. This gives Paradigm confidence in a successful pivotal Phase 3 OA/BMEL clinical trial, setting the foundation to register a treatment for osteoarthritis pain.

This confidence is supported by the following factors:

- **The proposed phase 3 clinical trial will have a larger sample size.** *“With a sufficiently large sample, a statistical test will almost always demonstrate a significant difference, unless there is no (clinically meaningful) effect whatsoever.”<sup>14</sup>*
- A commonly cited example of this phenomenon is the Physicians Health Study of aspirin to prevent myocardial infarction (MI). In more than 22,000 subjects over an average of 5 years, aspirin was associated with a reduction in MI (although not in overall cardiovascular mortality) that was highly statistically significant:  $P < .00001$ . The study was terminated early due to the conclusive evidence, and aspirin was recommended for general prevention. However, the effect size was very small: a risk difference of 0.77% with  $r^2 = .001$ —an extremely small effect size. As a result of that study, many people were advised to take aspirin who would not experience benefit yet were also at risk for adverse effects. Further studies found even smaller effects, and the recommendation to use aspirin has since been modified.

Paradigm’s phase 2b clinical trial (n=112) demonstrated a clinically meaningful effect and statistical significance across a number of endpoints and measures. **A moderately larger sample size will only improve the levels of statistical significance.**

- **The proposed phase 3 clinical trial design will expand upon what has been learned from the successful phase 2b trial and this will also likely enhance trial outcomes.** The phase 2b clinical trial provided

<sup>14</sup> 1. Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *J Grad Med Educ.* 2012;4(3):279–282. doi:10.4300/JGME-D-12-00156.1

Paradigm invaluable information that will guide the design of the phase 3 clinical trial. Paradigm will use this information to enhance the: target population (NRS 4-6, by far the most responsive patient strata), inclusion/exclusion criteria (knowing specific patients/disease states that have the greatest response) and the trial day at which primary and secondary endpoint data is collected.

Additionally, Paradigm may utilize a 'placebo run-in' to normalize the placebo effect associated with pain trials. A 'Placebo Run-in' at the start of their Phase 3 OA trial will serve a valuable role in screening out ineligible or non-compliant participants (i.e. participants who may be likely to return high placebo responses), in ensuring that participants are in a stable condition and providing stronger baseline observations. This will likely further enhance the prospects of Phase 3 trial success.

## Comparing the results of similar OA pain trials

### Nerve Growth Factor (NGF) Inhibitors

Nerve growth factor (NGF), a member of the neurotrophin family, is known to regulate the development and survival of a select population of neurons through the binding and activation of the TrkA receptor. Elevated levels of NGF have been associated with painful pathologies. These NGF drugs block the NGF from binding to the pain receptors.

Clinically, NGF concentration is increased in chronic pain conditions such as interstitial cystitis, prostatitis, arthritis, pancreatitis, chronic headaches, cancer pain, diabetic neuropathy and noncancer pain, suggesting that NGF-mediated signalling is an ongoing and active process in chronic pain.

In 2012, the FDA commissioned an independent arthritis advisory committee to further investigate NGF treatment related adverse events and concluded that joint failures were probably related to anti-NGF treatment and represented a unique clinical form of rapidly progressive OA, citing rapid and considerable joint destruction, typically within 6–12 months of exposure.

**Concern about the NGF treatment related adverse event of rapidly progressive osteoarthritis remains the single biggest concern for this class of drug.**

Teva (TEVA) and Regeneron's (REGN) collaboration on the anti-NGF drug (Fasinumab) has previously been put on clinical hold by the FDA after safety concerns of the drug persisted. This deal was valued up to US\$1.3b.

Tanezumab, another anti-NGF drug being developed by Pfizer (PFE) and Eli Lilly (LLY), recently released Phase 3 clinical trial that was very concerning on the safety front, in particular it points to rapid joint destruction in patients treated with the drug vs placebo or standard of care.

### iPPS versus Anti-nerve growth factor antibodies (Anti-NGF's)

#### **What are Anti-NGF's**

Years ago, the promise of anti-nerve growth factor antibodies inspired analysts to project multibillion-dollar markets for the class of drugs. But a slew of safety issues forced the FDA to impose clinical holds on keenly watched drugs after reports of patients blowing their joints out.

Nonetheless, such safety setbacks forced Pfizer to cut back on Tanezumab doses, although it did not deter Lilly from setting aside as much as US\$1.8 billion to buy into the drug. Teva and Regeneron too were compelled to trim down their dose of anti-NGF drug Fasinumab after similar concerns, while drug makers such as Johnson & Johnson (JNJ), AstraZeneca (AZN) and AbbVie (ABBV) washed their hands of their anti-NGF offerings.<sup>15</sup>

<sup>15</sup> <https://endpts.com/pfizer-and-lillys-tanezumab-largely-makes-the-efficacy-cut-in-second-phiii-study-but-safety-issues-continue-to-blight-anti-ngf-drug/>

### What is Tanezumab (Pfizer & Lilly)?

Tanezumab, an investigational humanized monoclonal antibody, is a potential first-in-class, non-opioid treatment being evaluated for OA pain, CLBP and cancer pain (due to bone metastases). Tanezumab works by selectively targeting, binding to and inhibiting NGF.

### Tanezumab Phase 3 OA Trial Results (Study A4091058) – released 18<sup>th</sup> April 2019

Pfizer and Eli Lilly on Thursday 18<sup>th</sup> April 2019 announced top-line results from their Phase 3 (A4091058) study evaluating their anti-NGF compound ‘Tanezumab’ at the 2.5 mg and 5 mg sub-cutaneous dose.

The objective of the study was to compare the long-term joint safety and 16-week efficacy of Tanezumab relative to nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with moderate-to-severe osteoarthritis (OA) of the hip or knee.

The release of these results were highly anticipated as it has been a long held view that the anti-NGF’s may offer a non-opioid treatment for joint pain.

The Tanezumab 5 mg (higher dose) treatment arm met two of the three co-primary efficacy endpoints (pain and physical function) compared to NSAIDs at the 16-week analysis, while patients’ overall assessment of their OA was not statistically different than that of NSAIDs.

Patients who received Tanezumab 2.5 mg (lower dose) did not experience a statistically significant improvement in pain, physical function or patients’ overall assessment of their OA at 16 weeks compared to NSAIDs.

**In the safety analysis, there was a higher rate of joint safety events in the Tanezumab arms compared to NSAIDs at 80 weeks; the difference was statistically significant.**

The full announcement can be read: here: <https://www.businesswire.com/news/home/20190418005771/en/Pfizer-Lilly-Announce-Top-Line-Results-Long-Term-Phase>

### Implications for Paradigm Biopharmaceuticals

We have previously considered Pfizer’s anti-NGF agent (Tanezumab) as Paradigm’s #1 competitor treatment for OA pain. This is despite the serious ongoing safety concerns with this class of drug and the US FDA putting the anti-NGFs on clinical hold at various stages in their development.

***These latest phase 3 trial results highlight Tanezumab’s problem i.e. the higher doses have efficacious pain reduction, but alarming safety issues and the lower doses still have safety issues but muted efficacy.***

Analysts and journalists extensively covered the story (see below links):

“There was a dose dependent increase for the primary composite joint safety endpoint: 7.1% in the 5 mg arm, 3.8% in the 2.5 mg group and 1.8% for NSAIDs. Rapidly progressive osteoarthritis was the main concern, while “total joint replacement was 8% percent in the Tanezumab 5 mg arm, 5.3% in the Tanezumab 2.5 mg arm and 2.6% in the NSAIDs arm.”

**"To us, the product is likely dead, if not from a regulatory standpoint (i.e., is it even approvable?) then from a commercial one (i.e., will it ever sell?)," Anderson wrote in a note to investors.**

<https://endpts.com/rip-tanezumab-eli-lilly-pfizer-spotlight-alarming-safety-data-for-ngf-pain-drug-in-phiii/>

<https://www.fiercebitech.com/biotech/lilly-pfizer-s-phase-3-pain-data-shows-mixed-efficacy-clear-safety-issues>

There were strong trends pointing to safety issues in Pfizer/Lilly’s Phase 2 OA clinical trials and this has been shown again in this most recent Phase 3 clinical trial.

We note, Eli Lilly paid Pfizer US\$200m upfront and promised US\$1.6bn in milestones prompting SVB Leerink’s analyst note to suggest that Eli Lilly should have kept their money.

“The significant safety imbalances in the study, and the marginal efficacy of the drug, effectively signalled the end of this program, in our view, and probably puts the outlook for the entire class in (more) jeopardy. It is hard for us to imagine how these results could have been much worse.”

They also highlighted the big problem for the class, which may well doom another drug in late-stage testing.

“Regeneron (REGN) and Teva (TEVA) are jointly collaborating on a different NGF antibody called Fasinumab, and we believe the Tanezumab results are likely to have a negative impact on the outlook for that program.”

Interestingly, Amgen/Janssen dropped their anti-NGF compound, Fulranumab, in 2016 after inking a US\$435m deal in 2008.

All of this should not come as a surprise given the FDA’s view towards this class of drugs and multiple occasions where anti-NGF clinical trials have reported AEs. **Despite this the FDA granted Tanezumab Fast-Track status in 2017**, most likely due to the Opioid Epidemic prompting the regulator to consider other non-addictive pain treatments.

### Current status of anti-NGFs in development

The sheer size of these transactions highlights Big Pharma’s desire to find a non-opioid based OA pain treatment.

Compound Name	Partner Companies	Deal Size	Status
Tanezumab	Pfizer and Eli Lilly	US\$1.8bn	Recent Phase 3 results demonstrated efficacy for 2 of 3 endpoints at high dose, but also confirmed serious safety concerns.
Fasinumab	Regeneron and Teva	US\$1.25bn	Currently being assessed in three Phase 3 trials, long-term safety (1), comparison to standard pain treatments (2). Fasinumab likely presents the same safety concerns as Tanezumab.
Fulranumab	Janssen and Amgen	US\$435m	In 2016, Janssen terminated the license with Amgen, discontinuing the Fulranumab clinical program at Phase 3

There is an old saying in drug development of “Safety First” and this appears to be ringing true for the anti-NGF class from what we are reading from the analysts and journalists in pharma world.

If Tanezumab ever gets approved for joint pain (unlikely on these data and according to various analysts) it would be hard to see how a doctor could prescribe it in a joint pain scenario. It is unlikely to be a first line therapy for OA.

### Tanezumab Phase 2 Study 1027 vs iPPS Phase 2b Clinical Trial

Tanezumab Study 1027 (NCT01089725), a placebo-controlled trial, evaluated the efficacy of sub-cutaneous Tanezumab (i.e., 2.5, 5, and 10 mg) and the therapeutic equivalence of 10 mg Tanezumab given subcutaneously versus intravenously every 8 weeks in the symptomatic treatment of OA.

Co-primary endpoints were:

- Change from baseline in Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) Pain and Physical Function indices; and
- Patient’s Global Assessment (PGA) of OA.

These endpoints were very similar Paradigm’s Phase 2b OA/BMEL Clinical Trial.

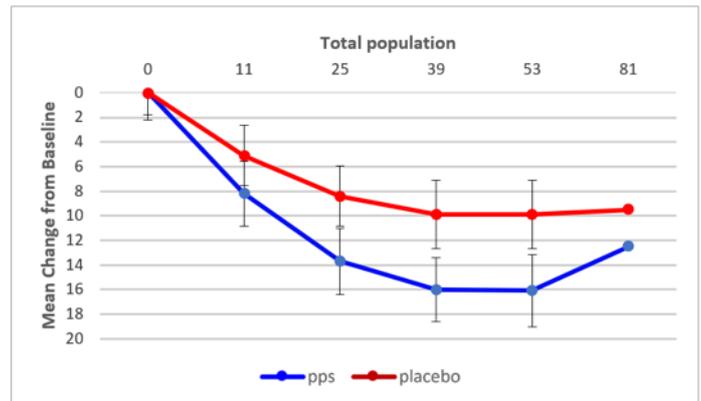
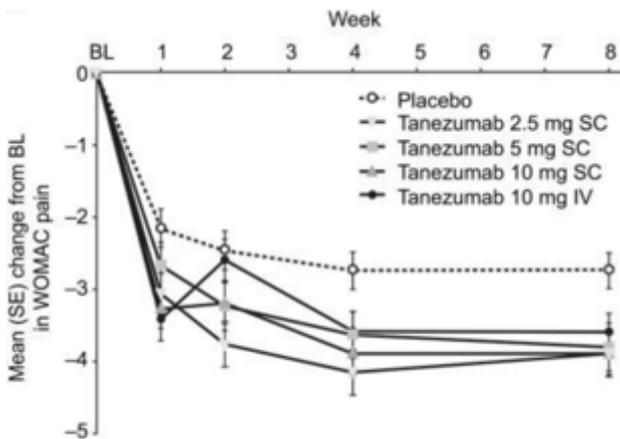
**Results**

Due to the clinical hold, Study 1027 was underpowered, and no statistical analyses were performed.

- Mean change from baseline to week 8 in WOMAC Pain in Tanezumab groups ranged from -3.59 (0.26) to -3.89 (0.32), versus -2.74 (0.25) with placebo.
- Mean (SE) change from baseline to week 8 in WOMAC Physical Function ranged from -3.13 (0.25) to -3.51 (0.28) with Tanezumab and was -2.26 (0.24) with placebo.
- PGA mean (SE) change from baseline to week 8 ranged from -0.90 (0.11) to -1.08 (0.12) with Tanezumab and was -0.78 (0.10) with placebo.
- Five patients required total joint replacements in Study 1027 (placebo, n=2 [2.8%]; Tanezumab 2.5 mg, n=3 [4.1%])

**Mean Pain Reduction from Baseline**

In the same fashion as Paradigm’s Phase 2b OA trial, the Tanezumab Study 1027 reported a mean change from Baseline. It is difficult to provide a clear comparison between the two results due to the differing pain scales WOMAC and KOOS. Additionally, the baseline figures have not been released by either company further complicating the ability to directly compare the results. Our analysis suggests that Study 1027 recruited patients with a higher (more severe) baseline pain score than Paradigm’s Phase 2b OA trial.



**Key observations:**

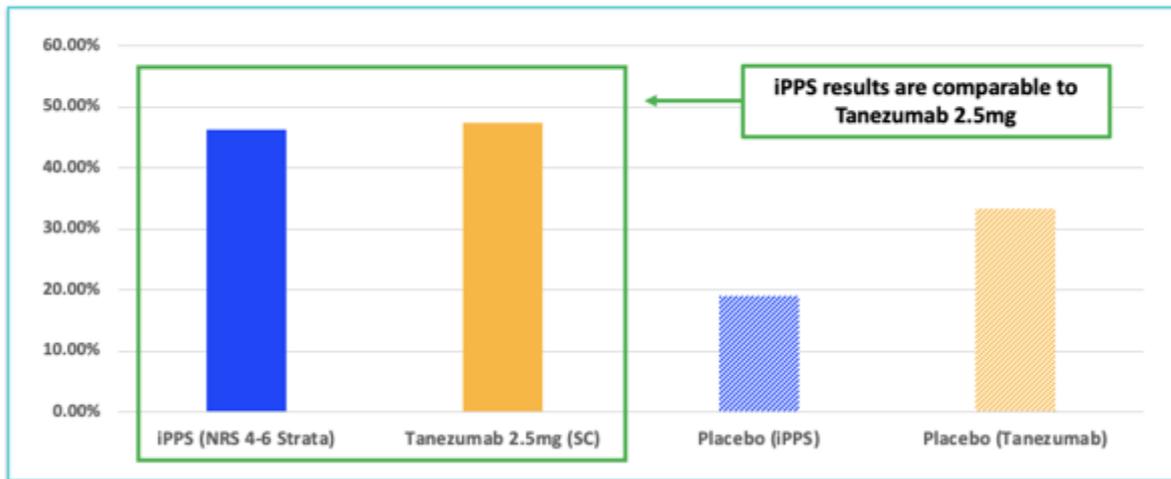
- **Clinical Efficacy** – Considering that it is difficult to compare efficacies, it appears that Tanezumab, at the higher doses, has a higher clinical effect compared to iPPS. We are not overly concerned by this, as iPPS’ results are very much considered clinically meaningful, resulting in a notable patient benefit. **We note, that the higher Tanezumab doses have all been discontinued due severe AEs and we have reservations that even the low doses will ever make it to market for OA pain.**

**Percentage of patients that achieved a greater than 50% improvement in pain**

The graph below compares the percentage of iPPS, Tanezumab and placebo control patients that achieved a greater than 50% improvement in pain. iPPS achieved a similar result to Tanezumab at a 2.5mg dose, 46.2% versus 47.3% respectively.

This comparison is very powerful as it highlights that iPPS has achieved similar results to Tanezumab, demonstrating its viability as a commercial product. To once again reiterate the point, any outperformance of Tanezumab over iPPS is counter balanced back into iPPS’ favour due it the starkly contrasted safety profiles.

**Percentage of subjects with >50% improvement in KOOS/WOMAC pain score at day 53**



- iPPS results are comparable to Tanezumab 2.5mg (46.20% vs. 47.30%)
- Tanezumab clinical trials have been plagued by significant Adverse Events (rapidly progressive osteoarthritis and osteonecrosis (a loss of blood to the bone that causes the bone to die))
- iPPS has an excellent safety profile, established over the past 70 years

**The significance of a >50% reduction in pain**

It is generally considered that a 30% reduction in pain corresponds with a “much improved” or “very much improved” response from patients on a global impression of change, or 2 points on a 0 to 11 pain intensity numerical rating scale for example from 6/10 down to 4/10”<sup>16</sup>.

While a 30% reduction in pain is significant and is described by participants reporting a much improved or very much improved reduction in pain, **Paradigm used the more stringent measure of a 50% reduction in pain.**

**A 50% reduction in pain represents a highly clinically meaningful effect, resulting in a significant shift in ‘intensity of pain’ i.e. from persistent moderate pain to mild/minor pain.**

We spoke to several clinicians who are experienced with iPPS as to why there was an uptrend in the trial data from Day 53 to Day 81 i.e. pain relief reducing. These clinicians said it was likely due to the fact that trial participants felt less pain and therefore commenced more rigorous physical activity than they normally would have done. It was reported that some trial participants had started hiking and playing sports they hadn’t played in a years again. This would naturally put more stress on the knee joint and therefore reduce the improvement in pain.

<sup>16</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891384/>

# Existing OA Treatments & OA Treatments in development

## Paradigm’s iPPS (ZILOSUL®) treatment vs current OA treatments

Current therapies treat the symptoms of osteoarthritis and bone marrow edema lesions but prolonged use results in undesirable side-effects. It is widely accepted that NSAIDs and corticosteroids are contraindicated having a detrimental effect on the metabolism of bone and cartilage. Opioid’s are widely misused globally as patients form serious addictions whilst mitigating pain.

There is currently no effective treatment for osteoarthritis and BMELs that treats the underlying pathology of the disease.

ZILOSUL® treats the underlying pathology of osteoarthritis by reducing inflammation, resolving the bone marrow edema lesions and down regulating cartilage degrading enzymes (MMP’s and ADAMTS-5). We believe that because of this ZILOSUL® has the potential to be a Disease Modifying OA Drug (DMOAD) and that the release of MRIs from the Phase 2b trial show iPPS (ZILOSUL®) having a positive effect on the disease state of the BMEL, like it did in the majority of cases is the Phase 2a trial.

	paradigm (ZILOSUL®)	NSAID (ibuprofen etc)	Opioid (oxycodone etc)	Corticosteroid / Cortisone	Joint Replacement
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology	✓				✓
No undesirable side-effects	✓				
Non-addictive	✓	✓		✓	✓
Anti-inflammatory	✓	✓		✓	
Non-Surgical	✓	✓	✓	✓	

## Paradigm’s iPPS (ZILOSUL®) treatment vs OA drug candidates currently in development

To fully appreciate just where iPPS sits vs its competition in development we have prepared the below table which shows iPPS is the only OA drug/treatment in its class that treats pain and has undisputed safety profile.

	paradigm (ZILOSUL®)	Anti-NGFs (Tanezumab®)	Stem Cell & PRP treatments	Invossa® TissueGene’s Cell/Gene Therapy	CNTX-4975 Centrexion’s trans-capsaicin
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology (potentially Disease Modifying)	✓	✗	✓	✓	✗
No undesirable side-effects (safe for repeat use)	✓	✗	?	?	?
Non-addictive	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✗	?	✓	✗
Non-Surgical	✓	✓	✗	✓	✓
Affordable	✓	✗	✗	✗	?

# Rare Joint Diseases – MPS

## What is MPS?

Mucopolysaccharide (MPS) are Lysosomal Storage Diseases. These are rare, life-limiting, progressive, genetic conditions.

MPS diseases are caused by a missing enzyme ( $\alpha$ -L-iduronidase), which inhibits the body's ability to metabolise certain molecules called GAGs (Glycosaminoglycans). GAGs are structural molecules that are integral to connective tissues such as cartilage, tendons and other tissues in the body. They accumulate in cell structures called lysosomes. Without essential enzymes to break down, recycle and build new mucopolysaccharides they continue to be stored inside the lysosome. This causes the lysosome to swell and disrupts cell functioning.

These are multi-organ storage diseases which cause progressive physical disability and, in many cases, severe neurological deterioration and can result in death in childhood.

Paradigm announced on 14<sup>th</sup> February 2019 that it had conducted a satellite meeting on 3-4<sup>th</sup> February at the "World Symposium 2019, 15<sup>th</sup> Annual Research Meeting on Lysosomal Disease Research" in Orlando, USA to discuss plans for its upcoming randomised double-blind placebo-controlled multicentred multinational Phase 2/3 Mucopolysaccharidosis (MPS) clinical trial.

The current standards of care are not adequate in treating pain associated with joint inflammation and musculoskeletal issues and **these drugs currently equate to a market size of around US\$1.4b per annum.**

**There is a growing collection of data which support iPPS as a potential treatment for MPS.**

1. **Professors Schuchman and Calogera (Mt Sinai) defined the rationale for iPPS in human clinical trials.** Their pioneering pre-clinical work on the effects of iPPS in animal models of MPS demonstrated that iPPS was able to:
  - reduce the levels of Glycosaminoglycans (GAGs), which accumulate as a result of enzyme deficiency in cells and tissues leading to joint pain and dysfunction; and
  - inhibit the inflammatory responses due to TLR-4 signalling by the accumulated GAGs.
2. **Paradigm/Hennermann et al. Phase 2a open label study (n=4) had promising results which warrant further studies.** The conclusions of this trial were:
  - iPPS treatment was well tolerated (safe), resulting in a significant reduction of urinary GAG excretion (Chart 6) and in an improvement of joint/mobility and pain (Chart 7) above any beyond ongoing/existing ERT treatment.

Chart 6 – Urinary GAG excretion

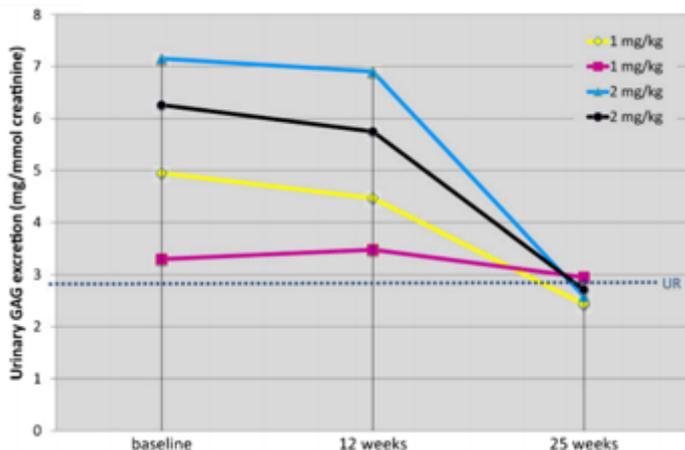
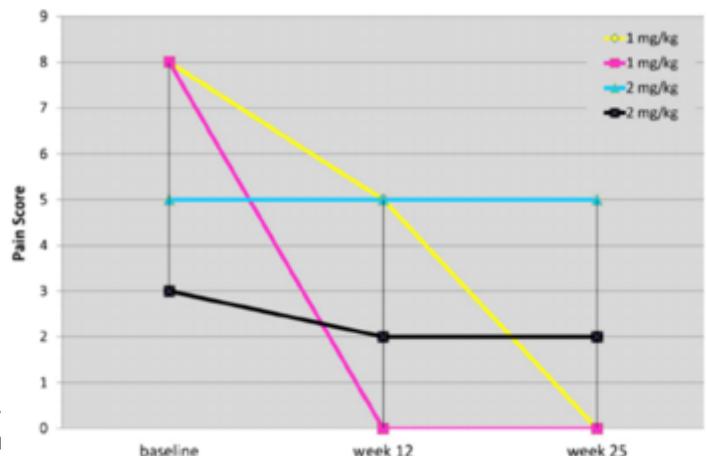
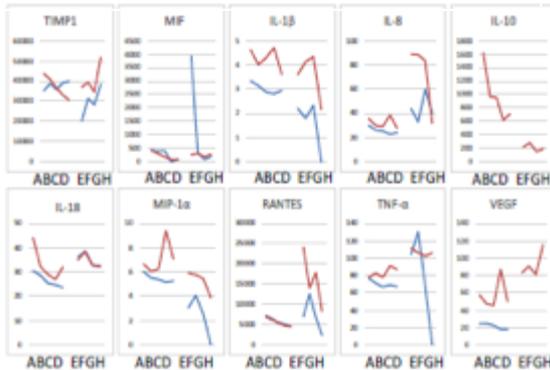


Chart 7 – Pain Score

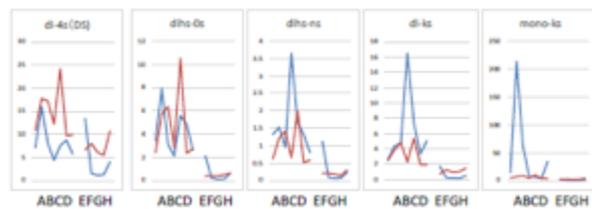


- The results below show that there was a reduction in the inflammatory markers (Graph 8) and urinary GAG levels (Graph 9) with no serious adverse events.
- The preliminary findings of this open label study were encouraging, demonstrating a reduction in the inflammatory markers and urinary GAG levels with visible signs of improved joint function and pain reduction.

Graph 8 Inflammatory Markers



Graph 9 Urinary GAG Levels



## Orphan Drug Status

Due to MPS' rarity and seriousness, it has received Orphan Designation across its various types. Utilising the above cumulative occurrence of 3.5/100,000 live births, there are approximately 140<sup>17</sup> cases per year, easily satisfying the FDA ceiling of 200,000 total cases in the US.

### Faster Approval – May only need one Phase 2/3 Clinical Trial

The FDA typically requires one or two phase 3 clinical trials for approval of a drug, but the legislation authorises the FDA to approve a drug based on one multi-centre study in appropriate circumstances. Because the number of patients available to participate in a clinical trial involving a rare disease is often very small, FDA frequently approves orphan drugs with less extensive requirements for clinical studies

#### An example of this is:

**Alglucosidase alfa (Myozyme)**, which was approved in April 2006 as enzyme replacement therapy for Pompe disease. **Pompe disease is also a rare autosomal recessive lysosomal storage disease.** Without treatment, infants with the disease usually die by 18 months of age from respiratory and heart failure. Myozyme was approved based primarily on the results of a randomized, open-label, historically controlled study in 18 infantile-onset patients. ([Beitz, 2006](#)).

### Leading MPS Treatments in market

	YEAR APPROVED	COMPANY AT APPROVAL	CONDITION	2017 REVENUES (USD MILLION)
<b>Aldurazyme™</b>	2003	BioMarin Pharmaceuticals	MPS I	\$90.02 <sup>1</sup>
<b>Elaprase®</b>	2006	Shire Pharmaceuticals	MPS II	\$615.7
<b>Naglazyme®</b>	2005	BioMarin Pharmaceuticals	MPS VI	\$332.2
<b>VIMIZIM®</b>	2014	BioMarin Pharmaceuticals	MS IVA	\$413.3
<b>Mepsevii™</b>	2017	Ultragenyx Pharmaceuticals	MPS VII	\$5.43 <sup>2</sup>

The FDA attached further post-marketing requirements

1. The bulk of Aldurazyme® revenues are reported by its co-developer Sanofi-Genzyme, which were €207m (USD235.4m) in 2017

2. Q1 to Q3 FY18. Product only approved in November 2017

Source: Company SEC Filings

<sup>17</sup> Based on 4m new births per annum in the USA - <https://www.cdc.gov/nchs/fastats/births.htm>

### Potential for this Orphan Indication

It is difficult to estimate the number of people living with the various types of MPS across Paradigm's patented regions. Due to the limited life expectancy of MPS sufferers (ranging from 10-30 years), we have discounted the 1:26,000 birth rate, formulating a conservative figure of 10,000 patients.

We anticipate that MPS sufferers will require weekly injections of iPPS.

We do not anticipate that Paradigm will be able to charge the same extremely high yearly treatment cost of other Orphan Drugs (\$500,000 - \$1,000,000), although, even a more modest price results in blockbuster market potential.

Therefore, we assume a potential yearly price of iPPS: US\$50,000 – US\$100,000 is possible, especially in light of the more constant dosing regimen.

Based on these assumptions, the market potential for iPPS across the patented regions may be US\$500m – US\$1bn p.a.

We understand that due to the severity of the condition, MPS sufferers generally live in close proximity to hospitals and health centres that can specifically cater for their treatment. This means that treating physicians/specialists and the various MPS communities would be more aware of iPPS being a new MPS treatment. Therefore, we anticipate that iPPS treatment would not only be much more accessible for these patients but that take-up (market penetration) would occur much quicker than for other more mainstream pharmaceutical products. All of this enhances the commercial aspects of the iPPS MPS treatment for either Paradigm or an interested pharma partner.

### Straight to a pivotal phase 2/3 clinical trial

Paradigm has positive phase 2a data (Hennermann et al.), which is supported by the preliminary work Mt Sinai Icahn School of Medicine and other scientists that have worked with PPS and MPS. As a result of this compelling data and the orphan status of MPS we believe that a pivotal FDA compliant phase 2/3 placebo (standard of care) controlled trial could be initiated by Q3 CY2019. The trial would likely run for 12-18 months including recruitment (treatment with drug would likely be 12 months) and consist of 30-50 patients (in line with other orphan indications). Assuming positive results and due to its Orphan Designation and accelerated regulatory dialogue with the FDA, it is possible to achieve drug registration and first sales by Q3 CY2021, i.e. 24 months after initiating the Phase 2/3 clinical trial.

### Big Pharma interest in rare diseases

On 8<sup>th</sup> May, Pfizer announced it intended to buy rare disease biotech Therachon a private Swiss biotech, for its experimental therapy to treat dwarfism for US\$810 million (US\$340m upfront), putting them on a path to compete with BioMarin

Full story: <https://endpts.com/pfizer-bags-a-rare-disease-drug-for-340m-plus-putting-them-on-a-path-to-compete-with-biomarin/>

The pharma giant is paid this large sum to acquire TA-46 for the treatment of achondroplasia. **Interestingly, the drug only has Phase 1 proof-of-concept data.** Pfizer Ventures had invested previously in Therachon.

“The acquisition makes them a rival to BioMarin, which has been attracting considerable attention for its own drug in the field.”

Achondroplasia is the most common type of short-limbed dwarfism. The condition occurs in 1 in 15,000 to 40,000 newborns.

BioMarin (BMRN, mkt cap US\$14.8Bn) is a leader in the field of enzyme replacement with several drugs in market to treat various MPS disorders.

**This has a number of positive implications for Paradigm?**

1. This shows the growing big pharma interest in orphan indications;
2. Pfizer, like many other big pharma, previously did not focus on orphan indications and so are finding that they have to acquire companies or in-licence these assets to get exposure to the niche, but high value, markets;
3. US\$810m (A\$482 upfront with total deal value A\$1.15Bn) is a large amount of money to pay for a drug asset that only has Phase 1 proof-of-concept data. Admittedly, Pfizer has been close to the drug, but it is very early in the stages of development for the drug.

This bodes well for Paradigm from a commercial point of view because:

- it once again shows pharma interest in orphan indications;
- the large amount of value being ascribed to early stage orphan indication data,
- Paradigm has impressive Phase 2a data showing iPPS as a potential treatment for several MPS indications, i.e. more advanced data than Therachon;
- iPPS has the potential to be an adjunct treatment for BioMarin's enzyme treatments; and
- Paradigm will be entering Phase 2/3 clinical trials in the coming months and this will no doubt be of great interest to both BioMarin and Pfizer.

Ultimately, we would not be surprised to see pharma interest in Paradigm's MPS program's and this interest could likely come from BioMarin looking to protect its markets or from Pfizer looking to enter new markets, as it did with Therachon.

## Upcoming Newsflow & TGA Provisional Approval

From an investor viewpoint, CY2019 will be a busy year for Paradigm as it achieves milestones that relate to its key objectives for OA & MPS:

1. Enter Phase 3 trials for OA – this will involve:
  - a. Pre-IND meeting with the US FDA to discuss Phase 3 trial
  - b. Amending trial design if/as necessary
  - c. IND meeting with the FDA
  - d. Potential for Fast-Track designation for the treatment of KOA pain
  - e. Commence recruitment of Phase 3 trial
  - f. Dose first patients
2. Treating ex-NFL players via US Expanded Access Program (EAP)
  - a. Commencement of US Intermediate Sized EAP
  - b. Associated media surrounding the successful treatment of high profile athletes/ex-NFL players
3. Further release of OA pain results (including joints other than the knee) under the TGA Special Access Scheme throughout remainder of CY2019.
4. Potential for Peer Review Publications re the OA program:
  - a. Potential for Peer Review Publication of MoA of iPPS in addressing KOA pain via moderation of NGF – “Human osteocyte expression of Nerve Growth Factor (NGF): the effect of Pentosan Polysulphate Sodium (PPS) and implications for pain associated with knee osteoarthritis”
  - b. Potential for Peer Review Journal publication of the Phase 2b results
5. TGA Provisional Approval for iPPS, a process that could ~12 months from submission and involves the following primary activities:
  - a. Pre-submission meetings
  - b. Submission of PFF

- c. First round of assessment
  - d. Company response
  - e. Second round of assessment
  - f. Expert advisory review
  - g. Decision (approve or not)
  - h. Post decision and Provisional Approval
6. In regard to, MPS we see the key objectives and newsflow as being:
- a. Design of pivotal Phase 2/3 trial (n=30-50 with centres in US, EU & Australia)
  - b. Pre-IND meeting with the US FDA to discuss Phase 2/3 trial
  - c. Initiation of treatment of MPS patients in Australia via the TGA SAS program & associated newsflow
  - d. IND Meeting with FDA
  - e. Commence recruitment of Phase 3 trial
  - f. Dose first patients
7. Ross River Phase 2a (safety study) trial results release – Q2/Q3 CY2019

## Provisional Approval – Potential Early Revenues

If Provisional Approval is received, Paradigm will be able to price and sell iPPS in Australia for a two-year period whilst it conducts further trials and collects additional data to support a full registration. Paradigm would be able to extend on a rolling two-year basis for a maximum of 6 years before a full application (with accompanying Phase 3 data) is received by the TGA.

Selling iPPS (ZILUSOL®) in Australia would result in Paradigm's first revenues, which given demand for the drug via the TGA SAS, we estimate that the company would generate revenue in the millions. There are approximately 2.1 million OA sufferers in Australia, which represents a respectable initial target market.

Let's assume 10,000 of these Australian OA sufferers were treated in the first 12 months post receiving TGA Provisional Approval, which is not unreasonable given over 500 patients were treated in under 12 months via the SAS program. The cost of a course of treatment (12 injections) could be A\$2,500, as per company announcements, then the total potential revenues would be A\$25m – for the first year. We believe OA sufferers will have a re-run or booster every 12 months on average, therefore we would expect the A\$25m to grow exponentially year on year.

**We note that other ASX listed healthcare companies such as Polynovo Ltd (ASX:PNV) had revenues of A\$1.7m last FY, which grew to a recently reported H1 FY19 of A\$3.75m. PNV now commands a market capitalisation of ~A\$700m and Clinuvel Ltd (ASX:CUV), which recently saw revenue grow to around A\$25m and expects to double this with upcoming potential FDA approvals has seen their market cap grow to A\$1.3bn.**

## Investment View

Rightly or wrongly we previously considered Pfizer/Eli Lilly's lead compound, Tanezumab, as the most advanced drug in development for the treatment of OA pain and therefore Paradigm's/iPPS's main competitor. However, post their most recent Phase 3 trial results, which detail Tanezumab's serious adverse events, we believe iPPS is now the front-runner in regard to being the next OA pain treatment.

Furthermore, with the successful completion of the Phase 2b OA clinical trial, Paradigm has now completed all the necessary stages that a Pharma company would require to enter into a partnership/licensing transaction, **the Foundations to a Pharma transaction are:**

1. **Strong Patent and IP Position,**

2. **Exclusive Supply and Manufacturing Confirmed,**
3. **Confirmed Market Demand,**
4. **Efficacy and Safety of PPS has been proven in Humans,**
5. **Mechanism of Action (MOA),**
6. **Positive Phase 2b Placebo controlled data, and**
7. **File Investigative New Drug Application Agency (only essential for US pharma deal)**

There have been a number of other drug candidates that have already been transacted on in OA space, for significant sums, that we consider inferior based on a number of factors and most importantly safety. Therefore, we are of the opinion that Paradigm's OA program will be of significant commercial interest to a pharma company.

When we compare Paradigm's results to the other companies developing treatments for OA, in particular Tanezumab, which we have grave reservations as to ever making it to market, we find that iPPS:

- has a very similar reduction in pain, circa 45-50% from baseline (even the low dose anti-NGFs have high AEs i.e. 2-3 x the chance of joint replacement over 1 year);
- excellent safety profile, very well-known drug tolerability and therefore will lend itself to repeat treatments, we expect for years;
- easy to store and has a strong shelf life;
- is not overly expensive and is much cheaper than the cell treatments and will be cheaper than the anti-NGF molecules; and
- has demonstrated strong pain reduction results across the >500 SAS treated patients and the Phase 2b clinical trial.

This combined with the exclusive supply agreement with bene pharmaChem (the only maker of PPS with a biologics master file (BMF) registered with the FDA), and Paradigm's family of specific use patents, all make for a compelling proposition for partnering from a large or regional pharmaceutical companies' point of view.

It would not be unreasonable for Paradigm to partner with a regional pharma company based in Asia or the EU as the first step in commercialising iPPS before partnering with a large western pharma company down the track for the US market. There is strong desire from Asian pharma companies to partner on OA treatments as evidenced by the deals done on Fasinumab and Invossa, US\$425 and US\$600m total deal size (upfront and milestones) respectively.

However, we would view even a small regional deal with a pharma company from one of the developed Asian countries being irrefutable proof of validation.

This would provide definitive validation for iPPS as an OA treatment, without impacting the scope of a partnering transaction with a western pharma, as long as US rights were not compromised.

One of the largest physical health issues that governments are facing is the treatment of osteoarthritis within the aging population. 31+ million people in the US and 2.1 million people in Australia are large markets that are currently very poorly served in the area of joint pain treatment. There is literally nothing currently in the market to treat the underlying cause of chronic knee OA pain. Current treatments, NSAIDS, opioids, corticosteroids or an eventual knee replacement treat the symptoms of OA and all have serious negatives and drawbacks. Other non-opioid drugs in development for pain, such as NGF inhibitors, have unknown long-term safety or 'serious adverse event' issues and have been put on clinical hold by the FDA at various points along their development.

One of the key factors in making Paradigm a desirable biotech investment revolves around the repurposing of an existing, safe drug that is known to work on various inflammatory pathways. The established medical evidence and extensive publications confirm PPS's use in other areas of inflammation and importantly confirm and reconfirm its safety profile. Thus, we feel there is good potential down the track for Paradigm to seek the label of Disease Modifying OA Drug (DMOAD). Should Paradigm be successful in achieving this label from the FDA it would be very significant as there are no other OA drugs in the market that have that label.

In addition, we see the recent in-licensing of the Rare Joint Disease indication of MPS as not only being a company maker in its own right but potentially being the first product to market for iPPS.

We have previously modelled the potential value of the MPS indication for Paradigm and estimate it to be worth A\$119m (via risked NPV) conservatively. MPS in its own right could attract a licence agreement with an established speciality pharma company that focuses on orphan indications. In this circumstance, it could attract a US\$250m+ licensing transaction (subject to standard milestones) with net royalties being 10-20%. However, for the purposes of this report and in light of the recent \$78m capital raising we feel Paradigm now has the resources to take the MPS program through to registration and sales. We have therefore modelled and incorporated this pathway in our valuation.

**Our risked DCF valuation on PAR, which is derived from using a probability weighted DCF analysis of future US only iPPS sales, ranges from A\$1.006 Bn on a fully diluted basis, down to A\$680m depending on the size of partnership agreement and expected treatment cost. We have selected the mid-point of these valuations to arrive at a \$843m valuation which equates to \$4.29 per share on a fully diluted basis.** We have detailed the sensitivity analysis below in the Valuation and Assumptions section.

**Additionally, to provide a different measure as this report also focuses on what pharma transactions have been completed in the OA space, we look at what iPPS would potentially be worth under licensing/partnership transaction.**

Therefore, we look at the corporate transactions in this space that demonstrate the interest by big pharma and the large sums they are willing to put up in partnerships. **We believe a regional pharma partnership could vary in total deal size from US\$150-600m (+ royalties of 10-20%), depending on the size, geographic area and reputation of the partnering company.** The average for recent regional pharma deals in the OA space is US\$424m (upfront of 5-10% equates to US\$21-42m) plus royalties.

**On the other hand, a licensing agreement with a global pharma company encompassing rights for the US and EU as a minimum could range from ~US\$700m to well over a US\$1bn but we believe will require further positive indications from the US FDA before eventuating (i.e. Fast Track designation or Phase 3 clinical trial commencement post IND approval). Thus, a circa US\$700m-\$1Bn licensing transaction (+ 10-20% royalties) with potential \$70-100m upfront payment is not out of the realm of possibility.**

Our Probability of Success (POS) of iPPS being approved and entering the US market has increased to 49% due to Phase 2b trial meeting its primary endpoint and on the assumption of OA entering Phase 3 clinical trials.

## Valuation & Assumptions

Given the inherent difficulty in valuing junior biotech companies we have had to make a series of assumptions and use the probability weighted valuation methodology which we feel is most appropriate for a company like Paradigm.

- Market size and sales are predicted in US\$ but revenues to PAR are converted to AU\$ using a AUD:USD exchange rate of 0.70
- Market size. We have conservatively estimated the target market size at 23% of the total OA patients in the US, that represents the segment of patients suffering from moderate to severe knee OA that have had sufficient progression of OA that would make them eligible for knee replacement. We have used 31.0m patients as 2018 base and applied a 3% growth rate to forecast future market size.
- Penetration rate. Given the move away from Opioids and Corticosteroids, we have assumed the non-opioid/non-corticosteroid/less invasive ZILOSUL<sup>®</sup> eventually takes 25% of the “injection” market in the US.
- Peak penetration. We have used “industry rule of thumb” ramp-up rates to peak sales as applicable to innovative drugs. We believe the drug would reach peak penetration in the 7<sup>th</sup> year and enjoy full penetration till patent expiry.
- Our peak sales assumption for ZILOSUL<sup>®</sup> is FY29, with the ramp-up assumptions tabled below.

**Table heading: ZILOZUL ramp-up rate to peak penetration post market launch**

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
11%	24%	48%	68%	80%	91%	100%	100%	80%	30%

Source: AEP Estimates

- Price per treatment. We have adopted Paradigm’s estimated treatment cost of \$US2,000 (for 12 injections over 6-weeks) in the first year of launch, noting this price point is yet to be tested commercially and excludes related nurse/doctor costs.
- We have assumed a steady price until FY30, at which time we forecast a 60% reduction (near patent expiry).
- Upfront and milestone payments. Perhaps the most subjective assumption in our valuation is the structure of a licensing deal, incorporating upfront payments and milestones.
- We have assumed a US\$850m deal comprising, being the mid-point of the \$700-\$1bn deal range:
  - US\$85m upfront payment in FY20 upon execution of transaction
  - US\$170m milestone for successful Phase 3 completion in FY22
  - ~US\$213m milestone for NDA registration in FY23
  - ~US\$383m for the first year of sales above US\$1Bn (FY24)
- Royalty rate. We have assumed a 15% royalty rate on all ZILOSUL® revenue to Paradigm. We have been guided by a Medtrack analysis across 2,100 indications and 105,000 deals looking at mean royalty rates struck across various Phases and various Therapies.

Of particular relevance to Paradigm is the mean rate struck in Phase 3 (14.1%) and the mean rate for Musculoskeletal Therapies (10%), which appear the two key drivers in setting royalty rates. We have taken slightly above the mid-point of both given accompanying supportive RWE data.

For the MPS indication we have applied the following assumptions:

- Total cost of full year treatment with iPPS is \$75,000 being mid-point of estimated \$50,000-\$100,000 pa cost and note this is significantly lower than existing enzyme replacement treatments which range from \$500,000-\$1m p.a.
- We believe there is strong potential for iPPS to be used in combination with existing enzyme replacement treatments due to its very strong safety profile and high reduction in joint pain data.
- We estimate the target market to be ~10,000 patients per year, but this could well be conservative.
- We believe due to concentration of patient treatment centres that an iPPS treatment would be publicised and promoted in the MPS community and therefore would be adopted rapidly. Thus, we believe market penetration could be as high as 20-25% in the first 1-2 years.
- We have assumed a peak market penetration of 25% for MPS and constant for the life of the patent (10 years).
- We believe these market metrics fairly justify a US\$250m partnering transaction with an established specialty pharmaceutical company (subject to industry standard milestones and 10-20% royalties).
- We do note, that due to the attractive potential marketability of a MPS iPPS treatment, Paradigm may be in a position to pursue this indication itself (i.e. would not need to partner) and therefore would receive full drug sale revenues less marketing and manufacturing costs.
- Probability weighting to reach market. Using the Biotechnology Innovations Organisation (BIO) “Phase Transition Success & Likelihood analysis” (n: 3,582) as a guide, we attribute a 49% weighted average probability of success of ZILOSUL® getting to market for OA.
- We attribute a 37% weighted average chance of success of iPPS for MPS treatment getting to market. This is higher than the strict application of BIO model (15%), as we have applied a 75% probability weighting for Phase 2b success given that Paradigm has already acquired successful Phase 2a safety and efficacy data.
- Our probability weighting for MPS would increase to 49%, upon positive FDA feedback regarding Phase 2/3 trial design and initiation of the Phase 2/3 trial. The table below summarises our weightings.

Table heading: Analysis of weighted probability to market

Transition	BIO Guideline	AEP estimate	Successful P2
Phase 2 to 3	31%	75%	100%
Phase 3 to NDA	58%	58%	58%
NDA to market	85%	85%	85%
<b>Weighted Probability</b>	<b>15%</b>	<b>37%</b>	<b>49%</b>

Source: BIO and AEP estimates

- All revenue assumptions (royalties and upfront/milestone payments) are probability weighted.
- Operating costs. We have assumed an ongoing cash burn rate of ~A\$5m/year, which covers head office, modest pipeline R&D and relationship costs but excludes recent elevated trail costs.
- Capital management. We have assumed that Paradigm will undertake Phase 3 trials for ZILOSUL® & MPS themselves, as they have the necessary capital to fund this pursuit estimated to be A\$40m.
- Given our analysis is solely based on the US OA opportunity we have not forecast additional trial or R&D costs that may be associated with other indications or jurisdictions.
- Manufacturing royalty costs. We assume 2% of gross sales are paid to manufacturer Bene for both manufacturing costs and royalties. In the event of partnering we assume this cumulative 4% to Bene will continue to be paid and will need to come out of what Paradigm receives from the transaction.
- Discounted cash flow. The resulting probability weighted royalty rates, upfront/milestone payments and costs are then discounted by a further 15% (in-line with industry standards for early stage drug development companies) and taxed at a 30% corporate tax rate to arrive at a probability weighted DCF.
- Summary. After all the assumptions above, we arrive at a mid-point valuation of **A\$843m (A\$4.29 per share)**, with significant flex on both the upside and downside.
- Sensitivities. There are a multitude of sensitivities in this valuation, with some key sensitivities listed below:

		Expected OA treatment cost (USD)				
		1,500	1,800	2,000	2,200	2,500
Deal Value (USD)	450	3.46	3.80	4.03	4.26	4.61
	650	3.58	3.93	4.16	4.39	4.74
	850	3.71	4.06	<b>4.29</b>	4.52	4.86
	950	3.84	4.18	4.41	4.64	4.99
	1,050	3.97	4.31	4.54	4.77	5.12

Cross checking our deal size assumption we highlight the following:

On the low end:

- Galapagos licensed GLPG1972, a potential disease-modifying oral therapy for osteoarthritis to Servier, for US\$346m EU Rights Only.

On the highend:

- Teva entered a US\$1.25 billion partnership with Regeneron for their Phase 3/2 anti-NGF pain relief program, with US\$250m being the upfront component and US\$1bn in development milestones.
- Sanofi was rumoured to looking to acquire FLXN for US\$1bn post FLXN's successfully Phase 3 trial for treating OA pain.
  - Pfizer entered into a US\$1.8bn transaction with Eli Lilly, to jointly develop its anti-nerve growth (NGF) factor drug, Tanezumab. Eli Lilly's paid \$200 million upfront and once the FDA addresses its hold on the program, another \$350 million in regulatory milestones and \$1.23 billion in sales milestones.
- We would also note the market cap of FLXN during their phase 2 study was US\$200-300m.

# Recent Big Pharma OA Transactions

## Recent OA Pharma Transactions

The below chart highlights the large amounts paid for drug candidates in the OA space over recent years by large and regional pharmaceutical companies. In comparison to each of the compounds listed below iPPS has significant benefits, especially in terms of safety and repeat use.

### Recent transactions highlight big pharma interest in OA

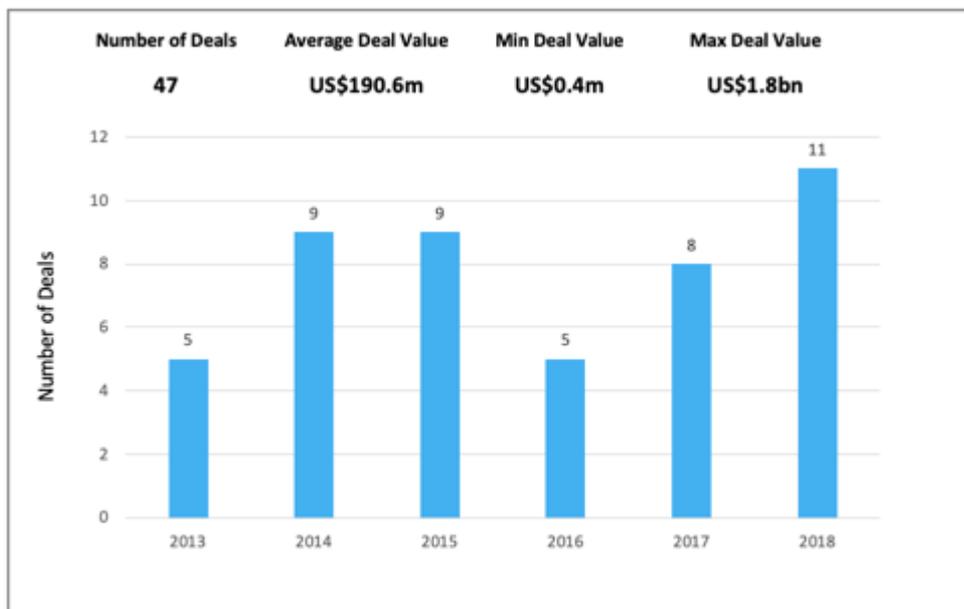
Safety Issues

COMPANIES	COMPOUND	REGION	UPFRONT	TOTAL VALUE	STATUS
	Anti-NGF	Global	US\$200m	US\$1.8bn	Phase 3
	Anti-NGF	Global	US\$250m	US\$1.25bn	Phase 3
	Corticosteroid	Global	Take-over*	US\$1.0bn*	Commercialised
	Anti-NGF	Global (ex Japan)	US\$50m	US\$435m	Discontinued
<b>GLOBAL AVERAGE</b>			<b>US\$166m</b>	<b>US\$1.12bn</b>	
	ADAMTS-5 Inhibitor	EU	Unknown	US\$346m	Phase 1
	Gene therapy	Japan	US\$24m**	US\$434m**	Handed Back
	Gene therapy	Japan	US\$27m	US\$591m	Phase 3
	Anti-NGF	Asia	US\$55m	US\$325m	Phase 3
<b>REGIONAL AVERAGE</b>			<b>US\$35m</b>	<b>US\$424m</b>	

Sources: Bloomberg, company filings; \*Sanofi-Flexion take-over rumoured – Fierce Biotech; \*\*Mitsubishi handed back rights to TissueGene who executed deal with Mundipharma

## All OA Transactions in the biotech/pharma sector 2013-2018

There have been 47 licensing and asset acquisition deals involving osteoarthritis drugs during 2013-18. This shows there is considerable interest in this sector, which is not surprising, but that there is also big pharma interest in the sector, as evidenced by the global names and sizes of the large transactions.



Source: Datamonitor Healthcare – Osteoarthritis and Osteoarthritis Pain Market Research Report & AEP estimates

### Recent transactions highlight big pharma interest in Osteoarthritis

There have been 47 licensing and asset acquisition deals involving osteoarthritis drugs for the period of 2013-2018. Below we have listed details of the OA transactions that are relevant to Paradigm because these transactions:

- specifically relate to treating OA;
- were done at phase 2b or later;
- involve an actual drug candidate or homogenous cell treatment, i.e. would be an off-the-shelf treatment and does not involve surgery for the administration; and
- have been executed with a large pharma or regional pharma companies.

Pfizer – Eli Lilly	
Details	<ul style="list-style-type: none"> <li>• Pfizer struck a deal with Eli Lilly to jointly develop its anti-nerve growth (NGF) factor drug, Tanezumab.</li> <li>• Eli Lilly committed to:               <ul style="list-style-type: none"> <li>– US\$200 million upfront once the FDA addresses its hold on the program, another US\$350 million in regulatory milestones and US\$1.23 billion in sales milestones.</li> <li>– share the cost of the Phase III, trials have been put on hold at various stage due to safety risks highlighted in 2009</li> <li>– Phase 3 results released April 18 highlighted significantly higher AEs vs Placebo (Standard of Care)</li> </ul> </li> </ul>
When:	<ul style="list-style-type: none"> <li>• January 2014</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li>• <b>US\$1.8bn<sup>18</sup></b></li> </ul>

Regeneron – Teva	
Details	<ul style="list-style-type: none"> <li>• Teva Pharmaceutical Industries Ltd executed a global agreement to develop and commercialize Fasinumab, Regeneron's investigational NGF antibody in Phase 3 clinical development for osteoarthritis pain and in Phase 2 development for chronic low back pain.</li> <li>• Under the terms of the agreement, Teva paid Regeneron US\$250 million upfront and share equally in the global commercial value, as well as ongoing research and development costs of approximately US\$1 billion.</li> <li>• Phase 3 clinical trials due to report CY2019</li> <li>• Analyst/Commentator concern of safety as same class of molecule as Tanezumab as FDA will likely view entire of drugs as having safety issues.</li> </ul>
When:	<ul style="list-style-type: none"> <li>• September 2016</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li>• <b>US\$1.25bn</b></li> </ul>

Flexion – Sanofi (Rumoured deal)	
Details	<ul style="list-style-type: none"> <li>• In March 2017 Sanofi was rumoured to be in talks to buy Flexion Therapeutics for &gt;US\$1 billion in cash<sup>1</sup>.</li> <li>• Flexion's knee injection for osteoarthritis, ZILRETTA®, said to fit in with Sanofi's bio surgery division.</li> <li>• Both companies did not comment on why transaction did not occur.</li> <li>• Post phase 3 – Pre FDA-approval</li> </ul>
When:	<ul style="list-style-type: none"> <li>• March 2017</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li>• <b>US\$1bn+ (Rumoured – did not occur)<sup>19</sup></b></li> </ul>

<sup>18</sup> <https://www.fiercebiotech.com/partnering/eli-lilly-spells-out-1-8b-deal-to-partner-pfizer-on-Tanezumab>

<sup>19</sup> <https://www.fiercepharma.com/pharma/sanofi-verge-1b-plus-deal-for-arthritis-focused-biotech-flexion>

Amgen - Ortho-McNeil-Janssen Pharmaceuticals, Inc.	
Details	<ul style="list-style-type: none"> <li>Amgen licensed their anti-nerve growth factor (NGF) antibody to OMJPI</li> <li>The terms of the agreement include a US\$50 million upfront payment, the potential for US\$385 million in success-based milestones and additional sales based milestones and royalties on sales.</li> <li>The agreement provides OMJPI with global rights to the product, but excludes Japan where Amgen has entered into a previous license agreement with respect to the compound. OMJPI and its affiliates will be responsible for future development and commercialization of the compound, a fully human anti-nerve growth factor (NGF) antibody.</li> </ul>
When:	<ul style="list-style-type: none"> <li>August 2008</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li><b>US\$435m</b></li> </ul>

Galapagos – Servier	
Details	<ul style="list-style-type: none"> <li>Galapagos licensed GLPG1972, a potential disease-modifying oral therapy for osteoarthritis to Servier</li> <li>GLPG1972 is a potent and highly selective inhibitor of ADAMTS-5.</li> <li>Licensed post Phase 1</li> </ul>
When:	<ul style="list-style-type: none"> <li>July 2017</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li><b>US\$346m EU Rights Only</b></li> </ul>

TissueGene, Inc – Mitsubishi Tanabe Pharma	
Details	<ul style="list-style-type: none"> <li>TissueGene, Inc. licensed the rights for its degenerative osteoarthritis drug Invossa to Japan's Mitsubishi Tanabe Pharma</li> <li>Invossa is the world's first cell-mediated gene therapy for degenerative osteoarthritis</li> <li><b>Japan rights only</b></li> <li>Post phase 2 – pre-phase 3</li> <li><b>Distribution and Trials in US halted due to safety concerns – Kolon/TissueGene share price plunged ~30% on day of announcement circa 1<sup>st</sup> April 2019</b></li> </ul>
When:	<ul style="list-style-type: none"> <li>November 2016</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li><b>US\$434m<sup>20</sup></b></li> </ul>

<ul style="list-style-type: none"> <li><b>Kolon Life Science - Mundipharma Pharma Corporation</b></li> </ul>	
Details	<ul style="list-style-type: none"> <li>Kolon Life Science entered into an agreement with Mundipharma to license out Invossa, its gene therapy designed to treat osteoarthritis</li> <li>Kolon will receive non-refundable upfront fees of 30 billion won (US\$27m) and potential milestone payments, totalling 667.7 billion won (US\$591.60 million). The company is eligible to receive royalties on sales. The contract lasts for 15 years following Invossa's launch in Japan.</li> <li>Under the deal, Mundipharma will retain exclusive rights for the development, marketing and distribution of the cell-mediated gene therapy Invossa in <b>Japan</b>.</li> <li><b>Distribution and Trials in US halted due to safety concerns – Kolon/TissueGene share price plunged ~30% on day of announcement circa 1<sup>st</sup> April 2019</b></li> </ul>
When:	<ul style="list-style-type: none"> <li>November 2018</li> </ul>
Deal Value	<ul style="list-style-type: none"> <li><b>US\$591.6m</b></li> </ul>

<sup>20</sup> [https://www.tissuegene.com/en\\_US/investors/pr/detail/10/tissuegene-licensee-kolon-life-science-partners-with](https://www.tissuegene.com/en_US/investors/pr/detail/10/tissuegene-licensee-kolon-life-science-partners-with)

Regeneron Pharmaceuticals - Mitsubishi Tanabe Pharma Corporation	
Details	<ul style="list-style-type: none"> <li>• Collaboration agreement for the exclusive development and commercial rights to Fasinumab (REGN475), Regeneron's NGF antibody</li> <li>• Under the terms of the agreement, MTPC will obtain exclusive development and commercial rights to Fasinumab in Japan, Korea and nine other Asian countries, excluding China.</li> <li>• Under the agreement, Regeneron will receive up to US\$55 million in upfront and other near-term payments. The agreement provides for additional payments to Regeneron of up to \$170 million in R&amp;D reimbursement payments and development milestones. Regeneron is also eligible for additional one-time purchase price adjustment payments of up to \$100 million total upon achievement of specified annual net sales.</li> </ul>
When:	• October 2015
Deal Value	• US\$325m

## Peer Comparison

Peer	Ticker and exchange	Market cap (A\$m)	Rationale	Clinical stage of key product	Addressable market size
 BIOMARIN	BMRN.NASDAQ	~20.74Bn	World leader in developing and commercializing innovative biopharmaceuticals for rare diseases driven by genetic causes. 7 drugs in market. Leader in ERT for MPS diseases.	7 Drugs in market/commercialisation	US\$5.0Bn+
 flexion <small>Transformative Medicine. Where it Matters.</small>	FLXN.NASDAQ	663	Marketing a slow release corticosteroid that is injected into the knee joint to treat OA pain. Granted Fast Track Status by the FDA and drug registration in Nov 2017.	In market/Commercialisation	US\$4.6Bn+ (~7.8m ppl receiving IA corticosteroid injections in USA)
 AXSOME <small>THERAPEUTICS</small>	AXSM.NASDAQ	1.04Bn	Developing novel therapies for the management of central nervous system disorders, focusing on treatment of BMEL	Phase III	US\$2.5Bn+ <sup>2</sup>
 Medical Developments International	MVP.ASX	330	Developing new markets and applications for Pentrox for treatment of acute pain, recent focus on respiratory diseases, significant manufacturing IP	Phase III & commercialisation	US\$3Bn+
 CENTREXION <small>THERAPEUTICS</small>	Unlisted	N/A	Development of CNTX-4975, a selective, highly potent, ultra-pure, synthetic form of trans-capsaicin. It inactivates local pain fibres transmitting pain signals to the brain	Phase III	US\$5Bn+
 paradigm <small>BIOPHARMA</small>	PAR.ASX	285	Focused on the clinical development of PPS as a multi-target treatment for complex conditions, such as BMEL/OA, AV, Cardiovascular & AR	Multiple Phase II/III	US\$37Bn+ <sup>4</sup>

Source: Bloomberg, company filings  
<sup>1</sup> Market data as at 05 May 2019, exchange rates of AUD/USD 0.70  
<sup>2</sup> Based on BMEL addressable market size, excludes CRPS addressable market due to lack of available information and thus likely understates true market size  
<sup>3</sup> Only includes the market size for COPD which is US\$12bn, excludes market sizes for other respiratory disease indications  
<sup>4</sup> Includes All market US\$33bn+ and OA/BMEL market US\$8bn+ & \$0.5bn for viral arthritis, excludes COPD addressable market size of US\$12bn+ and Asthma addressable market size of US\$15bn+ and Heart Failure Figures between 2014 & 2016 - Statista \$13.2bn (Research and Markets - Global Statin Market 2015-2016), Clopidogrel bisulphate \$1.8bn, Beta-blockers \$1.55bn, ACE inhibitors 0.47bn, Aspirin \$0.54bn, Vitamin K antagonist \$0.5bn ([www.pharmacompass.com](http://www.pharmacompass.com))

## Key Risks

**Funding Risks:** A delay in achieving a partnership and subsequent upfront/milestone payments may have an impact on Paradigm's clinical program development.

**Competing products:** As highlighted, there are several OA drugs in or about to enter Phase 3, providing a potentially crowded market in outer years for the treatment of OA. That said OA is clearly being viewed as an "unmet need" by the FDA, particularly considering the desire to find alternatives to opioid treatments.

**Clinical Trial Risk:** Despite there being ample evidence that PPS could be an effective treatment for the indications that Paradigm is investigating, there is no guarantee that trials will be successful and that the Company's drugs will make it to market.

**Manufacturing Risk:** Given Bene-pharmaChem are the sole manufacturer of the only FDA approved Pentosan polysulfate sodium, there is a short-term manufacturing/supply, redundancy risk. Paradigm will likely address this risk on approach to commercialisation.

**Timing risks:** Delays in timelines may inhibit optimal partnerships, milestone payments and long-term revenues. Timeline delays can be caused by but not limited to:

- Trial requirements & recruitment rates
- The FDA approval process
- Other products reaching market

Given our valuation has a probability weighting and a WACC discount rate applied to it, delays in expected licencing deals and royalty rates have a negative impact on valuation.

**Regulatory compliance issues:** Anything from accounting issues, manufacturing practices and product recalls could materially impact our current earnings forecasts.

**Poor Design of Clinical Studies:** It is imperative that the correct personnel are in place to optimally design all clinical trials. As many biotech companies have experienced, an incorrectly designed study will inevitably lead to detrimental results, which will adversely affect our valuation and forecasts.

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### ANALYST CERTIFICATION

Each research analyst primarily responsible for the content of this research report, in whole or in part, certifies that with respect to each security or issuer that the analyst covered in this report: all of the views expressed accurately reflect his or her personal views about those securities or issuers and were prepared in an independent manner.

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