PARADIGM BIOPHARMACEUTICALS LTD

ASX RELEASE 31 JANUARY 2019

DECEMBER 2018 QUARTERLY REPORT

HIGHLIGHTS

- **Paradigm reported on the top-line results of its successful phase 2b randomised double-blind placebo-controlled multi-centre clinical trial** treating participants with knee osteoarthritis and concurrent bone marrow lesions with injectable Pentosan Polysulfate Sodium (iPPS).
- **Like Big Pharma top-line reporting in Osteoarthritis (OA) clinical trials, Paradigm reported** (i) mean change from baseline in KOOS Pain, (ii) Patient Global Impression of Change (PGIC) of OA and (iii) percentage of patients with ≥50% reduction in pain from baseline. Together these results demonstrate that the drug, iPPS, was clinically effective and statistically significant over placebo.
- **46.2% of subjects receiving iPPS showed a greater than 50% reduction in pain from baseline compared to 19% 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 reported 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.
- **Safety profile confirmed** – Expected Adverse Events (AE) mild severity with no life-threatening AE's – this is highly relevant when comparing iPPS to current Anti-NGF antibodies (biologicals).
- **Planning for Phase 3 Clinical Trials and Partnering discussions have already commenced** on the back of the robust Phase 2b data package.
- **Paradigm executed an exclusive In-License Agreement** with the Icahn School of Medicine at Mount Sinai, New York, for the **use of iPPS in the treatment of mucopolysaccharidoses (MPS)**, a group of inherited lysosomal storage disorders of which the patient suffers chronic joint pain and dysfunction akin to osteoarthritis.
- **Paradigm maintained a >51.4% reduction in pain (on average), from an additional 58 patients** (two groups reported on during the quarter) with osteoarthritis treated with iPPS via the TGA Special Access Scheme ("TGA SAS"). **Paradigm has now reported on 183 knee OA patients treated under the TGA SAS.**
- Approximately 500 patients have been treated or are currently being treated by their doctors via the TGA SAS for a variety of orthopaedic indications. Paradigm will continue to report on additional groups of patients treated with iPPS via the TGA SAS as the data becomes available.
- Phase 2a placebo controlled randomised pilot clinical trial in participants with viral arthralgia (Ross River virus) has completed with data analysis beginning shortly. **Results expected read-out late Q2CY2019**.

- Paradigm received **R&D Tax Incentive Refund of ~ $2.32m** and has an **end of quarter cash position of A$9.93m,** leaving the company in a strong financial position to execute on its commercial milestones for CY2019

Paradigm Biopharmaceuticals Limited (ASX:PAR) ("Paradigm" or " the Company") is pleased to provide its quarterly report for the three months ending 31 December 2018 to accompany its Appendix 4C cash flow report for the period.

SUCCESSFUL PHASE 2B OA/BMEL CLINICAL TRIAL WITH PRIMARY END-POINT MET

On the 18th December 2018 Paradigm announced it met the primary outcome of its phase 2b randomised double-blind placebo-controlled multi-centre clinical trial (n=112). 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.

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 the higher number of subjects with >50% reduction in pain from baseline.

In the NRS Pain = 4-6 strata 46.2% of subjects receiving iPPS showed a greater than 50% reduction in pain from baseline compared to 19% of subjects receiving Placebo under KOOS pain subscale. 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.

It is generally considered that a 30% reduction in pain corresponds with a "much improved" or "very much improved" response from patients on a global impression of change, or 2 points on a 0 to 11 pain intensity numerical rating scale for example from 6/10 down to 4/10" [1].

While a 30% reduction in pain is significant and is described by participants reporting a much improved or very much improved reduction in pain, **Paradigm used the more stringent measure of a 50% reduction in pain.**

A 50% reduction in pain represents a highly clinically meaningful effect, resulting in a significant shift in 'intensity of pain' i.e. from persistent moderate pain to mild/minor pain.

Analysis of the trial data is ongoing with full reporting on secondary endpoints to be provided in Q1CY2019. Due to robust nature of the data, Paradigm is confident of achieving peer review publication and/or presentation at a preeminent global orthopaedic conference.

Importantly, the safety profile if iPPS was confirmed with Adverse Events (AE) being mild in severity with no life- threatening AE's – this a major and important difference between iPPS and current Anti-NGF antibodies (biologicals) all of which have had severe AE's and been put on clinical hold at various stages of their clinical development by the US FDA. Due to these severe AE's several large

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891384/

pharma have abandoned their anti-NGF programs despite spending hundreds of millions of dollars on their programs.

Paradigm's objective is to advance the clinical development plan for iPPS as an effective treatment for osteoarthritis which means filing an Investigational New Drug application (IND) 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.

In parallel to this process Paradigm is in discussions with various interested parties regarding its OA program and firmly believes that a partnering/licensing transaction is a viable and attractive route to get iPPS to market for OA pain.

NEW INDICATION FOR iPPS - MUCOPOLYSACCHARIDOSES (MPS)

On the 22nd November Paradigm announced that it has executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders from the Icahn School of Medicine at Mount Sinai, New York.

A key unmet medical need in this class of inherited disease is the current enzyme replacement therapies (ERT) have little effect on the skeletal system. People with MPS have bone, joint and cartilage pathologies which are not treated by ERT. iPPS has been shown in both animal models and human clinical trials to significantly improve joint mobility and pain.

The Licensing Agreement and accompanying Phase 2a human data is very complementary and synergistic to the Company's OA/BMEL program.

The MPS market is currently estimated to be a US$1.4bn p.a. market which is dominated by Sanofi Genzyme SNY:USNASDAQ GS**,** BioMarin Pharmaceuticals Inc (NASDAQ: BMRN) and Shire Plc (recently acquired by Takeda for £46bn). Paradigm's iPPS treatment has the potential to be a billion dollar per annum (blockbuster) pharmaceutical product, assuming successful registration, as it likely could be prescribed across a number of MPS categories.

The Licensing Agreement was executed on attractive commercial terms (single-digit royalty – no payment of equity or dilution to existing shareholders), providing Paradigm with highly valuable Intellectual Property:

- Patents: Granted patents in all key regions, USA, Japan, Europe, Australia and New Zealand
- Clinical Data: Successful phase 2a clinical trial that demonstrated excellent safety and strong efficacy data. Importantly, the data set includes long term safety of iPPS in very sick and debilitated patients with chronic joint pain, which would be included in future FDA submissions for Paradigm's primary indications (Osteoarthritis/BMEL)
- High probability of developing a commercial product: Based on Paradigm's review of the human clinical data, the product development for the targeted population of people who have inherited the rare disease with joint pain and dysfunction could receive 'Fast-Track' approval following a pivotal phase 2b clinical trial.
- Indication will now be included under Paradigm's exclusivity agreement with bene pharmaChem: This new IP will fall under the same terms of exclusivity and supply that Paradigm currently enjoys with bene pharmaChem.

The mucopolysaccharidoses (MPS) are a family of disorders caused by inherited (genetic) defects in the catabolism of sulfated components of connective tissue known as glycosaminoglycans (GAGs). The estimated cumulative rate for all types of MPS is around 3.5 in 100 000 live births[2] and generally the patients present in one of three ways:

1. As a dysmorphic syndrome (MPS IH, MPS II, MPS VI) often with early onset middle ear disease, deafness, or upper airways obstruction
2. With learning difficulties, behavioural disturbance and dementia and mild somatic abnormalities (MPS III)
3. As a severe bone dysplasia (MPS IV)

REAL WORLD EVIDENCE – TGA SPECIAL ACCESS SCHEME

In addition to the two phase 2 clinical trials, doctors have treated or are currently treating approximately 500 patients via the TGA Special Access Scheme ("TGA SAS") for a variety of orthopaedic indications. During the quarter, Paradigm reported the results two more groups (n:38 & n:20) of patients treated and assessed via the TGA SAS, increasing the total number of reported knee OA patients to 183.

Paradigm is pleased that the results from the TGA SAS have been consistent. Patients, self-reported pain scores were reduced by 51.4% (on average) from baseline pain scores in 183 patients with knee osteoarthritis and concurrent bone marrow lesions.

The 51.4% reduction in pain scores observed with PPS in knee OA is very similar to the 46.4% reduction in pain observed in Paradigm's recently reported successful Phase 2b clinical trial and also demonstrates superiority over the "15% pain reduction scores reported for opioid treatments for chronic pain in OA of the knee and hip."[3]

The 183 patients [102 males and 81 females, median age of 56.4 years (range 18 to 84 years) had been clinically diagnosed with OA and subchondral BMELs (as determined by multiple MRI). At the onset of PPS treatment:

- All patients were symptomatic with OA pain for at least six months and had failed current standard of care, which involved treatment with analgesics, NSAIDs (non-steroidal anti-inflammatory drugs) or corticosteroids.
- 70% of the patients had moderate to severe BMLs with a size ranging from five millimetres to more than 20 millimetres in diameter.
- 30% had lesions less than five millimetres in diameter.

PHASE 2A – VIRAL ARTHRALGIA – ROSS RIVER VIRUS

During the quarter, Paradigm completed the treatment of patients in its Phase 2a randomised, double-blinded placebo-controlled clinical study in participants with persistent Ross River virus (RRV) induced arthralgia (painful joints) treated with iPPS.

The seasonal and epidemiological factors on recruitment and the low RRV infection incidence predicted for 2018 initially impacted recruitment and the timeline for treating patients.

[2] https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/mucopolysaccharidosis

[3] Seghal N, Colson J and Smith H; Expert Rev Neurother. 2013;13(11):1201-1220

Paradigm is satisfied that 20 participants will meet the outcome objectives for the pilot Phase 2a study and will provide valuable clinical data demonstrating safety (primary endpoint) and effects on disease symptoms (secondary endpoint) in participants with recent Ross River virus infection treated with iPPS.

The results from this viral arthralgia phase 2a clinical study are expected in late Q2CY2019.

TREATMENT OF PAST AND PRESENT ELITE ATHLETES

Australian Athletes

The treatment of past and present elite sportspeople continued by their doctors via the TGA SAS with iPPS for osteoarthritis and/or acute injuries, with concurrent bone marrow lesions, although it slowed towards the end of the quarter as Paradigm is waiting for new supplies of the final product to be delivered from Germany and Japan.

A growing number of club physicians from a variety of elite Australian sporting codes (AFL, NRL, A-League) have successfully treated players. Positive anecdotes from these respected physicians has led to an exponential number of inquiries and subsequent applications for access to iPPS, via the TGA SAS. This positive SAS anecdotal evidence mirrors the strongly positive Patient Global Impression of Change (PGIC) scores and pain reductions from the Phase 2b clinical trial which Paradigm finds very encouraging as it indicates that iPPS is having a positive benefit and also that there is strong demand from general public to pursue iPPS treatment for their OA pain.

United States Athletes

Post the previously announced Heads of Agreement (HoA) with the New York, USA, based retired professional sporting network organization, the Pro Players' Elite Network (PPEN) both the PPEN and Paradigm have been working with US based regulatory consultants to progress a US Compassionate Use/Expanded Access program.

Paradigm expects that the first retired athletes will commence treatment in the current quarter, Q1CY2019.

The US market is a key focus for Paradigm, given the significant number of OA sufferers (31 million[4]) and in particular the large number of sportspeople and NFL players suffering from OA who are being overprescribed/incorrectly treated with opioids[5].

The data gathered from the US Expanded Access program would also provide valuable RWE data that supplements and diversifies the data already produced in Australia.

FINANCIAL AND CORPORATE UPDATE

Paradigm is well capitalised post the finalisation of tranche 2 of the 25 October announced Placement and the receipt of the R&D rebate. As per the end of the quarter Paradigm has A$9.93m cash, providing sufficient capital to execute its business development strategies over the coming 12-18 months. In the event that Paradigm pursues and executes a licensing/partner transaction this runway may be significantly extended by associated upfront and subsequent milestone payments.

[4] https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf
[5] https://source.wustl.edu/2011/01/retired-nfl-players-misuse-painkillers-more-than-general-population/

ABOUT PARADIGM PHARMACEUTICALS 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 announced the successful results from their phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with osteoarthritis and concurrent bone marrow edema lesions (n=112). 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.

The Company is aiming to achieve Fast-Track designation and begin a phase 3 trial in the US in CY2019. 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 Q2CY2019.

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

CORPORATE ENQUIRES

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+Rule 4.7B

Appendix 4C

Quarterly report for entities subject to Listing Rule 4.7B

Introduced 31/03/00 Amended 30/09/01, 24/10/05, 17/12/10, 01/09/16

Name of entity

Paradigm Biopharmaceuticals Limited

ABN	**Quarter ended ("current quarter")**
94 169 346 963	31 December 2018

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (6 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	-	-
1.2	Payments for		
	(a) research and development	(1,679)	(3,543)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	-	-
	(d) leased assets	-	-
	(e) staff costs	(142)	(283)
	(f) administration and corporate costs	(246)	(449)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	4	11
1.5	Interest and other costs of finance paid	-	-
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	2,319	2,319
1.8	Other (provide details if material)	-	-
1.9	**Net cash from / (used in) operating activities**	**256**	**(1,945)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire:		
	(a) property, plant and equipment	-	-
	(b) businesses (see item 10)	-	-
	(c) investments	-	-

Consolidated statement of cash flows		Current quarter $A'000	Year to date (6 months) $A'000
	(d) intellectual property	-	(21)
	(e) other non-current assets	-	-
2.2	Proceeds from disposal of:		
	(a) property, plant and equipment	-	-
	(b) businesses (see item 10)	-	-
	(c) investments	-	-
	(d) intellectual property	-	-
	(e) other non-current assets	-	-
2.3	Cash flows from loans to other entities	-	-
2.4	Dividends received (see note 3)	-	-
2.5	Other (provide details if material)	-	-
2.6	**Net cash from / (used in) investing activities**	**-**	**(21)**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of shares	9,050	9,050
3.2	Proceeds from issue of convertible notes	-	-
3.3	Proceeds from exercise of share options	-	1,036
3.4	Transaction costs related to issues of shares, convertible notes or options	(632)	(632)
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings	-	-
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (provide details if material)	-	-
3.10	**Net cash from / (used in) financing activities**	**8,418**	**9,454**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of quarter/year to date	1,260	2,446
4.2	Net cash from / (used in) operating activities (item 1.9 above)	256	(1,945)
4.3	Net cash from / (used in) investing activities (item 2.6 above)	-	(21)
4.4	Net cash from / (used in) financing activities (item 3.10 above)	8,418	9,454

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (6 months) $A'000**
4.5	Effect of movement in exchange rates on cash held	-	-
4.6	**Cash and cash equivalents at end of quarter**	**9,934**	**9,934**

5.	**Reconciliation of cash and cash equivalents** at the end of the quarter (as shown in the consolidated statement of cash flows) to the related items in the accounts	**Current quarter $A'000**	**Previous quarter $A'000**
5.1	Bank balances	9,934	9,934
5.2	Call deposits	-	-
5.3	Bank overdrafts	-	-
5.4	Other (provide details)	-	-
5.5	**Cash and cash equivalents at end of quarter (should equal item 4.6 above)**	**9,934**	**9,934**

6.	**Payments to directors of the entity and their associates**	**Current quarter $A'000**
6.1	Aggregate amount of payments to these parties included in item 1.2	60
6.2	Aggregate amount of cash flow from loans to these parties included in item 2.3	-

6.3 Include below any explanation necessary to understand the transactions included in items 6.1 and 6.2

Payments to Chairman and Non-Executive Directors

7.	**Payments to related entities of the entity and their associates**	**Current quarter $A'000**
7.1	Aggregate amount of payments to these parties included in item 1.2	-
7.2	Aggregate amount of cash flow from loans to these parties included in item 2.3	-

7.3 Include below any explanation necessary to understand the transactions included in items 7.1 and 7.2

8.	**Financing facilities available** *Add notes as necessary for an understanding of the position*	**Total facility amount at quarter end $A'000**	**Amount drawn at quarter end $A'000**
8.1	Loan facilities	NIL	NIL
8.2	Credit standby arrangements	NIL	NIL
8.3	Other (please specify)	NIL	NIL

8.4 Include below a description of each facility above, including the lender, interest rate and whether it is secured or unsecured. If any additional facilities have been entered into or are proposed to be entered into after quarter end, include details of those facilities as well.

9.	**Estimated cash outflows for next quarter**	**$A'000**
9.1	Research and development	2,325
9.2	Product manufacturing and operating costs	-
9.3	Advertising and marketing	-
9.4	Leased assets	-
9.5	Staff costs	147
9.6	Administration and corporate costs	232
9.7	Other (provide details if material)	-
9.8	**Total estimated cash outflows**	**2,704**

10.	**Acquisitions and disposals of business entities (items 2.1(b) and 2.2(b) above)**	**Acquisitions**	**Disposals**
10.1	Name of entity	N/A	N/A
10.2	Place of incorporation or registration	N/A	N/A
10.3	Consideration for acquisition or disposal	N/A	N/A
10.4	Total net assets	N/A	N/A
10.5	Nature of business	N/A	N/A

Compliance statement

1 This statement has been prepared in accordance with accounting standards and policies which comply with Listing Rule 19.11A.

2 This statement gives a true and fair view of the matters disclosed.

31 January 2019

Sign here: ..... Date: .....
Company secretary

Kevin Hollingsworth

Print name: .....

Notes

1. The quarterly report provides a basis for informing the market how the entity's activities have been financed for the past quarter and the effect on its cash position. An entity that wishes to disclose additional information is encouraged to do so, in a note or notes included in or attached to this report.
2. If this quarterly report has been prepared in accordance with Australian Accounting Standards, the definitions in, and provisions of, *AASB 107: Statement of Cash Flows* apply to this report. If this quarterly report has been prepared in accordance with other accounting standards agreed by ASX pursuant to Listing Rule 19.11A, the corresponding equivalent standard applies to this report.
3. Dividends received may be classified either as cash flows from operating activities or cash flows from investing activities, depending on the accounting policy of the entity.