1 SYNOPSIS

Name of Company: **Chiesi Farmaceutici S.p.A.**	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CHF 1535 100/6 NEXT DPI®	**Volume:**	
Name of Active Ingredient: Beclomethasone Dipropionate plus Formoterol Fumarate	**Page:**	

Title of Study: A Single-Dose, Open Label, Two-Way Crossover, Clinical Pharmacology Study of Four Inhalations of CHF 1535 100/6 NEXT DPI® (Fixed Combination of Beclomethasone Dipropionate 100 µg Plus Formoterol Fumarate 6 µg) Versus The Same Dose of CHF 1535 100/6 pMDI Both Administered With Charcoal Block.

Investigators: Dr Dave Singh

Study Centre(s): Medicines Evaluation Unit

Publication (reference):

Studied Period: *(FPFV Date)* 12 May 2011 *(LPLV Date)* 09 June 2011	**Phase of development:** Phase II

Objectives:

Primary

- To compare the lung bioavailability of B17MP (active metabolite of Beclomethasone Dipropionate (BDP)) and formoterol (FF) after four inhalations using CHF 1535 100/6 NEXT DPI® and CHF 1535 100/6 pMDI with activated charcoal to block gastrointestinal absorption.

Secondary

- To evaluate the lung bioavailability of BDP.
- To assess the safety and tolerability of the study treatments.

Methodology *(Study Design):*

This study was performed according to an open-label, randomised, two-way crossover, single-dose design. The study comprised of two single dose treatment visits at clinic, separated by a wash-out period (seven days). At each treatment visit, blood samples were collected for pharmacokinetic evaluation.

A pre-screening visit (Visit 0) was performed to explain the study and to obtain signed informed consent. The screening visit (Visit 1) was performed within seven days of Visit 0. A maximum of 14 days was permitted between Visit 0 and Visit 2. Eligible patients entered the seven day run-in period and treatment visits (Visit 2 and Visit 3) were performed, separated by a seven days wash-out period. A follow-up phone contact was performed after seven days from the Visit 3 or after premature discontinuation.

Number of subjects *(planned and analyzed)* :

In order to obtain 18 evaluable subjects, 24 subjects (12 per sequence) were randomized. Anticipating a screen failure rate of 35 %, 36 subjects were screened. Twenty three evaluable subjects were obtained.

Diagnosis and main criteria for inclusion:
Adults (≥18 and ≤70 years old) diagnosed with asthma as defined by the Global Initiative for Asthma (GINA) guidelines, update 2009, at least in the six months before the screening visit:

1. undergoing treatment with low or medium daily dose of Inhaled Corticosteroids (ICS) (e.g. BDP or equivalent ≤1000 µg/die) or low dose of ICS/Long-Acting β2-agonists (LABA) fixed combination (e.g. salmeterol/fluticasone 100/500 µg/die).
2. with pre-bronchodilator forced expiratory volume in one second (FEV_1) ≥60 % and ≤90 % of the predicted values.

Test product, dose and mode of administration, batch number:
CHF 1535 100/6 NEXT DPI®: CHF 1535 dry powder for inhalation (fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation) administered via the NEXT DPI® dry powder inhaler with charcoal block.
Subjects were administered four puffs, giving a total dose of 400 µg BDP and 24 µg FF.
Batch number: NEXT DPI® ([redacted]).

Duration of treatment:
One-week run-in period followed by two one-day single-dose treatment periods, separated by a one-week wash-out period.

Reference therapy, dose and mode of administration, batch number:
CHF 1535 100/6 pMDI: Fixed combination of "extrafine" beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation administered via a pMDI standard actuator (marketed as Foster®) using AeroChamber Plus™ spacer, with charcoal block.
Subjects were administered four puffs, giving a total dose of 400 µg BDP and 24 µg FF.
Batch number: pMDI ([redacted]).

Criteria for evaluation :
Pharmacokinetics variables:
Primary variables:

- Plasma B17MP and formoterol AUC_{0-t}

Secondary variables:

- Plasma BDP AUC_{0-t}
- Plasma B17MP, formoterol and BDP, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{½}$

Safety variables

- Adverse Events
- Vital Signs: blood pressure and heart rate assessed at pre-dose and 30 mins, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose.

Statistical methods:
Pharmacokinetic variables:

- Plasma B17MP, formoterol and BDP AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were log-transformed and analysed using a linear model including treatment, sequence, period and subject within sequence as fixed effects. The ratios of adjusted geometric means between test and reference were calculated with their 90 % confidence intervals (CIs).
- Plasma B17MP, formoterol and BDP t_{max} and $t_{½}$ were summarised by treatment group using descriptive statistics.
- Plasma concentration/time curves, individual and based on mean values by treatment, were presented in linear/linear and log/linear scale.

Safety variables:

- The number and percentage of subjects experiencing adverse events, adverse drug reactions, serious adverse events and adverse events leading to subject withdrawal were presented for each treatment. Adverse events were summarised for each treatment by System Organ Class

and Preferred Term using the MedDRA dictionary.

- Mean changes from pre-dose to each time point post-dose in vital signs were calculated with their 95 % CIs.

Summary – Conclusions:

Pharmacokinetic Results:

The 90 % CIs for ratios between AUC_{0-t} of B17MP (active metabolite of BDP) and formoterol when comparing CHF 1535 100/6 via NEXT DPI® to CHF 1535 via pMDI fell entirely within the bioequivalence region of 80 %-125 %, therefore meeting the primary objective of the study. The estimates of the ratios and their 90 % CIs were 87.11 % (80.56 to 94.20 %) for AUC_{0-t} of B17MP and 110.40 % (102.75 to 118.61 %) for AUC_{0-t} of formoterol, respectively.

Analysis of the C_{max} for B17MP showed this was lower post CHF1535 via NEXT DPI® in comparison to pMDI. Furthermore (AUC_{0-t}) data provide demonstration that the amount of the ICS delivered to the lung with NEXT DPI® and pMDI in the target population is equivalent. The time to maximum exposure t_{max} was within 30 minutes for both treatments.

Conversely, the CI of the ratio NEXT DPI® /pMDI for formoterol C_{max} was marginally outside the upper limit of 125 %. However, it is of note that despite the slightly higher observed C_{max} value post delivery via NEXT DPI®, the AUC_{0-t} values were equivalent. The time to maximum exposure t_{max} was within 15 minutes for both treatments.

Safety Results:

In total across both delivery modes, 31 TEAEs were reported. One SAE was reported, which was considered unrelated to treatment. With the exception of the SAE, all TEAEs were classified as mild to moderate and resolved within a short time-frame.

Post CHF 1535 via NEXT DPI®, 15 TEAEs were reported in eight subjects (34.8 %). Related TEAEs observed in three subjects included tremors (n=3) and dizziness (n=1). Previous studies have also identified tremors as a related TEAE post- NEXT DPI®. These resolved rapidly with no lasting sequalae and therefore do not present a significant safety concern.

Post CHF 1535 via pMDI, 16 TEAEs were reported in ten subjects (41.7 %). Related TEAEs were observed in one subject who showed headache and dizziness. Both events resolved rapidly with no lasting effects.

There were no clinically significant trends or changes in blood pressure or heart rate post-administration of either NEXT DPI® or pMDI.

Conclusion:

Treatment with CHF 1535 100/6 via NEXT DPI® is safe, well tolerated with no major safety concerns. Furthermore, B17MP and formoterol lung bioavailability using the NEXT DPI® or the pMDI is equivalent and provide a robust demonstration that the amount of drug delivered to the lung in the target population is equivalent.

Date of report: 25 January 2012