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Original research

Assessment of lung deposition and analysis of the effect of fluticasone/salmeterol hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) in stable persistent asthma patients using Functional Respiratory Imaging

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Summary

Results using functional respiratory imaging (FRI) complement pharmacokinetic (PK) assessments. Unambiguously for inhaled products, PK measures are best suited for ensuring that the total systemic exposure is equivalent for two products, while FRI provides the confirmation that regional deposition is equivalent for two products by directly measuring regional functional and structural changes within the lungs following its administration. The added value of this approach to the conventional clinical methods could be significant. FRI has been demonstrated to be sensitive for distinguishing small but imperative differences related to a single treatment. The scope of this study was to evaluate whether or not there are any differences between the lung deposition patterns of two products, having the same formulation and manufactured by different organizations using FRI.

Keywords

Functional respiratory imaging, lung deposition, salmeterol, fluticasone propionate, asthma

1. Introduction

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction and bronchial hyperresponsiveness. This chronic inflammatory process leads to airway infiltration by inflammatory cells, subepithelial deposition of collagen, and hyperplasia of smooth muscle cells, goblet cells, and submucosal glands. Chronic inflammation in the airways may also lead to permanent changes in the airways, a process referred to as airway remodeling. The goal of therapy is to control asthma by reducing impairment and reducing risk for future loss of control [**1**].

Many treatment options exist for asthma. Several studies have shown the benefits of adding a long-acting beta-2 agonist (LABA) to an inhaled corticosteroid (ICS) for the treatment of asthma in patients who remain symptomatic despite the use of low to medium doses of an ICS and as needed short-acting beta 2 agonists [**2, 3, 4, 5, 6].** The rationale for combination therapy of an ICS with a LABA in the treatment of asthma is scientifically sound with LABAs counteracting smooth muscle constriction and ICSs treating the underlying airway inflammation. Combination therapy is now a mainstay of persistent asthma treatment and is a recommended option in current asthma treatment guidelines for patients with persistent asthma [1]. Moreover, clinical programs conducted with currently marketed combination products (Advair Diskus, Advair hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) and Symbicort HFA pMDI) have demonstrated that ICS/LABA combination products provide greater improvement in pulmonary function and other measures of asthma control than either individual component alone in children, adolescents and adults with persistent asthma [**7, 8, 9]**.

Functional Respiratory Imaging (FRI) applications based on Computerized Tomography (CT) analysis and Computational Fluid Dynamics (CFD) emerges as a novel technique that can simulate different outcomes such as ventilation, lung deposition and perfusion of airway blood vessels. The static images obtained with CT are made functional by means of CFD. Previous studies have demonstrated the value of CT in the assessment of lung diseases [10,11, 12,13]. The advantage of FRI is mainly the enhanced sensitivity to detect clinically relevant changes on a regional level, potentially leading to smaller, more cost effective clinical trials [**14, 15**]. The technique thus, emphasizes understanding of the lung pathology and simulation of inhaled drug delivery methods. Since particle deposition is significantly dependent on flow characteristics, which, in turn, are reliant on the geometrical configuration of airways and regional ventilation of the lungs, it is desirable to conduct subject-specific CFD with an anatomically realistic

model of airway geometry. Numerous reports have already demonstrated the feasibility of FRI to accomplish just that [**16, 17, 18]**.

Cipla has recently developed a Salmeterol/Fluticasone Cipla pMDI product that was designed to be equivalent to the marketed product, Seretide® Evohaler®. The scope of the study is to combine a new technique of using FRI in evaluating differences between lung deposition, airway resistance and airway volume parameters of Seretide® (reference product) and Salmeterol/Fluticasone Cipla pMDI (test product) in asthma patients after the administration of a single dose of each product in a crossover manner, using FRI.

2. Patient Population & Methods

2.1 Subjects

Male or female subject ≥ 18 years of age, with a documented diagnosis of persistent asthma that was stable and treated according to the GINA guidelines [**1]**, were eligible for the study. Eligible subjects also had to be non-smokers or ex-smokers who had stopped smoking at least 1 year prior to screening (visit 1) and had a smoking history of < 10 pack years.

Subjects were assessed for inclusion/exclusion criteria based on their demographic data, medical/surgical history, prior medication records (prior 3 months), physical examination, safety laboratory investigations, spirometry, body plethysmography and 6 minute walk test (6MWT). All participants provided written informed consent and the study was approved by the ethics committee of the Antwerp University Hospital (ref: 13/5/50). Subjects were also assessed for the correctness of their inhaler usage technique, and had to demonstrate correct inhaler technique in order to be eligible to participate in the study

Unstable patients with an exacerbation in the 8 weeks prior to the study and patients with an upper or lower airway infection or those unable to perform pulmonary function testing were not included in the study. Patients who received oral corticosteroids within the last 4 weeks prior to screening (visit 1), or who received any investigational new drug within the last 4 weeks prior to visit 1 or twice the duration of the biological effect of any drug (whichever was longer) were excluded. Patients with a history of alcohol or substance abuse that could be of clinical significance, major surgery in the last 12 weeks before visit 1 or planned a major surgery before the end of the trial were also excluded.

2.2 Study Design

This study was a randomized, double-blind, double-dummy, two-period crossover study in stable persistent asthma subjects (figure 1). A total of 16 stable persistent asthma subjects, treated in accordance with the GINA guidelines were included.

The run-in period ranged from a minimum of 7 days to a maximum of 11 days. On the first dosing day, asthma stability (lung function parameters, body plethysmography parameters and 6-minute walk test) was assessed during the pre-dose measurements and was evaluated for current pharmacologic and non-pharmacologic treatment. The stable asthma patients were then randomized into the study, allocated to a treatment sequence and received a single dose of 2 puffs of either the test product; Salmeterol /Fluticasone propionate HFA pMDI 25/250 µg per actuation (FS HFA Cipla Ltd) or the reference product; Salmeterol /fluticasone propionate 25/250 µg per actuation (Seretide® Evohaler® pMDI; Allen and Hanburys Ltd., UK), under the supervision of the investigator or authorized site personnel. Additionally, patients also received a matching placebo of the alternate treatment as a dummy inhaler. The patient inhaled two puffs from both treatment and placebo inhalers without the aid of a spacer device. Pre-dose and 2-hours post dose, lung images as well as lung function were measured as described below. The patient inhaled two puffs from both inhalers.

There was a washout period of at least 3 days (not more than 7 days) between dosing days. The inhalation profiles were measured during inhalation maneuvers for all patients for the test product and reference product, separately.

2.3 Computed tomography

High Resolution Computed Tomography (HRCT) scans were obtained at two different lung volumes (i.e. Total Lung Capacity (TLC) and Functional Residual Capacity (FRC)) before and after the administration of a single dose of either the test or the reference product. During the first treatment visit, (visit 2), an additional scan of the upper airway was taken for deposition analyses prior to dosing. The HRCT scans were taken with a multi-slice scanner with 64 detectors (GE VCT LightSpeed) and the lung levels were controlled using spirometry during the HRCT procedure. The HRCT data for the asthmatic subjects were utilized for constructing computer models which were analyzed numerically using CFD for airway

resistance and particle deposition, and for bronchodilation comparison in terms of airway volume and surface area for the test and reference products.

Deposition is determined using computational fluid dynamics or CFD. CFD requires boundary conditions related to the flow domain (in this case the respiratory system), the inhalation profile and the formulation characteristics such as MMAD, and GSD, FPF, ED. The flow domain is derived from the HRCT scans and hence is highly patient specific, the inhalation profile is measured during the study and the aerosol characteristics are derived using the Anderson Cascade Impactor which yields the required parameters.

2.4 Model development

The HRCT scans were loaded into the Mimics 15.0 software suite (Materialise, Leuven, Belgium). This validated package (FDA K073468, Conformité Européenne Certificate BE 05/1191.CE.01) was used to generate 3-dimensional representations of the airways and lobes. Airway geometries were extracted from the HRCT scan at TLC using a semi-automatic algorithm of the airways up to the point where no distinction could be made between the intra-luminal and alveolar air (7^{th}-10^{th} airway generation). The segmentation and three-dimensional reconstruction were performed, and subsequently, the segmented airway model was smoothed with a volume compensation algorithm. Additionally, the lung lobes at both FRC and TLC were extracted.

2.5 Simulation Methodology

The three dimensional airway models were converted to tetrahedral 3D volume meshes using TGrid 14.0 (Ansys Inc, Canonsburg, PA). Computational fluid dynamics flow simulations were performed in Fluent 14.0 (Ansys Inc, Canonsburg, PA). As boundary conditions, the percentage of flow exiting the model towards a lobe was used as this equals the relative lobar expansion as obtained from the patient-specific inspiratory and expiratory scans. This method has been described previously in De Backer et al and Vinchurkar et al [**19, 20]**. Deposition characteristics of both LABA and ICS can be assessed using the respective median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of both products that were measured using an Anderson Cascade Impactor (MMAD±GSD in μm: fluticasone test: 3.5±1.6, salmeterol test 3.6±1.5, fluticasone reference: 3.4±1.6, salmeterol reference 3.5±1.6).

2.6 Outcomes measured

The primary endpoints estimated in this study were the changes in airway surface area (iSaw), airway volume (iVaw), airway resistance (iRaw) and lung deposition after acute bronchodilator, which reflects the effect of the LABA component.

2.7 Statistical methods

Due to the novel nature of the FRI technology limited data exists to perform a comprehensive sample size calculation. Hence the current study design and associated sample size is judged to be adequate to demonstrate the potential of FRI to describe the effect of two drugs in the same patient population. However, the intent of this study is not to make explicit claims about bio-equivalence based on the results of this study alone. The non-parametric Wilcoxon matched pair test was used for the statistical analysis. The changes from baseline (i.e., pre- versus post-intervention) for the various endpoints were analyzed statistically for the test product and the reference product. The differences between the test product and reference product for the changes from baseline for these endpoints were then compared.

3. Results

3.1 Demographic and Other Baseline Characteristics

A total of 16 stable persistent asthma patients were enrolled in the study and received both treatments**. (Table 1**).

3.2 Airway Volume and Resistance

Airway volume, airway surface and airway resistance were measured using patient-specific anatomical images from CT scans. The differences in treatment effects between the test product and reference product were not statistically significant for any of the imaging endpoints. At 2 hours post-dose, a significant increase in iVaw was observed following administration of FS HFA pMDI 25/250 mcg (55.66 ±

25.85 ml) and Seretide® HFA pMDI 25/250 mcg (55.82 ± 25.16 ml) compared with their respective baselines (51.93 ± 23.59 ml and 52.59 ± 24.10 ml, respectively, p=0.3936). Two hours post-treatment, the total airway resistance decreased from 0.040 ± 0.024 to 0.028 ± 0.016 kPa/L/s with FS HFA and from 0.039 ± 0.023 to 0.025 ± 0.013 kPa/L/s with Seretide® HFA pMDI, (p= 0.4534) (**Figure 2)**. Two hours post-treatment, the iSaw increased from 290.24 ± 93.19 to 312.57 ± 103.03 and 295.50 ± 89.34 to 315.75 ± 94.06 cm^2, for FS HFA pMDI and Seretide® HFA pMDI, respectively, (p=0.6603) (**Table 2**).

3.3 Lung deposition imaging

The test and reference products were not statistically different for deep lung deposition (distal + peripheral airways) for the fluticasone propionate/salmeterol combination (**Figure 3 and Figure 4**). While there are no currently available techniques for separately assessing the deposition of the salmeterol and fluticasone propionate, salmeterol and fluticasone propionate are co-deposited in the airways when administered from the HFA pMDI. Based on the *in vitro* profiles of salmeterol and fluticasone propionate in the combination products, CFD estimates the percent deposition of salmeterol with Seretide® HFA pMDI to be 18.7±6.6 % and 18.6±5.7 % for FS HFA pMDI (p=0.897 for Seretide® HFA pMDI versus FS HFA pMDI) and 18.4±6.6 % with Seretide® HFA pMDI and 18.2±5.7 % with FS HFA pMDI for fluticasone propionate (p=0.856 for Seretide® HFA pMDI versus FS HFA pMDI).

3.4 Safety assessments

Overall, both treatments were well-tolerated. There were a total of 18 adverse events reported, of which 1 was serious. The single serious adverse event (pneumonia) was reported with the test product, however, it was not considered to be related to the study treatment**.** None of the reported AE`s were related to the study treatment except for one incident of heart palpitation (FS HFA) and one incident of headache (Seretide®).

4. Discussion

The current study was designed to evaluate whether or not there were differences between Seretide® and FS HFA in asthma patients after the administration of a single dose of each treatment in a crossover manner, using FRI. While the study was not designed to assess bioequivalence, the study demonstrated

that there were no appreciable differences between the two products as assessed by airway volume, resistance and deposition.

It is well known that evaluating inhaled products for bio-equivalence has particular challenges compared with oral drugs. The delivered dose to the lung is a function of, for example, the delivery device, the aerosol formulation, the patient's upper airway morphology and inhalation maneuver. Drug absorption is determined by the regional deposition and local bio-availability. In this regard, pharmacokinetic testing can evaluate systemic exposure, but this may not relate directly to whether or not two inhaled products are functionally equivalent. Additionally, conventional pulmonary function tests such as FEV_1 do not provide information about regional drug deposition and lack the sensitivity to distinguish clearly between doses. Hence, the assessment of bioequivalence of inhaled products requires either large multicenter clinical trials which have limited sensitivity for distinguishing small but important differences between products or very complex study designs such as the 4-way cross-over design specified in FDA's Albuterol guidance. The current study showed that FRI has the capability to provide regional information both in terms of actual bronchodilation and deposition. Furthermore, in previous studies it has been demonstrated that FRI has enhanced sensitivity (better signal to noise ratio) compared with conventional spirometry, thereby suggesting that products that are not different in terms of FRI endpoints are most likely therapeutically equivalent. Future studies with more elaborate sample size calculations need to be performed to confirm this.

While the current study focused on the bronchodilating effect of salmeterol, it is also possible to evaluate ICS-specific endpoints using FRI. The effect of ICS was determined in a asthmatic population **[7]** and COPD population [21] by studying the changes in FRI parameters after 6 months of treatment with the study drug and after washout of bronchodilation. Importantly, the results using FRI complement PK assessments. Specifically, PK measures are best suited for ensuring that the total systemic exposure is equivalent for two products while FRI provides the confirmation that regional deposition and associated in-vivo effect is equivalent for two products by directly measuring regional functional and structural changes within the lungs following administration of an inhaled product.

The current study had a number of limitations: the average FEV_1 at baseline was > 100% in the current study, potentially limiting the ability to distinguish between treatments. However, it is important to note that changes in airway resistance/volume following bronchodilator administration can be detected in healthy subjects and in patients with airway disease even when changes in FEV_1, for example, cannot be

detected [22]. This was the reason for selecting these outcome measures to be sure that changes following treatment administration could be detected. Additionally, FRI by itself has some limitations. The number of scans is limited due to radiation exposure and the resolution of the HRCT does not allow direct measurement of the very small airways (diameter < 2mm). However, this is also not believed to be a significant limitation of FRI since the latter can be inferred from assessing lobe expansion from expiration to inspiration. One final consideration is that the sample size of this study is relatively small. However, the results of this study will be used for sample size calculations for future comparative studies that use FRI endpoints.

Finally, variation in inhalation technique could alter efficacy outcomes independent of actual differences between the test and reference products. However, care was taken to be sure each patient was able to inhale correctly from the MDI in order to minimize variability due to inhalation technique. This was further substantiated by inhalation profiles which were measured during inhalation maneuvers for all subjects and were not appreciably different for the test product and reference product

5. Conclusion

FRI using CFD emerges as a potential tool for assessing clinical equivalence of two products. It acts as an efficient biomarker for respiratory diseases and adds value to both drug and device development. The geometry of the respiratory system differs for every individual and this can be analyzed using FRI technique which subsequently helps evaluate the pulmonary function and the aerosol deposition. This study demonstrated that there were no appreciable differences between the two products as measured by using FRI. The measurements of airway volume and resistance were not statistically different for the test and reference products. The lung deposition (both distal and peripheral) with the two products was also not statistically different.

While the current study was not designed to assess bioequivalence, the added value of this approach to conventional clinical methods could be significant, especially since FRI is sensitive for distinguishing small but important differences between products with small sample sizes.

6. Expert commentary

The advances in pulmonary medicine is a fundamental requirement, considering the composite dynamics of the pulmonary organization and the lung's response to a disease; however the global measurements obtained via clinical pulmonary function tests do not sufficiently capture lung complexity and may only be marginally transformed by significant local disease. Quantifiable image-based measurements, including assessment of the static and dynamic structure and function, are now acknowledged as very sensitive markers of localized disease and appear to designate intricate lung processes much better than clinical measurements. Functional respiratory imaging is a novel approach that shows alterations in respiratory functions that associate with the 'classical' clinical outcome parameters and consequently provide a deeper insight into the physiological aspects of bronchodilation. The imaging helps in determining airway volume and resistance along with the lung functions like forced expiratory volume and peak expiratory flow rate. The technique however has a few limitations like number of scans is restricted due to radiation exposure and the resolution of the HRCT does not permit uninterrupted measurement of the very small airways (diameter < 2mm). The drawbacks, nevertheless can be tackled and imaging can become a viable tool for simulation of airflow in the human pulmonary system.

7. Five-year view

In recent times imaging of the thorax has progressed extensively from an investigational tool that was only used in a limited number of centres to a routine test for clinical evaluation of the respiratory system. The development of high resolution computed tomography has enormously augmented the understanding of the fundamentals of pathophysiology of respiratory diseases such as asthma, COPD, cystic fibrosis etc. In the coming years, it is believed that the functional respiratory imaging using computed fluid dynamics would grow into a potential tool to determine the pattern of the deposition of the inhaled product and judge the changes it brings about as a function of time of time

8. Key issues

- Assessment of clinical equivalence of products with same formulation manufactured by different organizations.
- Conventional clinical assessment tests are cumbersome, hence the introduction of a novel technique; functional respiratory imaging (FRI) using computational fluid dynamics

- FRI has the capability to provide regional information both in terms of actual bronchodilation and deposition.
- FRI has enhanced sensitivity (better signal to noise ratio) compared with conventional spirometry
- Quantifiable parameters : iRaw (airway resistance), iSaw, (surface area of the airway), iVaw (airway volume) and lung deposition of the two products

9. Clinical Trial

This study is registered at EudraCT, with identifier number EudraCT No: 2012-005789-36, and was submitted to ClinicalTrials.gov (NCT01795664).

Financial and competing interests disclosure

Writing assistance was provided by Cipla in-house Global Medical Affairs team in accordance with the CONSORT statement. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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	Mean	Min	Max
Age [y]	58.88 (8.70)	44	73
Height [cm]	169.69 (9.46)	158	192
Weight [kg]	81.16 (16.25)	55	102.5
BP Sys [mmHg]	121.44 (7.70)	107	130
BP Dia [mmHg]	79.94 (9.65)	60	92
HR [bpm]	70.25 (12.73)	56	102
FVC [L]	4.23 (1.25)	2.46	6.74
FVC [%p]	120.53 (13.20)	90.4	141.9
FEV1 [L]	2.97 (0.91)	1.77	5.27
FEV1 [%p]	104.50 (18.87)	65.7	133.9
FEV1/FVC [%]	70.95 (9.61)	41.7	80.6
PEF [L/s]	8.21 (2.71)	5.59	15.75
MEF50 [L/s]	2.70 (2.71)	0.9	6.24
FEF75 [L/s]	0.73 (2.71)	0.23	1.69
FEF25 [L/s]	5.54 (2.71)	1.95	11.45
RV [L]	2.50 (0.75)	1.51	4.14
RV [%p]	116.19 (23.77)	90	170
TLC [L]	6.84 (1.88)	4.48	10.65
TLC [%p]	114.44 (13.79)	91	142
FRC [L]	3.45 (0.95)	2.06	5.36
FRC [%p]	109.88 (18.39)	77	149
Raw [kPas/L]	0.328 (0.130)	0.119	0.640
sRaw [kPas]	1.236 (0.533)	0.560	2.109
6MWT [m]	605.06 (75.15)	473	735
6MWT [%p]	92.75 (11.96)	75	118

Table 1: Demographic data at baseline

IMAGING TESTS		Pre Test	Post test	Change (Test)	Pre Reference	Post Reference	Change Reference	p value Change
		Mean(SD)	Mean(SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	(Reference-test)†
iVaw [cm^3]	**Total**	51.93 (23.59)	55.66 (25.85)	3.72 (3.36)*	52.59 (24.10)	55.82 (25.16)	3.23 (1.82)*	0.39360
	Central	40.36 (18.26)	41.74 (19.26)	1.39 (1.61)**	40.72 (18.92)	41.75 (19.26)	1.03 (1.17)***	0.26630
	Distal	11.58 (6.23)	13.91 (7.61)	2.34 (2.12)*	11.87 (6.04)	14.07 (6.67)	2.20 (1.37)*	0.69820
iSaw [cm^2]	**Total**	290.24 (93.13)	312.57 (103.03)	22.33 (17.37)*	295.50 (89.34)	315.75 (94.06)	20.25 (12.02)*	0.66030
	Central	128.03 (32.93)	131.26 (33.92)	3.23 (2.68)*	129.95 (34.29)	132.87 (34.53)	2.92 (3.12)*	0.33880
	Distal	162.22 (65.29)	181.32 (74.42)	19.10 (15.73)*	165.55 (60.75)	182.87 (64.96)	17.32 (12.00)*	0.58720
iRaw	**Total**	0.040 (0.024)	0.028 (0.016)	-0.012 (0.013) ***	0.039 (0.023)	0.025 (0.013)	-0.014 (0.013)*	0.45340
[kPas/L/s]	**Central**	0.014 (0.009)	0.012 (0.007)	-0.002 (0.003) ***	0.013 (0.010)	0.011 (0.007)	-0.002 (0.003) **	0.89710
	Distal	0.026 (0.017)	0.017 (0.011)	-0.010 (0.011)**	0.026 (0.017)	0.014 (0.007)	-0.012 (0.011) *	0.48510

Table 2: Imaging results for a) changes post treatment for the 'Test' product, b) changes post treatment for the 'Reference' product (*p < 0.001, **p<0.01, ***p<0.05, †p > 0.05 for all comparisons)

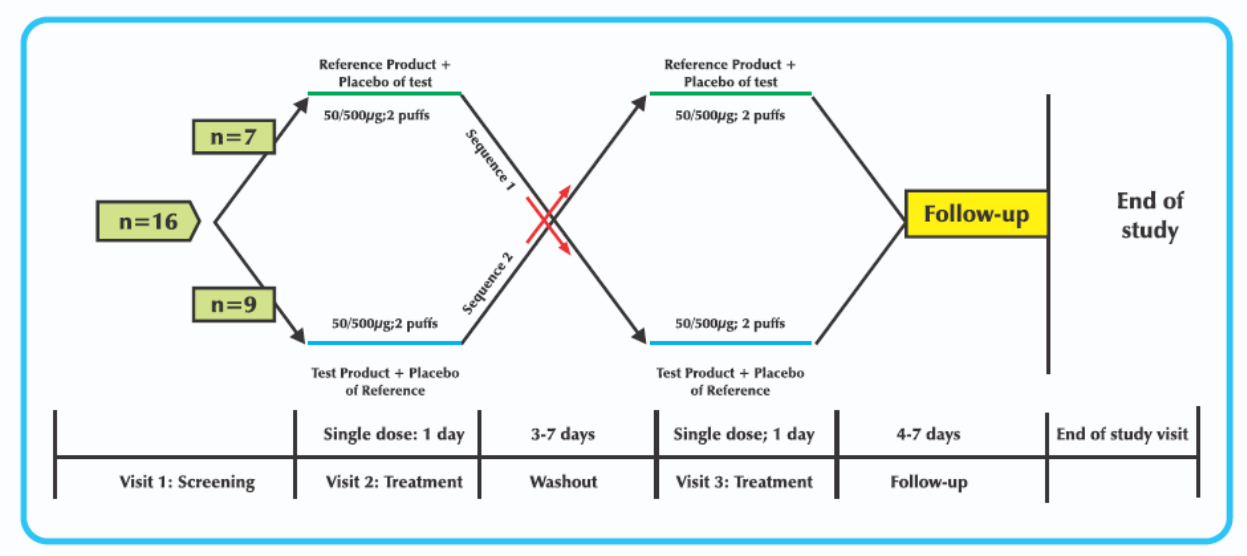

Figure 1: Study design

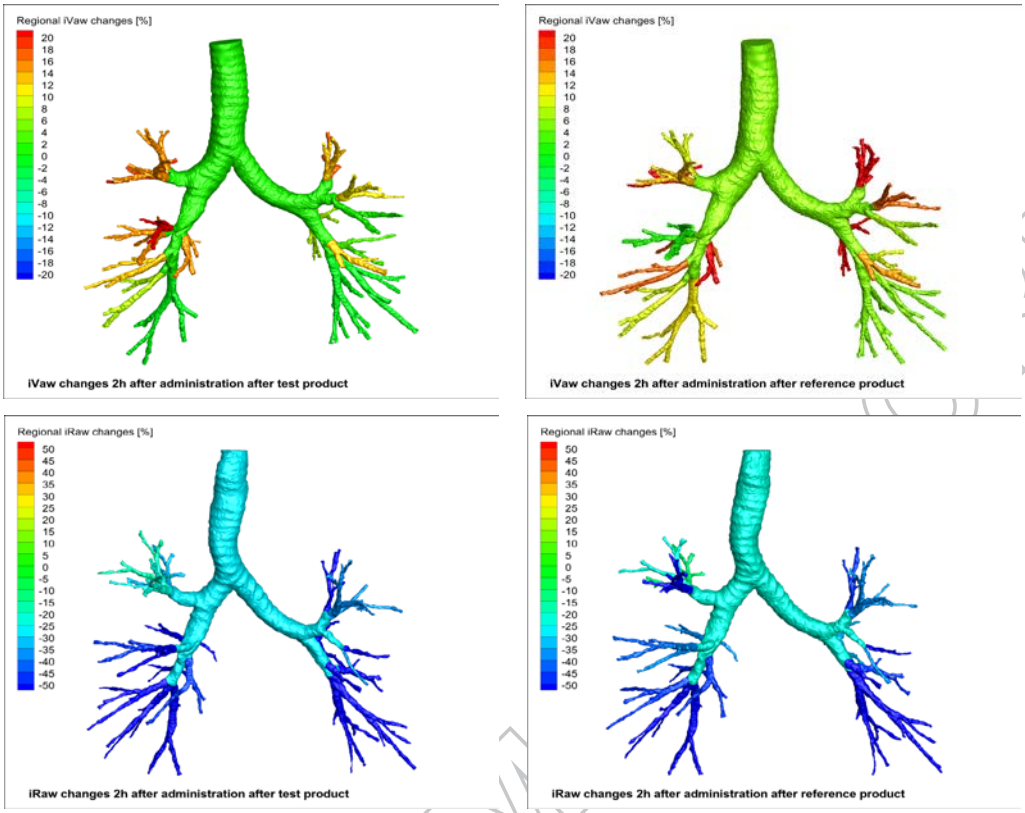

Figure 2: Difference in the effects of test and reference product on iVaw and iRaw two hours post–administration of study drug

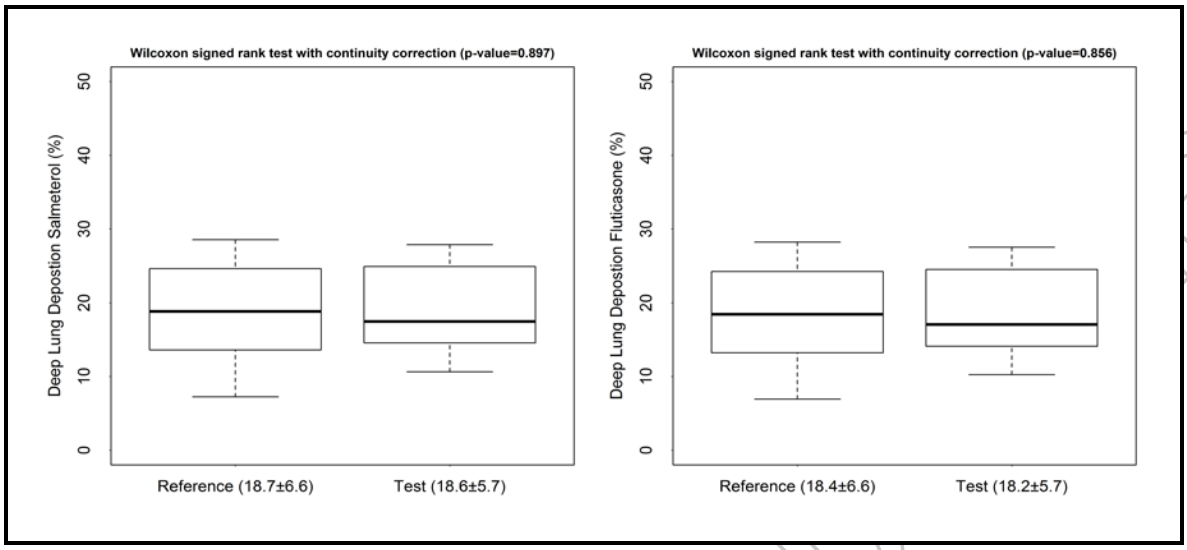

Figure 3: Lung deposition estimates for SM and FP for the reference and the Test Product

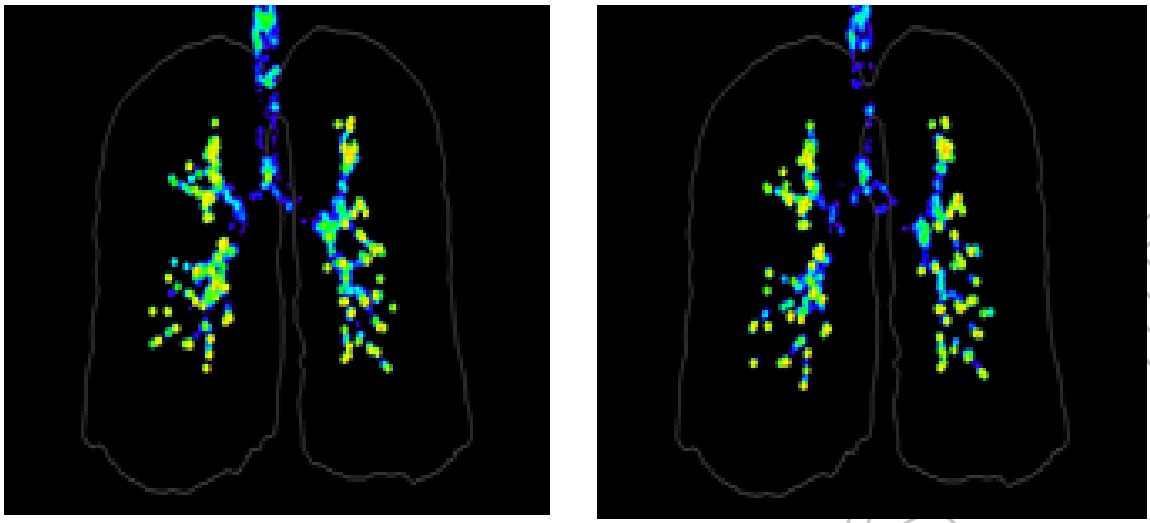

Figure 4: Lung deposition of inhaled salmeterol and fluticasone for the test (a) and the reference (b) product.