2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: Clenil® Modulite®	**Volume:**	
Name of Active Ingredient: beclomethasone dipropionate (BDP)	**Page:**	

Title of Study: Pilot, open-label, randomised, repeated dose, 4-way cross-over, clinical pharmacology study of beclomethasone dipropionate (Clenil® Modulite®) 250 µg HFA pMDI using the AeroChamber Plus™ spacer device versus the Volumatic™ spacer device without or with charcoal block in asthmatic adults patients

Investigator: Dr [redacted] (Principal Investigator)

Study Centre: [redacted]

Publication (reference): None at the time of reporting.

Studied Period:	**Phase of development:** II
FPFV: 01-Apr-2011 LPLV: 28-Jun-2011	

Objectives:

Primary:

- To evaluate, at steady-state, the systemic exposure and the lung deposition of beclomethasone 17-monopropionate (B17MP, active metabolite of BDP) as $AUC_{0\text{-}12h,ss}$ and $C_{max,ss}$, after inhalation of BDP (Clenil® Modulite®) with the AeroChamber Plus™ spacer device or with the Volumatic™ spacer device without and with charcoal block.

Secondary:

- To evaluate the pharmacokinetic (PK) profile of BDP and additional PK parameters of B17MP after inhalation of BDP (Clenil® Modulite®) with the AeroChamber Plus™ or the Volumatic™ spacer devices at steady-state without and with charcoal block;
- To evaluate the general safety and the tolerability profile after repeated treatment.

Methodology *(Study Design):*

This was a phase II, monocentre, open-label, randomised, 4-way crossover, repeated dose study with 4 active treatment periods. The study required seven visits in the clinic (Visit 0 to Visit 6)

and one follow-up phone contact (Visit 7). Screening consisted of a pre-screening visit (Visit 0) to obtain the patient's informed consent and record demographic data and a screening visit (Visit 1) to verify the eligibility of the patient. If eligible, patients were randomized at Visit 2 to a sequence of four subsequent treatment periods of 14 days each (Visits 2-6). Treatment sequences were defined such that each type of spacer device was used for two consecutive periods.

The four different treatments were:
- Clenil® Modulite® with AeroChamber Plus™;
- Clenil® Modulite® with AeroChamber Plus™ and charcoal block;
- Clenil® Modulite® with Volumatic™;
- Clenil® Modulite® with Volumatic™ and charcoal block.

The charcoal block was performed during the administration of Clenil® Modulite® with AeroChamber Plus™ and Volumatic™, respectively, on Day 14 of the respective treatment periods in the clinic.

A follow-up phone contact (Visit 7) was planned 3-5 days after end of the last treatment period. The study duration for each patient was approximately 10 to 11 weeks. The rescue medication in this study was salbutamol (Ventolin®), a short-acting β2-agonist (SABA).

On Day 14 of each treatment period, blood samples were collected at pre-dose and over a 12-hour period following study drug administration to evaluate the pharmacokinetics of BDP and its metabolite B17MP in plasma.

Number of patients *(planned and analysed)*:

Planned: 16 patients were to be randomised in order to obtain 12 completed patients

Analysed: *Safety Population:* 16 patients

Withdrawal: 1 patient

PK population: 15 patients

Diagnosis and main criteria for inclusion:

1. Male or female patients aged 18-65 years included.
2. Diagnosis of asthma according to Global Initiative for Asthma (GINA) guidelines 2009 made at least 6 months prior to screening.
3. Patients already treated with a dose of BDP or equivalent (according to GINA guidelines 2009) up to 2000 µg/day.
4. Forced Expiratory Volume in one second (FEV_1) ≥60% of predicted patient's normal value (after appropriate wash-out from bronchodilators) at screening and randomisation.
5. A documented positive response to the reversibility test, defined as an improvement in FEV_1 of at least 12% from baseline value and 200 mL 20 to 30 minutes after 4 puffs of inhaled salbutamol pressurised Metered Dose Inhaler (pMDI) (400 µg) at screening or within a year prior to screening and/or a documented (within 6 months prior to screening) hyper-responsiveness to methacholine on bronchial challenge testing (PC20 equal or less than 16 µg/mL).

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

- Treatment A: Beclomethasone dipropionate (Clenil® Modulite®) pMDI 250 µg with AeroChamber Plus™ spacer device without charcoal block; 4 inhalations bid (daily dose 2000 µg)
- Treatment B: Beclomethasone dipropionate (Clenil® Modulite®) pMDI 250 µg with AeroChamber Plus™ spacer device with charcoal block; 4 inhalations bid (daily dose 2000 µg)

Batch numbers:

BDP 250 µg hydrofluoroalkane (HFA) (Clenil® Modulite®) batch [redacted] AeroChamber Plus™ spacer batch [redacted]

Duration of treatment:

Repeated dose treatment over four 14-day periods

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

- Treatment C: Beclomethasone dipropionate (Clenil® Modulite®) pMDI 250 µg with Volumatic™ spacer device without charcoal block; 4 inhalations bid (daily dose 2000 µg)
- Treatment D: Beclomethasone dipropionate (Clenil® Modulite®) pMDI 250 µg with Volumatic™ spacer device with charcoal block; 4 inhalations bid (daily dose 2000 µg)

Batch numbers:

BDP 250 µg HFA (Clenil® Modulite®) batch [redacted], Volumatic™ spacer batch [redacted]

Pharmacokinetics:

Primary PK variables

- Plasma B17MP $AUC_{0\text{-}12h,ss}$ and $C_{max,ss}$ (at steady-state)

Secondary PK variables

- Plasma B17MP $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}0.5h,ss}$, $AUC_{0\text{-}8h,ss}$, $C_{min,ss}$, $t_{min,ss}$, $t_{max,ss}$ and $t_{½,ss}$ (at steady state)
- Plasma BDP $AUC_{0\text{-}t,ss}$, $C_{max,ss}$, $t_{max,ss}$ and $t_{½,ss}$ (at steady-state)

Safety:

- Adverse Events (AEs), Adverse Drug Reactions (ADRs), Serious Adverse Events (SAEs), Adverse events leading to study withdrawal;
- Vital signs: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP);
- Laboratory tests: haematology and blood chemistry;
- Pulmonary function test: FEV_1.

Statistical methods:

Sample size calculation

As this was a pilot study the sample size was not based on a formal power calculation. A total sample size of 12 completed patients (three patients per sequence) was deemed adequate to conduct an exploratory assessment of the pharmacokinetics of Clenil® Modulite® when used in

combination with a Volumatic™ or AeroChamber Plus™ spacer device.

16 patients (four patients per sequence) were to be randomised in order to obtain 12 completed patients.

Pharmacokinetic variables

Plasma B17MP $AUC_{0\text{-}12h,ss}$, $AUC_{0\text{-}t,ss}$ and $C_{max,ss}$ (at steady state), and plasma BDP $AUC_{0\text{-}t,ss}$ and $C_{max,ss}$ (at steady-state) were log-transformed and statistically evaluated using a linear model (analysis of covariance, ANOVA). Treatment, sequence, period of administration, and patient within sequence were considered fixed effects. The ratios of adjusted geometric means between test and reference without and with charcoal block were calculated with their 90% two-sided confidence intervals (CIs).

Plasma B17MP $AUC_{0\text{-}0.5h,ss}$, $AUC_{0\text{-}8h,ss}$, $C_{min,ss}$, $t_{min,ss}$, $t_{max,ss}$ and $t_{½,ss}$ (at steady-state) and plasma BDP $t_{max,ss}$ and $t_{½,ss}$ (at steady-state) were summarised by treatment group using descriptive statistics.

Plasma concentration/time curves, individual and based on mean values by treatment, were presented in linear/linear and log/linear scale.

Safety variables

The number and percentage of patients experiencing AEs, ADRs, SAEs and AEs leading to study withdrawal were presented for each treatment. Adverse events were summarised for each treatment by System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory tests (haematology and blood chemistry), vital signs (heart rate and blood pressure) and FEV_1 were summarised overall and by sequence using descriptive statistics. Shift tables from screening visit to Visit 6, with regard to normal range, were presented overall and by sequence for all relevant laboratory parameters.

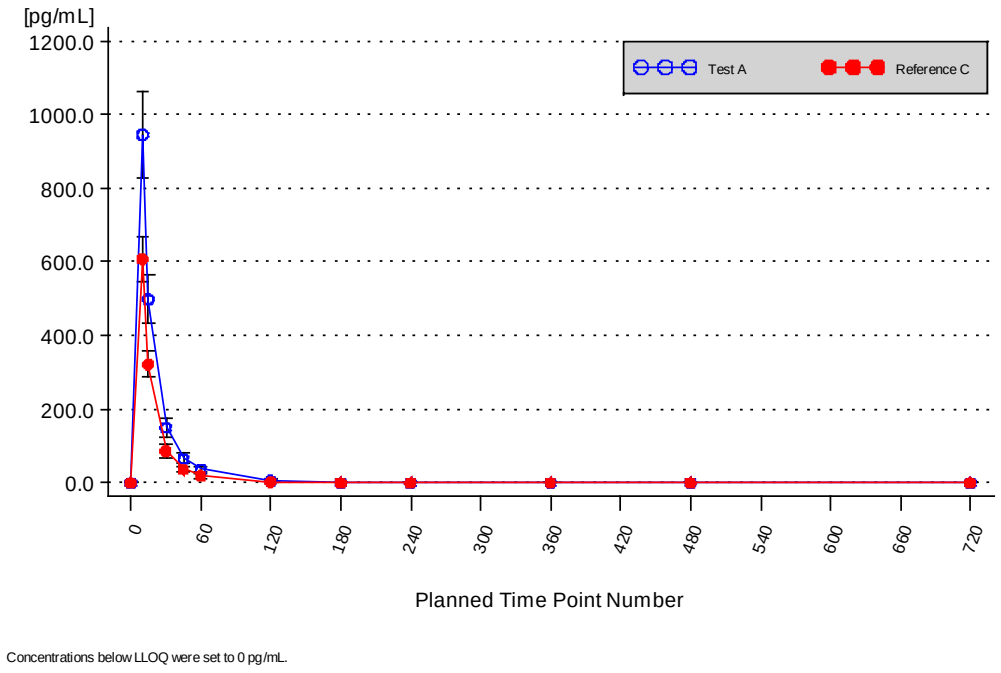
Summary – Conclusions:

Pharmacokinetic Results:

- **Pharmacokinetic comparison of *Clenil® Modulite® with AeroChamber Plus™* versus *Clenil® Modulite® with Volumatic™* both administered *without charcoal block*: TEST A - REFERENCE C (PK population)**

Pharmacokinetics of BDP

Concentration/time curves of BDP for Test A and Reference C (arithmetic means and standard deviations)



Concentrations below LLOQ were set to 0 pg/mL.

Test A: Clenil® Modulite® with AeroChamber Plus™; Reference C: Clenil® Modulite® with Volumatic™

Summary of PK parameters of BDP for Test A and Reference C

		$C_{max,ss}$ (pg/mL)	$T_{max,ss}$ (min)	$AUC_{0-t,ss}$ (min*pg/mL)	$t_{½,ss}$ (min)
Test A	Mean	945.9	10.0	16085.6	15.4
	SD	452.19	0.00	9856.42	9.02
	Median	872.0	10.0	13089.5	12.4
	Geometric Mean	860.5	10.0	14074.9	13.8
Reference C	Mean	608.4	10.1	9929.7	14.3
	SD	237.34	0.26	5504.75	10.92
	Median	628.0	10.0	9653.3	10.2
	Geometric Mean	564.6	10.1	8787.5	11.9

Statistical comparison of AUC and C_{max} for BDP between Test A and Reference C

Variable	Comparison of test and reference treatment (least square mean)		Ratio of geometric means	90%-CI for the ratio of means	Within-subject CV%
	Test A	Reference C			
$AUC_{0-t,ss}$	14085.3	8812.2	1.5984	(1.30 - 1.96)	34.4
$C_{max,ss}$	856.4	563.4	1.5201	(1.23 - 1.88)	35.7

$AUC_{0-t,ss}$ in min*pg/mL and $C_{max,ss}$ in pg/mL

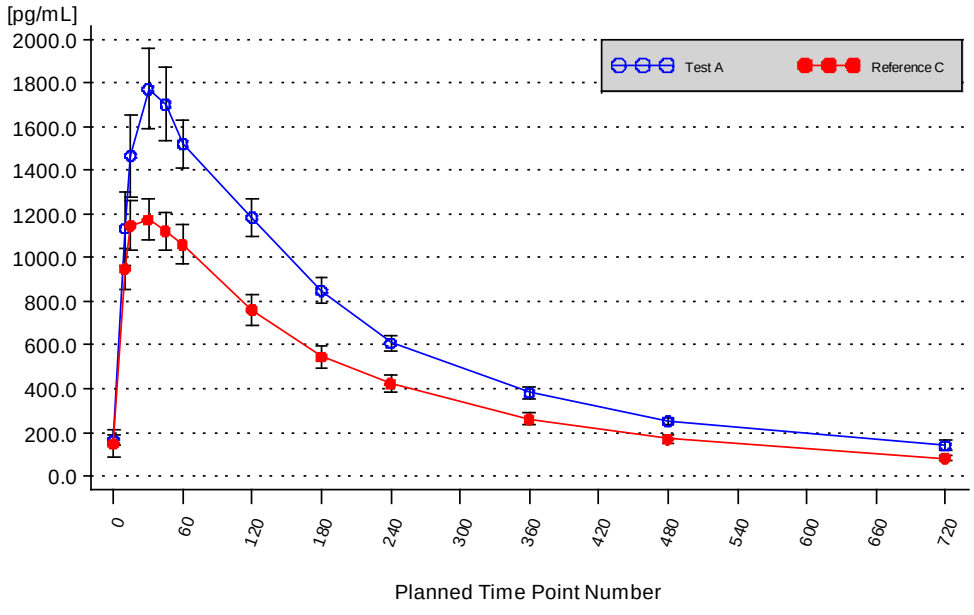
Test A: Clenil® Modulite® with AeroChamber Plus™; Reference C: Clenil® Modulite® with Volumatic™

The PK profile of BDP was characterized by rapid absorption with a median $t_{max,ss}$ of 10.0 min and rapid elimination with plasma concentrations decreasing to less than 10% of the $C_{max,ss}$ over the course of 45 min. The geometric mean $t_{1/2,ss}$ was 13.8 and 11.9 min for Test A and Reference C, respectively.

Steady-state systemic exposure to BDP and peak BDP concentration were, on average, 60% and 52% higher for Clenil® Modulite® with AeroChamber Plus™ as compared to Clenil® Modulite® with Volumatic™, as assessed by $AUC_{0-t,ss}$ and $C_{max,ss}$ respectively, with the 90% CIs for the comparison being 130 to 196% for $AUC_{0-t,ss}$ and 123 to 188% for $C_{max,ss}$, outside the bioequivalence acceptance interval (80.00-125.00%).

Pharmacokinetics of B17MP

Concentration/time curves of B17MP for Test A and Reference C (arithmetic means and standard deviations)



Concentrations below LLOQ were set to 0 pg/mL.

Test A: Clenil® Modulite® with AeroChamber Plus™; Reference C: Clenil® Modulite® with Volumatic™

Summary of PK parameters of B17MP for Test A and Reference C

		$Cmax_{,ss}$ (pg/mL)	$Tmax_{,ss}$ (min)	$AUC_{0\text{-}12h,ss}$ (min*pg/ mL)	$t_{½,ss}$ (min)
Test A	Mean	1891.1	36.1	419195.3	214.8
	SD	700.52	13.62	110725.61	41.77
	Median	1768.0	30.0	391107.5	218.3
	Geometric Mean	1786.3	33.5	406533.081	211.1
Reference C	Mean	1287.1	29.7	282707.6	197.9
	SD	390.81	15.41	89794.86	34.49
	Median	1279.0	30.0	273604.0	194.6
	Geometric Mean	1226.6	25.8	269479.488	195.2

Statistical comparison of AUC and C_{max} for B17MP between Test A and Reference C

Variable	Comparison of test and reference treatment (least square mean)		Ratio of geometric means	90%-CI for the ratio of means	Within-subject CV%
	Test A	Reference C			
$AUC_{0\text{-}12h,ss}$	409770.7	270529.8	1.5147	(1.31 - 1.75)	23.4
$AUC_{0\text{-}t,ss}$	409917.7	270600.0	1.5148	(1.31 - 1.75)	23.4
$C_{max,ss}$	1797.0	1228.9	1.4623	(1.27 - 1.69)	23.6

AUC in min*pg/mL and C_{max} in pg/mL

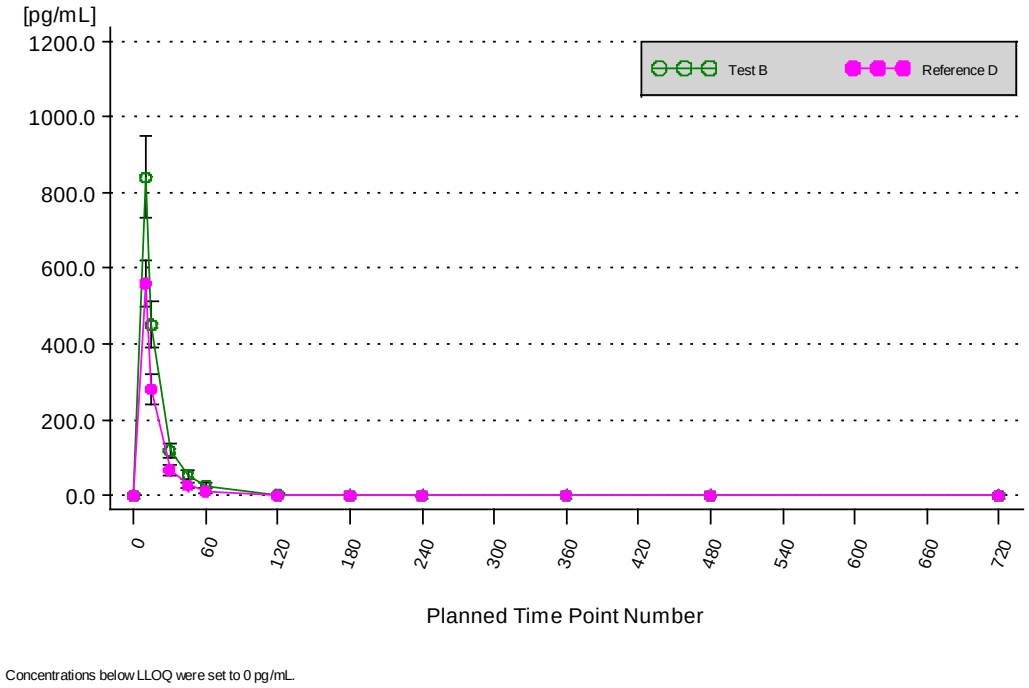
B17MP had a median $t_{max,ss}$ of 30.0 min for both treatments and a geometric mean $t_{1/2,ss}$ of 211.1 and 195.2 min for Test A and Reference C, respectively.

$AUC_{0\text{-}12h,ss}$ and $C_{max,ss}$ were the primary PK endpoints of the study. Steady-state systemic exposure to B17MP and peak B17MP concentration were, on average, 51% and 46% higher for Clenil® Modulite® with AeroChamber Plus™ compared to Clenil® Modulite® with Volumatic™, as assessed by $AUC_{0\text{-}12h,ss}$ and $C_{max,ss}$ respectively, with the 90% CIs for the comparison being 131 to 175% for $AUC_{0\text{-}12h,ss}$ and 127 to 169% for $C_{max,ss}$, outside the bioequivalence acceptance interval (80.00-125.00%).

- **Pharmacokinetic comparison of *Clenil® Modulite® with AeroChamber Plus™* versus *Clenil® Modulite® with Volumatic™* both administered *with charcoal block*: TEST B REFERENCE D (PK population)**

Pharmacokinetics of BDP

Concentration/time curves of the arithmetic means of BDP for Test B and Reference D



Concentrations below LLOQ were set to 0 pg/mL.

Test B: Clenil® Modulite® with AeroChamber Plus™ administered with charcoal block; Reference D: Clenil® Modulite® with Volumatic™ administered with charcoal block

Summary of PK parameters of BDP for Test B and Reference D

		$C_{max,ss}$ (pg/mL)	$T_{max,ss}$ (min)	$AUC_{0-t,ss}$ (min*pg/mL)	$t_{½,ss}$ (min)
Test B	Mean	840.3	10.1	13879.6	13.4
	SD	421.21	0.26	7525.27	5.83
	Median	775.0	10.0	13353.3	13.0
	Geometric Mean	740.5	10.1	12272.1	12.4
Reference D	Mean	559.9	10.0	8375.1	10.9
	SD	228.78	0.00	4637.31	5.47
	Median	509.0	10.0	7270.5	8.4
	Geometric Mean	527.3	10.0	7636.5	9.9

Statistical comparison of AUC and C_{max} for BDP between Test B and Reference D.

Variable	Comparison of test and reference treatment (least square mean)		Ratio of geometric means	90%-CI for the ratio of means	Within-subject CV%
	Test B	Reference D			
$AUC_{0-t,ss}$	12221.5	7610.0	1.6060	(1.31 - 1.97)	34.4
$C_{max,ss}$	731.1	522.0	1.4005	(1.13 - 1.73)	35.7

AUC in min*pg/mL and Cmax in pg/mL

Test B: Clenil® Modulite® with AeroChamber Plus™ administered with charcoal block; Reference D: Clenil® Modulite® with Volumatic™ administered with charcoal block

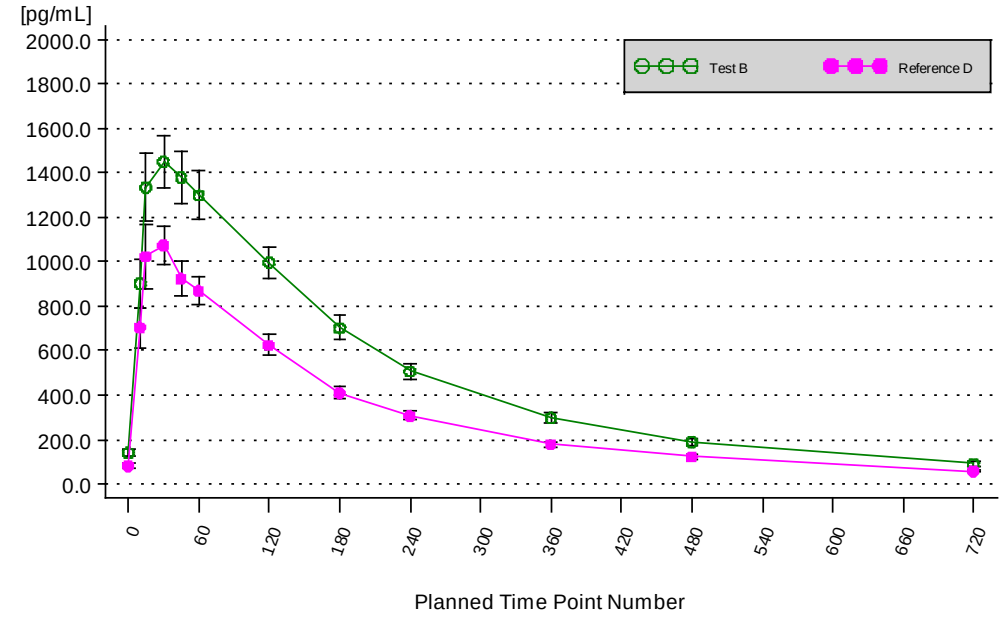
The PK profile of BDP was characterized by a median $t_{max,ss}$ of 10.0 min and rapid elimination with a geometric mean $t_{1/2,ss}$ of 12.4 and 9.9 min for Test B and Reference D, respectively.

Comparing Clenil® Modulite® with AeroChamber Plus™ to Clenil® Modulite® with

Volumatic™, both administered with charcoal block, the first one showed a 60% higher pulmonary absorption at steady-state as assessed by $AUC_{0\text{-}t,ss}$ and a 40% higher peak concentration as assessed by $C_{max,ss}$. The 90% CIs for the comparison were 131 to 197% for $AUC_{0\text{-}t,ss}$ and 113 to173% for C_{max} and in none of the cases bioequivalence was demonstrated.

Pharmacokinetics of B17MP

Concentration/time curves of the arithmetic means of B17MP for Test B and Reference D



Concentrations below LLOQ were set to 0 pg/mL.

Test B: Clenil® Modulite® with AeroChamber Plus™ administered with charcoal block; Reference D: Clenil® Modulite® with Volumatic™ administered with charcoal block

Summary of PK parameters of B17MP for Test B and Reference D

		$C_{max,ss}$ (pg/mL)	$T_{max,ss}$ (min)	$AUC_{0\text{-}12h,ss}$ (min*pg/ mL)	$t_{½,ss}$ (min)
Test B	Mean	1585.6	36.0	341840.9	195.0
	SD	476.27	15.83	79875.00	29.81
	Median	1394.0	30.0	341745.0	192.4
	Geometric Mean	1520.2	32.5	333346.662	192.9
Reference D	Mean	1194.7	31.0	219477.8	206.0
	SD	485.74	16.50	55065.63	45.97
	Median	1079.0	30.0	224384.1	216.1
	Geometric Mean	1119.1	27.4	212396.475	201.3

Statistical comparison of AUC and Cmax for B17MP between Test B and Reference D.

Variable	Comparison of test and reference treatment (least square mean)[1]		Ratio of geometric means	90%-CI for the ratio of means[2]	Within-subject CV%
	Test B	Reference D			
$AUC_{0\text{-}12h,ss}$	334451.8	213078.6	1.5696	(1.36 - 1.81)	23.4

$AUC_{0-t,ss}$	334583.4	213084.8	1.5702	(1.36 - 1.81)	23.4
$C_{max,ss}$	1514.8	1115.5	1.3580	(1.18 - 1.57)	23.6

AUC in min*pg/mL and $C_{max,ss}$ in pg/mL

B17MP had a median $t_{max,ss}$ of 30.0 min for both treatments and a geometric mean $t_{1/2,ss}$ of 192.9 and 201.3 min for Test B and Reference D, respectively.

$AUC_{0-12h,ss}$ and $C_{max,ss}$ were the primary PK endpoints of the study. When comparing Clenil® Modulite® with AeroChamber Plus™ to Clenil® Modulite® with Volumatic™, both administered with charcoal block, the first one showed a 57% higher pulmonary absorption at steady-state as assessed by $AUC_{0-12h,ss}$ and a 36% higher peak concentration as assessed by $C_{max,ss}$. The 90% CIs for the comparison were 136 to 181% for $AUC_{0-12h,ss}$ and 118 to157% for $C_{max,}$ and in none of the cases bioequivalence was demonstrated.

Safety Results:

The study treatments were well tolerated. Only eleven TEAEs (coded as PT) were recorded in 8 of the 16 patients. No AEs were considered to be related to the study treatments and there were no SAEs or AEs leading to study withdrawal reported.

No clinically significant laboratory abnormalities were observed. Vital signs did not clinically changed during the study. Mean FEV_1 actual values did not markedly differ between the test and reference treatments. Marked individual changes in FEV_1 actual values over time were not observed.

Conclusion:

Eleven male and five female adult patients with asthma were enrolled in this study. Fifteen patients completed the study as planned and received repeated doses of BDP (Clenil® Modulite®) 250 µg dispensed with the AeroChamber Plus™ spacer as compared to BDP dispensed with the currently standard Volumatic™ spacer, with and without charcoal block.

- In adult asthmatic patients, inhalation of Clenil® Modulite® with AeroChamber Plus™ resulted in a higher systemic exposure ($AUC_{0-12h,ss}$) to B17MP, the primary PK variable, as compared to Clenil® Modulite® with Volumatic™.
- Even when the same treatments were administered with charcoal block, the pulmonary absorption of B17MP ($AUC_{0-12h,ss}$) was higher for Clenil® Modulite® administered with AeroChamber Plus™ as compared to Volumatic™.
- Peak concentrations of B17MP were higher for Clenil® Modulite® with AeroChamber Plus™ as compared to Clenil® Modulite® with Volumatic™, both when administered with and without charcoal block.
- Both treatments resulted in comparable safety profiles. Overall, both treatments were well tolerated.

Date of report: 15 March 2012