Clinical studies in asthmatics with a new non-extra fine HFA formulation of beclometasone dipropionate (BDP Modulite®)

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Abstract The main objective of the clinical development programme for BDP Modulite®, a new non-extra fine formulation of beclometasone dipropionate (BDP) in hydrofluoroalkane (HFA), has been to demonstrate therapeutic equivalence compared with standard BDP chlorofluorocarbon (CFC) products at the recommended posology (delivered dose and patient population). A total of 1158 asthmatic patients were included in five clinical studies and 658 patients were treated with BDP Modulite®. Four studies were undertaken in mild or moderate-to-severe asthmatic adults, while one study was carried out in children. The duration of treatment was 12 weeks in three studies and 6 weeks in the other two studies. A range of doses of BDP Modulite® from 200 µg bid up to 1500 µg bid was evaluated against CFC comparators. The primary efficacy variable in all studies was morning PEFR while secondary variables included other lung function parameters, symptom scores and salbutamol use. All studies demonstrated equivalence of efficacy for morning PEFR for BDP Modulite® versus BDP-CFC when compared on a microgram for microgram basis. The secondary outcome variables also consistently support similar efficacy of the two products. The safety and tolerability profile for BDP Modulite® was similar to BDP-CFC; the incidence of adverse events was comparable between treatments and plasma and urinary cortisol were generally unchanged in patients receiving 1000 µg/day for 6-12 weeks. In conclusion, the results of the clinical studies with BDP Modulite® show that this new HFA formulation allows a seamless transition to CFC-free BDP, thus simplifying the changeover.

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INTRODUCTION

Inhaled corticosteroids (ICS) are recommended by all guidelines as first-line therapy in the control of persistent asthma (1), and are more commonly delivered via pressurized aerosols (metered dose inhalers-MDIs). Beclometasone dipropionate (BDP) was the first effective and safe ICS to be marketed (2). It is still largely used for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Chlorofluorocarbons (CFCs) are conventional propellants widely used in the delivery of MDIs. They have been administered to millions of asthmatics and COPD patients. They are inexpensive, reliable and effective but their use is now strictly limited under the Montreal Protocol because of their deleterious effects on ozone (3). Before the start of the phase-out of CFCs, alternative CFC-free propellants had been developed (4).

Hydrofluoroalkanes (HFAs) have been developed as alternative propellants to CFCs as they do not deplete the ozone layer (5). HFA 134a is one HFA that has been developed as a replacement propellant for use in MDIs since it is chemically inert, non-flammable and of low toxicity (6-10). In 1994, the European Committee for Proprietary Medicinal Products (CPMP) concluded that HFA 134a could be a suitable alternative to CFCs used in the formulation of medicinal products, including pressurized MDIs, for treatment of asthma (CPMP 1993) (11) and this has been borne out by the subsequent development of several inhaled asthma medicines containing this propellant.

CFCs and HFAs share a number of basic technical characteristics but differ in such physical properties as density, vapour pressure, molecular polarity and evaporation kinetics. These differences have necessitated the development of new formulations, valves and manufacturing processes for HFA 134a inhalers.

As a result of the technical difficulties encountered in formulating an HFA 134a BDP product, the aerosols produced by currently marketed products (Qvar™, 3M and Beclazone™, Norton Healthcare) are different to the BDP-CFC products (12-14). The size of the particles
released from the pressurized aerosol is smaller in order to target the lower airways and there appears to be a doubling potency of BDP-HFA compared with BDP-CFC (15,16). This implies that, in the switching phase from CFC to BDP-HFA, the dosage must be halved.

Therefore, in order to minimize disruption to prescribers and patients, a new HFA 134a formulation of BDP has been developed by Chiesi Farmaceutici with the objective of producing solution formulations of BDP-HFA 134a in pressurized MDIs that are equivalent in terms of efficacy, safety and dose per actuation performance to the currently marketed BDP-CFC containing products. The inclusion of glycerol as a non-volatile co-solvent has allowed the particle size of the inhaled drug to be rendered as close as possible to that of the conventional CFC. It has also been shown that the selection of an appropriate actuator orifice diameter contributes to the modulation of an aerosol cloud allowing the maintenance of an equivalence between the dose of HFA and CFC-formulated drugs. This new non-extra fine HFA 134a formulation, BDP Modulite®, allows a seamless transition to CFC-free BDP minimizing difficulties to both prescribers and patients.

Studies carried out with the BDP Modulite® formulation have been performed according to the recommendations of the European Guidelines for the phase-out of CFCs in the MDI (11).

CLINICAL TRIALS WITH NON-EXTRA FINE BDP-HFA FORMULATION (BDP MODULITE®)

I. Lefrançois et al: A new non-ultra fine BDP-HFA 134a formulation clinical equivalence of efficacy and safety vs. CFC formulation (17)

The clinical equivalence of efficacy and safety of the BDP Modulite® was compared with that of BDP-CFC in 498 clinically stable adult asthmatics treated by ICS delivered by MDI with or without a spacer and who required a daily dose of up to 1500 µg of BDP equivalent.

This was an equivalence multicentre, randomized (2 HFA, 1 CFC), double-blind parallel group study. After a 1-week run-in period, patients were randomized to BDP Modulite® or BDP-CFC. The treatment duration was 6 weeks. It was followed by an open-label safety study of 8 weeks treatment with BDP Modulite® (Figure 1).

Both drugs were delivered with the addition of the Jet® spacer (Chiesi Farmaceutici).

The treatment dosage was based on the replacement dose per dose, in term of BDP equivalent, of the previous treatment dosage with either BDP Modulite® or BDP-CFC.

Of the 498 patients included in the study, 473 were randomized and 443 were eligible for intent to treat analysis (293 patients in the group BDP Modulite® and 150 patients in the group BDP-CFC).

Patients demographics were similar in both groups in terms of age (44.8 ± 15.4 years in the BDP Modulite® group and 45.8 ± 15.4 years in the BDP-CFC group), previous and concomitant treatments. However, there were more men (59.3%) in the BDP-CFC group than in the BDP Modulite® group (47.8%).

FEV₁ values were also similar in the two groups.

The primary efficacy criterion recorded (PEFR) was recorded in the morning by an electronic flow meter (One Flow Meter). Morning PEFR was almost identical in both groups at randomization. There was an equivalence in morning PEFR between the two groups (Table I).

Several secondary efficacy criteria were used: evening PEFR, PEFR variability, morning and evening FEV₁, clinical symptoms, short-acting β₂-agonist rescue medications and the number of exacerbations defined as a PEFR variability > 20% for at least 2 consecutive days and/or β₂-agonist consumption > 3 double puffs per day for at least 2 consecutive days and/or woken at night with asthma for at least 2 consecutive days. The clinical equivalence of BDP Modulite® formulation was demonstrated for all parameters. In particular, the percentage of exacerbations was 12% in the BDP Modulite® group and 10.7% in the BDP-CFC group. Diurnal PEFR variability after 6 weeks of treatment was under 10% in both groups. Moreover, 46.9% in the BDP Modulite® group and 47.3% patients in the BDP-CFC group required rescue salbutamol during the treatment period.

The primary safety criterion was the adverse events spontaneously reported on the patient’s self-assessment diary or detected at each visit in reply to the

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investigator's standard questions. Adverse events essentially affected the respiratory system and gastrointestinal tract with no difference between groups; 82 adverse events were reported in the BDP-CFC group and 146 in the BDP Modulite® group. Only 8.8% of these events were scored as severe. The intensity and causality were similar in both groups. Only five patients dropped out from the study due to adverse events.

Urinary cortisol was used as a secondary safety criterion. There was no statistical difference between the two groups for the urinary cortisol/creatinine ratio.

Evaluation of laboratory parameters showed no difference between the two groups.

A reduction in the frequency of adverse events and exacerbations of asthma was observed during the open-label treatment period with BDP Modulite®.

In conclusion, analysis of morning PEFR, clinical and spirometric secondary parameters demonstrated the clinical equivalence of BDP Modulite® and BDP-CFC formulations. The stability and similar diurnal PEFR variability suggests that BDP Modulite® does not have any repercussion on bronchial hyperreactivity. The safety of BDP Modulite® and BDP-CFC was similar, in particular in terms of urinary cortisol.

The results of this study suggest that the non-extrafine BDP Modulite® formulation makes possible a seamless transition from BDP-CFC with evident advantages for both patients and practitioners.

2. Woodcock et al: Effects on lung function, symptoms and bronchial hyper-reactivity of low-dose inhaled BDP given via HFA 134a or CFC propellant (18)

The efficacy and safety of the BDP Modulite® was compared with that of BDP-CFC (Becotide®, GlaxoSmithKline) in 172 asthmatic adults with stable mild persistent asthma (1) (FEV₁ > 70%, mean FEV₁ predicted > 90% in both groups).

This was a single-centre, randomized, double-blind, double-dummy parallel group study. After a 1-week run-in period, patients were randomized to receive a 6-week treatment with 200 µg of BDP Modulite® or BDP-CFC bid (Figure 2).

In all, 84.9% of the patients in the BDP Modulite® group and 81.4% of the patients in the BDP-CFC group were receiving ICS at the screening visit. The treatment was continued during the run-in period.

Of the 172 patients included in the study, 164 completed the study (85 patients in the group BDP Modulite® and 79 patients in the group BDP-CFC).

Patients demographics were similar in both groups in terms of age (39.0 ± 13.1 years in the BDP Modulite® group and 37.0 ± 13.0 years in the BDP-CFC group), asthma severity, pulmonary function tests and previous and concomitant treatments.

The primary efficacy criterion was the morning PEFR recorded daily by the Mini-Wright Flow Meter. Morning PEFR was almost identical in both groups at randomization. There was an equivalence in morning PEFR between the two groups (Figure 3).

Several secondary efficacy criteria were used: evening PEFR, PEFR variability, FEV₁, FVC and MEF₂₅, clinical symptoms, number of night-time awakenings, short-acting β₂-agonist rescue medications and the number of day-time and night-time exacerbations. In accordance with asthma of a mild severity, a slight improvement in lung function compared with baseline was seen for both groups, significantly for FEV₁ in BDP Modulite® and MEF₂₅ in both groups. The clinical equivalence of BDP Modulite® and BDP-CFC formulations was demonstrated for all other parameters.

A methacholine challenge test was completed at baseline and at the end of the 6-week treatment period in 34 patients treated with BDP Modulite® and 31 patients treated with BDP-CFC. There were mild improvements in PD₂₀ and PC₂₀ methacholine in both groups with no significant difference between groups (Figure 4).

The primary safety criterion was the adverse events detected at each visit in reply to the investigator’s standard questions; 22 drug-related adverse events were recorded in the BDP Modulite® group and 19 in the BDP-CFC group. Most events were seasonal in nature or local effects due to the use of ICS. Only three patients in
the CFC-BDP group dropped out from the study due to adverse events.

In conclusion, BDP Modulite® seems to provide similar asthma control, compared with the same low daily dose of the active drug delivered via CFC. The safety of BDP Modulite® and BDP-CFC was similar.

The results of this study in mild-to-moderate persistent asthmatics suggest that the non-extra fine BDP Modulite® formulation makes possible a seamless transition from BDP-CFC.

3. Vondra et al: A new HFA 134a propellant in the administration of inhaled BDP via the Jet® Spacer: controlled clinical trial vs. the conventional CFC (19)

The efficacy and safety of the BDP Modulite® administered via a spacer device (Jet® spacer) was compared with that of BDP-CFC administered using the same device in 154 asthmatic adults with stable mild-to-
moderate persistent asthma (1) (FEV₁ ranging from 60 to 90% of predicted values).

This was a multicentre, randomized, double-blind, parallel group study. After a 2-week run-in period, patients were randomized to receive a 12-week treatment with 500 µg of BDP Modulite® or BDP-CFC bid (Clenil® Forte Jet®, Chiesi Farmaceutici) (Figure 5).

For patients receiving ICS at study entry, the treatment was continued during the run-in period.

Of the 154 patients included in the study, 147 completed it (77 patients in the group BDP Modulite® and 73 patients in the group BDP-CFC).

Patients demographics were similar in both groups in terms of age (38.0 ± 12.1 years in the BDP Modulite® group and 37.4 ± 13.3 years in the BDP-CFC group), asthma severity, pulmonary function tests and previous and concomitant treatments.

The primary efficacy criterion was the morning PEFR recorded daily by the Mini-Wright Flow Meter. Morning PEFR was almost identical in both groups at randomization. Morning PEFR increased from baseline to the final visit (Figure 6). There was an equivalence in morning PEFR between the two groups.

Several secondary efficacy criteria were used: evening PEFR, PEFR variability, pre-bronchodilator FEV₁, FVC, FEF₂₅-₇₅% and MEF₅₀, clinical symptoms, number of night-time awakenings, short-acting β₂-agonist rescue medications and the number of day-time and night-time exacerbations recorded on diary cards. Significant improvements over baseline were reported in both groups in terms of lung function (Figure 7), symptoms and use of rescue salbutamol. The clinical equivalence of BDP Modulite® and BDP-CFC formulations was demonstrated for all other parameters.

The primary safety criterion was the adverse events detected at each visit in reply to the investigator's standard questions. Adverse events were reported in 31% of patients in the BDP Modulite® group and 32% in the BDP-CFC group. No drug-related serious adverse events were reported in either group.

Morning serum cortisol (08.00 a.m. - 10:00 a.m.) was measured at the start and the end of the treatment period. Two patients went from normal to low levels in the two groups. One patient in the BDP-CFC group also had a low baseline value. The remaining patients had values within the normal range at both the baseline and end of treatment.

In conclusion, BDP Modulite® delivered using a spacer device (Jet® spacer) seems to provide similar asthma control, compared with the same high daily dose of the active drug delivered via CFC. The safety of BDP Modulite® and BDP-CFC was similar.

Figure 5. Study design.

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**Figure 6.** Evolution of morning PEFR in patients treated with BDP Modulite® and BDP-CFC via a spacer in mild-to-moderate asthmatics.
The results of this study in mild-to-moderate persistent asthmatics suggest that the non-extra fine BDP Modulite<sup>®</sup> formulation administered via a spacer device (Jet<sup>®</sup> spacer) makes possible a seamless transition from BDP-CFC.

4. Anderson et al: Equivalent efficacy and safety of a new HFA 134a formulation of BDP compared with the conventional CFC in adult asthmatics (20)

The efficacy and safety of the BDP Modulite<sup>®</sup> administered by MDI was compared with that of BDP-CFC administered by MDI (Becotide<sup>®</sup>, GlaxoSmithKline) in 116 asthmatic adults with stable mild, moderate-to-severe persistent asthma (1) (FEV<sub>1</sub> > 60% of predicted values).

This was a multicentre, randomized, double-blind, double-dummy parallel group study. After a 2-week run-in period, patients were randomized to receive a 12-week treatment with 500 µg of BDP Modulite<sup>®</sup> or BDP-CFC bid (Figure 8).

All of the patients in the BDP Modulite<sup>®</sup> and the BDP-CFC groups were receiving ICS (daily dose < 1 mg BDP equivalent) at the screening visit. Most patients were taking BDP. The treatment was continued during the run-in period.

Of the 116 patients included in the study, 91 completed the study (54 patients in the group BDP Modulite<sup>®</sup> and 52 patients in the group BDP-CFC).

Patients demographics were similar in both groups in terms of age (48.2 ± 13.7 years in the BDP Modulite<sup>®</sup> group and 46.7 ± 15.9 years in the BDP-CFC group), asthma severity, pulmonary function tests and previous and concomitant treatments.

The primary efficacy criterion was the morning PEFR recorded daily by the Mini-Wright Flow Meter. Morning PEFR was similar and non-significantly different in both groups at randomization. Morning PEFR slightly increased from baseline to the final visit. There was an equivalence in morning PEFR between the two groups.

Several secondary efficacy criteria were used: evening PEFR, PEFR variability, pre-bronchodilator FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub>% and MEF<sub>50</sub>; clinical symptoms, number of night-time awakenings, short-acting β<sub>2</sub>-agonist rescue medications and the number of daytime and night-time exacerbations recorded on diary cards. Values of pulmonary function tests were substantially unchanged during the entire study in both groups. Asthma control tended to improve during the study in both groups and there was no difference between groups in salbutamol rescue medication (Figure 9). The clinical equivalence of BDP Modulite<sup>®</sup>
and BDP-CFC formulations was demonstrated for all parameters.

The primary safety criterion was the adverse events detected at each visit in reply to the investigator's standard questions. Adverse events were reported in 57.6% of patients in the BDP Modulite® group and 52.6% in the BDP-CFC group. No drug-related serious adverse events were reported in either group. Local side-effects were observed in 11 patients in the BDP Modulite® group and in 12 patients of the BDP-CFC group.

Morning serum cortisol (08.00 a.m. – 10.00 a.m.) was measured at the start and the end of the treatment period. In the BDP Modulite® group, four patients went from normal to low levels, one patient had low levels at baseline and remained low, two patients went from low at baseline to normal levels at the end of the treatment period. In the BDP-CFC group, two patients went from normal baseline to low end of treatment level, one patient went from low to normal. The remaining patients had values within the normal range at both the baseline and end of treatment.

In conclusion, BDP Modulite® delivered using MDI seems to provide similar asthma control, compared with the same high daily dose of the active drug delivered via CFC. The safety of BDP Modulite® and BDP-CFC was similar.

The results of this study in mild, moderate-to-severe persistent asthmatics suggest that the non-ultra fine BDP Modulite® formulation administered via MDI makes possible a seamless transition from BDP-CFC.

5. Lee et al: Assessment of efficacy and systemic safety of a new CFC-free formulation of inhaled BDP in asthmatic children (21)

The efficacy and safety of the BDP Modulite® administered by MDI was compared with that of BDP-CFC (Becotide®, GlaxoSmithKline) administered by MDI in 218 asthmatic children (6–16 years) with stable mild-to-moderate persistent asthma (1) (FEV₁ between 60% and 90% of predicted values).

This was a multicentre, randomized, double-blind, double-dummy parallel group study. After a 2-week run-in period, patients were randomized to receive a 12-week treatment with 400 μg of BDP Modulite® (50 μg unit dose), BDP Modulite® (100 μg unit dose) or BDP-CFC (Becotide®, 50 μg unit dose) daily (Figure 10).

Due to practical difficulties encountered for a complete blinding of the trial (the use of four canisters would have been required), children assigned to the 100 μg dose strength were treated on an open-label design. Most of
the patients were already treated by ICS, mainly BDP, at a daily dose of up to 400 µg daily (95.8% in the BDP Modulite® 50 µg group, 91% in the BDP Modulite® 100 µg group and 84.5% in the BDP-CFC group). The treatment was continued during the run-in period.

Of the 218 patients included in the study, 207 completed the study (71 patients in the BDP Modulite® 50 µg group, 65 patients in the BDP Modulite® 100 µg group and 71 patients in the BDP-CFC group). The treatment was continued during the run-in period.

Patients demographics were similar in both groups in terms of age (10.8 ± 3.0 years in the BDP Modulite® 50 µg group, 11.4 ± 2.6 years in the BDP Modulite® 100 µg group and 10.8 ± 2.8 years in the BDP-CFC group), asthma severity, pulmonary function tests and previous and concomitant treatments.

The primary efficacy criterion was the morning PEFR recorded daily by the Mini-Wright Flow Meter. Morning PEFR was similar and non-significantly different in the three groups at randomization. Morning PEFR significantly increased from baseline after the 6th week of treatment in the three groups (P < 0.05). There was an equivalence in morning PEFR between the two groups (Figure 11).

Several secondary efficacy criteria were used: evening PEFR, PEFR variability, pre-bronchodilator FEV₁, FVC, FEF₂₅₋₇₅, FEF₁₂₀ and MEF₅₀, clinical symptoms, number of night-time awakenings, short-acting β₂-agonist rescue medications and the number of day-time and night-time exacerbations recorded on diary cards.

A statistically significant (P < 0.05) increase over baseline of FEV₁ was reported at each visit except at the final visit in the BDP-CFC group. The results of the other pulmonary function tests showed statistically significant improvements over baseline for BDP Modulite®. BDP-CFC appeared to be significantly less effective for some points (Table 2).

Superiority of BDP Modulite® over BDP-CFC was observed for some parameters.

Symptom scores significantly decreased at all times in the three groups except for BDP Modulite® 100 µg in the final 2 weeks (Table 3).

A significant decrease of salbutamol rescue medication occurred at all times in the BDP-CFC group and at weeks 7-8 in the BDP Modulite® 100 µg group.

The clinical equivalence of BDP Modulite® 50 µg, BDP Modulite® 100 µg and BDP-CFC formulations was demonstrated for most but not all parameters. However, differences were small albeit significant, and were not always found for the same formulation. Since patients in the BDP-CFC group tended to receive less salbutamol rescue medication, and these patients had a poorer control of the disease, it is possible that the differences seen were related to the amount of rescue medication, suggesting that there is an overall equivalence for the three formulations.

The primary safety criterion was the adverse events detected at each visit in reply to the investigator's standard questions. Drug-related adverse events were reported in 11.1% patients in the BDP Modulite® 50 µg group, 17.9% patients in the BDP Modulite® 100 µg group and 12.7% patients in the BDP-CFC group. The most common adverse events were respiratory tract
infections. Two other patients of the BDP Modulite® 100 µg group reported episodes of oral mycosis. No drug-related serious adverse events were reported in either group. Four patients in the BDP Modulite® 50 µg group, two patients in the BDP Modulite® 100 µg group and two patients in the BDP-CFC group discontinued the study medication due to adverse events.
Morning serum cortisol (08:00 a.m. – 10:00 a.m.) was measured at the start and the end of the treatment period in 25 patients in the BDP Modulite® 50 µg group, 33 patients in the BDP Modulite® 100 µg group and 35 patients in the BDP-CFC group. Only two patients in the BDP Modulite® 100 µg group had final values slightly below the lower limit of the normal range. On the other hand, an increase in the mean values was reported in the three patients groups.

In conclusion, BDP Modulite® delivered using MDI seems to provide similar asthma control, compared with the same daily dose of the active drug delivered via CFC. The safety of BDP Modulite® and BDP-CFC was similar.

The results of this study in mild, moderate-to-severe persistent asthmatic children suggest that the non-extra fine BDP Modulite® formulation administered via MDI makes possible a seamless transition from BDP-CFC.

CONCLUSIONS

The key objectives of the clinical development programme designed for BDP Modulite® were:
1. to confirm that the similar in vitro performance of BDP Modulite® and BDP-CFC MDIs translates into equivalent therapeutic efficacy,
2. to assess the local and systemic safety of the BDP Modulite® vs. BDP-CFC in asthma patients after prolonged administration,
3. to provide evidence that the risk/benefit ratio of the new BDP Modulite® formulation is comparable with currently available BDP-CFC products.

Studies carried out with the BDP Modulite® have been performed according to the recommendations of the European Guidelines for the phase-out of CFCs in the MDIs.

The following conclusions can be made:
1. Three pivotal clinical studies (18,20,21) have been undertaken to evaluate the performance of the BDP Modulite® 50 µg, 100 µg and 250 µg inhalers. One of the studies (21) was undertaken in a paediatric population of mild, moderate and severe asthmatics. The others were undertaken in mild or mild, moderate and severe asthmatic adults. A range of doses from 200 µg bid to 500 µg bid has been evaluated against BDP-CFC comparators.
2. Two supporting studies (17,19) have been performed in adults using the Jet® spacer actuator.
3. The primary efficacy variable in all studies was morning PEFR. Secondary variables included other lung function parameters, symptom scores and salbutamol use.
4. All studies demonstrated similarity for the BDP Modulite® products relative to the BDP-CFC products. The confidence intervals for this analysis were well within the equivalence hypothesis.
5. There were no apparent differences in the occurrence of general adverse events in patients treated with BDP Modulite® inhalers as opposed to BDP-CFC inhalers. The rates of occurrence of local adverse events (oropharyngeal and respiratory tract) were also similar for both types of treatment.
6. Morning serum cortisol values were measured in three studies. No significant decreases in the mean value were seen in any of the treatment groups.
7. A subset of adult patients treated with 200 µg bid was challenged with methacholine. There was no difference in the bronchial hyper-reactivity of patients treated with BDP-CFC and BDP Modulite® products.

These studies confirm that BDP Modulite® produces solution formulations of BDP-HFA 134a in pressurized MDIs that are equivalent in terms of efficacy, safety and dose per actuation performance to the currently marketed BDP-CFC containing products. This new non-extra fine HFA 134a formulation allows a seamless transition to CFC-free BDP in order to minimize difficulties to both prescribers and patients.

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