PARADIGM BIOPHARMACEUTICALS LIMITED

ASX RELEASE 6 April 2020

PARADIGM (PAR) RECEIVES CLARITY ON US REGULATORY PATHWAY

KEY HIGHLIGHTS FROM MEETING WITH US FDA

- The pre-IND meeting was both positive and informative for Paradigm. The positive outcomes from the meeting were clear guidance around the primary and secondary endpoints for the Phase 3 clinical trial, the number of Phase 3 studies required for registration and overall clarity and guidance over the requirements for the Phase 3 clinical trial design and NDA submission.

- For drug registration, it is typically expected that there be at least two successful Phase 3 trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as **FDA** (USA), or the **EMA** (European Union). The US FDA and EMA, generally require, a minimum of two adequately sized and well-controlled Phase 3 clinical trials. (One trial to investigate the safety and efficacy of the drug and second trial to confirm the results of the first trial (the confirmatory study)). There is a potential exception to this rule under the FDA 505(b)(2) regulatory pathway (Repurposed Drugs) where the sponsor can conduct one adequately sized and controlled Phase 3 and use (or bridge to) published literature to demonstrate or confirm efficacy. Paradigm presented its case to use the FDA 505(b)(2) pathway and conduct one Phase 3 clinical study and use published literature to confirm efficacy. The FDA advised that the literature would not serve as one of the two required efficacy studies. Paradigm's plans are now to conduct two efficacy studies (adequately sized and well-controlled) Phase 3 clinical trials as outlined below.

  ~ 750 patients in 1st Phase 3 trial (Seamless and adaptive Phase 3 clinical study design) 18 - 20 month duration)
  ~ 400 patients in 2nd Phase 3 trial (12-month duration but can be run concurrently).

  With data from both clinical trials being available at the same time Q3 CY2022.

- Under this schedule the additional Phase 3 clinical trial (400 subjects) should not delay the time to registration / first revenues in the USA.

- Paradigm has the potential to concurrently run the two Phase 3 clinical trials so as to optimise the timeline to registration.

- Paradigm now has clarity and certainty to what is required for execution of its Phase 3 clinical trials.

- A further positive outcome of the Pre IND meeting was the clear requirement, by the US FDA, for the bene pharmaChem PPS to be used in non-clinical and clinical studies. Paradigm confirmed all non-clinical, in vitro and all clinical trials were conducted with the bene PPS

product. The FDA noted that the bene PPS was comprised of multiple moieties[1] and those moieties and their levels were understood and acceptable to the US FDA. In contrast "PPS" from other manufacturers could have different levels of moieties and the safety and efficacy of those moieties were not well understood or controlled. A generic PPS could only be approved by the US FDA if the material was proven to be identical in molecular structure and purity to the bene PPS. Given PAR has an exclusive supply agreement in place with bene pharmaChem this puts PAR years ahead of any potential competition. This regulatory exclusivity is an additional level of its competitive advantage over and above Paradigm's granted patents.

- FDA indicated that Paradigm Phase 2b endpoints (pain and function) are appropriate for the Phase 3 clinical trial. In Paradigm's phase 2 clinical trial the primary endpoint was the mean reduction in pain from baseline at Day 53 and improvement in joint function (activities of daily living), bone marrow edema lesion volume, area and grade and biomarkers were evaluated.

- As a result of the meeting with the US FDA it was recommended that prior to US FDA New Drug Application (NDA) that PAR repeat some of the non-clinical toxicology studies under good laboratory practice (GLP) guidelines to bridge to the bene non-clinical data. PAR has already commenced those bridging GLP non-clinical toxicology studies in the USA. These studies will be finalised during 2020 and therefore the data will be available well before the NDA submission. Since the historical non-clinical toxicology studies were conducted (1960's) at a time before GLP guidelines were introduced (1970's) the current studies will be conducted under GLP conditions to consolidate the safety data.

- The US FDA was interested in the durability of the effects of PPS and wanted to understand how the duration of effect would impact possible retreatment cycles. Paradigm advised, that real world data from the SAS patients, suggested a duration of up to 12 months before re-dosing. The Agency requested Paradigm to confirm the durability of effect in one of its planned clinical studies.

- Paradigm intends to address the need for further understanding of dosing (minimum effective dose) and duration of treatment effect through a seamless adaptive Phase 3 clinical trial design. This study will evaluate dosing in an adequate and well controlled clinical trial (phase 2 component) and then will seamlessly move into the evaluation of the efficacy and safety in the phase 3 component. The trial size is expected to be n=750 subjects with dosing evaluation done 3 months or 6 months into the study. The study is expected to take approximately 18 - 20 months to complete.

Paradigm CEO Paul Rennie:
"As a pharmaceutical company having feedback which provides clarity and certainty about the Phase 3 clinical trial design from an agency such as the FDA is a huge milestone for our Company and we are delighted to have arrived at this outcome".

[1] In chemistry, a **moiety** is a specific group of atoms within a molecule that is responsible for characteristic chemical reactions of that molecule.

link to explain chemical moieties: https://www.thoughtco.com/definition-of-moiety-605357

Paradigm is now preparing the necessary documents to submit to the US FDA in Q4 CY 2020 with the expectation of opening its IND with the FDA in Q1 CY 2021.

FOR FURTHER INFORMATION PLEASE CONTACT:

Paul Rennie
Director & CEO
Paradigm Biopharmaceuticals Ltd
Level 2, 517 Flinders Lane, Melb, VIC, 3000, AUSTRALIA
ABN: 94 169 346 963
Web: http://paradigmbiopharma.com/