Paradigm Biopharmaceuticals (ASX: PAR) – Desk Note

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Zilosul Approaches Its First Phase 3 Read Out

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Company Snapshot

Company	Paradigm Biopharmaceuticals Limited (ASX: PAR)
Lead asset	Zilosul, injectable pentosan polysulfate sodium (iPPS).
Lead indication	Pain associated with knee osteoarthritis, Phase 3.
Shares on issue	606.8m
Share Price (Close 25 Aug 2026)	$0.225
Market Cap	$136.5m
Pro Forma Cash	$25.7m

Table 1: Cash of A$15.37m at 30 June 2026, plus A$5.69m of tax refunds received July 2026 and the A$4.6m Tranche 4 convertible note drawdown completed 13 July 2026

More than 500 million people live with osteoarthritis, yet treatment still largely comes down to managing pain until the joint becomes bad enough to replace. Paradigm's (PAR) work centres on Zilosul, an injectable drug for conditions where inflammation is a major driver. The lead program treats pain from knee osteoarthritis and is in Phase 3, the final and largest stage of human testing before a marketing application.

Osteoarthritis treatment remains largely focused on managing symptoms, and there are no approved disease modifying osteoarthritis therapies available today. Many patients cycle through painkillers, anti inflammatory drugs and injections into the joint before ending up in joint replacement surgery.

Safety Review Complete

On 13 August 2026 Paradigm reported that the independent Data Safety Monitoring Board, the outside committee that watches participant safety and trial integrity, had completed its planned review of safety data from approximately 80% of participants who had finished dosing at Day 39, and had recommended the trial continue without modification.

Paradigm reaffirmed that the interim analysis remains on track for September 2026 and that it will assess the treatment effect on the primary pain endpoint at Day 112. With the recommendation to continue unchanged the focus now turns to the September interim analysis.

Trial Design

Enrolment itself finished earlier this year. On 15 June 2026 Paradigm confirmed that 538 participants had commenced treatment, above the original target of 466, with the overshoot reflecting participants already progressing through screening when the target was reached. The study runs across 65 clinical sites in Australia, the United States, Hong Kong and Moldova.

PARA_OA_012 is randomised, double blind and placebo controlled, with participants allocated one to one to Zilosul or placebo over a six week treatment period. The primary endpoint is the change in pain intensity at Day 112, measured as the weekly average of daily pain scores.

One design point deserves flagging, because it is where osteoarthritis trials most often come unstuck. Paradigm uses the weekly average of daily pain recordings as the primary endpoint rather than a retrospective questionnaire, which aims to capture real time pain and reduces recall bias, with the

WOMAC questionnaire retained as a secondary measure. These refinements are intended to strengthen the ability to detect a real treatment effect while managing placebo response, a recognised challenge in osteoarthritis trials.

Next Steps

Paradigm has set out the sequence from here:

- Database lock and associated data preparation during August 2026.
- Independent DSMB meeting to review the interim analysis dataset targeted for September 2026, with the outcome and recommendation to be communicated to the market.
- Three possible outcomes from that meeting: continuation of the study as planned, early efficacy if the pre specified statistical threshold is achieved, or early termination for futility, meaning the trial is stopped because the drug is unlikely to show a benefit.
- Top line primary endpoint results are anticipated in the first quarter of calendar 2027.
- Continued regulatory and New Drug Application planning, manufacturing and commercial readiness activities.

During the June quarter Paradigm raised approximately A$21.38 million through a A$14.0 million institutional placement at A$0.19 per share and a A$7.38 million Share Purchase Plan at A$0.17 per share.

PAR's Phase Two Trial

PARA_OA_008 was a phase 2, randomised, double-blind, placebo-controlled trial in 61 people with moderate to severe knee osteoarthritis, split evenly between twice-weekly iPPS, once-weekly iPPS and placebo, given as injections under the skin for 39 days and followed for a year.

What it set out to measure was not pain but chemical markers in the fluid inside the knee at Day 56, with pain and function scores treated as secondary measures.

On the markers, a sign of cartilage breakdown in the joint fluid called ARGS fell significantly against placebo at Day 56 and again at Day 168, and a bone turnover marker in the blood rose significantly at both points, though most other markers moved in the expected direction without reaching significance.

On pain, the iPPS groups combined did not beat placebo at any timepoint, and the improvements came from the twice-weekly group, which was significant on WOMAC pain at Day 56 but not at Day 168 or Day 365.

Why Phase 3 Could Succeed on Pain Where Phase 2 Did Not

Dose: Phase 2 ran three arms and only twice-weekly worked. Once-weekly performed worse than placebo on WOMAC pain at Day 56 and never showed benefit at Day 168 or Day 365. Pooling the two dropped the treatment difference to essentially zero, which is why the headline Phase 2 pain result was negative. Phase 3 uses twice-weekly 2 mg/kg only, so the dilution is gone.

In the twice weekly arm there was a 20 percentage point advantage over placebo on WOMAC pain at Day 56, significantly better function and patient global impression at Day 365, and placebo patients consumed roughly nine times as much paracetamol.

Measurement: Phase 2 used WOMAC at scheduled visits. Phase 3 uses the weekly average of daily recordings as its primary, which averages out noise that a single recall-based snapshot carries.

The placebo arm no longer gets a knee procedure. Placebo participants received saline washing of the knee at each timepoint to obtain fluid samples, it's plausible the wash itself produced therapeutic benefit. Phase 3 does no synovial sampling, so the placebo arm receives only injections under the skin.

Recent Osteoarthritis Trial Outcomes

Three competitor events this year have reframed how the market should read Paradigm's September interim analysis, and two of them are cautionary.

Cynata Therapeutics

First, on 19 June 2026 Cynata Therapeutics (ASX: CYP) reported that its Phase 3 SCUlpTOR trial of CYP-004 in knee osteoarthritis missed both co-primary endpoints, with no statistical separation from placebo on either pain or cartilage loss. On the pain measure, 51.7% of treated patients reached the acceptable symptom threshold at 24 months against 48.1% on saline placebo, a p-value of 0.5907, and cartilage thickness loss was 0.27mm in the treated arm against 0.21mm on placebo.

The failure mechanism is what matters for Paradigm. Cynata had assumed 35% of placebo patients would reach the pain threshold and almost 50% did, so even a 26.8 point improvement out of 100 in the treated arm could not separate from 25.3 points in the placebo arm.

Three differences are worth holding in mind. Cynata injected its product into the joint against a saline injection control, whereas Paradigm gives Zilosul under the skin. Cynata's pain endpoint was the proportion of patients reaching a Patient-Acceptable Symptom State, defined as a pain score of 32 or less out of 100 on a single rating scale completed at scheduled visits every three months, rather than daily recording. PARA_OA_012 was designed with placebo response specifically in mind, using daily pain recording rather than a retrospective questionnaire, with WOMAC retained only as a secondary measure.

Kolon TissueGene

Second, on 20 July 2026 Kolon TissueGene reported that TG-C, a cell and gene therapy injected into the knee, missed both co-primary endpoints and every key secondary endpoint in its ACTiVION-II Phase 3 trial of 531 patients across 27 United States sites. Results from the second Phase 3 trial, ACTiVION-I, are expected in October 2026 and represent the last realistic route to a United States approval pathway for the program.

Biosplice Therapeutics

Third, and a success story, Biosplice Therapeutics submitted a New Drug Application to the United States FDA on 6 January 2026 for lorecivivint, a small molecule injected into the knee once or twice a year. Biosplice describes it as the first candidate with disease modifying potential for osteoarthritis to be submitted for approval, supported by improvements in pain, function and medial joint space width on imaging across its Phase 3 program. Biosplice is privately held, so it does not appear in the peer table below, but an approval would make it the first potential disease-modifying OA drug on the market and would set the regulatory precedent Paradigm is aiming at.

Upcoming Catalysts

Catalyst	Expected timing	Significance
Interim analysis outcome and independent DSMB review	September 2026	First Phase 3 read on the treatment effect on pain at Day 112. Can continue, stop early for efficacy, or stop for futility.
Expiry of PAROB attaching options	Earlier of 1 December 2026 or 20 business days after announcement of the interim analysis results	Up to approximately A$28 million of potential funding, tied to the interim result.
Top line Phase 3 primary endpoint results	Q1 CY2027	Full efficacy and safety readout across the 538 treated participants, underpinning any New Drug Application.
Publication of the PARA_OA_008 MRI structural data manuscript	Timing to be advised once the journal review process progresses	Adds imaging evidence to the disease modification argument.
City St George's, University of London research collaboration	About 12 months from 2 April 2026	Investigates the effect of PPS on bone marrow lesions, linked to osteoarthritis pain.

Table 2. Indicative timing only. Events may be delayed, modified or may not occur.

Peer Comparisons

The table below sets out listed companies developing therapies for osteoarthritis. United States dollar figures are converted at AUD/USD 0.7171, KRW/AUD 0.0010.

Eupraxia has completed Phase 2b and is seeking funding or a partner for the late phase program. Organogenesis is inside the regulatory process, with a Biologics License Application accepted for ReNu and a target decision date of 24 April 2027. Anika is the commercial benchmark, selling hyaluronic acid injections for osteoarthritis pain and working toward a United States filing for Cingal. Biosplice, which has the most advanced filing, is private and cannot be included.

One competitive dynamic sits outside this table. The STEP 9 trial found that once weekly semaglutide reduced knee osteoarthritis pain and improved physical function in people with obesity, alongside weight loss, and a study published on 2 June 2026 linked use of any GLP-1 drug to a reduced likelihood of knee replacement over eight years.

Company (Ticker)	Lead Asset, Indication and Delivery	Clinical Stage	Market capitalisation (AUD, m)
Kolon TissueGene (KOSDAQ: 950160)	TG-C, a cell and gene therapy for knee osteoarthritis, injected into the joint	Phase 3. ACTiVION-II failed Jul 2026, ACTiVION-I due Oct 2026	$1,695.7
Eupraxia Pharmaceuticals (NASDAQ: EPRX)	EP-104IAR, a slow-release steroid for knee osteoarthritis pain, injected into the joint. Phase 2b met its primary and three of four secondary endpoints	Phase 2b complete Seeking funding or a partner for late phase	$670.8
Anika Therapeutics (NASDAQ: ANIK)	Monovisc and Orthovisc hyaluronic acid injections for osteoarthritis pain, injected into the joint. Cingal outside the United States	Commercial. Cingal in US filing prep	$396.0
Organogenesis Holdings (NASDAQ: ORGO)	ReNu, an amniotic tissue suspension for knee osteoarthritis pain, injected into the joint	Under FDA review. Decision target 24 Apr 2027	$299.7
Paradigm Biopharmaceuticals (ASX: PAR)	Zilosul (iPPS) for pain in knee osteoarthritis, injected under the skin	Phase 3. Interim analysis Sept 2026	$136.5

Table 3. Source: Iress as of 25 Aug 2026

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