In comparison with the Integrated Safety Summary (ISS), the duration of exposure to formoterol in protocol #27 was somewhat longer and in FFOR14/F the duration was slightly shorter.

DEMOGRAPHICS

The majority of patients were in the age range of 19-64 years of age (80.0%); 1.3% was ≤ 18 years of age and 18.6% of the population was > 64 years old. Unlike data in the ISS, information about baseline $FEV_{1.0}$ was not collected and, for the most part, racial categorization was not performed. Patient counts and percents by treatment group are displayed in the table below [SU1:15-6].

SU1 – DEMOGRAPHIC CHARACTERISTICS AT BASELINE BY TREATMENT [SU1:16]			
	Formoterol n (%)	Salmeterol n (%)	All Patients n (%)
Total Patients	1636 (100)	239 (100)	1875 (100)
SEX:			
Male	820 (50.1)	113 (47.3)	933 (49.8)
Female	816 (49.9)	126 (52.7)	942 (50.2)
RACE:			
White	2 (0.1)	0	2 (0.1)
Black	8 (0.5)	0	8 (0.4)
Other	2 (0.1)	0	2 (0.1)
Not Stated	1624 (99.2)	239 (100)	1863 (99.4)
AGE RANGE:			
< 12	0	0	0
12-18	23 (1.4)	2 (0.8)	25 (1.3)
19-64	1295 (79.2)	206 (86.2)	1501 (80.1)
> 64	318 (19.4)	31 (13.0)	349 (18.6)

PREMATURE DISCONTINUATIONS DUE TO ADVERSE EVENTS

The single-dose protocol #54 produced no patients in this category. The method of displaying patients who terminated prematurely from trials is consistent with that found in the ISS. That is, the cause of early termination is not shown unless the underlying AE frequency is ≥ 2 %, which excludes about half of these patients in each treatment group. In the multiple-dose protocol #27, no patient discontinued due to a laboratory abnormality [SU1:28].

SU1 – FREQUENCY OF DISCONTINUATIONS DUE TO AE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN PROTOCOL #27 [SU1:28]		
	Formoterol n (%)	Salmeterol n (%)
Total Patients	241	239
Patients Stopping Early	11 (4.6)	11 (4.6)
Early Terminations Displayed	4	5

SU1 – FREQUENCY OF DISCONTINUATIONS DUE TO AE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN PROTOCOL #27 [SU1:28]		
	Formoterol n (%)	Salmeterol n (%)
Asthma	0	4 (1.7)
Headache	2 (0.8)	1 (0.4)
Tremor	2 (0.8)	0

Once again, tremor is identified as one salient contributor to this category. A similar display is presented for protocol FFOR14, where only two of the early terminating patients discontinued because of a laboratory abnormality.

SU1 – FREQUENCY OF DISCONTINUATIONS DUE TO AE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN PROTOCOL FFOR14 [SU1:29]	
	Formoterol n (%)
Total Patients	1383 (100)
Patients Stopping Early	82 (5.9)
Early Terminators Displayed	54
Tremor	12 (0.9)
Headache	13 (0.9)
Asthma	8 (0.6)
Rhinitis	1 (0.1)
Palpitation	8 (0.5)
Leg Cramps	1 (0.1)
Sinusitis	1 (0.1)
Pharyngitis	1 (0.1)
Nervousness	2 (0.1)
Insomnia	7 (0.5)

SERIOUS ADVERSE EVENTS (SAE'S)

No patient from protocol #54 experienced an SAE. Protocol #27 contributed 3 SAE's from the 480 patients enrolled. All SAE's came from the 241 patients exposed to formoterol and none from the 239 patients given salmeterol. They include respiratory failure, myocardial ischemia and surgical excision of indurated palate area to complete treatment for malignancy. The multiple-dose, uncontrolled protocol FFOR14/F contributed 6 patients with SAE's out of 1383 total patients. Three had asthma, and one each had a lung infection, cardiac insufficiency and rectal carcinoma [SU1:30-1].

DEATHS

No fatalities were reported for protocols #54, #27 or FFOR14/F in patients exposed to either formoterol or the active comparator during the update period [SU1:35].

LABELING

The proposed package insert included with the original submission of this New Drug Application stresses the following salient points and subpoints [1:1-16].

A full labeling review will be performed when all current deficiencies in this submission have been addressed.

APPEARS THIS WAY
ON ORIGINAL

FIGURE 8.1 - 1A

MEAN FEV - 1 (LITER) VERSUS SCHEDULED TIME AT VISIT 2
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

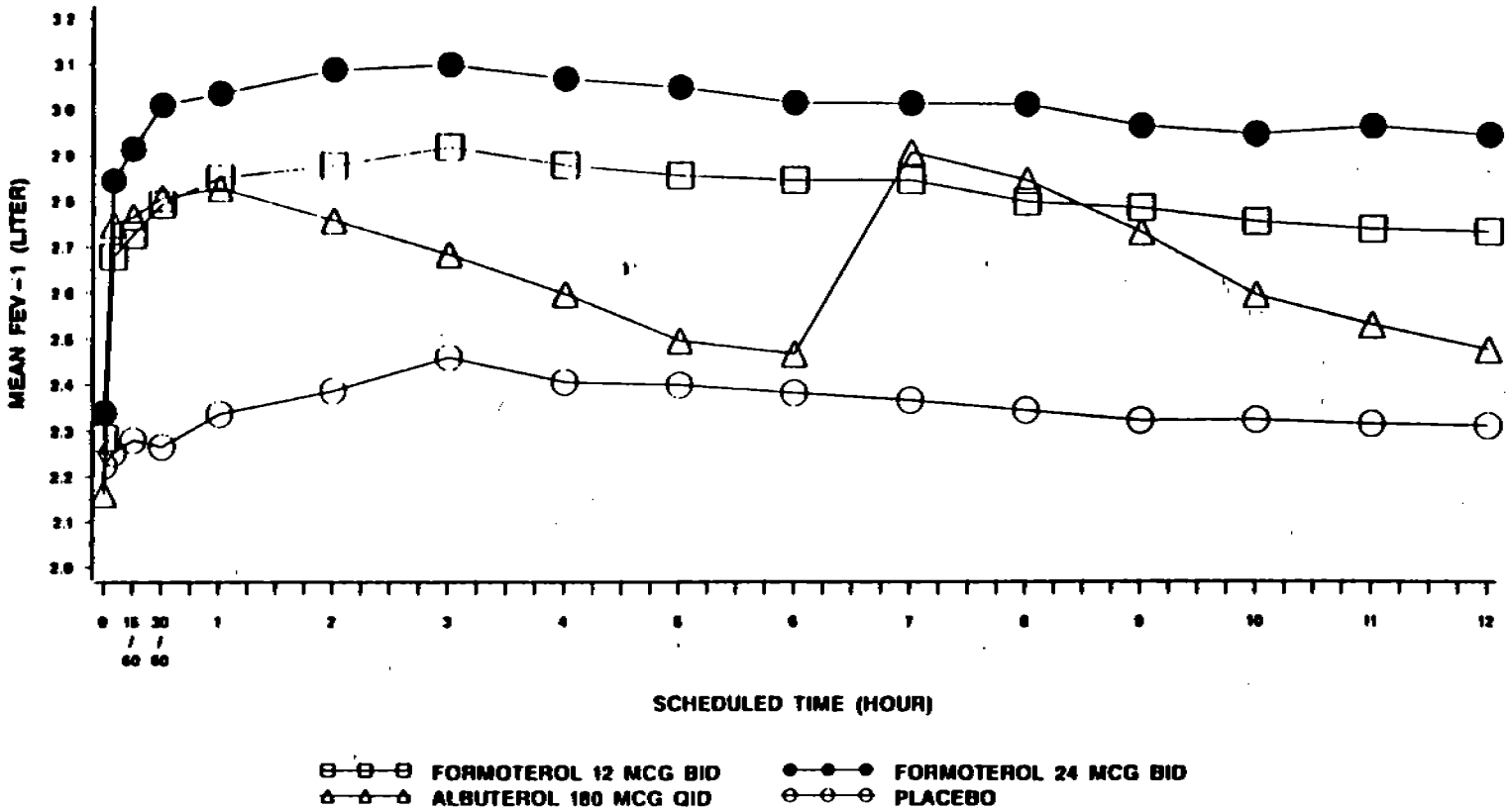


FIGURE 8.1 - 2A

MEAN FEV - 1 (LITER) VERSUS SCHEDULED TIME AT VISIT 4
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

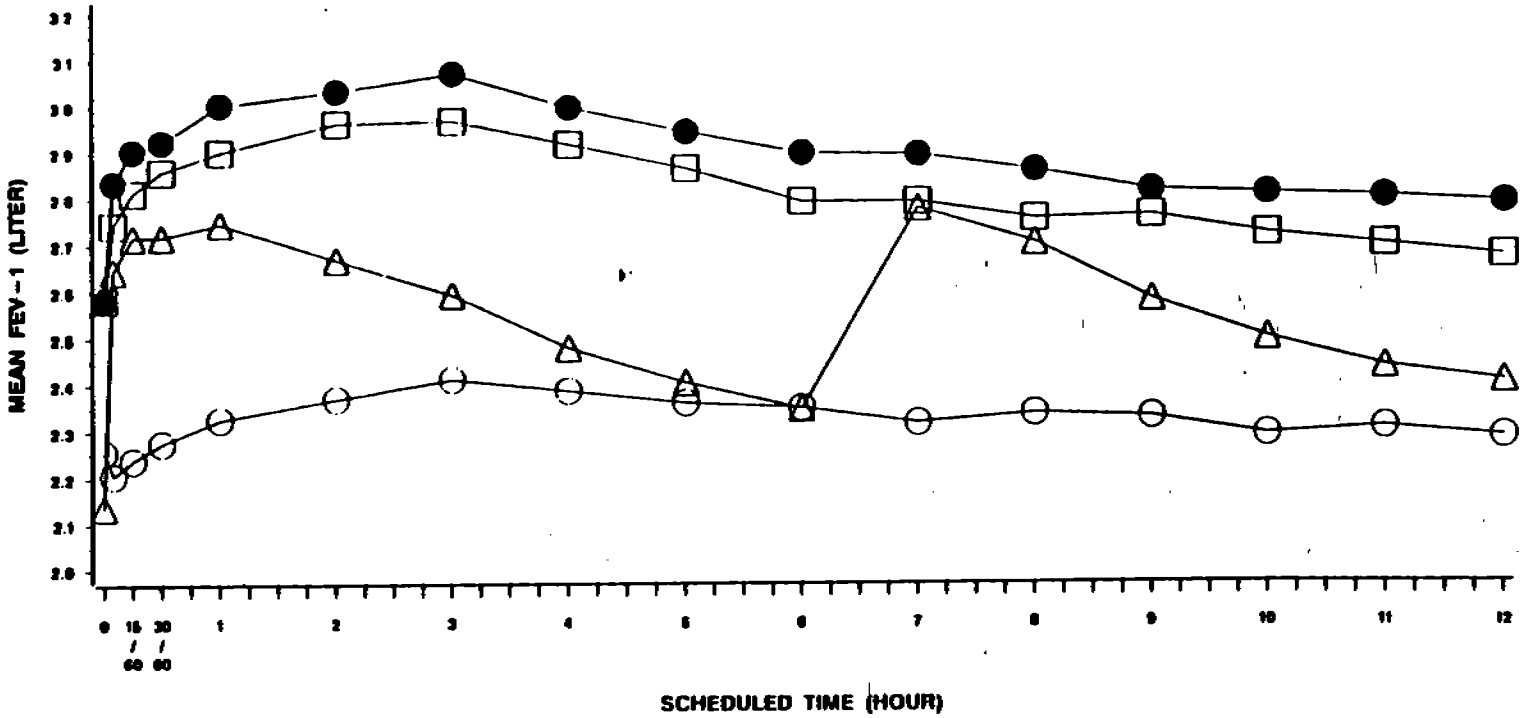


FIGURE 8.1 - 3A

MEAN FEV - 1 (LITER) VERSUS SCHEDULED TIME AT VISIT 5
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

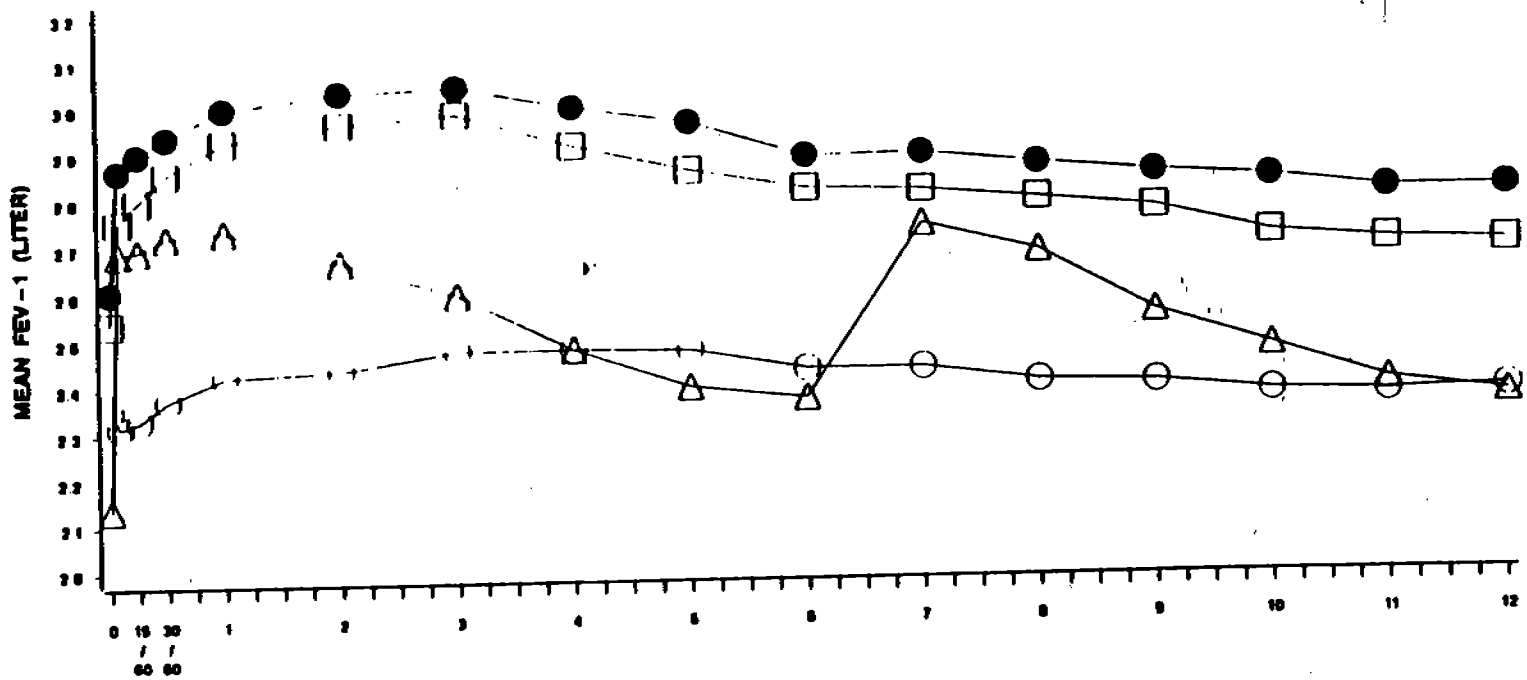


FIGURE 8.1 - 4A

MEAN FEV - 1 (LITER) VERSUS SCHEDULED TIME AT VISIT 6
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

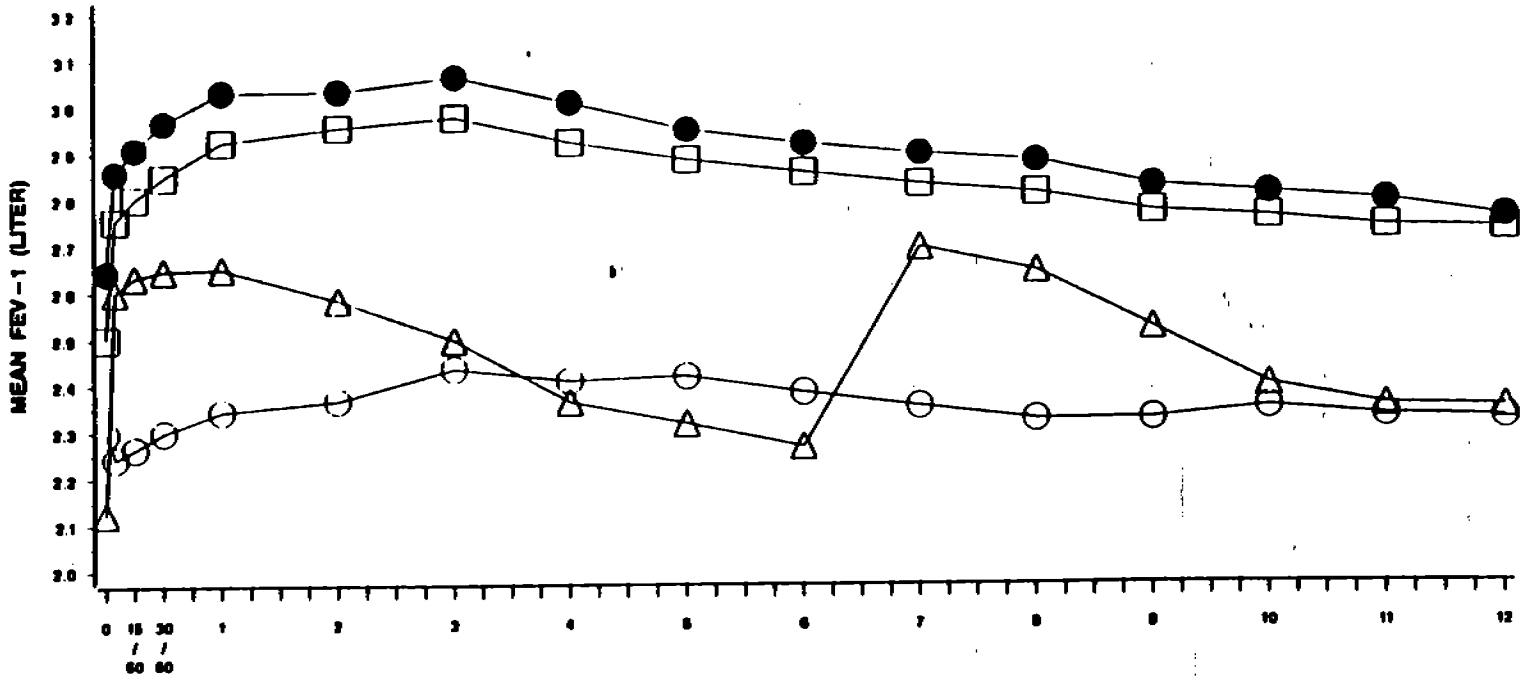


FIGURE 8.1-1A

MEAN FEV-1 (LITER) VERSUS SCHEDULED TIME AT VISIT 2
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

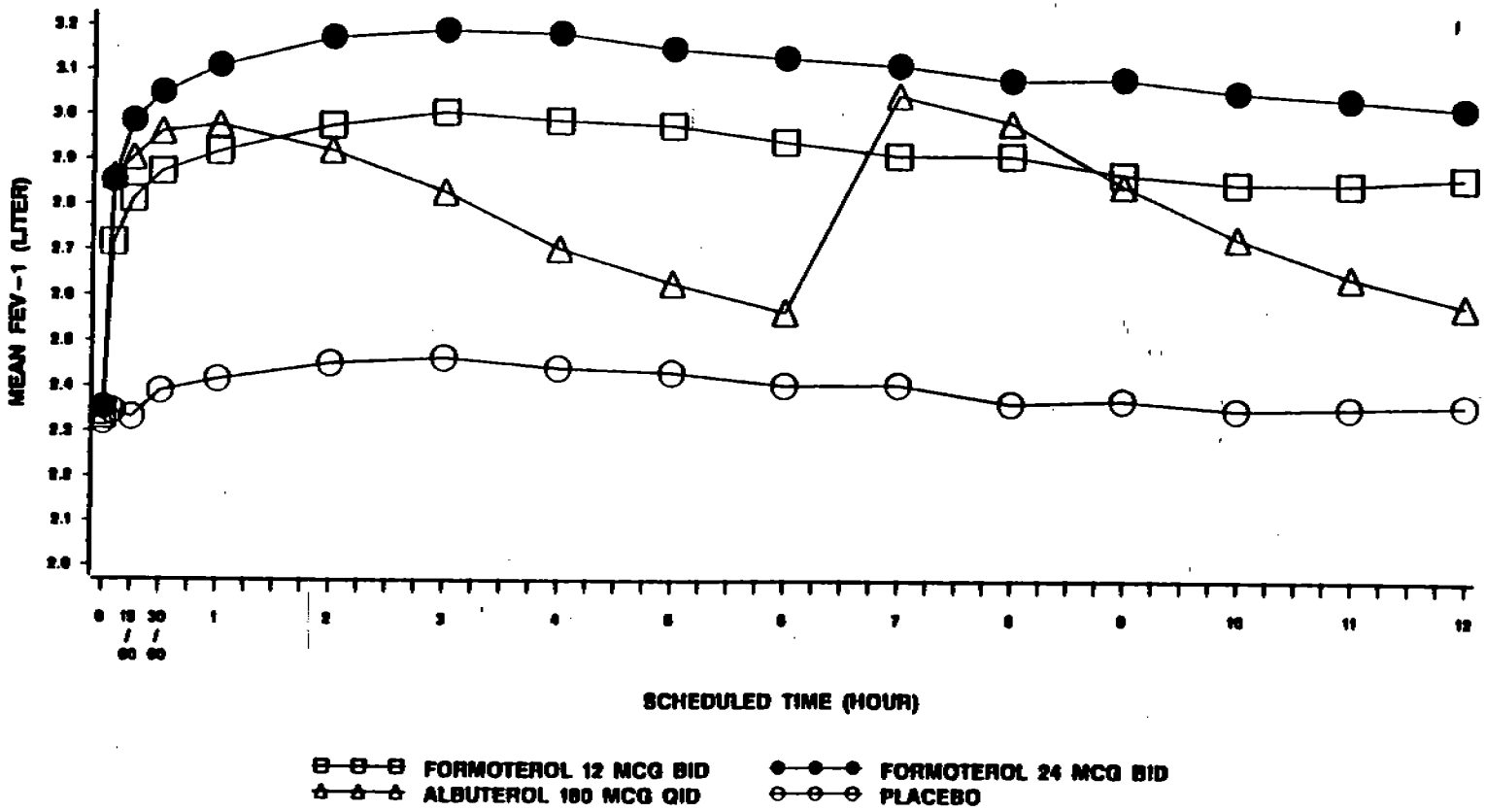


FIGURE 8.1-2A

MEAN FEV-1 (LITER) VERSUS SCHEDULED TIME AT VISIT 4
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

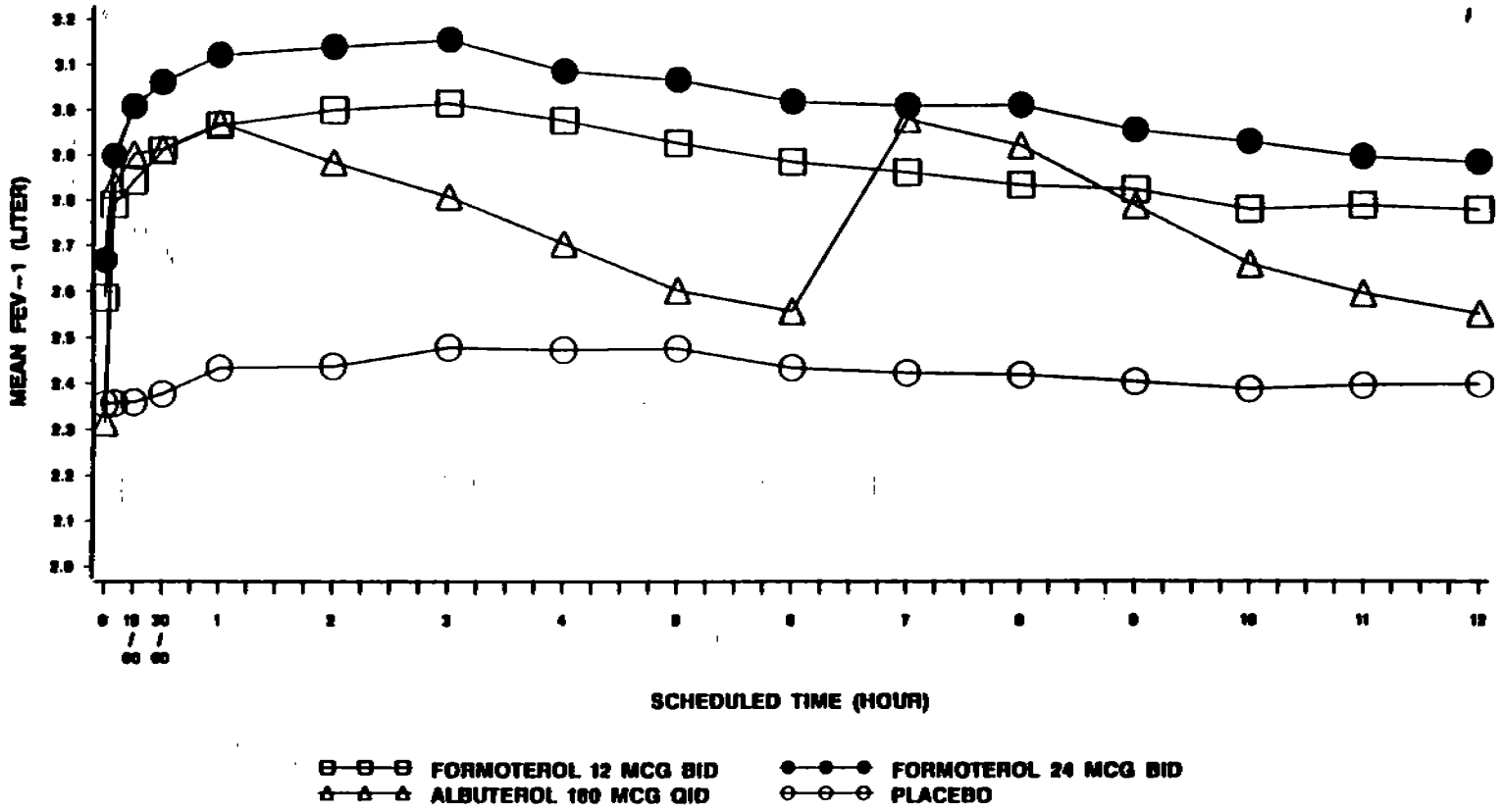


FIGURE 6.1-3A

MEAN FEV-1 (LITER) VERSUS SCHEDULED TIME AT VISIT 6
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

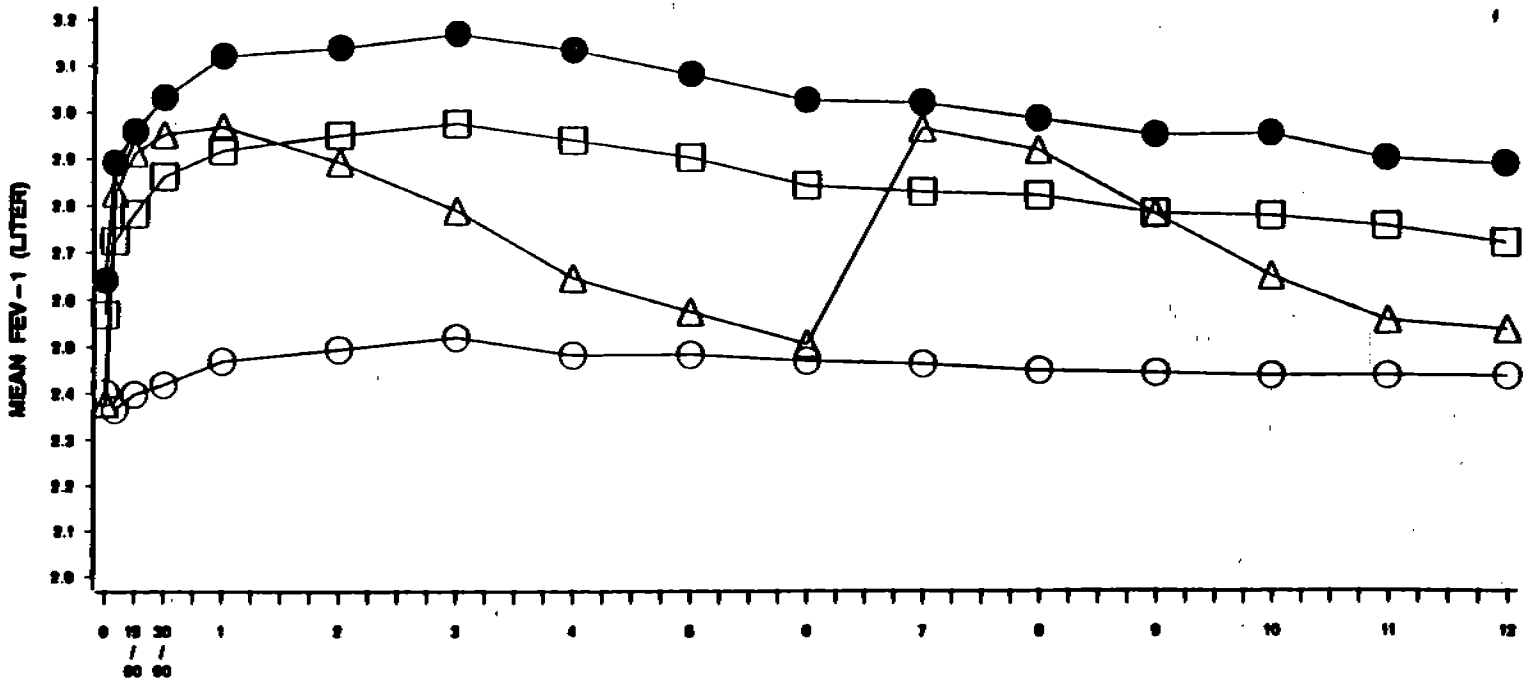


FIGURE 6.1-4A

MEAN FEV-1 (LITER) VERSUS SCHEDULED TIME AT VISIT 6
BY TREATMENT GROUP
(ALL RANDOMIZED PATIENTS)

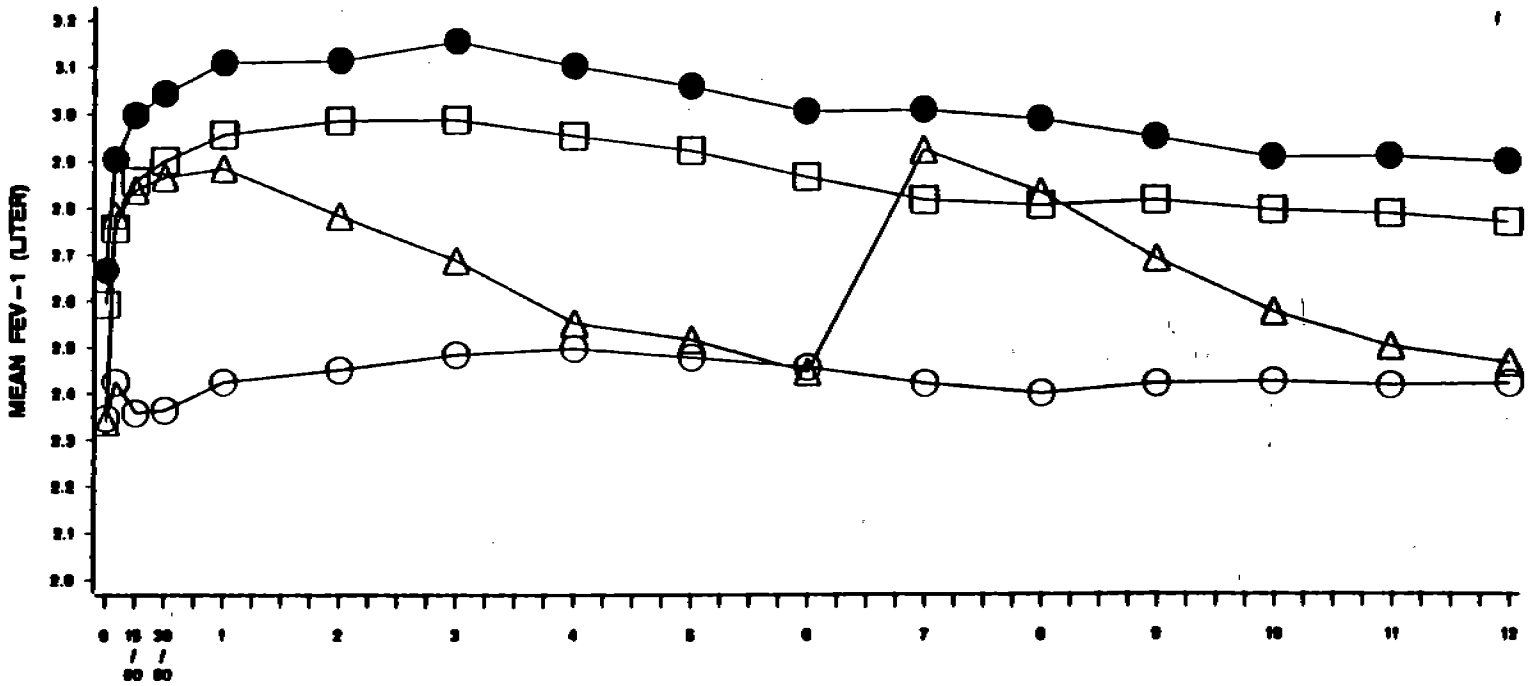
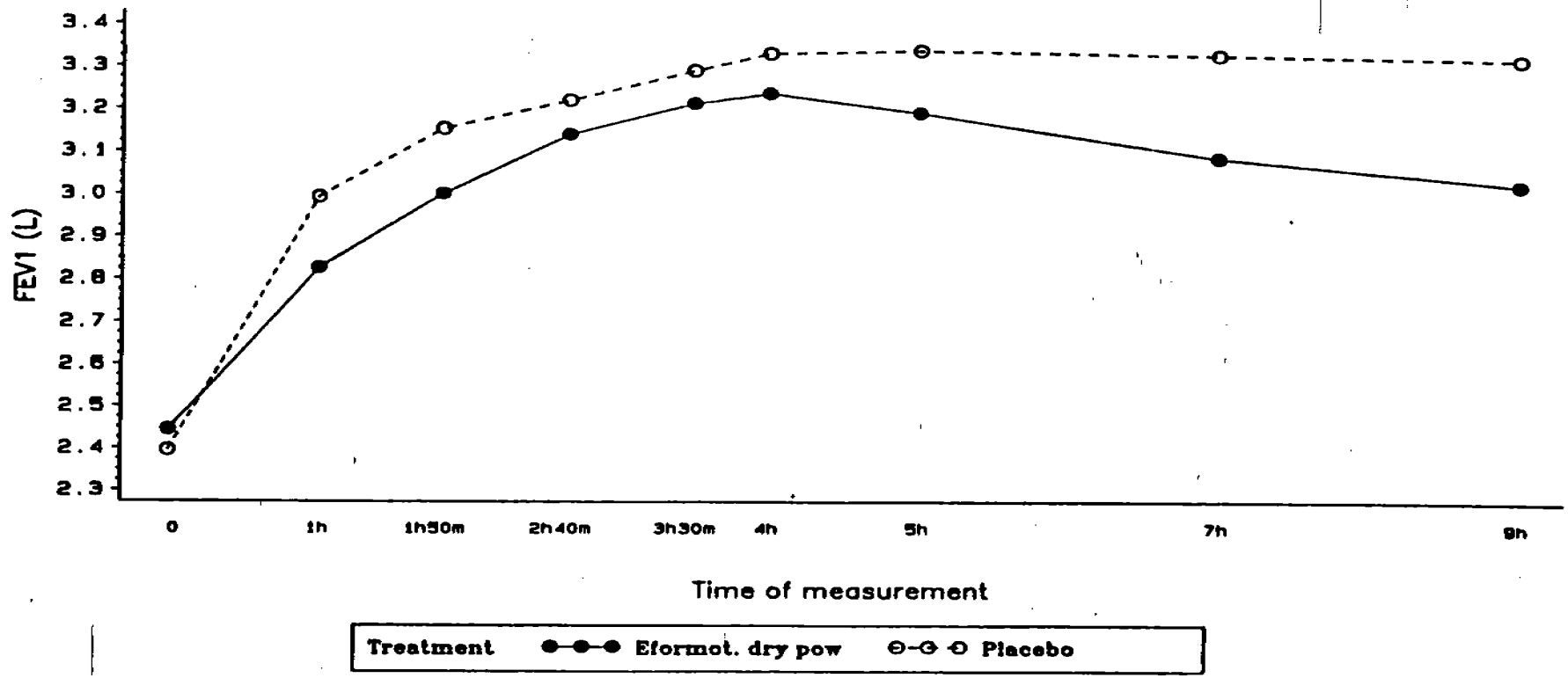
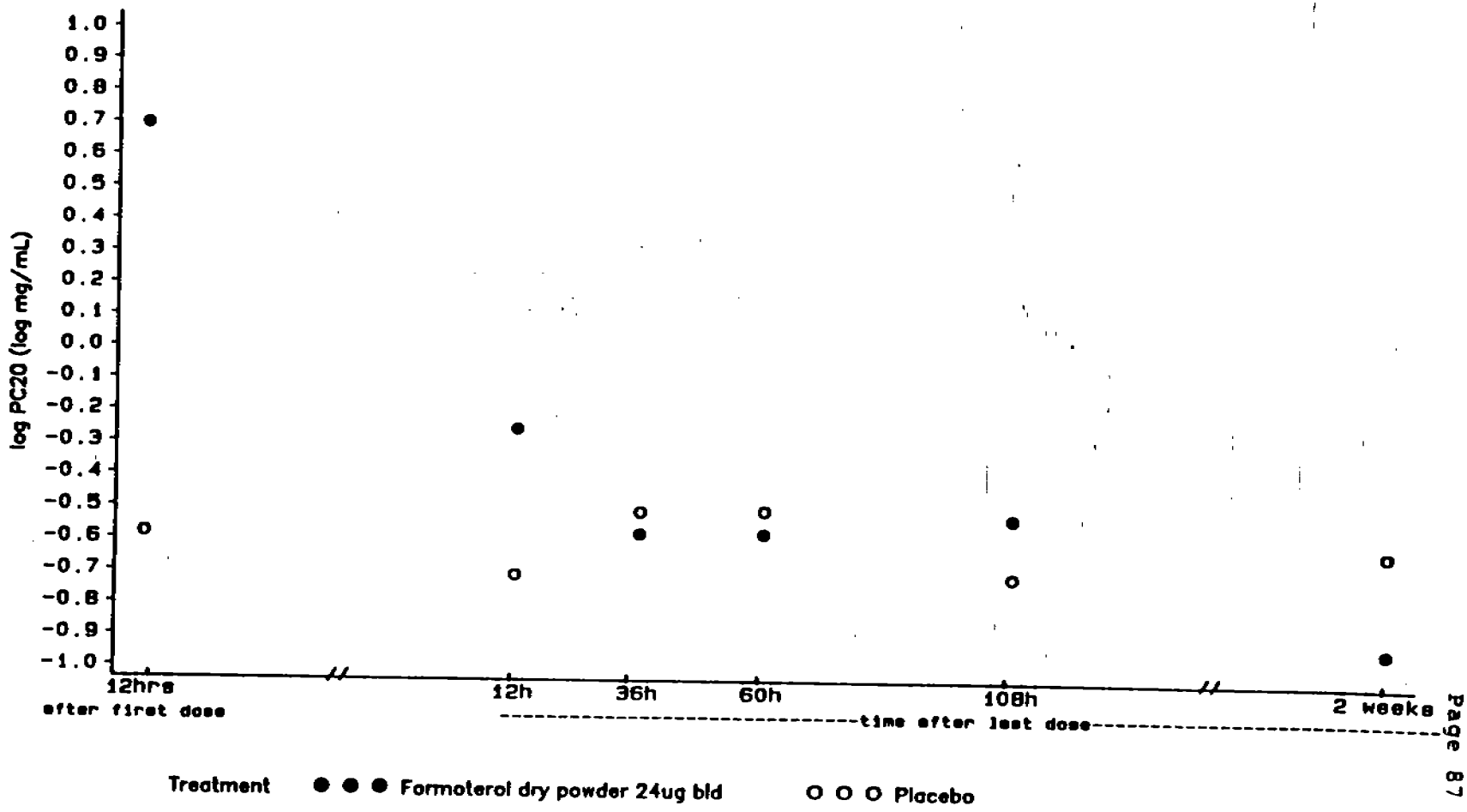


Figure 2 : Mean FEV1 (L) during dose-response curve
Patients who completed the study



Note: TIME OF MEASUREMENT : 0 = 30mins before 1st dose 1h = 30mins after 1st dose 1h30m = 30mins after 2nd dose
2h40m = 30mins after 3rd dose 3h30m = 30mins after 4th dose 4h = 1h after 4th dose
5h = 2hrs after 4th dose 7h = 4hrs after 4th dose 9h = 6hrs after 4th dose

Module I: Figure 8.1 – 2: Mean log methacholine PC20 measurements during and after each treatment period



Note: The time axis is not on a completely linear scale

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Labeling

3 PAGE(S) REDACTED

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