CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Medical Review(s)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	20-949	**Application Type:**	NDA
Sponsor:	Dey, L.P.	**Proprietary Name:**	AccuNeb™ Inhalation Solution
Investigator:	N/A	**USAN Name:**	Albuterol Sulfate
Category:	Bronchodilator	**Route of Administration:**	Oral Inhalation
Reviewer:	Eugene J. Sullivan, MD FCCP	**Review Date:**	April 17, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
April 4, 2001	April 5, 2001	Safety Update	

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY: This submission is a safety update for AccuNeb™ Inhalation Solution. AccuNeb Inhalation Solution is currently under review in DPADP for the treatment of bronchospasm in asthmatic children, aged 2-12 years. The submission contains the results of a literature search for all relevant information published since May, 1999. Five journal articles and two foreign language abstracts are included. These reports describe clinical and preclinical trials involving the use of nebulized albuterol sulfate in children. The submission does not include any new data from clinical trials involving AccuNeb. The information that is provided in this submission does not raise any new safety concerns regarding AccuNeb. No changes in the proposed label are necessary, based upon this submission.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION:

New clinical studies:	_____	**Clinical Hold**	____	**Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____	**Not Approvable**

SIGNATURES:

Medical Reviewer: _____ **Date:** _____

Eugene J. Sullivan, MD, FCCP

Medical Team Leader: _____ **Date:** _____

Badrul Chowdhury, MD, PhD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eugene Sullivan
4/17/01 10:56:11 AM
MEDICAL OFFICER

Badrul Chowdhury
4/17/01 01:34:03 PM
MEDICAL OFFICER
I concur

N, H, KeK

FEB 2 2 2000

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-949	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey, L.P.	**PROPRIETARY NAME:**	Accuneb™
CATEGORY:	Nebulized B-agonist	**USAN NAME:**	Albuterol Inhalation Solution 0.63mg and 1.25 mg
		ROUTE:	Oral
MEDICAL OFFICER:	Daniel J. O'Hearn, M.D.	**REVIEW DATE:**	~~12~~1/7/~~99~~2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 3, 1999	December 6, 1999	Response to Approvable Letter	

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments
March 27, 1998	NDA	

REVIEW SUMMARY: The sponsor of NDA 20-949 received an approvable letter dated March 30, 1999. The issues that prevented the application from being approved were largely related to chemistry and manufacturing concerns, however, there were a number of clinical points that required clarification and these were enumerated in the approvable letter. This is a review of the questions/comments or requests for clarification in the clinical review of safety and efficacy that were forwarded to the sponsor as part of the approvable letter. The sponsor appears to have adequately addressed the clinical comments and requests for clarifications. A labeling review is part of this review but further pharmacolgy and CMC revisions to the label may need to be made. ~~Pending~~

_____

OUTSTANDING ISSUES: Further pharmacolgy and CMC revisions to the label may need to be made to the labeling. ~~Pending~~

_____

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	_____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	X	**APPROVABLE**	_____	**NOT APPROVABLE**

DUE TO POOR COPIES AND PAGINATION PROBLEMS, A SEPARATE PAGE IS INCLUDED CONTAINING ONLY THE VARIOUS GRAPHS AND CHARTS AFTER EACH PERTINENT PAGE

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

SIGNATURES

Reviewer: /S/ Date: 2/17/00

Team Leader: /S/ Date: 2/22/00

I. Introduction and March 30, 1999 Approvable Letter

The sponsor of NDA 20-949 received an approvable letter dated March 30, 1999. The issues that prevented the application from being approved were largely related to chemistry and manufacturing concerns, however, there were a number of clinical points that required clarification and these were enumerated in the approvable letter. The following questions/comments or requests for clarification in the clinical review of safety and efficacy were forwarded to the sponsor as part of the approvable letter.

25. In a September 29, 1998, correspondence regarding DL-009, you stated that "when the ITT population (referred to as 'evaluable') was defined in accordance with the Investigator's final report, that population data did not match the report." You stated that the data diskette and the data used by — for the integrated analysis were compared and were identical. Therefore, the available population definitions from DL-019 were used for analysis. The data were sent with 2 fewer patients in each of the 0.75 mg and placebo groups. You further stated that the %ΔAUC FEV1 variable in the September 29 correspondence was consistent with the analysis of DL-019. Provide an explanation of why these 4 subjects were eliminated, and what is meant by the above statements.

26. There is a discrepancy between change in heart rate data from DL-009 (vol. 1-12, p. 99) and the data in Table 8.3.1 in Appendix B (vol. 1-38). Clarify if these discrepancies are solely due to the fact that the former includes 28 patients and the latter includes 29 patients.

27. Submit the case report form of the study subject (DL-019, Table 35, vol. 1-16) in the 1.5 mg group with a new instance of a depressed ST segment observed at Visit 2, 30 minutes post-dose. This depressed ST segment was not mentioned pre-dose and was still present at 60 and 90 minutes post-dose. Additionally, provide any details on this observation in this subject.

28. In Study DL-019, the 0.75 mg dose often had higher values than the 1.5 mg dose after the first dose of the drug at Visit 2. Verify that the 0.75 mg and 1.5 mg doses were not mislabeled and mistakenly switched at Visit 2 but were correctly labeled at Visit 4 or were not switched in the analysis.

29. According to the Integrated Clinical and Statistical Report narrative, Patient No. 157 had results interpreted by the centralized cardiologist as clinically relevant that were considered irrelevant by the investigator. Clarify what findings on the EKGs of Patient No. 157 were considered to be relevant.

30. In Data Listing 14 (vol. 1-26, data on DL-019 EKGs), there is a classification called "deteriorated (from baseline)." Clarify the meaning of this term.

31. With reference to the Integrated Clinical and Statistical Report for DL-019, Table M ("Summary of Adverse Events that occurred in > 2% of the ITT Population") and Table N ("Summary of Potentially Drug-Related Adverse Events") do not explain the difference between worsening of asthma symptoms versus an asthma exacerbation. Provide an explanation of how this distinction was made. More exact terms should be provided for these groupings.

32. For future study report submissions, also provide a more conventional method (e.g., ANOVA) for analyzing study data if a Nonlinear Mixed Effects Model (NONMEM) analysis is used.

The following preliminary labeling comments are provided. Additional comments will be forwarded following review of the response to this letter.

33. The proposed tradename, ——— , is not acceptable. Provide an alternative proposed tradename in writing.

34. Revise the tradename to describe the product in terms of dose instead of concentration. For example, the tradename should be expressed as albuterol sulfate inhalation solution, 0.75 mg, instead of albuterol sulfate inhalation solution, 0.021%. This comment applies equally to the 0.042% strength.

35. Include in the package insert the graphs from Study DL-019 regarding the % change in FEV_1 from pre-dose versus time at Visits 2 and 4 for both doses of albuterol sulfate and

placebo. Include a horizontal line depicting the 15% level on the graph so that one can see where the curve crosses the line.

36. Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in patients 2-12 years of age. Clarify this age range in the package insert and all carton and container labeling to avoid misintended use of these products in adults. Specify appropriate age groups in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert.

37. In the draft package insert, reference [ ] actually refers to rescue medication use. Therefore, this reference appears to be wrong. Provide the correct reference.

38. Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in subjects 2-12 years of age. Efficacy data referring to subjects greater than 12 years of age should not be included in the package insert.

39. Revise the CLINICAL PHARMACOLOGY, Pharmacokinetics subsection of the package insert according to the most recently approved package insert for Ventolin™ (albuterol sulfate) Inhalation Solution. In addition, add the following sentence to the end of this subsection: '[ ]

The sponsor provided a response to the comments/clarifications in the order that the comments were received from the FDA.

II. The Response

A. Comment #25

"In a September 29, 1998, correspondence regarding DL-009, you stated that "when the ITT population (referred to as 'evaluable') was defined in accordance with the Investigator's final report, that population data did not match the report." You stated that the data diskette and the data used by — for the integrated analysis were compared and were identical. Therefore, the available population definitions from DL-019 were used for analysis. The data were sent with 2 fewer patients in each of the 0.75 mg and placebo groups. You further stated that the %ΔAUC FEV_1 variable in the September 29 correspondence was consistent with the analysis of DL-019. Provide an explanation of why these 4 subjects were eliminated, and what is meant by the above statements."

The sponsor's response to this comment remained confusing. While it is understood how the evaluable population in each group changed from 23 to 21 (removal of subjects 202 and 203), it

is still not clear from the sponsor how two subjects from each of the placebo and 0.75 mg groups were removed)

		Placebo	0.75 mg	1.5 mg	3.0 mg
ITT Population (formerly known as Evaluable)	Original (Vol. 1-12, p.160)	25	29	28	27
	New (9/29/98)	23	27	28	27
Evaluable Population (formerly known as Completers)	Original (Vol. 1-12, p.160)	23	23	23	23
	New (9/29/98)	21	21	21	21

The sponsor provided a clearer answer to comment #25 in a fax dated 1/4/00. In the fax, the sponsor again points out that there were 25 subjects in the placebo group and 29 subjects in the 0.75 mg group in [ ] original analysis. In the [ ] re-analysis, there were 23 subjects in the placebo group and 27 subjects in the 0.75 mg group. Two subjects in the 0.75 mg group and two subjects in the placebo group had values of –99 for FEV_1 on one occasion each. "-99" means that this was a missing value and therefore, in the [ ] re-analysis, these values were set to missing and dropped from the analysis.

When 29 subjects for the 0.75 mg treatment group were included in the sponsor's original analysis [ ] for the comparison of the FEV_1-AUC –Change from Baseline with the 25 subjects in the placebo group, the p value was 0.05. When 27 subjects for the 0.75 mg treatment group were included in the sponsor's re-analysis [ ] for the comparison of the FEV_1-AUC – Change from Baseline with the 23 subjects in the placebo group, the p value was 0.055. Thus, the two analyses provide for similar results. The discrepancy in the numbers between the two analyses has been adequately explained as has the explanation for Comment #25.

B. Comment #26

"There is a discrepancy between change in heart rate data from DL-009 (vol. 1-12, p. 99) and the data in Table 8.3.1 in Appendix B (vol. 1-38). Clarify if these discrepancies are solely due to the fact that the former includes 28 patients and the latter includes 29 patients."

The sponsor replies that there were errors in the computations represented by not only the change in heart rate means, but in other vital signs as well. "The change in pre-dose values appear to be the actual timepoints minus a constant." The sponsor was asked for clarification on 12/23/99, as it was not understood how this answer related to the original comment. A brief teleconference was held with Dey on 12/29/99 at 1:30 p.m. EST – Peggy Berry represented Dey

and [ ] represented [ ] The sponsor maintained that they would get back to us after looking into it further.

The sponsor provided clarification for Comment #26 in the same fax dated 1/4/00 that contained the clarification for Comment #25. The sponsor says that the discrepancy in heart rate can be explained by two factors:

1. The sample sizes used for the computations differed between [ ]'s analysis and [ ]'s re-analysis. [ ] included all non-missing data on a visit-by-visit and by-timepoint basis. Therefore, the sample size fluctuated from 28 to 30 across the treatment arms and timepoints. [ ] analysis completely dropped two subjects (#103 and 213) due to missed visits, thus having only 28 subjects for all treatment arms and timepoints.
2. [ ] analysis and [ ] original analysis incorrectly analyzed –99 values as data points instead of missing values. These were corrected in the revised Table 8.3.1.

In the response to the approvable letter, the sponsor submitted a revised Table 8.3.1 listing the mean vital signs for Study DL-009. This table contains two changes compared with the original Table 8.3.1 (Volume 1.38) submitted with the NDA. There are changes in the "N" (number of subjects) and the means for 30 minutes post-dose and 6 hours post-dose for the 0.75 mg treatment group. While there were also two new "-99" values in the [ ] re-analysis for the FEV_1 data for the placebo group(as noted in the Table 2 received by fax 1/4/00 as part of a clarification.), there were no changes in this revised Table 8.3.1 for the placebo group. I asked the sponsor on 1/18/00 whether the fact that the revised Table 8.3.1 did not contain changes in the placebo group meant that the missing "-99" values were only for the FEV_1 data and not the vital sign data. After speaking with [ ] the sponsor confirmed on 1/20/00 that the subjects with "-99" values in the placebo group had already been eliminated in the original Table 8.3.1.

It appears that the incongruencies originally identified in Comment #26 have been adequately explained by the sponsor.

C. Comment #27 (with information related to Comment #29)

"Submit the case report form of the study subject (DL-019, Table 35, vol. 1-16) in the 1.5 mg group with a new instance of a depressed ST segment observed at Visit 2, 30 minutes post-dose. This depressed ST segment was not mentioned pre-dose and was still present at 60 and 90 minutes post-dose. Additionally, provide any details on this observation in this subject."

This subject was identified by the sponsor to be Subject #157 at Site 006. This subject also happens to be the topic of Comment #29 in which there appeared to be a discrepancy between the interpretation of the clinical relevance of some ECG findings between the site investigator and the pediatric cardiologist who overreads the ECGs.

The request for the case report form was based largely on what were thought to be new ECG findings. It was not clear from the original submission that this subject was #157, hence,

the apparent ~~duplicity~~redundancy in our request with Comment #29. The subject was a pre-menarchal 11 year-old female in the 1.5 mg albuterol group.

The screening Visit 1 ECG on 2/3/97 is listed by the pediatric cardiologist as abnormal with "clinical relevance" and inverted T waves and normal ST segments. It is not readily apparent from the form exactly what part of the ECG was the clinically relevant abnormal part. At Visit 2, the pre-dose ECG is listed as normal with normal ST segments and T waves while depressed ST segments and inverted T waves were identified 30, 60 and 90 minutes post-dose on 2/15/97 and was listed as mild in severity and unrelated to study drug. Dr. Thomas Edwards, the clinical investigator at the site, notes that this depressed ST segment was not clinically significant and that it was a juvenile variant. No action was taken and there does not appear to be a note in the CRF that the patient was having any symptoms consistent with cardiac disease at the time of the visits.

For Visit 3, the predose ECG is listed as normal with the 30 minute post-dose ECG listed with as abnormal and clinically relevant with normal ST segment and inverted T waves. No ECGs were performed at 60 and 90minutes post-dose. At Visit 4, the pre-dose ECG is listed as being abnormal but clinically irrelevant with depressed ST segments and normal T waves. The 30 minute post-dose was originally listed as normal in 3/18/97 with a depressed ST segment and then was revised to clinically irrelevant abnormal with depressed ST segment on 5/6/99 when the cardiologist at [redacted] was asked to re-read the ECGs. The ECGs at 60 and 90 minutes post-dose are listed as normal with normal ST segments and T waves.

In a letter dated 5/26/99, the pediatric cardiologist, [redacted] states that 11 ECGs were "evaluated for an eleven year old child with nonspecific ST and T wave changes which fluctuate over time from ECG to ECG. These findings were not clinically relevant." This appears to be the same physician who originally listed a number of these ECGs as clinically relevant abnormal ECGs. A letter dated 5/13/99 is also available from Dr. Thomas Edwards, the site investigator, who reviewed copies of the subject's records. He states "there appeared to be no clinically significant changes throughout the study. The visit one screening EKG exhibited a T wave and ST segment pattern which remained relatively consistent throughout the subsequent EKG tracings reviewed.

Actual copies of the ECGs were submitted by the sponsor in this response. It does not appear that there were overt changes amongst the ECGs aside from what appear to be very slight, if any, changes in the ST segments and minor variation in the T waves. T wave inversions and/or flattening were present in V1 – V4 in the ECGs throughout, including the Visit 2 pre-dose ECG.

It does not appear that there were important ECG changes in this subject.

D. Comment #28

"In Study DL-019, the 0.75 mg dose often had higher values than the 1.5 mg dose after the first dose of the drug at Visit 2. Verify that the 0.75 mg and 1.5 mg doses were not mislabeled and

mistakenly switched at Visit 2 but were correctly labeled at Visit 4 or were not switched in the analysis."

Because of the observation that the mean value of %Δ AUC FEV_1 and MAX FEV_1 for 0.75 mg was higher than that for 1.5 mg, the FDA speculated that the data was potentially mixed up between the doses. The sponsor says that they verified, back to the randomization file, that the treatment groups were appropriately assigned and not switched in the analysis.

E. Comment #29

"According to the Integrated Clinical and Statistical Report narrative, Patient No. 157 had results interpreted by the centralized cardiologist as clinically relevant that were considered irrelevant by the investigator. Clarify what findings on the EKGs of Patient No. 157 were considered to be relevant."

Please see the response for Comment #27.

F. Comment #30

"In Data Listing 14 (vol. 1-26, data on DL-019 EKGs), there is a classification called "deteriorated (from baseline)." Clarify the meaning of this term."

The sponsor says that [ ], who was responsible for the centralized reading of the EKGs, provided the following clarification: "Deterioration from Baseline is defined as any change or changes that are less than normal when compared to the baseline EKG interpretation of the [ ] cardiologist. These changes may or may not be clinically significant based on the complete evaluation." The terms were utilized in the evaluation of the EKGs for Subject #157 that was previously discussed in the response to Comment #27.

G. Comment #31

"With reference to the Integrated Clinical and Statistical Report for DL-019, Table M ("Summary of Adverse Events that occurred in > 2% of the ITT Population") and Table N ("Summary of Potentially Drug-Related Adverse Events") do not explain the difference between worsening of asthma symptoms versus an asthma exacerbation. Provide an explanation of how this distinction was made. More exact terms should be provided for these groupings."

The sponsor replies that the adverse events were first coded using a COSTART version that coded any investigator adverse event related to asthma to the preferred term 'asthma' so asthma exacerbations were not differentiated from worsening of asthma. To be more specific, a convention for coding was adopted and defined in the statistical report provided as Appendix A in the ISS of the NDA. The preferred term "asthma exacerbation" was used for the investigator's term of "asthma exacerbation" and the preferred term "worsening asthma" was used for the investigator's term of "asthma flare."

The sponsor says that it reviewed the data listings and: "asthma exacerbation" was used when asthma symptoms worsened enough to require therapeutic intervention with oral or parenteral steroids, or medication other than the study medication, as judged necessary by the investigator, or if asthma symptoms interfered with the completion of the post-dose PFT measurements during a clinic visit. "Worsening of asthma" was used when symptoms of asthma were noted, such as inspiratory and/or expiratory wheezing, that did not require any concomitant medications other than the albuterol rescue medication.

These clarifications provided by the sponsor appear adequate and do not appreciably change the interpretation of the adverse event data.

Preferred Term	1.5 mg Albuterol N=115	0.75 mg albuterol N=117	Placebo N=117
Asthma exacerbation	13%	11%	9%
Worsening asthma	7%	4%	10%
1and/or 2	18%[a]	15%	19%[b]

[a] Two subjects had both an asthma exacerbation and worsening asthma.
[b] One subject had both an asthma exacerbation and worsening asthma.

There appears to be somewhat of a negative dose response with asthma exacerbations as it appears to more common with 1.5 mg albuterol, followed by 0.75 mg and then placebo. When either Worsening asthma or Asthma exacerbation is considered, there is not much of a discrepancy between the groups.

H. Comment #32

"For future study report submissions, also provide a more conventional method (e.g., ANOVA) for analyzing study data if a Nonlinear Mixed Effects Model (NONMEM) analysis is used."

The sponsor says that more conventional methods of analysis will be provided in the future.

I. Comment #33

"The proposed tradename, [ ] is not acceptable. Provide an alternative proposed tradename in writing."

The sponsor has changed the tradename of the drug to AccuNeb™.

III. Labeling Review

Some preliminary labeling comments were forwarded to the sponsor as part of the March 30, 1999 approvable letter. It should be noted that the revised package labeling included in this response was not annotated. Comments #34-39 are included below.

- (Comment #34) Revise the tradename to describe the product in terms of dose instead of concentration. For example, the tradename should be expressed as albuterol sulfate inhalation solution, 0.75 mg, instead of albuterol sulfate inhalation solution, 0.021%. This comment applies equally to the 0.042% strength.

FDA response - The comment regarding the change from 0.021% to 0.75 mg and 0.042% to 1.5 mg have not been made to most sections of the proposed vial/box labeling. The sponsor has instead decided to list the dose in terms of the albuterol base in lieu of the albuterol sulfate dose (i.e., 0.63 mg instead of 0.75 mg and 1.25 mg instead of 1.5 mg. While the sponsor has included an asterisk followed by "* potency expressed as albuterol," some patients, and even therapists and prescribers may not realize that albuterol is part of the salt albuterol sulfate. For this reason, the weight of the product as albuterol sulfate should also probably be listed. This, however, is debatable because it should be noted that the convention for other albuterol products such as Proventil or Ventolin, when listed as "%" instead of milligrams, is to list the % as albuterol, not albuterol sulfate.

The change from % to milligrams has not yet been made to the "Percent Incidence of Moderate to Severe Adverse Events" table in the Adverse Reactions Section of the package insert.

- (Comment #35) Include in the package insert the graphs from Study DL-019 regarding the % change in FEV_1 from pre-dose versus time at Visits 2 and 4 for both doses of albuterol sulfate and placebo. Include a horizontal line depicting the 15% level on the graph so that one can see where the curve crosses the line.

FDA response – These graphs have been included for both Visits 2 and 4 and for both the ITT and the evaluable population. Because the user of the package label will not know what is Visit 2 or Visit 4, further identification of what is Visit 2 (an evaluation of the first dose effect of the drug) and Visit 4 (after 4 weeks of tid dosing of albuterol inhalation solution) should be included in these graphs. The graphs for the ITT population should be presented, not the graphs for the evaluable population.

- (Comment #36) Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in patients 2-12 years of age. Clarify this age range in the package insert and all carton and container labeling to avoid misintended use of these products in adults. Specify appropriate age groups in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert.

FDA response – No changes to highlight this age range have been made to the package insert or to the container labeling as requested. This will need to be done by the sponsor. This is particularly important because the potential exists for the off label use of this product in asthmatics greater than 12 years of age. This off label use could prove to be potentially dangerous as the efficacy data from this product indicate that the 0.75 mg AccuNeb product did not produce a statistically significant improvement in the %ΔAUC FEV_1 at Visit 4 for subjects in the age group 11-12 years of age, or those subjects in the weight group > 40 kg.

- (Comment #37) In the draft package insert, reference [ ]," actually refers to rescue medication use. Therefore, this reference appears to be wrong. Provide the correct reference.

FDA response – This reference has not been provided by the sponsor.

- (Comment #38) Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in subjects 2-12 years of age. Efficacy data [ ] should not be included in the package insert.

FDA Response – It appears that efficacy data [ ] remains in the package labeling in the section on Pharmacokinetics [ ], and the first proposed paragraph of the Clinical Trials section [ ] If this data is to be included in the AccuNeb labeling, [ ] The sponsor has made little to no changes in the Clinical Trials section other than to include the graphs asked for in Comment #35.

- (Comment #39) Revise the CLINICAL PHARMACOLOGY, Pharmacokinetics subsection of the package insert according to the most recently approved package insert for Ventolin™ (albuterol sulfate) Inhalation Solution. In addition, add the following sentence to the end of this subsection: [ ]

FDA response – This change has not been made by the sponsor as requested. This change will need to be implemented as requested previously by the FDA.

IV. The Package Label

AccuNeb™

Albuterol Sulfate Inhalation Solution 1.25mg/3 ml* and 0.63mg/3 ml*

(*Potency expressed as albuterol base)

19 pages redacted from this section of the approval package consisted of draft labeling

MEDICAL OFFICER REVIEW

MAR 16 1999

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-949	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey Laboratories, L.P. (Napa, CA)	**PRODUCT NAME:**	Albuterol sulfate
		USAN / Established Name:	Accuneb
CATEGORY OF DRUG:	B-agonist	**ROUTE OF ADMINISTRATION:**	Nebulized
MEDICAL REVIEWER:	Daniel J. O'Hearn, M.D.	**REVIEW DATE:**	March 11, 1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
March 27, 1998	March 30, 1998	New NDA	Submitted in 57 volumes.
October 6, 1998	October 7, 1998	Amendment	Tables/Listings DL-009
September 8, 1998	September 9, 1998	Orig. New Corres.	Data Listings DL-019
September 15, 1998	Sept. 17, 1998	Orig. Amendment	
September 29, 1998	Sept. 30, 1998	Amendment	
July 17, 1998	July 20, 1998	Orig. Amendment	DL-019 Data Listings and NONMEM Data for DL-009 and DL-010
June 15, 1998	June 16, 1998	Orig. Amendment	Final Study Report DL-019
June 9, 1998	June 10, 1998	Amendment	
May 18, 1998	May 19, 1998	Amendment	

Overview of Application/Review:

The submission includes three clinical trials: One large Phase III (DL-019) and two smaller dose-response trials (DL-009 and DL-010) to support the safety and efficacy of albuterol sulfate administered at 1.25 and 0.623 mg of albuterol base per dose. The sponsor is seeking approval for Accuneb 0.042% and 0.021% with the indication [redacted]

DL-009 is a two-center, 4-way crossover study in 30 patients 6 through 12 years of age with moderate to severe asthma. One of 4 nebulizer treatments (0.75 mg, 1.5 mg and 3 mg single doses of albuterol sulfate or placebo) was administered at each of four sessions, separated by 3-9 days. The main measure of bronchodilation will be FEV_1 - the forced expiratory volume in one second. Both non-compartmental and non-linear mixed effects modeling (NONMEM) were used in the analysis of this study. The drug in all three doses administered was efficacious compared to placebo in the ITT population when FEV_1 AUC (L-hr) and maximal % change in FEV_1 were examined. The median onset of action appeared to be 5 minutes but it is important to note that 5 minutes was the earliest time point tested. The median duration of effect was 4 hours for 0.75 mg and 3.0 mg while it was 6 hours for 1.5 mg. The duration of effect was clearly longer compared with placebo with the 1.5 mg and 3.0 mg dose. The duration of the 0.75 mg dose was very nearly significantly different from placebo with a p value of 0.054.

The purpose of DL-010 was to characterize the effect of nebulized placebo, 0.75 mg, 1.5 mg, and 3.0 mg nebulized albuterol sulfate on the PC_{20} of the methacholine challenge test in 25 subjects within the age range of 6-12 years. The analysis of this study was complicated by the fact that several subjects demonstrated a ceiling effect with post-treatment PC_{20} of > 128 mg/ml (the highest dose administered). Including these data points, the dose response curve was flat. NONMEM was used to analyze the data and the PC_{20} was extrapolated beyond 128 mg/ml. By fitting an E max model to the data a D_{50} and E_{max} could be identified. Because D_{50} values were significantly greater than zero, efficacy was thought to be established. The observed mean change in PC_{20} values were significantly different from baseline for all doses compared to placebo using a Generalized Linear Model. While this study appears to demonstrate efficacy, it could only be demonstrated only through extrapolation of the data and NONMEM modeling. This study should be thought of as supportive of Accuneb's efficacy but cannot be thought of as a

pivotal trial and used for basis of approval.

In the parallel 4-week Study DL-019, both 1.5 mg and 0.75 mg showed significant increases in the primary efficacy endpoint of %Δ AUC FEV_1 at Visit 4 versus placebo. Significant improvements were also noted with both albuterol solutions in the %Δ AUC FEV_1 at Visit 2, maximum percent change in FEV1, and duration of response.

Outstanding Issues: This NDA has notable CMC deficiencies. Please see Dr. V. Shah's CMC review for further details. The CMC issues will need to be adequately addressed before this product is approved.

Recommended Regulatory Action: | N drive location: None

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs: __X__ Approvable _____ Not Approvable

Signed

Medical Reviewer: /S/ MD Date: 3/15/99

Medical Team Leader: /S/ Date: 3/16/99

APPEARS THIS WAY
ON ORIGINAL

I. NDA #20-949

A. Introduction and Overview to the NDA

NDA #20-949 seeks the approval of Accuneb – Albuterol Sulfate Inhalation Solution 0.042% and 0.021% for TID-QID administration [redacted] The NDA consists of three clinical trials – DL-009, DL-010, and DL-019. DL-009 and DL-010 are clinical pharmacology, crossover, single-dose studies. DL-019 is a Phase II, parallel, 4-week study. DL-009 and DL-019 are considered the two pivotal trials for approval purposes.

B. NDA Demographics

404 pediatric patients, ages 6-12, with asthma were evaluated in the trials. DL-019 is the largest safety and efficacy trial with 349 participants. 55 patients participated in the randomized, double-blind, placebo-controlled, single-dose, 4-way crossover trials DL-009 and DL-010.

C. Review Process/Electronic Data Issues

The pivotal trials, DL-009 and DL-019, were reviewed in great detail. DL-010 was also reviewed thoroughly, but not to the extent of the other trials primarily because it was a bronchoprovacation study and the efficacy could only be discerned through data modeling. A consultation was received from the Division of Pharmacometrics at CDER to help discern the NONMEM data analysis in DL-009 and DL-010 that was utilized in part by the sponsor's consultants at [redacted]

DSI audits were performed at three of the sites in DL-019. The details of these audits are presented later within this NDA review.

This NDA review was largely performed by paper hard copy. Data from DL-019 was available in ACCESS but its use during this review was limited.

D. Regulatory History

A pre-IND meeting was held between the FDA and Dey Laboratories, L.P. on August 25, 1993. IND #44,281 was submitted on December 30, 1993. On August 11, 1997, Dey Laboratories met with the FDA to review the proposed content of the planned NDA submission. The NDA was submitted on March 27, 1998. The clinical review for the 45-day filing meeting was completed on April 19, 1998 and the NDA was allowed to be filed.

II. DL-009 Protocol date: 3/10/94 (Vol. 1. 9 and 12)

"A Placebo-Controlled, Double-Blind, Dose-Ranging Study Of Albuterol Sulfate, Using A Bronchodilation Design, In Pediatric Patients With Asthma"

A. Investigators and investigational centers.

1. Investigator

   Paul V. Williams, M.D.
   A.S.T.H.M.A., Inc. and
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   120 North 17th
   Mt. Vernon, WA 98273

   Michael Noonan, M.D.
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2. Investigational Centers

   Two centers participated.

B. Objective.

Establish the dose-response curve of albuterol sulfate as a nebulized treatment for asthma in children, ages 6 through 12 years. The dose-response curve would be used to estimate the lowest effective dose, and the shape, magnitude and variability of albuterol response in children.

C. Study Design.

This is a two-center, randomized, double blind, placebo-controlled, 4-way crossover study in 30 patients 6 through 12 years of age with moderate to severe asthma. One of 4 nebulizer treatments (0.75 mg, 1.5 mg and 3 mg single doses of albuterol sulfate or placebo) will be administered (in 3-ml normal saline) at each of four sessions, separated by 3-9 days. The main measure of bronchodilation will be FEV_1 - the forced expiratory volume in one second. FEV_1 will be recorded, at indexed times, for 6 hours post-dose during each treatment session to assess the bronchodilatory effects of study drug on pulmonary response.

Reviewer's note: Two centers participated in the trial.

1. **Population.**

a) **Inclusion Criteria**

(1) **History of moderately severe asthma**

(2) **FEV_1 between 50 and 70% with demonstrated reversibility of at least 15% of baseline within 30 minutes of inhalation of albuterol sulfate (3 mg).**

(3) **Specified asthma symptoms daily and/or nocturnal awakening 3-4 times weekly during at least 6 months in the year prior to randomization; or daily asthma medication for at least six months during the past year.**

Reviewer's note: On August 25, 1994, the protocol was amended to include patients with resting FEV_1 between 50 and 70% predicted - it is not clear whether the patients were off bronchodilators for the "resting FEV_1" testing.

b) **Exclusion Criteria**

(1) **Any serious medical condition or use of drug with which albuterol administration is contraindicated.**

(2) **Known hypersensitivity to albuterol.**

(3) **Any chronic condition other than asthma which would interfere with successful completion of the trial or its interpretation.**

(4) **Steroid dependence or use of systemic steroids 4 weeks before screening visit.**

(5) **Any patient who is currently experiencing clinically significant signs and symptoms of allergy to tree pollen or grasses, and such allergy has been documented by skin testing within the past 12 months**

(6) **Active pulmonary disease including: cystic fibrosis, bronchiectasis, tuberculosis, or immunodeficiency leading to recurrent sino-pulmonary infections.**

(7) **Clinical features suggestive of a history of respiratory infection within the month prior to enrollment.**

(8) **Pulmonary function tests suggesting a ventilatory defect other than asthma, or evidence of existing irreversible lung damage.**

(9) **Severe chronic sinusitis or nasal polyposis.**

(10) **The introduction of, or a change in, allergen immunotherapy within the month prior to enrollment.**

(11) **Treatment for gastrointestinal reflux.**

(12) **Administration of an investigational drug within 30 days prior to enrollment.**

(13) **An inability to perform three acceptable forced vital capacity maneuvers with two FEV_1 values within 10% of the largest FEV_1 value.**

(14) **Evidence that the patient or family may have been unreliable or noncompliant, or may have moved from the area before completing the study.**

(15) **A history of tobacco use.**

2. **Concomitant Medications**

Chronic usage of cromolyn sodium and approved dosages of inhaled steroids are permissible during the course of the study except 2 weeks before and during the screening period. Patients should stop inhaled cromolyn and inhaled steroids 2 weeks before the screening visit and continue abstaining from those medications during the 7-14 day screening period, unless they meet the entry criteria while on those medications. In terms of other washout periods, the specific list of medications and duration of abstinence from use prior to each study day are listed below:

• Inhaled β-agonists	
Short acting (albuterol, terbutaline)	8 hours
Long acting (e.g., salmeterol)	48 hours
• Oral β-agonists	
Conventional release	12 hours
Modified release	24 hours
• Theophylline products (all forms)	48 hours
• Antihistamines	
Astemizole	3 months
Hydroxyzine	96 hours
All others	48 hours
• Aspirin	5 days
• Other nonsteroidal anti-inflammatory drugs	5 days
• Anticholinergics	
Inhaled	24 hours
Oral	7 days

3. Study Procedures

A) <u>Screening Visit</u> (Visit 1 = Day –14) – After being determined eligible by history, the patient will:

- Be given a detailed explanation of the study
- Undergo a physical examination including measurements of height, weight, blood pressure, pulse, respiratory rate and body temperature.
- Provide written informed consent (by patient and parent/guardian).
- Be given a pregnancy test if female of childbearing potential
- be assigned a study drug number (and associated study drug package).
- Be administered a 12-lead electrocardiogram at baseline and after test for reversibility (administered nebulized albuterol sulfate 3mg).
- Have blood sample tested for theophylline levels (must be ≤ 6 mcg/ml), CBC, SMAC-12 and have urine sample obtained for urinalysis.
- Have skin tests (if not performed within 12 months prior to screening) to rule out patients with allergy to tree pollen or grasses. (This only applies to patients whose study participation would occur during the pertinent allergy season and who are currently experiencing clinical signs and symptoms of such allergy.)
- Perform a spirometric evaluation to document pulmonary function and bronchodilator reversibility.

- Be given training in nebulizer usage.
- Be scheduled for follow-up visits to the clinic for all four study treatment evaluation sessions.

B) Following the screening visit, patients will be assigned to a patient identification number in order of entrance into the study.

C) Study Visits 2-5 (Visit 2 = Day 0) - All patients received all doses with a different dose at each Visit 2-4 separated by 3-9 days. All treatment sessions were to begin at approximately the same time (+/- one-hour). At each visit (including Visit 5), patients had:
   - A blood sample tested for theophylline levels (must be $\leq$ 6 mcg/ml). (Theophylline levels were repeated each visit only if the subject had a history of taking theophylline within the past three years.)
   - A 12-lead electrocardiogram recorded immediately prior to, and two hours following, study drug administration.
   - Training in standardized nebulizer drug administration procedures and be administered study drug.
   - Baseline and post-dose spirometry and vital signs (heart rate, respiratory rate, and blood pressure) recordings conducted were done at baseline and repeated at 5, 15, 30, 60, 90, 120 minutes, and hourly, for a total of 6 hours after administration of study treatment.
   - A final evaluation (i.e., study exit evaluation) by the investigator following the final study session (Visit 5; or at time of discontinuation from study).

4. Randomization procedures

   The order of treatment across the four visits was determined by a computer-generated randomization schedule using a 4-way crossover design.

5. Administration and dosage

   A single brand nebulizer was used (Pari-jet) and the nebulization lasted about 15 minutes, via a mouthpiece with nose clip, using oxygen at 6 to 8 L/min. An in-line valve was used to allow nebulization only during inspiration.

   The sponsor supplied the drugs in identical vials containing the following concentrations in 3 ml of normal saline:
   - albuterol sulfate 0.75 mg.
   - albuterol sulfate 1.5 mg.
   - albuterol sulfate 3 mg.
   - placebo isotonic saline

6. Rescue Medication

   If FEV_1 falls below baseline prior to completion of the six hours of testing, two inhalations of albuterol MDI (90 μg /inhalation) were allowed for the treatment of acute exacerbations (the decision was up to the investigator). If albuterol MDI rescue attempts were inadequate, nebulized albuterol (3 mg) was administered. Further

spirometric testing were terminated for that study day. Patients requiring rescue medication on three separate sessions were dropped from the study.

7. Statistical Analysis

a) Sample size

The sample size was calculated to detect a 15% difference in the AUC FEV_1 relative to placebo, with an alpha level of 0.05 and a 90% power. This sample size calculates to 18 but because there was a desire to balance the data with respect to the number of subjects completing each sequence, the sample size was increased to 24.

b) Primary efficacy endpoint analysis

The analysis of the data was performed [redacted]

] The data set was analyzed with: 1) all patients who complete the study, or 2) all patients (intention-to-treat). Spirometric data was analyzed with the use of nonlinear mixed effects models, also known as NONMEM, for dose response, and generalized linear models for efficacy.

D. Results.

Of 57 patients evaluated on screening day, 30 patients were entered into the trial, from June 1994 through May 1995 (See Table 1 for details on disposition of patients enrolled). Two patients discontinued the study for adverse events (Patients 0103 (Moderate sinusitis) and 0217(asthma exacerbation) dropped out due to concurrent illnesses). These concurrent illnesses were judged by the investigators to not be related to the drug therapy. However, the data from all patients were included in the analysis. The 30 patients supplied 1,139 post-dose measurements from 116 treatments (1 patient missed 1 treatment and another patient missed 3 treatments). Among the 116 treatments, 109 included complete sets of observations (7 treatments of 5 patients were incomplete). The data from the 109 treatments of the 30 patients were analyzed as from the "evaluable" population. A total of 23 patients received all 4 treatments and completed all scheduled observations (these are considered " the completers").

Table 1

[redacted]				
	4	1	3	5
	24	1	20*	25
	28	2	23*	30

Reviewer's Note – 21 subjects had data points for all measurements. * Subject 202 was missing a data point at 30 minutes post-0.75 mg and Subject 213 was missing a data point at 5 minutes for the placebo group. Both were included in our efficacy analysis. Therefore, 23 subjects total were included in the efficacy analysis. The reviewer went over the line listings for the spirometry for all 30

Table 1

	4	1	3	5
	24	1	20*	25

patients enrolled and confirmed that 7 patients were missing significant data points to prevent analysis.

1. Demographic Characteristics.

There were 18 males and 12 females, all Caucasians, with a mean age of 9.4 years and a mean weight of 97.4 pounds. The mean duration of asthma was 6.5 years, and all of them were on or had taken concomitant medications at the time of entry (see Table 2 for details).

Table 2

	8.9 0.6 9.0 6	10.0 0.8 11.0 7	9.0 0.8 9.0 6	9.9 0.7 10.5 7	9.4 0.3 10.0 6
	3 (43)	5 (71)	5 (63)	5 (63)	18 (60)
	7 (100)	7 (100)	8 (100)	8 (100)	30 (100)
	4.9	7.6	5.6	7.9	6.5
	98.0 16.0	104.1 11.9	82.9 8.7	104.8 13.4	97.4

* Treatment sequences: 1= C/B/D/A; 2= D/C/A/B/; 3= A/D/B/C; 4= B/A/C/D; where A= placebo, B= albuterol 0.75 mg; C= albuterol 3.00 mg; D= albuterol 1.5 mg.

2. Type of analysis:

<u>Evaluable patients/treatments</u>: includes the data for the 109 treatments (from 30 patients) with 6 hours of observations.

<u>Completers:</u> includes the data from 92 treatments (from 23 patients) who completed all scheduled observations from all 4 treatments.

Reviewer's note: Dey notified the FDA in a letter dated 29 September 1998 of a discrepancy which existed between the investigator's Final Report dated 12 April 1996 and the DL-009 data. Two of the "completers" (ID's 202 (Noonan -0.75 mg at 30 minutes) and 213 (Noonan - Placebo at 5 minutes) were missing one post-PFT measurement and were erroneously analyzed by the investigator as completers. The ITT population as reported by Dey actually contained two less patients than what was reported in the Final Report.

We have included 23 patients in our analysis and have not disregarded the two patients, 202 and 213, who were each missing only one data point.

3. Efficacy

Reviewer's note: Data for this study was analyzed both with noncompartmental analysis as well as non-linear mixed-effect modeling (NONMEM). [redacted] under the guidance of [redacted] performed the statistical analysis for Study DL-009 on behalf of Dey Pharmaceuticals with data supplied by [redacted] A consultation

[redacted]	28	2	23*	30

Table 2

[redacted]					
	8.9 0.6 9.0 6	10.0 0.8 11.0 7	9.0 0.8 9.0 6	9.9 0.7 10.5 7	9.4 0.3 10.0 6
	3 (43)	5 (71)	5 (63)	5 (63)	18 (60)
	7 (100)	7 (100)	8 (100)	8 (100)	30 (100)
	4.9	7.6	5.6	7.9	6.5
	98.0 16.0	104.1 11.9	82.9 8.7	104.8 13.4	97.4

* Treatment sequences: 1= C/B/D/A; 2= D/C/A/B/; 3= A/D/B/C; 4= B/A/C/D; where A= placebo, B= albuterol 0.75 mg; C= albuterol 3.00 mg; D= albuterol 1.5 mg.

was received from the Division of Pharmacometrics which reperformed both types of analyses of the data for the purposes of our review.

The general model for the 0-6 hour post-dose area under the response time curve (AUC) was as follows:

$$AUC = AUC_{baseline} + AUC_{placebo} + AUC_{drug}$$

$AUC_{baseline}$ is the observed value of the pre-dose response (pre-dose FEV_1) multiplied by the duration of the study (6 hours). $AUC_{placebo}$ is the incremental change from baseline in AUC attributable to placebo and AUC_{drug} is the incremental change attributable to drug effect.

On Dey's behalf, [redacted] utilized nonlinear mixed effects models for dose response and generalized linear models (GLM) for efficacy.

For the FEV_1 0-6 hr area under the curve (AUC) - evaluable patients:

- **The mean incremental increase in AUC attributable to placebo ($AUC_{placebo}$) was 1.12 L/ hr.**
- **The mean maximum drug effect (E_{maxAUC}) was 1.30 L /hr. (see Table 3).**
- **The mean dose that produces 50% of the maximum effect (D_{50AUC}) was 0.69 mg. This parameters is significantly influenced by body weight, height and body surface, i.e., the larger the child the smaller albuterol is required to achieve a given increase in FEV_1.**

Table 3 Parameter estimates (95% CI) for FEV_1 AUC

[redacted]	9.60 (6.35, 12.9)	1.12 (0.71, 1.71)	1.30 (0.80, 1.80)	0.69 (0.28, 1.10)	1.85 (0.59, 3.11)
	9.56 (6.38, 12.8)	1.23 (0.67, 1.79)	1.20 (0.76, 1.64	0.67 (0.43, 0.91)	5.03 (0, 11.5)

The sponsor 's analysis utilizing a nonlinear mixed effects model also revealed:

The response-dose-time was described for both placebo effect (as a function of time) and drug effect (as a function of amount of drug at a given time). For FEV_1 :

- **The mean maximum drug effect (E_{max}) was 0.46 L**
- **The mean amount of drug that produces 50% of the maximum effect (A_{50}) was 0.67 mg.**

The lowest effective dose (LED) was defined as the lowest dose associated with an incremental change in AUC of FEV_1 plus the incremental change attributable to placebo.

- **The LED was 1.59 mg for a typical child.**

The highest reasonable dose (HRD) was defined as the dose that produces a drug effect that is 85% of the E_{maxAUC} (and that is safe).

- **The HRD was 1.76 mg for a typical child.**

Table 3 Parameter estimates (95% CI) for FEV_1 AUC

	9.60 (6.35, 12.9)	1.12 (0.71, 1.71)	1.30 (0.80, 1.80)	0.69 (0.28, 1.10)	1.85 (0.59, 3.11)
	9.56 (6.38, 12.8)	1.23 (0.67, 1.79)	1.20 (0.76, 1.64	0.67 (0.43, 0.91)	5.03 (0, 11.5)

The sponsor 's analysis utilizing a nonlinear mixed effects model also revealed:

Reviewer's Note - A similar NONMEM analysis was also performed by the Division of Pharmacometrics. NONMEM version 5 was used for the analysis. For each patient/treatment, the AUC of the FEV_1 measurements were computed. The overall AUC data were modeled as:

$$AUC = AUC_{baseline} + AUC_{placebo} + AUC_{drug} + \varepsilon$$

where $AUC_{baseline}$ is the observed value of the pre-dose response multiplied by the duration of the study (6 hours), $AUC_{placebo}$ is the change in AUC due to placebo, and AUC_{drug} is the change in AUC due to the drug. The term ε is an error term representing residual error.

The model for AUC_{drug} is based on the Hill equation as follows:

$$AUC_{drug} = \frac{E_{max,AUC} D^{\gamma}}{D^{\gamma} + D_{50,AUC}^{\gamma}}$$

where $E_{max,AUC}$ is the maximum AUC_{drug}, D is the dose, D_{50} is the dose that produces ½ $E_{max,AUC}$, and γ is a shape factor which controls the slope of the line. Covariates (weight, BSA, height) were also tested for their effects on the model, but were found not to have a significant impact.

Table 4 shows the results of the NONMEM analysis. A significant placebo effect is noted in the study, as $AUC_{placebo}$ is significantly greater than zero. The dose required to produce 50% of the maximum effect (0.69 mg) is very close to the minimum recommended dose in the labeling (0.62 mg), although this parameter is not especially well-estimated.

Table 4: Parameter estimates (and 95% confidence intervals for AUC_{FEV1}) n=23 for all.

$AUC_{placebo}$	1.12 (0.71, 1.71)
$E_{max\ AUC}$	1.30 (0.80, 1.80)
D_{50}	0.69 (0.28, 1.10)
γ	1.85 (0.59, 3.11)

Using the model, it was possible to estimate the AUC_{drug} for each subject/treatment. The results are shown in Table 5 and Figure 1.

Table 5: AUC_{drug} for each treatment.

Placebo	0
0.75 mg	0.72 (0.48, 0.96)
1.5 mg	1.08 (0.79, 1.36)
3.0 mg	1.33(1.00,1.66)

The above data shows the difference in the AUC attributable to the Accuneb dose and that of placebo (and the baseline AUC). It can be noted that each treatment has a significant effect over placebo but there is considerable overlap between active treatment arms. The analysis appears very similar to the analysis performed through Dey.

Table 4: Parameter estimates (and 95% confidence intervals for AUC_{FEV1}) n=23 for all.

Parameter	
$AUC_{placebo}$	1.12 (0.71, 1.71)
$E_{max\ AUC}$	1.30 (0.80, 1.80)
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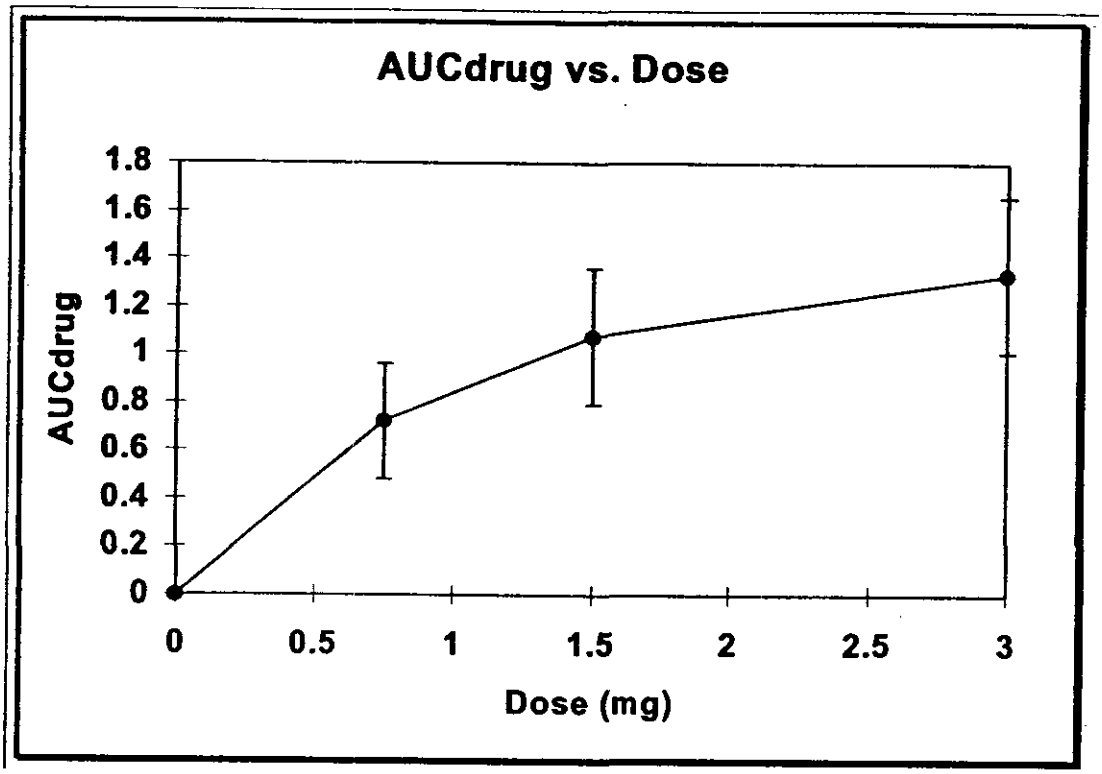
γ	1.85 (0.59, 3.11)

Using the model, it was possible to estimate the AUC_{drug} for each subject/treatment. The results are shown in Table 5 and Figure 1.

Table 5: AUC_{drug} for each treatment.

Figure 1: AUC_{drug} as a function of dose. Mean ± 2 SE shown



From Figure 1, it can be noted that each treatment has a significant effect over placebo; however, there is considerable overlap between the active treatment arms.

Data was also analyzed with generalized linear models.

Table 6 Dey's Analysis -FEV_1 AUC (L-hr) - Change from baseline (ANOVA- evaluable patients)(p. 160, Vol. 1-12)

	25 1.11 0.06	29 1.90* 0.05	28 2.30* 0.06	27 2.45* 0.07
	23 1.24 0.06	23 1.98* 0.06	23 2.45* 0.07	23 2.41* 0.08

*p< 0.005 vs. placebo

Each active treatment differed significantly from placebo for evaluable patients/treatments and completer patients. Dey also says that it found that 3.0 mg differed significantly from 0.75 mg in the evaluable population. (See also FDA analysis in Table 10)

Reviewer's Note – Two of the "completers" (#202 and 213) were each missing one post-dose PFT measurement and were originally analyzed by the investigators as "completers." Dey submitted a re-analysis in a correspondence dated Sept 29, 1998 utilizing 21 patients who had

Table 6 Dey's Analysis -FEV_1 AUC (L-hr) - Change from baseline (ANOVA- evaluable patients)(p. 160, Vol. 1-12)

	25 1.11 0.06	29 1.90* 0.05	28 2.30* 0.06	27 2.45* 0.07
	23 1.24 0.06	23 1.98* 0.06	23 2.45* 0.07	23 2.41* 0.08

*p< 0.005 vs. placebo

Each active treatment differed significantly from placebo for evaluable patients/treatments and completer patients. Dey also says that it found that 3.0 mg differed significantly from 0.75 mg in the evaluable population. (See also FDA analysis in Table 10)

Table 7 –Summary of Area Under the FEV_1 % Change from Pre-Dose Versus Time Curve (Dey's ANOVA- Intent to Treat population) (This %ΔAUC FEV_1 variable represents the percent change from pre-dose FEV_1 over time.)

	23 79.9 80.3	27 113.6 80.8 0.055	28 150.4 106.1 <0.001	27 156.3 119.1 <0.001
	21 73.4 87.9	21 114.3 84.8 0.023	21 157.9 113.4 <0.001	21 140.9 119.7 <0.001

complete data for every time point instead of 23 (Table 7). Furthermore, Dey said that when the ITT population was defined in accordance with the investigator's final report, the population data did not match the report. Dey says that the data diskette and the data used by — for the integrated analysis were compared and were identical. Therefore, the available population definitions from DL-019 were used for analysis. Dey sent data with two less patients in 0.75 mg and placebo groups. Dey said the %ΔAUC FEV_1 variable in the correspondence dated Sept 29, 1998 was consistent with the DL-019 analysis. This needs to be clarified in the action letter.

It also seems that with the new analysis submission on 9/28/98 that the population the sponsor was calling evaluable before is now the ITT population and the completers are now the evaluable/completers (simplified in the tables as "completers.")

Table 7 –Summary of Area Under the FEV_1 % Change from Pre-Dose Versus Time Curve (Dey's ANOVA- Intent to Treat population) (This %ΔAUC FEV_1 variable represents the percent change from pre-dose FEV_1 over time.)

	23 79.9 80.3	27 113.6 80.8 0.055	28 150.4 106.1 <0.001	27 156.3 119.1 <0.001
	21 73.4 87.9	21 114.3 84.8 0.023	21 157.9 113.4 <0.001	21 140.9 119.7 <0.001

Reviewer's Note – Based on the sponsor's submitted ANOVA, the nebulization of 1.5 and 3.0 mg is again significantly different from placebo in both the completer and the intention-to-treat population. The nebulization of 0.75 mg does not have a p value < 0.05 in the ITT population when compared with placebo but it is close at p=0.055. The same comparison in the completer population does have a p value< 0.05. In the completer population, 0.75 mg was significantly different from placebo.

Table 8 – Summary of % Change in Maximum FEV_1 from Pre-Dose (Dey's ANOVA - Intent to Treat Population)

	23 23.4 20.3	27 31.3 13.5 0.037	28 39.1 22.5 <0.001	27 38.9 23.1 <0.001

Table 8 – Summary of % Change in Maximum FEV_1 from Pre-Dose (Dey's ANOVA - Intent to Treat Population)

	23 23.4 20.3	27 31.3 13.5 0.037	28 39.1 22.5 <0.001	27 38.9 23.1 <0.001
	21 22.3 19.4	21 30.7 14.1 0.037	21 39.5 25.2 <0.001	21 34.4 22.8 0.002

At this reviewer's request, some additional analyses were carried out through the Pharmacometrics consultation which included the following:

[redacted]	21 22.3 19.4	21 30.7 14.1 0.037	21 39.5 25.2 <0.001	21 34.4 22.8 0.002

At this reviewer's request, some additional analyses were carried out through the Pharmacometrics consultation which included the following:

- **Non-compartmental analyses including AUC $_{FEV1}$, FEV1$_{max}$ (maximum FEV$_1$ reached over the 6 hours), t$_{max}$ (time post-dose the maximum was reached), and FEV1$_{ave}$ (the average FEV1 over the 6 hr interval, computed as the AUC $_{FEV1}$/6.**

A noncompartmental analysis (ANOVA) was performed on the 23 subjects whom this reviewer considered compieters. Only one data point was missing from 2 subjects so it was considered reasonable to include them in the completer population. This analysis with a 95% confidence interval revealed that 0.75 mg, 1.5 mg, and 3 mg were significantly different from placebo when the sum of the area under the FEV$_1$ percent change (AUC$_{FEV1}$), average FEV$_1$, and maximal FEV$_1$ were analyzed.

The data are summarized in Table 9. These results are in basic agreement with the preceding analyses, in that they clearly show that albuterol at all doses is having a pharmacological (albeit modest) effect as compared with placebo.

Table 9: Results of non-compartmental analysis of FEV1 data.

	Mean ± SD			
Dose	AUC $_{FEV1}$	FEV1 $_{ave}$	FEV1 $_{max}$	t$_{max}$
placebo	10.8 ± 3.2	1.8 ± 0.5	1.9 ± 0.5	2.0 (0.1, 6.0)
0.75 mg	11.6 ± 3.5	1.9 ± 0.6	2.1 ± 0.6	1.0 (0.1, 5.0)
1.5 mg	12.0 ± 3.6	2.0 ± 0.6	2.2 ± 0.6	1.5 (0.1, 6.0)
3.0 mg	12.2 ± 3.8	2.0 ± 0.6	2.2 ± 0.7	1.0 (0.1, 4.0)
Pairwise comparisons (95% CI of the least-square mean ratios)				
0.75 mg vs. placebo	112 (108, 116)	112 (108, 116)	113 (108, 118)	na
1.5 mg vs. placebo	110 (106, 114)	110 (106, 114)	112 (107, 117)	na
3.0 mg vs. placebo	107 (103, 111)	107 (103, 111)	109 (104, 113)	na

The results of this analysis are in reasonable agreement with the NONMEM analysis. For example, from Table 9, comparing the AUC $_{FEV1}$ between 1.5 mg and placebo, the increase that may be attributable to drug is about 1.2 L over 6 hours. This estimate compares well with the estimate from NONMEM (1.08). Thus, the two approaches may be considered equivalent.

A pairwise comparison of doses was also performed at the FDA.

Table 10 – Pairwise comparison of Doses (based on CI of 95%)

[redacted]

A pairwise comparison of doses was also performed at the FDA.

Table 10 – Pairwise comparison of Doses (based on CI of 95%)

	p=0.4209	p=0.4366	p=0.6385
	p=0.0138	p=0.0145	p=0.0405
	p=0.0881	p=0.0865	p=0.1086

Table 11- Onset and Duration of 23 Completers (FDA analysis-Pharmacometrics Consult))

	0.083	1	0.083	4	0.083	6	0.083	4
	NA	NA	0.225	0.0537	0.1934	0.0016	0.2256	0.0097

***Significance compared with placebo – sign test.**

[redacted]	p=0.4209	p=0.4366	p=0.6385
	p=0.0138	p=0.0145	p=0.0405
	p=0.0881	p=0.0865	p=0.1086

This analysis revealed that there was a significant difference between doses. From an AUC_{FEV1}, $FEV_{Average}$, and $FEV1_{Max}$ standpoint, 3.0 mg was significantly different from 0.75 mg, however, a significant difference could not be found between 0.75 and 1.5.

At this reviewer's request, analyses were carried out to study the estimation of onset and duration of action - this was performed by the pharmacometric reviewer by defining onset as the first of two consecutive points that were ≥15% over baseline. Duration of action was taken as the difference between onset and offset of action (defined as the first of two consecutive points that fell below the onset value).
The duration is that amount of time which the FEV_t has been increased by 15% over pre-dose values for at least 2 contiguous measurements.

Table 11- Onset and Duration of 23 Completers (FDA analysis-Pharmacometrics Consult))

[redacted]								
	0.083	1	0.083	4	0.083	6	0.083	4
	NA	NA	0.225	0.0537	0.1934	0.0016	0.2256	0.0097

*Significance compared with placebo – sign test.

The defined onset of action for all four treatments do not differ significantly from one another. The duration of effect for the 1.5 mg and 3.0 mg doses are greater than placebo. The comparison between 0.75 mg and placebo approaches statistical significance.

<u>In conclusion</u>, the analysis of efficacy from DL-009 reveals that at all doses studied, albuterol administered as Accuneb solution for inhalation demonstrates a measurable pharmacologic effect over placebo. The results from both the NONMEM analysis and the non-compartmental analysis are similar, suggesting that the two approaches may be considered equivalent.

4. Safety

The location of safety data in this NDA was not indexed well. Physical examination, urinalysis, CBC, and SMA-12 were done during the screening visit and were not repeated later in the course of the study except for theophylline levels. Theophylline levels were repeated during each treatment session.

Of the three subjects felt to be of child-bearing potential, pregnancy tests were performed in two and was negative.

A 12-lead electrocardiogram was recorded immediately prior to, and two hours following, study drug administration. There were 14 instances of an abnormality found in the post-dose ECG in 11 subjects (p. 280-284 and 308-309, Vol. 1.12).

The following post-dose abnormalities were observed. On Visit 2, subject 202 had a PVC and QT prolongation pre-dose and PR segment prolongation and sinus arrhythmia post-dose. PR prolongation was also seen post-dose on Visits 3 and 5. A comment on Subject 203's Visit 1 post-dose ECG says, "Dr. does not agree with QT prolongation." Subject 209 had a "slight ST abnormality" post-dose on Visit 1 – no further detail is given. Subject 211 had a flat T wave on Visit 2 post-dose – a flat T wave was also seen pre-dose on Visit 3. Subject 213 had "right ventricular deviation and right axis deviation" post-dose on Visit 1 - no other abnormality is listed for this patient. Subject 214 had "sinus arrhythmia and flat T waves" on post-dose Visit 1. Subject 216 had "right axis deviation", also seen pre-dose on Visit 1. Subject 217 had "slight ST-T abnormality" post-dose on Visit 2 – no further detail is given. Subject 219 demonstrated "slight ST abnormalities" post dose on visits 1, 3, and 5 – no further detail is given. Subject 224 had a "borderline wide P wave, and ST elevation" – no further detail is given.

None of the post-dose ECG abnormalities were felt to be clinically significant by the investigators involved. The actual ECGs were not submitted with the NDA nor were the specific lengths of PR and QT segments involved. Analysis of dose effect on arrhythmia was not performed.

Vital signs (pulse, blood pressure, and respiratory rate) were performed for each dose and the data was submitted.

Table 12 – Mean Change in Heart Rate with Treatment (Table 8.3.1, Vol. 1-38)

0.8	4.1	8.8	-0.7
-0.4	1.8	11.5	2.2
-4.5	2.8	10.7	2.5
1.3	0.7	9.1	2.0
-0.6	-1.9	8.0	0.9
-1.4	-3.1	4.5	1.2
-1.5	1.6	4.0	3.1
-1.4	-1.2	5.1	3.7
-2.6	-4.7	4.9	3.3
-7.7	-2.0	3.6	3.0

Table 12 – Mean Change in Heart Rate with Treatment (Table 8.3.1, Vol. 1-38)

0.8	4.1	8.8	-0.7
-0.4	1.8	11.5	2.2
-4.5	2.8	10.7	2.5
1.3	0.7	9.1	2.0
-0.6	-1.9	8.0	0.9
-1.4	-3.1	4.5	1.2
-1.5	1.6	4.0	3.1
-1.4	-1.2	5.1	3.7
-2.6	-4.7	4.9	3.3
-7.7	-2.0	3.6	3.0

Reviewer's Note - On p. 99, Vol. 1-12, there is a discrepancy between this change in heart rate data and the data in Table 8.3.1 in Appendix B of Vol. 1-38. The fact that the former includes 28 patients and the latter 29 patients cannot account for all the discrepancies. It appears that the Vol. 1-12 involves errors in subtraction between mean at Time X and baseline mean heart rate.

There appears to be an increase of ~ 8-11 bpm for 3.0 mg while there is not much of an increase for the other doses. There did not appear to be a difference between the treatment groups in the respiratory rate and diastolic blood pressure (Table not shown). Significance was also not noted between treatment groups in the systolic pressure.

The area under the curve (AUC) of pulse rate and peak pulse rate underwent further statistical scrutiny and modeling at —

AUC of pulse rate - The difference in the average pulse rate over 0-6 hours between placebo and active treatments was not statistically significant.

AUC of peak pulse rate - Peak pulse rate increased relative to the dose. The maximum increase in peak pulse rate due to drug was estimated at 4.96 beat/minute and there was a relationship between peak pulse rate and dose. The D_{50} for increase in peak pulse rate due to drug was estimated to be 1.59 mg (95% CI, 0.68, 2.46). The sponsor found that the peak pulse rate for both placebo and active drug is influenced by the observed value of the baseline pulse rate.

Table 13. Predicted peak pulse rate in beats/minute

	0	0.5	1.0	1.5	2.0	2.5	3.0
	91.9	91.9	92.4	94.9	97.5	98.3	98.6
	94.1	94.1	94.5	96.6	98.8	99.5	99.8
	99.6	99.6	99.9	101.7	103.5	104.1	104.3
	106.8	106.8	107.1	108.6	110.1	110.7	110.9
	115	115	115.2	116.5	117.9	118.4	118.5
	123.8	123.8	124	125.1	126.3	126.7	126.8

Reviewer's Note – This analysis of pulse rate data for this trial was submitted by the sponsor and was not re-analyzed by the reviewer.

Table 13. Predicted peak pulse rate in beats/minute

	0	0.5	1.0	1.5	2.0	2.5	3.0
	91.9	91.9	92.4	94.9	97.5	98.3	98.6
	94.1	94.1	94.5	96.6	98.8	99.5	99.8
	99.6	99.6	99.9	101.7	103.5	104.1	104.3
	106.8	106.8	107.1	108.6	110.1	110.7	110.9
	115	115	115.2	116.5	117.9	118.4	118.5
	123.8	123.8	124	125.1	126.3	126.7	126.8

Table 14: Adverse Events

					1							
								1				
	1											
		1										

				1								
					1							
		1										
								1				
	1											

5. Adverse Events

Adverse event tabulation was performed on the intention to treat population consisting of 30 patients. Of these patients, 6 (20%) reported one or more adverse events. There were no deaths. There were two patients withdrawn because of adverse events. Patient 217 withdrew because of a URI that was judged as mild in severity. Patient 103 withdrew after completing 3 of the 4 treatment sessions because of an exacerbation of asthma after completing 1 of the 4 treatment sessions. The most frequent adverse events were otorhinolaryngologic in nature. Patient 207, a 12-year-old boy, completed Visit 5 on 1/15/95 and was hospitalized for acute appendicitis [ ]

Table 14: Adverse Events

				1							
							1				
1											
	1										
		1									
			1								
				1							
1											
							1				
1											

None of the adverse events were attributed to the drug by the investigators.

Only one patient in DL-009 experienced a serious AE – he was hospitalized with appendicitis two days after receiving his final dose of 1.5 mg.

E. Discussion/Conclusions

DL-009 was a randomized crossover trial in which mild-moderate asthmatics were administered 0.75 mg, 1.5 mg, and 3.0 mg of nebulized albuterol or placebo and spirometry was followed for 6 hours. The drug in all three doses administered were efficacious compared to placebo in the completer population when AUC_{FEV1} and maximal % change in FEV_1 were examined.

Pairwise comparisons between the albuterol treatments revealed that 3.0 mg improved the AUC_{FEV1}, average FEV_1, and maximal FEV_1 significantly better than 0.75mg. No such difference was noted in efficacy between 1.5 mg and 3.0 mg

or .75 mg. The median onset of action appeared to be 5 minutes but it is important to note that 5 minutes was the earliest time point tested. No difference in the median onset of action was noted between albuterol treatments or compared with placebo. The median duration of effect was 4 hours for 0.75 mg and 3.0 mg while it was 6 hours for 1.5 mg. The duration of effect was clearly longer compared with placebo with the 1.5 mg and 3.0 mg dose. The 0.75 mg dose was very nearly significantly different with a p value of 0.054.

Blood work, except for theophylline levels, was not repeated during the study so no comment could be made from this study on the effect of treatment on electrolyte levels. No theophylline levels greater than 2.5 mcg/ml were noted in the study and only one patient was concurrently on theophylline. There appeared to be no drug-related adverse reactions. There was an increase in the peak pulse rate of 4.96 beats/minute, however, there was no statistically difference in the average pulse rate over 0-6 hours post-dose.

III. DL-0010 Protocol date: 3/2/95 (Vol. 1.13)

"A Placebo-Controlled, Double-Blind Dose-Ranging Study Of Albuterol Sulfate, Using A Bronchoprovocation Design, In Pediatric Patients With Asthma."

A. Investigators and investigational centers.

1. **Investigator**
   - **Paul V. Williams, M.D.**
     A.S.T.H.M.A., Inc.
     Seattle, WA (2 patients)
   - **James Baker, M.D.**
     Allergy Associates, P.C.;
     Portland, OR (rest of patients)
2. **Investigational Centers**

   Two centers participated.

B. Objective.

To establish the dose-response curve of nebulized albuterol sulfate as a nebulized treatment for asthma in children, ages 6 through 12 years. This curve will be used to estimate the lowest effective dose for use in a follow-up treatment protocol.

C. Study Design.

This is a multi-center, double blind, placebo- controlled, crossover study in 24 patients 6 through 12 years of age with moderate asthma. The primary parameter is airway responsiveness using a methacholine challenge test. Methacholine challenge test is a provocative challenge to determine the concentration of methacholine that reduces FEV_1 by 20% (PC_{20}).

1. **Population.**

a) **Inclusion Criteria**

(1) History of moderate asthma in a child from 6 to 12 years of age

(2) FEV_1 between 70 -95% with demonstrated reversibility of at least 15% of baseline within 30 minutes of inhalation of albuterol sulfate (3 mg.).

(3) Specified asthma symptoms daily and/or nocturnal awakening 3-4 times weekly during at least 6 months in the year prior to randomization; or daily asthma medication for at least six months during the past year.

(4) Methacholine PC_{20} baseline at Visit 2 must be $\leq$ 4 mg/ml to demonstrate airway responsiveness to methacholine

b) **Exclusion Criteria**

(1) Any serious medical condition or use of drug with which albuterol administration is contraindicated.

(2) Known hypersensitivity to albuterol, methacholine or similar agents.

(3) Any chronic condition which would interfere with successful completion of the trial or its interpretation.

(4) PFTs suggesting a ventilatory defect other than asthma, or evidence of existing irreversible lung damage.

(5) Steroid dependence or use of systemic steroids in 4 weeks before screening visit.

(6) Treatment of gastroesophageal reflux

(7) Received an immunization or flu vaccine within 30 days prior to entering or during the study.

(8) Active pulmonary disease including cystic fibrosis, bronchiectasis, tuberculosis, or immunodeficiency leading to recurrent sino-pulmonary infections.

(9) Clinical features suggestive of a history of respiratory infection within the month prior to enrollment.

(10) Chronic conditions other than asthma (i.e., physical disability, mental, neurological or psychiatric problems) which would have interfered with successful completion of the protocol, or confound its interpretation.

(11) Severe chronic sinusitis or nasal polyposis.

(12) The introduction of, or a change in, allergen immunotherapy within the month prior to enrollment.

(13) Administration of an investigational drug within 30 days prior to enrollment.

(14) An inability to perform three acceptable forced vital capacity maneuvers with two FEV_1 values within 10% of the largest FEV_1 value.

(15) Evidence that the patient or family may have been unreliable or noncompliant, or may have moved from the area before completing the study.

(16) A history of tobacco use.

(17) Experienced clinically significant signs and symptoms of allergy to tree pollen or grasses during the study period, as

documented by skin testing within the 12 months prior to enrollment or at screening. On the basis of history and skin tests, patients did not participate in the study during their pollen allergy season.

2. Concomitant Medications

Patients remained on stable doses of their current medications and/or prn B-agonists throughout the study. Varying washout times prior to each study day were required by the protocol for β-agonists (short acting – 8 hours, long-acting 48 hours, oral conventional release – 12 hours, oral modified release- 24 hours), theophylline (48 hours), antihistamines (astemizole-3 months, hydroxyzine – 96 hours, all others- 48 hours), aspirin and other non-steroidal anti-inflammatory drugs (5 days), and anticholinergics (inhaled – 24 hours, oral 7 days). Patients taking cromolyn, nedocromil, or inhaled steroids withheld their morning dose and all subsequent doses during the study session. These patients then resumed their regularly scheduled dosing after the study session.

3. Randomization procedures

The order of administration of the 4 nebulized treatments was allocated using a computer-generated randomization schedule.

4. Study Flow Chart

APPEARS THIS WAY
ON ORIGINAL

	X				
	X				X[2]
	X				
	X				
	X				
	X				
	X	X[3]	X[3]	X[3]	X[3]
	2X	2X	2X	2X	2X
	X				
	X	X	X	X	X
	2X	4X	4X	4X	4X
	2X	~10X	~10X	~10X	~10X
		2X[4]	2X	2X	2X

1 The time between screen/baseline visit to the first treatment visit must not be greater than 14 days; time between treatment visits = 3-9 days.

2 Final physical evaluation will be conducted at the end of the final visit (i.e., Visit 5 or at time of discontinuation from study).

3 Theophylline levels are tested for all patients at screening and only at treatment visits for patients who have taken theophylline in past 3 years.

4 Baseline PC_{20} at Visit 2 will serve as screening value and must be = 4 mg/ml to demonstrate methacholine responsivity.

5. Administration of study drug

Patients returned to the clinic within 14 days after screening and began a series of four separate treatment sessions (Visits 2-5), separated by 3-9 days. Two methacholine challenge tests were taken, 3 hours apart, on each treatment day: baseline (pre-treatment) and then starting again 15 minutes post–treatment with

4. Study Flow Chart

	X				
	X				X^2
	X				
	X				
	X				
	X				
	X	X^3	X^3	X^3	X^3
	2X	2X	2X	2X	2X
	X				
	X	X	X	X	X
	2X	4X	4X	4X	4X
	2X	~10X	~10X	~10X	~10X
		$2X^4$	2X	2X	2X

1 The time between screen/baseline visit to the first treatment visit must not be greater than 14 days; time between treatment visits = 3-9 days.

2 Final physical evaluation will be conducted at the end of the final visit (i.e., Visit 5 or at time of discontinuation from study).

3 Theophylline levels are tested for <u>all patients at screening</u> and only at treatment visits for patients who have taken theophylline in past 3 years.

4 Baseline PC_{20} at Visit 2 will serve as screening value and must be ≤ 4 mg/ml to demonstrate methacholine responsivity.

study medication. All patients received all doses, one at each visit separated by 3 - 9 days. A single brand nebulizer was used and the nebulization lasted about 10 minutes, via a mouthpiece with nose clip. Each treatment took place at about the same time of day.

Study treatment was given 2 hours 40 minutes after the baseline methacholine challenge.

The sponsor supplied the drugs in identical vials containing the following concentrations in 3 mL. of normal saline:

- Albuterol sulfate 0.75 mg.
- Albuterol sulfate 1.5 mg.
- Albuterol sulfate 3 mg.
- Placebo isotonic saline

The sponsor also supplied the Methacholine in the concentrations to be used.

6. Methacholine Provocation Challenge Test

Two methacholine challenge tests were conducted, three hours apart, on each study treatment day:

- at baseline, before study treatment, and
- starting 15 minutes after study treatment

Ascending concentrations of methacholine (0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 16.0, 32.0, 64.0, 128.0 mg/mL) were administered every 2 - 5 minutes to determine the PC_{20} relative to the pre-baseline or pre-treatment FEV_1 .

FEV_1 was measured 30 - 90 seconds after each methacholine dose was completed. The methacholine challenge test was stopped after the FEV_1 decreased at least 20% from the saline FEV_1 or when the highest methacholine dose, 128 mg/ml, had been delivered. Patients also underwent additional spirometry during Visit 2 at 2, 5, 10, 20, and 40 minutes after the last methacholine dose for both the pre-treatment and post-treatment challenge tests.

The post treatment challenge test was started at one concentration level lower than that which produced the patient's PC_{20} during the pretreatment challenge on that day. The pre-treatment PC_{20} from visit 2 served as the "screening PC_{20}". The screening PC_{20} had to be $\leq$ 4 mg/ml for the patient to continue in the study. Subsequent pre-treatment PC_{20} measurements had to fall between 50% and 200% of the screening PC_{20} (a two-fold dilution). Patients were rescheduled for another day if the Baseline FEV_1 was < 65% or if the FEV_1 dropped more than 10% from the pre-methacholine baseline following the saline dose. Those subjects who evidenced methacholine responsiveness at concentrations too low for safety, or at concentrations too high to be considered responsive, were to be dropped from the study at the discretion of the investigator.

All pulmonary function tests were obtained in triplicate according to American Thoracic Standards (ATS). All spirometric observations were obtained in the standing position using a dry spirometer. Parameters recorded included FEV_1, FEF_{25-75}, PEFR, and FVC. The "best effort" (e.g., the highest value) of the three recordings (or from at least two values not varying more than five percent) were taken as the "measured value" for data analysis. Pre-methacholine challenge FEV_1 measurements were not permitted to vary by more than 12% from the initial (Visit 1) baseline value. The FEV_1 measurements taken between methacholine challenges were also not permitted to vary by more than 12%. If greater than 12% variation occurred, the study was deferred until the variance was $\leq$ 12%. In addition, an absolute minimum baseline FEV_1 of at least 65% of predicted was required at each session. Any patient who failed to meet these criteria after three consecutive attempts was dropped from the study. Patients with a FEV_1 of less than 40% of predicted, during any treatment period, were to be dropped from the study.

7. Rescue Medication

If the FEV_1 did not return to baseline within 10 minutes of the second methacholine challenge, a rescue bronchodilator could be administered at the discretion of the investigator. The primary rescue medication was an albuterol MDI (90 mcg/inhalation). If this was unsuccessful, then albuterol sulfate 3 mg was administered via nebulizer. Any patients requiring rescue after the pre-treatment methacholine challenge at any session did not undergo any further testing and were instructed to return at a later date. Any patients requiring rescue medications on three separate occasions were to be dropped from the study.

8. Statistical Analysis

a) Sample size

A sample size of 24 patients was calculated to detect a 100% difference in PC_{20} attributable to albuterol relative to placebo, with an α level of 0.05 and a 90% power.

b) Analysis of the primary endpoint of efficacy

The change in the methacholine response from baseline to post-treatment PC_{20} was compared among the 4 treatment groups with the use of a General Linear Model, and Waller Duncan K-ratio T test.
The analysis of the data was performed at

D. Results.

Twenty-five of fifty pediatric patients were randomized to a treatment. Twenty-four of the 25 patients enrolled in the study completed all four

treatments sessions. Patient 0217 dropped-out at Visit 4 due to an asthma exacerbation that prevented the patient from meeting the protocol-defined minimum spirometry criteria required for continuation.

1. **Demographic Characteristics.**

There were 15 males and 10 females, all Caucasians, with a mean age of 10.0 years (range = 6-12 years). Mean height was about 57.5 inches (range = 48-66 inches) and weight was about 110 lbs. (range = 41-200 lbs.). The mean duration of asthma was 7.5 years, and all of them were on or had taken concomitant medications at the time of entry (most of them were taking medications for asthma).

2. **Efficacy**

The data was visually explored by this medical officer and it is clearly evident that the post treatment PC_{20} were much higher in most cases. While the manner in which they were explored did not have the doses of albuterol labeled, in many cases one PC_{20} was lower than the others and was most likely placebo.

Dose-response was assessed by measuring FEV_1 and then evaluating the calculated pre-treatment PC_{20} against the post-treatment PC_{20} for all three albuterol doses and placebo.

The analysis of efficacy for this study was complicated by the fact that the PC_{20} could not be reached in several sessions and some subjects demonstrated mean baseline PC_{20} values greater than 4 mg/ml.

All doses of albuterol produced significant benefit when compared to placebo, however, the dose response curve was very flat. One reason for the lack of dose response was due to the fact that a 20% reduction in FEV_1 (PC_{20}) could not be obtained for 17 treatments due to the limitation of methacholine dose. Because the ceiling of PC_{20} was reached during 17 treatments in eight subjects, and because the mean baseline PC_{20} was >4 mg/ml in 6 subjects (even though the baseline PC_{20} at visit 2 was required to be $\leq$4 mg/ml), 4 sets of data were analyzed: A) all data; no extrapolation of PC_{20} beyond 128 mg/ml, B) data of individuals with mean baseline PC_{20} values of $\leq$ 4 mg/ml only (which required the exclusion of 6 children with mean baseline PC_{20} values >4mg/ml); no extrapolation of PC_{20} beyond 128 mg/ml, C) all data; extrapolation of PC_{20} beyond 128 mg/ml, and D) data of individuals with mean baseline PC_{20} values of $\leq$ 4 mg/ml only; extrapolation of PC_{20} beyond 128 mg/ml. Data were analyzed with the use of nonlinear mixed effects models (the NONMEM program). The analysis was performed at

To evaluate efficacy of albuterol in the dose range studied, comparison of observed PC_{20} (data set A) values among the 4 treatment groups was made with the use of a General Linear Model (GLM Procedure of SAS-Version 6.08), and Waller Duncan K-ratio T test.

In the original data, there were 17 PC20 values out of 98 in eight subjects associated with methacholine challenge that exceeded the highest methacholine dose. It was surmised that because of the ceiling of methacholine doses that were found, there was a blunted differentiation between the doses. Without making a correction for this feature, the dose response is flat and the D_{50} is below the lowest dose studied at 0.31 mg. Even with the exclusion of subjects with a mean baseline PC_{20} > 4 mg/ml (Set B), the dose response is flat and the D_{50} is 0.25 mg. A model was developed for FEV_1 vs. time that allowed for the extrapolation of the PC_{20} beyond 128 mg/ml in order to predict the PC_{20} values subjects would have had if allowed to receive higher doses of methacholine.

The PC_{20} vs. albuterol dose relationship was analyzed using the following model:

$$PC_{20} = PC_{20,\ baseline} + PC_{20,placebo} + PC_{20,drug}$$

The PC_{20} vs. albuterol dose relationship was modeled with a saturable, monotonic curve (an E_{max} model) and various hypotheses were tested.

$$PC_{20,drug} = E_{max} \times Dose / \ Dose + D_{50}$$

D_{50} is the dose that is estimated to produce 50% of the maximum effect and E_{max} is the maximum drug effect.

	1.13 (0.68,1.89)	5.06 (2.81,9.09)	41.3 (25.1,68.0)	0.31 (0.05,2.08)
	0.72 (0.43,1.22)	3.59 (4.87,15.8)	17.7 (10.4,30.2)	0.25 (0.02,3.11)
	1.13 (0.68,1.89)	4.75 (3.78,12.1)	62.8 (37.1,106)	0.87 (0.76,1.00)
	0.72 (0.43,1.22)	3.63 (3.05,10.6)	24.1 (13.8,42.3)	1.00 (0.88, 1.14)

When reasonable predictions of PC_{20} beyond 120 mg/ml are made (Sets C and D), the D_{50} is estimated to be 0.87 mg (0.76, 1.00 mg) and 1.00 mg (0.88, 1.14 mg) respectively. Excluding individuals with a mean baseline PC_{20} greater than 4 mg/ml did result in a lowering of the E_{max} in data sets B and D. The model did not detect a significant effect of body weight. Efficacy was demonstrated because the mean change in PC_{20} with each active treatment differed significantly from that of placebo and the fact that the D_{50} was significantly greater than zero. In all models, the 95%

	1.13 (0.68,1.89)	5.06 (2.81,9.09)	41.3 (25.1,68.0)	0.31 (0.05,2.08)
	0.72 (0.43,1.22)	3.59 (4.87,15.8)	17.7 (10.4,30.2)	0.25 (0.02,3.11)
	1.13 (0.68,1.89)	4.75 (3.78,12.1)	62.8 (37.1,106)	0.87 (0.76,1.00)
	0.72 (0.43,1.22)	3.63 (3.05,10.6)	24.1 (13.8,42.3)	1.00 (0.88, 1.14)

confidence interval of the difference for E_{max} did not include 0, supporting the fact that the drug is efficacious.

Another test for a graded-dose response relationship is to test the goodness of fit of the E_{max} model (the model used in the analysis) to that obtained with a step model (that is, an E_{max} model with a D_{50} fixed to be very small, 0.0001mg). The goodness of fit according to the — analysts of these two models did not differ significantly confirming the absence of a graded dose response when the ceiling of PC_{20} is not accounted for.

The sponsor states in the Final report that based on the results of this study, an albuterol dose of 1.0 to 1.5 mg is recommended for study in a larger patient population.

3. Safety

Safety was assessed by recording the occurrence of adverse events and monitoring changes in vitals signs and 12-lead EKG taken pre and one hour post-treatment. Vital signs (pulse, blood pressure and respiratory rate) were recorded immediately prior to, and at the completion of, each of the two methacholine challenges.

One patient (#217) dropped from the study during Visit 4 due to an asthma exacerbation after completing three of the four treatments. The patient was unable to meet PFT requirements after 3 attempts at Visit 4.

No clinically lab abnormalities (CBC, SMAC-12) were noted in the 25 subjects but it is important to note that such blood work only done at screening and was not repeated.

There were no statistically or clinically significant differences in the means or changes in the means for the vital signs between treatment sequence groups or doses. In an analysis using the 24 subjects who completed all four treatments, there was no carryover or period effect in the means with systolic blood pressure, diastolic blood pressure, heart rate, or respiratory rate.

There was a statistically significant difference in the distribution of patients with any EKG abnormalities among the treatment sequence groups at pre-procedure during the screening visit (p=0.49). Two out of six subjects in Treatment Sequence 4 had a pre-procedure EKG abnormality, one of which resolved post-procedure. There were no pre-procedure EKG abnormalities in the other Treatment Sequence groups.

There were no statistically significant differences in the distribution of patients with any EKG abnormalities among the treatment sequence groups at post-procedure and change from pre-procedure during the screening visit. Two new abnormalities were noted post procedure with one in the placebo group and one in the 0.75-mg group. None of the new abnormalities noted on EKGs 2 hours after study drug administration were considered clinically significant by the investigator.

Four subjects were noted to have abnormalities on the post dose EKG as compared to the pre-dose EKG. Subject 205 was noted to have high T waves,

which was deemed not clinically significant. Subject 206 was noted to have a ST-T wave abnormality on a post dose EKG while the pre-dose was considered normal on Visits 1 and 3 – notably an ST-T wave abnormality had been noted on both pre and post dose EKGs on Visit 2. On Visit 4, this same subject had a wide P and ST elevation pre-dose and sinus arrthymia and ST abnormality post–dose. Subject 210 was noted to have a slight ST-T wave abnormality on a post dose EKG that was deemed not clinically significant on Visit 1. Subject 215 developed a sinus arrhythmia post dose EKG that was deemed not clinically significant on Visit 1.

Three subjects required 180-mcg B-agonist rescue medication – each on one visit.

Two of the 25 patients (8%) reported a total of three adverse events. Two of the reported events were rated as moderate in intensity, and one as mild.

	0218	1	1	0	0	0
	0222	1	0	0	0	1
	0222	1	0	1	0	0
		3	1	1	0	0

None of the events were serious or considered related to blinded study drug by the investigators. Two of the reported adverse events resolved. One adverse event, otitis media, was ongoing at study completion. There were no clinically significant laboratory abnormalities reported during the study.

E. Discussions/Conclusions

The purpose of this study was to characterize the effect of nebulized placebo, 0.75 mg, 1.5 mg, and 3.0 mg nebulized albuterol sulfate on the PC_{20} of the methacholine challenge test in 25 subjects within the age range of 6-12 years. The analysis of this study was complicated by primarily two circumstances: 1) while all subjects had to have a baseline PC_{20} of < 4 mg/ml at Visit 2 in order to be randomized, several subjects had pre-treatment PC_{20} of > 4 mg/ml, and 2) several demonstrated a ceiling effect with post-treatment PC_{20} of > 128 mg/ml (the highest dose administered). Including these data points, the dose response curve was flat. A nonlinear mixed effects model was used to analyze the data and the PC_{20} was extrapolated beyond 128 mg/ml. By fitting an E max model to the data a D_{50} and E_{max} could be identified. This model was evaluated by a consult through the Pharmacometrics Branch and because D_{50} values were significantly greater than zero, efficacy was thought to be established. The observed mean change in PC_{20} values were significantly different from baseline for all doses compared to placebo using a Generalized Linear Model.

Otitis Media Left Ear	0218	1	1	0	0	0
Cold Sore	0222	1	0	0	0	1
Tooth Ache	0222	1	0	1	0	0
Total		3	1	1	0	0

While this study appears to demonstrate efficacy, it could only be demonstrated only through extrapolation of the data and NONMEM modeling. This study should be thought of as supportive of Accuneb's efficacy but cannot be thought of as a pivotal trial and used for basis of approval.

This study demonstrated only three adverse events in two subjects. There were no serious adverse events. None of the events were considered related to blinded study drug by the investigators. An analysis of the effect of the drug on pulse rate and peak pulse rate was not submitted. Subject 206 appeared to have ST-T wave abnormalities at varying times both pre- and post-dose. In the action letter, asking for Subject 206's case report would be helpful. Overall, none of the new abnormalities noted on EKG's two hours after study drug administration were considered clinically significant by the investigator.

IV. DL-019 Protocol - last amendment 01/28/97 (Vol. 1.15)

"A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of the Safety and Efficacy of a Low-dose Albuterol Sulfate Inhalation Solution for Pediatric Subjects with Asthma"

A. Investigators and investigational centers.

This was a multi-center study. The number of centers was not established in the protocol. The study report states that 42 sites were involved.

One study site was disqualified by the FDA due to problems found at the site during an audit of another sponsor's asthma study. This site was Dr. Edwards at Site 006. The disqualification occurred just prior to the completion of this NDA. The site enrolled nine patients so the efficacy data was reanalyzed, removing those patients (3 in each treatment group) from the efficacy section and the ISE. Their data is included in the safety analysis because these people were exposed to the drug.

B. Objective.

The objective of this study was to evaluate the safety and efficacy of 2 doses of albuterol sulfate inhalation solution (0.75 and 1.50 mg), relative to placebo, in the treatment of asthma in children 6 to 12 years of age.

C. Study Design.

This was a multi-center, randomized, double-blind, placebo controlled, parallel group, 4 week treatment study to evaluate the safety and efficacy of 2 doses (0.75 and 1.50 mg) of albuterol sulfate solution for inhalation administered by Pari LC+™ nebulizer, TID, to 300 children ages 6 to 12 years, with moderate asthma. The study consisted of an optional pre-screening visit, a screening visit,, followed by a two-week placebo washout phase to confirm the need for regular symptomatic β-agonist therapy, and a 4-week treatment phase.

1. **Population.**

a) **Inclusion Criteria**

(1) **Males and females between the ages of 6 and 12 years;**
(2) **History of moderate asthma for a minimum of six months that required daily medication, but was otherwise in good health;**
(3) **FEV_1 between 50 and 80% at baseline and at the beginning of the double-blind treatment phase. At the screening visit, reversibility of at least 15% of baseline following the administration of albuterol sulfate had to be demonstrated;**
(4) **Asthma symptoms experienced (cough, wheezing, shortness of breath, nocturnal asthma awakenings) during the placebo controlled period between Visits 1 and Visit 2 which requires the use of prn β_2-agonists on at least 6 of the 14 days ±3 of observation.**

Reviewer's Note: Note that subjects had to demonstrate a response to albuterol sulfate before they could even be entered into the study.

b) **Exclusion Criteria**

(1) **Any serious medical conditions or use of drug with which albuterol administration is contraindicated;**
(2) **Known hypersensitivity to albuterol;**
(3) **Any chronic condition which would interfere with successful completion of the trial or its interpretation;**
(4) **Steroid dependence or use of systemic steroids 4 weeks before screening visit;**
(5) **Patients meeting protocol specified definition of severe asthma.**

2. **Concomitant Medications**

Patients who met the inclusion criteria while on their regular asthma medications, as prescribed by their physician, continued on those medications except β-agonists during the course of the study as long as the doses remained stable.

Regular asthma medications which were <u>not</u> permitted during this study were theophylline, oral β_2-agonists, and systemic steroids. Medications allowed to be maintained during the course of the study included the chronic usage of cromolyn sodium, nedocromil, approved dosages of inhaled steroids, excluding salmeterol xinafoate and prn albuterol MDI. Patients must have met the inclusion criteria while using such medications at stable doses and all medications were withheld during each study session. Patients continuing cromolyn, nedocromil, or inhaled steroids will, for each study visit, withheld their morning dose. After the patient completed the study session, the regularly scheduled dosing resumed the same day. Patients unable to meet inclusion criteria while remaining on cromolyn, nedocromil, or inhaled steroids, could discontinue these medications two weeks before the initial screening visit and, if they then met entry criteria, they continued abstaining from those medications for the entire course of the study. All medications were withheld during the entire study session (e.g., approximately 6 hrs for Visit 2 & 4 and for 2 hours at Visit 3. Moreover, in terms of specific washout periods, the list of medications and duration of abstinence from use prior to each study visit are listed below:

Inhaled β_2-agonists		
	Albuterol (study medication only)	6 hours
Antihistamines		
	Astemizole	3 months
	Hydroxyzine	96 hours
	All others	48 hours
Anticholinergics		
	Inhaled	24 hours
	Oral	7 days

The following medications are exclusionary throughout the study and should be washed out prior to screening Visit 1 according to the specified washout periods below:

Inhaled β_2-agonists		
	Short acting (not study related (albuterol, terbutaline))	6 hours
	Long acting (e.g., salmeterol)	48 hours
Oral β_2-agonists		
	Conventional release	12 hours
	Modified release	24 hours
Theophylline products (all forms)		48 hours
Corticosteroids (systemic)		4 weeks

In summary, patients on regular asthma medications, other than theophylline, β_2-agonists, and systemic steroids, were allowed to continue on those medications during the course of the study if the doses remained stable.

3. Randomization

Eligible patients were randomized at Visit 2 to a treatment group in sequential order for the double-blind treatment phase of the study. Random assignment to a treatment, albuterol sulfate 0.75mg (100 patients), albuterol sulfate 1.5 mg (100 patients) and placebo (100 patients) with stratification by study site were determined by a computer-generated randomization schedule provided by [redacted]

4. Procedures

a) Wash out period. Prior to randomization, all patients enrolled in the study completed an initial 2 week placebo washout period during which the dosages of inhaled corticosteroids, cromolyn sodium, or nedocromil were held constant and the use of β_2-agonists was limited to albuterol PRN. The placebo phase was to confirm the need for regular β_2-agonist therapy and to give patients experience with daily diaries. At the

start and end of the placebo washout phase (Visits 1 & 2), spirometric evaluations were conducted to confirm diagnostic inclusion criteria of FEV_1 between 50 and 80% of predicted normal.

b) **At the Screening Visit I, patients demonstrated reversibility by nebulization. Reversibility of FEV_1 by at least 15% was documented following the administration of an inhaled beta agonist by the standard nebulizer. Reversibility was assessed utilizing the KOKO Spirometry standard.**

c) **Double blind period. On the first day of the double blind treatment period, the patients were randomized to receive one of the three test drugs (albuterol sulfate 0.75 mg, 1.50 mg or placebo) TID for 4 weeks. The patients (and their caregivers) recorded the following safety and efficacy data on daily diaries throughout the study period: Pre-treatment peak flow readings, asthma symptoms, night awakenings, use of supplemental albuterol to control exacerbations of asthma, any changes in concurrent medications, and any adverse events. Following the first dose of their test drug, the patients were followed with spirometry and safety measurements at 30 and 60 minutes after the end of nebulization and then hourly for 6 hours post dose. The forced vital capacity maneuver was performed in triplicate by all subjects in the study and the highest value for FEV_1 and FVC from the three maneuvers was recorded. Peak flow rates were otherwise followed by the patient every morning before going to bed and every night before going to bed.**

Reviewer's Note –In is stated in Section 8.6 (p.211, Vol.1-16) of the protocol that: " Following the determination of qualifications for study inclusion at Visit 1 and Visit 2 (to exclude "placebo responders"), patients will be provided with a list of dates for the subsequent study treatment visits." It is not clear to this reviewer what is meant by excluding placebo responders.

Patients returned to the study center after 14 days $\pm$3 days of treatment (Visit 3) for exchange of study medication and diaries and to perform spirometric evaluations before and 30 minutes after the morning administration of the study drug.

At the completion of 28 days $\pm$3 days of treatment (Visit 4), the patient returned to the study center for a 6-hour evaluation of safety and efficacy after test drug administration.

Schedule of Assessments

	Prescreening	Visit 1	Visit 2	Visit 3	Visit 4
Weeks	(-) 3-7 days	0	2	4	6
Procedures Informed Consent	X	X (if applicable)			
Inclusion/Exclusion		X	X		
Physical Exam		X			X
Medical History		X			
Clinical Labs/Urinalysis		X			X
Urine Pregnancy		X	X	X	X
Theophylline Levels[1]		X	X	X	X
12-Lead ECG[2]		X	X	X	X
PFT[3]	X	X	X	X	X
PFT Reversibility[4]		X			
Vitals Signs[3]		X	X	X	X
Review Nebulizer/ MDI Technique		X	X	X	
Review Diary			X	X	X
Assess AEs			X	X	X
Assess Concomitant Medications			X	X	X
Global Assessment					X

[1] All patients had a theophylline level measured at the screen visit. Only patients with a level ≥ 6 mcg/mL of theophylline at Visit 1 had a level drawn at all visits.

[2] ECGs were done at screening and pre-dose and post-dose at 30, 60 and 90 minutes at Visits 2 and 4, and pre-dose and post-dose 30 minutes at Visit 3.

[3] PFTs and vital signs were measured pre-dose, 30 minutes, and hourly for 6 hours post-dose at Visits 2 and 4. At Visit 3, they were measured pre-dose and 30 minutes post-dose. PFTs were measured using the KOKO Spirometer.

[4] All patients had reversibility measured at Visit 1 by KOKO Spirometer, 30 minutes following inhaled albuterol.

5. Administration and dosage

Dosing was TID: upon arising, mid-day, and prior to bedtime.

The sponsor supplied the following drugs:

- **albuterol sulfate 0.75 mg. nebulized (0.623 mg as 0.021% soln)**
- **albuterol sulfate 1.5 mg. nebulized (1.25 mg as 0.042% soln)**
- **placebo isotonic saline (0.9%)**

6. Rescue Medication

The sponsor supplied the following drugs:

- **albuterol sulfate 3 mg nebulized (prn)**
- **albuterol sulfate 90 mcg MDI (prn)**

Albuterol MDI canisters (90 mcg/inhalation; 200 inhalations/canister) were used prn to treat breakthrough symptoms. The supplemental nebulized albuterol (3.0 mg) was used only if albuterol MDI did not provide adequate relief of symptoms

7. Statistical Analysis

a) Sample size

Sample size was not discussed in the protocol. The study report stated that "efficacy could have been demonstrated in a relatively small number of patients for each

drug treatment group (30 children); however, in order to accumulate sufficient safety data to demonstrate both clinical and statistical significance, a greater number of children were needed." Thus, 100 children were randomized to each treatment group.

b) Efficacy endpoints

The %Δ AUC FEV_1 defined, as the area under the FEV_1 percent change from pre-dose versus time curve at Visit 4, was the primary efficacy endpoint. Secondary efficacy endpoints were the %Δ AUC FEV_1 at Visit 2, the maximum FEV_1 (MAX FEV_1), and the duration of response (defined as the minutes between the time the patient reached a 15% increase in FEV_1 over pre-dose FEV_1 and then returned to below 115%). These measures at Visits 2 and 4 were analyzed by analysis of variance (ANOVA) or by nonparametric methods (e.g., Kruskal-Wallis Test) if assumptions of normality were not met.

Secondary efficacy parameters also consisted of peak expiratory flow readings, asthma symptoms, (including global assessment) night awakenings, frequency of rescue medication use for the treatment of asthma exacerbations, and frequency of study discontinuation due to treatment failure.

The analysis of the data was performed at [ ]

8. Safety analyses

The safety analysis included adverse events and the results of physical examinations, vital sign measurements, ECGs, and clinical laboratory tests. Treatment comparison of adverse events were evaluated by nonparametric analysis (Fisher's Exact Test) of the number and percent of patients with at least one adverse event.

The physical examinations were done at the screening visit and upon completion or termination from the study. Vital signs were taken at the same timepoints as the PFTs. ECGs were done at Visit 1 (screening), at Visits 2 and 4 pre-dose and 30, 60, and 90 minutes post-dose and at Visit 3 pre-dose and 30 minutes post-dose. The ECG parameters, including ventricular heart rate, P-R interval, R-R interval, QRS duration, Q-T interval, QTc interval, and overall ECG interpretation were collected at screening, pre-dose and 30 minutes post-dose at Visits 2, 3, 4, and, if early termination occurred, at Visit 4/Study Termination and at the follow-up Visit 5. Additional ECGs were taken at 60 and 90 minutes post-dose at Visits 2 and 4. To standardize the interpretations of the ECG, the rhythm strips were faxed to a central institution, [ ] for reading by a pediatric cardiologist. The interpretations were sent back to the study site for review by the investigator. The investigator, who had first-hand knowledge of the patient's medical history and health status, re-assessed any abnormal interpretations for their clinical relevance.

Clinical laboratory tests were done at the screening visit to determine eligibility and pre-dose at Visit 4 to monitor safety.

D. Disposition of Patients

A total of 349 patients were enrolled in the study: 115 patients were randomized to the 1.5 mg albuterol sulfate group; 117 patients were randomized to the 0.75 mg albuterol sulfate group; and 117 patients were randomized to the placebo (0.9% saline) group. Eighty-three percent (288/349) of the patients completed the study: 98 (85.2%) patients in

the 1.5 mg albuterol sulfate group; 97 (82.9%) in the 0.75 mg albuterol sulfate group; and 93 (79.5%) patients in the placebo group.

The number of patients discontinuing overall was similar across treatment groups, with slightly more patients in the placebo treatment group discontinuing. Of the 61 patients who withdrew from the study, 45 patients (73.8%) discontinued due to an adverse event. There were no differences in the number of patients discontinuing due to adverse events across treatment groups.

Reasons for discontinuations coded as "other" were due to the following: one subject was withdrawn under advisement by [redacted] due to a decrease in FEV_1 during the first treatment visit; one subject was randomized in error; one subject was taking [redacted] an investigational drug for pediatrics; one subject used exclusionary medication; and one subject did not meet inclusion criteria. The latter three patients could have been considered protocol violations, but the investigator checked the 'other' category.

E. Results.

1. Demographic Characteristics

Three hundred and forty nine patients were included in the ITT population (115 albuterol 0.042%, 117 albuterol 0.021% and 117 placebo). Because of the disqualification of one of the sites, the efficacy data were from 340 patients while the safety data was from 349 patients. The ITT population included all patients who took at least one dose of study medication. The ITT population was used for all safety analyses. The ITT efficacy population consisted of all patients randomized to the trial that had a minimum number of

Number of Patients in Each Study Population for DL-019

Study population		1.5 mg Albuterol	0.75 mg Albuterol	Placebo
ITT		115	117	117
Visit 2	ITT Efficacy	112	110	110
	Evaluable	75	70	67
Visit 4	ITT Efficacy	94	90	89
	Evaluable	75	70	69

non-missed PFT data points at Visit 2 and/or Visit 4. The minimum required PFT points were pre-dose, post-dose 30 minutes, 1 hour, 2 hours and 6 hours. Missing PFT data was the only reason why patients were excluded from the ITT Efficacy population. The evaluable population was a subgroup of the ITT efficacy population consisting of patients who completed the study in accordance with the protocol. Efficacy analyses were done on the ITT efficacy and the evaluable populations.

Summary of Demographics for the ITT Population (n=349)

	1.5 mg Albuterol N =115	0.75 mg Albuterol N =117	Placebo N =117	P-value[1]
Age				
Mean (SD)	9.3 (1.8)	9.4 (1.8)	9.6 (1.7)	0.488
Median	9.0	10.0	10.0	
Min, Max	6.0, 12.0	6.0, 12.0	6.0, 12.0	
Gender (%)				
Female	39 (33.9)	47 (40.2)	42 (35.9)	0.596
Male	76 (66.1)	70 (59.8)	75 (64.1)	
Race (%)				
Caucasian	81 (70.4)	79 (67.5)	82 (70.1)	0.841
Black	23 (20.0)	24 (20.5)	24 (20.5)	
Asian	2 (1.7)	1 (0.9)	3 (2.6)	
Hispanic	5 (4.3)	9 (7.7)	7 (6.0)	
Other	4 (3.5)	4 (3.4)	1 (0.9)	
Height (cm)				
Mean (SD)	140.2 (11.6)	140.0 (12.1)	141.3 (11.4)	0.635
Median	140.0	140.7	141.4	
Min, Max	103.6, 178.0	115.2, 170.2	117.0, 170.0	
Weight (kg)				
Mean (SD)	39.0 (12.9)	38.1 (12.3)	40.3 (14.2)	0.431
Median	37.0	35.4	37.2	
Min, Max	16.8, 90.8	19.1, 79.4	21.8, 86.6	
% FEV_1 Predicted				
Mean (SD)	69.0 (8.0)	67.8 (8.1)	68.5 (7.9)	0.494
Range	51.1 - 89.9	50.6 - 82.6	48.9 - 81.3	
% FEV_1 Reversibility				
Mean (SD)	29.0 (14.2)	33.6 (19.3)	30.4 (16.1)	0.107
Range	12.4 - 87.4	14.6 - 141.2	14.5 - 97.7	

[1] ANOVA for H0: Treatment means are equal for Age, Height, Weight; FEV_1 % Predicted or % Reversibility; or Fisher's Exact Test for H0: No association between Gender or Race and treatment.

The treatment groups appear to compare well and there were no statistical differences across the groups for any of the demographic parameters. When comparing the ITT population with the evaluable population, the only noticeable shift was in gender which was approximately 2:1, males to females, in the ITT placebo population and nearly 1:1 in the evaluable population placebo treatment group.

All patients had a history of asthma ≥ 6 months; the majority of patients experienced asthma for a duration of 5 to 10 years (60.0%, 66.7% and 59.8% in the 1.5 mg, 0.75 mg, and placebo groups, respectively). Most patients experienced both intrinsic and extrinsic asthma (73.9%, 77.8% and 83.8% in the 1.5 mg, 0.75 mg, and placebo groups, respectively), and the patients' asthma exacerbations were most often due to respiratory infection, exercise, and allergens. The percentages of patients whose mothers were currently using tobacco during the study were 20.9%, 18.8% and 14.5% in the 1.5 mg

albuterol sulfate, 0.75 mg albuterol sulfate, and placebo groups, respectively. The percentages of patients whose fathers were currently using tobacco during the study were 30.4%, 21.4% and 25.6% in the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo groups, respectively.

Baseline physical examinations (PE) were done at Screening (Visit 1). In the ITT population, 49.6% (57/115) of the 1.5 mg albuterol sulfate group, 58.1% (68/117) of the 0.75 mg albuterol sulfate, and 49.6% (58/117) of the placebo group reported with abnormalities of the EENT system. . No significant differences in any of the vital sign parameters were seen in patients assigned to the three treatment groups. ECG interpretations at baseline were normal, except for 10 (2.9%) out of the 349 patients. Five of those patients were enrolled in the 1.5 mg albuterol sulfate group. Four of those 1.5 mg patients had clinically insignificant abnormalities involving an inverted T-wave, two with left atrial hypertrophy, and/or two with ectopic atrial rhythm. One patient, Subject No. 531, reported with WPW syndrome, but the patient had participated in other beta-agonist studies with no problems, so the investigator elected to enroll the patient in this study. In the 0.75 mg albuterol sulfate group, four patients were enrolled with clinically insignificant abnormal ECG interpretations involving one incomplete right bundle branch block (IRBBB), one flat T-wave, and two cases of sinus tachycardia considered abnormal. In the placebo group, one patient was enrolled with a clinically insignificant abnormal ECG with sinus tachycardia.

Baseline laboratory data from Visit 1 revealed that all patients in the ITT population had clinically acceptable baseline laboratory results. Approximately 50% of the patients in each treatment group had elevated eosinophils, consistent with the allergic individuals. The mean value for serum potassium was 3.9 meq/L for the three treatment groups, with individual values ranging from 2.9 - 5.8 mEq/L. Low potassium levels were reported for 12% (14/115), 24% (28/117) and 9% (10/117) of the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo groups, respectively. Only 1% (4/349) reported high potassium levels at baseline. The mean baseline serum glucose levels were 103.7 mg/dL, 98.9 mg/dL, and 101.2 mg/dL for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo groups, respectively. High levels of glucose were detected at baseline in 23% (26/115), 13% (15/117) and 15% (17/117) of the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo groups, respectively. One percent (5/349) of the patients had low glucose levels at baseline).

Approximately 50% of all patients were on a stable regimen of inhaled corticosteroids during the study [55.7% (64/115), 58.1% (68/117), and 51.3% (60/117) for 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo, respectively]. Twenty-seven patients were listed as taking concomitant oral corticosteroids or theophylline. All but one of those patients dropped from the study due to an AE for which the medication was taken. The one exception was Subject No. 661 who had an asthma exacerbation around Visit 3, was treated with prelone (as per report), but then completed the study violating the protocol. All but two patients listed albuterol as a prior medication. Eighteen patients reported using non-study albuterol at some time during the study. For 11 of those 18 patients, the use of non-study albuterol was related to an AE that resulted in discontinuation from the study. Of the other 7 patients, 5 patients were in the placebo group and 2 patients were in the 0.75 mg albuterol sulfate group.

2. Compliance

All three treatment groups in the ITT population had a mean duration of drug intake of about 26 days with 2.8 nebules per day). Mean compliance in the ITT efficacy population was 94% - 95% in all groups. Compliance was defined as use of study

medication for > 75% and < 125% of the required dosing which was based on 3 nebules per day times the number of days enrolled in the study. The number of days enrolled was determined either by the date of the last dose recorded on the Study Termination page (if withdrawn prematurely) or the last recorded date of dosing on the patient's diary card.

In the ITT efficacy population, all treatment groups had a mean duration of drug intake of 26 days. The minimum number of days study drug was taken ranged from 1 to 4 days across the treatment groups. The maximum number of days drug was taken was 32 days in the two active treatment groups and 36 days in the placebo group. The mean number of nebules taken per day for all treatment groups was 2.8 for the active treatment groups and for the placebo group, but ranged from 1.0 to 5.0 nebules per day. Three patients had nebule use rate of 4.8 - 5.0 per day, and those three patients discontinued the study within 15 days of enrollment.

For the evaluable population, the mean duration of drug treatment was 28 days with a mean of 2.9 nebules per day for all three treatment groups. Compliance based on the > 75% and < 125% criteria was 95% - 96% for all treatment groups. The range of nebules per day was 2.3 - 3.6.

3. Efficacy

a) %Δ AUC FEV_1

The primary efficacy endpoint was the %Δ AUC FEV_1 at Visit 4. The null hypothesis was that the %Δ AUC FEV_1 at Visit 4 was equal across all treatment groups. The sponsor's statisticians at [ ] used a statistical modeling strategy utilizing non-parametric analyses of variance for the ranks of %Δ AUC FEV_1.

The %Δ AUC FEV_1 was calculated for the percent change in post-dose FEV_1 from the pre-dose FEV_1. The %Δ AUC FEV_1 data from the ITT efficacy population show that both the 1.5 mg and the 0.75 mg albuterol sulfate solutions produced significant improvement in FEV_1 ($p=<0.001$) over placebo following acute exposure (Visit 2) and chronic exposure (Visit 4). There were no significant differences between the 1.5 mg and the 0.75 mg of albuterol sulfate doses at either visit ($p=0.566$ Visit 2; $p=0.255$ Visit 4.)

Summary of %Δ AUC FEV_1 for the ITT Efficacy Population (Sponsor's analysis)

%Δ AUC FEV_1 (%·hr)[1]	1.5 mg Albuterol N = 112	0.75 mg Albuterol N =110	Placebo N = 110
Visit 2			
N	112	109	105
Mean (SD)	99.5 (75.4)	104.5 (97.6)	43.6 (82.0)
Median	91.5	88.8	35.5
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean (SD)	90.3 (93.6)	73.6 (76.5)	34.2 (53.1)
Median	64.7	57.2	27.3
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	< 0.001	<0.001	

[1] The %Δ AUC FEV_1 was based on the area under the FEV_1 percent change from pre-dose versus time curve. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

The FDA performed an analysis comparing the efficacy between each dose and between visits. No difference was found between 1.5 mg and 0.75 mg for %Δ AUC FEV_1 at either visit. While it is noted that there appeared to be a decrease in the mean %Δ AUC FEV_1 from 99.5 %-hr to 90.3 %-hr with 1.5 mg, this difference was not significant (p=0.436). A significant difference was found between visits for 0.75 mg (p=0.0145). No significant difference was found for placebo

The evaluable population data produced comparable results to the ITT efficacy population. Significant improvements in FEV_1 were seen following either 1.5 mg albuterol sulfate or 0.75 mg albuterol sulfate compared to placebo.

Summary of %Δ AUC FEV_1 for the Evaluable Population

%Δ AUC FEV_1 (%·hr)[1]	1.5 mg Albuterol N =75	0.75 mg Albuterol N = 70	Placebo N = 69
Visit 2			
N	74	70	67
Mean (SD)	99.6 (77.4)	102.5 (104.5)	34.8 (58.7)
Median	95.4	74.0	37.5
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	<0.001	<0.001	
Visit 4			
N	75	70	69
Mean (SD)	86.6 (78.5)	77.9 (78.9)	32.4 (42.4)
Median	65.1	60.1	31.5
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	<0.001	0.001	

[1] %Δ AUC FEV_1 was calculated for the percent change in post-dose FEV_1 from the pre-dose FEV_1. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

Testing was also performed after 2 weeks of treatment during Visit 3. Spirometry was performed pre-dose and 30 minutes post dose.

FEV_1 (only) at Visit 3 (ITT Efficacy population)

[redacted]	[redacted]	[redacted]	[redacted]
	99	100	96
	1.5	1.5	1.6
	0.4	0.5	0.5
	0.115	0.143	[redacted]
	0.96	[redacted]	[redacted]
	99	100	96
	1.8	1.9	1.7
	0.4	0.5	0.4
	0.022	0.003	[redacted]
	0.476	[redacted]	[redacted]
	0.001	0.001	0.415

Thus it appears that there is a significant increase in the FEV_1 with either dose at Visit 3. The increase with albuterol is significantly greater than the increase with placebo. There is no significant difference between the doses in the change in FEV_1 at Visit 3.

A subgroup analysis was performed by the sponsor' statisticians. The %Δ AUC FEV_1 data for the ITT efficacy population were analyzed by the following age groups: 6 - 8 year olds, 9 - 10 year olds, and 11 - 12 year olds.

Summary of the FEV_1 Percent Change From Pre-Dose – by Age (ITT –Efficacy)

			1.5 mg	0.75 mg	Placebo	p-value
Ages 6-8	Visit 2	N	35	34	28	<.001
		Mean	114.3	117.6	29	
		Std Dev.	79.3	102.3	68	
		p val vs. PBO	<.001	<.001		
		p val 1.5 =.75	.0852			
	Visit 4	N	31	26	22	.011
		Mean	103.9	83.7	44.8	
		Std Dev.	92.9	74.5	78.6	
		p val vs. PBO	.005	.019		
		p val 1.5 =.75	.0506			
Ages 9-10	Visit 2	N	46	41	45	<.001
		Mean	87.2	99.6	48.2	
		Std Dev.	71.8	72.7	99	
		p val vs. PBO	<.001	<.001		
		p val 1.5 =.75	0.693			
	Visit 4	N	38	35	37	.033
		Mean	66.9	76.7	43.3	
		Std Dev.	60	81.6	33.3	
		p val vs. PBO	.022	.029		
		p val 1.5 =.75	.679			
Ages 11-12	Visit 2	N	31	34	32	.005
		Mean	101.1	97.4	50	
		Std Dev.	75.2	73.3	40.6	
		p val vs. PBO	.002	.031		
		p val 1.5 =.75	.230			
	Visit 4	N	25	31	30	.002
		Mean	109.1	61.6	25.6	
		Std Dev.	127	73	39.8	
		p val vs. PBO	<.001	.082		
		p val 1.5 =.75	.084			

In all age groups in the ITT efficacy population, both active treatment groups produced significant improvement at ≤ 0.05 p-value in the FEV_1 at Visit 2 and Visit 4 except at Visit 4 for the 11- 12 year olds exposed to the 0.75 mg albuterol sulfate dose (p=. 082). It is worth noting that the 9 - 10 year olds receiving 0.75 mg albuterol sulfate, although not statistically significant, had mean and median values slightly higher than the 1.5 mg albuterol group at Visit 4. No significant differences in any of the age subgroups were seen between the 1.5 mg and the 0.75 mg albuterol sulfate doses.

When the evaluable population data were analyzed by age group, both the 1.5 mg and the 0.75 mg albuterol sulfate produced significant improvements in all age groups at both Visit 2 and Visit 4 (See Vol. 1-15, Table 9.2A) except for patients ages 9-10. The sponsor maintains that the improvements in %Δ AUC FEV_1 at Visit 4 for the 9 - 10 year olds did not reach statistical significance over placebo for either active treatment group because of two factors: 1) the placebo group had an increase in %Δ AUC FEV_1 at Visit 4 compared to Visit 2 (37.7 and 24.6%·hr, respectively); and 2) the improvements at Visit 4 for the active treatment groups were less than at Visit 2 (60.8 and 79.7 %·hr at Visit 4 vs. 81.7 and 91.9%·hr at Visit 2 for 1.5 mg and 0.75 mg albuterol sulfate, respectively). Both reasons seem plausible as: 1) the augmentation of pulmonary function appears to be less impressive after chronic use (Visit 4) as compared to acute usage (Visit 2) in other analyses (please see sections of Efficacy analysis on FEV1% change and the duration of response) and 2) the placebo response for ages 6-8 was similar at Visit 4 at 35.7 and yet the 0.75 mg dose was still significantly improved over placebo in this age group.

Not unexpectedly, the analysis by weight in the ITT population showed similar results to the age analysis. Patients in the two lower weight groups, i.e., those weighing $\leq$ 40 kg had significant improvements following either active treatment group at both Visits 2 and 4. The heavier weight children (> 40 kg) showed significant improvement at Visit 2 regardless of the active treatment group, but at Visit 4, the improvement in the 1.5 mg albuterol group was significantly better than the 0.75 mg group (109.7 %·hr vs 58.9 %·hr, respectively, p=0.050). The improvement in the 0.75 mg group of heavier children was not significantly better than placebo at Visit 4 (58.9 %·hr vs 30.9 %·hr, p=0.101) (See NDA: Vol. 1.15- Table 9.7B).

As in the ITT efficacy population, the evaluable populations analyzed by weight show that the heavier weight children (>40 kg) exposed to 0.75 mg albuterol did not show significant improvement at Visit 4 (p=0.203), while the 1.5 mg albuterol group did (p=0.006). The two lower weight groups (<30 kg and 30-40 kg) had significant improvements at both visits regardless of the active treatment. (See NDA: Vol. 1.15, Table 9.7A.)

Both doses were significantly effective when males and females were analyzed separately in the ITT and evaluable population. (See NDA: Vol. 1.15- Table 9.3B and Table 9.3A). The effect of race on the outcome was also examined.

Summary of the FEV_1 Percent Change From Pre-Dose -- by Race (ITT population)

			1.5 mg	0.75 mg	Placebo	p-value
Caucasians	Visit 2	N	78	74	74	
		Mean	110.7	112.1	49.8	
		Std Dev.	75.4	101.8	76	<.001
		p val vs.PBO	<.001	<.001		
		p val 1.5 =.75	0.404			
	Visit 4	N	66	63	64	<.001

		Mean	99.9	76.7	26.8	
		Std Dev.	100	77	41.6	
		p val vs.PBO	<.001	<.001		
		p val 1.5 =.75	0.227			
Non-Caucasians	Visit 2	N	34	35	31	
		Mean	74	88.6	28.9	
		Std Dev.	69.8	87.4	94.3	<.001
		p val vs.PBO	<.001	<.001		
		p val 1.5 =.75	0.697			
	Visit 4	N	28	29	25	
		Mean	67.7	66.9	52.9	
		Std Dev.	73.3	76.2	72.7	.671
		p val vs.PBO	.368	.544		
		p val 1.5 =.75	0.892			

Both the 1.5 mg and 0.75 mg albuterol sulfate doses were significantly better than placebo for the caucasian population at Visits 2 and 4 ($p<0.001$ compared to placebo). At Visit 4, while still significantly better than placebo, the 0.75 mg albuterol mean improvement for the caucasian group was less than at Visit 2 (112.1 %·hr at Visit 2 vs. 76.7 %·hr at Visit 4). The improvement with 1.5 mg albuterol sulfate was similar at both visits (110.7 %·hr at Visit 2 vs. 100.0 %·hr at Visit 4). For the non-caucasian ITT efficacy population, both active treatments were less effective than in the caucasian group, but still significantly better than placebo at Visit 2 (74.0, 88.6, and 28.9 %·hr for the 1.5 mg, 0.75 mg albuterol sulfate and placebo, respectively). At Visit 4, the improvements with the active treatments for the non-caucasians were not significantly different from placebo. This was thought due to an increase from Visit 2 in the placebo group (67.7, 66.9, and 52.9 %·hr for 1.5 mg, 0.75 mg albuterol sulfate, and placebo, respectively). There was no difference in the comparison of 1.5 mg with 0.75 mg at Visit 2 in the non-caucasians.

For the non-caucasian, as with the ITT efficacy population, both active treatments were significantly effective at Visit 2 ($p \leq 0.018$). At Visit 4, the improvements were at least double the placebo effect, but they did not reach statistical significance for either active treatment group ($p \geq 0.255$) due probably to a higher mean for placebo at Visit 4 and less improvement than seen at Visit 2 with the active treatments.

The effect of concomitant use of nasal or oral inhaled corticosteroids on the efficacy of albuterol sulfate was examined. The percentages of patients on inhaled corticosteroids during the study were similar across the treatment groups after randomization (55.7%, 58.1% and 51.3% for 1.5 mg, 0.75 mg albuterol sulfate and placebo, respectively) (See Vol. 1.15, Table 8.1). Both active treatments produced significant improvements in the %Δ AUC FEV_1 whether or not the patients were taking concomitant inhaled corticosteroids (See Vol. 1.15, Table 9.5) at Visit 2. For comparison with placebo, the p-values were ≤ 0.033 for both treatment groups at both Visits 2 and 4, except with 0.75 mg albuterol sulfate without corticosteroids which had a p-value of 0.151 at Visit 4. The greatest improvement was measured at Visit 2 in the patients using corticosteroids (103.2 and 112.3%·hr for 1.5 mg and 0.75 mg albuterol sulfate compared to 49.0%·hr for placebo). For patients using corticosteroids, the mean increase in %Δ AUC FEV_1 for 0.75 mg albuterol sulfate was greater at Visit 2 than at Visit 4 (112.3 vs. 83.3%·hr, respectively). For

the patients not using corticosteroids, the mean increase of %Δ AUC FEV_1 was less at Visit 4 than at Visit 2 for both the 1.5 mg and the 0.75 mg albuterol sulfate groups.

In studying concomitant corticosteroid use, the evaluable population data supported the ITT finding. The use or non-use of concomitant corticosteroids did not impact the ability of the 1.5 mg or the 0.75 mg albuterol sulfate doses to produce significant improvements in the %Δ AUC FEV_1 following acute exposure (Visit 2) or chronic exposure (Visit 4). Again, similar to the ITT efficacy data, while still significantly different from placebo, the two active treatment groups not using corticosteroids had less improvement at Visit 4 than those patients on corticosteroids (102.4 and 87.7 %·hr vs 66.4 and 63.9 %·hr for 1.5 mg and 0.75 mg albuterol sulfate with corticosteroids versus without corticosteroids, respectively)

The impact of a bronchodilator may depend on the severity of the asthma and the data were examined separately for patients who had $FEV_1 \leq 60\%$ of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose). There were 56 patients in the ITT efficacy population who had $FEV_1 \leq 60\%$.

%Δ AUC FEV_1 by Disease Severity in ITT Efficacy Population

%Δ AUC FEV_1 (%-hr)[1]	1.5 mg Albuterol	0.75 mg Albuterol	Placebo
$FEV_1 \leq 60\%$ Predicted			
Visit 2			
N	19	24	13
Mean (SD)	149.7 (92.0)	162.4 (94.6)	60.6 (131.8)
Median	128.3	157.7	6.9
Min, Max			
Treatment vs Placebo			
P-value[2]	0.011	0.005	
Visit 4			
N	12	18	8
Mean (SD)	144.6 (108.4)	96.9 (94.6)	40.9 (51.8)
Median	145.2	104.9	32.8
Min, Max			
Treatment vs Placebo			
P-value[2]	0.049	0.141	
$FEV_1 > 60\%$ Predicted			
Visit 2			
N	93	85	92
Mean (SD)	89.3 (67.6)	88.2 (92.6)	41.2 (73.1)
Median	77.9	72.7	36.5
Min, Max			
Treatment vs Placebo			
P-value[2]	<0.001	<0.001	
Visit 4			
N	82	73	76
Mean (SD)	82.4 (89.3)	68.2 (71.5)	29.4 (42.0)
Median	63.3	53.3	26.8
Min, Max			
Treatment vs Placebo			
P-value[2]	<0.001	<0.001	

[1] %Δ AUC FEV_1 was calculated for the percent change in post-dose FEV_1 from the pre-dose FEV_1. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

For Visit 4 in patients with $FEV_1 \leq 60\%$, 0.75 mg albuterol was not statistically different form placebo. Indeed for this subgroup of patients, 1.5 mg albuterol was barely different from placebo with a p value of 0.049. For the more severe asthmatic patients, both the 1.5 mg and the 0.75 mg albuterol sulfate produced significant improvements in FEV_1 at Visit 2, but by Visit 4 the 0.75 mg albuterol sulfate, was less effective than the 1.5 mg albuterol sulfate dose for this subgroup. The same trend was detected with the less severe patients, with both active treatments producing comparable improvements at Visit 2, and the 0.75 mg albuterol sulfate producing less of an improvement at Visit 4, but even that response was still greater than double the placebo group response.

Despite the fact that it was the group with $FEV_1 \leq 60\%$ predicted which did not have significant efficacy with 0.75 mg over placebo, this group nonetheless had a mean %Δ AUC FEV_1 (96.9 %-hr) greater than the subjects with $FEV_1 > 60\%$ (68.2 %-hr).

When the evaluable data were examined separately for patients who had $FEV_1 \leq$ 60% of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose), there were only 25 patients in the evaluable population that met that criteria (10, 12 and 4

for 1.5 mg, 0.75 mg albuterol sulfate and placebo, respectively). The sample size was thought to be too small to detect statistically significant differences.

b) Maximum Percent Change in FEV_1 (MAX FEV_1)

The MAX FEV_1 percent change from pre-dose at Visit 2 and Visit 4 was analyzed for the ITT efficacy population and the evaluable population (See Vol.1- 15, Tables 11.1B and 11.1A, respectively). In the ITT efficacy population, the MAX FEV_1 significantly increased following 1.5 mg and 0.75 mg albuterol sulfate compared to placebo at both Visit 2 and Visit 4. The mean maximum percent increases across visits ranged from 26.0% to 31.8% for the active treatment groups compared to 13.4% to 15.5% for the placebo group. The mean MAX FEV_1 were similar at Visit 2 and Visit 4 for the 1.5 mg albuterol sulfate group, but for the 0.75 mg albuterol sulfate group, the Visit 4 mean MAX FEV_1 was less than at Visit 2.

MAX FEV_1 for the ITT Efficacy Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol N =112	0.75 mg Albuterol N = 110	Placebo N = 110
Visit 2			
N	112	109	105
Mean % (SD)	29.3 (17.1)	32.0 (21.4)	15.5 (15.9)
Median	24.8	26.5	11.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean % (SD)	28.6 (22.6)	26.3 (17.4)	13.4 (12.5)
Median	19.8	21.1	10.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	

[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 percent change from pre-dose.

In the evaluable population, as in the ITT efficacy population, the mean MAX FEV_1 were significantly increased at Visit 2 and Visit 4 following the administration of the 1.5 mg and 0.75 mg albuterol sulfate compared to placebo. The mean increases in MAX FEV_1 for the active treatment groups were comparable between active treatment groups and between visits (26.8% to 30.8%) and more than double the mean percent changes in the placebo (13.2% at Visit 2 and 12.9% at Visit 4). No significant differences were identified for this variable between 1.5 mg and 0.75 mg in a FDA analysis. No significant difference was found between Visits 2 and 4 for 1.5 mg (p= 0.775) but a significant difference was identified for 0.75 mg with a p value of 0.0425. No differences were identified between visits for placebo.

MAX FEV_1 for the Evaluable Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol N =75	0.75 mg Albuterol N = 70	Placebo N = 69
Visit 2			
N	74	70	67
Mean % (SD)	29.0 (17.0)	30.8 (22.5)	13.2 (11.0)
Median	24.9	25.4	11.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	
Visit 4			
N	75	70	69
Mean % (SD)	28.1 (19.7)	26.8 (18.2)	12.9 (10.7)
Median	20.0	21.9	11.4
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	

[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 % change from pre-dose.

In the ITT population, all three age groups at both Visit 2 and Visit 4 had significant increases in MAX FEV_1 following 1.5 mg or 0.75 mg albuterol sulfate compared to placebo (See Vol. 1-15, Table 11.2B), as did all three weight groups. At Visit 4 for the maximum improvement, the 1.5 mg albuterol group was better than the 0.75 mg group for the heavier children (> 40 kg) (33.4% vs. 24.1%, respectively; See Vol. 1- 15, Table 11.7B).

In the evaluable population, both the 1.5 mg and the 0.75 mg albuterol sulfate doses produced significant improvements in MAX FEV_1 in all age groups at both visits (p-value <0.021), except at Visit 4 for the 9 - 10 year olds in the 1.5 mg albuterol sulfate group (See Vol. 1-15, Table 11.2A). The mean MAX FEV_1 for that group (20.7%) did not quite reach significance (p=0.068), but the trend was similar. No significant differences were detected between 1.5 mg and 0.75 mg albuterol sulfate within any of the age groups. The MAX FEV_1 data for the evaluable population show a significant improvement with both active treatments for each of the three weight groups.

In both the ITT and evaluable populations, significant increases in MAX FEV_1 were seen for both the female and male subgroups and regardless whether the patients were taking or not taking concomitant corticosteroids. There were no significant differences between the MAX FEV_1 for the two albuterol sulfate doses in those subgroups.

In the race ITT subgroups, significant increases were seen with both active treatment groups in the caucasian group at Visits 2 and 4, and the non-caucasian group at Visit 2. At Visit 4, the increases with either active treatment were not significantly different from placebo (25.2%, 21.8%, and 17.4% for the 1.5 mg, 0.75 mg albuterol sulfate, and placebo, respectively) thought due to the increase in the placebo at Visit 4 and the small sample size in that subgroup; n= 28, 29 and 25 for the 1.5 mg, 0.75 mg albuterol sulfate, and placebo, respectively. No significant improvement was also seen in the evaluable population at Visit 4 for the non-caucasian taking 0.75 mg.

As with the %Δ AUC FEV_1 data, the MAX FEV_1 were examined separately for patients who had $FEV_1 \leq 60\%$ of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose).

MAX FEV_1 by Disease Severity in ITT Efficacy Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol	0.75 mg Albuterol	Placebo
$FEV_1 \leq 60\%$ Predicted			
Visit 2			
N	19	24	13
Mean % (SD)	43.7 (22.0)	47.5 (17.5)	23.5 (24.2)
Median	39.0	45.1	16.2
Min, Max	[		]
Treatment vs Placebo P-value[1]	0.010	0.002	
Visit 4			
N	12	18	8
Mean % (SD)	45.01 (26.3)	36.6 (17.3)	18.7 (16.8)
Median	41.6	31.9	13.1
Min, Max	[		]
Treatment vs Placebo P-value[1]	0.034	0.024	
$FEV_1 > 60\%$ Predicted			
Visit 2			
N	93	85	92
Mean % (SD)	26.4 (14.3)	27.6 (20.5)	14.4 (14.2)
Median	23.7	23.8	11.1
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	
Visit 4			
N	82	73	76
Mean % (SD)	26.1 (21.1)	23.9 (16.6)	11.8 (9.6)
Median	18.4	18.9	9.9
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	

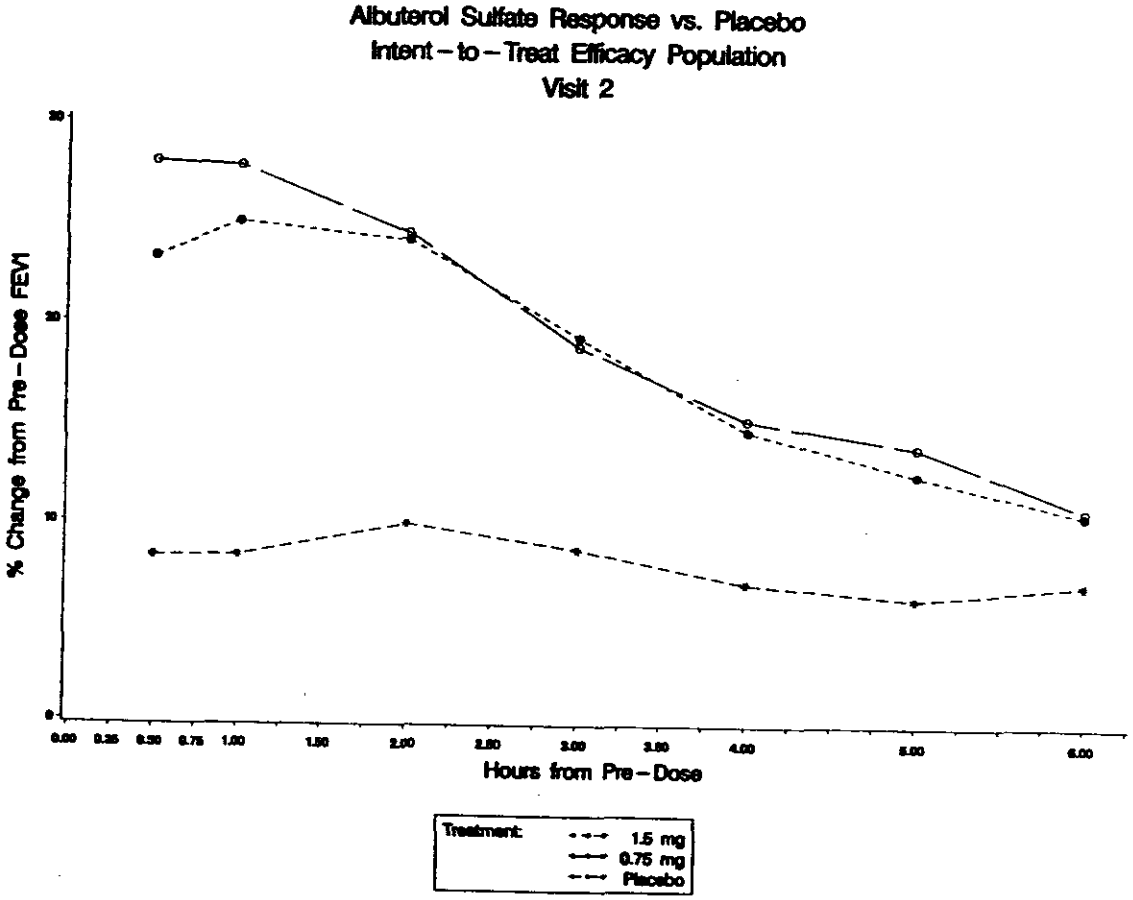
Note: MAX FEV_1 is selected as the maximum percent change in post-dose FEV_1 from the pre-dose FEV_1.
[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 percent change from pre-dose.

For the more severe asthmatic (≤ 60%) patients, both the 1.5 mg and the 0.75 mg albuterol sulfate produced significant improvements in FEV_1 at Visit 2 and Visit 4. The 0.75 mg albuterol sulfate produced less improvement at Visit 4 compared to Visit 2 and compared to the 1.5 mg albuterol sulfate dose at Visit 4. In the > 60% group, comparable mean maximum percent improvements were seen at both visits for both active treatment groups (23.9% to 27.6%). The mean maximum percent improvements seen with the active treatments for the ≤ 60% group, were higher than seen in the > 60% group, reflecting the greater area for improvement in the more severe subject.

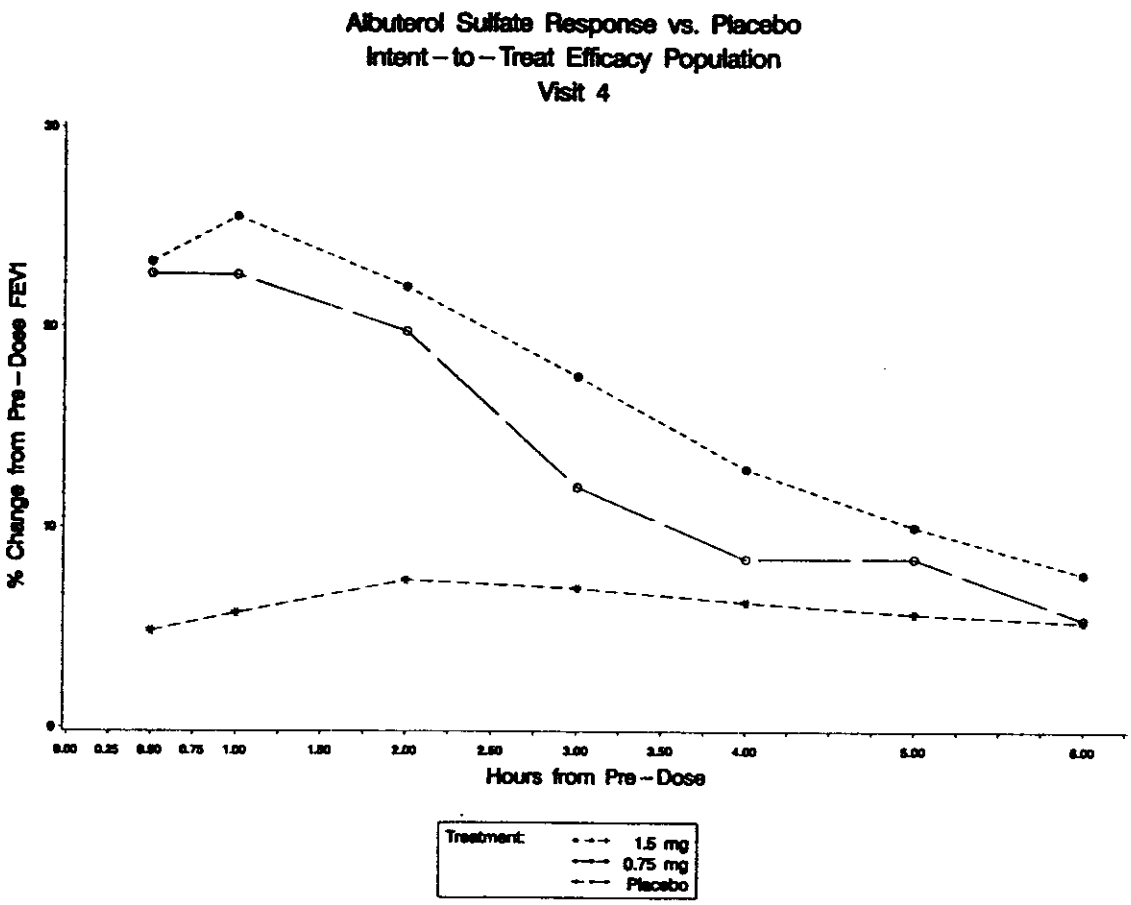
The evaluable population included only 26 patients with $FEV_1 \leq 60\%$ predicted. While increases in the MAX FEV_1 were noted at both visits with both treatments, it was not statistically significant compared with placebo and this was thought secondary to the small sample size. In the > 60% group, comparable mean improvements in MAX FEV_1 were seen at both visits for both active treatment groups (24.6% to 28.1% compared to placebo at 12.0% to 12.6%).

c) FEV_1 Percent Change

The percent changes in FEV_1 over time are shown in the following two graphs.



In the ITT efficacy population, significant changes in FEV_1 occurred within 30 minutes, the earliest FEV_1 measurement, post treatment, in the 1.5 mg albuterol sulfate and 0.75 mg albuterol sulfate groups compared to placebo (23.2%, 28.0%, 8.3%, respectively). The improvement in FEV_1 remained elevated for both the 1.5 mg and the 0.75 mg albuterol sulfate group compared to placebo for over 5 hours. However, the mean improvement dropped below 15% at the 4-hour timepoint for the 1.5 mg treatment group at Visit 2.



At Visit 4, similar results were obtained at 30 minutes post-dose. The mean improvement for the 1.5 mg albuterol sulfate group dropped below 15% at 4 hours as in Visit 2, but the 0.75 mg albuterol sulfate group dropped below 15% by 3 hours at Visit 4. Comparable results were obtained with the evaluable population.

Reviewer's Note: Pairwise comparisons were performed at the FDA at each time point to compare the pre-dose FEV1 of each of the treatments against each other or placebo for both Visits 2 and 4. No significant differences were noted in the pre-dose FEV1 at time 0 although it is interesting to note that the p value of 1.5 mg vs. placebo is close at 0.0774. It is important to note here that B_2-agonists were held 6 hours prior to each study visit.

FEV_1 Over Time (t test, CI = 95%) (FDA analysis)

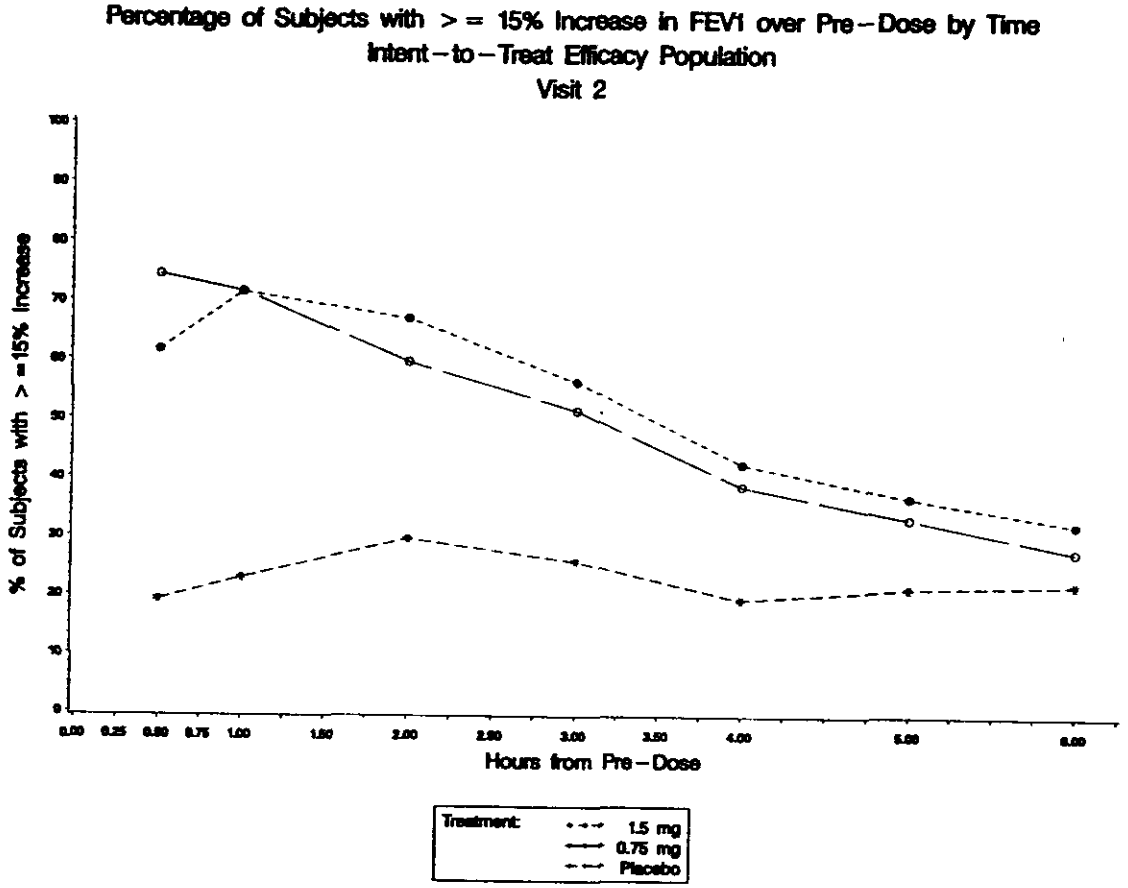
	Time	0.75 mg vs. Placebo	1.5 mg vs. Placebo	0.75 mg vs. 1.5 mg
Visit 2	0	.2286	.3910	.7199
	30 minutes	.0013	.0084	.5306
	60 minutes	.0015	.0033	.7990
	120 minutes	.0424	.0190	.7571
	180 minutes	.2812	.1080	.5963
	240 minutes	.5390	.3294	.7164
	300 minutes	.7252	.6946	.9688
	360 minutes	.6111	.8603	.7344
Visit 4	0	.2765	.0774	.4957
	30 minutes	.0047	.0326	.4701
	60 minutes	.0136	.0223	.8417
	120 minutes	.1069	.1770	.7836
	180 minutes	.9420	.6706	.6152
	240 minutes	.4892	.6774	.7782
	300 minutes	.6434	.4299	.7436
	360 minutes	.2431	.1899	.8894

It is interesting to note that the difference in FEV_1 between both albuterol treatments and placebo dissipates sometime between 120 and 180 minutes at Visit 2 and somewhere between 60 and 120 minutes at Visit 4.

d) Proportion of Responders

The FEV_1 data over time were further analyzed to determine the percentage of responders at each timepoint. A response was defined as a $\geq$ 15% increase in the FEV_1 from pre-dose. At Visit 2 in the ITT efficacy population 61.6% of the 1.5 mg albuterol sulfate group

74.1% of the 0.75 mg albuterol sulfate group responded within 30 minutes (the earliest time point measured) compared to 19.0% of the placebo group. At Visit 2, 56.3% (63/112) of the patients receiving 1.5 mg albuterol sulfate and 51.4% (56/109) of patients receiving 0.75 mg albuterol sulfate had a response at 3 hours compared to 25.7% (27/105) receiving placebo. By 6 hours post-dose, 32.1% and 27.5% of patients receiving 1.5 mg and 0.75 mg albuterol sulfate were responding compared to 21.9% of patients receiving placebo.



At Visit 4, a lower percentage of patients had a response within 30 minutes (56.4%, 59.8%, and 10.1% for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo, respectively). The percentage of patients receiving albuterol with a response at 3 hours was 44.7% (42/94) for 1.5 mg albuterol sulfate and 31.5% (29/92) for the 0.75 mg albuterol sulfate, but the percentage of placebo patients was 15.7% (14/89).

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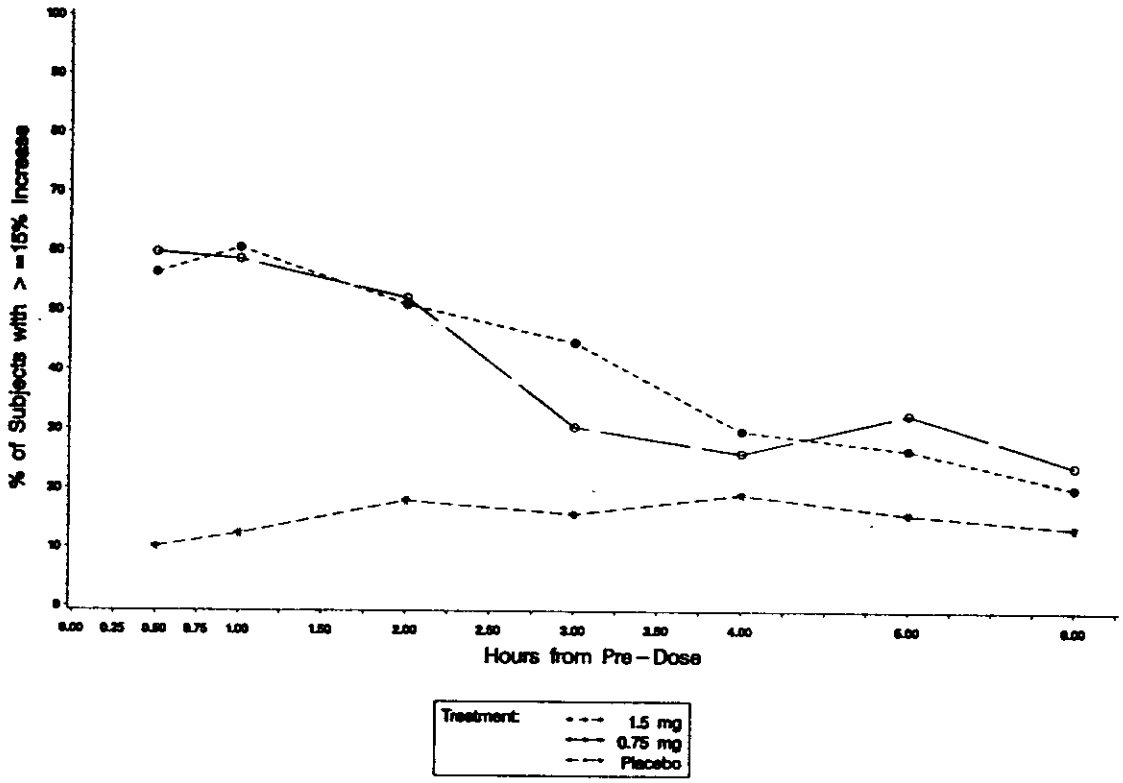
Percentage of Subjects with >= 15% Increase in FEV1 over Pre-Dose by Time
Intent-to-Treat Efficacy Population
Visit 4



e) Duration of Response

The duration of response was defined as the first time at which a ≥ 15% increase in FEV_1 over pre-dose was observed to the first time the percent change in FEV_1 from pre-dose returned to below the 15% increase. Patients who did not have an increase of ≥ 15% in FEV_1 from pre-dose were assigned a duration of 0 minutes.

At Visit 2 the mean duration of response for the ITT efficacy population was 2.67 hours following 1.5 mg albuterol sulfate, 2.45 hours following 0.75 mg albuterol sulfate, and 1.0 hour following placebo (See Vol. 1-15, Table 12.1.1B, p.225). At Visit 4, the mean duration was decreased from the Visit 2 response for both the 1.5 mg albuterol sulfate group (1.95 hours) and the 0.75 mg albuterol sulfate group (1.93 hours).

Duration of Response in ITT Efficacy Population by Treatment

	1.5 mg Albuterol N =112	0.75 mg Albuterol N = 110	Placebo N = 110
Visit 2	(N = 112)	(N = 109)	(N = 105)
0 to 30 mins	8 (7.1)	7 (6.4)	14 (13.3)
>30 mins to 1 hr	5 (4.5%)	9 (8.3%)	5 (4.8%)
>1 hr to 2 hr	13 (11.6%)	15 (13.8%)	5 (4.8%)
>2 hr to 3 hr	16 (14.3%)	12 (11.0%)	2 (1.9%)
>3 hr to 4 hr	12 (10.7%)	16 (14.7%)	5 (4.8%)
>4 hr to 5 hr	11 (9.8%)	6 (5.5%)	1 (1.0%)
>5 hr to 6 hr	26 (23.2%)	24 (22.0%)	12 (11.4%)
Visit 4	(N = 94)	(N = 92)	(N = 89)
0 to 30 mins	12 (12.8%)	5 (5.4%)	5 (5.6%)
>30 mins to 1 hr	5 (5.3%)	5 (5.4%)	7 (7.9%)
>1 hr to 2 hr	12 (12.8%)	12 (13.0%)	6 (6.7%)
>2 hr to 3 hr	9 (9.6%)	15 (16.3%)	5 (5.6%)
>3 hr to 4 hr	8 (8.5%)	4 (4.3%)	1 (1.1%)
>4 hr to 5 hr	6 (6.4%)	2 (2.2%)	4 (4.5%)
>5 hr to 6 hr	15 (16.0%)	18 (19.6%)	2 (2.2%)

Reviewer's Note - Statistical analysis was performed at the FDA in the ITT Efficacy population (based on Table 12.1.1B, Vol. 1-15) to determine if there was a statistical difference in the duration of effect between Visits 2 and 4 for each of the doses and placebo. The p value for 1.5 mg albuterol was 0.0133 with a significant decrease found in the duration of response found at Visit 4 (mean 116.8 minutes) compared with Visit 2 (mean = 160.4 minutes. The p value for 0.75 mg albuterol was 0.072 so the decrease between Visit 2 (147.3 minutes) and Visit 4 (115.9 minutes) was not statistically significant. While the mean for placebo appeared to decrease between Visit 2 (60.7) and Visit 4 (39.2), the p value was 0.1225. Thus, it appears, at least for the 1.5 mg dose of albuterol, that there is a decrease in the duration of effect after 4 weeks of t.i.d. use.

The mean duration of response was also examined by ITT efficacy subgroups. The mean duration of response was shorter at Visit 4 for most subgroups as well as the whole ITT Efficacy population. For instance the means for Visit 2 were 160.4 and 147.3 for 1.5 mg. and 0.75 mg. respectively while they were 116.8 and 115.9 minutes for Visit 4 in the ITT population. Overall, all subgroups had a duration of response significantly greater than placebo except for:

- **1.5 mg albuterol group ages 9-10, Visit 4 (evaluable, not ITT) – mean of 75 minutes vs. 122.6 for 0.75 mg and 40.2 minutes for placebo. The mean of 75 minutes is**

uncharacteristically low for an albuterol subgroup. Reviewer' Note - While the reason for this low response in this age group remains obscure, this reviewer believes it is not clinically significant.

- **0.75 mg albuterol group, non-caucasians, Visit 4 (evaluable and ITT)– mean of 104 minutes vs. 104.3 for 1.5 mg and 46.1 for placebo (evaluable). It is not clear why this difference between 0.75 mg and placebo is not significant.**
- **Patients without concomitant corticosteroid use, 0.75 mg group at Visit 4 (evaluable and ITT).**

There appeared to be an impressive difference in the duration of response between patients with and without concomitant corticosteroid use.

Summary of Duration (minutes) of >=15% increase from pre-dose in FEV_1

			1.5 mg	0.75 mg	placebo	p value(1)
Patients without Concom -itant Steroid Use	Visit 2	N	33	29	32	0.022
		Mean	121.7	109.2	61.4	
		Std. Dev.	123.2	112.4	112.2	
		p value (2)	0.021	0.013		
	Visit 4	N	33	29	33	0.046
		Mean	93.5	85.5	40.2	
		Std. Dev.	108.6	114.2	73.6	
		p value (2)	0.011	0.178		
Patients with Concom -itant Steroid Use	Visit 2	N	67	69	63	<0.001
		Mean	173.7	160.7	60.7	
		Std. Dev.	133.6	129.9	78	
		p value (2)	<0.001	<0.001		
	Visit 4	N	52	56	50	<0.001
		Mean	136.4	139.3	32.8	
		Std. Dev.	133.6	129.9	78	
		p value (2)	<0.001	<0.001		

(1) H_0 = Treatment means are equal across dose in duration.
(2) H_0 = Active treatment arm is equal to placebo in duration.

No significant difference in duration of effect was noted between 1.5 mg and 0.75 mg within either steroid use group at either Visit 2 or 4.

Patients already on concomitant steroids appear to have a more impressive response to albuterol at both doses. This finding could potentially be related to a similar difference in the FEV_1 between those with or without an FEV_1 < 60% predicted – notably the difference in this subanalysis appeared to be smaller. More analysis would have to be done to discern whether concomitant corticosteroid use is an independent predictor of response to albuterol; such an analysis does not need to be done for the purposes of

NDA. Note that at Visit 4, there was no significant difference noted between 0.75 mg and placebo in the patients not on concomitant steroids.

For the evaluable population, the percentages of patients with a longer duration of response were similar to those seen with the ITT efficacy population. At Visit 2, 59.5% (44/74) of patients receiving 1.5 mg albuterol sulfate and 48.6% (34/70) of patients receiving 0.75 mg albuterol sulfate had a duration of response > 2 hours compared to 14.9% (10/67) receiving placebo. The percentage of patients with a duration of response > 4 hours was 39.2% (29/74) in the 1.5 mg albuterol sulfate group compared to 20.0% (14/70) in the 0.75 mg albuterol sulfate, group and 9.0% (6/67) in the placebo group. At Visit 4, the percentage of patients receiving albuterol with a duration of response > 2 hours was 42.7% (32/75) for 1.5 mg albuterol sulfate and 42.9% (30/70) for 0.75 mg albuterol sulfate compared to 11.6% (8/69) for placebo.

f) Changes in FEF and FVC

$FEF_{25\%-75\%}$ and FVC measures and their percent changes from pre-dose were summarized in the NDA using descriptive statistics for each treatment visit.

Increases in $FEF_{25\%-75\%}$ were noted at 30 minutes post dose (the earliest measurement). The percent increases over pre-dose at 30 minutes at Visit 2 were 58.5%, 75.6%, and 14.4%, and at Visit 4, 59.2%, 63.5%, and 10.2% for the 1.5 mg, 0.75 mg albuterol sulfate, and placebo groups, respectively. The improvement in $FEF_{25\%-75\%}$ remained elevated over placebo even at 6 hours post-dose at Visit 2 and for up to five hours at Visit 4 following either 1.5 mg or 0.75 mg albuterol sulfate. Statistical comparisons were not performed on the FEF between doses..

Increases in FVC were seen within 30 minutes for both the 1.5 mg and the 0.75 mg albuterol sulfate groups. The percent increases over pre-dose at 30 minutes at Visit 2 were 11.9%, 13.4%, and 7.1 %, and at Visit 4, 11.8%, 9.5%, and 2.6%, for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo, respectively, for the ITT efficacy population. The improvements in FVC over placebo were maintained for up to 5 hours at Visit 2; and up to 5 hours for 1.5 mg albuterol sulfate and up to 3 hours for 0.75 mg albuterol sulfate at Visit 4. These changes in FVC were not reviewed statistically by the FDA.

Reviewer's Note – While the sponsor maintains that significant increases were seen in the FVC with Accuneb treatment, again only descriptive statistics were presented and a comparative statistical analyses was not performed. When the mean changes in FVC were reviewed, this reviewer does not believe that important increases in FVC were demonstrated with the use of Acuneb.

g) Peak Expiratory Flow Rates

The mean peak flow for each week, including the placebo phase at the start of the study, was calculated. There were no detectable differences in the means across

treatment groups (1.5 mg, 0.75 mg and placebo) for both morning and evening peak flow values.

h) Daily Asthma Symptom Score/Nocturnal Awakenings

The subject or parent/guardian in the study diary recorded daily cards recording whether or not asthma symptoms occurred during the night and upon awakening, and scoring the severity of the daytime symptoms according to the following system: 0 = no symptoms, 1 = mild (did not interfere with activities), 2 = moderate (interfered with some activities), 3 = severe (interfered with many activities.) For the ITT population, summaries and descriptive statistics for the symptom scores were provided in the NDA.

The occurrence of asthma symptoms showed a gradual decrease from 1.3 symptoms per day during the placebo phase (Weeks 1 and 2) to 0.9, 1.0 and 1.1 symptoms per day for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo groups, respectively, following the 4-week active treatment phase of the study (Week 6).

Nocturnal awakenings occurred at the rate of 0.1 to 0.2 per night during the placebo phase. There were no significant differences in the rate of nocturnal awakenings during the treatment phase of the study, regardless of the treatment group.

i) Rescue Medication Use

The study-supplied Dey MDI or nebulizer vials were allowed for rescue medication on a prn basis if additional albuterol was needed during the study. Parent/guardians and patients were given individualized guides for decision making and rescue management needed outside the clinic visits. Rescue medication was to be employed when an increase in symptoms and/or a decrease in peak flow required treatment. Patients were medicated according to the best medical judgment of the investigator. Patients were required to record the use of all rescue medication in their diaries. If rescue medication was required during a study visit, because the FEV_1 dropped below the pre-dose value prior to completion of the 6 hours of testing, the use of rescue medication was entered on the CRF.

Changes in the use of the Dey MDI provided for rescue medication were seen over the course of the placebo phase and the treatment phase of the study. Use of the nebulizer solution provided for rescue medication did not change over the course of the study or differ across treatment groups. The mean use of the nebulizer was 0.1- 0.3 vials per week and there did not appear to be a difference between the groups.

Use of Rescue Medication (albuterol MDI) in the ITT Population

Albuterol MDI Puffs/Day	1.5 mg Albuterol N=112	0.75 Albuterol N=114	Placebo N=114
Week 1 (Start of placebo phase)			
N	112	114	114
Mean (SD)	2.1 (1.7)	2.3 (1.7)	2.4 (1.8)
Min, Max	[		]
Week 2			
N	112	114	114
Mean (SD)	2.3 (1.8)	2.5 (1.6)	2.6 (1.9)
Min, Max	[		]
Week 3 (Start of treatment phase)			
N	108	113	111
Mean (SD)	1.6 (1.5)	1.7 (1.6)	2.1 (1.8)
Min, Max	[		]
Week 4			
N	104	108	105
Mean (SD)	1.5 (1.4)	2.0 (1.8)	2.4 (2.1)
Min, Max	[		]
Week 5			
N	99	98	99
Mean (SD)	1.4 (1.4)	1.6 (1.7)	2.2 (2.0)
Min, Max	[		]
Week 6			
N	97	94	98
Mean (SD)	1.4 (1.4)	1.4 (1.4)	2.1 (2.0)
Min, Max	[		]

During the first week of the placebo phase, patients randomized to the 1.5 mg albuterol sulfate and 0.75 mg albuterol sulfate groups and to the placebo group used means of 2.1, 2.3 and 2.4 MDI puffs/day, respectively. The mean number of puffs increased by 0.2 puffs/day for each of the groups during the second week of the placebo phase. All three groups, including the placebo group, decreased their mean use of rescue albuterol during the first two weeks of the active treatment phase. There was a difference in MDI use at Week 4 between the 1.5 mg group (1.5) and the 0.75 mg group (2.0) but by the third week of active treatment, the mean use of rescue medication continued to decrease in the 1.5 mg and 0.75 mg albuterol sulfate groups, while remaining the same for the placebo group. By the fourth week of active treatment (Week 6 of the study) the 1.5 mg and 0.75 mg albuterol sulfate groups were each using a mean of 1.4 puffs/day compared to a mean of 2.1 puffs/day for the placebo group. This data on MDI rescue medication use do not include the use of such medication by patients who ultimately discontinued the study due to asthma exacerbations.

Patients also had the option to use 2.5 mg nebulized albuterol as a rescue medication. The means for use generally varied from 0.1 to 0.2 vials/day. The 0.75 mg group had a mildly higher use of this form of rescue than the other two groups, but the difference should not be considered clinically significant.

j) Summary of Global Assessment

At the end of study participation, patients/guardians were asked for a global assessment of the effect of the study medication on asthma symptoms. The percentage of patients in the active treatment groups reporting substantial improvement were nearly double the percentage in the placebo group. If the substantial and moderate improvement categories are combined, the patients in the active treatment groups had ≥ 50% of the patients in the combined category compared to 36% in the placebo group. No change or worsening change were reported by 15.2%, 22.8%, and 35.1% for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo, respectively.

Summary of Global Assessment at Visit 4

Improvement in Asthma Symptoms	1.5 mg Albuterol N = 112 N (%)	0.75 Albuterol N = 114 N (%)	Placebo N = 114 N (%)
Substantial Improvement	18 (16.1%)	17 (14.9%)	9 (7.9%)
Moderate Improvement	48 (42.9%)	40 (35.1%)	32 (28.1%)
Doubtful/Minor Improvement	28 (25.0%)	30 (26.3%)	33 (28.9%)
No Change	7 (6.3%)	12 (10.5%)	31 (27.2%)
Worsening	10 (8.9%)	14 (12.3%)	9 (7.9%)
Did Not Assess Symptoms	1 (0.9%)	1 (0.9%)	0 (0.0%)

Reviewer's Note - The original protocol says that the investigator and subject *mutually* will evaluate how the subject's overall asthma symptoms responded to treatment according to the following system. Thus it appears that the investigator, although blinded did appear to have influence on the subject's global assessment. It is also not clear whether the subjects are assessing changes over the course of the trial or are asked to compare with their condition before the trial even began. These are clarifications that could be petitioned for in the action letter because it would assist in the understanding of the global assessment.

4. Safety

The total number of subjects receiving study drug for the safety section was 349 compared to 340 for the efficacy section. FDA discredited one investigator due to an unrelated investigation of another type of asthma medication. The investigators' data (n=9: 3 per treatment group) were excluded from the efficacy data but the safety data for those 9 patients were kept in the safety section of this report.

Patients receiving active albuterol totaled 232: 115 patients received 1.5 mg albuterol sulfate and 117 patients received 0.75 mg albuterol sulfate. In addition, patients received placebo (0.9% saline) for a two-week placebo screening phase of the study.

a) Adverse Events

A total of 350 AEs were reported by 164 of 349 (47.0%) patients. Of the 350 AEs, 28 (8.0%) AEs were considered to be potentially related to treatment and those were similarly

distributed across the treatment groups. The majority of AEs were considered to be moderate in severity for all treatment groups; however, in the 0.75 mg albuterol sulfate treatment group, 8.5% of patients reported AEs which were considered to be severe as compared to 0.9% in the 1.5 mg albuterol sulfate treatment group and 4.3% in the placebo treatment group. The largest number of AEs reported for all treatment groups was related to the respiratory system, with asthma exacerbation and rhinitis being reported with the highest frequencies.

Six serious adverse events (SAEs) were reported during the study. Two patients in the 1.5 mg albuterol sulfate treatment group experienced SAEs related to the respiratory system. Four patients in the 0.75 mg albuterol sulfate treatment group experienced SAEs: two related to the respiratory system, one related to the body as a whole, and one related to metabolic and nutritional disorders. Placebo patients reported no SAE.

The adverse events were first coded using COSTART version 5 preferred terms and were categorized by body system. The COSTART grouped URI under infections but the Medical Director modified the COSTART coding to allow URI to be counted separately and placed under the respiratory system grouping. COSART was also modified to make a distinction between asthma exacerbation and worsening asthma symptoms.

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Summary of Adverse Events that Occurred in ≥ 2% of the ITT Population

Modified COSTART Term	1.5 mg Albuterol (N=115)	0.75 mg Albuterol (N=117)	Placebo (N=117)
Total patients reporting events[1] (%)	54 (47.0)	51 (43.6)	59 (50.4%)
Total number of events	117	102	131
Body as a Whole	19 (16.5)	16 (13.7)	26 (22.2)
Allergic reaction	1 (0.9)	4 (3.4)	2 (1.7)
Fever	7 (6.1)	2 (1.7)	7 (6.0)
Flu syndrome	4 (3.5)	3 (2.6)	3 (2.6)
Headache	3 (2.6)	3 (2.6)	5 (4.3)
Infection bacterial	2 (1.7)	1 (0.9)	2 (1.7)
Infection viral	0	0	1 (0.9)
Injury accident	1 (0.9)	0	3 (2.6)
Pain	1 (0.9)	0	3 (2.6)
Cardiovascular System[2]	3 (2.6)	3 (2.6)	0
Digestive System	4 (3.5)	7 (6.0)	6 (5.1)
Heme & Lymphatic System	3 (2.6)	1 (0.9)	2 (1.7)
Lymphadenopathy	3 (2.6)	1 (0.9)	2 (1.7)
Respiratory System	36 (31.3)	36 (30.8)	45 (38.5)
Asthma[3]	8 (7.0)	5 (4.3)	12 (10.3)
Asthma exacerbation	15 (13.0)	13 (11.1)	10 (8.5)
Bronchitis	1 (0.9)	2 (1.7)	1 (0.9)
Cold symptoms	0	4 (3.4)	2 (1.7)
Cough increase	3 (2.6)	0	5 (4.3)
Pharyngitis	6 (5.2)	5 (4.3)	6 (5.1)
Rhinitis	10 (8.7)	10 (8.5)	17 (14.5)
Sinusitis	5 (4.3)	4 (3.4)	5 (4.3)
URI	8 (7.0)	5 (4.3)	8 (6.8)
Skin & Appendages	9 (7.8)	2 (1.7)	7 (6.0)
Rash	3 (2.6)	1 (0.9)	5 (4.3)
Special Sense	7 (6.1)	3 (2.6)	4 (3.4)
Otitis Media	5 (4.3)	1 (0.9)	0

1 Totals may include an adverse event with an unknown severity.
2 The cardiovascular events were tachycardia 0.9% in 1.5 mg albuterol sulfate group and 0% in other groups; migraine, ST depression and hypertension occurred in < 2% of the patients per group.
3 Asthma = worsening of asthma symptoms
Note: Patients may have more than one adverse event per body system or more than one occurrence of the same adverse event. Only one occurrence of the highest severity is counted for each patient.

Note that only one occurrence of an AE with the highest severity is counted for each patient in the tabulations. Notable among the adverse events include a mild "ST depressed" with 1.5 mg and seen only in this group. Other cardiovascular events include mild tachycardia with 1.5 mg, moderate migraine with 1.5 mg, and one mild migraine and one severe migraine with 0.75 mg. Only one mild hypokalemia is listed with the 0.75 mg dose. One moderate case of hyperkinesia and one moderate case of insomnia was noted with the 1.5 mg dose. One moderate twitch was seen with 0.75 mg.

Asthma exacerbation was seen in 13% of 1.5 mg, 11.1% of 0.75 mg and 8.5% of placebo. Worsening asthma was noted in 7%, 4.3%, and 10.3%, respectively. A discrepancy among the groups is noted with otitis media and was seen in 4.3%, 0.9%, and 0%, respectively – an explanation for the increase in otitis media in the 1.5 mg group is not known.

Reviewer's Note – While one could speculate what the difference is between a worsening of asthma symptoms and an asthma exacerbation, this needs to be clarified. An explanation should be provided by the sponsor as to how exactly this distinction was made. Is it simply a matter of degree of asthma worsening? The sponsor says that Chi-Square testing did not pick up any differences between doses but p-values were only available between the doses with body systems

listed as a whole. Perhaps the fact that the variable Special Sense was compared as a whole was the reason that otitis media did not stand out as different in a statistical analysis.

Sponsor's Summary of Potentially Drug-Related Adverse Events[1]

Modified COSTART Term	1.5 mg Albuterol (N=115)	0.75 mg Albuterol (N=117)	Placebo (N=117)
Total patients reporting ≥ 1 event(s) (%)	5 (4.3%)	5 (4.3%)	8 (6.8)
Total number of events	8	9	11
Body as a Whole	2 (1.7)	2 (1.7)	1 (0.9)
Allergic reaction	0	1 (0.9)	0
Flu Syndrome	0	1 (0.9)	0
Headache	1 (0.9)	0	1 (0.9)
Infection-bacterial	0	1 (0.9)	0
Pain chest	1 (0.9)	0	0
Cardiovascular System	1 (0.9)	0	0
Tachycardia	1 (0.9)	0	0
Digestive System	1 (0.9)	1 (0.9)	0
Nausea	1 (0.9)	1 (0.9)	0
Nervous System	1 (0.9)	0	0
Hyperkinesia	1 (0.9)	0	0
Insomnia	1 (0.9)	0	0
Respiratory System	2 (1.7)	3 (2.6)	6 (5.1)
Asthma Exacerbation	1 (0.9)	1 (0.9)	3 (2.6)
Asthma, worsening	1 (0.9)	1 (0.9)	1 (0.9)
Cough increase	0	0	1 (0.9)
Rhinitis	0	1 (0.9)	1 (0.9)
Sinusitis	0	0	1 (0.9)
Skin & Appendages	0	0	2 (1.7)
Acne	0	0	1 (0.9)
* Rash	0	0	1 (0.9)

1 Potentially drug-related adverse events are those that have "possible", "probable", "definite", or missing study drug relationship.

Note: Patients may have more than one adverse event per body system or more than one occurrence of the same adverse event. Only one occurrence of the highest severity is counted for each patient.

Notable again on this list of drug-related adverse events is the tachycardia, hyperkinesia, and insomnia. Nausea is also listed and was not seen in the placebo group. There was no significant p-values between the doses but, again, Chi-Square testing was only done on the body systems as a whole.

Overall, the placebo treatment group experienced slightly more adverse events than the albuterol treatment groups. The body as a whole category and the respiratory system had the greatest frequency of adverse events among patients in each treatment group. Rhinitis and asthma exacerbation were the most frequent type of events.

Reviewer's Note – Again, the sponsor should clarify what the difference is between a worsening of asthma symptoms and an asthma exacerbation.

Overall, beta-agonist related AEs were reported by 7 (6.0%) patients receiving 1.5 mg albuterol sulfate; 5 (4.3%) patients receiving 0.75 mg albuterol sulfate; and 2 (1.7%) patients receiving placebo. The beta-agonist related AEs reported by patients during the study were dizziness, dyspnea, hyperkinesia, insomnia, nausea, tachycardia, and

twitching. There was one case of hypokalemia reported during the study, in the 0.75 mg albuterol sulfate group. Most of these specific beta-agonist related AEs were reported by fewer than 3 out of the 232 (1.3%) patients receiving albuterol in this study.

b) Serious/Significant Adverse Events

Summary of Serious Adverse Events and Significant Adverse Events

	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
SAEs	2 (1.7)	4 (3.4)	0
Significant AEs	15 (13.0)	15 (12.8)	15 (12.8)
Total	15 (13.0)	17 (14.5)	15 (12.8)

Six patients experienced six SAEs during the study. Two patients in the 1.5 mg albuterol sulfate group experienced SAEs related to the respiratory system (one asthma, one pneumonia). Four patients in the 0.75 mg albuterol sulfate group experienced SAEs: two related to the respiratory system (one asthma, one pneumonia), one related to the body as a whole (fever), and one related to metabolic and nutritional disorders(dehydration). None of the SAEs were considered by the investigator to be related to study drug. Placebo patients reported no SAE. There were no deaths reported during this study

Patient No. 156, an 11 year old female, was randomly assigned to the 0.75 mg albuterol sulfate treatment group on February 1, 1997. The patient had a documented medical history of allergic rhinitis, pneumonia, idiopathic urticaria and both intrinsic and extrinsic asthma for a duration of at least 5 to 10 years. On —— she experienced a flu syndrome resulting in dehydration and hospitalization. The subject was rehydrated with normal saline and given Tylenol, and study medication was interrupted. Labs were within normal ranges and stool cultures were negative for enteric pathogens. She was discharged the following afternoon and resumed all asthma medications. The date of resolution was —— This serious adverse event was considered by investigators to be unrelated to the study medication. The patient completed the study (Vol-16.2, Data Listings 4and 22).

Patient No. 967, a 6 year old female, was randomly assigned to 0.75 mg albuterol sulfate treatment group on April 12, 1997. The patient had a documented history of rhinitis, sickle-cell anemia, extrinsic asthma with a duration of at least 1 to 5 years. Approximately 16 days after the patient's first dose of study medication, she developed a fever of 102° F. The fever continued, and the patient was hospitalized on —— for observation due to her past history and diagnosis of sickle-cell anemia. Study medication was interrupted while hospitalized. The fever resolved on —— and the subject was discharged from the hospital on —— This serious adverse event was considered by the investigator to be unrelated to the study medication. The patient completed the study (Vol-16.2, Data Listings 4, 5 and 22).

Patient No. 336, a 9 year old male, was randomly assigned to the 1.5 mg albuterol sulfate treatment group on January 04, 1997. The patient had a documented history of pneumonia, reflux and intrinsic asthma for a duration of at least 5 to 10 years. On —— the investigator was contacted because the patient experienced an increase in asthma symptoms and a decrease in PEFR beginning the evening before. The investigator

prescribed 40 mg of prednisone and nebulized treatment every two hours. Later in the day, the patient responded well, and the investigator decreased the dose of prednisone to 20 mg. The patient immediately worsened, went to the ER and was hospitalized. The patient received more nebulized albuterol treatments and oxygen while in the hospital; a moderate fever also developed while hospitalized and resolved later the same day. The asthma exacerbation resolved on —— This serious adverse event was considered by the investigator to be unrelated to the study medication. The patient discontinued from the study and his last dose of study medication was January 4, 1997 (Vol-16.2, Data Listings 4, 5 and 22).

Patient No. 547, a 7 year old male, was randomly assigned to the 0.75 mg albuterol sulfate treatment group on February 17, 1997. The patient had a documented history of allergic rhinitis, intermittent headaches and mixed asthma for a duration of at least 1 to 5 years. On March 4, 1997, the patient saw the investigator for an unscheduled visit with a complaint of increased asthma symptoms. The investigator prescribed albuterol nebulized treatments, four times daily, with instructions to continue study medication. On —— —— the patient's condition worsened and he was taken to the ER. He was admitted and treated with prednisone and continuous nebulization treatments. The date for hospital discharge is unavailable. The date of resolution was —— This serious adverse event was considered by the investigator to be unrelated to the study medication. The patient discontinued from the study and his last dose of study medication was March 5, 1997 (Vol-16.2, Data Listings 4, 5, and 22).

Patient No. 1114, a 6 year old female, was randomly assigned to the 0.75 albuterol sulfate treatment group on March 28, 1997. The patient had a documented history of otitis media, sinusitis, allergic rhinitis, upset stomach, headache, chicken pox and asthma for a duration of at least 5 to 10 years. On —— the patient developed increased cough and chest congestion. The following day, symptoms worsened and patient was taken to the hospital where she was admitted for possible pneumonia. Upon admission, chest x-ray showed that changes were most likely related to atelectasis rather than infiltrate. The patient was discharged on —— This serious adverse event was considered by the investigator to be unrelated to the study medication. The patient discontinued the study and received her last dose of study medication April 10, 1997 (Vol.-16.2, Data Listings 4, 5 and 22).

Patient No. 370, a 10 year old male, was randomly assigned to the 1.5 mg albuterol sulfate treatment group on November 20, 1996. The patient had a documented history of sinusitis, allergic rhinitis, allergies and mixed asthma for a duration of at least 5 to 10 years. The subject was admitted to the hospital on —— with symptoms associated with an asthma exacerbation; he was using nebulized albuterol 3 to 4 times daily and in addition to his nebulizer treatments, he was using his MDI up to 6 times a day. Physical examination at the time of hospitalization revealed mild hypoxemia that was refractory to nebulized albuterol. The patient was treated with supplemental oxygen, Solu-medrol and nebulized albuterol. The patient was discharged on —— . This serious adverse event was considered by the investigator to be unrelated to the study medication. The patient discontinued the study and his last dose of study medication was December 9, 1996 (Vol.-16.2, Data Listings 4, 5 and 22).

The serious adverse events were considered not related to the study medication.

The 45 patients who discontinued the study due to AEs and are thus called significant AEs were equally distributed across the three treatment groups. Four patients who discontinued with serious AEs are included in the table. Asthma exacerbation was the most frequent AE that led to discontinuation.

Adverse Events Associated with Study Discontinuation

Reason for Discontinuation	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
Asthma exacerbation	5 (4.3%)	8 (6.8%)	6 (5.1%)
Secondary Asthma exacerbation[1]	6 (5.2%)	3 (2.6%)	2 (1.7%)
Pneumonia/Bronchitis	1 (0.9%)	0	2 (1.7%)
Strep Throat	0	1 (0.9%)	1 (0.9%)
Upper Respiratory Infection	3 (2.6%)	5 (4.3%)	2 (1.7%)
Rhinitis/Sinusitis/Pharyngitis	0	0	2 (1.7%)
Headache/Nausea	1 (0.9%)	0	0
Ear infection	2 (1.7%)	0	1 (0.9%)
Total # of Patients Discontinuing with AEs	15 (13.0%)	15 (12.8%)	15 (12.8%)

[1]Additional asthma exacerbations were associated with the occurrence of an upper respiratory or ear infection.

Most (84%) of the AEs resulting in discontinuation from the study were considered unrelated to study drug. Four asthma exacerbations were considered potentially drug related: one event in the 1.5 mg albuterol sulfate group, one event in the 0.75 mg albuterol sulfate group, and two events in the placebo group. The strep throat listed for a 0.75 mg albuterol sulfate patient was considered related to study drug, as was one of the sinusitis AEs in a placebo patient and the headache and nausea reported for a 1.5 mg albuterol patient. The narratives for the remaining 41 patients who discontinued from the study due to an AE are provided in Vol. 16-1. These narratives were reviewed by this medical officer and were largely related to asthma exacerbations.

c) Clinical Laboratory Evaluations

Laboratory measurements, including hematology, serum chemistry, and urinalysis, were taken at Visit 1 (Screening) for baseline values to establish inclusion/exclusion criteria, and *prior to dosing* at Visit 4. Thus, other than serum theophylline levels and urine pregnancy tests, clinical laboratories were only checked at screening and at the last visit.

Hematology: Hemoglobin, total and differential WBC, hematocrit, and platelet count.

Clinical Chemistry: Creatinine, blood urea nitrogen (BUN), calcium, total protein, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate transaminase (AST, SGOT), alanine transaminase (AST, SGPT), Potassium, Sodium and Chlorides.

Urinalysis: color, appearance, specific gravity, ketones, pH, microscopic exam of the sediment (field counts of WBC's, RBC's, bacteria and casts), urine glucose, bilirubin and urine protein.

If a subject discontinued prematurely from the study, laboratory measures were taken at the subject's 'Early Termination' Visit, which is referred to as Visit 4, regardless of the actual visit sequence and potentially again at the Visit 5 follow-up. Laboratory data were summarized using descriptive statistics for each scheduled laboratory assessment time and were reviewed by the medical officer.

Glucose and Potassium Levels

	1.5 mg albuterol N = 115 N (%)	0.75 albuterol N = 117 N (%)	Placebo N = 117 N (%)
Glucose (mg/dL)			
Visit 1			
N	111	115	114
Mean (SD)	103.7 (17.5)	98.9 (13.3)	101.2 (15.5)
Min, Max	[		]
Visit 4			
N	98	100	100
Mean (SD)	100.0 (18.7)	92.6 (14.9)	90.4 (14.5)
Min, Max	[		]
Potassium (mEq/L)			
Visit 1			
N	111	115	114
Mean (SD)	3.9 (0.4)	3.9 (0.5)	3.9 (0.4)
Min, Max	[		]
Visit 4			
N	98	100	100
Mean (SD)	4.2 (0.5)	4.2 (0.4)	4.3 (0.4)
Min, Max			

Note that the acute effects of albuterol on laboratory parameters were not examined in this study. Patients were required to not take their morning albuterol prior to an office visit. Therefore, the laboratory measurements at Visit 4, taken prior to dosing, would have been taken at the trough of the previous albuterol dosing.

Reviewer's Note: In Table 26 (p.12, Vol-1-16), the data for glucose in urine has only data for 4 timepoints total and appears incomplete. It was stated in the protocol that glucose in the urine would be checked. It is not expected that albuterol would have an important effect on urine glucose. Urine protein and WBC also appears incomplete.

The laboratory data were also examined for shifts from normal to abnormal results during the study. Comparable shifts were seen across treatment groups for the serum chemistries, hematology, and urinalysis results, except for alkaline phosphatase. A higher percentage of patients in the placebo group shifted from normal to high during the study (2%, 5% and 9% for the 1.5 mg and 0.75 mg albuterol sulfate, and placebo groups)(Table 30, Vol. 1.16) but even this was not so impressive. Only 2% patients had a shift from normal to low in potassium levels and they were in the 1.5 mg albuterol sulfate group, but to put them in perspective, 2% of patients in that group had shifts from normal to high and 11% had shifts from low to normal. The 0.75 mg albuterol sulfate and placebo groups had comparable potassium shifts from low to normal (12% and 8%, respectively).

d) Vital Signs

Vital signs, including heart rate, blood pressure, respirations, and body temperatures were recorded at baseline (Visit 1), at Visits 2 and 4 pre-dose, 30 minutes and then hourly for 6 hours post-dose, and at Visit 3 at pre-dose and 30 minutes post dose. There were no significant changes from pre-dose in any of the parameters at any visit.

When pulse rate at Visit 2 is examined, the mean of the rate increased by 2.9 – 3.3 bpm at the post-2 hour mark for 1.5 mg while the increase for 0.75 mg was up to 2.6 and for placebo, 0.7 bpm. There did not appear to be an appreciable change for blood pressure or respiratory rate. Similar findings were noted at Visit 4.

Below the sponsor has charted the ventricular rate as read from the ECG.

Ventricular Heart Rate Over Time

Heart Rate established from ECG (bpm)	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
Visit 2			
Pre-dose			
N	115	116	117
Mean (SD)	84.9 (13.4)	82.4 (12.6)	81.9 (12.8)
30 min. Post			
N	112	110	113
Mean (SD)	88.3 (13.2)	84.3 (12.1)	81.4 (13.2)
60 min. Post			
N	111	110	111
Mean (SD)	88.2 (13.6)	84.4 (12.7)	79.6 (11.6)
90 min. Post			
N	110	109	110
Mean (SD)	88.3 (12.9)	85.4 (13.8)	81.4 (12.4)
Visit 4			
Pre-dose			
N	98	97	99
Mean (SD)	84.3 (13.9)	81.2 (12.0)	80.9 (13.5)
30 min. Post			
N	97	96	98
Mean (SD)	88.0 (12.1)	83.3 (12.1)	79.2 (11.4)
60 min. Post			
N	97	97	96
Mean (SD)	87.3 (12.4)	82.5 (12.6)	78.2 (12.2)
90 min. Post			
N	97	96	96
Mean (SD)	87.3 (12.2)	82.1 (12.6)	78.4 (12.7)

Only slight increases (< 4 bpm) occurred in the active treatment groups within 30 minutes post-dose and were still present at 90 minutes post-dose at Visits 2 and 4.

e) Physical Examinations

A physical examination was performed at the screening visit (Visit 1) and at Visit 4/Study Termination Visit and, if prematurely discontinued, potentially again at Visit 5. Any abnormality or change that occurred during the course of the study was evaluated as a potential AE. The medical officer reviewed the table of changes. A similar percentage of patients in each treatment group had unfavorable changes at Visit 4 in the respiratory system (13.0%, 12.0%, and 13.7% for 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo, respectively) and the EENT system (17.4%, 16.2%, 16.2% for 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo, respectively).

f) Electrocardiogram

A 12-lead ECG was performed on study patients prior to the PFT measurements at all visits. At Visits 2 and 4, ECGs were also taken 30, 60, and 90 minutes post-dosing. Summary statistics for the ECG parameters were provided. ECG data for individual patients are provided in Appendix 16.2, Data Listings 13 and 14.

To provide consistent interpretation across study sites, the ECG results were faxed to [redacted] reading by a pediatric cardiologist and the interpretations were then sent back to the site. If an interpretation was reported by the centralized cardiologist as clinically relevant, the investigator, who had direct knowledge of the patient's medical status, could choose to re-classify the interpretation as not clinically relevant. Two patients had results interpreted by the centralized cardiologist as clinically relevant that were considered irrelevant by the investigator: Patient No. 157 (in the 1.5 mg albuterol group) at Visit 1 pre-dose and at Visit 2 at 30, 60, and 90 minutes post dose; and Patient No. 605 (in the placebo group) at Visit 2 at 90 minutes post dose. Patient No. 157 had an inverted T-wave at Visit 1 and then at Visit 2 post dose had a depressed ST segment (according to the narrative p. 91 in Vol 1-15; it is not mentioned in the Data Listing 14. Vol. 1-26) with the inverted T-wave. Patient No. 605 had an interpretation of sinus bradycardia at Visit 1 and Visit 2 at 30, 60, and 90 minutes, but only the 90 minutes event was interpreted as abnormal. Patient No. 1025 had an abnormal interpretation with a ST rhythm that was marked on the CRF as clinically significant. However, a query confirmed that it was clinically irrelevant but the CRF had not been corrected as a follow-up.

Reviewer's Note – Patient 157 is noted to have an abnormal EKG at Visit 1, 2 (only post-dose) which is called "clinically relevant" in the Data Listing 14, Vol. 1-26. There is mention of inverted T waves at Visit 1 and Visit 2 post-dose but it is not clear whether the investigator is referring to the inverted T waves as the clinically relevant abnormality. The EKG is again called abnormal and has inverted T waves at Visit 3 post-dose but is labeled clinically irrelevant. These discrepancies in the clinical relevance of the inverted T waves are apparently what the sponsor is referring to in the Integrated Clinical and Statistical Report narrative when it is said that the relevance or irrelevance of a finding could be reclassified by the investigator after an initial reading and judgement is given by the centralized cardiologist. At Visit 4 pre-dose, the EKG is called abnormal but it is not clear why. (See Vol. 1-26, pp. 57-60) The reviewing officer could not locate further information on Patient 157's depressed ST segment. The question should be posed to the sponsor, what findings on Patient No. 157 EKGs were relevant or irrelevant?

Patient 605's heart rate is listed as 49 at 90 minutes post-placebo. Patient 1025' EKG are all listed as normal in Data Listing 14 – Vol. 1-27.

The baseline for the treatment phase of the study was the Visit 2 pre-dose. At the Visit 2 pre-dose, five patients (4 randomized to 1.5 mg albuterol sulfate and 1 randomized to 0.75 mg albuterol sulfate) had abnormal clinically irrelevant ECG interpretations, and one patient in the 1.5 mg group had a clinically relevant abnormal interpretation. The latter patient had been enrolled in the study with WPW-syndrome. The subject with WPW had done studies in the past with B-agonists with no problems and had had no problems with her current use of a Ventolin inhaler.

Reviewer's Note – There is a classification called "deteriorated (from baseline)" but it is not clear what is meant by this.

At Visit 2, 30 and 60 minutes post-dose, 6 patients were reported to have clinically irrelevant deterioration in their ECGs compared to their Visit 2 pre-dose ECG (3, 1, and 2 patients in the 1.5 mg, 0.75 mg albuterol sulfate, and placebo groups, respectively). Two of the 1.5 mg patients and the one 0.75 mg patient had the same abnormalities in their Visit 1 ECG, and therefore, those were not new events. By 90 minutes post dose, one of the 1.5 mg patients and the 0.75 mg patient returned to normal, while an additional 0.75 mg patient and another placebo patient showed clinically irrelevant abnormalities of sinus bradycardia or sinus tachycardia.

Reviewer's Note – The above represents the sponsor's narrative. From my review, it appears that at 30 minutes post-dose in the 1.5 mg group, there was 1 new report of VPC (no report on it at 60 minutes), 1 more report of ectopic atrial contraction (still one extra at 90 minutes), 1 new report of inverted T wave (still one extra at 90 minutes), and 1 new report of a depressed ST segment (one new one still present at 90 minutes). At 30 minutes for the 0.75 mg group, there was a new report of flat T wave which apparently remained at 30 minutes. A LAH (?left anterior hemiblock) was present in Patient 722 throughout the study.

At Visit 3, 4 out of 97 patients (4.1%) in the 1.5 mg albuterol sulfate group had shifts to an abnormal ECG, related to changes in pre-existing rhythm abnormalities, 30 minutes post-dose compared to the Visit 2 pre-dose, while only 1 out of 97 patients (1.0%) did so in the 0.75 mg albuterol sulfate group and 1 out of 98 patients (1.0%) in the placebo group. All of the abnormalities were categorized by the investigators as not clinically relevant.

Reviewer's Note – At 30 minutes in the 1.5 mg group, there was a new report of a flattened T wave and an inverted T wave. EKG's were not done at 60 and 90 minutes.

At Visit 4 pre-dose, 5 out of 98 patients (5.1%) in the 1.5 mg albuterol group had shifts to an abnormal ECG compared to pre-dose Visit 2, while only 2 out of 97 patients (2.1%) did so in the 0.75 mg albuterol sulfate group. Again, those abnormalities were categorized as not clinically relevant. Most of the abnormalities were related to sinus tachycardia, ectopic atrial rhythm, or other rhythm changes, except one of the 1.5 mg patients had evidence of an incomplete right bundle branch block (Patient No. 092) and another patient in that group (Patient No. 1232) had a reoccurring APC (atrial premature contraction) with a flat T-wave, which was first noted at Visit 2.

Reviewer's Note – You cannot tell from the line listing that 1232 had APC's. Furthermore, the flat T wave for Patient 1232 was first noted at Visit 3, not 2, according to the line listings. Patient .092 showed an IRBBB on Visit 4 only and it was present pre-dose: the IRBBB was thought to be clinically irrelevant. One of the 99 patients in the placebo group had a deterioration of an ECG during the post-dose testing (60 minutes post) at Visit 4.

Reviewer's Note – At 30 minutes in the 1.5 mg group there was a new report of VPC (there was still one report at 90 minutes.). There was one report of IRBBB throughout the visit.

No significant changes were detected in the mean QTc intervals for the different treatment groups. The QTc intervals ranged from 319 to 474 msec.

g) Safety Conclusions

During this study, 164/349 (47%) of patients reported 350 AEs, with asthma exacerbation and rhinitis being the most commonly reported AEs. The majority (92%) of the AEs were considered unrelated to the study medication. No significant difference in the incidence of AEs was detected across the treatment groups but beta-agonist related events were higher in the albuterol groups, showing a dose response effect, but each type of beta-agonist related event was reported by $\leq$ 1.3% of the total number of patients in both albuterol groups.

No acute effects of albuterol on laboratory parameters were examined in this study but the study did not really appear adequate to discern subtle and acute changes in laboratory parameters. No deleterious systemic effects as measured by changes in vital signs and ECG parameters were detected during the 4-week exposure. The mean of the increases in pulse appears to be approximately 3 bpm, which is not clinically significant in the pediatric patient population.

A discrepancy among the groups is noted with otitis media and was seen in 4.3%, 0.9%, and 0%, for 1.5 mg albuterol, 0.75 mg and placebo, respectively – an explanation for the higher incidence of otitis media in the 1.5 mg group is not known. The sponsor says that Chi-Square testing did not pick up any differences between doses but p-values were only available between the doses with body systems listed as a whole. Perhaps the fact that the variable Special Sense was compared as a whole was the reason that otitis media did not stand out as different in a statistical analysis.

F. Discussions/Conclusions on DL-019

Overall, it appears that this study demonstrates that Accuneb Albuterol sulfate Inhalation Solutions of 1.5 mg and 0.75 mg produce statistically significant improvements in the pulmonary function of asthmatic children with a few notable exceptions. It also appears that the risk/benefit ratio is acceptable based on a review of the safety data in this important pivotal study.

The exceptions to the demonstration of efficacy found in the subgroup analysis in the primary endpoint (%Δ AUC FEV_1 at Visit 4) are as follows:

a) Visit 4 for the 11- 12 year olds exposed to the 0.75 mg albuterol sulfate dose (p=. 082) (ITT Efficacy)

b) At Visit 4, the improvements with both 0.75 mg and 1.5 mg for the non-caucasians were not significantly different from placebo. (ITT Efficacy)

c) At Visit 4 for the 9 - 10 year olds did not reach statistical significance over placebo for either active treatment group in the evaluable population (Table 9.2 A – Vol. 1-15) while it did in the ITT efficacy population.

d) 0.75 mg dose in patients not on concomitant glucocorticoids had a p-value of 0.151 at Visit 4.

e) For Visit 4 in patients with $FEV_1 \leq 60\%$, 0.75 mg albuterol was not statistically different form placebo. Indeed for this subgroup of patients, 1.5 mg albuterol was barely different from placebo with a p value of 0.049 at Visit 4.

f) Heavier children (>40 kg) exposed to 0.75 mg albuterol did not show significant improvement in the %Δ AUC FEV_1 at Visit 4.

It appears that by Visit 4 – four weeks of chronic usage t.i.d. – 0.75 mg no longer had statistically significant improvement in 11-12 year olds, children > 40 kg, patients not on concomitant glucocorticoids, and subjects with an $FEV_1 \leq 60\%$. In each of these groups, 1.5 mg demonstrated a significant improvement over placebo at Visit 4 with the near exception of patients with an $FEV_1 \leq 60\%$ as stated in e) above. Some of these findings of significant differences or lack of significant differences must be tempered. These differences found in subgroup efficacy represent post-hoc analysis in studies not originally designed to discern differences between subgroups.

In looking at %Δ AUC FEV_1 in the subgroup analysis of FEV_1, despite the fact that it was the group with $FEV_1 \leq 60\%$ predicted which did not have significant efficacy with 0.75 mg over placebo, this group nonetheless had a mean %Δ AUC FEV_1 (96.9 %-hr) greater than the subjects with $FEV_1 > 60\%$ (68.2 %-hr). Subjects with an $FEV_1 \leq 60\%$ predicted also appeared to have a greater MAX FEV_1 and duration of response.

This data also seems to support the idea that with chronic use, nebulized albuterol is less effective when compared to initial or non-chronic use. The duration of response (the time that FEV_1 >115% of pre-dose FEV_1) was a secondary endpoint explored in the study. It appears from the studies done for DL-019 that the duration of effect for Visit 2 is different from Visit 4. There was a statistical difference in the duration of effect in the ITT Efficacy population between Visits 2 and 4 for both 0.75 and 1.5 mg. The p value for the difference between Visit 2 and 4 for the 1.5 mg group was 0.0133 with a significant decrease found in the duration of response found at Visit 4 (mean 116.8 minutes) compared with Visit 2 (mean = 160.4 minutes. The p value for 0.75 mg albuterol was 0.072 so the decrease between Visit 2 (147.3 minutes) and Visit 4 (115.9 minutes) was not statistically significant. Thus, it appears, at least for the 1.5 mg dose of albuterol, that there is a decrease in the duration of effect after 4 weeks of t.i.d. use.

Examining the table regarding FEV_1 over time (in the section of FEV_1 percent change) shows that the difference in FEV_1 between both albuterol treatments and placebo dissipates sometime between 120 and 180 minutes at Visit 2 and somewhere between 60 and 120 minutes at Visit 4. This again supports the idea that the duration of effect decreases over time of albuterol usage.

For the ITT Efficacy population, the mean duration of response at Visit 2 was 160.4 minutes (~2.7 hours) for 1.5 mg, 147.3 minutes (~2.45 hours) for 0.75 mg and 1.0 hour for placebo. The mean duration of response at Visit 4 was 116.8 minutes (~1.9 hours) for 1.5 mg, 116 minutes (~1.9 hours) for 0.75 mg and ~0.6 hours for placebo. For the evaluable population, the mean duration of response at Visit 2 was 164 minutes (~2.7 hours) for 1.5 mg, 130.7 minutes (~2.2 hours) for 0.75 mg and ~0.8 hours for placebo. The mean duration of response at Visit 4 was 118.5 minutes (~2 hours) for 1.5 mg, 122 minutes (~2 hours) for 0.75 mg and (~0.6 hours) for placebo. Subgroup analysis of duration of response was

done and the mean duration of response was shorter at Visit 4 for most subgroups as compared to Visit 2.

Overall, all subgroups had duration of response significantly greater than placebo with the exception of:

- 1.5 mg albuterol group ages 9-10, Visit 4 (evaluable, not ITT) – mean of 75 minutes vs. 122.6 for 0.75 mg and 40.2 minutes for placebo. The mean of 75 minutes is uncharacteristically low for an albuterol subgroup.
- 0.75 mg albuterol group, non-caucasians, Visit 4 (evaluable and ITT)– mean of 104 minutes vs. 104.3 for 1.5 mg and 46.1 for placebo (evaluable).
- Patients without concomitant corticosteroid use, 0.75 mg group at Visit 4 (evaluable and ITT).

Other secondary endpoints explored in this DL-019 included maximum percent change in FEV_1 (MAX FEV_1), proportion of responders, changes in FEF and FVC, PEFR, daily asthma symptom scores, rescue medication use, and global assessment. Subgroup analysis was performed for MAX FEV_1 as it was for %Δ AUC FEV_1 and duration of response.

V. Integrated Summary of Safety

Albuterol has been in clinical use for nearly 25 years and is considered a well-tolerated medicine for the majority of patients suffering from asthma. The principal adverse events of beta-sympathomimetic agents are skeletal muscle tremor, metabolic effects and cardiovascular effects. Tremor is typically dose-related and resolves with discontinuation of therapy. The most notable metabolic effects include hypokalemia and probably hyperglycemia.

Safety data are provided on three doses of albuterol sulfate compared to placebo (0.9% saline). The three doses are 3.0 mg albuterol sulfate (2.5 mg albuterol base), 1.5 mg albuterol sulfate (1.25 mg albuterol base), and 0.75 mg albuterol sulfate (0.623 mg albuterol base). The safety population included all randomized patients who received at least one dose of study drug and who had at least one post-baseline assessment which corresponds with the ITT population. The safety measures summarized are adverse events, laboratory testing, vital signs, and ECG measurements.

Data was available from 55 pediatric asthmatics in single dose pharmacology studies and 349 pediatric asthmatics in the Phase III study. Of the 349 subjects in DL-019, 117 were assigned to the placebo group.

Patients Randomized to all Studies

	30	29	29	30	30	28
	25	25	24	25	25	24
	349	0	115	117	232	117

The DL-010 study was a bronchoprovacation study and its study population consisted of less severe asthmatics with an FEV_1 percent predicted between 70 and 95%. Non-caucasians in DL-019 were Blacks (20%), Hispanics (4.3%), Asians (1.7%), and some classified as "Other race" (3.5%).

Patients Randomized to all Studies

	30	29	29	30	30	28
	25	25	24	25	25	24
	349	0	115	117	232	117

The DL-010 study was a bronchoprovacation study and its study population consisted of less severe asthmatics with an FEV_1 percent predicted between 70 and 95%. Non-caucasians in DL-019 were Blacks (20%), Hispanics (4.3%), Asians (1.7%), and some classified as "Other race" (3.5%).

Summary of Demographics

	9.4 (2.1)	10 (2.0)	9.3 (1.8)	9.6 (1.7)
	6-12	6-12	6-12	6-12
	18	15	146	75
	12	10	86	42
	30	25	160	82
	0	0	72	35
	44.1	49.8	38.5	40.3
	18.6-72.6	18.6-90.7	16.8-90.8	21.8-86.6
	142.2	146	140.1	141.3
	116.8-165.1	121.9-175.3	103.6-178	117-170
	66.8 (8.1)	79.8 (8.0)	68.5 (8.1)	68.7 (7.9)
	53.8-79.7	70-94.5	50.6-89.9	48.9-81.3
	39.7	23.8	31.4	30.1
	15-99	15.4-48.4	12.4-141.2	14.5-97.7

As far as patient disposition for the pharmacologic crossover studies are concerned, only three patients were prematurely discontinued. From DL-009, two patients discontinued due to adverse events: Patient No. 0103 in the 1.5 mg group and Patient No. 0217 in the 0.75 mg group. In DL-010, Patient No. 217 in the 3.0 mg group discontinued due to an asthma exacerbation. No patients in the placebo groups discontinued. This patient was unable to satisfy spirometry requirements during a study visit and should be considered a discontinuation due to an adverse event.

Of the 349 enrolled in DL-019, 84.1% of the patients completed the study.

Patient Disposition in DL-019

	98 (85.2)	97 (82.9)	195 (84.1)	93 (79.5)
	17 (14.8)	20 (17.1)	37 (15.9)	24 (20.5)
	15 (13)	15 (12.8)	30 (12.9)	15 (12.8)
	0	0	0	0
	0	1 (0.9)	1 (0.4)	0

[redacted]	2 (1.7)	1 (0.9)	3 (1.3)	2 (1.7)
[redacted]	0	1 (0.9)	1 (0.4)	2 (1.7)
[redacted]	0	0	0	1 (0.9)
[redacted]	0	2 (1.7)	2 (0.9)	3 (2.6)

There were clinical differences across treatment groups in the number of patients discontinuing from the study due to adverse events. Only one patient, No. 500, a 0.75 mg albuterol patient, was thought to have discontinued because of lack of efficacy after 15 days of study medication.

Of the 61 discontinuing patients, 45 (73.8%) discontinued due to an AE. There were differences in the number of patients discontinuing because of AEs across treatment groups. Five discontinued because of "other": 1) under advisement by —— due to an increase in FEV1 during the first treatment visit, 2) one patient was randomized in error (which was not defined), 3) one was taking [redacted], 4) one used exclusionary medication, and 5) one did not meet exclusion criteria. The latter three should have been considered protocol violations but the investigator errantly checked the other category. The mean FEV1 percent predicted values were only marginally lower than the total population (approx. –3%).

Patients were allowed to use albuterol as a rescue medication. They were given the Dey MDI and the Dey Albuterol 0.083% solution and were instructed to use the MDI first if needed.

Rescue Medication Use

[redacted]	[redacted]	[redacted]	[redacted]	Placebo
[redacted]	106	111	217	109
[redacted]	92.2%	94.9%	93.5%	93.2%
[redacted]	25.5	25.4		25.5
[redacted]	36.7	42.5		54.9
[redacted]	0.005	0.151		
[redacted]	54	58	112	57
[redacted]	47%	49.6%	48.3%	48.7%
[redacted]	25.5	25.4		25.5
[redacted]	3.4	4.9		3.7
[redacted]	0.19	0.24		0.17

[redacted]	94.8%	94.9%		94.9%

The mean use of MDI medication was significantly lower in the 1.5 mg group compared to placebo, but not in the 0.75 mg group. For safety analyses, it was difficult to determine the total impact of the rescue medication on the safety profile of the study drugs. The patients in the1.5 mg group received per day approximately 5 mg of nebulized albuterol sulfate plus a mean of 136 mcg albuterol from an MDI. The patients in the 0.75 mg group on average received per day approximately 3 mg of nebulized albuterol sulfate plus a mean of 160 mcg of albuterol from an MDI.

The mean use of rescue MDI puffs per day for patients taking study drug > 28 days suggest a dose response trend with 1.18, 1.53, and 2.11 puffs for 1.5 mg, 0.75 mg, and placebo, respectively (Table 2.3, Appendix B). There was no difference between the groups in mean vial use for patients taking study drug for > 28 days (Table 2.4, Appendix B).

Because only three studies were involved in this NDA, the data on adverse events ahs largely been presented in the safety sections for each of the studies. An examination of the AEs should largely depend on the four week study, particularly as albuterol has been involved in clinical use for many years. No deaths occurred in the patient population of any of the studies. A total of seven patients experienced serious AEs. Only one patient in DL-009 experienced a serious AE – he was hospitalized with appendicitis two days after receiving his final dose of 1.5 mg. In DL-019, two in the 1.5 mg group experienced SAEs, both related to the respiratory system (asthma exacerbations). Four in the 0.75 mg group experienced SAEs – two related to the respiratory system (one asthma exacerbation, one pneumonia), one to the body as a whole (dehydration secondary to a flu syndrome) and one related to metabolic and nutritional disorders (fever in a sickle cell anemia patient). No SAEs occurred in the placebo group. All of the SAEs were considered by the investigators to be unrelated to the study drug.

Of the 404 patients enrolled in the three studies, 64 discontinued prematurely. The majority (48/64) discontinued due to AEs. One following exposure to 3.0 mg, 16 exposed to 1.5 mg, 16 exposed to 0.75 mg and 15 exposed to placebo were discontinued as a result of an AE. In DL-009, there were two patients withdrawn because of adverse events. Patient 217 withdrew because of a URI that was judged as mild in severity. Patient 103 withdrew after completing 3 of the 4 treatment sessions because of an exacerbation of asthma after completing 1 of the 4 treatment sessions. In DL-010, one patient (#217) dropped from the study during Visit 4 due to an asthma exacerbation after completing three of the four treatments. The patient was unable to meet PFT requirements after 3 attempts at Visit 4. Forty five of the 48 who discontinued with an AE were in DL-019.

Adverse Events Associated with Study Discontinuation in DL-019

Reason for Discontinuation	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
Asthma exacerbation	5 (4.3%)	8 (6.8%)	6 (5.1%)
Secondary Asthma exacerbation[1]	6 (5.2%)	3 (2.6%)	2 (1.7%)
Pneumonia/Bronchitis	1 (0.9%)	0	2 (1.7%)
Strep Throat	0	1 (0.9%)	1 (0.9%)
Upper Respiratory Infection	3 (2.6%)	5 (4.3%)	2 (1.7%)
Rhinitis/Sinusitis/Pharyngitis	0	0	2 (1.7%)
Headache/Nausea	1 (0.9%)	0	0
Ear infection	2 (1.7%)	0	1 (0.9%)
Total # of Patients Discontinuing with AEs	15 (13.0%)	15 (12.8%)	15 (12.8%)

[1]Additional asthma exacerbations were associated with the occurrence of an upper respiratory or ear infection

The 45 patients who discontinued the study due to AEs were generally distributed equally across the three treatment groups. Four patients who discontinued with SAEs are included in the table. Asthma exacerbation was the most frequent AE that led to discontinuation. Most (84%) of the AEs resulting in discontinuation from the study were considered unrelated to study drug. Four asthma exacerbations were considered potentially drug related: one event in the 1.5 mg albuterol sulfate group, one event in the 0.75 mg albuterol sulfate group, and two events in the placebo group. The strep throat listed for a 0.75 mg albuterol sulfate patient was considered related to study drug, as was one of the sinusitis AEs in a placebo patient and the headache and nausea reported for a 1.5 mg albuterol patient. The strep throat occurred six days after study drug exposure so it is unclear to this reviewer how it could have been related to the study drug.

Because of the more chronic and repeated exposures to Accuneb in DL-019, the discussion of all adverse events and their percentages should focus on this study. The occurrence of AEs in the two crossover studies have been presented previously in this NDA and are not particularly remarkable.

Adverse Events with Incidence ≥ 1% and > Placebo in All Albuterol Groups

	1.5 mg (N=115)n(%)	0.75 mg (N=117)n(%)	All Albuterol Groups (N=232)n(%)	Placebo (N=117)n(%)	p-value (all albuterol vs. placebo)
Total Patients reporting ≥1 event					
Total # Events	117	101	218	130	
Body as a Whole	19 (16.5)	16 (13.7)	35 (15.1)	26 (22.2)	0.103
Flu Syndrome	3 (2.6)	3 (2.6)	6 (2.6)	2 (1.7)	
Allergic Reaction	1 (0.9)	4 (3.4)	5 (2.2)	2 (1.7)	
Chest Pain	1 (0.9)	2 (1.7)	3 (1.3)	0	

Cardiovascular	3 (2.6)	3 (2.6)	6 (2.6)	0	0.185
Migraine	1 (0.9)	2 (1.7)	3 (1.3)	0	
Digestive	4 (3.5)	7 (6.0)	11 (4.7)	6 (5.1)	1.000
Nausea	2 (1.7)	1 (0.9)	3 (1.3)	1 (0.9)	
Gastroenteritis	1 (0.9)	4 (3.4)	5 (2.2)	1 (0.9)	
Nervous System	2 (1.7)	1 (0.9)	3 (1.3)	1 (0.9)	1.000
Respiratory System	36 (31.3)	36 (30.8)	72 (31)	45 (38.5)	0.187
Asthma Exacerbation	15 (13)	13 (11.1)	28 (12.1)	10 (8.5)	
Bronchitis	1 (0.9)	2 (1.7)	3 (1.3)	1 (0.9)	
Skin and Appendages	9 (7.8)	2 (1.7)	11 (4.7)	7 (6.0)	0.616
Urticaria	2 (1.7)	1 (0.9)	3 (1.3)	0	
Special senses	7 (6.1)	3 (2.6)	10 (4.3)	4 (3.4)	0.781
Otitis Media	5 (4.3)	1 (0.9)	6 (2.6)	0	

Additionally, the following moderate to severe adverse events were reported infrequently (incidence < 1%) in any treatment group, face edema, chest pain, hyperkinesia, insomnia, hypertension, migraine, constipation, diarrhea, vomiting, lymphadenopathy, dehydration, twitch, worsening asthma, dyspnea, pneumonia, infection, rash, urticaria, ear disease, ear pain, and urinary tract infection.

Potentially Beta-Agonist Associated Adverse Events in DL-019

	5 (4.3)	7 (6.0)	6 (5.1)
	9	7	7
	3 (2.6)	3 (2.6)	5 (4.3)
	2 (1.7)	1 (0.9)	1 (0.9)
	1 (0.9)	1 (0.9)	1 (0.9)
	0 (0)	1 (0.9)	0 (0)
	0 (0)	1 (0.9)	0 (0)
	1 (0.9)	0 (0)	0 (0)
	1 (0.9)	0 (0)	0 (0)
	1 (0.9)	0 (0)	0 (0)

Dey says that no one reported twitching, tremors or shaking from any of the studies involved with the clinical program.

In Dey's subgroup analysis of DL-019, no statistical difference in the % incidence of any of the AEs between all albuterol groups and placebo were detected due to gender, race or weight. The one exception was between all albuterol patients and placebo for the Body as a Whole in the mid-weight group (>30 kg and ≤ 40 kg). The albuterol group had a

Potentially Beta-Agonist Associated Adverse Events in DL-019

	5 (4.3)	7 (6.0)	6 (5.1)
	9	7	7
	3 (2.6)	3 (2.6)	5 (4.3)
	2 (1.7)	1 (0.9)	1 (0.9)
	1 (0.9)	1 (0.9)	1 (0.9)
	0 (0)	1 (0.9)	0 (0)
	0 (0)	1 (0.9)	0 (0)
	1 (0.9)	0 (0)	0 (0)
	1 (0.9)	0 (0)	0 (0)
	1 (0.9)	0 (0)	0 (0)

rate of 16.9% versus placebo group with 36.4%. Higher rates of fever, headaches and general pain contributed to the difference. A higher percentage of males receiving albuterol reported asthma exacerbation or worsening of asthma as compared to females (14.4% and 7.5% for the males vs. 8.1% and 2.3% for the females, respectively.)

For those not using concomitant corticosteroids, , a significant difference (p=0.029) between the albuterol and placebo patients was seen in the incidence of AEs involving the respiratory system (22.1% vs. 14.9%, respectively). In the placebo group, over twice the percentage of patients reported rhinitis and worsening of asthma symptoms as the albuterol patients (5.8% vs. 14.9%).

For DL-009 and DL-010, laboratory tests were only done during screening. For DL-019, laboratory measurements were taken at Visit1 (Screening) and prior to dosing at Visit 4. As previously shown in the safety section on DI-019, there was no clinically relevant change in any laboratory parameter.

The laboratory data were also examined for shifts from normal to abnormal results during the study. Comparable shifts were seen across treatment groups for the serum chemistries, hematology, and urinalysis results, except for alkaline phosphatase where a higher percentage of patients in the placebo group shifted from normal to high during the study (2%, 5% and 9% for the 1.5 mg and 0.75 mg albuterol sulfate, and placebo groups.) The clinical significance of this difference in alkaline phosphatase changes is unknown and highly doubtful.

The effects of Accuneb on potassium and glucose levels immediately following administration of the drug were not evaluated. Dey says that the published reports on those two parameters show them to be transient and to occur at albuterol base doses greater than the currently recommended 2.5 mg dose. Hypokalemia has been reported in a case series of four young children (1-6 years) receiving overdoses of 1.1-3.7 mg/kg. The serum potassium was 2.3-2.8 mmol/l.

There was a discernible increase in the heart rate with treatment. In DL-009, the mean heart rate following 3.0 mg albuterol increased between 8.0-11 bpm at 5, 15, 30, 60 and 90 minutes post-dose. The 1.5 mg and 0.75 mg doses showed less of a peak increase in heart rate. The sponsor had modeling performed of the heart rate data for this study but this reviewer did not find it particularly helpful.

In the DL-010 study, a slight increase in the heart rate of 5-7 bpm was noted in all treatment groups including placebo which indicates that the increase was more procedure related than medication related.

When pulse rate for the Phase II study, DL-019, at Visit 2 is examined, the mean of the rate increased by 2.9 – 3.3 bpm at the post-2 hour mark for 1.5 mg while the increase for 0.75 mg was up to 2.6 and for placebo, 0.7 bpm. There did not appear to be an appreciable change for blood pressure or respiratory rate. Similar findings were noted at Visit 4.

Overall, it appears that the increase in heart rate that can be expected with the Accuneb dosing of 0.75 bpm and 1.5 bpm is probably less than 5 bpm and is not clinically significant, particularly in the pediatric population.

For DL-009, A 12-lead electrocardiogram was recorded immediately prior to, and two hours following, study drug administration. The actual ECGs were not submitted with the NDA nor were the specific lengths of PR and QT segments involved. On Visit 2, subject

202 had PR segment prolongation and sinus arrhythmia post-dose. PR prolongation was also seen post-dose on Visits 3 and 5. Subject 209 had a "slight ST abnormality" post-dose on Visit 1 – no further detail is given. Subject 211 had a flat T wave on Visit 2 post-dose – a flat T wave was also seen pre-dose on Visit 3. Subject 213 had "right ventricular deviation and right axis deviation" post-dose on Visit 1 - no other abnormality is listed for this patient. Subject 214 had "sinus arrhythmia and flat T waves" on post-dose Visit 1. Subject 217 had "slight ST-T abnormality" post-dose on Visit 2 – no further detail is given. Subject 219 demonstrated "slight ST abnormalities" post dose on visits 1, 3, and 5 – no further detail is given. The ECG data from this study are somewhat sketchy – the clinical significance of these changes cannot be discerned. None of the post-dose ECG abnormalities were felt to be clinically significant by the investigators involved.

For DL-010, 4 subjects were noted to have abnormalities on the post dose EKG as compared to the pre-dose EKG. Subject 205 was noted to have high T waves, which was deemed not clinically significant. Subject 206 was noted to have a ST-T wave abnormality on a post dose EKG while the pre-dose was considered normal on Visits 1 and 3 – notably an ST-T wave abnormality had been noted on both pre and post dose EKGs on Visit 2. On Visit 4, this same subject had a wide P and ST elevation pre-dose and sinus arrhythmia and ST abnormality post–dose. Subject 210 was noted to have a slight ST-T wave abnormality on a post dose EKG that was deemed not clinically significant on Visit 1. Subject 215 developed a sinus arrhythmia post dose EKG that was deemed not clinically significant on Visit 1. Again, none of the post-dose ECG abnormalities were felt to be clinically significant.

Study DL-019 appears to be the only study where there is actual data for the ECG intervals. A 12-lead ECG was performed on study patients prior to the PFT measurements at all visits. At Visits 2 and 4, ECGs were also taken 30, 60, and 90 minutes post-dosing.

No clinically relevant changes were seen in the QTc intervals. The largest increase in the mean QTc interval was 7.2 msec which occurred 30 minutes post-dose in the 1.5 mg albuterol group following the first study drug exposure. At Visit 4, a similar increase was seen in the 1.5 mg group at 30 minutes post dose but it was back to pre-dose value by 60 minutes. While statistics were not performed, it does appear that there is a slight increase in QT with 1.5 mg relative to 0.75 mg and placebo. This increase does not appear to be clinically significant at the Accuneb doses.

QT change from Pre-dose for DL-019

	343.6	-2.1	339.6	-1.1	347.3	-2.5
	404.9	1.2	409	7.2	401	-4.4
	341.3	-4.3	337.7	-2.8	348.3	-1.2
	402.3	-1.4	406.5	4.5	398.2	-7.3

QT change from Pre-dose for DL-019

	343.6	-2.1	339.6	-1.1	347.3	-2.5
	404.9	1.2	409	7.2	401	-4.4
	341.3	-4.3	337.7	-2.8	348.3	-1.2

[redacted]	341.6	-3.9	337.1	-3.1	347.1	-3.1
	404.5	0.8	406.3	4.2	400.9	-4.6
	346.1	-3.0	340.5	-3.5	348.3	-2.2
	405.1	1.7	409.8	5.5	397.4	-5.8
	345.6	-3.7	337.1	-6.9	349.2	-2.1
	402	-1.3	404.1	-0.2	395.4	-7.7
	343.5	-6.0	338.5	-5.5	350.6	-0.7
	399.2	-4.5	405.8	1.6	397.4	-5.8

At Visit 2, Dey's narrative reveals that at 30 and 60 minutes post-dose, 6 patients were reported to have clinically irrelevant deterioration in their ECGs compared to their Visit 2 pre-dose ECG (3, 1, and 2 patients in the 1.5 mg, 0.75 mg albuterol sulfate, and placebo groups, respectively). Two of the 1.5 mg patients and the one 0.75 mg patient had the same abnormalities in their Visit 1 ECG, and therefore, those were not new events. By 90 minutes post dose, one of the 1.5 mg patients and the 0.75 mg patient returned to normal, while an additional 0.75 mg patient and another placebo patient showed clinically irrelevant abnormalities of sinus bradycardia or sinus tachycardia.

Reviewer's Note –From this reviewer's review of Table 35 (Vol. 1-16), it appears that at 30 minutes post-dose in the 1.5 mg group, there was 1 new report of VPC (no report on it at 60 minutes), 1 more report of ectopic atrial contraction (still one extra at 90 minutes), 1 new report of inverted T wave (still one extra at 90 minutes), and 1 new report of a depressed ST segment (one new one still present at 90 minutes). At 30 minutes for the 0.75 mg group, there was a new report of flat T wave which apparently remained at 30 minutes. A LAH (?left anterior hemiblock) was present in Patient 722 throughout the study.

It would be helpful if the subject in the 1.5 mg group with the new instance of a depressed ST segment seen at Visit 2 - 30 minutes post dose- could be identified for further review of the details. The reviewer is not certain whether this is Subject No. 157 discussed in the narrative. This depressed ST segment was not mentioned pre-dose and was still present at 60 and 90 minutes post-dose.

At Visit 4 pre-dose, 5 out of 98 patients (5.1%) in the 1.5 mg albuterol group had shifts to an abnormal ECG compared to pre-dose Visit 2, while only 2 out of 97 patients (2.1%) did so in the 0.75 mg albuterol sulfate group. Again, those abnormalities were categorized as not clinically relevant. Most of the abnormalities were related to sinus tachycardia, ectopic atrial rhythm, or other rhythm changes, except one of the 1.5 mg patients had evidence of an incomplete right bundle branch block and another patient in

	402.3	-1.4	406.5	4.5	398.2	-7.3
	341.6	-3.9	337.1	-3.1	347.1	-3.1
	404.5	0.8	406.3	4.2	400.9	-4.6
	346.1	-3.0	340.5	-3.5	348.3	-2.2
	405.1	1.7	409.8	5.5	397.4	-5.8
	345.6	-3.7	337.1	-6.9	349.2	-2.1
	402	-1.3	404.1	-0.2	395.4	-7.7
	343.5	-6.0	338.5	-5.5	350.6	-0.7
	399.2	-4.5	405.8	1.6	397.4	-5.8

that group) had a reoccurring APC (atrial premature contraction) with a flat T-wave, which was first noted at Visit 2.

In their literature review for the ISS, the sponsor notes Bonnin et. al. (Chest 1993) who reported the case of a 29 year-old woman with WPW who safely received three 2.5 mg doses of albuterol over one hour under cardiac monitoring. Notably, one patient in DL-019 was known to have WPW (Subject No. 531) and remained in normal sinus rhythm as per ECGs in the 1.5 mg albuterol group.

In concluding this section on the ISS, Accuneb at both concentrations appears to have a relatively low incidence of adverse events. The most prominent AE is that of asthma exacerbation which would not be atypical for this study population. While there is a trend for asthma exacerbations to have a higher incidence in the active treatment groups, it is more related to the nature of the disease rather than the study medications.

VI. The Integrated Summary of Efficacy

Because there were only three clinical trials involved in this NDA and the fact only two of them should be considered for the basis of approval (DL-010 and DL-009), most of the efficacy data has been previously presented in the respective sections on Results and Efficacy for these studies.

Data for this DL-009 was analyzed both with noncompartmental analysis as well as non-linear mixed-effect modeling (NONMEM).

The NONMEM general model for the 0-6 hour post-dose area under the response time curve (AUC) was as follows:

$$AUC = AUC_{baseline} + AUC_{placebo} + AUC_{drug} + \varepsilon$$

For the FEV_1 0-6 hr area under the curve (AUC) - evaluable patients, the NONMEM analysis identified that the mean incremental increase in AUC attributable to placebo ($AUC_{placebo}$) was 1.12 L/ hr. and the mean maximum drug effect (E_{maxAUC}) was 1.30 L /hr. Thus, a significant placebo effect was noted in the study. The mean dose that produces 50% of the maximum effect (D_{50AUC}) was 0.69 mg. Dey's sponsored analysis revealed that this the D_{50AUC} is significantly influenced by body weight, height and body surface, i.e., the larger the child the smaller albuterol is required to achieve a given increase in FEV_1.

The NONMEM analysis was also performed on this data through a consultation with the Division of Pharmacokinetics.

AUC_{drug} for each treatment.

Dose	Mean (95% CI)
Placebo	0
0.75 mg	0.72 (0.48, 0.96)
1.5 mg	1.08 (0.79, 1.36)
3.0 mg	1.33(1.00,1.66)

The above data shows the difference in the AUC attributable to the Accuneb dose and that of placebo (and the baseline AUC). It can be noted that each treatment has a significant effect over placebo but there is considerable overlap between active treatment arms.

Data was also analyzed with generalized linear models by Dey's consultant.

AUC FEV_1 (L-hr) - Change from baseline (ANOVA- evaluable patients) (Dey's analysis)

	25 1.11 0.06	29 1.90* 0.05	28 2.30* 0.06	27 2.45* 0.07

*p< 0.005 vs. placebo

Each active treatment differed significantly from placebo for evaluable patients/treatments and completer patients (shown previously) for the AUC FEV_1.

Summary of % Change in Maximum FEV_1 from Pre-Dose (Dey's analysis)

	23 23.4 20.3	27 31.3 13.5 0.037	28 39.1 22.5 <0.001	27 38.9 23.1 <0.001

Pharmacometrics also performed a noncompartmental analysis (ANOVA) on the 23 subjects whom this reviewer considered completers. This analysis with a 95% confidence interval revealed that 0.75 mg, 1.5 mg, and 3 mg were significantly different from placebo when the sum of the area under the FEV_1 percent change (AUC_{FEV1}), average FEV_1, and maximal FEV_1 were analyzed.

A pairwise comparison of doses was also performed at the FDA. This analysis revealed that there was a significant difference between doses. From an AUC_{FEV1}, $FEV_{Average}$, and $FEV1_{Max}$ standpoint, 3.0 mg was significantly different from 0.75 mg, however, a significant difference could not be found between 0.75 and1.5.

Analyses were carried out to study the estimation of onset and duration of action - the Pharmacometric reviewer performed this by defining onset as the first of two consecutive points that were ≥15% over baseline. Duration of action was taken as the difference between onset and offset of action. The duration is that amount of time which the FEV_1 has been increased by 15% over pre-dose values for at least 2 contiguous measurements.

Onset and Duration of 23 Completers

[redacted]	0.083	1	0.083	4	0.083	6	0.083	4
	NA	NA	0.225	0.0537	0.1934	0.0016	0.2256	0.0097

*Significance compared with placebo – sign test.

The defined onset of action for all four treatments does not differ significantly from one another. The duration of effect for the 1.5 mg and 3.0 mg doses are greater than placebo. The comparison between 0.75 mg and placebo approaches statistical significance.

The analysis of efficacy for DL-009 reveals that at all doses studied, albuterol administered as Accuneb solution for inhalation demonstrates a measurable pharmacologic effect over placebo. The results from both the NONMEM analysis and the non-compartmental analysis are similar, suggesting that the two approaches may be considered equivalent. While the NONMEM models indicated a significant influence of body weight, height and body surface, it seems that an opposite effect (i.e. higher dose is needed for effect (at 4 weeks) for heavier children) was identified in the larger DL-019 which utilized more conventional analysis.

Dey itself acknowledged in the ISE (Vol. 1-34, p.25) that the DL-009 data was retrospectively re-examined following completion of DL-019. Scatterplots of the AUC FEV_1 versus age, weight, height, and baseline FEV_1 were examined to discern if any AUC FEV_1 versus weight relationship might be explained by weight serving as a surrogate for age or disease severity. The scatterplots showed no discernible trends.

DL-010 required that extrapolation be done on the PC_{20} dose above 128 mg/ml to produce a steeper response curve. When predictions of PC_{20} beyond 120 mg/ml are made, the D_{50} is estimated to be 0.87 mg (0.76, 1.00 mg). The model did not detect a significant effect of body weight. The sponsor indicates that efficacy was demonstrated because the mean change in PC_{20} with each active treatment differed significantly from that of placebo and the fact that the D_{50} was significantly greater than zero. In all models, the 95% confidence interval of the difference for E_{max} did not include 0, apparently supporting the fact that the drug is efficacious.

While DL-010 appears to demonstrate efficacy, it could only be demonstrated only through extrapolation of the data and NONMEM modeling and should not be thought of as a pivotal trial to be used for the basis of approval.

In DL-019, the bronchodilating effect of Accuneb was evaluated immediately following the first exposure after a 2-week placebo washout phase and following a 4-week TID stable regimen.

The primary efficacy endpoint was the %Δ AUC FEV_1 at Visit 4. Secondary analyses were done on the following subgroups: age, weight, gender, race, inhaled corticosteroid use, and asthma severity. Secondary efficacy endpoints were the %Δ AUC FEV_1 at Visit 2, the maximum FEV_1 (MAX FEV_1), and the duration of response.

Secondary efficacy parameters also consisted of peak expiratory flow readings (a.m. and p.m.), asthma symptoms (daily score), global assessment of how symptoms responded to treatment, night awakenings, frequency of rescue medication use for the treatment of asthma exacerbations, and frequency of study discontinuation due to lack of efficacy.

Summary of %Δ AUC FEV_1 for the ITT Efficacy Population

%Δ AUC FEV_1 (%·hr)[1]	1.5 mg Albuterol N = 112	0.75 mg Albuterol N =110	Placebo N = 110
Visit 2			
N	112	109	105
Mean (SD)	99.5 (75.4)	104.5 (97.6)	43.6 (82.0)
Median	91.5	88.8	35.5
Min, Max			
Treatment vs Placebo P-value[2]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean (SD)	90.3 (93.6)	73.6 (76.5)	34.2 (53.1)
Median	64.7	57.2	27.3
Min, Max			
Treatment vs Placebo P-value[2]	< 0.001	<0.001	

[1] The %Δ AUC FEV_1 was based on the area under the FEV_1 percent change from pre-dose versus time curve. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

Significant improvements in FEV_1 were seen following either 1.5 mg albuterol sulfate or 0.75 mg albuterol sulfate compared to placebo. The FDA performed an analysis comparing the efficacy between each dose and between visits. No difference was found between 1.5 mg and 0.75 mg for %Δ AUC FEV_1 at either visit. While it is noted that there appeared to be a decrease in the mean %Δ AUC FEV_1 from 99.5 %-hr to 90.3 %-hr with 1.5 mg, this difference was not significant (p=0.436). A significant difference was found between visits for 0.75 mg (p=0.0145). No significant difference was found for placebo.

A subgroup analysis was performed by the sponsor' statisticians. The %Δ AUC FEV_1 data for the ITT efficacy population were analyzed by the following age groups: 6 - 8 year olds, 9 - 10 year olds, and 11 - 12 year olds. In all age groups in the ITT efficacy population, both active treatment groups produced significant improvement in the FEV_1 at Visit 2 and Visit 4 except at Visit 4 for the 11- 12 year olds exposed to the 0.75 mg albuterol sulfate dose (p=. 082). It is worth noting that the 9 - 10 year olds receiving 0.75 mg albuterol sulfate, although not statistically significant, had mean and median values slightly higher than the 1.5 mg albuterol group at Visit 4. No significant differences in any of the age subgroups were seen between the 1.5 mg and the 0.75 mg albuterol sulfate doses.

When the evaluable population data were analyzed by age group, both active treatments produced significant improvements in all age groups at both Visit 2 and Visit 4 except for patients ages 9-10 at Visit 4. The sponsor maintains that the improvements in %Δ AUC FEV_1 for the 9 - 10 year olds did not reach statistical significance over placebo for either active treatment group because of two factors: 1) the placebo group had an increase in %Δ AUC FEV_1 at Visit 4 compared to Visit 2 (37.7 and 24.6%·hr, respectively); and 2) the improvements at Visit 4 for the active treatment groups were less than at Visit 2 (60.8 and 79.7 %·hr at Visit 4 vs. 81.7 and 91.9%·hr at Visit 2 for 1.5 mg and 0.75 mg albuterol sulfate, respectively).

An analysis by weight showed that patients in the two lower weight groups, i.e., those weighing ≤ 40 kg had significant improvements following either active treatment

group at both Visits 2 and 4. The heavier weight children (> 40 kg) showed significant improvement at Visit 2 regardless of the active treatment group, but at Visit 4, the improvement in the 0.75 mg group of heavier children was not significantly better than placebo at Visit 4.

Both doses were significantly effective when males and females were analyzed separately in the ITT population.

The non-Caucasian group in DL-019 consisted of 20% Blacks, 2% Asians, 4% Hispanics and 3% persons of other ethnic background. Both the 1.5 mg and 0.75 mg albuterol sulfate doses were significantly better than placebo for the caucasian population at Visits 2 and 4. For the non-caucasian ITT efficacy population, both active treatments were generally 35-40% less effective than in the caucasian group, but still significantly better than placebo at Visit 2. At Visit 4, the improvements with the active treatments for the non-caucasians were not significantly different from placebo. This was thought due to an increase from Visit 2 in the placebo group and because perhaps the study was not powered to discern a difference in this relatively smaller subgroup. It is important to not that no other single placebo population had this level of response to performing the pulmonary functions. Thus, it is probably not plausible to believe that either dose of Accuneb does not work after four weeks in non-Caucasians.

The effect of concomitant use of nasal or oral inhaled corticosteroids on the efficacy of albuterol sulfate was examined. The percentages of patients on inhaled corticosteroids during the study were similar across the treatment groups at ~51-58%. At Visit 2, both Accuneb treatments produced significant improvements in the %Δ AUC FEV_1 whether or not the patients were taking concomitant inhaled corticosteroids. At Visit 4, the mean %Δ AUC FEV_1 for the 0.75 mg group not on inhaled corticosteroids was not statistically different from placebo (p-value = 0.151).

The impact of a bronchodilator may depend on the severity of the asthma and the data were examined separately for patients who had $FEV_1 \leq 60\%$ of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose). There were 56 patients in the ITT efficacy population who had $FEV_1 \leq 60\%$. At Visit2, both doses were effective in both FEV_1 groups. For Visit 4 in patients with $FEV_1 \leq 60\%$, 0.75 mg albuterol was not statistically different form placebo. Indeed for this subgroup of patients, 1.5 mg albuterol was barely different from placebo with a p value of 0.049.

In looking at %Δ AUC FEV_1 in the subgroup analysis of FEV_1, despite the fact that it was the group with an $FEV_1 \leq 60\%$ predicted which did not have significant efficacy with 0.75 mg over placebo, this group nonetheless had a mean %Δ AUC FEV_1 (96.9 %-hr) greater than the subjects with $FEV_1 > 60\%$ (68.2 %-hr). Subjects with an $FEV_1 \leq 60\%$ predicted also appeared to have a greater MAX FEV_1 and duration of response. Thus, it should probably not be said that Accuneb works better in those with an $FEV_1 > 60\%$ as compared to those with an $FEV_1 \leq 60\%$ predicted.

The MAX FEV_1 percent change from pre-dose at Visit 2 and Visit 4 was analyzed for the ITT efficacy population.

MAX FEV_1 for the ITT Efficacy Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol N =112	0.75 mg Albuterol N = 110	Placebo N = 110
Visit 2			
N	112	109	105
Mean % (SD)	29.3 (17.1)	32.0 (21.4)	15.5 (15.9)
Median	24.8	26.5	11.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean % (SD)	28.6 (22.6)	26.3 (17.4)	13.4 (12.5)
Median	19.8	21.1	10.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	

[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 percent change from pre-dose.

In the ITT efficacy population, the MAX FEV_1 (%) significantly increased following 1.5 mg and 0.75 mg albuterol sulfate compared to placebo at both Visit 2 and Visit 4. No significant differences were identified for this variable between 1.5 mg and 0.75 mg.

Comparing the efficacy of Accuneb between Visits 2 and 4, the variable MAX FEV1 was also examined in the ITT Efficacy population. No significant difference was found between visits for 1.5 mg (p= 0.775). A significant difference was identified for 0.75 mg with a p value of 0.0425.

Subgroup analysis was also performed for MAX FEV_1. All age groups, weight divisions and genders showed significant increases with either albuterol dose at both visits. Non-caucasians, unlike caucasians, showed no significant increase in MAX FEV_1 (%) at Visit 4 with 0.75 mg only. Whether or not a patient was on inhaled corticosteroid or had an FEV_1 >60%predicted, the MAX FEV_1 (%) was significantly improved compared with placebo for both doses.

The duration of response was defined as the first time at which a ≥ 15% increase in FEV_1 over pre-dose was observed to the first time the percent change in FEV_1 from pre-dose returned to below the 15% increase. The mean duration of response for Visit 2 was 160.4 and 147.3 for 1.5 mg. and 0.75 mg. respectively while it was 116.8 and 115.9 minutes for Visit 4 in the ITT population. Each dose had a significantly longer effect than placebo at both visits. No significant difference was found between doses at either visit.

Statistical analysis of the ITT Efficacy population was performed to assess a difference in the duration of effect between Visits 2 and 4 for each of the doses and placebo. The p value for 1.5 mg albuterol was 0.0133 with a significant decrease found in the duration of response found at Visit 4 (mean 116.8 minutes) compared with Visit 2 (mean = 160.4 minutes.) The p value for 0.75 mg albuterol was 0.072 so the decrease between Visit 2 (147.3 minutes) and Visit 4 (115.9 minutes) was not statistically significant. While the mean for placebo appeared to decrease between Visit 2 (60.7) and Visit 4 (39.2), the p value was not significant. At least for the 1.5 mg dose of albuterol, there is a decrease in the duration of effect after 4 weeks of t.i.d. use.

Each subgroup had a duration of response significantly greater than placebo for each dose and each visit with the exception of:

- 1.5 mg albuterol group ages 9-10, Visit 4 (evaluable, not ITT).
- 0.75 mg albuterol group, non-caucasians, Visit 4 (evaluable and ITT).
- Patients without concomitant corticosteroid use, 0.75 mg group at Visit 4 (evaluable and ITT).

The 0.75 mg albuterol solution produced equivalent results to the 1.5 mg solution following the first exposure at Visit 2 except for a shorter duration of response in the 11-12 year olds and the > 40 kg children. Reviewer's Note – These differences were apparent, but not statistically significant according to the analyses submitted. After a 4 week regimen of stable TID treatment, the 1.5 mg solution produced longer duration of responses, than the 0.75 mg solution, but especially in the 11-12 year olds, the heavier children, children not using concomitant steroids, and the more sever asthmatic with an $FEV_1 \leq 60\%$ predicted. Reviewer's Note – Again, these differences were apparent, but not statistically significant according to the analyses submitted

The duration of response, in general, was greater in the Caucasian group as compared to the non-Caucasian group.

Graphs showing the % change from pre-dose FEV_1 were presented for each visit in the Results section for DL-019 and shall not be reproduced here. The figure for Visit 4 appears to illustrate than 0.75 mg dose , while better than placebo, was less than the 1.5 mg albuterol response. The response was more comparable at Visit 2. It must be noted, however, that the difference in FEV_1 between each albuterol treatment and placebo dissipates together sometime between 120 and 180 minutes at Visit 2 and somewhere between 60 and 120 minutes at Visit 4. (See "FEV_1 Over Time" table in Results Section.)

Important increases were noted in the FEF after both albuterol doses as compared to placebo. Only descriptive statistics were presented in the NDA and a comparative analysis was not performed. At both Visit 2 and Visit 4, the difference between 0.75 mg and placebo appeared to dissipate between post- 2 and 3 hours while for 1.5 mg it occurred between post- 3 and 4 hours.

While the sponsor maintains that significant increases were seen in the FVC with Accuneb treatment, again only descriptive statistics were presented and a comparative statistical analyses was not performed. When the mean changes in FVC were reviewed, this reviewer does not believe that important increases in FVC were demonstrated with the use of Accuneb.

The mean peak flow for each week was examined. There were no detectable differences in the means across treatment groups (1.5 mg, 0.75 mg and placebo) for both morning and evening peak flow values.

Only descriptive statistics were presented for the Daily Asthma Symptom Scores. No comparative analysis between treatments was performed but it did not appear that there was an appreciable difference between groups. There was a trend for the scores to decrease somewhat in the albuterol groups. The occurrence of asthma symptoms showed a gradual decrease from 1.3 symptoms per day in Weeks 1 and 2 during the placebo phase to 0.9, 1.0 and 1.1 symptoms per day for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo groups, respectively, following the 4-week active treatment phase of the study (Week 6). Before Week 6, the placebo score was 1.2.

Nocturnal awakenings occurred at the rate of 0.1 to 0.2 per night during the placebo phase. There were no significant differences in the rate of nocturnal awakenings during the treatment phase of the study, regardless of the treatment group.

The use of rescue medication was examined in DL-019. Changes in the use of the DEY rescue MDI were seen over the course of the placebo phase and the treatment phase of the study. All three groups, including the placebo group, decreased their mean use of rescue albuterol during the first two weeks of the active treatment phase. There was a difference in MDI use at Week 4 between the 1.5 mg group (1.5) and the 0.75 mg group (2.0) but by the third week of active treatment, the mean use of rescue medication continued to decrease in the 1.5 mg and 0.75 mg albuterol sulfate groups, while remaining the same for the placebo group. By the fourth week of active treatment (Week 6 of the study) the 1.5 mg and 0.75 mg albuterol sulfate groups were each using a mean of 1.4 puffs/day compared to a mean of 2.1 puffs/day for the placebo group. Overall, a dose response can be seen in the use of MDI rescue medication by the number of total puffs and the number of puffs/day with the fewest puffs used by the 1.5 mg albuterol group and the most puffs used by the placebo group.

Reviewer's Note - This data on MDI rescue medication use do not include the use of such medication by patients who ultimately discontinued the study due to asthma exacerbations.

Patients also had the option to use 2.5 mg nebulized albuterol as a rescue medication. The means for use generally varied from 0.1 to 0.2 vials/day. The 0.75 mg group had a mildly higher use of this form of rescue than the other two groups, but the difference should not be considered clinically significant.

During the global assessment performed at the end of four weeks of treatment, the % of patients in the active treatment groups reporting substantial improvement were nearly double the % in the placebo group. If the substantial and moderate improvement categories are combined, the patients in the active treatment groups had $\geq$ 50% of the patients in the combined category compared to 36% in the placebo group. No change or worsening change were reported by 15.2%, 22.8%, and 35.1% for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate and placebo, respectively.

In conclusion on the Integrated Summary of Efficacy, Studies DL-009 and DL-019 support the efficacy of Accuneb 0.021% and 0.042% in asthmatic children ages 6-12. Study DL--009 demonstrated that single treatment of either 3.0, 1.5 or 0.75 mg of albuterol sulfate significantly increases the AUC FEV_1 (L-hr) and % Change in maximum FEV_1 compared with placebo. The duration of effect for the 1.5 mg and 3.0 mg doses were significantly greater than placebo while the comparison between 0.75 mg and placebo approaches statistical significance. No significant influence of weight, height or body surface could be definitively identified.

In the parallel 4-week Study DL-019, both 1.5 mg and 0.75 mg showed significant increases in the primary efficacy endpoint of %Δ AUC FEV_1 at Visit 4. Exceptions to this efficacy were identified in subgroup analysis: 1) 11-12 year olds in the 0.75 mg group, 2) children of > 40 kg, 3) non-Caucasians in the 0.75 mg and 1.5 mg group, 4) subjects not on concomitant inhaled corticosteroids in the 0.75 mg group, and 5) patients with $FEV_1 \leq 60$ % predicted in the 0.75 mg group. Based on these exceptions, the 1.5 mg dose, rather than the 0.75 mg dose, may be a more appropriate dose for 11-12 year olds, patients > 40 kg, and probably those moderate asthmatics not being managed on inhaled corticosteroids. Basing dosing decisions on post-hoc analysis in studies not designed originally to discern differences between subgroups can be problematic.

As far as subjects with an $FEV_1 \leq 60$ % predicted, it has already been pointed out they may, in fact, have a better response to Accuneb than those with an $FEV_1 > 60\%$. It is believed that the lack of efficacy shown in non-Caucasians is based on the unusually large placebo effect seen at Visit 4 in this group.

The mean duration of response was just under 2 hours for both albuterol doses after 4 weeks of TID treatment.

In general, after a 4 week regimen of stable TID treatment, the 1.5 mg solution tended to produce larger improvements in pulmonary function with longer duration of responses, than the 0.75 mg solution in all subgroups, but especially in the 11-12 year olds, the heavier children, children not using concomitant steroids, and the more severe asthmatic with an $FEV_1 \leq 60\%$ predicted. Caucasians responded better overall to both 1.5 mg and 0.75 mg albuterol sulfate than the non-Caucasians. Patients using inhaled corticosteroids appeared to have greater responses than patients not using them.

In general, Accuneb tended to be more effective after initial exposure than it was after four weeks of therapy, especially with the 0.75 mg dose.

VII. Division of Scientific Investigations Activity

Three centers in DL-019 were audited by DSI. They were Anjuli Seth Nayak, M.D. of Normal, Illinois, Steven F. Weinstein, M.D. of Huntington Beach, California, and Michael Noonan, M.D. of Portland, Oregon. The DSI auditors, in addition to their own reviews, were asked to compare the FEV_1 and FVC data at each time point for each patient at each site.

a) Anjuli Seth Nayak, M.D. – The FEV_1 and FVC data from the NDA were compared with the source records for all 20 study subjects. No discrepancies were noted. The conclusion was made that the site adhered to pertinent federal regulations and/or good clinical practices. Data from this site appeared acceptable for use in support of drug claims.

b) Steven F. Weinstein, M.D – 19 subjects were enrolled in the study and the records for these 19 subjects was reviewed. No discrepancies in the PFTs were noted between the sponsor supplied Data Listing Tables and the original records.

DSI did find deviations from federal regulations and/or good clinical investigational practices. The deviations included a failure to adhere to the protocol with the timing the ECGs for subjects #821 and 824, and 829. The 4-hour PFT on Visit 2 for Subject #828 was not done. Explanations were provided to DSI during the exit interview. Overall, the site was classified as VAI - no response required. Data from this study appeared acceptable for use in support of drug claim.

c) Michael Noonan, M.D. – Deviations were found from federal regulations and/or good clinical investigational practices. Inspectors found that: 1) the calibration of the Koko spirometer was not performed according to the instruction manual, 2) the instruction video did not match the instruction manual, 3) there was no place on the diary to record concurrent medications and adverse

events (All this information was received from the patient verbally by the study coordinator and recorded on the CRF.)

Discrepancies were noted for the drug accountability among the clinic comments (original data), monitoring reports and sponsor report (data report to FDA) for 13 subjects. Discrepancies were noted for "the number of days between visits" among CRFs (original data) and monitor report and data summary (submitted to FDA) for 10 subjects. Discrepancies were noted for the tests performed within $\pm$ 5 minutes among the FDA inspector, the clinical data, monitor or sponsor for 20 subjects.

The final classification was VAI – no response required. The CIB reviewer's note was that data generated from the site was far from perfect, however, the data appeared acceptable for use in support of drug approval.

Overall, it appeared that the DSI audit no serious discrepancies that would call into question the validity and accuracy of data in support of drug approval.

VIII. Discussion of Relevant Regulatory Issues

1. Use in Adults

The sponsor makes no clarification or justification for the use of Accuneb in adults. There is no mention of specific adult use in the package insert labeling or in the package design. This may be potentially dangerous for the public as the Accuneb nebules may be perceived as equivalent to albuterol sulfate preparations of a higher concentration. The package insert and label must make it clear that this is a pediatric preparation.

2. Support for Safety in Children $\geq$ 2 years of Age

Dey is requesting that Accuneb 0.042% and 0.021% be approved for children > 2 years of age based on published literature and the recent FDA approval for Ventolin®Nebules for children $\geq$ 2 years of age and weighing more than 15 kg. Ventolin Inhalation Solution 0.5% is also indicated for the relief of bronchospasm in patients 2 years of age and older. Dey has only conducted studies in subjects down to 6 years of age. Dey performed a literature review in order to justify the safety of dosing their product in patients $\geq$ 2 years of age.

Dey notes that Glaxo Wellcome was given FDA approval to reduce the age indication for their Ventolin Nebules® (2.5 mg) at 0.083%) to 2 years of age if the child weighed more than 15 kg. They say the drop in the age was based on the published literature. Dey's review of the literature was not as extensive as Ventolin's because "if the 2.5 mg albuterol dose is safe for children, then the 1.5 mg and 0.75 mg albuterol sulfate doses would be, as well."

Reviewer's Note – The recommended dose for the Nebules is 2.5 mg three to four times daily as needed. In the Ventolin Nebules label, it is stated that children less than 15 kg should use the Ventolin Inhalation Solution instead.

For Ventolin Inhalation Solution, initial dosing should be based on body weight (0.1 to 0.15 mg/kg per dose) with subsequent dosing titrated to achieve the desired clinical response. For weight of 10-15 kg (22-33 lb), the dose is 1.25 mg. For > 15 kg, the dose is 2.5 mg.

Pearce and Wesley reported on 100 children, 1-15 years of age, experiencing acute asthma episodes and reporting to the ER. Children under 5 were given 2.5 mg albuterol and children older than 5 were given 5 mg albuterol. The study demonstrated that such doses could reduce hospitalizations. The ISS reports that no adverse events were reported, but the implication was that albuterol at those doses was safe for the children.

Reviewer's Note – This was a limited report. Symptoms of tremor, vomiting and irritability were seen in three children, aged 2 and under, who received 2.5 mg salbutamol. It is not clear what other treatment these patients received. It is not accurate, therefore, to report that no adverse events occurred. It is also not clear how many treatments of salbutamol children under age 6 received.

Rayner, et. al. reported on 28 children, 2-15 years of age, who were admitted to the hospital for acute asthma. The children received nebulized albuterol at 2.5 mg for those < 6 years and 5.0 mg for those > 6years of age on admission and then every four hours, with or without ipratropium every 8 hours. No AE's were reported and the implication again was that albuterol at those doses was safe for children.

Reviewer's Note – This again was a very limited report. While the mean age was 6.5, it is hard to say how many were actually under 6 years of age. AEs were not specifically mentioned.

Bentur, et. al (Pediatrics, 1992). studied the response to nebulized albuterol in 28 children, ages 3 months to 2 years (weights 6.9-14.5 kg), experiencing acute asthma exacerbation. The children received two doses of 0.15 mg/kg albuterol per dose of a 0.5% solution suspended in 3 cc saline or placebo one hour apart. The mean weight of the children was 10.1 kg, which means an average of 1.5 mg of albuterol base was administered twice, 1 hour apart, for a total of 3.0 mg albuterol base. The amount of albuterol base given in two doses ranged from 2.1 mg to 4.4 mg. The nebulized albuterol was found to be effective in treating asthma while producing no adverse events. The mean clinical score, a sum between 0-3 for each of heart rate, respiratory rate, the degree of accessory muscle use and wheezing, decreased by 2.9 in the albuterol group versus a decrease of 0.4 in the placebo group (p=0.02). The change in heart rate from baseline did not differ significantly between the albuterol (-3± 19) and placebo groups (+4±23). The highest individual heart rate during the study was 180 beats per minute. The administration of 0.15 mg/kg of albuterol twice within an hour was considered safe for the infant experiencing an acute asthma exacerbation.

Reviewer's Note – This was a more definitive report but was in a small study population and their were differences in the randomized groups. Only 13 children received albuterol. As a whole the albuterol group had a more severe attack pre-dose. Notably, the pre-dose heart rate was significantly increased in the albuterol group so it might be expected that it would have decreased

more than placebo. The authors report that the study does not necessarily establish the safety or efficacy of nebulized albuterol as maintenance treatment in very young subjects.

Schuh et. al (Pediatrics, 1992), conducted a randomized, double blind placebo-controlled trial in 69 infants, 6 weeks to 2 years of age (mean age ~ 9 months), who exhibited the first episode of bronchiolitis. Patients received either nebulized albuterol (0.15 mg/kg/dose) or nebulized albuterol with ipratropium bromide (0.15 mg/kg/dose and 250 mcg ipratropium per dose). The drugs were given twice, 1 hour apart. Both groups improved but no benefit was found with the addition of ipratropium. No side effects were reported in either study group. The total amount of albuterol cannot be calculated because the weights of the infants were not provided in the article. At two doses of 0.15 mg/kg, it can be assumed that most infants received a total albuterol dose greater than 1.25 mg.

Reviewer's Note – Oddly, the weights are not given in the article. But after both doses of albuterol were given, it is probably safe to assume that over 1.25mg was generally administered.

In Dey's literature review, the sponsor maintains that the literature does not address the effect of acute or chronic albuterol treatment on ECG parameters such as ventricular rate and QTc interval in the pediatric population. Katz et. al. (Pediatrics 1993), in a study whose objective was to study the cardiotoxicity of continuous nebulized albuterol in infants and children, examined 19 patients (mean age 20.7 months ± 38 months) who received treatment for at least 24 hours. The mean dose was approximately 3.4 mg/kg/hour at 24 hours. CPK was within normal limits for 16 patients. Three had elevated CPK (260 with MB <1, 360 with MB 37, 272 with MB 27) and in two, the MB fraction was elevated. In each patient, the elevated CPK-MB fractions returned to normal at the time of the next sampling despite continued albuterol therapy. The significance of these elevations to the authors was unknown. None of the ECGs showed ischemia (one done at 24 hours of therapy) nor were "significant" arrthymias seen on continuous cardiac monitoring. Five patients had non-specific ST-T wave changes; two of these had elevated CK-MB fractions. Two other patients had intraventricular conduction delay. These findings were felt to be nondiagnostic by the authors and were difficult to interpret in the stressed patient with significant respiratory distress. Maguire et. al. (Pediatrics 1991) noted marked elevations of CPK and MB in those patients who received intravenous isoproterenol compared with those who received usual therapy for severe asthma.

Stimulation of the β_2 receptor can produce muscle and hepatic glycogenolysis and gluconeogenesis. Dawson, Penna and Manglick (Acta Paediatr 1995) studied the effect of albuterol on 12 patients (2-9 years, mean 61 months). Salbutamol was administered by nebulization at 0.15 mg/kg every 15 minutes for 1.5 hours (total 0.9 mg/kg). Serum glucose rose from 6.5 mmol/L to 10.5 mmol/L at 2 hours post-dose.

Singhi et. al. (J. Paediatr 1996) looked at 46 children, 10 months to 12 years, who received three doses of 0.15 mg/kg – 0.3 mg/kg over 1.5 hours. The mean serum potassium level decreased from 3.9 mEq/L to 3.7 mEq/L ($p < 0.05$). Hypokalemia < 3.5 mEq/L was noted in 35% of the patients. The hypokalemia was more frequent in patients who had been receiving oral salbutamol prior to the asthma attack.

Dey concludes that these studies indicate that the practicing research physician treating asthmatics routinely uses 0.15 mg/kg for their young patients for an acute episode. The 1.5 mg albuterol sulfate dose would be a 0.15 mg/kg dose for a 10 kg (22 lb) child.

Reviewer's Note – Notably, the NAEPP Expert Panel Report 2 (2/97) recognizes the use of short-acting B_2 agonists as needed for symptoms up to 3 times a day in infants and young children as a Quick Relief medication.

Doses listed in Figure 3-10 of NAEPP Expert Panel Report 2 for children (age not specified) is 0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.

IX. Action Letter

An ITT (Intention to Treat) population should refer to patients who were randomized and received a dose of medication. In the DL-009 Final Report, Dey appears to equate evaluable population with ITT population. In tables submitted in a 29 September 1998 correspondence to the FDA, however, "evaluable" is then equated with "completers." The number of "All Patients" is 30 while the ITT population is listed as 27 for 3.0 mg and 0.75 mg, 28 for 1.5 mg, and 23 for placebo. Please account for the difference between the group listed as "all patients" and the ITT population.

In a correspondence to the FDA dated 29 September 1998 referring to DL-009, Dey maintained "when the ITT population (referred to as "evaluable") was defined in accordance with the investigator's final report, the population data did not match the report." Further detail is needed. Dey says that the data diskette and the data used by — for the integrated analysis were compared and were identical. Therefore, the available population definitions from DL-019 were used for analysis. Dey sent data with two less patients in 0.75 mg and placebo groups. Dey said the %ΔAUC FEV_1 variable in the correspondence dated Sept 29, 1998 was consistent with the DL-019 analysis. Please give further detail on why these two subjects were eliminated and what is meant by "the data diskette and the data used by — for the integrated analysis were compared and were identical."

On p. 99, Vol. 1-12, there is a discrepancy between this change in heart rate data from DL-009 and the data in Table 8.3.1 in Appendix B of Vol. 1-38. The fact that the former includes 28 patients and the latter 29 patients cannot account for all the discrepancies. It appears that the Vol. 1-12 involves errors in subtraction between mean at Time X and baseline mean heart rate. Please clarify.

Referring to DL-019, Table 35, Vol. 1-16, it would be helpful if the subject in the 1.5 mg group with the new instance of a depressed ST segment seen at Visit 2 - 30 minutes post dose- could be identified for further review of the details. This depressed ST segment was not mentioned pre-dose and was still present at 60 and 90 minutes post-dose. Is this Subject No. 157? Please provide details on the depressed ST segment seen post-dose Visit 2.

It is mentioned in the Integrated Clinical and Statistical Report narrative that Patient No. 157 had results interpreted by the centralized cardiologist as clinically relevant that were considered irrelevant by the investigator. What findings on Patient No. 157 EKGs were considered relevant?

In Data Listing 14, Vol.1-26 (data on DL-019 EKGs), there is a classification called "deteriorated (from baseline)." Please clarify what is meant by this term.

Please include in package insert labeling graphs from Study DL-019 of the % change in FEV_1 from pre-dose vs. time at Visits 2 and 4 for both doses of Accuneb and placebo. Please include a horizontal line depicting the 15% level on the graph on the graph so one can see where the curve crosses the line.

A clarification in the packaging and labeling regarding the use of this product in adults must be made. It should be made clear that Accuneb 0.021% and 0.042% are indicated for use in subjects 2-12 years of age. Please make note of this in the package insert labeling and package and box label.

In the submitted NDA package label, the reference [ ] actually refers to Rescue Medication Use. Therefore, it appears to be the wrong reference. Furthermore, while it is true that "Accuvent may last up to 6 hours," it is a misleading statement as part of the Information for Patients section. Your ITT Efficacy analysis reveals that 23.2% may have a response to 1.5 mg on first use (Visit 2) lasting between 5 and 6 hours. Because the aim of your original statement is that patients avoid more frequent dosing, it is better stated that " [ ] the action of Accuneb may last for up to 6 hours [ ], it should not be used more frequently than recommended [ ]

Accuneb is indicated for use in subjects 2-12 years of age. Efficacy data referring to [ ] should not be part of the insert labeling, i.e., in the Clinical Pharmacology section it is stated: [ ]

]

In referring to the Integrated Clinical and Statistical Report for DL-019, Table M "Summary of Adverse Events that occurred in > 2% of the ITT Population" and Table N "Summary of Potentially Drug-Related Adverse Events," it is not clear what is meant by a worsening of asthma symptoms versus an asthma exacerbation. An explanation should be provided by the sponsor as to how exactly this distinction was made. More exacting terms should be identified for these groupings.

Additional comments will be generated at a later date when a full labeling review is done.

/S/

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/S/ mo 3/16/99

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