Investigation of the effect of the angiotensin II type 2 receptor (AT2R) agonist C21 on plasma NT-proBNP, a diagnostic biomarker, in subjects hospitalised with COVID-19

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The prohormone N-terminal pro-B-type natriuretic peptide (NT-proBNP) is released from stretched cardiac myocytes and is a diagnostic biomarker for heart failure and cardiac dysfunction as well as pulmonary embolism and pneumonia that are frequent complications to severe Coronavirus Disease 2019 (COVID-19). NT-proBNP is frequently elevated in COVID-19. In a recent publication, it was demonstrated that NT-proBNP was strongly associated with mortality in patients with COVID-19, and further investigation of its usefulness as a prognostic tool to predict disease outcomes in COVID-19 was suggested (1).

In the recently completed phase 2 trial (angiotensin II type 2 receptor agonist COVID-19 trial [ATTRACT]; NCT04452435) in subjects hospitalised with COVID-19, it was investigated whether treatment with the AT2R agonist C21 for 7 days affected the release of the plasma biomarker NT-proBNP.

ATTRACT was a randomised, double-blind, placebo-controlled, phase 2 trial that investigated the safety and efficacy of C21 treatment (100 mg twice daily) for 7 days in hospitalised subjects with COVID-19, not requiring mechanical ventilation. The results of the trial demonstrated that treatment with C21 on top of standard of care (vast majority of patients received glucocorticoids) significantly reduced the proportion of subjects requiring supplemental oxygen at Day 14, indicating faster recovery with C21 treatment compared to placebo. Blood samples for exploratory analysis were taken before and after 7 days of treatment with C21 or placebo.

Plasma NT-proBNP was markedly elevated in both treatment groups before treatment, with average values of 357 and 438 pg/mL in the placebo and C21 groups, respectively, as compared to normal levels of approximately $<$100 pg/mL. After 7 days of treatment, the C21 group experienced a dramatic reduction in plasma NT-proBNP (by 259 pg/mL) as compared to the placebo group (63 pg/mL) ($p=0.02$).

The results show that short-term C21 treatment decreased the release of NT-proBNP in subjects hospitalised with COVID-19. Further investigations are needed to elucidate whether this is related to effects on COVID-19-induced pulmonary damage or direct protective effects on the heart. We are currently conducting a global phase 3 trial (VP-C21–008) further investigating the effect of C21 in subjects hospitalised with COVID-19 including determination of NT-proBNP.