2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A. – Via Palermo 26/A – 43122 Parma – Italy	Individual Study Table Referring to Part of the Dossier Volume: Page:	(for National Authority Use Only)
Name of Finished Product: CHF 1535 NEXT DPI®		
Name of Active Ingredient: Fixed combination beclomethasone dipropionate 100 µg/unit dose plus formoterol fumarate 6 µg/unit dose		

Title of Study: A phase II, multinational, multicentre, double blind, double dummy, randomised, 5-way cross-over, placebo and active controlled clinical study to test the non-inferiority of a single dose of CHF 1535 (fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg dry powder) via NEXT DPI® 1 or 4 inhalations versus CHF 1535 (beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg) pMDI with HFA-134a propellant 1 or 4 puffs on FEV_1 AUC_{0-12h} in partly controlled adult asthmatic patients.

Investigators: Dr Singh (UK), Pr [redacted] Pr [redacted] Pr [redacted] Dr [redacted]), Dr [redacted] then Dr [redacted]

Study Centre(s): 6 sites in Europe (1 in the UK, 3 in France and 2 in Italy)

Publications (reference): None

Studied Period: First patient enrolled: 27 February 2009 Last patient out: 09 July 2009	**Phase of Development**: Phase II

Objectives:

Primary objective:

To demonstrate the non-inferiority in terms of FEV_1 AUC_{0-12h} between a single dose of CHF 1535 "extrafine" via NEXT DPI® (4 inhalations of beclomethasone dipropionate + formoterol fumarate, total dose: 400 + 24 µg) and CHF 1535 "extrafine" via pMDI (4 puffs of beclomethasone dipropionate + formoterol fumarate, total dose: 400 + 24 µg) and between a single dose of CHF 1535 "extrafine" via NEXT DPI® (1 inhalation of beclomethasone dipropionate + formoterol fumarate, total dose: 100 + 6 µg) and CHF 1535 "extrafine" via pMDI (1 puff of beclomethasone dipropionate + formoterol fumarate, total dose: 100 + 6 µg) in partly controlled adult asthmatic patients.

Secondary objectives:

- To compare for each treatment, CHF 1535 NEXT DPI® and CHF 1535 pMDI, the higher dose (400/24 µg) versus the lower dose (100/6 µg) in terms of FEV_1 AUC_{0-12h},
- To evaluate the efficacy of the two treatments on pulmonary function in terms of FVC and peak FEV_1,
- To evaluate the safety profile in terms of adverse events (AEs) and adverse drug reactions (ADRs) reporting, and vital signs.

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Methodology (Study Design):

This was a multinational, multicentre, randomised, double-blind, double-dummy, placebo and active-controlled, 5-way crossover study in patients with asthma.

At Visit 2 eligible subjects were equally randomised to one of five study treatment sequences to receive the 5 treatments (one per visit) according to a random order

- Treatment A: CHF 1535 NEXT DPI®, 4 inhalations (total dose: BDP 400 µg/FF 24 µg) + placebo pMDI, 4 puffs.
- Treatment B: CHF 1535 pMDI, 4 puffs (total dose: BDP 400 µg/FF 24 µg) + placebo NEXT DPI®, 4 inhalations.
- Treatment C: CHF 1535 NEXT DPI®, 1 inhalation (total dose: BDP 100 µg/FF 6 µg) + placebo NEXT DPI®, 3 inhalations + placebo pMDI, 4 puffs.
- Treatment D: CHF 1535 pMDI, 1 puff (total dose: BDP 100 µg/FF 6 µg) + placebo pMDI, 3 puffs + placebo NEXT DPI®, 4 inhalations.
- Treatment E: placebo NEXT DPI®, 4 inhalations + placebo pMDI, 4 puffs.

The study entailed a pre-screening visit (Visit 0) followed by a period of at least 14 days, a screening visit (Visit 1) followed by a run-in period of 7 to 10 days duration, and then the randomisation visit (Visit 2) followed by five randomised single dose treatment sequences. A wash-out period of 7±4 days separated each treatment visit (Visit 2 –Visit 6). A telephone follow-up (Visit 7) took place 7±4 days after the last treatment visit.

Number of Patients (Planned and Analysed):

Planned:

A total of 50 patients were planned to be evaluated. Assuming a drop-out rate of about 20%, a total of at least 65 patients were planned to be randomised.

Randomised:

The actual number of randomised and completed patients was 69 (out of 88 screened patients).

Efficacy population:

69 patients were included in the ITT population. One patient was excluded from the PP population for treatment period 3, and was valid for 4 sequences out of five.

Safety population:

69 patients were included in the safety population.

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Diagnosis and Main Criteria for Inclusion:

Patients could enter the study if they met all of the following criteria, checked at Visits 0, 1 and/or 2:

- Patient's written informed consent obtained prior to any study-related procedures. Patients not able of giving consent personally or vulnerable patients (except women of childbearing potential with acceptable method of contraception) cannot be included in the study.
- Male or female outpatients aged ≥ 18 years.
- Evidence for "partly controlled" asthma in the 2 weeks before the screening visit according to the Classification of Asthma Severity and Levels of Asthma Control of the Global Strategy for Asthma Management and Prevention (GINA guidelines 2006) i.e. one or more of the following:
  - daytime symptoms more than twice/week;
  - any limitations of activities or nocturnal symptoms/awakening;
  - need for reliever/rescue treatment more than twice/week.
- Daily dose of previous inhaled corticosteroids (ICS) treatment at the screening visit:
  - ≤ 2000 µg of CFC BDP or BDP "non-extrafine";
  - ≤ 800 µg of BDP "extrafine" HFA;
  - ≤ 1600 µg of budesonide;
  - ≤ 1000 µg of fluticasone;
  - ≤ 2000 µg of flunisolide;
  - ≤ 1200 µg of mometasone;
  - ≤ 1280 µg of ciclesonide.
- Forced expiratory volume in the first second (FEV_1) ≥ 60% and ≤ 90% of the predicted normal value at the screening visit.
- A documented positive response to the reversibility test at the screening visit, defined as $\Delta FEV_1 \geq 12\%$ and ≥ 200 mL over baseline, 30 minutes after 400 µg salbutamol pMDI (ATS/ERS Task Force 2005).
- Patients free of long-acting β_2-agonists (LABAs) treatment for at least 2 weeks before the screening visit.
- Patients free of short-acting β_2-agonists (SABAs) treatment for at least 6 hours before the screening visit.
- Non-smokers or ex-smokers with a cumulative tobacco exposure less than 5 pack-years and who have stopped smoking since more than 1 year.
- A cooperative attitude and ability to be trained in the proper use of a pMDI and a DPI.

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Test Product, Reference Therapy, Dose and Mode of Administration, Batch Number:

Test Product /Reference Therapy	Mode of administration	Batch number
Test Product: Treatment A CHF 1535 NEXT DPI® (total daily dose: BDP 400 µg/FF 24 µg)	4 inhalations of CHF 1535 NEXT DPI® **and** 4 puffs of placebo pMDI	[redacted]
Reference Therapy: Treatment B CHF 1535 pMDI (total daily dose: BDP 400 µg/FF 24 µg)	4 puffs of CHF 1535 pMDI **and** 4 inhalations of placebo NEXT DPI®	[redacted]
Test Product: Treatment C CHF 1535 NEXT DPI® (total daily dose: BDP 100 µg/FF 6 µg)	1 inhalation of CHF 1535 NEXT DPI® **and** 3 inhalations of placebo NEXT DPI® plus 4 puffs of placebo pMDI	[redacted]
Reference Therapy: Treatment D CHF 1535 pMDI (total daily dose: BDP 100 µg/FF 6 µg)	1 puff of CHF 1535 pMDI **and** 3 puffs of placebo pMDI plus 4 inhalations of placebo NEXT DPI®	[redacted]
Reference Therapy: Treatment E Placebo NEXT DPI® and Placebo pMDI	4 inhalations of placebo NEXT DPI® plus 4 puffs of placebo pMDI	[redacted]

Duration of Treatment: 5 single administrations (8 inhalations/puffs at each administration), separated by a wash-out period of 7±4 days.

Criteria of Evaluation:

Primary efficacy variable:

- FEV_1 $AUC_{0\text{-}12h}$ standardised by time (FEV_1 taken 10 min pre-dose and 10 min, 30 min, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours post-dose).

Secondary efficacy variables:

- FVC as assessed at the same time points as for FEV_1;
- Peak FEV_1 and peak FVC in terms of absolute values and % of change from baseline.

Safety evaluation

- Adverse events and adverse drug reactions;
- Heart rate, systolic and diastolic blood pressure in sitting position, pre-dose at each visit.

Statistical Methods:

The primary efficacy variable, FEV_1 $AUC_{0\text{-}12h}$, was submitted to an ANCOVA model with subject as random effect, treatment, country and period as fixed effects and pre-dose value as covariate. The ANCOVA provided the Least Square Means (LSMeans) estimation as well as the treatment differences along with the relative 95% CIs and p-values.

The inferential statistical analysis followed hierarchical rules along with a closed testing procedure.

For all the inferential analyses, p-value was rounded to three decimal places. Statistical significance was declared if the rounded p-value was less or equal to 0.050.

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Summary – Conclusions:

Efficacy Results:

The primary efficacy analysis demonstrated the non-inferiority of CHF 1535 NEXT DPI® (400/24 µg) vs. CHF 1535 pMDI (400/24 µg), as well as of CHF 1535 NEXT DPI® (100/6 µg) vs. CHF 1535 pMDI (100/6 µg) in terms of FEV_1 $AUC_{0\text{-}12h}$, in partly controlled adult asthmatic patients. In the ITT population, the lower limit of the 95% CI of the LSMeans difference between CHF 1535 NEXT DPI® and CHF 1535 pMDI was equal to -0.02 L for the 400/24 µg dosage, and equal to -0.06 L for the 100/6 µg dosage. With a pre-specified margin set at -0.2 L, the non-inferiority of the DPI formulation vs. the pMDI one was demonstrated for both dosages. The PP analyses confirmed these results. Comparable efficacy was observed also for secondary endpoints (peak FEV_1, FVC $AUC_{0\text{-}12h}$ and peak FVC), where LSMean differences between the two formulations at both dosages were always not statistically significant and clinically not relevant.

All active treatments showed marked superiority over placebo for all the clinical endpoints evaluated.

A statistically significant dose-response was found with both formulations. For the NEXT DPI® formulation, the estimated FEV_1 $AUC_{0\text{-}12h}$ difference between 400/24 µg and 100/6 µg was of 0.09 L with 95% CI ranging from 0.04 to 0.13 L ($p<0.001$); for the pMDI formulation, the estimated FEV_1 $AUC_{0\text{-}12h}$ difference between 400/24 µg and 100/6 µg was of 0.05 L with 95% CI ranging from 0.01 to 0.10 L ($p<0.027$).

Safety Results:

A total of 25 subjects (36.2%) reported at least one AE after the first study drug administration, 16 patients (23.2%) while on CHF 1535 NEXT DPI® 400/24 µg, 6 patients (8.7%) while on CHF 1535 NEXT DPI® 100/6 µg, 6 patients (8.7%) while on CHF 1535 pMDI 400/24 µg, 7 patients (10.1%) while on CHF 1535 pMDI 100/6 µg and 3 patients (4.3%) while on placebo. All events were mild or moderate in intensity.

The most frequently reported events were tremor (11.6% patients while on CHF 1535 NEXT DPI® 400/24 µg and 4.3% while on CHF 1535 pMDI 400/24 µg, none with the low dosages or placebo), and tachycardia or palpitations (7.2% patients while on CHF 1535 NEXT DPI® 400/24 µg and 2.9% while on CHF 1535 pMDI 400/24 µg, none with the low dosages or placebo). These events were always considered related to study treatment, with one exception for tremor in the CHF 1535 NEXT DPI® 400/24 µg group (related tremors were 7, corresponding to 10.1%). The reported events were generally mild in intensity (only one tremor and one palpitation moderate in intensity). Tremor and palpitation are events already expected with formoterol administered via pMDI or DPI, and documented in the CHF 1535 pMDI formulation already marketed (Foster®).

There was no serious or fatal event during the trial in any group and no severe AEs after treatment with CHF 1535. No event led to discontinuation.

Both formulations demonstrated a good safety profile.

Conclusion:

The present study demonstrated that CHF 1535 NEXT DPI® is non-inferior to the marketed CHF 1535 pMDI in terms of pulmonary function improvement, after a single administration of CHF 1535 100/6 µg or 400/24 µg in the morning. In particular this study confirmed the bronchodilator effect of formoterol up to twelve hours after inhalation both as a new dry powder formulation and as the marketed pMDI.

Overall, the study medication CHF 1535 NEXT DPI® is effective and well tolerated at both dosages when used in partly controlled asthmatic patients.

Date of Report: 23 July 2010