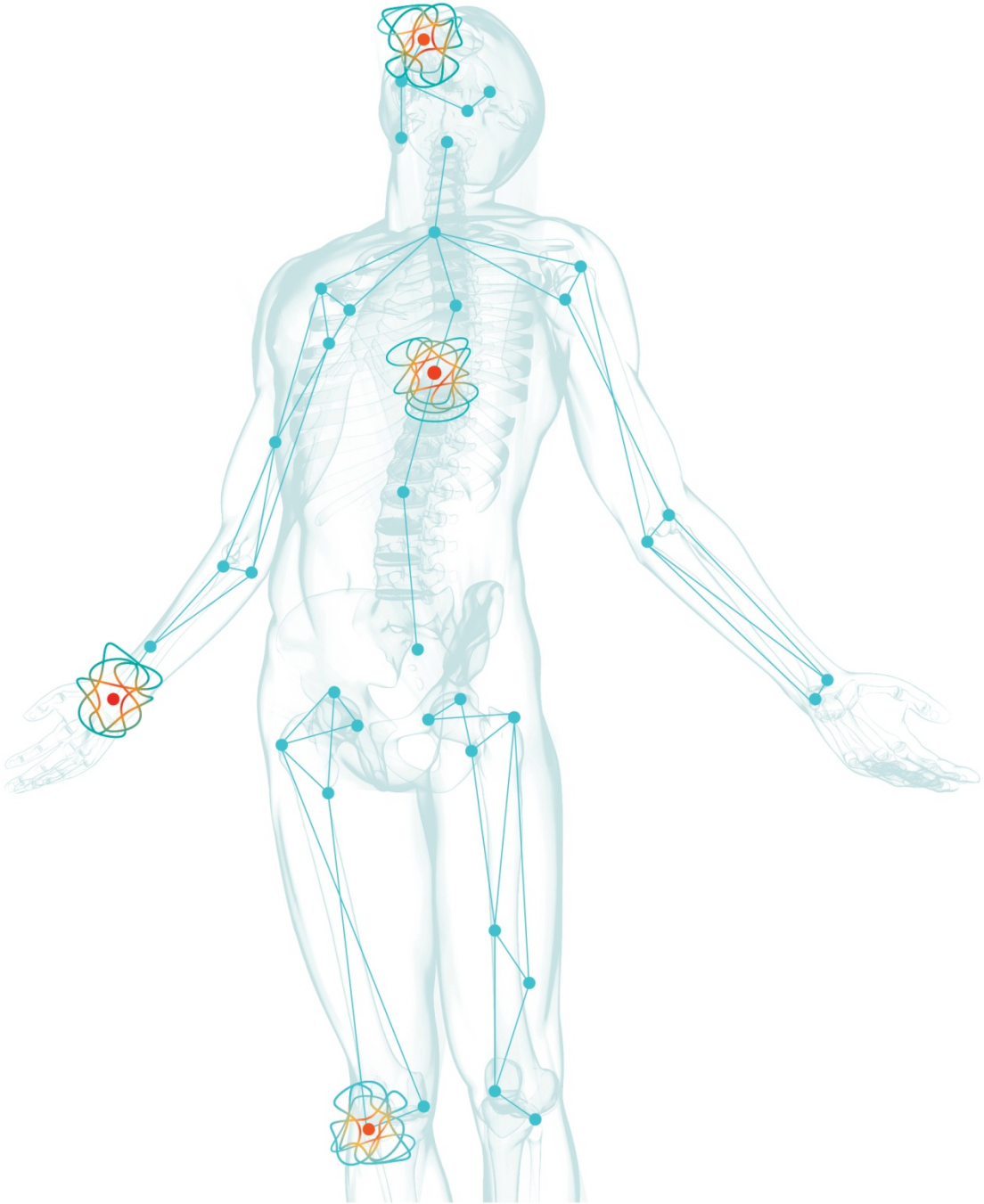
paradigm
BIOPHARMA

# 2018 AGM Presentation

Paul Rennie, CEO & MD

26 November 2018



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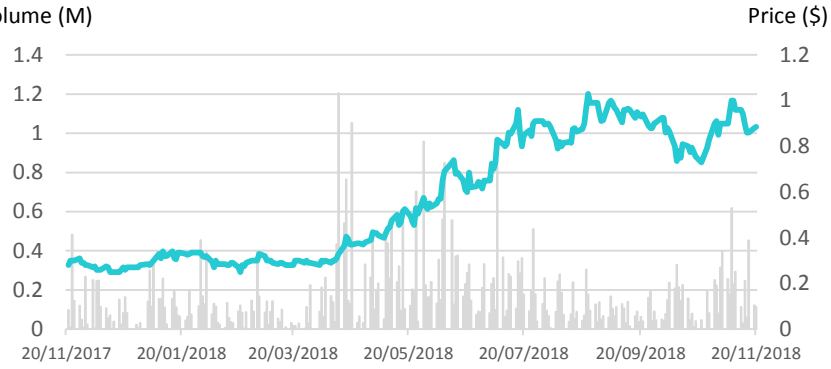
# Corporate Overview

- **Paradigm Biopharmaceuticals Ltd** is an 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
- Paradigm is repurposing PPS for a number of applications with a focus on treatment of **orthopaedic and viral arthritic** indications
- Drug repurposing uses the 505(b)(2) pathway - **lower cost, minimises risk** and has accelerated development timelines
- **Several clinical indications** such as Osteoarthritis/Bone Marrow Edema Lesions, Ross River virus and Chikungunya, giving us **"multiple shots on goal"**
- Strategy is to **establish commercial partnerships** with multiple leading pharmaceutical companies

**Financial information -** post $9m placement

| | |
|---|---|
| Share price (21-November-2018) | A$0.88 |
| Number of shares (post $9m placement) | 136.4m |
| **Market capitalisation** | **A$120m** |
| Cash Post Placement (Nov 2018) – no debt | ~A$10.5m |

| **Top shareholders**[1,2] | Shares (m) | % |
|---|---|---|
| Paul Rennie (Managing Director) | 21.6 | 15.8% |
| MJGD Nominees *(technology vendor)* | 6.9 | 5.1% |
| Other Board and management | 7.1 | 5.4% |
| Irwin Biotech *(technology vendor)* | 6.3 | 4.6% |




Note: 1. Blue shading represents Board and management holdings 2. MJGD Nominees and Irwin Biotech are select vendors of Xosoma, which was acquired by Paradigm prior to listing

# Investment Highlights

- Focus on repurposing PPS (under the name ZILOSUL®) to treat **Osteoarthritis (OA) – 31 million sufferers in the US alone** – Large Market with unmet Need for new treatments
- iPPS is expected to be **a more effective, safer, lower cost and longer term alternative to steroids and opioids** for the treatment of OA
- **Combating the Opioid Epidemic** – Significant demand for the development of new disease modifying treatment options that do not have the addictive/negative features of opioids
- Released data from 145 patients treated under TGA "special access scheme" – showing a clinically meaningful >50% reduction in pain
- Read out of **Phase 2b 110 patient trial results in mid December 2018 – Major value Inflexion point**
- Subject to successful Phase 2b results, the Company is aiming to achieve Fast-Track designation and conduct a pivotal **Phase 3 trial in the US in 2019**
- Fully Funded to **accelerate preparation for Phase 3 OA trial in the US and fund a Compassionate Use program** to be conducted in the US
- **Aim to replicate TGA SAS success in the US** with the Pro Players' Elite Network ( >11k retired NFL players and elite athletes)
- **Highly credentialed board and management team** with top tier experience at CSL Limited (CSL.ASX) and Mesoblast Limited (MSB.ASX)

# Drug Repurposing Strategy

## Much lower cost, accelerated timeline, lower risk and with higher rates of success

- **Lower cost:** average development cost of ~US$30-50m compared to US$1.3bn for "de novo" development[1]
- **Faster:** FDA 505(b)(2) pathway leveraging previous clinical efforts**,** which accelerates the development timeline
- **Lower risk:** safety already established so less chance of failure (safety issues account for 30% of clinical failures[1])
- **Higher success rates:** 25% chance of successful commercialisation compared to 10% for "de-novo" drugs[1]
- **Repurposed drugs have the same potential** to reach 'blockbuster drug status' as de novo drugs

**Standard clinical development[1,2]**

10-17 year process

| Discovery & pharmacology | Preclinical testing | Phase I clinical trials | Phase II clinical trials | Phase III clinical trials | Regulatory approval |
|---|---|---|---|---|---|
| 2 – 3 years | 5 – 6 years | | 2 – 6 years | | 1 – 2 years |

**Paradigm's drug repurposing timeline**

3-5 year process to approval

| Often only 1 pivotal Phase II trial Can use RWE open label case studies | 1 pivotal Phase III trial for each indication | Regulatory approval |
|---|---|---|
| 1 year | 1 – 2 years | 1 – 2 years |

Source:
1. Khanaoure A, Chuki P & De Sousa A (2014)
2. Ashurn T & Thor K (2004)

# Board and Management

## High quality Board and management, with top-tier pharmaceutical experience

- Board and management are renowned leaders in the biopharmaceutical industry, having held senior management positions with top ASX-listed companies, CSL (CSL.ASX) and Mesoblast (MSB.ASX)
- Extensive experience bringing biopharmaceutical products from clinical development to commercialisation
- Small and highly specialised team focused on product development utilising outsourcing effectively

### Board and management

**Graeme Kaufman – Non-executive Chairman**
- Broad experience in development and commercialisation of pharmaceutical drugs, previously CFO at CSL, executive VP of Mesoblast and Chairman of Bionomics (BNO)

**Paul Rennie – Managing Director**
- Extensive experience in drug development and commercialisation, previously COO & Executive VP, New Product Development of Mesoblast

**John Gaffney – Non-executive Director**
- 30+ years experience as a lawyer, previously Director of Patrys (PAB.ASX)

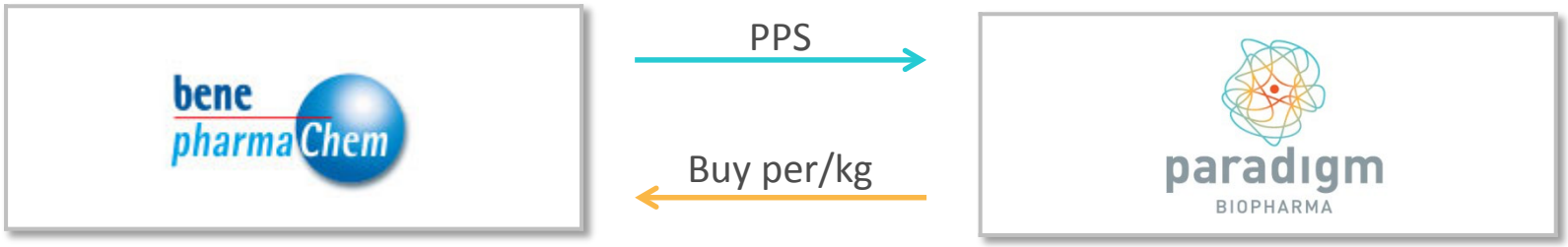
**Christopher Fullerton – Non-executive Director**
- Chartered Accounting and investment banking expertise, previously Non-executive Chairman of Bionomics and Cordlife (now Life Corporation (LFC.ASX))

**Dr Ravi Krishnan – Chief Scientific Officer**
- Significant experience in experimental pathology and investigating novel compounds with immune modulatory effects and anti-inflammatory properties

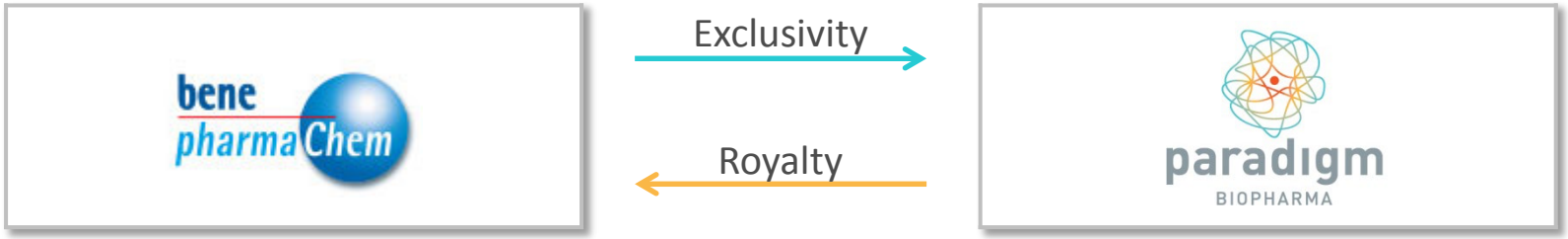
**Kevin Hollingsworth – CFO & Company Secretary**
- Previously CFO and Co-Sec of Mesoblast and Patrys (PAB.ASX)

# Pentosan Polysulfate Sodium – Supply & License

## Exclusive Supply




## License




- Paradigm has executed a 20 year exclusive supply agreement with bene PharmaChem Gmbh & Co. KG
- Bene pharmaChem are the original developer of PPS and the only FDA-approved manufacturer
- Agreement grants exclusive supply of only FDA approved PPS for all orthopaedic (inc. alphavirus), respiratory and cardiovascular indications
- Paradigm to pay bene pharmaChem small single digit royalty on commercial sales

# IP Protection

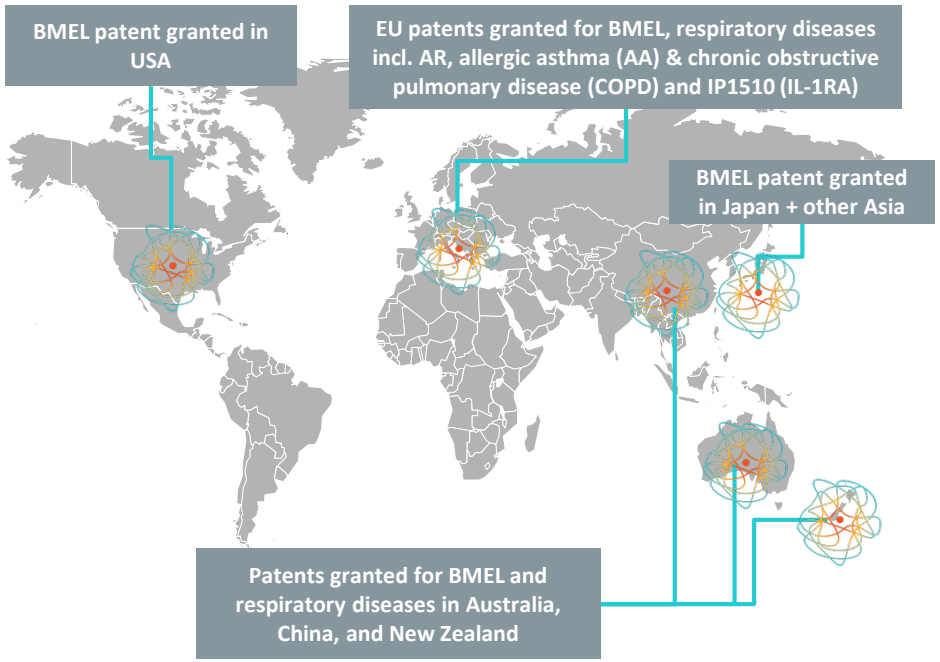
## Multi-faceted IP protection increases barriers to entry for potential competitors

### 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
- Patents granted for specific indications
- Established regulatory exclusivity and trademarks
- Patent applications for Ross River virus and Chikungunya virus
- Patent applications for osteoarthritis and concurrent BMEL
- Global patent for Heart Failure indication
- Assessing additional patent applications

### Secure manufacturing and supply

- Exclusive 20 year 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**
- Reduces risks associated with manufacturing and supply




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

# Broad Product Pipeline

| Drug Candidate | Indication(s) | Preclinical | SAS Pilot/Phase 1 | Phase 2a | Phase 2b | Phase 3 |
|---|---|---|---|---|---|---|
| **Orthopaedic - OA/Bone Marrow Edema Lesions** | | | | | | |
| PPS | Knee Osteoarthritis/BMEL | | 145 TGA SAS Patients | | 110 Knee OA Patients | |
| | Acute Injuries/BMEL (ACL etc) | | | 10 ACL Patients | | |
| | OA/BMEL - Other Joints | | TGA SAS Scheme | | | |
| **Viral Arthritis – Alphavirus** | | | | | | |
| PPS | Ross River Virus (RRv) | | 30 SAS RRv Patients | 20 RRv Patients | | |
| | Chikungunya virus (CHIKV) | | | | | |
| **Genetic Disorder** | | | | | | |
| PPS | Mucopolysaccharide (MPS) | | | 4 MPS patients | | |
| **Respiratory** | | | | | | |
| PPS | Allergic rhinitis (hay fever) | | 20 Phase 1 safety | | 40x2 patient crossover | Assessment needed |
| | COPD | | | | | |
| **Cardiovascular** | | | | | | |
| PPS | Heart failure | | | | | |
| **Inflammation & autoimmune** | | | | | | |
| Anti IL-1 RA inhibitor Peptide | Auto-immune disorders | | | 26 patients phase 2a | | |

# The AGM – The Company Scoreboard

# Milestones achieved - **CY2017**

## BME Milestones for CY2017

Close-out open-labelled acute BME study Q2 2017. ✓ Results Q4 CY2017 or Q1 CY 2018

Commence Phase 2b randomised, double-blind placebo-controlled clinical trial in subjects with osteoarthritis and concurrent BML (n=100) ready out CTQ4 2018 – CYQ1 2019 ✓

## Respiratory Milestones for 2017

Complete Phase 2 clinical trial with read-out Q3 2017 ✓

Commence commercial partnership opportunities ✓

Product development for a new product to treat other allergic conditions ✓

## Alphavirus Milestones for 2017

Commence RDBPC Phase 2 clinical trial Ross River ✓

Commence Chikungunya Phase 2 clinical trial (Brazil) (Planning has commenced) ✓

## Additional Milestones Achieved CY2017

Twenty-Four Doctor's patients with advanced OA treated with PPS under the TGA SAS. ✓
83% response rate to reduction in pain;
80% response rate to improved knee function.
Another Twenty-Five Doctor's patients treated under the TGA SAS expected to be reported in Q1CY 2018

Ross River Phase 2A commenced – expected readout Q2 or Q3 CY 2018 ✓

Over subscribed capital raise ($5.75 Million) ✓
R&D Tax ($1.7M) ✓

Publication peer-reviewed and published for Patient with OA and concurrent BML – A case study ✓

Implemented a Company Quality System ✓

Replaced E-DMS ✓

R&D undertook DD on four new projects ✓

# Milestones achieved - **CY2018**

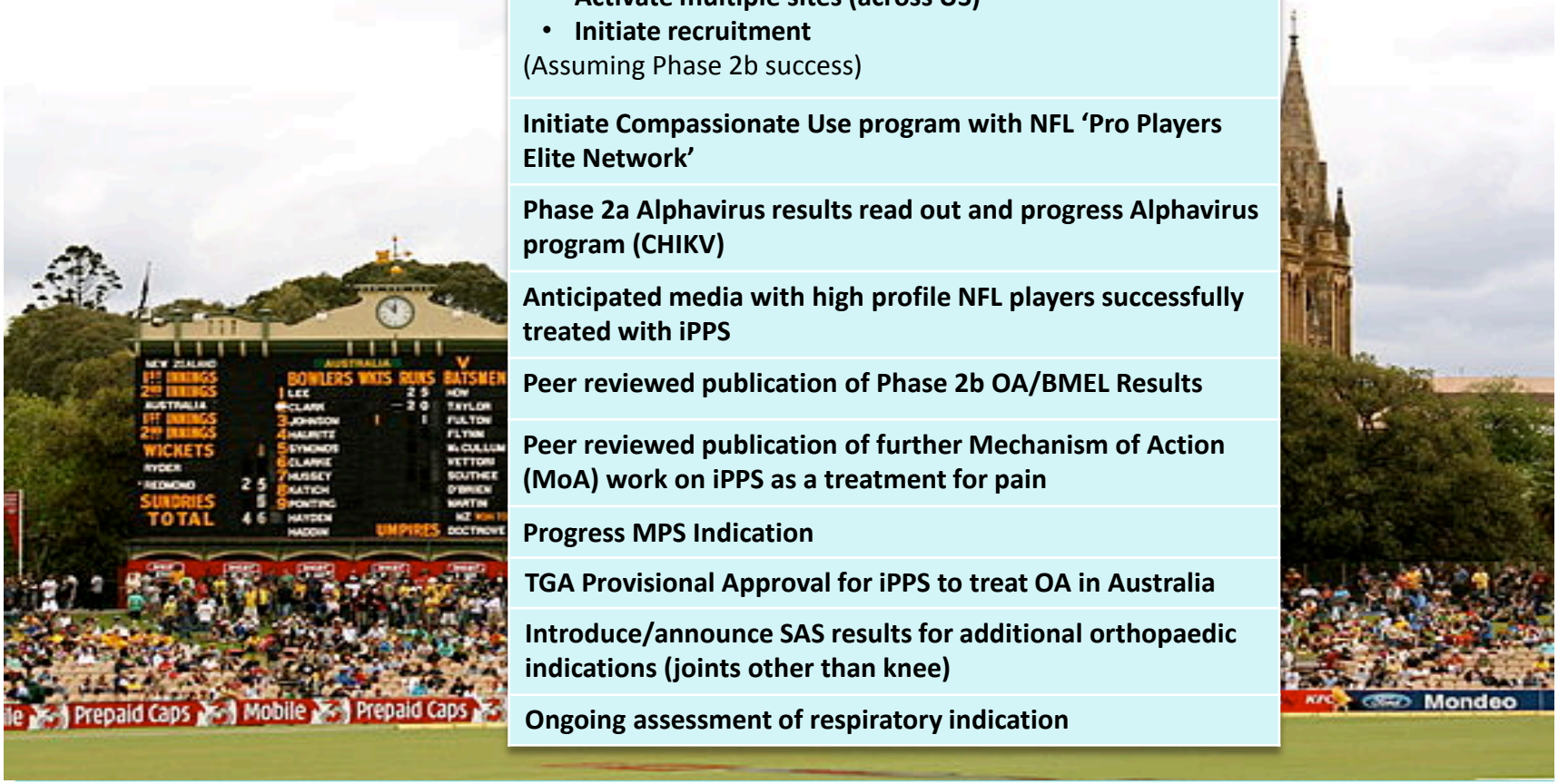
| OA/BMEL Milestones for CY2018 |
|---|
| Complete Phase 2b randomised, double-blind placebo-controlled clinical trial in subjects with osteoarthritis and concurrent BMEL ✓ |
| Results due on time – December 2018 ✓ |
| TGA Special Access Scheme – 500+ patients treated ✓ |
| TGA SAS Knee OA Results (RWE Data) – 145 patients >50% reduction in pain ✓ |
| TGA SAS Acute Injuries (RWE Data) – Elite sporting clubs using PPS to treat players ✓ |

| Alphavirus Milestones for 2018 |
|---|
| Finalise recruitment for Phase 2a Alphavirus clinical trial ✓ |
| Phase 2a Alphavirus results – pending ✓ |
| Commence Chikungunya Phase 2 clinical trial X |

| Additional Milestones Achieved CY2018 |
|---|
| Successfully treated AFL stars: Andrew Walker and Greg 'Diesel' Williams ✓ |
| Widespread use of PPS by elite sporting codes via the TGA SAS ✓ |
| Heads of Agreement with US based NFL 'Pro Players Elite Network' to initiate treatment of past NFL players via 'Compassionate Use Program' ✓ |
| Over subscribed capital raise ($9.0 Million) ✓ R&D Tax ($2.32M) ✓ |
| Large number of institutions have joined the register ✓ |
| Significant share price appreciation ✓ |
| In-licensing of MPS indication – Received valuable long term safety data ✓ |
| DD/R&D on a range of projects ✓ |

# Milestones for **CY2019**

| Milestones for CY2019 |
| --- |
| **Phase 3 OA/BMEL Clinical Trial:**<br>• **Plan/Design**<br>• **File Investigational New Drug (IND) Application**<br>• **Activate multiple sites (across US)**<br>• **Initiate recruitment**<br>(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** |



# Opioid Epidemic – Demand for New Treatments

## What is the Opioid Epidemic?

- The opioid epidemic is a crisis throughout North America and now in Australia, that involves the widespread use of prescription painkillers and subsequent popularity of illegal opioids, resulting in unprecedented addiction and consequential overdoses, many of which are fatal

## Opioids:

- **A class of narcotic substances**, both legal and illicit, derived from the opium poppy plant (synthetic or naturally occurring)
- **Not disease modifying** (only mask pain)
- **Highly addictive** with crippling withdrawals
- **Highly dangerous** – significant risk of overdose/death
- **Are incorrectly used** in chronic pain settings (i.e. Osteoarthritis)

## Demand for new effective treatments

- **FDA Commissioner Scott Gottlieb -** "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."**[1]

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

**115**

**opioid overdose deaths per day in the United States[2]**

**US$78.5 billion**

**total economic burden of prescription opioid misuse in the United States p.a.[3]**

**Given PPS is non-addictive and possibly disease modifying, it has the potential to receive FDA Fast-Track/Break-through Designation to address the Opioid Epidemic**

1. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm 2. CDC/NCHS, National Vital Statistics System, Mortality. CDC Wonder, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://wonder.cdc.gov.
3. 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 with BMEL: The Market for ZILOSUL®

## ZILOSUL® has the potential to fill the current gap in osteoarthritis treatment options

- There is currently **no effective treatment for osteoarthritis and BMELs** that treats the underlying pathology of the disease.
- **Current therapies treat the symptoms** of osteoarthritis and bone marrow edema lesions but **prolonged use results in undesirable side-effects.** It is widely accepted that NSAIDs and corticosteroids are contraindicated having a detrimental effect on the metabolism of bone and cartilage.
- **Opioid's are widely misused globally as patients form serious addictions whilst mitigating pain.**[1]
- **ZILOSUL® treats the underlying pathology of osteoarthritis** by reducing inflammation, resolving the bone marrow edema lesions and down regulating cartilage degrading enzymes (MMP's and ADAMTS-5).

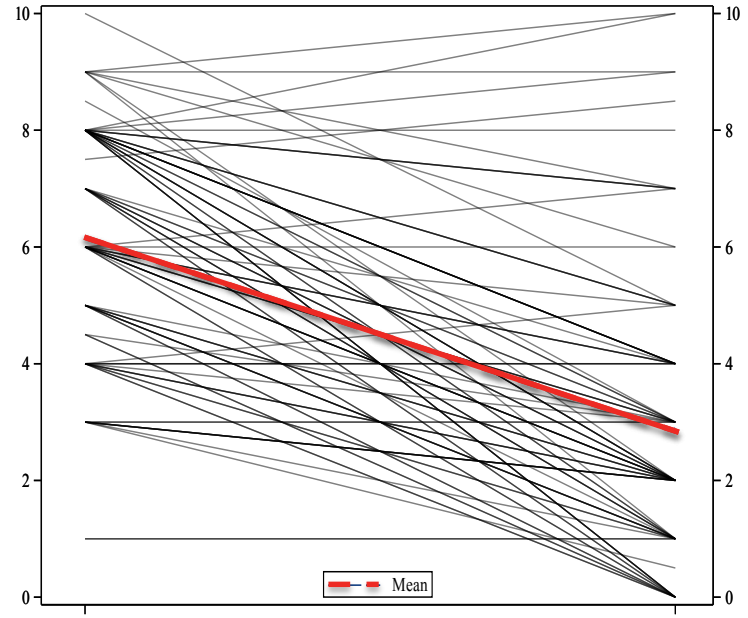
| | paradigm (ZILOSUL®) | NSAID (ibuprofen etc) | Opioid (oxycodone etc) | Corticosteroid / Cortisone | Joint Replacement |
|---|---|---|---|---|---|
| Treats the symptoms of OA (pain & function) | ✓ | ✓ | ✓ | ✓ | ✓ |
| Treats underlying pathology | ✓ | | | | ✓ |
| No undesirable side-effects | ✓ | |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

1. https://www.drugabuse.gov/news-events/news-releases/2017/07/pain-relief-most-reported-reason-misuse-opioid-pain-relievers

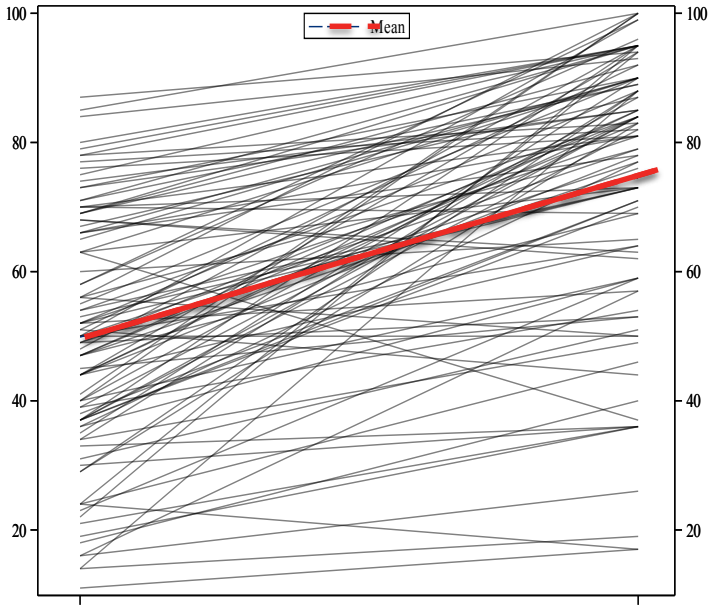
# OA/BML – First 125 Patients treated via TGA SAS

**A Paired t-test was used to compare the before and after scores for knee pain (NRS) and knee function (LKS).**

| Pain (NRS) Before – After = 3.2 p<0.0001<br>51.5 % reduction in knee pain | Function (LKS) Before – After = 25.1 p<0.0001<br>69.1% improvement in knee function |
|---|---|




Before 6.2 After* 3.0




Before 49.0 After* 74.1

***After = Results taken from patients six weeks post final treatment, i.e. twelve weeks from first dose, therefore it is anticipated that any placebo response will be somewhat reduced. Injections are Subcutaneous, NOT intra-articular.**

# Paradigm to Treat Elite Athletes in the US

## Heads of Agreement with the Pro Players Elite Network

Paradigm has executed a Heads of Agreement (HoA) to form a partnership with the Pro Players Elite Network (PPEN) to assist with commencing treatment of US based sportspeople under the FDA Expanded Access program.

### Pro Players Elite Network & Foundation

- The PPEN is a membership organisation of **over 11,000 retired NFL players & elite athletes**
- The **PPEN Foundation is committed to creating awareness about the National Opioid Epidemic**. Through strategic partnerships the PPEN Foundation is focused on helping their members and the Public to understand the effects of opioids and the identification less harmful alternatives (such as iPPS)
- The PPEN has **strong relationships with the NFL Past Players Association and numerous high profile ex-NFL players**
- **The proposed partnership provides Paradigm access to these high profile athletes, many of which have existing knee and joint pathologies**

### FDA Expanded Access Program

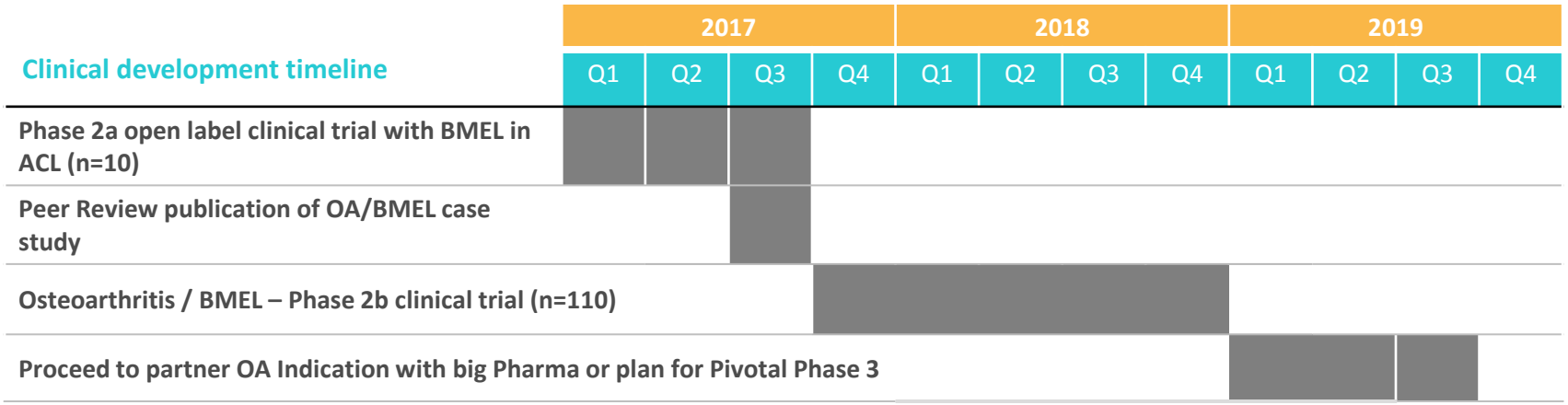
- The FDA Expanded Access program commonly referred to as the 'Compassionate Use' program is the US equivalent to Australia's TGA Special Access Scheme
- The program enables the use of investigational drugs, biologics or medical devices outside the clinical trial setting for treatment purposes.

**Paradigm intends on replicating the success of the TGA Special Access Scheme by treating elite athletes in the United States via the FDA Expanded Access Program**

# OA with BMEL: Clinical Timeline

## Comprehensive clinical pathway to commercialisation

- **OA/BMEL case study published in peer reviewed scientific journal**
- **Successful completion of the Phase 2a open label clinical trial**
  - Trial demonstrated the safety, tolerability and efficacy of ZILOSUL® in patients with a bone marrow edema lesions from a recent ACL (acute knee) injury
- **350+ additional patients treated under the TGA SAS scheme. Very positive clinical signals from BMEL patients with osteoarthritis (OA)**
- **100% recruited for Phase 2b placebo controlled (110 patient) clinical trial for BMEL with OA – Results due late Q4 CY2018**
- **Plan to undertake pilot studies in BMEL patients with other joint issues and rheumatoid arthritis (RA)**



# Viral Arthritis: Clinical Timeline

## Potential to gain Orphan status, resulting in fast-tracked clinical development

- **Pre-clinical studies have been conducted by the Institute of Glycomics at Griffith University. The results suggested that:**
  - PPS significantly alleviated the severity of disease and reduced both the inflammatory response and the loss of articular cartilage;
  - PPS has the potential to treat both acute and chronic symptoms associated with mosquito transmitted alphavirus infections (Ross River virus (RRV) and chikungunya virus (CHIKV);
  - There currently is no effective disease modifying treatment for RRV or CHIKV.
- **Patients with RRV-arthralgia (joint pain) already treated with PPS under the TGA Special Access Scheme** demonstrating tolerability and potential clinical effects
- **Phase 2 Clinical Trial – PPS to treat RRV and CHIKV– Potential for Fast-Track /Breakthrough/Accelerated Approval**
  - Queensland Government have provided a A$300,000 grant for Ross River research
  - Phase 2a, randomised, double-blinded placebo-controlled clinical trial treating RRV induced arthritis and arthralgia **– 100% recruited – Read-out Q1CY2019**
  - Phase 2 clinical trial in CHIKV-induced arthritis and arthralgia to be initiated post RRV read-out

| Clinical development timeline | 2017 | | | | 2018 | | | | 2019 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Proof of concept study under SAS (n=30) | Completed CY2016 | | | | | | | | | | | |
| Design and Ethics approval for Phase 2 Trial | | | | | | | | | | | | |
| **Phase 2a Clinical Trial Ross River (n=20)** | | | | | | | | | | | | |
| **Plan for a Phase 2 Clinical Trial - Chikungunya** | | | | | | | | | | | | |

# Global Big Pharma Interest

## Recent transactions highlight big pharma interest in BMEL/OA and Heart failure

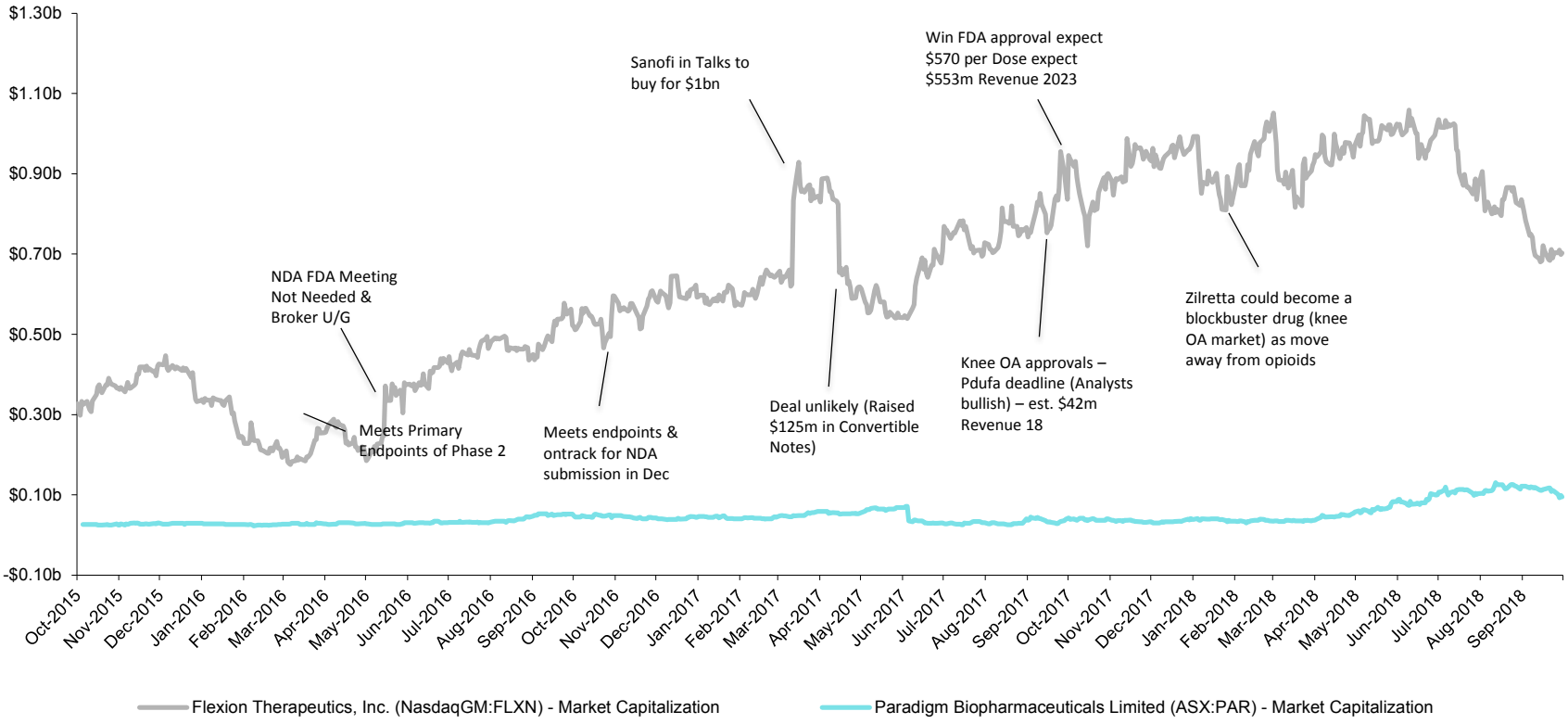
| Date ↓ | Target | Acquirer | Deal value (US$) | Relevance |
|---|---|---|---|---|
| Jul - 17 | Galápagos | SERVIER | **$346m** EU Rights Only | ▪ Galapagos licensed GLPG1972, a potential disease-modifying oral therapy for osteoarthritis to Servier<br>▪ GLPG1972 is a potent and highly selective inhibitor of ADAMTS-5. |
| Mar-17 | flexion Transformative Medicine... Where It Matters | SANOFI | **Rumoured $1 Billion+** *(did not occur)* | ▪ In March 2017 Sanofi was rumoured to be in talks to buy Flexion Therapeutics for >US$1 billion in cash[1].<br>▪ Flexion's knee injection for osteoarthritis, Zilretta, said to fit in with Sanofi's biosurgery division.<br>▪ Both co's did not comment on why transaction did not occur. |
| Nov-16 | TissueGene, Inc. Cell Technologies | | **$434m** | • TissueGene, Inc. Licensed the rights for its degenerative osteoarthritis drug Invossa to Japan's Mitsubishi Tanabe Pharma |
| Jan-14 | Pfizer | Lilly | **$1.8bn** | ▪ Pfizer struck a deal with Eli Lilly of Indianapolis, to jointly develop its anti-nerve growth factor (anti-NGF)drug, tanezumab. |
| May-13 | | ZIMMER BIOMET | **Undisclosed** | ▪ Zimmer Biomet acquired Knee Creations for its Subchondroplasty procedure, designed to treat BMEL |

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

Source: Bloomberg, company filings

# Flexion Case Study (FLXN.NASDAQ)

- Flexion is marketing a slow-release corticosteroid for the treatment of OA in the knee.
- 6x increase in valuation to A$1.4bn post meeting Ph2 endpoints in April 2016. Also received big pharma interest.



# Potential Share Price Catalysts / Newsflow

**There is potential for significant news flow in the 1-12 months**

- ✓ OA Phase 2b trial results released – mid/late December 2018
- ✓ Further release of up to 50 patients OA data under the TGA special access scheme (by end of CY18)
- ✓ Progression of the newly in-licensed MPS indication
- ✓ Ross River Phase 2a trial results release – Q1CY2019
- ✓ Dose first Compassionate Use OA patient in the US
- ✓ Potential for significant media attention assuming successful treatment of high profile NFL players (past and present)
- ✓ Finalise and announce recruitment of US based staff
- ✓ File IND and meet with FDA around Phase 3 trial in OA/BMEL
- ✓ Possibility of being granted “fast track status” for the Phase 3 trial
- ✓ Possibility of early revenue in 2019 via receiving ‘Provisional Approval’ from TGA to sell Zilosul (iPPS)
- ✓ Upcoming release of peer review scientific paper/s

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