# PARADIGM BIOPHARMACEUTICALS LIMITED

ASX RELEASE 18 December 2018

## PARADIGM ANNOUNCES POSITIVE RESULTS FROM 112 SUBJECTS IN PHASE 2B CLINICAL TRIAL OF iPPS IN KNEE OSTEOARTHRITIS PAIN

### KEY HIGHLIGHTS

- Clinical trial met the primary endpoint with a change in the Knee Injury and Osteoarthritis Outcome Score (KOOS) from baseline at Day 53; this confirms the potential for iPPS (ZILUSOL®) to be a safe and effective treatment of knee osteoarthritis pain
- Clinically meaningful and statistically significant results between iPPS and Placebo in the total population (p=0.031) and highly clinically meaningful and highly statistically significant in the Numeric Rating Scale (NRS) = 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 in the NRS Pain = 4-6 strata. This is highly statistically significant at p=0.026 and highly clinically meaningful i.e. subjects received a pain reduction of 50% or more
- In regard to secondary endpoints, to date, in comparisons with placebo, statistical differences were achieved in NRS pain score (day 39 and 53), Patient Global Impression of Change (PGIC, p=0.0062), and proportions of subjects with 50% reductions in timepoints other than day 53. With analysis ongoing, full reporting on secondary endpoints will be provided in Q1CY2019, likely in conjunction with a peer reviewed publication and/or presentation at a preeminent global orthopaedic conference
- Data from the trial is consistent with the 183 patients treated on thus far via the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) with an average of 51.4% reduction of pain from baseline with average NRS scores reduced from 6.3 to 3.1
- Safety profile confirmed – Expected Adverse Events (AE) mild severity with no life-threatening AE's – this is highly relevant when comparing iPPS and current Anti-NGF antibodies (biologicals)
- The robust data package from the Phase 2b clinical trial has confirmed the ideal target population for the Phase 3 clinical trial which Paradigm plans to design and commence in CY2019
- Phase 2b results strengthen iPPS (ZILUSOL®) licensing package and provide a significant boost to partnering prospects, of which early stage discussions have already commenced
- Paradigm will continue to report over the coming months on the groups of patients that are currently undergoing treatment from their doctors under the TGA SAS, thus adding more Real-World Evidence (RWE) cases to the orthopaedic data package
- Paradigm intends on commencing treatment of US Elite Sportspeople with iPPS in Q2CY2019

**Paradigm Biopharmaceuticals Ltd (ASX: PAR)** is pleased to announce it has met its primary endpoint of its phase 2b randomised double-blind placebo-controlled multi-centre clinical trial. The primary outcome of the trial is to evaluate the effects of injectable pentosan polysulfate sodium (iPPS) on knee pain in subjects with knee osteoarthritis and subchondral bone marrow edema lesions (BMELs) as assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale.

Paradigm's CEO, Mr Paul Rennie said that "*the Paradigm clinical & regulatory team along with all the clinical trial recruitment and treatment centres have done an extraordinary job to conclude this Phase 2b clinical trial in just over 12 months. The whole Paradigm team are incredibly happy with these positive Phase 2b trial results and are very excited for the future of the Company.*"

*"To achieve clinically meaningful and statistically significant results between iPPS and Placebo in the total population and highly clinically meaningful and highly statistically significant results in the NRS = 4-6 strata is truly an outstandingly positive trial outcome. If you have clinical significance and statistical significance you have a high probability the drug will pass a Phase 3 clinical trial and once registered a drug that can penetrate the market. We are further impressed with the results given the widespread difficulty ASX Listed biotechnology companies have had in achieving positive phase 2b trial results over the last few years."*

To further assist the market's understanding of the significance of this successful Phase 2b trial the company, with the input from independent doctors from several of the clinical trial sites, has produced a video describing the OA market, the importance of the data and of having a product that is *both clinically meaningful and statistically significant*. The video presenters are Prof. Andrew Östör (Principal Investigator), Dr David Martin (orthopaedic surgeon), Dr Phil Bloom (sports physician) and retired AFL footballer Andrew Walker. This video can be found on the following link - *Paradigm Biopharmaceuticals Results Announcement Video* - and also on Paradigm's website at www.paradigmbiopharma.com

Paradigm's objective is to advance the clinical development plan for iPPS as an effective treatment for osteoarthritis which means filing a New Drug Application (NDA) with the USA Food and Drug Administration (FDA) for a pivotal Phase 3 clinical trial in CY2019. The Company will also be engaging with their US based regulatory consultants and the FDA in regard to seeking Fast-Track designation.

Today, the Company reported only top line data from the Phase 2b clinical trial which successfully met the primary endpoint.

The analysis of the secondary endpoint data is ongoing but today we can report in comparisons with placebo, clinical and statistical differences are achieved in NRS pain score (day 39 and 53), Patient Global Impression of Change (PGIC, p=0.0062), and proportions of subjects with 50% reductions in timepoints other than day 53.

With analysis ongoing, full reporting on secondary endpoints will be provided in Q1CY2019 likely in conjunction with a peer reviewed publication and/or presentation at a preeminent global orthopaedic conference.

Given Paradigm's clinical teams experience with pain studies, Paradigm implemented a clinical trial strategy to identify and define the subject population most likely to succeed in a Phase 3 clinical trial with pain as a primary endpoint. Hence the use of predetermined stratification of subjects into 2 strata: moderate pain stratum (NRS pain = 4-6) or severe pain stratum (NRS pain = 7-8) as detailed in the trial design:
(https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373400&isReview=true).

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

## Trial Design and Description

The trial was conducted across 6 sites in Queensland, Victoria, South Australia and Western Australia. The recruitment was supported by strong media coverage and public referral from patients treated by their doctors via the TGA Special Access Scheme. The rapid recruitment in this trial has reflected the inadequacy of current standard of care and the unmet need for effective treatment of osteoarthritis associated pain and dysfunction.

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|---|---|
| **Trial Design** | Phase 2b, randomised double blind placebo controlled multicentre study |
| **Primary Endpoint** | **Change in KOOS Pain score from baseline to Day 53** |
| **Secondary Endpoints** | Safety, KOOS Pain, KOOS Symptom, KOOS Function, KOOS Quality of Life, BMEL Volume, Patient Global Impression of Change (PGIC) |
| **No. Participants** | 112 completed study protocol |
| **Active : Placebo** | First stratified by baseline pain score:<br><br>NRS 4-6 (moderate pain)<br><br>NRS 7-8 (high pain)<br><br>Then randomised 1:1 PPS: Placebo |
| **Dosing** | 2mg/kg Pentosan Polysulfate Sodium (100mg/ml injectable solution), administered by subcutaneous injection, twice weekly for 6 weeks. |
| **Placebo** | Saline (0.9% saline solution) |
| **Recruitment Sites** | 6 sites throughout Australia (VIC, SA, WA and QLD) |

The design of the phase 2b trial was designed by Paradigm to identify which category of OA suffers would best respond to treatment with iPPS in the clinical trial setting. It was important for Paradigm to identify which groups will have the best response to treatment in order to enhance the chance of success in the Phase 2b clinical trial and then the subsequent pivotal Phase 3 clinical trial.

Importantly, the trial results are consistent with the results being reported on in the real-world evidence (TGA SAS cases) with those with a less severe or progressive OA have responded better to treatment with iPPS (ZILUSOL®).

## Summary of Top-line Trial Results

**Clinically meaningful and statistically significant results between iPPS and Placebo were demonstrated across the total trial population (n = 112), therefore resulting in the primary endpoint being successfully met.**

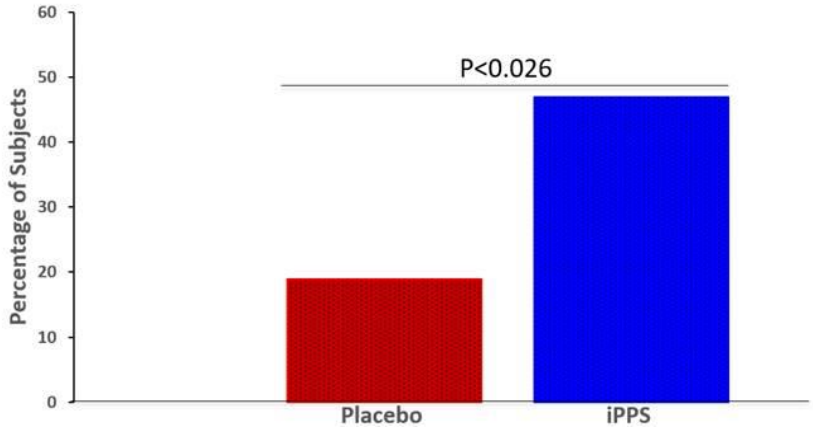
**NRS Pain = 4-6 Strata - Moderate self-reported pain** (39 subjects receiving iPPS : 40 receiving Placebo)

Looking specifically at the moderate pain group within the phase 2b study, the results are considered highly clinically meaningful and highly statistically significant when compared to the placebo control arm of the study:

- Met the primary endpoint - Change in KOOS Pain score from baseline to Day 53 reached statistical significance compared with placebo at day 39 and 53 (refer to graph 1 below);
- Highly clinically meaningful and highly statistically significant result between iPPS and Placebo;
- 46.2% of subjects receiving PPS showed a greater than 50% reduction in pain from baseline compared to 22.5% of subjects receiving Placebo. This is statistically significant at p = 0.026 and clinically meaningful i.e. subjects received a pain reduction of 50% or more;
- Data are consistent with TGA-SAS with an average of 51.4% reduction of pain from baseline with NRS scores reduced from 6.3 to 3.1;
- Safety profile confirmed – Expected AE's mild/moderate severity with no life-threatening AE's. This a major and important difference between iPPS and current Anti-NGF compounds all of which have had severe AE's and been put on clinical hold by the FDA. Due to these severe AE's several large pharma have abandoned their anti-NGF programs despite spending hundreds of millions of dollars on their programs;
- Pfizer/Lilly's NGF antibody (biological) Tanezumab (which Elly Lilly paid Pfizer US1.8bn to partner in to), as a comparator to iPPS, showed 33.3% of placebo displayed a greater than 50% reduction in pain from baseline vs 47.3% Tanezumab treated subjects);
- Importantly, robust data package from the Phase 2b clinical trial has conclusively confirmed the target population for the Phase 3 clinical trial to focus on moderate pain score subjects of NRS 4-6. Paradigm is confident of improving future clinical trial results by focussing on this group; and
- To achieve such highly clinically meaningful and highly statistical results from what is generally considered a relatively small strata further highlights the strength of these results and larger subject numbers would be expected to only improve these results.

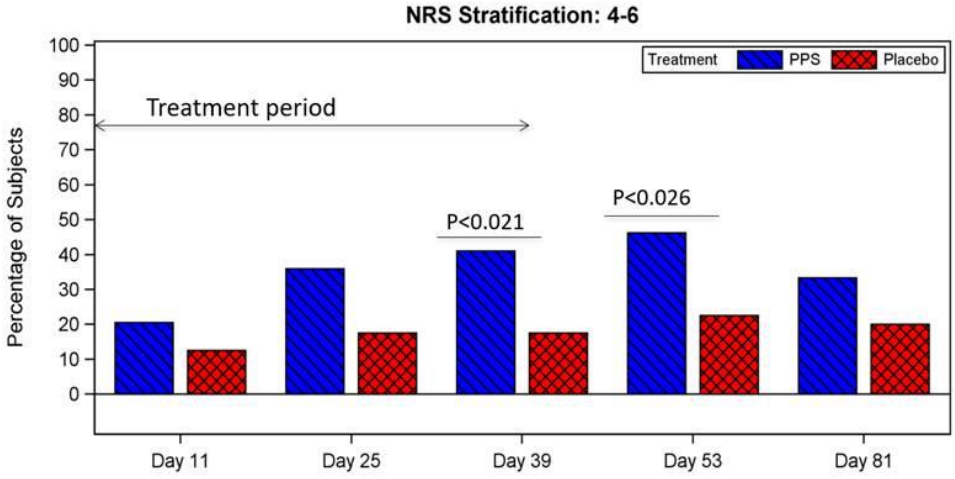
**Chart 1: Primary End Point met in NRS Pain strata 4-6**

**Change in KOOS pain score from baseline to Day 53 (NRS=4-6 stratum)**



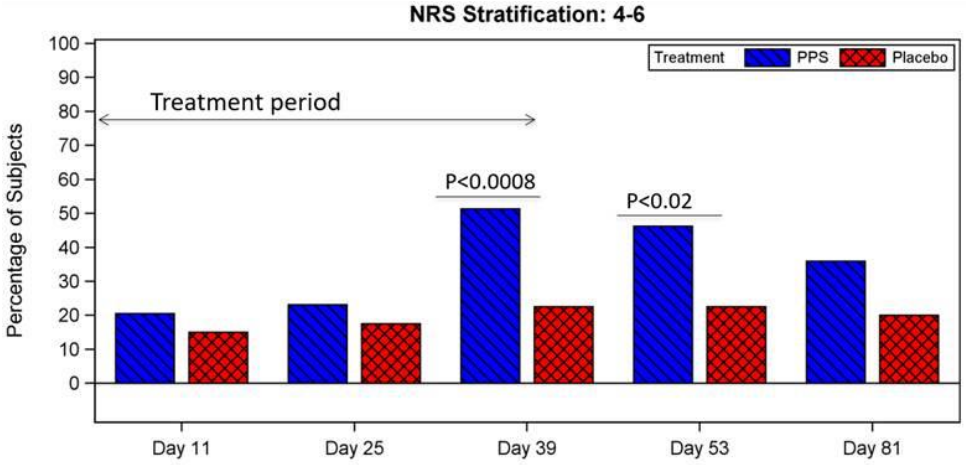

- **>50% Reduction from Baseline in KOOS Pain Score at Day 53**
- iPPS treatment is statistically significant compared to placebo (Chi-square analysis)
- iPPS treatment showed a clinically meaningful response to pain

**Chart 2: Clinically Meaningful Pain Reduction of >50% from Baseline (KOOS) Pain**




- Statistically greater proportions of subjects with >50% reduction in pain from Baseline after iPPS as measured by KOOS Pain subscale (Chi-square analysis)
- > 50% pain reduction corresponds to high reduction in pain (OARSI definition)

**Chart 3: Clinically Meaningful Pain Reduction of >50% from Baseline (NRS pain)**




- Statistically greater proportions of subjects with >50% reduction in pain from Baseline after iPPS as measured by *NRS pain score* (Chi-square analysis)
- > 50% pain reduction corresponds to *high reduction in pain* (OARSI definition)

## Secondary Endpoints

The secondary end point of the Patient Global Impression of Change (PGIC) from baseline to Day 53 between iPPS treatment and Placebo was statistically significant at p=0.0062.

The complete Secondary Endpoint Data is still being evaluated, however in regard to secondary endpoints that have been analysed to date, in comparisons with placebo, statistical differences are

achieved in NRS pain score (day 39 and 53), Patient Global Impression of Change (PGIC, p=0.0062), and proportions of patients with 25% and 50% reductions in timepoints other than day 53.

The complete Secondary Endpoint Data will be reported on in Q1CY2019, but initial internal evaluation has the Company feeling very confident that the full report will likely be accepted in a peer reviewed publication and/or presented at a preeminent global orthopaedic conference.

The low level of adverse events is also highly relevant given the unmet need for a drug to treat OA. This is also consistent with the SAS data that has been reported on which also had no major adverse events reported on. This consistently shows that iPPS is a safe treatment option for OA. Given the major competitor compounds in development, the anti-NGF's, have known serious AE's, such as rapid progression of OA (RPOA). Paradigm is very confident this key differentiator will be of great interest to potential partner pharma companies.

From a commercial perspective the goal of the Phase 2b OA/BMEL RCT was to identify the target population for a pivotal Phase 3 OA/BMEL RCT and the Company can unequivocally report the trial has done this with the NRS pain = 4-6 to be the target group for the Phase 3 clinical trial.

**NRS Pain = 7-8 Stratum – High self-reported pain group** (16 subjects receiving iPPS : 17 receiving Placebo)**.**

- The response from patients in the 7-8 pain group that received iPPS showed a response of >50% – which is in line with expectations, the other strata and what the TGA SAS patients reported, therefore showing iPPS still has a strong effect on this group of treated subjects.
- The small same size of the NRS 7-8 stratum combined with the high placebo response made it difficult to reach conclusive outcomes from these data. The analysis of the secondary endpoints is required to generate additional data to interpret the effect in this strata.
- This was not unexpected given data from the numerous other pain trials (anti-NGF's and opioid clinical trials) shows the 7+ NRS pain groups typically return a very high placebo response and therefore it would have been abnormal if this had not occurred with this strata in this clinical trial.
- The company is currently evaluating the full trial data for secondary endpoints to form final conclusions in this stratum (joint functions scores, BMEL Volume as per MRI and biomarkers). Based on what is known about subjects with severe chronic pain in clinical trials, combined with the Company's own data it is likely that NRS Pain = 7+ subjects will not to be included in the Phase 3 study design, thus indicating that a phase 3 trial would likely return even stronger results than this trial by focussing on the moderate pain group i.e. NRS 4-6.

## Consistency of pain reduction and safety from Phase 2b and TGA SAS

Today's positive Phase 2b randomised, double-blind, placebo-controlled multicentre clinical trial results combined with the 183 reported TGA SAS (still approximately 300 more TGA SAS patients to report on) consistently show the strong effect of iPPS treating Knee OA pain.

The TGA SAS case had pre-PPS pain scores (on average NRS=6.2) improving by greater than 50% from baseline. This level of pain reduction is very similar to the phase 2b clinical trial and shows:

- Consistency of safety and effect in various different groups both in placebo controlled and open label settings;
- Consistency of safety and effect across a very large patient population (183 SAS + 55 Phase 2b); and
- Consistency with the orphan MPS indication patients treated with iPPS.

The percentage of people who responded to treatment was 90% in the SAS program which was consistent with the results from those who received iPPS in the clinical trial. This high level of responders gives Paradigm confidence that iPPS can assist with pain reduction in a high percentage of people suffering from Knee OA pain.

Paradigm Chairman, Graeme Kaufman stated "*The combined data from this trial support the high number of patients treated by their doctors via the TGA SAS and give us confidence that iPPS has the potential to be a safe, effective, long lasting, non-opioid based treatment for Knee OA. Going forward we will be releasing additional SAS data on Knee OA but also other joints which will broaden the applicability of the potential of iPPS as an OA pain reduction treatment. Today's ground-breaking data also greatly strengthens the iPPS/OA licensing package and provides a significant boost to partnering prospects."*

## The OA Market

OA also remains the most common form of joint disease globally. In the US alone, it affects over 30 million adults, while in Australia, arthritis affects around 3 million people. In both countries, the condition is a leading cause of pain and disability among the elderly and a cause of life-years lost due to disability.[1]

The demand for a new effective treatment is significantly amplified by the opioid epidemic throughout the United States ("US"). Every day, more than 115 people in the US die after overdosing on opioids.[2] The misuse of and addiction to opioids is a serious national crisis that affects public health as well as social and economic welfare. The Centers for Disease Control and Prevention estimates that the total "economic burden" of prescription opioid misuse alone in the United States is $78.5 billion a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.[3]

## Potential for US Fast-Track Designation

Paradigm believes iPPS has the potential to receive Fast Track designation from the US Food and Drug Administration (FDA) which is greatly concerned about the opioid epidemic. In particular, the FDA Commissioner Scott Gottlieb was recently quoted as saying "The opioid epidemic continues to take an emotional, physical and financial toll on Americans. The U.S. Food and Drug Administration is committed to taking every possible step to address the many facets of this complex public health crisis"[4] and furthermore "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***."[5]

Fast-Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Filling an unmet medical need is defined by the FDA as providing a therapy where none exists or providing a therapy which may be potentially better than an available therapy.

Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some

[1] https://www.cdc.gov/arthritis/basics/osteoarthritis.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] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm
[4] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm

advantage over available therapy, such as avoiding serious side effects of an available therapy or an ability to address emerging or anticipated public health need.[5]

Paradigm's iPPS is neither an opioid nor a steroid and most importantly is non-addictive, thus has the potential to positively impact the opioid epidemic and treat OA pain.

## INVESTOR CONFERENCE CALL

Paradigm will **host a conference call at 9:00am (AEDT) Tuesday 18th December 2018** to present and discuss the results from the Phase 2b, randomised double blind placebo controlled multicentre study. The clinical trial was conducted to evaluate the effects of injectable Pentosan Polysulfate sodium (iPPS) on the treatment of pain in subjects with osteoarthritis of the knee and concurrent subchondral bone marrow edema lesions.

**Phase 2b OA/BMEL Results Teleconference Details**

You are invited to participate in a conference call held by Mr. Paul Rennie (CEO), Prof. Andrew Östör (Principle Investigator), Dr. Ravi Krishnan (CSO) & Dr. Claire Kaufman (COO).

**The call is scheduled for 9:00am (AEDT) Tuesday 18th December (US PST 2:00pm / EST 5:00pm on Monday 17th; UK 5:00am on Tuesday 18th).**

**Conference ID - 221766**

## Dial-in Details

**Diamond Pass Registration Link**

In order to pre-register for this conference and avoid a queue when calling, please follow the link below. You will be given a unique pin number to enter when you call which will bypass the operator and give you immediate access to the event.
https://services.choruscall.com.au/diamondpass/paradigmbiopharma-221766-invite.html

If you are unable to register, then at the time of the conference you can call one of the numbers below and provide the **Conference ID 221766** to an operator

| | | | |
|---|---|---|---|
| **Australia Toll Free:** | **1800 908 299** | **Australia Alt. Toll Free:** | **1800 455 963** |
| **Australia Local:** | **+61 2 9007 8048** | **Australia Alt. Local:** | **+61 7 3145 4005** |
| New Zealand Toll Free: | 0800 452 795 | Auckland Local: | +64 9 929 3905 |
| Germany Toll Free: | 0800 183 0918 | China Toll Free: | 1080 0140 1776 |
| USA/Canada Toll Free: | 1855 624 0077 | France Toll Free: | 0800 913 734 |
| Hong Kong Toll Free: | 800 968 273 | UAE Toll Free: | 8000 3570 2706 |
| UK Toll Free: | 0800 051 1453 | Switzerland Toll Free: | 0800 802 498 |
| Singapore Toll Free: | 800 101 2702 | India Toll Free: | 000 800 100 8070 |
| Japan Toll Free: | 0066 3386 8000 | Indonesia Toll Free: | 007 803 321 8057 |

[5] https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm

**Q&A Instructions**

In order to ask a question during the Live Question and Answer Session:
Press *** then 1 on your telephone keypad** to enter the Q&A queue
Press *** then 2 on your telephone keypad** to withdraw your question

## ABOUT PARADIGM BIOPHARMACEUTICALS LTD

Paradigm Biopharmaceuticals Limited (ASX: PAR) 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 over 60 years.

On 18 December 2018 the Company will announce the results of a phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with osteoarthritis and concurrent bone marrow edema lesions. The recruitment of the 126 subjects into the clinical trial commenced in November 2017 and concluded in August 2018. There is a global trend for safe and effective non-opioid and non-steroid pain relief for chronic disease such as osteoarthritis which presents a huge market opportunity for Paradigm's PPS treatment.

Post these successful phase 2b results, the Company is aiming to achieve Fast-Track designation and begin a phase 3 trial in the US in CY2019. Successful phase 2b trials and Fast-Track designation would be expected to generate significant big pharma interest.

In July 2017 the Company commenced a phase 2a clinical trial to treat people recently infected with the Ross River virus. The results of this trial are also expected to be released in Q1CY2019.

Paradigm recently executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders. A key unmet medical need in this class of inherited disease is the lack of treatment of joint pain and dysfunction akin to osteoarthritis, hence the applicability of iPPS in treating these rare joint diseases.

The Company continues to execute on its drug repurposing strategy. The key benefits of this strategy are lower costs, accelerated development timelines and higher success rates than the standard clinical development timeline.

To learn more please visit: www.paradigmbiopharma.com

**For more information, please contact**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