PARADIGM BIOPHARMA

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Paradigm reports significant pain and function findings in ROW Phase 3 analysis

Key Highlights

- **Further analysis identifies significant pain relief outside the US.** Following the overall interim futility result and findings in the US data, Paradigm investigated whether the result was consistent across regions. Analysis of 16 sites in Australia, Hong Kong and Moldova, collectively the rest of world (ROW), showed statistically significant improvement in weekly average daily pain (wADP) with iPPS compared with placebo at Day 112 (p=0.0007).
- **The benefit represents additional pain relief beyond placebo.** ROW participants receiving iPPS experienced an adjusted average pain reduction approximately 1.1 points greater than placebo on a 0–10 scale. The reported standardised effect size was 0.71 in favour of iPPS, measuring the size of the treatment benefit relative to variability in patient outcomes. This analysis included 95 participants with available Day 112 pain assessments.
- **The positive findings extended beyond daily pain.** At Day 112, ROW participants receiving iPPS also demonstrated statistically significant benefits in physical function (p=0.0026), pain assessed using the WOMAC questionnaire (p=0.0147), and patients' overall assessment of improvement (p=0.0032), compared with placebo.
- **The ROW findings add to the evidence from earlier studies.** The ROW group included 114 randomised participants, 58 receiving iPPS and 56 receiving placebo, approximately 2.8 times the corresponding twice-weekly iPPS and placebo population in PARA_OA_008. Day 112 pain assessments were available for 95 participants, representing 83.3% of the randomised ROW group.
- **Missing Day 112 pain data was concentrated in the US.** US participants accounted for 91 of the 97 participants with missing Day 112 wADP data at the interim analysis. The review identified a number of factors affecting dosing, including laboratory delays. Further analysis is assessing how these factors and the statistical handling of missing data may have contributed to the different regional outcomes.
- **The Administrators have received notice that the former Board is preparing a proposal** to preserve the program. The proposal is being prepared for consideration by the Administrators and aims to establish a funded path for continued development of iPPS. No proposal has yet been received or assessed, and any proposal will be considered alongside other options in the administration. Further details will be provided when available.

Paradigm Biopharmaceuticals Limited (Administrators Appointed) (ASX: PAR) (Paradigm or the Company) reports statistically significant and clinically meaningful improvements in pain, physical function and patient-reported overall improvement at Day 112 in a regional analysis of its Phase 3 PARA_OA_012 knee osteoarthritis trial. The analysis covered 16 sites across Australia (12), Moldova (3) and Hong Kong (1), collectively referred to as the rest of world (ROW). For the trial's primary measure of weekly average daily pain (wADP), iPPS delivered 1.1 points greater pain reduction than placebo on a 0–10 scale (p=0.0007), with a reported standardised effect-size magnitude of 0.708 in favour of iPPS.

The trial met its interim futility criteria and the overall interim result did not meet the threshold required for continuation. Following that result, Company management immediately initiated a review of the available data, both overall and by region, to understand the outcome and determine whether it was consistent across the trial.

The review identified a marked difference between the US and ROW results. The US dataset contained substantial missing assessments and dosing interruptions, including missed doses associated with specialist laboratory delays. Missing assessments required statistical imputation, meaning replacement values were assigned or returned to baseline under the trial's analysis rules. The US Day 112 pain and function results favoured placebo. In contrast, the ROW analysis favoured iPPS across average daily pain, WOMAC pain, WOMAC physical function and patients' overall assessment of improvement, with statistically significant and clinically meaningful differences on all four measures.

The consistency of the ROW findings across pain, function and patient-reported improvement provides an important basis for assessing the program's development options. The Company is investigating the extent to which operational issues, treatment exposure and missing-data handling contributed to the regional differences, alongside its assessment of a funded path forward.

These findings arise from an internal, post hoc regional analysis of observed data extracted from the electronic data capture (EDC) system as at 30 September 2026. The overall interim futility outcome remains unchanged and as previously announced, the trial will not proceed.

The ROW pain results show a clear difference

The forest plot compares the additional pain reduction with iPPS relative to placebo at each assessment. It puts the ROW and US results side by side so investors can see the direction, size and precision of the treatment differences.

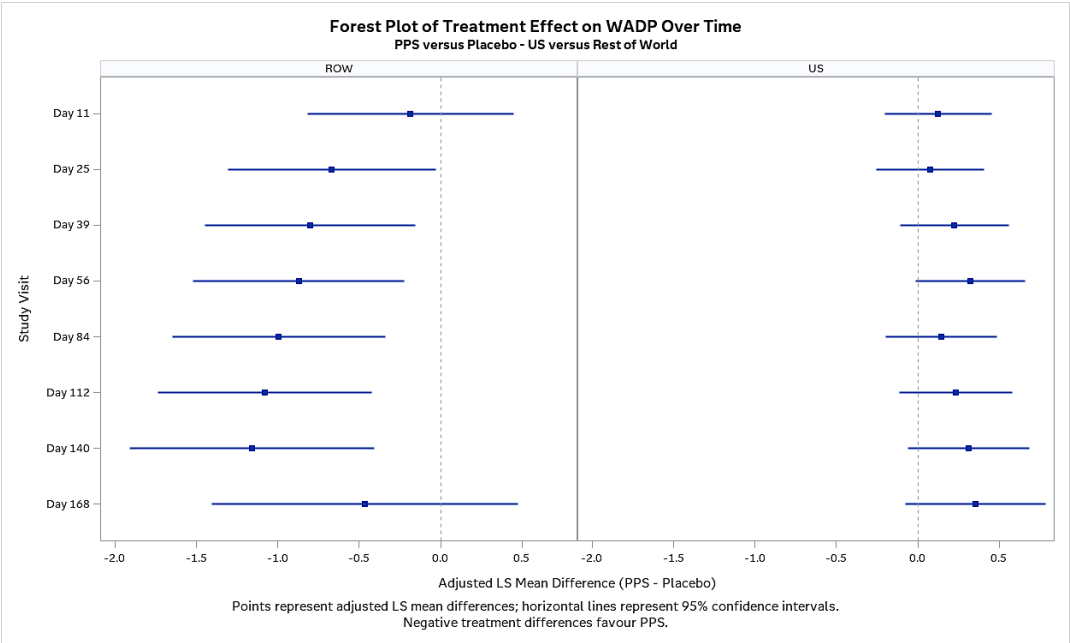

Figure 1. Adjusted wADP treatment differences by region and timepoint, with 95% confidence intervals.

Each point shows the adjusted treatment difference between iPPS and placebo at that timepoint. Points to the left of zero favour iPPS; points to the right favour placebo. The horizontal bars show the 95% confidence intervals. Where an entire bar sits to the left of zero, the comparison shows statistically significant greater pain relief with iPPS.

The ROW results show a sustained benefit in favour of iPPS. Every plotted timepoint favours iPPS, with statistically significant differences from Day 25 through Day 140, including the primary assessment at Day 112. At Day 112, iPPS delivered 1.105 points of additional pain reduction versus placebo on the 0–10 scale, with a 95% confidence interval of 0.476 to 1.733 points in favour of iPPS.

The US results show a different pattern. At Day 112, the treatment difference favours placebo, while the confidence intervals cross zero at every plotted visit, meaning no statistically significant difference between treatments was demonstrated at those visits. The Company's review is examining the reasons for this regional contrast, including operational issues, dosing interruptions and missing-data handling.

The key finding is that the ROW pain benefit was seen across multiple assessments and is supported by improvements in physical function and patients' overall assessment of benefit at Day 112**.** The Administrators understand that the Board considers that these findings support the case for pursuing a funded path for further development of iPPS, subject to the matters described in this announcement.

Primary endpoint measure shows additional pain relief at Day 112

Weekly average daily pain (wADP) measures patients' day-to-day pain on a 0–10 scale. At Day 112, observed assessments were available for 45 ROW participants receiving iPPS and 50 receiving placebo. Adjusted pain reductions were 2.098 points with iPPS and 0.993 points with placebo. The difference was 1.105 points in favour of iPPS (95% CI –1.733 to –0.476; p=0.0007, ES=-0.708).

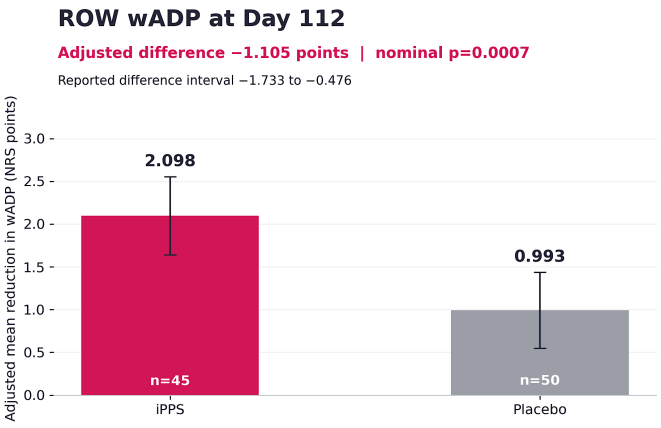

Figure 2. ROW Day 112 wADP: adjusted LS mean changes from baseline, shown as positive reductions. Supplied intervals; n assessed at visit.

The Day 112 comparison (Fig 2) shows the benefit beyond placebo: patients receiving iPPS had approximately 1.1 points more improvement on the 0–10 pain scale. The treatment difference, rather than the improvement in the iPPS group alone, is the key measure of additional benefit.

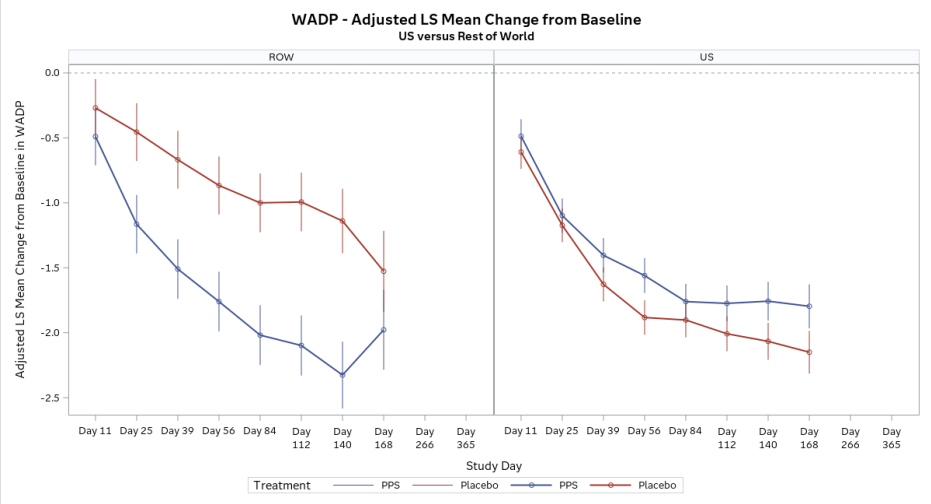

Figure 3. wADP adjusted LS mean change from baseline. Blue: iPPS; red: placebo. More negative values mean greater pain relief. ROW: left; US: right.

The time-course graphs (Fig 3) show how that difference developed. In ROW, the curves separate early, widen towards Day 112 and remain separated at Day 140 before narrowing at Day 168. At Day 168, the ROW analysis included only 25 observed assessments, compared with 95 at Day 112. The treatment difference continued to numerically favour iPPS but narrowed, with a wider confidence interval that included zero. The substantially smaller number of observations limits the precision of this later estimate, and further analysis is needed to establish the reasons for the narrowing. In the US, placebo generally shows greater improvement from Day 39.

Understanding the strength of the ROW pain result

The ROW pain analysis showed a sizeable treatment benefit over placebo, with an effect size of −0.708 and strong statistical evidence supporting the difference (p=0.0007). In practical terms, the treatment group achieved better pain relief, and a result this extreme would be very unusual if there were no genuine treatment difference.

A growing global need for better OA treatments

A 2023 study in The Lancet Rheumatology projects nearly one billion people living with OA by 2050 if current trends continue. This growing burden underscores the need for additional treatments for pain and impaired function, reinforcing the importance of evaluating the potential shown by iPPS[1].

Day 112 findings extend beyond daily pain

Endpoint	iPPS / placebo n	Adjusted difference Reported interval	p-value	Reported effect size
WADP	45 / 50	-1.105 -1.733 to -0.476	0.0007	-0.708
WOMAC function	39 / 46	-1.017 -1.675 to -0.359	0.0026	-0.659
WOMAC pain	39 / 46	-0.821 -1.480 to -0.163	0.0147	-0.532
PGIC	39 / 46	+1.077 +0.366 to +1.788	0.0032	+0.646

Table 1. ROW results at Day 112. Negative differences favour iPPS for pain and function; positive differences favour iPPS for PGIC. Number of participants (N) are observed assessments at the visit. Regional analyses are internal analyses on observed data.

Physical function improved alongside pain

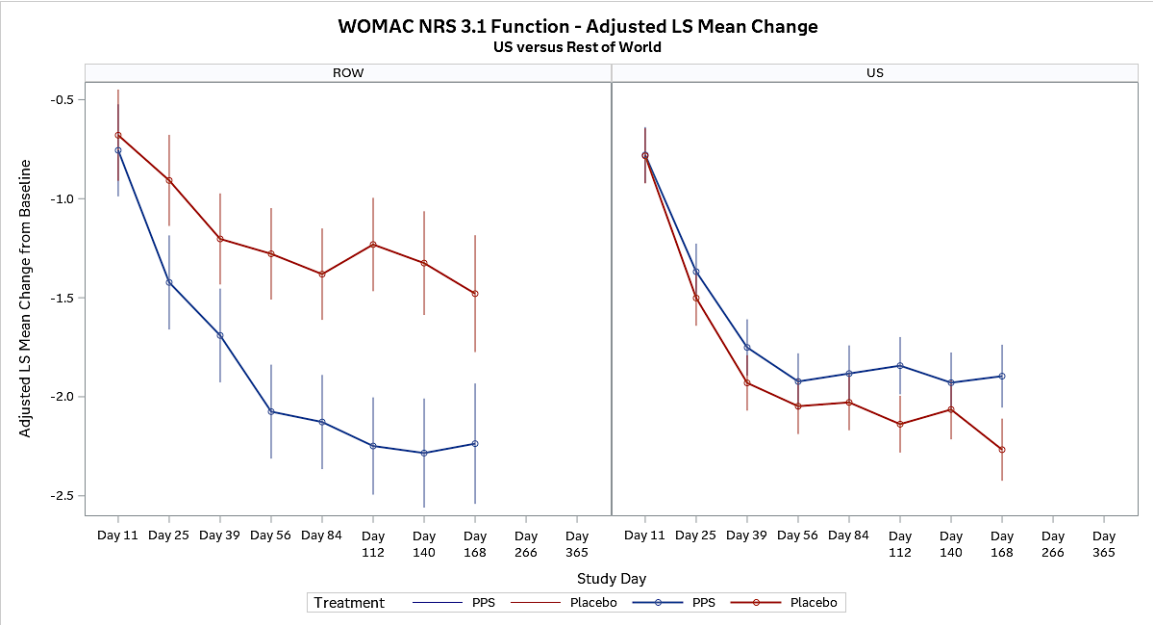

Figure 4. WOMAC function adjusted LS mean change from baseline. Blue: iPPS; red: placebo. More negative values mean greater improvement.

WOMAC function measures difficulty with everyday activities. At Day 112, adjusted ROW improvement was 2.249 points with iPPS versus 1.231 with placebo, an additional 1.017-point improvement (95% CI −1.675 to −0.359; p=0.0026; 39 and 46 observed assessments respectively). The graph (Fig 4) shows a ROW function benefit alongside pain relief; the US results do not show the same advantage at Day 112 (ES=0.169).

A second pain measure supports the daily pain finding

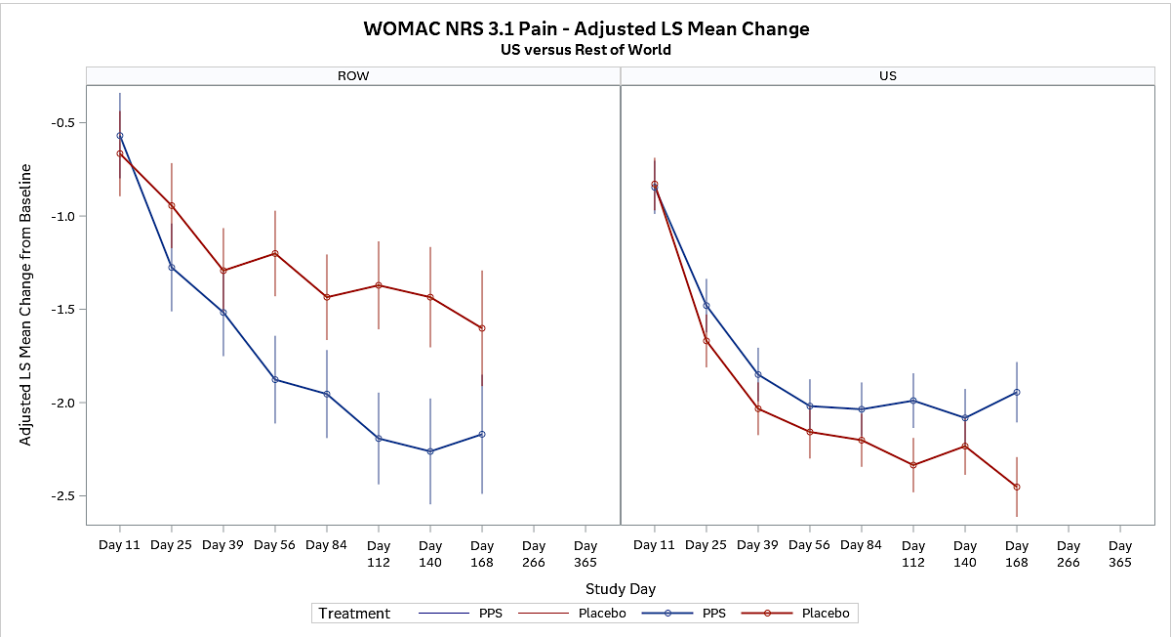

Figure 5. WOMAC pain: adjusted LS mean change from baseline. Blue: iPPS; red: placebo. More negative = more relief.

WOMAC pain captures pain during activities and situations relevant to osteoarthritis. At Day 112, adjusted ROW reductions were 2.192 points with iPPS and 1.371 with placebo. The additional reduction was 0.821 points (95% CI −1.480 to −0.163; p=0.0147; ES = -0.532; 39 and 46 observed assessments respectively). This supports the direction of the wADP finding. The US Day 112 estimate (ES =0.195) favoured placebo.

Patients also reported greater overall improvement

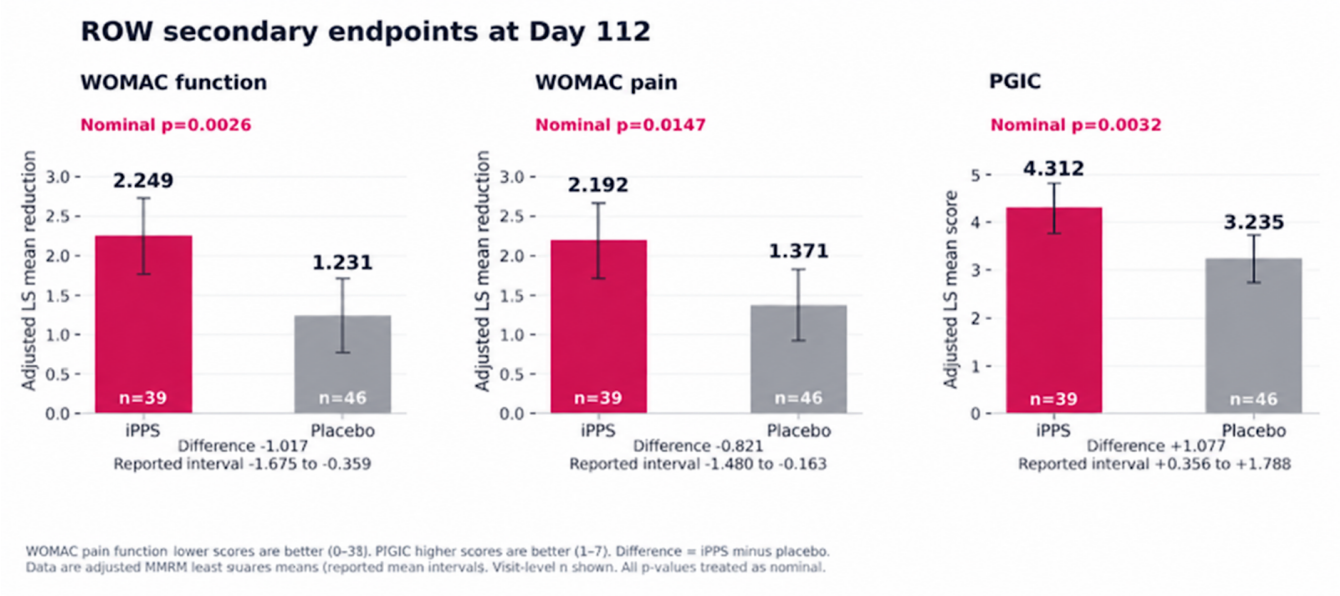

Figure 6. ROW Day 112. Pain/function: adjusted LS mean changes from baseline, shown as positive reductions. PGIC: adjusted LS mean score. Whiskers: supplied model mean intervals.

Patient Global Impression of Change (PGIC) asks patients to assess their overall improvement. Adjusted ROW scores were 4.312 with iPPS versus 3.235 with placebo, a 1.077-point advantage (95% CI 0.366 to 1.788; p=0.0032; 39 and 46 observed assessments respectively). Higher scores on the supplied 1–7 scale indicate greater improvement. Together, the ROW findings connect reduced pain with better function and a stronger patient perception of benefit.

Prior studies show pain benefit across multiple timepoints

The current ROW findings build on earlier pain and patient-reported improvements in PARA_005 and PARA_OA_008. The June 2025 CMO presentation reports positive pain effect sizes at every listed assessment in both studies. In PARA_OA_008, the WOMAC pain effect size was -0.66 at Day 56, -0.46 at Day 112 and -0.74 at Day 365, providing evidence of a sustained treatment difference after the six-week dosing course.

The ROW pain finding is supported by a larger assessed population than the relevant comparison in PARA_OA_008. That earlier study randomised 19 participants to twice-weekly iPPS and 22 to placebo, a total of 41. Its separate once-weekly arm is excluded from this comparison because the twice-weekly regimen was taken forward into Phase 3. The current ROW analysis has Day 112 pain assessments from 95 participants: 45 receiving iPPS and 50 placebo, more than twice that earlier randomised comparison population.

Pain assessment	PARA_005 effect size (WOMAC Pain)	PARA_OA_008 effect size (WOMAC Pain)	PARA_OA_012 effect size ROW	
			WOMAC Pain	wADP
Day 39	-0.33	-0.38	--0.135	-0.525
Day 56 (Day 53 for 005)	-0.25	-0.66	--0.41	-0.562
Day 112 (Day 109 for 005)	-0.20	-0.46	-0.532	-0.708

Pain assessment	PARA_005 effect size (WOMAC Pain)	PARA_OA_008 effect size (WOMAC Pain)	PARA_OA_012 effect size ROW	
			WOMAC Pain	wADP
Day 168 (Day 165 for 005)	-0.28	-0.26	Not Reported	0.412
Day 365	Not reported	-0.74	Not reported	Not reported

Table 2. Reported pain effect sizes from the June 30, 2025, Phase 3 Clinical Trial Webinar Presentation. Negative value favours iPPS over placebo.

Patient-reported and functional outcomes add to the pain evidence

Study and assessment	Reported result	p-value
005 | PGIC Day 56	4.42 with iPPS versus 3.42 with placebo; difference 1.0 (95% CI 0.24–1.8).	0.0106
008 | WOMAC Pain Day 56	Pain reduction approximately 50% versus 30%; function improvement approximately 50% versus 25%.	Pain 0.05 Function 0.017
008 | PGIC Day 112	4.07 with twice-weekly iPPS versus 3.10 with placebo; descriptive difference 0.97.	0.078
008 | PGIC Day 365	3.55 with iPPS versus 2.06 with placebo; descriptive difference 1.49.	0.005

The recurring pattern of pain relief and patient-reported benefit is relevant to any assessment of whether continued development is warranted. The current ROW Day 112 effect-size magnitude is -0.708.

Understanding the US outcome is the next critical step

At the interim analysis, 97 of 277 participants had missing Day 112 wADP data. Of those 97, 91 were in the US and six in ROW. This concentration made the US operational and data review central to understanding the trial outcome.

The review separated missed doses, missing pain assessments and statistical handling of unavailable assessments. Specialist laboratory delays appear to have contributed to missed US doses. The findings may inform any future development plan, regulatory discussions and the design of future trials.

Imputation assigns a value when an assessment cannot be used. Carrying baseline forward assigns no improvement. Missed doses instead affect treatment exposure. Each issue's impact depends on the patients affected, their treatment allocation and the analysis rules.

Reviews examined laboratory delays, dosing, diary completion, site follow-up, monitoring and sponsor oversight.

US observed-data results did not show an iPPS advantage at Day 112 (wADP p=0.1933; function p=0.1188; WOMAC pain p=0.0728; PGIC p=0.8216). Imputation alone cannot be

assumed to explain the regional difference, and the review is assessing whether operational factors may also have contributed.

Administration process and proposal from former Board

The Administrators understand that the Board is finalising a proposal to preserve iPPS and establish a funded path forward, which may combine clinical development, regulatory engagement, funding and restructuring options. Any proposal received will be assessed by the Administrators in the interests of creditors as a whole, alongside other options available in the administration. There is no certainty that any proposal will be received or accepted, that funding will be obtained or that further development of iPPS will proceed.

The Company expects to update the market on the data in the coming weeks and provide further details of the Board proposal when available. Progress will depend on the proposal being finalised, funding, applicable approvals and the administration process.

The Company's securities remain suspended from trading.

-ENDS-

Forward-Looking Statements and Disclaimer

The analysis was prepared by Company management and its clinical advisers. The Administrators have not independently verified the data or the analysis and make no representation as to their accuracy or completeness. The Administrators are releasing this information to keep the market informed.

Authorised for release by the Voluntary Administrators*.

References

1. GBD 2021 Osteoarthritis Collaborators (2023). Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet Rheumatology*, 5, e508–e522.

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*Christopher Pattinson and Hayden White of FTI Consulting were appointed as joint and several voluntary administrators of Paradigm Biopharmaceuticals Limited (Administrators Appointed) ACN 169 346 963 on 29 September 2026.