19 SAFE AND EFFICIENT TRANSDUCTION OF SYNOVIAL TISSUE AFTER LOCAL INJECTION OF AAV5.HIFN β IN NON-HUMAN PRIMATES WITH COLLAGEN-INDUCED ARTHRITIS

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Background and objectives Recombinant AAV5.NFkB.hIFN- β (ART-I02) is an adeno-associated type 5 (rAAV5) vector expressing the human interferon β (hIFN- β) under development for local treatment of rheumatoid arthritis (RA). The authors investigated biodistribution and safety after intra-articular (ia) injection of the gene construct in rhesus monkeys with CIA.

Materials and methods Arthritis was induced in 15 monkeys (13 male and 2 female) with chicken type II collagen (ChCII, 4

mg). All monkeys were naïve or showed limited (1:10–1:31,6) neutralising antibody (Nab) titers to AAV5 at the start of the study. All animals (N=5 per group) were treated with a single dose of ART-I02 (1.10^{13} vg/ml or $1.4.10^{12}$ vg/ml) or placebo in the first involved PIP joint (0,1 ml) and in the ipsilateral knee (1 ml) and ankle joint (0,5 ml). Clinical signs and symptoms were monitored for a maximum of 4 weeks until the human end-point in the study was reached. Serum, joints and organs were collected for histological analysis. Serum was analysed for acute phase response (CRP, IL-6 levels), ChCII antibodies and Nab. Presence of ART-I02 vector genomes in 16 tissues was analysed using qPCR. Expression of hIFN β was analysed in knee synovial tissue (ST) samples by ELISA. Histological evaluation by an experienced pathologist was performed on all organs collected to evaluate toxicity induced by the vector.

Results No adverse events were observed after ia injection of ART-I02. All animals experienced an acute phase response (CRP>50 mg/L-752 mg/L) with simultaneous rising of IL-6 levels and the production of anti-ChCII IgG antibodies associated with the development of arthritis. High titers of Nab to rAAV5 were observed (between 1:3.160 and 1:100.000) at the end of the study. Vector DNA was detected in ST of the injected knee joint and the popliteal (draining) lymph node (injected side) at the highest copy numbers. No vector DNA was detected in ovaries (2/2). In four out of eight animals testes was positive for vector DNA (100 copies/ug DNA). In animals which had a longer follow up after injection (>14 days) the testes were negative for vector DNA, indicating this could be a transient effect. In knee ST samples a varied level of expression of hIFN β was observed. No abnormalities were observed after histological evaluation of all organs.

Conclusions Intra-articular injection of ART-I02 at high doses is well-tolerated and does not induce adverse events in the monkey CIA model of RA. This study represents an important step towards a phase I clinical trial in RA patients.