ASX RELEASE 30 October 2023

SEPTEMBER 2023 QUARTERLY ACTIVITIES REPORT

Key Highlights (including significant events post end of quarter)

- **PARA_OA_002 Stage 1 100% Recruitment:** In July 2023, Paradigm reported the completion of enrolment of all subjects into stage 1 of the two-stage adaptive PARA_OA_002 phase 3 clinical trial.
- **Global Clinical Trial Site Activation:** Paradigm achieved the target of 120 clinical trial site activations to support the recruitment initiatives undertaken by Paradigm. The PARA_OA_002 clinical trial has activated sites across seven countries, comprising Australia, the US and Canada in North America, and the UK, Belgium, Poland, and Czechia in the EU. An additional 40 sites were added to the Phase 3 PARA_OA_002 trial following interest from clinicians and patients in the US compared to the original budget of 80 sites. The additional sites are expected to accelerate patient recruitment in the next stage of Phase 3 program.
- **PARA_OA_008 12 month 'Durability of Effect' Data:** Paradigm reported significant new phase 2 PARA_OA_008 data of demonstrating improvements in patient-reported outcomes of WOMAC pain and function and patient global impression of change (**PGIC**) scores for participants receiving 2mg/kg twice weekly iPPS compared to placebo at Day 365 in the phase 2 PARA_OA_008 clinical trial.
- **6-month MRI Cartilage Thickness Data:** Paradigm's phase 2 PARA_OA_008 trial also demonstrated that a 6-week 2mg/kg twice weekly course of subcutaneous iPPS was shown to increase cartilage thickness and volume and reduce bone marrow lesions and synovitis on MRI follow-up at 6 months.
- **Optimal iPPS Dosing Regimen:** Paradigm now has multiple data sets supporting the 2 mg/kg twice weekly dose of iPPS is highly effective in treating knee osteoarthritis and this dosing regimen will form the focus for future clinical development and registration programs.
- **Commercial Partnering:** Discussions with potential regional partners are progressing following the release of the 12-month durability data and 6-month MRI data, which is supportive of iPPS slowing the progression of OA.

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) ("Paradigm" or "the Company") is pleased to provide its quarterly update for the three months ended 30 September 2023 to accompany its Appendix 4C cash flow report for the period.

- Cash balance as of 30 September 2023 was $33.6m (on 30 June 2023 it was $56.4m).
- Research and development expenditure for the quarter was $21.9m compared to the previous quarter of $16.15m. The increased spend in Q1 FY24 was related to the subject recruitment initiatives and enrolment of the final subjects for the completion of stage 1 of the PARA_OA_002 study, as well clinical and quantitative MRI data analysis and completion of study activities for the PARA_OA_008 phase 2

clinical trial. The addition of 40 clinical trial sites were added to the Phase 3 PARA_OA_002 trial following interest from clinicians and patients in the US vs original budget of 80 sites. Accelerated recruitment via additional sites and changes in FX have resulted in higher than budgeted costs. Favourably, these trained additional sites are expected to accelerate patient recruitment in the next stage of Phase 3 program.

- The spend also included site operations for the MPS VI phase 2 study, and an ongoing New Drug Application (**NDA**) enabling nonclinical studies relating to our MPS and OA clinical programs. The quarter also saw payments related to continuing activities described in the outlook below.

- The anticipated spend for Q2 FY24 is expected to be at a lower level to the previous two quarters. Paradigm has concluded spend on the PARA_OA_008 clinical trial following the 12-month follow up of participants. The MPS VI clinical trial cost is also expected to reduce significantly with the final participant completing treatment in the study and top-line data to be reported during the current quarter. Stage 1 PARA_OA_002 has completed recruitment of all participants with screening and recruitment comprising a large portion of the spend in the program. Spend on the PARA_OA_002 program is expected to reduce significantly for the next two quarters.
- The Company has streamlined operations and improved efficiencies over the previous two quarters to ensure capital is being focussed on progressing the OA clinical program towards registration.
- A FY23 R&D Tax Incentive refund of $7.3m is expected to be received during Q2 FY24 to be reinvested into further continuing R&D activities for the quarter.
- 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 September 2023 were fees of $70K, which includes $67K for payment of Director fees, and $3K for legal fees to BioMeltzer (a company related to Paradigm NED, Amos Meltzer).

QUARTERLY ACTIVITIES & OUTLOOK

Paradigm is pleased to provide an update on continuing activities.

PARA_OA_002 Phase 3 Clinical Trial

The September quarter saw the completion of stage 1 of the two-stage, adaptive, randomised, double-blinded, placebo controlled, phase 3 PARA_OA_002 clinical trial. Paradigm recruited approximately 600 participants and achieved the goal of activating 120 sites across 7 countries comprising Australia, the US and Canada in North America, the UK, Belgium, Poland and Czechia in the EU. These activated sites will remain on standby and ready for the commencement of the next stage of the phase 3 OA clinical program. An additional 40 sites were added to the Phase 3 PARA_OA_002 trial following interest from clinicians and patients in the US compared to the original budget of 80 sites. Favourably, these trained additional sites are expected to accelerate patient recruitment in the next stage of Phase 3 program.

During the quarter, Paradigm requested the independent Data Monitoring Committee, to the phase 3 trial, to undertake an interim analysis of the performance of all treatment arms in stage 1 of the phase 3 trial. It was reported in October that all doses (less than 2 mg/kg twice weekly) included in the dose determination part of phase 3 trial did not meet the prespecified performance threshold, (which was based on prior outcomes with the 2mg/kg twice weekly dosing. The interim analysis was performed when 300 patients reached 56 days of follow up. The timing of this interim analysis was chosen to inform the program in advance of the formal dose selection procedure scheduled for CY Q1 2024.

The findings of the interim analysis determined that the PARA_OA_002 stage 1 doses did not demonstrate the performance of 2 mg/kg twice weekly as demonstrated in the PARA_OA_008, PARA_005 (previous phase 2b) studies and the TGA Special Access Scheme. On that basis, the Company has determined that the 2 mg/kg twice weekly is the optimal dose regimen to be included in Paradigm's OA development and registration programs and are preparing a request to the US FDA for a protocol review to move forward with this dose regimen into the next stage of the OA phase 3 program, anticipated in Q1 CY2024.

Paradigm is also progressing opportunities for the provisional approval of Zilosuul in Australia based on the PARA_OA_008 data.

The OA development program is expected to now focus on achieving the results of 2 mg/kg twice weekly regimen going forward in the phase 3 OA program. Paradigm anticipates timeline of the enrolment into the next stage of Phase 3 program in H1CY2024, subject to regulatory approval of the dosing protocol amendment.

PARA_OA_008 Phase 2 Clinal Trial

Paradigm's PARA_OA_008 clinical trial has now successfully completed the study of participants out to 12-months. The clinical trial has delivered a successful primary endpoint and delivered positive clinical data at Day 56, 168 and 365 and structural improvements through MRI quantitative analysis at 6-months.

Durable and significant responses were reported in WOMAC scores for pain, function, stiffness and overall are observed for iPPS twice weekly compared to placebo control through to Day 365. Reported figures included:

- Significant pain reduction (p=0.054).
- Significant functional improvement (p=0.048).
- Durable improvements in stiffness.
- Significant improvement in overall WOMAC scores (p=0.054).
- Significant improvement in patient global impression of change scores (p=0.005).
- Cumulative rescue pain medication use was over five times higher in the placebo group at Day 365.

This data is a significant outcome for Paradigm as no OA drug has previously shown durable and meaningful improvements in pain and function at 12 months after a single course of treatment.

The Company also reported in October quantitative MRI analysis data from the phase 2 PARA_OA_008 clinical trial, demonstrating that a single 6-week treatment of injectable pentosan polysulfate sodium (**iPPS)** treatment at 2mg/kg twice weekly results in:

- An increase in overall cartilage thickness, across all compartments of the knee, of 0.17mm (p=0.05) compared to overall decrease of -0.09mm in placebo;
- An increase of overall cartilage volume by 1.9% (p=0.07) compared to a decrease of -1.58% in the placebo group;
- Resolution or decrease in bone marrow lesions (BML) volume by 17% in the iPPS group, whereas placebo subjects saw a 2% increase in BML and;
- Reduced area and intensity by 1% of synovitis in the iPPS group compared to an increase 0f 4% in synovitis intensity in placebo.

The above results of the successful phase 2 clinical trial demonstrate that iPPS both treats the symptoms of OA and preserves and/or regenerates joint tissues. This is significant from a commercial perspective because the disease modifying effects of iPPS observed in the PARA_OA_008 phase 2 clinical trial are expected to support a greater reimbursement compared to that which would be expected for a therapeutic that only treat the symptoms of OA**.**

This successful phase 2 clinical trial has provided important data for Paradigm to progress with the TGA Provisional Approval application, which would expedite the pathway to marketing approval of iPPS in Australia.

Mucopolysaccharidosis VI

MPS VI: The MPS VI study is nearing completion with data to be reported during the December quarter. This placebo-controlled, double-blind, and randomised 24-week Phase 2 study compares iPPS to placebo in participants with the ultra-rare disease MPS VI, with Dr Roberto Giugliani as Principal Investigator. This is a large Phase 2 placebo-controlled study in this ultra-rare disease (n=13) with the primary objective of the study is to evaluate the safety and tolerability of iPPS in subjects with MPS VI at 6, 12, and 24 weeks. Throughout the study, multiple safety reviews have been completed by the safety monitoring physician allowing enrolment of participants aged 5 and over into the study.

The data produced from this program is expected to provide important information for discussions with the Brazilian Regulatory Authority (ANVISA) on a rare disease accelerated approval pathway for iPPS.

Partnering Update

Paradigm is currently in licensing discussions for the OA and MPS programs for China, Latin America and Middle East regions. Discussions have accelerated with potential partners following the release of 12-month durability and 6-month MRI data, which is supportive of a potential disease modification effect.

The company is aiming to secure a licensing agreement in one or multiple regions over the next 6 months, which would provide a material source of non-dilutive funding.

Conferences

PAINWeek Conference 2023: Dr Mukesh Ahuja, Paradigm Global Head of Osteoarthritis, presented a poster at the PAINWeek Conference 2023 held in Las Vegas, USA from 5–8 September 2023. The poster covered the multiple mechanisms of action of iPPS and its positive impact in wide-ranging applications in the treatment of musculoskeletal disorders with pain and inflammation. This is supported by clinical evidence from various Paradigm-

sponsored clinical trials, which have pain-based outcomes, in OA (PARA_008, PARA_005), alpha virus (PARA_004), and MPS type I (MPSV1_001).

Symposium on Glycosaminoglycans: Dr Ravi Krishnan, Paradigm Chief Scientific Officer, presented virtually at the 30th Symposium on Glycosaminoglycans on the 23rd of September. Dr Krishnan presented data on the various mechanism of iPPS supporting the treatment of acuter and chronic diseases.

Outlook

- Top-line data from the phase 2, double-blinded and randomised MPS VI clinical trial is expected during Q4 CY2023. Participants in the study are dosed weekly for 24 weeks with the primary endpoint being safety, followed by secondary endpoints of improvements in pain and function.
- Paradigm will be presenting two posters at the upcoming prestigious American College of Rheumatology Conference held on 10-15 November. Dr Mukesh Ahuja will present a poster detailing data from the PARA_OA_008 clinical trial on the therapeutic effects of iPPS on clinical and DMOAD outcomes in subjects with knee osteoarthritis. Dr Ravi Krishnan will also be presenting a poster on iPPS durable effects on pain, function, and MRI (joint structure) in canine naturally occurring osteoarthritis. The posters will be available and reported to the market at the conclusion of the conference.
- Paradigm has lodged the FY23 R&D Tax Incentive Scheme refund claim. The refund of approximately $7.3m is anticipated to be received during the Q4 FY2023.
- Paradigm is progressing with the TGA Provisional Approval application, which is expected to expedite the pathway to revenues via marketing approval in Australia. The next stage determination application is planned to be submitted to the TGA in Q1 CY2024. Should this prove successful, Paradigm will prepare a full dossier for submission for the TGA provisional approval application.
- PAR is preparing a request to the FDA for a protocol review. The program has FDA granted Fast-track designation and the timeline for the review is expected in Q1 CY2024. The program plans to proceed with the dose of 2mg/kg twice weekly for registration studies. Enrolment into the next stage of the program is expected to commence in 1H CY2024.
- Paradigm expects to conduct a pre-submission meeting with the Brazilian Regulatory Authority ANVISA, following the data read out of the MPS VI phase 2 trial. This is a large phase 2 study in an ultra-rare disease. Paradigm expects to pursue a rare disease accelerated approval pathway in Brazil for MPS VI. The meeting with ANVISA is planned in the 1H CY 2024.
- The overall results produced in the PARA_OA_008 phase 2 clinical trial and MPS-I study are currently being compiled into a manuscript for peer review and publication. Both are expected to be published during CY2024.

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:

Simon White
Director of Investor Relations
Tel: +61 404 216 467
Paradigm Biopharmaceuticals Ltd.
ABN: 94 169 346 963
Level 15, 500 Collins St, Melbourne, VIC, 3000, AUSTRALIA
Email: investorrelations@paradigmbiopharma.com

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 2023

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	30	30
1.2	Payments for		
	(a) research and development	(21,939)	(21,939)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	-	-
	(d) leased assets	(11)	(11)
	(e) staff costs	(563)	(563)
	(f) administration and corporate costs	(528)	(528)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	549	549
1.5	Interest and other costs of finance paid	(3)	(3)
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**	**(22,465)**	**(22,465)**

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)	-	-
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	-	-
		-	-
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings (lease liabilities)	(43)	(43)
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**	**(43)**	**(43)**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	**56,379**	**56,379**
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(22,465)	(22,465)

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)	(43)	(43)
4.5	Effect of movement in exchange rates on cash held	(312)	(312)
4.6	**Cash and cash equivalents at end of period**	**33,559**	**33,559**

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	33,559	56,379
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)**	**33,559**	**56,379**

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	70
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)	(22,465)
8.2	Cash and cash equivalents at quarter end (item 4.6)	33,559
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	33,559
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	1.49

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: Yes, the Company is undertaking a Capital Raise in order to raise further funding for operating activities. The Company also expects operating costs to be lower in the next two quarters as a result of cost containment strategies, and the finalisation of recruitment in the Stage 1 of the Phase III Clinical Trial.

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: Yes, the Company is undertaking a Capital Raise in order to raise further funding for operating activities. The Company is confident that this process will be successful.

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: Yes, as a result of the above.	

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: ..30 October 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.