CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

STATISTICAL REVIEW(S)

1. COVER PAGE

Date	September 26, 2003
NDA #	21-592
Applicant	Novartis Pharmaceuticals Corporation
Name of Drug	Foradil® Certihaler™ (Formoterol fumarate inhalation powder)
Indication	Maintenance treatment of asthma in adults and children ≥ 5 years of age.

Documents Reviewed	The documents:
	• Vol. 1.1, 1.2, 1.3
	• Clinical studies:
	  • Study protocol: 0604, 0605, 2302, and 2303
	  • Clinical trial report: 0604, 2302, and 2303
	  • Electronic data submitted on 12/27/2002

Statistical Reviewer	Feng Zhou, Division of Biometrics II/OPASS (HFD-715)
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3. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

3.1 Overview of the Clinical Program and Studies Reviewed

The sponsor submitted this NDA to demonstrate the efficacy and safety of a new delivery device for Foradil, the multi-dose dry powder inhaler (MDDPI), Foradil® Certihaler™ 10µg twice daily with the indication of *"long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older,* [redacted] *. (P10, Label)"*

b(4)

Study Design – To demonstrate efficacy, the sponsor submitted two phase III adolescent/adult studies (2302 & 2303) and one pediatric study (0604) as described in Table 1 below.

Table 1. Characteristics of Studies

Study No./ Centers #	*Study Objective/ Population*	*No. of Patients/ Gender*	*Treatment Duration*	*Medication Dose/Day*	*Primary Efficacy Endpoint*
2302 US – 22	Double-blind, double-dummy, parallel group for efficacy and safety In target population aged ≥ 13years	265	12 weeks (plus 2 weeks run-in)	10µg Formoterol via. MDDPI b.i.d. 180µg Albuterol via. pMDI q.i.d. Placebo q.i.d.	12-hour AUC of FEV1(relative to the baseline) at 3-month visit Baseline - the pre-dose FEV1 at visit 2
2303 US - 18	Double-blind, double-dummy, parallel group for efficacy, safety, and PK In target population aged ≥ 13years	239	12 weeks (plus 2 weeks run-in)	10µg Formoterol via. MDDPI b.i.d. 180µg Albuterol via. pMDI q.i.d. Placebo q.i.d.	12-hour AUC of FEV1(relative to the baseline) at 3-month visit Baseline - the pre-dose FEV1 at visit 2
0604 US - 22	Double-blind, parallel group for efficacy, safety, and PK In target population aged 5-12 years	249	12 weeks (plus 2 weeks run-in)	10µg Formoterol via. MDDPI b.i.d. Placebo b.i.d.	12-hour AUC of FEV1(relative to the baseline) at 3-month visit Baseline - the pre-dose FEV1 at visit 2
0605 28 Centers in 6 Countries	Double-blind, parallel group for efficacy and safety In target population aged ≥ 13years	365	12 weeks (plus 2 weeks run-in)	10µg Formoterol via. MDDPI b.i.d. 12µg Formoterol via. Aerolizer™ b.i.d. Placebo b.i.d.	Pre-dose FEV1 at 3-month visit

Studies 2302 and 2303 had the same design and duration. Study 0604 was a pediatric study. Study 0605 failed to achieve its objective of demonstrating non-inferiority of formoterol delivered via the MDDPI versus formoterol delivered by Aerolizer™. The

sponsor submitted this study only for its contribution to the safety evaluation. Since this study was a part of a clinical program which was designed to demonstrate efficacy, this reviewer included this study in the efficacy review.

Study Objective –
For adolescent/adult studies (2302 and 2303):

- Primary objective was to determine if 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) is superior to placebo with respect to lung function measurements (12-hour AUC of FEV1) in males and females aged 13 years and older with persistent asthma.

For pediatric study (0604):

- Primary objective was to determine if 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) is superior to placebo with respect to lung function measurements (12-hour AUC of FEV1) over a 12-week period in male and female children aged 5-12 years with persistent asthma.

For adolescent/adult study (0605):

- Primary objective was to determine if 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) is comparable to 12μg of formoterol fumarate delivered by Aerolizer™ administered twice daily (b.i.d.) with respect to lung function measurements (morning Pre-dose FEV1 performed at the study center during the final visit) in males and females aged 13 years and older with persistent asthma.

Study Population –
For Studies 2302, 2303, and 0605, the study population consisted of male and female outpatients aged 13 or older with persistent asthma. All patients had to demonstrate either a $\geq$ 15% increase or a $\geq$ 12% and at least 200ml increase in FEV1 over baseline within 30 minutes of inhaling albuterol at visit 1. Patients were permitted to take anti-inflammatory therapy provided they had been treated with stable, daily anti-inflammatory therapy up to the maximum recommended daily dose for at least one month prior to visit 1.

For Study 0604, the study population consisted of male and female outpatients aged 5 to 12 years, whose baseline FEV1 at visit 1 was $\geq$ 50% of the predicted normal value, with an increase of $\geq$ 15% in FEV1 over baseline after inhalation of albuterol or with a change in FEV1 (in ml) > 7% of the patient's predicted normal value in patients who were receiving, either regularly or on-demand, treatment with a bronchodilator. Patients were permitted to take anti-inflammatory therapy provided they had been treated with stable, daily anti-inflammatory therapy up to the maximum recommended daily dose for at least one month prior to visit 1.

3.2 Principal Finding

The following are the statistical findings for Studies 2302, 2303, 0604, and 0605 with emphasis on the effectiveness of 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) over the 12-week study period:

- Table 2 shows the comparison between the treatment groups for 12-hour AUC of FEV1 (relative to baseline) at the last spirometry evaluation which was the primary efficacy endpoint. The statistical results show that the three studies demonstrate that 10μg b.i.d. formoterol delivered by the MDDPI was statistically significantly better than placebo, at α=0.05, as an initial therapy for patients 5 years of age and older with persistent asthma based on the primary endpoint.

Table 2. The Comparison between the Treatment Groups for 12-hour AUC of FEV1 (Relative to Baseline) at the Last Spirometry Evaluation (Month 3 Imputed)

Study	*Population Visits*	*Treatment/ Treatment Contrast*	*N*	*LS Mean (SE)*	*95% CI*	*p-Value (two-sided)*
2302	ITTE Patients	*MDDPI*	86	5.21 (0.49)	-	-
	3 Month imputed	*Albuterol*	88	3.78 (0.49)	-	-
		Placebo	91	1.47 (0.48)	-	-
		MDDPI – Placebo	-	3.74 (0.66)	(2.44, 5.04)	<0.0001
		MDDPI – Albuterol	-	1.43 (0.67)	(0.11, 2.74)	0.0332
		Albuterol – Placebo	-	2.31 (0.65)	(1.03, 3.60)	0.0005
2303	ITTE Patients	*MDDPI*	80	4.45 (0.49)	-	-
	3 Month imputed	*Albuterol*	79	2.80 (0.49)	-	-
		Placebo	80	1.79 (0.49)	-	-
		MDDPI – Placebo	-	2.65 (0.69)	(1.29, 4.01)	0.0002
		MDDPI – Albuterol	-	1.64 (0.69)	(0.30, 3.00)	0.0184
		Albuterol – Placebo	-	1.01 (0.69)	(-0.35, 2.37)	0.1461
0604	ITTE Patients	*MDDPI*	127	2.45 (0.28)	-	-
	3 Month imputed	*Placebo*	120	1.50 (0.28)	-	-
		MDDPI – Placebo	-	0.95 (0.38)	(0.21, 1.70)	0.0119

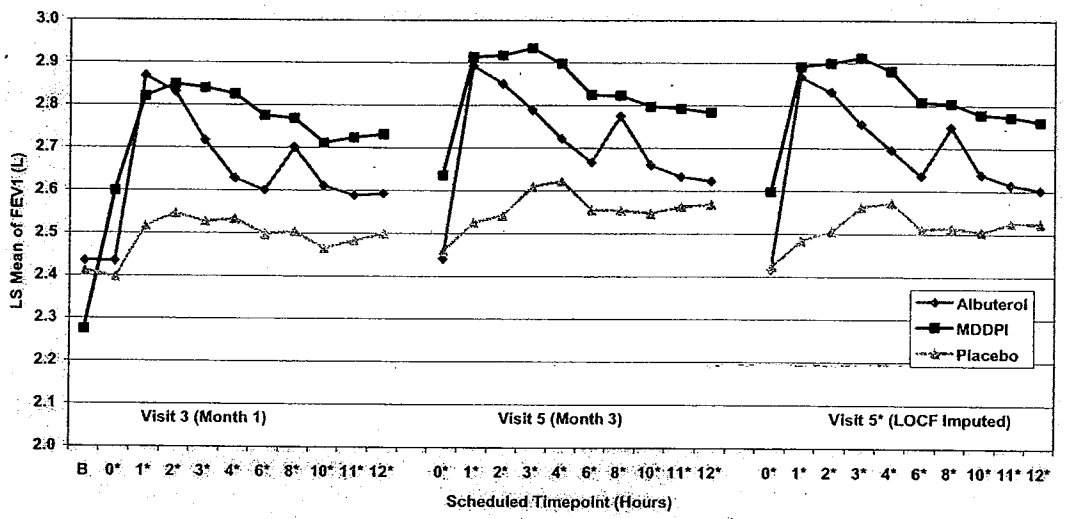
- Table 3 shows the comparison between the treatment groups for pre-dose FEV1 at the last spirometry evaluation which was the primary efficacy endpoint for Study 0605. Study 0605 failed to show efficacy for pre-dose FEV1 level at the final visit.

Table 3. The Comparison between the Treatment Groups for Pre-Dose FEV1 at the Last Spirometry Evaluation (Month 3 Imputed)

Study	*Population Visits*	*Treatment/ Treatment contrast*	*N*	*LS mean (SE)*	*95% CI*	*p-value (two-sided)*
0605	ITTE Patients	*MDDPI 10μg*	118	2.18 (0.04)	-	-
	3 Month imputed	*Aerolizer 12μg*	118	2.26 (0.04)	-	-
		Placebo	115	2.23 (0.04)	-	-
		MDDPI – Placebo	-	-0.05 (0.07)	(-0.16, 0.07)	.4234
		Aerolizer – Placebo	-	0.03 (0.06)	(-0.08, 0.14)	.5485
		MDDPI – Aerolizer	-	-0.08 (0.06)	(-0.19, 0.03)	.1603

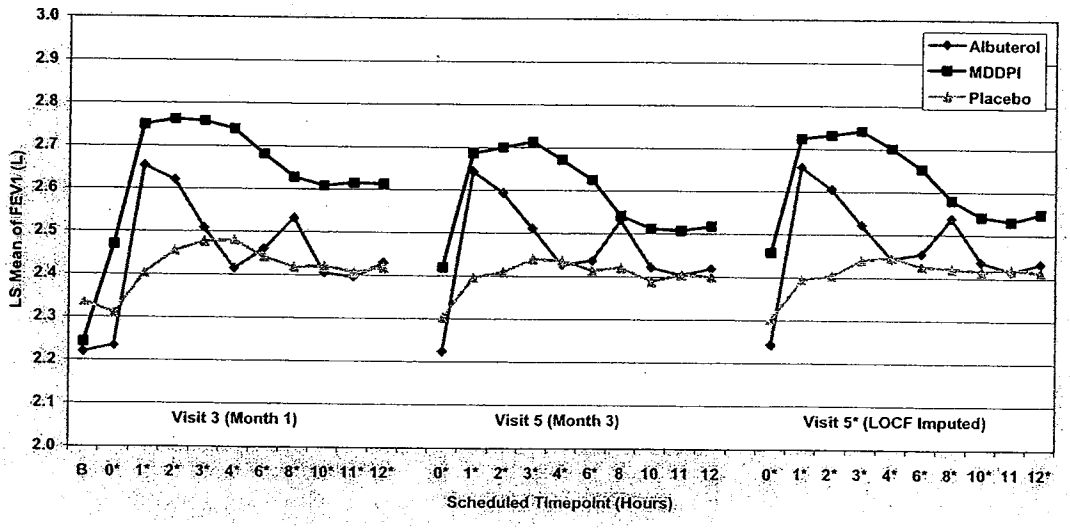
- Figure 1 and Figure 2 depict hourly FEV1 measurements at the three visits for Study 2302 and Study 2303. Formoterol 10μg via MDDPI demonstrates superiority to placebo. Both figures show that the FEV1 lines of Albuterol 180μg and formoterol 10μg are similar within 1 hour but the MDDPI had better maintenance of effect over the 12 hours. Study 2303 shows that the MDDPI did not maintain effectiveness after 6 hours compared to placebo at the 3 month visit.

Figure 1. LS Mean of Serial FEV1 (L) over 12-hours at Three Visits, Study 2302



* Indicated the significance at 0.05 level (MDDPI – Placebo).

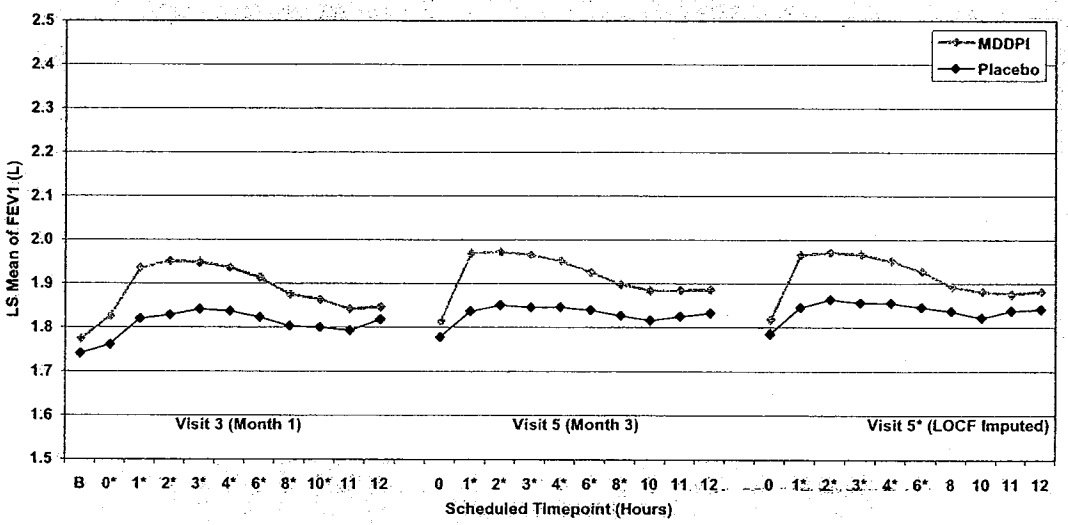
Figure 2. LS Mean of Serial FEV1 (L) over 12-hours at Three Visits, Study 2303



* Indicated the significance at 0.05 level (MDDPI – Placebo).

- Figure 3 depicts hourly FEV1 measurements at each visit for Study 0604. Formoterol 10μg via MDDPI demonstrates superiority to placebo, but the differences between MDDPI and placebo were quite small and MDDPI did not maintain effectiveness after 6 hours at the 3 month visit with LOCF imputation.

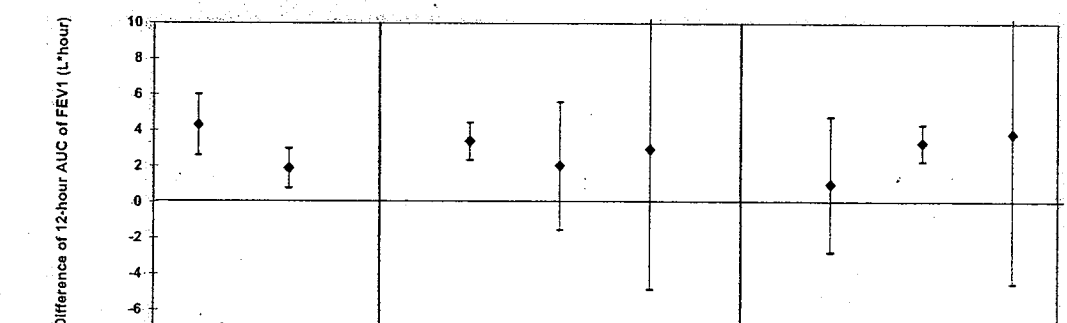
Figure 3. LS Mean of Serial FEV1 (L) over 12-hours at Three Visits, Study 0604



* Indicated the significance at 0.05 level (MDDPI – Placebo).

- Figure 4 shows the subgroup analyses for the pooled adult Studies 2302 and 2303 which show that the treatment effect of MDDPI was numerically better in male than in female patients.

Figure 4. LS Mean Difference and 95% CI for the Comparison between the MDDPI and Placebo for 12-hour AUC of FEV1 (Relative to Baseline) at End of 3-Month Study Period by Subgroup (Pooled Studies 2302 and 2303)

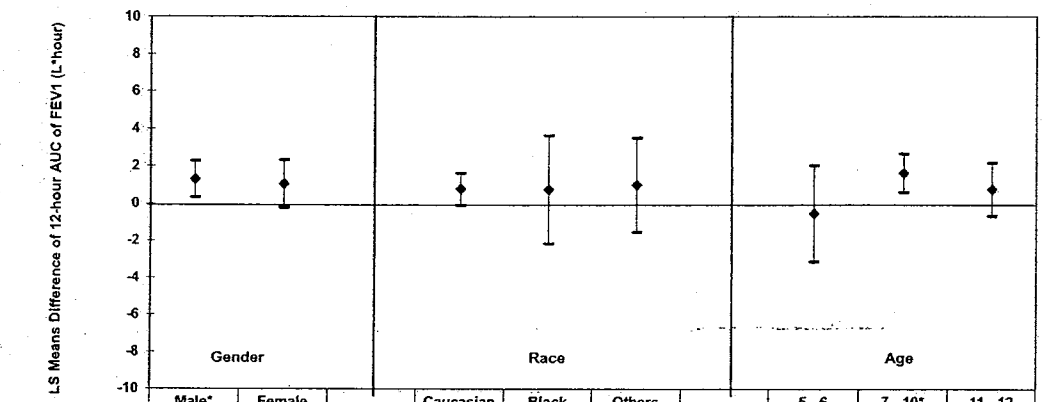


	Male* (n=138)	Female* (n=199)		Caucasian* (n=278)	Black (n=41)	Others (n=18)		<18 (n=34)	18 - 64* (n=289)	>=65 (n=14)
- 95% CI LL	2.60	0.80		2.36	-1.52	-4.84		-2.76	2.30	-4.51
- 95% CI UL	6.00	3.00		4.45	5.61	10.76		4.81	4.34	12.17
◆MDDPI - Placebo	4.30	1.90		3.41	2.04	2.96		1.03	3.32	3.83

* Indicated the significance at 0.05 level (MDDPI – Placebo).

- Figure 5 shows the subgroup analyses for the pediatric Study 0604 which shows consistent results in gender subgroups, race subgroup, and age subgroups except for the younger age group (5- 6 years old). However, the number of patients in this group was very small (n= 26) and therefore no definitive conclusion could be drawn from this factor.

Figure 5. LS Mean Difference and 95% CI for the Comparison between the MDDPI and Placebo for 12-hour AUC of FEV1 (Relative to Baseline) at End of 3-Month Study Period by Subgroup (Study 0604)



	Male* (n=166)	Female (n=81)		Caucasian (n=165)	Black (n=54)	Others (n=28)		5 - 6 (n=26)	7 - 10* (n=125)	11 - 12 (n=96)
—95% CI LL	0.31	-0.26		-0.11	-2.18	-1.55		-3.15	0.56	-0.69
—95% CI UL	2.27	2.31		1.62	3.63	3.49		2.02	2.64	2.15
◆MDDPI - Placebo	1.29	1.03		0.75	0.73	0.97		-0.57	1.60	0.73

* Indicated the significance at 0.05 level (MDDPI – Placebo).

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3.3 Conclusion and Recommendation

Based on the efficacy evaluation of 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) over the 12-week study period, as an initial therapy for patients 5 years of age and older with persistent asthma, in Studies 2302, 2303, and 0604, this reviewer concludes:

- Formoterol 10μg b.i.d. delivered by the MDDPI, demonstrated more efficacy than placebo as an initial therapy for patients 5 years of age and older with persistent asthma, based on the statistically significant difference for the 12-hour AUC of FEV1 at the end of the 3-month study period in the three studies (p-value ≤ 0.0119 in all studies).

- Compared with placebo, formoterol 10μg b.i.d. delivered by the MDDPI significantly improved the pre-dose FEV1 in the two adult Studies 2302 and 2303.

- Formoterol 10μg b.i.d. delivered by the MDDPI showed limited efficacy at the end of the 3-month study period in the pediatric study in terms of improving the pre-dose FEV1 level and maintaining a long term effect over 12 hours.

- Study 0605 was underpowered due to the primary variable being changed from the average of the last 7 available daily morning pre-dose PEF to the morning pre-dose FEV1 at the final visit in the middle of the study. The sponsor realized this but chose not to adjust the sample size. The study did not show any meaningful statistical difference between the three treatment groups (formoterol 10μg b.i.d. delivered by the MDDPI, formoterol 12μg b.i.d. delivered by the Aerolizer™, and Placebo). However, numerically, formoterol 12μg b.i.d. delivered by the Aerolizer™ showed better efficacy than formoterol 10μg b.i.d. delivered by the MDDPI.

- The subgroup analysis of the two adult studies numerically showed the MDDPI had a larger treatment effect in male than in female patients. The subgroup analysis of the pediatric study showed consistent results in gender subgroups, age subgroups, and race subgroups.

4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

4.1 Introduction and Background

The sponsor proposes that twice a day treatment regimen with 10µg FORADIL® CERTIHALER™ *"is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older,* [redacted] b(4)

Foradil® (formoterol fumarate) is a formylamino-substituted catecholamine derivative which exerts a preferential effect on β2-adrenergic receptors of bronchial smooth muscle. Bronchodilator activity seen in patients with asthma after inhalation of formoterol is characterized by a rapid onset of action (within 3 minutes), and a long duration of action (up to 12 hours duration). Foradil® Aerolizer™ is currently marketed as a dry powder capsule for oral inhalation with the Aerolizer™ device for bronchial asthma. Foradil® Aerolizer™ (NDA20-831) is approved for maintenance treatment of asthma in adults and children aged 5 years and older at a dosage of 12µg twice daily.

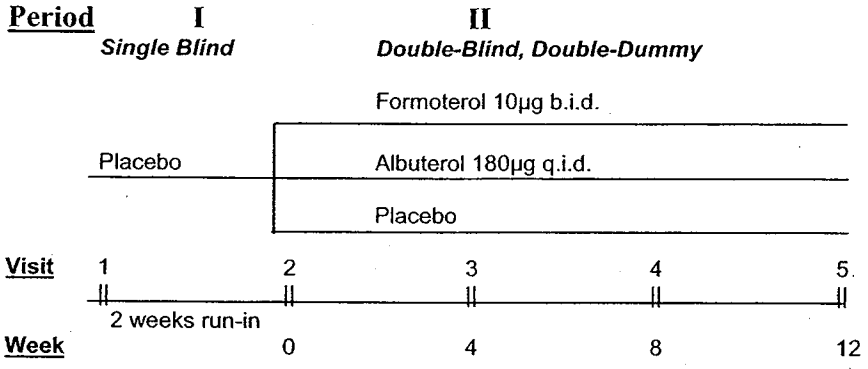
4.1.1 Study Design

To support the efficacy claim for the Foradil® Certihaler™, the Sponsor submitted two Phase-III adolescent/adult studies and one Phase-III pediatric study as described in Table 4 below.

Table 4. Characteristics of Studies

Study # / Center/ Period	*Age Range(y)/ Gender*	*Treatment Arms (# Of Patients) Randomization Ratio*	*Design*	*Duration of Treatment*
2302 US – 22 11/01/01 – 06/17/02	13-81 M (113) F (152) Adult with persistent asthma	Formoterol via MDDPI 10µg b.i.d. (86) Albuterol via pMDI 180µg q.i.d. (88) Placebo via MDDPI & pMDI q.i.d. (91) 1:1:1 Patients used open-label albuterol during both phases of the study on an as needed basis.	Multiple-center Randomized Double-blind Double-dummy Placebo-controlled Active-controlled Parallel-group	Period I: 1 week (Placebo run-in) Period II: 12 weeks
2303 US – 18 08/02/01 – 06/15/02	13-85 M (92) F (147) Adult with persistent asthma	Formoterol via MDDPI 10µg b.i.d. (80) Albuterol via pMDI 180µg q.i.d. (79) Placebo via MDDPI & pMDI q.i.d. (80) 1:1:1 Patients used open-label albuterol during both phases of the study on an as needed basis.	Multiple-center Randomized Double-blind Double-dummy Placebo-controlled Active-controlled Parallel-group	Period I: 1 week (Placebo run-in) Period II: 12 weeks
0604 US – 22 07/27/01 – 07/15/02	5-12 M (167) F (82) Adult with persistent asthma	Formoterol via MDDPI 10µg b.i.d. (127) Placebo via MDDPI b.i.d. (122) 1:1 Patients used open-label albuterol during both phases of the study on an as needed basis.	Multiple-center Randomized Double-blind Placebo-controlled Parallel-group	Period I: 1 week (Placebo run-in) Period II: 12 weeks

Studies 2302 and 2303 had the same design and duration and the study schematic is given in the following chart.



There were two periods in the studies.

Period I consisted of a 2-week (minimum 7 days) single-blind, placebo run-in period. Patients received placebo matched to MDDPI and albuterol pMDI in a single-blind manner. Albuterol was provided as an open label medication to all patients for use as needed during the run-in period.

Period II (Visits 2-5) consisted of a 12-week double-blind, double-dummy treatment period in which patients were randomly assigned to receive either formoterol 10µg b.i.d. via MDDPI, albuterol 180µg q.i.d. via pMDI, or placebo. Twelve-hour spirometry (FEV1) observation data were collected at Visits 2, 3, and 5.

The pediatric study 0604 had a similar design with no active-control.

4.1.2 Study Objective

For adolescent/adult studies (2302 and 2303):

- Primary objective was to determine if 10µg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) is superior to placebo with respect to lung function measurements (12 hour AUC of FEV1);

- Secondary objectives were:
  (1) to determine if 10µg of formoterol fumarate delivered by the MDDPI administered b.i.d. is superior to placebo with respect to symptom control, and quality of life (QoL) rating in male and female patients with persistent asthma over a 12-week period;
  (2) to compare the relative safety and tolerability of 10µg of formoterol fumarate delivered by the MDDPI administered b.i.d. versus albuterol 180µg via pMDI administered q.i.d., and placebo over a 12-week period;
  (3) to compare 10µg of formoterol fumarate delivered by the MDDPI administered b.i.d. to 180µg of albuterol via pMDI administered q.i.d. with respect to lung

function measurements, symptom control, and quality of life rating in male and female patients with persistent asthma over a 12-week period;

For pediatric Study 0604:

- Primary objective was to determine if 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) is superior to placebo with respect to lung function measurements (12 hour AUC of FEV1) and symptoms control over a 12-week period in male and female children aged 5-12 years with persistent asthma;

- Secondary object were:
  (1) to evaluate the relative safety and tolerability of 10μg of formoterol fumarate delivered by the MDDPI administered twice daily (b.i.d.) compared to placebo over a 12-week period in this patient population;
  (2) to evaluate the pharmacokinetics of dry powder formoterol fumarate delivered via the MDDPI device after multiple dosing to children with persistent asthma in a subgroup of patients.

4.1.3 Study Population

For Studies 2302 and 2303, the study population consisted of male and female outpatients aged 13 or older with persistent asthma. All patients had to demonstrate either a ≥ 15% increase or a ≥ 12% with at least 200ml increase in FEV1 over baseline within 30 minutes of inhaling albuterol at Visit 1. Patients were permitted to take anti-inflammatory therapy provided they had been treated with stable, daily anti-inflammatory therapy up to the maximum recommended daily dose for at least one month prior to visit 1.

For Study 0604, the study population consisted of male and female outpatients aged 5 to 12 years, whose baseline FEV1 at Visit 1 was ≥ 50% of the predicted normal value, with an increase of ≥ 15% in FEV1 over baseline after inhalation of albuterol or with a change in FEV1 (in ml) > 7% of the patient's predicted normal value in patients who were receiving, either regularly or on-demand, treatment with a bronchodilator. Patients were permitted to take anti-inflammatory therapy provided they had been treated with stable, daily anti-inflammatory therapy up to the maximum recommended daily dose for at least one month prior to visit 1.

4.2 Sponsor's Statistical Methodologies

4.2.1 Endpoints

The primary endpoint was 12 hour AUC of FEV1 (relative to baseline) in the unit of liter x hour at the 3 month timepoint (imputed if necessary) for the intent-to-treat of efficacy (ITTE) population.

The main secondary endpoint was quality of life. The other secondary endpoints were serial FEV1, forced vital capacity measurements, number of asthma exacerbations, daily

morning and evening peak expiratory flows, asthma symptom scores, and use of as needed asthma relief medication.

4.2.2 Treatment Groups

The qualified subjects for Studies 2302 and 2303 were randomly assigned at baseline to one of the following treatment groups:

- Formoterol 10μg via MDDPI b.i.d. plus placebo via the pMDI q.i.d.
- Albuterol 180μg via pMDI q.i.d. plus placebo via the MDDPI b.i.d.
- Placebo from both the MDDPI b.i.d. and the pMDI q.i.d.

The qualified subjects for Study 0604 were randomly assigned at the baseline to one of the following treatment groups:

- Formoterol 10μg via MDDPI b.i.d.
- Placebo via MDDPI b.i.d.

4.2.3 Analysis Population

ITTS (Intent-to-treat for safety) - the randomized patients who took study drug at least once during double-blind treatment.

ITTE (Intent-to-treat for efficacy) - the randomized patients who took study drug and had at least one 12-hour spirometry evaluation (scheduled or unscheduled) during the double-blind treatment period.

PP (Per Protocol) - the ITTE patients who completed 12 weeks of double-blind treatment therapy, have the 12-week spirometry evaluation (with a calculable AUC), and do not have any major deviations from the protocol procedure.

The sponsor's statistical analysis was based on the ITTE patients. The analysis of covariance (ANCOVA) was applied to all ITTE patients. The statistical methods employed are summarized in the following points:

1. **Randomization** – All randomized patients were assigned to the lowest available randomization number. Each center was supplied with blocks of sequentially increasing numbers to be used during the treatment period. So, randomization was stratified by center.

2. **Assessment of the 12-hour AUC of FEV1 at the 3 month spirometry evaluation -** AUC of FEV1 was calculated relative to baseline, i.e., the pre-dose FEV1 value measured at visit 2 prior to the first dose of study drug was subtracted from each of the serial FEV1 values taken over the 12-hour period. The following analysis of covariance (ANCOVA) model was used:

3-month 12-hour AUC of FEV1 = treatment + center + baseline + error

The baseline value was defined as 'the patient baseline minus an overall baseline average' where 'the patient baseline' was the pre-dose FEV1 value at Visit 2 prior to the first inhalation of study drug and the 'overall baseline average' was determined for each respective analysis population ignoring the treatment group.

Exploratory analyses were performed to investigate the treatment-center interaction and the treatment –baseline interaction. No adjustment for multiple comparisons was made. Regarding the 12-hour AUC of FEV1, five end points were analyzed:

- 3-month (imputed, if necessary) value for the ITTE population,
- 3-month value for the PP population (i.e., after at least 75 days of treatment),
- 3-month value for the ITTE population (i.e., after at least 75 days of treatment),
- 1-month value for the ITTE population,
- 1-day value for the ITTE population.

3. Missing data – Missing FEV1 values were imputed for the calculation of 12-hour AUC of FEV1. See protocol CFOR258F2302 for detail. (Vol. 17, pg584)

4. Sample Size and Power –
For Studies 2302 and 2303, using a two-sided significance level of 0.05 with 95% power, 70 patients for each treatment group were required to detect a difference of 4 (liter x hour) between the means of 12-hour AUC of FEV1 for the placebo and the MDDPI 10μg treatment groups (SD=6.5 (liter x hour)).

For Study 0604, using a two-sided significance level of 0.05 with 95% power, 103 patients for each treatment group were required to detect a difference of 1.8 (liter x hour) between the means of 12-hour AUC of FEV1 for the placebo and the MDDPI 10μg treatment groups (SD=3.96 (liter x hour)).

4.3 Sponsor's Results and Conclusions

Table 5 summarized the sponsor's efficacy results (Module 2 Vol. 1.1A, p18)

Table 5. Primary Efficacy Analysis (12-hour AUC of FEV1) at the Last Spirometry Evaluation (Month 3 Imputed)

Study	*Treatment/contrast*	*N*	*LS mean (SE)*	*95% CI*	*p-value (two-sided)*
2302	MDDPI	86	5.21 (0.49)	-	-
	Albuterol	88	3.78 (0.48)	-	-
	Placebo	91	1.47 (0.48)	-	-
	MDDPI – Placebo	-	3.74 (0.66)	2.44 – 5.04	<0.0001
	MDDPI – Albuterol	-	1.43 (0.67)	0.11 – 2.74	0.0332
	Albuterol - Placebo	-	2.31 (0.65)	1.03 – 3.60	0.0005
2303	MDDPI	80	4.45 (0.49)	-	-
	Albuterol	79	2.80 (0.49)	-	-
	Placebo	80	1.79 (0.49)	-	-
	MDDPI – Placebo	-	2.65 (0.69)	1.29 – 4.01	0.0002
	MDDPI – Albuterol	-	1.64 (0.69)	0.28 – 3.00	0.0184
	Albuterol - Placebo	-	1.01 (0.69)	-0.35 – 2.37	0.1461
0604	MDDPI	127	2.45 (0.28)	-	-
	Placebo	120	1.50 (0.28)	-	-
	MDDPI – Placebo	-	0.95 (0.38)	0.21 – 1.70	0.0118
Pooled Studies 2302 & 2303	MDDPI	166	4.85 (0.35)	-	-
	Albuterol	167	3.29 (0.35)	-	-
	Placebo	171	1.61 (0.34)	-	-
	MDDPI – Placebo	-	3.24 (0.48)	2.30 – 4.18	<0.0001
	MDDPI – Albuterol	-	1.57 (0.48)	0.62 – 2.51	0.0012
	Albuterol – Placebo	-	1.67 (0.48)	0.74 – 2.61	0.0005

The sponsor's efficacy conclusions were quoted as follows (p24; v1.1A):

"Foradil MDDPI 10μg b.i.d. is superior to placebo with respect to lung function measurements as demonstrated by 12-hour AUC of FEV1 in adults, adolescents and in children aged 5-12 years with persistent asthma. Foradil MDDPI 10μg b.i.d. is superior to Albuterol 180μg q.i.d. via the pMDI device with respect to lung function measurements as demonstrated by 12-hour AUC of FEV1 in adults, adolescents and in children aged 5-12 years with persistent asthma."

The Sponsor's safety conclusions were quoted as follows (p34; v1.1A):

"Foradil MDDPI was very well-tolerated. The safety profile of the drug as demonstrated in the clinical development program was very similar to that of placebo, with similar incidence of both AEs overall and most specific AEs."

4.4 Data Analyzed and Sources

The sponsor submitted the electronic documentation and SAS transport data sets of four phase III studies, 0604, 0605, 2302, and 2303. This reviewer checked raw data files and derived data files; the quality of the data is acceptable. The statistical results in this review were generated from both raw and derived data files.

4.5 Statistical Evaluation of Evidence on Efficacy

4.5.1 Focus of Review

1. This reviewer evaluated the statistical evidence presented in the four Phase-III studies: 2302, 2303, 0604, and 0605 by reanalyzing the sponsor's data. The purpose of the analyses was to verify that the sponsor's analyses were carried out as planned. The efficacy analysis focused on the comparison of three treatment groups: Formoterol 10μg via MDDPI b.i.d., Albuterol 180μg via pMDI q.i.d., and Placebo. The review of Study 0605 is described in section 4.5.4.

2. This reviewer used the sponsor's model but defined the baseline value as patient pre-dose FEV1 measured at Visit 2 prior to first inhalation of study drug.

3-month 12-hour AUC of FEV1 = treatment + center + baseline + error

The changing of the definition of baseline has no impact on the significance value and estimates of treatment effects.

3. The sponsor imputed FEV1 for mistimed or missing assessments. The imputation was reasonable and this reviewer used imputed FEV1 values to calculate the 12-hours AUC relative to the baseline.

4. This reviewer's statistical analysis was based on the ITTE population.

4.5.2 Detailed Review of Adolescent/Adult Studies 2302 & 2303

Introduction

Two phase III adolescent/adult studies (2302 and 2303) were multi-center, double-blind, double-dummy, randomized, placebo- and active-controlled clinical trials investigating the clinical effect of formoterol 10µg via MDDPI b.i.d. in patients aged ≥ 13 years with persistent asthma. The primary objective was to assess the treatment effect of formoterol 10µg via MDDPI b.i.d. versus Placebo with respect to the 12-hour AUC of FEV1 after 12 weeks of treatment.

Accountability of Patients

Table 6 shows the final status of the ITT population. The patient dropout rates were similar in the three treatment groups. In the MDDPI treatment group, the patient dropout rates caused by adverse events were higher than in the other two treatment groups.

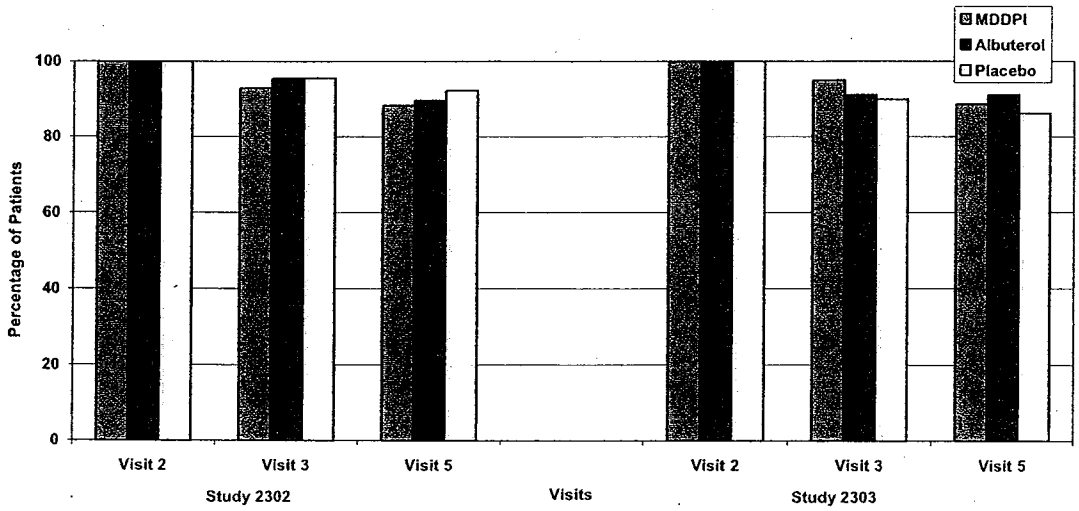
Table 6. ITT Patient Disposition by Final Status, N (%)

Study		MDDPI 10µg	Albuterol 180µg	Placebo	Total
2302	**Entered**	**86**	**88**	**91**	**265**
	Completed	**74 (86.05)**	**78 (88.64)**	**83 (91.21)**	**235 (88.68)**
	Discontinued	**12 (13.95)**	**10 (11.36)**	**8 (8.79)**	**30 (11.32)**
	Adverse event	4 (4.65)	3 (3.41)	0	7 (2.64)
	Consent withdrawn	5 (5.81)	3 (3.41)	3 (3.3)	11 (4.15)
	Lack of efficacy	1 (1.16)	3 (3.41)	3 (3.3)	7 (2.64)
	Lost to follow up	1 (1.16)	1 (1.16)	0	2 (0.75)
	Protocol violation	1 (1.16)	0	2 (2.2)	3 (1.13)
	Age				
	13 to 17	12 (13.95)	12 (13.64)	20 (21.98)	44 (16.60)
	18 to 64	69 (80.23)	71 (80.68)	67 (73.63)	207 (78.11)
	65+	5 (5.81)	5 (5.68)	4 (4.40)	14 (5.28)
	Gender				
	Male	37 (43.02)	37 (42.05)	39 (42.86)	113 (42.64)
	Female	49 (56.98)	51 (57.95)	52 (57.14)	152 (57.36)
	Race				
	Caucasian	68 (79.07)	77 (87.50)	72 (79.12)	217 81.89)
	Black	11 (12.79)	6 (6.82)	14 (15.38)	31 (11.70)
	Oriental	1 (1.16)	1 (1.14)	1 (1.10)	3 (1.13)
	Other	6 (6.98)	4 (4.55)	4 (4.40)	14 (5.28)
2303	**Entered**	**80**	**79**	**80**	**239**
	Completed	**70 (87.50)**	**72 (91.14)**	**67 (83.75)**	**209 (87.45)**
	Discontinued	**10 (12.50)**	**7 (8.86)**	**13 (16.25)**	**30 (12.55)**
	Adverse event	5 (6.25)	3 (3.80)	4 (5.00)	12 (5.02)
	Consent withdrawn	2 (2.50)	2 (2.53)	4 (5.00)	8 (3.35)
	Abnormal test results	0	2 (2.53)	0	2 (0.84)
	Lost to follow up	2 (2.50)	0	4 (5.00)	6 (2.51)
	Protocol violation	0	0	1 (1.25)	1 (0.42)
	Administrative problem	1 (1.25)	0	0	1 (0.42)
	Age				
	13 to 17	1 (1.25)	7 (8.86)	1 (1.25)	9 (3.77)
	18 to 64	76 (95.00)	68 (86.08)	77 (96.25)	221 (92.47)
	65+	3 (3.75)	4 (5.06)	2 (2.50)	9 (3.77)
	Gender				
	Male	32 (40.00)	30 (37.97)	30 (37.50)	92 (38.49)
	Female	48 (60.00)	49 (62.03)	50 (62.50)	147 (61.51)
	Race				
	Caucasian	69 (86.25)	68 (86.08)	69 (86.25)	206 (86.19)
	Black	8 (10.00)	7 (8.86)	8 (10.00)	23 (9.62)
	Oriental	1 (1.25)	0	0	1 (0.42)
	Other	2 (2.50)	4 (5.06)	3 (3.75)	9 (3.77)

Data source: \raw\cmp.xpt, \derived\ident_d.xpt; Program: summary.sas

Figure 6 shows the percentage of patients at each visit in the 12-week study period. The dropout rate at each visit was similar among the treatment groups.

Figure 6. Patients Allocation by Visits in the 12-Week Study Period



Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: FEV1.SAS, allocation.xls

Drug Exposure

Table 7 shows the drug exposure in days by treatment groups. The drug exposure in days was similar among the treatment groups. There were 31 patients who dropped out after the first day of the treatment. (See following table for detail)

Table 7. Drug Exposure Days by Visit

	MDDPI 10µg 2302	*Albuterol 180µg 2302*	*Placebo 2302*	*MDDPI 10µg 2303*	*Albuterol 180µg 2303*	*Placebo 2303*
Visit 3						
Mean (std)	29.80 (2.53)	29.85 (3.05)	29.48 (3.54)	29.92 (2.62)	29.44 (3.39)	29.74 (1.99)
Median	29	29	29	29	29	29
(Min, Max)	(25, 43)	(26, 43)	(21, 54)	(24, 39)	(22, 41)	(26, 37)
Visit 5						
Mean (std)	84.82 (5.48)	85.31 (2.86)	85.21 (5.77)	84.15 (5.60)	85.61 (3.35)	85.51 (8.11)
Median	85	85	85	85	85	85
(Min, Max)	(46, 98)	(78, 96)	(50, 103)	(57, 107)	(76, 97)	(29, 111)
Last Visit						
Mean (std)	76.42 (24.35)	77.93 (21.33)	79.70 (20.40)	77.45 (22.90)	78.11 (24.41)	74.58 (27.77)
Median	85	85	85	85	85	85
(Min, Max)	(1, 98)	(1, 96)	(1, 103)	(1, 107)	(1, 97)	(1, 111)
Dropped out after the first day of the treatment						
Consent withdrawn	3	1	3	1	2	3
Adverse event	2	0	0	1	3	2
Lost to follow up	1	1	0	2	0	2
Lack of efficacy	0	1	1	0	0	0
Abnormal test results	0	0	0	0	2	0

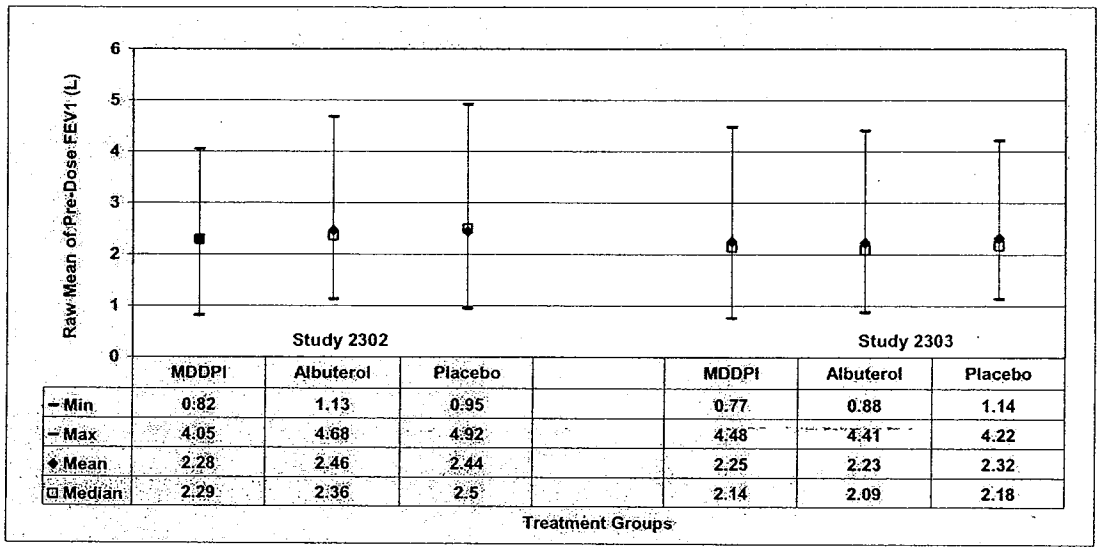
Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: AUC_FEV1.SAS

Baseline (Pre-dose FEV1 at visit 2)

The primary endpoint was the 12 hour AUC of FEV1 (relative to baseline), in the unit of liter x hour, at the 3 month timepoint (imputed if necessary) for the intent-to treat of efficacy (ITTE) population. The baseline was defined as the pre-treatment FEV1 value at visit 2 (reviewer's definition; see section 4.5.1 for detail).

Figure 7 shows the mean baseline FEV1 value by treatment groups.

Figure 7. Raw Mean of Pre-Dose FEV1 at Visit 2 (Baseline)

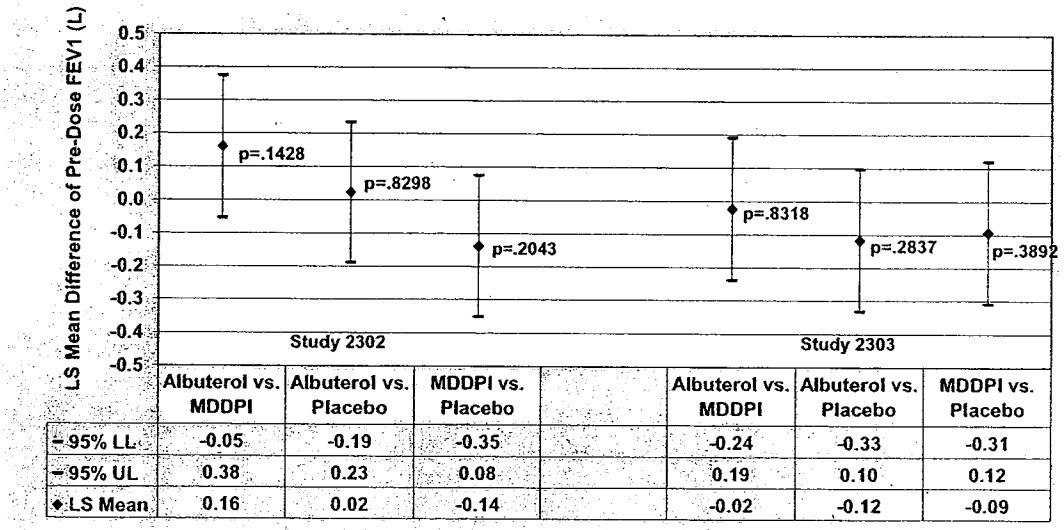


	MDDPI	Albuterol	Placebo		MDDPI	Albuterol	Placebo
– Min	0.82	1.13	0.95		0.77	0.88	1.14
– Max	4.05	4.68	4.92		4.48	4.41	4.22
◆ Mean	2.28	2.46	2.44		2.25	2.23	2.32
⊡ Median	2.29	2.36	2.5		2.14	2.09	2.18

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: FEV1.SAS

Figure 8 shows the pairwise LS mean differences of the three treatment groups. The p-values of the pairwise test for treatment group difference were more than 0.1428. The treatment groups were similar in baseline FEV1.

Figure 8. Pairwise Comparison of Pre-Dose FEV1 at Visit 2 (Baseline)



	Albuterol vs. MDDPI	Albuterol vs. Placebo	MDDPI vs. Placebo		Albuterol vs. MDDPI	Albuterol vs. Placebo	MDDPI vs. Placebo
– 95% LL	-0.05	-0.19	-0.35		-0.24	-0.33	-0.31
– 95% UL	0.38	0.23	0.08		0.19	0.10	0.12
◆ LS Mean	0.16	0.02	-0.14		-0.02	-0.12	-0.09

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: FEV1.SAS

12-hour AUC of FEV1

Table 8 shows the statistical results of 12-hour AUC of FEV1 at each visit and 3 month imputed value (LOCF imputed AUC of FEV1) for Studies 2302 and 2303.

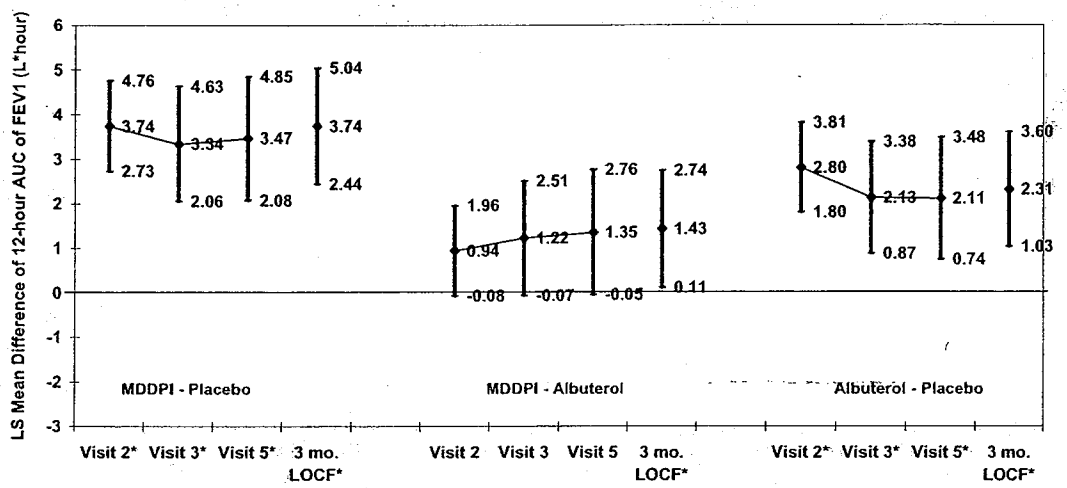
Table 8. 12-hour AUC of FEV1 (relative to baseline) by Visits

Study	Population Visits	Treatment/ Treatment Contrast	N	LS Mean (SE)	95% CI	p-Value (two-sided)
2302	ITT patients					
	Visit 2 (Randomization)	*MDDPI*	86	4.14 (0.38)	-	-
		Albuterol	88	5.08 (0.38)	-	-
		Placebo	91	1.34 (0.37)	-	-
		MDDPI – Placebo	-	3.74 (0.52)	(2.73, 4.76)	<.0001
		MDDPI – Albuterol	-	0.94 (0.52)	(-0.08, 1.96)	.0713
		Albuterol – Placebo	-	2.80 (0.51)	(1.80, 3.81)	<.0001
	Visit 3 (Month 1)	*MDDPI*	80	4.60 (0.49)	-	-
		Albuterol	84	3.38 (0.47)	-	-
		Placebo	86	1.26 (0.47)	-	-
		MDDPI – Placebo	-	3.34 (0.65)	(2.06, 4.63)	<.0001
		MDDPI – Albuterol	-	1.22 (0.65)	(-0.07, 2.51)	.0635
		Albuterol - Placebo	-	2.13 (0.64)	(0.87, 3.38)	.0010
	Visit 5 (Month 3)	*MDDPI*	76	5.15 (0.53)	-	-
		Albuterol	78	3.79 (0.52)	-	-
		Placebo	84	1.68 (0.50)	-	-
		MDDPI – Placebo	-	3.47 (0.70)	(2.08, 4.85)	<.0001
		MDDPI – Albuterol	-	1.35 (0.71)	(-0.05, 2.76)	.0591
		Albuterol - Placebo	-	2.11 (0.69)	(0.74, 3.48)	.0026
	3 Month imputed (LOCF Imputed)	*MDDPI*	86	5.21 (0.49)	-	-
		Albuterol	88	3.78 (0.49)	-	-
		Placebo	91	1.47 (0.48)	-	-
		MDDPI – Placebo	-	3.74 (0.66)	(2.44, 5.04)	<.0001
		MDDPI – Albuterol	-	1.43 (0.67)	(0.11, 2.74)	.0332
		Albuterol - Placebo	-	2.31 (0.65)	(1.03, 3.60)	.0005
2303	ITT patients					
	Visit 2 (Randomization)	*MDDPI*	80	4.80 (0.36)	-	-
		Albuterol	79	3.53 (0.34)	-	-
		Placebo	80	1.39 (0.36)	-	-
		MDDPI – Placebo	-	3.40 (0.50)	(2.41, 4.39)	<.0001
		MDDPI – Albuterol	-	1.26 (0.50)	(0.27, 2.26)	.0128
		Albuterol - Placebo	-	2.14 (0.50)	(1.15, 3.13)	<.0001
	Visit 3 (Month 1)	*MDDPI*	76	5.08 (0.54)	-	-
		Albuterol	72	2.83 (0.55	-	-
		Placebo	72	2.11 (0.55)	-	-
		MDDPI – Placebo	-	2.97 (0.76)	(1.47, 4.48)	.0001
		MDDPI – Albuterol	-	2.25 (0.76)	(0.74, 3.75)	.0036
		Albuterol - Placebo	-	0.73 (0.78)	(-0.80, 2.26)	.3494
	Visit 5 (Month 3)	*MDDPI*	71	4.34 (0.54)	-	-
		Albuterol	72	2.92 (0.54)	-	-
		Placebo	68	1.97 (0.55)	-	-
		MDDPI – Placebo	-	2.37 (0.76)	(0.87, 3.87)	.0021
		MDDPI – Albuterol	-	1.42 (0.75)	(-0.07, 2.91)	.0615
		Albuterol - Placebo	-	0.95 (0.76)	(-0.55, 2.45)	.2138
	3 Month imputed (LOCF Imputed)	*MDDPI*	80	4.45 (0.49)	-	-
		Albuterol	79	2.80 (0.49)	-	-
		Placebo	80	1.79 (0.49)	-	-
		MDDPI – Placebo	-	2.65 (0.69)	(1.29, 4.01)	.0002
		MDDPI – Albuterol	-	1.64 (0.69)	(0.30, 3.00)	.0184
		Albuterol - Placebo	-	1.01 (0.69)	(-0.35, 2.37)	.1461

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: AUC_FEV1.SAS

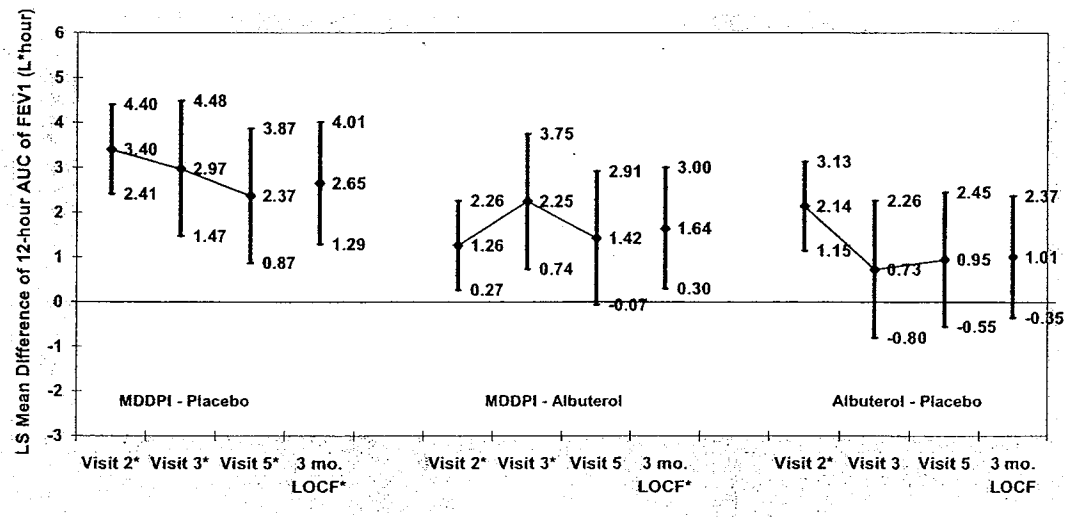
Figure 9 and Figure 10 show the LS mean differences and 95% confidence intervals of the pairwise comparisons of the three treatment groups for Studies 2302 and 2303. There were statistically significant increases in 12-hour AUC of FEV1 at the three visits for MDDPI compared to placebo. The MDDPI was statistically superior to Albuterol at some visits. Albuterol was statistically significant superior to placebo in Study 2302 but did not reach statistical significance in Study 2303 except at visit 2.

Figure 9. Pairwise Comparison of 12-hour AUC of FEV1 at Each Visit (Relative to Baseline, unit: L x hour) (LS Mean Difference and 95% CI, Study 2302)



Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: AUC_FEV1.SAS; mean_diff_auc.exl
* Indicated the significance at 0.05 level.

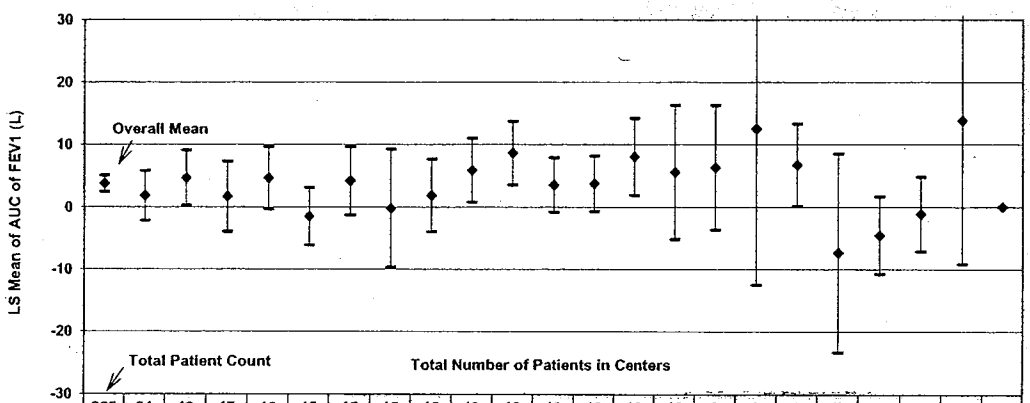
Figure 10. Pairwise Comparison of 12-hour AUC of FEV1 at Each Visit (Relative to Baseline, unit: L x hour) (LS Mean Difference and 95% CI, Study 2303)



Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: AUC_FEV1.SAS; mean_diff_auc.exl
* Indicated the significance at 0.05 level.

Figure 11 and Figure 12 show the LS mean difference and 95% confidence intervals of pairwise comparisons of MDDPI and Placebo at 3-month (imputed) by center for Studies 2302 and 2303. The treatment*center interaction was significant (p=0.0124) in Study 2302, but was not seen in Study 2303 (p=0.9483). In Study 2302, most of the centers favoring placebo had a small number of patients.

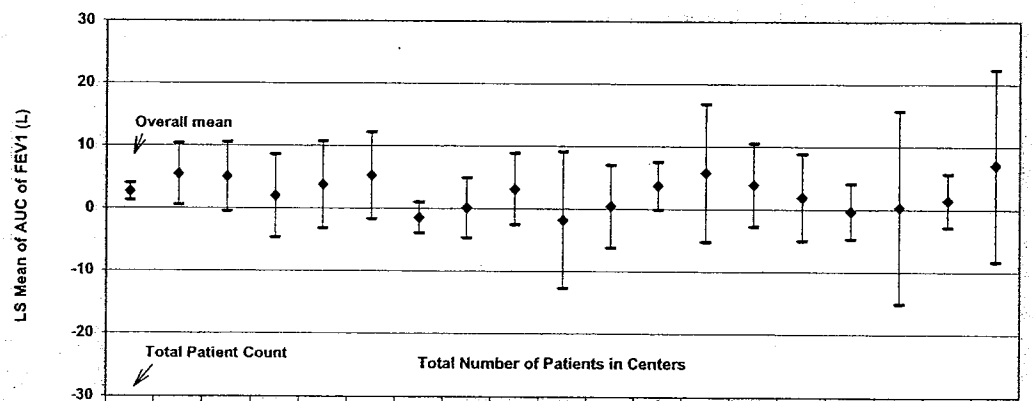
Figure 11. Pairwise Comparison of 12-hour AUC of FEV1 at Month 3 by Centers (LS Mean Difference and 95% CI of MDDPI vs. Placebo, Study 2302)



Total Patient Count	265	24	18	17	16	15	15	15	15	13	13	13	12	12	12	9	9	9	7	6	6	6	3
–95% CI LL	2.4	-2.2	0.3	-3.9	-0.3	-6.1	-1.3	-9.7	-4.0	0.8	3.5	-0.8	-0.7	1.9	-5.2	-3.7	-12.5	-0.2	-23.3	-10.8	-7.1	-9.2	0.0
–95% CI UL	5.0	5.8	9.1	7.3	9.6	3.1	9.6	9.3	7.6	11.0	13.7	7.9	8.2	14.2	16.3	16.3	37.5	13.3	8.5	1.7	4.8	36.9	0.0
◆MDDPI - PL	3.7	1.8	4.7	1.7	4.6	-1.5	4.2	-0.2	1.8	5.9	8.6	3.5	3.7	8.0	5.5	6.3	12.5	6.7	-7.4	-4.6	-1.2	13.9	0.0

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: cnt_efct.sas; center treatment effect with ci and mean.xls

Figure 12. Pairwise Comparison of 12-hour AUC of FEV1 at Month 3 by Centers (LS Mean Difference and 95% CI of MDDPI vs. Placebo, Study 2303)



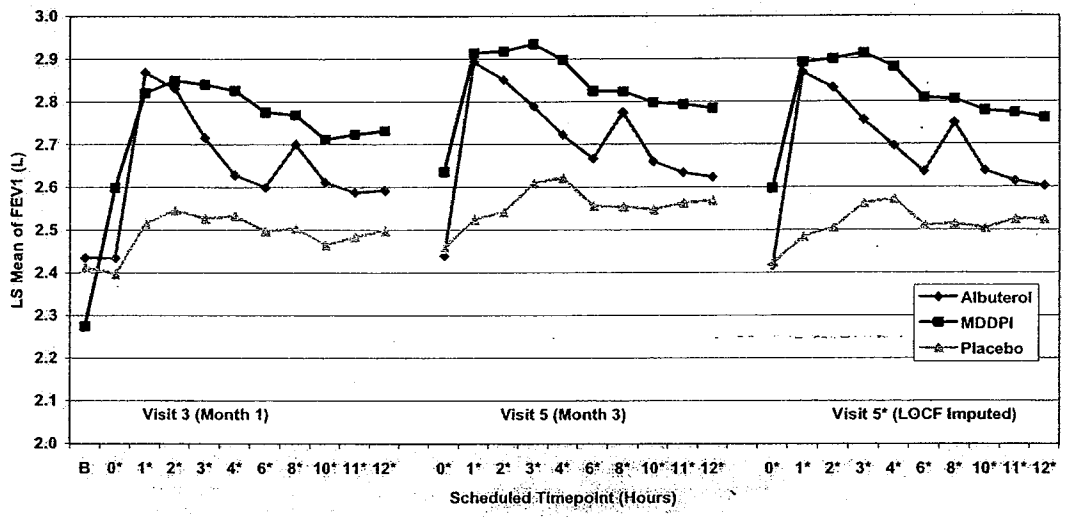
Total Patient Count	239	20	18	18	17	14	14	14	14	13	12	12	12	12	11	10	10	10	8
–95% CI LL	1.3	0.6	-0.5	-4.6	-3.2	-1.7	-3.9	-4.7	-2.5	-12.7	-6.2	-0.1	-5.2	-2.8	-5.0	-4.7	-15.1	-2.8	-8.3
–95% CI UL	4.0	10.4	10.6	8.6	10.7	12.2	1.0	4.9	8.8	9.1	7.0	7.5	16.8	10.5	8.9	4.1	15.7	5.6	22.3
◆MDDPI - PL	2.7	5.5	5.0	2.0	3.8	5.2	-1.4	0.1	3.1	-1.8	0.4	3.7	5.8	3.9	1.9	-0.3	0.3	1.4	7.0

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: cnt_efct.sas; Center treatment effect with ci and mean.xls

Serial FEV1

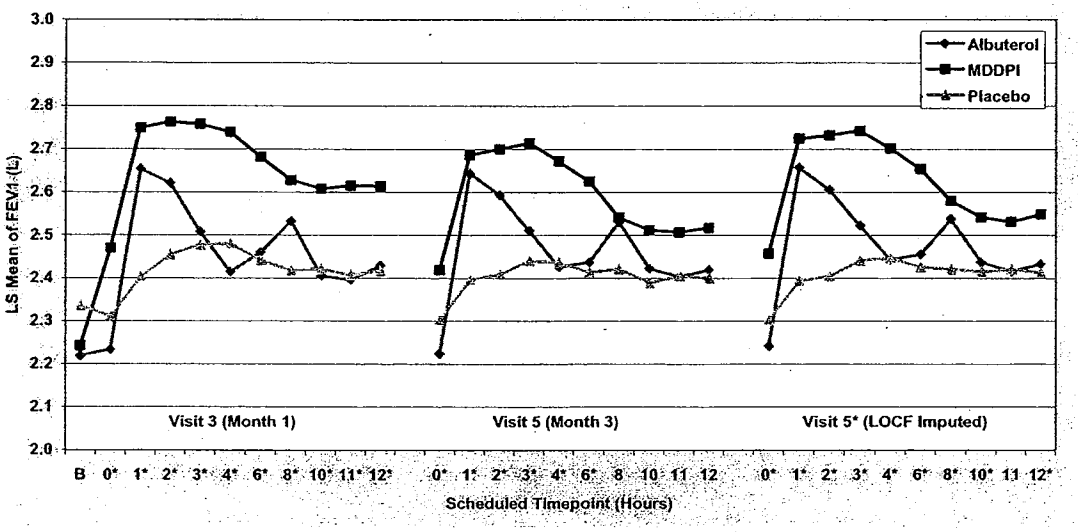
To visualize spirometric differences in FEV1 values over time, Figure 13 and Figure 14 depict hourly FEV1 measurements at the three visits for Study 2302 and Study 2303. Formoterol 10µg via MDDPI demonstrates superiority to placebo. Both figures show that the FEV1 lines of Albuterol 180µg and formoterol 10µg are similar within 1 hour but the MDDPI had better maintenance of effect over 12 hours. The Study 2303 shows that the MDDPI did not maintain effectiveness after 6 hours compared to placebo at the 3 month visit.

Figure 13. LS Mean of Hourly FEV1 at Three Visits, Study 2302



Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: fev1.sas; fev1.xls
* Indicated the significance at 0.05 level (MDDPI – Placebo).

Figure 14. LS Mean of Hourly FEV1 at Three Visits, Study 2303



Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: fev1.sas; fev1.xls
* Indicated the significance at 0.05 level (MDDPI – Placebo).

Table 9 shows the pre-dose FEV1 by visit which shows that 10μg b.i.d. formoterol delivered by the MDDPI was better than placebo in terms of increasing the morning pre-dose FEV1 level.

Table 9. Pre-Dose FEV1 at Each Visit, Studies 2302 and 2303

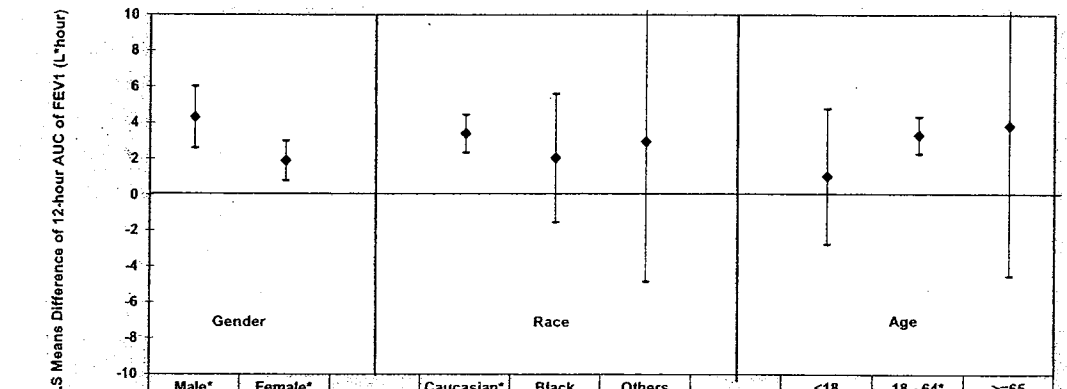
Visit	*Treatment/ Treatment Contrast*	*Study 2302*				*Study 2303*			
		N	LS Mean (SE)	95% CI	p-value	N	LS Mean (SE)	95% CI	p-value
3	*MDDPI*	80	2.60 (.04)	-	-	76	2.47 (.04)	-	-
	Albuterol	84	2.43 (.04)	-	-	72	2.23 (.04)	-	-
	Placebo	86	2.40 (.04)	-	-	72	2.31 (.04)	-	-
	MDDPI – Placebo	-	0.20 (.05)	(.11, .30)	<.0001	-	0.16 (.06)	(.04, .28)	.0100
	MDDPI – Albuterol	-	0.16 (.05)	(.07, .26)	.0009	-	0.24 (.06)	(.11, .36)	.0002
	Albuterol – Placebo	-	0.04 (.05)	(-.06, .13)	.4402	-	-0.08 (.06)	(-.20, .05)	.2248
5	*MDDPI*	76	2.64 (.04)	-	-	71	2.42 (.05)	-	-
	Albuterol	78	2.44 (.04)	-	-	72	2.22 (.05)	-	-
	Placebo	84	2.46 (.04)	-	-	68	2.30 (.05)	-	-
	MDDPI – Placebo	-	0.18 (.06)	(.06, .29)	.0022	-	0.12 (.07)	(-.01, .25)	.0818
	MDDPI – Albuterol	-	0.20 (.06)	(.08, .31)	.0008	-	0.20 (.07)	(.07, .33)	.0034
	Albuterol – Placebo	-	-0.02 (.06)	(-.13, .09)	.7213	-	-0.08 (.07)	(-.21, .05)	.2332
*5**	*MDDPI*	86	2.60 (.04)	-	-	80	2.47 (.04)	-	-
	Albuterol	88	2.42 (.04)	-	-	79	2.23 (.04)	-	-
	Placebo	91	2.42 (.04)	-	-	80	2.31 (.04)	-	-
	MDDPI – Placebo	-	0.18 (.05)	(.08, .29)	.0011	-	0.15 (.06)	(.04, .27)	.0111
	MDDPI – Albuterol	-	0.18 (.05)	(.07, .28)	.0008	-	0.22 (.06)	(.10, .33)	.0004
	Albuterol – Placebo	-	-0.02 (.05)	(-.11, .10)	.9012	-	-0.06 (.06)	(-.18, .06)	.3143

* noted: 3 month LOCF imputed

Subgroup Analyses

Figure 15 shows the subgroup analyses for the pooled adult Studies 2302 and 2303 which showed the MDDPI had larger treatment effect in male than in female patients.

Figure 15. Pairwise Comparison of 12-hour AUC of FEV1 at Month 3 by Subgroups (LS Mean Difference and 95% CI of MDDPI vs. Placebo, Pooled Studies 2302 & 2303)



	Male* (n=138)	Female* (n=199)		Caucasian* (n=278)	Black (n=41)	Others (n=18)		<18 (n=34)	18 - 64* (n=289)	>=65 (n=14)
- 95% CI LL	2.60	0.80		2.36	-1.52	-4.84		-2.76	2.30	-4.51
- 95% CI UL	6.00	3.00		4.45	5.61	10.76		4.81	4.34	12.17
◆ MDDPI - Placebo	4.30	1.90		3.41	2.04	2.96		1.03	3.32	3.83

Data source: \raw\cmp.xpt, \derived\fevauc_d.xpt; Program: subgrp.sas;subgroup.xls
* Indicated the significance at 0.05 level.

Conclusion

Following are the statistical results for Studies 2302 and 2303 with emphasis on the effectiveness of 10μg b.i.d. formoterol delivered by the MDDPI at the end of the 3-month study period:

- Both studies demonstrated that 10μg b.i.d. formoterol delivered by the MDDPI was superior over placebo, at α=0.05, as initial therapy for 13 years of age and older patients with persistent asthma. (See Table 8 for details.)

- Both studies demonstrated that 10μg b.i.d. formoterol delivered by the MDDPI was better than placebo in term of increasing the pre-dose FEV1 level and maintaining the effectiveness over 12-hours. (See Figure 13 and Figure 14 for details.)

- Subgroup analyses showed that 10μg b.i.d. formoterol delivered by the MDDPI had a larger treatment effect in male than in female patients. (See Figure 15 for detail.)

4.5.3 Detailed Review of Pediatric Study 0604

Introduction

The pediatric study (0604) was a multi-center, double-blind, randomized, placebo-controlled clinical trial investigating the clinical effect of formoterol 10µg via MDDPI b.i.d. in patients aged 5 to 12 years with persistent asthma. The primary objective was to assess the treatment effect of formoterol 10µg via MDDPI b.i.d. versus placebo with respect to the 12-hour AUC of FEV1 after 12 weeks of treatment.

Accountability of Patients

Table 10 shows the final status of the ITT population. The patient dropout rates were similar in both treatment groups.

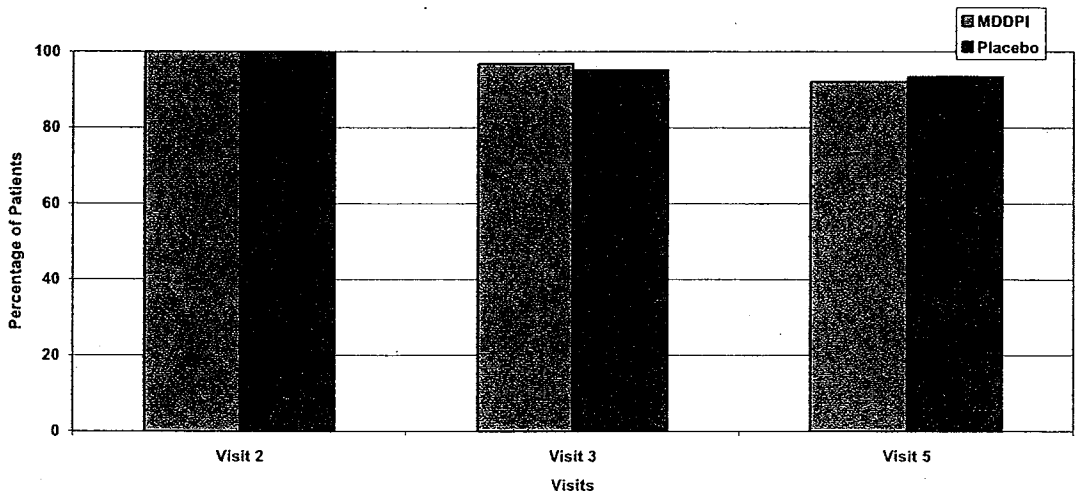
Table 10. ITT Patient Disposition by Final Status, N (%), Study 0604

Study		*MDDPI 10µg*	*Placebo*	*Total*
0604	Entered	127	122	249
	Completed	116 (91.34)	111 (90.98)	227 (91.16)
	Discontinued	11 (8.66)	11 (9.02)	22 (8.84)
	Clinical adverse experience	2 (1.57)	1 (0.82)	3 (1.20)
	Lack of efficacy	0	1 (0.82)	1 (0.40)
	Lost to follow-up	3 (2.36)	1 (0.82)	4 (1.61)
	Patient withdrew consent	1 (0.79)	4 (3.28)	5 (2.01)
	Protocol violation	2 (1.57)	3 (2.46)	5 (2.01)
	Abnormal test results	2 (1.57)	1 (0.82)	3 (1.20)
	Administrative problems	1 (0.79)	0	1 (0.40)

Data source: \raw\cmp.xpt, \derived\ident_d.xpt, \raw\dem.xpt; Program: summary.sas

Figure 16 shows the percentage of patients at each visit in the 12-week study period. The dropout rate at each visit was similar in the treatment groups.

Figure 16. Patients Allocation by Visits in 12-week Study Period, Study 0604



Data source: \raw\cmp.xpt, \derived\ident_d.xpt;\derived\fevauc_d.xpt; Program: fev1.sas, allocation.xls

12-hour AUC of FEV1

Table 11 shows the statistical results of 12-hour AUC of FEV1 at each visit and last valid value (LOCF imputed AUC of FEV1). Formoterol 10µg via MDDPI demonstrates superiority to the placebo at each visit.

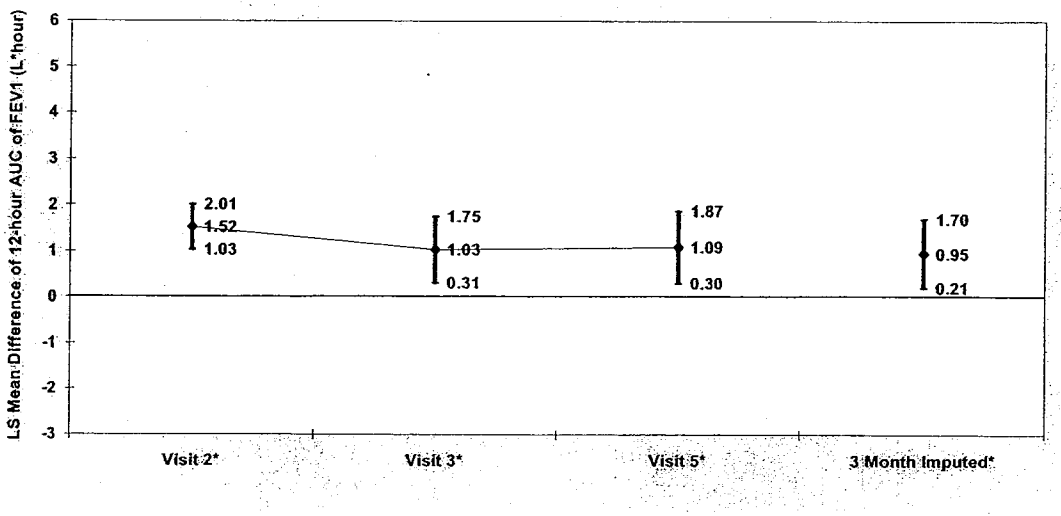
Table 11. 12-hour AUC of FEV1 (Relative to Baseline) by Visits, Study 0604

Visits	*Treatment Days Mean (std)*	*Treatment/ Treatment contrast*	*N*	*LS mean (SE)*	*95% CI*	*p-value (two-sided)*
Visit 2	1	*MDDPI*	127	2.16 (0.18)	-	-
(Randomization)	1	*Placebo*	120	0.64 (0.19)	-	-
		MDDPI – Placebo	-	1.52 (0.25)	(1.03, 2.01)	<.0001
Visit 3 (Month 1)	29.4 (2.7)	*MDDPI*	121	2.24 (0.27)	-	-
	29.8 (3.7)	*Placebo*	114	1.24 (0.28)	-	-
		MDDPI – Placebo	-	1.03 (0.37)	(0.31, 1.75)	.0052
Visit 5 (Month 3)	85.4 (3.8)	*MDDPI*	116	2.26 (0.29)	-	-
	83.5 (9.5)	*Placebo*	112	1.53 (0.30)	-	-
		MDDPI – Placebo	-	1.09 (0.40)	(0.30, 1.87)	.0069
Last Valid Visit	79.6 (19.6)	*MDDPI*	127	2.45 (0.28)	-	-
(LOCF Imputed)	79.1 (19.5)	*Placebo*	120	1.50 (0.28)	-	-
		MDDPI – Placebo	-	0.95 (0.38)	(0.21, 1.70)	0.0119

Data source:\raw\cmp.xpt, \derived\fevauc_d.xpt; Program: auc_fev1.sas

Figure 17 shows the LS mean difference and 95% confidence intervals of the pairwise comparisons of three treatment groups for the study. There were statistically significant increases in 12-hour AUC of FEV1 at the three visits for MDDPI compared to placebo.

Figure 17. LS Mean Difference and 95% CI of MDDPI vs. Placebo for 12-hour AUC of FEV1 (Relative to Baseline) at 3 Month, by Visits, Study 0604

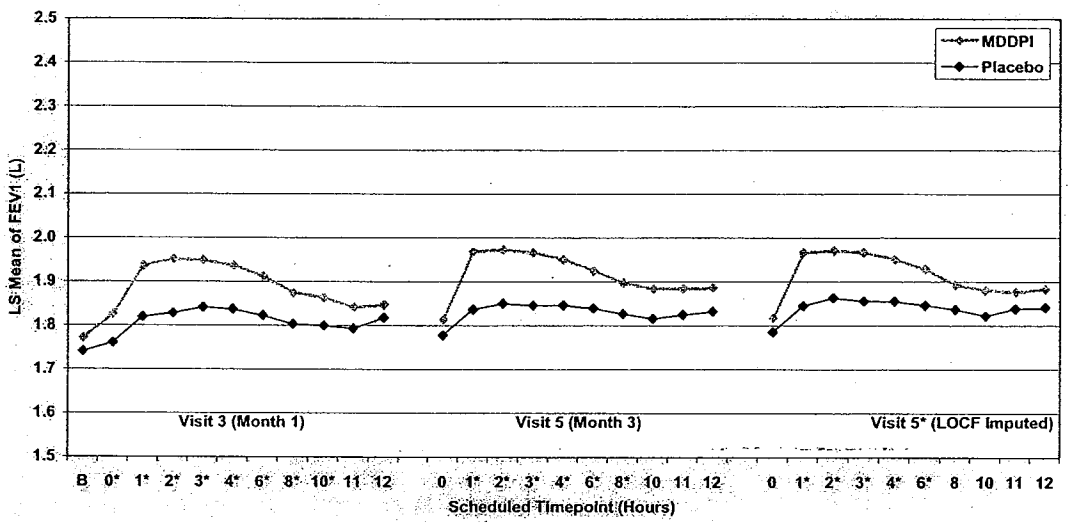


Data source:\raw\cmp.xpt, \derived\fevauc_d.xpt; Program: auc_fev1.sas; mean_diff_auc.exl
* Indicated the significance at 0.05 level.

Serial FEV1

To visualize spirometric differences in FEV1 values over time, Figure 18 depicts hourly FEV1 measurements at each visit for Study 0604. Formoterol 10µg via MDDPI demonstrates superiority to placebo, but the differences between MDDPI and placebo were quite small and MDDPI did not maintain effectiveness after 6 hours at the 3 month visit with LOCF imputation.

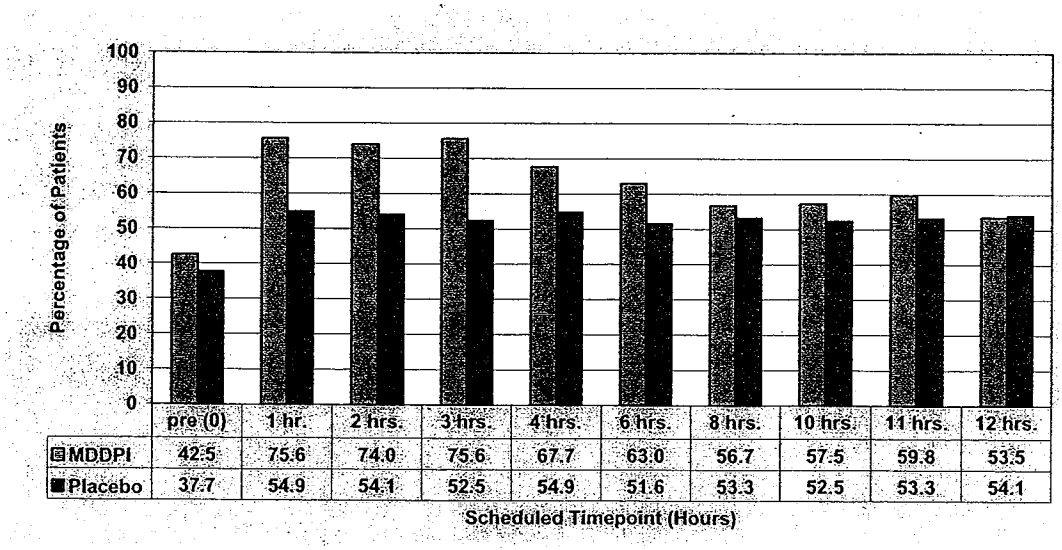
Figure 18. LS Mean of Hourly FEV1 at Three Visits, Study 0604



Data source:\raw\cmp.xpt, \derived\fevauc_d.xpt; Program: auc_fev1.sas; fev1.exl
* Indicated the significance at 0.05 level.

Figure 19 shows the percentage of patients whose change from baseline of FEV1 was more than 0.1(L) at last spirometry (3-month imputed). Only 56% of MDDPI patients improved by this amount after 6 hours compared to 53% of placebo patients.

Figure 19. Percentage of Patients Who's Change from Baseline of FEV1 More than 0.1(L) at 3-Month Visit (Imputed), Study 0604

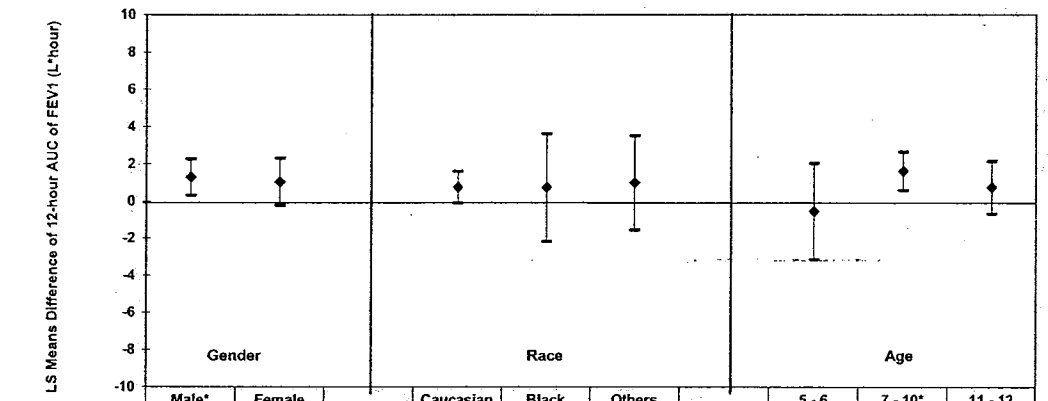


	pre (0)	1 hr.	2 hrs.	3 hrs.	4 hrs.	6 hrs.	8 hrs.	10 hrs.	11 hrs.	12 hrs.
MDDPI	42.5	75.6	74.0	75.6	67.7	63.0	56.7	57.5	59.8	53.5
Placebo	37.7	54.9	54.1	52.5	54.9	51.6	53.3	52.5	53.3	54.1

Subgroup Analyses

Figure 20 shows the subgroup analyses for the pediatric Study 0604 which shows consistent results in gender subgroups, race subgroup, and age subgroups except for the younger age group (5- 6 years old). In the youngest age group, 10µg b.i.d. formoterol delivered by the MDDPI numerically showed less effect than placebo. However, the number of patients in this group was very small (n= 26) and therefore no definitive conclusion could be drawn from this factor.

Figure 20. LS Mean Difference and 95% CI of MDDPI vs. Placebo for 12-hour AUC of FEV1 (relative to baseline) at 3 Month by Subgroup, Study 0604



	Male* (n=166)	Female (n=81)		Caucasian (n=165)	Black (n=54)	Others (n=28)		5 - 6 (n=26)	7 - 10* (n=125)	11 - 12 (n=96)
–95% CI LL	0.31	-0.26		-0.11	-2.18	-1.55		-3.15	0.56	-0.69
–95% CI UL	2.27	2.31		1.62	3.63	3.49		2.02	2.64	2.15
◆MDDPI - Placebo	1.29	1.03		0.75	0.73	0.97		-0.57	1.60	0.73

* Indicated the significance at 0.05 level.

Conclusion

The following are the statistical results for Study 0604 with emphasis on the effectiveness of 10µg b.i.d. formoterol delivered by the MDDPI at the end of the 3-month study period:

- Study 0604 demonstrated that 10µg b.i.d. formoterol delivered by the MDDPI was superior over placebo, at α=0.05, as initial therapy for 5 to 12 years of age patients with persistent asthma. (See Table 11 for details.)

- Study 0604 showed that 10µg b.i.d. formoterol delivered by the MDDPI had limited efficacy, compared to placebo, in terms of increasing the pre-dose FEV1 level and maintaining the effectiveness after 6 hours. (See Figure 18 for details.)

- Subgroup analysis showed MDDPI consistently better than placebo in gender subgroups, age subgroups, and race subgroups. (See Figure 20 for details.)

4.5.4 Detailed Review of Adolescent/Adult Study 0605

Introduction

This multi-center, double-blind, double-dummy, randomized, placebo- and active-controlled study in patients aged ≥ 13 years with persistent asthma evaluated the efficacy and safety of formoterol (10μg b.i.d.) delivered from the multi-dose dry powder inhaler (MDDPI).

The qualified subjects for the studies were randomly assigned at baseline to one of the following treatment groups:

- Formoterol 10μg via MDDPI b.i.d. plus placebo via the Aerolizer™ b.i.d.
- Formoterol 12μg via Aerolizer™ b.i.d. plus placebo via the MDDPI b.i.d.
- Placebo from both the MDDPI bid and the Aerolizer™ b.i.d.

The primary objective was to compare and evaluate the efficacy of 10μg b.i.d. formoterol delivered by the MDDPI versus 12μg b.i.d. formoterol delivered by the Aerolizer™.

Primary efficacy parameter: Peak Expiratory Flow (PEF) in the morning before taking study drug (Original efficacy parameter before Protocol Amendment #3). Morning Pre-dose FEV1 performed at the study center during the final visit (Protocol Amendment #3, Vol. 47).

The original sample size estimate, 110 per treatment group, was based on using morning PEF as the primary variable. Using a one-sided significance level of 0.025 with 80% power, 110 patients for each treatment group were required to detect that MDDPI would be 1 L/min worse (on average) than the Aerolizer™. Owing to the unreliability of the PEF data, the primary variable was changed to morning pre-dose FEV1.

Based on the data, the common standard deviation was .6L. Assuming that the difference was 0L but we want to rule out the difference could be 0.133L, we only have 37% power with a sample size of 110 patients per group.

The sponsor chose not to increase the sample size for this study, therefore for the new primary efficacy parameter, morning pre-dose FEV1 at end of 3-month study period, it was very likely that no definitive conclusion would be reached at the end of study.

Accountability of Patients

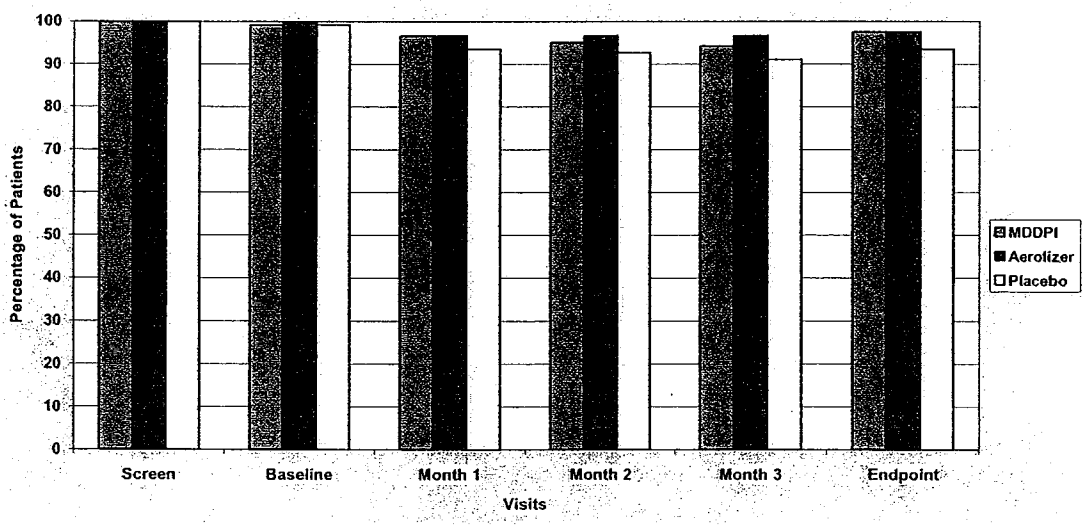
Table 12 and Figure 21 show the final status of the ITT population. More than 90% of patients completed the study. The patient distribution was similar among the treatment groups.

Table 12. ITT Patient Disposition by Final Status, N (%), Study 0605

Study		MDDPI 10µg	Aerolizer 12µg	Placebo	Total
0605	Entered	121	121	123	365
	Completed	113 (93.39)	116 (95.87)	114 (92.68)	343 (93.97)
	Discontinued	8 (6.61)	5 (4.13)	9 (7.32)	22 (6.03)
	Adverse event	0	2 (1.65)	2 (1.63)	4 (1.10)
	Consent withdrawn	3 (2.48)	0	2 (1.63)	5 (1.37)
	Lack of efficacy	0	0	0	0
	Lost to follow up	2 (1.65)	2 (1.65)	2 (1.66)	6 (1.64)
	Protocol violation	3 (2.48)	1 (0.83)	3 (2.44)	7 (1.92)
	Age				
	13 to 17	2 (1.65)	6 (4.96)	4 (3.25)	12 (3.29)
	18 to 64	106 (87.60)	104 (85.95)	104 (84.55)	314 (86.03)
	65+	13 (10.74)	11 (9.09)	15 (12.20)	39 (10.68)
	Gender				
	Female	80 (66.12)	79 (65.29)	84 (68.29)	243 (66.58)
	Male	41 (33.88)	42 (34.71)	39 (31.71)	122 (33.42)
	Race				
	Caucasian	95 (78.51)	94 (77.69)	92 (74.80)	281 (76.99)
	Black	3 (2.48)	2 (1.65)	2 (1.63)	7 (1.92)
	Oriental	0	0	3 (2.44)	3 (0.82)
	Other	23 (19.01)	25 (20.66)	26 (21.14)	74 (20.27)

Data source: \raw\cmp.xpt, \derived\ident_d.xpt; Program: SUMMARY.SAS

Figure 21. Patients Allocation by Visits, Study 0605



Data source:\raw\cmp.xpt, \derived\fevauc_d.xpt; Program: fev1.sas, study605.xls

Primary Efficacy Analyses

The primary efficacy parameter was the Morning Pre-dose FEV1 performed at the study center during the final visit (Protocol Amendment #3, Vol. 47).

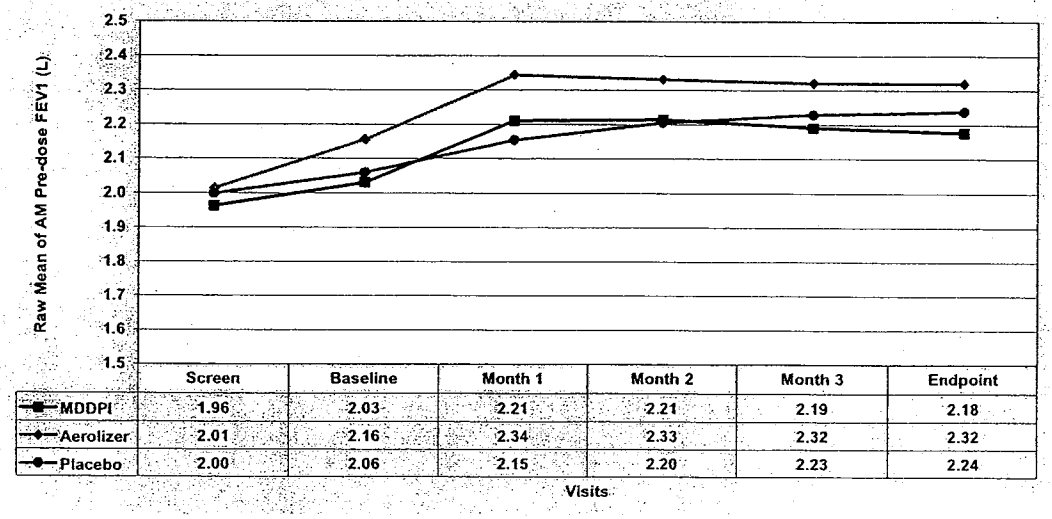
Table 13 and Figure 22 show the mean values of morning pre-dose FEV1 at each visit for the treatment groups. Due to the small sample size, no statistical significance was reached. The 12µg b.i.d. formoterol delivered by the Aerolizer™ numerically showed more effect than 10µg b.i.d. formoterol delivered by the MDDPI. At the end of study period, the MDDPI was similar to placebo.

Table 13. Morning Pre-Dose FEV1 by Visits, ITT Population for Study 0605

Visits	*Statistics*	*MDDPI 10µg*	*Aerolizer 12µg*	*Placebo*
Visit 1 (Screening)	N	121	121	123
	Mean (SD)	1.96 (0.58)	2.01 (0.53)	2.00 (0.51)
	Range	(0.97, 3.81)	(0.96, 3.56)	(0.80, 3.55)
	Test for Group Difference	F value=0.29	DF=2	P value=0.746
Visit 2 (Randomization)	N	120	121	122
	Mean (SD)	2.03 (0.65)	2.16 (0.66)	2.06 (0.59)
	Range	(1.00, 3.99)	(0.96, 4.40)	(1.04, 3.99)
	Test for Group Difference	F value=1.27	DF=2	P value=0.282
Visit 3	N	117	117	115
	Mean (SD)	2.21 (0.76)	2.34 (0.75)	2.15 (0.68)
	Range	(0.96, 4.84)	(0.80, 4.79)	(0.93, 4.09)
	Test for Group Difference	F value=2.04	DF=2	P value=0.131
Visit 4	N	115	117	114
	Mean (SD)	2.21 (0.73)	2.33 (0.75)	2.20 (0.72)
	Range	(1.02, 4.13)	(0.92, 4.67)	(0.82, 4.20)
	Test for Group Difference	F value=1.05	DF=2	P value=0.352
Visit 5 (Final Visit)	N	114	117	112
	Mean (SD)	2.19 (0.71)	2.32 (0.78)	2.23 (0.69)
	Range	(0.68, 4.01)	(0.82, 4.45)	(0.88, 3.78)
	Test for Group Difference	F value=0.96	DF=2	P value=0.383
Last Valid Reading (LOCF Imputed)	N	118	118	115
	Mean (SD)	2.18 (0.72)	2.32 (0.78)	2.24 (0.69)
	Range	(0.68, 4.01)	(0.82, 4.45)	(0.88, 3.78)
	Test for Group Difference	F value=1.15	DF=2	P value=0.318

Data source: \raw\cmp.xpt, \derived\fev1_d.xpt; Program: study605.sas

Figure 22. Raw Mean of Morning Pre-Dose FEV1 by Visits, Study 0605



	Screen	Baseline	Month 1	Month 2	Month 3	Endpoint
MDDPI	1.96	2.03	2.21	2.21	2.19	2.18
Aerolizer	2.01	2.16	2.34	2.33	2.32	2.32
Placebo	2.00	2.06	2.15	2.20	2.23	2.24

Data source: \raw\cmp.xpt, \derived\fev1_d.xpt; Program: study605.sas, study605.xls

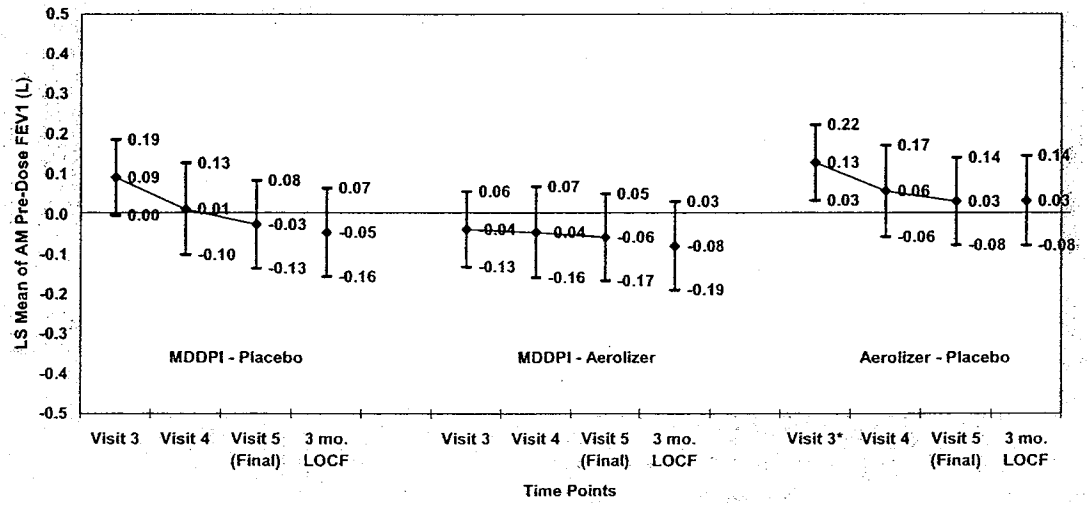
Table 14 and Figure 23 show the statistical analysis results of morning pre-dose FEV1. The Aerolizer™ was numerically better than the MDDPI at all visits and was numerically better than placebo at all visits and reached statistical significance at visit 3.

Table 14. Morning Pre-Dose FEV1 by Visits, Study 0605

Study	Population Visits	Treatment/ Treatment contrast	N	LS mean (SE)	95% CI	p-value (two-sided)
0605	ITTE patients					
	Visit 3 (Month 1)	*MDDPI 10µg*	117	2.25 (0.04)	-	-
		Aerolizer 12µg	117	2.29 (0.04)	-	-
		Placebo	115	2.16 (0.04)	-	-
		MDDPI – Placebo	-	0.09 (0.05)	(-0.00, 0.19)	.0574
		Aerolizer – Placebo	-	0.13 (0.05)	(0.03, 0.22)	.0076
		MDDPI – Aerolizer	-	-0.04 (0.05)	(-0.13, 0.06)	.4352
	Visit 4 (Month 2)	*MDDPI 10µg*	115	2.20 (0.04)	-	-
		Aerolizer 12µg	117	2.25 (0.04)	-	-
		Placebo	114	2.19 (0.04)	-	-
		MDDPI – Placebo	-	0.01 (0.06)	(-0.10, 0.13)	.8236
		Aerolizer – Placebo	-	0.06 (0.06)	(-0.05, 0.17)	.3195
		MDDPI – Aerolizer	-	-0.04 (0.06)	(-0.16, 0.07)	.4401
	Visit 5 (Month 3)	*MDDPI 10µg*	114	2.20 (0.04)	-	-
		Aerolizer 12µg	117	2.26 (0.04)	-	-
		Placebo	112	2.23 (0.04)	-	-
		MDDPI – Placebo	-	-0.03 (0.06)	(-0.13, 0.08)	.6489
		Aerolizer – Placebo	-	0.03 (0.06)	(-0.08, 0.14)	.5615
		MDDPI – Aerolizer	-	-0.06 (0.06)	(-0.17, 0.05)	.2996
	Last Valid Visit (LOCF Imputed)	*MDDPI 10µg*	118	2.18 (0.04)	-	-
		Aerolizer 12µg	118	2.26 (0.04)	-	-
		Placebo	115	2.23 (0.04)	-	-
		MDDPI – Placebo	-	-0.05 (0.07)	(-0.16, 0.07)	.4234
		Aerolizer – Placebo	-	0.03 (0.06)	(-0.08, 0.14)	.5485
		MDDPI – Aerolizer	-	-0.08 (0.06)	(-0.19, 0.03)	.1603

Data source: \raw\cmp.xpt, \derived\fev1_d.xpt; Program: study605.sas

Figure 23. LS Mean Difference and 95% CI of Pairwise Comparison of FEV1 at Each Visit, Study 0605



Data source: \raw\cmp.xpt, \derived\fev1_d.xpt; Program: study605.sas, study605.xls
* Indicated the significance at 0.05 level.

Conclusion

- Study 0605 was underpowered after changing the primary variable to morning pre-dose FEV1 in the middle of the study. The study did not show any meaningful statistical differences between the three treatment groups (formoterol 10µg b.i.d. delivered by the MDDPI, formoterol 12µg b.i.d. delivered by the Aerolizer™, and placebo). Numerically, formoterol 12µg b.i.d. delivered by the Aerolizer™ showed better and longer term efficacy than formoterol 10µg b.i.d. delivered by the MDDPI.

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/s/

Feng Zhou
9/26/03 11:56:33 AM
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James Gebert
9/26/03 12:58:54 PM
BIOMETRICS
I concur.