Research

Baker Young Limited

Wednesday, 24 February 2021

EQUITIES

Recommendation	BUY
Valuation	$4.75
Price (at 23 Feb 2021)	$2.60
Discount rate	20%
GICS Industry	Pharmaceuticals
Market Cap	$587m
30- day avg turnover	665,773 shares
52-week range	$4.22 - $1.08
Avg Daily value (3 month)	$2.50
Number shares on issue	225.9m
Sold short	3.99%

INVESTMENT FUNDAMENTALS

End 30 June	2020a$m	2021e$m	2022e$m	2023e$m
Revenue	-	-	-	41.4
EBITDA	-13.2	-30.7	-47.7	-10.8
NPAT	-12.3	-30.1	-47.3	-10.8
EPS	-0.054	-0.13	-0.209	-0.047
Total DPS	n/a	n/a	n/a	n/a
Cash	103.9	73.7	26.3	15.6
R&D rebate	3.6	2	1.5	9
EV	484	514	560	572
NAV	108	75	27	16.6
P/BV	0.18	0.13	0.046	0.028
EV/EBITDA	n/a	n/a	n/a	n/a
P/E	n/a	n/a	n/a	n/a

TOP 10 SHAREHOLDERS

Shareholder	Shares	%
Paul Rennie	20,109,222	8.77%
RBC Global Asset Man.	8,786,561	3.83%
The Vanguard Group, Inc.	6,337,381	2.77%
Nancy Wilson-Ghosh	3,860,835	1.68%
BSMI Trust	2,768,232	1.21%
V Redford Pty Ltd	2,505,419	1.09%
Brett Langan	2,403,432	1.05%
J G M Investment Group	2,185,715	0.95%
Collins St Asset Management	2,177,947	0.95%
The Himstedt Family Trust	1,921,871	0.84%

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Paradigm Biopharmaceuticals Limited (ASX:PAR AU)

All the makings of a front line, first in class Blockbuster Drug.

Key Points:

- Outlook remains strong, with several key milestones to drive material upside.
- Safety across all patients maintains 100% tolerance, with pain and function improvement up to 50%.

Our View - BUY

Paradigm begins 2021 on the cusp of several pivotal phase 3 clinical trials, with aspirations of successfully commercialising pentosan polysulfate sodium (PPS) for the treatment of the world's third largest unmet medical need osteoarthritis (OA). Paradigm via an exclusive supply agreement with bene pharmaChem GmBH, have access to a semi-synthetically produced heparin-like macromolecular carbohydrate derivative (extracted from beech trees), that for decades Big Pharma has failed at developing a bio-equivalent molecule. Paradigm has accumulated compelling data that confirms PPS is effective in reducing pain, whilst improving function and mobility, and is well tolerated.

In addition, radio graph (X-ray), and MRI images provide evidence that PPS slows the advancement of OA, indicating disease modifying characteristics. This is significant, as current treatments and competing products in development have mono specific applications, and in many cases have limited tolarability due to adverse effects. Paradigm has a multi model product, with several patents across many applications. 2021 is a year for anticipated partnerships, and/or commercial discussions for any one of the company's applications. Paradigm is well positioned to successfully commercialise Zilosul® (injectbale PPS) as a first in class, blockbuster drug.

Key Points

Exclusive supply agreement with bene pharmaChem GmBH (BPC) for PPS, extended on the 29th September 2020 for 25 years from first day of marketing approval. BPC are the only FDA approved supplier of PPS, with no other company achieving a bio-equivalent molecule. This agreement is crucial to the long term success of Paradigm.

Clinical and preclinical evidence demonstrate injectable PPS is active across multiple modes of action (MOA), including decreasing inflammation by downregulating inflammatory cytokines, reducing the production of NGF, protecting cartilage by downregulating degrading enzymes, and repairing bone through improved blood flow.

Disease modifying osteoarthritis drug (DMOAD), clinical trials OA_008 to begin Q2 CY 2021 (p.20). The study will evaluate biomarkers in the blood and synovial fluid as indicators of the MOA of PPS in the Knee OA. These results will support Paradigm's value proposition and market pricing for Zilosul®.

Mucopolysaccharidoses (MPS) Type 1 & 6 confirmed as orphan diseases by the Food and Drug Administration (FDA), and the European Medicines Agency (EMA). Two MPS-1 patients 7 & 11 weeks into treatment respectively, showing PPS to be well tolerated.

Phase 3 efficacy and safety read out for Knee osteoarthritis (OA) expected Q1 2023, with data from all supportive trials expected no earlier than Q3 2023. Filing and registration for PPS as a new drug with the FDA envisaged for CY Q1 2024 / Q3 2024. The OA indication is pending fast track designation.

Expanded Access Scheme (U.S.), and Therapeutic Goods Administration (TGA) Australia via the Special Access Scheme (SAS) continue to achieve results in line with Knee OA Phase 2b clinical trials.

Early stage discussions of three potential projects for the repurposing of molecules other than PPS. Paradigm is persuing adding new products to the pipeline via merger or acquisition, underpinning board and managements confidence in PPS.

Action and Recommendation

BUY - Paradigm trades at a significant discount to our valuation. Subsequent to IND approval, we believe it highly likely to spark the interest of large global institutional investors, identifying the companies enviable market positioning, and value proposition.

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Executive Summary

The crown jewel - bene pharmaChem GmbH & Co (BPC)

A meeting of two minds over a decade ago forms the backbone of Paradigm's existence. In 2009 Paul Rennie presented his interest in PPS for repurpose, and subsequently was introduced to Dr Harald Benend. Since this time, the two have formed a close relationship (noticed from our discussion with Dr Benend), underpinning the bond of their commercial interests. BPC is a family business, spanning three generations, established in 1947, with an inherent culture illustrated by its loyalty in long standing relationships with staff, suppliers, and customers. The pride Dr Benend's family has in their origins is evident in the legacy they have successfully built, not only in their community, but the broader commercial pharmaceutical market. BPC, despite the tenure of its existence has remained relatively small by choice, entrenching a philosophy built on quality and service, excelling and perfecting German ingenuity. Many decades of excellence, and the recent collaboration with Paradigm, has the potential to act as a springboard solving one of the world's biggest problems, improving the lives of millions of people, whilst saving billions of dollars.

Paradigm's success is highly dependent on their exclusive 25 year supply agreement with BPC for pentosan polysulfate sodium (PPS). BPC holds the only Drug Master File (DMF) with the FDA to manufacture PPS for human applications. During this period no other pharmaceutical group may reference the DMF in a future submission without BPC's approval. Several attempts to replicate PPS have failed, placing Paradigm in a unique position to take full advantage of this pivotal relationship. A full understanding can be sought on p.22.

Solving a global problem

Paradigm is on the cusp of a being a front line, first in class treatment, to an initial addressable market of 72 million OA sufferers throughout North America, Europe and Australia, with the Centre for Disease Control (CDC) estimating a compound annual growth rate in the U.S. of 8.1% to 2040 (p.5). Unbeknown to many, more than 128 people in the U.S. die overdosing on opioids daily. The misuse and addiction of opioids is a serious national crisis that affects public health, and social and economic welfare. The CDC estimates that the total economic burden of prescription opioid misuse alone in the U.S. is US$78.5 billion per annum (P.4). Currently there are no treatments that do not have adverse effects, treating only pain, without having any positive impact on the underlying pathology of the disease (p.39). Most, if not all alternate drugs in trial phases have been proven to lack either efficacy or safety, and in some cases accelerate the disease (p.27&32). Based on current studies, Paradigm has successfully repurposed PPS (p.17) and navigated its way through many regulatory obstacles, positioning the company on the verge of an Investigative New Drug (IND) submission with the FDA for global phase 3 clinical trials (p.25). Paradigm has proven PPS is safe and well tolerated, has pain and function improvement up to 50%, and evidence showing that BPC PPS slows the rate of progression of OA, halting, and in some cases reversing the progression of the disease (p.19). After receiving positive feedback from Paradigm's FDA Type C meeting, we believe the company will receive IND approval within months.

Paradigm has successfully treated over 700 patients, either through the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS)(p.12), FDA Expanded Access Program (EAP) (p.16), and Phase 2b clinical trials (p.17), transforming the lives of hundreds of OA sufferers, as is evidenced by the inclusion of a group of high profile success stories (p.15). We are extremely encouraged by statistically significant Phase 2b OA clinical trials, and the consistent high level of pain and function improvement in SAS patients, as well as countless anecdotal accounts from knee and hip OA suffers, many of whom have off label OA conditions, such as hand and feet. The feedback has been overwhelmingly positive, including medical cynics and ex professional athletes who were given no alternative options other than knee replacement. Whilst the science continues to consistently impress, our exposure to Real World success stories provides an extra layer of confidence. Despite the above, the most critical aspect is safety, and in all cases, PPS has shown to be well tolerated across patients treated with PPS.

Blue sky

The blue sky for Paradigm is vast, not only repurposing PPS for OA. The company is also well advanced with several other indications, none more so that orphan designation drug Mucopolysaccharidosis (MPS) 1 & 6 (p.33), having shown safety and efficacy in early-stage trials leading into upcoming phase 2/3 trials in both Australia and Brazil. Further, Ross River virus (RRV) / chikungunya virus (CHIKV), and Heart Failure (p.44&46) are at various stages of trials, all showing promise. MPS-6 is a crucial indication for Paradigm, success, with supporting data from MPS-1 trials having potential to unlock a lucrative market incorporating all other forms of MPS. Further, M&A activity for additional molecules for repurpose is now a real possibility, as indicated by Paul Rennie, and supported by the recent transformation of board and management (p.58). Paradigm during the past year has made several pivotal and key appointments that are crucial in seeing Paradigm through to commercialisation. We expect Paradigm to continue to add to what is fast becoming a star-studded line up.

At what price

Opinions will vary on valuation methods (p.48), for what is a fair and reasonable price for Paradigm today. Investment in Paradigm requires vision, forward thinking, patience, and an understanding of the risks associated with what many would consider a speculative investment. We derive all our assumptions based on the highest level of understanding across all aspects of the business, acknowledging the known benefits and pitfalls in the highly binary environment in which Paradigm operates. That being said, and as explained in our valuation methods, we are confident in attributing the highest level of belief across a broad range of possible outcomes. Given the conservative nature of our base level assumptions, the model leaves significant room for improvement across a range of outcomes we believe to be realistic, and well within reach. In all instances, we believe our starting position has the potential to significantly understate Paradigm's earning potential in providing a successful harmonised global roll out within the timeframes allowed, favourable exchange rate, Zilosul® pricing, milestone payments, and the percentage rate applied to royalty payments. In all instances, if Paradigm marginally improves on our base assumptions, the discounted value of forecast cash flows increases swiftly, and could considerably understate our NPV's and valuation of $4.75.

The Paradigm story

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, having established anti-inflammatory and anti-thrombotic properties. It has been in use for approximately 70 years and has a well established safety profile. This report refers extensively to the injectable format of the drug 'iPPS'.

Paradigm addresses conditions that start with, and are sustained by inflammation. Lead clinical indications involve treating OA (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.

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, ageing or genetic predisposition. Paradigm's core business revolves around the repurposing of PPS for a number of newly targeted indications.

Drug repurposing generally requires half the required time and budget to successfully commercialise a new product. This approach takes an existing approved drug which has demonstrated safety in its approved indication/s and repurposing that drug in a new patented therapeutic application.

What is Osteoarthritis (OA)

Osteoarthritis is a joint degenerative disorder that affects various joints, mostly affecting the elderly population. In OA, the smooth gliding surface between joints that provides easy movement is affected with age. This leads to swelling, pain, tenderness, and stiffness in joints, and affects the normal movement and quality of life of an individual. There is no permanent cure for this condition. However, medicines help in suppressing the symptoms to a certain extent, thereby offering relief to patients. Medications used for OA treatment include pain relievers, such as Paracetamol, ibuprofen and naproxen. OA affects the knee, shoulder, lower back, hip, and hands.

OA is the most prevalent form of joint disease, affecting as much as 13% of the world's population. An estimated 33 million people in the U.S., and over 3 million people in Australia suffer from degenerative OA .In the U.S. alone, the financial burden of OA has been estimated to be US$81 billion in medical costs, and US$128 billion in total cost.

The OA market

The global OA drug market is classified into drug class, route of administration, and distribution channel. The OA drug market is segmented into corticosteroids, NSAID's, viscosupplementation agents, and others. Route of administration; this market is segmented into oral, parenteral, and topical. The parenteral segment is expected to dominate the global market. Distribution channel segment; includes hospital pharmacies, retail pharmacies, and online pharmacies.

Opioid medicines are used by a large percentage of patients who have advanced knee, hip, or spine OA to manage their chronic pain. Dr Scott Gottlieb, M.D., ex-Commissioner of the U.S. Food and Drug Administration said on 14 May 2018, "The biggest public health crisis facing the FDA is opioid addiction. Not a day goes by in my role at FDA without hearing stories of the emotional, physical, and financial toll this epidemic is taking on Americans". There is an unmet medical need for people suffering from OA. IPPS is a non-opioid product, which is non-additive and has potential to become a first in class, front line treatment for OA.

Opiods

The demand for an effective treatment is significantly amplified by the opioid epidemic throughout the U.S.. Daily, more than 128 people in the die overdosing on opioids. The misuse and addiction of opioids is a serious national crisis that affects public health, and social and economic welfare. The Centers for Disease Control and Prevention estimates that the total 'economic burden' of prescription opioid misuse alone in the U.S. is US$78.5 billion a year. This includes healthcare costs, lost productivity, addiction treatment, and criminal justice involvement.

Opioids are potent analgesic medications that offer pain relief for severe acute pain associated with major trauma or surgery. Opioids are useful in chronically painful conditions in situations with limited life expectancy (such as metastatic cancer). Traditional treatments include non-opioid analgesics (acetaminophen), and non-steroidal anti-inflammatory drugs (NSAID's). During the past three decades, the use of opioids for the non-operative treatment of arthritic conditions has increased, with numerous negative consequences.

It is well recognised the U.S. is in the midst of an opioid crisis, representing less than 5% of the world's population, yet consumes approximately 80% of the world's prescription opioid production. The U.S. ranks second only to Canada in per capita opioid consumption.

Despite recommendations against opioid use, nearly 27% of patients with OA still receive opioids and benzodiazepines, with about 36% demonstrating at least one risk factor for prescription misuse.

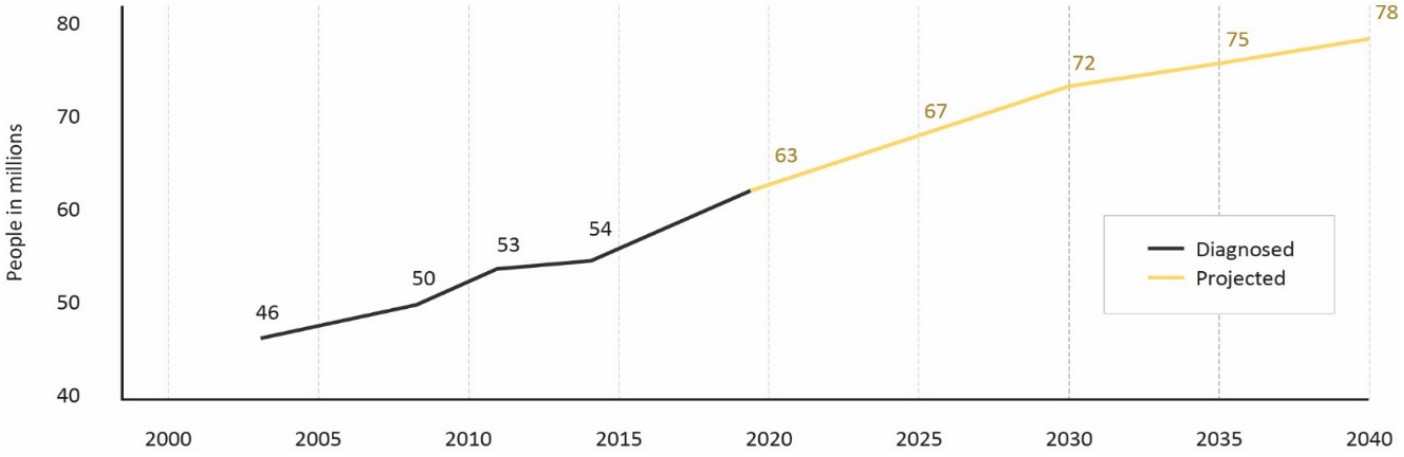
The past two decades have seen a significant increase in the prescription of opioids and benzodiazepines in the U.S. Physicians treating musculoskeletal conditions and injuries have played a significant role. It is reported opioid overdoses were involved in more than 46,802 deaths in 2018, representing a fivefold increase since 1999.

Evidence-based guidelines do not support long-term improvements in pain or function in patients with OA when treated with opioids. Clinical Practice Guidelines released by the American Association of Orthopaedic Surgeons (AAOS) in 2017 recommend against the use of the opioid pain medication for the treatment of OA.

Addressable Market

Centers for Disease Control estimates that 63 million U.S. adults have some form of arthritis, a figure that is projected to reach 78 million by 2040. Whilst there is estimated to be more than 100 types of arthritis, OA is the most common form of arthritis, affecting 33 million U.S. adults. This number is expected to grow in coming years at a CAGR of 8.1%, driven by ageing, obesity, and increasing sports injuries.

Compound annual growth rate for OA in U.S.



Source: Centers for Disease Control and Prevention

Statistics

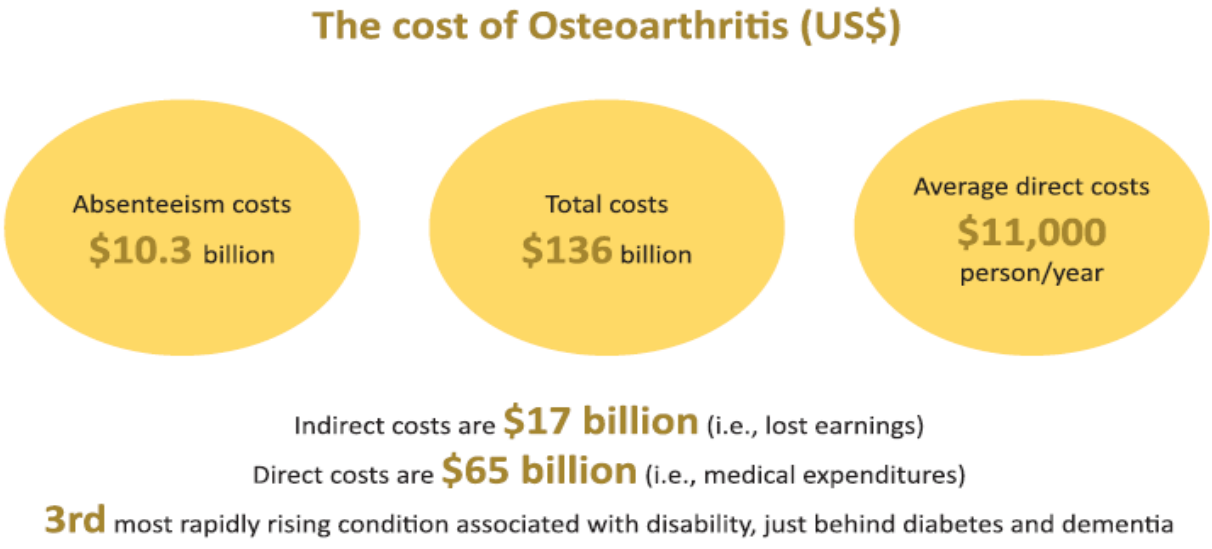
Since the 1990's the average age at diagnosis of OA has fallen from age 72 to 56, affecting 14% of adults aged 25 and older, 34% of those 65 and older, and 88% of people 45 or older. The annual incidence of Knee OA is highest between ages 55 and 64. OA is most common in women making up 62% of total sufferers.

The overall economic burden of OA in the U.S. is estimated at US$128 billion annually. This figure has more than doubled over the last decade. For perspective, the annual economic cost of arthritis surpasses that of tobacco related health effects, cancer, and diabetes. Direct medical costs reach US$65 billion annually.

In 2013 OA was the second most expensive health condition treated in U.S. hospitals. An estimated one million knee and hip replacements are completed each year, with lost wages per annum estimated at US$164bn, or US$4,040 per adult with OA compared to those without.

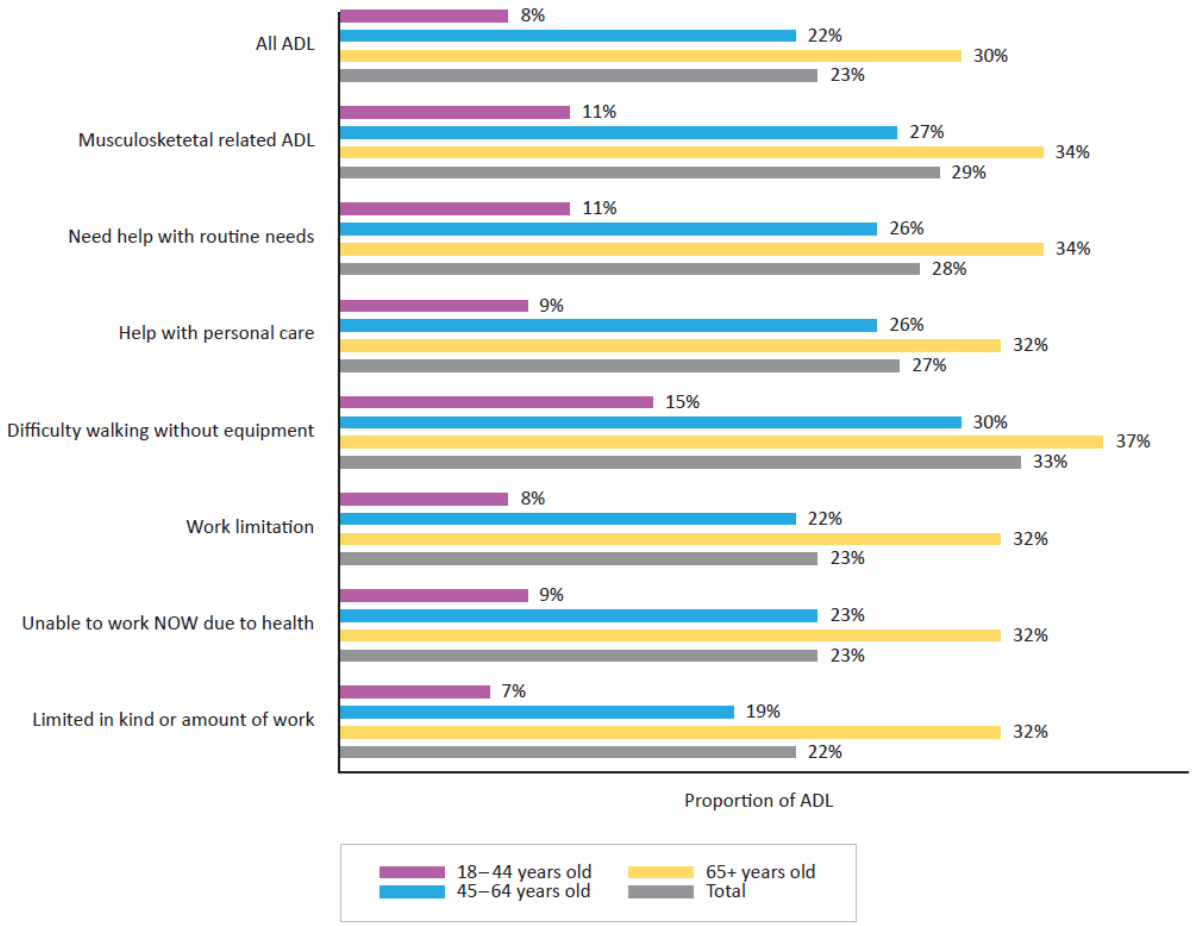
Increased absenteeism among workers with OA is well documented, missing an average of two more days per year than workers without OA. Presenteeism, or loss of productivity while on the job, is less easy to calculate but is no less costly for workers or businesses.

In the U.S. there are 14 million individuals who have symptomatic Knee OA, with more than half eligible for knee replacement. Seven million individuals with moderate to severe OA are Paradigm's immediate target market.



Source: Centers for Disease Control and Prevention

Proportion of adults age 18 and over with self-reported doctor – diagnosed arthritis reporting limitations of daily living (ADL) and activiety attributed arthritis. By age, U.S. 2013-2015 (below).



Source: Centers for Disease Control and Prevention

Currently there are no pharmaceutical products registered to treat the underlying cause of OA. Disease-modifying endpoints, such as BME which can be detected by MRI and other biomarkers, while not fully validated and accepted by regulatory agencies will be evaluated in ongoing and future studies by Paradigm.

Traumatic – Being the most frequent cause of BME arising from acute joint injuries such as sporting injuries, car accidents, or accidental falls leading to bruising within the subchondral bone (bone under the cartilage of a joint such as knee, hip or ankle).

Non traumatic – Bone bruising without an obvious traumatic event. For example, in rheumatoid arthritis edema (fluid build-up) inside the bone is commonly observed. BME is a signal of disease progression (rheumatoid arthritis), a marker of poor prognosis predicting joint damage and bone erosion.

There are two examples of acute traumatic injuries from which the market size may be estimated. In both cases, 80% of injuries were associated with BME:

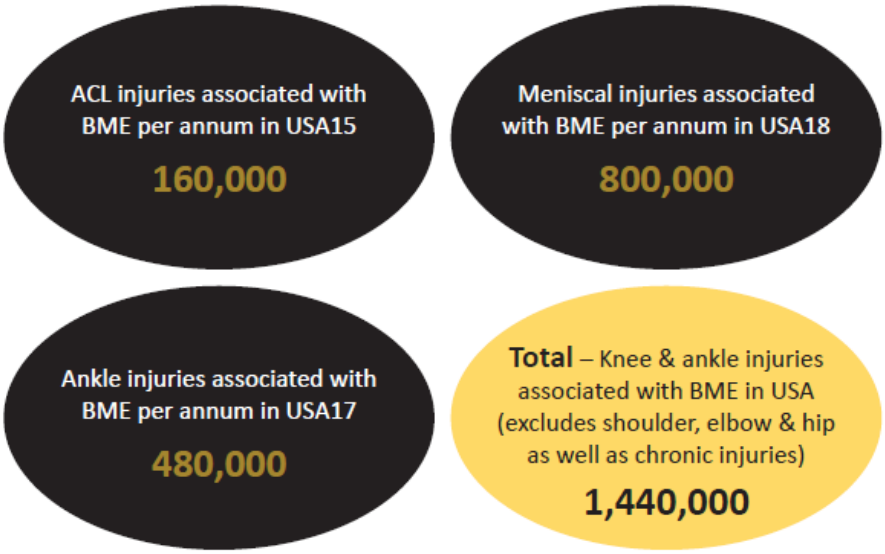
Anterior cruciate ligament (ACL): Injuries in the U.S. have an incidence rate of 40 ACL reconstructions per 100,000 people per year, equating to approximately 131,200 ACL reconstructions.

Tear of the meniscal cartilage: In the knee in the U.S has an incidence rate of 90 meniscal tears per 100,000 people per year, equating to approximately 295,200 meniscal injury operations.

12% of all patients with lower extremity OA have a history of joint injury (ligament strain/rupture, meniscal tear or joint surface injuries). The number of patients, in the U.S. with disabling PTOA of the hip, knee or ankle approaches six million, and accounts for approximately 12% of annual expenditures for OA i.e. about US$3 billion per year, or approximately 0.15% of the total U.S. health care direct cost outlay.

The current focus is on knee injuries, however there is potential for PPS to treat other major joints (ankle, shoulder, elbow, hip, etc.) and chronic injuries.

Addressable market based on acute traumatic injuries:



Source : Centers for Disease Control and Prevention

The addressable market in the U.S. alone, based on a treatment cost of US$2,000 is US$2.88bn. This figure does not include shoulder, elbow, hip injuries, and BME associated with invasive surgery.

More simplistically, the number of people with OA in the U.S. is approximately 33 million, 14 million of who have moderate to severe Knee OA. The addressable market in the U.S. based on a treatment cost of US$2,000 per annum is US$28bn.

The U.S. typically accounts for 50% of the global pharmaceutical OA sales.

Pentosan polysulfate sodium (PPS)

PPS is manufactured in Germany by bene pharmaChem GmBH (BPC), as a semi-synthetic compound made from sugar extracted from the bark of European beech trees, sharing structural similarities with glycosaminoglycans (GAGs), and heparin. These complex carbohydrates have a modulatory role in the body, via interactions with proteins involved with inflammation enhancing the body's defence and repair systems, and assisting in the growth of new tissue.

Approved indications for injectable PPS (iPPS) include prevention of thromboembolism, and the treatment of acute blood vessel occlusions. PPS has been available as an injectable treatment since 1949, with over 100 million performed doses, and no reported serious adverse events (AE's).

Currently iPPS is not approved for human use, with only an oral form approved by the TGA in Australia, and the U.S. Food and drug Administration (FDA), marketed by Janssen Pharmaceuticals (a subsidiary of Johnson & Johnson) under the brand name Elmiron®, for the treatment of a bladder condition, interstitial cystitis. Additionally, PPS acts as a supportive therapy for arterial vascular diseases (Claudicatio intermittens), and as a medicinal veterinary product used in the treatment of OA.

The FDA approved PPS over 30 years ago for oral use, known for anti-inflammatory, anti-histamine, anti-clotting, and prevents necrosis (premature cell death), and cartilage degeneration. Paradigm's focus is on repurposing PPS in an injectable format to treat OA and multiple other indications for human use.

Drug Repurposing

Drug repurposing is defined as identifying and developing new uses for existing drugs. There are three key advantages when compared to new drug (de novo) development:

1. The drug development cycle times are generally much shorter.

2. The development costs are expected to be less.

3. The success rates can be higher.

De novo drug discovery and development 11–18 year process | <10% overall probability of success

Target discovery	Discovery & screening	Lead optimization	ADMET	Development	Registration
> Expression analysis > In vitro function > In vivo validation; e.g knockouts > Bioinformatics	**Discovery** > Traditional > Combinatorial chemistry > Rational based drug design **Screening** > *Ex vivo* and *in vivo* > High throughput	> Traditional medicinal chemistry > Rational drug design	> Bioavailability and systemic exposure (absorption clearance and distribution)	> Must start clinical testing as Phase I (Phase VII for cancer)	> United States (FDA) > Europe (EMEA or country by country > Japan (MHLW) > Rest of world
2–3 yrs	0.5–1 yrs	1–3 yrs	1–2 yrs	5–7 yrs	2–4 yrs

Source Paradigm prospectus

Drug repurposing 3–10-year process | reduced safety and pharmacokinetic uncertainty

Compound identification	Compound acquisition	Development	Registration
> Targeted searches > Novel insights > specialized screening platforms > Serendipity	> Licensing > Novel IP > Both licensing and novel IP > Internal sources	> Can start at Phase I or Phase II stages > Ability to leverage existing data packages > Manufacturing complete	> United States (FDA) > Europe (EMEA or country by country > Japan (MHLW) > Rest of world
1–2 yrs	0–2 yrs	2–3 yrs	2–3 yrs

Source Paradigm prospectus

For most repurposed drugs, a single pivotal trial may be sufficient for regulatory clearance and marketing approval utilising the FDA's 505(b)(2)(U.S. Federal Food, Drug and Cosmetic Act of 1938) regulatory pathway in the U.S.. This can significantly reduce time and financial resources in the development process. However, the FDA has requested two studies for PPS due to the new indication, mode of delivery, and treatment regimen.

The 505(b)(2) pathway is generally open to companies where the compound being developed has already been granted approval as a New Chemical Entity (NCE), but for which the data exclusivity period has expired. In addition to a reduced clinical trial burden, this pathway also allows data collected on the compound by other drug developers, as well as research published in peer-reviewed journals to be used in support of the company's ultimate marketing application.

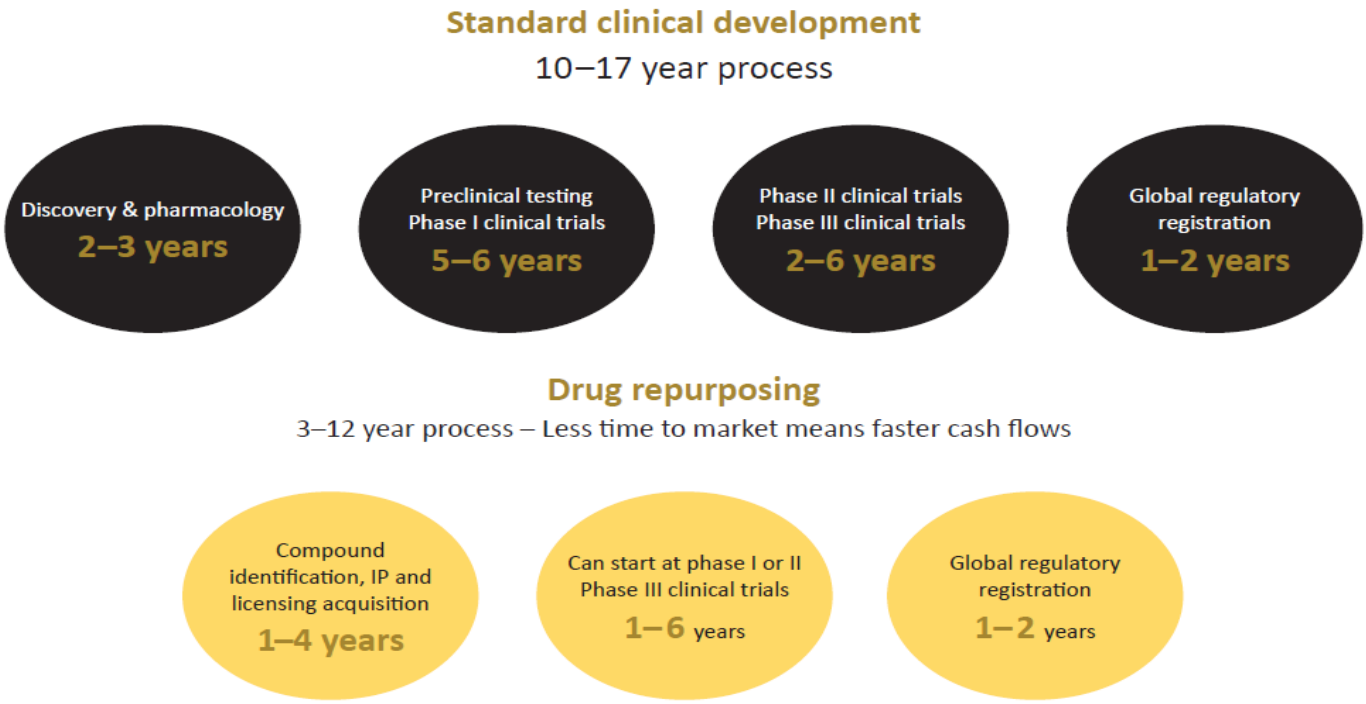
New Drug Application (NDA) section 505(b)(2) is a NDA that contains full reports of investigation of safety and efficacy where some of the information required for approval comes from studies not conducted by the applicant. Therefore, this provision expressly permits the FDA to rely, for approval of a NDA, on data not developed by the applicant.

There are a number of benefits of utilising a Drug Repurposing/Repositioning/Rescue (DRPx) strategy in comparison to conventional de novo drug development programs.

Cost savings – The cost to launch a repurposed drug can range anywhere between US$100-300 million if the DRPx drug has to undergo complex phase 2 and phase 3 clinical trials. This figure represents a fraction of the average de novo drug development cost of US$1.778 billion.

Time savings – Repurposing a compound dramatically reduces the clinical approval process due to the established clinical data that accompanies it. The average cycle time of a DRPx drug is approximately 3-12 years, considerably less than de novo drug development of 10-17 years.

(All dollars referred to in this report are in Australian dollars unless otherwise stated)



Source: Science Direct

Risk/productivity – The attrition rate of conventional de novo drugs is a 95%. The leading factor is due to a compound's lack of safety (45% failure in phase 1), and efficacy (65% failure in phase 2). As a result of the high attrition, there is an increased pressure on the drug pipeline.

Higher success rates – DRPx drugs have either been approved, or shown to be safe in late stage trials, and can enter the clinical cycle at the efficacy stage, therefore the failure rate is significantly decreased, promoting the chances of a successful launch. Approximately 25% of DRPx drugs successfully make it from phase 2 to launch, in comparison to 10% of conventional de novo drugs.

Market potential – The market potential for a DRPx drug is subject to the same market forces as a conventional de novo drug, such as market need, patient acceptance, market strategy, and intellectual property. A DRPx drug has the same potential to reach 'blockbuster' drug status as a de novo drug. An example of a DRPx blockbuster drug is dimethyl fumarate (brand name Tecfidera®) from Biogen & IDEC Pharmaceuticals. Tecfidera® was approved for a new indication to treat multiple sclerosis (MS) in 2013 and achieved revenue sales excess of US$2.5 billion worldwide in 2014.

Intellectual property –A DRPx strategy can help elongate a drugs patent life, thus prolonging product lifecycle and reducing the 'patent cliff' effect. Illustrated below are a few well known repurposed drugs (some of which have been used to assist in determining Paradigm's possible growth rates).

Brand name	Original indication	New indication	Pharma company	(US$) 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	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	Janssen/J&J	280M (2015)

Source: Paradigm

Bone Marrow Edema (BME)

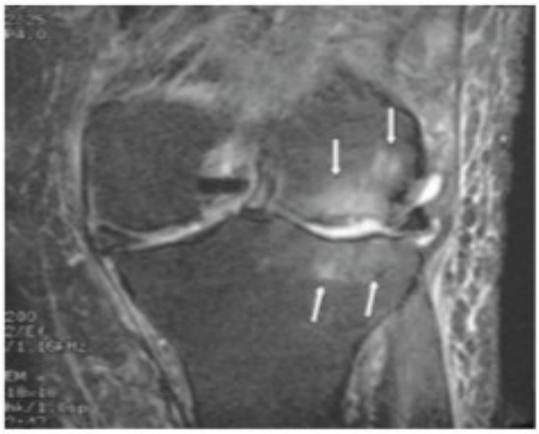
BME is a complex disorder causing excess fluid build-up inside the bone. BME typically occurs at the end of long bones adjacent to the cartilage of the hip, knee or ankle joints. BME (commonly referred to as bone bruising, or bone marrow lesions (BML)), is a painful condition. If untreated can be associated with negative long term health consequences for the patient's affected joint – including progression to OA.

Over the last decade the increased use of magnetic resonance imaging (MRI) for musculoskeletal injuries has alerted clinicians to the existence of BME, a clinical condition previously undetected by conventional radiographic techniques (X-Rays).

BME is considered a distinct clinical condition that is normally associated with constant bone pain, functional disability, quality of life issues, and poor long-term prognosis for the affected joint.

On an MRI scan, BME can be seen as an abnormality under the surface of the bone, particularly in joints presenting with OA, or at the location adjacent to significant ligament or meniscus tears or bone contusions (sporting injuries and accidents).

BME lesions are typically associated with, or a consequence of a direct impact to the bone, bone fractures, ligament injury, bone tumours, invasive surgery, OA or synovitis. Among medical professionals it is accepted there are two distinct forms of BME.



Traumatic BME – The rupture of the anterior cruciate ligament of the knee.

Atraumatic BME - Which occurs without trauma and may be associated with the rapid progression of OA.

Apart from prolonged rest and immobilisation of the affected joints/anatomical region, there is currently no effective, regulatory approved, therapeutic treatment available for patients. Traditional treatment of rest and immobilisation may result in the resolution of symptoms of pain & joint dysfunction, and normalisation in MRI within 6-18 months, however during this period the patient's quality of life is usually considerably diminished.

The image to the right is a T1 weighted MRI scan of a knee joint with the BME highlighted by the arrows.

Other treatments may include analgesics and anti-inflammatory drugs, physiotherapy and surgical treatment (core decompression). Analgesics or NSAID's, are usually prescribed to provide some relief for BME, although it is widely accepted that NSAID's and corticosteroids have detrimental side-effects on the metabolism of bone and cartilage. All current treatments are considered as symptomatic therapy, since they have little or no effect on the underlying pathophysiology.

Acute impact injuries, Bone Marrow Lesions and BME

There is a substantial body of research demonstrating that BME lesions are associated with acute joint injury, cartilage loss, and progressive joint degeneration, as evidenced by the following studies:

1. Acute-impact joint injuries initiate a sequence of biologic events that cause the progressive joint degeneration that leads to a condition known as Post Traumatic OA(PTOA) (J Orthop Res 2011, 29:802–809).
2. Joint injuries cause striking alterations in synovial fluid levels of compounds that may contribute to joint degeneration, including pro-inflammatory cytokines, and mediators such as tumor necrosis factor alpha (TNF-a), interleukin (IL)-1, nitric oxide, and matrix metalloproteinases (MMPs) (Biorheology 2006, 43:517–521).
3. People who suffered knee ligamentous and meniscal injuries demonstrated a 10-fold increased risk of OA as compared with those who did not have a joint injury (Sports Med 1999, 27:143–156) and (Arthritis Rheum 1998, 41:687–693).
4. Patients with a torn ACL develop OA of the knee irrespective of current treatment (BMJ 2013:346:f232 doi: 10.1136/bmj.f232).
5. Many acute joint injuries are characterised by Bone Marrow Lesions (BML's) as detected by Magnetic Resonance Imaging (MRI).
6. The occurrence and progression of BML's have been shown to be associated with progression to OA and joint pain (Osteoarthritis and Cartilage 2012, 20:1514-1518).
7. BML's are associated with structural changes in bone and cartilage that lead to joint pain and OA (Rheumatology 2010, 49:2413-9).
8. Patients who present with BML were nearly 9 times as likely to progress towards total knee replacement (Skeletal Radiol 2008, 37:609–617).

There is a growing link between BME and joint cartilage degeneration that leads to OA. This is evidenced by the above studies. It is believed there is chronic health impacts associated with untreated BME, with patients having a significantly greater likelihood of developing OA. Industry specialists believe that nearly 100% of people who have had an ACL injury will develop OA at some point in their lives.

To date, current treatment options are largely aimed at relieving symptoms of BME, with all failing to resolve the underlying pathology of BME.

Zilosul® injectable pentosan polysulfate sodium (iPPS)

Paradigm's injectable form of PPS trademarked as Zilosul® is produced by bene pharmaChem GmbH (see p.22). Zilosul® is used in all Paradigm's clinical trials, and is the only known compound that addresses multiple pathways to treat BME.

Zilosul® has demonstrated it has the characteristics to treat BME, which are not present in alternate options. Competing treatments have failed to capture market share due to limited efficacy, and sub-standard safety profiles, enabling Zilosul® to establish itself as the market leader if successful in phase 3 clinical trials.

The emergence of BME is understood to be the initial signal demonstrating the pathophysiology of cartilage breakdown. The synovial fluid of patients with an acute injury and consequent BME, present substantial increases in inflammatory cytokines (principally TNF alpha and IL-1), cartilage degrading enzymes (MMP's and ADAMTS5) and signs of hypercoagulability. To effectively address this pathophysiology, a compound must have multiple pharmaceutical actions, namely, anti-inflammatory (importantly Anti TNF alpha and anti IL-1), block matrix metalloproteinases (MMP's and ADAMTS), and improve microcirculation. It has been published in a variety of peer-reviewed studies that PPS has the aforementioned pharmaceutical actions, supporting the rationale for use treating BME.

Zilosul® has demonstrated:

- The inhibition of cartilage degrading enzymes that are released post-acute injury.
- Anti-inflammatory effects, whilst blocking the effects of the pro-inflammatory cytokine TNF and pro-inflammatory interleukin IL-1 beta.
- Antithrombic and antilipadaemic effects, which enhance microvascular circulation in the subchondral bone. Improving the microvascular circulation believed to be a critical factor in resolving BME.
- To be safe and well tolerated in patients.

PPS is likely to reduce swelling (anti-inflammatory) as well as improve blood flow greatly assisting the healing process.

Pain Scale - WOMAC & KOOS

A basic knowledge of the pain and function scoring frameworks is required to adequately understand how subjects participating in clinical trials accurately report their experiences.

Note, Phase 2b OA clinical trials used the KOOS pain scale. Phase 3 OA clinical trials will use WOMAC. Recent SAS results have used WOMAC (having previously used KOOS. The Expanded Access Program (EAP) (FDA) used WOMAC (see p.2 for EAP results).

KOOS - The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a questionnaire designed to assess short and long-term patient-relevant outcomes following knee injury. KOOS is self-administered, and assesses five outcomes: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. The KOOS meets basic criteria of outcome measures and can be used to evaluate the course of knee injury and treatment outcome. KOOS is patient-administered, the format is user-friendly and it takes roughly 10 minutes to complete.

Scoring instructions

The KOOS's five patient-relevant dimensions are scored separately: Pain (nine items); Symptoms (seven items); Activities of daily living function (ADL) (17 items); Sport and recreation function (five items); quality of life (four items). A Likert scale is used and all items have five possible answer options scored from 0 (no problems) to 4 (extreme problems) and each of the five scores is calculated as the sum of the items included.

Interpretation of scores

Scores are transformed to a 0–100 scale, with zero representing extreme knee problems, and 100 representing no knee problems (common in orthopaedic scales and generic measures).

WOMAC - The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used in the evaluation of hip and Knee OA. It is a self-administered questionnaire consisting of 24 items divided into 3 subscales. The test questions are scored on a scale of 0-4, which correspond to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4).

The scores for each subscale are summed, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical function. Usually a sum of the scores for all three subscales gives a total WOMAC score, however there are other methods that have been used to combine scores. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright.
- Stiffness (2 items): after first waking and later in the day physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

Patient global impression of change (PGIC) The self-report measure patient global impression of change (PGIC), reflects a patient's belief about the efficacy of treatment. PGIC is widely used in chronic pain clinical trials. PGIC is a seven point scale depicting a patient's rating of overall improvement. Patients rate their change as 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', or 'very much worse'.

KOOS pain questionnaire	Rating scale	WOMAC pain questionnaire	Rating scale
P1 How often do you experience knee pain	0–4 where 0 = never, 4 = always	–	–
P2 Pain twisting/ pivoting on your knee	0–4 where 0 = never, 4 = extreme pain	–	–
P3 Pain straightening knee fully	0–4 where 0 = never, 4 = extreme pain	–	–
P4 Pain bending knee fully	0–4 where 0 = never, 4 = extreme pain	–	–
P5 Pain walking on flat surface	0–4 where 0 = never, 4 = extreme pain	Pain walking on flat surface	0–4 where 0 = never, 4 = extreme pain
P6 Pain going up and down stairs	0–4 where 0 = never, 4 = extreme pain	Pain going up/ down stairs	0–4 where 0 = never, 4 = extreme pain
P7 Pain at night while in bed	0–4 where 0 = never, 4 = extreme pain	Pain at night	0–4 where 0 = never, 4 = extreme pain
P8 Pain sitting or lying	0–4 where 0 = never, 4 = extreme pain	Pain sitting/lying	0–4 where 0 = never, 4 = extreme pain
P9 Pain standing upright	0–4 where 0 = never, 4 = extreme pain	Pain standing upright	0–4 where 0 = never, 4 = extreme pain
KOOS Pain score	**0-100 where 100 = no pain, 0 = extreme pain**		**0-20 where 0 = no pain, 20 = extreme pain**

Source: Paradigm

Kellgren and Lawrence system - Classifies the severity of OA using five grades.

- **grade 0 (none)**: definite absence of x-ray changes of OA.
- **grade 1 (doubtful)**: doubtful joint space narrowing and possible osteophytic lipping.
- **grade 2 (minimal)**: definite osteophytes and possible joint space narrowing.
- **grade 3 (moderate)**: multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
- **grade 4 (severe)**: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

Special Access Scheme (SAS)

Zilosul® has been accessible since October 2017 through the Therapeutic Goods Administration (TGA), via the Special Access Scheme (SAS) pathway. As of today over 550 patients have completed this treatment. Patients have received a similar dosing regimen to Paradigm's 110 participant Phase 2b OA randomied, double-blind, placebo controlled, clinical trial, which was completed successfully. Results can be viewed on page 17.

When a pharmaceutical agent is used in patients outside a clinical trial it is referred to as Real World Data (RWD), RWD provides important clinical evidence (safety and efficacy), on how the agent works in people outside the confines of a clinical trial population, known as Real World Evidence (RWE).

SAS Results provide important RWE, which can be used in combination with randomised controlled clinical trials to support product registration for repurposed pharmaceuticals under the US FDA 505(b)(2) regulatory pathway.

Using KOOS scoring (refer p.11) 51.1% (average) reduction in pain scores (using Numeric Pain Scale (NRS) pain score), observed with iPPS patients (n:205) with Knee OA, continues to demonstrate superiority over the 30% average pain reduction reported for opioid treatments for chronic pain in OA of the knee and hip (refer p.4 Opioids).

On aggregate, of 205 patients treated prior to 28th May 2020, 89.7% (under KOOS) responded with a reduction in joint pain and 91.2% an improvement in knee function. Pain scores reduced over 51.3% and function improved 58.4% (on average) in patients with Knee OA. RWE across 205 patients (using KOOS) with Knee OA, who failed standard of care, responded with an average reduction in excess of 50% from baseline.

Comparative effects of iPPS therapy against opioid treatments imply that patient reported data shows evidence of clinically meaningful improvements in chronic pain. 'Clinically meaningful' reduction of chronic pain is defined to be between 25-30% pain reduction.

Patients

SAS patients 118 males/ 87 females, with a median age of 56.5 years (18 to 84 years), clinically diagnosed with OA and subchondral BML's (as determined by MRI), at the onset of iPPS treatment:

- All patients were symptomatic with OA pain for at least six months, and had failed current standard of care, i.e. treatment with analgesics, NSAID's, or corticosteroids.
- 70% of the patients had moderate to severe BML's, with a size ranging from five millimetres, to more than 20 millimetres in diameter.
- 30% had lesions less than five millimetres in diameter.

Patients were administered two PPS injections per week for three, four, or six weeks (a total of six, eight or twelve injections). Patients were followed at four, to six weeks following last dosage. During the course of iPPS treatment, patients did not receive NSAID's or corticosteroid treatment.

April 2020 - First SAS results using phase 3 WOMAC scoring

SAS results of a further 76 patients (n: 34 6th April / n: 42 1st October) with encouraging RWD ahead of phase 3 OA clinical trials using endpoints:

1. Reduced WOMAC pain from baseline (refer p.11 WOMAC definition).
2. Improved patient global impression of change (PGIC) at as secondary endpoint (refer p.12).

Results 6th April showed chronic pain response as measured by WOMAC pain score demonstrated a mean reduction of 44.9%. Consistent with previously reported reductions using the NRS pain score measure.

Patient's showed that the phase 3 iPPS formulation was well tolerated and demonstrated a continued excellent safety profile with no serious AE's. These results provide important RWE and inform us of anticipated responses in everyday clinical practice.

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

1st October 2020 - Further results continue to outperform

WOMAC pain questionnaire	Mean baseline value (95% confidence interval)	Mean post-treatment value (95% confidence interval)	Mean % reduction in pain (95% confidence interval)
1. Pain walking on flat surface (0-10)	5.8 (5.3, 6.2)	3.1 (2.6, 3.6)	45.57 (54.4, 36.8)
2. Pain going up/downstairs (0-10)	7.1 (6.7, 7.6)	4.3 (3.7, 4.9)	39.1 (49.6, 29.2)
3. Pain at night (0-10)	4.8 (4.1, 5.4)	1.9 (1.4, 2.3)	63.75 (73.2, 54.4)
4. Pain sitting/lying (0-10)	4.2 (3.7, 4.7)	1.9 (1.4, 2.3)	56.12 (69.8, 42.5)
5. Pain Standing upright (0-10)	5.3 (4.8, 5.8)	2.5 (2.1, 3.0)	49.83 (61.1, 38.5)
WOMAC pain subscale (0-50)	**27.1 (25.0, 29.3)**	**13.6 (11.3, 15.9)**	**47.30 (59.7, 34.9)**

Source: Paradigm

SAS WOMAC Pain Reduction at week 12 (N=76)

Patients were administered two injections of PPS per week for six weeks (a total of 12 injections), and were reviewed at six weeks following the last dosage. During the course of PPS treatment, patients did not receive NSAID's or corticosteroid treatment.

(All dollars referred to in this report are in Australian dollars unless otherwise stated)

Comparisons

Opioid use has resulted in significant dependency issues (p.4) with non-addictive alternatives being scarce. Zilosul® is a strong candidate to fill a needed gap in treatment options available to clinicians. IPPS has effectively the same mean reduction in pain compared to Tramadol, without the addictive side effects.

Comparing iPPS WOMAC pain reduction with daily opioids (opiate once a day) for 12 weeks.

Mean reduction in WOMAC pain score week 12			
Paradigm results iPPS under SAS	45%	The WOMAC pain score reduction of treatment with Zilosul® from baseline to 12 weeks is 45%. This means the pain reduction result is still present 6 weeks after the last Zilosul® injection.	**Source:** Paradigm data
Tramadol (Opiate) 300 mg	46%		**Source:** Fishman RL et al Efficacy and safety of 12 weeks of osteoarthritic pain therapy with one-daily tramadol (Tramadol Contramid OAD).2007. J Opioid Manag. 2007 Sep-Oct;3(5):273-80.
Tramadol (Opiate) 300 mg	43%		

Source: Paradigm

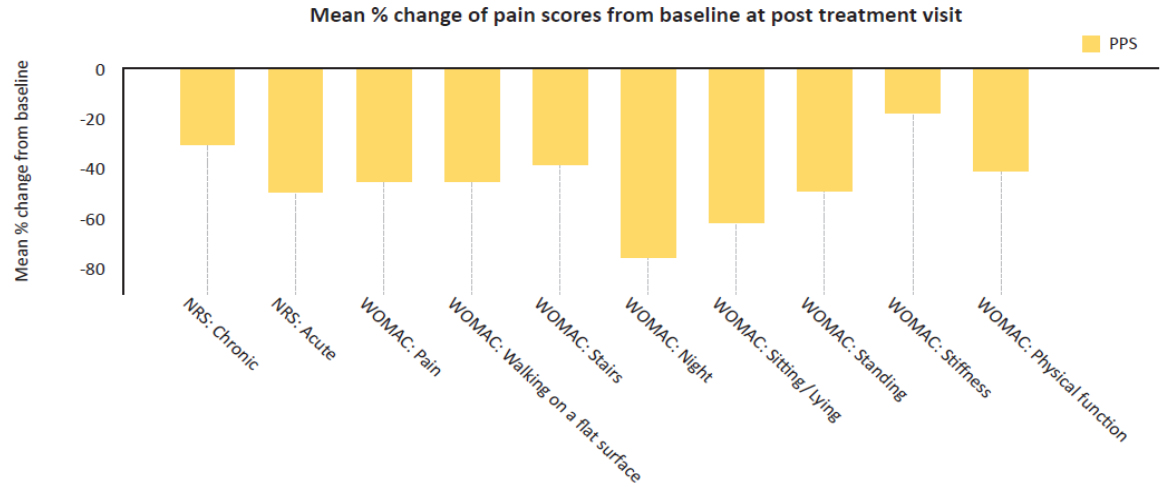
Patient global impression of change (PGIC): Is a self-reported measure that reflects the patient's belief about the overall efficacy of the treatment. Patient's rate their experience from 'no change', or 'condition worsened', through to 'considerable improvement that has made all the difference', (see p.12). The table below shows the PGIC Scores for 34 patients under the TGA SAS.

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

Source: Paradigm (below)

April 2020 PGIC results

85.7% (30 out of 34) SAS patients had reported PGIC of moderate, to definite and considerable improvement in their OA condition with Zilosul®.



(All dollars referred to in this report are in Australian dollars unless otherwise stated)

SAS Success Stories

Greg Williams - Is a former Australian rules footballer who represented Geelong, the Sydney Swans and Carlton in the Australian Football League during the 1980s and 1990s. A midfielder, he is a dual Brownlow Medal winner and at his peak was the then highest-paid player in the history of the sport. Greg is 57 years of age.

Three years ago Greg was told he was required to have a knee replacement. He spoke to Andrew Walker who introduced Paul Rennie. Subsequently Greg opted to try PPS treatment, and had two injections every four weeks (8 total), and states his pain went away in three weeks. Previously he was in a great deal of pain, and had difficulty walking, couldn't play golf, struggled getting out of bed, and general movement around the house was difficult. Prior to treatment, Greg had 10 arthroscopies on his knees, with bone on bone issues. Now he states an 80% improvement in pain, can play golf again (couldn't play any sport previously, due to pain during and after). Greg was 50 years of age when he had his first treatment, having his second treatment 18 months later, he was feeling ok, but did not want the pain to come back. Greg remains pain free stating ''PPS has changed my life, taking painkillers and anti inflammatory drugs every day is not a good place to be, I was feeling like crap all the time''. Greg is playing tennis again, and is the most active he has been in years. Greg reports no AE's, is active in society, and details a dramatic improvement in his standard of daily living, and quality of life. Greg no longer requires a knee replacement.

Andrew Walker - Is a former Australian rules footballer who played with the Carlton Football Club in the Australian Football League. Andrew is 34 years of age.

Andrew had his first treatment in 2016, after the Carlton Football Club doctor put him in contact with Paul Rennie. Andrew's condition prior, ''I could not walk from the kitchen to the bathroom, could not do anything, and was booked in for a partial knee replacement. I was 29/30 at this stage''. Andrew stated that within 2-3 months of completing PPS treatment he began to feel much better, and during the past four years has played over 70 division one games in both the GVFL and Northern League. Andrew had a second round of treatment three years later in 2019, but states ''he wouldn't have if he was not still playing at a high level, my pain scores went right down, from 10 out of 10 for severity of pain, to 1 and sometimes nothing, with less fluid around the knee, the best outcome has been the ability to strengthen the joint again, this is something that needs to be discussed and reported in more detail''. Andrew no longer needs an operation on his knee.

Michael Boileau – Is a former ice hockey professional representing Australia in 1973-79. Michael is 74 years of age.
Michael sated, ''PPS has been the greatest thing I have ever had'', Don Angus (Michaels doctor) stated, "Michael was walking better than anyone he has ever seen with the product given the severity of his scans prior to PPS treatment''. Michael had his right knee replaced, and 18 months ago learned he required the same for his left knee. Michael opted for PPS treatment, having no pain since, he can ride his bike again and plays golf twice a week. 'The product is sensational', Michael had two injections every six weeks (12 injections), and stated ''I have no pain in the left leg at all to this day, I just can't believe it, walking freely considering the knee was bone on bone. The pain before was like a bad tooth ache, I would get up during the middle of the night, I haven't had that since''. Michael stated ''he wants another dosage so the pain doesn't come back, doesn't want another knee replacement''. Michael no longer needs a knee replacement for his left knee.

Wayne Richardson - Is a former Australian rules footballer in the Victorian Football League. Wayne spent most of his 277-game, 323 goal VFL career between 1966 and 1978 as either a rover or ruck-rover, and captained the Magpies from midway through the 1971 season until 1975.

Wayne was treated with PPS in September 2019, and had 12 injections over 6 week period. MRI scans determined he had OA of the knee. Wayne was 73 when he started PPS treatment, and similarly to others required a knee replacement. Wayne stated ''it took a month or so for the treatment to settle. Getting out of bed and walking was a problem, now I can play golf, walk, and ride again no problems''. Wayne stated ''no return of pain, with walking up steps and long distances not a problem anymore''. Wayne no longer requires a knee replacement.

Mark Riccuito - is a former Australian rules footballer who played for the Adelaide Football Club in the AFL. Mark was consistently considered one of the best midfielders in the competition during the early 2000s (decade), Ricciuto shared the 2003 Brownlow Medal with Nathan Buckley and Adam Goodes, and was selected in the All-Australian team for four consecutive seasons between 2002 and 2005, captaining the side in both 2004 and 2005

Mark is 45 years of age and has had two PPS treatments. Mark stated he ''doesn't run much anymore, and doesn't want to get sore again, having no pain at all doing general day to day stuff''. Marks condition prior was stiffness and swollen joints, at times with significant inflammation based on the intensity of exercise. Mark was told he would need a knee replacement, as there was nothing further doctors could do for him, having had several arthroscopies over the course of his career. The past three years, Mark has been able to perform all his requirements of daily living pain free. Mark stated he had his second round of PPS treatment six months ago for a top up, ''didn't get sore again, just didn't want the pain to get back to what it was in the old days. Quick jab in the arm, takes five minutes, around the corner from work''. Mark no longer needs a knee replacement.

Brett Sands - Widely regarded as one of the most talented barefoot water-skiers to ever represent Australia, Brett wore the green and gold for the first time at age 14, to coming out of retirement and winning three gold medals at the world championships in Canada in 2018.

Brett Sands is now one of the most experienced Instructors globally. Brett was not in immense pain and did not have a history of knee problems. However, in recent years Brett developed aching pain in both knees, whether it be walking or running. He states his treatment was effortless and painless and has made an immense difference to the point where he trains 12-14 hours a week at high intensity and has no discomfort to speak of. Brett had his treatment in October 2019 and has no pain or stiffness. He mentioned his ancles have improved as well.

Doctor Roger Patterson - Is the co-founder of Sportsmed SA, a leading healthcare provider. Roger is a specialist in the field of anterior cruciate ligament biomechanics and reconstruction, patella- femoral pain and instability, meniscal and chondral injuries and repair, knee replacement, and ankle ligament injuries and sequelae.

Doctor Patterson stated ''we were all very skeptical at the start, nothing can work like that! There was a limited take-up to begin with, but as word of mouth reports started coming through prior to official results, everyone started getting on board, we were hearing up to, and possibly more than six months pain relief for two thirds or more of patients, clearly this was no placebo. We had no idea at the time as to reasons why, but started looking further to understand. There is large cohort of patients who are past the treatment of arthroscopy, but are not ready for a knee replacement, it's this group of sufferers which is huge, and stand to benefit from PPS. I will be very surprised if the product doesn't hit the market with a bang, given what we have seen in phase 2 studies. PPS is a unique product, what it does in the joint is like nothing we have seen before, it alters the biochemistry for the good, we are starting to believe that PPS improves the joint, which nothing has ever done before. PPS can potentially fill a massive black hole, and overall I am very excited to see what it can do. As a shareholder I am excited of course, but as a doctor equally as excited, as it gives us a more reliable product than anything we currently have at our disposal. There is a crying need for an acceptable alternative, which is evident in the opioid crisis. Sufferers are in desperate need of an alternative, if it's shown to work, and is cost effective, there will be huge demand for it. Alternate products we use currently are A$475 for a single injection, which patients can have every eight months, however these treatments have very limited efficacy. PPS needs to be cost effective, sufferers will take opioids because they are cheaper.

Doctor Donald Angus – Founder of Health on Grange (1978)

Doctor Angus stated ''I have been very impressed with the efficacy of PPS. I had a patient come in with two walking sticks, shortly after treatment he was playing golf without a buggy, an incredibly dramatic recovery. I had another patient who benefited from PPS in the finger joints, rather than for the knee. All patients I have seen there has not been one person who has not benefited and believed the treatment to be worthwhile. PPS appears to allow regrowth of cartilage, which normally if you lose it, it's gone forever''. Dr Angus assists with knee replacement procedures, being witness to many knees devoid of remaining cartilage, he states ''that if this can be avoided then it is a great outcome for the patient, and all concerned''. Doctor Angus had nothing negative to say, having been administering PPS injections for the past 18 months. Dr Angus was clearly very impressed by the efficacy of PPS. ''PPS is not much different from a flu injection from pain perspective, and it takes about 4-5 injections before patients begin reporting an improvement, it would be great to treat the cause of pain rather than masking it with Panadeine Forte, I shudder every time I need to write a script, there is nothing worse than hiding the symptoms''.

FDA Expanded Access Program (EAP)

EAP (or 'compassionate use'), provides a pathway for doctors and patients to gain access to investigational drugs, biologics, and medical devices used to diagnose, monitor or treat patients with serious diseases or conditions for which there are no comparable or satisfactory therapy options available outside of clinical trials.

Through the EAP, Paradigm submitted a new drug application (IND) for PPS to treat 10 retired NFL players with knee OA(KOA). All patients had concurrent bone marrow lesions (BML's), and failed to respond to current standard of care. The U.S. FDA provided clearance for this program to proceed in September 2019.

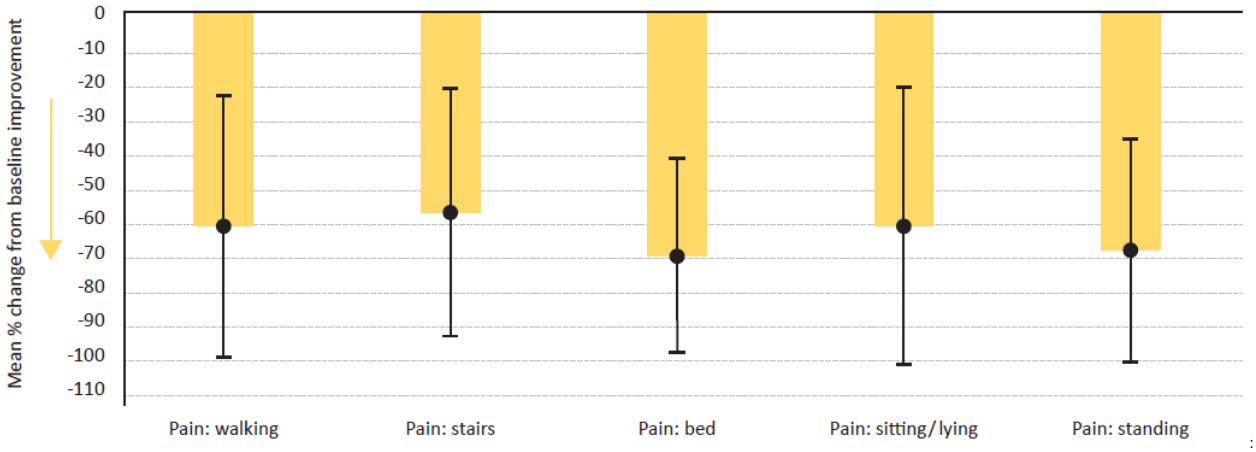
Arthritis is over three times more prevalent in retired NFL players than in the general U.S. population.

Results: Paradigm's Zilosul® demonstrated a 65% reduction in pain (from baseline), 12 weeks following initiation of treatment.

Comparative treatments are half as effective with marginal improved mobility. Oral NSAID treatment, and potent oral opioids (oxycodone), reduce pain with similar effect (around a 30% reduction). Zilosul® has demonstrated a significant improvement in pain, reducing effects over current therapies (65% vs 30%). Both NSAID's and opioids have undesirable side effects.

Each patient enrolled in the program was screened to measure their baseline pain scores under the WOMAC OA index and were evaluated with MRI scans to determine the presence of BMEL's within the knee joint.

PPS treatment demonstrated reduction in WOMAC pain scores at 12 weeks after the initiation of treatment.



Source: Paradigm

Shows average WOMAC pain reduction (5 items) for 10 patients treated with PPS under the FDA EAP.

WOMAC pain questionnaire	Mean baseline value (95% confidence interval)	Mean post-treatment value (95% confidence interval)	Mean reduction in pain (percentage) (N=10 patients)
1. Pain walking on flat surface	5.5 (3.8, 7.2)	1.8 (0.3, 3.3)	**61.64 (99.10, 24.18)**
2. Pain going up/downstairs	7.5 (5.9, 9.1)	2.8 (1.3, 4.3)	**57.59 (93.39, 21.79)**
3. Pain at night	4.5 (2.7, 6.3)	1.1 (-0.1, 2.3)	**69.67 (97.76, 41.58)**
4. Pain sitting/lying	4.9 (3.0, 6.8)	1.3 (-0.2, 2.8)	**61.57 (101.59, 21.55)**
5. Pain standing upright	5.8 (4.1, 7.5)	1.7 (0.4, 3.0)	**68.27 (100.31, 36.23**
WOMAC pain subscale	28.2 (20.3, 36.1)	8.7 (2.2, 15.2)	**65.73 (97.08, 34.38)**

Source: Paradigm

A company presentation and video detailing the patient's experiences can be can be found at the following links:

- https://paradigmbiopharma.com/investors/presentations/
- https://krld.radio.com/media/audio-channel/former-nfl-players-seeing-success-with-new-drug-for-knee-pain

Phase 2b OA clinical trial

Phase 2b OA clinical trials was a double-blind, placebo-controlled, multi-centre, clinical trial with two clearly defined endpoints, evaluating the effects of iPPS on knee pain and mobility in patients with KOA and BMEL's. Previous SAS results have illustrated a regression in the prevalence of BME, reducing pain with no AE's, showing PPS has the capability to be a DMOAD.

Pleasingly, on the 18th December 2018, Paradigm announced all endpoints of its Phase 2b clinical trial were achieved. Meaningful and statistically significant results between iPPS and placebo were demonstrated across the total subject population. Notably, highly clinically meaningful and statistically significant results were demonstrated in the NRS pain = 4-6 stratum.

Most importantly, PPS continues to be safe, well tolerated and clinically meaningful, as demonstrated by the higher number of subjects with a greater than 50% reduction in pain from baseline.

Chart 1

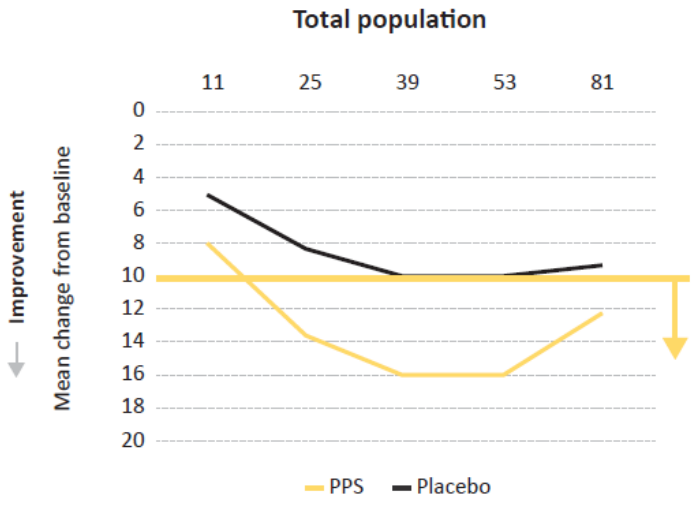
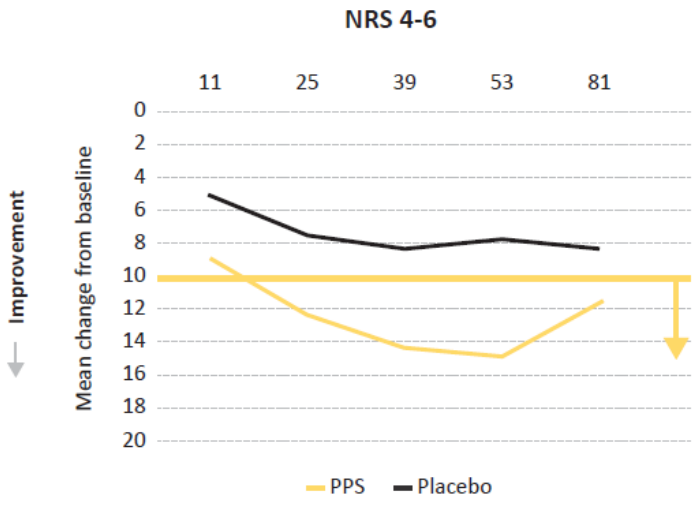


Chart 2



Source: Paradigm

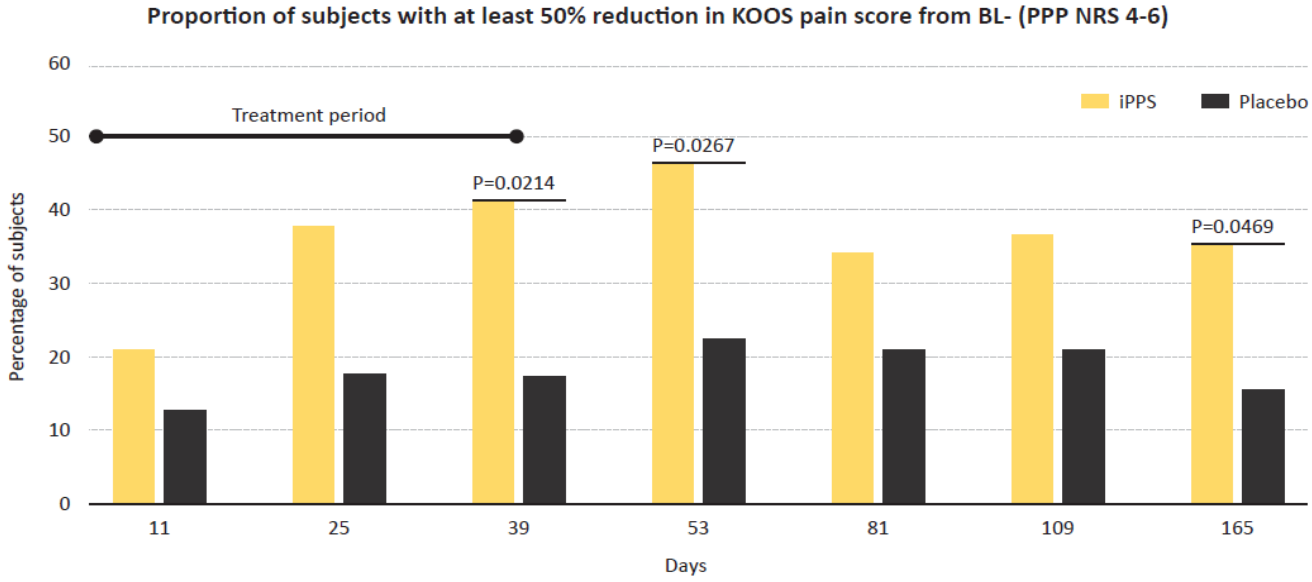
A change of 10 from baseline is considered a clinically meaningful change in KOOS Pain Subscale (gold line).

Chart 1: Mean change in KOOS pain from baseline – Total population: Paradigm demonstrated a statistically significant mean change in KOOS pain from baseline versus placebo at day 39, and day 53.

Chart 2: Mean change in KOOS pain from baseline – NRS: 4-6 Strata: In the NRS: 4-6 strata Paradigm demonstrated a statistically significant mean change in KOOS pain from baseline versus placebo at day 39, and day 53.

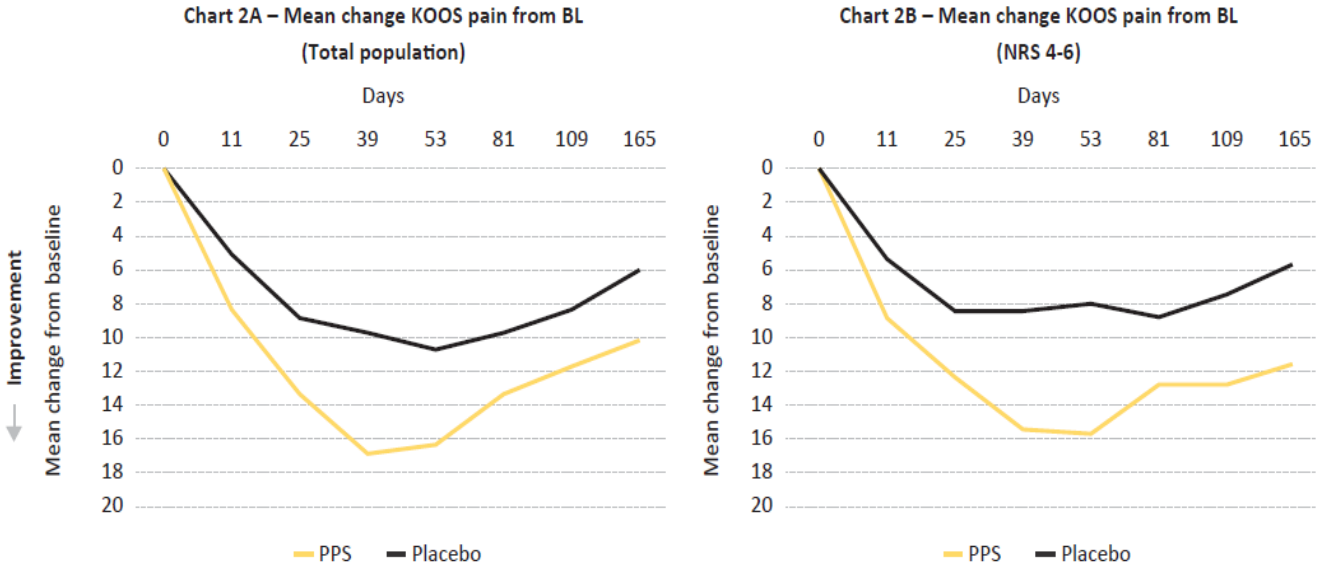
At day 165 (shown below), NRS Pain = 4-6 strata 46.2% of subjects receiving iPPS showed a greater than 50% reduction in pain from baseline, compared to 22.5% of subjects receiving placebo under KOOS pain subscale. This is statistically significant at p=0.026, and clinically meaningful, i.e. subjects received a pain reduction of 50% or more.

(All dollars referred to in this report are in Australian dollars unless otherwise stated)



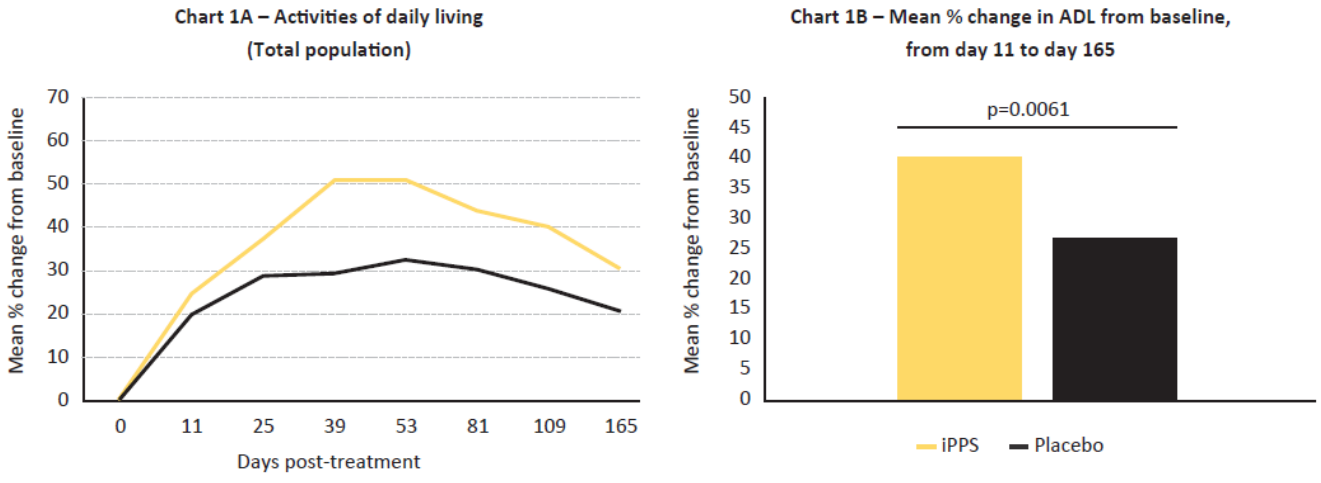
Source: Paradigm

From a PGIC perspective, a 30% reduction in pain is classified as being 'very much improved' (equivalent to a two point change on a sale of 0 to 11, i.e. 6/10 to 4/10). In this instance, Paradigm chose to use a higher metric of 50 % reduction in pain. This rating illustrates a highly clinically meaningful effect and known to represent a significant change in the intensity of pain.



Source: Paradigm

Mean change in KOOS pain score (from baseline) at day 165 for both the Total population and the NRS 4-6 stratum. Subjects receiving iPPS continue to show a greater than 50% reduction in KOOS pain score. These results are clinically meaningful and statistically significant (p=0.0469) over placebo.



Source: Paradigm

Chart 1C – Activities of daily living (NRS 4-6)

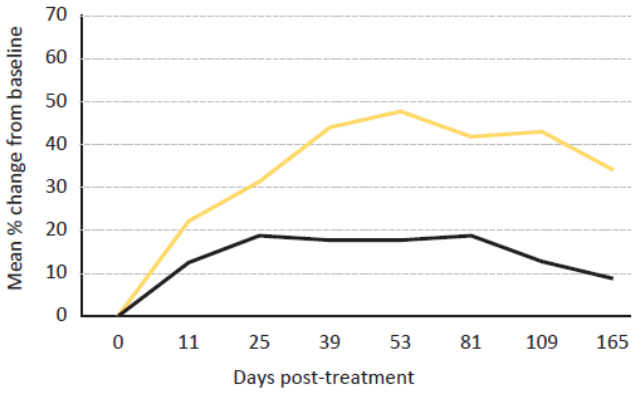
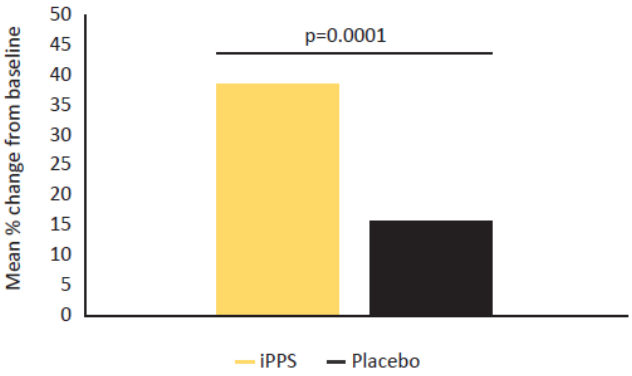


Chart 1D – Mean % change in ADL from baseline, from day 11 to day 165 (NRS 4-6)



Source: Paradigm

At day 165 the Mean % change ADL for PPS (39.6%) versus placebo (26.6%), being statistically significant (p=0.0061). ADL showed improved knee function confirming PPS is durable over placebo at six months with a greater than 50% reduction in KOOS pain score.

Disease modifying osteoarthritis drug potential (DMOAD)

MRI results at day 53 show significant regression in BME, indicating that PPS has the potential to be a DMOAD. MRI demonstrated that a 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 statistically significant over placebo (P=0.03).

BML appear as increased signal intensity within the bone marrow

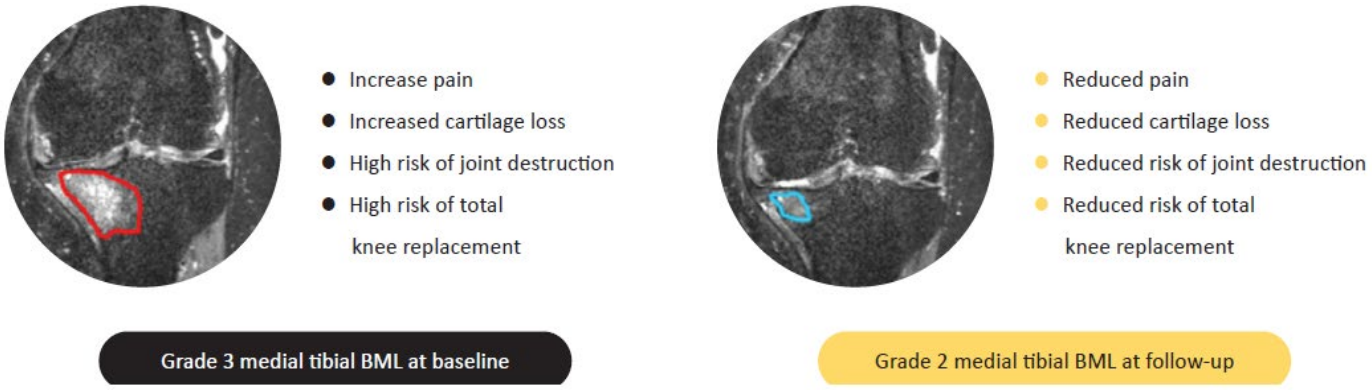


Chart 4A – Median % change from baseline BML volume in knee (total population)

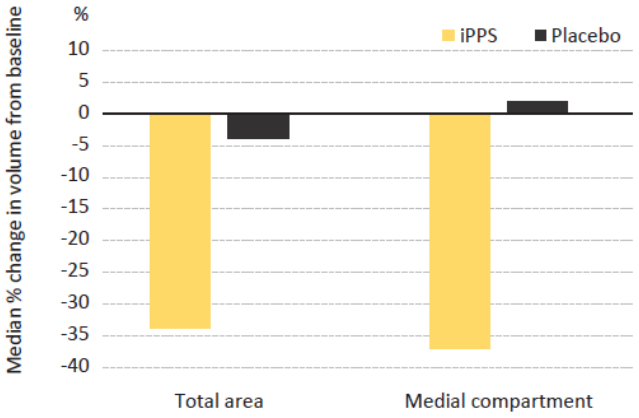
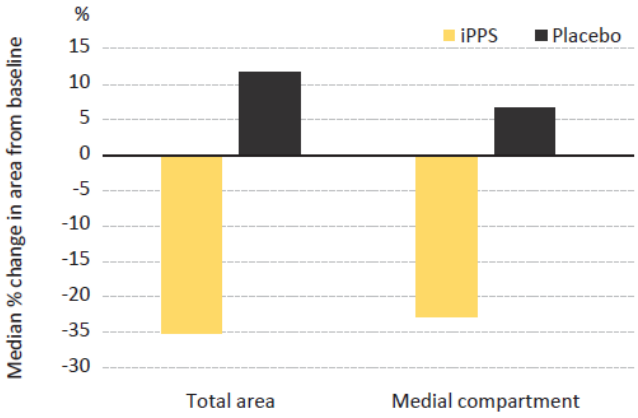


Chart 4B – Median % change from baseline BML area in knee (total population)



Source: Paradigm

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

Chart C

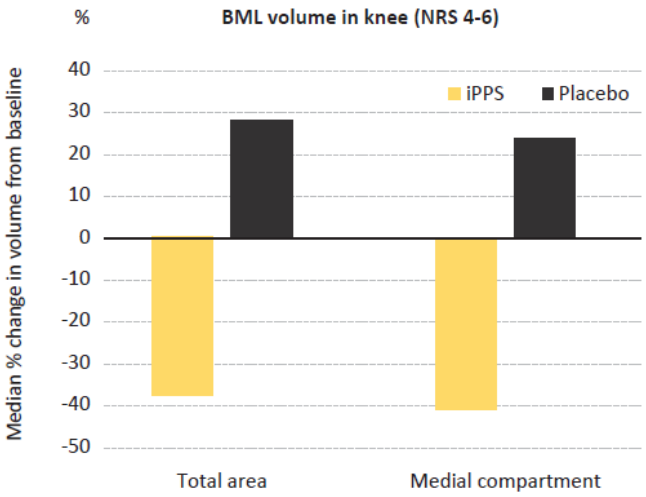
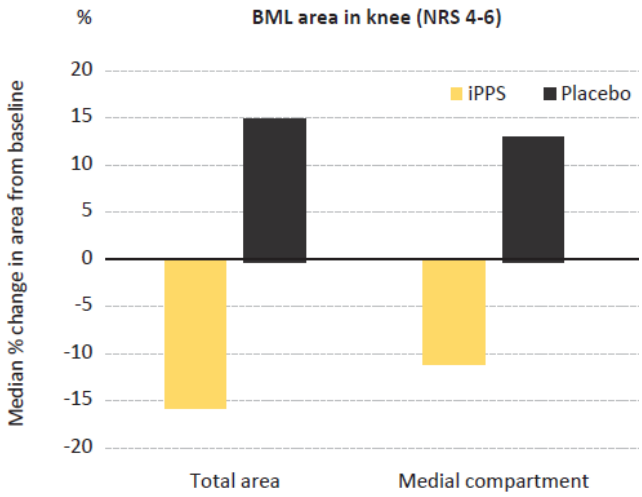


Chart D



Source: Paradigm

- iPPS treatment reduced BML volume by (-)37.3% in contrast to an increase of (+)28.5% in the placebo. Chart C
- iPPS treatment reduced BML area by (-)15.6% in contrast to an increase of (+)15.2%, in the placebo group. Chart D

What this means

Both durable pain reduction and ADL (improved knee function and mobility) data have returned statistically significant and clinically effective outcomes. Additionally, the reduction in grade, volume, and area of BML at day 53 is evident. These results are compelling, and suggest that PPS is likely to be effective in halting the progression of BML, and in many cases showing regressive properties. As mentioned previously, a successful phase 3 is not dependant on PPS having DMOAD capabilities, however indications at day 53 certainly illustrate its potential. MRI data shows the reduction in grade, volume, and area of BML are clinically meaningful, and statistically significant over placebo. Pleasingly, the safety of PPS is once again confirmed, unlike Paradigm's closest competitor tanezumab, (anti-NGF), has reported to rapidly progress OA and osteonecrosis. If Paradigm's phase 3 clinical trials are to achieve the same results, it would be highly likely for iPPS to be commercialised as a first in class, front line treatment for OA.

Paul Rennie, Paradigm Biopharmaceuticals CEO:

"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."

Synovial fluid biomarker study in participants with Knee OA

Paradigm on the 18th of February 2021 received ethics approval for its Phase 2 clinical trial to evaluate the treatment effects of PPS against placebo on synovial fluid biomarkers in participants with KOA pain. The randomised, double-blind, placebo-controlled phase 2 study will investigate PPS or placebo treatment in a total of 60 (n=60) patients. Participants with Kellgren-Lawrence grade 2, 3 or 4 and have OA pain will be enrolled and randomised 1:1 to receive either PPS (n=30) or placebo (n=30). Participants will receive twice weekly subcutaneous injections for six weeks.

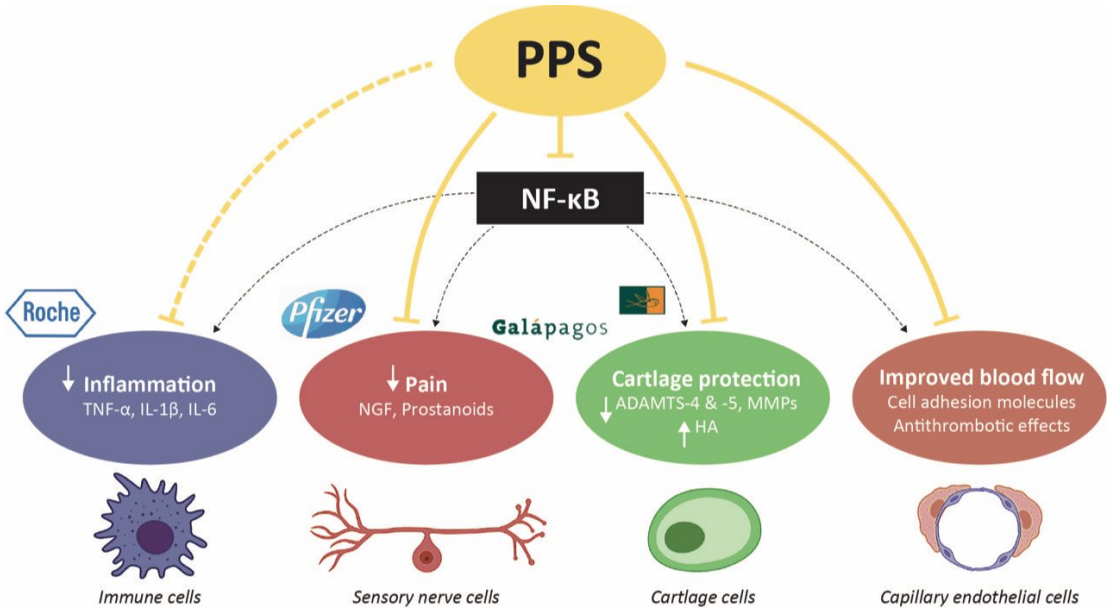
Previous trials have shown clinical evidence demonstrating PPS reduces pain by reducing the production of NGF, decreases inflammation by down-regulating inflammatory cytokines, and protects cartilage by downregulating degrading enzymes and repairing bone through improved blood flow. These multiple modes of action indicate that PPS has potential to be more than just pain medication.

Primary Endpoint

To identify the change from baseline at day 56 (two weeks post final injection) in one or more synovial fluid biomarkers, including but not limited to: C-Terminal Telopeptide (CTX) -II; Nerve Growth Factor (NGF); Interleukin (IL) -1 β; Tissue inhibitor matrix metalloproteinase 1 (TIMP-1); CTX-I; and Type II collagen fragment (C2C); Cartilage Oligomeric Matrix Protein (COMP); Tumour Necrosis Factor Alpha (TNFα);IL-6; A disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS5); Aggrecan ARGS fragment;

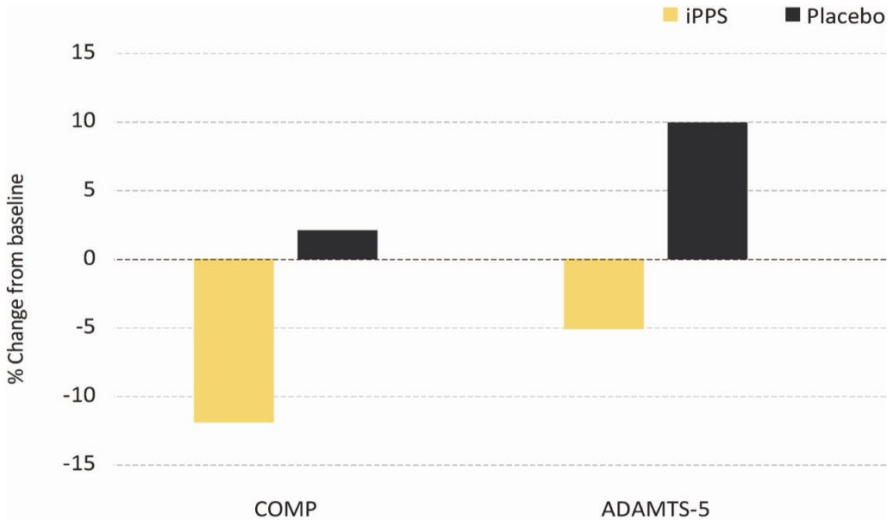
This study hopes to provide evidence that certain biomarkers are more prevalent in the synovial fluid of symptomatic OA patients with radiographic evidence of joint damage, and determine if biomarker concentrations change in the synovial fluid with PPS treatment, and to assess possible disease modifying effects of PPS on patients with Knee OA pain.

Title TBT



Source: Paradigm

As shown in the below table, previously reported exploratory endpoint data for Phase 2b OA clinical trial (August 2019) demonstrated a reduction of two key biomarkers (COMP and ADAMTS5) in the serum which are associated with cartilage degradation, in patients treated with Zilosul® compared to increase levels placebo.



Source: Paradigm

Biomarker analysis in synovial fluid samples will provide key scientific evidence as to whether PPS is acting locally in the knee joint of OA subjects and may further support the multiple actions of PPS in OA. The biomarkers analysed will include inflammatory cytokines (TNF-α, IL-1β and IL-6); pain mediator NGF and cartilage degrading enzymes ADAMTS4 and 5 in association with other molecular biomarkers potentially associated with disease modification.

Secondary and Exploratory Endpoints

1. Radiographic changes in the bone and joint - structural changes from baseline of the participants joint using MRI to day 168. Changes in BML area and volume will be assessed as well as structural changes to the joint. This data will add to previous evidence on reduction of BML's from baseline to day 53 following PPS treatment in its Phase 2b clinical trial.
2. Changes at baseline to 6 months in one or more synovial fluid biomarkers – Paradigm previously reported data from the Phase 2b clinical trial of a reduction from baseline of COMP and ADMTS-5 levels in the serum to day 53 following PPS treatment. Changes of one or more synovial fluid biomarkers from baseline out to day 168 will be measured to provide Paradigm important data on the durability of effect of PPS against placebo.
3. Correlation between synovial fluid biomarker changes and clinical outcomes - synovial fluid biomarkers will be assessed to investigate whether the down regulation of certain biomarkers post PPS treatments is related to patient reported outcomes compared to placebo.
4. Changes from baseline at designated timepoints of WOMAC® Pain, PGIC - Paradigm's primary endpoints in upcoming phase 3 trial design will be an improvement in pain and function from baseline at day 56 using the WOMAC® OAindex. This study will provide further clinical data will have pain scores measured at predetermined time points out to day 168.

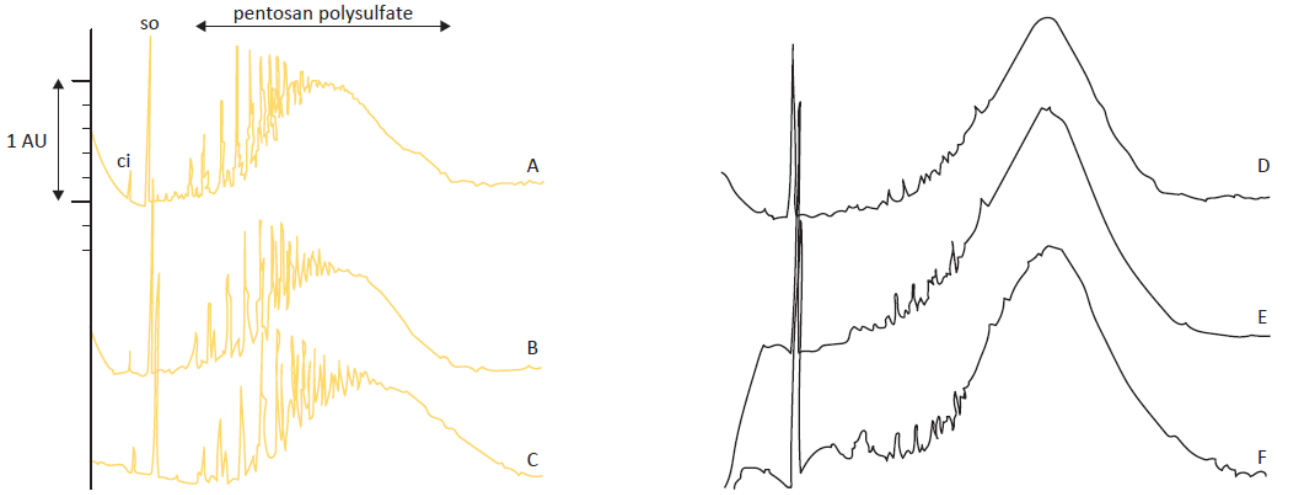
Bene pharmaChem GmbH & Co (BPC)

Paradigm's success is highly dependent on their exclusive supply agreement with BPC. BPC holds the only Drug Master File (DMF) on record with the FDA to manufacture PPS for human applications. Given Paradigm's exclusive agreement, no other pharmaceutical group may reference the DMF in a future submission without BPC approval. Several attempts to replicate BPC PPS DMF have failed.

There are other manufacturers of PPS, however only for veterinary use. PPS has been used in over 100 million injections, and is proven to be safe within animals. There are no other applications of PPS registered for human use. BPC PPS is being used in Paradigm's phase 3 clinical trials. A successful trial will see BPC become the first PPS manufacturer approved for human application on a commercial scale.

The manufacturing procedure of turning beech tree bark into PPS is exceptionally complex, with numerous highly sophisticated steps in each phase of production. Cumulatively this equates to hundreds of potential variations based on a single change.

Monograph of two different PPS manufactures (A,B,C BPC) – competing products have yet to achieve Good Manufacturing Practice & batch consistency to replicate the molecule produced by BPC.



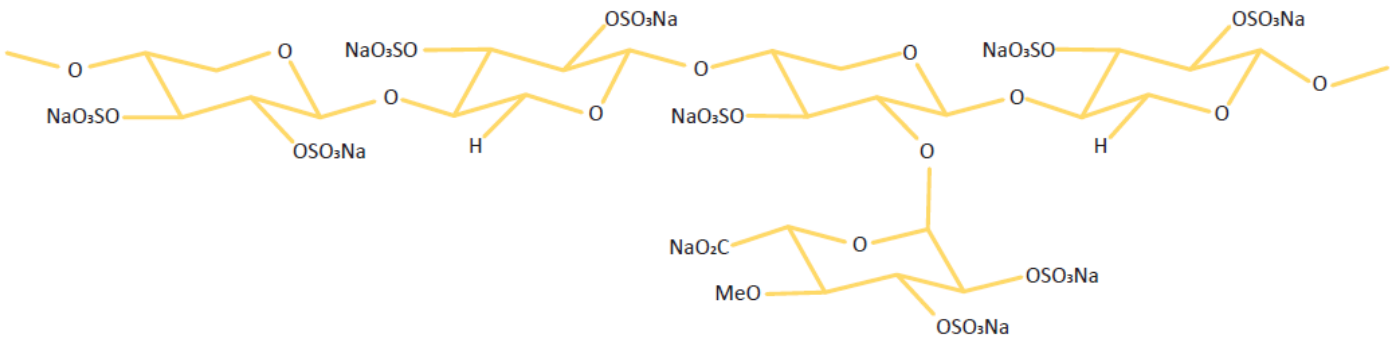
Source: Paradigm

The above illustration highlights the difference between BPC PPS, and competing efforts to replicate BPC DMF (study on PPS by Degenhardt M et.al). This monograph illustrates the difficulty manufacturers have in replicating PPS. Degenhardt also noted that 'minor variations in the molecular shape and size of a drug can have profound effects on pharmacological activities'.

One small alteration in any one of the steps, such as the quality of the charcoal, beech-wood chips, or temperature can alter the drug molecule. If a competing PPS molecule does not match the BPC approved PPS on file with the FDA, it cannot be classed as PPS (not a bio-equivalent).

Currently BPC is looking at methodologies to distinguish the PPS molecule against any generic attempt of replication. As it stands, the FDA have placed a pivotal hurdle in the process making it essentially impossible for competing products to synthesise a bio-equivalent. PPS is produced in two stages, with pentosan being the core ingredient (first stage), the DMF on record with the FDA states that the PPS molecule must have particular attributes that only BPC have knowledge of. This process acts as a fingerprint for BPC's PPS, if a generic form was to surface it would need to comprise of key ingredients found only in BPC pentosan.

PPS Molecule



Source: Paradigm

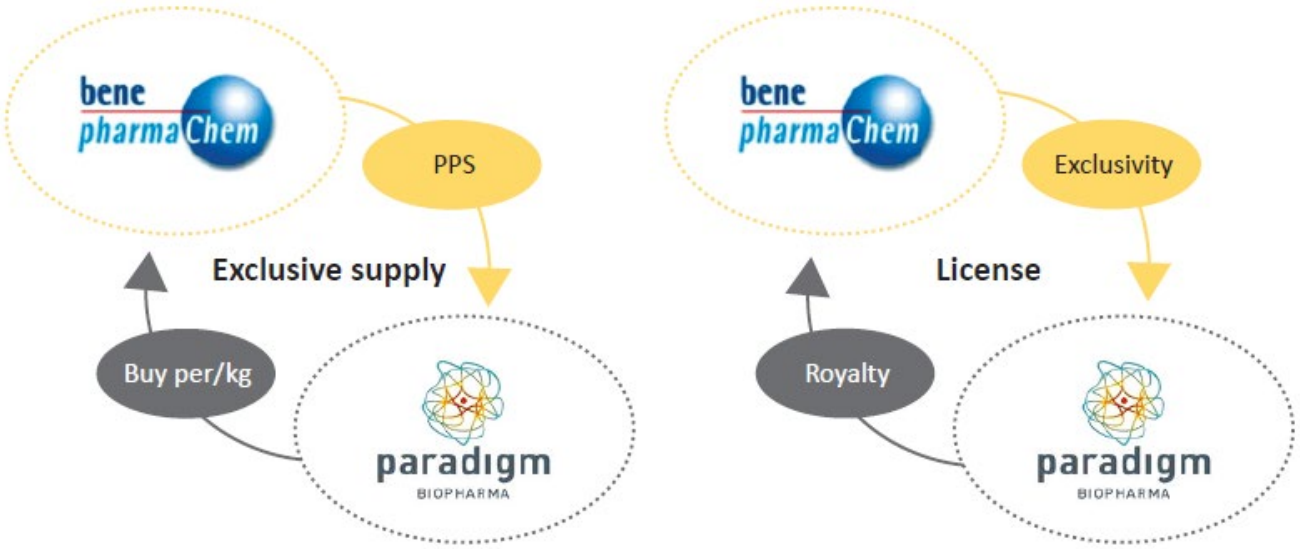
Due to the complexities mentioned, as long as Paradigm remains an exclusive customer of BPC, it is highly unlikely competing products will jeopardise Paradigm's market position. It would take years for an alternative PPS manufacturer to commercialise PPS given the strict regulatory process any new drug needs to withstand to be deemed safe. A new PPS molecule would need to satisfy safety and efficacy, over several clinical trials.

A Real World example - Elmiron®

Elmiron® is sold by Janssen Pharmaceutica (a subsidiary of Johnson & Johnson (J&J). BPC has a long standing exclusive agreement with J&J for the supply of PPS which is used to treat a rare condition relating to inflammatory bladder syndrome, interstitial cystitis. BPC has honoured this agreement as the sole provider of PPS since 1996. Remarkably, there has been no generic form of Elmiron® developed despite corresponding patents having expired in 2010. This is a testament to the loyalty of BPC, as well as highlighting the difficulty in replicating PPS. In the U.S. BPC remain the only recognised FDA approved supplier of PPS. In turn, this enabled J&J to increase the price of Elmiron® (not possible if a generic version was available).

Fortuitously, Paradigm is in a similar position. Not only do they have multiple patents for various indications, the company is placed to service a market where no competing FDA PPS molecules are approved. Given the complexities in replicating BPC PPS, it is reasonable to have a high degree of confidence in the pricing power of Zilosul® if phase 3 clinical trials are successful.

This cannot be overlooked, as it gives Paradigm a near monopoly if further attempts to replicate a PPS bio-equivalent fail. Additionally, it would be counterproductive for BPC to supply competitors PPS for OA, it would be to their detriment given Paradigm's exclusive long term supply agreement. The absence of a generic offering would enable Paradigm to benefit from favourable margins, with no pressure on pricing. Given BPC receive a 2% royalty on sales, it is undoubtedly in their interests to act in good faith throughout the duration of the agreement.



Source: Paradigm

Every year, or as Paradigm in-licences new patents, the exclusivity agreement between the two parties is updated. As Paradigm holds multiple patents for the use of PPS to treat various indications, supplying PPS to a competitor would be pointless. Such actions would violate these patents if there was an attempt to commercialise. The above diagram explains the supply and license agreement with BPC.

Paradigm updated the market on 29th September 2020 announcing the company will have 25 years of exclusive supply from the date of marketing approval. As Paradigm moves towards commercialisation, the agreement greatly elevates the level of commercial protection. BPC product exclusivity, along with regulatory exclusivity and patents, combine to provide Paradigm with a multi-tiered protective moat around the business.

Not only does this agreement now include all major pharmaceutical markets, Paradigm has been able to expand the number of clinical indications, with potential to add many more.

Supply

BPC has manufactured PPS since 1940, supplying Elmiron® consistently and uninterrupted since 1996. The facility at present is running well below maximum throughput producing seven tonnes of PPS per annum, and has the ability to produce 12-14 tonnes at maximum capacity. BPC's facility was designed for expansion if the requirement became necessary, it would take 1-2 years for a second shift to be built, this would add an additional 12 tonnes of production. After speaking with Dr Harald Benend, he stated, colleagues ask him regularly about increasing production not only for Paradigm PPS, but for growth in European Elmiron® sales. Dr Benend said it was a great 'problem to have, one he never could have expected, but handling an increase in demand is no problem, we have more than enough lead time'. BPC is audited frequently by regulators and the FDA, as well as major customers, ensuring the highest quality of product is maintained.

The company - bene pharmChem GmBH

In 1947, Dr W. Benend succeeded in developing a standardised process for manufacturing a type of sulphated polysaccharides, pentosan polysulphate sodium, which has an anticoagulant, fibrinolytic and thrombolytic quality with comparatively limited side effects. As a medicinal product, pentosan polysulphate sodium was first authorised and marketed in Germany in 1949, and afterwards in other European countries, primarily for thromboembolism. In the following years, pentosan polysulphate sodium was investigated on a global scale by research groups and its anti-inflammatory, antiviral and anti-carcinogenic effects, as well as its use for prion diseases, OA, nephropathy, sickle cell anaemia, MPS, and HTLV associated myelopathies.

BPC is a family run, private business operating from four production sites. PPS is manufactured in a state of the art facility ensuring goods are manufactured to a reliable and consistent quality. Equipment used to produce PPS has been custom built by BPC, using in house intellectual property. Given the bespoke nature of equipment and technology, this significantly strengthens the integrity of PPS. BPC employs 175 staff.

Bene pharmaChem and bene-Arzneimittel GmbH are separate companies within the Dr Beneng Holding Company. Equity stakes are divided equally between the families three siblings. BPC employs both the daughter and son of Dr Harald Beneng, making BPC a third-generation business. BPC is responsible for the medical and chemical science of PPS, employing 16 people and generates €10 million in sales per annum. Bene-Arzneimittel GmbH is responsible for the production and distribution of PPS, and other products, employing 120 people, and generates €22 million in sales.

Patents

Mucopolysaccharidosis (MPS) – Awarded an exclusive in –licence agreement for the use of iPPS for the treatment of MPS on the 22nd November 2018 from Mount Sinai hospital. Paradigm has registrations in key regions, such as the United States, Europe, Australia, and New Zealand (excluding Japan). MPS patients suffer similar symptoms to OA (see p.33).

Bone marrow edema – Granted European patent January 2018 for the treatment of BMEL with iPPS. In addition to previously granted registrations in Australia, the United States, Japan, China, Canada, Taiwan, Singapore, and other countries across the Asia-Pacific.

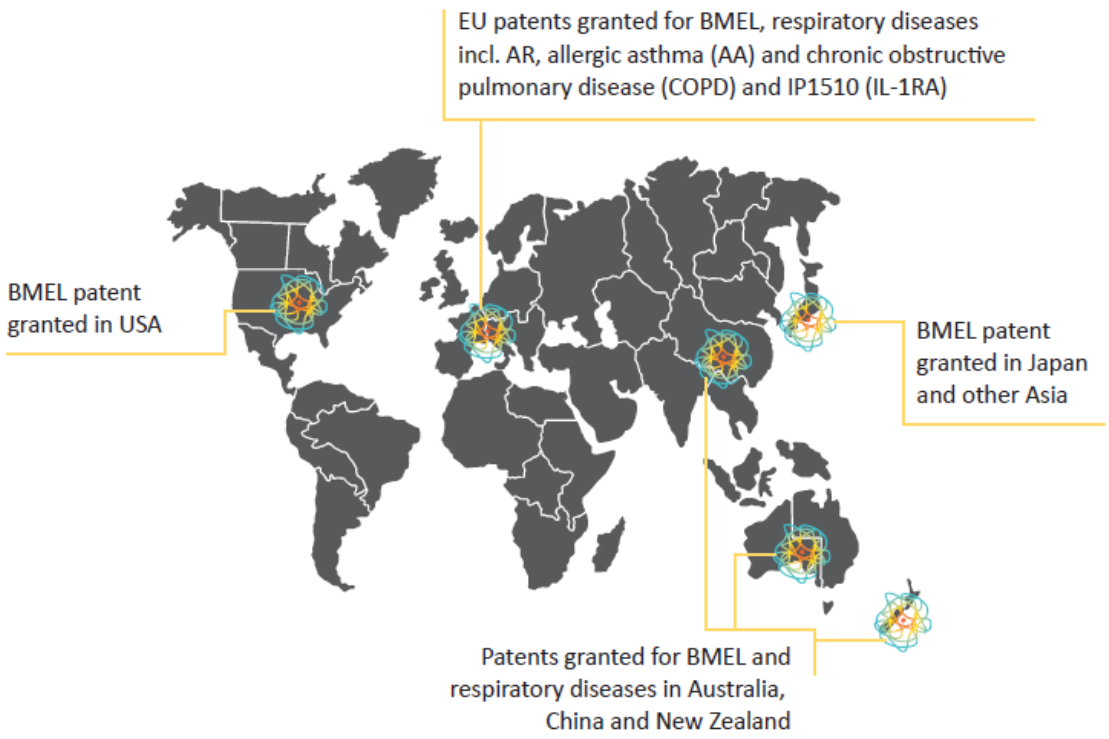
Alphavirus – Collaborative partnership announced September 2016 with the Institute for Glycomics at Griffith University, whereby Paradigm was granted exclusive world-wide rights to commercialise a patent covering the use of iPPS to treat alphavirus arthritis and joint pain.

Respiratory disease – Various patents cover the use of iPPS for many respiratory diseases such as Allergic Rhinitis (AR), Allergic Asthma (AA), and Chronic Obstructive Pulmonary Disease (COPS). These patents are registered in Australia, Canada, Europe, New Zealand and China.

Additional – Application for Ross River virus, chikungunya virus and patent for Heart Failure indication.

The second half of CY2020 Paradigm filed two patents for the use of iPPS in reducing pain. In particular, the patent relates to use of polysulfated polysaccharides, such as PPS, for the treatment of pain, or pain conditions mediated by mature Nerve Growth Factor (NGF) or its precursor pro-Nerve Growth Factor (pro-NGF) both of which are known pain mediators in chronic diseases such as OA.

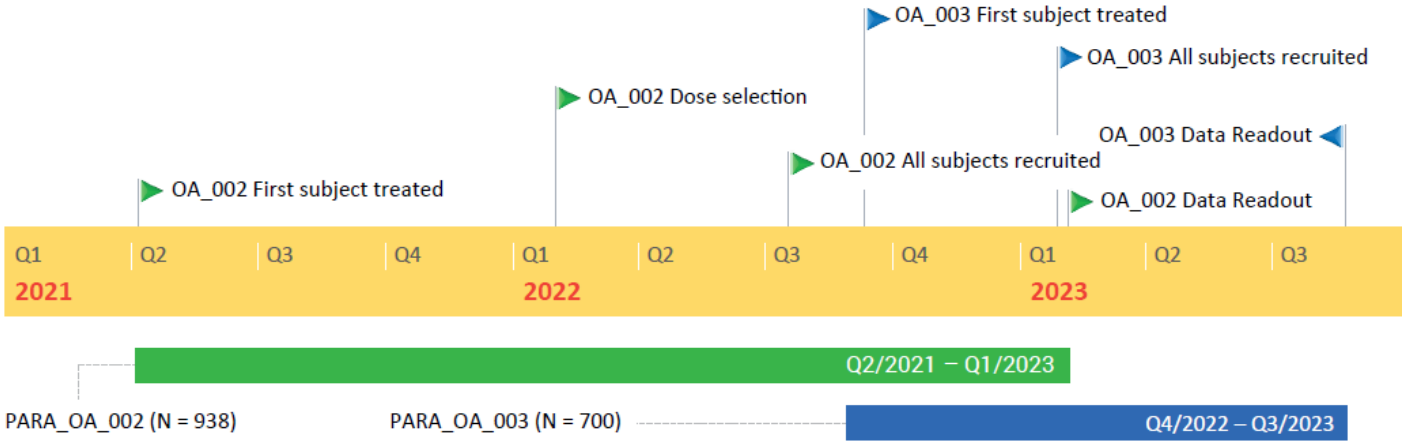
Treatment is administered by an injection including intra-muscular (IM), or subcutaneous (SC) routes, intravenously (IV), intra-articularly (IA), and periarticular injections, as well as topical or oral administration. Oral use of PPS for the indications mentioned are covered under Paradigm's patents. Any oral use by others would be an infringement of Paradigm's patent.



Source: Paradigm

Phase 3 OA clinical trials

Paradigm has received clear guidance from the FDA in relation to primary and secondary endpoints. In order to obtain approval from the appropriate regulatory agencies, both the FDA (U.S.) and EMA (European Union) require at least two successful phase 3 clinical trials demonstrating safety and efficacy (one trial to investigate safety and efficacy, and the second trial to confirm the first trial (confirmatory study)).



Source: Paradigm

The meeting concluded all non-clinical and clinical studies are required to use BPC PPS. Acknowledging multiple moieties (a specific group of atoms within a molecule that is responsible for characteristic chemical reactions of that molecule) that are understood and deemed safe, and therefore is the only accepted form of PPS. Detailed under BPC (p.22) any generic version of PPS would have to be identical in molecular structure and purity for the FDA to grant approval. There are no known generic PPS products, placing Paradigm in an enviable position.

Endpoints: Primary and secondary ;

1. Reduced WOMAC pain from baseline (efficacy and safety).
2. Improved patient global impression of change (PGIC).

Target Population: Based on Phase 2b clinical data, it was evident the patient population with a NRS pain score 4-6 responded more favorably to treatment showing a greater that 50% reduction in KOOS (refer p.17 for Phase 2b clinical trials). Given the significance of these results, phase 3 clinical trials will focus on recruiting patients with moderate to severe pain using WOMAC NRS 4-9. Further, results highlighted the importance of having exclusion/inclusion criteria for screening specific patients and disease states. For example, phase 3 clinical trials will consist of patients with clinically diagnosed OA with a radiographic diagnosis (X-ray) showing a Kellgren Lawrence (refer p.12) score of 2, 3, or 4 (when the knee shows no signs of OA, it is classified as stage 0, which is normal knee health, with no known impairment or signs of joint damage. 1 = minor, 2 = mild, 3 = moderate, 4 = severe) (stage 4 being severe sclerosis and bone deformity).

The inclusion criteria for phase 3 clinical trials are straight forward and removes any confusion with results across different subgroups that could have been created by inaccurate NRS pain scores.

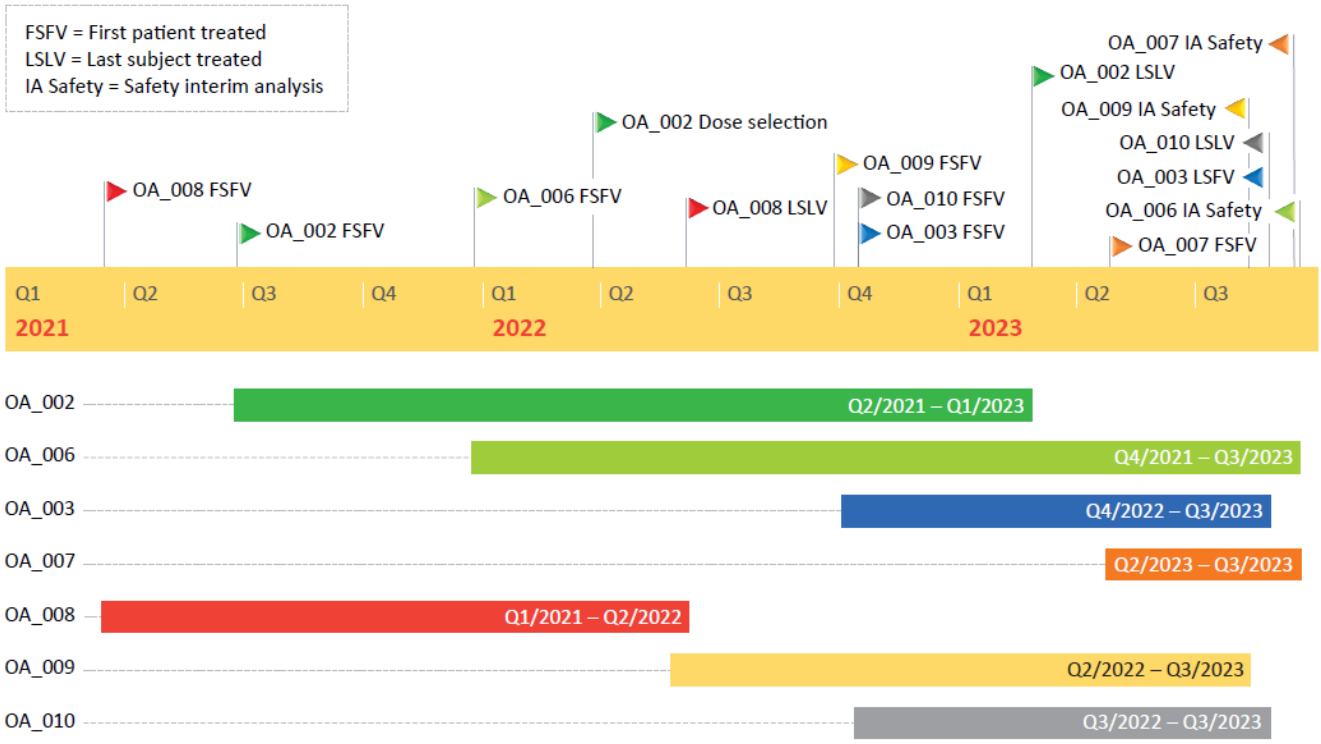
Paradigm may perform a placebo run-in trial. The rationale for a run-in period is to adjust the selection of patients for the post-randomisation phase of the trial. The principal difference between standard screening by eligibility criteria in a trial, and the procedures for a run-in phase is the latter permits exclusions based on observations of patient's compliance or responses to trial interventions. Both active and placebo run-in periods enable the exclusion of patients who do not comply with trial procedures

Phase 3 clinical trials will aim to confirm the findings of Paradigm's Phase 2b clinical trial. Subjects will be dosed twice for six weeks and observed for 24 months, for evidence of durability (re-administration data). The primary endpoint is day 56 for mean pain change from baseline using WOMAC. They key secondary endpoint is day 56 for mean change from baseline in WOMAC function. Phase 2b clinical trials demonstrated a clinically meaningful effect for pain, function, and PGIC. A larger sample size in phase 3 clinical trials will improve the power to detect meaningful differences between treatment groups.

KOOS pain rating scale was used in Phase 2b clinical trial. Phase 3 clinical trials will use WOMAC, the preferred rating scale of the FDA. A 25% reduction in WOMAC pain score from baseline is regarded as clinically meaningful. WOMAC scores for 42 patients in the most recent SAS results returned a mean pain reduction of 47% from baseline. In Phase 2b clinical trial, patients returned a mean pain score reduction of 50% from baseline. The mean reduction in pain scores is comparable under both measures (refer to Phase 2b clinical trials p.17, and SAS results p.12).

Secondary

- Change in BME/BML and other structural findings in bone and cartilage. Phase 2b clinical trial reported a reduction in the size, volume and grade of BMEL. This was a significant result as it indicates the potential for iPPS to be a DMOAD (p.17). These results were shown at day 165 by MRI.
- Phase 3 will collect PGIC using WOMAC. (refer p.11)
- At day 165 will assess the mean % change of activities of daily living.
- Biomarkers including ADAMTS5 and COMP data for discussion around insurer reimbursement based on potential DMOAD status.



Source: Paradigm

Understanding the trials

Paradigm's primary/pivotal, and dosage study 002 will begin Q3 2021. Paradigm's confirmatory study 003 will be complete around the end of 2023. Extension study 006 will be used to evaluate patients who complete the dosage study 002, designed to provide additional information to enhance the label, demonstrating the duration of treatment effect, responses to re-treatment with PPS, and evaluate biomarker assessments either by radio graph or chemical biomarkers to determine if DMOAD effects are demonstrated.

007 is an extension study to confirmatory study 003 and has the purpose to provide similar information to extension study 006 (important once again for developing the label for OA of the knee).

008 will be conducted in Australia and will be the first study to begin in 2021. This study will evaluate biomarkers in the blood and synovial fluid, as indicators of the mechanism of action (MOA) of PPS in Knee OA. The results of the study will inform our understanding of how PPS works by evaluating the synovial fluid, and support a provisional approval application with the TGA (early 2024).

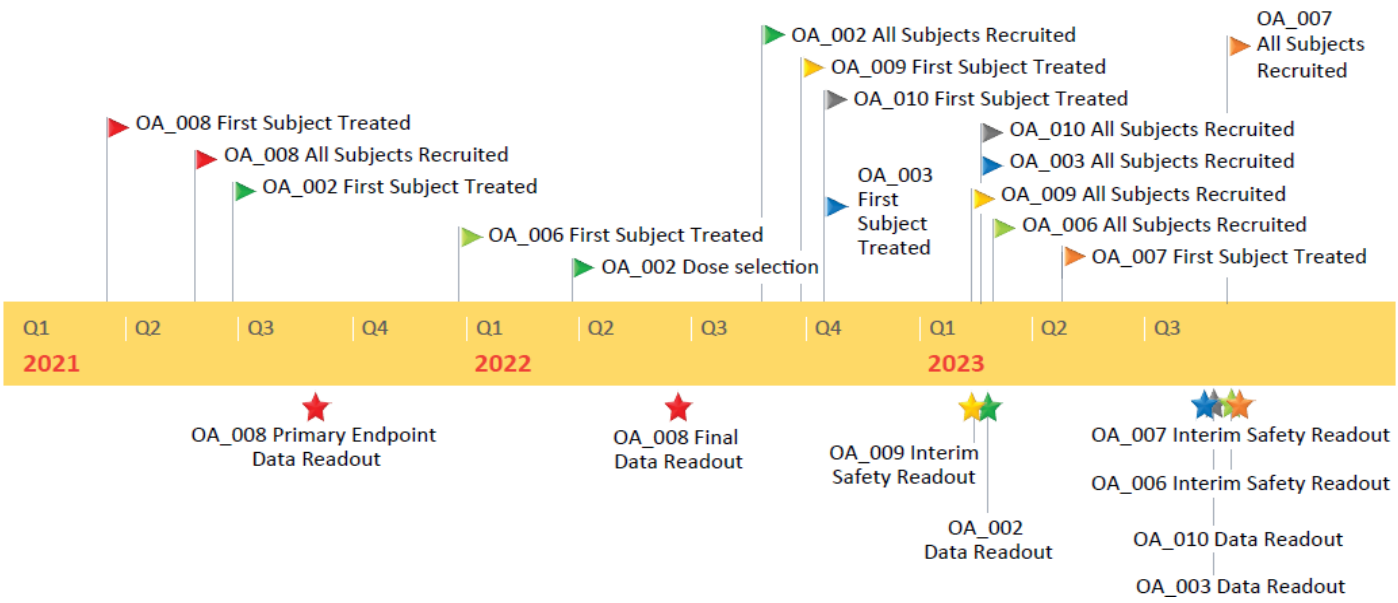
009 will evaluate re-treatment of PPS in OA patients at various intervals to support the use of PPS for multiple cycles over a patient's course of OA. OA is known as a chronic disease with patients likely needing multiple repeat courses over a prolonged period. This is required to establish an understanding of the benefits from various intervals of re-treatment for physician information.

0010 will evaluate patients with OA of the hip, and will be done simultaneously without delaying the overall timeline of the program. There are many similarities between Knee OA and hip OA, with a clinical need for both. The TGA regulatory pathway is similar for both. This study could also increase the value of the label.

Study	Region	N	PPS selected dose (initial course)	Placebo	Subjects for safety DB
PARA_OA_002 (phase 2b/3	US/AU	938	352	352	352
PARA_OA_006 (2B/3 extension)	US/AU	750*	282	–	282
PARA_OA_003 (PH3 confirm)	EU/US	700	350	350	350
PARA_OA_007 (PH3 extension)	EU/US	560*	280	–	60
PARA_OA_008 (synovial fluid)	AU	60	30	30	60
PARA_OA_009 (retreatment)	TBD	270	180	90	225
Previous studies	US/AU	243	99	72	99
Total			**1573**	**894**	**1428**
PARA_OA_010 (hip)	TBD	TBD	TBD	TBD	TBD

Source: Paradigm

Phase-3 readout timeline



Source: Paradigm

Nerve Growth Inhibitors (NGF)

Nerve Growth Factor (NGF) was discovered in the 1950's as a small protein with actions of promoting survival and differentiation of sensory and sympathetic neurons, and is a member of a family of growth and survival factors known as neurotrophins. NGF is a critical protein required for the development of nerve cells, primarily those that transmit temperature, pain and touch sensations.

Whilst anti-NGF therapy has potential to reduce pain associated with OA, clinical trials have revealed serious adverse effects that are yet to be fully understood. Studies have shown that anti-NGF therapy, including tanezumab and fasinumab (see p.27 and p.32), is efficacious in improving pain and function, however there is evidence of these treatments rapidly progressing OA and osteonecrosis. Subsequently in 2010, the FDA imposed a hold on all clinical trials of NGF antagonists, which was extended due to the observation of autonomic nervous system toxicity in preclinical models. In 2015, the hold was lifted subject to the imposition of stringent monitoring, dose limitations, and enrolment restrictions.

Preclinical testing has revealed effects of NGF blockade on both pain behaviours and joint structure in experimental models of OA. Similar to clinical trial results, studies in laboratory animals demonstrated analgesic efficacy of NGF blockade. Interestingly, several animal studies run in parallel to human trials have illustrated detrimental effects on joint integrity as a result of treatment, particularly when dosage is started early in the disease, when joint damage is mild.

It was discovered monoclonal antibodies can be used to inhibit the binding of NGF to its high-affinity cognate receptor, tropomyosin-related kinase (TrkA), and thus block its biological activity suppressing pain. As a result, there was a vigorous effort by the pharmaceutical industry to develop humanised monoclonal antibodies that bind NGF with high specificity and affinity. These include tanezumab (Pfizer and Eli Lilly Pharmaceuticals), fasinumab (Regeneron and Teva Pharmaceuticals), and fulranumab (Janssen and Amgen Pharmaceuticals). Of these, tanezumab has been the most widely studied, and formed the basis of the first randomised, double blind, controlled clinical trial of anti-NGF therapy for OA pain, which was published in 2010 revealing dramatic pain relief among many study subjects.

Although these findings produced initial optimism, as highlighted, there has been a high prevalence of rapidly progressive OA (RPOA) and osteonecrosis in non-target joints among subjects who had received anti-NGF treatment.

Tanezumab, and others mentioned have either completed further trials under strict guidelines, or discontinued efforts. Billions have been invested despite clear concerns around safety. Anti-NGF products were highly anticipated to be the cure for a disease that had failed repeatedly to find adequate treatment. Given the opioid epidemic across all geographies, it could be argued the FDA was motivated to fast track anti-NGF trials as an alternative was nonexistent. Today, it is evident safety remains a considerable concern.

Tanezumab by Pfizer & Eli Lilly Pharmaceuticals (anti - NGF)

Efficacy is proven, safety is not. There are two anti-NGF products which remain in contention, however from recent phase 3 clinical data the probabilities of becoming a commercial product is remote. There have been nine tanezumab controlled phase 3 OA studies performed to date. This segment focuses on a pool of 696 patients with a baseline Kellgren Lawrence score of 3-4 compared to placebo (not NSAID's).

Tanazumab is a non-opioid, anti-NGF treatment. NGF levels increase in the body as a result of injury, inflammation or in chronic pain states. Tanezumab is a monoclonal antibody (antibodies that are made by identical immune cells which are clones belonging to a unique parent cell). These cells target and bind to NGF reducing pain. Tanezumab to date has demonstrated efficacy, however with ongoing safety concerns.

In 2013, Pfizer and Eli Lilly Pharmaceuticals partnered with the objective to co-develop tanezumab. This is after several companies (including Pfizer) in 2010 were instructed by the FDA to cease clinical studies as a result of serious bone disorders occurring with a study participant. A confirmed case of avascular necrosis of a joint was encountered (death of bone tissue due to a lack of blood supply), also known as osteonecrosis.

- Regeneron and Sanofi-Aventis Pharmaceuticals were ordered to cease trials (2010).
- Johnson & Johnson were ordered to cease trials of its anti-NGF fulranumab and subsequently elected to discontinue their phase 3 clinical trial in 2016.
- Pfizer put on hold tenezumab after 16 patients showed radiographic evidence of bone necrosis leading to the requirement of total joint replacement.
- AstraZeneca developing MEDI-578 voluntarily delayed their program and has not attempted further trials.
- Fasinumab by Regeneron Pharmaceuticals is the only other anti-NGF continuing trials (see p.32).

Pfizer and Eli Lilly Pharmaceuticals were permitted by the FDA in 2015 to continue trials, on the provision patients taking NSAID's were to be excluded. Pfizer through this partnership received a US$200m payment from Eli Lilly under the terms of the Collaboration Agreement.

Phase 3 Clinical trials - United States, Canada and Puerto Rico (patient n: 698)

A randomised, double blind, placebo controlled, parallel-group, multicenter, dose-titration study run over a 16 week treatment period, followed by a 24 week observation period. 89 clinical research sites were used for 698 patients across the United States, Canada and Puerto Rico, from January 2016 to May 2018. Patients with a Kellgren Lawrence score (p.12) greater than two were selected via radiographic (X-ray) confirmation. Patients who scored five or greater using the WOMAC pain subscale, and WOMAC physical function subscale, at both screening and baseline were enrolled (WOMAC 11-point numerical rating scale from 0 = no difficulty to 10 = extreme difficulty, 5 = indicating a mild-moderate baseline pain status).

Treatment - Patients received by subcutaneous administration either tanezumab 2.5 mg at day 1, and week 8 (n = 231); tanezumab 2.5 mg at day 1, and 5 mg at week 8 (i.e. tanezumab, 2.5/5 mg) n = 233), or placebo at day 1 and week 8 (n = 232).

Primary objective – Establish efficacy of two subcutaneous tanezumab treatment regimes at week 16— fixed dosing (2.5 mg administered at baseline and week 8) and forced dose titration (2.5 mg administered at baseline and 5 mg at week 8)—compared with placebo treatment.

Secondary objective - Evaluate the efficacy of tanezumab titrated from 2.5 mg to 5 mg at week 8 compared with 2 administrations of tanezumab, 2.5 mg, 8 weeks apart, and observe the AE profile of both tanezumab dosing regimens.

Results – released 18th April 2019

Among 698 randomised patients (mean age 61 years; 65% women) with 582 patients (83.6%) completing the trial.

- Mean WOMAC pain scores from baseline to 16 weeks, decreased from 7.1 to 3.6 (49%) in the tanezumab 2.5 mg group. 7.3 to 3.6 (51%) in the tanezumab 2.5/5 mg group. 7.3 to 4.4 (40%) in the placebo group.
- Mean WOMAC physical function scores decreased from 7.2 to 3.7 (49%) in the 2.5-mg group. 7.4 to 3.6 (51%) in the 2.5/5-mg group, and 7.4 to 4.5 with placebo (39%).
- Mean PGA-OA scores decreased from 3.4 to 2.4 (29%) in the 2.5 mg group. 3.5 to 2.4 (31%) in the 2.5/5 mg group. 3.5 to 2.7 (23%) with placebo.
- Rapidly progressive OA occurred only in tanezumab treated patients (2.5 mg n = 5, 2.2%), (2.5/5 mg n = 1, 0.4%). The incidence of total joint replacements was 8 (3.5%), 16 (6.9%), and 4 (1.7%) in the tanezumab, 2.5 mg, tanezumab, 2.5/5 mg, and placebo groups respectively.

Phase 3 clinical trials (n: 698), shows clear evidence of joint safety events for both 2mg and 2mg-5mg groups against placebo (consistent with other tanezumab phase 3 clinical trials). Of the 37 cases, 30 were adjudicated as a result of normal OA progression. These cases are known by two predetermined terms:

Type 1, Defined as, a significant loss of joint space with >2 mm within approximately one year without gross structural failure, cases reported n=4.

Type 2, Defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface that is not normally present in conventional end-stage OA, cases reported n=2.

Both type 1 and 2 were only seen in tanezumab treated patients 6/464. Type 1 and 2 occurred more frequently in 2.5mg group (2.2%) with group 2.5-5 mg reporting (0.4%).

The majority of safety events were total joint replacements (28/37 patients 75%). Eight tanezumab 2.5 mg treated patients (3.5%), 16 tanezumab 2.5/5 mg treated patients (6.9%), and four placebo treated patients (1.7%). Illustrating a higher correlation with tanezumab patients. All total joint replacements were for patients who returned a 3 to 4 at screening using Kellgren Lawrence grading scale.

Change from baseline to week 16 in WOMAC pain, physical function, and patient global assessment of OA subscale

	Tanezumab		
	2.5mg (n = 231)	2.5/5 mg (n = 233)	Placebo (n = 232)
WOMAC Pain[b]			
Baseline pain score, mean (range)	7.1 (4.8 to 10.0)	7.3 (5.0 to 10.0)	7.3 (4.2 to 10.0)
Least squares change from baseline, mean (95% CI)	-3.23 (-3.67 to -2.79)	-3.37 (-3.81 to -2.93)	-2.64 (-3.08 to -2.19)
Difference of least squares vs placebo, mean (95% CI)	-0.60 (-1.07 to -0.13)	-073 (-1.20 to -0.26)	
WOMAC Physical Function[c]			
Baseline physical function score, mean (range)	7.2 (5.1 to 9.9)	7.4 (3.2 to 9.9)	7.4 (4.4 to 10.0)
Least squares change from baseline, mean (95% CI)	-3.22 (-3.66 to -2.79)	-3.45 (-3.88 to -3.03)	-2.56 (-3.00 to -2.12)
Difference of least squares vs placebo, mean (95% CI)	-0.66 (-1.14 to -0.19)	-0.89 (-1.37 to -0.42)	
Patient Global Assessment of Osteoarthritis[d]			
Baseline score, mean (range)	3.4 (2 to 5)	3.5 (3 to 5)	3.5 (3 to 5)
Least squares change from baseline, mean (95% CI)	-0.87 (-1.02 to -0.72)	-0.90 (-1.05 to -0.75)	-0.65 (-0.80 to -0.50)
Difference of least squares vs placebo, mean (95% CI)	-0.22 (-0.39 to -0.05)	-0.25 (-0.41 to -0.08)	

Source: ClinicalTrials.gov

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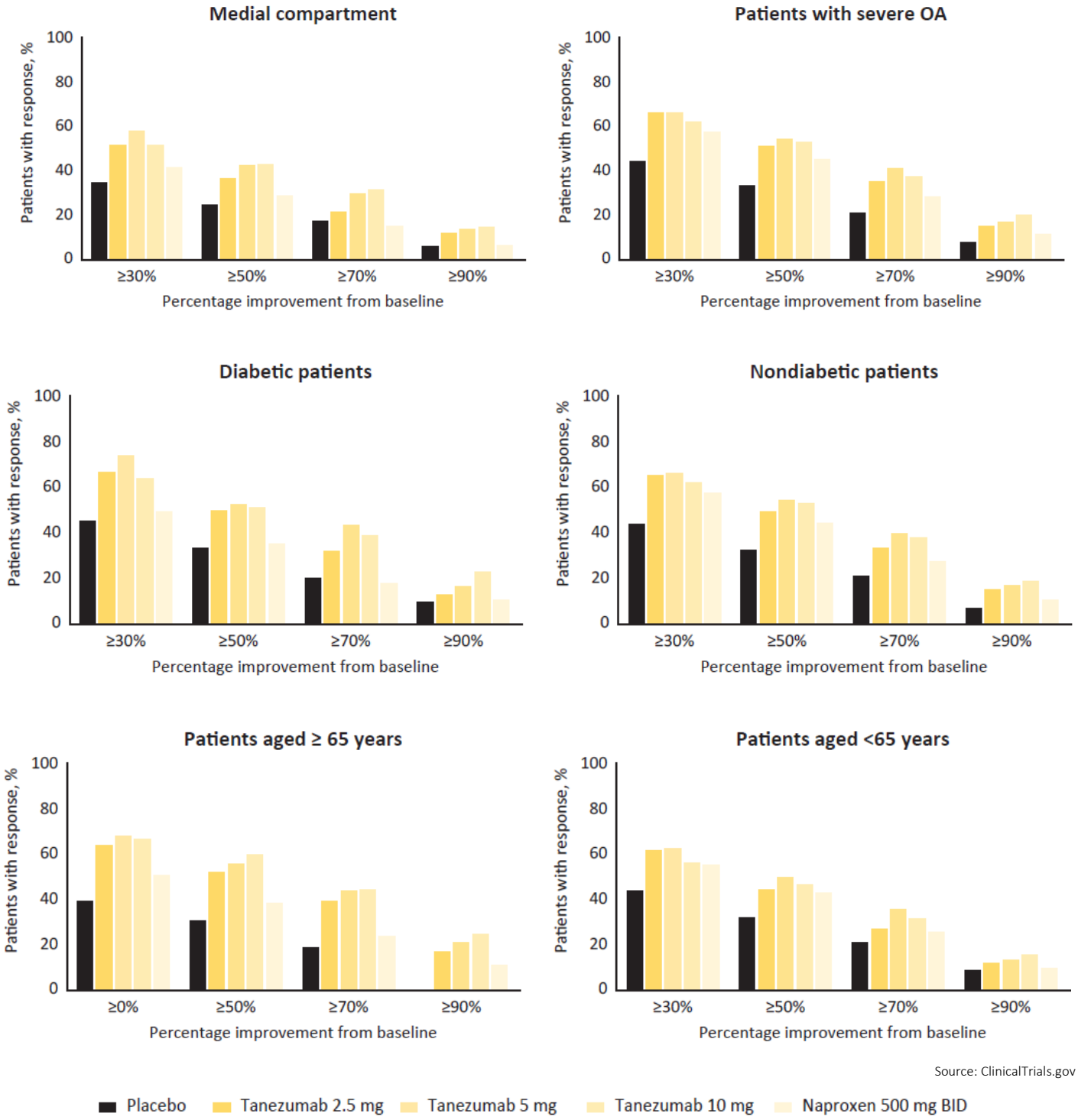
Reduction from baseline in WOMAC pain at Week 16: Proportion of Patients With >30%, >50%, >70%, and >90% reduction.

	Tanezumab		
	2.5 mg (n = 231)	2.5/5 mg (n = 233)	Placebo (n = 232)
≥30% Reduction			
Patients, No. (%)	157 (68.0)	164 (70.4)	127 (54.7)
Difference from placebo, %	13.2	15.6	
≥50% Reduction			
Patients, No. (%)	126 (54.5)	133 (57.1)	88 (37.9)
Difference from placebo, %	16.6	19.2	
≥70% Reduction			
Patients, No. (%)	80 (34.6)	85 (36.5)	58 (25.0)
Difference from placebo, %	9.6	11.5	
≥90% Reduction			
Patients, No. (%)	34 (14.7)	33 (14.2)	22 (9.5)
Difference from placebo, %	5.2	4.7	

Source: ClinicalTrials.gov

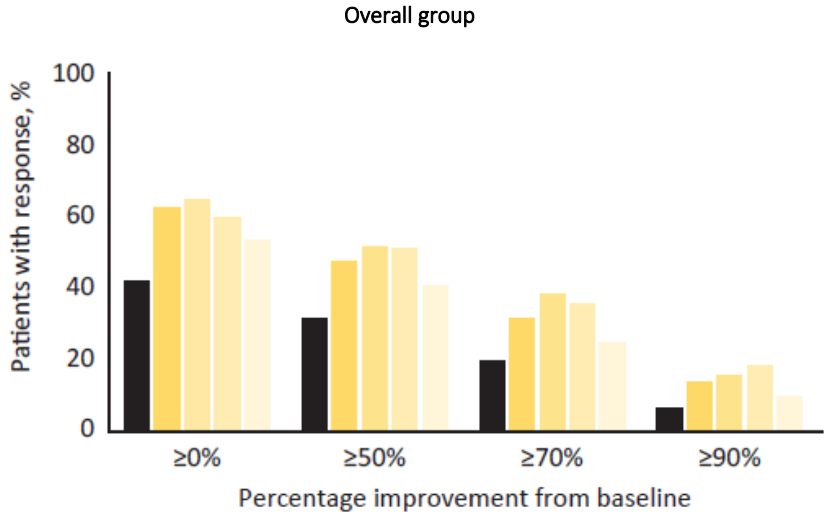
Multiple phase 3 studies

Overall, nine placebo controlled phase 3 OA clinical studies have been completed with tanezumab (efficacy = 4/9) and (safety = 9). Four of these studies had treatment periods completed prior to clinical suspension, with data pooled to evaluate efficacy. Patients received intravenous tanezumab, tanezumab + an oral NSAID (naproxen, celecoxib, diclofenac, diclofenac, oxycodone) or placebo. These studies have included patients across a range of conditions, such as diabetic vs non-diabetic, severity of OA, and patients aged >65 vs <65. Tanezumab dosages ranged between 2.5mg and 10mg.



Source: ClinicalTrials.gov

Pooled data for safety outcomes showed that incidence rates of AE, withdrawals due to AE, and serious AE's in patients was higher compared to placebo treated patients. Further, a combination of tanezumab with NSAID's was responsible for slightly higher rates of AE's compared to all other (FDA reasons for clinical hold in 2010). Overall, the most common AE's were hypoesthesia, peripheral edema, nasopharyngitis, arthralgia, pain in extremity, and headache.



Source: ClinicalTrials.gov

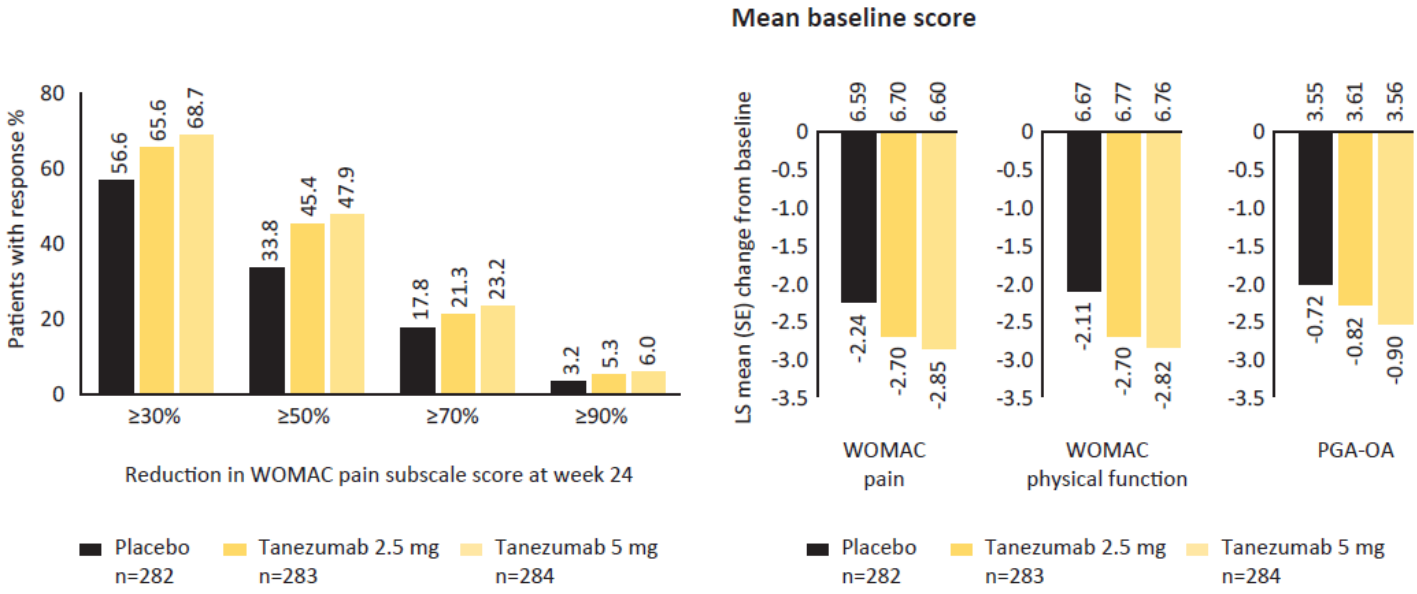
The percentage of patients with WOMAC >30%, >50%, >70%, and >90% pain reduction compared with placebo, tanezumab dosage 2.5-10 mg returned the best results. Further, 5 - 10mg illustrated across all categories (compared with naproxen) a larger percentage improvement. Statistical significance vs naproxen and placebo was higher amongst non diabetic patients over 65 with higher baseline pain scores.

Phase 3 clinical trials – Europe & Japan (patient n: 849)

Over a 24 week period (March 2016 – December 2017) 849 patients with moderate to severe OA that had not responded or could not tolerate analgesics were enrolled in a double blind, randomised trial, and were administered tanezumab 2.5mg and 5mg against placebo every 8 weeks. Similarly to other phase 3 clinical trials, co-primary endpoints were pain reduction, improved physical function, and PGIC of OA. Following final treatment, patients were monitored for a further 24 week period, and assessed for joint safety and neurological AE's.

Results – Tanezumab 2.5mg n=283, 5mg n=284, and Placebo n=282. Tanezumab 5 mg compared with placebo using WOMAC returned statistically significant improvements in all endpoints, especially reduction in pain. 2mg achieved a statically significant outcome for 2/3 endpoints, not PGA-OA. Rapidly progressive OA (RPOA) was observed in 2.5mg (4/283 or 1.4%), 5mg (8/284 or 2.8%) and none for placebo. Tanezumab patients who received both dosages experienced greater paraesthesia and hypoaesthesia than placebo.

Whilst efficacy is proven, RPOA remains concerning. 5mg achieves all endpoints yet continues to show the largest number of RPOA AE.



Source: ClinicalTrials.gov

Aggregated phase 3 clinical trials – (patient n: 3,021)

In addition, Pfizer released data in April 2019 for tanezumab dosage 2.5 – 5mg administered subcutaneously over a 56 week period (in 8 week intervals). Safety endpoints were mostly consistent with previous studies. Incidence of joint safety 7.1 % (5mg), 3.8% (2.5mg), 1.5% (NSAID's). RPOA overall 6.3% (5mg arm), 3.2% (2.5mg arm) and NSAID's (1.2%). 81% of RPOA events observed with tanezumab were type 1 (refer p.28). Subchondral insufficiency fracture was evident with 5mg (7 people), 2.5mg (6 people), NSAID's (4 people). The requirement for joint replacement was 8% (5mg), 5.3% (2,5mg) and 2.6% (NSAID's).

Tanezumab 5mg reached two of three co-primary endpoints, demonstrating statistically significant improvement in pain and physical function compared to NSAID's at 16 weeks. Tanezumab 2.5mg did not produce a statistically significant outcome with any endpoint. Joint safety incidences was statistically significant with both type 1 & 2 (p.28) RPOA evident compared to NSAID's at 80 weeks.

This study was conducted worldwide (United States, Europe, Asia and Latin America) performed over a 56 week period combining a total of 3,021 people. All patients were randomised in a 1:1:1 ratio and received tanezumab 2.5mg, 5mg or oral NSAID's (either naproxen 500mg, celecoxib 100mg, diclofenac extended release 75mg), 2 times per day over 56 weeks. There was a safety review following the trial at week 24.

Overall

Tanezumab is most effective with people suffering from moderate to severe OA. Subcutaneous tanezumab 2.5/5mg is statistically significant over placebo and NSAID's for pain and physical function. However, nine phase 3 trials spanning over ten years continue to highlight safety concerns (39 total trials phases 1-3). Irrespective of this, as at March 2020 the FDA accepted regulatory submission for tanezumab, and will review a Biologics Licence Application (BLA) for tanezumab 2.5mg to be administered subcutaneously. If granted tanezumab would be cleared for commercial distribution.

Given the tanezumab 2.5mg dose did not lead to a statistically significant improvement in either pain or function over the NSAID arm, it is perplexing as to why Pfizer and Eli lilly Pharmaceuticals continue trials. Given the time and invested capital, it is seen as a final effort to recover costs. If the 2.5mg dosage was to be approved by the FDA, it is unknown if doctors would prescribe tanezumab. The known safety concerns for a marginal reduction in pain, and increased function could be deemed unnecessary and hazardous. The lack of alterative treatment to opioids could be seen as a reason why tanezumab has not been discontinued. Regardless of the FDA decision, it is hard to imagine tanezumab being a front line/ first in class treatment given the aforementioned safety concerns.

Fasinumab by Regeneron Pharmaceuticals (anti – NGF)

Fasinumab by Regeneron Pharmaceuticals is the second of two remaining fully human monoclonal antibodies being trialed for use against NGF. Similarly to tanezumab, several fasinumab phase 3 clinical trials in recent years have been run in parallel. As with tanezumab, efficacy is proven to be statistically significant across varying dosages, however safety remains the defining factor for a successful New Drug Registration (NDR).

Patients in Phase 2b/3 clinical trial were randomised and administered subcutaneous dosages of 1mg, 3mg, 6mg, and 9m, or placebo over a 16 week period (every 4 weeks). 421 patients between the ages of 40-80 with moderate to severe OA pain were deemed appropriate based on pre-trial radiologic scans identifying patients with a Kellgren Lawrence score greater than 2 (66% of patients), as well as demonstrating a baseline WOMAC pain subscale score of 4 or greater. The index joint was mostly the knee (88%), the remainder had OA of the hip.

The primary endpoint was pain reduction, with physical function and patient global assessment (PGA) secondary. Patients were monitored for a 36 week period, with joints observed regularly by plain film radiography (X-ray), and magnetic resonance imaging (MRI). 342 of 421 patients completed the trial with all doses returning statistically significant and clinically meaningful reductions in pain compared to placebo at week 16 using WOMAC pain subscale. PGA and physical function scores improved in line. During the follow up period (after week 16), all pain scales returned almost to preclinical baseline levels (see tables below).

Viability for commercialisation

Despite achieving efficacy with all endpoints, fasinumab at every dosage, (as with all other trialed anti- NGF's) continues to show treatment emergent adverse events (TMAE), 17% in fasinumab treated patients, and 10% placebo treated patients. The incidence of TEAS's at week 20 was higher in the fasinumab group compared to placebo (48% vs 38%). Analysis was performed to detect both symptomatic arthropathy given the history of elevated incidences with anti-NGF treatment. Throughout the trial, regular radiologic monitoring was performed without the requirement for pain as the catalyst. Adjudicated arthropathies were detected in 5% (23 patients) overall, involving 25 joints. 7% of patients in the combined fasinumab group and 1% of patients in the placebo group.

Chart A

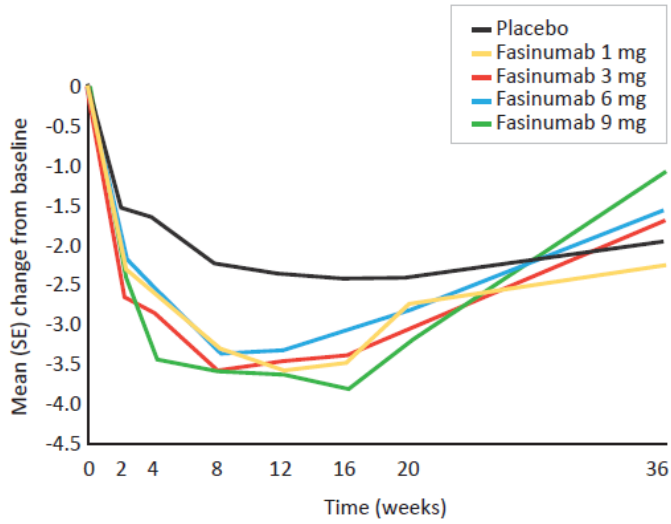
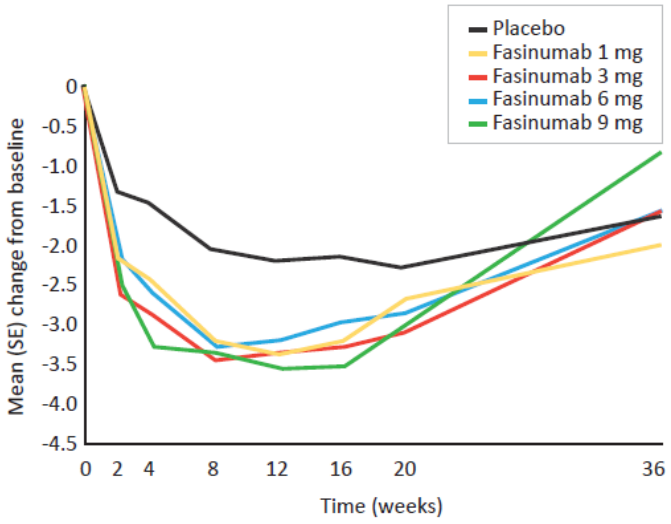
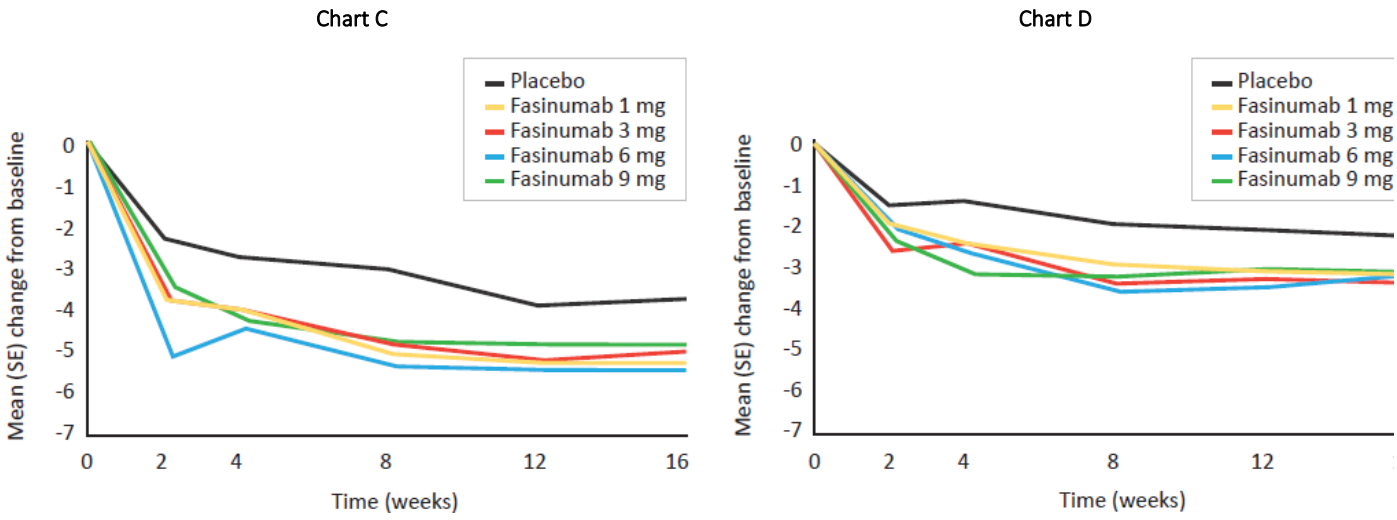


Chart B



Source: PubMed.com



Source: PubMed.com

Change from baseline in (WOMAC) pain (A), and physical function (B), subscale scores by visit, and change from baseline in WOMAC pain subscale score in patients exhibiting pain flare (C), compared to those not exhibiting pain flare (D), upon withdrawal of a prior analgesic (full analysis set). Pain and physical function subscales were each normalised to a scale of 0–10.

Two phase 3 clinical trials (FACT 0A1 & FACT0A2) demonstrated improvements in pain and physical function achieving co-primary endpoints for fasinumab 1mg monthly, at both week 16 and 24. However initial safety analyses from all phase 3 clinical trials show an increase in arthropathies. In the long term sub group Phase 3 clinical trial, an increase in joint replacement was reported with fasinumab 1mg during the off-drug follow-up period. Whilst efficacy is evident, fasinumab continues to experience TMAE's across all dosages, similar to tanezumab. Long term safety data from ongoing trials is being collected and expected to be reported first half of calendar year 2021.

The highlighted phase 3 clinical studies are part of a longer term 52 week active treatment study designed to discover safety and tolerability of fasinumab. Primary safety analysis for all aggregated trials occurs at 72 weeks. (52 week active treatment, with 20 week follow-up periods). In January 2018 an Independent Data Monitoring Committee (IDMC) began evaluating the ongoing efficacy and safety of fasinumab. During mid 2018 the IDMC advised that both 3mg, and 6mg dosage every eight weeks be discontinued.

August 18th Regeneron Pharmaceuticals decided against continuing dosing patients in an optional second year extension of their only remaining phase 3 clinical trial. This is a result of further IDMC recommendations suggesting the program be terminated. If the decision is made to file for regulatory approval, current core efficacy data will be sufficient. Regeneron Pharmaceuticals will continue to gather long term safety data which they expect to report in 2021.

Mucopolysaccharidosis (MPS)

Paradigm in-licensed the MPS indication from the Icahn School of Medicine at Mount Sinai, New York and has recently received approvals for two Orphan Designations, MPS-1 and MPS-6 from both the FDA and EMA to progress MPS clinical and commercial development. Both agencies agreed on the rare nature of MPS-6 and provided clarification on both the clinical trial design, and regulatory path forward. Paradigm seeks to establish whether PPS may be an effective adjunct/combination therapy with current enzyme replacement therapy treatments.

What is MPS?

Mucopolysaccharides are long chains of sugar molecules that are found throughout the body that are unable to be broken down by a group of inherited conditions. This results in the accumulation of these polysaccharides in cells, blood and connective tissue often leading to a variety of health problems.

Seven distinct subtypes of MPS have been identified. Signs and symptoms, and the severity of the condition vary significantly by form. In general, most people appear healthy at birth and experience a period of normal development, followed by a decline in physical and/or mental function. As the condition progresses, it may affect appearance, physical abilities, organ and system functioning, and in most cases development. Treatment is based on the signs and symptoms present in each person.

The cumulative rate for all types of MPS is around 3.5 in 100,000 live births, and generally patients present in one of three ways:

1. As a dysmorphic syndrome (MPS-IH, MPS-2, MPS-6) often with early onset middle ear disease, deafness, or upper airways obstruction.

2. With learning difficulties, behavioural disturbance and dementia and mild somatic abnormalities (MPS-3).

3. As severe bone dysplasia (MPS-4).

Estimates for the specific types of MPS range from; one in 100,000 for Hurler syndrome (MPS-1H); one in 500,000 for Scheie syndrome (MPS-1S); one in 115,000 for Hurler-Scheie syndrome (MPS-1H/S); one in 70,000 for Sanfilippo syndrome (MPS-3); one in 200,000 for Morquio syndrome (MPS-4); and fewer than one in 250,000 in Sly syndrome (MPS-7). Hunter syndrome occurs predominantly in males. In extremely rare cases, affected females have been reported. The incidence of Hunter syndrome is estimated at one in 100,000-150,000 male births (MPS-2).

Phase 2 MPS-1 /MPS-6 clinical trial

Paradigm announced on the 12th 2020 November dosage of its first Phase 2 clinical trial patient evaluating PPS in MPS-1. The trial is open label and will recruit up to 10 participants (male and female) aged 5 years or greater who meet inclusion criteria. Participants enrolled into the study will be sequentially assigned to one of two dosing cohorts (0.75mg/kg and 1.5mg/kg). The study drug is administered via subcutaneous injection weekly for the first 12 weeks, and then every second week until week 48.

Two subjects diagnosed with MPS-1 have been treated for four, and eight weeks respectively, with no negative effects evident. Priority is to assess the safety of PPS in patients with MPS-1. Secondary objectives will be to evaluate if PPS can successfully alleviate pain and functional symptoms in patients who have received ERT and/or HSCT, where these patients continue to have residual musculoskeletal symptoms (joint pain, muscle pain and limited range of motion in various joints).

The study is being conducted at the Adelaide Women's and Children's Hospital (WCH) with Dr David Ketteridge, the Principal Investigator, and Dr Drago Bratkovic (Head of the Metabolic Clinic) leading the clinical trial. Dr David Ketteridge, is a Paediatrician and Metabolic Physician at the Adelaide WCH, and has extensive experience in treating lysosomal storage disorders.

MPS-6 clinical trials will be conducted in Brazil due to a large patient population. This will be a double blinded, placebo trial with 12 subjects, dosed weekly for 24 weeks. Primary endpoint is safety, key secondary endpoints are pain and function, and pharmacokinetics. Read out of top line data is anticipated for the end CY 2022/early 2023, this can change subject to regulatory approvals.

This trial will provide Paradigm with comparator data of the activity of PPS versus placebo in the MPS- 6 population. ANVISA, the Brazilian regulatory agency has confirmed acceptability of Paradigm's clinical program and study endpoints. This is a good first step that will build on commercial studies to follow across further MPS conditions.

Mucopolysaccharidosis type 1 (MPS-1)

MPS-1 is a condition that affects many parts of the body. It is a progressively debilitating disorder; however, the rate of progression varies among affected individuals. The condition is caused by mutations in the IDUA gene. These mutations lead to reduced levels, or the complete lack of the IDUA enzyme. Without the proper amount of this enzyme, large sugar molecules called glycosaminoglycans (GAGs) accumulate within cells called lysosomes. This causes the lysosomes to increase in size, causing many different organs and tissues of the body to become enlarged. This leads to the medical problems seen in the condition.

People with severe MPS-1 typically have earlier onset of symptoms, a decline in intellectual function, and a shorter lifespan. Although there is no cure, bone marrow transplant, and enzyme replacement therapy are treatment options that may help manage the symptoms of this condition.

Signs and symptoms are not present at birth, they begin to appear during childhood. People with severe MPS-1 develop features of this condition earlier than those with attenuated MPS-1. The following are most common signs and symptoms:

- Enlarged head, lips, cheeks, tongue, and nose.
- Enlarged vocal cords, resulting in a deep voice.
- Frequent upper respiratory infections.
- Hepatosplenomegaly (enlarged liver and spleen).
- Narrowing of the spinal canal (spinal stenosis).

Mucopolysaccharidosis type 6 (MPS-6)

Mps-6, also known as Maroteaux-Lamy syndrome, is a progressive condition that causes many tissues and organs to enlarge and become inflamed or scarred. Skeletal abnormalities are also common in this condition. The rate at which symptoms worsen varies among affected individuals.

People with MPS-6 generally do not display any features of the condition at birth. They often begin to show signs and symptoms during early childhood. The features of the condition include a large head (macrocephaly), a buildup of fluid in the brain (hydrocephalus), distinctive-looking facial features that are described as "coarse," and a large tongue (macroglossia). Affected individuals also frequently develop heart valve abnormalities, an enlarged liver and spleen (hepatosplenomegaly), and a soft out-pouching around the belly-button (umbilical hernia) or lower abdomen (inguinal hernia)

The life expectancy of individuals depends on the severity of symptoms. Without treatment, severely affected individuals may survive only until late childhood, or adolescence. Those with milder forms of the disorder usually live into adulthood, although their life expectancy may be reduced. Heart disease, and airway obstruction are major causes of death in people with MPS-6

Current treatments

Current treatment for MPS patients includes enzyme replacement therapy (ERT) which acts to reduce non-neurological symptoms and pain and improve survival. MPS patients undergoing approved ERT however continue to report ongoing stiffness, pain, inflammation, and heart and airway soft tissue manifestations. The current standards of care are not adequate in treating pain associated with joint inflammation and musculoskeletal issues. Current treatment costs equate to a market size of around US$1.4bn per annum, with BioMarin Pharmaceuticals ERT treatments costing US$300,000 – US$600.000 per annum.

Orphan Drugs

In 2019 The Centre for Drug Evaluation and Research (CDER) approved 21 of 48 novel drugs (44%) to treat rare or 'orphan' diseases. As so few patients suffer from these rare diseases, there are often scarce, or no drugs available to treat these conditions. Paradigm has received confirmation from both the FDA and EMA that MPS-1 and MPS-6 are orphan diseases. Generally, orphan drug clinical trials are single arm (no placebo), non-randomised, and open label. A safety phase 1 clinical trial is seldom required, with phase 2 and 3 able to be combined with a low patient population.

The benefits orphan designation approval provides to Paradigm:

- Tax credits for qualified clinical testing.
- Waiver of New Drug Application (NDA)/Biological Licensing Application (BLA) user fees.
- Eligibility for a 7-year marketing exclusivity upon marketing approval. If granted, the drug will have a status which gives companies exclusive marketing and development rights along with other benefits to recover the costs of researching and developing the orphan drug.

Why PPS?

Studies have shown there to be a strong indication of iPPS being an effective and potential treatment for MPS-1 and MPS-6.

Professors Schuchman and Calogera (Mt Sinai) defined the rationale for iPPS in human clinical trials. Their pioneering preclinical work on the effects of iPPS in animal models of MPS demonstrated that iPPS was able to:

1. 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,
2. Inhibit the inflammatory responses due to TLR-4 signaling by the accumulated GAGs.

Phase 2a open label study (n=4)

Paradigm/Hennermann et al showed promising results which warrant further studies. The conclusions of this trial were:

IPPS treatment was well tolerated and showed a significant reduction of urinary GAG excretion (Chart 6). Chart 7 shows improvement of joint/mobility and pain, above any beyond ongoing/existing ERT treatment.

Chart 6 – Urinary GAG excretion

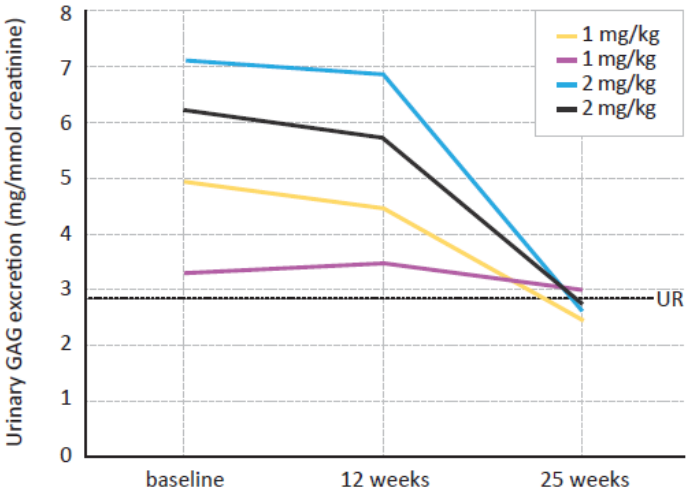
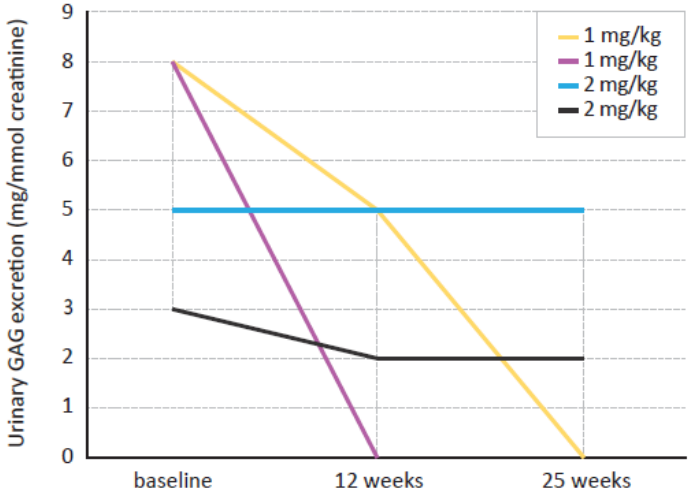


Chart 7 – Pain score



Source: Paradigm

The findings presented by Dr Furujo at the WORLD Symposium further demonstrate that iPPS could have a positive impact on pain and physical function in patients suffering from MPS.

The results (right), show there was a reduction in the inflammatory markers (Chart 8), and urinary GAG levels (Chart 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.

Understanding the results

In MPS animal models, PPS reduces the concentrations of glycosaminoglycans (GAGs) in tissues and body fluids and improves cartilaginous and osseous pathologies. The objective of this study was to investigate safety, clinical effects, mobility, and pain reduction of PPS treatment in MPS-1 patients.

Four MPS-1 Hurler-Scheie/-Scheie patients (three female and one male) were included in the study. All patients were on enzyme replacement therapy since 9.45 ± 3.75 years. PPS was applied subcutaneously in two patients with 1 mg/kg, and in two patients with 2 mg/kg, weekly for 12 weeks and then fortnightly for 12 weeks. The 24-week treatment with iPPS was well tolerated by all patients.

Chart 8 Inflammatory markers

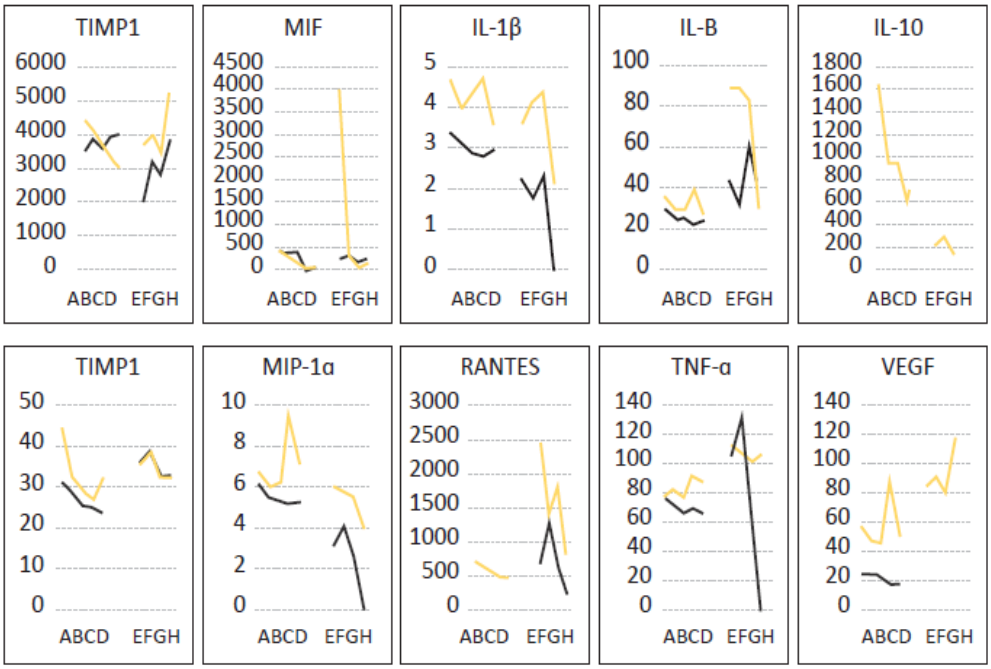
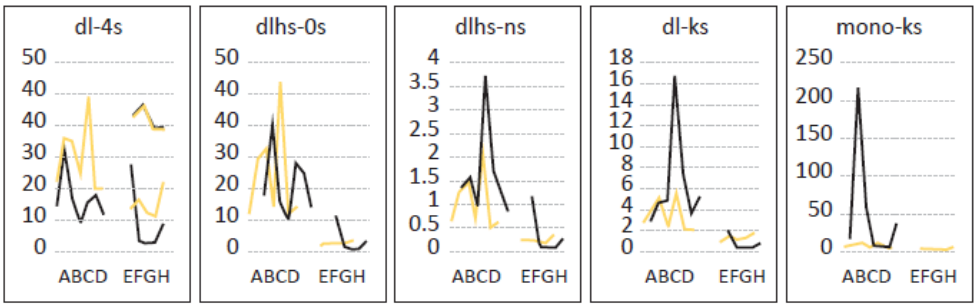


Chart 9 Urinary GAG levels



Source: Paradigm

Urinary GAG concentrations were reduced from 4.13 ± 1.17 at baseline, to 2.69 ± 0.36 mg/mmol creatinine after 24-week treatment with 1 mg/kg iPPS, and from 6.71 ± 0.62 to 2.65 ± 0.09 mg/mmol creatinine with 2 mg/kg iPPS. An improvement in range of motion was noted in three out of four patients. The pain intensity score was reduced from 4.5 ± 1.77 at baseline to 1.8 ± 0.47 after 24-week treatment with 1 mg/kg iPPS; patients with 2 mg/kg iPPS already had minimal pain at the start of the study.

IPPS treatment in a small number of adult MPS-1 patients was well tolerated and resulted in a significant reduction of urinary GAG excretion and an improvement of joint mobility and pain.

How is MPS currently treated.

There is no cure for these disorders. Medical care is directed at treating systemic conditions and improving the person's quality of life. Changes to the diet will not prevent disease progression.

Surgery can help drain excessive cerebrospinal fluid from the brain and free nerves and nerve roots compressed by skeletal and other abnormalities. Corneal transplants may improve vision among individuals with significant corneal clouding. Removing the tonsils and adenoids may improve breathing among individuals with obstructive airway disorders and sleep apnea. Some people may require surgical insertion of an endotracheal tube to aid breathing.

ERT is currently in use for MPS-1, MPS-2, MPS-4A, MPS-4, MPS-7, and tested in other MPS disorders. ERT involves an intravenous solution containing an enzyme that is deficient or missing from the body. It does not cure the neurological manifestations of the disease but has proven useful in reducing non-neurological symptoms and pain.

Bone marrow transplantation (BMT), and umbilical cord blood transplantation (UCBT), have had limited success in treating MPS. Abnormal physical characteristics, except for those affecting the skeleton and eyes, may be improved, but neurologic outcomes have varied. BMT and UCBT are high-risk procedures and are usually performed only after family members receive extensive evaluation and counseling. All forms of treatment for MPS are expensive.

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

Enzyme replacement treatment options

Drug	Year approved	Company at approval	Condition	2017 Revenues (US$ million)	Patients in NDA
Aldurazyme™	2003	BioMarin Pharmaceuticals	MPS I	90.0	45
Elaprase®	2006	Shire Pharmaceuticals	MPS II	615.7	96
Naglazyme®	2005	BioMarin Pharmaceuticals	MPS VI	332.2	56
VIMIZIM®	2014	BioMarin Pharmaceuticals	MPS IVA	413.3	176
Mepsevii™	2017	Ultragenyx Pharmaceuticals	MPS VII	5.4	23

Despite the small populations each ERT drug serves, they remain enticing markets. The above table details the five MPS ERT treatments.

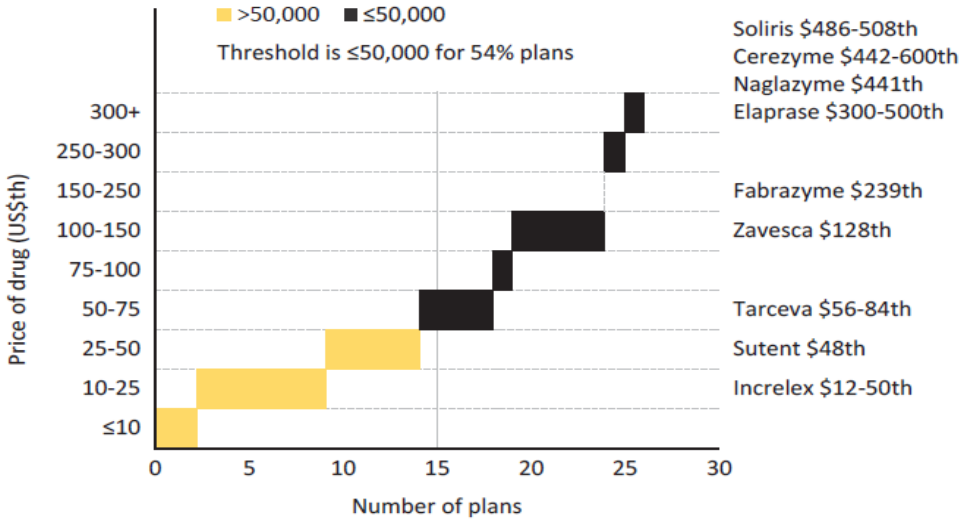
Addressable market – Pricing

Given the life expectancy for MPS suffers is unpredictable (7-30 years), arriving at an accurate addressable market becomes blurred.

Drug	Indication (US pravelence)	Mode of administration	Therapeutic options available	Annual cost, US$thousands
Sunitinib malate (Sutent)	Advanced renal-cell carcinoma (~90,000) Gastrointestinal stromal tumor (2040	Oral	X	48,000
Erlotinib (Tarceva)	Non-small-cell lung cancer (148,800) Pancreatic cancer (~33,000)	Oral	X	56,000–84,000
Miglustat (Zavesca)	Gaucher disease type I (~4000)	Oral	X	128,000
Mecasermin (Increlex)	Growth failure (~30,000 overall, ~6000 severe form)	Subcutaneous injection	X	12,000–50,000
Agalsidase beta (Fabrazyme)	Fabry disease (2564)	Infusion	X	239,000
Idursulfase (Elaprase)	Hunter syndrome (~1500)	Infusion		300,000–500,000
Galsulfase (Naglazyme)	Mucopolysaccharidosis VI (1200)	Infusion		441,000
Imiglucerase (Cerezyme)	Gaucher disease type I (~4000)	Infusion	X	442,000–600,000
Eculizumab (Soliris)	Paroxysmal nocturnal hemoglobinuria (~1505)	Infusion		486,000–508,000

Source: InVentiv Advance Insights, Somerset, NJ.

Potential revenue is estimated on regular treatments, weekly and fortnightly, as designed in current Phase 2 MPS-1 clinical trial. A broad pricing range will capture the scope of possible outcomes. The above & to the right table provide an example of the pricing per annum of current orphan drugs (note: MPS-6 US$441,000).



Source: Per above

Notable activity in the orphan drugs by Big Pharma

In May 2019, Pfizer Pharmaceuticals paid €303m (US$370m) upfront for Therachon Pharmaceuticals, (a private Swiss biotech known for its experimental therapy to treat dwarfism). The acquisition makes Pfizer a rival to BioMarin Pharmaceuticals Inc (NASDAQ: BMRN US$13.8bn), a leader in the field of ERT with several drugs in market to treat various MPS disorders. Pfizer will follow up with a payment up to €420m (US$516m) dependent on Therachon reaching milestones in the development of its drug improving bone growth in achondroplasia. This genetic condition inhibits bone growth, resulting in dwarfism, short limbs, and other complications such as arthritis and bowed legs. Achondroplasia is the most common type of short-limbed dwarfism. The condition occurs in 1 in 15,000 to 40,000 newborns.

Phase 1 clinical trial to evaluate pharmacokinetics, safety and tolerability of single, or multiple subcutaneous doses of recifercept is now active. 18 healthy adults will receive recifercept, an innovative medicine for achondroplasia. This is the first step in the evaluation for safety, results are not expected until April 20th 2021.

Why is this relevant? The dominance by large pharmaceutical companies of the orphan market has fueled calls to reform the Orphan Drug Act. Regardless, orphan drug sales are forecast to increase from US$119bn in 2018, to US$217bn in 2024. With an estimated 7,000 orphan diseases, one out of every 10 Americans lives with a rare condition. After nearly four decades of relatively consistent growth, orphan drugs now comprise a cornerstone of the pharmaceutical market, with this category predicted to generate more than 18% of overall prescription sales by 2024. As mentioned earlier, in 2019 just under half (44%) of new FDA approvals were for orphan drugs.

How does this relate to Paradigm

Pending successful clinical trials for MPS conditions, PPS has the potential to be equally important as the treatment for KOA. The capital outlay by Pfizer is a clear indicator of how attractive orphan drugs are becoming by Big Pharma. We would not be surprised if a number of eyes aren't following with close interest given Paradigm's initiation of clinical trials.

It is possible phase 2 clinical trials alone will satisfy a NDA by the FDA. Further, if iPPS is successful in treating both MPS-1 & MPS-6 it could indicate potential efficacy for other forms of MPS. This remains to be seen, however based on early indications as illustrated above, successful MPS trials have the potential to dramatically increase Paradigm's value offering. This is incredibly exciting as a good portion of US$1.4bn revenue currently generated on an annual basis becomes well within Paradigm's reach.

Provisional Registration Pathway

The standard registration process for prescription medicines consists of eight phases, with eight milestones. Internal business practices (milestone process) for the standard registration process aim to process submissions within a target timeframe of 220 working days (refer graph p.39).

The provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data is still required.

Status at present – The TGA is known to be less advanced / organised to their global counter parts EMA and FDA. Whilst both agencies have accepted Paradigm's Japanese populated pharmacokinetic data, the TGA has requested further data to be collected from a Western population. There are two pathways PPS is broken down, having the potential for large genetic variation dependant on ethnicity. One pathway is independent of race, and consistent with all types, whilst the second pathway is not. The TGA has requested Australian pharmacokinetic data.

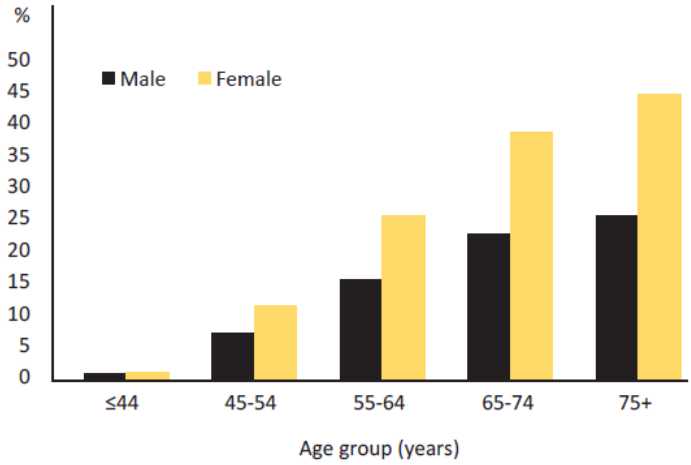
The TGA has also requested a durability study in conjunction with updated domestic pharmacokinetics. Whilst the TGA has approved iPPS administration through SAS for some time, they seek understanding of tenure before re-dosage is required.

Pending approval by the TGA, Paradigm will have a rolling two-year period in which they can distribute PPS. The company would have a total of six years to provide ongoing efficacy and safety data for full registration.

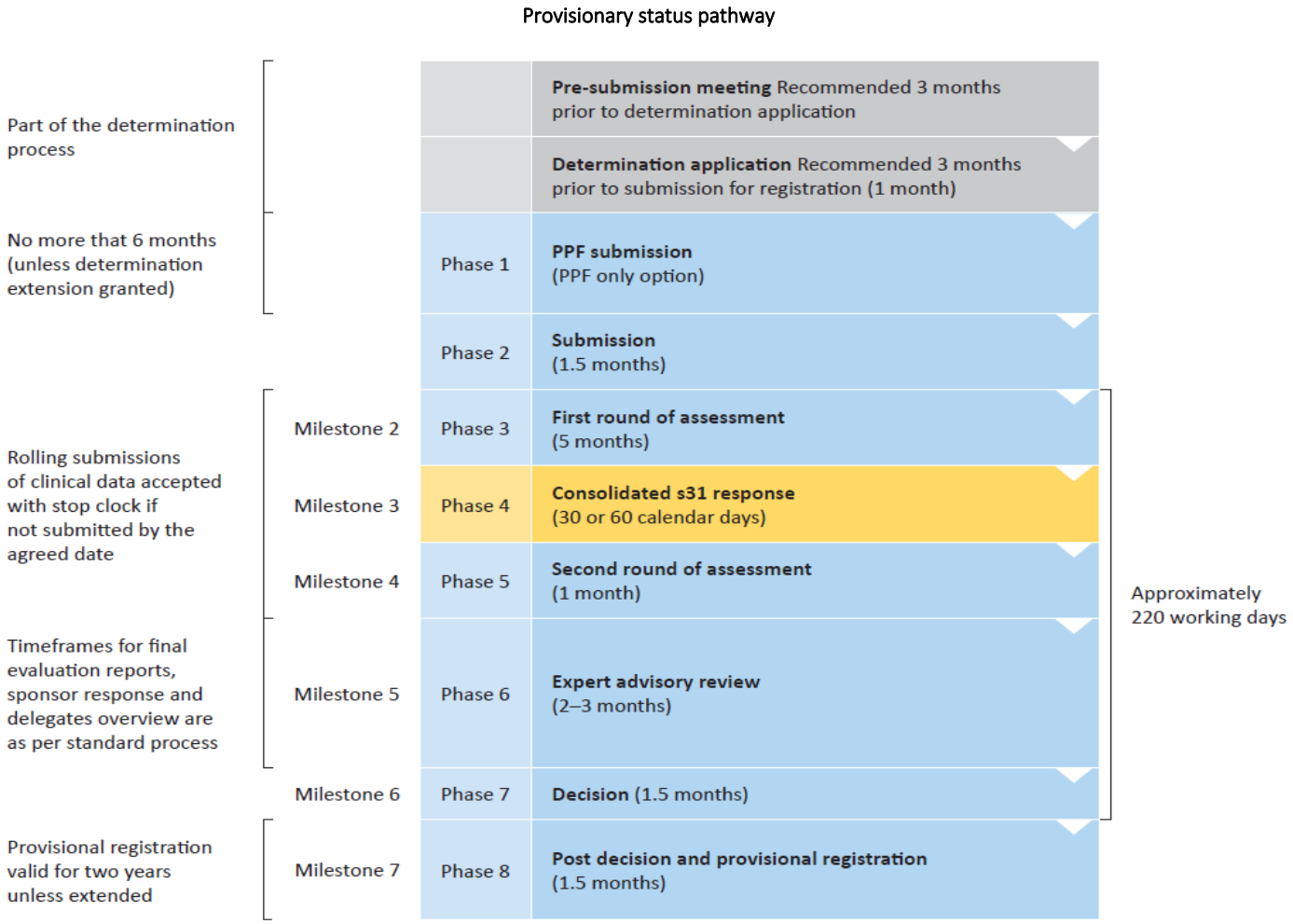
Revenue - There is an estimated 2.2 million (9.3%) Australians who have OA, representing over half (62%) of all arthritic conditions. OA affects people of all ages, the prevalence increases sharply from the age of 45 years. 1 in 5 Australians (22%) over the age of 45 has OA, and is most common in adults aged 75 and over, with just over one third (36%) of people in this age group with the disease (Figure 2). OA is more common among females than males, affecting 10% of females compared with 6.1% of males (total population after adjusting for age).

At present the market price is yet to be determined. Biomarker clinical trial results are scheduled for read out 2H CY2021. These results will influence the price of PPS if proven to have DMOAD capabilities. Pricing per person is likely to be no less than US$2,500, with potential to increase based on trial results as mentioned.

Figure 2: Prevalence of self-reported osteoarthritis, by age and sex 2017-18



Source: https://www.aihw.gov.au/



Source: Therapeutic Good Administration (TGA)

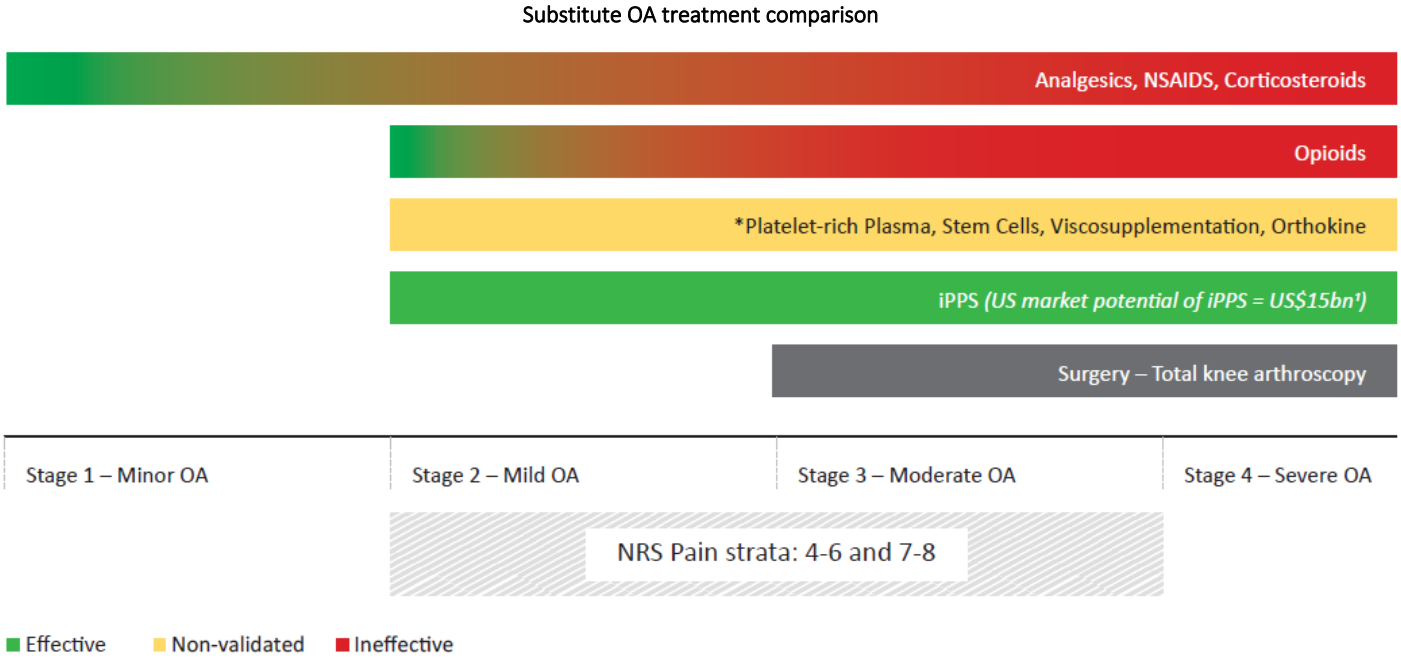
Substitute treatments

Given the size of the OA market it is expected that continuing attempts to develop a cure will be made in perpetuity. As it stands there are few safe treatments that have the potential to adequately treat moderate to severe OA.

Biosimilars – do they pose a threat? Therapeutic proteins are next-generation drugs in the prevention and treatment of diseases, in particular human critical illness. The expiration of patents in originally approved biopharmaceutics has stimulated great excitement, and subsequent development of 'follow-on' versions of these first-in-line biotherapeutic products, known as biosimilars or biobetters. Biosimilars are a new class of drugs intended to offer comparable safety and efficacy, (or clinical equivalence) to their original reference products which are brand name drugs and no longer under patent coverage. However, preparing exact copies of biologicals is more challenging than replicating small molecules due to their structural complexity, intricate manufacturing processes, and their potential risks for increased immunogenicity. Therefore, specific regulatory approval pathways and guidelines must be followed when creating biosimilars.

Real life example – Abbvie Pharmaceuticals (NYSE: ABBV) Humira® (adalimumab – a monoclonal antibody) indicated for the treatment of rheumatoid arthritis and other inflammation. Generic competition to Humira ®, which in2019 generated sales just over US$19 billion, is not expected until 2023. Humira® was first approved in the U.S. in December 2002 and the first biosimilar was not approved until 2016. As a result, Abbvie decided to discontinue the production of Humira® by 2023 when its patent expires. Fortunately, in this instance Abbvie has been able to replace its top-selling drug Humira® with two newer medicines Skyrizi® and Rinvoq®. Given Abbive has exclusivity until 2023, the company has increased its price by 16%. There are eight FDA approved copies of Humira® that will be available from 2023.

The diagram below lists the various treatments that are currently available for the treatment of OA. First line therapy is for anyone suffering from minor to mild OA, sufferers will typically be advised to lose weight and prescribed NSAID's or analgesics. For more severe cases this treatment is not effective, with longer term use linked with serious gastrointestinal and cardiovascular side effects.



Source: Paradigm

Corticosteroids are considered second line therapy, and effective anti-inflammatory drugs, however are contra-indicated for long term/repeat use. Failing first line therapy, General Practitioners have limited options, none of which treat underlying pathology (accept total knee arthroscopy) and only treating pain.

Opioids - Are effective for short term use post surgery reducing pain up to 45% (on average 30%). However, opioids can be abused and incorrectly prescribed for extended periods. Incorrect opioid consumption is considered an epidemic in the U.S. (see Opioids p.4).

Platelet-rich plasma, stem-cell, viscosupplementation, orthokine - These treatments come with complications and biases as they are still in early stages of research. A great deal of published data acknowledges a lack of quality of clinical trials (as double-blinded, placebo-controlled studies), creating difficulty for sustaining the clinical use of PRP. Thus, are many years from being considered an acceptable option. These treatments are invasive and expensive, with the added risk of complications from surgery.

Surgery, total knee arthroscopy – Last resort, only when chronic pain is restricting a person from simple everyday requirements. Post surgery patients should be able to stop using crutches or walking frames resuming normal leisure activities after six weeks. However, it may take up to three months for pain and swelling to settle, and up to a year for leg swelling to disappear. Total knee arthroscopy can cost A$30,000 or more.

Given the above, PPS could be both a second, and first line treatment. Providing Phase 3 OA clinical trial endpoints are achieved in line with Phase 2b OA clinical trial, the above available treatments will be no comparison. PPS has the ability to revolutionise the OA market in its entirety. PPS would be superior for safety, cost, accessibility and administration, and would have huge benefits for the medical insurance industry, as well as improve the lives of countless suffers who are addicted and dependant on opioids.

There are no available treatments that improve the underlying pathology of OA. All approved treatments deal with symptoms, whilst having no positive impact on joint integrity. It is widely accepted, the prolonged use of the above options contribute to the advancement of BME, and the deterioration of joints.

ADAMTS5 – A 'disintegrin and metalloproteinase with thrombospondin motifs 5'(distinct protein module/or enzyme that breaks down cartilage), was focused on by Servier and Galapagos Pharmaceuticals in light of evidence that increases in the activity of the aggrecanase triggers OA by driving cartilage aggrecan loss. However, as at October 16th 2020, Galapagos and Servier's GLPG1972 inhibitor failed to improve outcomes in knee OA during a phase 2 clinical trial.

The primary endpoint looked at changes in cartilage thickness from baseline to week 52 in patients administered placebo compared to their peers who received one of three doses of GLPG1972. Cartilage thickness reduced by 0.116 mm in placebo patients over the course of the clinical trial. The smallest reduction, 0.068 mm, was seen in the low-dose group, but fell short of statistical significance.

With medium and high doses performing comparably to placebo, with reductions of 0.097 mm and 0.085 mm respectively, the primary endpoint was largely devoid of positive signs. The decision to discontinue was confirmed by the failure of GLPG1972 to beat placebo against secondary endpoints.

IPPS - Zilosul® has the ability to inhibit ADAMTS5

PPS targets NF-kappaB (transcription factor) which leads to the cascade of pro inflammatory mediators of pain and destruction of cartilage. Cytokines up regulate enzymes such as ADAMTS5 increasing the amount of protein content which leads to the destruction of cartilage. PPS targets inflammation which is a key driver of pain and tissue enzyme degradation. PPS has been shown to switch off this process whilst at the same time directly inhibiting ADAMTS5.

Through this process of downregulating cartilage degrading enzymes, BME's have been shown to regress. This indicates that PPS has the potential to reverse the breakdown of cartilage, thus having DMOAD potential. Phase 3 trials will have this as a secondary endpoint having returned promising results in Phase 2b clinical trials (refer p.17).

Paradigm's iPPS (Zilosul®) treatment vs OA drug candidates currently in development

	Paradigm (ZILOSUL®)	NSAID (ibuprofen etc)	Opioid (oxycodone etc)	Corticosteroid/ Cortisone	Joint Replacement
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology	✓				✓
Well-tolerated	✓				
Non-addictive	✓	✓		✓	✓
Anti-inflammatory	✓	✓		✓	
Non-surgical	✓	✓	✓	✓	

Source: EBSCO

Zilosul® - the only OA drug/treatment in its class that treats pain, is safe, and preserves joint integrity.

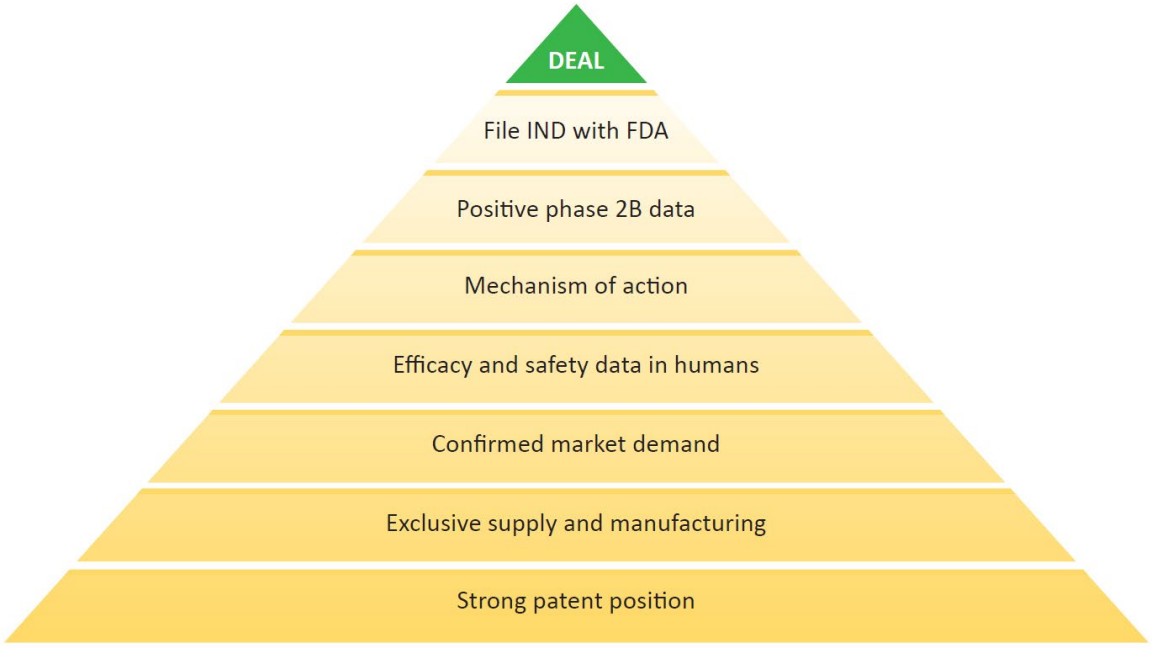
	Paradigm (ZILOSUL®)	Anti-NGFs (Tanezumab®)	Stem Cell & PRP treatments	Invossa® TissueGene's Cell/ Gene Therapy	CNTX-4975 Centrexion's trans-capsaicin
Treats the symptoms of OA (pain & function)	✓	✓	✓	✓	✓
Treats underlying pathology (potentially disease modifying)	✓	✗	✓	✓	✓
No undesirable side-effects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

Source: EBSCO

Partnership eligibility

Paradigm on the 8th April 2020 completed a placement of A$35 million thought to see the company through to read out of phase 3 OA clinical trials. Prior to this, a deal with Big Pharma was more likely. As at February 2021 it is evident Paradigm will require additional capital to fund a revised phase 3 clinical trial program, as well as further capital to fund trials for other PPS indications. The company has openly stated they are strengthening the board and management for commercialisation, acknowledging that a partnership and distribution agreement is necessary to reach global markets. Milestone payments through partnerships may be preferable to issuing equity.

The below stages are complete with Paradigm in ongoing discussions with several interested Big Pharma.



Source: Research Gate

1. Strong patent position / 2. Exclusive supply and manufacturing – 29th September 2020 BPC and Paradigm amended the previous agreement extending the exclusive supply of PPS for a term of 25 years from the date of marketing approval. This is crucial to Paradigm's commercial plans and represents a further significant de-risking for the company. Patents for MPS, BME, Alphavirus, Respiratory Disease and others extend many years (see p.24 for further patents across all indications).

3. Confirmed market demand - Centers for Disease Control estimates that 63 million U.S. adults have some form of arthritis, a figure that is projected to reach 78 million by the year 2040. While there are estimated to be more than 100 types of arthritis, OA is the most common form, affecting 33 million U.S. adults. This number is expected to grow in the coming years at a CAGR of 8.1%, driven by ageing, obesity and increasing sports injuries (see p.5 for addressable market).

4. Efficacy and safety in humans - Pain reduction in 76 SAS patients (using WOMAC), showed that iPPS formulation is well tolerated and demonstrated continued safety with no serious adverse events. These results provide important RWE illustrating anticipated responses in everyday clinical practice supporting Paradigm's phase 3 OA clinical trials (detailed results can be found in SAS p.12, EAP p16, and Phase 2b clinical trials p.17).

5. Mechanism of action (MOA) – In a peer reviewed article published September 26th 2019 shows for the first time the effects of PPS on human primary osteocytes isolated from the subchondral bone in patients with OA of the knee. It is the first demonstration of the production and secretion of NGF/proNGF by this cell type. PPS inhibited basal and TNFα-induced levels of proNGF secretion and TNFα induced NGF mRNA expression. PPS also inhibited TNFα-induced levels of the collagenase MMP-13. Together, this provides evidence that PPS may act at multiple levels to suppress the release of NGF and potentially other pain mediators in the subchondral bone, to ameliorate pain associated with Knee OA. (See p.20 for in depth background).

6. Positive Phase 2b clinical data – Paradigm achieved primary and secondary endpoints of improved knee function (activities of daily living (ADL)) and pain reduction to 6 months (reduction in KOOS pain score from baseline to day 165). Additionally, reduction in BML grade, size and volume in the iPPS groups as measured on MRI, highlighting the potential of PPS to slow the progression of the OA. This data corroborates previously reported top-line-data that PPS is safe, clinically effective, and statistically significant.

7. File Investigative New Drug application (IND) with the FDA – Paradigm received Type C meeting response for the purpose of protocol design for a successful IND, this was done via a written application. Whilst the written response is not binding, the FDA is more likely to accept any arguments years later providing the FDA's instructions are followed throughout any subsequent trials. There have been examples where companies have proceeded to late stage clinical trials to be refused registration due to lack of applicable data. This has the potential to be costly and delay the progression to commercialisation.

Paradigm has openly stated they are regularly talking to interested global pharmaceutical companies for potential licensing and distribution partnerships.

Historical Big Pharma interest in OA

Recent OA transactions

Companies		Compound	Region	US$ Upfront	US$ Total value	Status
Pfizer	Lilly	Anti-NGF	Global	200m	1.8bn	Submitted
Regeneron	Teva	Anti-NGF	Global	250m	1.25bn	Phase 3
Inflazome	Roche	NLRP3 inhibitor	Global	445m	Undisclosed milestones	Phase 1
		Global average		298m	1.5bn	
Galapagos	Servier	ADMATS-5 Inhibitor	EU	Unknown	346m	Discontinued Oct 20
Tissuegene, Inc.	Mundi Pharma	Gene therapy	Japan	27m*	591m	Phase 3
Regeneron	Mitsubishi Tanebe Pharma	Anti-NGF	Asia	55m	325m	Phase 3
Regeneus	Kyocera	Stem cells	Japan	9m	10m	Phase 2
		Regional average		30m	318m	

Source: Paradigm

Pfizer/Lilly Pharmaceuticals -Tanezumab: Based on results from 2,996 patients who participated in phase 3 clinical trials, researchers reported increased doses of tanezumab was associated with a higher incidence of AE's, Specifically, the rates of AE's were 6.2% for patients receiving 2.5 mg doses of tanezumab, and 9% for those receiving 5 mg doses. For the group receiving NSAID's twice daily (and not tanezumab), the incidence was 4.5%. Whilst important endpoints were met across varying dosages, the incidence of AE's are concerning (p.27 for complete overview).

Regeneron/Teva Pharmaceuticals - Fasinumab: Patients with moderate to severe OA pain (knee or hip) and a history of inadequate response or intolerance to analgesics were randomised to receive fasinumab 1 mg, 3 mg, 6 mg, 9 mg, or placebo every four weeks over a 16 week period and were monitored up to week 36. Of the 421 randomised patients, 342 completed the 36-week study. All doses of fasinumab yielded statistically significant and clinically important reductions in pain compared to placebo. However, treatment emergent AE's were 17% with fasinumab, and 10% with placebo. As with tanezumab, AE's are concerning (p.32 for a complete overview).

Inflazome/Roche Pharmaceuticals - NLRP3 inhibitor : Inflazome announced on the 21st September 2020 that it closed a share purchase agreement with Roche (SIX: RO, ROG; OTCQX: RHHBY) in which Inflazome's shareholders received an upfront payment of €380m (US$ 467m), and are eligible to receive additional contingent payments to be made based on the achievement of predetermined milestones. The acquisition gives Roche full rights to Inflazome's entire portfolio which is composed of clinical and preclinical orally available small molecule NLRP3 inhibitors. Roche intends to develop NLRP3 inhibitors across a wide variety of indications with unmet medical need.

Galapaogs/Servier Pharmaceuticals – ADAMTS5 Inhibitor: Galapagos and Servier's GLPG1972 failed to improve outcomes in Knee OA patients in a phase 2 clinical trial. The failure of the ADAMTS5 inhibitor is a setback for Galapagos to expand its opportunities beyond its faltering JAK1 inhibitor filgotinib.

TissueGene Inc/Mandipharma Pharmaceuticals - Invossa-K™: Kolon Life Science announced on Nov 19th 2018 that the company signed a technology export contract with multinational company Mundipharma Pharmaeticals to launch Invossa-K, a cell gene therapy for OA treatment, developed by its subsidiary Kolon TissueGene in Japan. However, Kolon Life Science's Invossa-K (which was once considered a promising candidate as a new global drug), disgraced itself by being thrown out of the market two years after its approval. The problem regarding Invossa-K was ingredients used were different from those specified at the time of permission. It was revealed that the transgenic cells (TC), which was initially reported as cartilage-derived cells, were kidney-derived cells (GP2-293). The FDA has since approved the resumption of an Invossa-K phase 3 clinical trial to be conducted in the U.S.

Regeneron/Mitsubishi Tanabe Pharmaceuticals - Fasinumab : October 1ST 2015 announced a collaboration with Mitsubishi Tanabe Pharmaceutical Corporation (TSE: 4508) (MTPC) providing MTPC with exclusive development and commercial rights to fasinumab (REGN475), Regeneron's anti-NGF antibody in late stage development for musculoskeletal pain. 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. Multiple phase 3 trials have been conducted globally achieving statistically significant endpoints. However, safety remains an ongoing concern (p.32).

Regeneus/Kyocera Corporation – Progenza™**:** This partnership provides Kyocera with an exclusive licence in Japan to develop and commercialise Regeneus's lead mesenchymal stem cell (MSC) and secretome technology Progenza™, for the treatment of Knee OA. Progenza's™ mechanism of

actions turns inflammatory immune cells into anti-inflammatory cells, thereby addressing inflammation at its source. This downregulates pain causing signals and repairs damaged tissues, such as cartilage tissue, commonly found in joints such as knees and elbows. The company is currently in phase 2 clinical trial.

Ross River virus (RRV) / chikungunya virus (CHIKV)

Arthritogenic alphaviruses such as Ross River virus (RRV), and chikungunya virus (CHIKV) cause large scale epidemics of severe musculoskeletal disease and has been spreading globally since the introduction of CHIKV in July 2014, the virus now circulates the U.S.. The hallmark of alphavirus disease is crippling pain and inflammation of the joints that can persist for months or years and impact life quality, a similar immunopathology to rheumatoid arthritis. Chikungunya virus is the most well-known member of this family since it was responsible for two worldwide epidemics with millions of cases in the last 15 years. The disease mostly occurs in Africa, Asia and the Indian subcontinent.

Paradigm in partnership with Griffith University's Institute for Glycomics on December 9th 2019 reported impressive results from their Phase 2a clinical trials of a new drug candidate to treat viral arthritis caused by mosquito-borne alphavirus infections, including the debilitating Ross River virus (RRV) and chikungunya virus (CHIKV).

"We are extremely pleased that Paradigm's Phase 2a clinical trials have passed both safety and efficacy measures amongst participants with chronic RRV-induced arthralgia who were treated with the injectable pentosan polysulfate sodium (iPPS) drug candidate,"

"At patients their three-month follow-up, 72.7% of those participants treated with iPPS showed near remission of symptoms in contrast to those participants who were administered with a placebo (14.3%)." said Dr Lara Herrero, research leader at the Institute for Glycomics and lead inventor of the technology.

Participants with RRV-induced arthralgia treated with iPPS met the aims for the pilot Phase 2a clinical study by demonstrating safety outcomes (primary endpoint) and effects on reduced disease symptoms (secondary endpoint). Five sites in Queensland and Victoria recruited 20 subjects with 18 completing treatment and follow up according to the protocol. The recruited RRV subjects were diagnosed by laboratory tests based on the Australian Government Ross River virus case definition and progressed from the acute phase of RRV fever (two weeks post infection) with sustained chronic symptoms between three to twelve months post-infection. During the onset of the chronic phase these patients sustained debilitating musculoskeletal pain for which there is no adequate standard of care treatments.

Paradigm's aim was to demonstrate PPS was safe in subjects with chronic and sustained RRV symptoms (arthralgia or joint pain). Additionally, the clinical trial aim was to obtain signals of efficacy of iPPS with regard to alleviation of disease symptoms. The per protocol population (a total of 18 subjects) in this pilot trial consisted of 11 iPPS treated and 7 placebo treated subjects.

Chart 1) Statistically significant at p<0.05 from baseline

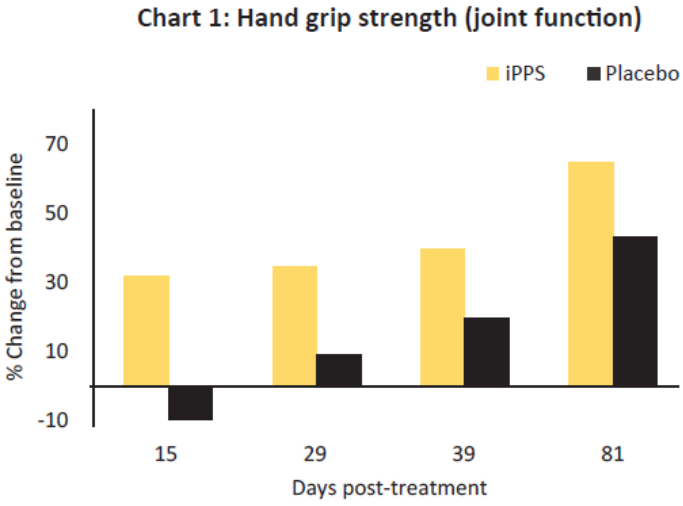
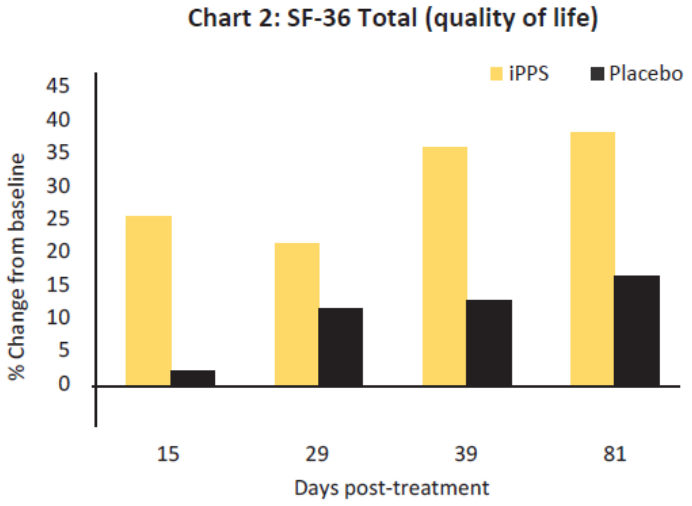


Chart 2) Statistically significant at p<0.05 from baseline

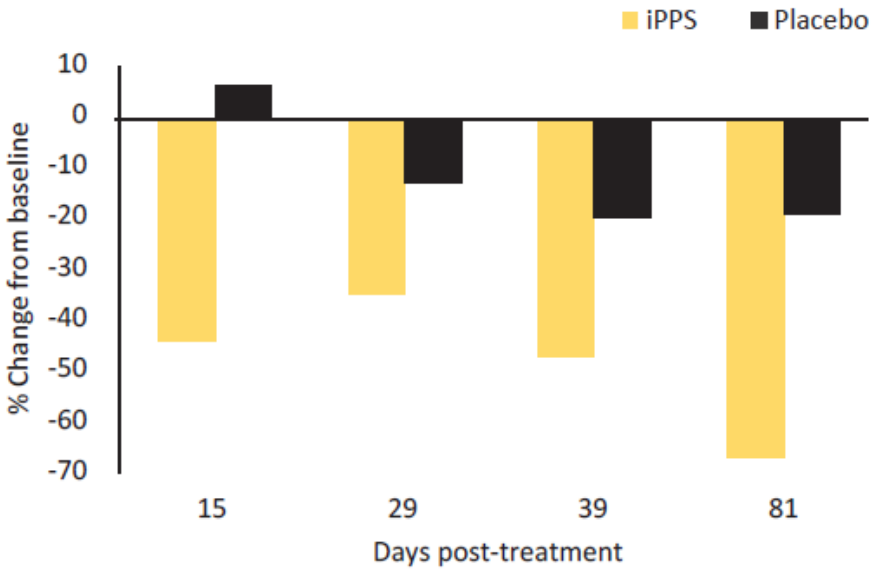


Source: Paradigm

Chart 1, In iPPS treated subjects, hand grip strength which measures the maximum isometric strength of the hand and forearm muscles using handgrip dynamometer showed clinically and statistically significant improvements from baseline throughout the study from day 15 to day 81. As shown in Chart 1, there were statistically significant differences from baseline at all time points in the iPPS treated group, 32% at day 15, 40% at day 39, and 66% at day 81. In contrast, the placebo group showed a 9% weakening of hand grip at day 15, which was statistically lower than the iPPS group. Furthermore, the changes in the placebo group did not demonstrate statistically significant improvement from baseline. Moreover, the improvement in hand grip strength in the iPPS group was clinically significant at all time points represented by changes of 5-6.5 kg increase from baseline.

Chart 2, The SF36 total scores showed statistical and clinical significant improvements from baseline at all post-treatment time points, peaking at 38.2 % at day 81. In contrast, placebo treated patients showed lower responses. Statistically significant differences were noted between PPS and placebo groups at day 15, day 39, and day 81.

Chart 3: RAPID-3 total (joint symptoms)



Source: Paradigm

Chart 3, RAPID-3 scores are correlated with clinical disease activity and enable the quantitative monitoring and documenting of improvement or worsening over time. A reduction in Rapid-3 signifies improvement in clinical disease activity. As shown in Chart 3, Rapid 3 total scores consisting of pain and function assessments showed statistical and clinically significant reduction in disease activity from baseline at all post treatment time points in the iPPS group. Statistically significant differences were shown between iPPS and placebo at day 15, however the placebo treated subjects showed a lower level of disease reduction compared to the iPPS group throughout the remainder of the treatment period.

Ross River virus (RRV): Most commonly occurs in adults aged 25–44 years, with males and females equally affected. The incubation period is 7–9 days, with a range of 3–21 days. In the acute phase, functional ability can be significantly impaired, with about half of patients requiring time off work. Joint pain is present in more than 95% of patients, and most commonly involve the fingers, toes, wrists, ankles, knees and elbows. Clinical manifestations of RRV disease could be prolonged, with reports of arthralgia, tiredness and depression persisting years after diagnosis.

Chikungunya (CHIKV): Is closely related to RRV, with symptoms of joint pain, fever, headache, conjunctivitis, and rash. The disease course is divided into an acute stage, lasting approximately one week, and a chronic stage, also known as the persistent stage, which can last from months to years. Acute fever and polyarthralgia are highly indicative of an infection, with arthralgia (joint pain) appearing in 30–90% of cases. Joint pain is often bilateral, symmetric, and debilitating. There are occasional ophthalmic, neurological, and cardiac symptoms. CHIKV causes more than three million infections worldwide each year. PPS offers hope in the global fight against these debilitating mosquito-borne alphaviruses. During the 21st century there have been two worldwide epidemics causing close to 10 million cases. CHIKV is undoubtedly a re-emerged disease threatening both tropical and temperate regions.

Several studies have searched for efficient antiviral molecules that have a broad-spectrum activity inhibiting all arthritogenic alphaviruses; however, despite a long list of antivirals efficient in vitro or in vivo, no treatment is currently available. Indeed, all clinical trials conducted until now have either failed, or have been inconclusive because of small test groups. Despite ongoing trials by other researchers, PPS appears to be the most promising. Dr Ravi Krishnan is in the process of completing documents for peer review.

Competition: Currently, there are two candidates in phase 2 clinical trials. One is a recombinant measles virus encoding the CHIKV structural proteins. The first results of the phase 2 clinical trial show encouraging signs. The second candidate is a VLP vaccine containing CHIKV structural proteins that is immunogenic and protective against a challenge infection in mice and rhesus macaques. Phase 1 clinical trial confirmed immunogenicity in humans after two injections and the absence of serious adverse events. A phase 2 clinical trial is currently underway.

Overall: The pilot RRV study has yielded promising safety data and key efficacy outcomes in the reduction of disease symptoms in this debilitating chronic phase of the disease. The human data on the effects of iPPS in RRV-induced arthralgia together with Paradigm's preclinical work on CHIKV will progress commercial discussions with the U.S. Department of Defense, and pharmaceutical companies with tropical disease programs.

RRV is Australia's most common arbovirus, which causes epidemic polyarthritis and arthralgia, with about half of patients experiencing fever and a rash. There is no current treatment available to shorten the duration or alter the course of RRV-induced arthritis.

Heart failure

Paradigm continues to develop Intellectual Property which it licensed from the University of Oslo (Norway) for the use of iPPS for the treatment of heart failure. Significant non-clinical work was performed in the past 12 months of which paradigm plans to build upon with non-clinical studies.

PPS: Inhibitor of Myocardial Extracellular Matrix Enzyme ADAMTS4 for treatment of Heart Failure and its progression

The primary objective of preclinical studies was to identify alterations in expression of ADAMTS versicanases and aggrecanases during development of heart failure, while evaluation of the effects of in vivo modulation of relevant changes in ADAMTS activity constituted the secondary objective.

The study discovered that iPPS-treatment improved systolic function in the pressure -overloaded heart. Findings suggest that a beneficial effect of PPS was mediated through a reduction in ADAMTS4 versicanase activity, based on the following main findings:

1) Increased ADAMTS4 expression and altered ADAMTS-induced versican degradation during heart failure development.
2) Inflammation-induced ADAMTS4 and versican synthesis in cardiac cells.
3) Improved contractile performance accompanied by indications of reduced ADAMTS4 versicanase activity in AB-rats receiving PPS. The findings shed light on a novel mechanism for heart failure development, and a promising novel heart failure therapy.

The trial : Myocardial levels of versican, aggrecan, and their ADAMTS cleaving proteases were examined in Wistar rats six weeks after aortic banding (AB), and versican and selected ADAMTS versicanases were further analysed in neonatal cardiomyocytes (NCM) and cardiac fibroblasts (NFB) after stimulation by inflammatory mediators. Based on the initial findings, ADAMTS4 was selected the most promising therapeutic target. Thus, rats with AB were treated with PPS, a polysaccharide with known ADAMTS4-inhibitory properties, and effects on versican fragmentation. Left ventricular function and geometry were evaluated.

Limitations

Further studies are needed to establish the cause-effect relationship between PPS, ADAMTS4-inhibition and improved contractile performance. Due to the lack of opportunity to subdivide AB-rats into the failing and non-failing phenotype during in vivo ADAMTS4-inhibition, the rats with AB receiving vehicle or PPS treatment should be regarded as a group consisting of both phenotypes. Although PPS treatment led to a significant improvement in parameters for systolic function, the heterogeneity within the group regarding heart failure development could render the study underpowered to detect other pathophysiological characteristics, such as left atrial diameter and lung weight. Studying the effects of PPS treatment at different time points after induction of pressure overload may reveal effects on these pathophysiological characteristics, however it was beyond the scope of this study. Furthermore, ADAMTS4-independent effects of PPS need to be explored in further detail in future studies. PPS also suppresses the activity of ADAMTS5, inflammatory mediators, and coagulation factors, effects that may contribute to the observed beneficial effect in the pressure overloaded heart. The role of aggrecanase activity exerted by ADAMTS1, -4, and -8 in heart failure progression will also be addressed in studies to come. A complete overview of preclinical studies can be found at :
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3940660/pdf/pone.0089621.pdf

The problem and the role PPS could play

Cardiac overload due to aortic stenosis or myocardial infarction causes adverse cardiac tissue remodelling which progresses to heart failure. As heart disease progresses into chronic heart failure, there is continued remodelling of the left ventricle. Muscle mass increases, the left ventricle enlarges, cardiac systolic and/or diastolic function declines, and symptoms of heart failure become evident. Current therapy with ß-blockers, ACE-inhibitors and AT2-antagonists are initiated soon after heart failure development but are inadequate in slowing disease progression. As mentioned above, PPS treatment demonstrated improved contractility of the heart in the pressure-overloaded heart failure preclinical model with an associated reduction in the enzyme ADAMTS4 versicanase, which is a proteoglycan degrading enzyme involved in adverse cardiac tissue remodelling. Paradigm believes its product (IM or SC administered PPS) can meet market needs that are not effectively managed by current cardiac drugs.

Why the excitement:

- PPS demonstrated benefits associated with unique anti-remodelling action in an established preclinical heart failure model.
- PPS provides a novel therapeutic modality not reported in other heart failure agents.
- No significant safety issues compared to significant side effects reported with current cardiac drugs.
- PPS has the potential to reverse progression of heart failure addressing unmet medical need.
- The heart failure market is projected to increase from US$3.2 billion in 2015 to US$11.8 by 2025.

Data supporting PPS as a treatment for Heart Failure in the aortic banding rat model:

- ADAMTS4-versicanase is a key target for treatment due to the pronounced increase in heart failure rats showing reduced Fractional shortening in aortic banding rats.
- Improved contractile function in PPS compared to vehicle-treated rats in AB-rats demonstrated by:
- 25% higher fractional shortening ($p<0.01$)
- 33% lower left ventricular diameter in systole ($p<0.01$).
- PPS-treatment reduced myocardial ADAMTS4 mRNA Levels
- PPS-treatment inhibited myocardial versican cleavage in AB-rats.

Figure A

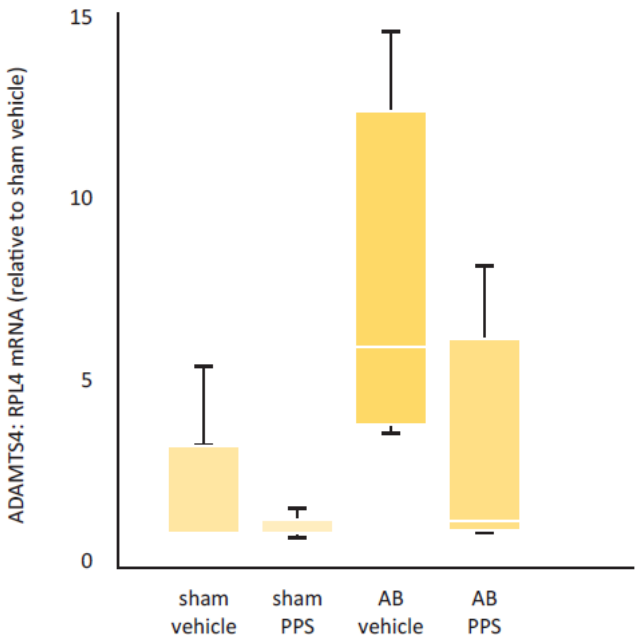
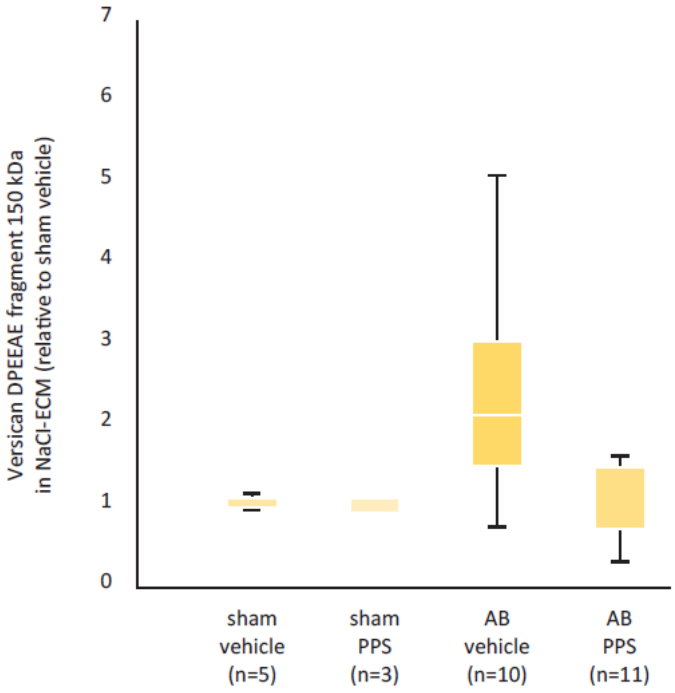


Figure B



Preclinical data : showing efficacy of PPS in aortic rat model of Heart Failure (Vistnes et al 2014).

PPS downregulates ADAMTS4 activity at the mRNA level (Figure A) in the aortic banding (AB) rat model which translated to reduction of ADAMTS4 enzymatic activity shown by reduction in versican cleavage fragments (Figure B). Versican cleavage fragments also contribute to cardiac edema

Valuation

A weighted probability of outcomes is not factored into our model. An investment in Paradigm is highly dependent upon successful phase 3 trials and considered binary. Traditionally phase 3 trials have a 50% success rate. The purpose of our forecasts is to illustrate how investors could be rewarded if Paradigm is successful. Given the conservative nature of our assumptions and the deliberate omission of several factors that could improve our final NPV's, we believe our final estimates reflect a generous margin of safety accommodating the requirement for a probability weighting.

We acknowledge Paradigm's success is based solely on PPS continuing to perform as it has in all trials and surveys to date, Phase 2b clinical trials, TGA SAS, and FDA EAP. Our assumptions reflect our best estimates of current market conditions and historical transactions. The ability to successfully commercialise Zilosul® pending successful phase 3 trials is a key risk. Paradigm's management has stated on several occasions the requirement to have all data necessary at the time of filing for NDA. The company is aware of past mistakes made by biopharmaceutical companies having to perform multiple further trials due to not following suggestions of the FDA. We feel comfortable Paradigm from their Type C meeting feedback, and subsequent alterations and extensions to their trial design mitigate this risk.

The current share price represents a substantial discount to what we consider is Paradigm's intrinsic value across multiple FCF variations. Given the nature of biopharmaceutical companies operations prior to commercial approval, we encourage our audience to look beyond the immediate to identify future value. The speculative nature of such positioning creates substantial scope for heavily skewed asymmetric returns. To encapsulate the vast number of possible outcomes we have moved away from a 'one size fits all approach' allowing the investor to decide what scenarios seem fair and reasonable. Across all assumptions our model uses the lowest number in a range of reasonable probabilities having significant flexibility to surprise on the upside, without needing to adjust for sizable deviations.

Assumptions.

- Paradigm is likely to establish multiple global partnerships after successful Phase 3 clinical trial readouts. We therefore believe that it is reasonable for Paradigm to demand higher royalty and milestone payments. Our estimates allow for royalty payments to Paradigm of between 15% and 35 %, (after marketing and distribution expenses). Royalty payments (%) from all global partners are expected to be aligned. Note: The average royalty rate for pre-phase 3 trials across 1000 companies as stated by Quintiles IMS Institute is 5-15%. 'Pending approval' royalty rates are shown to reach in excess of 25%. Royalty payments on all top line sales of 2% is payable to BPC.
- Given the size of historical milestone payments for OA (shown on p.43) we believe our model has potential to significantly understate the value of milestone payments. A successful phase 3 read out will significantly strengthen Paradigm's value proposition, and essentially provide any potential global partner with a risk free investment. Our range of US$100-400m is considered highly conservative assuming this outcome.
- It is reasonable to expect Paradigm to demand up to, and above US$ 600 million for North America alone. Equal milestone payments of US$ 200 million, 1) Submission of NDA, 2) FDA NDA approval, and, 3) Initial commercial sales. We would expect Europe and Australia to follow similar structures but at a lower amounts, US$400 & US$100 respectively. Japan is estimated at US$200+.
- Forecasting the balance of both royalty and milestone payments is difficult, and therefore our model illustrates a matrix of cash flows factoring in several outcomes. We acknowledge milestone payments could be trimmed considerably in favour of higher royalties.
- Our FCF is reverse engineered from conservative estimates of top line revenue, earnings before depreciation & amortisation, interest, and tax, and capital expenditure on R&D, (and other). We have used a discount rate of 20%. Our NPV does not include sales from any other PPS indication. Further evidence of safety and efficacy for other indications will allow us to adjust our forecasts appropriately in due course.
- Three main drivers of revenue for OA underpin our range of chosen growth rates, 1) OA sufferers will likely require re-dosage every year, 2) year on year additional patients will begin treatment (with a high % remaining as ongoing users), 3) Off label use will contribute to the addressable market.
- Given the above, and internal growth figures provided by Paradigm's statisticians, we are confident that our growth rates allow for significant upside. Our base growth rate of 33% is taken from an average of 15 repurposed molecules since 1995. All products had uninterrupted runways over a period of 10 years with no competing generic products. In some instances, growth rates exceeded 50% on average. We believe Paradigm can match, and possibly exceed 50%, significantly understating our forecasts.
- Paradigm is in a unique position, and whilst patents are important (expiring 2035 and beyond), the jewel in the crown for Paradigm is the company's exclusive supply agreement of PPS with BPC for 25 years from marketing approval. This agreement supersedes any patents Paradigm has (refer p.24) For this reason we believe Paradigm will be able to maintain pricing power for the duration of our forecasts (and beyond), allowing us to use a 15 year NPV with 10 years FCF, (see Elmiron® on p.23 for a RWE). For interest, we have provided shorter NPV scenarios, all of which are attractive given our assumptions.
- Our uptake curve to peak penetration is difficult to ascertain. Over the past 20 years 700 New Active Substances have on average reached this milestone after 12 years. We have provided a range of scenarios taking this into consideration. We believe our year on year growth figures, and medium term runway are conservative given structural tailwinds.

- A competing molecule identical to BPC PPS would take at least 10 years to pass all regulatory hurdles (as Paradigm is experiencing now). Given the DMF on file with the FDA has a fingerprint unique to BPC, the likelihood of an exact replica is essentially nil. Further, any other PPS molecule would take up to 20 years to develop, given the requirement to undertake toxicology trials, amongst other pre-clinical requirements. Considering numerous failed attempts over the past 75+ years, we feel confident in our 15-year NPV.
- Full year revenue is anticipated for CY 2026. We have not included any revenue in our model for CY2025, however it is likely first sales will commence midyear CY2025 (or earlier). Our NPV allows for delays in first revenue providing a margin of safety.
- Pending a harmonised global roll out in CY2026 we believe Paradigm can reach 1.4% of the addressable market. This being a conservative figure and forecast first full year revenue to range between 1% & 1.4% of the addressable market, for both Knee and Hip OA. We acknowledge some independent research suggests 2.2% is achievable, whilst this may be so, we prefer to remain conservative across all assumptions.
- Paradigm's addressable market is based on advanced Western demographics, USA, Canada, Europe 5 (UK, France, Germany, Italy, and Spain), and Australia. There are 72 million OA sufferers, 69% with Knee and Hip OA, and 81% dissatisfied with current treatments. We believe Paradigm can penetrate at least 10% of this market by 2035.
- Pricing of Zilosul® remains uncertain, however we do not envisage the price to be lower than US$ 2000. Paradigm has publicised US$ 2500 as its current go to market price. We believe this figure could be higher based on biomarker results from study OA-008, showing PPS to have DMOAD capabilities. Paradigm's closest competitor tanenzumab charges US$8000, with Humira (rheumatoid arthritis) costing US$5,500+ for a 30-day treatment. We understand for TGA SAS PPS 'pay-for-use' Paradigm is looking to charge up to A$4000. Our model assumes US$2000-US$2500 acknowledging that any price above US$2500 would understate our valuation.
- Global sales will be valued in US$, therefore our FCF figures are in US$. We have chosen not to covert to A$ despite Paradigm being listed in Australia. It is our belief Paradigm will become a global company with the majority of sales generated abroad. Currently US$ trades at a premium to A$ therefore understates the value of our NPV figures. Over the past 20 years the AUD/USD exchange rate has ranged from .51 to 1.10 averaging 76.8.

Taken into consideration (not included)

- Revenue from MPS is not included in our model, however MPS-6 & 1 are the most likely indications to modestly contribute to Paradigm's bottom line (earliest CY2025). MPS-6 if proven across all endpoints will likely be used as an adjunctive treatment alongside ERT. We consider it highly likely Paradigm will partner with a current ERT provider. Once again, partnering agreements would not be likely until after completion of phase 2/3 trials improving Paradigm's value proposition. At this stage it is premature to speculate on what figure we could attribute to a milestone payment, however we can estimate that PPS would likely demand 10% of the total cost of ERT treatment. MPS-6 treatment currently costs between US$400,000-500,000 (hence US$ 40,000-50,000 for Zilosul®). Brazil has circa 200 sufferers with an estimated 1100 globally. Before any royalty payments, sales would generate at full market penetration up to US$ 55 million per annum.
- If MPS-1 & 6 prove to be safe and have efficacy, it is possible Zilosul® will be approved for the treatment of all other MPS types. A better understanding of total MPS revenue will be determined as further data becomes available. We acknowledge our NPV and DCF is well understated if the above was to materialise. As with OA, we would expect higher royalty and milestones payments based on the asset being de-risked.
- Japan, China, and India remain incredibly attractive markets, however these regions will be required to perform their own independent domestic trials. Providing Paradigm's phase 3 trials are successful, these countries will be able to reduce the size of their trials to 1/10$^{th\ of}$ the size of Paradigm's 1500 participants phase three trials, requiring 150 participants.
- Revenue or milestone payments from any other MOA are not considered, however a milestone payment for MPS is believed likely. No allowances are made for M&A activity for additional repurposed molecules.
- Dilution of shareholder equity from exercised options or performance shares awarded to board and management (considered to be immaterial to overall cash flows and EV).
- Dilution of shareholder equity subsequent to the failure to attract capital via other avenues. We believe Paradigm will explore debt options, as well as stepping stone deals where potential global partners invest for the option (first right of refusal), of the asset pending successful phase 3 OA endpoints. This process is common in Europe and standard practice. Further, notching rights can be used allowing multiple interested parties to improve the price of this option.

- Revenue is based on the current addressable market as at 2021. Whilst growth in global OA sufferers is expected to increase steadily due to an ageing population and obesity, it was decided not to incorporate these aspects to illustrate the strength of Paradigm's forecast cash flows, providing a margin of safety.
- New global regions 2030 and beyond will likely approve Zilosul® (China, Japan, broader Asia,) as well as further European nations. No revenue from these regions is included in our model.
- Revenue from the TGA SAS 'pay for use' program is anticipated 12-18 months prior to global registration. However, this is not included and considered immaterial to our valuation.
- Griffiths University pre-clinical data for CHIKV is anticipated for 2H CY 2021, and will likely be Paradigm's first revenue. We anticipate a licence-out opportunity to a vaccine provider, as well as potential agreements with the U.S. Department of Health, and U.S. Defence Force. For the time being quantum around these relationships is difficult to assess

First three years X% growth, following four years X% growth, final two years X% growth (15 year time NPV) 10 Years FCF, first year revenue 2026 (cash at bank X m)

Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-3 = 33%, Year 4-7 = 25%, Year 8-10 = 15%)				
Market Cap. ($m)	790.00	1,020.00	1,250.00	1,480.00
Share Price ($) Cash = $100m	3.50	4.52	5.53	6.55
Market Cap. ($m)	890.00	1,120.00	1,350.00	1,580.00
Share Price ($) Cash = $200m	3.94	4.96	5.98	6.99
Market Cap. ($m)	990.00	1,220.00	1,450.00	1,680.00
Share Price ($) Cash = $300m	4.38	5.40	6.42	7.44
Market Cap. ($m)	1,090.00	1,320.00	1,550.00	1,780.00
Share Price ($) Cash = $400m	4.82	5.84	6.86	7.88

** 1.0% Addressable market / / Zilosul® price = US$2,000 / Lower range royalty = 15% after marketing and distribution costs*

*** 1.4% Addressable market / / Zilosul® price = US$2,500 / Higher range royalty = 35% after marketing and distribution costs*

Note: This is our most conservative base model, with a first year growth rate of 33%, in line with our assumption in reference to the average of 15 repurposed molecules over the past 25 years. We believe the year of peak sales, and prospective growth rates could be significantly understated in Paradigm's case.

Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-3 = 40%, Year 4-7 = 30%, Year 8-10 = 20%)				
Market Cap. ($m)	968.00	1,257.00	1,546.00	1,836.00
Share Price ($) Cash = $100m	4.28	5.56	6.84	8.12
Market Cap. ($m)	1,068.00	1,357.00	1,646.00	$1,936.00
Share Price ($) Cash = $200m	4.73	6.01	$7.29	8.57
Market Cap. ($m)	1,168.00	1,457.00	1,746.00	2,036.00
Share Price ($) Cash = $300m	5.17	6.45	$7.73	9.01
Market Cap. ($m)	1,268.00	1,557.00	1,846.00	2,136.00
Share Price ($) Cash = $400m	5.61	6.89	$8.17	9.45

** 1.0% Addressable market / / Zilosul® l price = US$2,000 / Lower range royalty = 15% after marketing and distribution costs*

*** 1.4% Addressable market / / Zilosul® price = US$2,500 / Higher range royalty = 35% after marketing and distribution costs*

Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-3 = 45%, Year 4-7 = 35%, Year 8-10 = 25%)				
Market Cap. ($m)	1,154.00	1,506.00	1,858.00	2,209.00
Share Price ($) Cash = $100m	5.11	6.67	8.22	9.78
Market Cap. ($m)	1,254.00	1,606.00	1,958.00	2,309.00
Share Price ($) Cash = $200m	5.55	7.11	8.66	10.22
Market Cap. ($m)	1,354.00	1,706.00	2,058.00	2,409.00
Share Price ($) Cash = $300m	5.99	7.55	9.11	10.66
Market Cap. ($m)	1,454.00	1,806.00	2,158.00	2,509.00
Share Price ($) Cash = $400m	6.44	7.99	9.55	11.10

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Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-3 = 50%, Year 4-7 = 35%, Year 8-10 = 20%)				
Market Cap. ($m)	1,235.00	1,613.00	1,992.00	2,370.00
Share Price ($) Cash = $100m	5.47	7.14	8.82	10.49
Market Cap. ($m)	1,335.00	1,713.00	2,092.00	2,470.00
Share Price ($) Cash = $200m	5.91	7.58	9.26	10.93
Market Cap. ($m)	1,435.00	1,813.00	2,192.00	2,570.00
Share Price ($) Cash = $300m	6.35	8.03	9.70	11.37
Market Cap. ($m)	1,535.00	1,913.00	2,292.00	2,670.00
Share Price ($) Cash = $400m	6.79	8.47	10.14	11.82

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First 5 years X% growth, following 5 years X% growth, (15 year time NPV) 10 Years FCF, first year revenue 2026 (cash at bank X m)

Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 33%, Year 6-10 = 20%)				
Market Cap. ($m)	831.00	1,075.00	1,319.00	1,563.00
Share Price ($) Cash = $100m	3.68	4.76	5.84	6.92
Market Cap. ($m)	931.00	1,175.00	1,419.00	1,663.00
Share Price ($) Cash = $200m	4.12	5.20	6.28	7.36
Market Cap. ($m)	1,031.00	1,275.00	1,519.00	1,763.00
Share Price ($) Cash = $300m	4.57	5.65	6.72	7.80
Market Cap. ($m)	1,131.00	1,375.00	1,619.00	1,863.00
Share Price ($) Cash = $400m	5.01	6.09	7.17	8.25

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Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 37%, Year 6-10 = 25%)				
Market Cap. ($m)	962.00	1,250.00	1,537.00	1,825.00
Share Price ($) Cash = $100m	4.26	5.53	6.80	8.08
Market Cap. ($m)	1,062.00	1,350.00	1,637.00	1,925.00
Share Price ($) Cash = $200m	4.70	5.97	7.25	8.52
Market Cap. ($m)	1,162.00	1,450.00	1,737.00	2,025.00
Share Price ($) Cash = $300m	5.14	6.42	7.69	8.96
Market Cap. ($m)	1,262.00	1,550.00	1,837.00	2,125.00
Share Price ($) Cash = $400m	5.59	6.86	8.13	9.40

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Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 45%, Year 6-10 = 30%)				
Market Cap. ($m)	1,244.00	1,625.00	2,007.00	2,388.00
Share Price ($) Cash = $100m	5.51	7.19	8.88	10.57
Market Cap. ($m)	1,344.00	1,725.00	2,107.00	2,488.00
Share Price ($) Cash = $200m	5.95	7.64	9.32	11.01
Market Cap. ($m)	1,444.00	1,825.00	2,207.00	2,588.00
Share Price ($) Cash = $300m	6.39	8.08	9.77	11.45
Market Cap. ($m)	1,544.00	1,925.00	2,307.00	2,688.00
Share Price ($) Cash = $400m	6.83	8.52	10.21	11.90

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Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 50%, Year 6-10 = 35%)				
Market Cap. ($m)	$1,495.00	$1,961.00	$2,426.00	$2,891.00
Share Price ($) Cash = $100m	$6.62	$8.68	$10.74	$12.80
Market Cap. ($m)	$1,595.00	$2,061.00	$2,526.00	$2,991.00
Share Price ($) Cash = $200m	$7.06	$9.12	$11.18	$13.24
Market Cap. ($m)	$1,695.00	$2,161.00	$2,626.00	$3,091.00
Share Price ($) Cash = $300m	$7.50	$9.56	$11.62	$13.68
Market Cap. ($m)	$1,795.00	$2,261.00	$2,726.00	$3,191.00
Share Price ($) Cash = $400m	$7.95	$10.01	$12.06	$14.12

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Note: The above four models are more aggressive suggesting consistent straight-line growth. It is not unreasonable to expect peak sales to extend well into 5-10 years. Given the size of the addressable market, with additional global regions approving Zilosul® Paradigm's uptake curve could track the above profiles.

First 5 years X% growth (6NPV) 6 Years FCF, first year revenue starting immediately (cash at bank X m)

Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 33%)				
Market Cap. ($m)	$1,084.00	$1,413.00	$1,741.00	$2,068.00
Share Price ($) Cash = $100m	$4.80	$6.25	$7.71	$9.16
Market Cap. ($m)	$1,184.00	$1,513.00	$1,841.00	$2,168.00
Share Price ($) Cash = $200m	$5.24	$6.70	$8.15	$9.60
Market Cap. ($m)	$1,284.00	$1,613.00	$1,941.00	$2,268.00
Share Price ($) Cash = $300m	$5.69	$7.14	$8.59	$10.01
Market Cap. ($m)	$1,384.00	$1,713.00	$2,041.00	$2,368.00
Share Price ($) Cash = $400m	$6.13	$7.58	$9.03	$10.49

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Discount Rate, 20%	Addressable Market / Zilosul® Price / Royalty Range			
	Lower Estimates*		Higher Estimates**	
Free Cash Flow - Year 1 ($m)	**150.00**	**200.00**	**250.00**	**300.00**
Estimated Growth Rates (Year 1-5 = 40%)				
Market Cap. ($m)	$1,241.00	$1,621.00	$2,002.00	$2,382.00
Share Price ($) Cash = $100m	$5.49	$7.18	$8.86	$10.54
Market Cap. ($m)	$1,341.00	$1,721.00	$2,102.00	$2,482.00
Share Price ($) Cash = $200m	$5.93	$7.62	$9.30	$10.98
Market Cap. ($m)	$1,441.00	$1,821.00	$2,202.00	$2,582.00
Share Price ($) Cash = $300m	$6.38	$8.06	$9.74	$11.43
Market Cap. ($m)	$1,541.00	$1,921.00	$2,302.00	$2,682.00
Share Price ($) Cash = $400m	6.82	8.5	$10.19	$11.87

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Note: The purpose of the above model is for illustration only. Given we have used a 6 year NPV (with no initial years of zero cash flow) it cannot be compared as like for like with our longer term cash flows. If the company was to begin first sales immediately, the above values are a starting point, keeping in mind these values would be larger with an extended cash flow period similar to our 10-15 year NPV's.

Profit & Loss	2020a	2021e	2022e	2023e	2024e	2025e
Revenue				41,443,000	200,000,000	400,000,000
R&D Tax Rebate	3,697,847	2,000,000	1,500,000	9,000,000	2,000,000	1,000,000
R&D expenses	-12,793,576	-25,000,000	-40,000,000	-50,000,000	-10,000,000	-10,000,000
Employee expenses	-1,226,649	-3,700,000	-4,700,000	-5,300,000	-6,000,000	-8,000,000
Sales, general and administration expenses	-2,939,988	-4,000,000	-4,500,000	-6,000,000	-7,000,000	-10,000,000
EBITDA	**-13,262,366**	**-30,700,000**	**-47,700,000**	**-10,857,000**	**179,000,000**	**373,000,000**
Intangible amortisation	-37,124	-35,000	-32,000	-30,000	-30,000	-30,000
Depreciation	-20,722	-25,000	-35,000	-35,000	-35,000	-35,000
Interest income/expense	997,647	630,000	441,053	91,654	2,300,000	3,357,000
Profit/Loss before income tax	**-12,322,565**	**-30,130,000**	**-47,325,947**	**-10,830,346**	**181,235,000**	**376,292,000**
Tax					-34,370,500	-112,887,600
Profit after tax	-12,380,411	-30,130,000	-47,325,947	-10,830,346	144,629,500	263,404,400
Balance Sheet	**2020a**	**2021e**	**2022e**	**2023e**	**2024e**	**2025e**
Current assets						
Cash	103,922,241	73,792,241	26,533,294	15,635,948	160,265,448	423,669,848
Trade & receivables	3,509,777	3,500,000	3,500,000	3,500,000	3,500,000	3,500,000
Prepaid expenses	192,380	150,000	150,000	150,000	150,000	150,000
Financial assets held at amortised cost	746,200					
Total current assets	**108,370,598**	**77,442,241**	**30,183,294**	**19,285,948**	**163,915,448**	**427,319,848**
Non- current assets						
Intangible assets	2,947,588	2,700,000	2,500,000	2,300,000	2,300,000	2,300,000
Right-of-use assets	832,917	500,000	250,000	1,000,000	850,000	532,917
Security deposits receivable	102,616					
Other	109,913					
Total non-current assets	**3,993,034**	**3,200,000**	**2,750,000**	**3,300,000**	**3,150,000**	**2,832,917**
Current liabilities						
Trade & other payables	2,784,324	4,000,000	5,000,000	5,000,000	5,000,000	5,000,000
Employee benefits	455,510	455,510	455,510	455,510	455,510	455,510
Lease Liabilities	124,731	115,000	100,000	180,000	150,000	125,000
Total current liabilities	3,364,565	4,570,510	5,555,510	5,635,510	5,605,510	5,580,510
Non-current liabilities	817,348	432,023	235,023	235,023	235,023	235,023
Net assets	**108,181,719**	**75,618,708**	**27,142,761**	**16,688,415**	**161,204,915**	**424,337,232**
Equity						
Issued capital	145,865,076	145,865,076	145,865,076	145,865,076	145,865,076	145,865,076
Share based payments reserve	3,585,189	3,585,189	3,585,189	3,585,189	3,585,189	3,585,189
Accumulated losses	-41,268,546	-71,398,546	-118,724,493	-129,554,839		
Total equity	**108,181,719**	**74,851,719**	**30,725,772**	**19,895,426**	**149,450,265**	**412,854,665**
Cashflow	**2020a**	**2021e**	**2022e**	**2023e**	**2024e**	**2025e**
Cash flows from operating activities						
Operational Income				40,000,000	200,000,000	400,000,000
Research and development and other tax incentive received	3,621,355	3,697,847	2,000,000	9,000,000	2,000,000	1,000,000
Clinical trial payments		-25,000,000	-40,000,000	-50,000,000	-10,000,000	10,000,000
Payments to suppliers and employees	-14,797,407	-7,700,000	-9,200,000	-11,300,000	-13,000,000	18,000,000
Interest received	1,120,163	630,000	441,053	91,654	2,300,000	3,357,000
Net cash outflow from operating activities	**-10,090,057**	**-28,372,153**	**-46,758,947**	**-12,208,346**	**181,300,000**	**432,357,000**
Cash flows from investing activities						
Payments for intangible assets	-3,353					
Payments for plant and equipment	-127,537					
Proceeds/(Payments) for financial assets held at amortised cost	5,753,800					
Net cash inflow (outflow) from investing activities	**5,622,910**					
Cash flows from financing activities						
Proceeds from the issue of share capital	35,000,000					
Proceeds from the exercise of share options	1,839,328			1,443,750		
Limited recourse loan repayment under ESP	1,895,907					
Payments of share issue costs	2,588,451					
Net cash inflow from financing activities	**36,053,215**					
Net increase in cash and cash equivalents	31,586,068	-30,130,000	-47,325,947	-10,830,346	144,629,500	263,404,400
Cash at the beginning of the financial period	72,336,173	103,922,241	73,792,241	26,466,294	15,635,948	160,265,448
Cash at the end of the financial period	**103,922,241**	**73,792,241**	**26,466,294**	**15,635,948**	**160,265,448**	**423,669,848**

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Recommendation

The share price during the timeline required for Paradigm to achieve regulatory NDA approval is likely to remain volatile (as it has been to date), requiring the investor to have a clear understanding of why the stock is owned. We acknowledge there are many variables that have potential to impact Paradigm's course of business, however many of these nonsystematic risks have been accommodated in our model. We have highlighted that a favourable outcome for Paradigm is binary, as it is for most biopharmaceutical companies hoping to achieve medical breakthrough. We have seen on many occasions promising phase 2 trials lead to disappointment, with failure to achieve success in subsequent trials, however we have also seen a success rate of circa 50% of all successful phase 2 trials leading to NDA approval. For this reason, companies such as Paradigm receive considerable attention, from the cynic and the optimist. When thinking about Paradigm it is imperative that the investor understands the risk/return profile, and how it fits with their objectives and expectations. If Paradigm achieves statistically significant, and clinically meaningful results for OA Phase 3 clinical trials, and awarded a NDA , the payoff will be significantly asymmetric, as essentially all risks will evaporate.

We are confident that using a 20% discount rate, and modest base figures across all assumptions, that our estimates could materially understate Paradigm's true net present value. As we have repeatedly stated, our objective has been to remain highly conservative, allowing Paradigm the opportunity to overshoot our estimates. The current share price trades at a significant discount to our forward earnings estimates, allowing for a margin of safety. As Paradigm continues to reach its stated milestone, we believe interest from larger institutional investors will become apparent, reducing the number of short-term shareholders, forming a more stable base in Paradigm's market capitalisation.

2021 is highly anticipated, beginning with FDA approval of Investigative New Drug status, followed by OA 008 biomarker clinical trials. If PPS is shown to have DMOAD capabilities, this would be of significance, as pain and function are bi-products of OA progression. Whilst achieving DMOAD status is not a primary endpoint for larger phase 3 trials, it would be a very positive result, which could see the market re-rate Paradigm significantly. We would expect the share price, providing broader market stability, to edge up leading into PAR 008 primary endpoint data readout scheduled for Q3 CY 2021.

What we have not mentioned, is the possibility of Big Pharma acquiring Paradigm. We have purposely avoided doing so given the future for Paradigm as a standalone entity with global partners. It is our belief, that the investor who is patient, and stays the journey, could be compensated well in excess of any takeover bid.

Summary

As is evidenced throughout this report, Paradigm has come a long way since listing in August 2015. The company now embarks on 2021 for what will be a crucial year, setting the tone for what we believe will transform Paradigm into a multibillion-dollar company. It is now critical for the company to progress and execute on well planned, uninterrupted phase 3 OA clinical trials.

Most pleasing, is Paul Rennie's success in transforming Paradigm into an ASX 300 company, whilst recruiting a highly experienced, and well qualified Board and Management. Paradigm boasts a team with decades of combined knowledge in progressing early-stage biopharmaceutical companies through to successful New Drug Application. This provides us with great confidence given the number of companies who meet phase 3 trial endpoints, only to be rejected for not following, or failing entirely to adhere to FDA guidelines. Paradigm's revised phase 3 clinical trials, whilst not ideal from a timeline perspective, are welcomed as they are in keeping with FDA Type C meeting feedback. This gives us further confidence that pending phase 3 success, Paradigm will be adequately prepared to execute on a harmonised global marketing and distribution campaign for OA without delay.

From a broader perspective, Paradigm possesses an exciting and growing development pipeline across several applications with an unmet medical need, helping to de-risk the company. Whilst many of these indications are in early-stage trials, they will continue to run concurrently thereby contributing to Paradigm's value proposition. As highlighted, MPS-1 & 6, have potential to be a significant, and a steady source of annuity style revenue for decades. Paradigm will continue to file for further patents, as well as seek to discover additional molecules for repurpose. Given the pedigree of Paradigm's board and management, we eagerly anticipate further updates.

We acknowledge it is easy to be consumed by Paradigm's OA trials, considering the size of the addressable market, however the aforementioned initiatives should not be underestimated. Whilst we have confidence Paradigm can meet its funding obligations through non-dilutive sources, these indications have potential to provide the source of Paradigm's first revenue, which clearly is important from a shareholder perspective.

Overall, we believe Paradigm is in an enviable position, with the current share price trading significantly below its all-time high of $4.22, almost precisely a year ago, this is quite astounding given the company Paradigm is today in comparison. Despite this, and as mentioned several times, an investment in Paradigm requires patience, with a clear understanding of the risks associated with such and investment. We have no doubt if Paradigm continues to perform in line with what we have come to expect in recent years, it will not be long before the current share price reflects its earning potential, and in line with our valuation of $4.75.

Risks

Clinical trial risk

The Company may be unable to secure necessary approvals from regulatory agencies and institutional bodies (clinics and hospitals) to conduct future clinical trials. There is also no assurance that products developed using the Company's technology will prove to be safe and efficacious in clinical trials, or that the regulatory approval to manufacture and market its products will be received. Clinical trials might also potentially expose the Company to product liability claims in the event its products in development have unexpected effects on clinical subjects. Clinical trials undertaken by the Company have many associated risks which may impact the Company's profitability and future productions and commercial potential. They may prove unsuccessful or non efficacious, impracticable or costly. The clinical trials could be terminated which will likely have a significant adverse affect on the Company, the value of its securities and the future commercial development of its technology.

Regulatory and reimbursement approvals

The research, development, manufacture, marketing and sale of products using the Company's technology are subject to varying degrees of regulation by a number of government authorities in Australia and overseas. Products developed using the Company's technology must undergo a comprehensive and highly regulated development and review process before receiving approval for marketing. The process includes the provision of clinical data relating to the quality, safety and efficacy of the products for their proposed use. Products may also be submitted for reimbursement approval. The availability and timing of that reimbursement approval may have an impact upon the uptake and profitability of products in some jurisdictions. Furthermore, any of the products utilising the Company's technology may be shown to be unsafe, non-efficacious, difficult or impossible to manufacture on a large scale, uneconomical to market, compete with superior products marketed by third parties or not be as attractive as alternative treatments.

Commercialisation of products and potential market failure

The Company has not yet commercialised its technology and as yet has no revenues. The Company is also dependent on commercially attractive markets remaining available to it during the commercialisation phase and there is a risk that, once developed and ready for sale, commercial sales, to fund sufficient revenues for continued operations and growth, may not be achieved.

Pipeline product in development and not approved for commercial sale

Paradigm's ability to achieve profitability is dependent on a number of factors, including its ability to complete successful clinical trials, obtain regulatory approval for iPPS technology and successfully commercialise that product. There is no guarantee that Paradigm's product will be commercially successful. Paradigm does not currently generate revenue from product sales. There are many reasons why initially promising products fail to be successfully commercialised. For example, clinical trials may be suspended for safety or efficacy reasons. Following development it may prove difficult or impossible to manufacture the products on a large scale, or, during the period of development, competitors (including those with greater resources) may emerge with competing or alternative treatments.

Reliance on key personnel

The Company currently employs and has plans to recruit additional key management and scientific personnel; the Company's future depends on retaining and attracting suitably qualified personnel. The Company has included in its employment with key personnel provisions aimed at providing incentives and assisting in the recruitment and retention of such personnel. It has also, as far as legally possible, established contractual mechanisms through employment and consultancy contracts to limit the ability of key personnel to join a competitor or compete directly with the Company. Despite these measures, however, there is no guarantee that the Company will be able to attract and retain suitably qualified personnel, and a failure to do so could materially and adversely affect the business, operating results and financial prospects.

Risk of delay and continuity of operations

Paradigm may experience a delay in achieving a number of critical milestones, including securing commercial partners, completion of clinical trials, obtaining regulatory approvals, manufacturing, product launch and sales. Any material delays may impact adversely upon the Company, including the timing of any revenues under milestone or sales payments.

Competition

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. A number of companies, both in Australia and abroad, may be pursuing the development of products that target the same markets that Paradigm is targeting. The Company's products may compete with existing alternative treatments that are already available to customers. In addition, a number of companies, both in Australia and abroad, may

be pursuing the development of products that target the same conditions that the Company is targeting. Some of these companies may have, or develop, technologies superior to the Company's own technology. The Company may face competition

Risk of supply of cGMP product

The Company has engaged a third party cGMP (Good Manufacturing Practice) contract manufacturer for PPS (BPC). The manufacturing of PPS is very complex and associated with uncertainties in relation to issues such as the price of manufacture, impurities and manufacturing capacity for large scale manufacturing. While BPC has significant experience in the manufacture of cGMP commercial quantities of PPS and the Company has the ability to order significant forward quantities of PPS, should difficulties or delays occur in the cGMP production of PPS or the supply agreement be terminated for any reason – the timing of the clinical development and/or commercialisation may be affected and may have an adverse impact on the financial performance of the Company.

Patent rights

The Company heavily relies for its success on its ability to obtain and maintain patent protection for the relevant therapeutic products. There is no guarantee that the patent applications will be granted. Further, if the Company's intellectual property rights are ever challenged it may be that the Company's entitlement is subsequently revealed not to have existed, may not have any exclusive patent rights or any patent rights at all and may be prevented from developing and/or commercialising its products.

Trade secrets

The Company relies on trade secrets, which include information relating to the manufacture, development and administration of its therapeutic products. The protective measures employed may not provide adequate protection for those trade secrets. This could erode the Company's competitive advantage and materially harm its business. The Company cannot be certain that others will not independently develop the same or similar technologies on their own or gain access to trade secrets or disclose such technology.

Dependence on service providers

The Company intends to operate a significant amount of its key clinical activities through a series of contractual relationships with independent contractors and suppliers. The Company relies on and will continue to rely on a number of its contractors for their expertise in manufacture and clinical development. All of the Company's contracts carry a risk that the third parties do not adequately or fully comply with its or their respective contractual rights and obligations. Such failure can lead to termination and/or significant damage to the Company's product development efforts.

Infringement of third party intellectual property

If a third party accuses the Company of infringing its intellectual property rights or if a third party commences litigation against the Company for the infringement of patent or other intellectual property rights, the Company may incur significant costs in defending such action, whether or not it ultimately prevails. Costs that the Company incurs in defending third party infringement actions would also include diversion of management's and technical personnel's time. In the event of a successful claim of infringement against the Company, it may be required to pay damages and obtain one or more licenses from the prevailing third party. If it is not able to obtain these licenses at a reasonable cost, if at all, it could encounter delays in product introductions and loss of substantial resources while it attempts to develop alternative products.

Product liability

As with all new therapeutic products, even after the granting of regulatory approval, there is no assurance that unforeseen adverse events or manufacturing defects will not arise. Adverse events could expose the Company to product liability claims or litigation, resulting in the removal of the regulatory approval for the relevant products and/or monetary damages being awarded against the Company. In such event, the Company's liability may exceed the Company's insurance coverage.

Healthcare insurers and reimbursement

In both domestic and foreign markets, sales of products are likely to depend in part upon the availability and amounts of reimbursement from third party health care payer organisations, including government agencies, private health care insurers and other health care payers such as health maintenance organisations and self-insured employee plans. There is considerable pressure to reduce the cost of therapeutic products, particularly biologics, and government and other third party payers are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement for new therapeutic products and by refusing, in some cases, to provide any coverage for uses of approved products for disease indications for which the Food and Drug Administration has not granted marketing approval. No assurance can be given that reimbursement will be provided by such payers at all or without substantial delay, or, if such reimbursement is provided, that the approved reimbursement amounts will be sufficient to enable the Company to sell products developed on a profitable basis.

Coronavirus

The outbreak of the coronavirus disease (COVID-19) has had a significant impact on the global economy and the ability of individuals, businesses and governments to operate. Travel, trade, business, working arrangements and consumption have been materially impacted by the outbreak. The nature and extent of the outbreak on Paradigm's performance remains unknown, including in relation to government, regulatory or health authority actions, work stoppages, lockdowns, quarantine and supply restrictions. The impact of some or all of these factors could cause an adverse impact to Paradigm's financial performance.

Board and Management

Paul Rennie, Managing and Executive Director (Appointed 2014)

Paul Rennie BSc, MBM, Grad Dip Commercial Law, MSTC, has sales, marketing, business development, operational and IP commercialisation experience in the biopharmaceutical sector. Paul's experience includes working for Boehringer Mannheim (now Roche Diagnostics), Merck KGGA as national sales and marketing manager and Soltec (FH Faulding Ltd) as their Director of business development. Paul also led the commercialisation of Recaldent® a novel biopharmaceutical arising from research at the dental school, University of Melbourne. Paul took an R&D project from the laboratory bench to a commercial product now marketed globally as an additive to oral care products. More recently Paul worked in a number of positions with Mesoblast Ltd. Paul was the inaugural COO and moved into Executive Vice President New Product Development for the adult stem cell company. For the past 6 years, Paul has worked full time at Paradigm Biopharmaceuticals Limited.

Chief Scientific Officer – Dr Ravi Krishnan (Appointed 2015)

Dr Ravi Krishnan has had extensive research experience in areas of research encompassing cancer pathology, organ transplantation immunology and discovery of novel therapeutic molecules originating from marine organisms. The past five years Dr Krishnan has played an instrumental role alongside Paul Rennie transforming Paradigm to an ASX top 200 company. Prior to this Dr Krishnan held the role of Senior Vice President of Research for Diabetes , Metabolic Syndrome & Immunological Diseases with Mesoblast Limited for a period of four years.

Dr Krishnan spent the previous 21 at The Queen Elizabeth Hospital as the Senior Medical Scientist (with Excellence), Renal Unit, Transplantation Immunology Laboratory (12 years, 1999 – 2011). The remaining 9 years (1990-1999) was Senior Medical Scientist Renal Unit, Transplantation Immunology Laboratory at The Queen Elizabeth. Dr Krishnan has held affiliate senior lectureships at the Department of Medicine University of Adelaide and the Department of Medical Biotechnology at Flinders University of South Australia which enabled him to mentor more than 12 PhD students and 25 Honours Research students.

John Gaffney, Non-Executive Director (Appointed 2014)

John Gaffney LL.M is a lawyer with over 30 years' experience and has undertaken the AICD Company Directors qualification. He brings to the board a compliance and corporate governance background and is experienced in financial services compliance. John also has corporate and commercial experience having worked with a major national law firm as a senior lawyer and also practised as a Barrister at the Victorian Bar. Previously John has been a Non-Executive Director of a US based biotechnology company.

Dr. Donna Skerrett, Executive Director (Appointed 2020)

Dr. Donna Skerrett, has more than 30 years' experience in transfusion medicine, cellular therapy, and regenerative medicine. She brings a wealth of experience in medical, clinical, and regulatory affairs. Donna served previously as Chief Medical Officer at Mesoblast. She was Director of Transfusion Medicine and Cellular Therapy at Weill Cornell Medical Center in New York (2004 – 2011) and prior to that was Associate Director of Transfusion Medicine and Director of Stem Cell Facilities at Columbia University's New York-Presbyterian Hospital. She previously chaired the New York State Governor's Council on Blood and Transfusion Services, previously served on the Board of Directors of the Fox Chase Cancer Centre, and currently serves on the Board of Visitors for the Lewis Katz School of Medicine of Temple University.

Chief Operating Officer – Dr Jeannie Joughin, (Appointed 2020)

Dr Jeannie Joughin prior to joining Paradigm spent nine years in the U.S. where she held senior executive roles with Enable Injections, and CSL Behring. Upon her return joined an ASX-listed company as a Non –Executive Director and provided guidance as a principal commercial adviser to Australian biotechnology and medical technology companies.

Jeannie is an experienced biopharmaceutical and medical device leader with over 20 years experience in global biopharmaceutical companies and start-up environments. Her responsibilities and experience have included extensive post-doctoral research, clinical trial management, brand management, licensing and business development, team leadership, strategic planning, capital raising, as well as partner relationship/alliance management. Jeannie holds a Bachelor of Science (Hons) and a Doctor of Philosophy (Immunology).

Global Head of Safety – Dr Michael Imperiale (Appointed 2020)

Dr Michael Imperiale has more than 25 years of international drug development experience in the biotechnology and pharmaceutical industry. Dr. Imperiale worked at Nektar Therapeutics, where he led the development of their Immuno-Oncology and Pain programs. Prior to joining Nektar, Dr. Imperiale was the Global Medical Lead in Medical Affairs at Bio Marin where he managed the Lysosomal Storage disease and PKU franchises. Dr. Imperiale also held the Vice President of Clinical Research position at Talon Therapeutics (Hana Biosciences), where he successfully developed Marqibo® for adult Acute Lymphocytic Leukemia (ALL).

Dr Imperiale began his career in drug development at Boehringer- Ingelheim, where he initiated the International Medical Affairs division for Virology. In recognition for his achievements, he received the Medical Marketing Award. He received a Doctor of Medicine with an Academic Distinction in Medicine, from Hahnemann University School of Medicine and a Bachelor of Arts degree from Villanova University.

Dr. Imperiale will head up Paradigm's MPS IV clinical program with his significant experience in Lysosomal Storage Diseases.

Commercial Head – Beverley Huttmann (Appointed 2020)

Beverley Huttman is a highly experienced pharmaceutical commercial leader, with more than 25 years experience with global pharmaceutical companies including CSL and GSK. Her past responsibilities have encompassed all facets of pharmaceutical commercial management including market and product analysis, strategic planning and budgeting, licencing, pricing and reimbursement, government Liaison, in-market promotion,

demand forecasting and team leadership. She has held senior commercial roles in many therapeutic areas including pain, rheumatology, respiratory disease, allergy, immunology, and dermatology.

Beverley will be responsible for developing and implementing commercial strategy including partnerships, licencing, pricing and reimbursement, product differentiation, patient and physician acceptance and life cycle management.

Chief Financial Officer – Justin Cahill (Appointed 2020)

Justin Cahill has over 20 years experience in strategic finance roles across a broad spectrum of industries and global organisations. In one of his more prominent roles, Justin sent nine years at CSL, including five years in the U.S. as Divisional CFO of CSL Plasma. Justin is a CPA and holds a master's in accounting.

As Paradigm's operations expand and become more global, Justin will oversee the financial management of, and control over Paradigm's increasingly complex activities.

R&D Translational Scientist, Catherine Stapledon, PhD (Appointed 2020)

Catherine Stapledon – Will work alongside Chief Science Officer, Ravi Krishnan. Catherine had undertaken her PhD studies at the Centre for Orthopaedic & Trauma Research, Faculty of Health and Medical Sciences, University of Adelaide. Catherines research involved multidisciplinary approach to investigate the roles of neurotrophic factors on osteocyte function in osteoarthritis. Of significance were Catherines studies which elucidated the mode of action of PPS related to the regulation of Nerve Growth Factor as a mediator of pain in bone osteocytes derivded from OA patients.

Catherine has extensive experience in the development and design of a number of studies ranging from basic call culture to animal and human studies. Her expertise is considerd a valuable asset to Paradigm's R&D programs, involving GLP and GLP-like preclinical proof-of conecept studies, and in translational disease models.

Amos Meltzer (Refer dec announcement)

Amos Meltzer is a scientist and an intellectual property lawyer with over 25 years of experience in international trade and in commercialising technologies, overwhelmingly in the life sciences. Amos' experience and expertise is drawn from having worked in both large law firms (Freehills and K&L Gates) and in house counsel and IP director at two Nasdaq-listed companies (Nasdaq:Cgen and Nasdaq:Gilt), as a non-executive director of a biotechnology company (Nasdaq:evgn), and as VP of Business Development and then CEO of an ASX-listed biopharmaceutical company Immuron Ltd ASX:IMC).

Amos currently serves Chief Operating Officer of neuro-medical device company Synchron Ltd, chairman of the board of surgeon education services company Vasculab Ltd, and as a legal advisor to a number of ASX listed and private life science companies. Amos brings to the Paradigm board his intellectual property expertise and a proven track record of successful commercial transactions.

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Corporate Advisory Disclosure

Baker Young acted as Co-Manager to the company's capital raise in April 2020 and received fees for that service

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