

Investigation of Lung Pharmacokinetic of the Novel PDE4 Inhibitor CHF6001 in Preclinical Models: Evaluation of the PreciseInhale Technology

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Abstract

Background: Preclinical evaluation of new chemical entities (NCEs) designed to be administered by inhalation route requires lung administration to rodents, especially in the discovery phase. Different administration methods have been used until now, but more efforts are required to obtain controlled and reproducible lung deposition when only small amounts of neat powder material are available.

Methods: The PreciseInhale platform used in the present study enables well-controlled powder aerosol exposures with only small amounts of micronized neat material, providing data on inhalation pharmacokinetic (PK) of NCEs at a very early stage. The DustGun aerosol technology uses compressed air to generate a respirable aerosol from milligram-amounts of powder that is delivered to one animal at a time. The new methodology was used to investigate the inhalation PK and lung retention in the rat of the novel Chiesi PDE4 inhibitor CHF6001 in three exposure models of the PreciseInhale platform: nose-only, intratracheally intubated rat, and the isolated, ventilated, and perfused rat lung. Results were compared with data from two other pulmonary delivery systems commonly used in preclinical studies: liquid instillation and powder insufflation.

Results: Administration of micronized CHF6001 using the PreciseInhale system yielded lung exposures in the same range as the other tested devices, but the reproducibility in lung deposition was improved. The initial amount of CHF6001 in lungs at the first sampling time point was close to the predetermined target dose. Tracheal deposition with PreciseInhale ($0.36 \pm 0.22 \mu\text{g}$) was significantly less than with other tested delivery systems: PennCentury ($23.7 \pm 3.2 \mu\text{g}$) and Airjet ($25.6 \pm 7.2 \mu\text{g}$).

Conclusions: The PreciseInhale platform enabled the administration of CHF6001 powder with good accuracy and reproducibility, with low tracheal deposition. The new platform can be used at an early discovery stage to obtain inhalatory PK data for respirable aerosols of neat NCE powder without excipients and with minimal use of dry powder formulation work.

Keywords: CHF6001, dry powder aerosol, endotracheally intubated rat, inhalation pharmacokinetic, isolated perfused lung, nose-only exposure

Introduction

INHALATION ADMINISTRATION TO RODENTS is an important step in preclinical development of new drugs designed for the inhalation route.⁽¹⁾ Different administration methods have been developed with the aim of obtaining a reproducible and controlled lung deposition using a small amount of substance.^(2,3)

Liquid formulation of new chemical entities (NCEs) can be obtained by using solubilizing excipients and delivered by intratracheal (IT) instillation or nebulization to anesthetized animals.⁽⁴⁾ These methods require a low amount of substance, but are characterized by uneven distribution of the formulation in the lung and poor dose control.⁽⁵⁾ Furthermore, liquid formulation is often different from the

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