Title

Early clinical proof of effect of inhaled lung therapies in Phase 1 : Evaluation of mode of action and drug deposition in the target organ of healthy subjects

Introduction

Generation of evidence for clinical effect and of drug availability in the lung is essential for inhaled lung therapies and is generated in first phase 1 studies, as shown for 3 project examples:

Ex.1: The established therapy of respiratory bacterial infections with Ciprofloxacin shall be optimised by inhalation as dry powder formulation with a handheld device. Reliable, reproducible lung deposition in man has to be shown.

Ex2:D, L-lysine acetylsalicylate glycine (Aspirin i.v.®) inhalation reduces lung influenza virus titer in mice and dose-dependently decreases disease severity.

Ex3:A novel inhalable soluble guanylate cyclase activator, designed for local application to lung for improvement of cardiopulmonary circulation in pulmonary hypertension is evaluated in FiM studies with SAD and MAD dry powder inhalations.

Methods and Materials

Example 1:

A phase I study in 12 patients with non-cystic fibrosis bronchiectasis or COPD, and 12 healthy volunteers, evaluated pulmonary drug deposition after 99mTc-Ciprofloxacin DPI 32.5 mg dose by quantitative scintigraphy. 81mKrypton ventilation scans were performed to map lung contours. Gastrointestinal absorption was excluded using charcoal block, pulmonary drug deposition from plasma PK.

Example 2:

First-in-man study with inhalation of up to 750 mg ASA nebulized by Akita® device used plasma TXB2 and functional platelet aggregation assay in serum to quantify activity and PK analysis for proof of effective administration.

Example 3:

Pharmacological target engagement is quantified as cGMP, product of direct sGC activation after drug inhalation, functional effects are cardiovascular and lung function parameters.

References

Ex.1: H. Stass, **J.H. Nagelschmitz**, D. Kappeler et al; Ciprofloxacin Dry Powder for Inhalation in Patients with Non-Cystic Fibrosis Bronchiectasis or Chronic Obstructive Pulmonary Disease, and in Healthy Volunteers; July 2016Journal of Aerosol Medicine and Pulmonary Drug Delivery 30(1); DOI: 10.1089/jamp.2015.1282