ASX RELEASE 28 April 2023

MARCH 2023 QUARTERLY ACTIVITIES REPORT

Key Highlights

- **Top-line PARA_OA_008 Six-month Data Release:** Paradigm reported exciting novel 6-months data from the phase 2 study, that is complementary to the ongoing phase 3 clinical trial. The phase 2 study is exploring the disease modifying and clinical effects of injectable pentosan polysulfate sodium (**iPPS**) compared to placebo in 61 subjects with knee osteoarthritis (**OA**). Disease modifying therapies are expected to attract a significantly higher price. Six-month data reported participants receiving iPPS treatment demonstrated improvement in cartilage loss, reductions in bone marrow lesions, and reductions in marginal osteophytes as measured by MRI compared to placebo. The disease modifying OA drug (**DMOAD**) potential for iPPS in knee OA treatment was also supported by changes and trends in four key biomarkers (ARGS, COMP, C2C, and CTX-II) at six months. The PARA_OA_008 trial successfully achieved its primary endpoint of a change from baseline at Day 56 in one or more synovial fluid biomarkers, with Paradigm reporting a positive change in six biomarkers associated with OA disease progression following iPPS treatment compared to placebo. Additionally, iPPS-treated subjects demonstrated statistically significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) pain and function scores at Day 56 for the twice-weekly group compared to placebo. This measurement is also the primary endpoint for the ongoing phase 3 clinical trial.
- **Global Phase 3 Progress:** In March, Paradigm reported that regulatory and ethics approvals were received via Europe's Clinical Trial Information System for Paradigm's pivotal PARA_OA_002 clinical trial. These approvals enabled Paradigm to commence PARA_OA_002 clinical trial site start-up activities in Belgium, Poland, and the Czech Republic.
- **OARSI 2023 World Congress on Osteoarthritis:** During March, Paradigm's management and clinical team conducted three presentations at the Osteoarthritis Research Society International (**OARSI**) 2023 World Congress held in Denver, Colorado. Dr. Donna Skerrett, Paradigm's Chief Medical Officer, was invited to present iPPS technology, its mechanism of action, and clinical translation potential for Paradigm's ongoing global OA program at the Clinical Trial Symposium, held the evening prior to the congress commencement. Dr. Mukesh Ahuja, Paradigm's Global Clinical Head of OA, presented a poster detailing the clinical trial design and Day 56 top-line data from the PARA_OA_008 clinical trial exploring the disease modifying potential of iPPS. Paradigm's Chief Scientific Officer Dr. Ravi Krishnan and Dr. Mukesh Ahuja gave an oral presentation covering Paradigm's global OA program, including the Day 56 top-line data from the PARA_OA_008 clinical trial.

Paradigm Biopharmaceuticals Ltd. (ASX:PAR) ("Paradigm" or "the Company") is pleased to provide its quarterly update for the three months ended 31 March 2023 to accompany its Appendix 4C cash flow report for the period.

- Cash balance as of 31 March 2023 was $73.20m (on 31 December 2022 it was $83.92m).
- Research & development expenditure for the quarter was $8.95m compared to the previous quarter of $13.2m. The spend in Q3 FY23 is related to ongoing subject recruitment and new site identification and activation for the PARA_OA_002 study, as well as subject monitoring and analytical activity regarding biomarker and MRI analysis for the PARA_OA_008 phase 2 clinical trial. The spend also included site operations for MPS I and MPS VI phase 2 studies, and an ongoing New Drug Application (**NDA**) enabling nonclinical studies related to our MPS and OA clinical programs. The quarter also saw payments related to 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 March 2022 were fees of $77K, which includes $66K for payment of Director fees, and $10K 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 2-stage adaptive clinical trial. Site activation continues to increase with a total of 102 sites activated across 6 countries out of a planned 120 sites.
- Paradigm is scheduled to complete enrolment of stage 1 of the PARA_OA_002 clinical trial by the end of the current quarter.
- Paradigm continues to progress its partnership with NFL Alumni Health to inform interested alumni and affiliates regarding developments in OA drug development. Paradigm is scheduled to conduct multiple webinars with NFL Alumni chapter presidents during the quarter, with evidence of strong interest in the phase 3 program through ethics-approved pre-screening activities.

PARA_OA_008 Synovial Fluid Biomarker Study

Paradigm's PARA_OA_008 clinical trial has now met the primary endpoint and delivered positive clinical data at both Day 56 and Day 168. The trial demonstrated both symptomatic relief through reduction in pain and improvement in function and additionally showed structural improvement as measured by molecular and structural biomarkers associated with OA disease progression. Highlights from both the Day 56 and Day 168 top-line data releases include:

Day 56

- Successfully met the study's primary endpoint with a change from baseline in one or more molecular biomarkers associated with OA disease progression following iPPS treatment compared to placebo. Paradigm reported positive changes in 6 key biomarkers (NGF, TNF-α, IL-6, COMP, ARGS, and TIMP-1).
- iPPS treatment showed statistically significant improvements at Day 56 in pain, function and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm. The primary endpoint for Paradigm's Phase 3 program is a change from baseline in WOMAC pain and function at Day 56.

Day 168 (6 months)

- Structural changes in several disease features as measured by MRI were consistent with potential DMOAD activity in iPPS-treated participants compared to placebo. Most notably, iPPS demonstrated:
    - 21% improvement in mean cartilage loss score compared to 4% worsening in the placebo group,
    - Statistically significant reductions in bone marrow lesions compared to placebo, and
    - Reduction of marginal osteophytes compared to an increase in the placebo group.
- Reductions in molecular biomarkers of cartilage degradation (C2C, CTX II, COMP, ARGS) were observed in iPPS-treated subjects compared to placebo control. Following discussions with a leading expert in the research of predictive biomarkers and their role in OA progression, it was suggested that these four biomarkers be highlighted during discussions with the key regulatory agencies.
- Durable clinical responses were reported out to Day 168 in WOMAC index scores for pain, function, stiffness, and overall for twice-weekly iPPS compared to placebo control. The placebo group reported using rescue medication on an average of 23 days compared to an average of only 5 days in the twice-weekly iPPS group. This comparison is highly relevant as rescue medication was not permitted prior to Day 56, as per the clinical protocol.

Discussions will be undertaken with key regulatory agencies (FDA and EMA) in order to reach agreement on disease modification labelling pathways for iPPS. Paradigm's current Phase 3 clinical trials have been designed to collect molecular (serum and urine) and structural (MRI) biomarker data. Paradigm expects to conduct these meetings prior to the commencement of the PARA_OA_003 confirmatory trial.

The PARA_OA_008 clinical trial continues to monitor participants out to 12 months, with this follow-up data expected to be reported in the 2H CY2023.

Canine OA Model

The complete study report examining both week 8 and week 26 responses in the final cohort of dogs is expected to be reported during the current quarter. This study data aims to provide informative data in conjunction with the data released from the PARA_OA_008 phase 2 clinical trial in humans to assess the potential of iPPS as a DMOAD. The key data being analysed from this study are changes from baseline at week 8 and week 26, in:

- Joint function as measured by percentage body weight distribution (**BWD**%) in the affected limb as measured by the total pressure index percentage (TPI%).
- Biomarkers of joint degeneration; and
- Structural changes determined by OA clinical scores as assessed by X-ray and MRI.

The longer follow-up period at week 26 (roughly equivalent to 3 human years) aims to provide data on the long-term durability of effect of iPPS compared to placebo on structural and molecular biomarkers.

Mucopolysaccharidosis (MPS I and VI)

The open-label MPS I trial has been completed and data analysis is currently underway. iPPS is well tolerated in this population with no serious adverse events reported to date. Additionally, to date, there appears to be an overall trend toward meaningful improvements in pain, function, activities of daily living (ADL) , and overall improvement in quality of life. Further data will be reported on this study once the analysis and clinical study report has been completed.

Paradigm's MPS VI phase 2 trial based in Brazil has completed enrolment of participants. This placebo-controlled, double-blind, and randomised 24-week study compares iPPS to placebo in participants with the ultra-rare disease MPS VI. 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.

Upcoming Conferences

- **NFL Alumni Health Symposium:** Paradigm has been invited to present at the NFL Alumni Health Symposium being held at the NFL Draft on April 28 in Kansas City, MO. Paradigm's Global Head of OA, Dr Mukesh Ahuja, will participate in a live panel discussion to discuss conditions relevant to the NFL Alumni, of which OA being a major concern. The symposium is free to the public and will provide a platform for medical experts to discuss the latest advancements in osteoarthritis research and development, as well as the challenges and opportunities for developing new therapies. NFL Alumni Health hopes to raise awareness about the importance of addressing osteoarthritis in NFL players and the wider community.
- **Bio 2023 International Conference:** Paradigm has been accepted to present at the upcoming Bio International Conference that will be conducted in Boston on June 5–8. Paradigm's Managing Director, Mr. Paul Rennie and Chief Medical Officer Dr. Donna Skerrett, will be in attendance to present Paradigm's clinical development program and conduct 1x1 meetings in conjunction with Plexus Ventures, Paradigm's Business Development Consultant.

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 March 2023

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (9 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	-	23
1.2	Payments for		
	(a) research and development	(8,953)	(30,805)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	(79)	(387)
	(d) leased assets	(16)	(70)
	(e) staff costs	(1,195)	(2,317)
	(f) administration and corporate costs	(736)	(2,729)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	649	805
1.5	Interest and other costs of finance paid	(4)	(13)
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	-	7,405
1.8	Other (provide details if material)	-	-
1.9	**Net cash from / (used in) operating activities**	**(10,334)**	**(28,088)**

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 (9 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	-	(3,765)
		-	-
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings (lease liabilities)	(23)	(80)
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (Limited recourse loan repaid under ESP)	56	188
3.10	**Net cash from / (used in) financing activities**	**33**	**62,331**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	83,926	39,721
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(10,334)	(28,088)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (9 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)	33	62,331
4.5	Effect of movement in exchange rates on cash held	(422)	(761)
4.6	**Cash and cash equivalents at end of period**	**73,203**	**73,203**

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	73,203	83,926
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)**	**73,203**	**83,926**

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	77
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)	(10,334)
8.2	Cash and cash equivalents at quarter end (item 4.6)	73,203
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	73,203
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	7.08

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: ..28 April 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.