COMPANY UPDATE

SA | Level 6, 121 King William Street
Adelaide SA 5000 | P +61 (0)8 8236 8888
QLD | Level 2, Building A, 6 Innovation Parkway
Birtinya QLD 4575 | P +61 (0)7 5329 4122
ABN 92 006 690 320 AFSL 246735

PARADIGM BIOPHARMACEUTICALS LTD (ASX:PAR)

Investigative New Drug (IND) update

We are pleased to provide the most recent market update from **Paradigm**, including questions and answers from their presentation (*watch it* **here**).

Paradigm CEO, Paul Rennie, and Paradigm management have provided a thorough update which we believe encapsulates the company's current state of affairs. In addition, we encourage the reader to view both our **Paradigm research report** and previous **market update**.

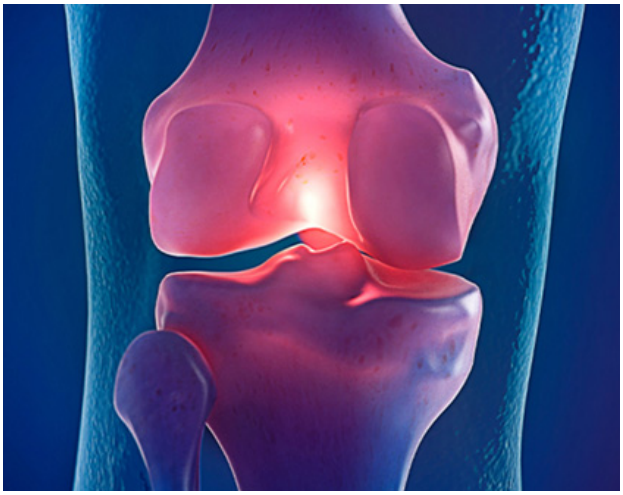
The FDA has one question remaining to be answered by Paradigm (of the six questions previously submitted). The remaining question pertains to good laboratory practice (GLP), and pre-clinical studies completed in rats.

Paul Rennie stated on August 3, 2021, ''We are very confident, very confident we can respond within the month''.

The response will include clarification on the non-clinical finding and the mitigation plan in the protocol.

The good news is Paradigm is very close to IND approval (as Paul states above), however, there remains uncertainty around when the company can expect to be given the green light. Based on the timeline of events (below), we are confident that, providing the company provides the FDA's required information within the month, we can expect to know the outcome by October 3, 2021 (no later than 30 days from submission to the FDA).

We acknowledge there are many questions surrounding what another delay of this nature means for the company. Rather than speculate, we have included detailed information below about how the timeline may be impacted, and at what cost. Paradigm has stated that once they receive IND approval they will be in a position to update the market more specifically.



Whilst any delay is not ideal, we maintain that Paradigm remains on course to unlock Pentosan Polysulfate Sodium (PPS) as a front line, first in class, blockbuster drug. As our research report states, Paradigm is on a multi-year journey, and we look forward to further updates.

Understanding Paradigm's current state of operations - knee Osteoarthritis

Paradigm states that it is common practice for the FDA to be incredibly thorough, considering the impact a new drug of this nature could have on such a large patient population, and admits the process has been slow due to changes in communication with the FDA - mostly due to COVID-19.

Australia

1. Eight sites have been selected.
2. Protocol has received ethics approval.
3. Paradigm has began contracting sites in WA, Victoria, NSW, SA and QLD.
4. Screening of participants in the study to commence in Q4.
5. Lead investigator confirmed.

Europe

1. Six sites to be initiated.
2. Paradigm is finalising discussions with the lead investigator.

United States

1. Approximately 56 sites have been selected.
2. Meeting with clinical and non-clinical experts to respond to the FDA's outstanding question.
3. Lead investigator confirmed.

Current trials

PARA_OA_008 – Australia

1. Biomarker study assessing the change from baseline in multiple objective measures associated with disease progression of osteoarthritis (OA) . Will allow the ability to explore the relationship between biomarkers and clinical endpoints in OA.
2. Study is currently underway at one site in Box Hill, Victoria.
3. Study will randomise 60 participants to receive PPS or placebo.
4. To date the exploratory clinical trial is 50% recruited.

MPS 1 – Australia

1. Open label trial currently enrolling up to 10 subjects. Dosed weekly for 12 weeks then every other week for a total of 52 weeks.
2. Being conducted at the Women's & Children's Hospital, Adelaide, South Australia.
3. Primary endpoint is safety, key secondary endpoints are pain and function, as well as pharmacokinetics.
4. Three subjects currently in treatment: enrolment of additional patients ongoing.
5. PPS has been well tolerated in this trial.

MPS VI – Brazil

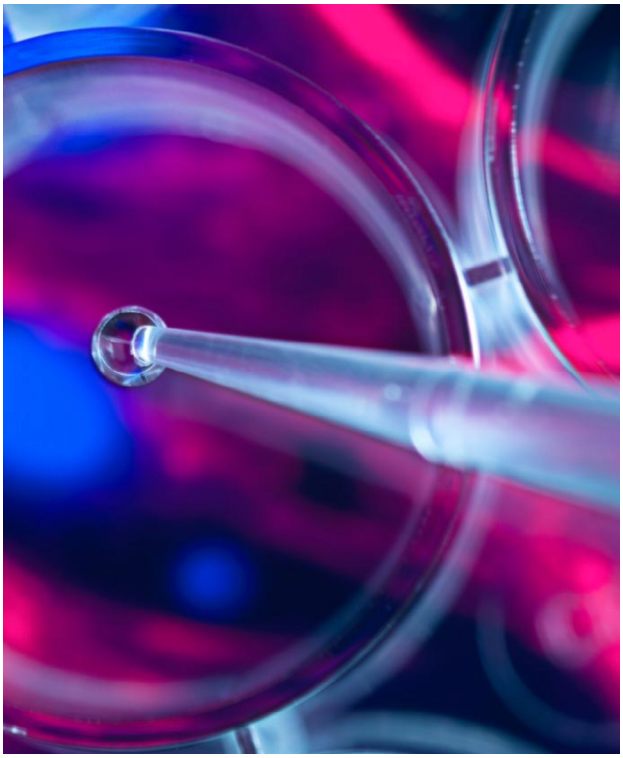
1. A double- blind placebo-controlled trial with 12 subjects. Dosed weekly for 24 weeks.
2. Primary endpoint is safety, key secondary endpoints are pain and function.
3. The Brazilian regulatory agency, ANVISA, and Brazilian ethics committee CONEP have approved Paradigm's clinical program and study endpoints.
4. Program update Q3 2021.

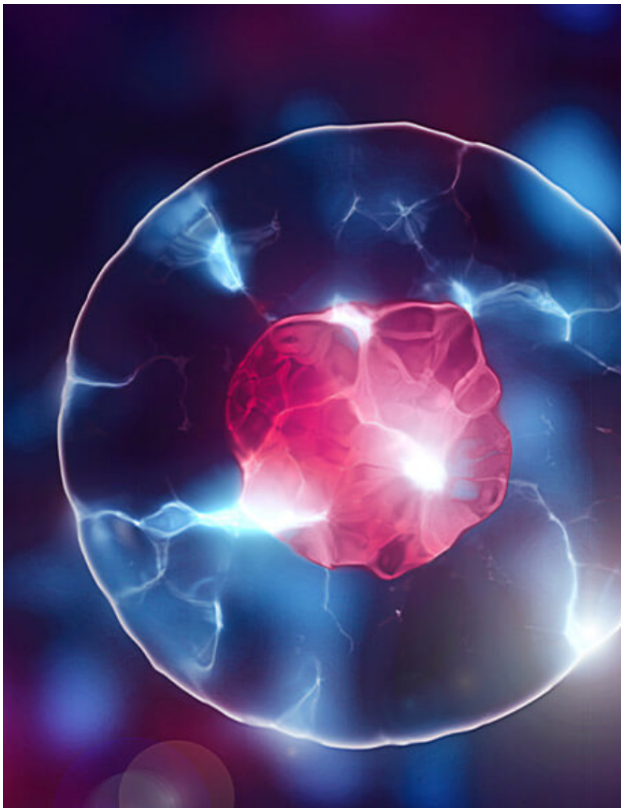
Future iPPS indications

Paradigm has other ongoing exploratory pre-clinical work and proof-of-concept work for future iPPS indications in ARDS and heart failure. Paradigm will continue to widen the pipeline looking for other indications for PPS as the company moves forward with OA.

Timeline of events

- After the pre IND meeting with the FDA (Feb 2020), the company then conducted 26 additional non-clinical evaluations, to provide toxicology profile for the injectable PPS formulation. Prior profiles submitted were for oral administration.
- **September 20, 2020** feedback from the European Medicines Agency (EMA) confirms clinical trial design to be acceptable.
- **December 20, 2020** clinical trial design was submitted to the FDA through a Type C meeting, receiving confirmation the FDA understood their view on the primary endpoint, patient population, statistical analysis plan and safety population, therefore allowing Paradigm to acquire all clinical information for the IND submission in 2021.
- **March 26, 2021** Paradigm submitted an IND application to the FDA (response due from the FDA within 30 days).
- **April 25, 2021** Paradigm advised the FDA will require an additional 30-days to submit questions to Paradigm.
- **May 25, 2021** Paradigm receives FDA questions (Paradigm received six questions from the agency principally relating to recently completed non-clinical studies). As stated, there were 26 non-clinical studies in the IND designed to answer general and specific questions based on the toxicity profile, as much as can be gained, from animal studies. The IND contained a substantial amount of new, non-clinical information.
- **June 30, 2021** Paradigm submits response to FDA questions (FDA had 30 days to review Paradigm's responses to their questions).
- **July 30, 2021** Paradigm received a written response from the FDA accepting answers to five of the six questions received.





Q & A

Q ***How does the FDA response influence the clinical timeline?***

A The review process from the FDA is longer than we originally anticipated or would have liked to have experienced, and it will pose a slight delay in the overall clinical program timelines. We are working to find ways to reduce the timeline and an update will be provided to the market at the time when we have worked out the overall strategy to reduce the overall program time. That may include additional site initiation. It also includes moving forward with initiation of participant activity in Australia and Europe, while we clear this one remaining issue with the FDA.

Q ***What impact does the FDA response have on Paradigm's cash position?***

A We currently have A$71m cash on hand as at June 30, 2021. This is sufficient capital to continue to progress the OA phase 3 pivotal, and PARA_OA_008 clinical trials, the MPS clinical studies, and the pipeline research for potentially using iPPS in indications for Acute Respiratory Disease and Chronic Heart Failure. Once we have finalised this process with the FDA the company will have a clearer view on the financial impact of the clinical program and will update the market as required.

Q ***Is the focus on the rat GLP study a normal part of the process, or are there any other reasons why the FDA would be quite particular on this issue.***

A The non-clinical study requirements are that we look at more than one species. One of those species is almost always a rodent, and for our studies we used rats. I'd like to stress the question that is outstanding with the FDA is for further clarification regarding a tissue finding in one organ, without associated clinical side effects in the rats and no deaths in the study. Additionally, there were no similar findings noted in dogs that were part of the non-clinical study program. In our clinical experience, which consists of approximately 600 clinical subjects, there are no suggestions of any impact of these findings in the clinic. While we need to provide the clarification that the FDA is asking for regarding this finding, we don't expect this to be of clinical significance and we also understand the best evidence of understanding if something is clinically significant is to monitor it carefully in the clinical program. The discussion around the significance in the rat, as well as the mitigation in the clinical program on the topic of the response, will be provided to the agency within the next 30 days.

Q ***Paradigm stated it had several experts review and assist with the previous response to the FDA. Why is the company confident the response this time around will be received more positively?***

A The responses submitted previously to the FDA were received positively. I mentioned we responded to six questions, and only one question has come back with further clarification. We have convened our panel of experts to assure that we provide the FDA with all of the evidence they need to understand the lack of significance of this tissue finding, and our ability to very thoroughly mitigate for such a finding in the clinic. Given our experience to date with 26 non-clinical studies, six prior questions are now coming down to a clarification around one of these studies, and we feel confident that we have provided all the information to the FDA that is needed to understand how PPS works, not only from a toxicology aspect in animals, but also in humans based on a pharmacokinetics recently conducted this year in humans. This aggregate information is in the IND and will also be included in our response to the FDA. We do believe that this will provide the final clarification that the FDA needs in order to give us clearance to proceed.

Q ***Has Paradigm considered seeking advice from an additional independent consultant to review the remaining question to see if they can shed any further light on the issue?***

A Yes, I mentioned we've previously worked with a panel of experts not only from the clinical side but also from a non-clinical side. We have expanded that panel to include some very well acknowledged experts in the field including individuals with former and current FDA relationships. That is often very insightful when it is time to put our responses together so that they are not only valid scientifically but also from the regulatory perspective presented in a way the FDA understands our intent, and our plans for the clinical trial.

Q ***Is there a risk that the FDA could require more testing if they are not satisfied with Paradigm's response?***

A I think the risk of them requesting more non-clinical work before going into the clinic is extremely unlikely. I mentioned a couple of times, we have done a large number of studies in two species looking at everything they've asked for (the portfolio of injectable PPS), so we fully expect that the questions that we have will be answered by the existing non-clinical work. We need to provide this information to the FDA in such a way that it's very clear to them that the answers they are looking for are in the data that already exists.

Q ***Have agreements been made, or put in place, for clinical research organisations in Europe and in Australia?***

A Yes, a lot of activity has been going on prior to the IND submission. We have selected and are in contact with a clinical research organisation that has been working with us for several months to identify sites and site feasibility. We have established our relationship with a statistical group that is working with us to improve the databases that will be required for the study, and the randomisation scheme. All of this background work has been done so that when we receive clearance from the FDA we will move quickly into the active site that will allow for involvement of patients. Preparation for patient enrolment has been performed simultaneously across the U.S., Australia and Europe.

Q ***When is the company likely to partner with knee OA?***

A Our immediate goal is to get the IND open, and we think the number of pharma companies we have had discussions with thus far will turn their attention to a more intense discussion when the IND is open. We have one partnering discussion later this week, and our position will be to have the IND open first. I think potential partners will want to see the IND open as well. We've been open and transparent with potential partners to date, explaining this process. We have one final question, once that's resolved and the IND is open then we believe potential partners will be more willing to talk to us in more specific detail. It's on our agenda and we do have pharma companies which have expressed interest. As I said, we are waiting for the IND to be open to demonstrate we have clearance through the FDA and clearance in Australia and Europe. I think this will be a very significant position for the company to be in, and certainly increase the value of the asset.

Disclosures

Baker Young acted as Co-Lead to the company's capital raise in April 2020 and received fees for that service. • Baker Young, its employees, consultants, and associates within the meaning of Chapter 7 of the Corporations Law may receive commissions, underwriting, and management fees from transactions involving securities referred to in this document (which its representatives may directly share) and may from time to time hold interests in the securities referred to in this document. At the time of publication, Baker Young, its Directors and related parties (including immediate family), employees and consultants held positions (including Principal) in Paradigm Biopharmaceuticals (PAR.ASX) consisting of shares, options, or both. The analyst responsible for preparing this report holds an immaterial interest in the security at the time of publication which may change throughout the lifetime of this document.