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Sharing Clinical Study Report Synopsis

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Chiesi

2 SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43100 Parma, Italy **Name of Active Ingredient:** Beclomethasone dipropionate 100 µg/unit dose plus formoterol fumarate 6 µg/unit dose **Name of Finished Product:** Foster®	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(for National Authority Use only)*

Title of the study: a 48-week, double blind, double dummy, randomised, multinational, multicentre, 3-arm parallel group clinical study of "fixed combination" Beclomethasone dipropionate plus Formoterol fumarate administered via pMDI with HFA-134a propellant (CHF 1535) versus "fixed combination" Budesonide plus Formoterol DPI (Symbicort® Turbohaler®, AstraZeneca) versus Formoterol DPI (Oxis® Turbohaler®, AtraZeneca) in patients with stable severe chronic obstructive pulmonary disease (COPD)

Investigators: 76 principal investigators, 6 in Bulgaria, 4 in France, 12 in Italy, 28 in Poland, 9 in Russia, 3 in Spain, 12 in Ukraine and 2 in the UK at sites that screened at least one patient. Further investigational centres were opened (see complete list in Appendix 16.1.4), but no patients were enrolled in these centres.

Study centres: 76 centres, 6 of which located in Bulgaria, 4 in France, 12 in Italy, 28 in Poland, 9 in Russia, 3 in Spain, 12 in Ukraine, 2 in the UK, were authorized by Ethic Committees and Regulatory Authorities and screened at least one patient.

Publication (reference): None

Study period: FPFV: 22.12.2006; LPLV: 07.08.2008	**Phase of development:** III

Objectives: The primary objectives of the study were to demonstrate that Foster® is non-inferior to Symbicort® in terms of pulmonary function (change in pre-dose morning FEV_1 from baseline to 48 weeks) and superior to formoterol alone in terms of number of COPD exacerbations [rate of exacerbations (number/patient/year) over 48 weeks] in patients with stable severe COPD.

The secondary objectives of this study were:

- To assess the efficacy of the test treatments in: St Georges Respiratory Questionnaire (SGRQ), COPD symptoms; other pulmonary function parameters (FVC, PEF, $FEF_{25-75\%}$); use of "rescue" medication; number of moderate (requiring treatment with oral corticosteroids and/or antibiotics, or a visit to an emergency department) and severe (requiring hospitalization) COPD exacerbations; time to first moderate and severe COPD exacerbation; dyspnoea index; BODE index;
- To evaluate the safety profile of the test treatments in: rate of adverse events (AEs) and adverse drug reactions (ADRs); electrocardiography (ECG); blood chemistry (serum potassium, serum cortisol and plasma glucose levels); vital signs.

Methodology (Study Design):

This was a phase III, double blind, double dummy, randomised, multinational, multicentre, 3-arm parallel group clinical study in patients with stable severe COPD to compare the efficacy and safety of CHF 1535 pressurized metered dose inhaler (pMDI) vs. the fixed combination budesonide plus formoterol dry powder via Turbohaler® (Symbicort®, AstraZeneca) and formoterol dry powder via Turbohaler® (Oxis® AstraZeneca), over a 48-week treatment period.

The treatment period was preceded by a 4-week run-in period, during which patients discontinued all COPD treatments and were treated with the combination ipratropium/salbutamol 20µg /100µg, two puffs t.i.d. and "rescue" salbutamol given on an as needed basis. Subjects satisfying all the inclusion and exclusion criteria then entered the randomised treatment period. Clinic visits took place at the start and end of the run-in period, and after 4, 12, 24, 36 and 48 weeks after randomisation.

Number of patients:

	Planned	Randomised	ITT	PP	Safety	Completed
Total	576	718	703	679	716	621
BDP/Formoterol pMDI	192	237	232	223	236	205
Budesonide/formoterol DPI	192	242	238	231	242	212
Formoterol DPI	192	239	233	225	238	204

Diagnosis and main criteria for inclusion:

- Written informed consent obtained;
- Male and female outpatients, aged ≥ 40 years;
- Patients with a clinical diagnosis of COPD (according to GOLD guidelines);
- FEV_1 ≥ 30% and < 50% of the predicted normal values post-bronchodilator (and at least 0.7 L absolute value);
- FEV_1/FVC ratio ≤ 70%;
- FEV_1 reversibility test: ΔFEV_1 30 minutes following inhalation of 200 µg of salbutamol pMDI less than 12% of predicted normal value
- COPD symptoms for at least 2 years;
- At least 1 exacerbation requiring medical intervention (oral corticosteroid and/or antibiotic treatment and/or need for a visit to an emergency department and/or hospitalisation) within 2-12 months before the screening visit;
- Current or previous smoker (in both cases with a cumulative exposure to cigarette smoke of more than 20 pack-years);
- A cooperative attitude and ability to be trained to use correctly the pMDI and the DPI inhalers.

Test product, dose and mode of administration, batch no: Beclomethasone dipropionate plus formoterol (CHF 1535, Foster®, Chiesi Farmaceutici S.p.A.), unit doses 100 µg beclomethasone dipropionate + 6 µg formoterol, administered via pMDI using an HFA-134a propellant. Dose: 2 puffs (plus placebo matching Budesonide plus Formoterol Turbohaler®, 2 inhalations, and placebo matching Formoterol Turbohaler®, 1 inhalation) morning and evening; total daily dose of active drug: BDP 400 µg plus formoterol 24 µg. Batch numbers: refer to Section 9.4.2.

Duration of treatment: 48 weeks.

Reference therapy, dose and mode of administration, batch no:

a) Budesonide plus formoterol dry powder (Symbicort®, AstraZeneca), unit doses 160 µg budesonide + 4.5 µg formoterol administered via a dry powder inhaler (Turbohaler®, AstraZeneca). Dose: 2 inhalations (plus placebo matching CHF 1535 pMDI, 2 puffs, and placebo matching Formoterol Turbohaler®, 1 inhalation) morning and evening; total daily dose of active drug: budesonide 640 µg plus formoterol 18 µg, corresponding to a delivered dose of budesonide 800 µg plus formoterol 24 µg.

b) Formoterol fumarate dry powder (Oxis® AstraZeneca), unit doses 12 µg administered via a dry powder inhaler (Turbohaler®, AstraZeneca). Dose: 1 inhalation (plus placebo matching CHF 1535 pMDI, 2 puffs, and placebo matching Budesonide plus Formoterol Turbohaler®, 2 inhalations) morning and evening; total daily dose of active drug: formoterol 24 µg.

Batch numbers: refer to Section 9.4.2.

SYNOPSIS

Criteria for evaluation:

Efficacy:

The primary efficacy variables of the study were: change in pre-dose morning FEV_1 from baseline to 48 weeks and number of COPD exacerbations (mean rate per patient per year).

The secondary efficacy variables of the study were: the time to first COPD exacerbation; the number of severe COPD exacerbations; the time to first severe COPD exacerbation; the number of moderate COPD exacerbations; the time to first moderate COPD exacerbation; morning pre-dose FEV_1 at all clinic visits; the 3-hour post-dose average FEV_1 at Visit 2, 3, 5 and 7; peak FEV_1 at Visit 2, 3, 5 and 7; FVC, PEF, $FEF_{25-75\%}$ as for FEV_1; Health Related Quality of Life (HRQOL) according to St. George's Respiratory Questionnaire (SGRQ); dyspnoea scores – Modified Medical Research Council (MMRC) questionnaire; BODE Index scores; six-minute walking test (6MWT); COPD symptoms' scores; use of rescue medication.

Safety:

The safety variables of the study were: AEs and ADRs; cardiovascular parameters (vital signs, 12-lead ECG, Holter monitoring in a subgroup of 15% of patients); routine haematochemical parameters; biochemical parameters (serum potassium, plasma glucose, serum cortisol).

Statistical methods:

The following populations were considered for analysis: the intention-to-treat (ITT) population included all randomised patients who received at least one administration of the treatment and with at least post-baseline efficacy evaluation; the per-protocol (PP) population included all patients in the ITT analysis set who did not have any major protocol violation; the safety population included all randomised patients who took at least one dose of study medication.

Summary statistics (mean, standard deviation, minimum, maximum, and 95% CI) were provided for continuous variables, and the number and percentage of patients in each category were provided for categorical data.

For the analysis within group, 95% CI for the mean changes from baseline was calculated. For the superiority of CHF 1535 vs. formoterol alone (FORM), the number of COPD exacerbations (mean rate per patient per year) was analysed using Poisson regression. Log-time on study was used as an offset and SEs were estimated allowing for extra-Poisson variation. Superiority test was performed at the 5% significance level (significant if $p \leq 0.050$). For the non-inferiority of CHF 1535 vs. Budesonide plus Formoterol (BUD/FORM), change in pre-dose morning FEV_1 at the 'End of Treatment' was submitted to an ANCOVA model with treatment and centre as factors and baseline (V2) pre-dose FEV_1 as a covariate. Non-inferiority was declared if the lower limit of the two-sided 95% CI for the difference between adjusted treatment means was above (i.e. closer to zero) the non-inferiority margin fixed at -100 ml. Moreover, CHF 1535 was also compared to BUD/FORM in terms of number of COPD exacerbations and to FORM in terms of change in pre-dose morning FEV_1.

A Kaplan-Meier plot for time to first COPD exacerbation was presented. Time to first COPD exacerbation was described further by a Cox proportional hazards regression analysis with treatment and centre included in the model. Treatment effect was presented as a hazard ratio with 95% CI.

All other pulmonary functions tests and secondary efficacy variables were analysed by means of an ANCOVA model with treatment and centre as factors and baseline as a covariate. For use of rescue medication, the median data for 1-48 weeks were analysed using the Wilcoxon rank-sum test.

The proportion of patients presenting AEs, AEs leading to withdrawal, ADRs and serious AEs (SAEs) were tabulated for each treatment group by system organ class (SOC) and preferred term (PT) using MedDRA dictionary and were compared using Chi-square test or Fisher's exact test.

Laboratory parameters, vital signs and ECG QTc intervals were described using summary statistics. Relevant parameters were also compared using an ANCOVA model. Shift tables from baseline to each visit, with regard to normal range (low, normal, high), were constructed for relevant safety parameters.

Efficacy results:

Primary efficacy variables

Change in pre-dose morning FEV_1:

The non-inferiority of CHF 1535 vs. BUD/FORM in terms of pre-dose morning FEV_1 improvement (co-primary endpoint related to lung function) was demonstrated as shown in the table below, with the lower limit of the 95% CI of the difference between treatments well within the pre-specified margin (-0.100 L).

The results in the PP population, as well as those of the sensitivity analysis (that considered FEV_1 values measured before the intake of oral steroids if taken in the two months prior to the final visit) were consistent with those obtained in the primary ITT analysis.

ITT POPULATION			
	CHF 1535 (N = 231)	**BUD/FORM (N = 236)**	**FORM (N = 231)**
Change from baseline, *L* (mean, SD)	0.080 (0.28)	0.079 (0.28)	0.027 (0.27)
Adjusted means	0.077	0.080	0.026
Difference (97.5% unilateral CI) of CHF 1535 vs. BUD/FORM		-0.002 (-0.052)	
Difference (bilateral 95% CI) of CHF 1535 vs. FORM			0.051 (0.001 to 0.102)
PP POPULATION			
	CHF 1535 (N = 222)	**BUD/FORM (N = 230)**	**FORM (N = 223)**
Change from baseline, *L* (mean, SD)	0.081 (0.28)	0.077 (0.28)	0.025 (0.28)
Adjusted means	0.071	0.072	0.016
Difference (97.5% unilateral CI) of CHF 1535 vs. BUD/FORM		-0.001 (-0.052)	
Difference (bilateral 95% CI) of CHF 1535 vs. FORM			0.055 (0.003 to 0.106)

Number of COPD exacerbations (mean rate per patient per year):

As shown in the table below, the number of patients with at least one COPD exacerbation and the mean rate of COPD exacerbations per patient per year in the ITT population were similar in the three treatment groups. No statistically significant differences among groups in both comparisons were detected and the results in the PP population were consistent with those observed in the ITT analysis.

ITT POPULATION			
	CHF 1535 (N = 232)	**BUD/FORM (N = 238)**	**FORM (N = 233)**
Number (%) of patients with COPD exacerbations	64 (27.6%)	64 (26.9%)	66 (28.3%)
Mean rate per patient/year	0.414	0.423	0.431
Rate ratio (95% CI) of CHF 1535 vs. the other groups		0.979 (0.722 to 1.326)	0.961 (0.707 to 1.305)
p value		0.889	0.798
PP POPULATION			
	CHF 1535 (N = 223)	**BUD/FORM (N = 231)**	**FORM (N = 225)**
Number (%) of patients with COPD exacerbations	59 (26.5%)	60 (26.0%)	64 (28.4%)
Mean rate per patient/year	0.395	0.405	0.433
Rate ratio (95% CI) of CHF 1535 vs. the other groups		0.975 (0.712 to 1.335)	0.912 (0.667 to 1.248)
p value		0.872	0.564

Secondary efficacy variables:

COPD exacerbations:

Time to first COPD exacerbation:

Considering the low number of COPD exacerbations, the median time to the first COPD exacerbation estimated by means of Kaplan Meier method was not applicable. The analysis of time to first exacerbation using a Cox proportional hazards regression model, in which subjects without exacerbations were considered 'censored' at the last day in the study, did not show statistically significant differences between the CHF 1535 group and the BUD/FORM group (p = 0.781), and between the CHF 1535 group and the FORM group (p = 0.754).

COPD exacerbations leading to hospitalization:

The number of patients with COPD exacerbations leading to hospitalization was 13 (5.6%) in the CHF 1535 group, 7 (2.9%) in the BUD/FORM group and 8 (3.4%) in the FORM group. The mean rate per patient/year was 0.074 in the CHF 1535 group, 0.033 in the BUD/FORM group and 0.040 in the FORM group. The comparison among groups showed that the rate of COPD exacerbations leading to hospitalization in the CHF 1535 group was statistically significantly higher than that reported both in the BUD/FORM group (p<0.001) and in the FORM group (p = 0.008). The analysis of the time to first exacerbation leading to hospitalization using a Cox proportional hazards regression model did not show statistically significant differences between the CHF 1535 group and the BUD/FORM group (p = 0.172), and between the CHF 1535 group and the FORM group (p = 0.313).

Since after the Blind Review Meeting it became evident that in some countries/hospitals ER visits/unscheduled visits with the treating investigator were performed in place of hospitalisation, a post-hoc analysis was carried out in patients with COPD exacerbation leading to hospitalization including also patients requiring ER/unscheduled visits for COPD exacerbation at which oral corticosteroids and/or antibiotic treatments were started. This analysis showed that the resulting number of patients with COPD exacerbations requiring institutionalised treatment or hospitalisation was 28 (12.1%) in the CHF 1535 group, 26 (10.9%) in the BUD/FORM group and 30 (12.9%) in the FORM group, with no statistically significant differences among treatment groups. The mean rate per patient/year was 0.162 in the CHF 1535 group, 0.180 in the BUD/FORM group and 0.180 in the FORM group. The comparison among groups showed that the rate of COPD exacerbations leading to ER/unscheduled visits/hospitalization in the CHF 1535 group was not statistically significantly higher than that reported both in the BUD/FORM group (p=0.597) and in the FORM group (p = 0.607). The analysis of the time to first exacerbation leading to ER/unscheduled visit/hospitalization using a Cox proportional hazards regression model did not show statistically significant differences between the CHF 1535 group and the BUD/FORM group (p = 0.613), and between the CHF 1535 group and the FORM group (p = 0.813).

Moderate COPD exacerbations:

The number of patients with moderate COPD exacerbations was 56 (24.1%) in the CHF 1535 group, 60 (25.2%) in the BUD/FORM group and 60 (25.8%) in the FORM group. The mean rate per patient/year was 0.340 in the CHF 1535 group, 0.389 in the BUD/FORM group and 0.390 in the FORM group. The comparison between groups did not show statistically significant differences in both comparisons (p = 0.398 vs. the BUD/FORM group and p = 0.394 vs. the FORM group). The analysis of the time to first moderate exacerbation using a Cox proportional hazards regression model did not show statistically significant differences between the CHF 1535 group and the BUD/FORM group (p = 0.920), and between the CHF 1535 group and the FORM group (p = 0.607).

As a result of the above reclassification of ER visits into the severe category for consistency with the concept of insitutionalised treatment of COPD exacerbations, the number of patients with moderate COPD exacerbations was 43 (18.5%) in the CHF 1535 group, 41 (17.2%) in the BUD/FORM group and 44 (18.9%) in the FORM group, with no statistically significant differences among treatment groups. The mean rate per patient/year was 0.251 in the CHF 1535 group, 0.242 in the BUD/FORM group and 0.250 in the FORM group. The comparison among groups showed that the rate of moderate COPD exacerbations in the CHF 1535 group was not statistically significantly higher than that reported both in the BUD/FORM group (p=0.835) and in the FORM group (p = 0.985). The analysis of the time to first moderate exacerbation using a Cox proportional hazards regression model did not show statistically significant differences between the CHF 1535 group and the BUD/FORM group (p = 0.646), and between the CHF 1535 group and the FORM group (p = 0.782).

Pulmonary function tests:

FEV_1:

Pre-dose

As shown in the previous table, the mean changes from baseline at the final visit were higher in CHF 1535 group (0.080 L) than in the FORM group (0.027 L). The bilateral 95% CI for the difference was 0.001 to 0.102, thus showing that the difference was statistically significant, in favour of the CHF 1535 group. The results in the PP population, as well as those of the sensitivity analysis (that considered FEV_1 values measured before the intake of oral steroids if taken in the two months prior to the final visit) were consistent with those obtained in the primary ITT analysis.

Post-dose:

The mean changes of area under the curve (AUC) FEV_1 standardized for time measured in the 3 hours post-dose from baseline to the final visit were 0.20 (0.26) L in the CHF 1535 group, 0.20 (0.29) L in the BUD/FORM group and 0.14 (0.29) L in the FORM group (p<0.001 in all groups). A statistically significant difference was found in the comparisons b h CHF 1535 d h FORM (0 039) hil h diff b h CHF 1535 d h

Post-dose:

The mean changes of AUC FVC measured in the 3 hours post-dose from baseline to the final visit were 0.26 (0.44) L) in the CHF 1535 group, 0.26 (0.51) L in the BUD/FORM group and 0.19 (0.46) L in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Peak FEV_1:

The mean changes from baseline at the final visit were 0.42 (0.51) L in the CHF 1535 group, 0.39 (0.55) L in the BUD/FORM group and 0.35 (0.47) L in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

PEF:

Pre-dose:

The mean changes from baseline at the final visit were 0.22 (0.85) L/sec in the CHF 1535 group, 0.25 (0.81) L/sec in the BUD/FORM group and 0.12 (0.88) L/sec in the FORM group. The change from baseline was significant in all treatment groups ($p<0.001$ in the CHF 1535 group and in the BUD/FORM group, $p = 0.033$ in the FORM group). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Post-dose:

The mean changes from baseline of AUC PEF measured in the 3 hours post-dose at the final visit were 0.43 (0.8) L/sec in the CHF 1535 group, 0.47 (0.84) L/sec in the BUD/FORM group and 0.36 (0.85) L/sec in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Peak:

The mean changes from baseline at the final visit were 0.71 (0.92) L/sec in the CHF 1535 group, 0.70 (0.88) L/sec in the BUD/FORM group and 0.62 (0.86) L/sec in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

$FEF_{25-75\%}$:

Pre-dose:

The mean changes from baseline at the final visit were 0.05 (0.24) L/sec in the CHF 1535 group, 0.06 (0.27) L/sec in the BUD/FORM group and 0.02 (0.23) L/sec in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p = 0.002$) and in the BUD/FORM group ($p<0.001$), and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Post-dose:

The mean changes from baseline of AUC $FEF_{25-75\%}$ measured in the 3 hours post-dose at the final visit were 0.12 (0.25 L/sec in the CHF 1535 group, 0.13 (0.23) L/sec in the BUD/FORM group and 0.10 (0.27) L/sec in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Peak:

The mean changes from baseline at the final visit were 0.22 (0.30) L/sec in the CHF 1535 group, 0.22 (0.29) L/sec in the BUD/FORM group and 0.19 (0.35 L/sec) in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

SGRQ:

Symptoms score:

The mean changes from baseline at the final visit were -7.55 (21.9) in the CHF 1535 group, -6.28 (19.1) in the BUD/FORM group and -6.61 (20.9) in the FORM group. The change from baseline was significant in all treatment groups ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Activity score:

The mean changes from baseline at the final visit were -2.33 (14.8) in the CHF 1535 group, -2.60 (14.7) in the BUD/FORM group and -1.23 (15.4) in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p = 0.020$) and in the BUD/FORM group ($p = 0.008$), and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Impacts score:

The mean changes from baseline at the final visit were -3.66 (16.4) in the CHF 1535 group, -4.62 (14.0) in the BUD/FORM group and -2.80 (15.7) in the FORM group. The change from baseline was significant in all treatment groups ($p<0.001$ in both CHF 1535 and BUD/FORM groups, $p = 0.008$ in the FORM group). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Total score:

The mean changes from baseline at the final visit were -3.75 (13.9) in the CHF 1535 group, -4.28 (11.9) in the BUD/FORM group and -2.90 (13.3) in the FORM group. The change from baseline was significant in all treatment groups ($p<0.001$ in both the CHF 1535 group and the BUD/FORM group, $p = 0.001$ in the FORM group). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Dyspnoea score:

The mean changes from baseline at the final visit were -0.19 (0.74) in the CHF 1535 group, -0.18 (0.78) in the BUD/FORM group and -0.07 (0.76) in the FORM group. The change from baseline was significant in the CHF 1535 group and in the BUD/FORM group ($p<0.001$ in both groups), and was not significant in the FORM group. No statistically significant differences were found n the comparisons between the CHF 1535 group and the other two groups.

BODE index:

The mean changes from baseline at the final visit were -0.61 (1.23) in the CHF 1535 group, -0.64 (1.36) in the BUD/FORM group and -0.44 (1.26) in the FORM group ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

6MWT:

The mean changes in the covered distance from baseline at the final visit were 41.08 (85.09) metres in the CHF 1535 group, 35.39 (86.04) metres in the BUD/FORM group and 35.20 (78.63) metres in the FORM group. ($p<0.001$ in all groups). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

COPD symptoms' score:

Ability to perform the usual daily activities:

The mean changes from baseline to the last two weeks of treatment were 0.04 (0.65) in the CHF 1535 group, -0.01 (0.66)in the BUD/FORM group and 0.02 (0.66) in the FORM group. The change from baseline was not significant in any treatment group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Breathlessness:

The mean changes from baseline to the last two weeks of treatment were -0.13 (0.67) in the CHF 1535 group, -0.13 (0.62) in the BUD/FORM group and -0.09 (0.65) in the FORM group. The change from baseline was significant in all treatment groups ($p = 0.003$ in the CHF 1535 group, $p = 0.002$ in the BUD/FORM group and $p = 0.031$ in the FORM group). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Waking at night:

The mean changes from baseline to the last two weeks of treatment visit were -0.04 (0.54) in the CHF 1535 group, -0.04 (0.48) in the BUD/FORM group and -0.04 (0.59) in the FORM group. The change from baseline was not significant in any treatment group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Breathlessness on rising:

The mean changes from baseline to the last two weeks of treatment were -0.10 (0.64) in the CHF 1535 group, -0.11 (0.60) in the BUD/FORM group and -0.02 (0.62) in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p = 0.023$) and in the BUD/FORM group ($p = 0.006$), and was not significant in the FORM group. No statistically significant differences were found n the comparisons between the CHF 1535 group and the other two groups.

Cough:

The mean changes from baseline to the last two weeks of treatment were -0.18 (0.67) in the CHF 1535 group, -0.10 (0.63) in the BUD/FORM group and -0.14 (0.61) in the FORM group. The change from baseline was significant in all treatment groups ($p<0.001$ in the CHF 1535 group and in the FORM group, $p = 0.021$ in the BUD/FORM group). No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Sputum:

The mean changes from baseline to the last two weeks of treatment were -0.08 (0.65) in the CHF 1535 group, -0.08 (0.63) in the BUD/FORM group and -0.13 (0.60) in the FORM group. The change from baseline was significant in the FORM group ($p = 0.001$), and was not significant in the other two groups. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Percentage of days without COPD symptoms:

The mean changes from baseline to the last two weeks of treatment were 3.17 (23.80) % in the CHF 1535 group, 3.15 (24.13) % in the BUD/FORM group and 3.07 (27.78) % in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p = 0.046$) and in the BUD/FORM group ($p = 0.047$, and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

The mean changes from baseline of the total percentage of days without COPD symptoms in the overall treatment period were 3.44 (17.49) % in the CHF 1535 group, 4.67 (19.98) % in the BUD/FORM group and 1.84 (19.27) % in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p = 0.003$) and in the BUD/FORM group ($p<0.001$), and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Use of rescue medication:

The mean changes from baseline at the final visit were -0.27 (1.20) puffs in the CHF 1535 group, -0.24 (1.41) puffs in the BUD/FORM group and -0.04 (1.28) puffs in the FORM group. The change from baseline was significant both in the CHF 1535 group ($p<0.001$) and in the BUD/FORM group ($p = 0.013$), and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

The mean changes from baseline to the last two weeks of treatment of the percentage of days without use of rescue medication during the study were 4.68 (42.89) %) in the CHF 1535 group, 9.83 (38.59) % in the BUD/FORM group and -1.79 (43.69) % in the FORM group. The change from baseline was significant in the BUD/FORM group ($p<0.001$), and was not significant in the other two groups. The percentage of days without use of rescue medication in the last two weeks of treatment increased significantly in the BUD/FORM group compared to the CHF 1535 group ($p = 0.049$), while no significant differences were found in the comparison between the CHF 1535 group and the FORM group.

The mean changes from baseline of the total percentage of days without use of rescue medication in the overall treatment period were 7.90 (34.89) % in the CHF 1535 group, 10.59 (31.11) % in the BUD/FORM group and 0.85 (33.46) % in the FORM group. The change from baseline was significant in both the CHF 1535 group and in the BUD/FORM group ($p<0.001$ in both groups), and was not significant in the FORM group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Safety results:

Adverse Events:

AEs were reported in 101 patients (42.8%) in the CHF 1535 group, 99 (40.9%) in the BUD/FORM group and 105 (44.1%) in the FORM group (NS between the CHF 1535 group and the other two groups). ADRs were reported in 22 patients (9.3%) in the CHF 1535 group, 12 (5.0%) in the BUD/FORM group and 20 (8.4%) in the FORM group (NS between the CHF 1535 group and the other two groups). SAEs were reported in 24 patients (10.2%) in the CHF 1535 group, 19 (7.9%) in the BUD/FORM group and 14 (5.9%) in the FORM group (NS between the CHF 1535 group and the other two groups). AEs leading to study discontinuation were reported in 20 patients, 9 (3.8%) in the CHF 1535 group, 6 (2.5%) in the BUD/FORM group and 5 (2.1%) in the FORM group (NS between the CHF 1535 group and the other two groups). Pneumonia was reported in 5 patients (2.1%) in the CHF 1535 group, 7 (2.9%) in the BUD/FORM group and 1 (0.4%) in the FORM group (NS between the CHF 1535 group and the other two groups).

In the Safety population, COPD exacerbation or worsening was the most common event, and was reported in 65 patients (27.54%) in the CHF 1535 group, 65 (26.86%) in the BUD/FORM group and 66 (27.73%) in the FORM group.

The rate of adverse events likely to be caused by the deposition of ICS on the oral mucosa (e.g. oral candidosis or pharyngo-laryngeal discomforts), by the systemic absorption of ICS (decrease in cortisol levels) or by the systemic absorption of long-acting β2-agonists (e.g. tachycardia, palpitations, tremors, hypokaliemia, hyperglycaemia or worsened glucose tolerance) were reported in a small number of patients, similarly distributed in the three treatment groups.

A total of 7 fatal events occurred during the study period. One patient had a fatal event during the run-in phase of the study. The other fatal events occurred in 2 patients in the CHF 1535 group and in 4 in the BUD/FORM group: none of them was judged as related with study medication. Two other patients died after the end of the study: one in the FORM group due to a rectal adenocarcinoma and the other one in the CHF 1535 group due to disseminated neoplasmatic disease.. One SAE only in the BUD/FORM group (atrial flutter) was considered as drug-related, as well as only 3 patients in the CHF 1535 group and 1 in the FORM group discontinued the study due to drug-related adverse events.

Laboratory parameters:

Serum Potassium:

A statistically but not clinically significant increase vs. baseline was observed in the CHF 1535 group and in the FORM group. The mean changes from baseline at the final visit were 0.09 (0.57) mmol/l in the CHF 1535 group, 0.03 (0.59) mmol/l in the BUD/FORM group and 0.13 (0.53) mmol/l in the FORM group. The change from baseline was statistically significant both in the CHF 1535 group ($p = 0.020$) and in the FORM group ($p<0.001$), and was not significant in the BUD/FORM group. There were small and not clinically significant changes in all the treatment groups between values measured pre- and post-dose at baseline, and after 24 and 48 weeks of treatment.

Plasma glucose:

No clinically or statistically significant changes vs. baseline were observed in any treatment group. There were small changes in all the treatment groups between values measured pre- and post-dose at baseline, and after 24 and 48 weeks of treatment.

Serum cortisol:

The mean changes from baseline at the final visit were 5.70 (161.26) nmol/l in the CHF 1535 group, 1.81 (166.0)1 nmol/l in the BUD/FORM group and -1.59 (141.44) nmol/l in the FORM group. The change from baseline was not statistically significant in any treatment group. No statistically significant differences were found in the comparisons between the CHF 1535 group and the other two groups.

Other haematology and blood chemistry parameters:

The analysis of the mean changes from baseline of the other haematology and blood chemistry parameters did not show clinically relevant changes relative to the COPD context: BUN and sodium levels significantly increased from baseline to endpoint in all groups, while alkaline phosphatase, ALT levels significantly decreased in all groups.

For all the examined variables (including serum potassium, plasma glucose and serum cortisol), there were no substantial differences between the three treatment groups in the number and rate of patients with normal values at baseline and abnormalities at the final visit, or in those with abnormal baseline values that were normalised at the final visit.

Vital signs:

Mean systolic and diastolic blood pressure did not change in any group from baseline to week 48, as well as in pre- and post-dose measurements. Mean heart rate did not change in any group in the analysis from baseline to week 48, while the results of measurements pre- and post-dose showed small increases in all groups, however of no clinical relevance (the mean increases did not exceed 2 bpm).

ECG:

QTc interval:

The mean changes from baseline at the final visit in the Bazett's equation were -4.60 (22.45) msec in the CHF 1535 group, -1.29 (23.46) msec in the BUD/FORM group and 2.20 (25.34) msec in the FORM group. The change from baseline was significant in the CHF 1535 group ($p=0.004$) and was not significant in the other two groups. The comparison between the CHF 1535 group and the other two groups showed a statistically significant difference vs. the FORM group ($p = 0.003$), due to the decrease in the CHF 1535 group and the small increase in the FORM group, while the difference vs. the BUD/FORM group was not statistically significant.

The mean changes from baseline at the final visit in the Fridericia's equation were -3.49 (19.54) msec in the CHF 1535 group, -0.50 (20.74) msec in the BUD/FORM group and 2.40 (21.38) msec in the FORM group. The change from baseline was significant in the CHF 1535 group ($p = 0.012$) and was not significant in the other two groups. The comparison between the CHF 1535 group and the other two groups showed a statistically significant difference vs. the FORM group ($p = 0.004$), due to the decrease in the CHF 1535 group and the small increase in the FORM group, while the difference vs. the BUD/FORM group was not statistically significant.

Measurements carried out pre- and post-dose showed a prolongation in the formoterol monotherapy group at baseline and after 24 week of treatment, with no substantial changes in the other two groups and in measurements in all groups at week 48.

24-hour Holter monitoring:

The results of the 24-hour Holter monitoring, which was carried out in 64 patients, did not show clinically significant changes or abnormalities in any group. There were no cases of torsades de pointes, ventricular flutter and/or ventricular fibrillation, and ventricular asystole.

Conclusions:

The results of the present study have shown that:

- CHF 1535 was not inferior to budesonide/formoterol in improving pre-dose morning FEV_1 from baseline to 48 weeks of treatment.
- The mean rate of COPD exacerbations per patient/year was lower than expected and was similar in the three treatment groups. No statistically significant differences in the mean rate of COPD exacerbations per patient during the 48-week treatment period among the three treatment groups were observed.
- CHF 1535 was superior to formoterol alone in improving morning pre-dose, 3 hours post-dose and peak FEV_1 from baseline to 48 weeks of treatment period.
- Morning pre-dose FVC significantly improved in the CHF 1535 group only, although no statistically differences were observed among the three treatment groups.
- The improvements from baseline of the other pulmonary function parameters (PEF and $FEF_{25-75\%}$) measured pre-dose, in the 3 hours post-dose and as peak values, did not substantially differ among the three treatment groups.
- Health-related quality of life (measured by SGRQ), dyspnoea score, BODE index, performance in the 6MWT and COPD symptoms improved in all groups, without statistically significant differences among them, even though there was a trend favouring CHF 1535 on 6MWT.
- The use of rescue medication decreased in the CHF 1535 group and in the BUD/FORM group, although no statistically differences were observed among the three treatment groups
- All the investigational study drugs were safe and well tolerated as demonstrated by the adverse events' profile, effects on adrenal function, systemic effects, vital signs and ECG, and the safety results did not raise any unexpected safety concern regarding the known profile of inhaled corticosteroids and long-acting β_2-agonists in the treatment of COPD.

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