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The aptamer BC 007 completely neutralizes agonistic autoantibodies directed against β1-adrenoceptors: Results of a phase 1 trial

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Background: 80 percent of patients with non-ischemic heart failure (HF) and reduced ejection fraction have autoantibodies against β1- adrenoceptors (β1-AAB), which cause and/or sustain HF. The removal of β1-AAB by immunoadsorption (IA) leads to an improvement of cardiac function and significantly reduced mortality. With the aptamer BC 007, a new drug is under study that neutralizes autoantibodies against G-Protein-coupled receptors (GP-AAB) including β1-AAB. Aptamers are often referred to as "chemical antibodies" and offer a number of advantages over e.g. peptides and biologics when used for treatment. Based on in vitro studies followed by animal testing, BC 007 was recently step-by-step transferred to humans. We present here a Phase I study investigated the safety, tolerability, and pharmacological effect of BC 007.

Methods: In a randomized, double blind, placebo controlled single ascending dose study, 3 cohorts of 8 male healthy subjects each (age 18 - 45 yrs) were dosed with 15, 50 and 150 mg of BC 007 by i. v. infusion over 20 min. Additional 8 elderly healthy subjects of both sexes (55 - 70 yrs) received 150 mg BC007 or placebo. Subsequently, in an open labelled study part with 5 cohorts of 6 elderly volunteers each (55 - 75 yrs), who showed evidence for GP-AAB dosages of 50, 150, 300, 450, and 750 mg were tested. Infusion duration was 20 min in the 50 and 150 mg and 40 min in the 300, 450 and 750 mg cohort. Subjects safety was carefully monitored during the study (ECG, blood pressure, lab, injection site reactions, VS, physical examination, adverse events). 12 blood samples were taken from before the infusion began until 24 h thereafter for clinical chemistry, hematological and pharmacokinetic analysis. Urine was collected.

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Results: BC 007 was extremely well tolerated and without clinically relevant adverse events. GP-AAB neutralization has been seen 24 h after BC 007 infusion in 1 of 6 individuals in the 150 mg cohort, in 2/6 in the 300 and 400 mg and 5/6 in the 750 mg cohort. A slightly elevated aPTT (max 49 s) was observed in 5 subjects of the 300, 450, and 750 mg cohort which quickly normalized after end of infusion. AUC increased by rising dosage from 21 to 556 µg*min/mL, Cmax increased from 1610 to 15832 ng/mL. The half-life was short at appr 4 min.

Conclusion: BC 007 is a powerful new drug for the neutralization of β1-AAB with a favorable side-effect profile which will be tested as the first causative acting drug for patients with β1-AAB induced heart failure. Derived from IA data, a huge number of patients with HF will profit from this new drug.