

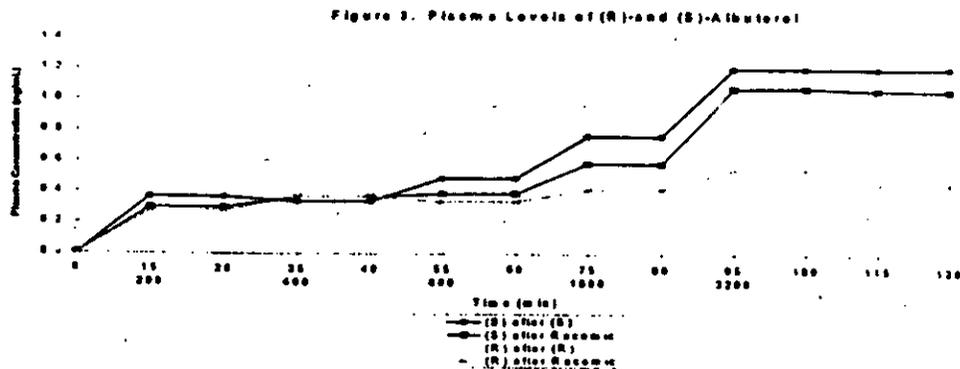
seen after racemic albuterol. However, the 95% confidence intervals around the relative potency estimates included 2 units and, therefore, a 1:2 ratio could not be excluded." This is a reasonable interpretation by the sponsor and consistent, at least in part, with the placebo response in regard to serum potassium, seen in figure 2 on page 60.

Table 4. Summary of Relative Potency of (R)-Albuterol with Racemic Albuterol as the Standard

	Treatment Group
	(R)-albuterol
	n=12
Finger Tremor (cm/s ²)	
Relative potency	1.662
Plasma Potassium (mmol/L)	
Relative potency	1.431

Note: One subject has been dropped from finger tremor analysis due to missing data.
Reference: Section 14.2, Table 14.2.6.

□ Plasma levels of (R)-albuterol and (S)-albuterol can be seen in the figure below. There was generally a higher plasma concentration achieved with each successfully higher dose administered. Increased plasma levels of (R)-albuterol were associated with increased pharmacodynamic effects after administration of both (R)-albuterol and racemic albuterol. The levels of (S)-albuterol were higher than the levels of (R)-albuterol after administration of either the (S) isomer or the racemic mixture. At some doses, the plasma levels of (R)-albuterol were slightly higher after administration of (R)-albuterol than after administration of racemic albuterol. However, there was no concomitant increase in pharmacodynamic effects seen after (R)-albuterol administration. The sponsor states that there was no interconversion of (R)-albuterol to (S)-albuterol or (S)-albuterol to (R)-albuterol when the single isomers were administered. The table showing mean levels of (R)-albuterol after administration of (S)-albuterol (page 72) is misleading since 9/12 patients had undetectable levels of (R)-albuterol after administration of (R)-albuterol.



□ This data is consistent with beta receptor binding studies which showed a much higher affinity of the (R)-isomer, as compared to the (S)-isomer, since the extrapulmonary effects of albuterol appear to be due primarily to the (R)-isomer. Since virtually all of the pharmacologic activity is related to the (R)-isomer, the extrapulmonary safety of (R)-albuterol can be expected to be similar to the extrapulmonary safety of twice the dose of racemic albuterol, unless the (S)-enantiomer somehow protects against extrapulmonary adverse effects. Although other data suggests that this could occur, this possibility requires further study. There were no serious adverse events in this study, with 6 adverse events (3 patients) after racemic albuterol, 4 adverse events (3 patients) after (R)-albuterol, and 7 adverse events (3 patients) after placebo administration. None of the adverse events was felt to be related to treatment.

CONCLUSIONS: There were no safety concerns raised by the data from this study, despite administration of cumulative doses of 6.2 mg of (R)-albuterol compared to cumulative doses of 12.6 mg of racemic albuterol. There were no statistically significant changes in vital signs, with the exception of heart rate, but the change was not significantly different than the change seen after administration of racemic albuterol. Expected increase in tremor and decrease in potassium were seen after administration of (R)-albuterol, but the effect was no greater than that seen after racemic albuterol on a mg/mg basis.

- **Study 005: entitled, "Dose-response study of inhaled (R)-albuterol in the reversal of bronchconstriction in asthmatic patients"; Principal Investigators: DG Tinkelman MD, MJ Noonan MD, Atlanta GA, Portland OR.**

Study Characteristics

- ◆ **number of patients: 22 screened; 20 randomized; 20 completed**
- ◆ **age range: 22-51 years**
- ◆ **patient population: asthma, chronic; mild-moderate; FEV-1 50-80% predicted; non-smokers; inhaled corticosteroids were allowed during the study; 75% of the patients were women; on inhaled racemic albuterol (Ventolin or Proventil)**
- ◆ **study design: randomized, double-blind, crossover, placebo-controlled, single dose, two center study**
- ◆ **drug administration: 0.31 mg (lot # 2195) 0.0105%, 0.63 mg (lot # 2295) 0.021%, and 1.25 mg (lot # 2595) 0.042% of (R)-albuterol; 2.5 mg of racemic albuterol 0.083% (lot # 941636); placebo was 0.9% saline (lot # 2495); drug delivered by Pari LC Jet Nebulizer with Pari Master compressor**
- ◆ **periods of study: 5 treatment visits separated by a minimum of 2 days and a maximum of 8 days; screening visit and final visit within 48 hours of the last pulmonary function testing session, i.e. last treatment day**
- ◆ **parameters evaluated: The objectives of the study were to determine the comparative efficacy and safety of (R)-albuterol relative to racemic albuterol and the effect of increasing doses of (R)-albuterol on the magnitude and duration of bronchodilation. The primary efficacy variables were overall change in FEV-1 from baseline to 6 hours after drug administration and time of onset and duration of effectiveness. The primary comparisons of**

interest were between 1.25 mg of (R)-albuterol and placebo and between 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol.

- PFTs (FEV-1): at screening visit and on treatment visits prior to drug administration and every 15 minutes following drug administration (start of nebulization) for 2 hours and hourly thereafter for a minimum of 6 hours or until FEV-1 was within 10% of the baseline average; if the FEV-1 fell by more than 20% after administration of treatment medication, further testing on that day was terminated; at the final visit
- 12 lead ECGs and Holter monitoring: 12 lead ECG 30 minutes after drug administration on treatment days and at the final visit; Holter monitoring for 150 minutes following drug administration
- serum glucose, potassium and calcium: one hour prior to administration of study medication and 1 hour after drug administration
- adverse events
- other laboratory tests: at visit 1 and visit 7
- vital signs: at visits 1 and 7 and prior to drug administration and at the conclusion of evaluation on study days 2-6

Study Results:

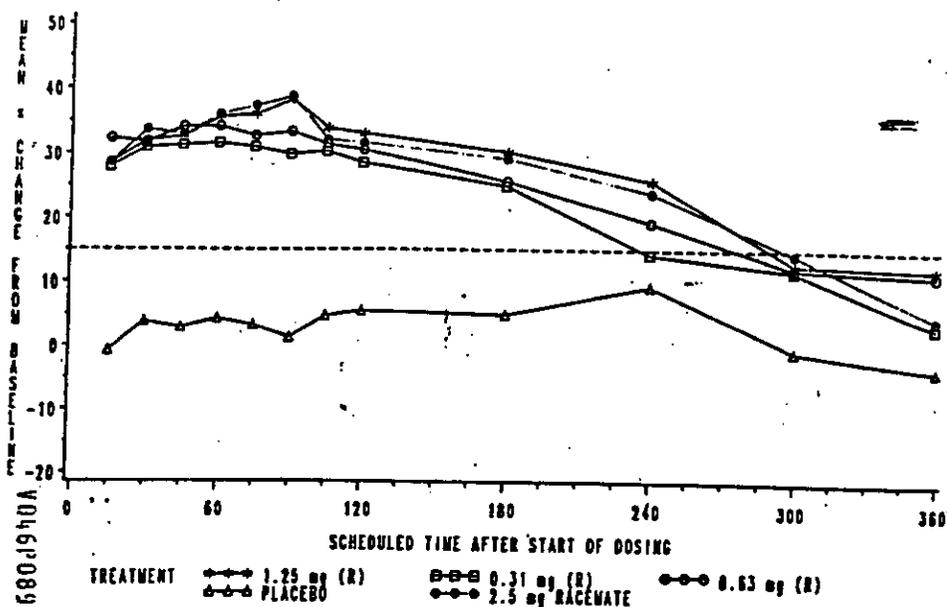
- ◆ Mean percent change from baseline in FEV-1 was highest after administration of 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol, but there was a statistically significant difference between treatments only for (R)-albuterol and placebo (see table and figure below). There was no statistically significant difference between improvement after administration of 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol. There was a dose-

response trend for the 3 doses of (R)-albuterol. At least one patient did not respond after administration of each treatment.

Table 3. Mean FEV₁ Data over Time (Percent Change from Pre-Dose)

Scheduled Assessment Time	Placebo	0.31 mg (R)-Albuterol	0.63 mg (R)-Albuterol	1.25 mg (R)-Albuterol	2.5 mg Racemic Albuterol
15 min	-1	28	32	29	29
30 min	4	31	32	32	34
45 min	3	31	34	33	33
60 min	4	32	34	36	36
75 min	3	31	33	36	37
90 min	1	30	33	38	39
105 min	5	30	31	34	32
120 min	5	28	31	33	32
3 hr	5	25	26	30	29
4 hr	9	14	19	26	24
5 hr	-1	12	12	13	14
6 hr	-4	3	11	12	5
Overall Average	1	25	27	29	29

FEV₁ DATA (VISITS 2-6)

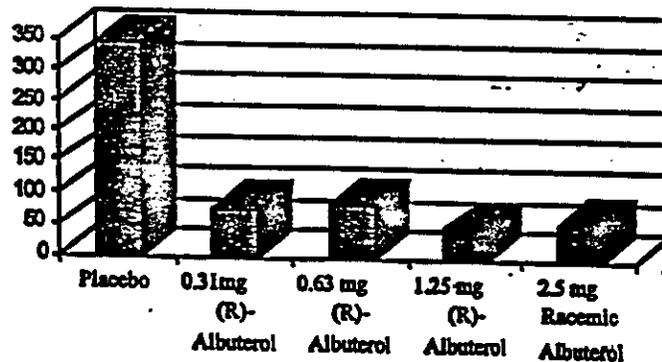


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There was no statistically or clinically significant difference in terms of time to onset of action (the first time point at which a 15% increase in FEV-1 was observed) (see table and figure below) between any of the treatments, but there was a dose-response in terms of duration of action (the time from onset of action to the time at which the FEV-1 first fell below 15%), ranging from [redacted] minutes after administration of 0.31 mg of (R)-albuterol to [redacted] minutes after administration of 1.25 mg of (R)-albuterol. Duration of activity was comparable after administration of 0.63 mg of (R)-albuterol and 2.5 mg of racemic albuterol (see table and figure below). The mean onset of action was 78 minutes, 83 minutes, 46 minutes, 54 minutes and 345 minutes after administration of 0.31 mg (R)-albuterol, 0.63 mg (R)-albuterol, 1.25 mg (R)-albuterol, 2.5 mg racemic albuterol and placebo, respectively. There was no significant difference in regard to the duration of effectiveness between patients who were not receiving corticosteroids and those with chronic corticosteroid use.

Figure 1. Mean Time to Onset of Activity (Minutes)



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Figure 3
DISTRIBUTION OF ONSET (MINUTES) BY TREATMENT

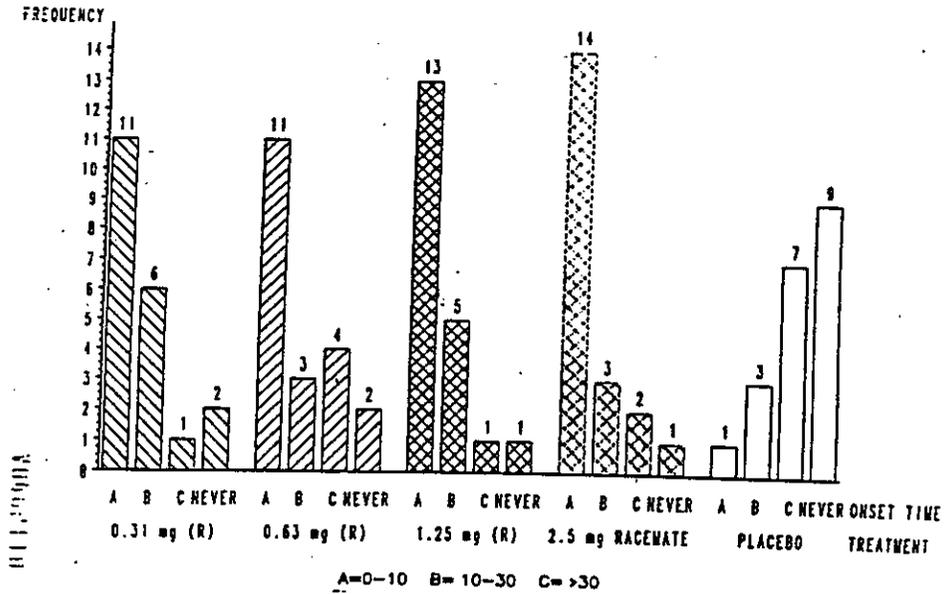


Figure 4
DISTRIBUTION OF DURATION (MINUTES) BY TREATMENT

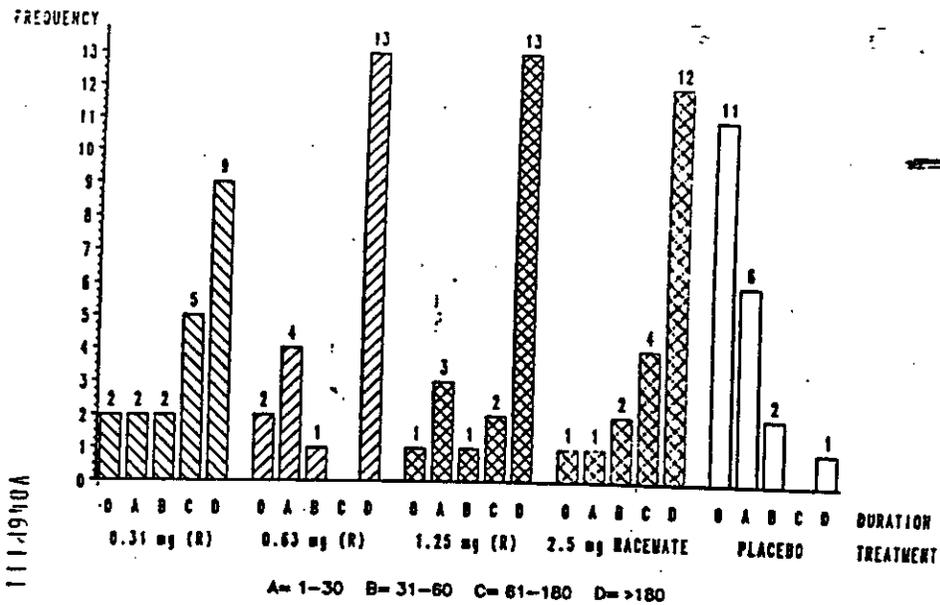
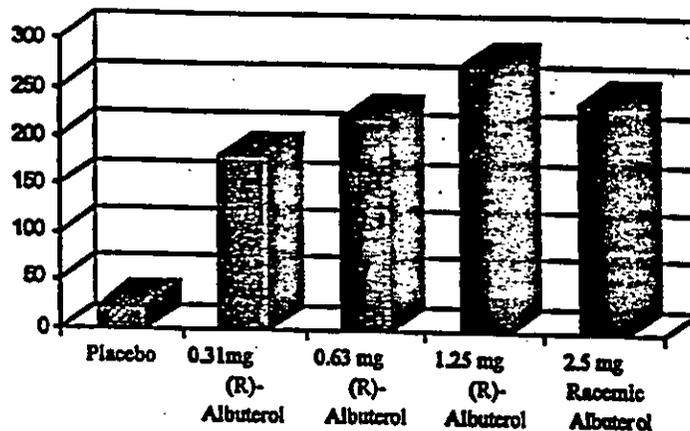


Figure 2. Mean Duration of Activity (Minutes)



◆ The percentage of patients experiencing adverse events, as well as the total number and type of adverse events, were comparable after administration of the three (R)-albuterol doses, 2.5 mg of racemic albuterol and placebo (see table below). No serious or unexpected adverse events were noted. The most frequent treatment-related adverse events were nervousness and wheezing/chest tightness. Nervousness was most frequently reported after administration of 1.25 mg (R)-albuterol and 2.5 mg of racemic albuterol.

Table 4. Summary of Adverse Events

	Placebo	0.31 mg (R)-Albuterol	0.63 mg (R)-Albuterol	1.25 mg (R)-Albuterol	2.5 mg Racemic Albuterol
All Adverse Events					
No. (%) of Patients	4 (20)	6 (30)	4 (20)	7 (35)	6 (30)
No. of Events	6	9	4	7	6
Treatment-Related Adverse Events					
No. (%) of Patients	3 (15)	5 (25)	2 (10)	7 (35)	6 (30)
No. of Events	3	7	2	7	6

◆ **12 lead ECGs:** In regard to QTc interval, all albuterol treatments differed significantly from placebo and there was a statistically significant difference between the 1.25 mg (R)-albuterol and the 0.31 mg (R)-albuterol treatments (see tables below). The percentage of patients without normal sinus rhythm varied from 0% after 2.5 mg racemic albuterol to 20% after 0.31 mg (R)-albuterol. The percentage of abnormal ECGs varied from 5% after administration of placebo to 15% after administration of 2.5 mg or racemic albuterol and 0.31 mg of (R)-albuterol.

QTc INTERVAL (ms)	Baseline Mean	One Hour Post-Treatment Mean	Difference ²
Placebo	421.1	413.0	-8.1 A
0.31 mg (R)-Albuterol	421.1	422.5	1.5 B
0.63 mg (R)-Albuterol	421.1	427.6	6.6 BC
1.25 mg (R)-Albuterol	421.1	433.2	12.1 C
2.5 mg Racemic Albuterol	421.1	429.2	8.2 BC

² Means with a letter in common are not significantly different at the 0.05 level (Fisher's protected LSD test).

◆ **Holter monitoring:** There were no significant differences in heart rate after administration of 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol at any time period. Heart rate was increased during the first 30 minutes following administration of albuterol, relative to placebo and there was a dose-response relationship with respect to increasing heart rate with increasing doses of (R)-albuterol.

◆ **laboratory tests:** Mean serum glucose levels were significantly increased after administration of all albuterol treatments compared with placebo, which was decreased (see tables below). Mean serum potassium levels remained the same or increased slightly relative to baseline for all albuterol treatments.

GLUCOSE (mg/dl)	Baseline Mean	Post-Treatment Mean	Difference ²
Placebo	101.8	94.8	-7 A
0.31 mg (R)-Albuterol	101.8	107.9	6.2 B
0.63 mg (R)-Albuterol	101.8	103.5	2.3 B
1.25 mg (R)-Albuterol	101.8	110.5	8.7 B
2.5 mg Racemic Albuterol	101.8	103.4	1.7 B

Note: t-statistics (above diagonal) and two-sided p-values (below diagonal) for comparison of least squares means (Fisher's protected LSD test)

GLUCOSE (mg/dl)	Placebo	0.31 mg (R)-Albuterol	0.63 mg (R)-Albuterol	1.25 mg (R)-Albuterol	2.5 mg Racemic Albuterol
Placebo	-	-3.20	-2.13	-3.83	-2.11
0.31 mg (R)-Albuterol	0.002	-	1.02	-0.62	1.10
0.63 mg (R)-Albuterol	0.04	0.31	-	-1.63	0.06
1.25 mg (R)-Albuterol	0.000	0.54	0.11	-	1.72
2.5 mg Racemic Albuterol	0.04	0.28	0.96	0.09	-

² Means with a letter in common are not significantly different at the 0.05 level (Fisher's protected LSD test).

◆ vital signs: There were no clinically or statistically significant changes in vital signs either prior to treatment or following treatment, although the greatest effect was seen after administration of 1.25 mg of (R)-albuterol (see tables below).

PULSE (bpm)	Pre-Treatment Mean	Post-Treatment Mean	Difference ²
Placebo	73.3	76.3	0.2 A
0.31 mg (R)-Albuterol	81.1	77.6	0.1 A
0.63 mg (R)-Albuterol	77.6	78.7	0.0 A
1.25 mg (R)-Albuterol	76.7	81.5	0.0 A
2.5 mg Racemic Albuterol	78.4	81.2	0.1 A

SYSTOLIC BP (mm Hg)	Pre-Treatment Mean	Post-Treatment Mean	Difference ²
Placebo	114.9	118.1	2.8 A
0.31 mg (R)-Albuterol	118.4	118.9	-0.2 A
0.63 mg (R)-Albuterol	119.9	119.5	-0.4 A
1.25 mg (R)-Albuterol	115.9	123.4	7.6 A
2.5 mg Racemic Albuterol	116.7	118.8	1.7 A

DLASTOLIC BP (mm Hg)	Pre-Treatment Mean	Post-Treatment Mean	Difference ²
Placebo	74.7	76.5	1.9 A
0.31 mg (R)-Albuterol	72.4	75.6	3.2 A
0.63 mg (R)-Albuterol	75.2	74.3	-0.9 A
1.25 mg (R)-Albuterol	74.5	77.8	3.4 A
2.5 mg Racemic Albuterol	74.4	76.2	1.6 A

² Means with a letter in common are not significantly different at the 0.05 level (Fisher's protected LSD test).

CONCLUSIONS: There were no clinically significant differences in terms of mean FEV-1 over the 6 hour period of evaluation after administration of 0.63 mg of (R)-albuterol, 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol. Onset of effectiveness and duration of effectiveness were comparable after administration of these three treatments. The proposed dosing interval is supported by this study, based on mean percent change from baseline for FEV-1.

Although there were no serious or unexpected adverse events noted after administration of (R)-albuterol, the incidence of adverse events was less after administration of 0.63 mg of (R)-albuterol than after administration of 1.25 mg (R)-albuterol and 2.5 mg racemic albuterol. The greatest increase in the QTc interval was seen in patients who received 1.25 mg of (R)-albuterol. Increase in serum glucose was also greatest after administration of 1.25 mg of (R)-albuterol, as were heart rate and blood pressure. The changes in these parameters that were seen after administration of 1.25 mg of (R)-albuterol are consistent with the changes that can be seen after administration of other beta agonists and are not clinically significant. Moreover, 1.25 mg of (R)-albuterol is proposed only for patients with more severe asthma, where the potential benefits should outweigh any increased risk.

The data from this study suggests that 0.63 mg of (R)-albuterol produces the same degree of efficacy, based on change in FEV-1, as 1.25 mg of (R)-albuterol, and less systemic effect, based on adverse events, serum glucose, QTc interval and vital signs. Therefore, the 0.63 mg dose of (R)-albuterol has a better benefit:risk ratio than the 1.25 mg dose, based on this study's data.

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ABSTRACT OF STUDY 024

METHODS: This randomized, double-blind, placebo and active treatment-controlled repetitive dose study compared the response in 362 adult patients with moderate asthma to (R)-albuterol at doses of 0.625 and 1.25 mg TID and racemic albuterol at doses of 1.25 and 2.5 mg TID over a period of 4 weeks. Patients were evaluated in regard to change in FEV-1 over 8 hours after drug administration compared with prestudy baseline after the first dose and with both prestudy and onstudy baselines when evaluated after 2 and 4 weeks of treatment. In addition, comparison of onstudy baselines were made with the prestudy baseline. Treatment arms were also compared in terms of other pulmonary function parameters, as well as patient peak flow measurements, use of rescue medication, symptoms, corticosteroid use, and withdrawals due to lack of efficacy. The primary efficacy variable was the peak change in FEV-1 after 4 weeks of treatment relative to the onstudy baseline. Safety was assessed by adverse events, vital signs, laboratory tests, and ECGs.

RESULTS: A dose of 0.625 mg of (R)-albuterol was comparable to 2.5 mg of racemic albuterol in terms of onset of action, peak effect, AUC, and duration of action based on change from baseline in FEV-1. A dose of 1.25 mg of (R)-albuterol produced more bronchodilatation (as measured by peak effect and AUC based on FEV-1 change from baseline) than 2.5 mg of racemic albuterol. Significant bronchodilatation over an 8 hour period after drug administration was demonstrated for both the 0.625 and the 1.25 mg dose of (R)-albuterol.

The same degree of bronchodilatation was demonstrated for 8 hours after administration of 0.625 and 1.25 mg of (R)-albuterol at a time when the drug had been administered at these doses TID for 2 and 4 weeks. In addition, there was an increase from the prestudy baseline to the onstudy baseline after 4 weeks of treatment with 0.625 mg (6%) and 1.25 mg (7%) of (R)-albuterol. Although there was an increase in the onstudy baseline in the placebo group of 6% after 4 weeks of treatment, no significant increase in the onstudy baseline was seen in either of the groups receiving racemic albuterol after 4 weeks of treatment. There was a further increase in the onstudy baseline in all treatment groups at week 5, i.e. 1 week after the last dose of albuterol.

The response to the different treatment arms was not significantly different when evaluated in terms of change in FVC or FEF 25-75. The mean peak change in FEV-1 after 4 weeks of treatment was generally higher in patients 12-16 years of age and in patients not receiving corticosteroids, although this pattern was not seen in the 2.5 mg racemic albuterol group in terms of age or in the 1.25 mg racemic albuterol group in terms of corticosteroid use.

Use of rescue medication was greater in patients who received racemic albuterol than in the patients who received (R)-albuterol. The number of symptom-free days was greatest in the 1.25 mg (R)-albuterol group, while the number of symptom-free days in the 2.5 mg racemic albuterol and placebo groups was not statistically different. There was less nocturnal awakenings due to wheeze and cough in the 1.25 mg (R)-albuterol group during each week of treatment, and symptoms were generally less severe in this group, especially during the last week of treatment. Use of oral corticosteroids for > 5 consecutive days was necessary in 2 patients in the 0.625 mg (R)-albuterol, the 1.25 mg (R)-albuterol and the 1.25 mg racemic albuterol groups, while no patients in the 2.5 mg racemic albuterol group required this amount of oral corticosteroids. There were 2 patients, one in the 1.25 mg (R)-albuterol group and one in the placebo group who withdrew because of perceived lack of efficacy.

The 1.25 mg dose of (R)-albuterol produced a greater number of nervous system adverse effects, especially anxiety, dizziness, and tremor than did the 2.5 mg dose of racemic albuterol. No such adverse effects were seen in the placebo group. One patient developed non-specific T wave abnormalities associated with numbness of the left hand after the first dose of 1.25 mg (R)-albuterol. Another patient developed ST-T wave changes 2-3 hours after receiving the first dose of 1.25 mg of (R)-albuterol but remained in the study without recurrence. There were a slightly greater number of patients in the 1.25 mg (R)-albuterol as compared to the 2.5 mg racemic albuterol group who had an increase in serum glucose from normal to above the upper limit of the normal reference range after treatment. There was also a slightly greater mean change in heart rate seen after the first dose of 1.25 mg of (R)-albuterol as compared to the first 2.5 mg dose of racemic albuterol. No clinically significant difference in prolongation of the QTc interval was noted after

administration of the 1.25 mg dose of (R)-albuterol compared with other active treatment groups.

DISCUSSION: The sponsor has demonstrated the comparative efficacy of (R)-albuterol and racemic albuterol in reversing bronchoconstriction (producing bronchodilatation). Specifically, 0.625 mg of (R)-albuterol was demonstrated to be comparable to 2.5 mg of racemic albuterol and 1.25 mg of (R)-albuterol produced more bronchodilatation than 2.5 mg of racemic albuterol. The sponsor has demonstrated the ability of (R)-albuterol to produce bronchodilatation acutely following the first dose, without a decrease in this ability after 2 and 4 weeks of treatment. There is, in addition, a suggestion that (R)-albuterol produces chronic bronchodilatation, based on an increase in the onstudy baseline for FEV-1 of 6-7% from prestudy baseline after 4 weeks of treatment, which increased further 1 week after (R)-albuterol was discontinued. The increase in onstudy baseline was significantly less in the groups which received racemic albuterol. The sponsor has not demonstrated that (R)-albuterol prevents bronchoconstriction because the study was not designed to do so. The recommended dose for racemic albuterol solution for nebulization is 2.5 mg TID or QID. Since a dose of 0.625 mg of (R)-albuterol TID produced the same degree of bronchodilatation as 2.5 mg of racemic albuterol in this study, the dose and dosing interval are appropriate for patients 12 years of age and older. Since a dose of 1.25 mg of (R)-albuterol produced a greater degree of bronchodilatation than 0.625 mg of (R)-albuterol, it is appropriate to recommend that this dose be used for patients with more severe disease. The use of the 1.25 mg dose of (R)-albuterol should, however, be accompanied by a careful benefit:risk assessment, especially from a cardiac standpoint, since the safety data from this study indicates that a greater systemic effect can be seen with this dose.

After submission of this NDA, it was determined by the sponsor that one site for this study (Edwards site) was flawed (numerous altering of ECG tracings, possible fabrication of chest x-ray report). An internal audit by the sponsor concluded that the integrity of the data had been maintained. The sponsor was, nevertheless, asked to analyze the data from this study excluding this site. There were no clinically significant changes in the efficacy or safety data when the study was reanalyzed excluding the Edwards site. Therefore,

interpretation of the data from this study was not changed because of this finding.

In summary, the sponsor has demonstrated that a dose of 0.625 mg of (R)-albuterol is safe and effective, and comparable in effect to the recommended dose of nebulized albuterol, 2.5 mg, when given acutely. A dose of 1.25 mg of (R)-albuterol produces a slightly greater effect locally and systemically than 2.5 mg of racemic albuterol but is safe and effective for treatment of patients with more severe asthma, especially if they have not responded adequately to a dose of 0.625 mg of (R)-albuterol. The proposed TID dosing interval is supported by the 8 hour duration of action. With chronic administration, there is no deterioration of asthma and some improvement, based on symptoms and use of rescue medication, especially in the 1.25 mg (R)-albuterol group. There is also a suggestion that patients may do better with chronic administration of (R)-albuterol than with racemic albuterol, based on improvement in onstudy baseline FEV-1.

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◆ REPETITIVE DOSE STUDY ◆

- **Study 024:** A phase III randomized, double-blind, placebo-controlled parallel-group study to evaluate (R)-albuterol in terms of effectiveness in reversing bronchoconstriction, preventing bronchoconstriction and in the safe management of asthma.

◆ STUDY CHARACTERISTICS:

- number of patients:** 424 enrolled; 362 randomized to treatment; 328 patients completed the study
- age range:** 12-80 years
- patient population:** asthma; FEV-1 45%-70% predicted; stable on medication for at least 6 months; stable dose of inhaled sympathomimetic for 90 days and stable dose of inhaled corticosteroids for 30 days prior to the study; see table below for disallowed medications

Disallowed Medications	
Drug	Withdrawal Time (Prior to Visit 1)
<u>Corticosteroids</u>	
parenteral	≥ 8 weeks
oral	≥ 2 weeks
<u>Theophylline</u>	
short-acting	≥ 12 hours
BID controlled release	≥ 24 hours
QD controlled release	≥ 36 hours
<u>Adrenergic bronchodilators</u>	
Nebulized or inhaled, short-acting	≥ 8 hours
Oral TID or QID preparations	≥ 24 hours
Oral BID preparations	≥ 36 hours
Inhaled, long acting	≥ 24 hours
Ipratropium bromide (Atrovent)	≥ 24 hours
Nonprescription asthma medications	≥ 7 days
Cromolyn sodium, nedocromil sodium	≥ 7 days

- study design:** randomized, double-blind, placebo-controlled, parallel, multicenter, repetitive dose study
- drug administration:** 0.625 mg or 1.25 mg of R-albuterol; 1.25 mg or 2.5 mg of racemic albuterol as a nebulized solution TID; albuterol MDI as rescue medication; single use vials containing 3 ml; administered by PARI LC PLUS nebulizer with a DURA-NEB 200 Portable compressor; patients were instructed to allow a minimum of 4 hours between doses, with the first dose in the morning after the morning PEF, the second dose in the afternoon, and the third dose in the evening h.s.
- periods of study:** 1 week of single-blind treatment with placebo followed by 4 weeks of randomized treatment which was in turn followed by 1 week of single-blind treatment with placebo; there were 5 visits, a screening visit, 3 treatment visits (week 0, week 2, and week 4)(visits 2-4)
- parameters evaluated:** see flow chart below.

Schedule of Assessments

	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5
Week	-1	0	2	4	5
Informed Consent	X				
Medical History	X				
Physical Exam	X				
Vital Signs	X	X	X	X	X
Chest X-ray	X ^a				
Laboratory Tests	X	X	X	X	X
Pregnancy Test	X				
Randomization		X		X	
12-lead ECG	X	X ^d	X ^d	X ^d	X
Non-serial PFTs	X				X
Serial PFTs		X ^e	X ^e	X ^e	X
Review Diary Card		X	X	X	X
Issue Diary Card	X	X	X	X	X
Review AEs		X	X	X	X
Review Concurrent Meds	X	X	X	X	X
Dispense Study Drug	X	X	X	X	X
Collect Previous Medication		X	X	X	X
Dispense Compressor, Nebulizer	X				
Inspect and Dispense Albuterol MDI	X	X ^f	X ^f	X ^f	
Inspect Nebulizer		X	X	X	X

^a Vital signs were recorded prior to dosing and at 15, 30 and 60 minutes post-dose and then hourly for 6 hours thereafter.

^b The most recent chest X-ray taken within 12 months of Visit 1 was allowable.

^c Electrolyte and glucose levels were determined prior to dosing and at 60 minutes post-dose.

^d An electrocardiogram (standard 12-lead ECG) was performed prior to the pre-dose PFT and at 15, 30, 60, 120 and 180 minutes post-dose.

^e Spirometry was performed prior to dosing, immediately post-dose, 15 minutes post-dose, at 30 minute intervals for the first 2 hours and hourly for 6 hours thereafter.

^f New albuterol MDI was dispensed as needed.

EFFICACY: The primary efficacy endpoint was the peak change in FEV-1 after 4 weeks of treatment relative to visit baseline; secondary analysis evaluated the peak change in FEV-1 after 4 weeks of treatment relative to the study baseline (week 0); secondary analyses included peak change in FEV-1 at week 0 and week 2, as well.

- **spirometry: (FEV-1, FVC, FEF 25-75):** single spirometric measurements were obtained at visits 1 and 5; serial spirometry for 8 hours was done at visits 2-4, prior to drug administration, immediately after drug administration, 15 minutes after drug administration, every 30 minutes for the first two hours and hourly for 6 hours thereafter; AUC under the FEV-1 curve was a secondary efficacy outcome variable.
- **AM and PM PEFr:** recorded on diary card daily
- **use of rescue medication:** recorded on diary card daily
- **rates of acute exacerbations:** an exacerbation of asthma was defined as a worsening of asthma symptoms or pulmonary function requiring therapeutic intervention.
- **use of oral corticosteroids:** patients were allowed to receive one course of oral corticosteroids for 5 continuous days at a maximum of 40 mg per day.
- **symptom scores:** recorded on diary card daily; scale of 0-4 used for individual symptoms (0 = none, 1 = barely noticeable, 2 = noticed from time to time, 3 = noticed often and interfere with daily routine, and 4 = present most of the day and radically changed daily routine; the total asthma symptom score was based on a scale of 0-3 with 0 = none, 1 = mild, 2 = moderate and 3 = severe.
- **withdrawals due to initiation or increase in dose of oral corticosteroids or withdrawal due to perceived lack of efficacy;** a survival plot was used for visual comparison

SAFETY:

- **adverse events**
- **vital signs: prior to drug administration on visits 2-4 and then at 15, 30, and 60 minutes after drug administration and then hourly for 7 hours; at visit 5 (at the end of the placebo run-out period)**
- **laboratory tests: prior to drug administration at visits 2 and 3; prior to drug administration for electrolytes and glucose only at visit 4; in addition, at visits 2, 3, and 4 electrolytes and glucose were obtained 60 minutes after drug administration; at visit 5 (at the end of the placebo run-out period) laboratory tests were repeated.**
- **ECGs: prior to drug administration and pulmonary function testing and then at 15, 30, 60, 120, and 180 minutes after drug administration at visits 2-4; an ECG was also done at visit 5 (at the end of the placebo run-out period)**

Statistical Considerations:

- **All efficacy analyses were performed on the ITT population; the primary efficacy endpoint was also analyzed using the "efficacy population" defined as all patients who completed 4 weeks of double-blind treatment without major protocol violations. Analyses were done as well after stratifying for concomitant use of corticosteroids, age, gender and ethnic background. If patients used rescue medication during serial spirometry, the PFTs recorded on and after the time of rescue were not included in the efficacy analysis.**
- **Treatment groups were compared for differences in peak change in FEV-1 based on analysis of variance comparing the week 4 mean peak change in FEV-1 to the visit FEV-1 before treatment; as a secondary analysis, peak change in FEV-1 at week 0 and after 2 weeks of treatment were**

compared to the FEV-1 prior to treatment on that visit; in addition, peak change in FEV-1 after 2 and 4 weeks of treatment were compared to baseline FEV-1.

- For all end-of-study data, categorical data were summarized using the frequency and percentage of patients with a particular attribute. Continuous data were summarized using descriptive statistics including the mean, median, standard deviation, range and number of patients.

◆ **STUDY RESULTS:**

□ **Disposition of Patients:** see table below.

Subject Disposition.

	Treatment Group					Total (n=362)
	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	placebo (n=75)	
Number of Subjects						
Completed Study	68 (94.4%)	62 (84.9%)	63 (92.6%)	68 (91.9%)	67 (89.3%)	328 (77.4%)
Terminated Study	4 (5.6%)	11 (15.1%)	5 (7.4%)	6 (8.1%)	8 (10.7%)	34 (9.4%)
Last Completed Visit Week						
Week 0	3 (4.2%)	8 (11.0%)	5 (7.4%)	4 (5.4%)	4 (5.3%)	24 (6.6%)
Week 2	1 (1.4%)	3 (4.1%)	0 (0.0%)	1 (1.4%)	3 (4.0%)	8 (2.2%)
Week 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.3%)	2 (0.6%)
Week 5	68 (94.4%)	62 (84.9%)	63 (92.6%)	68 (91.9%)	67 (89.3%)	328 (90.6%)
Reason for Early Termination After Randomization						
Adverse Event	3 (4.2%)	8 (11.0%)	2 (2.9%)	4 (5.4%)	5 (6.7%)	22 (6.0%)
Major Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	2 (0.5%)
Voluntarily Withdrew	1 (1.4%)	1 (1.4%)	2 (2.9%)	1 (1.4%)	0 (0.0%)	5 (1.4%)
Lost to Follow-Up	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Treatment Failure	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (0.5%)
Other	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.4%)	0 (0.0%)	2 (0.5%)

Note: Subjects participating through Week 4 completed the double-blind treatment period. Subjects completing Week 5 completed the study without terminating early.

Reference: Sections 14.1.2 and 14.1.3.

COMMENT: *There were more patients who were withdrawn from the study because of an adverse event after randomization in the 1.25 mg (R)-albuterol group than in the other treatment groups, 4 of whom were withdrawn within the first week of*

double-blind treatment for adverse events potentially related to the study drug. The sponsor is proposing a usual dose of 0.63 mg in the labeling for this drug product, with use of 1.25 mg only for those patients with more severe disease where the potential benefits outweigh any increased risk. This is appropriate (see discussion under Adverse Events in this review).

- Protocol Deviations:** The protocol deviations which resulted in exclusion of patients from the efficacy analysis can be seen in the table below.

Protocol Deviations Resulting in Exclusion from Efficacy Analysis.

Protocol Deviation	Treatment Group					Total (n=362)
	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	placebo (n=75)	
Violation of Inclusion Criterion 3 (FEV ₁ out of Range)	1 (1.4%)	2 (2.7%)	1 (1.5%)	2 (2.7%)	2 (2.7%)	8 (2.2%)
Compliance <80% for the Double-Blind Treatment Period	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	3 (4.0%)	4 (1.1%)

Reference: Section 14.1.4.

COMMENT: *The protocol deviations which occurred were neither sufficiently great in number nor related to one treatment group to have affected the analysis of this study.*

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□ Demographics: see table below

Subject Demographics						
	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	placebo (n=75)	All Subjects (n=362)
Age						
Mean (SD)	36.2 (13.94)	35.0 (13.34)	37.9 (14.58)	38.3 (15.94)	35.2 (14.61)	36.5 (14.50)
Min, Max	13.0, 75.0	12.0, 72.0	13.0, 74.0	13.0, 80.0	12.0, 78.0	12.0, 80.0
Sex						
Male	26 (36.1%)	35 (47.9%)	28 (41.2%)	28 (37.8%)	29 (38.7%)	146 (40.3%)
Female	46 (63.9%)	38 (52.1%)	40 (58.8%)	46 (62.2%)	46 (61.3%)	216 (59.7%)
Race						
Caucasian	62 (86.1%)	60 (82.2%)	60 (88.2%)	65 (87.8%)	59 (78.7%)	306 (84.5%)
Black	8 (11.1%)	6 (8.2%)	6 (8.8%)	6 (8.1%)	6 (8.0%)	32 (8.8%)
Asian	0	1 (1.4%)	2 (2.7%)	2 (2.7%)	0	4 (1.1%)
Hispanic	2 (2.8%)	5 (6.8%)	1 (1.5%)	0	7 (9.3%)	15 (4.1%)
Other	0	1 (1.4%)	0	1 (1.4%)	3 (4.0%)	5 (1.4%)
Height (cm)						
Mean (SD)	168.4 (9.10)	170.4 (9.98)	168.2 (8.70)	167.7 (9.25)	166.1 (9.49)	168.2 (9.38)
Weight (kg)						
Mean (SD)	79.8 (20.43)	79.8 (16.67)	76.8 (20.21)	76.1 (15.59)	78.2 (22.52)	78.2 (19.20%)
FEV ₁ Percent of Predicted						
Mean (SD)	60.0 (8.32)	60.0 (7.29)	60.0 (6.91)	59.5 (7.29)	59.7 (7.62)	59.8 (7.47)
Min, Max						
FEV ₁ Percent Reversibility						
Mean (SD)	40.9 (19.80)	41.6 (22.31)	39.9 (21.33)	39.7 (19.75)	37.1 (17.37)	39.8 (20.10)
Min, Max						

Reference: Section 14.1.5.2

COMMENTS: *The PEF was higher during the placebo run-in period in the group which received 1.25 mg of (R)-albuterol than in the other treatment groups, a mean value of 346 L/min with a maximum of 609 L/min compared to the other groups which had a mean of 304-323 L/min and a maximum value of [redacted] L/min. This is supported by the symptom assessment in the run-in week during which there were significantly less patients in the 1.25 mg (R)-albuterol group who had severe symptomatology. This suggests that the 1.25 mg (R)-albuterol group had somewhat milder asthma than the other treatment groups, and, therefore, might not be capable of responding as much as the groups which had lower PEF values and/or less symptomatology. In this reviewer's opinion, this difference in baseline severity is not likely to have influenced the study results. In fact, the 1.25 mg (R)-*

albuterol group showed the greatest degree of improvement.

The racemic albuterol 1.25 mg group had a significantly greater percentage of patients with asthma duration greater than 15 years; 71% compared to 56% in the (R)-albuterol groups and 57% in the placebo group. It could be argued that this discrepancy in some way biased the study results.

However, it is not clear that greater duration of asthma can be equated with more severe asthma or that the response in more severe asthmatics, if indeed such were the case, to inhaled beta agonists is likely to be more or less than in patients with less severe asthma. Therefore, it is unlikely that this difference in asthma duration influenced the study results significantly.

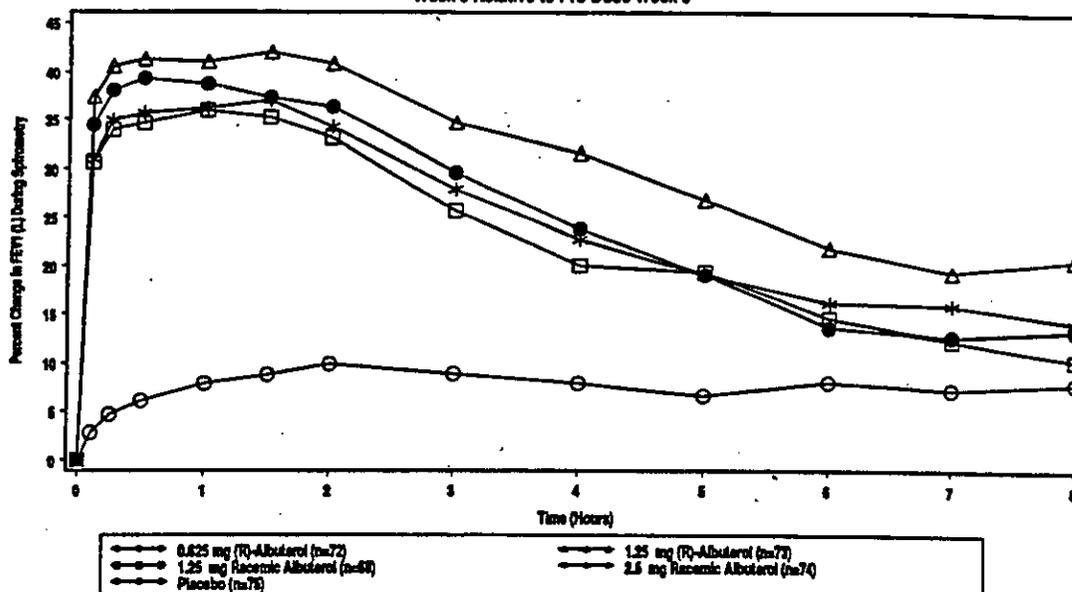
- Center issues:** There were 32 centers. At 6 centers, there were no patients in at least one of the five treatment groups. Of these centers, 5 enrolled between 1-6 patients and a total of 16 patients.

COMMENT: *After discussion with our statisticians, it is acceptable to include patients from centers which did not have patients in each treatment group, in the overall analysis. There is no indication by the sponsor of any attempt to pool the data from centers with small numbers of patients. Nevertheless, it is unlikely that the inclusion in the analysis of the 16 patients from the 5 centers which did not have patients in each treatment group significantly changed the conclusions which can be drawn from this study.*

Efficacy Evaluation:

- **change in FEV-1 over 8 hours following the first dose of study medication (see figure and table below).**

Summary of Percent Change in FEV1 Over Time
Week 0 Relative to Pre-Dose Week 0



- ◆ There was a clinically significantly greater response with both doses of the R enantiomer and the racemic mixture of albuterol than there was with placebo.
- ◆ This difference in response lasted for 6 hours with the 1.25 mg dose of racemic albuterol, for 6 hours with the 0.625 mg dose of (R)-albuterol, for 8 hours with the 2.5 mg dose of racemic albuterol and for 8 hours with the 1.25 mg dose of (R)-albuterol.
- ◆ In terms of peak effect, 0.65 mg and 1.25 mg of (R)-albuterol had a greater effect than either dose of racemic albuterol.
- ◆ Onset of action was immediate and was essentially the same for both doses of racemic albuterol and (R)-albuterol.

- ◆ The AUC was comparable for the 2.5 mg dose of racemic albuterol and the 0.625 mg dose of (R)-albuterol.
- ◆ The AUC was greater with the 1.25 mg dose of (R)-albuterol than with the 2.5 mg dose of the racemic mixture.
- ◆ The AUC was greater for the 0.625 mg dose of (R)-albuterol than for the 1.25 mg dose of racemic albuterol.

Summary of Percent Change in FEV₁ from Study Baseline⁽¹⁾ - Week 0

	-Treatment Group				
	(R)-albuterol 0.625 mg	(R)-albuterol 1.25 mg	racemic albuterol 1.25 mg	racemic albuterol 2.5 mg	placebo
Immediately Post Dose					
Mean (SD)	34.4 (20.74)	37.3 (22.48)	30.7 (19.47)	30.9 (19.16)	2.8 (15.02)
n	69	73	68	73	75
Post-15 Minutes					
Mean (SD)	38.1 (21.90)	40.6 (24.17)	33.9 (21.25)	34.8 (21.43)	4.7 (16.85)
n	71	73	68	74	74
Post-30 Minutes					
Mean (SD)	39.3 (23.34)	41.3 (24.92)	34.6 (22.58)	35.6 (20.26)	6.1 (18.52)
n	72	73	68	73	75
Post-60 Minutes					
Mean (SD)	38.7 (22.58)	41.0 (25.81)	35.9 (20.89)	36.1 (21.09)	7.9 (17.78)
n	72	73	68	74	73
Post-90 Minutes					
Mean (SD)	37.3 (23.03)	42.0 (26.78)	35.2 (21.37)	37.0 (22.28)	8.8 (17.87)
n	70	72	67	73	67
Post-2 Hours					
Mean (SD)	36.3 (23.15)	40.9 (24.81)	33.1 (20.73)	34.2 (22.51)	9.9 (17.44)
n	72	73	68	74	70
Post-3 Hours					
Mean (SD)	29.7 (20.93)	34.6 (24.31)	25.7 (19.65)	28.0 (23.82)	8.9 (19.71)
n	71	73	68	74	70
Post-4 Hours					
Mean (SD)	23.9 (20.03)	31.6 (24.93)	20.1 (19.22)	22.8 (22.51)	7.9 (17.94)
n	70	72	68	74	69
Post-5 Hours					
Mean (SD)	19.2 (19.35)	26.9 (23.55)	19.4 (17.96)	19.2 (20.22)	6.7 (16.46)
n	69	72	65	73	68
Post-6 Hours					
Mean (SD)	13.7 (20.94)	21.9 (21.34)	14.6 (18.68)	16.2 (19.39)	8.0 (20.36)
n	66	69	65	72	65
Post-7 Hours					
Mean (SD)	12.7 (20.42)	19.4 (22.52)	12.4 (17.13)	15.9 (18.13)	7.3 (18.38)
n	66	68	63	67	63
Post-8 Hours					
Mean (SD)	13.5 (21.88)	20.8 (22.81)	10.4 (17.93)	14.3 (18.83)	8.0 (19.01)
n	63	68	60	67	62

⁽¹⁾ Percent change in forced expiratory volume from pre-dose Week 0.
Reference: Summarized from Section 14.2.1.7.

Analysis of data excluding the Edwards site:

◆ As noted in the abstract of this study (see page 97), there was no clinically significant changes in the efficacy or safety data when the study was reanalyzed excluding the Edwards site. As an example, the percent change from study baseline in FEV-1 and the mean peak change in FEV-1 relative to visit pre-dose measurement after 4 weeks of treatment (the primary efficacy variable) with exclusion of the Edwards site can be seen in the tables below (they should be compared with the tables on pages 108 and 111).

Table 14.2.1.7
Summary of Percent Change in FEV1 from Study Baseline (1)
Week 0

	Treatment Group				
	(R)-Albuterol 0.625 mg (n= 67)	(R)-Albuterol 1.25 mg (n= 68)	Racemic Albuterol 1.25 mg (n= 64)	Racemic Albuterol 2.5 mg (n= 70)	Placebo (n= 70)
Immediately Post-Dose					
Mean (SD)	34.4 (21.21)	30.5 (22.37)	30.9 (19.02)	30.6 (18.45)	3.0 (15.42)
Min, Max	-6.0, 85.6	-2.7, 88.1	-4.1, 82.5	-0.2, 75.0	-22.7, 76.6
n	64	65	64	69	70
Post-15 Minutes					
Mean (SD)	28.3 (22.55)	41.6 (24.51)	34.2 (21.70)	34.0 (19.00)	4.0 (17.20)
Min, Max	0.0, 88.0	-13.6, 91.3	-4.1, 95.9	0.7, 75.0	-22.1, 72.0
n	66	65	64	70	69
Post-30 Minutes					
Mean (SD)	29.7 (24.06)	42.1 (25.35)	34.4 (22.53)	35.0 (18.90)	6.0 (19.00)
Min, Max	-1.2, 109.9	-25.2, 94.9	-14.2, 99.0	0.7, 81.1	-20.3, 86.2
n	67	68	64	69	70
Post-60 Minutes					
Mean (SD)	28.9 (23.32)	42.0 (26.17)	36.3 (21.27)	25.5 (19.34)	7.2 (18.10)
Min, Max	-1.6, 93.0	-7.6, 99.3	2.0, 96.4	-4.5, 83.1	-24.2, 81.5
n	67	68	64	70	68
Post-90 Minutes					
Mean (SD)	27.2 (23.07)	42.6 (26.06)	35.2 (21.64)	26.4 (20.81)	9.0 (18.17)
Min, Max	-1.1, 113.4	-0.7, 98.1	0.0, 94.4	-17.2, 93.9	-26.2, 86.2
n	65	68	63	69	63
Post-2 Hours					
Mean (SD)	26.0 (22.72)	41.0 (25.20)	33.2 (20.94)	22.6 (21.27)	10.1 (17.72)
Min, Max	-6.0, 119.7	-2.2, 100.7	-4.0, 92.4	-26.9, 87.2	-32.0, 75.2
n	67	68	64	70	65
Post-3 Hours					
Mean (SD)	29.4 (21.59)	35.5 (24.69)	26.0 (20.06)	27.5 (22.74)	9.2 (20.02)
Min, Max	-16.9, 91.5	-19.7, 106.5	-7.0, 87.5	-44.0, 84.6	-19.6, 83.3
n	66	68	64	70	65
Post-4 Hours					
Mean (SD)	24.0 (20.42)	32.2 (25.22)	20.2 (19.64)	22.6 (21.02)	7.0 (18.28)
Min, Max	-25.0, 69.7	-9.8, 114.4	-26.2, 85.0	-36.7, 83.1	-25.0, 82.7
n	63	67	64	70	64
Post-5 Hours					
Mean (SD)	19.0 (19.94)	27.2 (24.07)	20.0 (18.20)	19.1 (19.09)	6.2 (16.01)
Min, Max	-20.7, 68.0	-18.2, 96.1	-11.1, 76.4	-27.1, 85.0	-38.8, 81.5
n	64	67	61	69	63
Post-6 Hours					
Mean (SD)	12.0 (21.28)	22.4 (21.07)	15.0 (18.20)	16.3 (19.62)	7.6 (21.22)
Min, Max	-29.9, 63.0	-19.9, 82.1	-16.6, 76.4	-24.4, 81.1	-37.0, 82.0
n	63	64	61	69	60
Post-7 Hours					
Mean (SD)	12.0 (20.84)	20.0 (23.02)	12.5 (17.40)	15.7 (18.12)	6.5 (18.07)
Min, Max	-31.5, 67.3	-20.2, 83.5	-28.0, 72.2	-27.5, 73.0	-32.7, 86.4
n	63	63	61	64	58
Post-8 Hours					
Mean (SD)	12.2 (22.10)	21.5 (22.24)	10.9 (18.05)	14.2 (18.97)	7.6 (19.61)
Min, Max	-45.7, 60.3	-26.9, 87.9	-29.1, 82.5	-24.2, 83.0	-32.8, 76.2
n	61	63	58	64	57

(1) Percent change in forced expiratory volume from pre-dose Week 0.

Table 14.2.1.10
Comparison of Mean Peak Change in FEV1 Relative to Visit Pre-Dose
Week 4

	Treatment Group					Overall p-value {2}	Pairwise p-value {3}
	(R)-Albuterol 0.625 mg (n= 67)	(R)-Albuterol 1.25 mg (n= 68)	Racemic Albuterol 1.25 mg (n= 64)	Racemic Albuterol 2.5 mg (n= 70)	Placebo (n= 70)		
Peak Change in FEV1 {1}							
Mean (SD)	0.70 (0.37)	0.75 (0.36)	0.67 (0.41)	0.77 (0.41)	0.24 (0.25)	<.0001	
LS Mean (SD)	0.71 (0.40)	0.75 (0.40)	0.67 (0.39)	0.79 (0.39)	0.25 (0.39)		
Min. Max	0.14, 1.56	0.25, 1.63	0.09, 1.74	0.09, 2.14	-0.50, 0.91		
n	63	57	60	65	62		
							0.625 mg (R) v P <.0001 1.25 mg (R) v P <.0001 1.25 mg (RS) v P <.0001 2.5 mg (RS) v P <.0001 (RS) v (R) 0.98

{1} Peak change in FEV1 refers to the peak change in forced expiratory volume in one second relative to pre-dose at Week 4.
 {2} Overall treatment test was conducted using an ANOVA. Effects included study site and treatment.
 {3} Pairwise tests of active treatment versus placebo and an overall test of racemic albuterol versus (R)-Albuterol (1 df) were presented if the overall test was significant.

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COMMENT: *Greater than twice the dose of racemic albuterol is needed to produce an effect comparable to a given dose of (R)-albuterol. There was still a 20% improvement in FEV-1 over baseline 8 hours after administration of 1.25 mg of (R)-albuterol. Not only is (R)-albuterol effective acutely at this dose but at both the 0.625 mg and the 1.25 mg dose, (R)-albuterol produces more bronchodilatation than twice the dose of racemic albuterol.*

However, the proposed dosage of (R)-albuterol is 0.63 mg TID, with the option of treating patients "with more severe disease" with a dosage of 1.25 mg TID. It is unclear how "more severe disease" will be defined. If "more severe disease" is defined as those patients who do not respond sufficiently to 0.63 mg TID, this would be acceptable.

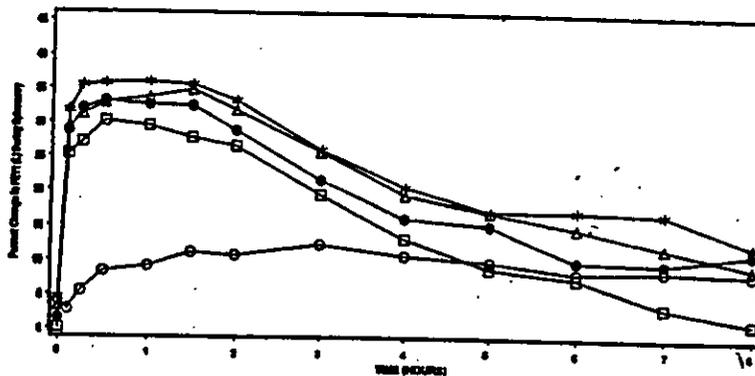
A dose of 0.63 mg of (R)-albuterol produced an increase in FEV-1 of 15% or greater for only 5 hours after administration. If TID is interpreted as every 5-6 hours while awake, then this dosage would be acceptable. If TID is strictly interpreted as q 8 hours, there would be concern about asthma control between 5-8 hours after chronic administration of (R)-albuterol at a dose of 0.63 mg., and in this situation a dose of 1.25 mg of (R)-albuterol should be used. On the other hand, the peak increase in FEV-1 from a dose of 0.63 mg of (R)-albuterol was essentially the same as the peak increase in FEV-1 from the higher dose of (R)-albuterol and the two doses of racemic albuterol. Therefore, a dose of 0.63 mg of (R)-albuterol is adequate for acute management of asthma, at least in the patient population evaluated in this study. The labeling should be changed to indicate: 1) the dose that is recommended acutely; and 2) based on the above comments, dosage considerations in regard to chronic administration, e.g. that drug administration should be every 6 hours while awake and if administered every 8 hours on a regular basis, the effect may be diminished at times beyond 5 hours after administration.

Change in FEV-1 over 8 hours after drug administration at weeks 2 and 4, i.e. after 2 and 4 weeks of treatment, compared to baseline FEV-1 prior to the first administration at week 0 can be seen in the figures below.

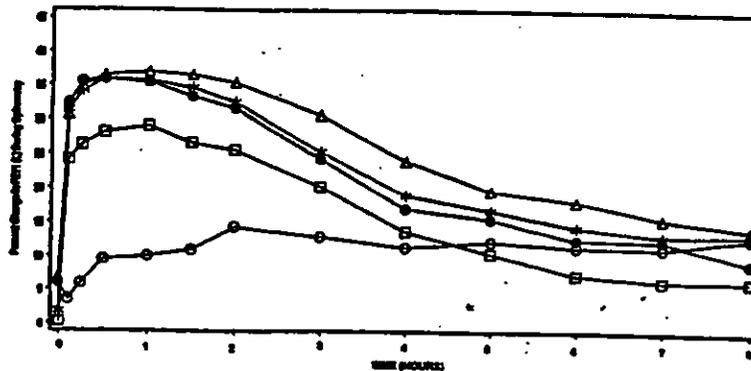
◆ The AUC after 2 weeks of treatment is very similar to the AUC after administration of the first dose for all treatments, except that the 2.5 mg dose of the racemic mixture and the 1.25 mg dose of (R)-albuterol are more comparable after 2 weeks of treatment than they were after the first dose, in terms of increase in FEV-1 from baseline.

◆ The AUC after 4 weeks of treatment is almost identical for each treatment group to the AUC after administration of the first dose for that treatment group.

Summary of Percent Change in FEV₁ Over Time - Week 2 Relative to Pre-Dose Week 0



Summary of Percent Change in FEV₁ Over Time - Week 4 Relative to Pre-Dose Week 0



○—○—○ 0.625 mg (R)-albuterol (n=64)	△—△—△ 1.25 mg (R)-albuterol (n=62)
□—□—□ 1.25 mg racemic albuterol (n=63)	—●—●—● 2.5 mg racemic albuterol (n=69)
○—○—○ Placebo (n=68)	

COMMENT: *While the change in FEV-1 over the 8 hours after drug administration following 2 and 4 weeks of treatment compared to the baseline FEV-1 on the first day of treatment can be useful for comparison of the different treatment arms, it does not provide information about the additional improvement that can be seen after a higher baseline has been established at weeks 2 and 4. Therefore, the discussion below, regarding change in FEV-1 after 2 and 4 weeks of treatment when the baseline used is the pre-dose determination of FEV-1 at weeks 2 and 4 is more clinically relevant.*

• peak change in FEV-1 relative to pre-dose at week 4: see table below.

Comparison of Mean Peak Change in FEV₁ [L]

	Treatment Group					Overall p-value ^[2]	Pairwise p-value ^[3]
	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	Placebo (n=75)		
Peak Change in FEV₁ (relative to visit pre-dose)							
Week 0-							
Mean (SD)	0.86 (0.44)	0.98 (0.48)	0.82 (0.51)	0.81 (0.41)	0.36 (0.35)	<.0001 [†]	(RS) v (R)=0.0339
n	72	73	68	74	75		
Week 2							
Mean (SD)	0.73 (0.44)	0.75 (0.42)	0.70 (0.43)	0.71 (0.36)	0.30 (0.39)	<.0001	(RS) v (R)=0.58
n	69	65	63	70	70		
Week 4							
Mean (SD)	0.70 (0.38)	0.75 (0.36)	0.68 (0.41)	0.76 (0.41)	0.24 (0.25)	<.0001	(RS) v (R)=0.90
n	68	62	63	69	67		
Peak Change in FEV₁ (relative to study baseline)							
Week 2							
Mean (SD)	0.75 (0.49)	0.82 (0.50)	0.68 (0.48)	0.80 (0.45)	0.38 (0.43)	<.0001	(RS) v (R)=0.55
n	69	65	63	70	70		
Week 4							
Mean (SD)	0.80 (0.50)	0.87 (0.52)	0.67 (0.50)	0.80 (0.40)	0.38 (0.52)	<.0001	(RS) v (R)=0.13
n	68	62	63	69	67		

^[1] Peak change in FEV₁ refers to the peak change in forced expiratory volume in one second relative to pre-dose at Week 0 or pre-dose at each visit.

^[2] Overall treatment test was conducted using an ANOVA. Effects included study site, treatment and their interaction (if significant)

^[3] Pairwise tests of active treatment versus placebo and racemic albuterol versus (R)-albuterol were presented if the overall test was significant. Pairwise comparisons of active treatment vs placebo were <.0001 for all analyses

Reference: Summarized from Sections 14.2.1.10, 14.2.1.11, 14.2.1.12, 14.2.1.13, and 14.2.1.15.

- ◆ After 4 weeks of TID treatment, peak change in FEV-1 was comparable between all albuterol groups ($p = 0.9$) but statistically different from placebo ($p < 0.0001$), based on change from baseline at 4 weeks of treatment. This was also true after 2 weeks of treatment, based on change from baseline at 2 weeks. However, as discussed above, after the first dose (week 0), there was a statistically significant difference between (R)-albuterol and racemic albuterol ($p = 0.03$), with (R)-albuterol being superior to the racemic mixture.

- ◆ Except for the 1.25 mg dose of racemic albuterol, as might be anticipated, there was a greater increase in FEV-1 using the week 0 baseline than using the baseline for weeks 2 or 4. With continued treatment on a regular basis, if the duration of action of the active treatment lasts throughout the dosage interval, it would be expected that the baseline would be higher at weeks 2 and 4 than at week 0, and that there would be less room for improvement. This effect can be seen in the table below comparing week 0, week 2 and week 4 baselines.

Comparison of Mean Percent Change in Pre-Dose FEV₁ to Study Baseline.

	Treatment Group					Overall p-value ²¹
	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	Placebo (n=75)	
Percent Change in Pre-Dose FEV₁²⁰						
Week 2-Week 0						
Mean (SD)	1.6 (19.20)	3.3 (22.19)	0.1 (18.34)	4.5 (21.65)	4.1 (19.21)	0.77
n	69	65	63	70	70	
Within Treatment p-value ²¹	0.56	0.26	0.86	0.09	0.11	
Week 4-Week 0						
Mean (SD)	6.0 (21.89)	6.9 (24.53)	0.3 (21.11)	1.7 (21.57)	6.0 (25.01)	0.48
n	68	62	63	69	68	
Within Treatment p-value ²¹	0.05	0.0311	0.80	0.58	0.09	
Week 5-Week 0						
Mean (SD)	10.5 (22.42)	16.4 (24.49)	11.1 (21.45)	7.7 (21.33)	12.1 (27.23)	0.27
n	72	72	68	74	75	
Within Treatment p-value ²¹	0.0003	<0.0001	0.0002	0.0030	<0.0001	

¹⁹Overall treatment test was conducted using an ANOVA. Effects included study site and treatment.

²⁰Percent change in pre-dose FEV₁ refers to the mean change in FEV₁ levels from Week 0 at Week 2 (pre-dose), Week 4 (pre-dose), and Week 5, respectively, as a percentage of pre-dose at Week 0.

²¹P-values were computed using a paired t-test to compare differences in pre-dose FEV₁ values within each treatment group. The p-values were obtained from the test that each Least Squares Means was significantly different from 0. Reference: Summarized from Section 14.2.1.21.

COMMENT: *After 4 weeks of treatment, the mean percent change in the pre-dose baseline, compared to the baseline prior to the first dose was 6% in the 0.625 mg (R)-albuterol group and 7% in the 1.25 mg (R)-albuterol group. The baseline also improved by 6% in the placebo group after 4 weeks. Interestingly, the baseline after 4 weeks did not improve to the same degree after receiving racemic albuterol, 0.3% and 1.7% in the 1.25 mg and the 2.5 mg groups, respectively. Especially in the 2.5 mg racemic albuterol group, where there was an improvement in on-study baseline of 4.5% after 2 weeks of treatment, but a decrease in the on-study baseline to 1.7% after 4 weeks of treatment, it is possible that a further decrease in on-study baseline FEV-1 could have been seen in a study of longer duration with continued administration of racemic albuterol. Also noteworthy, is the fact that the mean percent change in baseline FEV-1 was significantly greater in all the treatment groups at week 5, i.e. 1 week after the last dose of albuterol was received, e.g. 16% in the 1.25 mg (R)-albuterol group one week after treatment was discontinued compared to 7% after 4 weeks of treatment. This suggests that there is an effect from administration of albuterol on a repetitive basis over 4 weeks that persists after treatment is discontinued, although the same effect was seen in the placebo group. There is no apparent pharmacologic basis for why this might occur.*

- Onset of action after 4 weeks of treatment:** The median time that it took to demonstrate a 15% or greater improvement in FEV-1 over baseline at week 4 was approximately the same for all treatment groups, i.e. 6-9 minutes.
- Time to mean maximum response after 4 weeks of treatment:** The shortest time to reach the mean maximum response at week 4 relative to pre-dose at week 4 was 82 minutes in the 0.625 mg (R)-albuterol group, compared to 97-100 minutes in the other groups. The time to maximum response in the other active treatment groups, therefore, occurred 15-18 minutes later.

- **Duration of response after 4 weeks of treatment:** based on mean data, a 15% or greater improvement in FEV-1 was noted for 5 hours in the 0.625 mg (R)-albuterol and the 2.5 mg racemic albuterol groups, for 3 hours in the 1.25 mg racemic albuterol group and for 7 hours in the 1.25 mg (R)-albuterol group.
- **FVC:** The mean peak change in FVC relative to study baseline was essentially the same for the two (R)-albuterol groups and the 2.5 mg racemic albuterol group, less for the 1.25 mg racemic albuterol group and even less for the placebo group which was statistically significantly different than each of the albuterol groups, using either the ITT or efficacy population.
- **FEF 25-75:** The mean peak change in FEF 25-75 relative to study baseline was the same in the 0.625 mg (R)-albuterol and 2.5 mg racemic albuterol groups, greatest in the 1.25 mg (R)-albuterol group, less in the 1.25 mg racemic albuterol group and least in the placebo group with all active treatment groups showing a statistically significant improvement compared with placebo, based on either the ITT or efficacy population.

COMMENT: *The objectives of this study were to demonstrate the comparative efficacy of 2 doses of (R)-albuterol and racemic albuterol in reversing and preventing bronchoconstriction. The study, however, was not designed to demonstrate the prevention of bronchoconstriction and therefore this objective has not been achieved. The sponsor has demonstrated that 0.625 mg of (R)-albuterol is comparable to 2.5 mg of racemic albuterol and 1.25 mg of (R)-albuterol is generally more effective than 2.5 mg of racemic albuterol in reversing bronchoconstriction acutely. A determination of which of the two doses of (R)-albuterol should be recommended as the usual dosage for acute reversal of bronchoconstriction depends, therefore, on an assessment of the comparable safety of these two doses (see discussion of comparable safety below). The sponsor has not demonstrated that (R)-albuterol at either dosage, i.e. 0.625 or 1.25 mg TID will reverse bronchoconstriction when administered on a chronic basis, although such an effect was not*

demonstrated for racemic albuterol either, i.e. although there was an increase in the pre-dose baseline at week 4 as compared to week 0 (6.0 % and 6.9 % in the 0.625 mg and 1.25 mg TID (R)-albuterol groups, respectively) there was a 6.0 % increase in the placebo baseline. The sponsor has demonstrated that there is only a minimal decrease in the ability of (R)-albuterol to reverse acute bronchoconstriction after 4 weeks of treatment, to a degree comparable to racemic albuterol. It can be assumed, although it has not been proven, that the chronic administration of (R)-albuterol prevents bronchoconstriction to a degree comparable to that of racemic albuterol. Nevertheless, the comparability of (R)-albuterol and racemic albuterol in terms of acute effectiveness in reversing bronchoconstriction has been demonstrated. It has further been demonstrated that a dose of 0.625 mg, as well as a dose of 1.25 mg of (R)-albuterol is comparable in terms of this effect to a 2.5 mg dose of racemic albuterol. The dose and dosing interval proposed by the sponsor, i.e. 0.625 mg or 1.25 mg of (R)-albuterol TID, are supported by this study.

- Subgroup analysis: Across all treatment groups, males had a greater mean peak change in FEV-1 after 4 weeks of treatment compared to the baseline before initiation of treatment (week 0), than did females. In all the study groups except the 2.5 mg of racemic albuterol group, there was a greater mean peak change in FEV-1 after 4 weeks of treatment compared to the baseline before initiation of treatment in patients 12-16 years of age than in patients > 16 years of age (see table below). There was a greater mean peak change in FEV-1 after 4 weeks of treatment compared to the baseline before initiation of treatment in patients not receiving corticosteroids in the 0.625 mg and 1.25 mg (R)-albuterol and the 2.5 mg racemic albuterol groups (see table below).

Comparison of Mean Peak Change in FEV₁ Stratified by Age - Week 4.

	Treatment Group					Overall p-value ^[2]	Pairwise p-value ^[3]
	(R)-albuterol 0.625 mg n=72	(R)-albuterol 1.25 mg n=73	racemic albuterol 1.25 mg n=68	racemic albuterol 2.5 mg n=74	placebo n=75		
Peak Change in FEV ₁ ^[1]						<.0001	
12-16 Year Olds							.625(R) v P<.0001 1.25(R) v P<.0001 1.25(RS) v P=.0008 2.5(RS) v P<.0001 (RS) v (R)<.14
Mean (SD)	0.92(0.61)	1.40(0.43)	1.17(1.06)	0.79(0.62)	0.56(0.24)		
n	6	5	4	5	7		
Over 16							
Mean (SD)	0.79(0.49)	0.83(0.50)	0.63(0.44)	0.80(0.38)	0.36(0.54)		
n	62	57	59	64	60		

^[1] Peak change in FEV₁ refers to the change in forced expiratory volume in one second relative to pre-dose at Week 0.

^[2] Overall test was conducted using an ANOVA. Effects included study site, treatment and age (12-16, >16). The p-value corresponding to age was 0.0255.

^[3] Pairwise tests of active versus placebo and an overall test of (R)-albuterol versus racemic albuterol (1 df) were presented if the overall test was significant.

Reference: Summarized from Section 14.2.1.18.

Comparison of Mean Peak Change in FEV₁ Stratified by Corticosteroid Use - Week 4^[1]

	Treatment Group					Overall p-value ^[2]	Pairwise p-value ^[3]
	R-albuterol 0.625 mg	R-albuterol 1.25 mg	racemic albuterol 1.25 mg	racemic albuterol 2.5 mg	Placebo		
Peak Change in FEV ₁							
Not using Corticosteroids:							.625(R) v P<.0001 1.25(R) v P<.0001 1.25(RS) v P=.0010 2.5(RS) v P<.0001 (RS) v R=0.14
Mean (SD)	0.82(0.53)	1.06(0.42)	0.63(0.43)	0.91(0.41)	0.41(0.40)	<.0001	
n	38	29	35	26	37		
Using Corticosteroids:							
Mean (SD)	0.78(0.48)	0.71(0.54)	0.72(0.58)	0.73(0.37)	0.36(0.65)		
n	30	33	28	43	30		

^[1] Peak change in FEV₁ refers to the peak change in forced expiratory volume in one second relative to pre-dose at Week 0. Corticosteroid users are subjects who have used oral or inhaled corticosteroids during the study for the treatment of asthma according the concomitant medication log.

^[2] Overall treatment test was conducted using an ANOVA. Effects included study site, treatment and corticosteroid use indicator. The p-value corresponding to the use of corticosteroids was 0.07.

^[3] Pairwise tests of active treatment versus placebo and an overall test of (R)-albuterol versus racemic albuterol were presented if the overall test was significant.

Reference: Summarized from Section 14.2.1.17.

□ **Diary peak flow measurements:** see tables below. The variability of response makes this data uninterpretable (see tables below). It is interesting to note that in the week after stopping treatment (week 4 to week 5), both the mean AM and the PM PEFR were higher in the groups which received (R)-albuterol than in patients who received racemic albuterol.

Comparison of Mean Change in Peak Flow (L/min) Relative to Week -1 (Screening)

	Treatment Group					Overall p-value [1]
	(R)-Albuterol 0.625 mg (n= 72)	(R)-Albuterol 1.25 mg (n= 73)	Racemic Albuterol 1.25 mg (n= 68)	Racemic Albuterol 2.5 mg (n= 74)	Placebo (n= 75)	
Mean Change in Morning Peak Flow (L/min) [2]						
Week 1 Relative to Week -1						
Mean (SD)	11.6 (48.34)	6.4 (41.46)	-5.4 (42.10)	10.1 (35.62)	13.0 (26.12)	0.93
LS Mean (SD)	4.3 (42.92)	14.1 (43.77)	3.5 (45.14)	8.4 (44.99)	12.0 (43.53)	
Min, Max	-44.8, 187.1	-49.4, 136.4	-111.0, 94.5	-37.1, 97.0	-22.3, 67.9	
n	15	20	14	24	21	
Week 2 Relative to Week -1						
Mean (SD)	7.9 (40.70)	1.9 (38.02)	3.5 (23.78)	14.3 (42.19)	9.4 (26.11)	0.98
LS Mean (SD)	2.6 (39.38)	6.6 (40.13)	10.9 (40.49)	10.4 (40.07)	6.6 (39.95)	
Min, Max	-58.6, 118.0	-48.0, 118.3	-47.5, 49.0	-45.7, 114.0	-31.0, 66.7	
n	15	10	14	23	21	
Week 3 Relative to Week -1						
Mean (SD)	-0.6 (32.10)	10.0 (29.08)	-4.9 (31.87)	9.4 (48.02)	0.3 (26.79)	0.14
LS Mean (SD)	-1.4 (37.09)	6.5 (36.79)	-7.4 (36.82)	8.2 (36.92)	-2.3 (26.49)	
Min, Max	-87.0, 71.4	-36.3, 84.3	-78.2, 58.6	-77.1, 210.7	-85.7, 60.4	
n	57	51	84	49	53	
Week 4 Relative to Week -1						
Mean (SD)	0.5 (42.21)	7.5 (33.93)	-5.3 (30.14)	7.3 (47.13)	7.6 (34.73)	0.30
LS Mean (SD)	-4.2 (42.36)	5.7 (42.10)	-5.4 (41.10)	6.8 (42.08)	6.5 (41.64)	
Min, Max	-89.6, 122.7	-69.9, 121.5	-84.1, 69.5	-87.3, 236.3	-114.8, 114.6	
n	69	67	65	70	73	

[1] Overall treatment test was conducted using an ANOVA. Effects included study site and treatment.
 [2] Change in peak flow was computed by comparing the mean peak flow from Week 0 to Week 1, Week 1 to Week 2, Week 2 to Week 3, and Week 3 to Week 4, respectively, relative to the mean peak flow from screening (Week -1).

Comparison of Mean Change in Peak Flow (L/min) Relative to Week -1 (Screening)

	Treatment Group					Overall p-value [1]
	(R)-Albuterol 0.625 mg (n= 72)	(R)-Albuterol 1.25 mg (n= 73)	Racemic Albuterol 1.25 mg (n= 68)	Racemic Albuterol 2.5 mg (n= 74)	Placebo (n= 75)	
Mean Change in Evening Peak Flow (L/min) [2]						
Week 1 Relative to Week -1						
Mean (SD)	22.5 (45.14)	9.4 (48.17)	8.0 (31.88)	9.3 (23.97)	1.1 (22.62)	0.46
LS Mean (SD)	17.6 (41.38)	14.7 (41.23)	17.4 (42.83)	12.9 (42.28)	-2.5 (41.00)	
Min, Max	-28.0, 164.3	-45.0, 166.6	-22.9, 73.6	-30.9, 76.0	-59.1, 85.7	
n	15	20	14	24	21	
Week 2 Relative to Week -1						
Mean (SD)	18.0 (39.00)	4.0 (46.87)	10.3 (36.34)	8.0 (30.78)	10.8 (46.62)	0.95
LS Mean (SD)	16.4 (49.00)	5.0 (49.81)	13.4 (40.38)	13.5 (40.19)	7.6 (48.47)	
Min, Max	-47.7, 185.7	-77.5, 143.8	-35.0, 94.7	-60.9, 76.0	-77.6, 113.0	
n	15	10	14	24	21	
Week 3 Relative to Week -1						
Mean (SD)	9.1 (35.10)	11.0 (33.16)	2.3 (32.48)	15.6 (48.44)	-0.9 (28.47)	0.09
LS Mean (SD)	6.6 (30.00)	7.7 (37.70)	-1.0 (37.72)	13.2 (37.82)	-4.0 (37.28)	
Min, Max	-53.6, 107.1	-79.0, 91.4	-105.2, 73.0	-87.1, 213.9	-90.2, 76.9	
n	57	51	84	49	53	
Week 4 Relative to Week -1						
Mean (SD)	7.6 (49.89)	9.4 (35.71)	1.6 (33.61)	8.2 (44.77)	3.5 (27.42)	0.83
LS Mean (SD)	6.8 (45.37)	7.7 (45.09)	1.6 (44.02)	7.1 (45.04)	1.8 (44.87)	
Min, Max	-88.3, 219.7	-50.0, 165.8	-76.7, 88.8	-88.0, 210.0	-61.3, 114.2	
n	69	67	65	70	73	

[1] Overall treatment test was conducted using an ANOVA. Effects included study site and treatment.
 [2] Change in peak flow was computed by comparing the mean peak flow from Week 0 to Week 1, Week 1 to Week 2, Week 2 to Week 3, and Week 3 to Week 4, respectively, relative to the mean peak flow from screening (Week -1).

Diary Card Peak Flow
Week 4 to Week 5

	Treatment Group					Overall p-value (1)
	(R)-Albuterol 0.625 mg (n= 72)	(R)-Albuterol 1.25 mg (n= 73)	Racemic Albuterol 1.25 mg (n= 68)	Racemic Albuterol 2.5 mg (n= 74)	Placebo (n= 75)	
Morning Peak Flow (L/min)						
Mean (SD)	324.2 (96.52)	346.1 (112.25)	319.6 (95.90)	307.7 (94.70)	318.2 (95.35)	0.68
Min, Max	126.7, 662.5	152.5, 585.0	156.0, 546.0	148.0, 530.0	142.5, 556.7	
n	68	61	62	67	67	
Evening Peak Flow (L/min)						
Mean (SD)	339.3 (102.63)	367.7 (102.55)	339.9 (94.48)	331.2 (88.81)	344.9 (95.73)	0.60
Min, Max	145.0, 750.0	180.0, 590.0	162.0, 546.7	166.7, 530.0	160.7, 630.0	
n	68	61	62	67	67	
Shift in Peak Flow (L/min) (2)						
Mean (SD)	35.2 (50.22)	20.1 (34.41)	19.9 (34.10)	23.2 (30.95)	26.7 (44.73)	0.70
Min, Max	-73.3, 220.0	-32.5, 136.7	-76.0, 105.0	-45.7, 114.2	-35.0, 266.0	
n	68	61	62	67	67	

(1) Overall p-values were computed using an analysis of variance (ANOVA) F test. The response variable of interest was the change in peak flow at the end of study (Week 5) relative to baseline (Week -1).
 (2) Shift in peak flow was the mean difference in the peak flow levels (evening minus morning).

Use of rescue medication: The two (R)-albuterol groups were comparable in terms of the mean number of days that rescue medication was needed per week. The mean rescue medication days/week was higher in the groups which received racemic albuterol, in particular patients who received 2.5 mg racemic albuterol in whom mean days/week of rescue medication was comparable to that of patients who received placebo. This same pattern was seen when the data was analyzed in terms of number of puffs of rescue medication used per day. The increase in number of symptom-free days was most prominent in the 1.25 mg (R)-albuterol group, while the number of symptom-free days in the 2.5 mg racemic albuterol group and the placebo group was not statistically significantly different. In the week following discontinuation of treatment (week 4 to week 5), the amount of rescue medication used was lowest and the number of symptom-free days was highest in the 1.25 mg (R)-albuterol and the 1.25 mg racemic albuterol groups.

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- symptom scoring:** There was no clinically significant decrease in symptoms on any active treatment and symptoms scores were comparable to those seen in the placebo group. However, there were less nocturnal awakenings due to wheeze and cough in the 1.25 mg (R)-albuterol group during each week of treatment and symptoms were generally less severe in this group, especially during the last week of treatment. In the week following discontinuation of treatment (week 4 to week 5), symptoms were generally less severe in the group which received 1.25 mg (R)-albuterol.

- corticosteroid use:** Use of oral corticosteroids for > 5 consecutive days occurred in 2 patients in the 0.625 mg (R)-albuterol, the 1.25 mg (R)-albuterol and the 1.25 mg racemic albuterol groups, and in 4 patients in the placebo group. No patients in the 2.5 mg racemic albuterol group required oral corticosteroids for this length of time.

- withdrawals due to lack of efficacy:** There were 2 patients, one in the 1.25 mg (R)-albuterol and one in the placebo group who withdrew because of perceived lack of efficacy.

- Safety Evaluation:**

- Adverse events:** see tables below. In regard to potentially related adverse events, there were more patients who developed tachycardia, and nervous system effects, such as anxiety, dizziness, nervousness and tremor in the two (R)-albuterol groups than in the racemic albuterol or placebo groups. In particular, the difference seen in nervous system adverse events potentially related to treatment in the 1.25 mg (R)-albuterol and the 2.5 mg racemic albuterol groups and the placebo group were statistically significantly different ($p = < 0.0001$ and $p = 0.003$ respectively). Five of the nervous system adverse events were considered severe; 1 anxiety, 1 dizziness and 3 nervousness. Interestingly, there were -

more asthma-related adverse events in the 0.625 mg (R)-albuterol group, with onset after week 4 of treatment, than in the 1.25 mg (R)-albuterol group. One possible explanation for this finding would be a greater carryover effect in the higher dose group.

Summary of Adverse Events With Frequency $\geq 2\%$ and $>$ Placebo, or Associated with the Use of (R)-Albuterol or Racemic Albuterol With Onset During the Double-Blind Treatment Period

Body System Preferred term	Treatment Group									
	(R)-albuterol 0.625 mg n = 72		(R)-albuterol 1.25 mg n = 73		racemic albuterol 1.25 mg n = 68		racemic albuterol 2.5 mg n = 74		placebo n = 75	
	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n
All Adverse Events	42(58.3)	78	45(61.6)	94	40(58.8)	75	45(60.8)	92	47(62.7)	91
Body as a Whole										
allergic reaction	0	0	0	0	0	0	2(2.7)	2	1(1.3)	1
headache	6(8.3)	6	7(9.6)	7	9(13.2)	12	6(8.1)	6	8(10.7)	9
flu syndrome	3(4.2)	3	1(1.4)	1	2(2.9)	2	2(2.7)	2	0	0
accidental injury	0	0	2(2.7)	2	0	0	0	0	0	0
pain	2(2.8)	2	1(1.4)	1	1(1.5)	2	2(2.7)	2	1(1.3)	1
back pain	0	0	0	0	1(1.5)	1	2(2.7)	2	0	0
chest pain	0	0	1(1.4)	1	3(4.4)	3	1(1.4)	1	0	0
Cardiovascular System										
migraine	0	0	2(2.7)	3	0	0	0	0	0	0
tachycardia	2(2.8)	3	2(2.7)	3	0	0	2(2.7)	2	0	0
Digestive System										
dyspepsia	1(1.4)	1	2(2.7)	2	1(1.5)	1	1(1.4)	1	1(1.3)	1
Musculoskeletal System										
leg cramps	0	0	2(2.7)	3	1(1.5)	1	1(1.4)	1	1(1.3)	1
Nervous System										
anxiety	0	0	2(2.7)	2	0	0	0	0	0	0
dizziness	1(1.4)	1	2(2.7)	2	0	0	0	0	1(1.3)	1
hypertonia	0	0	0	0	1(1.5)	1	2(2.7)	2	0	0
insomnia	0	0	1(1.4)	1	0	0	0	0	0	0
nervousness	2(2.8)	3	7(9.6)	8	3(4.4)	3	6(8.1)	6	0	0
tremor	0	0	5(6.8)	6	0	0	2(2.7)	2	0	0
Respiratory System										
asthma	13(18.1)	13	12(16.4)	12	12(17.6)	12	15(20.3)	16	18(24.0)	18
asthma inc. ⁽¹⁾	6(8.3)	7	8(11.0)	9	6(8.8)	6	4(5.4)	5	9(12.0)	9
cough increased	1(1.4)	1	3(4.1)	3	1(1.5)	1	2(2.7)	2	2(2.7)	2
viral infection ⁽²⁾	5(6.9)	5	9(12.3)	10	5(7.4)	5	9(12.2)	9	7(9.3)	7
pharyngitis	4(5.6)	4	0	0	1(1.5)	1	2(2.7)	2	6(8.0)	7
rhinitis	8(11.1)	8	2(2.7)	2	3(4.4)	3	5(6.8)	5	2(2.7)	2
sinusitis	3(4.2)	3	1(1.4)	1	3(4.4)	3	2(2.7)	2	2(2.7)	2
turbinate edema	2(2.8)	2	1(1.4)	1	0	0	0	0	0	0
wheezing	1(1.4)	1	0	0	4(5.9)	4	1(1.4)	1	2(2.7)	2
Urogenital System										
UTI	0	0	0	0	2(2.9)	2	0	0	0	0

Note: Subjects may have had the same adverse event more than once.

⁽¹⁾ Asthma inc. = asthma exacerbation. An asthma exacerbation was defined as a worsening of asthma symptoms or pulmonary function which required therapeutic intervention with oral or parenteral corticosteroids or other medications as judged necessary by the Investigator.

⁽²⁾ viral infection = upper respiratory infection.

Reference: Summarized from Sections 14.3.1.1 and 14.3.1.5.

Summary of Potentially Related Adverse Events With Frequency $\geq 2\%$ and $>$ Placebo, or Associated with the Use of (R)-Albuterol or Racemic Albuterol With Onset During Double-Blind Treatment Period.

Body System Preferred term	Treatment Group									
	(R)-albuterol 0.625 mg n = 72		(R)-albuterol 1.25 mg n = 73		racemic albuterol 1.25 mg n = 68		racemic albuterol 2.5 mg n = 74		placebo n = 75	
	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n
All Adverse Events	12 (16.7)	21	23 (31.5)	41	14 (20.6)	18	20 (27.0)	32	14 (18.7)	23
Body as a Whole	4 (5.6)	4	5 (6.8)	5	3 (4.4)	5	3 (4.1)	4	4 (5.3)	6
headache	3 (4.2)	3	4 (5.5)	4	2 (2.9)	4	2 (2.7)	2	3 (4.0)	4
Cardiovascular System	2 (2.8)	3	3 (4.1)	4	0	0	2 (2.7)	2	0	0
tachycardia	2 (2.8)	3	2 (2.7)	3	0	0	2 (2.7)	2	0	0
Musculoskeletal System	1 (1.4)	1	2 (2.7)	3	0	0	0	0	1 (1.3)	1
leg cramps	0	0	2 (2.7)	3	0	0	0	0	1 (1.3)	1
Nervous System	4 (5.6)	5	13 (17.8)	20	3 (4.4)	3	8 (10.8)	9	0	0
anxiety	0	0	2 (2.7)	2	0	0	0	0	0	0
dizziness	1 (1.4)	1	2 (2.7)	2	0	0	0	0	0	0
nervousness	2 (2.8)	3	7 (9.6)	8	3 (4.4)	3	6 (8.1)	6	0	0
tremor	0	0	5 (6.8)	6	0	0	2 (2.7)	2	0	0
Respiratory System	6 (8.3)	6	6 (8.2)	7	8 (11.8)	9	9 (12.2)	12	10 (13.3)	14
asthma	5 (6.9)	5	4 (5.5)	4	5 (7.4)	5	6 (8.1)	6	7 (9.3)	7
asthma inc. ^[1]	1 (1.4)	1	3 (4.1)	3	2 (2.9)	2	2 (2.7)	2	2 (2.7)	2
rhinitis	0	0	0	0	0	0	2 (2.7)	2	0	0

Note: Subjects may have had the same adverse event more than once.

[1] Asthma inc. = asthma exacerbation. An asthma exacerbation was defined as a worsening of asthma symptoms or pulmonary function which required therapeutic intervention with oral or parenteral corticosteroids or other medications as judged necessary by the Investigator.

Reference: Summarized from Sections 14.3.1.3 and 14.3.1.6.

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- ◆ A 42 year old female developed diffuse non-specific T wave abnormalities, associated with numbness of the left hand after her first dose of 1.25 mg (R)-albuterol, which had resolved when an ECG was repeated about 2 months later (patient 20194). This patient was discontinued from the study. Another patient (patient 43428) developed ST-T wave changes 2-3 hours after receiving the first dose of 1.25 mg (R)-albuterol, but in this case the patient remained in the study and had no recurrence.

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☛ **Laboratory tests:**

- ◆ **No clinically significant changes in mean serum potassium levels was noted 60 minutes after drug administration on day 1 or after 2 and 4 weeks of treatment for any of the treatment groups and there was no clinically significant difference between the treatment groups in regard to this parameter (see table below).**

Comparison of Mean Change in Potassium 60 Minutes Post-Dose^[1]

	Treatment Group					Overall p-value ^[2]	Pairwise p-value ^[3]
	(R)-albuterol 0.625 mg n=72	(R)-albuterol 1.25 mg n=73	racemic albuterol 1.25 mg n=68	racemic albuterol 2.5 mg n=74	placebo n=75		
Week 0							
Mean (SD)	-0.2 (0.32)	-0.3 (0.33)	-0.3 (0.26)	-0.3 (0.28)	-0.2 (0.31)	0.0004	0.625(R) v 1.25(R) =0.0130 0.625(R) v 1.25(RS) =0.13 0.625(R) v 2.5(RS) =0.0181 1.25(R) v 1.25(RS) =0.35 1.25(R) v 2.5(RS) =0.88 1.25(RS) v 2.5(RS) = 0.42
Pairwise p-value ^[3]	0.21	0.0002	0.0056	0.0003			
Week 2							
Mean (SD)	-0.2 (0.25)	-0.3 (0.31)	-0.2 (0.29)	-0.4 (0.31)	-0.1 (0.32)	<.0001	0.625(R) v 1.25(R) =0.09 0.625(R) v 1.25(RS) =0.87 0.625(R) v 2.5(RS) =0.0049 1.25(R) v 1.25(RS) =0.07 1.25(R) v 2.5(RS) =0.29 1.25(RS) v 2.5(RS) = 0.0038
Pairwise p-value ^[3]	0.0403	0.0002	0.07	<.0001			
Week 4							
Mean (SD)	-0.0 (0.30)	-0.1 (0.29)	0.1 (0.28)	-0.1 (0.36)	0.1 (0.32)	0.0032	0.625(R) v 1.25(R) =0.26 0.625(R) v 1.25(RS) =0.08 0.625(R) v 2.5(RS) =0.59 1.25(R) v 1.25(RS) =0.0050 1.25(R) v 2.5(RS) =0.54 1.25(RS) v 2.5(RS) = -0.0214
Pairwise p-value ^[3]	0.0336	0.0014	0.75	0.0072			

^[1] Change in the laboratory measure of interest was calculated by comparing the 60 minutes post-dose value relative to pre-dose on that day.

^[2] Overall treatment test was conducted using an ANOVA.

^[3] All pairwise tests were presented if the overall test was significant. Results of pairwise tests with placebo are reported by treatment group. Pairwise tests of R vs RS are reported separately.

Reference: Summarized from Sections 14.6.1.5, 14.6.2.5, and 14.6.3.5.

- ◆ **There was no clinically significant change in mean serum glucose in any treatment group. For all treatment groups, there was less increase in serum glucose after 4 weeks of treatment compared with the response after the first administration of the drug (see table below). There were more of the higher dose albuterol patients who had an increase in serum glucose from normal to above the upper limit of the normal reference range, i.e. ten 1.25 mg (R)-albuterol patients and eight 2.5 mg racemic albuterol patients as compared to five placebo patients.**

Comparison of Mean Change in Glucose 60 Minutes Post-Dose^[1]

	Treatment Group					Overall p-value ^[2]	Pairwise p-value ^[3]
	(R)-albuterol 0.625 mg n=72	(R)-albuterol 1.25 mg n=73	racemic albuterol 1.25 mg n=68	racemic albuterol 2.5 mg n=74	placebo n=75		
Week 0							
Mean (SD)	4.6 (11.88)	10.3 (9.33)	4.0(11.03)	8.2 (16.11)	-0.2 (9.73)	<.0001	.625(R) v 1.25(R) =0.0045 .625(R) v 1.25(RS) =0.76 .625(R) v 2.5(RS) =0.07 1.25(R) v 1.25(RS) =0.0018 1.25(R) v 2.5(RS) =0.28 1.25(RS) v 2.5(RS) =0.357
Pairwise p-value	0.0183	<.0001	0.0414	<.0001			
Week 2							
Mean (SD)	4.9 (13.99)	6.3 (8.55)	4.6 (8.71)	5.5 (14.29)	-0.3 (10.06)	0.0092	.625(R) v 1.25(R) =0.48 .625(R) v 1.25(RS) =0.90 .625(R) v 2.5(RS) =0.76 1.25(R) v 1.25(RS) =0.42 1.25(R) v 2.5(RS) =0.69 1.25(RS) v 2.5(RS) =0.67
Pairwise p-value	0.0088	0.0011	0.0150	0.0034			
Week 4							
Mean (SD)	2.4 (19.32)	4.2 (10.56)	2.6(11.82)	4.4 (12.72)	-2.0 (12.04)	0.06	

^[1] Change in the laboratory measure of interest was calculated by comparing the 60 minutes post-dose value relative to pre-dose on that day.

^[2] Overall treatment test was conducted using an ANOVA.

^[3] All pairwise tests were presented if the overall test was significant.

Reference: Summarized from Sections 14.6.1.5, 14.6.2.5, and 14.6.3.5.

◆ There was no significant difference between any of the treatment groups and placebo in terms of the mean values for any laboratory tests obtained prior to drug administration after 2 or 4 weeks of treatment. There were 4 patients in the 1.25 mg racemic albuterol group compared to one patient in the placebo group who had a normal value for SGPT at baseline whose SGPT was above the upper limit of the normal reference range after 4 weeks of treatment.

☛ Vital Signs: There were no clinically significant mean changes in vital signs during the study in any treatment group.

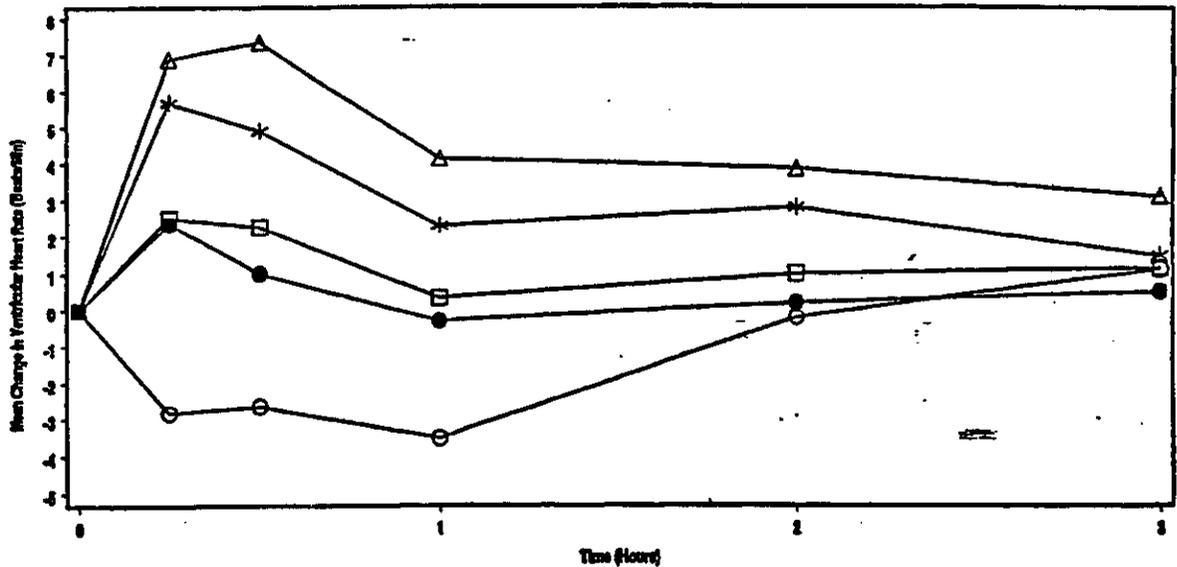
☛ ECGs:

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◆ heart rate: There were no clinically significant changes in mean heart rate in any treatment group (see figures below). The greatest change in mean heart rate occurred in the 1.25 mg (R)-albuterol group with a maximum increase of 7 bpm after the first dose and a decrease in mean maximum increase in bpm after 2 and 4 weeks of treatment. Increase in heart rate 15 minutes after the first administration of study medication was statistically significantly less at lower

doses of both the (R)-albuterol and the racemic albuterol ($p = 0.001$ and $p = 0.008$ respectively). The increase in heart rate seen after administration of the lower and higher doses of (R)-albuterol and racemic albuterol were comparable when measured 15 minutes after the first administration of study drug. Increase in heart rate 15 and 30 minutes after drug administration at week 4 was comparable in all active treatment groups, but less in the 0.625 mg (R)-albuterol group.

Mean Change in heart rate after first dose

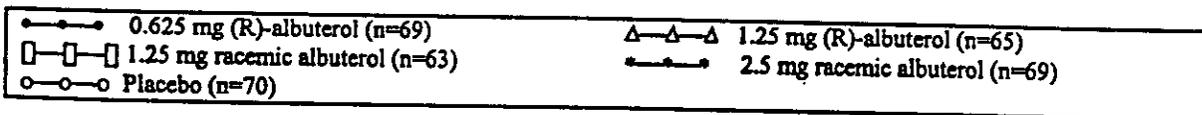
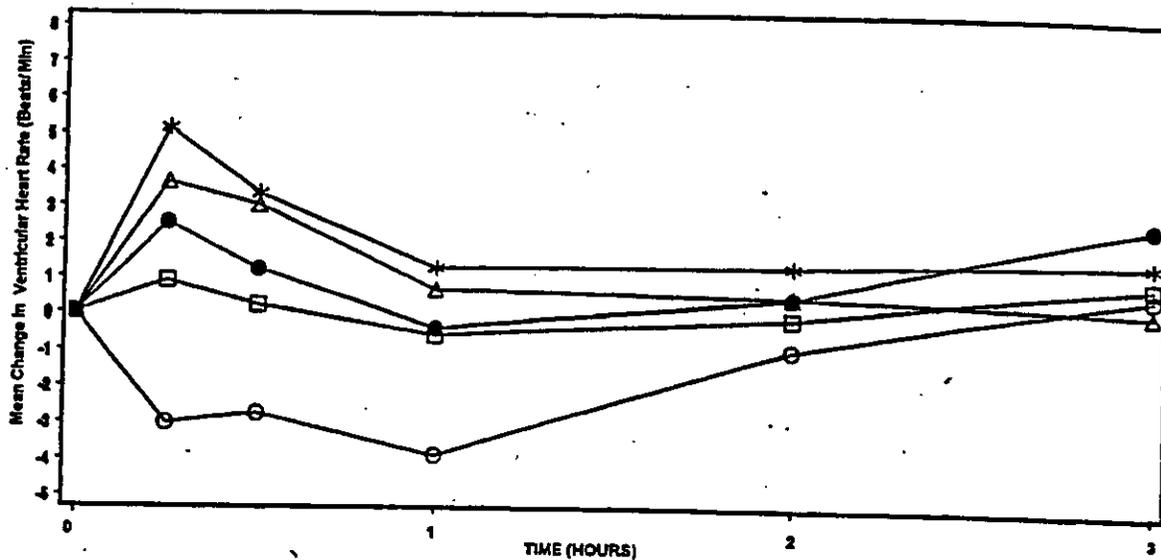


●—●—● 0.625 mg (R)-albuterol (n=72)	△—△—△ 1.25 mg (R)-albuterol (n=73)
□—□—□ 1.25 mg racemic albuterol (n=68)	*—*—* 2.5 mg racemic albuterol (n=74)
○—○—○ Placebo (n=75)	

Reference: Section 14.8.19.

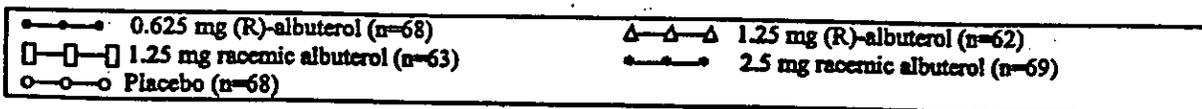
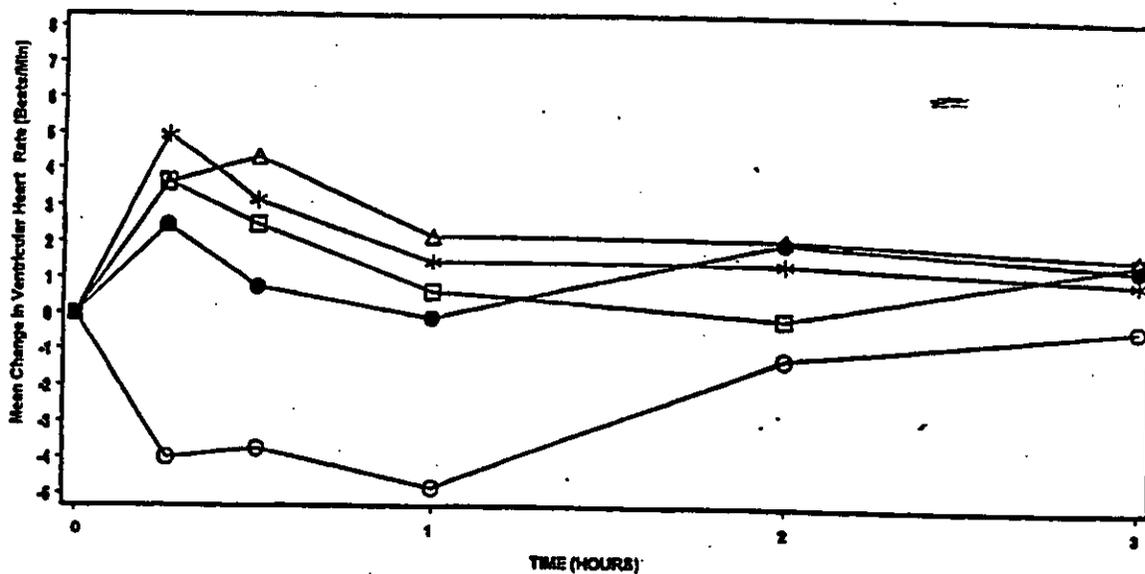
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Mean Change in heart rate after dose at 2 weeks



Reference: Section 14.8.20.

Mean change in heart rate after dose at 4 weeks

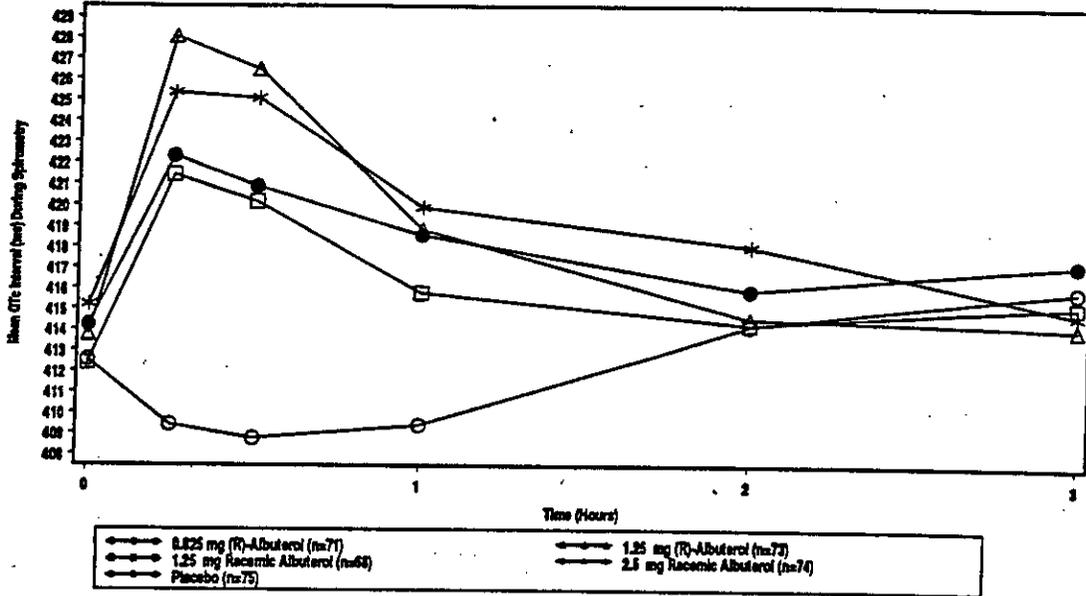


Reference: Section 14.8.21.

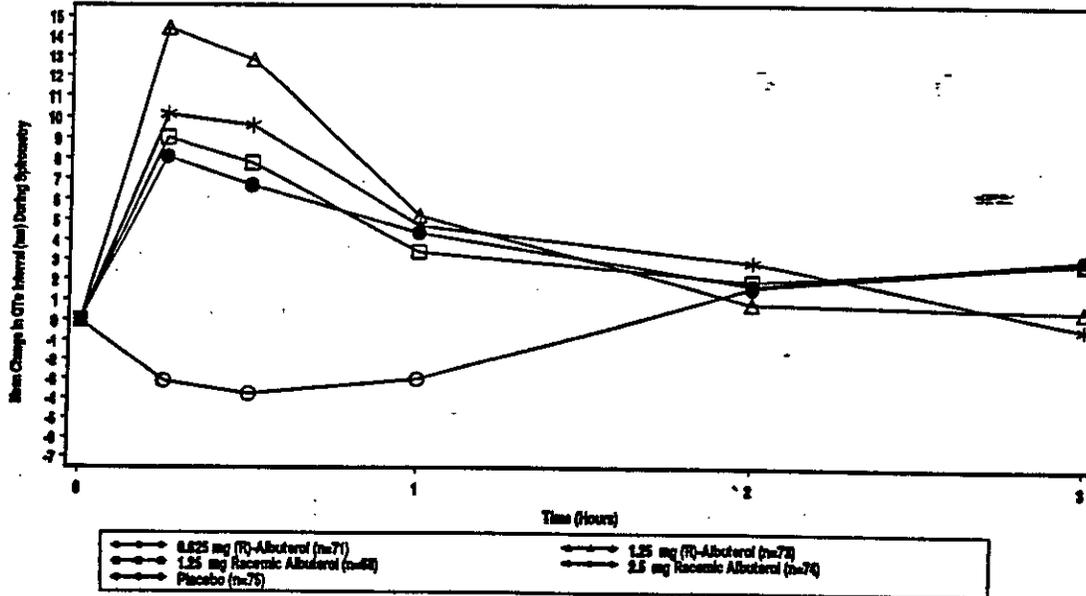
- ◆ **QTc interval:** After 4 weeks of treatment, there was a significant prolongation of the mean QTc interval relative to placebo in the active treatment groups but no significant difference between the active treatment groups. The largest mean increase in the QTc interval was 8.8 msec in the 2.5 mg racemic albuterol group. There were 11 patients who had a QTc interval > 500 msec after drug administration; 3 patients who received placebo, 3 patients who received 0.625 mg (R)-albuterol, 3 patients who received 2.5 mg racemic albuterol, and 2 patients who received 1.25 mg (R)-albuterol. The greatest increase in the QTc interval was from 400 msec to 677 msec in one patient after treatment with 2.5 mg racemic albuterol, but one patient who received 0.625 mg (R)-albuterol had an increase from 472 to 567 msec, one patient who received placebo had an increase from 412 to 545 msec, and one patient who received 1.25 mg (R)-albuterol had an increase from 426 to 564 msec. After the first administration of medication at week 0, mean increase in QTc interval was seen at 15 minutes and lasted until 30 minutes after administration of both (R)-albuterol and racemic albuterol (8 msec in 0.625 mg (R)-albuterol group, 15 msec in 1.25 mg (R)-albuterol group, 9 msec in 1.25 mg racemic albuterol group and 10 msec in 2.5 mg racemic albuterol group. At week 2, the maximum increase in mean QTc interval (again seen 15 minutes after drug administration and basically returning to baseline 60 minutes after drug administration) was 7 msec in the 0.625 mg (R)-albuterol, 11 msec in the 1.25 mg (R)-albuterol, 2 msec in the 1.25 mg racemic albuterol, and 10 msec in the 2.5 mg racemic albuterol groups. See figures below.

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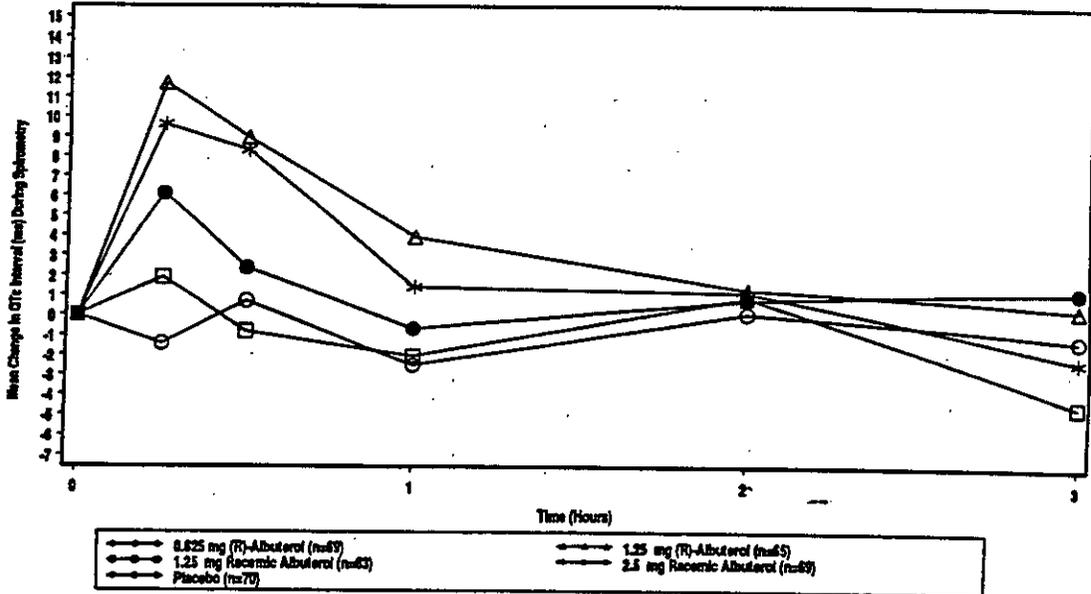
Summary of Mean QTc Interval Over Time
Week 0



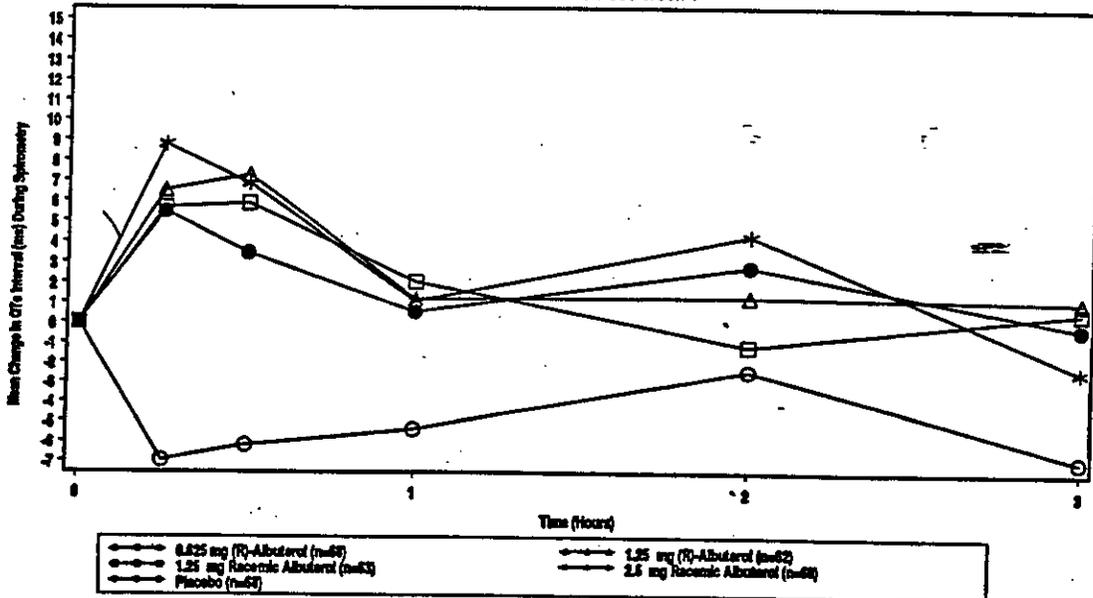
Summary of Mean Change in QTc Interval Over Time
Week 0 Relative to Pre-Dose Week 0



Summary of Mean Change in QTc Interval Over Time
Week 2 Relative to Pre-Dose Week 2



Summary of Mean Change in QTc Interval Over Time
Week 4 Relative to Pre-Dose Week 4



- ◆ overall interpretation: At week 0, there was one patient who developed a clinically significant abnormal ECG 15 minutes after receiving 1.25 mg of (R)-albuterol and another patient who developed a clinically significant abnormal ECG 2 hours after receiving the same active treatment. There was one placebo patient who developed a clinically significant abnormal ECG 2 hours after dosing as well.

◆ **EFFICACY CONCLUSIONS:** *The sponsor has demonstrated the comparative efficacy of (R)-albuterol and racemic albuterol in reversing bronchoconstriction (producing bronchodilatation). Specifically, 0.625 mg of (R)-albuterol was demonstrated to be comparable to 2.5 mg of racemic albuterol and 1.25 mg of (R)-albuterol produced more bronchodilatation than 2.5 mg of racemic albuterol. The sponsor has demonstrated the ability of (R)-albuterol to produce bronchodilatation (reverse bronchoconstriction) acutely following the first dose, without a decrease in this ability after 2 and 4 weeks of treatment. There is, in addition, a suggestion that (R)-albuterol produces chronic bronchodilatation based on an increase in the onstudy baseline for FEV-1 of 6-7% from prestudy baseline, which increased further 1 week after (R)-albuterol was discontinued (11-16% higher than prestudy baseline). Although there was a 6% increase in the placebo baseline for FEV-1 after 4 weeks of treatment, this effect becomes more significant when compared with the onstudy change in baseline FEV-1 from prestudy baseline in the groups that received racemic albuterol; 0.3-1.7% at week 4 and 8-11% one week after discontinuing treatment. This study was not designed to show that (R)-albuterol prevents bronchoconstriction. The recommended dose for racemic albuterol solution for nebulization is 2.5 mg TID or QID. Since a dose of 0.625 mg of (R)-albuterol produced the same degree of bronchodilatation as 2.5 mg of racemic albuterol in this study, it is appropriate, based on this study, to recommend a dose of 0.63 mg TID for most patients 12 years of age and older. Since a dose of 1.25 mg of (R)-albuterol produced a greater degree of bronchodilatation than 0.625 mg of (R)-albuterol, it is also appropriate to recommend that this dose be used for patients with more severe disease. The use of the 1.25 mg dose of (R)-albuterol should, however, be accompanied by a careful benefit: risk assessment (see discussion of safety), since the data indicates that a dose of 1.25 mg of (R)-albuterol has a greater effect than a dose of 2.5 mg of racemic albuterol and might, in particular, be considered if a dose of 0.625 mg of (R)-albuterol was not effective.*

◆ **SAFETY CONCLUSIONS:** *The 1.25 mg dose of (R)-albuterol produced a greater number of nervous system effects, especially anxiety, dizziness and tremor than did the 2.5 mg dose of racemic albuterol. No such effects were seen in the placebo group. Moreover, one patient (see discussion above) developed non-specific T wave abnormalities associated with numbness of the left hand after the first dose of 1.25 mg of (R)-albuterol. Another patient developed ST-T wave changes 2-3 hours after receiving the first dose of 1.25 mg of (R)-albuterol but remained in the study without recurrence. It is likely that these two patients developed coronary insufficiency from this dose of (R)-albuterol. The labeling for racemic albuterol indicates that it should be used with caution in patients with coronary insufficiency and there is ample evidence in the literature to indicate that beta agonists have the potential to produce coronary insufficiency. Based on these two patients and an increased incidence of nervous system adverse events, there is a strong indication that the 1.25 mg dose of (R)-albuterol has the potential to produce a greater systemic effect than 2.5 mg of racemic albuterol. This is supported by the slightly greater number of patients in the 1.25 mg (R)-albuterol group as compared to the 2.5 mg racemic albuterol group who had an increase in serum glucose from normal to above the upper limit of the normal reference range after treatment and by the slightly greater mean change in heart rate seen after the first dose of 1.25 mg of (R)-albuterol as compared to the 2.5 mg racemic albuterol group. Therefore, when prescribing this dose for patients with more severe asthma, a careful benefit:risk assessment is needed. No clinically significant difference in prolongation of the QTc interval was noted, however, after administration of the 1.25 mg dose of (R)-albuterol compared with other active treatment groups. This study supports the safe administration, in general, of both the 0.625 and the 1.25 mg doses of (R)-albuterol acutely and with repetitive TID administration over 4 weeks.*

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INTEGRATED SUMMARY OF SAFETY

- I. This integrated summary of safety includes data from the 9 studies that are reviewed above. This data was generated after administration of 0.1, 0.156, 0.312, 0.625, 1.25, 5, and 6.2 mg of (R)-albuterol and 0.2, 1.25, 2.5, 10, and 12.4 mg of racemic albuterol in comparison with 0.9% saline as placebo. The dose from cumulative dose studies was the total dose received on the day of the study, i.e. 6.2 mg was 200 mcg + 400 mcg + 800 mcg + 1600 mcg + 3200 mcg. The crossover studies 001, 006, 007, and 008 included administration of (S)-albuterol, although adverse event data after administration of (S)-albuterol has not been included in the integrated summary of safety (ISS). In the crossover studies, patients were counted only once for each study medication, regardless of the number of different doses of that medication the patient received. As a result, a complete assessment of safety of specific doses of (R)-albuterol is not possible, e.g. an adverse event in a study where the patient received different doses of (R)-albuterol will not be categorized as resulting from one specific dose.**
- II. The safety measures addressed in the ISS include: 1) patient withdrawal; 2) extent of exposure; 3) adverse events; 4) laboratory tests; 5) vital signs; and 6) electrocardiographic measurements. The data is also stratified and presented by: 1) type of study; 2) age; 3) gender; 4) race, 5) weight; and 6) percent of predicted FEV-1.**
- III. The safety database includes 490 asthmatic patients and 42 healthy volunteers. Of these, 292 received (R)-albuterol, of whom, 147 had single day exposures (106 patients with asthma) and 145 patients received (R)-albuterol on a repetitive dose basis in study 024 (see table below). The 42 healthy volunteers were in studies 006 and 008.**
- There were no significant demographic differences between treatment groups. There were 487 patients (92%) who completed the studies. There were 5% withdrawals due to adverse events (see table below). The duration of treatment for specific treatments can be seen in the table below. There were 145 patients who received (R)-albuterol for longer than a single day compared to 142 patients who received racemic albuterol and 75 who received placebo.**

Table 3.1: Enumeration of Subjects by Treatment Group for Each Completed Protocol

Study Type ¹	Total ² (n=532)	Placebo (n=164)	(R)-Albuterol ³ (n=292)	Racemic Albuterol ³ (n=281)
Phase I: Healthy Volunteers:				
051-006*	30	0	29	29
051-008*	12	12	12	12
Total	42	12	41	41
Phase II Asthmatics:				
Single Day Studies:				
051-001	30	10	10	10
051-005*	20	20	20	20
051-007*	12	12	12	12
051-021*	13	0	13	13
051-025*	12	12	12	12
Total	128	77	106	98
Phase III Study:				
051-024	362	75	145	142
All Studies				

Reference Appendix Tables 1.1 and 1.2

Note: The ISS does not include two subjects in [redacted] who were randomized to treatment but withdrew from the study without receiving any study drug.

¹ Cross-over studies are denoted with an asterisk. For cross-over studies, a subject contributes only once to each treatment total regardless of how many dose levels of each treatment the subject received.

² Because both of the Phase I studies and five of the Phase II studies were cross-over studies, this column reports the total number of individual subjects who participated in each study.

³ Subject No. 029 in Study 051-006 discontinued the study after having received only two doses; a second subject discontinued after racemic albuterol.

Table 4.4.1: Subject Disposition from All Studies by Treatment Group

	Total Number of Subjects ¹ (%)	Placebo n (%)	(R)-Albuterol n (%)	Racemic Albuterol ¹ n (%)
Number of Subjects				
Total Enrolled	[redacted]	[redacted]	[redacted]	[redacted]
Completed	[redacted] (91.5)	[redacted] (92.1)	[redacted] (92.1)	[redacted] (94.3)
Terminated	45 (8.5)	13 (7.9)	23 (7.9)	16 (5.7)
Reason for Withdrawal:				
Adverse event	27 (5.1)	8 (4.9)	15 (5.1)	8 (2.8)
Protocol violation	5 (0.9)	4 (2.4)	2 (0.7)	1 (0.4)
Subject voluntarily withdrew	8 (1.5)	0	4 (1.4)	5 (1.8)
Lost to follow-up	1 (0.2)	0	1 (0.3)	0
Lack of efficacy	2 (0.4)	1 (0.6)	1 (0.3)	0
Other	2 (0.4)	0	0	2 (0.7)

Reference Appendix Table 3.1

Note: In Study 051-024, subject No. 45450 (2.5 mg racemic albuterol) was discontinued during the second single-blind placebo period following the 4-week treatment period, so her AEs during that period are not included in the ISS.

¹ Because many of the studies were cross-over in design, the total number of individuals participating in the studies cannot be derived by adding the total number in the treatment columns. The total column represents the number of individual subjects participating in all the clinical trials.

Table 5.1: Duration of Treatment for Subjects in All Studies Receiving Placebo or (R)-Albuterol by Dose

Duration	(R)-Albuterol (mg)							
	Placebo (n=164)	0.1 (n=10)	0.156 (n=23)	0.312 (n=40)	0.625 (n=126)	1.25 (n=153)	5 (n=28)	6.2 (n=12)
One Day Single Dose	77	10	23	40	54	80	0	0
One Day Multiple Dose ¹	12	0	0	0	0	0	28	12
0 - 2 Weeks ²	7	0	0	0	4	11	0	0
3 - 4 Weeks	68	0	0	0	68	62	0	0

Reference Appendix Table 3.2

Note: For cross-over studies, a subject contributed to totals for each treatment dose level the subject received. One day single dose studies include 051-001, 051-005, 051-006 (Group A), 051-007, and 051-025. One day multiple dose studies include 051-006 (Group B), 051-008, and 051-021. The Phase III study, 051-024, was the only study contributing to categories 0-2 weeks and 3-4 weeks.

¹ Subjects in cumulative dose studies are grouped according to the total dose received in a day.

² The 22 subjects exposed to 0-2 weeks terminated early from Study 051-024, the 4-week exposure study.

Table 5.2: Duration of Treatment for Subjects in All Studies Receiving Racemic Albuterol by Dose

Duration	Racemic Albuterol (mg)				
	0.2 (n=10)	1.25 (n=88)	2.5 (n=153)	10 (n=27)	12.4 (n=12)
One Day Single Dose	10	20	79	0	0
One Day Multiple Dose ¹	0	0	0	27	12
0 - 2 Week ²	0	5	5	0	0
3 - 4 Weeks	0	63	69	0	0

Reference Appendix Table 3.2

¹ Subjects in cumulative dose studies are grouped according to the total dose received in a day.

² The 10 subjects exposed to 0 - 2 weeks terminated early from Study 051-024, the 4-week exposure study.

IV. Adverse Events:

- A. 10 SERIOUS AEs in 9 patients; 6 serious AEs in 5 patients who received active drug; 2 received 0.625 mg of (R)-albuterol, 2 received 1.25 mg of (R)-albuterol and 1 received 2.5 mg or racemic albuterol. Three ALARMING adverse events were reported (alarming = unusual, unexpected, and/or caused significant concern for the patient's safety), and included chest pain (after 2 doses of 1.25 mg of (R)-albuterol) and an abnormal ECG after receiving 1.25 mg of (R)-albuterol, both of which resolved.**

- B.** There were 25 patients who received at least one dose of study drug who **DISCONTINUED** prematurely because of an adverse event. Of these, 5 received placebo, 1 received 0.156 mg of (R)-albuterol, 4 received 0.625 mg of (R)-albuterol, 9 received 1.25 mg of (R)-albuterol 2 received 1.25 mg of racemic albuterol and 4 received 2.5 mg of racemic albuterol.
- C.** There were 363 reports of **MODERATE/SEVERE** adverse events in 200 patients. The most frequently reported moderate/severe adverse event was headache. Adverse events related to the respiratory (asthma exacerbation) and nervous systems (nervousness) were most frequently reported. There were 11 cardiovascular adverse events considered moderate/severe in 8-292 (3%) patients who received (R)-albuterol; 4 experienced moderate/severe tachycardia.
- D.** There was no significant differences between treatment groups in terms of **DRUG-RELATED** adverse events, the majority of which were respiratory in nature. Anticipated beta agonist adverse events were more frequent with higher doses of (R)-albuterol and racemic albuterol.
- E.** In studies involving healthy volunteers and single day studies in asthmatic patients, the incidence of adverse events was greater after administration of (R)-albuterol than after administration of placebo or racemic albuterol, although the incidence of adverse events in the one repetitive dose study was the same in the (R)-albuterol and racemic albuterol groups, which was comparable to the incidence of adverse events in the placebo group. The same relationship exists when only adverse events with a frequency of 2% or greater are considered.
- F.** Chest pain was more frequent after administration of racemic albuterol than after administration of (R)-albuterol. Beta adrenergic adverse events produced by different treatments can be seen in the table below.

Table 6.5.7: Overview of Beta-Mediated Adverse Events by Treatment Across All Studies and by Study

		Number of Subjects					
		Placebo		(R)-Albuterol All doses		Racemic Albuterol All doses	
		Total (n=164)	By Type ¹	Total (n=292)	By Type ¹	Total (n=281)	By Type ¹
All AEs		75 (45.7)		159 (54.5)		141 (50.2)	
	A		3 (25.0)		22 (53.7)		18 (43.9)
	B		25 (32.5)		50 (47.2)		38 (38.8)
	C		47 (62.7)		87 (60.0)		85 (59.9)
Cardiovascular Tachycardia		3 (1.8)		21 (7.2)		12 (4.3)	
	A	0	0	15 (5.1)	7 (17.1)	12 (4.3)	6 (14.6)
	B		0		4 (3.8)		4 (4.1)
	C		0		4 (2.8)		2 (1.4)
Hypertension		1 (0.6)		2 (0.7)		0	
	A		0		1 (2.4)		0
	B		0		1 (0.9)		0
	C		1 (1.3)		0		0
Digestive Dyspepsia		10 (6.1)		17 (5.8)		12 (4.3)	
	A	1 (0.6)	0	3 (1.0)	0	3 (1.1)	0
	B		0		0		1 (1.0)
	C		1 (1.3)		3 (2.1)		2 (1.4)
Nausea		1 (0.6)		3 (1.0)		5 (1.8)	
	A		0		0		2 (4.9)
	B		1 (1.3)		2 (1.9)		1 (1.0)
	C		0		1 (0.7)		2 (1.4)
Musculoskeletal Leg Cramps		1 (0.6)		4 (1.4)		3 (1.1)	
	A	1 (0.6)	0	2 (0.7)	0	2 (0.7)	0
	B		0		0		0
	C		1 (1.3)		2 (1.4)		2 (1.4)
Nervous System Dizziness		6 (3.7)		57 (19.5)		41 (14.6)	
	A	2 (1.2)	0	14 (4.8)	5 (12.2)	4 (1.4)	2 (4.9)
	B		1 (1.3)		6 (5.7)		2 (2.0)
	C		1 (1.3)		3 (2.1)		0
Insomnia		0		1 (0.3)		0	
	A		0		0		0
	B		0		0		0
	C		0		1 (0.7)		0
Nervousness		0		39 (13.4)		31 (11.0)	
	A		0		13 (31.7)		10 (24.4)
	B		0		17 (16.0)		12 (12.2)
	C		0		9 (6.2)		9 (6.3)
Tremor		0		5 (1.7)		2 (0.7)	
	A		0		0		0
	B		0		0		0
	C		0		5 (3.4)		2 (1.4)

Reference Appendix Tables 4.7 - 4.8.3

¹By Type presents numbers of subjects in each type of study (%) reporting events in the following order: (A) = normal healthy subjects (n=42), (B) = asthmatic subjects in single day studies (n=128), and (C) = subjects in the Phase III study (n=362).

G. The most frequent adverse events which were considered related to administration of (R)-albuterol when administered to healthy volunteers were nervousness and tachycardia in 30% and 17% of patients, respectively. The incidence of these adverse events were similar to the incidence seen after racemic albuterol. The most frequent adverse events which were considered related to administration of (R)-albuterol when administered on a single day to patients with asthma were nervousness and chest congestion, 15% and 6% respectively, an incidence that was not significantly different from that noted after administration of racemic albuterol. In the one repetitive dose study, the most frequently occurring adverse events were nervousness and asthma, occurring in 8% and 6% of patients receiving (R)-albuterol, respectively, an incidence that was not significantly different than that noted after administration of racemic albuterol. The incidence of adverse events occurring 2% of the time or more after administration of various doses of (R) albuterol and racemic albuterol can be seen in the tables below.

Table 6.5.11: Adverse Events with a Subject Incidence $\geq 2\%$ for (R)-Albuterol by Dose

Preferred Term	Placebo (n=164)		0.1 mg ¹ (n=10)		0.156 mg ¹ (n=23)		0.312 mg ¹ (n=40)		0.426 mg ¹ (n=126)		1.25 mg ¹ (n=153)		6.0 mg ¹ (n=28)		6.3 mg ¹ (n=12)	
	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n	Sub ² n (%)	Ev ³ n
All AEs	27 (17)	30	0	0	3 (13.0)	3	5 (12.5)	6	24 (19)	31	40 (26)	50	23 (82)	49	0	0
Body as a Whole																
Headache	13 (7.9)	14	0	0	1 (4.3)	1	4 (10.0)	4	8 (6.3)	8	11 (7.2)	11	6 (21.4)	7	0	0
Chest Pain	13 (7.9)	14	0	0	1 (4.3)	1	4 (10.0)	4	8 (6.3)	8	10 (6.5)	10	6 (21.4)	6	0	0
Chest Pain	0	0	0	0	0	0	0	0	0	0	1 (0.7)	1	1 (3.6)	1	0	0
Cardiovascular																
Tachycardia	0	0	0	0	0	0	0	0	2 (1.6)	3	2 (1.3)	3	11 (39)	13	0	0
Tachycardia	0	0	0	0	0	0	0	0	2 (1.6)	3	2 (1.3)	3	11 (39)	13	0	0
Nervous System																
Dizziness	2 (1.2)	2	0	0	0	0	1 (2.5)	1	2 (1.6)	2	4 (2.6)	4	7 (25)	7	0	0
Nervousness	0	0	0	0	0	0	1 (2.5)	1	3 (2.4)	4	19 (12)	20	18 (64)	20	0	0
Respiratory																
Infect Viral	14 (8.5)	14	0	0	2 (8.7)	2	0	0	12 (9.5)	14	11 (7.2)	12	2 (7.1)	2	0	0
Rhinitis	8 (4.9)	8	0	0	2 (8.7)	2	0	0	5 (4.0)	5	9 (5.9)	10	0	0	0	0
Rhinitis	3 (1.8)	3	0	0	0	0	0	0	8 (6.3)	8	2 (1.3)	2	1 (3.6)	1	0	0
Wheezing	3 (1.8)	3	0	0	0	0	0	0	1 (0.8)	1	0	0	1 (3.6)	1	0	0

Reference: Appendix Table 4.11

¹Subjects in cumulative dose studies are grouped according to the total dose received in a day.

²Ev = number of events

³The 0.1 mg dose was in Study 051-001 which was conducted in France and no AEs were reported. The 6.3 mg dose was in Study 051-008 which was conducted in Scotland and no AEs were reported. The lack of reported AEs is most likely related to reporting practices among non-U.S. investigators.

Table 6.5.12: Adverse Events with a Subject Incidence \geq 2% for Racemic Albuterol by Dose

Preferred Term	0.2 mg (n=10)		1.25 mg (n=88)		2.5 mg (n=153)		10.0 mg (n=27)		12.4 mg (n=12)	
	Subject n (%)	Ev ^a n	Subject n (%)	Ev ^a n	Subject n (%)	Ev ^a n	Subject n (%)	Ev ^a n	Subject n (%)	Ev ^a n
All AEs	0	0	22 (25.0)	31	35 (22.9)	47	19 (70.4)	39	0	0
Body as a Whole	0	0	12 (13.6)	16	12 (7.8)	14	6 (22.2)	6	0	0
Headache	0	0	10 (11.4)	13	11 (7.2)	12	4 (14.8)	4	0	0
Chest Pain	0	0	3 (3.4)	3	2 (1.3)	2	2 (7.4)	2	0	0
Cardiovascular	0	0	0	0	3 (2.0)	3	9 (33.3)	10	0	0
Tachycardia	0	0	0	0	3 (2.0)	3	9 (33.3)	10	0	0
Nervous System	0	0	3 (3.4)	3	14 (9.2)	14	16 (59.3)	20	0	0
Dizziness	0	0	0	0	0	0	4 (14.8)	4	0	0
Nervousness	0	0	3 (3.4)	3	14 (9.2)	14	14 (51.9)	16	0	0
Respiratory	0	0	11 (12.5)	12	15 (9.8)	16	3 (11.1)	3	0	0
Infect Viral	0	0	5 (5.7)	5	10 (6.5)	10	0	0	0	0
Rhinitis	0	0	3 (3.4)	3	5 (3.3)	5	0	0	0	0
Whooping	0	0	4 (4.5)	4	1 (0.7)	1	3 (11.1)	3	0	0

Reference Appendix Table 4.11

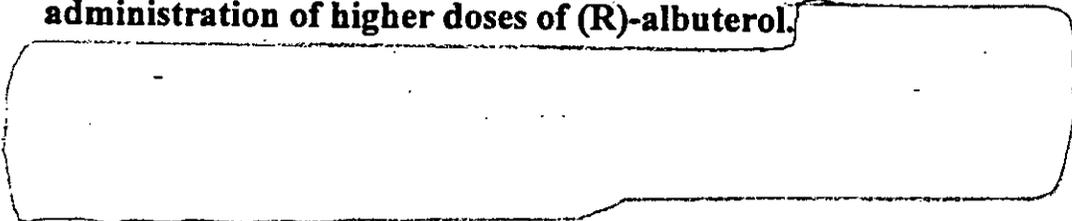
^aSubjects in cumulative dose studies are grouped according to the total dose received in a day.

^aEv = number of Events

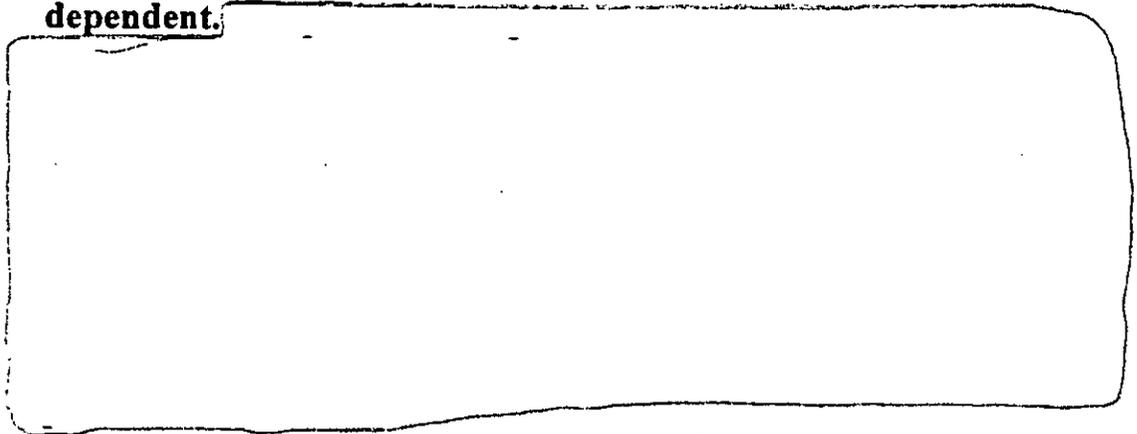
H. There was no significant difference in the incidence of adverse events based on age, gender, race, weight or percent predicted FEV-1.

V. Laboratory tests:

A. The percent change in serum POTASSIUM levels from baseline divided on the basis of the type of study and the patient population can be seen in the table below. This limited amount of data would suggest that serum potassium levels decrease more in healthy volunteers than in patients with asthma and decrease less after repetitive dosing. These changes are not clinically significant in patients with asthma. There was a slightly greater, but not clinically significant, decrease in serum potassium after administration of higher doses of (R)-albuterol.



B. The percent change in serum GLUCOSE levels from baseline divided on the basis of the type of study and patient population can be seen in the table below. Unlike serum potassium levels, mean glucose levels increased slightly more in asthmatic patients than in healthy volunteers. Similar to changes in serum potassium levels, there was less increase in mean serum glucose levels after repetitive administration than after single dose administration, and the amount of increase in mean serum glucose was dose-dependent.



C. There were no changes in other laboratory values that raised any concern about the safety of (R)-albuterol.

VI. Vital Signs:

A. The only data that can be used to assess treatment effect on vital signs is the data from studies 024 and [redacted] since vital signs in other studies were only done prior to drug administration and at the end of the study, between which times patients received more than one drug or more than one dose. In studies 024 and [redacted] higher doses produced more effect on heart rate than lower doses and changes in heart rate were modest and not clinically significant. Changes in systolic and diastolic blood pressure were minimal and not clinically significant. For more detailed information on vital signs, see the specific review of these two studies.

VII. ECG data:

A. There were no unexpected increases in mean ventricular rate in patients who received (R)-albuterol and there were no changes in ventricular rate that would produce concern about the administration of (R)-albuterol. The percent change in mean ventricular rate after administration of (R)-albuterol was slightly greater in the [redacted] For example, after a administration of a single dose of 0.625 mg of (R)-albuterol to adults, there was a 10% increase in ventricular rate, [redacted] and after administration of a dose of 1.25 mg of (R)-albuterol there was a 16% and a [redacted] increase in ventricular rate in adults [redacted]

B. QTc interval: There were 11 patients in study 024 who had a QTc interval of more than 500 ms on one or more occasions during the study, 3 in the 0.625 mg (R)-albuterol group, 3 in the 2.5 mg racemic albuterol group, 3 in placebo group, and 2 in the 1.25 mg (R)-albuterol group, all of whom were women. None of the patients who had a prolonged QTc interval had any adverse clinical event.

No clinically significant differences overall were seen in QTc interval based on age, gender, race, weight or baseline FEV-1.

The percent change in QTc interval in studies of healthy volunteers and asthmatic patients who received study drug on a single day can be seen in the table below. The mean changes for (R)-albuterol are not significantly different than the mean changes for racemic albuterol. The maximum QTc interval seen after administration of (R)-albuterol in the single day studies in asthmatic patients was less than the maximum QTc interval seen after administration of placebo and the maximum QTc interval noted after administration of (R)-albuterol to healthy volunteers was less than that noted after administration of racemic albuterol.

Table 9.3.1: Summary of QTc Interval Maximum Percent Change from Pre-Dose for Healthy Volunteers and Asthmatic Subjects in Single Day Studies

	Studies in Healthy Volunteers ¹		Single Day Studies in Asthmatic Subjects ¹		
	(R)-Albuterol	Racemic Albuterol	Placebo	(R)-Albuterol	Racemic Albuterol
Pre-Dose					
Mean (SD)	399.3 (27.57)	397.8 (27.03)	407.0 (22.67)	407.6 (21.41)	405.0 (23.21)
Min, Max	350.0, 460.0	350.0, 436.0	357.0, 447.0	366.0, 460.0	360.0, 459.0
n	29	29	23	100	53
Maximum Post-Dose					
Mean (SD)	436.9 (30.85)	434.0 (38.58)	405.7 (23.27)	416.1 (20.99)	415.2 (21.57)
Min, Max	393.0, 490.0	360.0, 520.0	374.0, 459.0	373.0, 455.0	367.0, 463.0
n	28	29	23	99	52
Percent Change from Pre-Dose²					
Mean (SD)	9.7 (10.05)	9.5 (12.01)	-0.3 (3.82)	2.1 (4.82)	2.8 (4.32)
Min, Max	-8.7, 36.6	-11.5, 40.5	-6.7, 8.7	-7.2, 13.0	-10.7, 12.2
n	28	29	23	99	52

Reference Appendix Tables 7.20.1-7.20.2

Note: For cross-over studies, a subject contributes only once to each treatment column header total, but contributes to each treatment summary for each dose level of the treatment received. Percent change was calculated by comparing the post-dose value to pre-dose on that day.

¹ Only subjects from Study 051-006 had both pre-dose and post-dose measurements.

² Only subjects from Studies 051-006 and 051-021 had both pre-dose and post-dose measurements.

The percent mean change in QTc interval in study 024, the repetitive dose study of 4 weeks duration, can be seen in the table below. The maximum increase in QTc interval was slightly greater in the (R)-albuterol group than in the placebo group after the first dose, but slightly greater in the placebo group than in the (R)-albuterol group after 4 weeks of treatment and less at both time points than the maximum increase seen in the racemic albuterol group. This lesser increase in QTc interval after 4 weeks of treatment in the (R)-albuterol group was independent of the dose administered (see table below)

Table 9.3.2: Summary of QTc Interval Maximum Percent Change from Pre-Dose for the Phase III Study at Week 0, Week 2, and Week 4¹

	Week 0			Week 2			Week 4		
	Placebo (n=75)	(R)-Albuterol (n=145)	Racemic Albuterol (n=142)	Placebo (n=75)	(R)-Albuterol (n=145)	Racemic Albuterol (n=142)	Placebo (n=75)	(R)-Albuterol (n=145)	Racemic Albuterol (n=142)
Pre-Dose									
Mean (SD)	412.5 (23.5)	414.0 (23.0)	413.8 (25.2)	413.3 (23.3)	413.9 (22.9)	415.1 (25.1)	416.2 (25.5)	414.9 (24.0)	414.3 (27.0)
Min, Max	369.0, 495.0	354.0, 484.0	352.0, 491.0	366.0, 508.0	348.0, 469.0	362.0, 491.0	361.0, 504.0	350.0, 491.0	355.0, 486.0
n	75	144	142	70	134	132	64	130	132
Max Post-Dose									
Mean (SD)	428.0 (29.5)	434.5 (29.0)	433.4 (25.9)	425.8 (26.7)	430.0 (21.2)	430.9 (28.5)	423.3 (23.0)	430.2 (25.0)	432.0 (33.6)
Min, Max	378.0, 545.0	363.0, 567.0	383.0, 499.0	363.0, 518.0	363.0, 482.0	370.0, 598.0	377.0, 515.0	369.0, 505.0	378.0, 677.0
n	75	144	142	70	134	132	67	130	132
Percent Change from Pre-Dose²									
Mean (SD)	3.8 (4.9)	5.0 (4.54)	4.8 (4.0)	3.1 (3.9)	4.0 (4.0)	3.9 (5.5)	1.9 (3.8)	3.7 (3.8)	4.4 (6.8)
Min, Max	-4.1, 32.3	-5.3, 32.4	-5.2, 21.4	-7.2, 20.5	-7.0, 18.5	-3.8, 50.3	-5.5, 11.0	-5.7, 20.7	-6.6, 69.3
n	75	144	142	70	134	132	67	130	132

Reference Appendix Tables 7.20.3-7.20.5

¹ Only Weeks 0, 2 and 4 pre-dose and post-dose measurements were summarized.

² Percent change was calculated by comparing the post-dose value to pre-dose on that day.

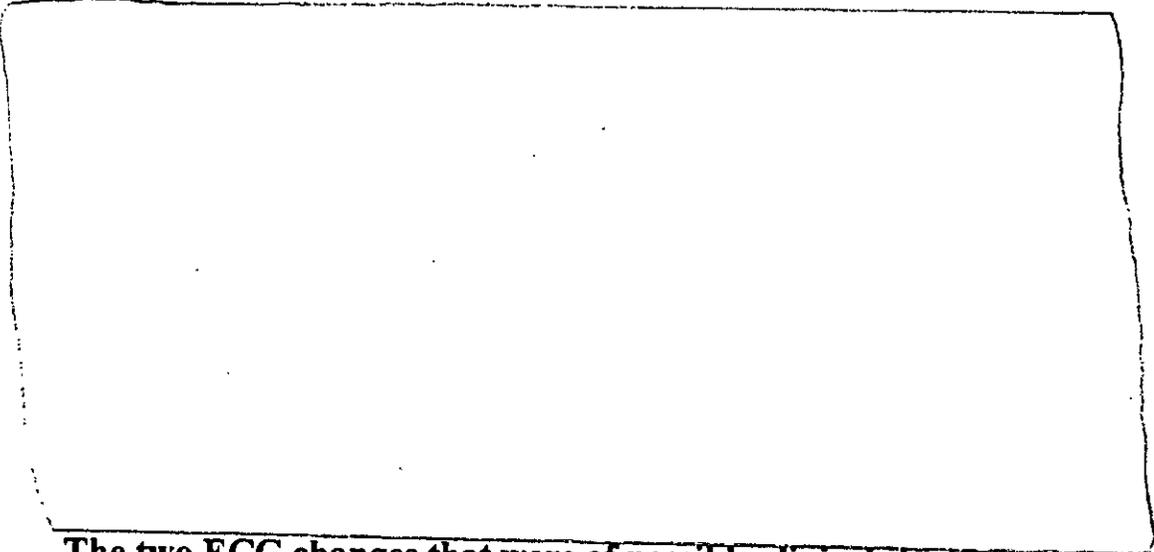
Table 9.3.3: Summary of QTc Interval Maximum Percent Change from Pre-Dose by Dose for the Phase III Study at Week 0 and Week 4¹

	Week 0					Week 4				
	Placebo (n=75)	(R)-Albuterol		Racemic Albuterol		Placebo (n=75)	(R)-Albuterol		Racemic Albuterol	
		0.625 mg (n=72)	1.25 mg (n=73)	1.25 mg (n=68)	2.5 mg (n=74)		0.625 mg (n=72)	1.25 mg (n=73)	1.25 mg (n=68)	2.5 mg (n=74)
Pre-Dose										
Mean (SD)	412.5 (23.5)	414.2 (22.6)	413.8 (23.6)	412.4 (21.3)	415.2 (27.0)	416.2 (25.5)	414.3 (22.6)	415.7 (25.5)	412.9 (25.6)	415.7 (28.2)
Min, Max	369.0, 495.0	354.0, 462.0	358.0, 484.0	352.0, 491.0	360.0, 475.0	361.0, 504.0	350.0, 469.0	361.0, 491.0	364.0, 481.0	355.0, 486.0
n	75	71	73	68	74	68	68	63	63	69
Max Post-Dose										
Mean (SD)	428.0 (29.5)	432.2 (28.2)	434.7 (29.7)	430.7 (24.3)	433.8 (27.1)	423.3 (23.0)	429.0 (23.0)	431.4 (27.1)	427.2 (25.4)	434.3 (39.3)
Min, Max	378.0, 545.0	363.0, 567.0	383.0, 564.0	384.0, 499.0	383.0, 492.0	377.0, 515.0	369.0, 502.0	364.0, 505.0	378.0, 498.0	384.0, 677.0
n	75	71	73	68	74	67	68	63	63	69
Percent Change from Pre-Dose²										
Mean (SD)	3.8 (4.9)	4.4 (3.9)	3.6 (5.1)	4.5 (3.9)	3.1 (4.1)	1.9 (3.8)	3.6 (4.1)	3.8 (3.5)	3.5 (3.4)	3.1 (8.9)
Min, Max	-4.1, 32.3	-3.8, 22.7	-5.3, 32.4	-8.0, 21.4	-5.2, 15.8	-5.5, 11.0	-5.7, 20.7	-3.2, 11.5	-5.7, 12.4	-6.6, 69.3
n	75	71	73	68	74	67	68	63	63	69

Reference Appendix Tables 7.21.1-7.21.2

¹ Only Weeks 0 and 4 pre-dose and post 1 hour measurements were summarized.

² Percent change was calculated by comparing the post-dose value to pre-dose on that day.



The two ECG changes that were of possible clinical significance both occurred in patients after administration of 1.25 mg of (R)-albuterol. One patient was a 48 year old female who developed extensive ST segment changes and first degree AV block approximately one hour after drug administration, which returned to normal within 30 minutes. This patient was discontinued from the study and did not receive any further doses of (R)-albuterol. The other patient was a 42 year old female who developed diffuse non-specific T wave abnormalities after the first dose of 1.25 mg of (R)-albuterol at visit 2 in study 024. The patient developed numbness of the left hand in conjunction with the ECG changes. The numbness of the hand resolved within 24 hours and the ECG changes had resolved when an ECG was repeated 2 months later.

COMMENT: In this reviewer's opinion, these changes were related to the administration of 1.25 mg of (R)-albuterol. Such changes are compatible with the administration of this class of drug and probably represent beta agonist-induced myocardial ischemia. The potential for this type of effect is present in the labeling for beta agonists in general and in the labeling for (R)-albuterol specifically. The sponsor has proposed a usual dose of 0.625 mg of (R)-albuterol, with the option of giving a dose of 1.25 mg if the patient has more severe asthma. This is acceptable

provided a statement is added to the labeling to indicate that patients receiving a dose of 1.25 mg of (R)-albuterol may need to be monitored more closely for cardiovascular effects.

IN SUMMARY, there were more alarming adverse events, premature discontinuations because of an adverse event, significant ECG changes, and percent increase in QTc interval after administration of 1.25 mg of (R)-albuterol than after administration of other doses of (R)-albuterol or racemic albuterol. Despite these findings, a dose of 1.25 mg of (R)-albuterol may be indicated for patients with more severe asthma. In general, the effect of (R)-albuterol on safety parameters was comparable to the effect of racemic albuterol. The data support the safety of (R)-albuterol for the treatment of acute asthma.

**APPEARS THIS WAY
ON ORIGINAL**

120 day safety update

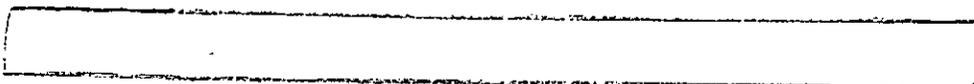
I. In this update, studies are classified as revised, i.e. additional data is supplied on studies included in the ISS, or new, i.e. safety data is being submitted for the first time. The database in this study includes information from studies completed prior to 30 September 1997.

- ◆ phase I clinical pharmacology studies in volunteers (revised)(studies 006, 008, 013)
- ◆ phase II single-day studies in asthmatics (revised)(studies 005, 007, 001, [] 021, 025)
- ◆ phase II multiple-day studies in asthmatics (new)(study 009)
- ◆ phase III pivotal four week, parallel group study (lab data revised)(study 024)

II. Additional safety data obtained since the submission of the ISS includes:

◆ 2 studies classified as ongoing, now completed

- study 009: 12 patients added to database (new)
- study 013: 12 patients added to database (revised)



◆ Data for 16 laboratory tests were updated

III. The demographics, when revised to contain new data, were similar to the demographics for the patient population included in the ISS, with a slight increase in the percentage of males and Caucasians.

IV. New phase II multiple-day study: This was a study in 37 mild asthmatics with an age range of 19-45 years, the data from which was incorporated into the revised analyses.

V. Adverse Events: There was no significant increase or decrease in the incidence of specific adverse events after administration of (R)-albuterol when data was included that had not been included in the ISS. As a result, there was no change in the interpretation of the data when evaluating the adverse events seen after (R)-albuterol administration or when comparing such adverse events to those seen after administration of racemic albuterol.

VI. Laboratory Tests: The changes that were seen after addition of new data, i.e. data that was not included in the ISS, were not significantly different than those seen after review of the ISS data. There were no changes in laboratory tests that reflected any safety issue inherent in the administration of (R)-albuterol.

VII. Vital Signs: There were no clinically mean significant changes in vital signs after administration of (R)-albuterol and interpretation of these data are not changed by the revised analysis based on the 120 day safety update.

VIII. ECGs: There were no clinically significant mean changes in ECGs after administration of (R)-albuterol and interpretation of these data are not changed by the revised analysis based on the 120 day safety update.

SUMMARY: The revised analyses submitted by the sponsor, as part of the 120 day safety update, do not change the conclusions reached previously about the safety of (R)-albuterol.

**APPEARS THIS WAY
ON ORIGINAL**

NOMENCLATURE

The sponsor initially chose [redacted] as the product name. In a conference call with the sponsor on 7 August 1997, we notified the sponsor that the name [redacted] was unacceptable for this product, based on audio and visual similarities with other medical products.

The sponsor requested in the submission of 13 October 1997 that we reconsider [redacted] as the proprietary name for this product, based on two market research studies. The conclusion from these studies was that: 1) there were no misprescriptions for [redacted]; 2) there was a low incidence of confusion with other marketed brands; 3) the name [redacted] was pronounced correctly by 97% of respondents; and 4) associations and connotations with [redacted] were low. There was, however, no indication by the sponsor that such studies had been validated. The Division concluded, as did the Labeling and Nomenclature Committee (LNC), that the name was still unacceptable for the reasons noted above.

A conference call was again held with the sponsor on 6 January 1998, at the sponsor's request. The Division conveyed to the sponsor that the market research studies submitted by the sponsor did not alleviate concern about potential prescribing errors based on the audio and visual similarities with other marketed products.

The sponsor then proposed the name [redacted] which the Division and the LNC also found unacceptable. A market research study submitted by the sponsor to support the name [redacted] was also felt to be unacceptable.

As a result, the sponsor has submitted the name Xopenex for our review. Both the LNC and the Division feel that this name is acceptable.

DSI Audits of Edwards Site

After submission of the NDA, it was determined by the sponsor that one site for this study (Edwards site) was flawed (numerous altering of ECG tracings, possible fabrication of chest x-ray report). An internal audit by the sponsor concluded that the integrity of the data had been maintained. The sponsor was, nevertheless, asked to analyze the data from this study excluding this site. The Division of Scientific Investigation (DSI) also audited the site on 22 October and 23 December 1997 and documented fabricated and/or altered source documents that were used to qualify ineligible patients for study 024. Audits of other sites involved in study 024 by DSI did not reveal any irregularities at these sites.

**APPEARS THIS WAY
ON ORIGINAL**