Comparative Pulmonary Function & Pharmacokinetics of Fluticasone Proprionate and Salmeterol Xinafoate in Asthmatics Using 3M Conix™ and Advair Diskus

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Introduction

Previous work demonstrated that the 3M Conix DPI system was capable of efficiently delivering a formulated sulfonate formulation in vivo (in drinking) (1). The purpose of this study was to take the 3M Conix technology, in the form of an inhalation pulsed device, into a clinical environment and demonstrate its capability of efficiently and safely delivering a combination therapy (fluticasone propionate and salmeterol xinafoate) to asthmatic patients. Response to both 3M Conix™ and Advair Diskus was assessed at FEV1 and blood plasma measurements.

The in vitro fine particle dose (FPD) performance of the Conix device was matched to that of Advair Diskus. 1000 DPI Advantage using Next Generation Impactor (NGI) testing, within a particle of 5 µm in diameter, unless otherwise stated by the manufacturer, there is a risk of greater lung deposition with the drug (2). This optimum size for deposition into the smaller spaces of the lung and clinical efficacy occurs in the region of 3 µm (3). Hence this size range was selected for in vivo testing of drug delivery from the study devices. This approach of matching FPD at 3 µm was also shown to the claim, testing for safety and efficacy, matching FPD at 5 µm would require a greater amount of each medication from Conix to be administered, particularly in the 5-µm region that was considered to be the most critical for systemic absorption.

Study Outline

The study was a single-centre, open label, subject in subjects with mild-to-moderate asthma who had been stable for at least 12 weeks prior to being enrolled. Subjects had to demonstrate 12% reversibility of bronchoconstriction with two inhalations of albuterol sulfate.

Safety was assessed by the occurrence of adverse events, including the need for rescue medication. Inhalation of the formulation from both 3M Conix and Advair Diskus were safe and well tolerated during the study. No adverse events were reported and no rescue medication was required.

Conclusions

The 3M Conix technology provided comparable improvement in pulmonary function compared with Advair Diskus while starting with drug in each pre-dose material. Those pulmonary function results suggest that both DPI devices can maintain efficacy but the estimated pharmacokinetic results help to underpin the fundamental differences between the devices, namely that the NGR data provides a greater amount of inter-individual variability with Advair Diskus. About 30% of the systemic activity of inhaled salmeterol from Advair Diskus comes from oral absorption of swallowed drug (4). Our study results show a greater amount of inter-individual variability with Advair Diskus than Conix. The advantage of Advair Diskus in this region correlated with greater bioavailability of the drug, leading to a greater percent of absorption on average with Advair Diskus which we attribute to inhaled drug. The advantage is due to greater mass of particles deposited by Advair in the 3-5 µm range (approximately between cups 2 and 3). Therefore electing to match the in vitro FPD cup-offs at 3 µm was not optimal for Advair because of the greater mass of particles produced by Advair in the 3-5 µm range. Therefore selecting to match the FPD cup-off point at 3 µm (approximately around cup 4 and below) Advair consistently produced more particles on each cup above this cut-off. Thus in matching to match FPD at a cut-off of 3 µm, Advair was delivered to approximately 28% more of each drug mass than Conix in the 5-µm range from Conix. This was due to the greater mass of particles produced by Advair in the 3-5 µm range (approximately between cups 2 and 3). Therefore matching to the in vitro FPD cup-offs at 3 µm did not match Advair properties when delivering all inhaled dose, the 3M Conix device delivered significantly more of each drug than Conix in the 5-µm region as a consequence.

As the Conix formulation was a development material, it was important that the formulation be shown to be stable. Stability was demonstrated after storage at 45°C for 6 months. The study was a single-centre, open label, trial in subjects with mild-to-moderate asthma who had been stable for at least 6 months. Subject No. 2 had contaminated predose values for both analytes, so the data from 17 subjects were evaluated for FEV1. Subject No. 2 had contaminated predose values for both analytes, so the data from 17 subjects were evaluated for FEV1. Subject No. 2 had contaminated predose values for both analytes, so the data from 17 subjects were evaluated for FEV1.

In summary, the stability and in vivo performance matching of 3M Conix to Advair demonstrates that the test device was suitable for the intended use and was not unfairly biasing the clinical study in favour of Conix.

Treatments

The reference treatment was one inhalation from an Advair Diskus label to deliver 100 µg Fluticasone propionate (Fluticasone) and 50 µg Salbutamol sulfate (Salmeterol) (4). The test treatment was delivered to be comparable to the in vivo FPD (<5 µm) of each drug in the reference, and was one inhalation from the Conix device which contained approximately 18% less of each drug per pre-dose dose relative to Advair due to the lesser in vitro efficiency of Conix. The Conix device contained a proprietary drug/liquid blend made using standard commercially available materials and was used from Loughborough. The two treatment conditions were compared in Table 1.

Table 1: Comparison of 3M Conix and Advair formulations

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<tr>
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<th>Fluticasone</th>
<th>Salmeterol</th>
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<tbody>
<tr>
<td>Conix</td>
<td>50.2%</td>
<td>49.8%</td>
</tr>
<tr>
<td>Advair</td>
<td>57.1%</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

The FPD of each drug delivered from the Conix Device was successfully matched (targeted to be within ±10%) that is from Advair using NGI matching (Table 2). The FPD of each drug delivered from the Conix Device was successfully matched (targeted to be within ±10%) that is from Advair using NGI matching (Table 2). The FPD of each drug delivered from the Conix Device was successfully matched (targeted to be within ±10%) that is from Advair using NGI matching (Table 2).

Table 2: Comparison of Conix and Advair DPI in Vivo Data

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone</th>
<th>Salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conix</td>
<td>75.7%</td>
<td>24.3%</td>
</tr>
<tr>
<td>Advair</td>
<td>81.2%</td>
<td>18.8%</td>
</tr>
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</table>

In summary, the stability and in vivo performance matching of 3M Conix to Advair demonstrates that the test device was suitable for the intended use and was not unfairly biasing the clinical study in favour of Conix.

Results

Implementation of the salmeterol pharmacokinetic data, without the need for an oral absorption mechanism, led to the following: 1. The extent of absorption (AUC) of fluticasone was ~30% greater with 3M Conix, whereas the extent of absorption of salmeterol was 41% greater with Advair Diskus. 2. Examination of the variability shown in Figures 3 and 4 illustrates that both DPI devices were equally consistent. 3. The study was a single-centre, open label, trial in subjects with mild-to-moderate asthma who had been stable for at least 12 weeks prior to being enrolled. Subjects had to demonstrate 12% reversibility of bronchoconstriction with two inhalations of albuterol sulfate.

Inhalation of the formulations from both 3M Conix and Advair Diskus were safe and well tolerated during the study. No adverse events were reported and no rescue medication was required.

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References