2. 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: **CHF6001 DPI**	**Volume:**	
Name of Active Ingredient: **CHF6001**	**Page:**	

Title of Study:	A randomised, double-blind, placebo-controlled, three-way crossover study to evaluate the efficacy after allergen challenge, safety, and tolerability of two doses of inhaled CHF6001 DPI after 9 days of treatment in adult patients with asthma.
Coordinating Investigator: Dave Singh, MD	
Study Centre(s):	3 clinical sites in UK. Coordinating site: Medicines Evaluation Unit (MEU). The Langley Building, Southmoor Road, Wythenshawe, Manchester, UK.
Publication (reference): None	

Studied Period: First Patient First Visit (FPFV): 01/Oct/2012 Last Patient Last Visit (LPLV): 10/Apr/2013	**Phase of development:** IIa

Objectives:

Primary Objective:

To determine the effect of CHF6001 Dry Powder Inhaler (DPI) in attenuating the late asthmatic response (LAR) after an allergen challenge (AC) following 9 days of inhaled dosing in adult subjects with allergic asthma.

Secondary Objectives:

- To determine the effect of CHF6001 DPI in attenuating the early asthmatic response (EAR) and responsiveness to MCh challenge 24 h after an AC,
- To assess the allergen induced changes in sputum eosinophils, neutrophils and mediators (eosinophilic cationic protein [ECP], neutrophil elastase [NE], Interleukin-5 [IL-5], IL-8) 10 h after an AC,
- To assess safety and tolerability,
- To measure systemic exposure to CHF6001 and its metabolites CHF5956 and CHF6095.

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Methodology *(Study Design):*

The study was a randomised, double-blind, placebo-controlled, 3-way crossover design evaluating the efficacy and safety of two doses of inhaled CHF6001 DPI administered for 9 days to non-smoking, mild to moderate steroid-naive allergic asthmatics before an AC test.

Number of subjects *(planned and analysed)*:

Approximately 30 subjects were to be randomised in order to have 24 evaluable subjects by the end of the study.

A total of 88 subjects were screened out of which 36 subjects were randomised to one of the six treatment sequences (L-H-P, L-P-H, H-L-P, H-P-L, P-L-H, or P-H-L) and received study drug, i.e., six subjects per treatment sequence. Thirty-three (91.7%) out of 36 randomised and treated subjects completed the study; three (8.3%) subjects discontinued the study (one subject withdrew consent and two subjects discontinued due to a treatment-emergent adverse event (TEAE).

Diagnosis and main criteria for inclusion:

Steroid-naive subjects, generally in good health with a history of atopy, episodic wheeze and shortness of breath, a diagnosis of intermittent or persistent mild to moderate allergic asthma, as defined by the Global initiative for management asthma (GINA) guidelines, and with a pre-bronchodilator FEV_1 ≥70% of the subject's predicted value at screening and on Day 1 of the first treatment period were eligible for enrolment.

In addition, at randomisation, subjects had to present a 'dual response' to AC, i.e., to demonstrate both a positive allergen-induced LAR as defined by a fall from post-diluent value in FEV_1 of ≥15% between 4 to 10 h following the final concentration of allergen was administered, on at least three occasions, two of which were consecutive, and a positive allergen-induced EAR as defined by a fall from post-diluent value in FEV_1 of ≥20% between 5 to 30 min following the final concentration of allergen was administered, on at least one occasion.

In the 'sputum producer' cohort (defined as a subgroup of a minimum 20 randomised subjects), subjects had to be able to produce an adequate induced sputum sample, 10 h after AC at screening. "Adequate sputum" was defined as a load of at least 75 mg with a viability factor equal or more than 40% (with ideally less than 30% epithelial cells).

Test product, dose and mode of administration, batch number:

CHF6001, oral inhalation in the morning through a single dose dry powder inhaler (SDDPI) for capsules (Aerolizer®).

- Dose 1: one capsule of CHF6001 400 µg with two capsules of CHF6001 placebo giving a total daily dose of 400 µg (low dose).
- Dose 2: three capsules of CHF6001 400 µg giving a total daily dose of 1200 µg (high dose).

Batch no.: [redacted], recheck date: [redacted]

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Duration of treatment:

Two screening visits were performed, 2 to 4 weeks before randomisation, to assess subjects' eligibility, followed by three 9-day treatment periods separated each by a 4 to 5-week wash-out period. A final safety phone call was done 1 to 2 weeks after the end of the last treatment period. The total duration of the study was approximately 15 to 20 weeks for each participant.

Reference therapy, dose and mode of administration, batch number:

Three capsules of CHF6001 placebo, oral inhalation in the morning through a SDDPI for capsules (Aerolizer®).

Batch no.: [redacted], recheck/expiry date: [redacted]

Criteria for evaluation:

Efficacy:

Primary Variable:

- The LAR on Day 9, defined as the weighted area under the curve (AUC) of the FEV_1 percent changes from post-diluent value from 4 to 10 h post-AC (FEV_1 $AUC_{4\text{-}10h}$).

Secondary Variables:

- The LAR on Day 9, defined as the weighted area under the curve (AUC) of the FEV_1 absolute changes from post-diluent value from 4 to 10 h post-AC (FEV_1 $AUC_{4\text{-}10h}$).
- The EAR on Day 9, defined as the weighted AUC of the FEV_1 percent and absolute changes from post-diluent value from 5 min to 2 h (FEV_1 $AUC_{0\text{-}2h}$);
- Maximum fall in FEV_1 during EAR and LAR on Day 9 defined as the maximum decrease in the percent and absolute change in FEV_1 between 5 min and 2 h post-diluent for EAR and between 4 and 10 h for LAR;
- Allergen induced changes in sputum eosinophils and neutrophils (absolute and %) and mediators (ECP, NE, IL-5, IL-8) at 10 h post-AC;
- Responsiveness to a MCh challenge 24 h post-AC defined as the provocative MCh challenge concentration causing a 20% decrease in FEV_1 ($PC_{20}FEV_1$);
- Pre-dose FEV_1 on Day 4, Day 9 and Day 10 (before MCh challenge).

Safety:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Lung function: FEV_1 to assess potential occurrence of paradoxical bronchospasm on Day 1 (2 h spirometry measurements);
- Vital signs: pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP);
- 12-lead electrocardiogram (ECG) parameters (heart rate [HR], PR, QRS, QT, QTcB, QTcF intervals) on Day 1, Day 9 and Day 10;
- Laboratory parameters (clinical chemistry, haematology and urinalysis) on Day 10;
- Body weight on Day 1 and Day 10.

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Pharmacokinetics:

$AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}24h,ss}$, $C_{max,ss}$, $C_{min,ss}$, $C_{av,ss}$, $t_{max,ss}$, $t_{min,ss}$, $t_{½,ss}$, CL/F_{ss} and V_z/F_{ss}, were calculated for CHF6001 and its metabolites CHF5956 and CHF6095 from the individual drug concentration versus time profiles on Day 9, at steady state.

Statistical methods:

Efficacy variables

- The LAR measured as the weighted mean FEV_1 $AUC_{4\text{-}10h}$ (primary endpoint) was compared by treatments by means of an analysis of variance (ANOVA), including treatment, subject and period as fixed effects;
- The maximum decrease in FEV_1 vs. post-diluent value in the 4-10 h interval post-AC, the EAR measured as the weighted mean FEV_1 $AUC_{0\text{-}2h}$, and maximum decrease in FEV_1 vs. post-diluent value in the 5 min - 2 h interval post-AC were analysed using the same model as for primary efficacy analysis;
- Methacholine challenge $PC_{20}FEV_1$ measurements were analysed using the same model as for primary efficacy analysis after log_2-transformation of data;
- The allergen-induced airway inflammatory cells, ECP, and NE were compared between treatments using an ANOVA, including treatment, subject and period as fixed effects. Non-normally distributed data were log-transformed before analysis. IL-5, and IL-8 data were summarised by means of descriptive statistics;
- The FEV_1 change from baseline to pre-dose value of Day 4, 9, and 10 was summarised by treatment using descriptive statistics.

Safety variables

- The number and percentage of subjects experiencing AEs, ADRs, serious AEs (SAEs) and AEs leading to study withdrawal were presented by treatment. Adverse events were summarised by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA);
- The mean FEV_1 on Day 1 as well as the percentage change from pre-dose values to each Day 1 post-dose time point (up to 2 h post-dose) were calculated with their 95% confidence intervals (CIs) by treatment;
- For vital signs (pulse rate, SBP, DBP), the mean absolute value, the mean change from pre-dose and mean placebo-adjusted change from pre-dose with related 95% CI were calculated by treatment at each post-dose time point on Day 1 and Day 9. In addition, the change from baseline and the placebo-adjusted change from pre-dose of each study day were presented;
- For 12-lead ECG parameters (HR, PR, QRS, QT, QTcB, QTcF), the mean absolute values with its 95% CI, the mean change from the pre-dose and the mean placebo-adjusted change from pre-dose with related 90% CI were calculated by treatment at each post-dose time point on Day 1 and Day 9. In addition, the change from baseline and the placebo-adjusted change from pre-dose of each study day were presented;
- Time profile plots by treatment were presented for the change from pre-dose (Day 1) value for vital signs and 12-lead ECG parameters;

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- For both QTcB and QTcF, the number and percentage of subjects with a:
  - QTc interval >450 ms, >480 ms and >500 ms at each time point and at any post-baseline study day/time point;
  - change from baseline (pre-dose Day 1) to pre-dose Day 9 and 10 in QTc interval >30 ms and >60 ms and at any study day;
  - change from pre-dose value on Day 1 and Day 9 in QTc interval >30 ms and >60 ms at each time point post-dose and at any time point post-dose.

  were presented by treatment.
- Abnormal findings on 12-lead ECG were summarised by treatment using descriptive statistics;
- Shift tables with regard to normal range were presented for all relevant laboratory parameters on Day 10;
- Mean changes in body weight from baseline (Day 1) to Day 10 with their 95% CI were calculated by treatment.

Pharmacokinetic (PK) variables

Plasma CHF6001 and its metabolites CHF5956 and CHF6095 PK variables were summarised using descriptive statistics.

Summary – Conclusions:

- **Efficacy Results (mITT population):**

Late and Early Asthmatic Response

❖ Primary efficacy variable: weighted AUC of the FEV_1 percent changes from baseline (post-diluent) value from 4 to 10 h post-AC

Adjusted mean (95% CI) LAR expressed as FEV_1 $AUC_{4\text{-}10h}$ percent changes from baseline (%*h) was -16.70 (-18.73; -14.68) %*h, -14.94 (-16.96; -12.92) %*h, and -20.80 (-22.98; -18.62) %*h after treatment with CHF6001 400 µg, CHF6001 1200 µg and placebo, respectively, for the mITT population.

Both doses of CHF6001 resulted in a significant attenuation of the LAR after 9 days of treatment. The low dose of CHF6001 (400 µg daily) caused a reduction of 19.7% (p=0.015) and the high dose (1200 µg daily) a reduction of 28.2% (p<0.001) of the weighted FEV_1 $AUC_{4\text{-}10h}$ (%*h) compared with placebo. No statistically significant difference in LAR expressed as $AUC_{4\text{-}10h}$ (%*h) was observed between CHF6001 400 µg and CHF6001 1200 µg.

Similar findings were observed in the PP population.

LAR $AUC_{4\text{-}10h}$, (%*h)	**CHF6001 400 µg vs. Placebo**			**CHF6001 1200 µg vs. Placebo**			**CHF6001 1200 µg vs. 400 µg**		
	PE	**95%CI**	**p-value**	**PE**	**95%CI**	**p-value**	**PE**	**95%CI**	**p-value**
mITT population	4.093	0.733; 7.454	0.015	5.858	2.489; 9.226	<0.001	1.764	-1.099; 4.628	0.223
PP population	3.611	0.210; 7.013	0.036	5.609	2.210; 9.008	<0.001	1.998	-0.926; 4.921	0.176

PE: point estimate; CI: confidence interval

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❖ Secondary efficacy variables:

o LAR expressed as weighted AUC of the FEV_1 absolute changes from baseline (post-diluent) value from 4 to 10 h post-AC

Similar results were obtained for FEV_1 $AUC_{4\text{-}10h}$ absolute changes from baseline (L*h), where the reduction was 20.3% with CHF6001 400 µg (p=0.014) and 29.9% with CHF6001 1200 µg (p<0.001) compared with placebo. No statistically significant difference in $AUC_{4\text{-}10h}$ (L*h) was observed between CHF6001 400 µg and CHF6001 1200 µg.

o LAR expressed as the maximum percent and absolute change in FEV_1 from baseline (post-diluent value) in the time interval 4-10 h post-AC

Reductions of 15.6% (p=0.028) and 22.9% (p=0.001) of the maximum FEV_1 % fall were observed respectively for CHF6001 400 µg and CHF6001 1200 µg compared with placebo. Similar results were obtained for the maximum absolute FEV_1 fall (L).

The reduction of the weighted FEV_1 AUC absolute changes and of the maximum fall in FEV_1 was higher with the CHF6001 high dose compared to the low dose, but the difference was not statistically significant.

o Early asthmatic response

The reductions in EAR for both doses were limited and not statistically significant compared with placebo (4.3% and 7.6%, respectively for the low and high dose in terms of weighted $AUC_{0\text{-}2h}$ [%*h] and 7.9% and 11.1%, respectively, for the low and high dose in terms of percent fall in FEV_1). Similar results were observed for EAR expressed as weighted $AUC_{0\text{-}2h}$ absolute FEV_1 change from post-diluent value (L*h) and as maximum absolute FEV_1 fall from post-diluent value (L).

Methacholine Challenge

Only the low dose of CHF6001 significantly reduced the response to MCh challenge post-AC by a 0.7 doubling dose of $PC_{20}FEV_1$ compared with placebo (p=0.028) while the difference over placebo with the high dose was only 0.4 doubling dose and did not reach statistical significance. The adjusted geometric mean (95% CI) MCh $PC_{20}FEV_1$ was 0.826 (0.627; 1.088) mg/mL, 0.652 (0.499; 0.851) mg/mL and 0.505 (0.378; 0.674) mg/mL after treatment with CHF6001 400 µg, CHF6001 1200 µg and placebo, respectively.

	CHF6001 400 µg vs. Placebo			**CHF6001 1200 µg vs. Placebo**		
MCh $PC_{20}FEV_1$	**PE**	**95%CI**	**p-value**	**PE**	**95%CI**	**p-value**
Treatment ratio	1.635	1.049; 2.548	0.028	1.290	0.826; 2.014	0.331
Adjusted mean difference (doubling concentrations)	0.710	0.144; 1.275		0.367	-0.200; 0.935	

PE: Point estimate; CI: confidence interval, mITT population

Induced Sputum Cells and Biomarkers

The assessment of these parameters was performed in a limited number of subjects (N=27), i.e., only subjects who were able to produce an adequate sputum sample during the treatment period (the '*sputum producer*' subset).

A trend in the reduction of eosinophil and macrophage counts (both absolute numbers and differential count) was observed with both doses of CHF6001 compared with placebo but none were statistically significant with the exception of the effect of CHF6001 low dose on macrophage differential count (p=0.029).

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- **Pharmacokinetic Results:**

The key plasma PK parameters for CHF6001 and its metabolites are summarised overleaf (geometric mean and geometric coefficient of variation [CV%] values unless otherwise stated).

PK Parameter, geometric mean (CV%)	CHF6001		CHF5956		CHF6095	
	CHF6001 400µg	CHF6001 1200 µg	CHF6001 400µg	CHF6001 1200 µg	CHF6001 400µg	CHF6001 1200 µg
$C_{max,SS}$ (pg/mL)	346 (44.2)	1025 (39.8)	34.6 (63.4)	95.8 (57.5)	NC	52.3 (55.8)
$C_{min,SS}$ (pg/mL)	133 (59.8)	393 (51.8)	NC	NC	NC	NC
$C_{avg,SS}$ (pg/mL)	207 (50.6)	614 (45.3)	9.56 (94.2)	36.0 (62.8)	2.92 (103)	17.4 (48.9)
$t_{max,SS}$ (h)[a]	2.00 (1.50-4.25)	2.00 (1.02-4.00)	3.00 (2.00-4.00)	3.00 (1.50-6.05)	2.97 (1.53-4.02)	2.00 (1.50-6.05)
$t_{min,SS}$ (h)[a]	24.00 (9.88-24.1)	24.00 (10.0-24.3)	24.00 (3.98-24.1)	24.00 (10.0-24.3)	6.00 (3.00-24.0)	24.00 (6.00-24.3)
$t_{1/2,SS}$ (h)	22.9 (38.9)	23.8 (28.9)	8.34 (150)	9.45 (82.8)	14.0 (253.0)	11.9 (95.6)
$AUC_{0-t, SS}$ (h*pg/mL)	4960 (50.6)	14746 (45.3)	166 (122)	813 (72.0)	NC	330 (74.9)
$AUC_{0-24h, SS}$ (h*pg/mL)	4959 (50.6)	14744 (45.3)	229 (94.2)	863 (62.8)	70.2 (103)	417 (48.9)
CL_{SS}/F (mL/min)	1344 (50.6)	1356 (45.3)	29071 (94.2)	23169 (62.8)	94984 (103)	47927 (48.9)
V_z/F_{SS} (L)	2659 (50.7)	2791 (44.0)	16462 (201)	18631 (86.8)	54739 (559)	47694 (89.8)

NC: value not calculated = number of subjects
[a] Median (range)

❖ CHF6001

The CHF6001 profile was similar across both doses. CHF6001 peaked at 2 h post-dose and a number of subjects exhibited a double peak around t_{max} and a secondary peak between 8 and 10 h post-dose. Subsequent to C_{max}, concentrations tended to decline in a biphasic manner with plasma CHF6001 remaining quantifiable for the duration of sampling in all subjects. Exposure to CHF6001 appeared to increase dose proportionally with similar elimination half-lives (geometric mean values of 23 and 24 h, respectively) and clearances (geometric mean values of 1344 and 1356 mL/min, respectively) at both dose levels.

❖ CHF5956

The CHF5956 profile was similar across both CHF6001 doses. CHF5956 peaked at 3 h post-dose and remained quantifiable in plasma for at least 8 to 10 h post-dose in most subjects after the CHF6001 400 µg dose and for the duration of sampling in most subjects after the CHF6001 1200 µg dose. Exposure to CHF5956 appeared to increase dose proportionally with similar elimination half-lives (geometric means of 8.3 and 9.5 h, respectively).

❖ CHF6095

The CHF6095 profile was similar across both CHF6001 doses. CHF6095 peaked at median 2 to 3 h post-dose and remained quantifiable in plasma for at least 4 to 6 h post-dose in most subjects after the CHF6001 400 µg dose and for 10 to 24 h after the CHF6001 1200 µg dose. CHF6095 C_{max} appeared to increase sub-proportionally to the CHF6001 dose while AUC_{0-t} increased supra-proportionally. CHF6095 showed similar elimination half-lives after the two CHF6001 doses (geometric means of approximately 14 and 12 h, respectively).

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- **Safety Results:**

Treatment-Emergent Adverse Events (TEAE)	CHF6001 400 µg N=34	CHF6001 1200 µg N=33	Placebo N=35	Wash-Out N=35	Total[a] N=36
Most frequently reported TEAEs (in >2 subjects per treatment period)					
Headache	7 (20.6)	4 (12.1)	4 (11.4)	6 (17.1)	15 (41.7)
n (%) with at least one TEAE	13 (38.2)	10 (30.3)	13 (37.1)	16 (45.7)	28 (77.8)
n (%) of deaths	0	0	0	0	0
n (%) with at least one serious TEAE	0	0	1 (2.9)	0	1 (2.8)
n (%) with at least one TEAE leading to withdrawal	1 (2.9)	0	1 (2.9)	0	2 (5.6)
n (%) with at least one severe TEAE	0	0	1 (2.9)	0	1 (2.8)
n (%) with at least one TEAE considered to be treatment-related by the Investigator	1 (2.9)	1 (3.0)	1 (2.9)	1 (2.9)	3 (8.3)

N = number of subjects; n = number of subjects with that observation
[a] Any TEAEs during wash-out and follow-up are included in the total column, no TEAEs occurred during follow-up.

No deaths were reported during the study. Two subjects were withdrawn prematurely from the study due to TEAEs: one subject due to hypersensitivity (a severe reaction to AC) during treatment with placebo reported as an SAE and one subject due to a mild and non-serious exacerbation of asthma during treatment with CHF6001 400 µg.

Treatment-emergent AEs were observed in approximately one third of the study population: 13 (38.2%), 10 (30.3%), and 13 (37.1%) subjects during treatment with CHF6001 400 µg, CHF6001 1200 µg, and placebo, respectively. No relevant differences in incidence of TEAEs between the treatments were observed. The most frequent TEAE was headache reported in 7 (20.6%), 4 (12.1%) and 4 (11.4%) subjects during treatment with CHF6001 400 µg, CHF6001 1200 µg, and placebo, respectively. Of interest, gastrointestinal disorders were scarce. One treatment-related AE was reported with each treatment: dyspepsia in one subject while on CHF6001 400 µg and insomnia, one subject each during treatment with placebo and CHF6001 1200 µg.

No clinically relevant trends or changes in laboratory values were observed. None of the individual changes in laboratory parameters were considered clinically relevant and reported as TEAE.

Mean changes from pre-dose and post-dose in DBP and SBP on Day 1 and Day 9 were small as were mean changes in body weight. Of note, mean changes in body weight were larger after treatment with CHF6001 400 µg (-0.42 kg) and CHF6001 1200 µg (-0.95 kg) than after treatment with placebo (-0.23 kg). None of these changes were considered clinically relevant and reported as TEAE.

Likewise, mean changes from baseline in HR and ECG parameters (PR, QRS, QTcB and QTcF intervals) on Day 1 and Day 9 were generally small. No QTcB or QTcF values of >450 ms were reported in any subject. None of the subjects had an increase from baseline values of >60 ms in QTcB and none of the subjects had an increase of >30 ms in QTcF. With the exception of a first degree atrioventricular block reported in one subject during treatment with CHF6001 1200 µg, no other clinically relevant ECG abnormalities were reported.

No significant decrease in FEV_1 values after study drug administration was observed.

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Conclusion:

CHF6001 reduced the airway response to AC in asthmatic subjects by significantly attenuating the late response in a dose dependent manner. No effect was observed on the EAR. In the 'sputum producer' subgroup of subjects, a decrease in sputum total cell count, eosinophils and macrophages (absolute and percent count) was observed with both doses of CHF6001 compared with placebo, although the differences did not achieve statistical significance. No differences were observed in neutrophil count nor in sputum biomarkers (ECP and NE). The effect on methacholine reactivity 24 h after AC was limited, a statistically significant PC20 doubling dose difference of 0.7 was observed with CHF6001 low dose compared with placebo.

The systemic exposure to CHF6001 appeared proportional to the doses administered. The low systemic exposure of metabolites compared to the parent compound, suggests limited formation of CHF5956 and CHF6095 *in-vivo*.

Both doses of CHF6001 proved to be safe and well tolerated particularly with respect to gastrointestinal disorders. No serious or severe related AE was reported nor was there an apparent clinically relevant signal on laboratory, vital signs and ECG parameters.

Date of report: 25 February 2014