Efficacy of the novel thromboxane receptor antagonist NTP42 alone, or in combination with Sildenafil, in the sugen/hypoxia-induced model of pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is characterized by an elevated pulmonary vascular resistance resulting from excessive pulmonary arterial vasoconstriction and vascular remodelling, ultimately leading to right ventricular hypertrophy and right heart failure. NTP42 is a novel antagonist of the thromboxane (TX)A2 receptor (TP), currently in development for the treatment of PAH. Signalling through the TP, TXA2 is a potent vasoconstrictor, a driver of platelet aggregation and a pro-mitogenic and pro-inflammatory mediator. Moreover, the TP also mediates the actions of the isoprostane 8-iso-prostaglandin F2 alpha, a free-radical-derived product of arachidonic acid produced in abundance during oxidative injury. Mechanistically, TP antagonists should treat many of the hallmarks of PAH, including inhibiting the excessive vasoconstriction and pulmonary artery remodelling, in situ thrombosis, fibrosis and inflammation.

The aim of the study was to evaluate the effects of NTP42 when used alone, or as a dual-therapy in combination with a PAH standard-of-care (Sildenafil). Alongside control animals maintained in normoxia, PAH was induced in rats by injection of Sugen5416 (20 mg/kg) and exposure to hypoxia (10% O2) for 21 days. Thereafter, animals were returned to normoxia and treated for 28 days with either vehicle, NTP42 (0.05 mg/kg BID), Sildenafil (50 mg/kg BID), or NTP42+Sildenafil (0.05 mg/kg + 50 mg/kg BID, respectively).

While the standard-of-care PAH drug Sildenafil or NTP42 when used in mono-therapy led to non-significant reductions in the SuHx-induced rises in mean pulmonary arterial pressure (mPAP) or right ventricular systolic pressure (RVSP), combined use of NTP42+Sildenafil in dual-therapy significantly reduced these increases in mPAP and RVSP. Moreover, NTP42+Sildenafil also significantly reduced the SuHx-induced increase in cardiac hypertrophy. Detailed morphometric analysis of vessel remodelling confirmed that while both NTP42 and Sildenafil mono-therapy resulted in significant benefits, combined use of NTP42+Sildenafil showed an even greater benefit over either drug used in mono-therapy. Moreover, a multiparameter score of key PAH cardiac and pulmonary disease indices show that NTP42+Sildenafil when used in combination results in a highly significant treatment benefit, indicating a potential synergistic effect.

Assessment of key hemodynamic, cardiac hypertrophy and pulmonary vascular remodelling parameters shows equivalent or greater efficacy of the TP antagonist NTP42 compared with the standard-of-care Sildenafil when used as monotherapies in the SuHx-induced preclinical model of PAH. Combined use of both drugs in dual therapy form confirms an even greater benefit in treating or offsetting the key aetiologies underlying PAH. These findings suggest that NTP42 and antagonism of TP signalling may alleviate PAH pathophysiology, representing a novel therapeutic for use in mono- dual- or triple-therapy regimens.