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JUNE 2023 QUARTERLY ACTIVITIES REPORT

Key Highlights

- **Top-line PARA_OA_008 Six-month Data Release:** in April Paradigm reported exciting novel 6-month data from the exploratory phase 2 study investigating the disease modifying and clinical effects of injectable pentosan polysulfate sodium (**iPPS**) compared to placebo in 61 subjects with knee osteoarthritis (**OA**). Six-month data reported that 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 cartilage biomarkers (ARGS, COMP, C2C, and CTX-II) at six months.
- **Canine Model of Naturally Occurring OA:** iPPS demonstrated durable improvements in pain, joint function, and cartilage volume in canine osteoarthritis model at a 3-year human-equivalent time point.
- **MPS I Positive Top-line Phase 2 Results:** Primary and secondary endpoints were attained in this open-label study of the rare disease MPS I. iPPS was well tolerated with no serious adverse events reported out to 73 weeks. In the study, MPS I patients experienced meaningful improvements in pain, function, and activities of daily living and an overall improvement in quality of life.
- **MPS VI Study Completes Enrolment:** Paradigm's phase 2 MPS VI clinical trial based in Brazil completed participant enrolment in April. The placebo-controlled, double-blinded, randomised, 24-week phase 2 study compares iPPS to placebo in 13 participants with the ultra-rare disease MPS VI.

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

- Cash balance as of 30 June 2023 was $56.38m (on 31 March 2023 it was $73.2m).
- Research and development expenditure for the quarter was $16.15m compared to the previous quarter of $8.95m. The spend in Q4 FY23 is related to ongoing subject recruitment initiatives and new site identification and activation for the PARA_OA_002 study, as well as biomarker and MRI analysis for the PARA_OA_008 phase 2 clinical trial and the canine model of naturally occurring OA. The spend also included data review and analysis for the MPS I study and 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 the September 2023 quarter is expected to be at similar levels to the June 2023 quarter as the company continues to run several pivotal studies.
- 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 2023 were fees of $73K, which includes $66K for payment of Director fees, and $6K for legal fees to BioMeltzer (a company related to Amos Meltzer).

QUARTERLY ACTIVITIES & OUTLOOK

Paradigm is pleased to provide an update on continuing activities.

PARA_OA_002 Phase 3 Clinical Trial

The June quarter saw considerable progress in the Phase 3 clinical program for OA. Paradigm achieved the target of 120 clinical trial site activations to support the recruitment initiatives undertaken by the Company. 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. As Paradigm has reached its target for site activation and these clinical trial sites have become familiar with the study design, Paradigm has been able to increase the number of participants directed to these sites through the utilisation of diverse recruitment initiatives.

During the quarter, the independent data monitoring committee (**DMC**) conducted a second formal safety review of the PARA_OA_002 clinical trial with the recommendation that the trial proceed without modification.

To facilitate current and potential trial participants, Paradigm launched a new clinical trials website in May called Hope4OA.com. The website is designed for ease of use where potential participants can discover trial details and find answers to commonly asked questions. If interested, they are invited to complete an online questionnaire to determine their eligibility as a potential trial participant. The website hosts helpful explanations and instructional videos about clinical trials in general, as well as providing links to patient support and further information.

Canine Naturally Occurring OA Model

Top-line data from the final cohort of dogs at week 26 was reported in June. The canine model of naturally occurring OA was designed to gather further preclinical proof-of-concept and translational data to determine the long-term effects of iPPS out to an approximate equivalent of 3 years in humans. These durable effects of iPPS out to at least 26 weeks in dogs support the findings from the recently reported phase 2 PARA_OA_008 Day 168 clinical data.

The key data reported from this study at week 8 and 26, demonstrated iPPS:

- Reduces pain at week 8 and week 26 in osteoarthritic dogs with meaningful effect size,
- Improves joint function at week 8 and week 26 in osteoarthritic dogs with meaningful effect size,

- Inhibits OA disease progression by stabilising cartilage volume changes at week 8 and week 26 in the stifle joints (knee equivalent) of osteoarthritic dogs; and
- Favourably regulates serum levels of the biomarkers CTX-I, HA, and TIMP-1 with meaningful effect sizes at week 8 and week 26 in osteoarthritic dogs.

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.

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 Day 168 top-line data released during the June quarter include:

- 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 for twice-weekly iPPS compared to placebo control in Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) index scores for pain, function, stiffness, and overall. 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.

Mucopolysaccharidosis (MPS I and VI)

MPS I: During the June quarter, the open-label MPS I trial was completed, and data analysed. The primary objective of the study was to evaluate safety and tolerability of iPPS over an initial 48-week treatment period, with a 6-month treatment extension available, in patients treated with the current standard of care. Secondary and exploratory endpoints included examining the effects of iPPS on pain, function, and quality of life, pharmacokinetics, and biomarkers of inflammatory processes.

Paradigm reported top-line results on 6 June that the MPS I clinical trial met the primary and secondary endpoints. No serious adverse events were reported out to week 73 and iPPS showed

meaningful improvements in pain, function, and activities of daily living and an overall improvement in quality of life.

MPS VI: During the quarter, Paradigm reported on 13 June that the final participant had been enrolled in the phase 2 trial based in Brazil. This placebo-controlled, double-blind, and randomised 24-week study compares iPPS to placebo in participants with the ultra-rare disease MPS VI, with Dr Roberto Giugliani as Principal Investigator. 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.

Conferences

BIO International Convention 2023: Paradigm Senior Management attended and conducted a sponsored presentation at the BIO International Convention in Boston from June 5–8. Paradigm's Managing Director, Mr. Paul Rennie, Chief Medical Officer Dr. Donna Skerrett, and Chief Scientific Officer, Dr. Ravi Krishnan were in attendance to present Paradigm's clinical development program and conduct 1x1 meetings in conjunction with Plexus Ventures, Paradigm's Business Development Consultant.

Outlook

- Paradigm has confirmed that all participants have been identified for completion of stage 1 recruitment of the PARA_OA_002 clinical trial. Once all participants in stage 1 (n=468) are randomised and reach the pre-specified Day 84 timepoint, the DMC will recommend the optimal dose for proceeding to stage 2 (n=468). Following dose selection, which is expected early in Q1 CY2024, stage 2 and the PARA_OA_003 confirmatory trial (n=700) can commence.
- 12-month clinical outcome data from the PARA_OA_008 phase 2 clinical study is expected to be reported in late Q3 CY2023. Paradigm expects to report change from baseline in WOMAC pain, function, and stiffness data along with patient global impression of change (PGIC) measurements following iPPS treatment compared to placebo at the Day 365 time point.
- The clinical, MRI, and molecular biomarker data produced from the phase 2 PARA_OA_008 clinical trial—along with the data from the canine OA model—will be presented to the US and EU regulatory authorities (FDA and EMA). The aim is to reach agreement on the regulatory pathway for a DMOAD label extension. Paradigm's phase 3 confirmatory clinical trial plans to collect molecular (serum and urine) and structural (MRI) biomarker data in addition to the clinical data required for the WOMAC pain and function, primary and secondary endpoints, respectively. Paradigm plans for the meeting with the US FDA to take place in Q4 CY2023.
- 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 has estimated that the FY23 R&D Tax Incentive Scheme refund will equal approximately $6.3m. This is anticipated to be received in the December 2023 quarter.

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 June 2023

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (12 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	-	23
1.2	Payments for		
	(a) research and development	(16,148)	(46,953)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	(83)	(470)
	(d) leased assets	(15)	(85)
	(e) staff costs	(423)	(2,740)
	(f) administration and corporate costs	(577)	(3,306)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	145	950
1.5	Interest and other costs of finance paid	(3)	(16)
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**	**(17,104)**	**(45,192)**

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 (12 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)	(24)	(104)
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (Limited recourse loan repaid under ESP)	228	416
3.10	**Net cash from / (used in) financing activities**	**204**	**62,535**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	73,203	39,721
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(17,104)	(45,191)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (12 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)	204	62,535
4.5	Effect of movement in exchange rates on cash held	76	(685)
4.6	**Cash and cash equivalents at end of period**	**56,379**	**56,379**

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	56,379	73,203
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)**	**56,379**	**73,203**

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	73
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)	(17,104)
8.2	Cash and cash equivalents at quarter end (item 4.6)	56,379
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	56,379
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	3.3

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 July 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.