Bell Potter Emerging Leaders Conference
September 2020

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BIOPHARMA

PAUL RENNIE
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PARADIGM'S MISSION

Paradigm Biopharmaceuticals Limited (PAR) is a late stage drug development company

To develop and commercialise pentosan polysulphate sodium (PPS) for the treatment of pain associated with musculoskeletal disorders driven by injury, inflammation, aging, degenerative disease, infection or genetic predisposition.

EXECUTIVE SUMMARY

- **Repurposing an FDA-approved drug with 60-yr track record of treating inflammation:** Pentosan Polysulphate Sodium ("PPS," "ZILOSUL®")
- **Lead program:** Osteoarthritis (OA) **~ 31m+** sufferers in the US alone
- **Proven Safety and Efficacy: OA Phase 2b trial (n=112) met primary, secondary and exploratory endpoints:** Included pain, function, BML and biomarkers
- **IP:** Strong portfolio of IP protection and patents on Zilosul® – patents in all key markets from 2030 to 2039.
- **Manufacturing:** Secured scalable manufacturing supply from FDA approved facility – **exclusive agreement for 20 years**
- **Funded: A$104m cash on balance sheet (as at 30 June)** – fully funding company until end of 2022.

US

IND Submission upcoming for Phase 3 trial in OA. Pre-IND meeting has confirmed key endpoints as pain and function. Revenue potential in US @ 10% market share = **~US$9bn p.a**

EUROPE

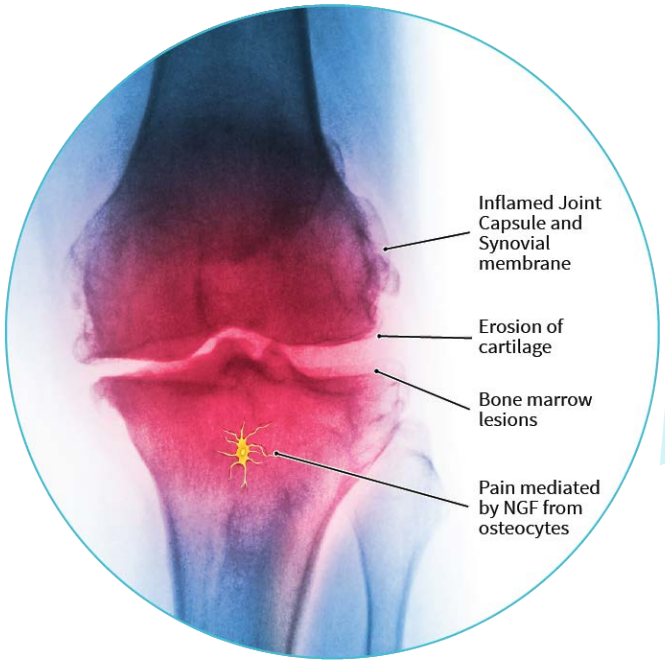
Meeting with EMA in September 2020, to ensure Phase 3 OA trial will also meet EU regulatory requirements.

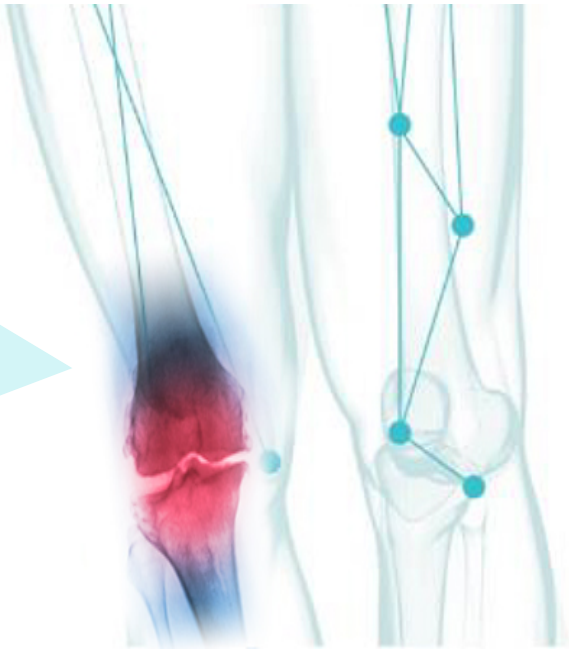
AUSTRALIA

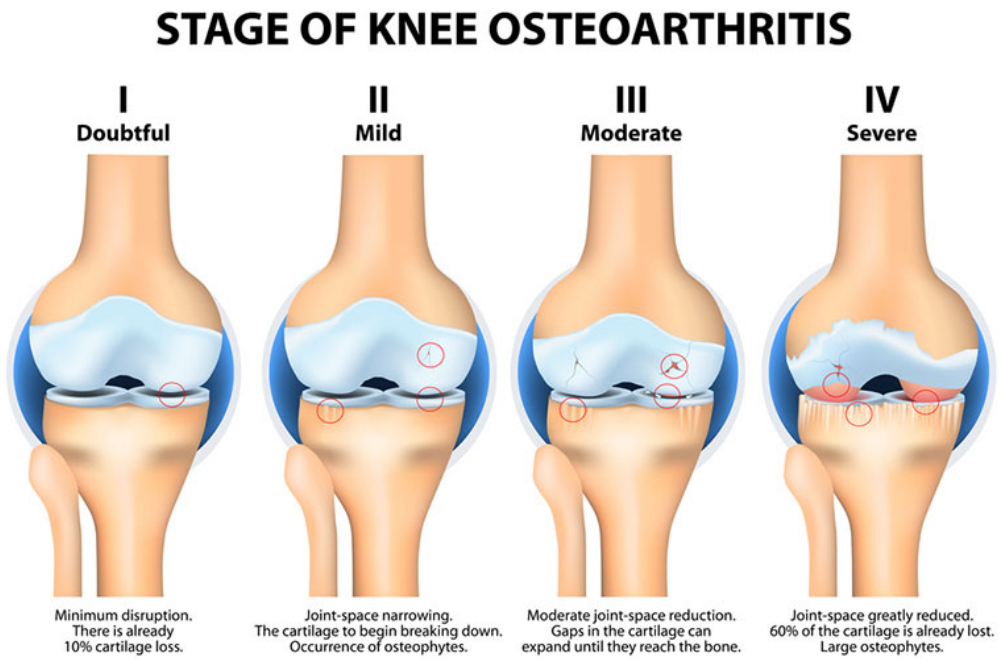
Seeking Provisional Approval in Australia with TGA prior to completing Phase 3 trial

- 3m sufferers, revenue potential in Australia @ 20% market share = **~AUD$1.5b p.a**

PATHOGENESIS IN KNEE OSTEOARTHRITIS







Symptoms of Osteoarthritis

Patients with OA may experience a spectrum of signs and symptoms that can include:

- joint specific pain at rest, walking/climbing stairs
- pain at night
- soreness to touch of the affected joint(s)
- decreased range of motion
- in some cases crepitus and/or bony enlargement.

Osteoarthritis leads to[1]:

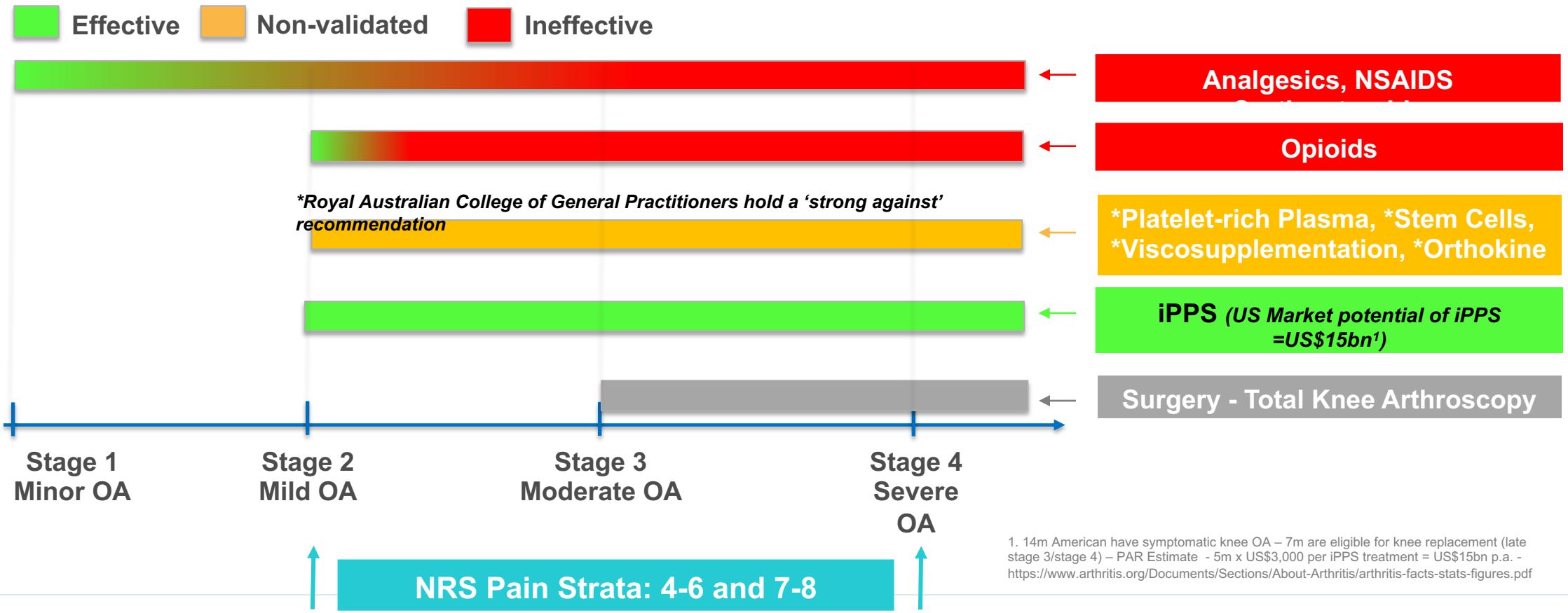
- Activity limitations
- Participation restrictions
- Sleep interruption
- Fatigue and depressed or anxious mood
- Loss of independence and reduced quality of life.

[1] Osteoarthritis Research Society International (OARSI). Osteoarthritis: A serious disease, submitted to the US Food and Drug Administration December 1, 2016.

MARKET DEMAND

OA STAGES AND TREATMENTS

There are no effective treatments for Moderate to Severe OA



1. 14m American have symptomatic knee OA – 7m are eligible for knee replacement (late stage 3/stage 4) – PAR Estimate - 5m x US$3,000 per iPPS treatment = US$15bn p.a. - https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf

OPIOID EPIDEMIC

DEMAND FOR NEW TREATMENTS

PPS has potential as a non-opioid treatment for osteoarthritis pain

Opioids

A class of narcotic substances derived from the opium poppy plant (synthetic or naturally occurring)

Not disease modifying (only mask pain)

Highly addictive with significant withdrawals

Serious adverse effects– significant risk of overdose/ death

Considered by TGA to be inappropriate for use in chronic non-cancer pain settings (e.g. OA)

US$78.5B

Annual economic burden of prescription opioid misuse in the US[4]

~42,000

Deaths from opioid overdose per year in the US[3]

Prescription opioid overdose is now the leading cause of accidental death in Australia

"Our goal is to support more rational prescribing practices, as well as **identify and encourage development of new treatment options that don't have the addictive features of opioids."**

Scott Gottlieb, Former FDA Commissioner[2]

2. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm
3. CDC/NCHS, National Vital Statistics System, Mortality. CDC Wonder, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://wonder.cdc.gov.
4. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Med Care. 2016;54(10):901-906. doi:10.1097/MLR.0000000000000625.

OSTEOARTHRITIS MARKET

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OSTEOARTHRITIS (OA)

SIGNIFICANT MARKET SIZE WITH UNMET NEED

300M+
The prevalence of OA Worldwide[8].

3M+
Australia

31M+
US

30M+
Japan

50M+
Top 5 European Markets

Most common form of joint disease and the leading cause of disability for people greater than 65 years of age[6]

Growing Crisis

67M+

US OA prevalence by 2030[7] due to aging pop and obesity.

US$128B+

Significant cost of OA to the US economy per annum[7].

Current treatment

Symptomatic pain relief.

91% are <u>not</u> ready for total joint replacement and 59% would try “almost anything” to avoid joint surgery[7].

81%

Number of OA patients dissatisfied with current treatments[7].

UNMET NEED

A treatment or medication that ***can alleviate the symptoms (pain and joint dysfunction) in a clinically meaningful manner <u>and</u> slow or halt the disease progression.***

5. http://ard.bmj.com/content/annrheumdis/early/2017/07/12/annrheumdis-2017-211396.full.pdf.
6. Neogi T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and cartilage*, *21*(9), 1145-53.
7. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September.
8 James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018; 392(10159): 1789-858.

RECENT OA TRANSACTIONS

HIGHLIGHTS PHARMA INTEREST IN OA

COMPANIES	COMPOUND	REGION	UPFRONT	TOTAL VALUE	STATUS
Pfizer / Lilly	Anti-NGF	Global	US$200m	US$1.8bn	Phase 3 (Failed)
Regeneron / teva	Anti-NGF	Global	US$250m	US$1.25bn	Phase 3
Flexion / Sanofi	Corticosteroid	Global	Take-over*	US$1.0bn*	Commercialised
Amgen / Janssen	Anti-NGF	Global (ex Japan)	US$50m	US$435m	Discontinued
	GLOBAL AVERAGE		**US$166m**	**US$1.12bn**	
Galápagos / Servier	ADAMTS-5 Inhibitor	EU	Unknown	US$346m	Phase 1
TissueGene, Inc. / Mitsubishi Tanabe Pharma	Gene therapy	Japan	US$24m**	US$434m**	Handed Back
TissueGene, Inc. / mundipharma	Gene therapy	Japan	US$27m	US$591m	Phase 3
Regeneron / Mitsubishi Tanabe Pharma	Anti-NGF	Asia	US$55m	US$325m	Phase 3
	REGIONAL AVERAGE		**US$35m**	**US$424m**	

Safety Issues

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

REVENUE POTENTIAL IN OA

Key Assumptions:

- 31m OA sufferers in the US
- 3m OA sufferers in Aus.
- Annual dosing/treatment – assumed 12 month duration of effect as observed in TGA special access scheme
- Pricing is indicative only

		US MARKET		
		10% Market Penetration	20% Market Penetration	30% Market Penetration
INDICATIVE POTENTIAL PRICING	US$1.5k p.a	US$4.65B p.a	US$9.3B p.a	US$13.95B p.a
	US$2.0k p.a	US$6.2B p.a	US$12.4B p.a	US$18.6B p.a
	US$2.5k p.a	**US$7.75B p.a**	**US$15.5B p.a**	**US$23.25B p.a**

		AUS MARKET		
		10% Market Penetration	20% Market Penetration	30% Market Penetration
INDICATIVE POTENTIAL PRICING	A$1.0k p.a	A$300M p.a	A$600M p.a	AUD$900M p.a
	A$2.0k p.a	A$ 600M p.a	A$1,200M p.a	AUD$1,800M p.a
	A$2.5k p.a	**A$ 750M p.a**	**A$1,500M p.a**	**AUD$2,250M p.a**

OVERVIEW OF PPS / ZILOSUL®

BACKGROUND

PENTOSAN POLYSULPHATE SODIUM (PPS) / ZILOSUL

PENTOSAN POLYSULPHATE SODIUM

- Semi-synthetic drug manufactured from beech-wood hemicellulose
- Has been used in humans for more than 60 years
- Oral formulation is FDA approved and sold under the name Elmiron, by Janssen Pharmaceuticals (J&J), for the treatment of interstitial cystitis and deep vein thrombosis.
- **Paradigm has been granted patents to use PPS for other indications**

EXCELLENT SAFETY PROFILE

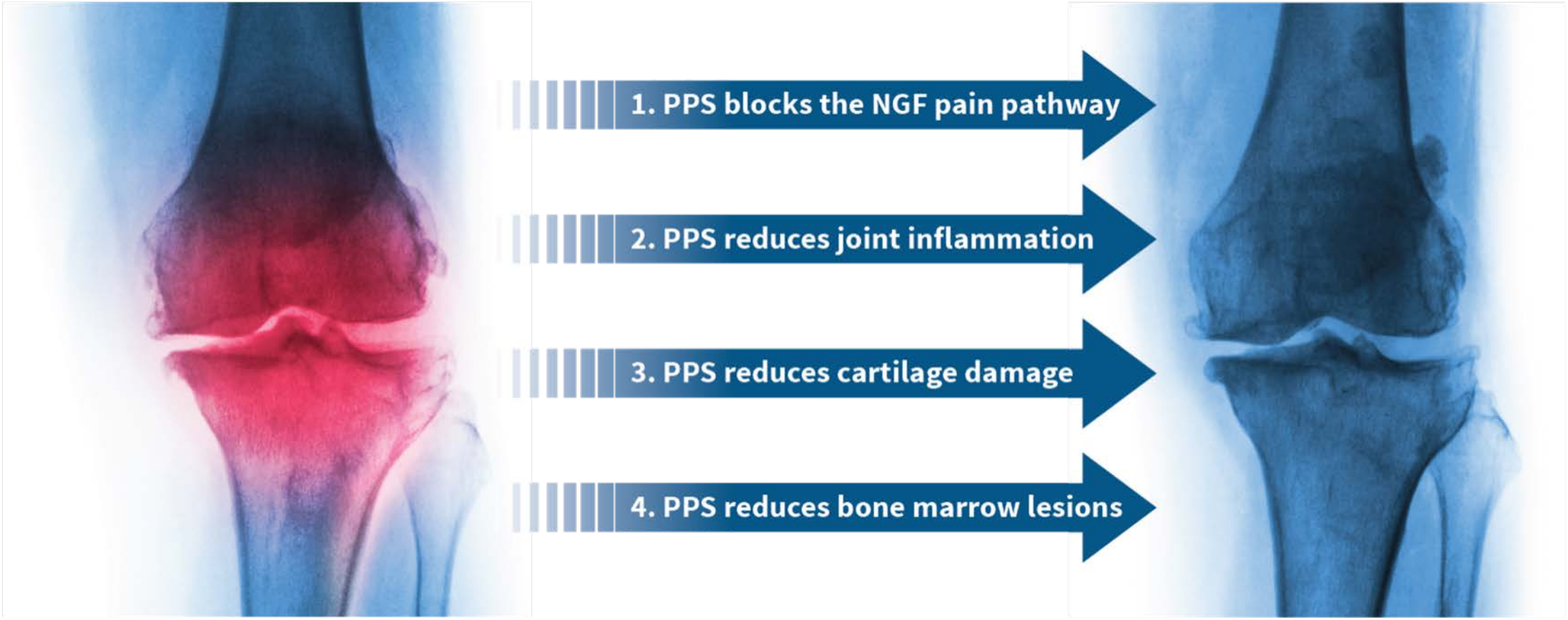
- **Well established safety profile**
- FDA Approved 30+ years ago for oral use, **100 m+** injectable doses administered
- Semi-synthetic, complex carbohydrate makes it well tolerated by the human body
- As of June 2020, **over 700 patients have received PPS** for injection in clinical studies or as part of an Expanded Access Program (EAP) or Special Access Scheme (SAS), as follows:
  - ✓ **Clinical studies (completed): 88 subjects**
  - ✓ **EAP (completed): 10 patients (USA)**
  - ✓ **SAS (ongoing): > 650 patients.**

Potential positioning of Zilosul® when used to treat OA

- Anti-inflammatory
- Reduction in degeneration of joint structures including bone, cartilage and synovium[7].
- Reduction in OA symptoms of pain and joint function.
- Durable effect (sustained pain reduction and improvement in joint function for months not weeks/hours)
- Short course therapy
- Non-performance enhancing (WADA & ASADA Cleared)
- Non-addictive (non opioid)

[9] Based on BML and cartilage biomarker data from Paradigm's phase 2 clinical and preclinical studies.

MECHANISM OF ACTION (MOA) OF PPS

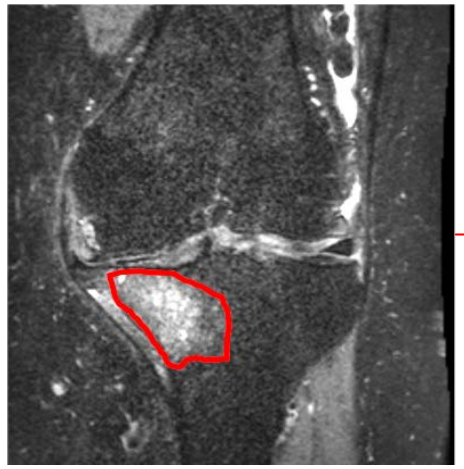


BONE MARROW LESIONS (BML)

CLINICAL IMPLICATIONS FOR KNEE OA AND DISEASE REGRESSION WITH IPPS THERAPY

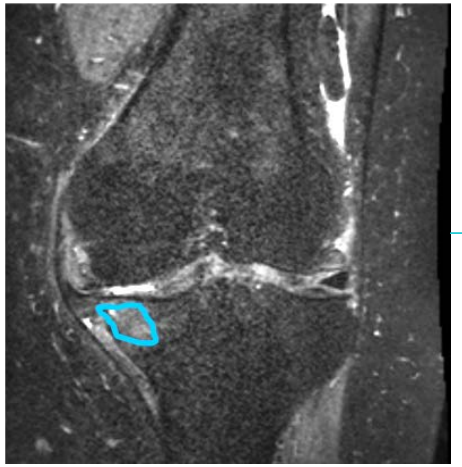
BML appear as increased signal intensity within the bone marrow

Grade 3 medial tibial BML at baseline



- INCREASING PAIN
- INCREASED CARTILAGE LOSS
- HIGH RISK OF JOINT DESTRUCTION
- HIGH RISK OF TOTAL KNEE REPLACEMENT

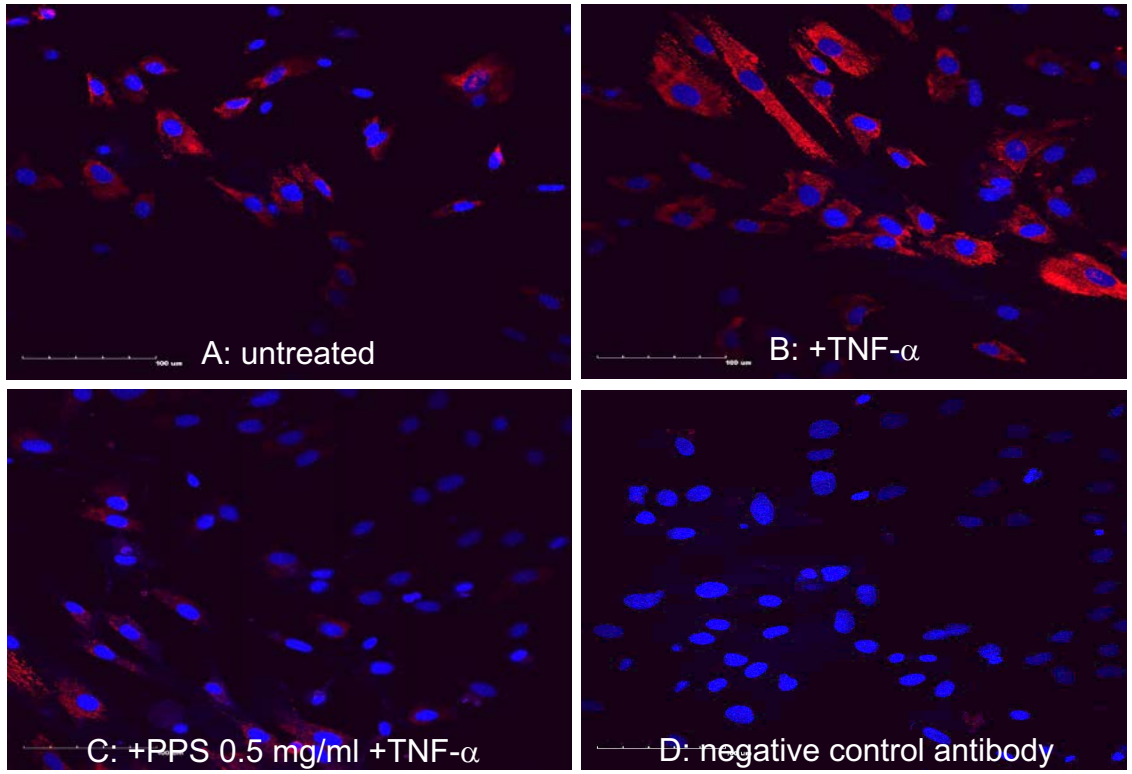
Grade 2 medial tibial BML at follow-up



- REDUCED PAIN
- REDUCED CARTILAGE LOSS
- REDUCED RISK OF JOINT DESTRUCTION
- REDUCED RISK OF TOTAL KNEE REPLACEMENT

MECHANISM OF ACTION (MOA)

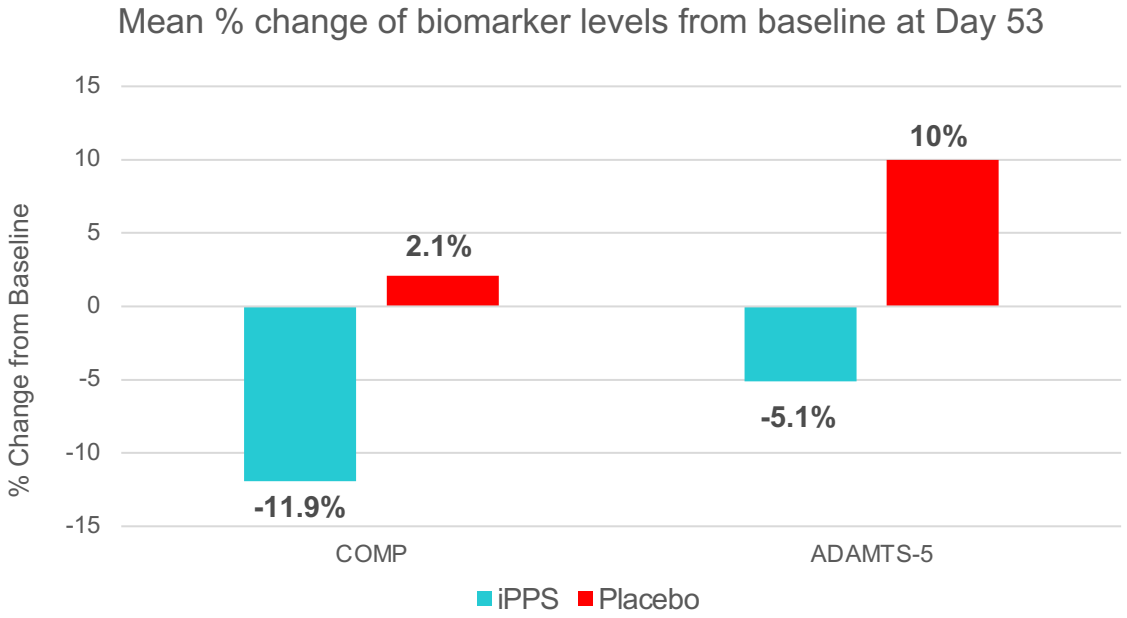
Reduction of NGF as mediator of PAIN.
PPS downregulates NGF expression in osteocytes knee OA patients



Confocal microscopy images showing NGF protein expression (red) by freshly harvested human osteocytes. Nuclei (blue) (***Stapeldon et al PLOS One 2019)***

Inhibition of the cartilage degrading enzymes that are known to play a key role in the progression of OA.

Reduction in serum **COMP** & **ADAMTS-5** in P2 study of knee OA.



Among subjects with symptomatic knee OA, <u>a single measurement of increased COMP predicted subsequent cartilage loss on MRI</u>. Hunter et al.

OA PHASE 2B TRIAL RESULTS

PRIMARY, SECONDARY & EXPLORATORY ENDPOINTS MET

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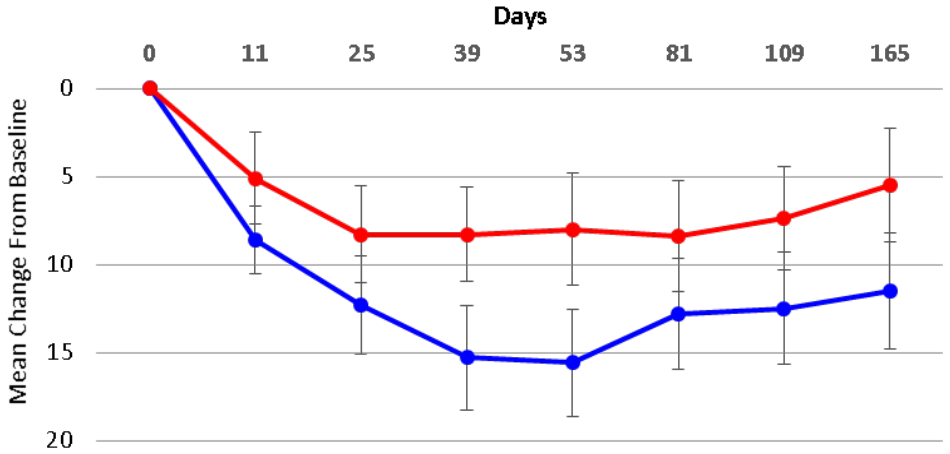
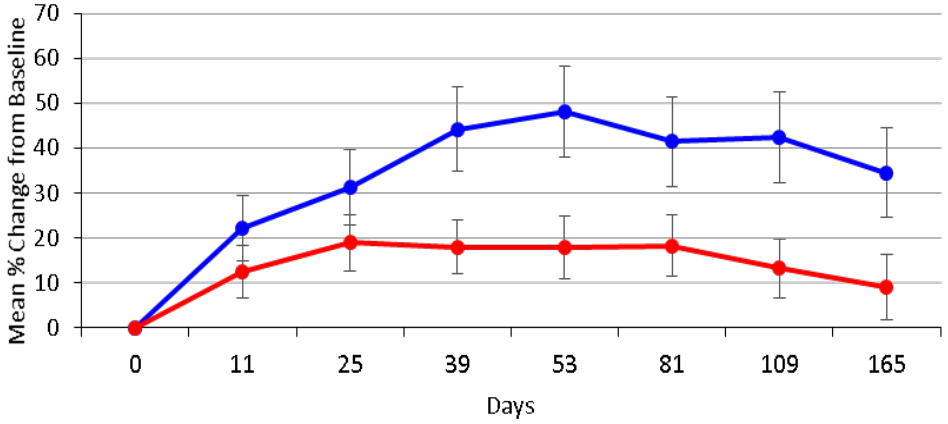
SUMMARY PHASE 2 DATA – PPP

PAIN – Mean Change KOOS Pain from BL (PPP NRS 4-6)

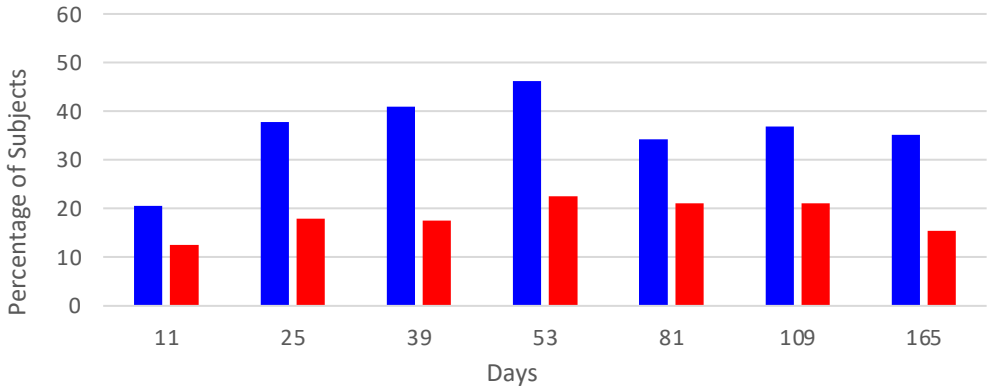


FUNCTION – Activities of Daily Living (PPP NRS 4-6)

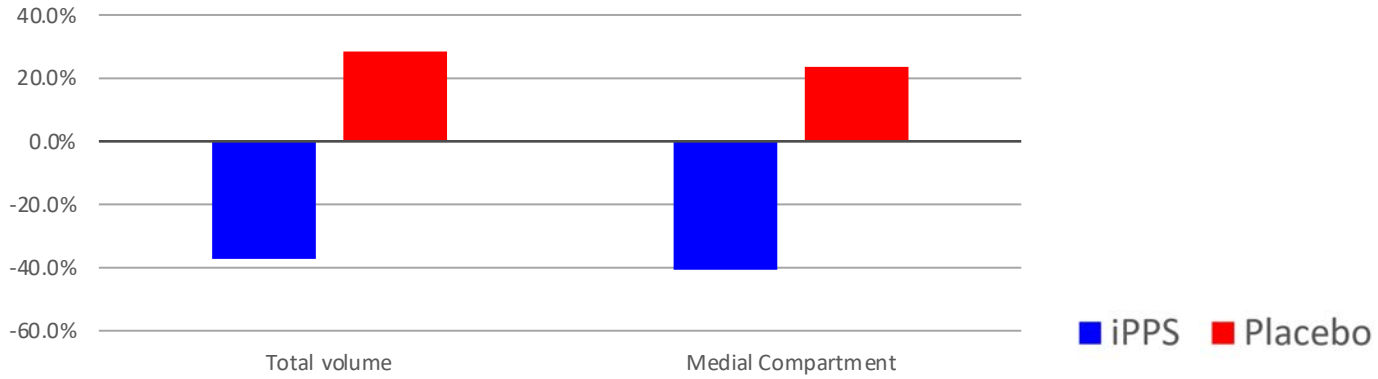


Paradigm also achieved statistically significant and clinically meaningful result in Patient Global Impression of Change (PGIC) (p=0.0062)

CLINICALLY MEANINGFUL - % of subjects with >50% reduction in KOOS pain from BL- (PPP NRS 4-6)



STRUCTURAL CHANGES - Median % Change from Baseline: BMEL Volume in Knee (PPP NRS 4-6)



PHASE 2B OA/BML CLINICAL TRIAL

PRIMARY AND SECONDARY ENDPOINTS

iPPS was well tolerated, effective and clinically meaningful in a Phase 2b randomised, double-blind, placebo-controlled, multi-centre clinical trial

- **Primary endpoint met** - change in KOOS pain score from baseline at Day 53 for total trial population ($p < 0.0001$)
- Number of subjects with **>50% Reduction from Baseline** in KOOS Pain Score at Day 53 – Clinically meaningful and stat sig results ($p<0.026$)
- **Patient Global Impression of Change (PGIC):** total iPPS population vs placebo was stat sig (PGIC, $p=0.0062$)
- BML data suggests iPPS has **potential to reduce progression of OA**
- Decreasing serum levels of COMP and ADAMTS-5 consistent with **iPPS preservation of cartilage**

Reduction in BML grade, volume and area indicates iPPS potential for reducing rate of progression of OA

Decreased serum levels of COMP and ADAMTS-5 indicate iPPS potential for reducing cartilage loss

EXPANDED ACCESS PROGRAM (EAP) RESULTS

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WOMAC® PAIN RESULTS WEEK 12

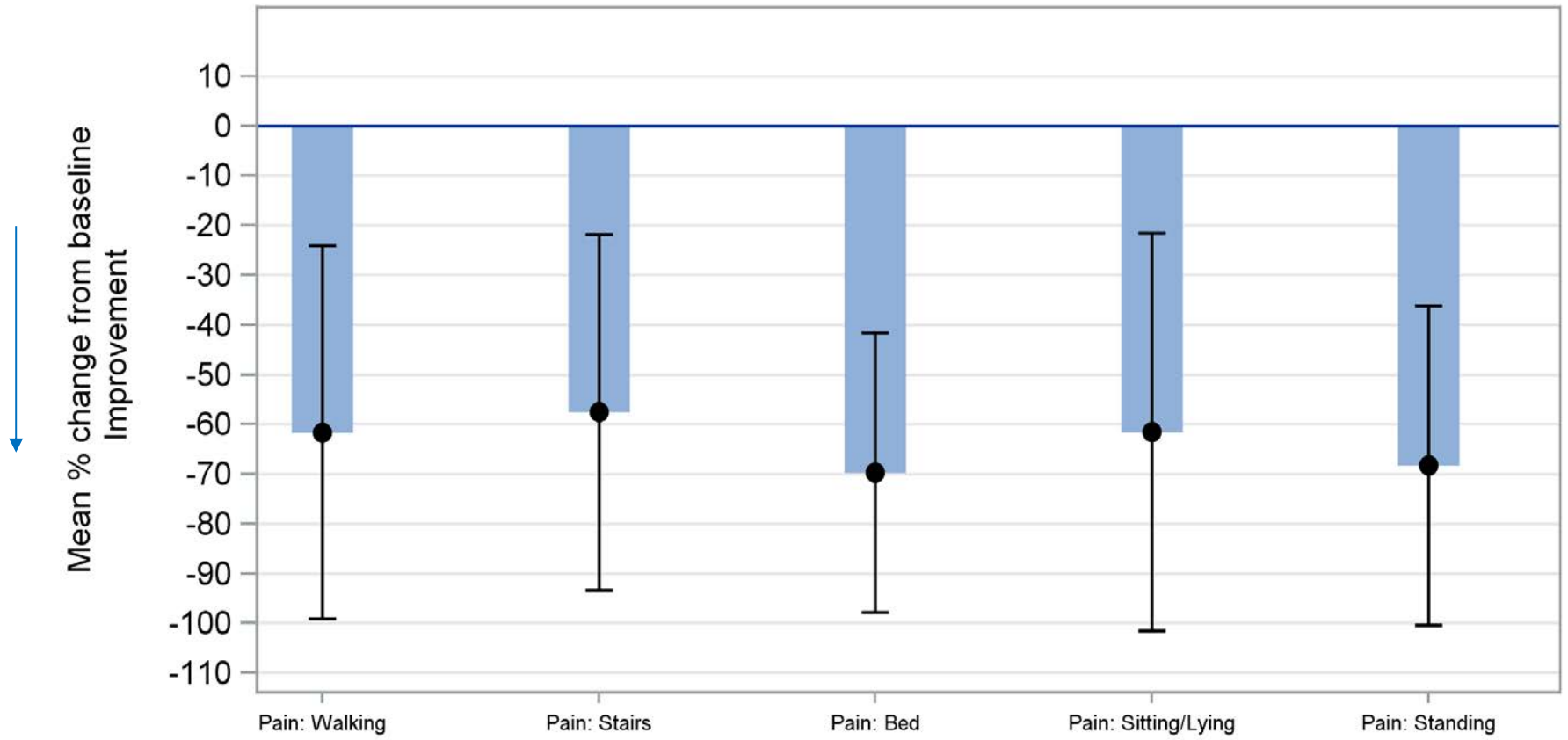
Summary of WOMAC Osteoarthritis Pain

WOMAC Pain Questionnaire (N=10 patients)	Mean Baseline value (95% CI)	Mean Post-treatment value (95% CI)	Mean % Reduction in Pain (95% CI)
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)

REDUCTION IN WOMAC PAIN SCORES

PPS TREATMENT DEMONSTRATED REDUCTION AT 12 WEEKS AFTER TREATMENT INITIATION

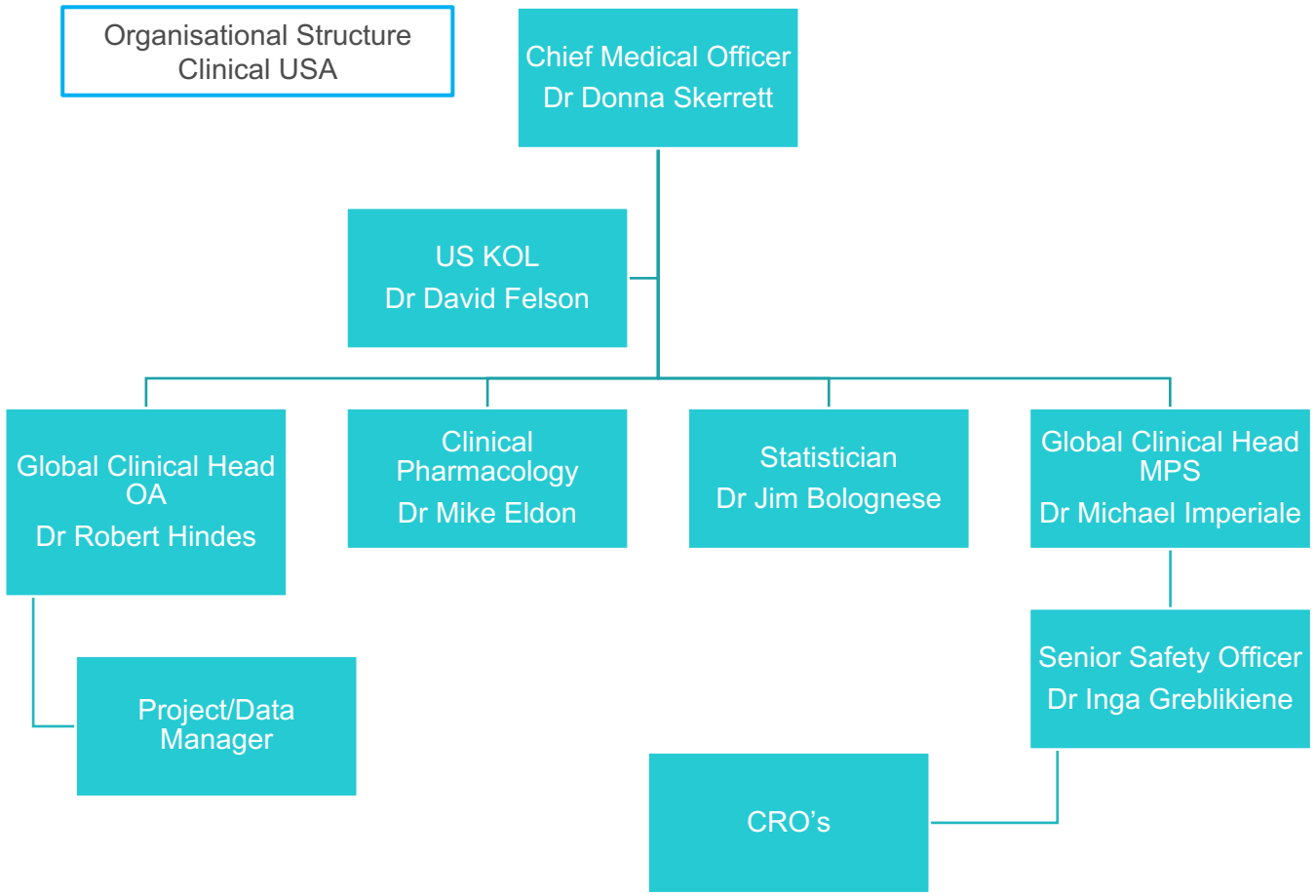
Relative (%) Change from Baseline in WOMAC Pain Scores



Toward Commercialisation

US CLINICAL TEAM

Experience presenting to the FDA and held senior executive roles with big pharma Companies.



FDA communication before opening IND

The Sponsor (PAR) is free to ask questions of the FDA at various points in the drug development process, including:

- ✓ Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance the Sponsors research.
- ✓ After Ph2, to obtain guidance on the design of large Ph3 studies (generally a pre-IND meeting).
- ➢ Any time during the process, to obtain an assessment of the IND application (generally a Type C meeting).

- ➢ OA KOL's have clinical experience with patients with OA and been involved in submissions or many products registered in the USA.
- ➢ Paradigm's Ph3 clinical trial design is being developed by a team of industry experienced experts including pharmacokinetics, statistical design, drug safety and translational experience with registered drugs.

KOL: Key Opinion Leader
CRO: Contract Research Organization

REGULATORY DISCUSSIONS

Streamlining trial design to satisfy multiple Agencies

Paradigm has had detailed discussions with the US FDA, EMA and TGA. The purpose of those discussions are to clarify the path to regulatory approval. Paradigm is designing its Phase 3 clinical trials to ensure it meets with the regulatory agency's advice and to concurrently generate clinical data:

- ✓ for market authorisation, product label, and prescribing information to assist physicians with the use of the product (package insert), time to re-dosing etc.
- ✓ to support potential unique selling advantages of iPPS post marketing approval.

- ➢ Phase 3 n=750 and confirmatory phase 3 n=400 (to be run concurrently) in USA, Europe and Australia. (possibly also Japan).
- ➢ Paradigm will apply to the US FDA for a Type C meeting for a written response to questions in relation to the clinical trial design and associated supporting clinical data. Once agreed and finalised with the US FDA, Paradigm will inform the market of the Phase 3 clinical trial design.

- The principal objective of labelling is to provide the information that is most useful to prescribers in treating their patients.
- If satisfied that the drug is safe and effective, the drug's manufacturer and the FDA agree on specific language describing dosage, route of administration, re-dosing and other information to be included on the drug's label. More detail is included in the drug's package insert.

LAYERS OF PROTECTION

Exclusive Supply Agreement with only FDA approved PPS Manufacturer

Secure manufacturing and supply

- Exclusive long-term supply agreement with bene PharmaChem. Current Agreement 20 years.
- **Only FDA-approved form of PPS Manufacturer**
- Manufacturing methods are highly complex and a well-kept trade secret

Strong Patent & IP Position

Multi-faceted IP protection

- Patent protection using PPS for new indications
- Minimum life on patents is 2030 and beyond for more recent patents
- Prosecuting new patent applications.
- Significant IP in Paradigm's process of turning PPS into its injectable form.

Regulatory Exclusivity* on Approval

Exclusivity on Registration

- MPS : Orphan Drug Exclusivity (ODE), 7 years
- OA: 505b2 pathway, 3 – 5 years of exclusivity

*Paradigm plans to commence its Ph3 clinical study in 2021

SUMMARY

Moving from a clinical development to commercial company

- Secured exclusive and scalable supply of PPS
- Lead program in OA backed by promising clinical results
- Received feedback from EMA and FDA to support next steps
- Established experienced clinical and commercial teams to deliver pivotal studies and commercial success
- Clinical protocols address data required by regulators for approval and funding agencies for optimal pricing and reimbursement
- Zilosul positioning, including physician and patient convenience, to provide for high unmet clinical need
- US market potential in OA US$15B+*

*PAR Estimate - 5m x US$3,000 per iPPS treatment = US$15bn p.a.
https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf

UPCOMING NEWS FLOW

2020	**Osteoarthritis**	▪ Official feedback from Scientific Advice meeting with the EMA ▪ Regulatory update on FDA IND submission and TGA Provisional application ▪ Official Feedback from Type-C meeting with FDA ▪ Additional TGA SAS patient WOMAC data ▪ Peer reviewed publication of Phase 2b OA/BMEL Results ▪ Evaluating once-weekly dosing and other patient convenience initiatives
	MPS	▪ Commencement of Phase 2 clinical trial in MPS I at Adelaide's Women and Children's Hospital ▪ MPS VI clinical program update
	Additional News Flow	▪ Peer reviewed publication of Phase 2a Viral Arthritis clinical trial ▪ Commencement of research program to investigate the safety and efficacy of PPS in a viral induced respiratory disease model ▪ Further strengthening of the Paradigm Management team to prepare for commercialisation ▪ Extension/Update of Bene pharmaChem Exclusive agreement

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