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PPS TREATMENT DEMONSTRATES IMPROVEMENT IN HEART FUNCTION AND TISSUE PRESERVATION IN PRECLINICAL HEART FAILURE MODEL

KEY HIGHLIGHTS

- Pentosan polysulfate sodium (**PPS**) treatment demonstrated potential improvement in cardiovascular function and tissue preservation in an industry standard model of heart failure with preserved ejection fraction (**HFpEF**).
- No therapeutics are commercially available for the treatment of HFpEF.
- PPS demonstrated improvement in diastolic function as measured by echocardiography.
- PPS potentially inhibits accumulation of versican cleavage products in the myocardium of ZSF1 obese rats, suggesting a beneficial effect of PPS on the myocardium.
- Paradigm intends to conduct a further preclinical study to confirm these observations and work with key opinion leaders to undertake market analysis to best understand the patient population for clinical translation.

Paradigm Biopharmaceuticals Ltd (ASX: PAR) (Paradigm or the Company), a clinical stage biopharmaceutical company focused on repurposing existing molecules for new indications with unmet clinical needs, is pleased to announce top line summary of results of the actions of PPS in its proof-of-concept heart failure model. The objective of this pilot study was to indicate the effects of PPS on heart function and cardiac extracellular matrix (**ECM**) changes in an animal model of HFpEF. The study was performed by the contract research organisation European Research Biology Center, while quantification of myocardial ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) activity was performed at the Institute for Experimental Medical Research at University of Oslo by lead researcher and cardiologist Dr Maria Vistnes.

The urgent need for novel HFpEF therapies

Heart failure is a clinical syndrome characterised by typical symptoms and signs caused by a structural and/or functional cardiac abnormality that results in reduced cardiac output and/or elevated intracardiac pressures (McDonagh et al, 2021 [1]). Heart failure is classified based on the pumping function of the heart as determined by the ejection fraction (**EF**) by echocardiography. The two subpopulations characterised are heart failure with reduced EF (**HFrEF**) and heart failure with preserved EF (**HFpEF**). Both HFrEF and HFpEF have different disease mechanisms, co-morbidities and response to treatment (McDonagh et al, 2021 [1], Butler et al, 2014 [2]).

While HFrEF is induced by direct and single myocardial insults like infarction or cardiomyopathy, HFpEF develops in response to a combination of risk factors like diabetes, hypertension and obesity (Sweeney et al, 2020 [3]). The prevalence estimates for HFpEF lie in the range from 1 to 3%, and is increasing (Dunlay et al, 2017 [4], Leszek et al, 2020 [5]). HFpEF is associated with high mortality rates of 20-29% annually, and 53-74% in 5 years (Dunlay et al, 2017 [4], Taylor et al, 2019 [6]). Due to the increase in prevalence and limited options for therapy, there is an urgent need for novel and improved treatment strategies for HFpEF patients. Despite a number of therapies having been found to improve patient morbidity and mortality with HFrEF, there are no therapeutics commercially available for the treatment of HFpEF (Mishra and Kass, 2021 [7], Kim and Park, 2021 [8]).

PPS demonstrated potential to improve heart function and reduce the accumulation of versican fragments

Diastolic heart function was improved in PPS-treated compared to vehicle-treated ZSF1 rats (see below for description of the ZSF1 rat model). Diastolic function was assessed by echocardiography by measuring the diastolic tissue velocity (e') alone and in a ratio with blood flow into the left ventricle (E/e'). These parameters reflect changes in the extracellular matrix of the myocardium and are the most commonly used functional parameters to assess cardiac function in HFpEF patients.

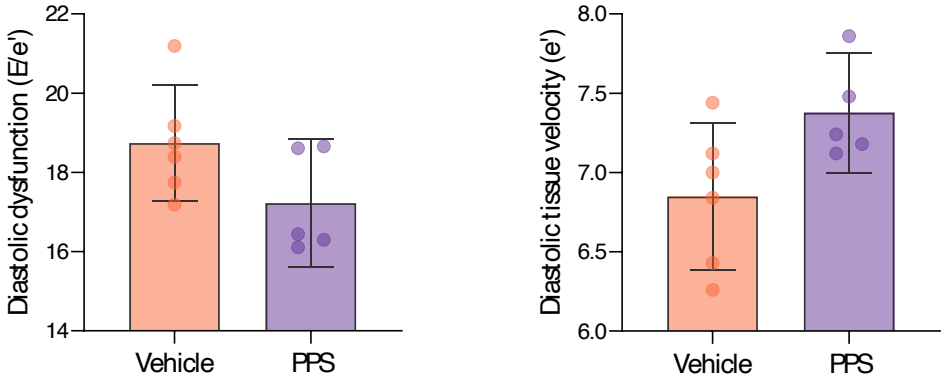
Moreover, the myocardial tissue content of versican, which is degraded to cleavage fragments produced by ADAMTS enzymes were reduced in PPS-treated rats, suggesting a beneficial effect of PPS on the myocardium. This observation is in line with previous studies which demonstrated a reduction in versican fragments upon PPS treatment in a model representing HFrEF (Vistnes et al, 2014 [9]). These promising results with PPS require further confirmation in a larger study in the ZSF1 animal model which evaluates additional biomarkers of inflammation associated with HFpEF.

Principal Investigator and Cardiology researcher at the Institute for Experimental Medical Research at University of Oslo, Dr Maria Vistnes, said: *"The findings in this pilot study in the ZSF1 model of HFpEF are promising data that support the mechanism of action of PPS as an inhibitor of ADAMTS enzymes that cleave the extracellular matrix component versican, which, in turn, drive heart failure development. I'm excited that this pilot study also suggests an improvement in cardiac function by PPS in this state-of-the-art model of HFpEF."*

Top line summary of data

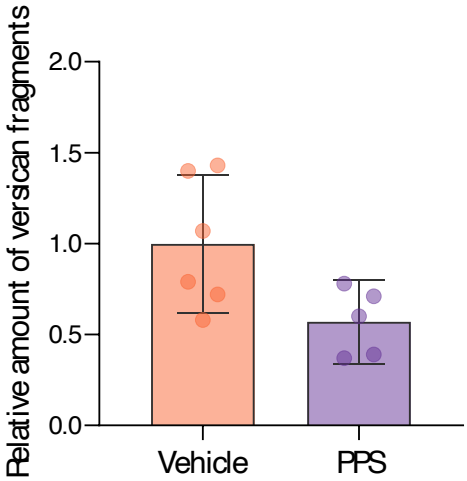
Twelve rats were enrolled in the pilot study, divided into two groups: 1) ZSF1 obese rats receiving PPS at a dose of 9.3 mg/kg once weekly, corresponding to a human equivalent dose of 1.5 mg/kg once weekly, 2) ZSF1 obese rats receiving vehicle (control). The pilot study was powered to detect differences at an α of 10 % (e.g. $p<0.1$). The rats were treated from 14 to 29 weeks of age, and examined by echocardiography and analyses of myocardial samples.

PPS demonstrated trends in improvement in diastolic function as measured by echocardiography.



Bar graphs showing trends of better diastolic function assessed by E/e' (left) and e' (middle) in PPS-treated (purple) than vehicle-treated ZSF1 obese rats (red). Dots indicate individual animals, and error bars indicate 95% confidence intervals. P-values <0.1 by comparison between groups by student t-test.

<u>PPS demonstrated trends in inhibiting accumulation of versican cleavage products in the myocardium of ZSF1 obese rats.</u>



Bar graphs showing less accumulation of versican cleavage products in PPS-treated (purple) than vehicle-treated ZSF1 obese rats (red). Dots indicate individual animals, and error bars indicate 95% confidence intervals. P-values <0.1 by comparison between groups by student t-test.

Dr Ravi Krishnan, Paradigm's Chief Science Officer, commented: *"Heart failure with preserved ejection fraction is an unmet medical need requiring urgent therapeutic attention. We are very pleased that the pilot study conducted in the laboratory of Dr Maria Vistnes has provided cutting edge data to further clarify the mechanism of action of PPS in HFpEF. The next steps for Paradigm are: firstly, to confirm these findings in*

a larger preclinical study, and, secondly, map out potential target patient populations for a pilot clinical trial."

Mechanism of Action

It has previously been demonstrated that PPS prevents heart failure development after aortic banding and myocardial infarction, evidenced by an increased fractional shortening in aorta-banded rats(Vistnes et al, 2014 [9]), and a lower lung weight and smaller left atria in post-infarction rats. PPS targets enzymes in the cardiac ECM, including ADAMTS-4 and -5 (Troeberg et al, 2008 [10], Takizawa et al, 2008 [11]). Along with the improvement in cardiac function, we observed reduced myocardial ADAMTS activity determined by the level of versican cleavage products, demonstrating that ADAMTS-mediated versican cleavage contribute to heart failure development (Vistnes et al, 2014 [9]). The human heart expresses ADAMTS-4 (Tucker et al, 2020 [12]), and versican cleavage by ADAMTS-4 promotes inflammation in other organs (Boyd et al, 2020 [13]). Since ECM changes and inflammation are central pathogenic factors in heart failure, PPS may have beneficial effects in both HFrEF and HFpEF populations of heart failure.

The ZSF1 rat model as the state-of-the-art preclinical HFpEF model

So-called 2-hit animal model for HFpEF combines increased afterload by aortic banding or hypertension, with insulin resistance through obesity or diabetes(Valero-Muñoz et al, 2017 [14]). By crossing a diabetic fatty (ZDF) rat with a spontaneously hypertensive heart failure rat, both carrying mutations in the leptin receptor, homozygous offspring develops hypertension, obesity and insulin resistance. These Zucker fatty and spontaneously hypertensive (ZSF1 obese) rats develop HFpEF with diastolic dysfunction by aging (Hamdani et al, 2013 [15], van Dijk et al, 2016 [16], Davila et al, 2019 [17]), and at week 15 to 20 of age, an HFpEF phenotype that resembles the human phenotype develops, including diastolic dysfunction (Schauer et al, 2020 [18]). The European Society of Cardiology in 2018 regards the ZSF1 obese rat to be the experimental model that most closely recapitulates the clinical phenotype (Lourenço et al, 2018 [19]), and the model is frequently used by pharmaceutical companies for preclinical testing of drugs (Signore et al, 2021 [20], Liu et al, 2020 [21], Stolina et al, 2020 [22], Zimmer et al, 2020 [23], Joshi et al, 2009 [24]).

About Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals LTD (ASX: PAR) is a late-stage drug development company with the mission to develop and commercialise PPS for the treatment of pain associated with musculoskeletal disorders driven by injury, inflammation, ageing, degenerative disease, infection or genetic predisposition. Paradigm is also exploring proof-of-concept studies for the use of PPS in respiratory and heart failure indications.

Forward Looking Statements

This Company announcement contains forward-looking statements, including statements regarding anticipated commencement dates or completions dates of preclinical or clinical trials, regulatory developments and regulatory approval. These forward-looking statements are not guarantees or predictions of future performance, and involve known and unknown risks, uncertainties and other factors, many of which are beyond our control, and which may cause actual results to differ materially from

those expressed in the statements contained in this presentation. Readers are cautioned not to put undue reliance on forward-looking statements.

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