PARADIGM BIOPHARMA

ASX RELEASE **31 January 2023**

DECEMBER 2022 QUARTERLY ACTIVITIES REPORT

Key Highlights

- **Top-line data PARA_OA_008:** Paradigm reported in October exciting top-line results from the phase 2 study exploring the disease modifying and clinical effects of injectable pentosan polysulfate sodium (**iPPS**) compared to placebo in 61 subjects with knee OA. The day 56 data demonstrated changes from baseline in multiple synovial fluid biomarkers for the iPPS treatment group. Reductions in levels of nerve growth factor (**NGF**) indicate that the effect of iPPS 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. The assessed 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 proportion of patients dosed twice-weekly with iPPS achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.
- **Successful PARA_OA_002 Formal Safety Review:** Paradigm completed the first formal safety review meeting of the Data Monitoring Committee (DMC) for the for the pivotal PARA_OA_002 clinical trial during the December quarter. The DMC review of trial progress and safety data concluded the clinical trial should proceed without modification. Paradigm Managing Director said of the DMC formal review process, *"this is a positive outcome for Paradigm that the early safety data from the pivotal PARA_OA_002 clinical trial has been reviewed by the DMC and it was recommended to continue without modification. Injectable PPS has been well tolerated throughout all of Paradigm's clinical programs, including real-world evidence with treatment of over 600 participants via the TGA Special Access Scheme".*
- **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%**). Of the 9 dogs treated with iPPS, 7 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. The dogs also demonstrated a response to iPPS treatment with changes in cartilage degradation biomarkers in the synovial fluid and serum reflecting results observed in the human PARA_OA_008 trial.

- **R&D Tax Rebate:** Paradigm lodged its income tax return and the R&D tax incentive claim for fiscal year 2022. The Company received a refund of approximately $7.4m during the December 2022 quarter.
- **Global Phase 3 Progress:** On 26 October 2022, the first subject in the United Kingdom (UK) was randomised and dosed in the pivotal PARA_OA_002 clinical trial. This subject was randomised at Leeds University by lead investigator Professor Hemant Pandit. Paradigm aims to activate a total of seven sites across the UK for this phase 3 study. Furthermore, it was confirmed during the quarter that the PARA_OA_006 extension study had enrolled its first participant from the PARA_OA_002 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 in PARA_OA_002 who reach the day 168 timepoint from initial dosing will be enrolled in PARA_OA_006 and monitored for an additional 34 weeks.
- **Key US Patent Allowance:** Paradigm received notification from the US Patent and Trademark Office (**USPTO**) in December 2022 that the patent application 16/636,545 had been examined and received a Notice of Allowance in the US. A summary of the first claim of the patent (16/636,545) refers to a method for improving knee function in a human having bone marrow edema lesions as assessed by magnetic resonance imaging (**MRI**) and osteoarthritis in a knee, the method including the treatment of the knee with administering an amount of pentosan polysulfate.

- **BIO-Europe 2022:** Paradigm's Managing Director, Mr Paul Rennie, attended the BIO-Europe conference from 24–26 October in Leipzig, Germany. Mr Rennie was accompanied by Plexus Ventures, Paradigm's business development consultant, to discuss partnering and investment opportunities with other biotech innovators. BIO-Europe is one of the biggest biotech BD&L conventions with over 4000 attendees from 2200 unique companies representing over 60 countries.

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) ("Paradigm" or "the Company") is pleased to provide its quarterly update for the three months ended 31 December 2022 to accompany its Appendix 4C cash flow report for the period.

- Cash balance as of 31 December 2022 was $83.92m (on 30 September 2022 it was $92.375m). During the December quarter Paradigm received a R&D Tax Incentive Rebate of $7.4m. Reported quarters cash on hand is 10.76, including the impact of the R&D rebate. Whilst this receipt is of an operating nature, Management and the Directors note this receipt does not related to Q2FY23 activity. After normalising Q2FY23 cash flow for this receipt, cash outflow is $15.2MAUD for the quarter which results in 5.5 quarters cash on hand. Management and the Directors note a similar R&D rebate being received in Q1/Q2FY24 is probable.
- Research & development expenditure for the quarter was $13.2m compared to the previous quarter of $8.6m. The spend in Q2 FY23 is related to ongoing subject recruitment and new site identification for the PARA_OA_002 study, as well as subject monitoring and ongoing analytical activity regarding biomarker and MRI analysis for the PARA_OA_008 phase 2 clinical trial. The spend also included site operations for the phase 2 studies for

MPS-VI and MPS-I, and ongoing New Drug Application (**NDA**) enabling nonclinical studies relating to our MPS and OA clinical programs. The quarter also included a milestone payment for the first subject enrolled in the PARA_OA_006 observational follow-up study 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 31 December 2022 were fees of $109.6K, which includes $103.1K for payment of Director fees, and $6.48K for legal fees to BioMeltzer (a company related to Amos Meltzer).

OUTLOOK

Paradigm is pleased to provide an update on continuing activities.

PARA_OA_002 Phase 3 Clinical Trial

- Recruitment remains ongoing for stage 1 of the pivotal PARA_OA_002 clinical trial. Site identification and activation continues to increase with a total of 120 sites planned to be activated during the PARA_OA_002 2-stage adaptive trial.
- The first Canadian site was activated in late 2022 and is expected to commence screening and enrolling participants shortly, with further site activations to follow.
- Paradigm has engaged recruitment firms with broad outreach to identify patients for referral to sites for screening and participation. Participant outreach is through social media and trial networks.
- Additionally, Paradigm continues to progress it engagement with the NFL Alumni Health to inform interested alumni and affiliates regarding trial activities.

PARA_OA_008 Synovial Fluid Biomarker Study

Paradigm expects to report on the 6-month data during Q1 CY2023. 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. Observations on changes to the joint structure by MRI of iPPS-treated subjects compared to placebo are also being assessed at 6 months. The secondary and exploratory endpoints at the 6-month timepoint include:

- Changes in one or more synovial fluid biomarkers;
- Changes and correlation between synovial fluid, serum, and urine biomarkers and correlation with changes in clinical outcomes;
- Changes in WOMAC pain, function, stiffness, and quality of life scores;
- MRI changes in the bone and joint; and
- Incidence of treatment-emergent adverse events (**TEAEs**), including serious adverse events (**SAEs**).

Following the readout of the PARA_OA_008 6-month data, Paradigm intends to initiate discussion with the key regulatory agencies (FDA and EMA) to reach agreement on disease modification label pathways for iPPS.

Canine OA Model Evaluating Disease Modification by iPPS

Recruitment for the canine OA model trial has now been completed and analysis is ongoing. 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. 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 (MRI), and biomarker levels (synovial fluid and serum) following iPPS therapy. This study data aims to provide informative data in conjunction with the PARA_OA_008 phase 2 clinical trial in humans to assess the potential of iPPS as a disease-modifying OA drug (**DMOAD**).

Conferences

- **JP Morgan 41st Annual Healthcare Conference:** Paradigm delivered a presentation at the JP Morgan Global Healthcare Conference held in San Francisco from 9–12 Jan 2023. Paradigm was represented at the conference by MD Paul Rennie, CMO Dr Donna Skerrett, and Global Head of Safety and MPS Dr Michael Imperiale. The Paradigm team conducted several 1x1 meetings during the conference with both potential investment funds and potential partnering companies.

- **International Conference on Lysosomal Diseases (ICLD):** Paradigm has been selected to present data from the MPS-I open-label phase 2 study, as an oral presentation at the 2023 ICLD meeting. The data from the four clinical trial participants treated to date is due 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.

- **WORLD*Symposium*™:** An abstract for the phase 2 clinical trial evaluating iPPS against placebo in mucopolysaccharidosis type VI (**MPS-VI**) patients was accepted for a poster presentation at the WORLD*Symposium*™ in 2023. The 19th annual WORLD*Symposium*™ conference will be held in Orlando, Florida during February 22–26, 2023. Dr Roberto Giugliani MD, PhD, MSc, the Principal Investigator of Paradigm's phase 2 clinical trial, is scheduled to present the poster, Ih provides an update on the enrolment and baseline characteristics of MPS-VI participants in the trial.
- **ACMG Annual Meeting**: Paradigm's submitted abstract "*Results of an Open-label, Single-Center, Clinical Study Evaluating the Safety and Tolerability of Pentosan Polysulfate Sodium in MucopolysaccharidoIis I Subjects*" has been accepted for a poster presentation at the 2023 ACMG Annual Clinical Genetics Meeting, to be held in Salt Lake City, UT, during 14–18 March 2023. Paradigm's Global Head of Drug Safety and the MPS Program, Dr Michael Imperiale, is scheduled to present the poster on Friday March 17.
- **World Congress on Osteoarthritis OARSI 2023:** An abstract detailing the day 56 results from the phase 2 synovial fluid biomarker clinical trial (PARA_OA_008) has been accepted for a poster presentation at the 2023 Osteoarthritis Research Society International (**OARSI**) World Congress on Osteoarthritis. Paradigm has also been officially invited to provide a presentation to the Clinical Trial Symposium a day prior to the conference and additionally is scheduled to conduct a sponsored oral theatre presentation to OARSI conference attendees. The planned presentation covers Paradigm's global OA program,

including the day 56 top-line data from the PARA_OA_008 clinical trial and proposed mechanism of action. The international conference will be held in Denver, Colorado from 17–20 March 2023.

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.

FOR FURTHER INFORMATION PLEASE CONTACT:

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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	31 December 2022

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	24	23
1.2	Payments for		
	(a) research and development	(13,258)	(21,852)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	(176)	(308)
	(d) leased assets	(26)	(54)
	(e) staff costs	(517)	(1,122)
	(f) administration and corporate costs	(1,375)	(1,993)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	131	156
1.5	Interest and other costs of finance paid	(3)	(9)
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	7,405	7,405
1.8	Other (provide details if material)	-	-
1.9	**Net cash from / (used in) operating activities**	**(7,795)**	**(17,754)**

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 (6 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
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	(301) -	(3,765) -
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings (lease liabilities)	(26)	(57)
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (Limited recourse loan repaid under ESP)	132	132
3.10	**Net cash from / (used in) financing activities**	**(195)**	**62,2989**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	92,375	39,721
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(7,795)	(17,754)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (6 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)	(195)	62,209
4.5	Effect of movement in exchange rates on cash held	(459)	(339)
4.6	**Cash and cash equivalents at end of period**	**83,926**	**83,926**

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	83,926	92,375
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)**	**83,926**	**92,375**

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	110
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)	(7,795)
8.2	Cash and cash equivalents at quarter end (item 4.6)	83,926
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	83,926
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	10.76^

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.

^The December quarter included a cash receipt of $7.4MAUD from the Australian Tax Office, relating to eligible FY22 R&D spend under the ATO R&D tax incentive scheme. Whilst this is considered an operating activity, given Paradigm is a late-stage clinical development company, Management and the Directors note that this receipt does not relate to the operating activity of Q2FY23. Normalising cash outflows, excluding the impact of this receipt, shows cash outflow of $15.2MAUD for the quarter, which results in 5.5 quarters cash on hand. Management and the Directors note a similar R&D rebate being receivable in Q1/Q2FY24 is probable.

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 January 2023.....

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.