

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Beclometasone dipropionate**

**IE/W/001/pdWS/001**

<b>Rapporteur:</b>	Irish Medicines Board
<b>Start of the procedure (day 0):</b>	07 April 2009
<b>Date of this report:</b>	16 June 2009
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):</b>	16 June 2009
<b>Deadline for CMS's comments (day 85):</b>	01 July 2009
<b>Date re-start procedure (day 90):</b>	08 December 2009
<b>Deadline for CMS's comments (day 115):</b>	06 January 2010
<b>Finalisation procedure (day 120):</b>	11 January 2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Beclometasone dipropionate
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	R03BA01
Pharmaceutical form(s) and strength(s):	
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## **I. EXECUTIVE SUMMARY**

In accordance with Article 45 of the Regulation (EC) No 1901/2006 the pharmaceutical company Cheisi has submitted data from ten studies of Beclometasone dipropionate (BDP) in asthmatic children. The studies have not previously undergone regulatory review, other than in the preliminary version of this report.

None of the studies contribute new safety or efficacy information to the clinical and scientific understanding of the product. Many have been made redundant by time, such as comparisons of CFC and HFA driven formulations; the former being no longer available. Some of the studies are either poorly designed, or poorly conducted, to such an extent as to render them uninterpretable.

## **II. RECOMMENDATION**

The data submitted do not warrant any regulatory action.

During the course of the procedure there were no comments from any EU Member State with the exception of the Netherlands. The Netherlands considered that the Article 45 procedure should lead to an SPC harmonisation exercise. Despite Chiesi's willingness to participate in such an exercise, the Rapporteur disagrees with that view. The purpose of the paediatric work sharing programme was and is, to review previously unseen material from a clinical safety and efficacy perspective; the driver for the programme being the discovery of the adverse effects of SSRI drugs in children, and the fact that it emerged from clinical trials which had not been seen by, or submitted to, regulatory authorities.

In the current instance no new data on BDP emerge and it is considered that a BDP product information review is outside the remit of the procedure. Furthermore, if such a procedure were to be undertaken the normal regulatory practice would be to begin with the product information of the innovator. The present report concerns generic products.

In summary, the BDP work sharing procedure is considered finalised with no requirement for regulatory action.

## **III. INTRODUCTION**

Several Marketing Authorisation Holders MAHs submitted 10 completed paediatric studies for Beclometasone dipropionate (BDP) in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for BDP and that there is no consequential regulatory action.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)**

No relevant information has been provided.

## IV.2 Non-clinical aspects

### IV.2.1. Introduction

The MAH has not submitted any reports.

### IV.2.2. Clinical study(ies)

**DM/PR/3303/004/03** was a single centre, double-blind; three ways cross over comparison of the safety of Beclometasone dipropionate (BDP) HFA administered by metered dose inhaler and BDP CFC administered by metered dose inhaler. It was conducted in Denmark from September to December 2003.

- Methods

The primary aim of the study was to compare lower leg growth rate, measured by knemometry, over a 2-week treatment period in asthmatic children treated with BDP HFA MDI 100 µg bid versus BDP CFC MDI 100 µg and 200 µg bid. There was a two week washout period between treatments. A secondary endpoint was to compare 24 hour cortisol excretion.

Eligible patients were children aged between 6 and 14 years inclusive defined as Tanner Stadium I, with a clinical diagnosis of mild asthma for at least two months prior to randomisation and taking β2 agonists as required or inhaled dry powder budesonide up to 400 µg daily or equivalent treatments.

The primary endpoint, growth rate measured by knemometry, was summarised per treatment and analysed across treatments by ANCOVA. The ANCOVA model included treatment and period as fixed effects, subject as a random effect and baseline growth rate as a covariate. Total cortisol and urinary free cortisol excretion was compared across treatment groups by an ANOVA model including treatment and period as fixed effect and subject as random effect.

- Results

Twenty-five patients were screened and twenty-four randomised. One patient withdrew during the placebo run-in period and three during the first treatment period. Twenty patients completed the study. Eleven patients were female and fourteen were male. Patients mean age was 9.2 years (s.d. 1.6).

The results for the primary endpoint and for 24 hour cortisol excretion are shown in Table 1 the difference for the primary comparison, growth rate on the HFA 100 µg and CFC 100 µg which was -0.2 was not statistically significant. The difference between HFA 100 µg and Run-in was -0.34 (95% CI -0.53, -0.13). The differences in cortisol excretion on active treatment are not statistically significant.

Table 1 – Safety results data are mean and s.d.

	Run in	HFA 100 µg	CFC 100 µg	CFC 200 µg
Growth rate (mm/week)	0.43 (0.23)	0.09 (0.29)	0.1 (0.45)	0.08 (0.27)
24 hour cortisol excretion (µg/day)	NA	523.0 (165.2)	596.5 (204.6)	561.4 (229.4)

**Rapporteur's comment:**

The basis for the sample size is difficult to find. Under the relevant heading there is a statement that the study was carried out according to the protocol but the basis for the relevant assumptions are not given. Despite this the size is comparable to that often found in crossover studies.

**DM/PR/3303/005/03** was a single centre, double-blind; three ways cross over comparison of the safety of Beclometasone dipropionate (BDP) HFA administered by metered dose inhaler and BDP CFC administered by metered dose inhaler. All treatments were administered via the Volumatic® spacing device. It was conducted in Denmark from January to May 2004.

- Methods

The primary aim of the study was to compare lower leg growth rate, measured by knemometry, over a 2-week treatment period with BDP HFA MDI 100 µg bid versus BDP CFC MDI 100 µg and 200 µg bid in children with mild asthma. There was a two week washout period between treatments. A secondary endpoint was to compare 24 hour cortisol excretion between treatments.

Eligible patients were children aged between 6 and 14 years inclusive defined as Tanner Stadium I, with a clinical diagnosis of mild asthma during at least two months prior to randomization treated with β2 – agonists as required or inhaled dry powder Budesonide (Spirocort®) up to 400 µg daily or equivalent treatments.

The primary endpoint, growth rate measured by knemometry, was summarized per treatment and analysed across treatments by ANCOVA. The ANCOVA model included treatment and period as fixed effects, subject as a random effect and baseline growth rate as a covariate. Total cortisol and urinary free cortisol excretion was compared across treatment groups by an ANOVA model including treatment and period as fixed effect and subject as random effect.

- Results

Thirty patients were screened and all were randomized. Two patients withdrew during the placebo run-in period and two during the treatment period. Twenty-six patients completed the study. Thirteen patients were female and seventeen were male. Patients’ mean age was 9.3 years (s.d. 2.2).

The results for the primary endpoint and for 24 hour cortisol excretion are shown in Table 2 the difference for the primary comparison, growth rate on the HFA 100 µg and CFC 100 µg which was not statistically significant. The differences in cortisol excretion on active treatment are not statistically significant.

*Table 2 – Safety results data are mean and s.d.*

	Run in	HFA 100 µg	CFC 100 µg	CFC 200 µg
Growth rate (mm/week)	0.45 (0.44)	0.29 (0.24)	0.33 (0.26)	0.31 (0.22)
24 hour cortisol excretion (µg/day)	358.2 (158.2)	339.4 (181.7)	404.8 (163.1)	331.1 (121.1)

**Rapporteur’s comment:**

As with the study without a spacing device the determination of the study size is unclear.

**DM/RS/3303/005/00** was a multi-centre, double-blind, twelve week parallel group comparison of the efficacy and tolerability of Beclometasone dipropionate (BDP) delivered by a HFA or by a CFC metered dose inhaler. It was conducted at twenty-three centres in the UK from January 1999 to June 2000.

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi-HFA 200 µg twice daily (50 µg/puff) with DBP Cheisi-HFA 200 µg twice daily with (100 µg/puff) and BDP-CFC (Becotide) (50 µg/puff) in children with mild to moderate persistent asthma. The primary endpoint was morning peak expiratory flow rate (PEFR) at study end; other pulmonary function values were secondary endpoints.

The primary endpoint was the treatment difference in FEV1 over the final 14 days of treatment analysed by ANCOVA. The ANCOVA model included terms for the investigator, treatment effects, and baseline PEFr as covariates, the non-inferiority margin was 10% of the FEV1 on reference treatment (Becotide).

Eligible patients were children aged at least 6 years and no more than 16 years; FEV1 was to be at least 60% and no more than 90% of predicted normal with FEV1 reversibility of at least 10% to inhaled salbutamol. Patients with an asthma exacerbation in the previous four weeks were excluded, as were patients receiving oral corticosteroids in the previous eight weeks and those receiving inhaled corticosteroids at doses higher than BDP 400 µg daily.

The sample size was based on an estimate of a mean of 300 mL/min for the reference (Becotide) treatment with standard deviation of 70 mL/min. A between treatment difference was estimated as zero. With  $\alpha = 0.05$  and  $\beta = 80\%$  the required sample size was 210. Non-inferiority was defined as a difference of more than 10% of the reference treatment.

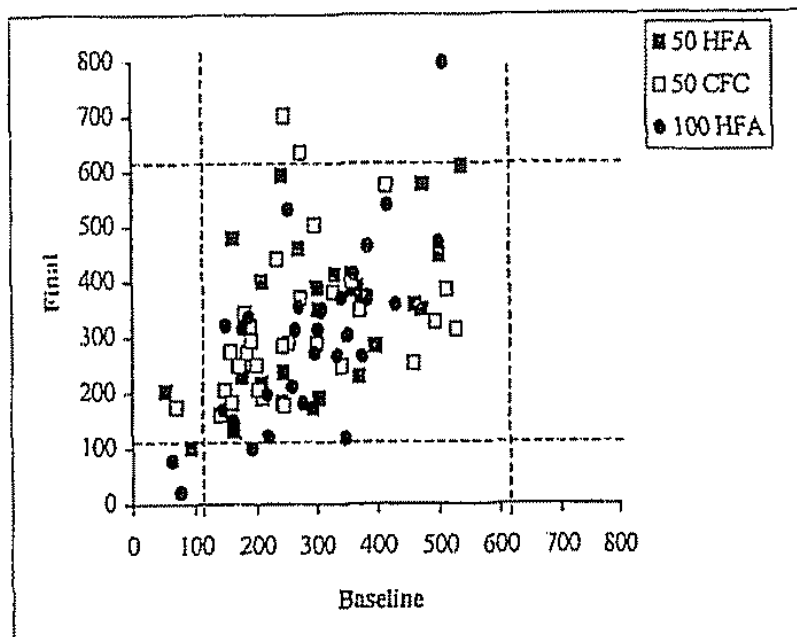
- Results

Two hundred and ninety-six patients were screened and 218 randomised, of whom 210 received trial medication.

Table 4 – Overview of study outcome (data are mean and s.d.)

	HFA 50 µg	CFC 50 µg	HFA 100 µg
Baseline demographics			
No. studied	71	71	65
No. of males	41	42	31
Mean age (years)	10.8 (2.9)	10.8 (2.7)	11.4 (2.6)
FEV1 predicted normal (%)	81.5 (9.4)	81.4 (7.5)	79.2 (8.5)
Primary efficacy endpoint			
PEFR – run in (L/min)	324 (99)	324 (96)	344 (89)
PEFR – final (L/min)	347 (98)	341 (95)	361 (93)
The treatment difference for HFA 50 µg vs. CFC 50 µg was 4.95 with a lower 95% CI of -7.3. The non-inferiority criterion was met.			
Safety variables			
Mean change in morning serum cortisol	+ 40.4	+ 51.3	+ 18.5
Treatment emergent ARs (no.)	14	20	13
AEs leading to study discontinuation (no.)	4	2	2

Figure 1 Individual values for morning cortisol by treatment



Source: Listing 14, Appendix 16 2.9

**Study 14.06/CT/01/91** was a double blind, two centre, comparison of the safety and efficacy of two preparations of BDP administered as a nasal spray; Clenil Acqua Cheisi and Beconase Aqua Glaxo. It was conducted in Italy from June to October 1991.

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi-and Glaxo products both administered as 100 µg by metered nasal spray twice daily for two weeks. The principal efficacy criterion was based on a scoring system for; rinorrhoea, nasal congestion, itching, weeping, each was scored as 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

The study was a non-inferiority evaluation assuming a 50% reduction in symptoms and with the limit of non-inferiority set as a 20% difference between treatments. Given  $\alpha = 0.05$  and  $\beta = 80\%$  the sample size was estimated at 38 patients.

Eligible patients were adolescents and adults aged at least 14 years and suffering from allergic rhinitis. Patients with nasal polyps and/or serious septal deviation were excluded. Patients with significant comorbidity were excluded.

- Results

Eighty patients were enrolled, 41 to the Clenil BDP treatment arm and 39 to Beconase. The two treatment arms were homogenous with regard to baseline rhinologic symptoms and examination.

Table 5 – Overview of study outcome (data are mean and s.d.)

	Clenil	Beconase
Demographics		
No. studied	41	39
Mean age (years)	33.5 (13.5)	34.3 (12.7)
Efficacy variables		
Rhinorrhoea baseline	2.19 (0.71)	2.13 (0.82)
Rhinorrhoea week 2	0.29 (0.52)	0.66 (0.68)
Nasal congestion baseline	2.41 (0.55)	0.29 (0.60)
Nasal congestion week 2	2.59 (0.60)	0.30 (0.47)
Itching baseline	1.60 (0.60)	1.70 (0.70)
Itching week 2	0.25 (0.50)	0.11 (0.31)
Weeping baseline	1.52 (0.58)	1.50 (0.71)
Weeping week 2	0.15 (0.36)	0.13 (0.34)

**Rapporteur's comment:**

As can be seen from Table 5 this was not a primarily a paediatric study. Review of the individual patient data shows that one patient was aged 16, one 17, and two 19, all others were aged at least 20 years.

**15.02/CT/03/92** was an open, four week, parallel group comparison of the efficacy and tolerability of Beclometasone dipropionate (BDP) delivered by dry powder inhaler (DPI) Chiesi and Glaxo. It was conducted at four centres in the Italy from November 1993 to January 1995.

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi multi-dose dry powder inhaler (MDPI) 100 µg four times daily with DBP Glaxo MDPI 100 µg four times daily in children with mild to moderate persistent asthma. The primary endpoint was FEV1 at study end; other pulmonary function values were secondary endpoints.

The primary endpoint was the success rate at study end, with success defined as more than 10% improvement in FEV1. The aim was to show that Cheisi-BDP was equivalent to Glaxo-BDP with equivalence defined as no more than 20% less successes. The number of children required for a study with  $\alpha = 0.05$  and  $\beta = 80\%$  was 72. Inference testing was by analysed by ANOVA.

Eligible patients were children aged at least 6 years and no more than 14 years; FEV1 was to be at least 60% and no more than 80% of predicted normal. They had stable lung function as identified by variability of FEV1 of no more than 15% in the previous four weeks and FEV1 reversibility of at least 10% to inhaled salbutamol. Patients with an asthma exacerbation in the previous four weeks were excluded, as were patients receiving oral corticosteroids in the previous eight weeks and those receiving inhaled corticosteroids at doses higher than BDP 400 µg daily.

- Results

Seventy four children participated in the study. The principal study results are shown in Table 6.

Table 6 – Overview of study outcome (data are mean and s.d.)

	Cheisi-BDP	Glaxo-BDP
Demographics		
No. studied	36	38
No. of males	23	27
Mean age (years)	9.8 (2.6)	9.9 (2.4)
FEV1 predicted normal (%)	73.2 (7.8)	73.9 (7.6)
FEV1 reversibility (%)	24.9 (12.6)	20.4 (7.6)
Efficacy variables		
FEV1 baseline (L)	1.78 (0.5)	1.75 (0.5)
FEV1 at four weeks (L)	2.00 (0.6)	2.00 (0.5)
Percentage of clinically relevant results [sic]*	84.85%	86.11 %
95% CI for treatment difference Percentage of clinically relevant results - 15.4, 17.9		
Safety variables		
Patients with adverse events	3	2
Trial discontinuation	1 (prohibited medication)	0

\* taken by Rapporteur to be equivalent to the proportion showing a response

**P/14.04/CT/02/97** was a multi-centre, open, twelve week parallel group comparison of the efficacy and tolerability of BDP Cheisi 800 µg twice daily delivered by nebuliser or budesonide 750 µg (Pulmicort®) twice daily by nebuliser. It was conducted at 24 centres in France from December 1997 to June 1999.

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi-800 µg twice daily with Pulmicort 750 µg twice daily both delivered by nebuliser (Pariboy Junior). The primary efficacy endpoint was the proportion (%) of patients not experiencing at least one major exacerbation during the study period. An exacerbation was defined as failure to respond to conventional inhaled rescue therapy and requiring oral corticosteroids for at least two consecutive days. Both treatment arms were administered as add-on to patients' usual bronchodilator therapy.

The primary safety endpoint was urinary deoxyipyridinoline (a marker of steroid induced bone resorption) expressed as the urinary deoxyipyridinoline/creatinine ratio.

The primary efficacy endpoint was analysed by applying the Chi-square test. The primary safety variable was analysed by two-way analysis of variance for repeated measurements.

The study size was based on data from a study in children aged 2 to 15 years where the mean urinary deoxyipyridinoline/creatinine ratio was 49.26 (s.d. 11.30) extrapolating to an expected mean of 80.3 in younger children and setting  $\alpha = 0.5$  and  $\beta = 10\%$  gave a required sample size 176 patients.

Eligible patients were children aged at least 6 months and no more than 6 years with of severe or persistent asthma based on a history of at least three episodes of wheezing dyspnoea and wheezing dyspnoea for at least two weeks before inclusion experiencing at least one exacerbation per month requiring oral steroid for the three months before inclusion. Patients receiving long acting  $\beta$ -agonists and those with significant co-morbidity were excluded.

- Results

One hundred and thirty patients were selected of whom 120 were randomised 58 to Clenil A and 62 to Pulmicort.

Table 7 – Overview of study outcome (data are mean and s.d.)

	Clenil A	Pulmicort
Demographics		
No. in ITT population	57	60
No. of males	38	45
Mean age (years)	2.02 (1.36)	2.09 (1.42)
Efficacy variables		
No. of major exacerbations	1.04 (1.18)	0.80 (1.01)
No. without major exacerbation (%)	23 (40.35)	31 (51.67)
Percentage of clinically relevant results [sic]*		
Primary safety variable		
deoxy pyridinoline/creatinine ratio	56.41 (25.22)	50.97 (50.97)

**Rapporteur's comment:**

The design, purpose, and conduct of this study are questionable.

The meaning of the term 'selected' in the patient disposition is unclear it seems to mean something more than the usual term screened.

The diagnosis of asthma at the lower end of the dose range might have been insecure – wheezy bronchitis being an alternative for at least some episodes.

The power calculation for the safety primary endpoint was based on an assumption about deoxy pyridinoline/creatinine ratio from older children which proved ill founded.

The recruitment target was not met.

The dropout rate was high 19/120, despite the relatively short duration. The duration was probably too short to show an effect on exacerbation rate or number. There were no baseline data other than satisfying the entry criteria against which to measure the effect of either treatment.

Given the above problems this study is considered uninterpretable for either safety or efficacy endpoints.

**14.04/CT/03/97** was a multi-centre, double-blind, four week parallel group comparison of the efficacy and tolerability of Beclometasone dipropionate (BDP) delivered by nebuliser and BDP delivered by metered dose inhaler with a spacing device. It was conducted at six centres in Romania from August 1998 to May 1999.

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi- 800 µg twice daily with DBP Cheisi 400 µg twice daily in children moderate to severe asthma. The primary endpoint was morning peak expiratory flow rate (PEFR) at study end; other pulmonary function values were secondary endpoints.

The primary efficacy endpoint was change from baseline in PEFR. The primary safety variable was change from baseline in morning serum cortisol. Analysis of efficacy was by ANCOVA. The ANCOVA model included terms for the investigator treatment effects and baseline PEFR as covariates. The primary safety variable was by unpaired Student's t-test. The sample size was based on a presumed treatment

effect of 300 L/min with a standard deviation of 70 L/min with  $\alpha = 0.05$  and  $\beta = 80\%$  the required sample size was 140 patients. Non-inferiority was set as no more than 10%.

Eligible patients were children aged at least 6 years and no more than 16 years; FEV1 was at least 50% and no more than 80% of predicted normal with FEV1 reversibility of at least 10% to inhaled salbutamol. Patients with an asthma exacerbation in the previous four weeks were excluded, as were patients receiving oral corticosteroids in the previous four weeks.

- Results

One hundred and sixty three patients were screened and 151 randomised.

Table 8 – Overview of study outcome (data are mean and s.d.)

	MDI	Nebuliser
Demographics		
No. in ITT population	76	75
No. of males	49	46
Mean age (years)	10.66 (2.71)	10.65 (2.89)
Efficacy variables		
Baseline PEFr (L/min)	222.94 (87.26)	231.44 (87.04)
Week 8 PEFr (L/min)*	345.57 (121.84)	360.74 (124.55)
Treatment difference was - 2.4 L/min = < 10% of the non-inferiority value (35 L/min)		
Primary safety variable		
Baseline a.m. cortisol ( $\mu\text{g}/100\text{ mL}$ )	18.6 (9.1)	17.5 (8.1)
Week 4 a.m. cortisol ( $\mu\text{g}/100\text{ mL}$ )	17.9 (10.2)	16.3 (6.6)
The ANCOVA p value for the treatment difference was 0.401.		

\*there was a four week additional efficacy period the non-inferiority margin is for four weeks.

**MC/RS/1400/001/05** was a multi-centre, double-blind, 12 week parallel group comparison of the efficacy and tolerability of Beclometasone dipropionate (BDP) 800  $\mu\text{g}$  once daily versus 400  $\mu\text{g}$  twice daily both delivered by nebuliser. It was conducted at 13 centres from January 2003 to June 2005.<sup>1</sup>

- Methods

The primary aim of the study was to compare the therapeutic equivalence of DBP Cheisi- 800  $\mu\text{g}$  daily with DBP Cheisi 400  $\mu\text{g}$  twice daily in children with moderate asthma. The primary endpoint was change from baseline in morning peak expiratory flow rate (PEFR).

The primary efficacy endpoint was change from baseline in PEFR. Analysis of efficacy was by repeated measures ANOVA. The sample size was based on a presumed mean of 320 L/min with a standard deviation of 70 L/min with  $\alpha = 0.05$  and  $\beta = 85\%$  the required sample size was 140 patients. Non-inferiority was set as no more than 10%.

Eligible patients were children aged at least 5 years and no more than 12 years; FEV1 was at least 70% and no more than 90% of predicted normal with FEV1 reversibility of at least 12% to inhaled salbutamol. Patients with an asthma exacerbation in the previous four weeks were excluded, as were patients receiving oral corticosteroids in the previous four weeks.

- Results

Seventy-four patients were screened of whom 67 entered the open run-in phase and 65 were randomised. Major protocol deviations occurred in 22 patients in the once daily group and 23 patients in the twice daily group. In the once daily group 12 patients withdrew during the study, in the twice daily group 10 patients withdrew during the study.

<sup>1</sup> The appendix giving details of the investigating centres is not available.

Table 9 – Overview of study outcome (data are mean and s.d.)

	Once daily	Twice daily
Demographics		
No. in ITT population	32	33
No. of males		
Mean age (years)	8.47 (2.08)	8.76 (2.29)
Efficacy variables		
Baseline PEF (L/s)	3.25 (0.92)	3.20 (0.93)
Week 12 PEF (L/s)	3.35 (1.13)	3.97 (1.01)

**Rapporteur's comment:**

Due to the low recruitment, high withdrawal rate, and high protocol violation rate this study is considered uninterpretable.

**MC/RS/1404/001/07** was a multi-centre, double-blind, 12 week parallel group superiority comparison of the safety and efficacy of Beclometasone dipropionate plus rescue salbutamol versus placebo plus rescue salbutamol. It was conducted at 19 centres in Poland and Ukraine from March 2006 to January 2007.

• Methods

There were three treatment arms to which patients were randomised 2:1:2 as follows;  
DBP Cheisi- 400 µg twice daily by nebulisation + rescue salbutamol 2.5 mg by nebulisation:

- Placebo + rescue salbutamol 2.5 mg by nebulisation.

- Placebo + rescue with a fixed dose combination of DBP Cheisi- 800 µg + 1.6 mg salbutamol.

The primary endpoint was the percentage of asthma symptom free days during the treatment period and treatment arms were compared using the Wilcoxon sum rank test. The sample size was based on a presumed treatment advantage of 15% in symptom free days for the double active treatment arm compared to rescue salbutamol with standard deviation of 30% with  $\alpha = 0.05$  and  $\beta = 80\%$  the required sample size was 240 patients.

Eligible patients were children aged at least 1 year and no more than 5 years; they had three or more episodes of wheeze or asthma like symptoms in the six months prior to recruitment. Patients with respiratory infections within the previous four weeks were excluded.

• Results

Two hundred and eighty three patients were screened of whom 276 entered the open run-in phase and 65 were randomised. Major protocol deviations occurred in 22 patients in the once daily group and 23 patients in the twice daily group. In the once daily group 12 patients withdrew during the study, in the twice daily group 10 patients withdrew during the study.

Table 10 – Overview of study outcome (data are mean and s.d.)

	Double active	Rescue salbutamol	Rescue FDC
Baseline demographics			
No. studied	110	56	110
No. of males	64	34	68
Mean age (years)	2.35 (0.81)	2.29 (0.87)	2.26 (0.79)
Baseline symptom score	2.47 (1.52)	2.23 (1.51)	2.37 (1.62)
Efficacy endpoints			
Percentage of symptom free days	69.6 (20.89)*	61.0 (24.83)	64.9 (24.74)
Reduction in symptom score	1.87 (1.63)	1.26 (1.92)	1.84 (1.71)
The treatment difference for HFA 50 µg/CFC 50 µg was 4.95 with a lower 95.5 CI of -7.3			
Safety variables			
Number of adverse events	30	28	50
Serious adverse events (No.)	1	0	0
Change in salivary cortisol at week 4 (µg/100 mL)	- 1.85 (6.99)	- 0.25 (3.41)	- 0.80 (17.24)

\*p = 0.034 for the comparison with rescue salbutamol.

**Rapporteur's comment:**

The efficacy and safety results of this study are presented as 63 pages of text; the tables and indices cited in the text are not available.

**MC/PR/1400/001/98** was an open multi-centre, 4 week parallel group comparison of the safety and efficacy of Beclometasone dipropionate 400 µg twice daily by nebuliser and budesonide 250 µg twice daily by nebuliser. It was conducted at 10 centres in Hungary and 1 centre in Serbia from March 1999 to July 1999.

• Methods

The primary aim of the study was to compare the therapeutic equivalence of Beclometasone dipropionate 400 µg twice daily by nebuliser and budesonide 250 µg twice daily by nebuliser in children with moderate asthma. The primary endpoint was change from baseline in peak expiratory flow rate (PEF). Analysis of efficacy between treatments was by ANCOVA and the Wilcoxon test for scored variables. Analysis of efficacy within treatment arms was by paired Student's t test. The sample size was based on a presumption of no treatment difference and a standard deviation of 22 L/min with  $\alpha = 0.05$  and  $\beta = 80\%$  the required sample size was 140 patients. Non-inferiority was set as 10 L/min.

Eligible patients were children aged at least 6 years and no more than 14 years; PEF was greater than 50% and less than 85% of predicted normal with FEV1 reversibility of greater than 15% to inhaled salbutamol. Patients receiving oral corticosteroids in the previous 12 weeks and with significant comorbidity were excluded.

• Results

One hundred and twenty-eight patients were recruited of whom 127 were randomised; all randomised patients completed the four week treatment period.

Table 11 – Overview of study outcome (data are mean and s.d.)

	BDP	BUD
<b>Demographics</b>		
No. in ITT population	66	61
No. of males	48	44
Mean age (years)	9.5 (2.3)	10.0 (2.3)
<b>Efficacy variables</b>		
Baseline PEF (% of predicted normal)	67.1	66.3
Week 4 PEF (% of predicted normal)	98.4	101.2
The p value for the inter treatment week 4 value was 0.5 the test is not stated see comment below.		
<b>Safety variables</b>		
No. of adverse events	7	2

**Rapporteur's comment:**

At various points in the study report reference is made to that fact that the p values are unimportant, presumably this refers to the under recruitment in the study but this is not formally stated or discussed.

The tables and indices referred to in the body of the report are not provided and this makes interpretation difficult. The conclusion presented in the report is that the treatments are therapeutically equivalent, the quality of study is not so poor as to make it uninterpretable and equivalence of treatments is highly probable anyway from existing knowledge of the treatments, the point of carrying out the study is therefore questionable.

Finally, the age group of the children is higher than might be expected. Although those at the youngest end of the eligibility range might have difficulty using a metered dose inhaler those in the middle and upper ends would generally be well capable of receiving treatment by that route.

**V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

➤ **Overall conclusion**

The studies provided are at best of average quality and some are of very poor quality. They do not add in any meaningful way to the sum of knowledge about beclometasone dipropionate administered by the inhalational route. Considering the length of time the substance has been in clinical use it would be surprising if they did.

➤ **Recommendation**

No further action required.

**VI. REQUEST FOR SUPPLEMENTARY INFORMATION**

Not applicable.