PARADIGM BIOPHARMACEUTICALS LIMITED

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PARADIGM REPORTS SUCCESSFUL ROSS RIVER PHASE 2A CLINICAL TRIAL.

KEY HIGHLIGHTS

- **Primary end point met in Paradigm's Phase 2a randomised, double-blinded placebo-controlled clinical trial in participants with Ross River virus (RRV).**
- **The secondary end points demonstrated injectable pentosan polysulfate sodium (iPPS) reduced RRV disease symptoms compared to placebo.**
- **At 3 months follow-up 72.7% (8/11) of subjects in the iPPS group showed near remission of symptoms based on Rapid-3 disease assessment in contrast to 14.3% (1/7) in the placebo group.**
- **Current treatments for RRV are pain relief (paracetamol) and anti-inflammatories (NSAID's). No current treatment has been shown to shorten the duration or alter the course of RRV[1].**
- **The RRV clinical data will support discussions with US Department of Defense and pharmaceutical companies with tropical disease programs.**

Paradigm Biopharmaceuticals Ltd (ASX: PAR) Paradigm is pleased to report that it met its primary end point of safety in its Pilot Phase 2a randomised, double-blinded placebo-controlled, multicentre clinical trial in participants with chronic Ross River virus (RRV) induced arthralgia (joint pain or joint stiffness) treated with injectable pentosan polysulfate sodium (iPPS).

Participants with RRV-induced arthralgia treated with iPPS met the aims for the pilot Phase 2a study by demonstrating safety outcomes (primary endpoint) and effects on reduced disease symptoms (secondary endpoint). Five sites in Queensland and Victoria recruited 20 subjects with 18 finally completing treatment and follow up according to the protocol. The recruited RRV subjects have been diagnosed by laboratory tests based on the Australian Government Ross River virus case definition and are those who have progressed from the acute phase of RRV fever (two weeks post infection) with sustained chronic symptoms between 3 to 12 months post-infection. During the onset of the chronic phase these patients have sustained debilitating musculoskeletal pain for which there are no adequate standard of care treatments.

Paradigm's aim was to demonstrate iPPS was safe in subjects with chronic and sustained RRV symptoms (arthralgia or joint pain). Additionally, the clinical trial aim was to obtain signals of efficacy of iPPS with regard to alleviation of disease symptoms. The per protocol population (a total of 18 subjects) in this pilot trial consisted of 11 iPPS treated and 7 placebo treated subjects who had completed the full course of treatment and final follow up.
For complete details of the Phase 2b clinical trial follow the link:
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372925&isReview=true

[1] https://www.racgp.org.au/download/Documents/AFP/2009/August/200908barber.pdf

Primary Endpoint: iPPS demonstrated safety in RRV subjects

The evaluation of the safety and tolerability of subcutaneous pentosan polysulfate sodium (PPS) in subjects with Ross River virus (RRV) induced arthralgia involved physical examination, observations on concomitant medication usage, changes in clinical laboratory findings and changes in vital signs. Paradigm is pleased to report that that the primary end points were achieved since there were no clinically significant differences between iPPS and placebo groups in the safety assessments. There were no serious adverse events.

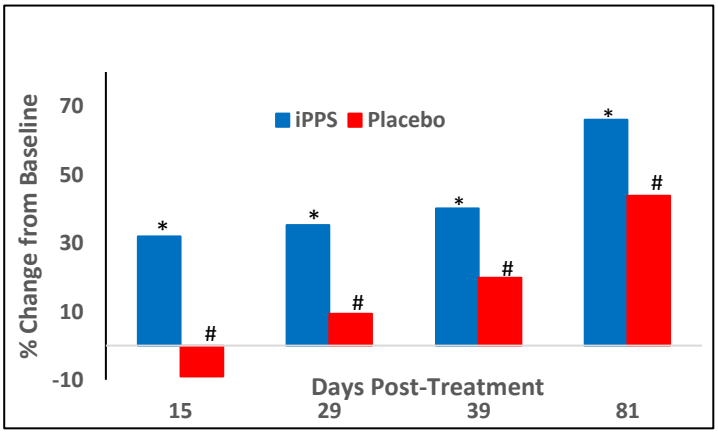
Secondary Endpoint: iPPS demonstrated reduction in RRV disease symptoms

The evaluation of secondary efficacy outcomes in RRV subjects with arthralgia involved assessments of disease symptoms at Day 15, Day 29, Day 39 and Day 81 post-treatment. These included changes from baseline of Quality of Life scores by SF-36 scores; patient questionnaire to assess joint symptoms by RAPID 3 scores and assessment of change from baseline in Hand grip strength scores which is an objective measure of joint function.

Effects of iPPS in Hand Grip Strength:

As shown in Chart 1, in the PPS treated subjects, hand grip strength which measures the maximum isometric strength of the hand and forearm muscles using handgrip dynamometer showed clinically and statistically significant improvements from baseline throughout the study from Day 15 to Day 81. As shown in Chart 1 there were statistically significant differences from baseline at all time points in the iPPS-treated group: 32% at Day 15; 40% at Day 39 and 66% at day 81. In contrast, the placebo group showed a 9% weakening of hand grip at Day 15 which was statistically lower than the iPPS group. Furthermore, the changes in the placebo group did not demonstrate statistically significant improvement from baseline. Moreover, the improvement in Hand Grip Strength[2] in the iPPS group was clinically significant at all time points represented by changes of 5-6.5 kg increase in hand grip from baseline.

Chart 1: Hand Grip Strength (Joint Function)



***** Statistically significant at p<0.05 from baseline; **#** Not significant from baseline

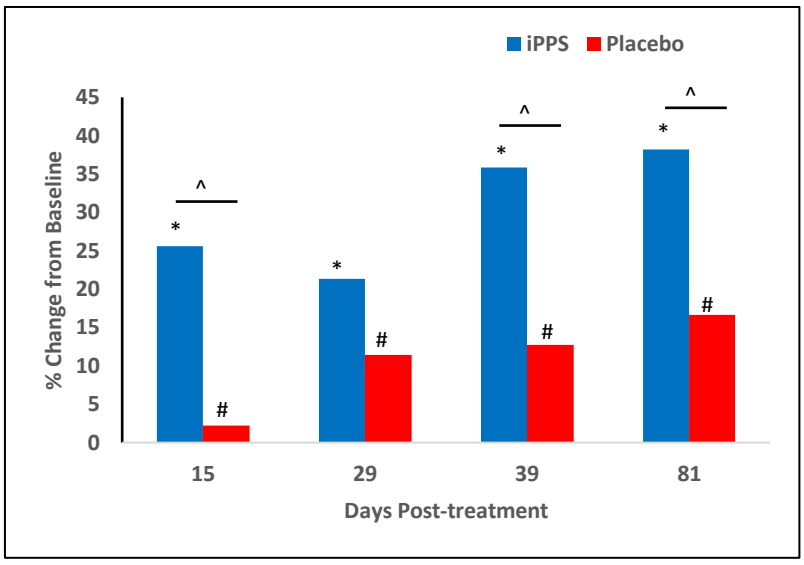
Effects of iPPS in Quality of Life assessment (SF-36):

The Short Form Health Survey SF 36 is a 36-item, patient-reported survey of patient health. The acute, or one week recall form asks the respondent to answer the questions as they pertain to the way he or she felt or acted during the past week. The sections include: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6348186/

As shown in Chart 2, the SF36 total scores[3] showed statistical and clinical significant improvements from baseline at all post-treatment timepoints, peaking at 38.2 % at Day 81. In contrast, placebo treated patients showed lower responses. Statistically significant differences were noted between PPS and Placebo groups at day 15, Day 39 and Day 81.

Chart 2: SF-36 Total (Quality of Life)



***** Statistically significant at p<0.05 from baseline ; **#** Not significant from baseline;

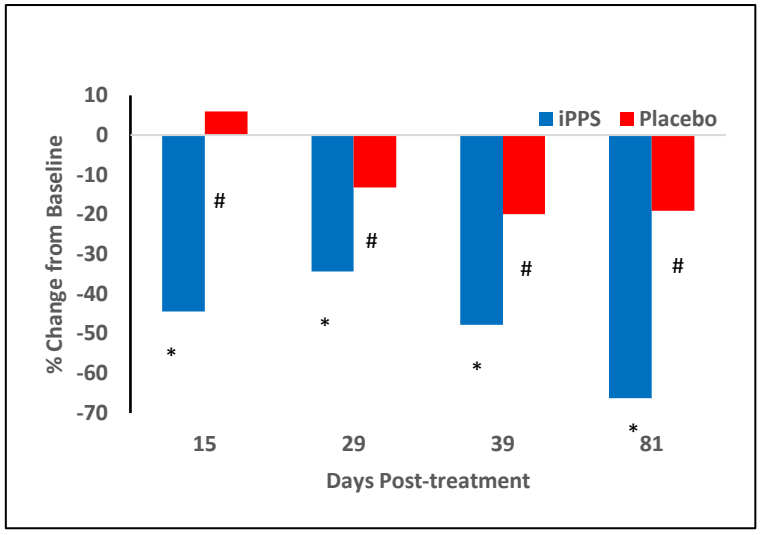
^ Statistically significant between iPPS and Placebo at p<0.05

Effects of iPPS in joint symptoms (RAPID-3)

RAPID3 scores[4] are correlated with clinical disease activity and enable the quantitative monitoring and documenting of improvement or worsening over time. A reduction in Rapid 3 signifies improvement in clinical disease activity. As shown in Chart 3, Rapid 3 total scores consisting of pain and function assessments showed statistical and clinical significant[5] reduction in disease activity from baseline at all post-treatment timepoints in the iPPS group. Statistical significant differences were shown between iPPS and placebo at Day 15 however, the placebo treated subjects showed a lower level of disease reduction compared to the iPPS group throughout the remainder of the treatment period.

[3] https://onlinelibrary.wiley.com/doi/pdf/10.1002/acr.22392
[4] https://www.ncbi.nlm.nih.gov/pubmed/18793006
[5] http://www.jrheum.org/content/early/2018/10/11/jrheum.180153

Chart 3: RAPID-3 Total (Joint Symptoms)



***** Statistically significant at p<0.05 from baseline; **#** Not significant from baseline

Potential effects of iPPS in RRV disease reduction

At baseline 90.9% (10/11) of subjects in the iPPS group and 100% (7/7) of subjects in the placebo group were categorised with clinical disease severity (Rapid-3) ranging from low, moderate and high severity. At follow up at 12 weeks, 72.7% (8/11) subjects in the iPPS group showed near remission in contrast to 14.3% (1/7) subjects in the placebo group.

These positive clinical observations of safety and efficacy of iPPS in chronic sufferers of RRV-induced arthralgia have confirmed preclinical findings and will progress discussions with the US DOD.

Mr. Paul Rennie, Paradigm's Chief Executive Officer said: ***"We are very pleased to see that this small pilot RRV study has yielded very promising safety data and key efficacy outcomes in the reduction of disease symptoms in this debilitating chronic phase of the disease".***
"The human data on the effects of iPPS in RRV induced arthralgia together with our preclinical work on CHIK-V will progress our commercial discussions with US Department of Defense".

About Ross River Virus[1]

Ross River virus (RRV) is a mosquito transmitted alphavirus that causes epidemic polyarthritis and arthralgias, with about half of patients also experiencing fever and rash. It is Australia's most common arbovirus with about 5000 cases notified.

Ross River virus most commonly occurs in adults aged 25–44 years, with males and females equally affected. The incubation period is 7–9 days, with a range of 3–21 days. In the acute phase, functional ability can be significantly impaired, with about half of patients requiring time off work. Joint pain is present in more than 95% of patients, and most commonly involve the fingers, toes, wrists, ankles, knees and elbows. Clinical manifestations of RRV disease could be prolonged, with reports of arthralgias, tiredness and depression persisting years after diagnosis. The disease is associated with significant morbidity during the first few months following diagnosis, with arthralgias more than 3 months after diagnosis in over two-thirds of patients.

No treatment has been shown to shorten the duration or alter the course of RRV. Although, analgesics (aspirin or paracetamol) and NSAIDS are recommended there is limited relief of

symptoms by most patients. There is no evidence to support corticosteroids in RRV fever patients and have not been recommended.

About Chikungunya Virus:
CHIKV is closely related to the Ross River virus (both of the alphavirus genera) and causes similar debilitating symptoms of joint pain, fever, headache, conjunctivitis, and rash. The disease course is divided into an acute stage, lasting approximately one week, and a chronic stage, also known as the persistent stage, which can last from months to years. Acute fever and polyarthralgia are highly indicative of an infection, with arthralgia (joint pain) appearing in 30–90% of cases. This joint pain is often bilateral, symmetric, and debilitating. There are occasional ophthalmic, neurological, and cardiac symptoms[2].

Causing more than 3 million[3] infections worldwide, CHIKV outbreaks have been reported in parts of Africa, Europe, South east Asia, and islands in the Indian and Pacific Oceans. In 2013, CHIKV was found for the first time in the Americas and has spread to the Caribbean, South and Central America and North America[4]. The expanding incidence and the lack of anti-viral agents, vaccines or effective pharmaceutical agents to treat the debilitating effects of CHIKV make iPPS a valuable product for this unmet medical need. In addition, to the clinical data from the RRV Phase2a clinical trial, Paradigm is in collaboration with the Institute of Glycomics at Griffith University to investigate the effects of iPPS in animal models of CHIKV infection which would further support future clinical trial design.

Link to paper demonstrating iPPS effect in RRV and CHIK-V in a preclinical model:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4505659/

About injectable PPS
Injectable PPS is not currently registered in Australia, but it is registered in four of the seven major global pharmaceutical markets. In those European markets, injectable PPS is registered as an antithrombotic agent. In Australia, injectable PPS for human use is not currently available for sale. Injectable PPS for human use is only available by inclusion into a Paradigm Sponsored clinical trial or via a treating physician applying for its use in patients via the TGA's SAS - Category B.

To learn more please visit: www.paradigmbiopharma.com

For more information, please contact

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