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Title: Advantageous toxicity profile of an inhaled GATA-3-specific DNAzyme intended for anti-inflammatory treatment of Th2-driven asthma

Dr. Rainer 28300 Fuhst rainer.fuhst@item.fraunhofer.de [1], Dr. Frank 28301 Runge frank.runge@nycomed.com [2], Dr. Jochen 28302 Buschmann jochen.buschmann@item.fraunhofer.de [1], Dr. Christiane 28303 Praechter christiane.praechter@nycomed.com [2], Dr. Jasmin 28304 von Erichsen jasmin.von-erichsen@nycomed.com [2], Dr. Agnieszka 28324 Turowska a.turowska@sterna-biologicals.com [3], Dr. Heinz-Gerd 28326 Hoymann hoymann@item.fraunhofer.de [1], Dr. Meike 28331 Müller meike.mueller@item.fraunhofer.de [1], Dr. Gerhard 28333 Pohlmann pohlmann@item.fraunhofer.de [1], Dr. Katherina 28344 Sewald katherina.sewald@item.fraunhofer.de [1], Dr. Christina 28345 Ziemann christina.ziemann@item.fraunhofer.de [1], Prof. Dr Gerhard 28348 Schlüter gerhard.schlueterGS1@gmx.net MD [4] and Dr. Holger 28349 Garn garn@staff.uni-marburg.de [5]. [1] General and Reproductive Toxicology, Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM), Hannover, Germany ; [2] Institute of Pharmacology and Preclinical Drug Safety, Nycomed, Barsbüttel, Germany ; [3] R&D, Sterna Biologicals, Marburg, Germany ; [4] Toxicology, Independent Consultant, Wuppertal, Germany and [5] Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University, Marburg, Germany .

Body: DNAzymes are single-stranded catalytic DNA molecules that specifically bind and cleave target mRNA sequences. Their potential as novel therapeutic agents has been demonstrated in a variety of disease models. However, no studies have yet addressed their toxicology and safety pharmacology profiles in detail. We have developed and characterized the human GATA-3-specific DNAyzme hgd40 intended for the treatment of Th2-driven asthma. Here we report results of a detailed toxicological analysis of inhaled hgd40. Subacute toxicity, immunotoxicity, and respiratory, cardiovascular, and CNS safety pharmacology were analyzed in rodents and non-rodents, and genotoxicity was assessed in human peripheral blood. Overall, hgd40 was very well tolerated when delivered by aerosol inhalation or slow intravenous infusion. Only marginal reversible histopathological changes were observed in the lungs of rats receiving the highest dose of inhaled hgd40. The changes consisted of slight mononuclear cell infiltration and alveolar histiocytosis, and moderate hyperplasia of bronchus-associated lymphoid tissue. No local or systemic adverse effects were observed in dogs. No compound-related respiratory, cardiovascular, or CNS adverse events were observed. The only relevant immunological findings were very slight dose-dependent changes in interleukin-10 and interferon-γ levels in bronchoalveolar lavage fluid that may represent pharmacological activity of hgd40. Taken together, these results support the direct delivery of the GATA-3-specific DNAzyme hgd40 via inhalation for the treatment of asthma in subsequent clinical studies.