2 SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43100 Parma, Italy **Name of Active Ingredient:** Beclomethasone dipropionate 250 µg/salbutamol 100 µg HFA pMDI fixed combination **Name of Finished Product:** N/A	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(for National Authority Use only)*

Title of the study: Multicentre, multinational, randomised, double blind, double dummy, active drug controlled, parallel group study design clinical trial of the efficacy and tolerability of beclomethasone dipropionate 250 mcg plus salbutamol 100 mcg in HFA pMDI fixed combination vs. beclomethasone dipropionate 250 mcg plus salbutamol 100 mcg in CFC pMDI (Clenil® Compositum 250) fixed combination in a 12-week treatment period of adult patients with uncontrolled asthma

Investigators: 23 principal investigators, 5 in Italy, 13 in Ukraine and 5 in Russia.

Study centres: 23 centres, located in Italy (5 sites), Ukraine (13 sites) and Russia (5 sites).

Publication (reference): None

Study period: First patient enrolled: 14/11/2007; Last patient completed: 29/01/2009 | **Phase of development:** III

Objectives: The primary objective of this study was to demonstrate that the test treatment BDP 250 µg/salbutamol 100 µg HFA pMDI fixed combination was non-inferior to the same BDP 250 µg/salbutamol 100 µg pMDI fixed combination given with the conventional CFC propellant (Clenil® Compositum 250, Chiesi Farmaceutici).

The secondary objectives of the present study were: to assess the efficacy of the two investigational study drugs on pulmonary function parameters, asthma symptoms, use of relief medications and frequency of asthma exacerbations; to assess the safety of the two investigational study drugs as regards frequency of adverse events, laboratory parameters (potassium, glucose, 12-hour overnight cortisol/creatinine ratio), ECG (with QTc interval) and vital signs (heart rate and blood pressure).

Methodology:

This was a phase III, multinational, multicentre, double-blind, double dummy, randomised, two-arm parallel groups, active drug controlled study design, to compare the efficacy and tolerability of BDP plus salbutamol given via pMDI with HFA-134a propellant and the same fixed combination given via CFC propellant, over a 12-week treatment period in a b.i.d. regimen.

The treatment period was preceded by a 2-week run-in period. Subjects satisfying all the inclusion and exclusion criteria then entered the 12-week treatment period. Clinic visits taken place at the start and end of the run-in period, and after 2, 4, 8 and 12 weeks after randomisation, with an acceptable variation of a maximum of ± 3 days in respect of the scheduled dates of the visits.

Number of patients (total and in each arm):

	Randomised	ITT/M-ITT	PP	Safety	Completed
Total	209	209	204	209	203
BDP/S HFA	106	106	104	106	103
BDP/S CFC	103	103	100	103	100

Diagnosis and main criteria for inclusion: written informed consent obtained; male or female out-patients aged ≥ 18 and < 65 years; uncontrolled asthma defined according to the GINA 2006 "Classification of Levels of Asthma Control"; FEV_1 ≥ 60% and < 80% of the predicted normal value; positive response to the reversibility test; 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 co-operative attitude and ability to be trained to correctly use the pMDIs; at the end of the 2-week run-in period, the condition of uncontrolled asthma was to be confirmed by reviewing the diary cards for run-in.

Test product, dose and mode of administration, batch no: BDP/salbutamol HFA pMDI 2 puffs twice daily (morning and evening), for a total daily dose of BDP 1000 µg/salbutamol 400 µg (plus placebo matching BDP/salbutamol CFC

pMDI 2 puffs twice daily, morning and evening). BDP/S HFA was provided in batch No. [redacted]; BDP/S CFC placebo was provided in batch No. [redacted].

Duration of treatment: 12 weeks.

Reference therapy, dose and mode of administration, batch no: BDP/salbutamol CFC pMDI (Clenil® Compositum 250, Chiesi Farmaceutici) received 2 puffs twice daily (morning and evening), for a total daily dose of BDP 1000 µg/salbutamol 400 µg, (plus placebo matching BDP/salbutamol HFA pMDI 2 puffs twice daily, morning and evening). BDP/S CFC was provided in batch No. [redacted]; BDP/S HFA placebo was provided in batch No. [redacted].

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the mean value of morning PEF daily measured by the patient in weeks 11-12.

The secondary efficacy variables were: morning PEF daily measured daily by the patient at any other time point to weeks 11-12; evening PEF and morning and evening FEV_1 daily measured by the patient; pulmonary function parameters (FEV_1, FVC, PEF and $FEF_{25-75\%}$) measured at clinic visits; changes from pre-dosing of pulmonary function parameters measured at baseline (visit 2) and end of treatment (visit 6) in the interval 0-60 minutes (pre-dose and 5, 15, 30 and 60 minutes post-dose); rates of asthma exacerbations (in total and by severity); time to first asthma exacerbation; night-time and daytime use of relief salbutamol, and number of days (both day and night) without intake of salbutamol; nighttime and daytime symptoms scores, and number of symptoms-free days (both day and night).

Safety:

Safety variables were: adverse events (AEs) and adverse drug reactions (ADRs); vital signs (heart rate and blood pressure, measured pre-dose and 60 minutes post-dosing at visit 2 and visit 6); ECG abnormalities and QTc interval (measured pre-dose and 60 minutes post-dosing at visit 2 and visit 6); serum potassium and glucose (measured pre-dose and 60 minutes post-dosing at visit 2 and visit 6); 12-hour urinary cortisol/creatinine ratio.

Statistical methods:

The following populations were considered for analysis: ITT population, defined as all randomised patients who received at least one dose of study drug and with at least post-baseline data; M-ITT population, defined as the ITT population with the exclusion of data measured in the 30 days after the intake of oral or additional inhaled corticosteroids for asthma exacerbation; PP population, defined as all subjects in the ITT population without major protocol violations; safety population, defined as all randomised subjects for which there was evidence of drug intake. Post-baseline missing data of patients who discontinued the study were replaced with the last observation carried forward (LOCF) method. Summary statistics (mean, standard deviation, minimum, maximum) were provided for continuous variables, and the number and percentage of patients in each category were provided for categorical data. Variables recorded in daily diary cards were averaged to obtain a mean value for each two-week treatment period.

The assessment of non-inferiority was performed by calculating the bilateral 95% CI for the difference between LSMs, from ANCOVA, in the two groups. The test treatment (BDP/salbutamol HFA) was defined as non-inferior to BDP/salbutamol CFC if the lower limit of the bilateral 95% CI for the difference between LSMs of morning PEF (weeks 11-12) was $\geq$ -20 L/min.

The results of the efficacy parameters measured daily by patients and at the clinic visits were analysed within treatment by calculating, in each 2-week period, the 95% CI for the mean change from baseline; comparisons between treatment groups were made using an ANCOVA model. The incidence of asthma exacerbation (and its intensity) and use of additional corticosteroids in the two groups was evaluated using Chi square test. Time to first asthma exacerbation was analysed by means of survival analysis (Kaplan-Meier estimates were calculated).

The incidence of AEs and ADRs was compared between groups using Chi-square test. The results of vital signs (heart rate and blood pressure) were summarised using descriptive statistics and 95% CI for the changes from baseline was calculated. The results of the ECG were presented in terms of normal/abnormal findings in the two groups, with no formal comparison between groups. Values of QTc interval were summarized using descriptive statistics and 95% CI for the changes from baseline was calculated: the comparison between treatment groups was performed using an ANCOVA model. The same method was used for the analysis of the laboratory parameters (serum potassium, fasting serum glucose and 12-hour (overnight) urinary cortisol/creatinine ratio), including the changes from pre-dose to 60 minutes post-dosing in serum potassium and fasting serum glucose after the first and the last dose of study drug. Shift tables from visit 2 (pre-dose) to end of treatment (visit 6, pre-dose) were provided by treatment for fasting plasma

glucose and serum potassium, with reference to normal range (low/normal/high).

Study population:

A total number of 209 patients were randomised to receive the assigned treatment; 106 were included in the HFA group and 103 were included in the CFC group. A total number of 6 patients included in the safety population, 3 (2.83%) in the HFA group and 3 (2.91%) in the CFC group, were withdrawn from the study after randomisation.

Extent of exposure and compliance:

The mean extent of exposure to study drug in the safety population was 82.9 ± 10.2 days (range 13-92) in the HFA group and 83.2 ± 11.0 days (range 3-98) in the CFC group.

The mean compliance to HFA was 98.3 ± 2.8 % (range 80.8-104.8) in the HFA group (active) and 97.0 ± 7.3 % (range 45.9-101.3) in the CFC group (placebo). The mean compliance to CFC was 98.2 ± 2.7 % (range 80.8-104.2) in the HFA group (placebo) and 96.9 ± 7.4 % (range 45.9-101.3) in the CFC group (active).

Efficacy results:

Primary efficacy variable: morning PEF

The results in the ITT population showed a statistically significant and clinically relevant increase from baseline at any time point in both treatment groups. The mean increases from baseline at endpoint were 42.1 ± 50.9 L/min (95% CI: 32.2 to 52.0) in the HFA group and 24.8 ± 42.2 L/min (95% CI: 16.5 to 33.1) in the CFC group. The results in the M-ITT and in the PP populations were consistent with those observed in the ITT analysis.

The analysis of non-inferiority and the comparisons between groups are presented in the table below:

	HFA (n = 106)		CFC (n = 103)	
	ITT POPULATION			
	Baseline	Endpoint	Baseline	Endpoint
Mean value ± SD (*L/min*)	290.6 ± 100.5	332.7 ± 100.8	287.0 ± 79.6	311.8 ± 84.3
Adjusted mean (*L/min*)	331.1		313.4	
Difference (*L/min*), p value (95.0% bilateral CI)	17.7, p value = 0.006 5.09 to 30.3			
	HFA (n = 106)		CFC (n = 103)	
	M-ITT POPULATION			
	Baseline	Endpoint	Baseline	Endpoint
Mean value ± SD (*L/min*)	290.6 ± 100.5	332.7 ± 100.8	287.0 ± 79.6	311.6 ± 84.4
Adjusted mean (*L/min*)	331.1		313.2	
Difference (*L/min*), p value (95.0% bilateral CI)	17.9, p value = 0.006 5.30 to 30.5			
	HFA (n = 104)		CFC (n = 100)	
	PP POPULATION			
	Baseline	Endpoint	Baseline	Endpoint
Mean value ± SD (*L/min*)	290.6 ± 101.0	333.4 ± 101.1	284.8 ± 78.8	309.9 ± 84.1
Adjusted mean (*L/min*)	330.9		312.5	
Difference (*L/min*), p value (95.0% bilateral CI)	18.3, p value = 0.005 5.61 to 31.0			

The analysis of non-inferiority in the ITT population showed that the difference between the adjusted means (last 2-week period) of the HFA (331.1 L/min) and of the CFC group (313.4 L/min) was equal to 17.7 L/min. The 95% bilateral CI for the difference between the adjusted means in the ANCOVA model was 5.09 to 30.3, and the lower limit was ≥ than the pre-specified limit of -20 L/min, thus showing that HFA was non-inferior to CFC in the ITT population. The difference between groups was statistically significant (p value = 0.006). The analysis of non-inferiority in the M-ITT and the PP populations showed similar results to those of ITT population.

Secondary efficacy variables (ITT population):

Pulmonary function tests daily measured by patients:

Evening PEF:
A statistically significant and clinically relevant increase from baseline was observed at any time point in both treatment groups. The mean increases from baseline at endpoint were 35.3 ± 54.3 L/min (95% CI: 24.8 to 45.9) in the HFA group and 22.7 ± 44.1 L/min (95% CI: 14.1 to 31.4) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last 2-week period) of the HFA group (335.2 L/min) and of the CFC group (322.0 L/min) was equal to 13.2 L/min. The 95% bilateral CI for the difference between the adjusted means was 0.03 to 26.4, thus showing that the difference between groups was statistically significant (p value = 0.049).

PEF daily variability:
A statistically significant decrease from baseline was observed at all time points in the HFA group (except at weeks 1-2) while the decrease from baseline in the CFC group was statistically significant only weeks 3-4. The mean changes from baseline at endpoint were -2.75 ± 9.24 % (95% CI: -4.55; -0.95) in the HFA group and -0.90 ± 8.60% (95% CI: -2.59 to 0.79) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last 2-week period) of the HFA group (1.04%) and of the CFC group (2.63%) was equal to -1.59 %. The 95% bilateral CI for the difference between the adjusted means was -3.41 to 0.23, thus showing that the difference between groups was not statistically significant (p = 0.087).

Morning FEV_1:
A statistically significant and clinically relevant increase from baseline was observed at any time point in both treatment groups. The mean increases from baseline at endpoint were 0.24 ± 0.41 L (95% CI: 0.16 to 0.32) in the HFA group and 0.13 ± 0.37 L (95% CI: 0.06 to 0.21) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last 2-week period) of the HFA group (2.25 L) and of the CFC group (2.15 L) was equal to 0.10 L. The 95% bilateral CI for the difference between the adjusted means was -0.01 to 0.21, thus showing that the difference between groups was not statistically significant (p = 0.063).

Evening FEV_1:
A statistically significant and clinically relevant increase from baseline was observed from weeks 1-2 onwards in both treatment groups. The mean increases from baseline at endpoint were 0.21 ± 0.39 L (95% CI: 0.14 to 0.29) in the HFA group and 0.15 ± 0.40 L (95% CI: 0.07 to 0.23) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last 2-week period) of the HFA group (2.29 L) and the adjusted mean of the CFC group (2.23 L) was equal to 0.06 L. The 95% bilateral CI for the difference between the adjusted means was -0.05 to 0.17, thus showing that the difference between groups was not statistically significant (p = 0.261).

Pulmonary function tests measured at clinics:

FEV_1:
The results expressed as absolute value showed statistically significant and clinically relevant increases from baseline from visit 3 (week 2) onwards in both treatment groups. The mean increases from baseline at endpoint were 0.32 ± 0.39 L (95% CI: 0.24 to 0.39) in the HFA group and 0.24 ± 0.33 L (95% CI: 0.18 to 0.31) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last visit) of the HFA group (2.44 L) and of the CFC group (2.37 L) was equal to 0.07 L. The 95% bilateral CI for the difference between the adjusted means was -0.03 to 0.17, thus showing that the difference between groups was not statistically significant (p = 0.150). The results expressed as percentage of predicted normal values were consistent with those of absolute values (however, the difference between groups at the end of treatment was statistically significant due to the greater increase in the HFA group compared to the CFC group). The analysis of the curve from pre-dose to 60 minutes after dosing showed no difference in the increases from pre-dose in the two groups at all time points both at visit 2 and at visit 6.

FVC:
The results expressed as absolute values showed statistically significant and clinically relevant increases from baseline from visit 3 (week 2) onwards in both treatment groups. The mean increases from baseline at endpoint were 0.24 ± 0.50 L (95% CI: 0.14 to 0.34) in the HFA group and 0.20 ± 0.44 L (95% CI: 0.11 to 0.29) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last visit) of the HFA group (3.16 L) and of the CFC group (3.13 L) was equal to 0.03 L. The 95% bilateral CI for the difference between the adjusted means was -0.09 to 0.15, thus showing that the difference between groups was not statistically significant (p = 0.625).
The results expressed as percentage of predicted normal values were consistent with those of absolute values. The analysis of the curve from pre-dose to 60 minutes after dosing showed no difference in the increases from pre-dose in the two groups at all time points both at visit 2 and at visit 6.

PEF:
The results expressed as absolute values showed statistically significant and clinically relevant increases from baseline from visit 3 (week 2) onwards in both treatment groups. The mean increases from baseline at endpoint were 49.1 ± 66.7 L/min (95% CI: 36.1 to 62.0) in the HFA group and 38.6 ± 64.3 L/min (95% CI: 26.0 to 51.2) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last visit) of the HFA group (366.3 L/min) and of the CFC group (355.9 L/min) was equal to 10.4 L/min. The 95% bilateral CI for the difference between the adjusted means was -7.21 to 28.0, thus showing that the difference between groups was not statistically significant (p = 0.246). The results expressed as percentage of predicted normal values were consistent with those of absolute values. The analysis of the curve from pre-dose to 60 minutes after dosing showed no difference in the increases from pre-dose in the two groups at all time points both at visit 2 and at visit 6.

FEF_{27-75}:
The results expressed as absolute values showed statistically significant and clinically relevant increases from baseline from visit 3 (week 2) onwards in both treatment groups. The mean increases from baseline at endpoint were 0.44 ± 0.82 L/sec (95% CI: 0.28 to 0.60) in the HFA group and 0.22 ± 0.68 L/sec (95% CI: 0.09 to 0.35) in the CFC group. The ANCOVA model showed that the difference between the adjusted means (last visit) of the HFA group (2.26 L/sec) and of the CFC group (2.05 L/sec) was equal to 0.20 L. The 95% bilateral CI for the difference between the adjusted means was 0.00 to 0.40, thus showing that the difference between groups was statistically significant (p = 0.046). The results expressed as percentage of predicted normal values were consistent with those of absolute values. The analysis of the curve from pre-dose to 60 minutes after dosing showed no difference in the increases pre-dose in the two groups at all time points both at visit 2 and at visit 6, except from a higher increase in the HFA group than in the CFC group 15 minutes post-dose in visit 2.

Symptoms' scores:
A statistically significant decrease from baseline in daytime scores was observed from weeks 1-2 onwards in both treatment groups. The mean decreases from baseline at endpoint were -0.66 ± 0.58 (95% CI: -0.77 to -0.55) in the HFA group and -0.60 ± 0.57 (95% CI: -0.71 to -0.48) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.832).

Similarly to daytime scores, a statistically significant decrease from baseline in night time scores was observed from weeks 1-2 onwards in both treatment groups. The mean decreases from baseline at endpoint were -0.43 ± 0.55 (95% CI: -0.54 to -0.32) in the HFA group and -0.43 ± 0.58 (95% CI: -0.55 to -0.32) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.762).

A statistically significant and clinically relevant increase from baseline in the percentage of days without symptoms was observed from weeks 1-2 onwards in both treatment groups. The mean increases from baseline at endpoint were 45.3 ± 32.3% (95% CI: 38.9 to 51.6) in the HFA group and 39.8 ± 31.3% (95% CI: 33.6 to 46.0) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.331).

Use of relief salbutamol:
A statistically significant decrease from baseline in daytime use of relief salbutamol was observed from weeks 1-2 onwards in both treatment groups. The mean decreases from baseline to endpoint were -1.24 ± 0.99 (95% CI: -1.43 to -1.04) in the HFA group and -1.03 ± 0.83 (95% CI: -1.20 to -0.86) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.437).

As regards night-time use, a statistically significant decrease from baseline was observed from weeks 1-2 onwards in both treatment groups. The mean decreases from baseline at endpoint were -0.45 ± 0.66 (95% CI: -0.58 to -0.32) in the HFA group and -0.36 ± 0.55 (95% CI: -0.47 to -0.24) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.356).

A statistically significant and clinically relevant increase from baseline of the percentage of days without use of salbutamol was observed from weeks 1-2 onwards in both treatment groups; the increases were generally of similar extent in the two groups. The mean increases from baseline at endpoint were 46.0 ± 32.3% (95% CI: 39.5 to 52.4) in the HFA group and 40.5 ± 33.5% (95% CI: 33.7 to 47.3) in the CFC group. The ANCOVA model showed that the difference between groups was not statistically significant (p = 0.336).

Asthma exacerbations:

A total number of 16 exacerbations, 2 in the HFA group and 14 in the CFC group, were reported in 12 patients, 2 (1.89%) in the HFA group and 10 (9.71%) in the CFC group. The comparison between groups of the incidence of asthma exacerbations showed a statistically significant difference (p = 0.015), in favour of the HFA group. Severe exacerbations were reported in 1 case (0.9% of the total number of exacerbations) in the HFA group and in 7 (6.8%) in the CFC group. A total number of 3 exacerbations requiring oral corticosteroids, 1 in the HFA group and 2 in the CFC group, were reported in 3 patients, 1 (0.94%) in the HFA group and 2 (1.94%) in the CFC group. The comparison between groups in the incidence of asthma exacerbations requiring oral corticosteroids did not show statistically significant differences (p = 0.618).

The mean time to the first exacerbation was 5.50 ± 6.36 days (range 1-10) in the HFA group and 25.4 ± 32.4 days (range 1-85) in the CFC group. The analysis of the Kaplan-Meier estimate of the survival analysis of the time to the first exacerbation showed a statistically significant difference between groups (p = 0.014), in favour of the CFC group.

Safety results:

Adverse events:

A total number of 60 adverse events (AEs), 33 in the HFA group and 27 in the CFC group, were reported in a total of 47 patients, 24 (22.6%) in the HFA group and 23 (22.3%) in the CFC group (p = 0.957 between groups). A total number of 38 adverse drug reactions (ADRs), 19 in the HFA group and 19 in the CFC group, were reported in a total of 29 patients, 14 (13.2%) in the HFA group and 15 (14.6%) in the CFC group (p = 0.777 between groups). No serious adverse events (SAEs) were observed in both groups for the total study period. One patient in CFC group discontinued the study due to adverse events (dysphonia). The most frequently reported events consisted of headache and gastrointestinal disorders (dry mouth, dyspepsia and nausea), which were reported with similar frequency in the two groups.

Vital signs:
The results of vital signs did not show any statistically significant change from baseline to week 12 in both groups as regards systolic blood pressure (mean changes were -0.88 mmHg in the HFA-134 a group and -1.58 mmHg in the CFC group), diastolic blood pressure (mean changes were -0.81 mmHg in the HFA-134 a group and -0.61 mmHg in the CFC group) and heart rate (mean changes were -1.03 bpm in the HFA-134 a group and -1.58 bpm in the CFC group).

Laboratory tests:
The results of laboratory parameters measured pre-dose at baseline and week 12 did not show any statistically significant change from baseline in both treatment groups for fasting serum glucose, serum potassium and 12-hour urinary cortisol/creatinine ratio (except a significant increase in serum potassium in the CFC group). The comparisons between groups showed a statistically significant difference for serum potassium (p = 0.024), due to the unexpected significant increase in the CFC group, while there were no statistically significant differences between groups for fasting serum glucose and 12-hour urinary cortisol/creatinine ratio. No differences between groups were found in the analysis of changes from baseline to week 12 of fasting serum glucose and serum potassium in terms of values below, within or above the range of normal values.

ECG:
No evidence of ECG changes or QTc interval prolongation was reported in both groups. The mean changes from baseline at the final visit of QTc interval were -2.08 ± 30.2 msec (95% CI: -7.98 to 3.83) in the HFA group and 0.35 ± 32.4 msec (95% CI: -6.08 to 6.78) in the CFC group (p = 0.568 between groups). There were also no significant changes in both groups or in the comparison between groups in the change of the QTc interval measured pre-dose and 60 minutes after dosing both at visit 2 and at visit 6.

Conclusions:

The main results of the present study have shown that:

- BDP 250 µg/salbutamol 100 µg HFA pMDI fixed combination was not inferior to the same BDP 250 µg/salbutamol 100 µg pMDI fixed combination given with the conventional CFC propellant in the primary efficacy variable morning pre-dose PEF daily measured by patients.
- The increase from baseline of morning and evening PEF daily measured by patients was higher in the HFA-134 than in the CFC group, while no statistically significant differences between groups were observed in changes from baseline to endpoint of morning and evening FEV_1, daily measured by patients.
- The results of pulmonary function measured at the clinic visits (FEV_1, FVC, PEF and FEF_{27-75}) showed relevant and significant increases from baseline in both treatment groups. Apart from FEV_1 expressed as percentage of predicted normal value and FEF_{27-75}, for which the increase was higher in the HFA-134a than in the CFC group, there were no significant differences between groups in all the other pulmonary function parameters, both expressed as absolute values or as percentage of predicted normal values.
- There were also no differences between groups in the extent of bronchodilation measured from pre-dose to 60 minutes post-dose at both visit 2 and visit 6.
- No difference between groups was shown in the improvements of daytime and night time clinical symptoms, as well as in use of rescue salbutamol.
- The rate of patients with asthma exacerbation was higher in the CFC than in the HFA-134a group, whereas no differences between groups were observed in the number of patients with asthma exacerbations requiring treatment with oral corticosteroids. The time to first exacerbation was significantly longer in the CFC group, as compared to the HFA-134a group.
- BDP 250 µg/salbutamol 100 µg HFA pMDI fixed combination was as safe as the CFC combination in terms of adverse events' profile, effects on serum potassium, fasting serum glucose and adrenal function, changes of heart rate and blood pressure, and ECG (including QTc interval).