BET PROTEIN INHIBITION FOR PULMONARY ARTERIAL HYPERTENSION: A PILOT STUDY

Background: While combination therapy delays clinical worsening of patients with pulmonary arterial hypertension (PAH), their long-term prognosis remains poor. The identification of complementary innovative therapeutic interventions is thus urgently needed in PAH. Bromodomain-containing proteins (BRDs) have been identified as a critical epigenetic driver for PAH. Apabetalone, a clinically available BRD2-4 antagonist, was shown to reverse pulmonary artery remodelling in diverse PAH rat models, as well as to support the pressure-loaded right ventricle. The aim of this pilot study was to assess the feasibility of a future early-stage clinical trial evaluating BRD inhibition in PAH, and provide preliminary evidence that apabetalone may be safe and effective in PAH.

Methods: This was an open-label, single-arm, 16-week study evaluating apabetalone 100mg BID in addition to guideline-recommended therapy in PAH. Within a 4-week screening period and at week-16 of treatment, eligible subjects completed a right heart catheterization, an optional cardiac MRI, a six-minute walk-test (6MWT) and lab tests including NT-proBNP. In addition to feasibility, change in pulmonary vascular resistance (PVR) was predefined as key exploratory efficacy endpoint. Changes in other hemodynamics parameters, 6MWT, NT-proBNP, as well as CD180 and CCR2 mRNA levels (qRT-PCR), blood-based biomarkers of BRD target engagement markers, were also explored. Given the pilot design of the study, there was no formal statistical hypothesis nor power calculations determined a priori.

Results: All participants completed the study procedures without dose reduction or discontinuation. Four patients had a contraindication to (n=2) or refused (n=2) the cardiac MRI. No serious adverse events were reported. Two patients experienced an asymptomatic 1.5 and 2.4 times the ULN increase in transaminases that spontaneously resolved despite continued treatment and 1 patient experienced iron deficiency anemia from angiodysplasia.

The mean changes in PVR, cardiac output and stroke volume were -140 (95%CI -200;-79)dyn.s.cm^{-5}, +0.73 (95%CI -0.22;+1.68)L.min^{-1} and +8 (95%CI -4;+20)ml, respectively. Minimal decreases in right atrial pressure and mean PA pressure were observed, whereas no changes in 6MWT and NT-proBNP were documented. Most subjects exhibited decreases in CD180 and CCR2 expression levels. Median changes in RV ejection fraction, RV end-systolic and end-diastolic volumes were +7%, -12ml and -30ml, respectively.

Conclusion: This single-arm open-label study documents that the evaluation of apabetalone for the treatment of PAH in future clinical studies is feasible. Further studies are needed to confirm the efficacy signal suggesting that apabetalone may be associated with beneficial effects when added to current therapies in PAH.