Paradigm Biopharmaceuticals Ltd (ASX:PAR)

Heart Failure product

Pentosan Polysulphate Sodium (PPS): Inhibitor of Myocardial Extracellular Matrix Enzyme ADAMTS4 for treatment of Heart Failure and its progression

Partnership Opportunity:

Anti-remodelling drug provides convincing preclinical data for heart failure treatment for unmet market demand. Preclinical study complete. Paradigm preparing for Phase 2a clinical trial.

Cardiac overload due to aortic stenosis or myocardial infarction causes adverse cardiac tissue remodelling which progresses to heart failure. As heart disease progresses into chronic heart failure, there is continued remodelling of the left ventricle. Muscle mass increases, the left ventricle enlarges, cardiac systolic and/or diastolic function declines, and symptoms of heart failure become evident. Current therapy with ß-blockers, ACE-inhibitors and AT2-antagonists are initiated soon after heart failure development but are inadequate in slowing disease progression. Pentosan polysulfate sodium (PPS) treatment demonstrated improved contractility of the heart in the pressure-overloaded heart failure preclinical model with an associated reduction in the enzyme ADAMTS4 versicanase, which is a proteoglycan degrading enzyme involved in adverse cardiac tissue remodelling. Paradigm believes its product (IM or SC administered PPS) can meet market needs that are not effectively managed by current cardiac drugs.

- Pentosan polysulfate sodium (PPS) demonstrated benefits associated with unique anti-remodelling action in an established preclinical heart failure model.
- PPS provides a novel therapeutic modality not reported in other heart failure agents.
- No significant safety issues compared to significant side effects reported with current cardiac drugs.
- PPS has the potential to reverse progression of heart failure addressing unmet medical need.
- The heart failure market is projected to increase from $3.2 billion at 2015 to $11.8 by 2025.

Data supporting PPS as a treatment for Heart Failure in the Aortic banding rat model of Heart Failure:

- ADAMTS4-versicanase is a key target for treatment due to the pronounced increase in Heart failure rats showing reduced Fractional shortening in aortic banding rats.
- Improved contractile function in PPS compared to vehicle-treated rats in AB-rats demonstrated by:
  - 25% higher fractional shortening ($p<0.01$)
  - 33% lower left ventricular diameter in systole ($p<0.01$).
- PPS-treatment reduced myocardial ADAMTS4 mRNA Levels.
- PPS-treatment inhibited myocardial versican cleavage in AB-rats.

Preclinical data showing efficacy of PPS in Aortic Banding rat model of heart Failure (Vistnes et al 2014)

PPS downregulates ADAMTS4 activity at the mRNA level (Figure A) in the Aortic banding (AB) rat model which translated to reduction of ADAMTS4 enzymatic activity shown by reduction in versican cleavage fragments (Figure B). Versican cleavage fragments also contribute to cardiac edema.

Figure A

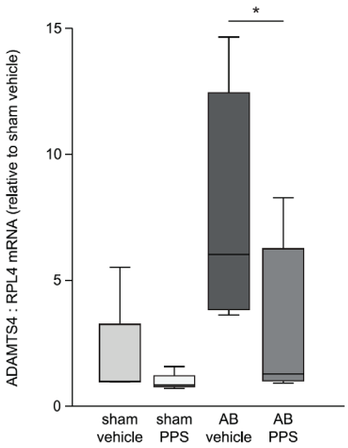

Figure B