PARADIGM BIOPHARMA

ASX RELEASE **31 October 2022**

SEPTEMBER 2022 QUARTERLY ACTIVITIES REPORT

Key Highlights (including significant events post end of quarter)

- **Successful AU$66m Capital Raise:** Paradigm reported a $66m fully underwritten capital raise to fund the Company into CY2024 on 16 August 2022. The capital raise comprised a $45.7m placement to international and domestic institutions and a $20.7m non-renounceable entitlement offer. The placement was supported by Paradigm's current institutional investors and new international and domestic institutional investors. As a result of the placement, a global long-only international fund increased their shareholding in Paradigm to become a substantial investor following the allotment of placement shares.
- **Synovial Fluid Biomarker PARA_OA_008 Phase 2 Trial:** 100% recruitment and top-line results were announced by Paradigm during the quarter. The day 56 data was analysed by an independent clinical research organisation. The primary endpoint was successfully met by demonstration of several synovial fluid biomarker changes from baseline that favoured iPPS over placebo. In addition, significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) scores relating to pain, function, and joint stiffness were demonstrated for injectable PPS (**iPPS**) in this phase 2 clinical trial**.** In PARA_OA_008 at day 56, the mean percentage change from baseline in WOMAC pain was -50% for the twice-weekly iPPS group compared to placebo at -30%, p=0.050. The mean percentage change from baseline in WOMAC function was +50% for the twice-weekly iPPS group compared to +25% for the placebo, p=0.017.
- **Naturally Occurring Canine OA Model**: In conjunction with results from the PARA_OA_008 study, early top-line results from the canine osteoarthritis (**OA**) model were also announced. Results indicated that iPPS treatment in osteoarthritic dogs demonstrated improvement in joint function in relation to body weight distribution percentage, as measured by the total pressure index percentage (**TPI%**). Dogs also demonstrated a response to iPPS treatment with changes in cartilage degradation biomarkers in the synovial fluid and serum.
- **Global Phase 3 Progress:** On 6 July 2022, Paradigm reported it had activated the first UK site in the global phase 3 clinical trial. This first site is located at the University of Leeds under lead investigator Prof. Hemant Pandit, with participant screening and enrolment commencing during Q3 CY2022. Paradigm aims to activate a total of 7 sites across the UK for the phase 3 study. Regulatory approval from Health Canada for the phase 3 study was also reported in July 2022. Paradigm can also confirm it has since achieved ethical approval from the research ethics board in Canada. The Company may now commence clinical trial site activation in Canada, where it plans to activate up to 10 sites. The first UK patient to be dosed following enrolment and randomisation into the PARA_OA_002 study was reported on 26 October 2022, and Canadian participants enrolled will be reported once achieved.
- **Mucopolysaccharidosis Type 6 (MPS-VI):** During the quarter, Paradigm reported two protocol mandated safety reviews for the randomised, double-blind, placebo-controlled MPS-VI study to evaluate the safety and tolerability of PPS compared to placebo in 12 patients with MPS-VI. The safety review was first undertaken in 3 adult subjects participating in the trial. A further review was completed in adolescent subjects (9 to 16 year-olds) who had

reached the specified time point. This allowed the inclusion of subjects aged 5 to 9 years to assess the safety and tolerability of PPS amongst this paediatric population.

- **NFL Alumni Health Partnership:** Paradigm reported on 13 July 2022 that it had entered a research partnership to inform NFL Alumni members about OA and potential clinical trial participation. Paradigm is working closely with the NFL Alumni Health team and Alumni members to inform them of the onset and progression of osteoarthritis and Paradigm's clinical progress through phase 3 clinical trials.
- **The Knee Society Annual Members Meeting:** A presentation detailing Paradigm's prior phase 2b clinical trial data (PARA_OA_005) was delivered to members of the Knee Society in Park City, Utah during September 2022. Prof. Hemant Pandit, a Professor of Orthopaedic Surgery at Leeds University in the UK and lead investigator in Paradigm's current phase 3 clinical trial delivered the presentation with Paradigm's Dr Mukesh Ahuja in attendance.

Paradigm Biopharmaceuticals Ltd (ASX:PAR) ("Paradigm" or "the Company") is pleased to provide its quarterly update for the three months ended 30 September 2022 to accompany its Appendix 4C cash flow report for the period.

- Cash balance as of 30 September 2022 was $92.375m (on 30 June 2022 it was $39.72m). The September quarter saw new and current investors strongly support a $66m capital raising undertaken in August.
- Research & development expenditure for the quarter was $8.6m compared to the previous quarter of $7.5m. The spend in Q1 FY23 is related to ongoing subject recruitment and site activation for the PARA_OA_002 study, as well as subject monitoring and ongoing analytical activity regarding biomarker analysis for PARA_OA_008. The spend also included site operations for the phase 2 studies for MPS-VI and MPS-I, and ongoing NDA enabling nonclinical studies relating to our MPS and OA clinical programs, as well as continuing activities described in the outlook below.
- In accordance with Listing Rule 4.7C.3 and as noted in item 6 of the Appendix 4C Cashflow Statement, payments to related parties and their associates during the quarter ended 30 June 2022 were fees of $130K, which includes $121.5K for payment of Director fees, and $8.5K for legal fees to BioMeltzer (a company related to Amos Meltzer).

OUTLOOK

Paradigm is pleased to provide an update on achievements and upcoming events.

PARA_OA_002 Phase 3 Clinical Trial

- The first formal review by the Data Safety Management Board (DSMB) for stage 1 of the PARA_OA_002 phase 3 trial is expected to occur in Q4 this calendar year. Paradigm will provide an update on the progress of the phase 3 clinical program following this review.
- Paradigm announced that the first subject in the United Kingdom (UK) has been randomised in this pivotal PARA_OA_002 clinical trial. The first subject was randomised at the Leeds University by lead investigator, Prof. Hemant Pandit. Paradigm aims to activate a total of seven sites across the UK for this phase 3 study.

- Paradigm continues its clinical phase 3 trial PARA_OA_002 activities in the European Union and will provide relevant updates as milestones are reached.
- Paradigm can confirm the first participant from the PARA_OA_002 study has now entered the PARA_OA_006 extension study. PARA_OA_006 is an observational follow-up study to investigate the duration of treatment effect with subcutaneous iPPS compared with placebo in participants with knee OA pain. It is planned that participants who reach the day 168 timepoint from initial dosing in PARA_OA_002, will be enrolled in PARA_OA_006 and will be monitored for an additional 34 weeks.

PARA_OA_008 Synovial Fluid Biomarker Study

- Paradigm reported exciting top-line results in October from the phase 2 study exploring the disease modifying and clinical effects of iPPS compared to placebo in 61 subjects with knee OA. The day 56 data demonstrated synovial fluid biomarker change from baseline for the iPPS treatment group with iPPS impacting multiple biomarkers measured in the synovial fluid. Reductions in nerve growth factor (**NGF**) indicate iPPS impacts on pain could be related to mechanisms linked to molecular pain pathways. Reductions in the biomarkers TNF-α and IL-6 indicate mechanistic effects on inflammatory pathways. Reductions in COMP and ARGS and an increase in TIMP-1 also provide important insights into iPPS mechanisms of action which may be linked to cartilage preservation and potential disease modification. In all cases, the synovial biomarker changes in iPPS-treated subjects at day 56 were favourable compared to placebo controls.

- WOMAC data was also collected from baseline. iPPS treatment showed statistically significant improvements at day 56 in pain, function, stiffness, and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm. The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.

- Paradigm expects to report on the 6-month data in Q1 CY2023. It is planned that data from this study will be prepared for peer-review publication, with the Company providing an update once timing can be confirmed.

The 6-month time point for PARA_OA_008 is expected to yield further data on the duration of effect of iPPS on WOMAC pain and function compared to placebo, further analyses and correlations of biomarker data, and structural changes assessed by MRI.

Canine OA Model Evaluating Disease Modification by PPS

Early interim observations in nine osteoarthritic dogs who had received subcutaneous iPPS at a dose of 3 mg/kg (human equivalent dose of 1.7 mg/kg) weekly for 6 weeks demonstrated:

- That 7 of the 9 dogs treated with iPPS had a clinically meaningful improvement in the affected limb as measured by TPI% at week 8 compared to baseline.
- A mean percentage change (improvement) from baseline in TPI% of 10.1 was observed for the affected hind limb (n=5) and 5.6% for the affected front limb (n=4). A mean increase of 5% in TPI% is considered a clinically meaningful improvement.

- Dogs demonstrated a response to iPPS treatment with changes in cartilage degradation biomarkers in the synovial fluid. Aggrecan degradation neoepitope (**ARG**) levels, the canine equivalent of human ARGS, were reduced in the synovial joint of 3/4 iPPS-treated dogs.
- Analysis of serum biomarkers demonstrated that 3 of 6 dogs showed a reduction in serum ARG, and 5 of 9 dogs had reduced serum HA, supporting the effect of iPPS on these biomarkers observed in the synovial fluid. Additionally, in the serum, it was demonstrated that 7 of 9 iPPS-treated dogs responded to treatment with reduced levels of C3M (a degradation fragment of type III collagen), 6 of 9 dogs had lower levels of CTX-I, and 4 of 9 dogs had reduced levels of CTX-II.

Recruitment for the canine OA model remains ongoing. The longer follow-up period at week 26 (equivalent to 3 years in human terms) should allow for collective analyses of pain, function, joint structure, and biomarker levels following iPPS therapy, and provide informative data to assess the potential of iPPS as a disease-modifying OA drug (**DMOAD**). The complete study report examining both week 8 and week 26 responses in the final cohort of dogs is expected to be reported in 1H CY2023.

Mucopolysaccharidosis Phase 2 Programs

- **Mucopolysaccharidosis Type 1 (MPS-I):** Paradigm has been selected to present data from the open-label phase 2 study of pentosan polysulfate sodium (PPS) for MPS-I as an oral presentation at the 2023 ICLD meeting. The data from the four clinical trial participants treated to date is expected to be presented at ICLD 2023 held in Sydney, Australia, February 20-21, 2023, by Dr Drago Bratkovic, Head of the Metabolic Clinic at the Adelaide Women and Children's hospital.
- **Mucopolysaccharidosis Type 6 (MPS-VI):** The phase 2 study being conducted at multiple sites in Brazil is expected to complete recruitment during CY2022. Paradigm plans to provide an update to investors once this milestone is achieved and detail a timeline for top-line data.

Past and Upcoming Conferences

- **Goldman Sachs SMID Cap Day**: Paradigm Chairman Mr Paul Rennie participated in the Goldman Sachs Small-Mid Cap Day, presenting the data from the PARA_OA_008 to the Goldman Sachs team and institutional investors during October 2022.
- **US Roadshow:** CEO Mr Marco Polizzi, CMO Dr Donna Skerrett and US IR Mr Mitch Marrow were in New York in October 2022 following the release of the PARA_OA_008 data presenting to several new US fund managers.
- **BIO-Europe 2022:** One of the biggest biotech BD&L conventions with over 4000 attendees from 2200 unique companies representing over 60 countries is occurring in Leipzig Germany, from 24-26 October 2022. Paradigm is attending the conference to discuss partnering and investment opportunities with other biotech innovators.
- **JP Morgan 41st Annual Healthcare Conference**: Paradigm intends to present at the JP Morgan Global Healthcare Conference in San Francisco between the 9-12 Jan 2023. The conference is returning to an in-person format with members from the Paradigm

management team attending the conference with CEO Marco Polizzi delivering a presentation during the conference and conducting several 1x1 meetings.

R&D Tax Incentive

- Paradigm has lodged its income tax return and the R&D tax incentive claim for fiscal year 2022. The Company expects to receive a refund of circa $7m during the December 2022 quarter.

Investor Webinars

- On 21 July 2022, Paradigm conducted an investor webinar introducing Paradigm's new CEO, Mr Marco Polizzi. Dr Donna Skerrett, CMO, provided a clinical program update for all shareholders. Mr Polizzi, Dr Skerrett, and Chairman Mr Paul Rennie also answered several investor questions at the conclusion of the presentation.
- Paradigm hosted an investor webinar on 15 August 2022 to discuss the capital raising that was undertaken by the Company and the upcoming near-term catalysts.
- Paradigm's senior management team also provided commentary to investors on the exciting top-line results from both the PARA_OA_008 and canine studies via a webinar on 4 October 2022.
- All webinars can be viewed on the Paradigm website under Presentations within the Investor menu at: www.paradigmbiopharma.com.

Change to AGM Date

Paradigm has made a change to the date of its Annual General Meeting. The date for the meeting originally communicated as 18 November 2022, will now be conducted on **Tuesday 29 November 2022 at 11:00 am** at the offices of K & L Gates Lawyers, Level 25, Rialto South Tower, 525 Collins Street, Melbourne, 3000, and also as a virtual meeting.

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) is a late-stage drug development company driven by a purpose to improve patients' health and quality of life by discovering, developing, and delivering pharmaceutical therapies. Paradigm's current focus is developing iPPS for the treatment of diseases where inflammation plays a major pathogenic role, indicating a need for the anti-inflammatory and tissue regenerative properties of PPS, such as in osteoarthritis (phase 3) and mucopolysaccharidosis (phase 2).

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments, and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

Authorised for release by the Paradigm Board of Directors.

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Appendix 4C

Quarterly cash flow report for entities subject to Listing Rule 4.7B

Name of entity	
Paradigm Biopharmaceuticals Limited	
ABN	**Quarter ended ("current quarter")**
94 169 346 963	30 September 2022

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (3 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	(1)	(1)
1.2	Payments for		
	(a) research and development	(8,594)	(8,594)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	(132)	(132)
	(d) leased assets	(28)	(28)
	(e) staff costs	(605)	(605)
	(f) administration and corporate costs	(618)	(618)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	25	25
1.5	Interest and other costs of finance paid	(6)	(6)
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	-	-
1.8	Other (provide details if material)		
1.9	**Net cash from / (used in) operating activities**	**(9,959)**	**(9,959)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	-	-
	(d) investments	-	-
	(e) intellectual property	-	-
	(f) other non-current assets	-	-

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
2.2	Proceeds from disposal of:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	-	-
	(d) investments	-	-
	(e) intellectual property	-	-
	(f) 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**	**-**	**-**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of equity securities (excluding convertible debt securities)	65,988	65,988
3.2	Proceeds from issue of convertible debt securities	-	-
3.3	Proceeds from exercise of options	-	-
3.4	Transaction costs related to issues of equity securities or convertible debt securities	(3,464)	(3,464)
		-	-
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings (lease liabilities)	(31)	(31)
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (Limited recourse loan repaid under ESP)	-	-
3.10	**Net cash from / (used in) financing activities**	**62,493**	**62,493**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	39,721	39,721
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(9,959)	(9,959)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
4.3	Net cash from / (used in) investing activities (item 2.6 above)	-	-
4.4	Net cash from / (used in) financing activities (item 3.10 above)	62,493	62,493
4.5	Effect of movement in exchange rates on cash held	120	120
4.6	**Cash and cash equivalents at end of period**	**92,375**	**92,375**

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	92,375	39,721
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)**	**92,375**	**39,721**

6.	Payments to related parties of the entity and their associates	Current quarter $A'000
6.1	Aggregate amount of payments to related parties and their associates included in item 1	130
6.2	Aggregate amount of payments to related parties and their associates included in item 2	

Note: if any amounts are shown in items 6.1 or 6.2, your quarterly activity report must include a description of, and an explanation for, such payments.

7.	**Financing facilities** *Note: the term "facility' includes all forms of financing arrangements available to the entity.* *Add notes as necessary for an understanding of the sources of finance available to the entity.*	**Total facility amount at quarter end $A'000**	**Amount drawn at quarter end $A'000**
7.1	Loan facilities	-	-
7.2	Credit standby arrangements	-	-
7.3	Other (please specify)	-	-
7.4	**Total financing facilities**	-	-

7.5	**Unused financing facilities available at quarter end**	-

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

8.	**Estimated cash available for future operating activities**	**$A'000**
8.1	Net cash from / (used in) operating activities (item 1.9)	(9,959)
8.2	Cash and cash equivalents at quarter end (item 4.6)	92,375
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	92,375
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	9.3

Note: if the entity has reported positive net operating cash flows in item 1.9, answer item 8.5 as "N/A". Otherwise, a figure for the estimated quarters of funding available must be included in item 8.5.

8.6 If item 8.5 is less than 2 quarters, please provide answers to the following questions:

8.6.1 Does the entity expect that it will continue to have the current level of net operating cash flows for the time being and, if not, why not?

Answer:

8.6.2 Has the entity taken any steps, or does it propose to take any steps, to raise further cash to fund its operations and, if so, what are those steps and how likely does it believe that they will be successful?

Answer:

8.6.3 Does the entity expect to be able to continue its operations and to meet its business objectives and, if so, on what basis?

Answer:

Note: where item 8.5 is less than 2 quarters, all of questions 8.6.1, 8.6.2 and 8.6.3 above must be answered.

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.

Date: ..31 October 2022.....

Authorised by: ...By the board.....
(Name of body or officer authorising release – see note 4)

Notes

1. This quarterly cash flow report and the accompanying activity report provide a basis for informing the market about the entity's activities for the past quarter, how they have been financed and the effect this has had on its cash position. An entity that wishes to disclose additional information over and above the minimum required under the Listing Rules is encouraged to do so.

2. If this quarterly cash flow 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 cash flow 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.

4. If this report has been authorised for release to the market by your board of directors, you can insert here: "By the board". If it has been authorised for release to the market by a committee of your board of directors, you can insert here: "By the [*name of board committee – eg Audit and Risk Committee*]". If it has been authorised for release to the market by a disclosure committee, you can insert here: "By the Disclosure Committee".

5. If this report has been authorised for release to the market by your board of directors and you wish to hold yourself out as complying with recommendation 4.2 of the ASX Corporate Governance Council's *Corporate Governance Principles and Recommendations*, the board should have received a declaration from its CEO and CFO that, in their opinion, the financial records of the entity have been properly maintained, that this report complies with the appropriate accounting standards and gives a true and fair view of the cash flows of the entity, and that their opinion has been formed on the basis of a sound system of risk management and internal control which is operating effectively.