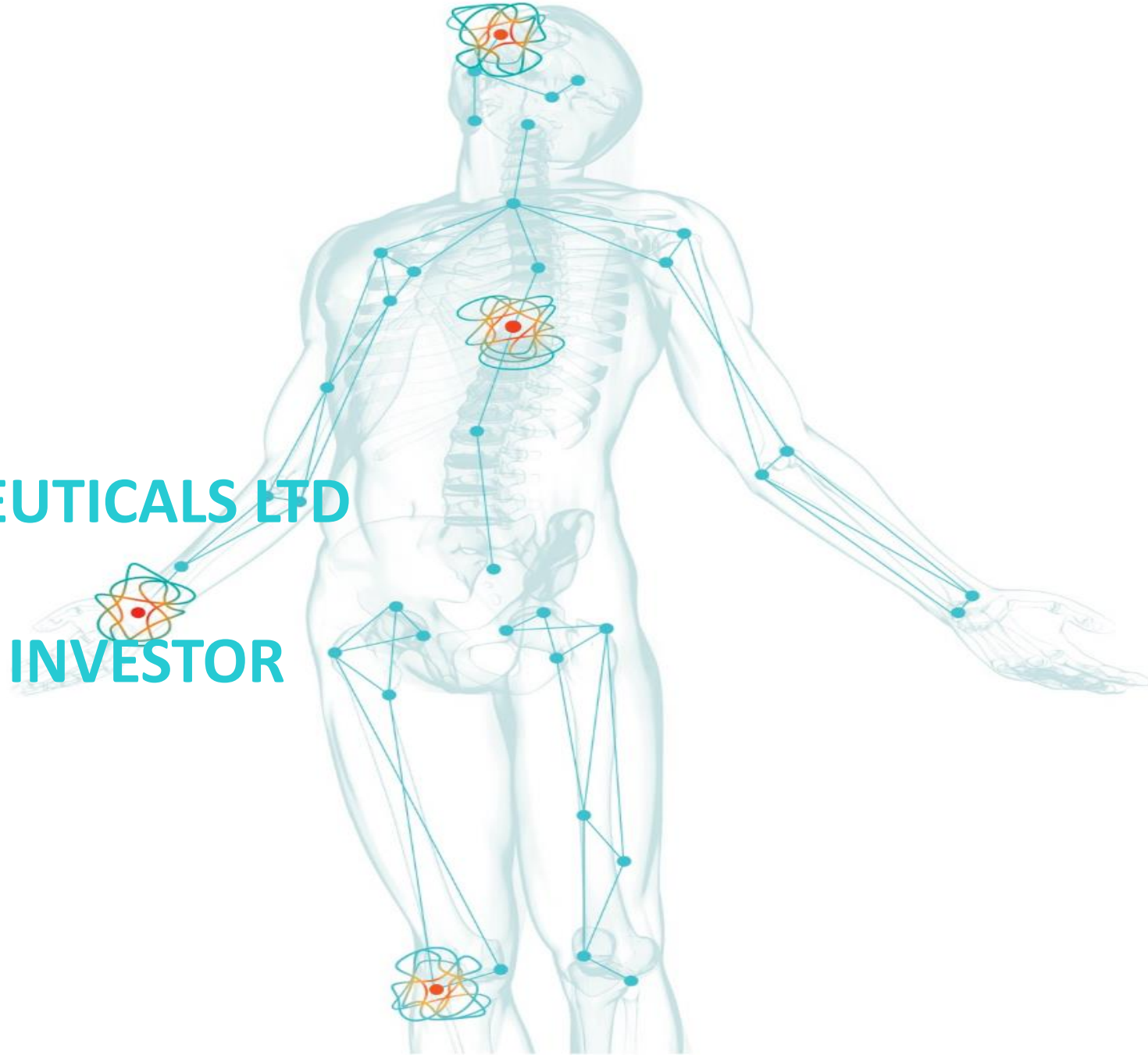
PARADIGM BIOPHARMACEUTICALS LTD (ASX: PAR) ANNUAL GENERAL MEETING (AGM) INVESTOR UPDATE

Paul Rennie, CEO & MD

7 November 2019



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EXECUTIVE SUMMARY

- **Paradigm Biopharmaceuticals Ltd (PAR.ASX)** is a late stage ASX-listed biotechnology company focused on repurposing Pentosan Polysulfate Sodium (PPS), an **FDA-approved drug** that has a **long track record** of safely treating inflammation over sixty years
- Our main focus is on repurposing PPS (under the name ZILOSUL®) to treat Osteoarthritis (OA) – market with over **31m sufferers in the US alone**
- **Expecting to file an IND with the FDA for a phase 3 clinical trial in OA in early 2020**, potential for trial readout and regulatory submission in the US as early as 2021
- **Phase 2b trial n OA successfully met primary, secondary and exploratory endpoints**
  - Primary endpoints - reduction in pain from baseline at Day 53.
  - Secondary endpoints – 6 month duration of effect, reduction in volume/size/grade of BML confirmed by MRI
  - Exploratory endpoints – material reduction in two key OA biomarkers COMP and ADAMTS-5
- Competing treatments (NGF, steroid, opioid) have not demonstrated this **combination of safety, subjective efficacy, objective efficacy, indicative regression of disease and reduction of key biomarkers**
  - **Revenue potential in US alone at 10% market share is as much as US$9bn p.a**
- **Mechanism of action has been established and peer reviewed –** down regulates Nerve Growth Factor in bone cells

EXECUTIVE SUMMARY

- Zilosul has also been **granted FDA approval under the Expanded Access Program (EAP)** to treat 10 patients
  - **First 10 patients are all ex-NFL players suffering OA – treatment begins Dec 2019**
- In Australia we are seeking Provisional Approval with the TGA prior to completing phase 3 trial
  - If successful, **Paradigm could be generating revenue in Australia as early as Q3 2020**
  - **With 3m sufferers, revenue potential in Australia alone at 20% market share is as much as AUD$1.5b p.a**
- **Meeting with EMA in Dec/Jan to ensure Phase 3 trial will also meet European regulatory requirements**
- In addition to OA, we are **seeking submission of Zilosul to treat rare disease Mucopolysaccharidosis (MPS) with FDA and EMA in a joint submission in Q1 2020 –** potential pivotal trial to read out in 2021
- Strong portfolio of IP protection and patents on Zilosul – **patents in all key markets from 2030 to 2039**
- Secured scalable manufacturing supply from FDA approved facility **– exclusive agreement for 20 years**
- **$75m of cash on balance sheet at Sept 2019**
  - **Fully funded for all major clinical trials and regulatory submissions** in OA and MPS
  - Strong position to negotiate a favorable outcome with big pharma post regulatory clearance

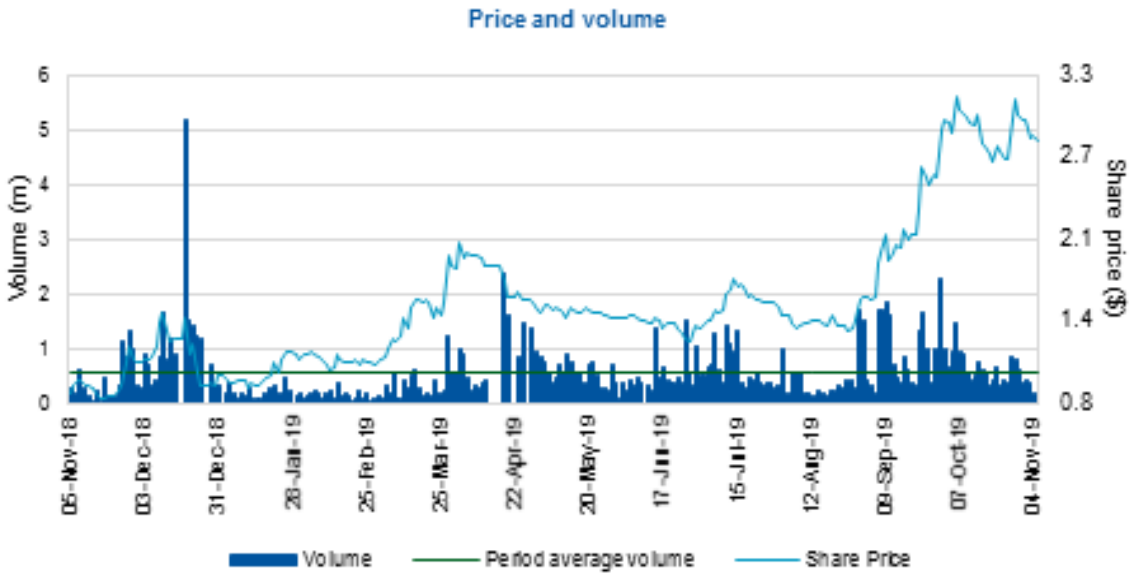
CORPORATE SNAPSHOT

Financial information

Share price (6-NOV-2019)	A$2.80
Number of shares	193m
Number of Options	5.2m
Market capitalisation	**A$538m**
Cash Mar-19	**A$75.4m**
Pro-Forma Cash Post Transaction	**A$462.6m**

Top Shareholders

	Volume Shares (m)	%
Paul Rennie	23.4m	12.12%
Other Board and Management	7.45m	3.86%
Citicorp Nominees	7.78m	4.03%
JP Morgan Nominees	5.47m	2.83%



BACKGROUND ON PENTOSAN POLYSULFATE SODIUM (PPS) / ZILOSUL

Pentosan Polysulfate Sodium

- Pentosan polysulfate sodium (PPS) is a semi-synthetic drug manufactured from beech-wood hemicellulose
- PPS has been used in humans for more than 60 years
- The oral formulation is FDA approved and sold under the name Elmiron, by Janssen Pharmaceuticals (Johnson & Johnson), for the treatment of interstitial cystitis (painful bladder syndrome). Also used to treat deep vein thrombosis
- Paradigm has been granted patents to use PPS for new indications

Potential biological characteristics

- ✓ Anti-inflammatory
- ✓ Prevents cartilage degeneration
- ✓ Anti-histamine
- ✓ Anti-clotting
- ✓ Prevents necrosis (premature cell death)
- ✓ Non performance enhancing (WADA & ASADA Cleared)
- ✓ Non-addictive

Excellent Safety Profile

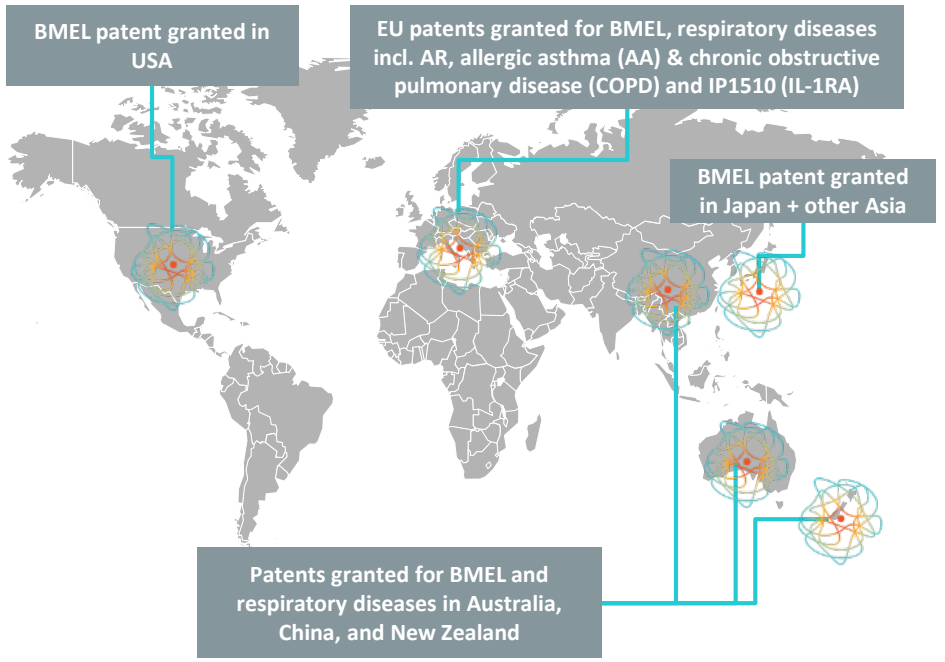
- PPS has a well established safety profile with no reported serious adverse events
- Approved by FDA over 30 years ago for oral use, over 100 million injectable doses of PPS have been administered
- PPS is a semi-synthetic, complex carbohydrate, which makes it well tolerated by the human body
- PPS is a weak anti-coagulant compared to Heparin. PPS has $1/15^{th}$ – $1/20^{th}$ the anti-coagulant activity of Heparin. Data on file with US FDA
- The clearance of PPS from the body, as measured by activated partial thromboplastin time (aPTT), is 300 minutes (5 hours).
- Suggested sports physician treatment protocol:
  - Administration at least 48 – 72 hours before any contact sport is played
  - Blood test prior to contact sport to test coagulation parameters are within the normal range
- Paradigm believes that the weak anti-coagulant properties of PPS should not present any notable issues

STRONG PATENTS & IP POSITION

Multi-faceted IP protection increases barriers to entry for potential competitors

Valuable patent portfolio

- Paradigm has patent protection because it is using PPS for new indications
- Minimum life on patents is 2030 and beyond for more recent patents **- i.e. 2035 - 2040**
- Established regulatory exclusivity and trademarks
- Patents for MPS (ex Japan) + Orphan Status
- Patent applications for Ross River virus and Chikungunya virus
- Patent applications for osteoarthritis and concurrent BMEL
- Patent for Heart Failure indication
- Prosecuting new patent applications



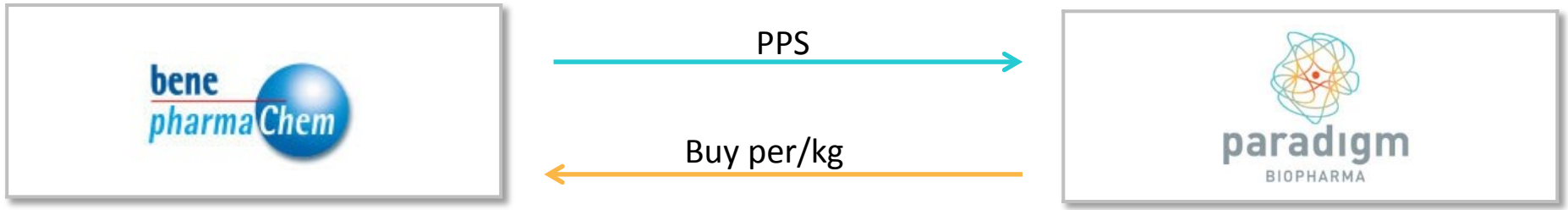
Secure **manufacturing** and supply

- Exclusive long term supply agreement with bene PharmaChem[1]
- bene pharmaChem makes the only FDA-approved form of PPS
- **Manufacturing methods are highly complex and a well kept trade secret**
- **bene pharmaChem has been supplying J&J for over 20 years for oral use**

1.bene pharmaChem is a private company located in Germany and manufactures the only officially approved and clinically tested medicinal PPS in the USA, Europe and Australia

EXCLUSIVE SUPPLY & MANUFACTURING

Exclusive Supply



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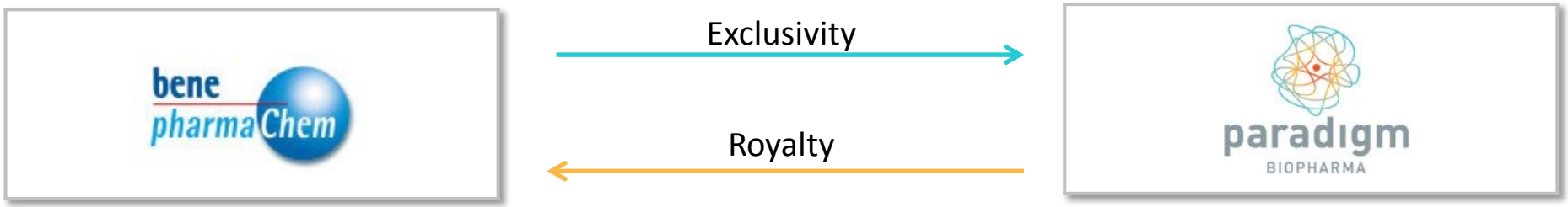
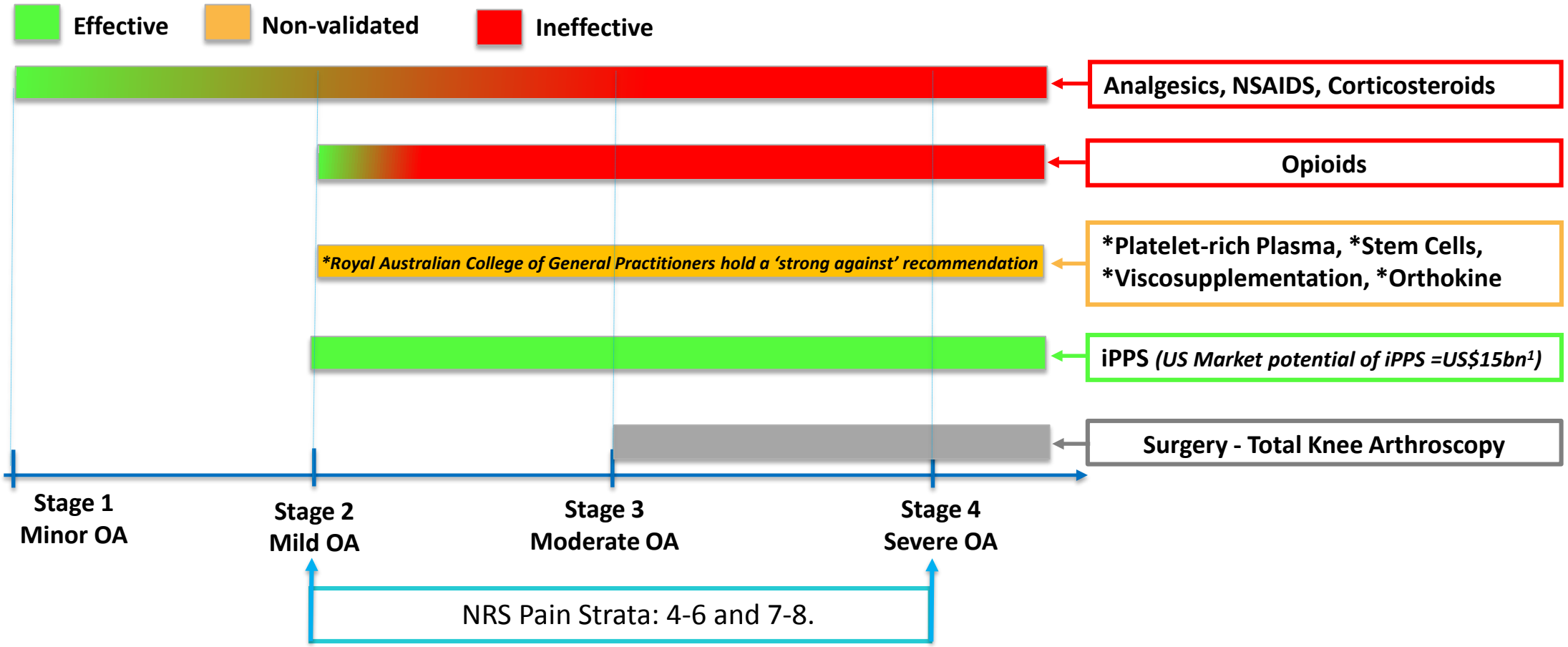


- **Paradigm has executed a long term exclusive supply agreement** with bene pharmaChem Gmbh & Co. KG
- Bene pharmaChem are the original developer of PPS and the only FDA-approved manufacturer
- Leading Big Pharma Co (J&J) source their PPS from bene for a different application (bladder pain).
- Agreement grants exclusive supply of only FDA approved PPS for Paradigm's orthopaedic and respiratory programs.
- Paradigm to pay bene pharmaChem small single digit royalty on commercial sales

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

BLOCKBUSTER POTENTIAL REVENUE P.A

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 <u>indicative</u> only

		US MARKET – aiming for approval 2021		
		10% Market Penetration	20% Market Penetration	30% Market Penetration
INDICITATIVE POTENTIAL PRICING	US$1.5k p.a	US$6.2bn p.a	US$12.4bn p.a	US$18.6bn p.a
	US$2.0k p.a	US$7.7bn p.a	US$15.5bn p.a	US$23.2bn p.a
	US$2.5k p.a	US$9.3bn p.a	US$18.6bn p.a	US$27.9bn p.a

		AUS MARKET – aiming for provisional approval 2020		
		10% Market Penetration	20% Market Penetration	30% Market Penetration
INDICITATIVE POTENTIAL PRICING	A$1.0k p.a	AUD$ 450M	AUD$ 900M	AUD$ 1.3b
	A$2.0k p.a	AUD$ 600M	AUD$ 1.2b	AUD$ 1.8b
	A$2.5k p.a	AUD $ 750M	AUD$ 1.5b	AUD$ 2.25b

DEALS – GLOBAL BIG PHARMA INTEREST IN OA

Safety Issues

Recent transactions highlight big 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. Cell Technologies	Mitsubishi Tanabe Pharma	Gene therapy	Japan	US$24m**	US$434m**	Handed Back
TissueGene, Inc. Cell Technologies	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**	

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

SUCCESSFUL RE-PURPOSED DRUGS

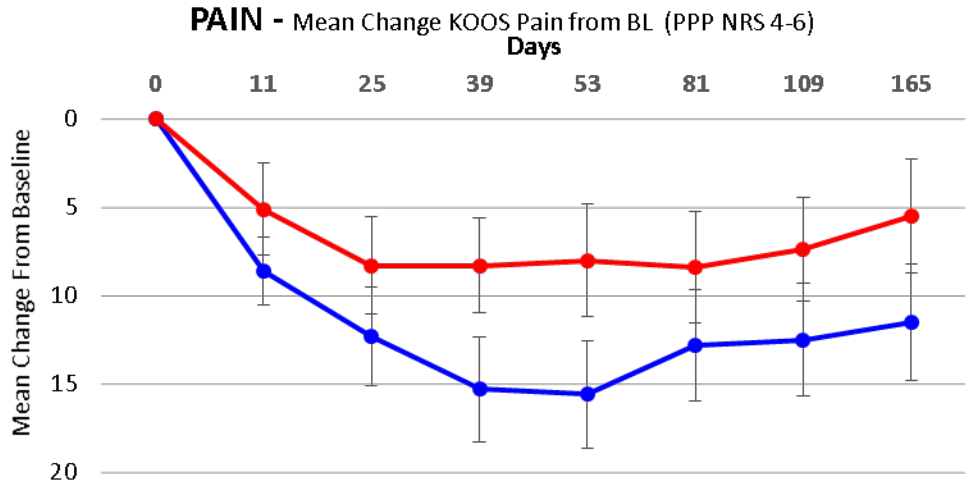
Re-purposed drugs have become true blockbusters

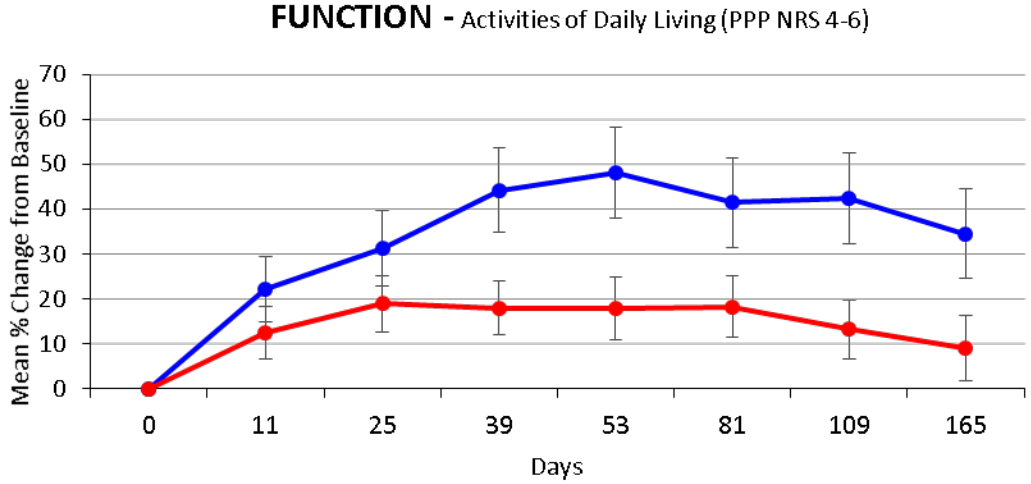
BRAND NAME	ORIGINAL INDICATION	NEW INDICATION	PHARMA COMPANY	PEAK ANNUAL SALES
SPRAVATO	Anaesthetic (Ketamine)	Treatment Resistant Depression	Janssen/J&J	**Approved March 2019**
REVLIMID	Structural Analogue of THALOMID (below)	Multiple Myeloma	Celgene	**$9.7B (2018)**
TECFIDERA	Psoriasis	Multiple Sclerosis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

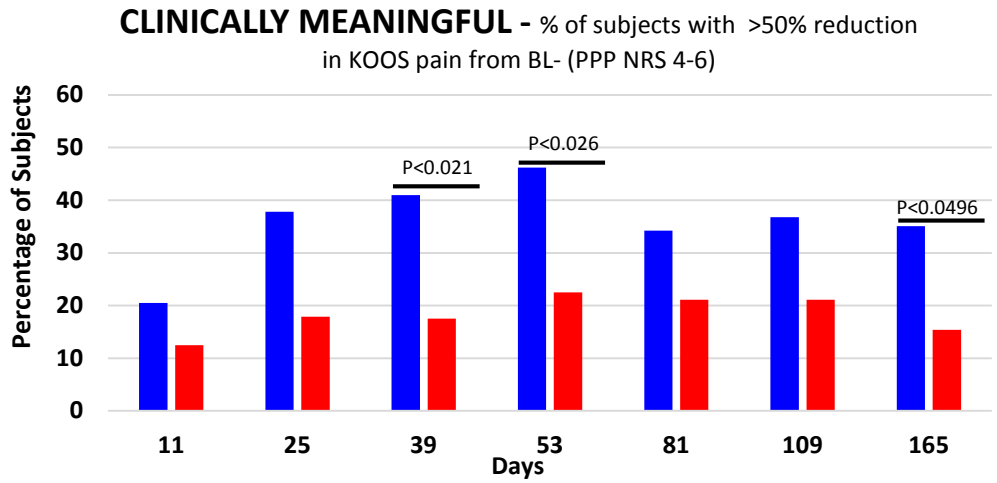
Source: Therapeutic Drug Repurposing, Repositioning and Rescue, Drug Discovery World Spring 2015; * Elmiron Use Patents ended in 2012, despite this no generic has been approved in US

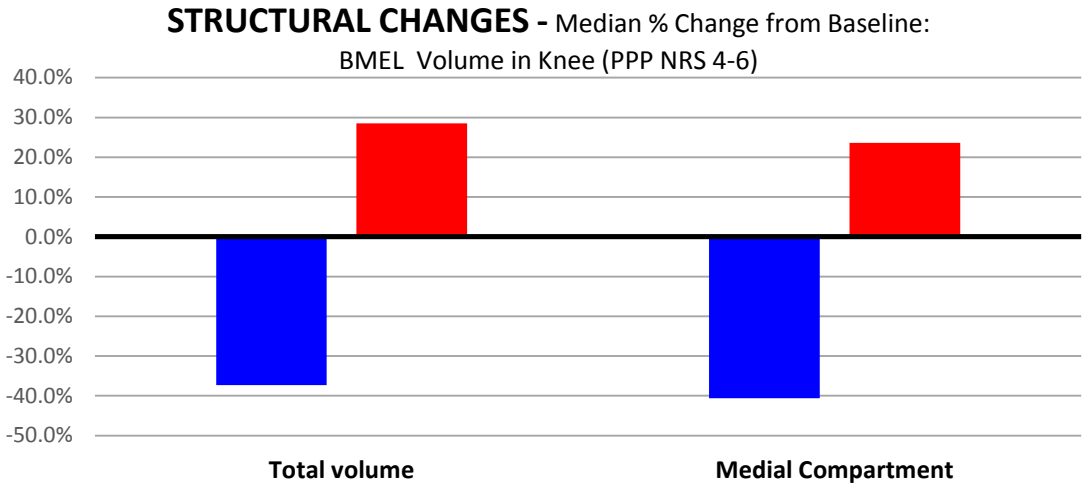
OA PHASE 2B TRIAL RESULTS PRIMARY & SECONDARY ENDPOINTS MET

SUMMARY PHASE 2B DATA – PPP NRS 4-6





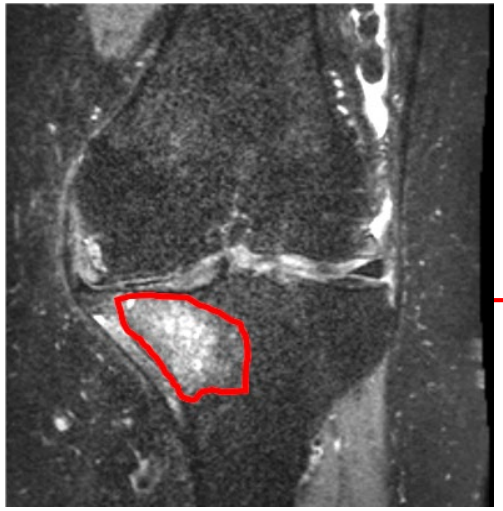




- **Paradigm also achieved a statistically significant and clinically meaningful result in Patient Global Impression of Change (PGIC) (p=0.0062)**

iPPS Placebo

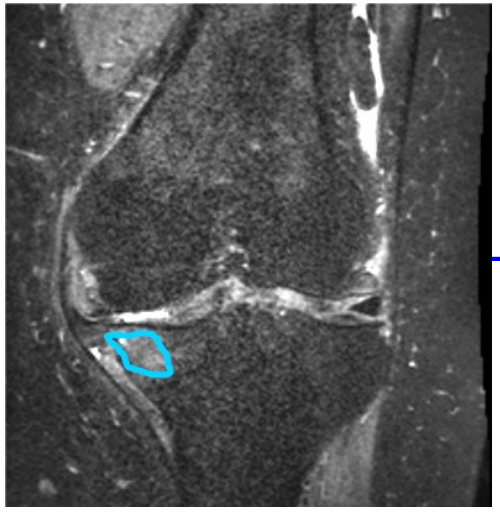
BONE MARROW LESIONS (BML): CLINICAL IMPLICATIONS FOR KNEE OA AND DISEASE REGRESSION WITH iPPS THERAPY



Grade 3 medial tibial BML at baseline

BML appear as increased signal intensity within the bone marrow

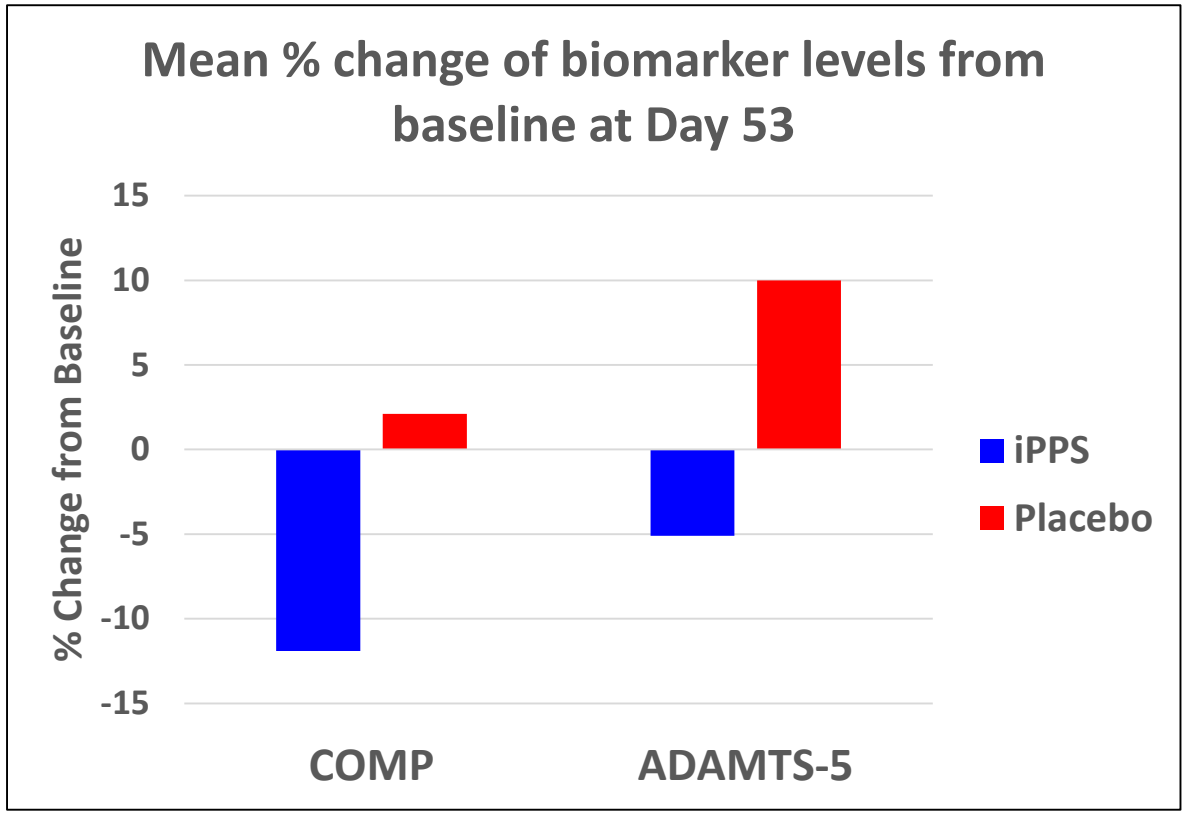
- INCREASING PAIN[1]
- INCREASED CARTILAGE LOSS[2]
- HIGH RISK OF JOINT DESTRUCTION[3]
- HIGH RISK OF TOTAL KNEE REPLACEMENT[4,5]



Grade 2 medial tibial BML at follow-up

- REDUCED PAIN[1]
- REDUCED CARTILAGE LOSS[2]
- REDUCED RISK OF JOINT DESTRUCTION[3]
- REDUCED RISK OF TOTAL KNEE REPLACEMENT[4,5]

iPPS as a cartilage-protective agent potentially blocks the progression of KOA: Reduction in serum COMP and ADAMTS-5 in KOA



- **COMP: mean percentage reduction of 11.9% from baseline at Day 1 to Day 53 in the iPPS treatment group vs increase of 2.1% in placebo (p=0.03).**
- **ADAMTS-5: mean percentage reduction of 5.1% from baseline at Day 1 to Day 53 in the iPPS treatment group vs increase of 10% in placebo.**

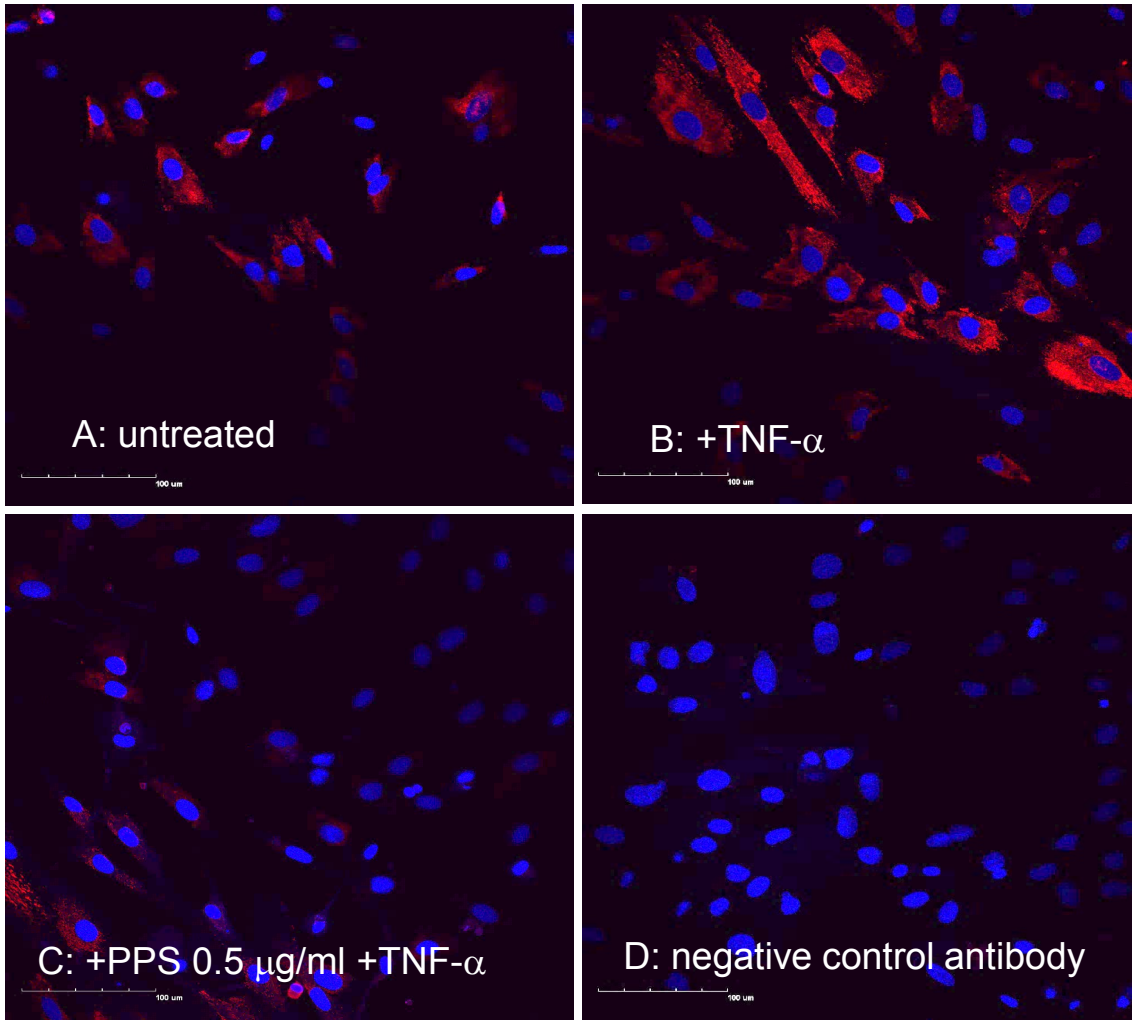
Among subjects with symptomatic knee OA, a single measurement of increased COMP predicted subsequent cartilage loss on MRI. Hunter D et al; Arthritis Research & Therapy 2007, 9:R108 (doi:10.1186/ar2314)

PHASE 2B OA/BML CLINICAL TRIAL – PRIMARY AND SECONDARY ENDPOINTS

- Clinical trial met the primary endpoint - change in the KOOS pain score from baseline at Day 53 for the total trial population ($p < 0.0001$);
- Number of subjects with a >50% Reduction from Baseline in KOOS Pain Score at Day 53 – Clinically meaningful and statistically significant results ($p<0.026$)
- Mean Percentage Change in NRS Pain from Baseline – NRS:4-6 Strata. Clinically meaningful and statistically significant results ($p<0.028$).
- A key measure in pain outcomes is the Patient Global Impression of Change (PGIC) the total iPPS population vs placebo was statistically significant (PGIC, $p=0.0062$);
- All data will be the subject of a peer-review publication;
- BML data confirms iPPS reduces progression of OA
- Decreasing serum levels of COMP and ADAMTS-5 confirms iPPS protects cartilage from breakdown.
- Safety of drug confirmed.
- Conclusion iPPS was safe, effective and clinically meaningful in a Phase 2b randomised, double-blind, placebo-controlled, multicentre clinical trial.
- **Of significant note is the reduction in BML grade, volume and area confirms iPPS reduces the rate of progression of OA and the decreased serum levels of COMP and ADAMTS-5 confirm iPPS reduces the amount of cartilage loss.**

Mechanism of Action: Reduction of NGF as mediator of Pain

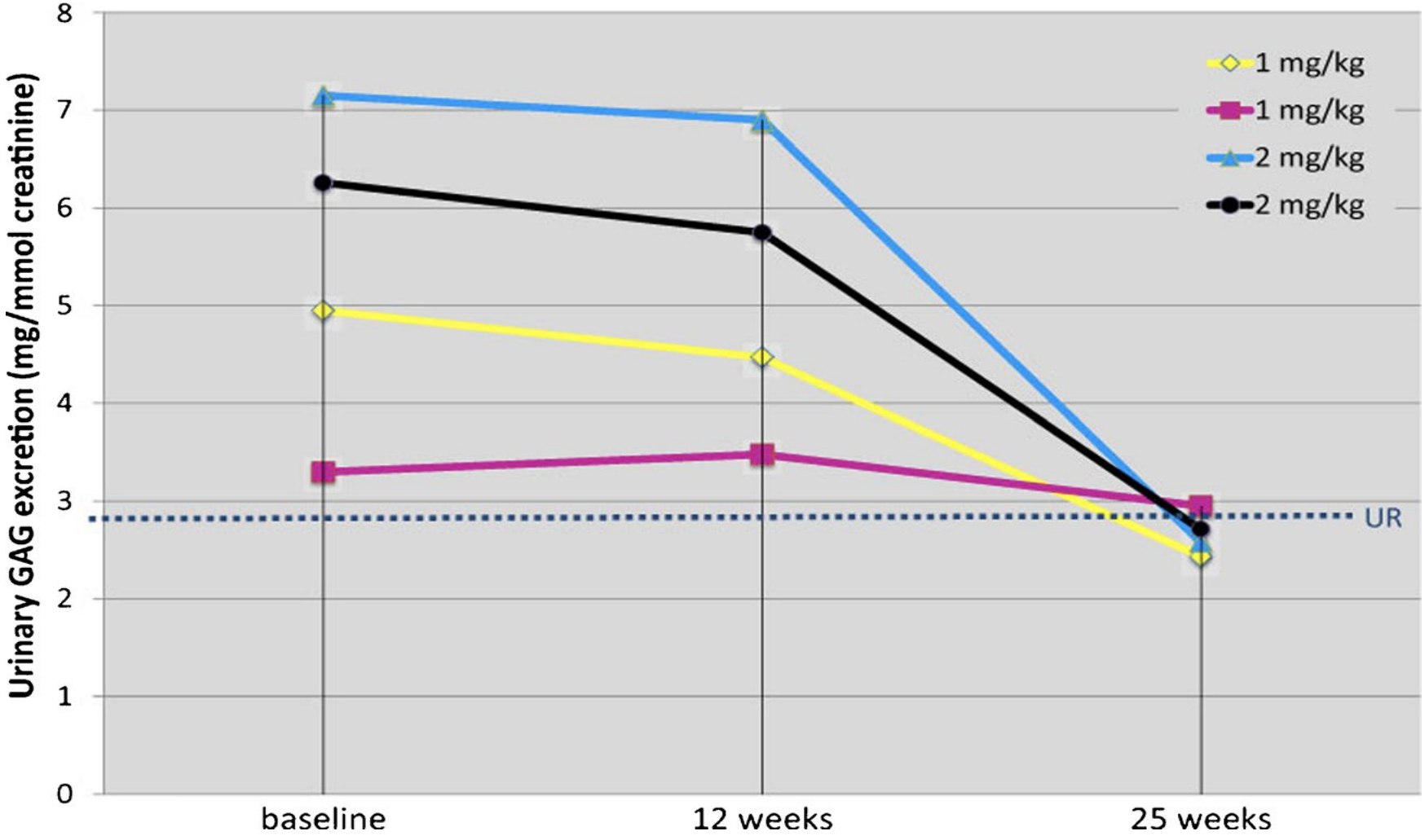
PPS downregulate NGF expression in Osteocytes Knee OA patients



Confocal microscopy images showing NGF protein expression (red) by freshly harvested human osteocytes compared (A, B, C) with isotype control IgG immunostain (D). Nuclei (blue) are stained with DAPI.

(***Stapeldon et al PLOS One 2019)***

MPS


Urinary GAG excretion (mg/mmol creatinine)
8
7
6
5
4
3
2
1
0
baseline
12 weeks
25 weeks
1 mg/kg
1 mg/kg
2 mg/kg
2 mg/kg
UR

ACHIEVEMENTS SINCE $77M CAPITAL RAISING IN APRIL 2019

- ✓ Mechanism of Action established and peer reviewed in scientific journal
- ✓ Release of exploratory endpoints from phase 2b trial – reduction in key OA biomarkers
- ✓ Expansion of team for regulatory approvals and pivotal trials – 5 new staff hired
- ✓ FDA approval for Expanded Access Scheme to treat 10 patients
  - ✓ Key doctor/site established
  - ✓ 10 high profile ex-NFL players recruited
  - ✓ Manufacturing completed and shipped
- ✓ Filed Pre-IND request for meeting with FDA – expected before end of Q1 CY 2020.
- ✓ Close to completing filings to EMA
- ✓ Submitted request for meeting for Provisional Approval with TGA – meeting mid Nov 2019
- ✓ Nearing completion of joint filing for IND with FDA and EMA for MPS

CATALYSTS & NEWS FLOW

- **Further release of patient results for treatment of OA under the TGA special access scheme -** imminent
- **Results of meeting for provisional approval of Zilosul with TGA –** end 2019
  - **Potential for approval to begin selling in Australia**
  - **Potential for first revenues in Q3 2020**
- **10 ex-NFL players with OA treated with Zilosul in the US–** end 2019
  - **Results to be released in mid 2020 – potential for significant media attention**
- **Pre-IND meeting with FDA for OA – end 2019**
- **Submit IND with FDA for OA – early 2020**
- **Phase 3 Pivotal clinical trial in OA begins – mid CY2020**
- **Joint filing of with FDA and EMA for pivotal trial for Mucopolysaccharidosis (MPS)** – early CY2020
  - **Pivotal trial in MPS to begin in US - 2020**
- **Potential to treat to MPS patients in Australia via the SAS** – CY2020
- **Ongoing partnering discussions with big pharma**

AGM BUSINESS

The AGM – the Company Scoreboard

Milestones for **CY2019**

Milestones for CY2019	
Phase 3 OA/BMEL Clinical Trial: • **Plan/Design** • **File Investigational New Drug (IND) Application** • **Activate multiple sites (across US)** • **Initiate recruitment** (Assuming Phase 2b success)	
Initiate Compassionate Use program with NFL 'Pro Players Elite Network'	
Phase 2a Alphavirus results read out and progress Alphavirus program (CHIKV)	
Anticipated media with high profile NFL players successfully treated with iPPS	
Peer reviewed publication of Phase 2b OA/BMEL Results	
Peer reviewed publication of further Mechanism of Action (MoA) work on iPPS as a treatment for pain	
Progress MPS Indication	
TGA Provisional Approval for iPPS to treat OA in Australia	
Introduce/announce SAS results for additional orthopaedic indications (joints other than knee)	
Ongoing assessment of respiratory indication	

Milestones for **CY2020**

Milestones for CY2020	
Initiate Compassionate Use program with NFL 'Pro Players Elite Network'	
Peer review publication of Phase 2a Viral Arthritis clinical trial.	
Phase 3 OA/BMEL Clinical Trial: • **Commence Phase 3 Clinical Trial in USA**	
Phase 2/3 MPS Clinical Trial: • **Commence Phase 2/3 Clinical Trial in USA and EU**	
Peer reviewed publication of Phase 2b OA/BMEL Results	
Progress MPS Indication	
TGA Provisional Approval for iPPS to treat OA in Australia	
Ongoing assessment of respiratory indication