2. SYNOPSIS

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

Title of Study: In-vivo Deposition Measurement of Beclomethasone and Formoterol after Inhalation of a single Dose of the Combination BDP plus Formoterol NEXT DPI® in Healthy Volunteers, Asthmatic and COPD Patients

Investigators: [redacted] MD
[redacted] - Germany

Study Centre(s): [redacted] - Germany

Publication (reference): Data not published

Studied Period: **First patient first visit:** 24 Aug 2010 **Last patient last visit:** 29 Sep 2010 (last follow-up: 06 Oct 2010)	**Phase of development:** I/II

Objectives:

Primary:

- To evaluate the amount of drug deposited within the lungs after inhalation of the radiolabeled fixed combination of BDP and Formoterol in healthy volunteers, asthmatic patients, and COPD patients, in terms of intrapulmonary deposition ($D_{L.E}$) relative to the emitted dose.

Secondary:

- To evaluate the intrapulmonary distribution and the extrathoracic deposition.
- To evaluate BDP, B17MP and Formoterol pharmacokinetics (PK).
- To evaluate the efficacy by lung function assessment.

Methodology *(Study Design):*
Open, uncontrolled, single dose study

Number of patients *(planned and analyzed)*:
Planned enrolment: 30 volunteers/patients, i.e. 10 subjects per group (healthy volunteers, asthmatic patients, COPD patients)
Planned completion: 8 subjects per group (healthy volunteers, asthmatic patients, COPD patients)
Actual enrolment: 12 healthy volunteers, 9 asthmatic patients, 9 COPD patients
Actual completion: 10 healthy volunteers, 9 asthmatic patients, 9 COPD patients

Diagnosis and main criteria for inclusion:
- Healthy volunteers
  - Male or female
  - Age 21–65 years
  - Non- or ex-smokers
  - Overall healthy
- Asthmatic patients
  - Male or female
  - Age 21–65 years
  - Non- or ex-smokers
  - Forced Expiratory Volume in the first second (FEV_1) ≥30% and <80% of predicted for the patient's normal value
  - Reversibility of FEV_1 ≥12% and at least 200 ml of the initial value 15 minutes after inhalation of Salbutamol, 200 µg
- COPD patients
  - Male or female
  - Age 40–70 years
  - Minimum smoking history of 10 pack-years
  - Stable COPD within the past four weeks
  - Post bronchodilator FEV_1 between 30% and 50% of predicted values
  - Post bronchodilator FEV_1/Forced Vital Capacity (FEV_1/FVC) ≤0.70 (absolute value)

Test product, dose and mode of administration, batch number:
Radiolabeled CHF 1535 100/6 NEXT DPI®
Inhalation of four single puffs, corresponding to total dose of 400 µg BDP + 24 µg Formoterol
Inhalation via DPI
Batch No.: [redacted]

Duration of treatment:
Each volunteer/patient received one single dose (one dose = four puffs)

Reference therapy, dose and mode of administration, batch number:
Not applicable

SYNOPSIS

Criteria for evaluation :

Efficacy:

- Drug deposition
  - Intrapulmonary deposition relative to the emitted dose ($D_{L,E}$)
  - Central to peripheral ratio (C/P)
  - Ratio of central, intermediate and peripheral deposition to total lung deposition
  - Variance of pixel counts (VAR)
  - Extrathoracic drug deposition ($D_{E,E}$)
  - Amount of exhaled activity ($M_{X,E}$)
- Lung function
  - FEV_1
  - FVC
  - Maximal expiratory flow at 25%, 50%, and 75% vital capacity (MEF_{25}, MEF_{50}, and MEF_{75})
- Pharmacokinetic parameters (BDP, B17MP and Formoterol)
  - Maximum plasma concentration (C_{max})
  - Time of maximal plasma concentration (T_{max})
  - Area under the plasma drug concentration-time curves (AUC_{0-t}, $AUC_{0-\infty}$; $AUC_{0-30\ min}$, (only for B17MP and Formoterol))

Safety:

- General medical examination
- Adverse events (AEs)
- Vital signs, electrocardiogram (ECG)
- Oxygen saturation

Statistical methods:

Descriptive statistics of parameters describing drug deposition (lung deposition, extrathoracic deposition, ratio central to peripheral, variance of pixel counts, exhaled activity) were calculated in each study group. Variables were compared between groups by an analysis of variance (ANOVA) using a linear model with subjects GROUP as independent variable. The model was calculated assuming group as fixed effect using the SAS procedure "Mixed" (see Appendix 16.1.9).

An exploratory data analysis was performed using Spearman Rank correlations analysis, to check correlation between baseline lung function and parameters quantifying drug deposition ($D_{L,E}$, $D_{E,E}$, C/P, VAR and $M_{X,E}$).

A second exploratory data analysis was done describing regions of interests: Ratio of central deposition to total deposition (C/T), ratio of intermediate deposition to total deposition (I/T), and ratio of peripheral deposition to total deposition (P/T).

Descriptive statistics were calculated in each group of subjects for lung function parameters (FEV_1, FVC, MEF_{25}, MEF_{50}, and MEF_{75}) as absolute and as percent of predicted values.

Descriptive statistics were calculated in each study group for PK parameters (C_{max}, T_{max}, AUC_{0-30}, AUC_{0-t}, and $AUC_{0-\infty}$). This analysis is presented as separate report and is included as an appendix to this clinical study report.

Summary – Conclusions:

The study enrolled 30 volunteers/patients: 12 healthy volunteers, 9 asthmatic patients, and 9 COPD patients. Of these, 28 subjects completed the study: 10 healthy volunteers, 9 asthmatic patients and 9 COPD patients. The 2 healthy volunteers which stopped prematurely were discontinued before receiving study medication. The safety population includes 28 subjects enrolled, who received at least one dose of study medication, and excludes 2 volunteers which were not exposed to study medication. The Intention-to-treat (ITT) population consists of 10 healthy volunteers, 9 asthmatic and 9 COPD patients. The per-protocol (PP) population consists of 9 healthy volunteers, 9 asthmatic and 9 COPD patients. One healthy volunteer was included in the ITT, but excluded from the PP population, because the weight of inhaled study medication was below the defined limit of 32 mg.

Efficacy Results:

Drug deposition of the inhaled fixed combination of Beclomethasone and Formoterol via the NEXT DPI® device was investigated in 10 healthy volunteers, 9 asthmatic patients, and 9 COPD patients (ITT-population). One healthy volunteer was not included in the PP analysis due to an insufficient amount of study drug inhaled. Similar lung deposition and extrathoracic deposition were observed among healthy volunteers, asthmatic patients and COPD patients. On both ITT and PP set average lung deposition was 55% relative to the emitted dose in healthy volunteers, 56% in asthmatic patients and 55% in COPD patients. Mean extrathoracic deposition was 43% in healthy volunteers, 42% in asthmatic patients and 42% in COPD patients. The exhaled amount was 1.63% in healthy volunteers, 1.92% in asthmatic patients and 3.28% in COPD patients. The difference in the exhaled amount between the healthy volunteers and the COPD patients was statistical significant (p=0.0116) but without any clinical relevance, due to the small amount of exhaled drug (< 3.3% of emitted dose). The distribution patterns in the lungs, evaluated by calculating the ratio between central and peripheral deposition (C/P ratio) and the variance of pixel counts (VAR) indicate that in COPD patients and in asthmatic patients the pulmonary deposition of radiolabeled drug was less homogeneous and more centralised compared to healthy volunteers. The C/P ratio and the variance of pixel counts were increased in patients compared to healthy volunteers (C/P ratio was 1.23, 2.02 and 1.57 and the VAR was 0.1, 0.3 and 0.18 for healthy volunteers, asthmatic and COPD patients respectively). Significant correlations between baseline lung function parameters and parameters describing lung deposition were found only in healthy volunteers and asthmatic patients regarding the C/P and the VAR parameters (see Table 14.2-6).

Additionally regions of interests were evaluated and the central/total, peripheral/total and intermediate/total (C/T, P/T, I/T) ratios were calculated. These parameters emphasized the results of the C/P ratio. The amount of drug deposited in the peripheral regions of the lungs was higher in healthy volunteers compared to the two patient groups.

Drug deposition in healthy volunteers, asthmatic and COPD patients following administration of one single dose of 4 puffs of the BDP/formoterol NEXT DPI® (100/6 µg) combination (mean ± s.d.)

	Healthy volunteers n=10	Asthmatic patients n=9	COPD patients n=9
Intrapulmonary drug deposition (% of the emitted dose)	55.2 ± 3.7	56.2 ± 5.8	54.9 ± 4.9
Extrathoracic deposition (% of the emitted dose)	43.2 ± 4.2	41.8 ± 5.6	41.8 ± 4.8
Exhaled fraction (% of the emitted dose)	1.63 ± 0.72	1.92 ± 1.55	3.28 ± 1.56
Ratio central to peripheral	1.23 ± 0.19	2.02 ± 0.59	1.57 ± 0.29
Variance of pixel counts	0.0001 ± 0.0000	0.0003 ± 0.0002	0.00018 ± 0.00007

After administration of BDP and Formoterol via the NEXT DPI®, lung function parameters improved over time reaching a maximum improvement generally within 1–2 hours and declining over the next 12–24 hours. As expected, FEV_1 improved most in asthmatic and COPD patients, and to a minor extent in healthy volunteers.
BDP and B17MP plasma profiles were comparable in healthy volunteers, asthmatic and COPD patients, well in agreement with the deposition results which were similar in the three study groups. Due to in-vitro contamination of plasma samples for Formoterol analysis during sample processing, the Formoterol plasma profiles could be evaluated only for 3 healthy volunteers and asthmatic patients and for 2 COPD patients. On average, individual profiles were almost similar in the three study groups.

Safety Results:
Overall, the AEs documented in this study were typical for variable day by day severity of the patient's disease. The Investigator considered all the events as not related to the study medication.
As a conclusion, the study did not elicit any new safety signals for the study medication BDP and Formoterol. Furthermore, no AEs or safety signs related to the inhalation device NEXT DPI® happened.

Conclusion:
The primary study endpoint showed that the fixed combination BDP plus Formoterol NEXT DPI® achieved similar and high mean intrapulmonary deposition relative to the emitted dose in healthy volunteers (55.2%), in asthmatic patients (56.2%) and in COPD patients (54.9%), indicating that a high and reproducible pulmonary dose was achieved in healthy volunteers and in asthmatic and COPD patients in different stages of their respective disease. Similar extra-thoracic deposition was observed in the three groups (43%, 42% and 42 % in healthy volunteers, asthmatic and COPD patients, respectively). Even if a statistically significant difference was detected (p=0.0116) between healthy volunteers and COPD patients the amount of drug was exhaled (< 3.3% of emitted dose) was devoid of clinical relevance.

Slightly lower homogeneity of the intrapulmonary distribution was observed in COPD patients and especially in asthmatic patients compared to healthy volunteers, being the amount of drug deposited into the intermediate and peripheral parts of the lungs lower in patients compared to healthy volunteers. Differences in homogeneity of drug distribution in the airways between healthy volunteers and patients reflect the characteristics of the lung diseases.

The correlation between baseline lung function parameters, i.e. pulmonary disease status, and parameters describing lung deposition was generally not relevant indicating that the deposition of drugs inhaled by the NEXT DPI® device is relatively independent of patient characteristics.

The intrapulmonary deposition of the fixed combination BDP plus Formoterol NEXT DPI® was very similar in all study groups thus confirming a good and reproducible delivery of the drug to the lung regardless the pathophysiological condition.

Administration of BDP/formoterol produced a FEV_1 increase in healthy volunteers and a more sustained bronchodilation in asthmatic and COPD patients. On average BDP and B17MP plasma profiles were comparable in healthy volunteers, asthmatic and COPD patients, in agreement with the deposition results which were similar in the three study groups

All AEs in this study were considered as not related to study medication or inhaler. Thus, the study did not elicit any new safety signals for BDP plus Formoterol or the inhalation device NEXT DPI®.