CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

S T A T I S T I C A L MEMORANDUM
Additional Statistical Analyses of Human Factor Study

NDA Number:	205920
Submission date:	06/28/2016
Drug Name:	(b) (4) 125 mcg/inhalation
Biometrics Division:	Division of Biometrics VII, Office of Biostatistics
Statistical Reviewer:	Rima Izem, Ph.D. (Team Leader)
Secondary Reviewer:	Mark Levenson, Ph.D. (Division Director)

Background for this memorandum: this memorandum summarizes for the record some analyses the statistical reviewer conducted for the human factor study in NDA 205920 submitted in 06/28/2016. In December 2nd 2016, reviewers from Division of Medication Error Prevention and Analysis (DMEPA) at FDA re-adjudicated the outcomes in the human factor study. The primary statistical review archived in DARRTS on December 7th 2016 used the sponsor adjudication rather than the re-adjudicated outcomes and did not include the additional analyses in this memorandum. We refer to the summary of human factor study and analyses with sponsor adjudication in primary statistical review. We refer to the completed safety review by Grace Jones in DMEPA for summary of study design and motivation for the re-adjudication.

Statistical analyses:

Table 1 presents the success rate and 95% confidence interval for the first three tasks of the human factor study based on the re-adjudicated data by DMEPA shown in Appendix A.

Results on sponsor's adjudication, previously reported in the statistical review, are presented in Appendix A for comparison purposes. More granular count results for the re-adjudicated data broken down by each task are shown in Appendix B and Appendix C.

Table 1: Success Rates for Each Task and for All Tasks in Human Factor Study

Tasks	DMEPA Re-Adjudicated Success Rates	95% Confidence Interval[1]
Task 1: First Use	**131/151 (87%)**	**(80%, 92%)**
Task 2: Cleaning	**133/151 (88%)**	**(82%, 93%)**
Task 3: Routine use	**132/151 (87%)**	**(81%, 92%)**
All three tasks[2]	**106/151 (70%)**	**(62%, 77%)**

1. Confidence interval use Clopper-Pearson exact method
2. This is a composite endpoint for success on all three tasks. That is, a subject is deemed successful if he completed each of three tasks correctly based on the re-adjudication.

Appendix A: Sponsor Adjudication Results

This Table is a subset of results reported in Table 22 of Yueqin Zhao's statistical review (archived in DARRTS on 12/7/2016). This table shows the results for the Applicant's definition of success and a stricter definition of success. The applicant counted as successes those who had completed the task (C) or those who completed with issues (CI). The stricter definition only count those who completed the task (C) as successes.

CBT/ALHFQ	Risk-Based Evaluation Dataset (N=151)				
	C	CI	NC	Applicant's definition (success as C or CI) (95% CI)	Stricter definition (success as C only) (95% CI)
Critical Behavioral Tasks					
Task 1: First Use*	105	**38**	**8**	95% (90%, 98%)	70% (62%, 77%)
Task 2: Cleaning	91	56	4	97% (93%, 99%)	60% (52%, 68%)
Task 3: Routine Use	128	21	2	99% (95%, 100%)	85% (78%, 90%)

Appendix B: DMEPA re-adjudication

Sponsor and DMEPA re-adjudicated dataset. Here is a documentation of each variable in this dataset

- Pid is the patient id as coded by the sponsor
- Task 1 to task 3 are the sponsor adjudicated results for each task with C for completed, CI for completed with issues and NC for not completed.
- Task1.DMEPA to Task3.DEMPA are the DMEPA re-adjudicated results for each task with C for completed and F for failed to complete.

	pid (b) (6)	task1	task2	task3	Task1.DMEPA	Task2.DMEPA	Task3.DMEPA
1		C	CI	C	C	A	C
		CI	C	C	A	C	C
		CI	CI	C	F	F	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		CI	C	C	A	C	C
		C	C	C	C	C	C
10		NC	C	C	F	C	C
11		C	C	C	C	C	C
12		C	C	C	C	C	C
13		CI	C	C	A	C	C
14		C	C	C	C	C	C
15		C	CI	C	C	A	C
16		NC	C	C	F	C	C
17		CI	CI	CI	A	A	F
18		C	C	C	C	C	C
19		C	C	C	C	C	C
20		C	C	C	C	C	C
21		C	C	C	C	C	C
22		NC	CI	C	F	A	C
23		C	C	C	C	C	C
24		C	C	C	C	C	C
25		C	CI	C	C	A	C
26		C	C	C	C	C	C
27		C	C	C	C	C	C
28		C	CI	C	C	A	C
29		CI	C	C	A	C	C
30		C	CI	C	C	A	C
31		C	C	C	C	C	C
32		CI	CI	C	A	A	C
33		C	CI	CI	C	A	F

	(b) (6)						
34		C	C	C	C	C	C
35		NC	CI	C	F	F	C
36		C	CI	C	C	F	C
37		NC	C	C	F	C	C
38		CI	CI	C	A	F	C
39		CI	C	C	A	C	C
40		C	C	C	C	C	C
41		C	C	C	C	C	C
42		C	C	C	C	C	C
43		CI	CI	C	F	A	C
44		C	CI	C	C	A	C
45		C	C	C	C	C	C
46		C	C	C	C	C	C
47		C	C	C	C	C	C
48		C	C	C	C	C	C
49		C	C	C	C	C	C
50		CI	C	C	A	C	C
51		C	CI	CI	C	A	A
52		C	CI	C	C	A	C
53		C	CI	C	C	F	C
54		CI	CI	C	A	F	C
55		C	C	C	C	C	C
56		CI	C	CI	A	C	F
57		CI	C	CI	F	C	F
58		C	CI	C	C	A	C
59		C	C	C	C	C	C
60		CI	C	C	A	C	C
61		C	C	C	C	C	C
62		C	C	C	C	C	C
63		C	C	C	C	C	C
64		CI	CI	C	A	A	C
65		C	CI	C	C	A	C
66		C	C	C	C	C	C
67		CI	C	CI	F	C	F
68		C	C	C	C	C	C
69		C	CI	C	C	A	C
70		CI	CI	C	A	F	C
71		C	CI	C	C	A	C
72		C	CI	CI	C	F	A
73		CI	C	C	A	C	C
74		C	C	C	C	C	C
75		CI	NC	C	F	F	C
76		C	C	C	C	C	C

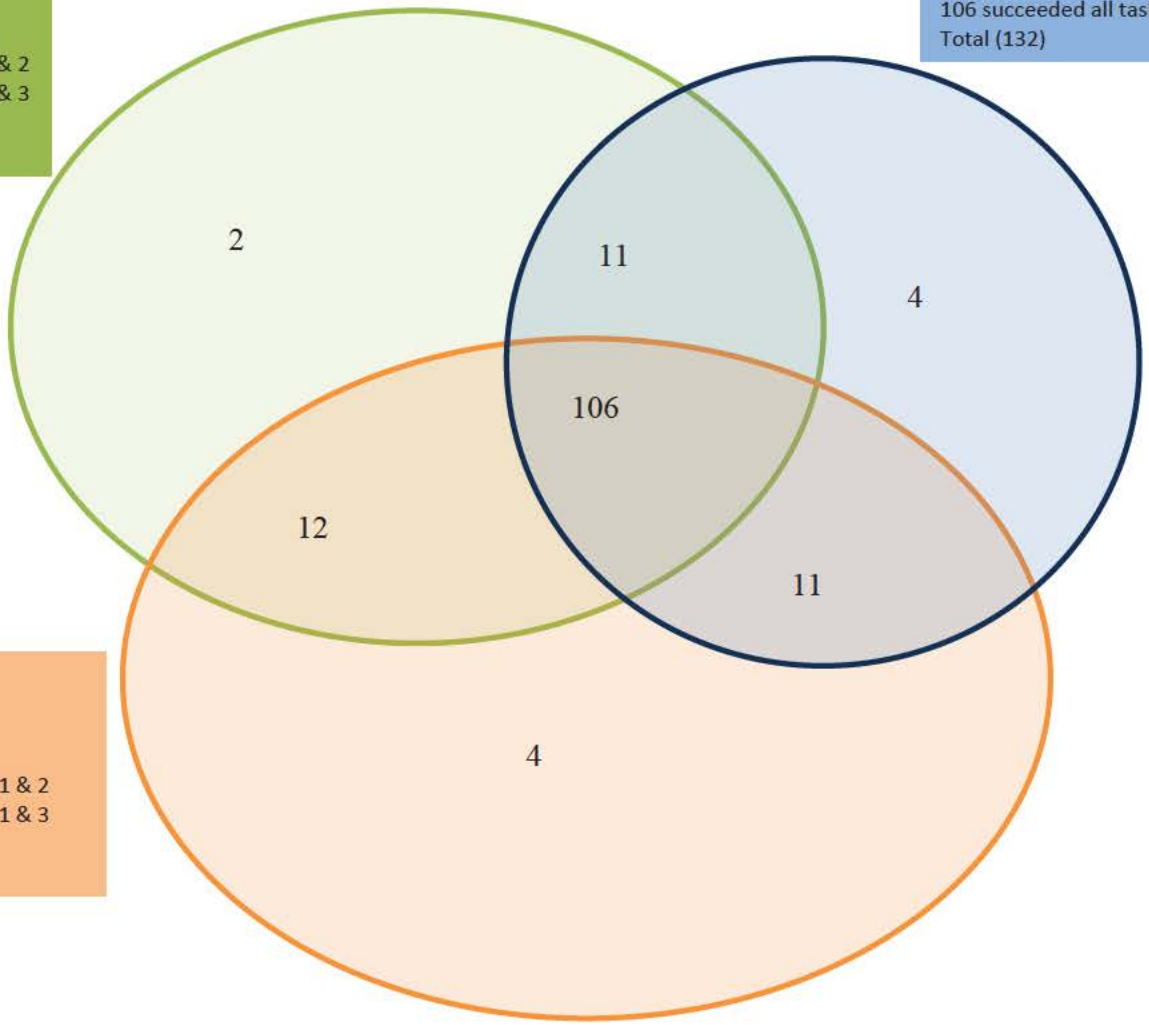
	(b) (6)						
77		CI	CI	C	A	A	C
78		C	C	C	C	C	C
79		C	C	CI	C	C	A
80		CI	C	C	A	C	C
81		CI	C	C	A	C	C
82		CI	C	CI	F	C	A
83		CI	C	C	F	C	C
84		C	CI	C	C	A	C
85		C	CI	C	C	F	C
86		C	C	C	C	C	C
87		C	CI	CI	C	A	F
88		CI	C	C	A	C	C
89		C	CI	C	C	A	C
90		C	CI	C	C	A	C
91		C	CI	C	C	A	C
92		C	C	C	C	C	C
93		C	C	C	C	C	C
94		CI	CI	C	A	A	C
95		C	C	C	C	C	C
96		C	CI	C	C	A	C
97		C	C	CI	C	C	F
98		CI	C	C	F	C	C
99		C	C	C	C	C	C
100		C	CI	C	C	A	C
101		C	CI	C	C	A	C
102		C	CI	C	C	A	C
103		C	CI	C	C	A	C
104		C	C	CI	C	C	F
105		CI	CI	C	F	A	C
106		NC	C	CI	F	C	F
107		NC	CI	NC	F	A	F
108		CI	C	CI	A	C	F
109		C	C	C	C	C	C
110		C	C	C	C	C	C
111		C	CI	C	C	A	C
112		CI	CI	C	A	F	C
113		C	C	C	C	C	C
114		CI	C	C	F	C	C
115		C	CI	C	C	A	C
116		C	C	C	C	C	C
117		C	CI	C	C	F	C
118		C	CI	C	C	A	C
119		C	C	CI	C	C	F

	(b) (6)						
120		C	C	C	C	C	C
121		C	C	C	C	C	C
122		C	C	C	C	C	C
123		C	C	C	C	C	C
124		C	C	CI	C	C	F
125		C	C	C	C	C	C
126		C	CI	C	C	A	C
127		C	CI	C	C	F	C
128		C	C	C	C	C	C
129		CI	C	CI	A	C	F
130		C	C	CI	C	C	F
131		CI	NC	CI	F	F	F
132		C	C	C	C	C	C
133		C	C	C	C	C	C
134		C	CI	CI	C	F	F
135		CI	C	C	A	C	C
136		C	C	C	C	C	C
137		C	C	CI	C	C	F
138		C	C	C	C	C	C
139		C	CI	C	C	A	C
140		C	CI	C	C	A	C
141		CI	CI	C	A	A	C
142		C	C	C	C	C	C
143		C	C	C	C	C	C
144		C	C	C	C	C	C
145		C	CI	C	C	F	C
146		C	CI	C	C	A	C
147		NC	CI	C	F	A	C
148		C	C	C	C	C	C
149		C	NC	NC	C	F	F
150		CI	NC	C	F	F	C
151		CI	CI	C	A	A	C

Appendix C: Venn Diagram for Successes (DMEPA Re-adjudication)

Task 1
First Use
2 succeed only task 1
12 succeeded only tasks 1 & 2
11 succeeded only tasks 1 & 3
106 succeeded all tasks
Total (131)

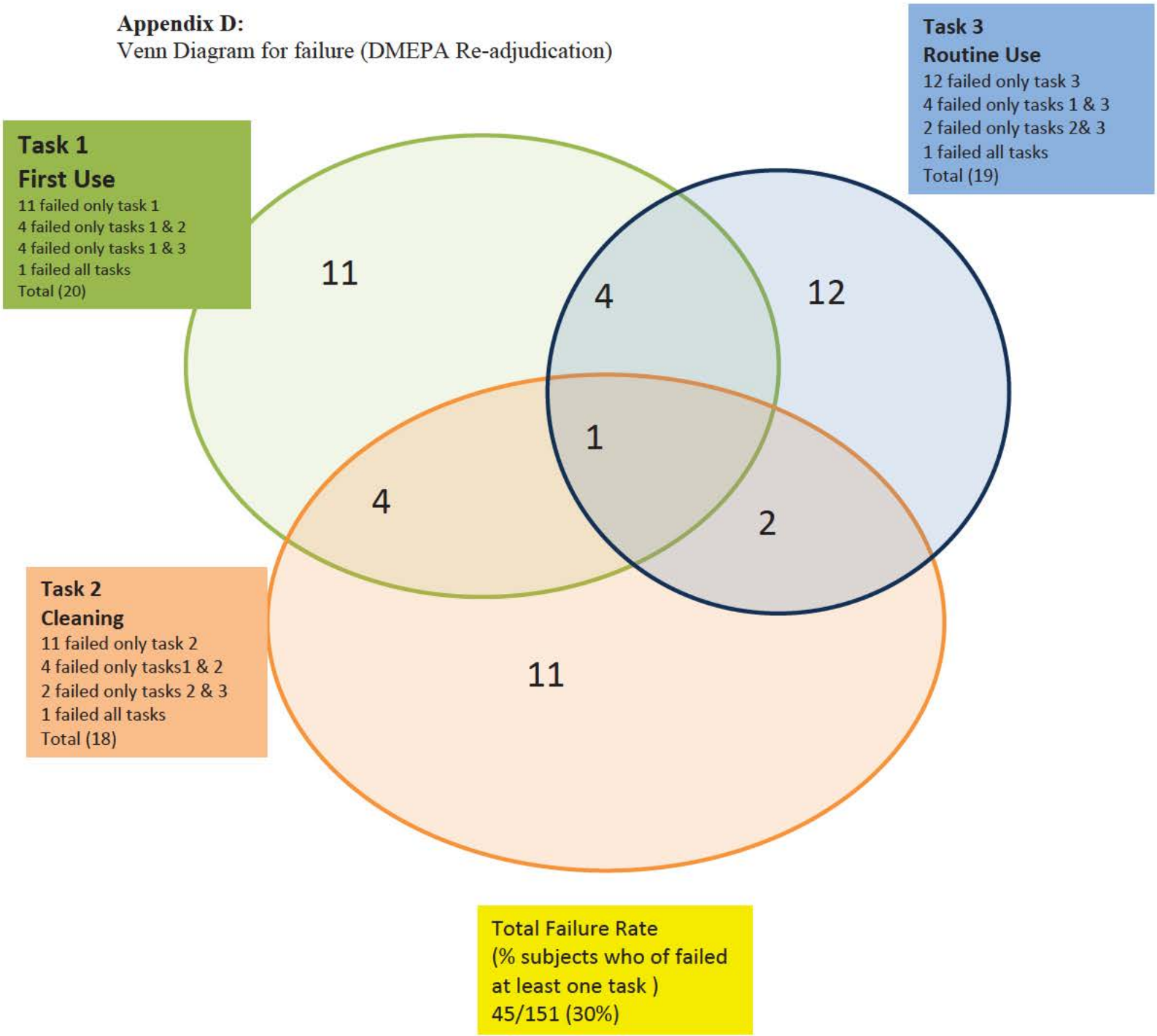
Task 3
Routine Use
4 succeed only task 3
11 succeeded only tasks 1 & 3
11 succeeded only tasks 2 & 3
106 succeeded all tasks
Total (132)



Task 2
Cleaning
4 succeed only task 2
12 succeeded only tasks 1 & 2
11 succeeded only tasks 1 & 3
106 succeeded all tasks
Total (133)

Total Success Rate
(% subjects who of succeeded in all three tasks)
106/151 (70%)

Appendix D:
Venn Diagram for failure (DMEPA Re-adjudication)



Participant ID for those who failed one task:

- Task 1 only: [redacted]
- Task 2 only: [redacted]
- Task 3 only: [redacted]"

Participant ID for those who failed multiple tasks:

- Task 1 and task 2: [redacted]
- Task 1 and task 3:
- Task 2 and Task 3:
- All tasks: [redacted]

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/s/

RIMA IZEM
12/21/2016

MARK S LEVENSON
12/21/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CONSUMER BEHAVIOR STUDIES

NDA/BLA #:	NDA205920
Supplement #:	Not Applicable
Drug Name:	(b) (4) 125 mcg/inhalation (Epinephrine Inhalation Aerosol USP)
Indication(s):	(b) (4)
Applicant:	Amphastar
Date(s):	Date re-submitted: 06/28/2016 PDUFA due date: 12/28/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Yueqin Zhao, Ph.D.
Secondary Reviewer:	Rima Izem, Ph.D., Team leader
Tertiary Reviewer:	Mark Levenson, Ph.D., (Acting) Division Director
Main Review Division:	OND/ODEIV/DNDP
Review Team for Consumer Behavior Studies:	Ryan Raffaelli (Primary Medical Reviewer, OND/ODEIV/DNDP) Francis Becker (Medical Team Leader, OND/ODEIV/DNDP) Barbara Cohen (Social Scientist Reviewer, OND/ODEIV/DNDP) Grace Jones(Health Scientist Reviewer, OSE/OMEPRM/DMEPA)
Project Manager:	Tinya Sensie
Keywords:	Label comprehension studies; Human factor studies

Table of Contents

1 LIST OF TABLES

2 LIST OF ACRONYMS

ALHFQ	Additional Labeling Human Factor Questions
AR	Acceptable Rate
CBT	Critical Behavioral Tasks
CI	Confidence Intervals
CRL	Complete Response Letter
DFL	Drug Fact Label
HF	Human Factor Study
IFU	Instruction For Use
ITPP	Intent-to-participate Population
LCS	Label Comprehension Study
MDI	Metered Dose Inhaler
OD	Original Datasets
OTC	Over-the-counter
PI	Package Insert
RBED	Risk-based Evaluation Datasets
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-Teen	Rapid Estimate of Adolescent Literacy in Medicine
SABA	Short-acting beta2-agonist
TEP	Task Evaluable Population

1 EXECUTIVE SUMMARY

This is a statistical review of an NDA resubmission for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) dispensed using a metered dose inhaler (MDI). Epinephrine-HFA is a short-acting beta2-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath.

This statistical review evaluates the consumer behavior studies submitted in this NDA. Those are three label comprehension studies (LCS IV, LCS V and LCS VI) and one human factor study (HFS). The Applicant conducted these studies to address deficiencies identified by FDA in a complete response letter (CRL) on 5/22/2014 in response to previous submission of the NDA on 7/22/13. This review did not evaluate other consumer behavior studies conducted under this NDA in the earlier submission.

The three label comprehension studies evaluated whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). Each of the three LCS enrolled more than 450 subjects (16 years of age or older) from multiple retail sites. The Applicant used iterative testing in which results from each LCS led to changes in labeling (DFL and PI) further tested in subsequent LCS.

In each LCS and comprehension objective, the Applicant assessed comprehension relative to the performance threshold of 85% for the general population. Thus, a study meets a communication objective if the lower bound of the 95% confidence interval of the comprehension rate exceeds 85%. LCS IV focused on subject comprehension of instructions for washing, priming, re-priming and using the device. All the comprehension objectives were met in LCS IV except the one for "priming the inhaler when wet or not used for 2 days". Thus, the label was revised and this latter comprehension objective was tested again in LCS V. This objective was still not met in LCS V, so the label was further revised and the objective was tested again in LCV VII where it was met. In addition, LCS V tested and met the objective for the prime before first use and place finger on center of dose indicator.

In LCS IV, LCS V and LCS VI, specific subject comprehension levels met the 85% threshold for the general population after the label was revised based on prior studies After all label revisions, the comprehension rate still fell below the 85% threshold in low literacy subjects for the following evaluation objectives:

1. Prime before first use;
2. Place fingers on center of dose indicator;
3. Do not use more than 8 inhalations in 24 hours;
4. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take;
5. Prime the inhaler if wet or not used for 2 days.

The human factor study was conducted in 151 subjects (>12 years old) from two sites. This study assessed consumers' ability to carry out three tasks related to use and maintenance of the MDI: First use (task 1), Cleaning (task 2) and Routine Use (Task 3). Correct completion rates were 85% or lower for each task. More specifically, completion rates and 95% confidence interval are 70% (62%, 77%) for first use task, 60% (52%, 68%) for cleaning task, and T 85% (78%, 90%) for

routine use task. When correct completion rates included not only performance coded as completed but also performance coded as completed with issues, as in Applicant's analyses, 95% confidence interval for each task was higher than 85%.

In addition to behavior tasks, the human factor study assessed understanding level of the labeling on three different items: (i) Dose Indicator, (ii) Dropped Device and (iii) Hold Inhaler Properly. The study met comprehension objectives on all the label comprehension items with correct comprehension rate significantly above 85% on each item.

Subgroup analyses in the human factor study showed that subjects with the following characteristics did not perform as well in all tasks (i) a very short reading time of E004 IFU (instruction for use), (ii) low literacy level, and (iii) carryover habit of prior inhaler experience.

The reviewer recommends that additional instructions about priming should be included in the Instructions for Use (IFU). The instructions for use of "Prime the inhaler again if it is wet or not used in 2 days" was difficult to understand relative to other tested messages in the label comprehension study. Comprehension rates for this instruction did not exceed 85% in LCS IV, LCS V but did exceed 85% in LCS VI. Although the PI and DFL were revised, the IFU was not revised. The reviewer believes that the additional instructions should be included in the IFU, so that potential consumers can safely use the product.

2 INTRODUCTION

This is a statistical review of new consumer behavior studies in an NDA resubmission for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA). The drug is dispensed using a metered dose inhaler (MDI) with a dose of 125mcg/inhalation. Epinephrine-HFA is a short-acting beta2-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath.

Epinephrine-HFA MDI is proposed as an alternative to the previously marketed Primatene® Mist epinephrine MDI, which was removed from the market in 2011 due to the phase out of ozone-depleting chlorofluorocarbon (CFC) propellants under the Montreal Protocol. Of note, this product was not removed from the market due to reasons of safety or efficacy. Proper use of the device includes shaking at every use, cleaning every day and priming frequently. The device must be shaken immediately prior to dosing because the product is a suspension and settling may occur if the device is not shaken. The device also requires cleaning by disassembling the device and washing with warm water on a daily basis. Priming is required at first ever use, first use in 2 days or more of no-use, after cleaning if it is wet, or after dropping device.

Instructions of use also include how to properly use the dose indicator. The epinephrine HFA MDI includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the MDI no longer advance the display. Instructions also note that if the MDI is dropped, the dose indicator is no longer reliable and patients must keep track of the number of sprays taken. The package instructions note that a finger must be placed on the center of the dose indicator during actuation.

The application contained three label comprehension studies (LCS) and a human factor study, The Applicant conducted the three LCS to evaluate whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, the human factor study was performed. In the human factor study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling.

This statistical review will address the consumer behavior studies, specifically the label comprehension and human factor studies, submitted in this NDA.

Regulatory history

Epinephrine, one of the first sympathomimetic agents in medicine, has been marketed in the United States in a variety of different formulations since 1901, with use in the treatment of asthma dating back to the early 1900s. Epinephrine in an MDI formulation utilizing CFCs (Primatene® Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967. Beginning in

1996, MDIs using CFC propellants began to be phased out to protect the environment under the Montreal Protocol. FDA published the Final Rule in 2008 and based upon a request from the manufacturer, the end date (effective date) for use of CFCs for epinephrine MDIs was December 31, 2011.

The FDA and sponsor met several times to discuss which consumer behavior studies are needed and what they should test. Please refer to Statistical Review by Scott Komo on 4/25/2014 for a detailed review of the regulatory history.

On 4/8/2013, the Applicant submitted an NDA (under NDA 205496) that the Agency refused to file due to a number of deficiencies that did not allow a substantive review. The NDA was resubmitted on 7/22/13 (under NDA 205920). The NDA contained three label comprehension studies and a human factor study. FDA reviewed the submission and sent the Applicant a complete response letter (CRL) on 5/22/2014 outlining multiple deficiencies. The letter states that the application could not be approved due to the failure to establish the product usability in the OTC setting. The following study deficiencies were included:

- The label comprehension studies identified limitations in consumers' understanding of the following critical information: the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to re-prime when wet, and not relying on the indicator if dropped.
- The human factor study did not assess whether consumers understood the need to initially prime and clean the product without prompting. The study did not provide sufficient information to assess whether cleaning and use of the device was performed appropriately. In addition, the human factor study did not adequately assess consumers with low literacy.

The NDA was resubmitted on 6/28/16 (under NDA 205920) to address these deficiencies. As stated above, the NDA contains new label comprehension studies and a new human factor study. A consumer behavioral actual use study, which collected device performance data, was not conducted. This review will focus on reviewing the studies submitted in this application and will not review studies submitted in the previous application.

2.1 Overview

The consumer studies submitted in the application are presented in Table 1.

Table 1: List of all studies included in the review

Applicant defined study number	Study Type	Number of subjects	Number of low literacy (%)
LCS IV	Label Comprehension	506	126 (25%)
LCS V	Label Comprehension	492	113 (23%)
LCS VI	Label Comprehension	485	98 (20%)
HF G3	Human Factor	151	24 (16%)

Source: The reviewer's table

2.2 Data Sources

List of materials used in this review along with the locations are listed in Table 2.

Table 2: List of review materials and locations

Applicant defined study number	Document type and name	Location
LCS IV	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f4\analysis\legacy\datasets
LCS V	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f5\analysis\legacy\datasets
LCS VI	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f6\analysis\legacy\datasets
HF G3	Study Protocol, Statistical Analysis Plan and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\amp-2016-e004-g3
	Analysis Datasets: **basic.xpt; demo.xpt; task1*-task6.xpt; task1od.xpt; task1rbd.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\g3\analysis\legacy\datasets \\cdsesub1\evsprod\NDA205920\0042\m5\datasets\g3\analysis\legacy\datasets \\cdsesub1\evsprod\NDA205920\0042\m5\datase

Applicant defined study number	Document type and name	Location
		ts\g3\analysis\legacy\datasets

Source: The reviewer's table.

*Our review found that one table submitted by the Applicant could not be reproduced by using the submitted datasets, and per our request the Applicant resubmitted two revised datasets: task1od.xpt and task1rbd.xpt.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and reports of this submission were submitted electronically. The data and analysis quality are adequate as it allowed us to reproduce most key safety findings and conduct additional analyses. The datasets were well documented in the define.pdf files. We could not originally reproduce one table in HF G3 study report by using the originally submitted datasets (task1*-task6.xpt). After an information request to Applicant, on July 25th, 2016 we received two revised datasets: task1od.xpt and task1rbd.xpt where we could reproduce the results.

3.2 Label Comprehension Study IV

The objective of this LCS was to evaluate the package insert for Epinephrine Inhalation Aerosol USP, and to test for consumer comprehension of the E004 instructions that differ from the already approved Primatene® Mist product.

The primary objectives of this study were to determine if participants understand the following messages from the package insert:

1) Wash the mouthpiece daily if used.

2) Prime before first use.

3) Prime the inhaler again if it is:

    a. Wet;

    b. Dropped;

    c. Not used for 2 days

4) Place finger(s) on center of dose indicator.

5) Remove the canister for cleaning mouthpiece.

6) Do not use in children under 12 years of age.

7) Do not use more than 8 inhalations in 24 hours.

8) See your doctor if you have more than 2 asthma attacks in a week.

The secondary objective was to determine if participants understand:

1) If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take.

3.2.1 Study Design

This was a multi-center consumer label comprehension study designed to determine the effectiveness of the E004 package insert information. Participants consisted of adults 16 years of age and older selected from the general population at seven retail sites across the United States, of whom approximately 25% would be identified as low literacy as defined by the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen), depending on the age of the participant.. All subjects answered comprehension questions about the proposed package insert.

The Applicant enrolled 506 subjects in this LCS IV at seven US retail sites as listed in Table 3.

Table 3: List of study sites-LCS IV

Site ID	Name	Frequency	Percent
1022	Chicago Ridge Mall, Chicago Ridge, IL	72	14%
2020	White Marsh Mall, Baltimore, MD	92	18%
3010	Sugarloaf Mills, Lawrenceville, GA	79	16%
3080	Citrus Park Mall, Tampa, FL	92	18%
4011	Colorado Mills Mall, Lakewood, CO	52	10%
4022	Mainplace Mall, Santa Ana, CA	51	10%
4070	Kitsap Mall, Silverdale, GA	68	13%

Source: The reviewer's table.

3.2.2 Endpoints

Table 4 below lists all communication objectives that were tested in this study along with the corresponding target threshold for each objective. All primary and secondary communication messages were assessed as primary or secondary endpoints, respectively.

The thresholds for the primary endpoints are set at 85% by the Applicant. Failure to understand primary objectives 1-5 could lead to malfunction. Most often, malfunction would lead to lack of effectiveness (under-dose) and more rarely to possible safety issue (over-dose under certain conditions of misuse). Failure to understand primary objectives 6-9 could lead to safety issues. Objective #2 was planned but never included in the study for further testing.

Failure to understand instructions in the secondary objective are not as critical as first objective. An in-vitro laboratory study showed that falling would not cause critical malfunctions of the device, but occasionally the dose indicator would advance by one count. (b) (4) the Applicant argued that the risk of dose indicator being damaged during dropping as having an impact to the safety is mitigated. Therefore the threshold for the secondary endpoint was assigned a target threshold of 75%.

Table 4: Communication Objectives and Target thresholds – LCS IV

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Wash the mouthpiece daily if used	85%
2	Prime before first use	85%
3	Prime the inhaler again if it is: a. wet; b. dropped; c. not used for 2 days	85%
5	Place finger(s) on center of dose indicator	85%
6	Instructions for removing the canister for cleaning mouthpiece	85%
7	Children under 12 years of age: do not use	85%
8	Do not use more than 8 inhalations in 24 hours	85%
9	See your doctor if you have more than 2 asthma attacks in a week	85%
Secondary Objectives		
1	If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	75%

Source: The Applicant's study report (API-E004-CL-F4), page 10 of 80.

3.2.3 Statistical Methods

3.2.3.1 Analyses of primary and secondary endpoints

Subjects' demographic characteristics were described with summary descriptive statistics (number of participants, mean, standard deviation, median, minimum and maximum) for continuous variables (age) and frequency distributions for categorical variables (e.g., sex, race and literacy level).

For each communication message, the report provided comprehension rates and 95% confidence intervals (exact Clopper-Pearson method). To satisfy the comprehension standard, the lower bound of the 95% confidence interval should exceed the target threshold.

The primary analysis was performed for all participants reviewing the package insert, by literacy level, Primatene® Mist use history, and by asthma status.

The nine primary endpoints were co-primary endpoints, i.e., all the nine endpoints were required to meet the 85% target threshold, therefore there was no need to adjust for multiplicity.

3.2.3.2 Subgroup analyses

Subgroup analyses of comprehension rates included the following subgroups: literacy level, Primatene® Mist use history, and asthma status. In addition to reproducing the sponsor's analyses, the reviewer conducted Fisher's Exact test and Mantel-Haenszel test to compare the findings between the subgroups. Note that confidence intervals of comprehension rates in subgroups will be generally wider confidence than in the general population because subgroups have smaller sample sizes.

3.2.4 Patient Disposition and Demographic Characteristics

A total of 529 participants were qualified for the study at seven sites around the US, 8 participants discontinued the interview prior to beginning the comprehension questions, and 15 participants did not proceed to take the REALM Test. In the end, a total of 504 participants completed the entire interview with the REALM Test.

Within this sample, the mean age was 36.9 (standard deviation was 17.1) and 8.3% of the participants were <18 years of age. Slightly less than half of the sample (45.6%) was male. Participants were reasonably well distributed across race categories; 55.1% were White, 21.9% Black or African American and 14.4% Hispanic or Latino. For education, 13.2% of participants reported that they did not complete their high school education, 27.7% were high school graduates, 35.6% had some college experience, and 23.5% were college graduates. 126 participants (25.0%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 13.8% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 36 participants (7.1% of the total cohort). The demographic characteristics are listed in Table 5.

Table 5: Demographic characteristics – LCS IV

Characteristics	
N	506
Age	
Mean (Std Dev)	36.9(17.1)
<18 years old, n(%)	42(8.3%)
Sex	
Male, n(%)	230(45.6%)
Race, n(%)	

Characteristics	
White	279(55.1%)
African America	111(21.9%)
Hispanic or Latino	73(14.4%)
Other	43(8.5%)
Education, n(%)	
Did not complete high school	67(13.2%)
High school	140(27.7%)
Some college experience	180(35.6%)
College degree or higher	119(23.5%)
Low literacy, n(%)	126 (25.0%)
Had asthma, n(%)	70(13.8%)
Ever use Primist, n(%)	36(7.1%)

Source: The reviewer's table.

3.2.5 Results

3.2.5.1 Primary analyses

As shown in Table 6, subjects demonstrated high comprehension rate on each of the primary endpoints. The lower bound of the 95% confidence interval for each comprehension rate exceeded the Applicant specified threshold of 85%, with the exception of #3, Prime the inhaler again if it is wet, dropped, or not used for 2 days, where the lower bound of the CI was below the 85% threshold .

Table 6: Results for the primary endpoints – LCS IV

Primary Endpoints	Question # and Text	Comprehension Level (95% CI) N=506
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	95% (93%, 97%)
3. Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#8: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	88% (85%, 90%)
	#4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	83% (79%, 86%)
4. Place finger(s) on center of dose indicator	**#5: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?**	89% (86%, 92%)
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	96% (93%, 97%)
6. Children under 12 years of age: do not use	**#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?**	97% (95%, 98%)
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	92% (89%, 94%)
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (96%, 99%)

*#2 objective, "Prime before first use" was originally planned, but never tested out in LCS IV. It was included in LCS V later.

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F4), page 23 of 80.

Reviewer's comments: The primary endpoint #2 "Prime before first use" was not evaluated in this study.

3.2.5.2 Secondary Analyses

As shown in Table 7, comprehension rate was high for the secondary endpoint. The lower bound of the 95% confidence interval for each exceeded the Applicant specified threshold of 85%.

Table 7: Results for the secondary endpoints – LCS IV

Secondary Endpoints	Question # and Text	Comprehension Level (95% CI) N=506
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**Question 9: Based on the package insert, what should you do if you drop your inhaler?**	94% (92%, 96%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F4), page 24 of 80.

A correct response for this secondary communication objective was a composite of multiple correct responses based on the label tested at the time. However, the current proposed label differs from the label tested in LCS IV. Thus, the reviewer recalculated comprehension for this objective only counting the statements displayed in the current proposed label. The comprehension rates only count those who checked the "Do not rely on dose indicator" and "Keep track of the number of sprays you take" in the questionnaire. The results are in Table 8. There were only 276 (54.6%) participants who checked both options, 77 (15.2%) only checked "Do not rely on dose indicator" and 19 (3.8%) only checked "Keep track of the number of sprays you take".

Table 8: Additional tabulation of Question 9

Question 9	n (%)
Checked "Do not rely on dose indicator" and "Keep track of the number of sprays you take"	276 (54.6%)
Only Checked "Do not rely on dose indicator"	77 (15.2%)
Only Checked "Keep track of the number of sprays you take"	19 (3.8%)
Others	134 (26.5%)

Source: The reviewer's table.

3.2.6 Findings in Subgroup Analyses

This section shows subgroup analyses for each of the primary and secondary endpoints by age, literacy level, experience with product, and asthma history. Below presents the literacy level subgroup analyses, and the Appendix 5.1 includes the results for other subgroup analyses.

3.2.6.1 Literacy Level

The results for literacy level subgroup analyses are in Table 9. Among the 379 participants with normal literacy level, the comprehension rate of each of the primary and secondary communication endpoints were similar to the overall estimates. The lower bound of the 95% confidence interval exceeded the a priori threshold of 85% for all the endpoints. However, the comprehension rates were lower within the 126 low literacy participants compared to the normal literacy group. The lower bound of the 95% confidence interval for the primary endpoints #3, #4, #7 and the secondary endpoint did not exceed the threshold of 85%. The lowest was 56% as for question 4 in the primary endpoint #3.

The reviewer applied Fisher's exact test to compare the comprehension levels between the normal vs and low literacy subgroups. There was significant difference between normal and low literacy groups on almost all the primary and secondary endpoints, except the primary endpoint #5 and #7.

Table 9: Results for literacy subgroup analyses – LCS IV

		Normal Literacy (95% CI) N=379	**Low Literacy (95% CI) N=126**	**p-value**
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	97% (94%, 98%)	91% (85%, 96%)	0.0265*
2. Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#8: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	90% (87%, 93%)	81% (73%, 87%)	0.0074*
	Question 4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	89% (85%, 92%)	65% (56%, 73%)	<0.0001*
3. Place finger(s) on center of dose indicator	**#5: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?**	91% (88%, 94%)	84% (77%, 90%)	0.0289*
4. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	97% (94%, 98%)	94% (88%, 97%)	0.195

		Normal Literacy (95% CI) N=379	Low Literacy (95% CI) N=126	p-value
5. Children under 12 years of age: do not use	**#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?**	98% (96%, 99%)	93% (87%, 97%)	0.0179*
6. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	93% (90%, 95%)	89% (82%, 94%)	0.1863
7. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	99% (98%, 100%)	95% (90%, 98%)	0.0093*
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	98% (96%, 99%)	85% (77%, 91%)	<0.0001*

Source: The reviewer's table.

* p-values<0.05.

3.3 Label Comprehension Study V

After LCS IV, the package insert was updated to improve communication on priming. The new instructions were tested in LCS V as the Applicant determined that other items were already demonstrated to be understood at an acceptable level in previous comprehension studies for this product. In addition, this study retested an instruction on appropriate finger placement for a puff.

More specifically, the primary objectives of this study were to determine if participants understand the following messages from the package insert:

1) Prime before first use;

2) Prime the inhaler again if it is wet;

3) Prime the inhaler again if it is not used for 2 days; and

4) Place finger(s) on center of dose indicator.

3.3.1 Study Design

This was a multi-center consumer label comprehension study designed to determine the effectiveness of the E004 package insert information. Participants consisted of adults 16 years of age and older selected from the general population at five retail sites across the United States. About 23% of participants were identified as low literacy as defined by the age specific tests of REALM or REALM-Teen. All subjects answered comprehension questions about the proposed package insert.

The Applicant enrolled 492 subjects in this LCS V from five US retail sites as listed below.

- Chicago Ridge Mall, 730 Chicago Ridge Mall, Chicago Ridge, IL. 60415
- Maplewood Mall, 3001 White Bear Ave. N. Space 1070, St. Paul, MN. 55109
- Neshaminy Mall, 109 Neshaminy Mall, Bensalem, PA. 19020
- Roseville Galleria, 1151 Galleria Blvd, Suite 277, Roseville, CA. 95678
- Vancouver Mall, 8700 NE Vancouver Mall Drive, Ste. 187, Vancouver, WA. 98662

3.3.2 Endpoints

Table 10 below lists all communication objectives that were tested in this study along with the corresponding target threshold determined by the Applicant. The thresholds for all the primary endpoints were set at 85%, to keep with previous label comprehension work conducted for E004.

Table 10: Communication Objectives and Target thresholds – LCS V

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Prime before first use	85%
2	Prime the inhaler again if it is wet	85%
3	Prime the inhaler again if it is not used for 2 days	85%
4	Place finger(s) on center of dose indicator	85%

Source: The Applicant's study report (API-E004-CL-F5), page 10 of 76.

3.3.3 Statistical Methods

This study used the same analyses of primary, secondary endpoints and subgroup analyses as the ones in LCS IV and described in Section 3.2.3.

3.3.4 Patient Disposition and Demographic Characteristics

A total of 517 participants were qualified for the study at five sites around the US, 22 participants discontinued the interview prior to beginning the comprehension questions, and 3 participants did not proceed to pass the REALM Test or start the interview. In the end, a total of 492 participants completed the entire interview.

Within this sample, the mean age was 33.5 years (standard deviation was 16.5) and 7.5% of the participants were <18 years of age. Less than half (47.2%) were male. Participants were reasonably well distributed across race categories; 63.4% were White, 20.5% Black or African American and 6.1% Hispanic or Latino. For education, 13.6% of participants reported that they did not complete their high school education, 38.6% were high school graduates, 35.0% had some college experience, and 12.8% were college graduates. 113 participants (23.0%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 17.7% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 25 participants (5.1% of the total cohort). The demographic characteristics are in Table 11.

Table 11: Demographic characteristics – LCS V

Characteristics	
N	492
Age	
Mean (Std Dev)	33.5(16.5)
<18 years old, n(%)	37(7.5%)
Sex	
Male, n(%)	232(47.2%)
Race, n(%)	
White	312(63.4%)
African America	101(20.5%)
Hispanic or Latino	30(6.1%)
Other	49(10.0%)
Education, n(%)	
Did not complete high school	67(13.6%)
High school	190(38.6%)
Some college experience	172(35.0%)
College degree or higher	63(12.8%)
Low literacy, n(%)	113(23.0%)
Had asthma, n(%)	87(17.7%)
Ever use Primist, n(%)	25(5.1%)

Source: The reviewer's table.

3.3.5 Results

3.3.5.1 Primary analyses

As shown in

Table 12, comprehension rates were high on each of the endpoints. The lower bounds of the 95% confidence intervals for the endpoints of "Prime before first use" and "Place finger on center of dose indicator" exceeded the Applicant threshold of 85%. However, the lower bounds of the 95% confidence intervals for the endpoints of "Prime the inhaler again if it is wet" and "Prime the inhaler again if not used for 2 days" were below the threshold.

Table 12: Results for the primary endpoints – LCS V

Endpoints	Question # and Text	Comprehension Level (95% CI) N=492
1. Prime before first use	**#1: Brenda just purchased [redacted](b) (4) What does she need to do to get a new inhaler ready for use?**	88% (85%, 91%)
2. Place finger on center of dose indicator	**#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff where should he place his finger?**	91% (88%, 94%)
3. Prime the inhaler again if it is wet	**#3: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	86% (82%, 89%)
4. Prime the inhaler again if it is not used for 2 days	**#4: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	83% (79%, 86%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F5), page 21 of 76.

3.3.6 Subgroup Analyses Results

Subgroup analyses were conducted for each of the primary endpoints within the normal vs low literacy subgroups and also the user vs. non-user subgroups. Below presents the literacy level subgroup analyses, and the Appendix 5.2 includes the results for other subgroup analyses.

3.3.6.1Literacy Level

The results for literacy level subgroup analyses are in Table 13. Comprehension rates were up to 18% lower in the low literacy group (113 participants) compared to the normal literacy group (379 participants). Differences were statistically significant for each of the four comprehension endpoint using Fisher's exact test (type 1 error 5%, two-sided).

Table 13: Results for literacy level subgroup analyses – LCS V

		Normal Literacy (95% CI) N=379	Low Literacy (95% CI) N=113	p-value
Primary Endpoints				
1. Prime before first use	**#1: Brenda just purchased (b) (4) What does she need to do to get a new inhaler ready for use?**	92% (89%,95%)	75% (66%, 83%)	<0.0001*
2. Place finger on center of dose indicator	**#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff where should he place his finger?**	93% (90%, 95%)	86% (78%, 92%)	0.0348*
3. Prime the inhaler again if it is wet	**#3: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	89% (85%, 92%)	75% (66%, 83%)	0.0007*
4. Prime the inhaler again if it is not used for 2 days	**#4: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	87% (83%, 90%)	69% (60%, 77%)	<0.0001*

Source: The reviewer's table.

* p-values<0.05.

3.4 Label Comprehension Study VI

The objective of this LCS is to test priming instructions. Some of the priming instructions failed to meet the target comprehension rates in LCS V. Thus, the package insert instructions were modified and the instructions were re-tested in this LCS (LCS VI).

The primary objectives of this study were to determine if participants comprehend the following messages from the package insert:

1) Prime the inhaler again if it is wet; and

2) Prime the inhaler again if it is not used for 2 days.

3.4.1 Study Design

This was a multi-center study. Participants consisted of adults 16 years of age and older selected from the general population at four retail sites across the United States. The study had 20% low literacy participants as determined by the REALM or REALM-Teen. All subjects answered comprehension questions about the proposed package insert.

This Label Comprehension Study (LCS VI) for E004 was conducted at four US retail sites as listed in Table 14.

Table 14: List of study sites-LCS VI

Roseville Galleria	1151 Galleria Blvd, Suite 277	Roseville	CA	95678
Kitsap Mall	10315 Silverdale Way, Suite E20	Silverdale	WA	98383
Citrus Park Mall	7852 Citrus Park Drive	Tampa	FL	33625
Sugarloaf Mills	5900 Sugarloaf Parkway, Suite 125	Lawrenceville	GA	30043

Source: The Applicant's table, page 10 of 63 in the LCS VI study report.

3.4.2 Endpoints

Table 15 below lists all communication objectives that were tested in this study along with the corresponding target threshold. All communication messages were assessed as primary endpoints. The target comprehension thresholds were set at 85% by Applicant, to keep with previous label comprehension work conducted for E004.

Table 15: Communication Objectives and Target thresholds – LCS VI

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Prime the inhaler again if it is wet	85%
2	Prime the inhaler again if it is not used for 2 days	85%

Source: The Applicant's study report (API-E004-CL-F6), page 10 of 63.

3.4.3 Statistical Methods

Statistical methods for primary endpoint and subgroup analyses in this LCS were similar to other two LCS studies as described in Section 3.2.3.

3.4.4 Patient Disposition and Demographic Characteristics

A total of 486 participants were qualified for the study at four sites around the US, 1 participant discontinued the interview prior to beginning the comprehension questions, and a total of 485 participants completed the entire interview.

Within this sample, the mean age was 31.9 (standard deviation was 15.2) and 5.4% of the participants were <18 years of age. A majority of participants (57.1%) were male. Participants were reasonably well distributed across race categories; 55.3% were White, 18.8% Black or African American and 13.0% Hispanic or Latino. For education, 13.6% of participants reported that they did not complete their high school education, 29.3% were high school graduates, 42.3% had some college experience, and 14.8% were college graduates. 98 participants (20.2%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 17.3% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 31 participants (6.4% of the total cohort). The demographic characteristics were listed in Table 16.

Table 16: Demographic characteristics – LCS VI

Characteristics	
N	485
Age	
Mean (Std Dev)	31.9(15.2)
<18 years old, n(%)	26(5.4%)
Sex	
Male, n(%)	277(57.1%)
Race, n(%)	
White	268(55.3%)
African America	91(18.8%)
Hispanic or Latino	63(13.0%)
Other	63(13.0%)
Education, n(%)	

Characteristics	
Did not complete high school	66(13.6%)
High school	142(29.3%)
Some college experience	205(42.3%)
College degree or higher	72(14.8%)
Low literacy	98 (20.2%)
Had asthma, n(%)	84(17.3%)
Ever use Primist, n(%)	31(6.4%)

Source: The reviewer's table. Similar results were also available in the Applicant's study report (API-E004-CL-F6), page 21 of 63.

3.4.5 Results

3.4.5.1 Primary analyses

As shown in Table 17, subjects demonstrated high comprehension level on both primary endpoints. The lower bound of the 95% confidence interval for each comprehension rate exceeded the Applicant specified threshold of 85%.

Table 17: Results for the primary endpoints – LCS VI

Endpoints	Question # and Text	Comprehension Level (95% CI) N=485
1. Prime the inhaler again if it is wet	**# 1: John cannot let his inhaler dry overnight and must use it when it is still wet. What does the package insert say John should do if he needs to use it when it is still wet?**	92% (89%, 94%)
4. Prime the inhaler again if it is not used for 2 days	**#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	90% (87%, 92%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F6), page 22 of 63.

3.4.6 Findings in Subgroup Analyses

Subgroup analyses were conducted for each of the primary and secondary endpoints within the normal vs low literacy subgroups and also the user vs. non-user subgroups. The reviewer also conducted subgroup analyses by age. Below presents the literacy level subgroup analyses, and the Appendix 5.3 includes the results for other subgroup analyses.

3.4.6.1 Literacy Level

The results for literacy subgroup analyses are in Table 18. However, the comprehension rates were 7%-8% lower in low literacy group compared to normal literacy group. This is a significant difference based on Fisher's exact test.

Table 18: Results for literacy level subgroup analyses – LCS VI

		Normal Literacy (95% CI) N=387	Low Literacy (95% CI) N=98	p-value
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	93% (90%, 96%)	86% (77%, 92%)	0.0224*
2. Prime the inhaler again if it is not used for 2 days	**#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	92% (89%, 95%)	80% (70%, 87%)	0.0006*

Source: The reviewer's table.

* p-values<0.05.

3.5 Human Factor Study

The study objective of this human factor study (G3) was to validate the usability of E004 by following its package insert IFU that is intended to be used in OTC settings. The usability was to characterize

(1) User interface, which consists of the following three tasks:
    (i) Device set-up: assembly;
    (ii) Device use: various aspects, including initial priming/re-priming and routine use; and
    (iii) Device cleaning
(2) Effectiveness;
(3) Efficiency;
(4) Ease of user learning; and
(5) User satisfaction.

3.5.1 Study Design

This study was a Human Factor and Usability Engineering study with 151 participants. The study consisted of approximately 1-hour long, one-on-one sessions with each participant. At the start of the session, study investigators gave participants an opportunity to familiarize themselves with the product. Then, participants were asked to perform a series of tasks with no additional instructions. Finally, participants answered a series of open-ended label comprehension questions.

These Critical Behavioral Tasks (CBTs) are:

(i) Initial priming of the inhaler to prepare it for use;

(ii) Cleaning the inhaler to prevent clogging; and

(iii) Routine use of the inhaler.

Site investigators coded each participant performance in these tasks based on the simulated use portion.

Investigators captured three (3) additional areas of product use and labeling comprehension in an open-ended interview approach using Additional Labeling Human Factor Questions (ALHFQs). The ALHFQs include questions on the following:

(i) How to interpret the dose indicator;

(ii) Not relying on the dose indicator if a device has been dropped; and

(iii) An understanding of the correct finger position required to ensure that the device expels medication properly with each spray.

The study period for this human factors pivotal study G3 for E004 is February to March 2016. This was a multisite study with two study sites listed in Table 19.

Table 19: List of study sites for human factor study (G3)

Site Name	Site Address
HF Labs	8041 Corporate Center Drive Suite 200, Charlotte, NC 28226
Plaza Research	9000 E. Lincoln Drive Building Two Suite 224, Marlton, NJ 08053

Source: The Applicant's table, page 30 of 80 in the HF G3 study report.

3.5.2 Endpoints

The primary and secondary endpoints of Study G3 were defined as follows:

Primary endpoints were the performance scores of the three CBTs, and secondary endpoints were the performance scores of the three ALHFQs.

3.5.3 Statistical Methods

Investigators coded participants' performance for each of the CBTs as completed(C), completed with issues (CI) or not completed(NC);

- Completed (C) — indicates that the participant can successfully perform the use task and demonstrate an understanding of the communication objective.
- Completed with Issues (CI) — indicates that the participant successfully performs the use task and demonstrates an understanding of the communication objective, but either struggles initially to do so, self-corrects during the testing session, or completes the task in such a way that varies from the specific direction provided in the IFU.
- Not Completed (NC) —indicates that the participant does not complete the task successfully and does not demonstrate an understanding of the communication objective.

Participants' performance for each of the ALHFQs were coded and evaluated as correct(C) or Not correct (NC).

- Correct (C) — indicates that the participant, independently and without prompting, can articulate a correct understanding of the communication objective, and can describe the appropriate (i.e., successful) strategy for achieving that objective.
- Not Correct (NC) — indicates that the participant does not articulate a correct understanding of the communication objective, and cannot describe an appropriate (i.e., successful) strategy for achieving that objective.

There were two study populations defined, intent-to-participate population (ITPP) and task evaluable population (TEP). The ITPP of the study is defined as the population of all subjects who was enrolled and was assigned with a participant ID. The TEP is defined as the population of all subjects whose investigator-reported performance score (C, CI, or NC) for all score-coding evaluable sub-items affiliated with this task are available.

The following two (2) datasets with different outcomes codes-were evaluated:

(1) Original Datasets (OD) – all data from the investigator; and

(2) Risk-based Evaluation Data (RBED) – same evaluable population as OD but with outcomes coded as "NC" in OD further assessed based on bench functional test results for E004 inhaler.

Besides the primary and secondary endpoints, the Applicant collected additional data including: Demographic characteristics of participants such as age, gender, race, literacy level (normal or low), participant qualification information, experience with using an MDI inhaler (naïve or experiences); Study basic information such as total time taken by the participant used to read E004 labeling, and whether or not the participant retrieved and reviewed the IFU(Yes/No).

3.5.3.1.1 Analyses of primary endpoint

The acceptable rate (AR) for a given Critical Task-k, denoted as Θ_k (k=1, 2, or 3), is the proportion of subjects who either completed the task correctly (C) or completed with issue (CI) out of all those in the study. More precisely,

$$\theta_k = \frac{N_k(C) + N_k(CI)}{N_k(C) + N_k(CI) + N_k(NC)} \times 100\%$$

Applicant was targeting acceptable rates significantly higher than 85% threshold (5% significance level (2-sided) using clopper-pearson exact method or normal approximation method).

- The primary analysis used RBED;
- For primary analysis, the population will be TEP.

Reviewer's comments: The acceptable rate for a given Critical Task was defined by the review division for this study, Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology, as the proportion of complete response among all the responses. The reviewer calculated the acceptable rate based on DMEPA's definition and performed Binomial tests to check whether AR is greater than the threshold 85%. Clopper-Pearson Exact method was used to construct the 95% confidence intervals.

3.5.3.2 Analyses of secondary endpoints

The AR for a given ALC question-*k*, denoted as Θ_k *(k*=4, 5, or 6), is defined as the proportion of correct responses out of all participants. More precisely,

$$\theta_k = \frac{N_k(C)}{N_k(C) + N_k(NC)} \times 100\%$$

Applicant planned similar statistical analyses for secondary endpoints as that for the primary endpoints.

3.5.3.3 Multiplicity adjustment

The three primary endpoints were co-primary endpoints, i.e., all the three endpoints were required to significantly exceed the 85% target threshold, therefore there was no need to adjust for multiplicity.

3.5.3.4 Subgroup analyses

The subgroup primary and secondary endpoints analyses were performed based on TEP per following categorical variables:

- Age group: Adult vs teen;
- Gender;
- Race;
- Literacy level: normal or low;

- Experience of use MDI inhaler: naïve (never used) or experienced;
- The total time taken by the participant used to read E004 Labeling.

3.5.4 Patient Disposition and Demographic Characteristics

A total of 151 participants enrolled in the study with a participant ID and thus are part of the ITPP. All of the 151 participants had their performance scores available and included in the TEP. So the ITPP population is identical to the TEP population.

The summary of the demographic and related characteristics of participants is in Table 20. There were 151 participants enrolled in this study, including 132 adults (79 women and 72 men) and 19 teens. The mean ages of subjects were 42 years with standard deviation of17 years, with a range of 12 to 78 years of age. The majority of participants were Caucasian (79.5%) with some African American (15.9%) and Hispanic (3%).

Literacy level was assessed by the REALM and REALM TEEN tools. Low literacy level group included 19 adult and 5 teen tested at low literacy level. Thirty-nine (39, 25.8%) participants had prior experience using an inhaler.

Reviewer comment: this review reports different numbers than the Applicant's report for low literacy: "there were 24 (15.9%) adults and 3 juveniles tested at low literacy levels".

Table 20: Demographic and study related information

Populations	Intent-To-Participate Population (ITPP)
# of Subjects	151
Age	
Age (yo), mean ± SD	41.6 ± 16.6
Age (yo), median (range)	42 (12 - 78)
Age Group, n(%)	
Adults	132 (87.4%)
Teens	19 (12.6%)
Gender, n(%)	
Male	72 (47.7%)
Female	79 (52.3%)
Race, n(%)	
Caucasian	120 (79.5%)
African American	24 (15.9%)
Hispanic	5 (3.3%)
Asian	1 (0.7%)
Others	1 (0.7%)
Literacy per REALM	
REALM scores, mean ± SD	63.0 ± 4.9
REALM scores, median (range)	65 (25 - 66)
Literacy Group n(%)▲	
Normal (REALM>60)	126 (83.4%)
Low (REALM≤60)	24 (15.9%)
Experience of Inhaler Usage, n(%)	
Naïve	112 (74.2%)
Experienced	39 (25.8%)
Categories per Multiple Factors, n(%)	
Adults, Naïve, Normal Literacy	86 (57.0%)
Adults, Naïve, Low Literacy	14 (9.3%)
Adults, Experienced, Normal Literacy	27 (17.9%)
Adults, Experienced, Low Literacy	5 (3.3%)
Teens	19 (12.6%)

Source: The Applicant's table, pg 37 of 80 in the HF G3 study report.

▲ One participant (PID=(b) (4) had no REALM score recorded).

3.5.5 Results

The Applicant conducted analyses using the Risk-based evaluation dataset and defined the acceptable rate (for CBTs) as the proportion of Complete and Complete with Issues responses among all the responses. The results from the Applicant's analyses are in Table 21. From the results, all ARs and their lower limits of 95% exact confidence intervals were above 85% for all CBTs/ALHFQs.

Table 21: Primary findings from the human factor study

CBT/ALHFQ	# of Paticipants (TEP*)	Global Results				Lower Limit of 95% confidence Interval, %		
		C	CI	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Critical Behavioral Tasks (CBT)								
Task 1 First Use	151	105	38	8	94.7%	89.8%	√	91.1%
Task 2 Cleaning	151	91	56	4	97.4%	93.4%	√	94.8%
Task 3 Routine Use	151	128	21	2	98.7%	95.3%	√	96.9%
Additional Labeling Human Factor Questions (ALHFQ)								
Question-4 Dose Indicator	151	149	-	2	98.7%	95.3%	√	96.9%
Question-5 Dropped Device	151	147	-	4	97.4%	93.4%	√	94.8%
Question-6 Hold Inhaler Properly	151	151	-	0	100.0%	97.6%	√	100.0%
All Tasks/Questions	151				**97.8%**	**94.1%**	√	**95.7%**

*T EP: Task-Evaluable Population; C: Completed (for CBT 1-3) or Correct (for ALHFQ 4-6);
CI: Complete with Issues (for CBT 1-3); NC: Not Completed (for CBT 1-3) or Not Correct (for ALHFQ 4-6).

Source: The Applicant's table, page 4 of 80 in the HF G3 study report.

For comparison purpose, the reviewer conducted additional analyses using both the Risk-based evaluation dataset and the original dataset, using both the applicant's and the DMEPA's definition of acceptable rate. DMEPA defines the CBT acceptable rate as the proportion of only Complete responses among all the responses. The results are listed in Table 22.

By using the original dataset and the Applicant's definition of acceptable rate, the acceptable rate for Task 1 First use was estimated as 91% with 95% confidence intervals as (85%, 95%). By using the DMEPA's definition of acceptable rate for CBTs and only count Complete responses as acceptable, the acceptable rate for Task 1 First use was estimated as 70 % with 95% confidence intervals as (62%, 77%), the acceptable rate for Task 2 Cleaning was estimated as 60% with 95% confidence intervals as (52%, 68%) and the acceptable rate for Task 3 Routine use was estimated as 85% with 95% confidence intervals as (78%, 90%).

The acceptable rates for the three ALHFQ remained the same.

Table 22: Primary analysis results, using both OD and RBED, and using Applicant's and DMEPA's definitions for acceptable rates.

CBT/ALHFQ	Original Dataset (N=151)					Risk-Based Evaluation Dataset (N=151)				
	C	CI	NC	Acceptable Rate by Applicant's definition (95% CI)	Acceptable Rate by DMEPA's definition (95% CI)	C	CI	NC	Acceptable Rate by Applicant's definition (95% CI)	Acceptable Rate by DMEPA's definition (95% CI)
Critical Behavioral Tasks										
Task 1: First Use*	105	**32**	**14**	91% (85%, 95%)	70% (62%, 77%)	105	**38**	**8**	95% (90%, 98%)	70% (62%, 77%)
Task 2: Cleaning	91	56	4	97% (93%, 99%)	60% (52%, 68%)	91	56	4	97% (93%, 99%)	60% (52%, 68%)
Task 3: Routine Use	128	21	2	99% (95%, 100%)	85% (78%, 90%)	128	21	2	99% (95%, 100%)	85% (78%, 90%)
Additional Labeling Human Factor Questions										
Question 4: Dose Indicator	149	--	2	99% (95%, 100%)	99% (95%, 100%)	149	--	2	99% (95%, 100%)	99% (95%, 100%)
Question 5: Dropped Device	147	--	4	97% (93%, 99%)	97% (93%, 99%)	147	--	4	97% (93%, 99%)	97% (93%, 99%)
Question 6: Hold Inhaler Properly	151	--	0	100% (98%, 100%)	100% (98%, 100%)	151	--	0	100% (98%, 100%)	100% (98%, 100%)

Source: The reviewer's table.

*In this study, as opposed to repeatedly shaking and spraying for four times, seven participants shook the inhaler once and sprayed 4 to 5 times consecutively into the air, and six of them completed the priming within 10 seconds. The Applicant argued that the behaviors of these six participants would have no significant impact on user's effective and safe use since the priming were completed within 10 seconds. Thus, these six participants for Task 1 were assigned performance score of Complete with Issues (CI) in the RBE dataset.

3.5.6 Findings in Subgroup Analyses

The subgroup primary and secondary endpoints analyses were performed based on TEP per following categorical variables:

- Age group: Adult vs teen;
- Gender;
- Race;
- Literacy level: normal or low;
- Experience of use MDI inhaler: naïve (never used) or experienced;
- The total time taken by the participant used to read E004 Labeling; and,
- Participant categories.

The following section presents the literacy level subgroup analyses, and the Appendix 5.4 includes the results for other subgroup analyses.

3.5.6.1 Literacy level

The Applicant's results for ARs and their 95% LCI for the two literacy levels (Normal literacy and Low literacy) are summarized in Table 23. For normal literacy subgroup (n=126) subgroup, the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For low literacy subgroup (n=24), the ARs for 5 of 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 5 of 6 Tasks/Questions were lower than 85%.

The reviewer applied Fisher's exact test to compare the ARs between the normal vs and low literacy subgroups. There was significant difference between normal and low literacy groups for CBT Task 1, Task 3, ALHFQ Question 4 and Question 5.

Table 23: Subgroup Analysis for CBTs and ALHFQs by Literacy Level

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	> 85%?
Normal Literacy								
Task 1 First Use	126	92	30	4	96.8%	√	92.1%	√
Task 2 Cleaning	126	78	46	2	98.4%	√	94.4%	√
Task 3 Routine Use	126	111	15	0	100.0%	√	97.1%	√
Question-4 Dose Indicator	126	126	-	0	100.0%	√	97.1%	√
Question-5 Dropped Device	126	124	-	2	98.4%	√	94.4%	√
Question-6 Hold Inhaler Properly	126	126	-	0	100.0%	√	97.1%	√
All Task/Question-1 to 6					98.9%	√	95.4%	√
Low Literacy								
Task 1 First Use	24	12	8	4	83.3%	x	62.6%	x
Task 2 Cleaning	24	13	9	2	91.7%	√	73.0%	x
Task 3 Routine Use	24	16	6	2	91.7%	√	73.0%	x
Question-4 Dose Indicator	24	22	-	2	91.7%	√	73.0%	x
Question-5 Dropped Device	24	22	-	2	91.7%	√	73.0%	x
Question-6 Hold Inhaler Properly	24	24	-	0	100.0%	√	85.8%	√
All Task/Question-1 to 6					91.7%	√	73.4%	x

Source: The Applicant's table, page 58 of 80 in the HF G3 study report.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

This application includes results from three LCS and one HFS.

Label Comprehension Studies

The three LCS evaluated whether consumers could understand the information on the proposed DFL and PI.

Overall, the three label comprehension studies enrolled more than four hundred subjects, who were 16 years of age or older, from multiple retail sites. The studies used an iterative study design in which initial testing in the first LCS, LCS IV, led to modifications to the DFL and PI. The modified statements were tested in the second LCS, LCS V. In a similar fashion, labeling was refined prior to the start of the sixth LCS, LCS VI, to improve upon any items where consumers did not demonstrate adequate comprehension.

The first label comprehension study LCS IV focused on evaluating instructions for washing, priming, re-priming and using the device. In this study, comprehension rates were significantly higher than 85% for all communication messages, excluding the one for "priming the inhaler when wet or not used for 2 days". The label was revised by Applicant based on the results of LCS IV. Then, the second label comprehension study, LCS V, tested the objective not met in LCS IV, along with other messages on priming. Comprehension rates significantly exceeded 85% for the instruction of "prime before first use and place finger on center of dose indicator" but not "priming

the inhaler when wet or not used for 2 days" Thus, the Applicant further revised the label and re-tested this latter message in LCS VI. This communication objective was finally met in LCS VI with comprehension rate significantly above 85%. Results on all communication objectives in the studies were they were met are in Table 24.

Table 24: Summary Results of Communication Objectives and Rates in LCS IV, LCS V and LCS VI

Communication Objectives	LCS #/Question # and Text	Comprehension Rates (95% CI)
Wash the mouthpiece daily if used	**LCS IV/Q#6: According to the package insert, how often should the mouthpiece be washed?**	95% (93%, 97%)
Place finger(s) on center of dose indicator	**LCS IV/Q#5 and LCS V/Q#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?**	LCS IV 89% (86%, 92%) LCS V 91% (88%, 94%)
Instructions for removing the canister for cleaning mouthpiece	**LCS IV/Q#7: Susie needs to wash her inhaler. What is the first step she must take?**	96% (93%, 97%)
Children under 12 years of age: do not use	**LCS IV/Q#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?**	97% (95%, 98%)
Do not use more than 8 inhalations in 24 hours	**LCS IV/Q#2: Bill has taken 8 inhalations of (b) (4) (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	92% (89%, 94%)
See your doctor if you have more than 2 asthma attacks in a week	**LCS IV/Q#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (96%, 99%)
Prime before first use	**LCS V/Q#1: Brenda just purchased (b) (4) What does she need to do to get a new inhaler ready for use?**	88% (85%, 91%)
Prime the inhaler again if it is wet	**LCS VI/Q# 1: John cannot let his inhaler dry overnight and must use it when it is still wet. What does the package insert say John should do if he needs to use it when it is still wet?**	92% (89%, 94%)
Prime the inhaler again if it is not used for 2 days	**LCS VI/ Q#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	90% (87%, 92%)

Source: The reviewer's Table from individual study results reported in Table 6, Table 12 and Table 17 of this review.

The subgroup analyses in the LCS studies found the following: 1. Age, inhaler use experience and asthma history did not greatly impact comprehension rate; 2. Health literacy impacted comprehension. Comprehension rates were lower for subjects with lower health literacy, prior inhaler experience or asthma history.

The lower bound of 95% confidence intervals for the comprehension level still fell below the 85% threshold in low literacy subjects for the following evaluation objectives:

1. Prime before first use (LCS IV);
2. Place fingers on center of dose indicator (LCS V);
3. Do not use more than 8 inhalations in 24 hours (LCS IV);
4. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take (LCS IV);
5. Prime the inhaler if wet or not used for 2 days (LCS VI).

Human Factor Study

After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, the Applicant conducted a consumer behavior human factor study. In the human factor study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling. The Applicant carried out the study as a combination of behavioral, simulated use and label comprehension study. During the study, participants were asked to perform all the CBTs (1. Initial Priming; 2. Cleaning to prevent clogging; and 3. Routine use.) required for proper use of the product, and to answer ALHFQs exploring safe use of E004 and supporting labeling (4. How to interpret the dose indicator, 5. Not relying on the dose indicator if a device has been dropped and 6. Understanding the correct finger position when use).

By using the original dataset and the Applicant's definition of acceptable rate, all acceptable rates and their lower limits of 95% exact CI were above 85% for all CBTs/ALHFQs. This definition included not only performances coded as completed but also performances codes as completed with issues. By using the DMEPA's definition of acceptable rate for CBTs and only count Complete responses as acceptable, the acceptable rate for Task 1 First use was estimated as 70 % with 95% confidence intervals as (62%, 77%), the acceptable rate for Task 2 Cleaning was estimated as 60% with 95% confidence intervals as (52%, 68%) and the acceptable rate for Task 3 Routine use was estimated as 85% with 95% confidence intervals as (78%, 90%).

The subgroup analyses found the following 1. Demographic characteristics of age, gender and race did not impact comprehension; and 2. (i) a reading time of E004 IFU, (ii) literacy level, and (iii) prior inhaler experience impacted comprehension rates with lower comprehension rates for subgroup with short reading time, low literacy level or prior inhaler experience.

The comprehension objectives on "Prime the inhaler again if it is wet" and "Prime the inhaler again if not used in 2 days" were tested in all three Label comprehension studies. The thresholds of 85% comprehension level for these objectives were not met in LCS IV, LCS V but were met in LCS VI. Thus, based on the label comprehension studies, this is a challenging instruction for potential users to comprehend in the DFL and PI. However, instructions on using the inhaler if wet or not used in 2 days is not explained well in the proposed IFU ((see Appendices 5.7 and 5.8))

tested in the HFS. The reviewer believes that the additional instructions should be included in the final IFU so that the potential consumers can safely use the product.

4.2 Conclusions and Recommendations

The reviewer was able to reproduce the results provided by the Applicant. Subjects met the performance threshold of 85%, proposed by the Applicant for all the tasks related to priming, cleaning and routine use and all the label comprehension questions on dose indicator, dropped device and holding inhaler properly. The instructions on "Prime the inhaler again if it is wet or not used in 2 days" is an important information for correct use and should be added to the proposed IFU.

It is worth noting that the artificial nature of testing environment may have influenced the performance of subjects in the human factor study. The lack of data from an actual use study gives us no way to determine the consumer's performance in a less artificial setting.

5 APPENDICES

5.1 Additional Subgroup Analyses Results in Label Comprehension Study IV

5.1.1 Age

The results for age subgroup analyses, using categories suggested by Barbara, are in Table 25.

The reviewer applied Mantel-Haenszel test to compare the comprehension levels between the four age subgroups. There was no significant difference between different age groups for the primary endpoints #5, #6 but not for the others.

Table 25: Results for age subgroup analyses – LCS IV

		Age 16-17 (95% CI) N=42	Age18-25 (95% CI) N=147	Age 26-55 (95% CI) N=231	Age 55+ (95% CI) N=86	p-value
Primary Endpoints						
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	95% (84%, 99%)	95% (90%, 98%)	96% (92%, 98%)	94% (87%, 98%)	0.9682
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#8: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	93% (81%, 99%)	91% (85%, 95%)	85% (80%, 90%)	87% (78%, 93%)	0.1589
	Question 4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	71% (55%, 84%)	87% (81%, 92%)	83% (77%, 87%)	80% (70%, 88%)	0.9134
4. Place finger(s) on center of dose indicator	**#5: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?**	90% (77%, 97%)	90% (85%, 95%)	91% (86%, 94%)	83% (73%, 90%)	0.1481
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	98% (87%, 100%)	99% (95%, 100%)	95% (91%, 97%)	92% (84%, 97%)	0.0162*
6. Children under 12 years of age: do not use	**#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her**	93% (81%,	96% (91%,	97% (93%,	100% (96%, 100%)	0.0371*

		Age 16-17 (95% CI) N=42	Age18-25 (95% CI) N=147	Age 26-55 (95% CI) N=231	Age 55+ (95% CI) N=86	p-value
	son?	99%)	98%)	98%)		
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	90% (77%, 97%)	93% (87%, 96%)	92% (87%, 95%)	91% (82%, 96%)	0.8432
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (87%, 100%)	99% (96%, 100%)	98% (95%, 99%)	97% (90%, 99%)	0.2780
Secondary Endpoints						
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	90% (77%, 97%)	96% (91%, 98%)	94% (90%, 96%)	97% (90%, 99%)	0.4928

Source: The reviewer's table.

* p-values<0.05.

5.1.2 Experience with Primist

The results for Primist use subgroup analyses are in Table 26.The comprehension rate for each of the primary and secondary communication endpoints were up to 7% lower in the small Primist user subgroup (36 participant) compared to the large non-user subgroup (469 participants). Nevertheless, none of these differences were statistically significant using Fisher's exact test,

Table 26: Results for Primist use subgroup analyses – LCS IV

		Users (95% CI) N=36	Non-Users (95%CI) N=469	p-value
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	94% (81%, 99%)	95 % (93%, 97%)	0.6963
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#8: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	81% (64%, 92%)	88% (85%, 91%)	0.1857
	Question 4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	78% (61%, 90%)	83% (79%, 86%)	0.4922
4. Place finger(s) on center of dose indicator	**#5: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?**	94% (81%, 99%)	89% (86%, 92%)	0.4086
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	100% (90%, 100%)	95% (93%, 97%)	0.3907
6. Children under 12 years of age: do not use	**#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?**	94% (81%, 99%)	97% (95%, 98%)	0.3453
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	94% (81%, 99%)	91% (89%, 94%)	0.7573

		Users (95% CI) N=36	Non-Users (95%CI) N=469	p-value
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	100% (90%, 100%)	98% (96%, 99%)	1.0000
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	94% (81%, 99%)	94% (92%, 96%)	1.0000

Source: The reviewer's table.

* p-values<0.05.

5.1.3 History of asthma

The results for asthma history subgroup analyses are in Table 27. The comprehension rates for each of the primary and secondary communication endpoints were up to 7% lower among asthma sufferers (70 participants) compared to the non-asthma sufferers subgroup (436 subgroup). Nevertheless, none of these differences was statistically significant (Fisher's exact test).

Table 27: Results for asthma history subgroup analyses – LCS IV

		Asthma Suffers (95% CI) N=70	Non-Asthma Suffers (95%CI) N=436	p-value
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	94% (86%, 98%)	95% (93%, 97%)	0.7651
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#8: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	84% (74%, 92%)	88% (85%, 91%)	0.3297
	#4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler	80% (69%, 89%)	83% (79%, 86%)	0.5017

		Asthma Suffers (95% CI) N=70	Non-Asthma Suffers (95%CI) N=436	p-value
	again?			
4. Place finger(s) on center of dose indicator	#5: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?	83% (72%, 91%)	90% (87%, 93%)	0.0918
5. Instructions for removing the canister for cleaning mouthpiece	#7: Susie needs to wash her inhaler. What is the first step she must take?	96% (88%, 99%)	96% (93%, 97%)	1.0000
6. Children under 12 years of age: do not use	#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?	97% (90%, 100%)	97% (94%, 98%)	1.0000
7. Do not use more than 8 inhalations in 24 hours	#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?	86% (75%, 93%)	93% (90%, 95%)	0.0612
8. See your doctor if you have more than 2 asthma attacks in a week	#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?	97% (90%, 100%)	98% (96%, 99%)	0.6355
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	#9: Based on the package insert, what should you do if you drop your inhaler?	93% (84%, 98%)	95% (92%, 97%)	0.5703

Source: The reviewer's table.

* p-values<0.05.

5.2 Additional Subgroup Analyses Results in Label Comprehension Study V

5.2.1 Age

The results for age subgroup analyses are in Table 28.

The reviewer applied Mantel-Haenszel test to compare the comprehension levels between the four age subgroups. There was no significant difference between different age groups for all the primary endpoints.

Table 28: Results for age subgroup analyses – LCS V

		Age 16-17 (95% CI) N=37	Age18-25 (95% CI) N=196	Age 26-55 (95% CI) N=190	Age 55+ (95% CI) N=69	p-value
Primary Endpoints						
1. Prime before first use	**1. Prime before first use**	89% (75%, 97%)	90% (85%, 94%)	85% (79%, 90%)	91% (82%, 97%)	0.7728
2. Place finger on center of dose indicator	**2. Place finger on center of dose indicator**	89% (75%, 97%)	94% (90%, 97%)	91% (85%, 94%)	87% (77%, 94%)	0.2016
3. Prime the inhaler again if it is wet	**3. Prime the inhaler again if it is wet**	95% (81%, 99%)	86% (81%, 91%)	84% (78%, 89%)	83% (72%, 91%)	0.1179
4. Prime the inhaler again if it is not used for 2 days	**4. Prime the inhaler again if it is not used for 2 days**	84% (68%, 94%)	85% (79%, 90%)	82% (76%, 87%)	80% (68%, 88%)	0.3565

Source: The reviewer's table.

* p-values<0.05.

5.2.2 Experience with Primist

The results for literacy level subgroup analyses are in Table 29. Comprehension rates were up to 13% lower in the previous experience of using Primist group (25 participants) compared to non-user group (467 participants).

However, none of the differences was statistically significant using Fisher's exact test.

Table 29: Results for Primist use subgroup analyses – LCS V

		Users (95% CI) N=25	Non-Users (95%CI) N=467	p-value
Primary Endpoints				
1. Prime before first use	**#1: Brenda just purchased [redacted] (b) (4) What does she need to do to get a new inhaler ready for use?**	76% (55%, 91%)	89% (86%, 92%)	0.101
2. Place finger on center of dose indicator	**#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff where should he place his finger?**	80% (59%, 93%)	92% (89%, 94%)	0.057
3. Prime the inhaler again if it is wet	**#3: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	76% (55%, 91%)	86% (83%, 89%)	0.2356
4. Prime the inhaler again if it is not used for 2 days	**#4: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	80% (59%, 93%)	83% (79%, 86%)	0.5964

Source: The reviewer's table.

* p-values<0.05.

5.2.3 History of asthma

The results for asthma history subgroup analyses are in Table 30. The comprehension rates were up to 8% lower in asthma sufferers compared to the non-asthma sufferers group.

However, only comprehension rates of endpoint #2 were statistically significant between the two groups.

Table 30: Results for asthma history subgroup analyses – LCS V

	Asthma Suffers (95% CI) N=87	Non-Asthma Suffers (95%CI) N=405	p-value

		Asthma Suffers (95% CI) N=87	Non-Asthma Suffers (95%CI) N=405	p-value
Primary Endpoints				
1. Prime before first use	**#1: Brenda just purchased [redacted](b) (4) What does she need to do to get a new inhaler ready for use?**	84% (74%, 91%)	89% (86%, 92%)	0.1982
2. Place finger on center of dose indicator	**#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff where should he place his finger?**	85% (76%, 92%)	93% (90%, 95%)	0.0345*
3. Prime the inhaler again if it is wet	**#3: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?**	79% (69%, 87%)	87% (83%, 90%)	0.0909
4. Prime the inhaler again if it is not used for 2 days	**#4: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	84% (74%, 91%)	83% (79%, 86%)	0.876

Source: The reviewer's table.

* p-values<0.05.

5.3 Additional Subgroup Analyses Results in Label Comprehension Study VI

5.3.1 Age

The results for age subgroup analyses are in Table 31.

The Mantel-Haenszel shows no significant difference between different age groups for all the primary endpoints.

Table 31: Results for age subgroup analyses – LCS VI

		Age 16-17 (95% CI) N=26	Age18-25 (95% CI) N=214	Age 26-55 (95% CI) N=193	Age 55+ (95% CI) N=52	p-value
Primary Endpoints						
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	92% (75%, 99%)	92% (87%, 95%)	93% (89%, 96%)	87% (74%, 94%)	0.5622
2. Prime the inhaler again if it is not used for 2 days	**#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	81% (61%, 93%)	89% (84%, 93%)	92% (87%, 95%)	88% (77%, 96%)	0.3284

Source: The reviewer's table.

* p-values<0.05.

5.3.2 Experience with Primist use

The results for Primist use experience are in Table 32. Comprehension rates were lower (by 2% for one question and 6% in another question) for Primist users (31 participants) compared to non-user group (454 participants).

This difference was not statistically significant (Fisher's exact test)

Table 32: Results for Primist use subgroup analyses – LCS VI

		Users (95% CI) N=31	**Non-Users (95%CI) N=454**	**p-value**
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	90% (74%, 98%)	92% (89%, 94%)	0.7337
2. Prime the inhaler again if it is not used for 2 days	**#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	84% (66%, 95%)	90% (87%, 93%)	0.3523

Source: The reviewer's table.

* p-values<0.05.

5.3.3 History of asthma

The results for the asthma history subgroup analyses are in **Table 33**. The comprehension levels for each of the primary communication endpoints among asthma suffers were similar to the non-asthma suffers group (within 1%).

Table 33: Results for asthma history subgroup analyses – LCS VI

		Asthma Suffers (95% CI) N=84	Non-Asthma Suffers (95%CI) N=401	p-value
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	93% (85%, 97%)	92% (88%, 94%)	0.8289
2. Prime the inhaler again if it is not used for 2 days	**#2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**	89% (81%, 95%)	90% (86%, 93%)	0.8452

Source: The reviewer's table.

* p-values<0.05.

5.4 Additional Subgroup Analyses Results in Human Factor Study G3

5.4.1 Age

The results for ARs and their 95% LCI for the two age groups (Adult and Teen) are summarized in Table 34.

Table 34: Subgroup Analysis for CBTs and ALHFQs by Age Groups – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
Adults								
Task 1 First Use	132	91	34	7	94.7%	√	89.4%	√
Task 2 Cleaning	132	81	49	2	98.5%	√	94.6%	√
Task 3 Routine Use	132	110	21	1	99.2%	√	95.9%	√
Question-4 Dose Indicator	132	130	-	2	98.5%	√	94.6%	√
Question-5 Dropped Device	132	128	-	4	97.0%	√	92.4%	√
Question-6 Hold Inhaler Properly	132	132	-	0	100.0%	√	97.2%	√
All Task/Question-1 to 6					98.0%	√	94.0%	√
Teens								
Task 1 First Use	19	14	4	1	94.7%	√	74.0%	x
Task 2 Cleaning	19	10	7	2	89.5%	√	66.9%	x
Task 3 Routine Use	19	18	0	1	94.7%	√	74.0%	x
Question-4 Dose Indicator	19	19	-	0	100.0%	√	82.4%	x
Question-5 Dropped Device	19	19	-	0	100.0%	√	82.4%	x
Question-6 Hold Inhaler Properly	19	19	-	0	100.0%	√	82.4%	x
All Task/Question-1 to 6					96.5%	√	77.0%	x

Source: The Applicant's table, page 54 of 80 in the HF G3 study report.

5.4.2 Gender

The results for ARs and their 95% LCI for the gender groups were summarized in Table 35. The ARs and their 95% LCIs for 5 of 6 Tasks/Questions in male subgroup were above 85%, except the LCI for Task-1 was 79.3%. The ARs and their 95% LCIs for all 6 Tasks/Questions in female subgroup were above 85%.

Table 35: Subgroup Analysis for CBTs and ALHFQs by Gender – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
Males								
Task 1 First Use	72	43	21	8	88.9%	√	79.3%	x
Task 2 Cleaning	72	42	27	3	95.8%	√	88.3%	√
Task 3 Routine Use	72	60	11	1	98.6%	√	92.5%	√
Question-4 Dose Indicator	72	70	-	2	97.2%	√	90.3%	√
Question-5 Dropped Device	72	69	-	3	95.8%	√	88.3%	√
Question-6 Hold Inhaler Properly	72	72	-	0	100.0%	√	95.0%	√
All Task/Question-1 to 6					96.1%	√	89.0%	√
Females								
Task 1 First Use	79	62	17	0	100.0%	√	95.4%	√
Task 2 Cleaning	79	49	29	1	98.7%	√	93.2%	√
Task 3 Routine Use	79	68	10	1	98.7%	√	93.2%	√
Question-4 Dose Indicator	79	79	-	0	100.0%	√	95.4%	√
Question-5 Dropped Device	79	78	-	1	98.7%	√	93.2%	√
Question-6 Hold Inhaler Properly	79	79	-	0	100.0%	√	95.4%	√
All Task/Question-1 to 6					99.4%	√	94.3%	√

Source: the Applicant's table, page 55 of 80 in the HF G3 study report.

5.4.3 Race

The results for ARs and their 95% LCI for the three race groups (White, African-America and Others) were summarized in Table 36. For white (Caucasian, n=120) subgroup, the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For African-American (n=24) subgroup The ARs for 5 of 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 5 of 6 Tasks/Questions were lower than 85%. For other race subgroup (n=7), the ARs were higher than 85%; however, the 95% LCIs of ARs were lower than 85% due to the small sample size.

Table 36: Subgroup Analysis for CBTs and ALHFQs by Race – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
White (Caucasian)								
Task 1 First Use	120	88	29	3	97.5%	√	92.9%	√
Task 2 Cleaning	120	70	47	3	97.5%	√	92.9%	√
Task 3 Routine Use	120	105	15	0	100.0%	√	97.0%	√
Question-4 Dose Indicator	120	120	-	0	100.0%	√	97.0%	√
Question-5 Dropped Device	120	118	-	2	98.3%	√	94.1%	√
Question-6 Hold Inhaler Properly	120	120	-	0	100.0%	√	97.0%	√
All Task/Question-1 to 6					98.9%	√	95.1%	√
African-American								
Task 1 First Use	24	13	6	5	79.2%	x	57.9%	x
Task 2 Cleaning	24	15	8	1	95.8%	√	78.9%	x
Task 3 Routine Use	24	17	5	2	91.7%	√	73.0%	x
Question-4 Dose Indicator	24	22	-	2	91.7%	√	73.0%	x
Question-5 Dropped Device	24	22	-	2	91.7%	√	73.0%	x
Question-6 Hold Inhaler Properly	24	24	-	0	100.0%	√	85.8%	√
All Task/Question-1 to 6					91.7%	√	73.6%	x
Others								
Task 1 First Use	7	4	3	0	100.0%	√	59.0%	x
Task 2 Cleaning	7	6	1	0	100.0%	√	59.0%	x
Task 3 Routine Use	7	6	1	0	100.0%	√	59.0%	x
Question-4 Dose Indicator	7	7	-	0	100.0%	√	59.0%	x
Question-5 Dropped Device	7	7	-	0	100.0%	√	59.0%	x
Question-6 Hold Inhaler Properly	7	7	-	0	100.0%	√	59.0%	x
All Task/Question-1 to 6					100.0%	√	59.0%	x

Source: The Applicant's table, page 56 of 80 in the HF G3 study report.

5.4.4 Experience of use MDI inhaler

The results for ARs and their 95% LCI for the prior inhaler experience (Naïve and Experienced) were summarized in Table 37. For inhaler naïve subgroup (n=112), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For experienced subgroup (n=39), the ARs for all 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 4 of 6 Tasks/Questions were lower than 85%.

Table 37: Subgroup Analysis for CBTs and ALHFQs by Prior Inhaler Experience – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Inhaler Naïve								
Task 1 First Use	112	80	29	3	97.3%	√	92.4%	√
Task 2 Cleaning	112	65	45	2	98.2%	√	93.7%	√
Task 3 Routine Use	112	96	15	1	99.1%	√	95.1%	√
Question-4 Dose Indicator	112	112	-	0	100.0%	√	96.8%	√
Question-5 Dropped Device	112	111	-	1	99.1%	√	95.1%	√
Question-6 Hold Inhaler Properly	112	112	-	0	100.0%	√	96.8%	√
All Task/Question-1 to 6					99.0%	√	95.0%	√
Experienced								
Task 1 First Use	39	25	9	5	87.2%	√	72.6%	x
Task 2 Cleaning	39	26	11	2	94.9%	√	82.7%	x
Task 3 Routine Use	39	32	6	1	97.4%	√	86.5%	√
Question-4 Dose Indicator	39	37	-	2	94.9%	√	82.7%	x
Question-5 Dropped Device	39	36	-	3	92.3%	√	79.1%	x
Question-6 Hold Inhaler Properly	39	39	-	0	100.0%	√	91.0%	√
All Task/Question-1 to 6					94.4%	√	82.4%	x

Source: The Applicant's table, page 59 of 80 in the HF G3 study report.

5.4.5 The total time taken by the participant used to read E004 IFU

The results for ARs and their 95% LCI for the two labelling reading time categories (≥1 minute and <1 minute) were summarized in Table 38. For the subgroup who spent 1 minute or more (n=145), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For the subgroup who spent less than 1 minute (n=6), the ARs and 3 of 6 Tasks or Questions were less 85%.

Table 38: Subgroup Analysis for CBTs and ALHFQs by IFU Reading Time – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Total Reading Time ≥ 1 minute								
Task 1 First Use	145	104	36	5	96.6%	√	92.1%	√
Task 2 Cleaning	145	90	51	4	97.2%	√	93.1%	√
Task 3 Routine Use	145	122	21	2	98.6%	√	95.1%	√
Question-4 Dose Indicator	145	144	-	1	99.3%	√	96.2%	√
Question-5 Dropped Device	145	142	-	3	97.9%	√	94.1%	√
Question-6 Hold Inhaler Properly	145	145	-	0	100.0%	√	97.5%	√
All Task/Question-1 to 6					98.3%	√	94.7%	√
Total Reading Time: < 1 minute								
Task 1 First Use	6	1	2	3	50.0%	x	11.8%	x
Task 2 Cleaning	6	1	5	0	100.0%	√	54.1%	x
Task 3 Routine Use	6	6	0	0	100.0%	√	54.1%	x
Question-4 Dose Indicator	6	5	-	1	83.3%	x	35.9%	x
Question-5 Dropped Device	6	5	-	1	83.3%	x	35.9%	x
Question-6 Hold Inhaler Properly	6	6	-	0	100.0%	√	54.1%	x
All Task/Question-1 to 6					86.1%	√	41.0%	x

Source: The Applicant's table, page 61 of 80 in the HF G3 study report.

5.4.6 Participant Categories

The results for ARs and their 95% LCI for the 5 participant categories (Adult, naïve and normal literacy; Adult, experienced and normal literacy; Adult, naïve and low literacy; Adult, experienced and low literacy; and Teen) were summarized in Table 39.

For the "Adults, naïve, normal literacy" subgroup (n=86), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For the "Adults, experienced, normal literacy" subgroup (n=27), the ARs for all 6 Tasks/Questions were above 85%, and 3 of 6 LCI for ARs were lower than 85%. For the "Adults, naive, low literacy" subgroup (n=14), the ARs for all 6 Tasks/Questions were above 85%, and all of 6 LCI for ARs were lower than 85%. For the "Adults, experienced, low literacy" subgroup (n=5), the ARs for 2 of 6 Tasks/Questions were above 85%, and all of 6 LCI for ARs were lower than 85%. For "teens" subgroup (n=19), the ARs for all 6 Tasks/Questions were above 85%, but none of the 6 LCI for ARs were above 85%.

Table 39: Subgroup Analysis for CBTs and ALHFQs by Multiple Factors – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Adults, Naive, Normal Literacy								
Task 1 First Use	86	63	22	1	98.8%	√	93.7%	√
Task 2 Cleaning	86	49	37	0	100.0%	√	95.8%	√
Task 3 Routine Use	86	75	11	0	100.0%	√	95.8%	√
Question-4 Dose Indicator	86	86	-	0	100.0%	√	95.8%	√
Question-5 Dropped Device	86	85	-	1	98.8%	√	93.7%	√
Question-6 Hold Inhaler Properly	86	86	-	0	100.0%	√	95.8%	√
All Task/Question-1 to 6					**99.6%**	√	**95.1%**	√
Adults, Experienced, Normal Literacy								
Task 1 First Use	27	20	5	2	92.6%	√	75.7%	x
Task 2 Cleaning	27	21	5	1	96.3%	√	81.0%	x
Task 3 Routine Use	27	23	4	0	100.0%	√	87.2%	√
Question-4 Dose Indicator	27	27	-	0	100.0%	√	87.2%	√
Question-5 Dropped Device	27	26	-	1	96.3%	√	81.0%	x
Question-6 Hold Inhaler Properly	27	27	-	0	100.0%	√	87.2%	√
All Task/Question-1 to 6					**97.5%**	√	**83.2%**	x
Adults, Naive, Low Literacy								
Task 1 First Use	14	7	5	2	85.7%	√	57.2%	x
Task 2 Cleaning	14	7	6	1	92.9%	√	66.1%	x
Task 3 Routine Use	14	10	4	0	100.0%	√	76.8%	x
Question-4 Dose Indicator	14	14	-	0	100.0%	√	76.8%	x
Question-5 Dropped Device	14	14	-	0	100.0%	√	76.8%	x
Question-6 Hold Inhaler Properly	14	14	-	0	100.0%	√	76.8%	x
All Task/Question-1 to 6					**96.4%**	√	**71.8%**	x
Adults, Experienced, Low Literacy								
Task 1 First Use	5	1	2	2	60.0%	x	14.7%	x
Task 2 Cleaning	5	4	1	1	100.0%	√	47.8%	x
Task 3 Routine Use	5	2	2	1	80.0%	x	28.4%	x
Question-4 Dose Indicator	5	3	-	2	60.0%	x	14.7%	x
Question-5 Dropped Device	5	3	-	2	60.0%	x	14.7%	x
Question-6 Hold Inhaler Properly	5	5	-	0	100.0%	√	47.8%	x
All Task/Question-1 to 6					**76.7%**	x	**28.0%**	x
Teens								
Task 1 First Use	19	14	4	1	94.7%	√	74.0%	x
Task 2 Cleaning	19	10	7	2	89.5%	√	66.9%	x
Task 3 Routine Use	19	18	0	1	94.7%	√	74.0%	x
Question-4 Dose Indicator	19	19	-	0	100.0%	√	82.4%	x
Question-5 Dropped Device	19	19	-	0	100.0%	√	82.4%	x
Question-6 Hold Inhaler Properly	19	19	-	0	100.0%	√	82.4%	x
All Task/Question-1 to 6					**96.5%**	√	**77.0%**	x

Source: The Applicant's table, page 62 of 80 in the HF G3 study report.

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/s/

RIMA IZEM

12/07/2016

The primary statistical reviewer and author of this review is Dr. Yueqin Zhao. Dr. Zhao is not submitting this review because she is on maternity leave. Thus, this review is submitted by Team Leader Rima Izem after completion of the secondary and tertiary reviews.

MARK S LEVENSON

12/07/2016

Statistical Review and Evaluation

NDA #	205920
SDN # / eCTD SN #	37/0035
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Drug	Epinephrine Inhalation Aerosol (E004)
Indication	For the temporary relief of mild symptoms of intermittent asthma
Sponsor	Armstrong Pharmaceuticals Inc.
Document location	\\cdsesub1\evsprod\NDA205920\0035

Statistical Reviewer	Scott Komo
Concurring Reviewer	Karen Higgins
Biometrics Division	Division of Biometrics IV
Clinical Reviewer	Ryan Raffaelli
Social Scientist	Barbara Cohen
Project Manager	Daniel Reed
Medical Division	Division of Nonprescription Drug Products (DNDP)

1. Introduction and Background

This submission contains a meeting request and briefing document for a meeting held with the sponsor on 10/1/14. A complete response letter was issues by the Agency for this NDA on 5/22/14. This meeting was a type A meeting to discuss steps to be taken for the approval of NDA 208920.

The complete response letter stated that to address the clinical deficiencies the sponsor would need

- to revise the labeling to optimize comprehension and to assess the revised labeling with a label comprehension study,
- to conduct a behavioral (human factors) study with the revised labeling using the actual product to assess consumers' ability to use epinephrine HFA inhalation aerosol, and
- to conduct a randomized, actual use study with the revised labeling and proposed epinephrine HFA inhalation aerosol to quantify and evaluate complaints or problems associated with the use of the product and to characterize sources of user error.

This review will focus only on the consumer behavioral studies.

2. Submission Summary

To address the clinical deficiencies outlined in the complete response letter, the sponsor plans on conducting label comprehension studies, a human factors study and an actual use study. (b) (4)

The sponsor has completed two pilot label comprehension studies and a larger label comprehension study, Study E004-F4 (LCS-4), in approximately 500 subjects. A second label comprehension study, Study E004-F5 (LCS-5) also in approximately 500 subjects, is in progress. These studies include the following items:

i. Prime before first use
ii. Clean on each day of use
iii. Re-prime when wet
iv. Do not rely on the dose indicator if dropped
v. Instructions on removing the canister for cleaning
vi. Proper reassembly after cleaning
vii. Press on the center of the dose indicator
viii. Orientation of product during use and storage.

The sponsor states that subjects performed very well in LCS-4, though the item regarding re-priming was low. The insert has been modified to chance the position of the instructions regarding re-priming if wet. LCS-5 will be used to confirm if the improved labeling is effective.

A pilot behavior study in approximately 12 subjects will be performed prior to a larger behavioral study, E004-G2, in approximately 150 subjects. The following will be included as endpoints:

- Understanding of the need to initially prime and subsequently clean the product
- Performance of appropriate cleaning of the device with a sink.
- Understanding of the need to remove the canister in order to clean the product
- Demonstration that consumers can correctly reassemble the product after cleaning or before use
- Adequate assessment of consumers with low literacy

(b) (4)

[redacted]

3. Comments

The following comments are regarding the behavioral studies.

Question 2: The Company will conduct a behavioral (human factors) study with the revised label using the actual product to assess consumer's ability to use E004 in an

OTC setting. Would the Agency agree that the revised E004 insert has addressed the concerns of the Agency?

We are not able to answer this question without more information about the label comprehension studies that were conducted.

Question 3: (b) (4)

(b) (4)

Preliminary meeting comments were sent to the sponsor on 9/29/14. See meeting minutes for a summary of the discussion.

No comments need to be sent to the sponsor at this time.

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

/s/

SCOTT S KOMO
04/30/2015

KAREN M HIGGINS
05/01/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205,920
Drug Name:	(b) (4) (Epinephrine Inhalation Aerosol - hydrofluoroalkane, 125 mcg/actuation)
Indication(s):	Temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath
Applicant:	Armstrong Pharmaceuticals, Inc.
Date(s):	7/22/13 (received)
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, DrPH
Concurring Reviewers:	Karen Higgins, ScD Daphne Lin, PhD
Medical Division:	Division of Nonprescription Clinical Evaluation
Clinical Team:	Barbara Cohen, MPA Ryan Raffaelli, MD Theresa Michele, MD
Project Manager:	Daniel Reed, MPH

Keywords: labeling

Table of Contents

1 EXECUTIVE SUMMARY

An NDA was submitted for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) dispensed using a metered dose inhaler (MDI). Epinephrine-HFA is a short-acting $beta_2$-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath. This statistical review will focus on the consumer studies, specifically the label comprehension and behavioral studies, submitted in this NDA.

The application contained three label comprehension studies (LCS), conducted to evaluate whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). The Applicant was told that the LCS did not need to evaluate all the elements of the label; it would only need to test items that differed between the labels for the epinephrine HFA and epinephrine CFC products. After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, a consumer behavior study was performed, which was included in the application. In the behavioral study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling.

The label comprehension studies all enrolled more than four hundred subjects, who were 16 years of age or older, from multiple retail sites. The studies used an iterative study design in which initial testing in the first LCS, LCS1, led to modifications to the DFL and PI. The modified statements were tested in the second LCS, LCS2. In addition, changes were made to the questionnaire wording, where LCS1 responses indicated a question was unclear. In a similar fashion, labeling was refined prior to the start of the third LCS, LCS3, to improve upon any items where consumers did not demonstrate adequate comprehension.

The label comprehension studies focused on undercounting of the dose indicator. LCS3 showed improved subject comprehension over LCS1 and LCS2 for the objective that the dose indicator reading cannot be trusted if the inhaler is dropped. However, comprehension still fell slightly below the 85% threshold in normal literacy subjects. In LCS2, subject comprehension for the communication objectives related to what to do when the dose indicator reaches “0” met the 85% performance threshold in normal literacy subjects and was not re-tested in LCS3. It should be noted that the Applicant assessed comprehension relative to the performance threshold of 85% for only the normal literacy cohort rather than the general population in which this analysis is typically performed. The general population includes both normal and low literacy subjects. Assessing performance relative to the threshold in only the normal literacy cohort could potentially bias the decision toward meeting the threshold because normal literacy subjects usually have higher comprehension rates than low literacy subjects.

The behavioral study was conducted in 61 subjects (>12 years old) from two sites. This study assessed consumers’ ability to carry out tasks related to use and maintenance of the MDI: (i) prime/re-prime the inhaler, (ii) clean the inhaler, (iii) reassemble the inhaler, (iv) correctly position the inhaler, and (v) actually deliver a dose following the insert instructions only.

Subjects did not meet the performance threshold for any of the tasks related to priming, although the performance for one task almost met the threshold. Performance in the priming task related to shaking the inhaler fell far below the performance threshold. For the cleaning tasks, subjects met the performance threshold only for one subtask although performance in another subtask almost met the threshold. Performance in cleaning tasks related to washing the mouthpiece fell far below the threshold. For the finger placement task, the performance threshold was also not met. Finally, for the medicating tasks, the performance threshold was met for almost all of the subtasks with the exception of the shaking the inhaler subtask where the performance fell far below the performance threshold.

There are concerns with the ability of subjects to correctly use the product based on the results of the behavioral study where the performance for tasks related to shaking the inhaler and washing the mouthpiece fell far below the 85% performance threshold. Shaking the inhaler is a potential issue because the product is a suspension and lack of shaking could potentially result in dose variability leading to the administration of higher doses. Washing the mouthpiece properly is an issue because HFA inhalers are prone to clogging.

The Applicant posits that subjects' performance in the tasks of shaking the inhaler and washing the mouthpiece would be expected to improve with continued use and familiarity with the product. Unfortunately, they provided no evidence for this statement. They also stated that the artificial nature of testing environment may have influenced the performance. While this may be true, the lack of data from an actual use study gives us no way to determine the performance in a less artificial setting.

2 INTRODUCTION

2.1 Overview

An application was submitted for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) at a dose of 125 mcg/inhalation dispensed using a metered dose inhaler (MDI). Epinephrine-HFA is a short-acting beta$_2$-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed dosing is one or two inhalations; subjects should wait at least 4 hours between dosing and should not exceed 8 inhalations in 24 hours. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath.

The active ingredient, epinephrine, is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. It is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation.

Epinephrine-HFA MDI is proposed as an alternative to the previously marketed Primatene® Mist epinephrine MDI, which was removed from the market in 2011 due to the phase out of ozone-depleting chlorofluorocarbon (CFC) propellants under the Montreal Protocol. Of note, this product was not removed from the market due to reasons of safety or efficacy.

The product is a standard MDI that comes assembled. In order to use the device, it must first be shaken and primed. It must also be primed if not used for more than 2 days, if it is still wet after cleaning, or if it is dropped. In addition, the device must be shaken immediately prior to dosing because the product is a suspension and settling may occur if the device is not shaken. The device also requires cleaning by disassembling the device and washing with warm water on a daily basis.

The epinephrine HFA MDI includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the MDI no longer advance the display. Instructions also note that if the MDI is dropped, the dose indicator is no longer reliable and patients must keep track of the number of sprays taken. The inhaler should be held with the dose indicator facing upward during actuation otherwise only the propellant may be discharged. The package instructions note that a finger must be placed on the center of the dose indicator during actuation.

The application contained three label comprehension studies (LCS), conducted to evaluate whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). After the Applicant determined that the label comprehension studies

showed an adequate consumer understanding of the labeling, a consumer behavior study was performed, which was included in the application. In the behavioral study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling.

This statistical review will focus on the consumer studies, specifically the label comprehension and behavioral studies, submitted in this NDA.

Regulatory history

Epinephrine, one of the first sympathomimetic agents in medicine, has been marketed in the United States in a variety of different formulations since 1901, with use in the treatment of asthma dating back to the early 1900s. The first route of administration widely used was intravenous or subcutaneous injection; later, administration by oral inhalation was adopted. Epinephrine in an MDI formulation utilizing CFCs (Primatene® Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967. Beginning in 1996, MDIs using CFC propellants began to be phased out to protect the environment under the Montreal Protocol. The process for the phase out of CFC use for epinephrine MDIs began in 2006 with an FDA advisory committee meeting, a proposed rule in 2007, and a public meeting in 2007. In the 2007 proposed rule, FDA proposed an end date (effective date) of December 31, 2010, for the use of CFCs for epinephrine MDIs. In comments on the proposed rule, the manufacturer of epinephrine CFC MDIs requested additional time (December 31, 2011) to reformulate the product. The Final Rule was published in 2008 and based upon a request from the manufacturer, the end date (effective date) for use of CFCs for epinephrine MDIs was December 31, 2011.

At an EOP2 meeting that occurred on 10/29/2010, the Applicant was told that they would need to assess device performance, including ruggedness and reliability. Subsequently at the pre-NDA meeting, which occurred on 9/23/2011, the Sponsor was told a large (n~300) label comprehension/behavioral use trial was required and concerns were raised regarding the product's potential need for once-daily cleaning, which prompted the Agency to request device performance data under different in-use conditions to assess the impact of not cleaning the mouthpiece as directed. In addition, the Applicant was reminded to assess potential malfunctioning of the device with real-life usage. In addition, the Sponsor was also told that the label comprehension study would not need to evaluate all the elements of the label; it should test only items that differ between the labels for the epinephrine HFA and epinephrine CFC products. Finally, it was also stated by the Agency that if the directions with regard to administering the drug are not the same as Primatene Mist (e.g., priming, re-priming, cleaning the device and proper dosing which includes the timing of inhalation with respect to timing of actuation), a behavioral use study was needed to assure that consumers could administer and use the drug properly. Differences in the propellant resulted in changes in the directions for priming, re-priming, and cleaning of the device that necessitated a need for the behavioral study.

The Agency also provided feedback to the Applicant on 4/23/2012 on a proposed label comprehension study. Subsequently at a second Pre-NDA meeting, the Agency again recommended that the NDA submission include evaluations of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging as well as justification for device cleaning instructions.

On 4/8/2013, the Applicant submitted an NDA (under NDA 205,496) that the Agency refused to file due to a number of deficiencies that did not allow a substantive review. These deficiencies included:

- Poor organization of the application and the inability to navigate the application that did not allow substantive review to begin.
- Documents that did not conform to either specifications for eCTDs or the requirements stipulated in the CFR.
- The application did not include a formal benefit-risk analysis.
- Datasets were not provided for the consumer behavior studies
- Analysis datasets were not provided for the clinical efficacy studies

The NDA was resubmitted on 7/22/13 with these deficiencies addressed. As stated above, the NDA contains label comprehension studies and a behavioral study. A consumer behavioral actual use study, which collected device performance data, was not conducted. However, the Applicant stated that they collected information on device performance in the efficacy study that will not be addressed in this review.

2.2 Data Sources

The consumer studies submitted in the application are presented in the following table.

Table 1: List of all studies included in analysis

Applicant defined study number	*Study Type*	*# of Subjects*
E004-F-LCSI (LCS1)	Label Comprehension	432 (110 low literacy)
E004-F-LCSII (LCS2)	Label Comprehension	442 (125 low literacy)
E004-F-LCSIII (LCS3)	Label Comprehension	471 (122 low literacy)
E004-G	Behavioral Study	61 (5 low literacy)

Clinical study reports, datasets, and SAS programs are available at:

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission contained analysis datasets along with a define.pdf and an annotated CRF for the consumer studies (label comprehension and behavioral studies).

There were two data quality issues with the behavioral study datasets. The first issue was that the dataset did not have a variable representing the site where the subject was tested. The second issue was that the dataset did not contain the results of the reconciliation when the two interviewers initially disagreed.

The first data quality issue was that the dataset did not contain a site variable so it was not possible to determine at which site the subjects were tested. In response to an information request

(IR), the Applicant stated that Subjects 1 – 37 were tested at Site 1 (Salt Lake City) and Subjects 38 – 61 were tested at Site 2 (Los Angeles, CA).

The second data quality issue was that the dataset did not contain the results of the reconciliation when the two interviewers initially disagreed. In the behavioral study, two interviewers observed the subjects as they performed the required tasks. If they disagreed, the two interviewers jointly reviewed their ratings and determined if the discrepancy could be resolved through discussion. However, if they could not come to agreement, a third independent reviewer evaluated the video recordings and resolved the discrepancy. Based on the response to an IR, (b) (4) all three ratings should be captured in the dataset. After an IR was sent to the Applicant, they submitted a dataset for review that contained the ratings for the two reviewers as well as either the reconciled rating or the rating of the third reviewer when the two reviewers disagreed.

3.2 Evaluation of Efficacy

3.2.1 Label Comprehension Studies

3.2.1.1 Study Design and Endpoints

The application contained three label comprehension studies, LCS1, LCS2 and LCS3. These studies evaluated whether consumers could understand the information on E004 Drug Facts Label (DFL) and package insert (PI), particularly focusing on consumer comprehension of the updated elements related to (1) how to prime the inhaler; (2) how to clean the mouthpiece; (3) how to re-assemble the inhaler; (4) how to correctly place finger on the canister to actuate the inhaler; and (5) how to dose with the inhaler that were new or revised from the Primatene® Mist labels. As discussed earlier in the regulatory history section, the label comprehension studies focused on the updated elements of the label.

In all three (3) label comprehension studies, trials were designed to enroll approximately 470 subjects per trial aged >16 yr. old. The studies used an iterative study design in which initial testing in LCS1 led to modifications to the DFL (see Appendix A.1 for proposed DFL) and PI (see Appendices A.2 and A.3 for the proposed PI). The modified statements were tested in LCS2. In addition, changes were made to the questionnaire wording, where LCS1 responses indicated a question was unclear. In a similar fashion, labeling and questions were refined prior to the start of the LCS3 to improve upon any items where consumers did not demonstrate adequate comprehension.

In LCS1 and LCS2, the primary objectives in testing the labeling focused on consumer understanding of the following three label directions:

1. If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records.
2. The dose indicator will stop counting at "0" and the inhaler must be replaced.
3. Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.

In contrast, LCS3 focused only on the first primary objective because the Applicant determined that comprehension for the second and third objectives was demonstrated in LCS2.

The secondary objectives in all three label comprehension studies were:

- Never try to change the numbers or take the dose indicator off the metal canister.
- The inhaler should be cleaned at the end of the day after use.
- Once the red zone appears and the display reads — 20, you should obtain a new (b) (4) inhaler soon
- You must maintain (re-prime) your inhaler under specific circumstances
- (b) (6). The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler

Retail sites (large shopping malls) at which subjects were recruited were selected from across the United States. Recruiters from the research facility, who were themselves trained to use the screening instrument, approached and screened potential subjects in a consumer traffic area of the shopping center immediately around the research facility. The sites used in the studies are listed in Table 2.

Table 2: Sites for Label Comprehension Studies

Research Site	Geographical Area	Study I	Study II	Study III
Mall of America	Bloomington, MN	✓		
Mainplace Mall	Santa Ana, CA	✓		
Tacoma Mall	Tacoma, WA	✓		
Citrus Park Mall	Tampa, FL	✓		
Neshaminy Mall	Bensalem, PA	✓		
Discover Mills Mall	Lawrenceville, GA	✓		
North Star Mall	San Antonio, TX	✓		✓
Northlake Mall	Charlotte, NC	✓		
PEGUS Research	Salt Lake City, UT	✓	✓	✓
Twin Peaks Mall	Longmont, CO		✓	
Gateway Mall	Springfield, OR		✓	
Moreno Valley Mall	Moreno Valley CA		✓	
Spring Hill Mall	West Dundee, IL		✓	

Voorhees Mall	Voorhees, NJ	✓	
Greenspoint Mall	Houston, TX	✓	
Arsenal Mall	Watertown, MA	✓	
Colorado Mills Mall	Lakewood, CO		✓
Montclair Plaza	Montclair, CA		✓

Source: LCS Summary Report, Table 4

Subjects were recruited and screened for minimal entry criteria. One-on-one interviews were then conducted with participants, in which participants were asked questions from a standardized questionnaire to assess each communication objective and message. The questionnaire primarily consisted of open-ended questions, including direct questions and hypothetical scenarios. No multiple-choice questions were used. These responses were subsequently scored as correct or acceptable (with both counting towards comprehension statistics), or incorrect. At the conclusion of the label comprehension interview, incorrect responses were reviewed with participants to determine where confusion occurred and why incorrect responses were given. These debriefing responses were not used to mitigate incorrect responses.

Literacy was measured using Rapid Estimate of Adult Literacy in Medicine (REALM) for participants 18 years of age and older and Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) for participants 16-17. Low literacy was defined as a REALM score ≤60 or a REALM-Teen score ≤62 for LCS1 and LCS2 and REALM-Teen score≤61 for LCS3.

Approximately 25% of the subjects were targeted to be low literacy based on the REALM or REALM-Teen. In addition, the studies targeted to enroll approximately fifty (50) subjects who reported use of Primatene® MIST in the previous five years to ascertain if consumers with previous product experience would override the new information on the epinephrine HFA package and answer based on their experience with Primatene® MIST rather than on the new information on the label and/or package insert.

Subject's responses were classified as correct, acceptable, or incorrect with the classification of correct and acceptable response categories determined *a priori*. Assessment of subjects' comprehension will be based on the proportion of subjects who adequately comprehend the communication objectives with adequate comprehension defined as providing either a correct or acceptable response.

3.2.1.2 Statistical Methodologies

The sample size of approximately 470 analyzable subjects provided approximately 90% power for the study to meet the performance standard of 85% using a 2-sided alpha of 0.05 assuming a comprehension rate of 90%.

Comprehension of the specified communication messages was evaluated by determining whether the lower bound of a two-sided 95% confidence interval (calculated with binomial standard errors) for the proportion of subjects who responded with either a correct or acceptable response

exceeded the 85% performance threshold for the primary communication objectives. The primary analysis was performed for all participants reviewing the label and also by literacy level.

Though the Applicant appeared to have determined the sample size and power based on the assessment of the general population meeting the threshold, the Applicant stated in both protocols and study reports that comprehension should be assessed against the performance threshold for the normal literacy group only rather than for the general population, in which this analysis is typically performed. The general population includes both normal and low literacy subjects. Assessing performance relative to the threshold in only the normal literacy cohort is likely to bias the decision toward meeting the threshold because normal literacy subjects usually have higher comprehension rates than low literacy subjects.

To justify the performance thresholds used in the label comprehension studies, the Applicant stated that that the clinical risk of undercounting the number of doses was identified as of primary importance. They subsequently determined that undercounting could be caused by either the consumer not correctly understanding how to interpret the dose counter readings or due to a malfunction of the inhaler that causes an incorrect dosage use display, which for example could be caused by dropping the inhaler or a manufacturing defect.

They were concerned if consumers did not adequately comprehend these label messages, there would be a potential safety risk in the event that the amount of medicine remaining in the inhaler is overestimated. However, they felt that the potential safety risk was low because the proposed product is labeled for the temporary relief of mild symptoms of intermittent asthma. They also added instructions to the DFL providing consumers guidance on what to do if they did not experience relief after use of the product.

The other primary objectives used related to the risk that the consumer may continue to use the product when the dose indicator reads — 0. If this occurred, the dispensing of a correct amount of medication cannot be assured because an unknown amount of medication is left in the canister. They were concerned that the user may not achieve symptom relief because of inadequate dosing, potentially leading to safety risks. Again, they felt the risk of this was low because the proposed indication is for the temporary relief of mild symptoms of intermittent asthma.

However, while the Applicant did provide reasons why the safety risk for undercounting was low and also stated how they would mitigate the safety risk by adding instructions to the DFL to tell consumers what actions to take if they did not experience symptom relief, they did not explicitly state why the performance threshold should be 85%.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics for LCS1

The Applicant enrolled fewer subjects (432) than planned (471) because of recruitment difficulties, (e.g., low response rate and low foot traffic in some malls).

As can be seen in Table 3, there was approximately an equal representation of male and female subjects. In addition, for education, 27.5% were high school graduates, 35.9% had some college

experience, and 22.7% were college graduates and a total of 7.9% of subjects did not finish high school. The racial distribution in the study was: 46.8% White, 12.7% Hispanic or Latino, and 32.4% Black or African American, with other races accounting for the remaining 8.1%. The mean age of subjects was 39.4 years (SD = 15.8) with an age range of 16 to 85 years old. The study enrolled 110 subjects, representing 25.5% of the sample, considered low literacy (read at an 8th grade reading level or below) as determined by the REALM Test or REALM Teen Test. Note, this low literacy rate met the target recruitment goal for low literate subjects (25%). In addition, the study also enrolled 71 subjects who were previous Primatene Mist users, which met the target recruitment goal of 50 prior Primatene users. It should be noted that there was a large amount of missing data for the question of prior Primatene Mist use (71.8%). Finally, slightly less than a third of the subjects reported suffering from asthma (28.2%).

Table 3: Demographics for LCS1

	Total (N=432)	Normal Literacy (N=322)	Low Literacy (N=110)
Gender			
Male	217 (50.2%)	155 (48.1%)	62 (56.4%)
Female	215 (49.8%)	167 (51.9%)	48 (43.6%)
Education			
8th grade or less	4 (0.9%)	3 (0.9%)	1 (0.9%)
Some high school	30 (6.9%)	14 (4.3%)	16 (14.5%)
High school graduate, GED, or certificate	119 (27.5%)	81 (25.2%)	38 (34.5%)
Some college or technical school	155 (35.9%)	118 (36.6%)	37 (33.6%)
College graduate	98 (22.7%)	83 (25.8%)	15 (13.6%)
Post-graduate degree	26 (6.0%)	23 (7.1%)	3 (2.7%)
Race			
White	202 (46.8%)	173 (53.7%)	29 (26.4%)
Black or African American	140 (32.4%)	83 (25.8%)	57 (51.8%)
Hispanic	55 (12.7%)	41 (12.7%)	14 (12.7%)
Asian	4 (0.9%)	3 (0.9%)	1 (0.9%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	1 (0.3%)	0 (0%)
American Indian or Alaska Native	7 (1.6%)	4 (1.2%)	3 (2.7%)
Other	23 (5.3%)	17 (5.3%)	6 (5.5%)
Age Groups			
Under 18	13 (3.0%)	3 (2.7%)	3 (2.7%)
18 to 24	91 (21.1%)	31 (28.2%)	31 (28.2%)
25 to 34	71 (16.4%)	27 (24.5%)	27 (24.5%)

35 to 44	101 (23.4%)	18 (16.4%)	18 (16.4%)
45 to 54	73 (16.9%)	20 (18.2%)	20 (18.2%)
55 to 64	51 (11.8%)	6 (5.5%)	6 (5.5%)
65 to 74	25 (5.8%)	5 (4.5%)	5 (4.5%)
75 to 84	6 (1.4%)	6 (1.9%)	0 (0.0%)
>=85	1 (0.2%)	1 (0.3%)	0 (0.0%)
Age Distribution			
Mean (SD)	39.4 (15.8)	40.9 (16.1)	35.0 (14.0)
Median	38	40	31
Range	16 - 85	16 – 85	16 – 69
Do you have asthma?			
Yes	122 (28.2%)	88 (27.3%)	34 (30.9%)
No	309 (71.5%)	233 (72.4%)	76 (69.1%)
Don`t know	1 (0.2%)	1 (0.3%)	0 (0.0%)
Have you used Primatene Mist within the past five years?			
Yes	71 (16.4%)	57 (17.7%)	14 (12.7%)
No	51 (11.8%)	31 (9.6%)	20 (18.2%)
Missing	310 (71.8%)	234 (72.7%)	76 (69.1%)

Source: LCS Summary Report, Table 9

3.2.1.4 Results and Conclusions for LCS1

The results for the primary communication objectives are shown in Table 4.

The comprehension rate for the first primary communication objective to not rely on the dose indicator after dropping the inhaler and to keep track of the number of sprays you use on your own records (Q9) was only 51.4% with a 95% CI of (46.6%, 56.2%).

Comprehension for the first primary communication objective fell far short of the 85% performance threshold with only 55.6% of normal literacy subjects providing a correct or acceptable response with a 95% CI of (50.0%, 61.1%).

As expected, there was a statistically significant association of literacy and the first comprehension objective (Chi-square=8.9, df=1, p=0.0028) where normal literacy subjects demonstrated much higher comprehension (55.6%) than low literacy subjects (39.1%).

Previous Primatene Mist users (46.5%) performed similarly to non-users (52.4%) with no statistically significant association between previous Primatene use and comprehension of the first primary communication objective (Chi-square=0.82, df=1, p=0.36).

For the second and third primary communication objectives which were tested together in one question, subjects performed much better than for the first primary communication objective with a comprehension rate of 87.0% with a 95% CI of (83.5%, 90.1%).

Comprehension for the second and third primary communication objectives in normal literacy subjects met the 85% performance threshold with 91.3% of normal literacy subjects providing a correct or acceptable response with a 95% CI of (87.7%, 94.1%).

Again, as expected, there was a statistically significant association of literacy and comprehension of the second and third primary communication objectives (Chi-square=20.4, df=1, p<0.0001) where normal literacy subjects demonstrated much higher comprehension (91.3%) than low literacy subjects (74.5%) for these objectives.

Previous Primatene Mist users (91.5%) performed similarly to non-users (86.1%) with no statistically significant association between previous Primatene use and comprehension of the second and third primary communication objectives (Chi-square=1.53, df=1, p=0.22).

Table 4: Results for the Primary Communication Objectives (LCS1)

Primary Communication Objectives	**Question# and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Low Literacy**	**Normal Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non-Users**
1. If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records.	**Question 9:** *Robert uses Primatene several times a week and usually carries it around with him. This morning he dropped his inhaler in the parking lot, so he re-primed it. Is there anything else that the package insert says Robert should do?*	51.4% (222/432) (46.6%, 56.2%)	39.1% (43/110) (29.9%, 48.9%)	55.6% (179/322) (50.0%, 61.1%)	46.5% (33/71) (34.5%, 58.7%)	52.4% (189/361) (47.1%, 57.6%)

2. The dose indicator will stop counting at –0 and the inhaler must be replaced. **3.** Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.	**Question 10:** *After using the inhaler, Jen noticed that the dose indicator was zero, but when she shakes the device she can tell there is medicine left in it. What does the package insert say about this?*	87.0% (376/432) (83.5%, 90.1%)	74.5% (82/110) (65.4%, 82.4%)	91.3% (294/322) (87.7%, 94.1%)	91.5% (65/71) (82.5%, 96.8%)	86.1% (311/361) (82.2%, 89.5%)

Source: Table 10, LCS Summary Report
* 2-sided 95% exact confidence interval

The results for the secondary communication objectives are presented in Table 5. Note these objectives were not evaluated using a performance threshold. Subjects did not perform well on the two questions related to re-priming (Q2 & Q7) with a comprehension rate of 42.1% and 61.8% for Q2 and Q7 respectively. Subjects also demonstrated poor comprehension (39.6%) that the dose indicator counts down by 20 after you spray 20 times rather than decreasing by one each time you spray the inhaler.

Table 5: Results for the Secondary Communication Objectives (LCS1)

Secondary Communication Objectives	**Question # and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Low Literacy**	**Normal Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non-Users**
1. Never try to change the numbers or take the dose indicator off the metal canister.	**Question 11:** *Jean sees that the dose indicator reads zero but she knows there is more medicine in the inhaler so she decides to change the dose indicator to show more sprays. What does the package insert say about this*?	87.7% (84.3%, 90.7%)	77.3% (68.3%, 84.7%)	91.3% (87.7%, 94.1%)	94.4% (86.2%, 98.4%)	86.4% (82.5%, 89.8%)

2. The inhaler should be cleaned at the end of the day after use	**Question 1:** *According to the package insert, when should the mouthpiece be cleaned?*	76.4% (72.1%, 80.3%)	67.3% (57.7%, 75.9%)	79.5% (74.7%, 83.8%)	74.6% (62.9%, 84.2%)	76.7% (72.0%, 81.0%)
3. Once the red zone appears and the display reads "20", you should obtain a new (b) (4) inhaler soon	**Question 6:** *According to the package insert, what does it mean when the red zone appears on the dose indicator?*	96.5% (94.3%, 98.0%)	96.4% (91.0%, 99.0%)	96.6% (94.0%, 98.3%)	97.2% (90.2%, 99.7%)	96.4% (93.9%, 98.1%)
4. You must maintain (re-prime) your inhaler under specific circumstances – Not used for a week	**Question 7:** *Sally has not used her inhaler for a week. What, if anything, does she need to do to it before using it again?*	61.8% (57.0%, 66.4%)	38.2% (29.1%, 47.9%)	69.9% (64.5%, 74.8%)	62.0% (49.7%, 73.2%)	61.8% (56.5%, 66.8%)
5. You must maintain (re-prime) your inhaler under specific circumstances – After Cleaning; before it is dry	**Question 2:** After cleaning, if the inhaler must be used before the mouthpiece is dry, what should you do before you can use it?	42.1% (37.4%, 46.9%)	23.6% (16.1%, 32.7%)	48.4% (42.9%, 54.1%)	47.9% (35.9%, 60.1%)	41.0% (35.9%, 46.3%)
6. (b) (4)	Question 4: About how many sprays are there in a full inhaler?	79.4% (75.3%, 83.1%)	74.5% (65.4%, 82.4%)	81.1% (76.3%, 85.2%)	88.7% (79.0%, 95.0%)	77.6% (72.9%, 81.8%)
7. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler	Question 8: *Jessica has just started using this inhaler for the first time. She has used two inhalations but noticed that the dose indicator hasn't changed. What does the package insert say about this?*	39.6% (34.9%, 44.4%)	26.4% (18.4%, 35.6%)	44.1% (38.6%, 49.7%)	46.5% (34.5%, 58.7%)	38.2% (33.2%, 43.5%)

Source: Table 11, LCS Summary Report
* 2-sided 95% exact confidence interval

3.2.1.5 Patient Disposition, Demographic and Baseline Characteristics for LCS2

In LCS2, the Applicant enrolled fewer subjects than planned (442 vs. 470) because of recruitment difficulties (e.g., low response rate and low foot traffic in some malls).

As can be seen in Table 6, there was an equal representation of male and female subjects. In addition, for education, 30% were high school graduates, 34% had some college experience, and 17% were college graduates and a total of 13% of subjects reported some high school education. The racial distribution in the study was: 49% White, 12% Hispanic or Latino, and 29% Black or African American, with other races accounting for the remaining 8%. The mean age of subjects was 38 years (SD = 16.1) with an age range of 16 to 92 years old. The study enrolled 125 subjects, which constituted 28% of the sample, considered low literacy (read at an 8th grade reading level or below) as determined by the REALM Test or REALM Teen Test. Note, this low literacy rate met the target recruitment goal for low literate subjects of 25%. In addition, the study also enrolled 100 subjects who were previous Primatene Mist users, which met the target recruitment goal of 50 prior Primatene users. Finally, slightly more than a third of the subjects reported suffering from asthma (34 %).

Table 6: Demographics for LCS2

	Total (N=442)	Normal Literacy (N=317)	Low Literacy (N=125)
Gender			
Male	221 (50.0%)	152 (47.9%)	69 (55.2%)
Female	221 (50.0%)	165 (52.1%)	56 (44.8%)
Education			
8th grade or less	3 (0.7%)	1 (0.3%)	2 (1.6%)
Some high school	57 (12.9%)	31 (9.8%)	26 (20.8%)
High school graduate, GED, or certificate	135 (30.5%)	80 (25.2%)	55 (44%)
Some college or technical school	150 (33.9%)	117 (36.9%)	33 (26.4%)
College graduate	76 (17.2%)	68 (21.5%)	8 (6.4%)
Post-graduate degree	21 (4.8%)	20 (6.3%)	1 (0.8%)
Race			
White	218 (49.3%)	180 (56.8%)	38 (30.4%)
Black or African American	130 (29.4%)	79 (24.9%)	51 (40.8%)
Hispanic	55 (12.4%)	28 (8.8%)	27 (21.6%)
Asian	2 (0.5%)	2 (0.6%)	(0 0%)
Native Hawaiian or Other Pacific Islander	2 (0.5%)	2 (0.6%)	(0 0%)
American Indian or Alaska Native	5 (1.1%)	4 (1.3%)	1 (0.8%)
Refused to Answer	2 (0.5%)	1 (0.3%)	1 (0.8%)
Other	28 (6.3%)	21 (6.6%)	7 (5.6%)

Age Groups			
Under 18	38 (8.6%)	26 (8.2%)	12 (9.6%)
18 to 24	81 (18.3%)	45 (14.2%)	36 (28.8%)
25 to 34	74 (16.7%)	48 (15.1%)	26 (20.8%)
35 to 44	105 (23.8%)	87 (27.4%)	18 (14.4%)
45 to 54	75 (17%)	54 (17%)	21 (16.8%)
55 to 64	39 (8.8%)	32 (10.1%)	7 (5.6%)
65 to 74	20 (4.5%)	17 (5.4%)	3 (2.4%)
75 to 84	8 (1.8%)	6 (1.9%)	2 (1.6%)
>=85	2 (0.5%)	2 (0.6%)	0 (0.0%)
Age Distribution			
Mean (SD)	37.9 (16.1)	39.7 (16.2)	33.2 (15.0)
Median	36.5	39	30
Range	16 - 92	16 - 92	16 - 80
Do you have asthma?			
Yes	149 (33.7%)	114 (36.0%)	35 (28.0%)
No	289 (65.4%)	199 (62.8%)	90 (72.0%)
Don`t know	4 (0.9%)	4 (1.3%)	0 (0 0%)
Have you used Primatene Mist within the past five years?			
Yes	100 (22.6%)	79 (24.9%)	21 (16.8%)
No	342 (77.4%)	238 (75.1%)	104 (83.2%)

Source: LCS-tables-and listings, Table DMT_LIT

3.2.1.6 Results and Conclusions for LCS2

The results for the primary communication objectives are shown in Table 7.

The comprehension rate for the first primary communication objective to not rely on the dose indicator after dropping the inhaler and to keep track of the number of sprays you use on your own records (Q10) was only 67.9% with a 95% CI of (63.3%, 72.2%).

Comprehension for the first primary communication objective fell far short of the 85% performance threshold with 72.6% of normal literacy subjects providing a correct or acceptable response with a 95% CI of (67.3%, 77.4%).

There was a statistically significant association of literacy and the first comprehension objective (Chi-square=11.3, df=1, p=0.008) where normal literacy subjects demonstrated much higher comprehension (72.6%) than low literacy subjects (56.0%).

Previous Primatene Mist users (69.0%) performed similarly to the non-users (67.5%) with no statistically significant association between previous Primatene use and comprehension of the first primary communication objective (Chi-square=0.08, df=1, p=0.78).

For the second and third primary communication objectives tested in question 11, subjects had a comprehension rate of 91.9% with a 95% CI of (88.9%, 94.2%).

Comprehension for the second and third primary communication objectives in normal literacy subjects met the 85% performance threshold with 93.1% of normal literacy subjects providing a correct or acceptable response with a 95% CI of (89.7%, 95.6%).

Normal literacy subjects (93.1%) demonstrated similar comprehension as low literacy subjects (88.8%) for these communication objectives with no statistically significant association of literacy and comprehension of the second and third primary communication objectives (Chi-square=2.17, df=1, p=0.14).

Previous Primatene Mist users (90.0%) performed similarly to the non-users (92.4%) with no statistically significant association between previous Primatene use and comprehension of the second and third primary communication objectives (Chi-square=0.59, df=1, p=0.44).

Table 7: Results for Primary Objective Comprehension (LCS2)

Primary Communication Objective(s)	**Question # and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Normal Literacy**	**Low Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non- Users**
1. If the inhaler is dropped, do not rely on the dose indicator. Keep track of the number of sprays.	Question 10: *Robert dropped his inhaler so he cleaned and re-primed it. Is there anything else that the package insert says Robert should do as he uses his inhaler*	67.9% (300/442) (63.3%, 72.2%)	72.6% (230/317) (67.3%, 77.4%)	56.0% (70/125) (46.8%, 64.9%)	69.0% (69/100) (59.0%, 77.9%)	67.5% (231/342) (62.3%, 72.5%)

2. The dose indicator will stop counting at –0 and the inhaler must be replaced. 3. Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured	**Question 11:** *After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like there is medicine left in it. What does the package insert say about this?*	91.9% (406/442) (88.9%, 94.2%)	93.1% (295/317) (89.7%, 95.6%)	88.8% (111/125) (81.9%, 93.7%)	90.0% (90/100) (82.4%, 95.1%)	92.4% (316/342) (89.1%, 95.0%)

* 2-sided 95% exact confidence interval
Source: Table 15, LCS Summary Report

The results for the secondary communication objectives are presented in Table 8. Note these objectives were not evaluated using a performance threshold. Subjects did not perform that well on the two questions related to re-priming (Q3 & Q8) with a comprehension rate of 71.7% and 78.5% for Q3 and Q8 respectively. Subjects also did not perform that well (77.4%) for the objective related cleaning the inhaler daily.

Table 8: Results of Secondary Communication Objectives (LCS2)

Secondary Communication Objective	**Question # and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Normal Literacy**	**Low Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non- Users**
1. Never try to change the numbers or take the dose indicator off the metal canister.	Question 12: *Jean decides to change the dose indicator to show more sprays. It did not work so she tried to remove the dose indicator. What does the package insert say about this?*	93.2% (90.5%, 95.4%	95% (91.9%, 97.1%)	88.8% (81.9%, 93.7%)	96% (90.1%, 98.9%)	92.4% (89.1%, 95.0%)

2. The inhaler should be cleaned daily.	Question 2: *According to the package insert, how often should the mouthpiece be cleaned?*	77.4% (73.2%, 81.2%)	84.2% (79.7%, 88.1%)	60% (50.9%, 68.7%)	82% (73.1%, 89.0%	76% (71.1%, 80.5%)
3. Once the red zone appears and the display reads "20", you should buy a new (b) (4) inhaler soon.	Question 7: *According to the package insert, what does it mean when the red zone appears on the dose indicator?*	99.5% (98.4%, 99.9%)	100% (98.8%, 100.0%)	98.4% (94.3%, 99.8%)	100% (96.4%, 100.0%)	99.4% (97.9%, 99.9%)
4. Re-prime your inhaler • If you have not used it in more than 2 days • If it must be used before the mouthpiece is dry	Question 3: *John cleaned his inhaler and it is still wet. Now he must use it before it is dry. What does the insert say he should do?* *(If only 'Let it dry overnight' or 'Air dry' selected in Q3, 3a was asked)* *3a. If John cannot let it <dry overnight or air dry>, and still must use it before it is dry, what does the package insert say John should do?*	71.7% (67.3%, 75.9%)	81.4% (76.7%, 85.5%)	47.2% (38.2%, 56.3%)	71% (61.1%, 79.6%)	71.9% (66.8%, 76.6%)

	Question 8: *Sally has not used her inhaler for about a week. What, if anything, does she need to do to the inhaler before using it again?* *(If only 'clean it' selected in Q8, 8a was asked)* *8a. After Sally has cleaned the inhaler, is there anything else she should do?*	78.5% (74.4%, 82.2%)	86.8% (82.5%, 90.3%)	57.6% (48.4%, 66.4%)	81% (71.9%, 88.2%)	77.8% (73.0%, 82.1%)
Secondary Communication Objective 5: The dose indicator starts at 160. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray	Question 4: *How do you tell if you have any sprays left in the container?*	93.9% (91.2%, 95.9%)	97.8% (95.5%, 99.1%)	84.0% (76.4%, 89.9%)	97.0% (91.5%, 99.4%)	93.0% (89.7%, 95.5%)
	Question 5: *About how many sprays are there in a full container?*	96.6% 94.5%, 98.1%)	98.4% (96.4%, 99.5%)	92.0% (85.8%, 96.1%)	96.0% (90.1%, 98.9%)	96.8% (94.3%, 98.4%)
	Question 9: *How many sprays does it take for the dose indicator number to change?*	86.0% (82.4%, 89.1%)	91.5% (87.8%, 94.3%)	72% (63.3%, 79.7%)	87% (78.8%, 92.9%)	85.7% (81.5%, 89.2%)

* 2-sided 95% exact confidence interval
Source: Table 16, LCS Summary Report

3.2.1.7 Patient Disposition, Demographic and Baseline Characteristics for LCS3

In LCS3, four hundred seventy-one (471) subjects were interviewed and four hundred sixty-eight (468) subjects qualified for the study.

As can be seen in Table 9, there was an approximate equal representation of male and female subjects. In addition, for education, 29% were high school graduates, 35% had some college experience, and 20% were college graduates and a total of 9% of subjects reported some high school education. The racial distribution in the study was: 58% White, 18% Hispanic or Latino, and 18% Black or African American, with other races accounting for the remaining 6%. The mean age of subjects was 41.4 years (SD = 16.6) with an age range of 16 to 89 years old. The study enrolled 122 subjects, which constituted 26% of the sample, considered low literacy (read

at an 8th grade reading level or below) as determined by the REALM Test or REALM Teen Test. Note, this low literacy rate met the target recruitment goal of 25% for low literate subjects. In addition, the study also enrolled 62 subjects who were previous Primatene Mist users, which met the target recruitment goal of 50 prior Primatene users. Finally, slightly more than a fifth of the subjects reported suffering from asthma (22%).

Table 9: Demographics for LCS3

	Total (N=471)	Normal Literacy (N=348)	Low Literacy (N=122)
Gender			
Male	225 (47.8%)	158 (45.4%)	67 (54.9%)
Female	243 (51.6%)	190 (54.6%)	53 (43.4%)
Missing	3 (0.6%)	0 0)	2 (1.6%)
Education			
8th grade or less	5 (1.1%)	2 (0.6%)	3 (2.5%)
Some high school	41 (8.7%)	24 (6.9%)	17 (13.9%)
High school graduate, GED, or certificate	137 (29.1%)	84 (24.1%)	53 (43.4%)
Some college or technical school	166 (35.2%)	135 (38.8%)	31 (25.4%)
College graduate	92 (19.5%)	78 (22.4%)	14 (11.5%)
Post-graduate degree	27 (5.7%)	25 (7.2%)	2 (1.6%)
Missing	3 (0.6%)	0 (0.0%)	2 (1.6%)
Race			
White	272 (57.7%)	233 (67.0%)	39 (32.0%)
Black or African American	84 (17.8%)	46 (13.2%)	38 (31.1%)
Hispanic	84 (17.8%)	46 (13.2%)	38 (31.1%)
Asian	6 (1.3%)	5 (1.4%)	1 (0.8%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	2 (0.6%)	0 (0.0%)
American Indian or Alaska Native	5 (1.1%)	4 (1.1%)	1 (0.8%)
Other	15 (3.2%)	12 (3.4%)	3 (2.5%)
Missing	3 (0.6%)	0 (0.0%)	2 (1.6%)
Age Groups			
Under 18	15 (3.2%)	13 (3.7%)	2 (1.6%)
18 to 24	85 (18%)	54 (15.5%)	31 (25.4%)
25 to 34	69 (14.6%)	50 (14.4%)	18 (14.8%)
35 to 44	103 (21.9%)	71 (20.4%)	32 (26.2%)
45 to 54	81 (17.2%)	62 (17.8%)	19 (15.6%)

55 to 64	69 (14.6%)	54 (15.5%)	15 (12.3%)
65 to 74	40 (8.5%)	35 (10.1%)	5 (4.1%)
75 to 84	7 (1.5%)	7 (2%)	0 (0.0%)
>=85	2 (0.4%)	2 (0.8%)	0 (0.0%)
Age Distribution			
Mean (SD)	41.4 (16.6)	42.8 (17.1)	37.5 (14.4)
Median	41	41.5	36
Range	16 - 89	16 - 89	17 - 68
Do you have asthma?			
Yes	106 (22.5%)	83 (23.9%)	23 (18.9%)
No	361 (76.6%)	264 (75.9%)	97 (79.5%)
Don`t know / not sure	1 (0.2%)	1 (0.3%)	0 (0.0%)
Missing	3 (0.6%)	0 (0.0%)	2 (1.6%)
Have you used Primatene Mist within the past five years?			
Yes	62 (13.2%)	44 (12.6%)	18 (14.8%)
No	406 (86.2%)	304 (87.4%)	102 (83.6%)
Missing	3 (0.6%)	0 (0.0%)	2 (1.6%)

Source: LCS-tables-and-listing, Table DMG_LIT (LCS3)
1 subject did not take the REALM

3.2.1.8 Results and Conclusions for LCS3

The results for the primary communication objectives are shown in Table 10.

The comprehension rate for the first primary communication objective to not rely on the dose indicator after dropping the inhaler and to keep track of the number of sprays you use on your own records (Q4) was 83.0% with a 95% CI of (79.3%, 86.3%), which was an improvement over the first two label comprehension studies. It should be noted that the question testing this objective changed considerably from LCS2 to LCS3 with the introduction of text specifically mentioning the “dose indicator” and a box was placed around the section of the label that contained information relating to this objective.

Comprehension for the first primary communication objective fell slightly short of the 85% performance threshold with 87.1% of normal literacy subjects providing a correct or acceptable response with a 95% CI of (83.1%, 90.4%).

There was a statistically significant association of literacy with the primary comprehension objective (Chi-square=14.4, df=1, p=0.0001) where normal literacy subjects demonstrated higher comprehension (87.1%) than low literacy subjects (72.1%).

There was also a statistically significant association of previous Primatene Mist use with the primary comprehension objective (Chi-square=4.55, df=1, p=0.03) where previous Primatene Mist users subjects had lower comprehension (74.2%) than non-users (85.0%).

Table 10: Results for the Primary Communication Objective (LCS3)

Primary Communication Objective(s)	**Question # and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Normal Literacy**	**Low Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non-Users**
1. If you drop the inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take.	Question 4: *What does the package insert say about the dose indicator if the inhaler is dropped?*	83.0% (391/471) (79.3%, 86.3%)	87.1% (303/348) (83.1%, 90.4%)	72.1% (88/122) (63.3%, 79.9%)	74.2% (46/62) (61.5%, 84.5%)	85.0% (345/406) (81.1%, 88.3%)

* 2-sided 95% exact confidence interval
Source: Table 20, Label Comprehension Summary Report

The results for the secondary communication objectives are presented in Table 11. Note these objectives were not evaluated using a performance threshold. Overall, subjects performed relatively well for the cleaning objective with comprehension rate of 94.1%. The re-priming objective (Q2 and Q3) had comprehension rates of 82% and 87% respectively.

Table 11: Results for the Secondary Communication Objectives (LCS3)

Secondary Communication Objective	**Question # and Text**	**Comprehension Rate (Correct + Acceptable) % (n/N) (95% CI)***				
		Total	**Normal Literacy**	**Low Literacy**	**Prior Primatene Mist Users**	**Prior Primatene Mist Non- Users**
1. The mouthpiece should be cleaned daily	**Question 5:** *According to the package insert, how often should the mouthpiece be cleaned?*	94.1% (91.5%, 96.0%)	96.3% (93.7%, 98.0%)	88.5% (81.5%, 93.6%)	95.2% (86.5%, 99.0%)	94.6% (91.9%, 96.6%)

2. You must prime your inhaler under the following circumstances: a. If you have not used it in more than 2 days b. If you must use it when still wet after cleaning	**Question 2:** *John cleaned his inhaler and it is still wet. Now he must use it before it is dry. What does the insert say he should do?*	81.5% (77.7%, 84.9%)	83.9% (79.6%, 87.6%)	75.4% (66.8%, 82.8%)	75.8% (63.3%, 85.8%)	83% (79.0%, 86.5%)
	Question 3: *Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?*	87.0% (83.7%, 89.9%)	91.1% (87.6%, 93.9%)	76.2% (67.7%, 83.5%)	90.3% (80.1%, 96.4%)	87.2% (83.5%, 90.3%)

* 2-sided 95% exact confidence interval
Source: Table 21, LCS Summary Report

3.2.2 Behavioral Study

3.2.2.1 Study Design and Endpoints for Behavioral Study

After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, a consumer behavior study was performed in which subjects were instructed to actually demonstrate how to use the product, based upon the labeling. For this study, 61 subjects (>12 years old) were used. Comprehension objectives were established and subject performance was graded using two qualified evaluators. This study assessed consumers' ability to carry out tasks related to use and maintenance of the MDI: (i) prime/re-prime the inhaler, (ii) clean the inhaler, (iii) reassemble the inhaler, (iv) correctly position the inhaler, and (v) actually deliver a dose following the insert instructions only.

The behavioral study was conducted from October 29-November 2, 2012 in two sites. There were 37 subjects tested at the first site in Salt Lake City, UT and 24 subjects tested at the second site in Los Angeles, CA. Of the 61 subjects, eight were former Primatene Mist users; 19 were asthma sufferers; ten were ages 12-17 and five were low literacy. Placebo was utilized instead of active ingredient in this study.

The study focused on those steps in the proposed consumer package insert regarding priming, cleaning and medicating that are different from the previous product, Primatene Mist. The primary objectives were defined as those steps that represent a significant or moderate safety risk to consumers if not correctly performed.

Table 12: Behavioral Study Objectives

Task	Objective
Priming	
Remove the cap	Informational only
Shake inhaler	Primary
Hold inhaler with dose indicator up	Primary
Spray into air at least one time	Primary
Cleaning	
Remove the cap	Informational only
Remove container	Primary
Wash mouthpiece through opening	Primary
For 30 seconds	Primary
Wash mouthpiece through the top	Primary
With warm water	Primary
Shake off excess water	Informational only
Dry Completely (either by overnight or re- prime)	Informational only
Reassemble the inhaler	Informational only
Put the Inhaler Back together	
Attach removable cap to mouthpiece	Informational only
Insert container in mouthpiece	Informational only
Finger Placement	
Place forefinger in the center of the dose indicator	Primary
Dosing	
Take cap off mouthpiece	Information Only
Shake inhaler before inhalation	Primary
Place forefinger in center of dose indicator	Information Only
Empty the lungs by exhaling	Secondary
Place mouthpiece in mouth	Secondary
Lips closed around the mouthpiece	Secondary
Inhale	Primary
…while squeezing mouthpiece and container together	Primary
…pressing on center of dose indicator	Primary
Continue the deep breath	Secondary
Hold breath	Secondary
Release (by releasing forefinger from the container)	Information Only
Remove inhaler from mouth	Information Only
Exhale slowly	Secondary
Keep lips nearly closed	Secondary
Replace cap	Information Only

Source: Label-behavior-study-report, pp. 10-11

A subject's performance of the various subtasks was filmed and observed by two independent interviewers. The two independent interviewers, one considered the primary, observed the subjects to determine whether the subjects correctly performed the subtasks. In the event of a disagreement between the two interviewers, the two interviewers jointly reviewed their ratings and determined if the discrepancy could be resolved through discussion. If it was discovered that interviewers agreed and a discrepancy could be resolved by these discussions, the data were updated accordingly at that time. If the two on-site interviewers did not agree and a discrepancy still remained, a third independent reviewer/arbitrator evaluated the video recordings and resolved the discrepancy by rating each sub-procedure of the task where discrepancies occurred.

It should be noted that the washing subtasks were not performed at a sink with water. Instead, subjects verbally described and demonstrated (without water) how they would wash the mouthpiece. The Applicant stated that, "it was viewed that choosing to have subjects pantomime the steps for washing the mouthpiece required the subjects to think through the procedures themselves rather than being overly prompted to do this by being lead to an area with a sink".

There is some concern that the results for the cleaning tasks may not accurately reflect the subject's ability to correctly clean the device.

3.2.2.2 Statistical Methodologies

The objective of the analyses was to assess for each task the proportion of subjects who adequately performed the task. The proportion of subjects that adequately performed the given instruction for all steps was not done.

The percentage of participants who successfully demonstrated each direction in the package insert was calculated. Correct and (where defined) acceptable response rates were calculated along with 95% confidence limits (using binomial standard errors).

Performance threshold of 85% were set only for the tasks that tested the primary objectives listed above in Table 12.

The Applicant provided the following clinical justifications for the 85% performance thresholds used for the primary objectives:

- Priming
    - Shake the inhaler
      During the priming process, shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. This is achieved through shaking during the priming process. If shaking is not performed, it could create uneven distribution of the medication and ingredients during the subsequent actuation. For dosing immediately after the priming, the first actuation has the potential to provide an uneven amount of medication to the user and not provide immediate relief to the asthma symptoms.
    - Hold inhaler with dose indicator up

If the dose indicator is not in the up position during the actuation of the inhaler, it could cause the propellant only to be discharged. If this process continued over the life of the product, the propellant would be completely discharged and the inhaler would fail to provide any medication. This has the potential to not provide medication to the user when needed.

- Spray into the air at least one time
  If the inhaler is not sprayed during the priming process, priming would not be achieved. As a result, the first dose of medication the user received has the potential to be less than adequate.

- Clean the mouthpiece
  - Remove the container
    If the container (canister) is not removed during the cleaning process, the actuator opening could not be confirmed to be cleaned as an adequate amount of water would not be passed through the spray hole. This could lead to a clogging of the actuator and a failure of medication to be received during the dosing process.
  - Wash the mouthpiece through the opening
    If water is not passed through the opening during the washing process, the spray hole could become clogged.
  - …for 30 seconds
    If the opening is not washed for 30 seconds during the washing process, the spray hole could become clogged.
  - Wash the mouthpiece through the top
    If water is not passed through the top during the washing process, the spray hole could become clogged.
  - …for 30 seconds
    If the top is not washed for 30 seconds during the washing process, the spray hole could become clogged.
- Finger Placement
  - Place forefinger in the center of the dose indicator
    If the user does not place finger on the center of the dose indicator, it could cause the canister to be tilted to the side and cause a release of additional medication through the valve stem. This could cause less medication in the canister than accounted for on the dose indicator. The user could continue to use the inhaler as the dose indictor would show actuations left.
- Dosing
  - Shake the inhaler before inhalation
    Shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. This is achieved through shaking prior to dosing. If shaking is not performed, it could create uneven distribution of the medication and ingredients during the subsequent actuation. Failure to shake has the potential to provide an uneven amount of medication to the user and not provide immediate relief for the asthma symptoms.
  - Inhale
    Failure of the user to inhale during the dosing will not allow the user to inhale the medication. This will not allow for the medication to get into the lungs. The

consequence will be that the user may not get complete relief from their asthma symptoms.

- …while squeezing mouthpiece and container together (actuating the inhaler)
  If the user fails to squeeze the mouthpiece together there are two possible concerns. The first is completely failing to depress it and therefore not providing an actuation. If this happens, the user will not get any medication. The consequence will be that the user will not get complete relief from their asthma symptoms. The second possibility is that the user will not perform the sequence of the actuation of starting the inhalation and then actuating while continuing the breath. If this occurs, the user might not get a complete dose of medication. The consequence will be that the user may not get complete relief from their asthma symptoms.
- … pressing on the CENTER of the dose indicator
  If the user does not place finger on the center of the dose indicator, it could cause the canister to be tilted to the side and cause a release of additional medication through the valve stem. This could cause less medication in the canister than accounted for on the dose indicator. The user could continue to use the inhaler as the dose indictor would show actuations left.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics for the Behavioral Study

The demographics are presented in Table 13. The study consisted of 65.6% females, with the majority of adults having some education beyond high school. Nearly two-thirds were white. Ten participants were under age 18 and the median age was 35, with a range of 12-71. It should be noted that only 5 subjects (8.2%) were considered low literacy. Nearly a third (31%) of the subjects reported having asthma. Finally, 8 subjects (13%) reported using Primatene Mist within the last five years.

Table 13: Demographics for Behavioral Study

	Number of Subjects n (%)
Gender	
Male	21 (34.4)
Female	40 (65.6)
Education	
8th grade or less	3 (4.9)
Some high school	8 (13.1)
High school graduate, GED, or certificate	5 (8.2)
Some college or technical school	29 (47.5)
College graduate	12 (19.7)
Post-graduate degree	4 (6.6)
Race	

White	38 (62.3)
Black or African American	5 (8.2)
Hispanic	10 (16.4)
American Indian or Alaska Native	1 (1.6)
Other	7 (11.5)
Age Groups	
Under 18	10 (16.4)
18 to 24	8 (13.1)
25 to 34	11 (18.0)
35 to 44	14 (23.0)
45 to 54	9 (14.8)
55 to 64	7 (11.5)
65 to 74	2 (3.3)
Age Distribution	
Mean (SD)	35.8 (15.8)
Median	35.0
Range	(12, 71)
Literacy Level*	
Normal	56 (91.8)
Low	5 (8.2)
Do you have asthma?	
Yes	19 (31.2)
No	39 (63.9)
Don`t know	3 (4.9)
Have you used Primatene Mist within the past five years?	
No	53 (86.9)
Yes	8 (13.1)

Source: Reviewer's table
* Low literacy classified as either REALM≤60 or REALM-TEEN≤61

3.2.2.4 Results and Conclusion for the Behavioral Study

The results for the behavioral study are presented in Table 14.

For the priming tasks, subjects did not meet performance threshold for any of the tasks although the "Hold inhaler with dose indicator up" task performance almost met the threshold [rate=93.4%; 95% CI= (84.1%, 98.2%)]. Subjects fared much worse for the "Shake inhaler" task with a rate of 74% and a 95% CI of (61%, 84%) and for the "Spray into air at least one time" task with a rate of 82.0% with a 95% of (70%, 91%).

For the cleaning tasks, subjects met the performance threshold for only the task "Wash mouthpiece with warm water" [rate=97%; 95% CI= (88.7%, 99.6%)] although the "Remove container" task was close to the threshold [rate=93.4%; 95% CI= (84.1%, 98.2%)]. Subjects fared much worse for the "Wash mouthpiece through opening", "Wash mouthpiece through opening for 30 seconds", and "Wash mouthpiece through the top" tasks. It should be noted that the Applicant computed the "Wash mouthpiece through opening for 30 seconds" rate based only on the 47 subjects who washed the mouthpiece through the opening. I instead computed the rate using all of the subjects because this method provides an estimate of the proportion of subjects who washed the mouthpiece through the opening for the prescribed length of time.

For the "Finger Placement" task, the performance threshold was not met with a rate of 88.5% and a 95% CI of (77.8%, 95.3%).

For the medicating tasks, the performance threshold was met for almost all of the tasks with the exception of the "Shake inhaler before inhalation" task with a rate of 75.4% and a 95% CI of (62.7%, 85.5%).

The Applicant posits that subjects' performance in shaking the device prior to priming or dosing and cleaning the mouthpiece by washing through the opening and top for 30 seconds would be expected to improve with continued use and familiarity with the product. They also stated,

> *It is also likely that the artificial nature of the testing environment (including handling an empty container) may also have influenced participant performance, particularly in measurement of non-dosing behaviors such as cleaning (which participants likely perceive as less important than the dosing demonstration)*

Unfortunately, an actual use study was not conducted and there is no way to confirm their hypothesis. Also it should be remembered that the washing steps did not occur at a sink but were done as a "pantomime" with subjects describing what they would do. It is not clear what effect this had on the estimate of the washing rates.

Information on device performance was collected in the efficacy clinical trials, however the efficacy studies cannot be thought of as actual use studies because subjects were prompted to do things and that this prompting would not occur in the actual use setting.

Table 14: Results for the Primary Objectives in the Behavioral Study

	Response Rate % (n/N)	95% CI *
Priming		
Shake inhaler	73.8% (45/61)	(60.9, 84.2)
Hold inhaler with dose indicator up	93.4% (57/61)	(84.1, 98.2)
Spray into air at least one time	82.0% (50/61)	(70.0, 90.6)
Cleaning		
Remove container	93.4% (57/61)	(84.1, 98.2)
Wash mouthpiece through opening	77.0% (47/61)	(64.5, 86.9)
For 30 seconds+	72.1% (44/61)	(59.2, 82.8)
Wash mouthpiece through the top	63.9% (39/61)	(50.6, 75.8)
Wash mouthpiece with warm water	96.7% (59/61)	(88.7, 99.6)
Finger Placement		
Place forefinger in the center of the dose indicator	88.5 (54/61)	(77.8, 95.3)
Medicating		
Shake inhaler before inhalation	75.4% (46/61)	(62.7, 85.5)
Lips closed around the mouthpiece	98.4% (60/61)	(91.2, 100)
Inhale	100% (61/61)	(94.1, 100.0)
While squeezing mouthpiece and container together	98.4% (60/61)	(91.2, 100)
Pressing on center of dose indicator	98.4% (60/61)	(91.2, 100)

Source: Modified from Behavioral Study Report, pp. 25-26

* 2-sided 95% exact confidence interval

+ In the study report, the Applicant computed percentages based on only the #subjects who washed the mouthpiece through the opening (n=47). I have provided percentages based on the total number of subjects

In an information amendment submitted on 2/14/14, the Applicant stated, "the root cause of the tested steps being 'off goal' was likely due the fact that part of the Primatene Mist CFC previous users who were included in the study were too dependent on their prior experiences of using Primatene mist cfc and did not pay close attention to the changed/new instructions during the e004 behavioral study." They argued that the results for tasks in the shaded area of Table 15 support their hypothesis that the Primatene® Mist CFC users who were included in the study were too dependent on their prior experience of using Primatene® Mist CFC. However, it is important to the note that there were only 8 previous Primatene Mist users included in this study and their inclusion did not markedly change the results for the overall group, i.e. rate for the total group is similar to the rate for Primatene Mist CFC non-users and the rates for the shaking and washing task still fell far below the performance threshold for the Primatene Mist CFC non-user subgroup.

Table 15: Subgroup Analyses by Previous Primatene Mist Use in the Behavioral Study

	"Off Goal Step"	Total (n=61)	Primatene Mist CFC Previous User (n=8)	Primatene Mist CFC Non-Previous User (n=53)	Difference of Percentage of the Two Subgroups
1	"*Shake the inhaler*" prior to priming	45 (74%)	6 (75%)	39 (74%)	-1%
2	"*Shake the inhaler before inhalation*"	46 (75%)	6 (75%)	40 (76%)	1%
3	Priming prior to use ("*Spray at least 1 time into the air*")	50 (82%)	5 (62.5%)	45 (85%)	22.5%
4	"*Wash the mouthpiece through the top*"	39 (64%)	3 (38%)	36 (68%)	30%
5	"*Wash the mouthpiece through the opening*"	47 (77%)	5 (63%)	42 (79%)	16%

Source: 2/14/14 Information amendment

Disagreements between the two interviewers

The rate of disagreement between two interviewers was 5.6% (133/2379) for the demonstration data fields (actual subject rating procedures, which excludes the screening, demographic and debriefing data fields). The rate of disagreement was relatively constant across the tasks with no individual task having a much higher rate of disagreement.

3.3 Evaluation of Safety

Subjects in the consumer studies were not exposed to treatment; therefore, the evaluation of safety is not applicable for these studies

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Label Comprehension Studies

The results broken out by age, gender, and race are presented in Table 16 and Table 17. There are no consistent subgroup findings across the three label comprehension studies.

Table 16: Comprehension Rates for the 1st Communication Objective

Subgroup	1. If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records.		
	LCS1 % (n/N) (95% CI)*	LCS2 % (n/N) (95% CI)*	LCS3* % (n/N) (95% CI)*
Sex †			
Male	47.5 (103/217) (40.7, 54.3)	63.4 (140/221) (56.6, 69.7)	82.2 (185/225) (76.6, 87.0)
Female	55.4 (119/215) (48.4, 62.1)	72.4 (160/221) (66.0, 78.2)	84.8 (206/243) (79.6, 89.0)
Race †			
White	55.0 (111/202) (47.8, 61.9)	75.7 (165/218) (69.4, 81.2)	87.1 (237/272) (82.6, 90.9)
Black or African American	47.9 (67/140) (39.4, 56.5)	60.0 (78/130) (51.0, 68.5)	77.4 (65/84) (67.0, 85.8)
Hispanic	54.6 (30/55) (40.6, 68.0)	61.8 (34/55) (47.7, 74.6)	77.4 (65/84) (67.0, 85.8)
Asian	50.0 (2/4) (6.8, 93.2)	100.0 (2/2) (15.8, 100.0)	100.0 (6/6) (54.1, 100.0)
Native Hawaiian or Pacific Islander	0.0 (0/1)	50.0 (1/2) (1.3, 98.7)	50.0 (1/2) (1.3, 98.7)
American Indian or Alaska Native	28.6 (2/7) (3.7, 71.0)	80.0 (4/5) (28.4, 99.5)	100.0 (5/5) (47.8, 100.0)
Refused to answer or missing		0.0 (0/2) (0.0, 84.2)	0.0 (0/3) (0.0, 80.8)
Other	43.5 (10/23) (23.2, 65.5)	57.1 (16/28) (37.2, 75.5)	80.0 (12/15) (51.9, 95.7)
Age Groups			
<65 years	51.5 (206/400) (46.5, 56.5)	66.5 (274/412) (61.7, 71.0)	81.8 (345/422) (77.7, 85.3)
≥65 years	50.0 (16/32) (31.9, 68.1)	86.7 (26/30) (69.3, 96.2)	93.9 (46/49) (83.1, 98.7)

Source: Reviewer's table
* 2-sided 95% exact confidence interval
† Missing gender and race information for three subjects in LCS3

Table 17: Comprehension Rates for the 2nd and 3rd Primary Communication Objectives

Subgroup	2. The dose indicator will stop counting at –0‖ and the inhaler must be replaced. 3. Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.		
	LCS1 % (n/N) (95% CI)*	LCS2 % (n/N) (95% CI)*	LCS3 % (n/N) (95% CI)*
Sex†			
Male	85.2 (185/217) (79.8, 89.7)	92.3 (204/221) (88.0, 95.5)	NA
Female	88.8 (191/215) (83.8, 92.7)	91.4 (202/221) (86.9, 94.7)	NA
Race†			
White	90.6 (183/202) (85.7, 94.2)	92.7 (202/218) (88.4, 95.8)	NA
Black or African American	84.3 (118/140) (77.2, 89.9)	90.0 (117/130) (83.5, 94.6)	NA
Hispanic	81.8 (45/55) (69.1, 90.9)	96.4 (53/55) (87.5, 99.6)	NA
Asian	75.0 (3/4) (19.4, 99.4)	100.0 (2/2) (15.8, 100.0)	NA
Native Hawaiian or Pacific Islander	100.0 (1/1)	100.0 (2/2) (15.8, 100.0)	NA
American Indian or Alaska Native	85.7 (6/7) (42.1, 99.6)	100.0 (5/5) (47.8, 100.0)	NA
Refused to answer		50.0 (1/2) (1.3, 98.7)	NA
Other	87.0 (20/23) (66.4, 97.2)	85.7 (24/28) (67.3, 96.0)	NA
Age Groups			
<65 years	88.2 (353/400) (84.7, 91.2)	91.8 (378/412) (88.7, 94.2)	NA
≥65 years	71.9 (23/32) (53.2, 86.2)	93.3 (28/30) (77.9, 99.2)	NA

Source: Reviewer's table
* 2-sided 95% exact confidence interval
† Missing gender and race information for three subjects in LCS3
NA: LCS3 only had one primary communication objective

4.1.2 Behavioral Study

Subgroup analyses were not performed for this study because of the small number of subjects enrolled in this study (n=61).

4.2 Other Special/Subgroup Populations

The other important subgroup defined by literacy level and prior Primatene use have been discussed previously in Section 3.3.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Analysis population to assess comprehension in the LCS relative to the performance threshold

The Applicant states that comprehension should be assessed against the performance threshold of 85% for the normal literacy group only rather than the general population that includes both normal and low literacy subjects. Assessing performance relative to the threshold in only the normal literacy cohort could potentially bias the decision toward meeting the threshold because normal literacy subjects usually have higher comprehension rates than low literacy subjects. For the first primary communication objective, in LCS3 there was a statistically significant association (Chi-square=14.4, df=1, p=0.0001) between literacy level and comprehension where normal literacy subjects demonstrated higher comprehension (87.1%) than low literacy subjects (72.1%). However, in LCS2, normal literacy subjects (93.1%) demonstrated similar comprehension as low literacy subjects (88.8%) for the second and third primary communication objectives with no statistically significant association of literacy level and comprehension (Chi-square=2.17, df=1, p=0.14).

Performance thresholds

For the label comprehension studies, the Applicant did provide reasons why the safety risk for the issue felt to be of greatest import, undercounting the number of doses, was low and also stated how they would mitigate the safety risk by adding the following elements to the DFL (Appendix A.1):

> Asthma alert: Because asthma may be life threatening, see a doctor if you:
> - are not better in 20 minutes
> - get worse
> - need more than 8 inhalations in 24 hours
> - have more than 2 asthma attacks in a week
> - These may be signs that your asthma is getting worse

However, they did not explicitly state why the performance threshold should be 85%.

Behavioral study washing subtasks

There is some concern that the results for the cleaning tasks may not accurately reflect the subject's ability to correctly clean the device because the washing subtasks were not performed at a sink with water but instead, subjects verbally described and demonstrated (without water) how they would wash the mouthpiece.

Label Comprehension Performance

Comprehension of the first communication objective, "If the inhaler is dropped, do not rely on the dose indicator. Keep track of the number of sprays" fell far below the 85% performance threshold in normal literacy subjects for LCS1 [rate=55.6%; 95% CI=(50.0%, 61.1%)] and LCS2 [rate=72.6%; 95% CI=(67.3%, 77.4%)]. In LCS3, comprehension [rate=87.1%; 95% CI=(83.1%, 90.4%)] in normal literacy subjects improved from first two label comprehension studies but still fell slightly below the 85% threshold. It should be noted that the question testing this objective changed considerably from LCS2 to LCS3 with the introduction of text specifically mentioning the "dose indicator" and a box was placed around the section of the label that contained information relating to the objective.

Comprehension of the second and third communication objectives, "The dose indicator will stop counting at — 0 and the inhaler must be replaced" and "Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured" met the 85% performance threshold for normal literacy subjects in LCS2 [rate=93.1%; 95% CI=(89.7%, 95.6%)] and was not re-tested in LCS3.

Behavioral Study

In the behavioral study, the subjects' ability to correctly perform the task related to shaking the inhaler and washing the mouthpiece fell far below the 85% performance threshold. These difficulties could be of import because the Applicant in their justification explained the importance of these tasks. Specifically, shaking the inhaler is important because it ensures that the medication, which is a suspension, is evenly mixed and distributed. Lack of shaking could potentially result in dose variability leading to the administration of higher doses. Washing the mouthpiece properly is also important because without properly cleaning, the device could become clogged and medication would not be dispensed. The relatively low level of proper cleaning is an issue because as stated in the FDA correspondence of 9/23/11, "Experience has shown that HFA MDI devices are prone to clogging".

The Applicant argued that the results for the Priming prior to use ("Spray at least 1 time into the air"), "Wash the mouthpiece through the top", and "Wash the mouthpiece through the opening" tasks (shaded area of Table 15) support their hypothesis that the Primatene® Mist CFC users who were included in the study were too dependent on their prior experience of using Primatene® Mist CFC. However, it is important to the note that there were only 8 previous Primatene Mist users included in this study and their inclusion did not markedly change the results for the overall group, i.e. rate for the total group is similar to the rate for Primatene Mist CFC non-users and the rates for the shaking and washing tasks still fall far below the performance threshold for the Primatene Mist CFC non-user subgroup.

5.2 Conclusions and Recommendations

There are concerns with the ability of subjects to correctly use the product based on the results of the behavioral study where the tasks related to shaking the inhaler and washing the mouthpiece fell far below the 85% performance threshold.

The Applicant posits that subjects' performance in shaking the device prior to priming or dosing and cleaning the mouthpiece by washing through the opening and top for 30 seconds would be expected to improve with continued use and familiarity with the product. They also stated,

> *It is also likely that the artificial nature of the testing environment (including handling an empty container) may also have influenced participant performance, particularly in measurement of non-dosing behaviors such as cleaning (which participants likely perceive as less important than the dosing demonstration).*

Unfortunately, an actual use study was not conducted and there is no way to confirm their hypothesis. Also it should be remembered that the washing steps did not occur at a sink but were done as a "pantomime" with subjects describing what they would do. It is not clear what effect this had on the estimate of the washing rates.

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

/s/

SCOTT S KOMO
04/25/2014

KAREN M HIGGINS
04/25/2014
I concur.

TSAE YUN D LIN
04/25/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205-920 (cross reference IND 74286)
	S000
Drug Name:	Epinephrine HFA MDI, 125 mcg/inhalation
Indication(s):	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Applicant:	Armstrong Pharmaceuticals, Inc.
Date(s):	Received 7/22/2013; PDUFA due date 7/22/2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Joan Buenconsejo, Ph.D., Team Leader
	Thomas Permutt, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Jennifer Pippins, M.D.
	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Daniel Reed, MPH

Keywords: Clinical studies, NDA review, dropouts, missing data

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1 EXECUTIVE SUMMARY

The applicant submitted the results from one phase 3 adult study (API-E004-CL-C, hereafter referred to as C) and one phase 3 pediatric study (API-E004-CL-D, hereafter referred to as D), as well as two dose-findings studies (API-E004-CL-A, hereafter referred to as A and API-E004-CL-A2, hereafter referred to as A2) in support of the efficacy of epinephrine HFA-MDI (metered-dose inhaler)for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Epinephrine HFA-MDI (hereafter referred to as E004) is proposed as a replacement for epinephrine chlorofluorocarbon (CFC)-MDI, for over-the-counter (OTC) use, which stopped commercial distribution on December 31, 2011, due to the phase-out of products containing CFCs outlined by the Montreal Protocol.

Studies A and A2 were both randomized, multicenter, double-blinded/evaluator-blinded, placebo- and active-controlled 5-arm and 8-arm crossover studies, respectively. Study A was the first dose-ranging study which studied three doses of E004 (i.e., 250 mcg, 320 mcg, and 440 mcg), Primatene, and placebo HFA and Study A2 studied the five doses of E004 (i.e., 90 mcg, 125 mcg, 180 mcg, 200 mcg, and 250 mcg), placebo HFA, and two doses of Primatene (i.e., 220 mcg and 440 mcg). E004 250 mcg four times daily demonstrated a greater change in FEV_1 $AUC_{0\text{-}6h}$ and serial FEV_1 measurements compared to the other nominal doses of 90, 200, 320, 440 mcg. Both studies showed E004 250 mcg had better efficacy compared to Primatene doses.

Study C was a double blind, randomized, parallel group (E004 250 mcg four times daily (QID), placebo QID, or Primatene Mist 440 mcg QID), controlled, clinical trial in asthma patients aged 12 years and older. The primary measure of efficacy was $AUC_{0\text{-}6h}$ of $\Delta\%$ FEV_1, defined as the area under curve of post-dose FEV_1 percentage changes (Δ %) from the same-day pre-dose baseline FEV_1 up to 6 hours post-dose at week 12. E004 250 mcg showed a statistically significant greater improvement in lung function over 12 weeks of treatment compared to placebo, regardless of the imputation strategies used to handle missing data.

Study D had a similar design as Study C with the primary measure of efficacy being the $AUC_{0\text{-}6h}$ of $\Delta\%$ FEV_1 at the week 4. Study randomized the asthma patients aged 6 to 11 years old into two treatment arms (E004 250 mcg QID and placebo QID) with stratification of age group (4-8 and 9-11). Analyses of the primary efficacy endpoint using the pre-specified statistical method showed no statistically significant treatment effect between E004 250 mcg and placebo in the pediatric population.

In summary, there is statistical evidence of a difference between E004 and placebo in asthma patients aged 12 years and older based on Study C and supported by the two dose-finding studies (studies A and A2). In Study C, the estimated treatment difference in $AUC_{0\text{-}6hrs}$ of $\%\Delta$ FEV_1 at week 12 was about 28 (%xL) (95% CI of (12, 44) (%xL)). This finding is supported by the results from the analyses of the secondary endpoints. E004 treated patients had a higher mean $AUC_{0\text{-}6hrs}$ of FEV_1 of 15.8 (Lxhr) compared placebo group of 14.4 (Lxhr). At 5 minutes after dosing, the E004 treated patients had 0.25L FEV_1 improvement compared 0.02L for placebo group. The E004 treated patients reached the maximum FEV_1 in an hour compared to 2 hours in

the placebo group. These findings demonstrated E004's bronchodilator effect. The treatment effect observed in the Primatene arm was numerically smaller compared to E004.

In Study D, there is not enough evidence to support the efficacy of E004 in asthma patients aged 4 to 11 years old. The applicant is not seeking the approval for this age group in this current application.

The Joint Meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the US Food and Drug Administration (FDA) convened on March 25, 2014 to discuss the over-the counter (OTC) marketing of the epinephrine inhalation aerosol (HFA) 125 mcg/actuation for temporary relief of mild symptoms of intermittent asthma for patients aged 12 years or older. The panels voted in favor of the drug's efficacy (14 yes, 10 no, 1 abstain) and against its safety (7 yes, 17 no, 1 abstain) for OTC use. Several committee members voiced concern that if the inhaler is available OTC, people may be inclined to use it in lieu of seeking appropriate medical treatment. The HFA inhaler also requires special care to prevent inaccurate dosing, and some members were concerned that patients might not use and care for the inhalers properly.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

The applicant, Armstrong Pharmaceuticals (Armstrong), has submitted a New Drug Application (NDA 205920) to the Division of Nonprescription Clinical Evaluation (DNCE) for epinephrine HFA-MDI, referred to as E004 hereafter. The proposed indication is the "temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older".

E004 is proposed as a replacement for epinephrine chlorofluorocarbon (CFC)-MDI, for over-the-counter (OTC) use, which stopped commercial distribution on December 31, 2011, due to the phase-out of products containing CFCs outlined by the Montreal Protocol.

The innovator product, Primatene® Mist (NDA 16-126, Wyeth) was approved in 1967. A generic version, epinephrine CFC-MDI (ANDA 87-997, Armstrong [a subsidiary wholly owned by Amphastar]) was approved in 1984. Armstrong has since purchased the Primatene® Mist trademark and Wyeth has withdrawn NDA 16-126 and discontinued distribution of the product. The epinephrine CFC- MDI (Primatene® Mist, hereafter referred to as Primatene), is available in a 220 mcg/inhalation formulation, and is indicated for the "temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath" in adults and children 4 years of age and older. The dosing recommendation across the entire age spectrum is:

"Start with one inhalation, then wait at least 1 minute; if not relieved, used once more. Do not use again for at least 3 hours."

2.1.2 History of Drug Development

The initial development program for E004 was introduced to the Agency on March 27, 2007 via IND 74286 and discussed with the Division of Nonprescription Clinical Evaluation (DNCE).

Several interactions between the Agency and the Applicant have previously taken place. The following statistics-related comments were provided to the applicant at the January 31, 2013 pre-NDA meeting (meeting preliminary comments dated January 30, 2013 and meeting minutes dated February 28, 2013 in DARRTS):

1. *We request that you include efficacy analyses based on the mean change in FEV_1, in addition to the AUCΔFEV%.*

2. *In Studies C and D, you propose to evaluate the primary endpoint based on the evaluator per-protocol population. We remind you of our discussion at the first preNDA meeting held on September 23, 2011, during which we recommended that the primary analysis for Trial D be performed using the Intent-to-Treat (ITT) population. While your approach will likely produce no missing data since you are only including patients who completed the trial and who potentially adhered to the protocol, we are concerned that these post-baseline evaluator-based criteria will introduce bias. In many cases, the use of per-protocol population may not preserve the baseline comparability between treatment groups achieved by*

randomization. In addition, excluding patients who dropped out that are related to outcome may introduce bias and influence the results. Furthermore, it is unclear whether this subset of patients can adequately address the primary objective of the study since you are only evaluating those patients who complete the study and adhered to the protocol. You also propose to test the difference between treatment arms using one-side t-test with α=0.05. The primary analysis should be performed using two-sided t-test with α=0.05 based on the intent-to-treat population (defined as all randomized patients regardless of whether they discontinue from treatment or study).

3. *In your statistical analysis plan, provide a detail description on how you plan to handle missing data. Discuss potential mechanisms which may cause FEV_1 data to be missing, and how those mechanisms affected your selection of the primary analysis method. In addition, describe the underlying estimand, and explain why the estimand is appropriate for this study we also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in a different direction from the result of the primary analysis. We also recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned. " Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.*

4. *Should you intend to make labeling claims based on the results from the analyses of the other secondary endpoints, your statistical analysis plan must include sufficient details regarding missing data, and the method you will use to control the probability of Type 1 error.*

5. *In the NDA submission, provide all raw datasets (in SDTM format or in other format), as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*
    - *Include the programs used for creating main efficacy analysis datasets from submitted raw datasets (in SDTM format or in other format) and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains what each program is used for.*
    - *Provide the analysis datasets and programs used to generate the specific analyses results contained in the ISE reports.*
    - *Provide the analysis datasets and programs used to generate the inferential analyses results in the ISS.*
    - *You can check the FDA website to find the information about current document and guidance: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf*

2.1.3 Specific Studies Reviewed

The applicant submitted the results from 10 studies to support the indication of the OTC product of E004. The efficacy studies included two dose finding studies, one phase 3 adult study, and one phase 3 pediatric study. These four studies will be the focus of my review (Table 1). In this clinical program, the applicant included Primatene® Mist as an active control. The E004 and Placebo-HFA share identical product configuration and physical attributes, Primatene® Mist has different product configuration and physical appearance than other two arms. Therefore, Primatene® Mist arm could only be evaluator-blinded and was not patient-blinded.

Throughout this review, epinephrine HFA-MDI will be referred to as E004; Primatene® Mist will be referred to as Primatene.

Table 1: List of Studies Included in this Review

Study ID (Period)	Location	Design	Primary Endpoint	# of Patients per Arm (Completed)	Study population
Phase II API-E004-CL-A (A) (3/25/2010–6/30/2010)	4 sites in the US	R, DB or EB, MC, active-controlled, single-dose, five-arm crossover	AUC of Δ%FEV1, relative to the same day baseline	**E004 250 mcg, 26/24** E004 320 mcg, 26/24 E004 440 mcg, 26/24 Primatene 440 mcg, 26/24 Placebo, 26/24	18+ Adult patients with mild to moderate asthma
Phase II API-E004-CL-A2 (A2) (11/22/2010–2/10/2011)	5 sites in the US	R, DB or EB, MC, single-dose, eight-arm crossover	AUC of Δ%FEV1, relative to the same day baseline	E004 90 mcg, 30/29 E004 125 mcg, 30/29 E004 180 mcg, 30/29 E004 200 mcg, 30/29 **E004 250 mcg, 30/29** Primatene 220 mcg, 30/29 Primatene 440 mcg, 30/29 Placebo, 30/29	18+ Adult patients with mild to moderate asthma
Phase III API-E004-CL-C (C) (5/5/2011–11/16/2011)	34 sites in the US	R, DB or EB, PC, AC, MC, MD 12-weeks	AUC of Δ%FEV1, relative to the same day baseline	**E004 250 mcg QID, 248/205** Primatene 440 mcg, QID, 64/53 Placebo, 61/52	male and female asthma patients aged 12 – 75 years documented asthma requiring inhaled epinephrine or β-agonist treatment for at least 6 months, but who were otherwise generally healthy
Phase III API-E004-CL-D (D) (10/08/2011–3/14/2012)	8 sites in the US	R, DB, PC, AC, MC, MD, 4-weeks	AUC of Δ%FEV1, relative to the same day baseline for Week-4	**E004 250 mcg QID, 35/20** Placebo, 35/21	4-11 years pediatric patients with mild to moderate asthma

Abbreviations: DB = double blind; EB = evaluator-blinded OID = once daily; PC = placebo-controlled; QID = four times daily; R = randomized; MC=multi-cent, MD=multi-dose

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location \\...\205920.enx. The information needed for this review was contained in submission modules 1, 2.7, and 5.3.5 modules 5 datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the data and analysis quality are acceptable. An information request (IR) letter was sent to the applicant on October, 18, 2013 seeking additional data and results for the following measurements: $AUC_{0\text{-}6hrs}$ FEV1, Fmax, and Tmax for both studies E004-C and E004-D. The applicant submitted the requested information on November 5, 2013.

3.2 Evaluation of Efficacy

3.2.1 Dose Finding Studies

According to the applicant, the proposed dose for E004 (2×125 mcg) is 43% lower than that for Primatene (2×220 mcg) due to a higher delivery efficiency of the suspension formulation of E004. In this section, I examined and confirmed the results from the two dose-ranging studies (A and A2). Of note, the Division agreed on 5/10/2011 to start E004 Phase III studies with E004 formulation strength of 125 mcg per inhalation and 2 inhalations (250 mcg) per dose, based upon the initial review of the findings from the five phase I/II clinical studies of E004 that included two efficacy and initial single normal dose safety studies (studies A and A2) and three PK and safety studies at single high doses (studies B, B2, and B3),

Studies A and A2 were both randomized, multicenter, double-blinded/evaluator-blinded, placebo- and active-controlled 5-arm and 8-arm crossover studies, respectively. Study A was the first dose-ranging study which studied three doses of E004 (i.e., 250 mcg, 320 mcg, and 440 mcg), Primatene, and placebo HFA and Study A2 studied the five doses of E004 (i.e., 90 mcg, 125 mcg, 180 mcg, 200 mcg, and 250 mcg), placebo HFA, and two doses of Primatene (i.e., 220 mcg and 440 mcg).

Study A consisted of 5 periods with 5 scheduled visits and Study A2 consisted of 8 periods with 8 scheduled visits. Each qualified patient who demonstrated acceptable airway reversibility with Primatene® Mist epinephrine inhaler at screening participated in each study visits, generally with 2-14 day inter-visit intervals (wash-out period). During each visit, the patients randomly received one of the treatments and the serial FEV_1 were collected before and after dosing (pre-dose, 5min, 30min, 1hr, 2hrs, 3hrs, 4hrs, and 6hrs). The demographic profile of patients in both studies is generally well-balanced across treatment arms (Table 12 and Table 13, Appendix).

The primary endpoint for both studies was the $AUC_{0\text{-}6h}$ of post-dose FEV_1 percentage changes ($\Delta\%$) from the pre-dose baseline FEV_1 at Day 1. Based on the reviewer's and also pre-specified in SAP efficacy analysis results using the PP population for Study A, a significant (p-value $\leq$ 0.05) improvement in bronchodilatory effect is observed in asthma patients treated with E004 (i.e., 250 mcg, 320 mcg, and 440 mcg) per the primary endpoint compared to asthma patients treated with placebo (Table 2). There appears to be no dose response with the lowest dose of 250 mcg showing better efficacy compared to the two higher doses (Table 2). In Study A2, four E004 doses (125 mcg, 180 mcg, 200 mcg, and 250 mcg) also showed a significant bronchodilatory

effect in asthma patients (Table 2) compared to the two Primatene doses (220 mcg and 440 mcg). This is supported by findings from the analyses of secondary endpoints (Appendix, Table 14 and Table 15).

Table 2: Analysis Results on the Primary Efficacy Endpoint for Both Studies (PP population)

Treatment Group	*N*	*Mean (SD)*	*Treatment Comparison with Placebo*		
			Mean Diff. (SD)	*95%CI*	*p-value*
Study A					
E004 125 mcg/inh. x2, (E250)	21	88.9 (70.1)	67.2 (57.6)	(31.0, 103.3)	<0.001
E004 160 mcg/inh. x2, (E320)	20	62.8 (62.7)	44.9 (51.5)	(11.7, 78.0)	0.01
E004 220 mcg/inh.x2, (E440)	21	75.6 (53.6)	53.9 (45.1)	(25.8, 82.1)	<0.001
Primatene 220 mcg/inh. x2 (Prim440)	21	74.3 (56.3)	53.6 (49.4)	(21.7, 83.5)	0.001
Placebo	21	21.7 (41.4)	--	--	--
Study A2					
E004 90 mcg/inh. x1, (E90)	25	37.1 (50.0)	12.2 (53.5)	-18.2 (42.6)	0.424
E004 125 mcg/inh. x1, (E125)	25	72.5 (62.3)	47.6 (59.6)	(13.7, 81.5)	0.007
E004 90 mcg/inh. x2, (E180)	25	98.2 (58.6)	73.3 (57.7)	(40.5, 106.1)	<0.001
E004 100 mcg/inh. x2 (E200)	25	76.1 (57.7)	51.1 (57.3)	(18.6, 83.7)	0.003
E004 125 mcg/inh. x2, (E250)	24	84.7 (62.9)	61.0 (60.4)	(25.9, 96.1)	0.001
Primatene 220 mcg/ing. x1, (Prim220)	25	63.0 (56.7)	37.6 (56.7)	(5.4, 69.9)	0.023
Primatene 220 mcg/inh. x2, (Prim440)	24	47.4 (43.8)	23.7 (51.2)	(-6.1, 53.5)	0.117
Placebo	25	24.9 (56.8)	--	--	--

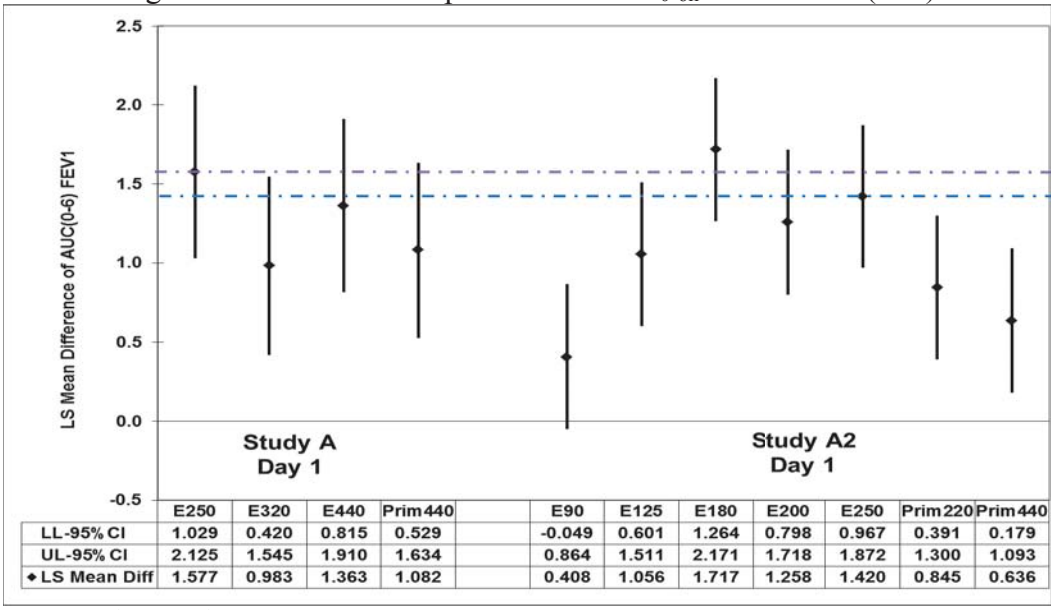
Note 1: p-value <0.05.
The mean, standard deviations, 95% confidence interval, and p−value are based on two-sided t-test analyses.

Instead of examining the difference in percentage change at Day 1, the clinical team requested additional analyses on the change from baseline in FEV_1 $AUC_{0\text{-}6h}$ [L] at day 1 for both studies. The analyses were done using a mixed effect model with sequence, treatment, and period as fixed effects, and with subject nested with sequence as a random effect. The period effect was not significant in either study (p-value=0.5379 for Study A and p=0.5472 for Study A2).

The results at Day 1 are generally consistent with what was observed by the applicant. All doses of E004 except 90 mcg showed statistically significantly improvement in FEV_1 $AUC_{0\text{-}6h}$ compared to placebo. The efficacy appears to plateau at doses around 180 mcg to 250 mcg. E004 250 mcg showed greater improvement in FEV_1 $AUC_{0\text{-}6h}$ compared to the two lowest doses in study A2 and compared to the two higher doses in study A. All E004 doses except 90 mcg dose showed better improvement in FEV_1 $AUC_{0\text{-}6h}$ compared to Primatene 440 mcg and 220 mcg doses (Figure 1). Based on the FEV_1 time serial profile for Study A (Figure 2), the curves for all E004 doses and the Primatene arm are clearly above the curve for the Placebo arm. There is also some separation among the E004 doses with the lowest dose (i.e., 250 mcg) appearing to be slightly more efficacious and had a much quicker onset time compared to the two higher E004 doses and the Primatene 440 mcg dose. Based on the time serial profile at Day 1 in study A2, there is some separation among the E004 doses with the 180 mcg dose appearing to be more efficacious and had a much quicker onset time compared to the other four E004 doses (including 250 mcg dose) and the two Primatene doses (Figure 3). The results from the analyses of the secondary endpoints support this finding.

In summary, E004 250 mcg four times daily demonstrated a greater change in FEV_1 $AUC_{0\text{-}6h}$ and serial FEV_1 measurements compared to the other nominal doses of 90, 200, 320, 440 mcg. E004 180 mcg four times daily showed a numerically greater improvement in FEV_1 $AUC_{0\text{-}6h}$ compared to 250 mcg arm, and this is supported by the serial FEV_1 measurements and the results from the analyses of secondary endpoints. Both studies showed E004 250 mcg has a better efficacy compared to Primatene doses.

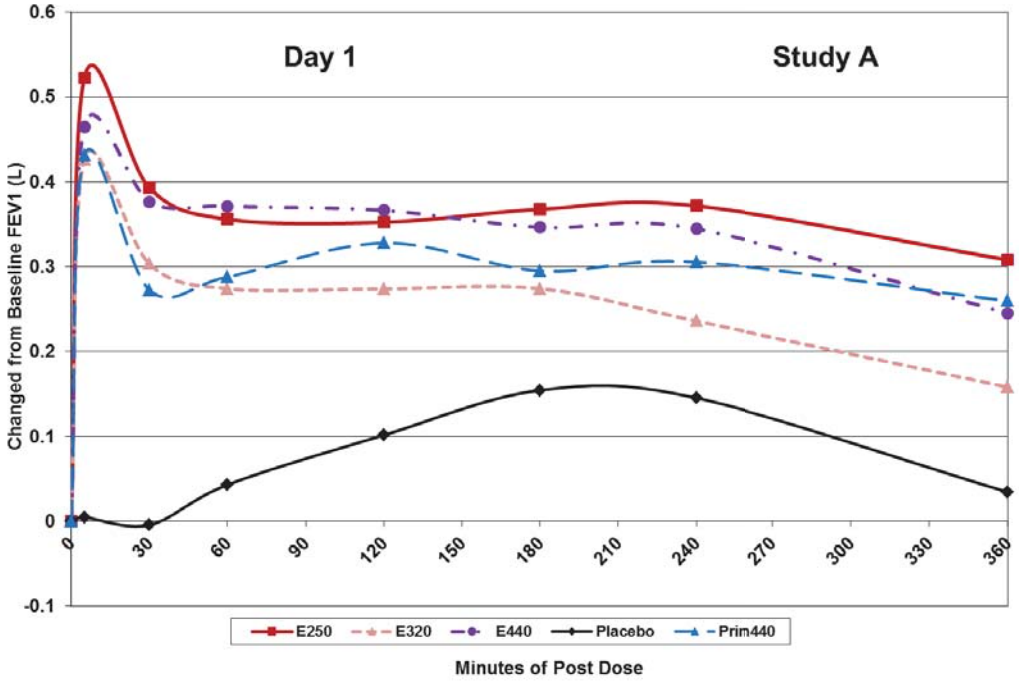
Figure 1: Treatment Comparison for $AUC_{0\text{-}6h}$ for Δ FEV1 (ITT)



	E250	E320	E440	Prim440	E90	E125	E180	E200	E250	Prim220	Prim440
LL-95% CI	1.029	0.420	0.815	0.529	-0.049	0.601	1.264	0.798	0.967	0.391	0.179
UL-95% CI	2.125	1.545	1.910	1.634	0.864	1.511	2.171	1.718	1.872	1.300	1.093
◆ LS Mean Diff	1.577	0.983	1.363	1.082	0.408	1.056	1.717	1.258	1.420	0.845	0.636

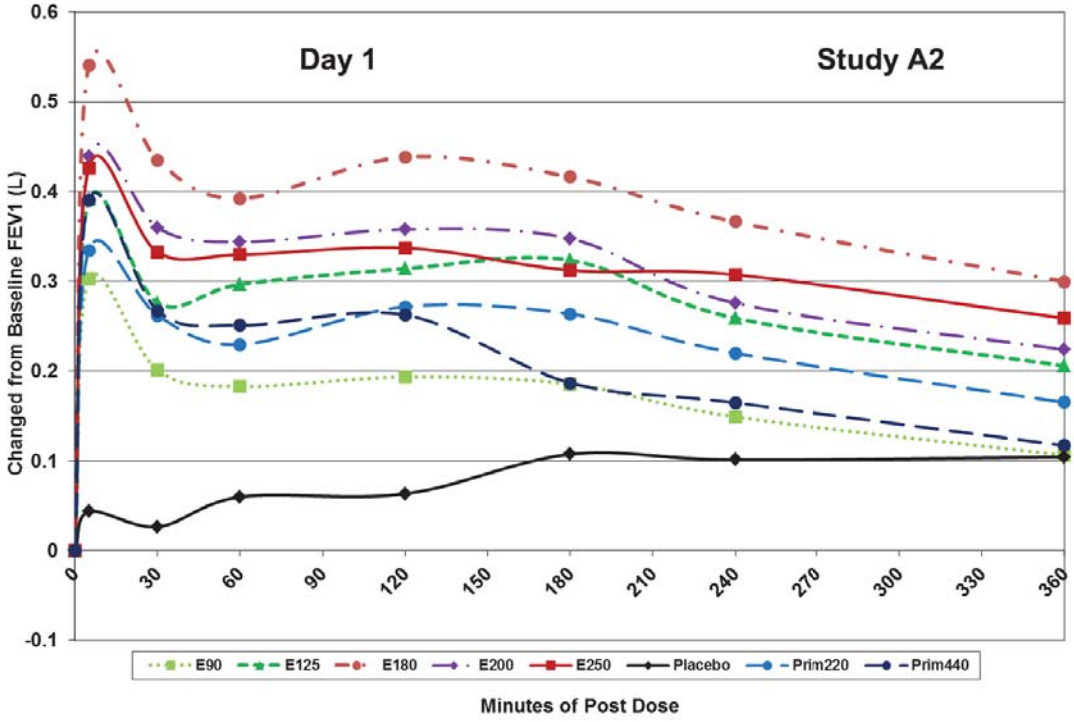
[Source: dose_auc.xlsx]

Figure 2: The 6-hour FEV_1 (L) Profile at Day 1 Study A (ITT)



[Source: dose_fev.xlsx]

Figure 3: The 6-hour FEV_1 (L) Profile at Day 1 for Study A2 (ITT)



[Source: dose_fev.xlsx]

3.2.2 Phase 3 Adult Study

3.2.2.1 Study Design and Endpoints, and Statistical Methodologies

Study C was a phase 3, 12-week, randomized, multicenter, double-blinded/evaluator-blinded, placebo- and active-controlled trial to evaluate the long-term efficacy and safety of E004 250 mcg four times daily (QID) HFA inhaler compared to placebo and the currently marketed Primatene® Mist (epinephrine CFC inhaler) in patients aged 12 years and older with intermittent or mild-to-moderate persistent asthma.

A total of 373 patients were randomized to Arm T (E004 2×125 mcg/inh), Arm A (Primatene 2×220 mcg/inh, active control) and Arm P (Placebo) with a 4:1:1 ratio. The Primatene had distinct physical attributes from those for E004 and Placebo; an evaluator-blinded technique was applied for arm A. This study consisted of a screening visit and five visits scheduled at 3-week intervals, as Visit-1 (Day 1 of study), Visit-2 (week 3), Visit-3 (week 6), Visit-4 (week 9), and Visit-5 (week 12). The patients self-administered one of the three treatments via inhalations to inhalations per dose, four times daily (QID) for 12 weeks. Dosing time was recommended to be before the 3 meals and before bedtime, approximately every 4-6 hours. For the days of study Visit 1, 3, and 5, the first AM dose was administered at the study sties.

The primary endpoint was $AUC_{0\text{-}6h}$ of Δ% FEV1, defined as the area under curve of post-dose FEV_1 percentage changes (Δ %) from the same-day pre-dose baseline FEV_1 (FEV_1 at t_0) versus

time (AUC Δ %) (Figure 14, Appendix). The analysis compared the $AUC_{0\text{-}6h}$ Δ% FEV1 between E004 and Placebo-HFA at Study Visit-5 using two-sided t-test.

Efficacy was assessed via pulmonary function testing at each of visits 1, 3 and 5 only and serial FEV_1 measurements up to 6 hours post-dose were collected, in addition to safety and compliance evaluations. Study Visits 2 and 4 were conducted for safety and compliance evaluations, without study drug dosing and serial FEV_1 measurement at the study sites. The 8 FEV_1 measures were taken at 0 (baseline), 5, 30, 60, 120, 180, 240, and 360 minutes post-dose.

The secondary efficacy endpoints included AUC of Δ volume for FEV_1, time to onset [tonset], peak bronchodilator response [Fmax], time to peak effect/response [tmax], duration of efficacy; % responder rate, PEF (peak expiratory flow), DASS (daytime asthma symptom scores), and NAS (nighttime awakening scores). The applicant's definitions of the primary endpoint and each secondary endpoint are listed in the Appendix.

All efficacy endpoints including $AUC_{0\text{-}6h}$, Fmax, duration, Time of onset, Tmax were calculated based on the percent change FEV_1 ($\Delta\%FEV_1$). In order to compare E004 with the same class of drug on the market, the clinical team requested that the applicant provide additional efficacy analyses based on the mean change in FEV_1 during the Pre-NDA meeting (meeting preliminary comments, dated January 30, 2013 in DARRTS). In the NDA submission, the applicant did not provide the results from the requested analyses. Instead, these data and analyses results for the efficacy measurements of $AUC_{0\text{-}6h}$ for FEV_1, Fmax of FEV_1 and Tmax for FEV_1 for both Studies E004-C and E004-D were submitted on November 5, 2013 per request in the IR letter dated October 18, 2013.

The Statistical Analysis Plan (SAP) for clinical efficacy Study C was prepared and initially submitted to the FDA on 10/16/11. Two (2) minor modifications to the SAP version 1.0 were submitted to the Agency on 4/13/12 and 4/26/12, respectively, for further clarification of study population, rescue drug use analysis and vital signs data analysis. Further, FDA's instructions on the SAP given during the 1/31/2013 pre-NDA meeting were incorporated into version 2.0 and version 2.1 of SAP and were submitted to the FDA for review on 2/14/2013.

The primary efficacy analysis was performed on the treated population (TP), defined as all randomized patients who had taken at least one dose of the randomized treatment. The safety evaluation was also performed on the TP population. The statistical analysis was performed to examine if Armstrong's E004 (Arm T), with a repeated dose for 12 weeks, has a significantly greater bronchodilatory effect compared to the Placebo-HFA control (Arm P) in terms of AUC of $\Delta\%FEV_1$. The trial would be declared a success if the statistical analyses based on TP showed that the E004 (Arm T) at Visit-5 has a significant bronchodilatory effect compared to Placebo (Arm P). Similar efficacy analyses of Primatene active control arm (Arm A) versus Arm P were also performed for the study validation purpose. Secondary efficacy endpoints were analyzed for all complete-cases only, i.e., the per protocol population (PPP), defined as patients who have successfully completed at least clinical Visit 5, and have evaluable AUC for clinical Visit 5 as specified below:

(1) Pre-dose Baseline FEV_1 was valid;

(2) Treated by the correct study drug at the correct dose (except for placebo) with the correct delivery procedure (except for placebo) as designed by the protocol of this study;
(3) Patient did not use rescue drug during the study visit;
(4) At least one out of the two FEV_1 measurements at 5 and 30 minutes post-dose was available; and
(5) FEV_1 at 360' post-dose was available; and
(6) At least 5 out of all 7 Post-dose Serial FEV_1 measurements were available.

The applicant did not provide detailed information about the sample size calculation. No interim efficacy analysis has been done.

Per FDA's recommendation, the primary efficacy analysis for efficacy (FEV_1) data observed in Visit 5 was performed for all randomized patients who took at least one dose of study drug (modified intent-to-treat or Treated population). There were many ways for FEV_1 data at Visit 5 to be missing as defined by the applicant. This includes:

- For patients who discontinued treatment prior to Visit-5, all FEV_1 data for these patients were considered missing;
- For patients who were treated at Visit-5, data may be disqualified for the following reasons
    - Required the use of rescue drug (UORD) after the dosing, then all FEV_1 data after the UORD for the patient were considered missing;
    - Baseline $FEV1_0$ was not observed (or qualified), then all FEV_1 data for that patient were considered missing;
    - The measurement of baseline $FEV1_0$ or FEV_1 after dosing have non-material deficiencies, observed FEV_1 data for the patients would NOT be considered as missing data. However, these deficiencies would be flagged and listed.

For these patients with missing data, the applicant applied the following three imputation strategies to handle missing data at Visit 5 for the primary endpoint (Table 3). The appropriateness of these imputation strategies is discussed in Section 3.2.2.3.

a) Closest Data Model (Primary approach):
    - For patients who were not treated at Visit 5, then entire 8 FEV_1 points are missing, impute the missing value of FEV_1 with the previous visit value at the same time point if it exists; otherwise impute missing value of FEV_1 with the group mean of the same arm at the same visit of the data from PPP;
    - For treated patients, if missing value due to the disqualification of using rescue drug, then impute the missing value of FEV_1 with the group mean of the placebo arm at the same visit of the data from PPP;
    - For treated patients, if missing value due to the disqualification of other reasons, then impute the missing value of FEV_1 with the group mean of the same arm at the same visit of the data from PPP.

b) Placebo Model: impute all missing value of FEV_1 with the group mean of the placebo arm at the same visit of the data from PPP.

c) Baseline Model: impute all missing value of FEV_1 with the baseline FEV_1 ($FEV1_0$) (BOCF).

Table 3: Imputation Methods for Primary Efficacy Endpoint (FEV_1) at Visit 5

Patient Sub-group in ITT Population	Method-A: Closest Data Model (Reasonable method, Primary Analysis)			Method-B: Placebo Model (Very Conservative Method)	Method-C: Baseline Model Most Conservative Method
	Classifi-cation	Description	Formula		
Not Treated at Visit-5	Visit-3 Data available	FEV1(t) (i) for the same subject *j* (ii) at the same treatment *X* (iii) the same time *t* (iv) but in Visit-3	$f_j^{X,5}(t)$	Arm mean FEV1(t) for Placebo Treatment at same visit (Visit-5) $\overline{f^{P,5}(t_i)}$	The same day baseline, $f_j^{X,5}(t) \equiv 0\%$
	No Visit-3 Data Available	Arm mean FEV1(t) at (i) the same treatment *X*, (ii) the same time *t* after dosing (iii) in the same visit (Visit-5)	$\overline{f^{X,5}(t_i)}$		
Treated at Visit-5, but disqualified,	Rescue Drug was used after Dosing	Arm mean FEV1(t) (i) in Placebo treatment at (ii) the same time *t* after dosing (iii) for the same visit (Visit-5)	$\overline{f^{P,5}(t_i)}$		
	Rescue Drug was used Before dosing	Arm mean FEV1(t) at (i) the same treatment *X*, (ii) the same time *t* after dosing (iii) in the same visit (Visit-5)	$\overline{f^{X,5}(t_i)}$		
	Others	ibid			
Treated at Visit-5, Qualified (PPP)	Missed schedule etc.	Interpolation	See Text	Interpolation	Interpolation

[Source: Table 5-10 of study report api-e004-cl-c.pdf]

For the analyses using the PP population, only a small portion of data were most likely to be missing since the criteria required that patients complete Visit 5 schedule, have baseline FEV value and have at least 5 of 7 post-dose serial FEV_1 measures. According to the applicant, this implied that patients in this group adhered to the protocol and tolerated the drug to stay in their assigned treatment group. Further, missing data occurred most likely at random. Therefore, the applicant applied the interpolation method for imputation and estimated as:

$$F_i = F_{i-1} + \frac{F_{i+1} - F_{i-1}}{t_{i+1} - t_{i-1}}(t_i - t_{i-1})$$

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Of 605 screened patients, only 373 patients were randomized to either E004 (248), Placebo (61) and Primatene (64). All of 373 patients were treated with at least one dose of study drug. Three hundred and eleven (87%) patients completed the entire 12-week study (Visit-5) and patients in placebo arm had the most completion rate (92%) compared to other two arms (Table 4). For

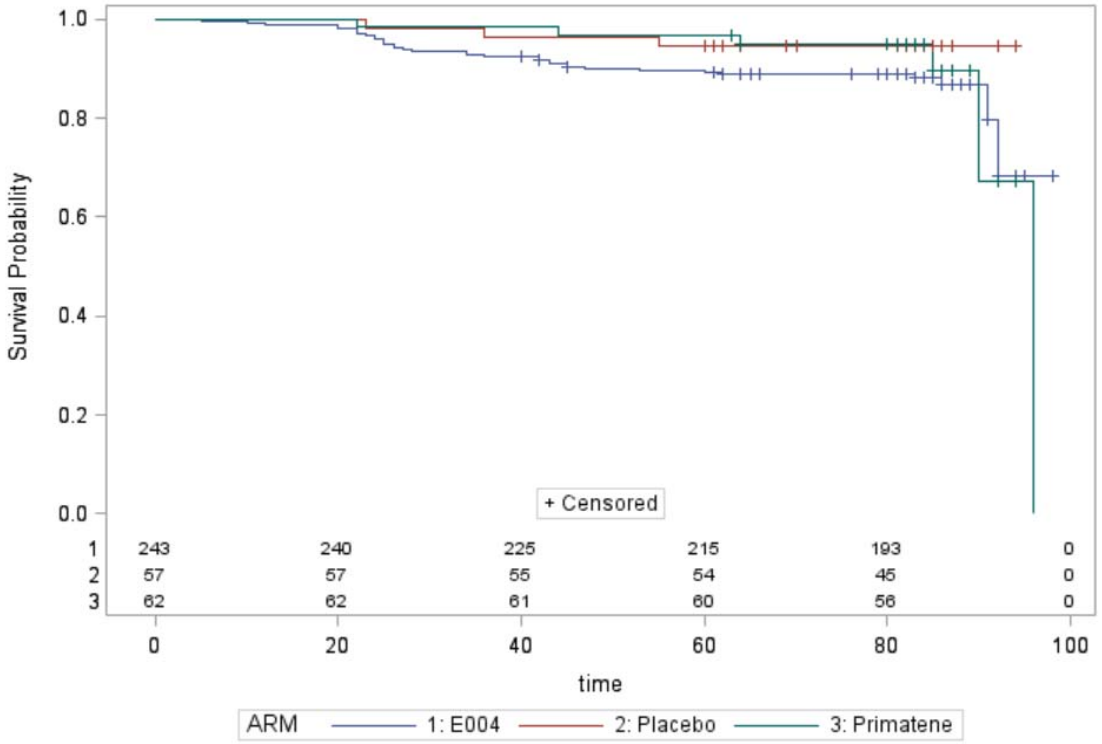
those 47 patients who prematurely discontinued treatment, the reasons were mainly due to adverse event (6%), personal reason (3%), and protocol violation (2%). The pattern of withdrawal is shown numerically in Table 4 and graphically with Kaplan-Meier plot of the time to early discontinuation of each treatment group in Figure 4. These illustrate the slightly faster withdrawal rate in the E004 group than the placebo group.

Table 4: Patient Disposition, N (%) ITT Population

			E004	***Placebo***	***Primatene***	***Total***
Population	Randomized		248	61	64	373
	ITT [a]		248	61	64	373
	TP [b]	Visit 1	248 (100)	61 (100)	64 (100)	373 (100)
		Visit 2	221 (89)	57 (93)	60 (94)	338 (91)
		Visit 3	215 (87)	56 (92)	55 (86)	326 (87)
	Per-protocol (PP) [c]	Visit 1	228 (92)	54 (89)	61 (95)	343 (92)
		Visit 2	198 (80)	54 (89)	57 (89)	309 (83)
		Visit 3	205 (83)	53 (87)	53 (83)	311 (83)
	Completed study		214 (86)	56 (92)	55 (86)	325 (87)
	Discontinued study treatment		34 (14)	5 (8)	9 (14)	48 (13)
Reasons for early Discontinuation From study	Due to AEs		17 (7)	3 (5)	3 (5)	23 (6)
	Consent withdrawn (not due to AE)		*9 (4)*	*0*	*3 (5)*	*12 (3)*
	Lost to follow-up		2 (1)	2 (3)	1 (2)	5 (1)
	Protocol violation		6 (2)	0	2 (3)	8 (2)

Percentages are based on the ITT population.
a. ITT – ITT population included all randomized patients, who had passed enrollment confirmation evaluation at Screen.
b. TP - The Treated Population included all randomized patients who had taken at least one dose of the randomized treatment
c. The Per Protocol population comprises all randomized patients with baseline and post treatment data and at least one drug intake without any relevant protocol violations.

Figure 4: Kaplan-Meier Plots on Time to the Discontinuation



Demographic and Baseline Characteristics

Study C consisted of slightly more female patients than male patients, with an average age of 40 years (range 18 to 64). The majority of these patients were Caucasian (70%). Patients in each treatment arms represented a broad range of disease severity with baseline FEV_1 values ranging from 1.0 L to 4.5 L (Table 5).

Table 5: Demographic and Baseline Characteristics of ITT Patients, N (%)

Demographic Parameter		***E004 250 mcg (N=248)***	***Placebo (N=61)***	***Primatene 440 mcg (N=64)***
Age at Randomization (yrs)	Mean (SD)	38.6 (15.0)	40.1 (14.3)	41.2 (15.9)
	Median (Range)	37 (12, 75)	38 (13, 69)	40 (13, 71)
Age Group, N (%)	12 - <18	18 (7)	4 (6)	3 (5)
	18 – 40	115 (46)	28 (46)	30 (47)
	41 – 64	109 (44)	25 (41)	25 (39)
	65+	6 (2)	4 (6)	6 (9)
Sex, N (%)	Male	99 (40)	21 (34)	29 (45)
	Female	149 (60)	40 (66)	35 (55)
Race, N (%)	Caucasian	177 (71)	40 (65)	49 (76)
	African-American	39 (16)	14 (23)	9 (14)
	Hispanic/Latino	23 (9)	4 (7)	5 (8)
	Asian	2 (1)	1 (2)	1 (2)
	Others	7 (3)	2 (3)	0
Height (cm)	Mean (SD)	168.6 (9.3)	167.0 (11.4)	168.8 (11.1)
	Median (Range)	168 (145, 201)	167 (115, 188)	167 (142, 197)
Weight (kg)	Mean (SD)	83.7 (20.0)	82.1 (19.6)	83.2 (24.0)
	Median (Range)	84 (47, 147)	77 (44, 138)	82 (43, 146)
Baseline FEV_1 (L)[1]	Mean (SD)	2.36 (0.59)	2.36 (0.58)	2.34 (0.64)
	Median (Range)	2.30 (1.19, 4.47)	2.29 (1.40, 4.09)	2.37 (1.04, 4.08)
Screen FEV_1% Predicted	<80%	213 (86)	52 (85)	52 (81)
	≥80%	35 (14)	9 (15)	12 (19)

Note: Baseline FEV_1 = Pre-dose FEV_1 at visit 1. Data source: dm01.xpt, ds.xpt, arm.xpt, demo.xpt, FEV.xpt.

3.2.2.3 Results and Conclusions

The primary efficacy analysis was conducted with FEV_1 data collected in Visit 5 (Week 12). Eight (8) FEV_1 data were expected to be measured for each patient. Table 6 displays the missing data patterns for FEV_1 at Visit 5. There were 15%, 13%, and 17% patients missing all FEV_1 measurement at visit 5 for E004, placebo, and Primatene respectively. The main reason for the treatment discontinuation and missing data was due to adverse event (Table 6). Post-discontinuation FEV_1 data were not collected. Therefore, the applicant applied several strategies to impute missing data. For patients who only missed 1 or 2 FEV_1 data points, these data will be imputed using the interpolation method. For patients who discontinued treatment prior to Visit 5, the applicant applied three imputation strategies described in detail in the preceding section, namely the closest data model (model A, primary approach), the placebo model (model B), and the baseline model (model C). Since the primary endpoint was at Visit 5, the applicant only imputed the missing data points at visit 5.

All three approaches used a single value imputation that assumed what the patient score would have been if he/she continued treatment. These approaches also did not account for the variance in the treatment effect, potentially overstating the significance of the treatment effect.

In model A, the approach imputes missing data based on measurements from previous visit or from the group mean of the same arm at the same visit from the per protocol population (i.e., missing at random assumption). This is concerning given that we are assuming that the behavior of the post-withdrawal data can be predicted from what was observed prior to discontinuation, preserving the treatment effect that was observed prior to discontinuation. Since half of the missing data in E004 treated patients discontinued due to AE, this approach may be imputing good scores to patients who were in fact not successfully treated. Further, the PP population (PPP) includes only patients who tolerated the drug or adhered to the protocol, such that the characteristics of the population who discontinued treatment and those that are in the per protocol population are more likely to be different. It is more likely that the status of those patients who discontinued treatment may be more severe compared to those who completed the study and were included in the PPP. Therefore, by taking the group mean of the same arm at the same visit from the PP population, you may be imputing a good score to a bad outcome, inadvertently making the treatment difference larger than it should be. Model B had similar limitation as model A. Placebo patients who adhered to the protocol and completed the trial (PP population) are more likely to be different from those who discontinued treatment. Therefore, you may still be imputing a good score to a potentially bad outcome. Therefore, models A and B are not the most ideal imputation strategies. The approach in Model C imputes missing data with patient's baseline score. While this approach is not perfect since this does not account for the variance and potentially overstates the statistical significance of results, in general this approach does provide a conservative point estimate of the treatment effect. Given the larger discontinuation rate in the E004 group compared to placebo, bringing these patients' scores to their baseline value may be conservative and its comparison to placebo or Primatene groups may be reasonable. An alternative strategy is to compare treatment effect by examining patients' response using multiple responder cut-offs (or continuous responder plots). Patients who discontinued treatments are considered non-responders.

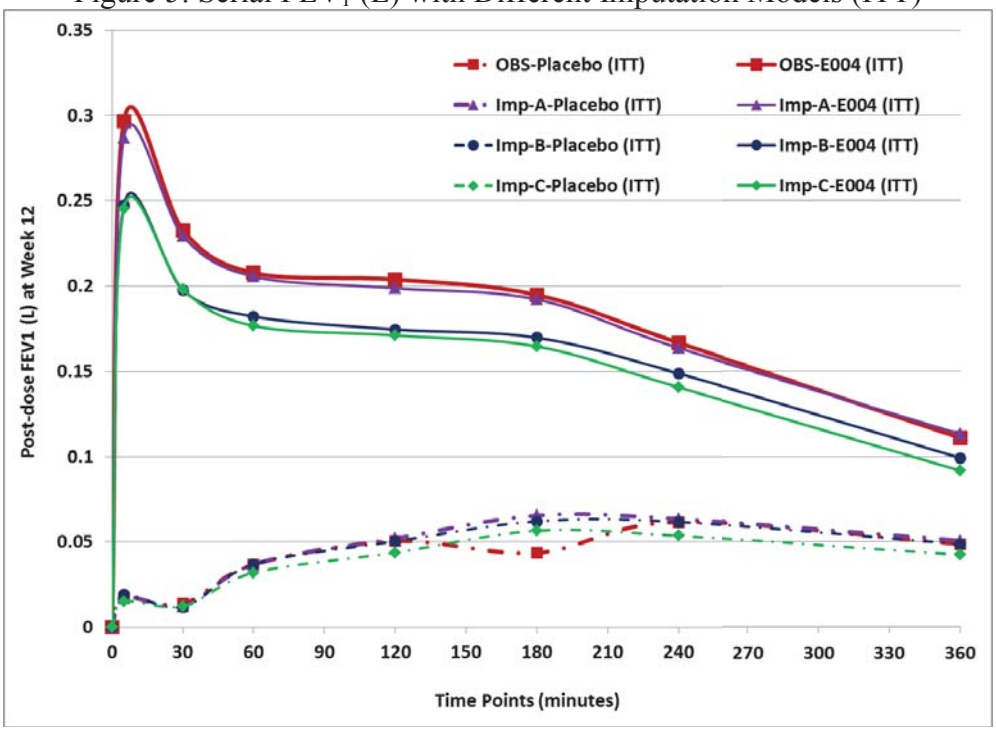
Examining the serial FEV_1 from 0 to 6 hours by imputation strategies showed a slightly narrower difference between E004 and Placebo when model C is applied suggesting a smaller treatment effect (Figure 5).

Table 6: Patient Missing FEV_1 at Each Time point and $AUC_{0\text{-}6h}$ at Visit 5, N (%) ITT Population

	E004 (N=248)	***Placebo (N=61)***	***Primatene (N=64)***
Patients with missing all FEV_1 measurement	37 (15)	8 (13)	11 (17)
Reason for missing FEV_1 measurement			
Adverse event	17 (7)	3 (5)	3 (5)
Lost to follow-up	2 (<1)	2 (3)	1 (1)
Major protocol violation and non-compliance	5 (2)	0	2 (3)
Personal reasons and other	6 (2)	0	1 (1)
Withdrawal of informed consent	3 (1)	0	2 (3)
No reason recorded	4 (2)	3 (5)	2 (3)

Percentages are based on the ITT population.

Figure 5: Serial FEV_1 (L) with Different Imputation Models (ITT)



[Source: seq_fev_study_c.xlsx]

Efficacy results

The primary analysis results based on imputation model A (primary approach) showed that E004 has a significant improvement in $AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ compared to placebo at week 12, which is consistent with the results applying models B and C (Table 16 and Table 17 in Appendix for detail). Of note, the results applying models A and C are shown in Table 7 as well. There is about a 15% reduction in the treatment effect when model C was applied instead of model A (treatment difference in $AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ for model A is 33% and for model C is 28%) but the results were still statistically significant. When compared to placebo, Primatene had similar conclusion as E004 (Please see Table 16 and Table 17 in Appendix for detail).

The clinical reviewer requested that the following efficacy results be summarized: $AUC_{0\text{-}6hrs}$ of FEV_1, FEV_1 at 5 minutes post-dose, Fmax, and Tmax. The analysis results (Table 7) based on the model C imputed data showed that E004 treated patients has a significant higher mean $AUC_{0\text{-}6hrs}$ of FEV_1 of 15.8 (Lxhr) compared to placebo group of 14.4 (Lxhr) at visit 5 (Week 12). At 5 minutes after dosing, the E004 treated patients had a 0.25L FEV_1 improvement compared to 0.02L in the placebo group. The E004 treated patients had a shorter time to reach the maximum FEV_1 (1 hour) compared to 2 hours in the placebo group. These efficacy results support the E004's bronchodilator effect. Similar to the primary endpoint, there is about a 15% reduction in the treatment effect when model C is applied instead of model A (for example: treatment difference in $AUC_{0\text{-}6hrs}$ of FEV_1 (Lxhr) for model A is 1.4 (Lxhr) and for model C is 1.2 (Lxhr)).

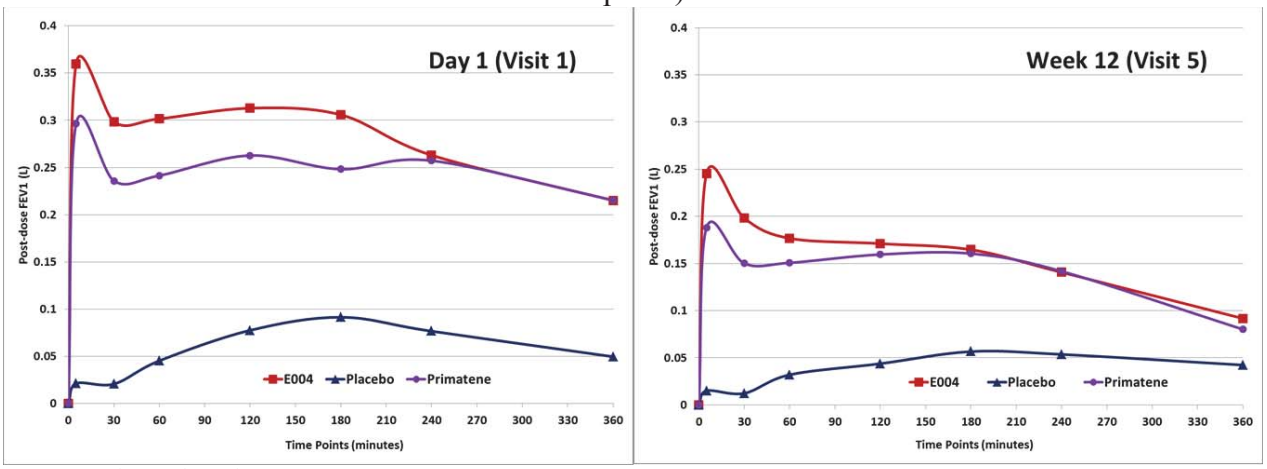
Table 7: Analyses Results on Selected Endpoints Based on the Imputation Model A and C (ITT)

	E004 (n=248) Mean (SD)	*Placebo (n=61) Mean (SD)*	*Primatene (n=64) Mean (SD)*	*Mean Difference (E004 - Placebo) 95%CI*
Based on Model A Imputed Data				
$AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ (%*hr)	**47.27 (54.16)**	**14.60 (55.60)**	**41.02 (43.39)**	**32.67 (16.97, 48.38)** [1]
$AUC_{0\text{-}6hrs}$ of FEV_1 (L*hr)	15.84 (3.90)	14.43 (3.57)	15.72 (4.18)	1.41 (0.37, 2.44) [1]
ΔFEV_1 at 5 min. post-dose (L)	0.29 (0.22)	0.02 (0.14)	0.23 (0.21)	0.27 (0.22, 0.31) [1]
Fmax of FEV_1 (L)	2.82 (0.67)	2.55 (0.60)	2.77 (2.59)	0.27 (0.09, 0.44) [1]
Tmax(hr)	1.17 (1.57)	2.46 (2.06)	1.38 (1.74)	-1.29 (-1.85, -0.73) [1]
Based on Model C Imputed Data				
$AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ (%*hr)	**40.59 (56.09)**	**12.76 (55.77)**	**35.67 (45.70)**	**27.83 (11.99, 43.68)** [1]
$AUC_{0\text{-}6hrs}$ of FEV_1 (L*hr)	15.57 (3.96)	14.36 (3.57)	15.39 (3.97)	1.22 (0.18, 2.25) [1]
ΔFEV_1 at 5 min. post-dose (L)	0.25 (0.24)	0.02 (0.14)	0.19 (0.23)	0.23 (0.18, 0.28) [1]
Fmax of FEV_1 (L)	2.75 (0.70)	2.53 (0.60)	2.70 (0.71)	0.22 (0.04, 0.39) [1]
Tmax(hr)	1.02 (1.43)	1.95 (2.12)	1.18 (1.70)	-0.93 (-1.50, -0.36) [1]

Note 1: p-value <0.05. ΔFEV_1= Change from baseline (pre-dose) FEV_1
The mean, standard deviations, 95% confidence interval, and p−value are based on two-sided t-test analyses.

The serial FEV_1 profile curves between 0 to 6 hours at day 1 and week 12 by treatment arms (i.e., E004 (red), placebo (blue), and Primatene (purple)) based on ITT population imputed by model C are presented in Figure 6. There is a clear separation between both E004 and Primatene and placebo which demonstrates a greater bonchodilatory effect among those treated with E004 and Primatene. There is also a small separation between E004 and Primatene around the first 3 hours at Day 1 and around the first 2 hours at week 12 suggesting a small benefit of E004 over Primatene in the first few hours of treatment.

Figure 6: Series Change from Baseline of FEV_1 (L) at Day 1 and Week 12 (ITT, Model C Imputed)



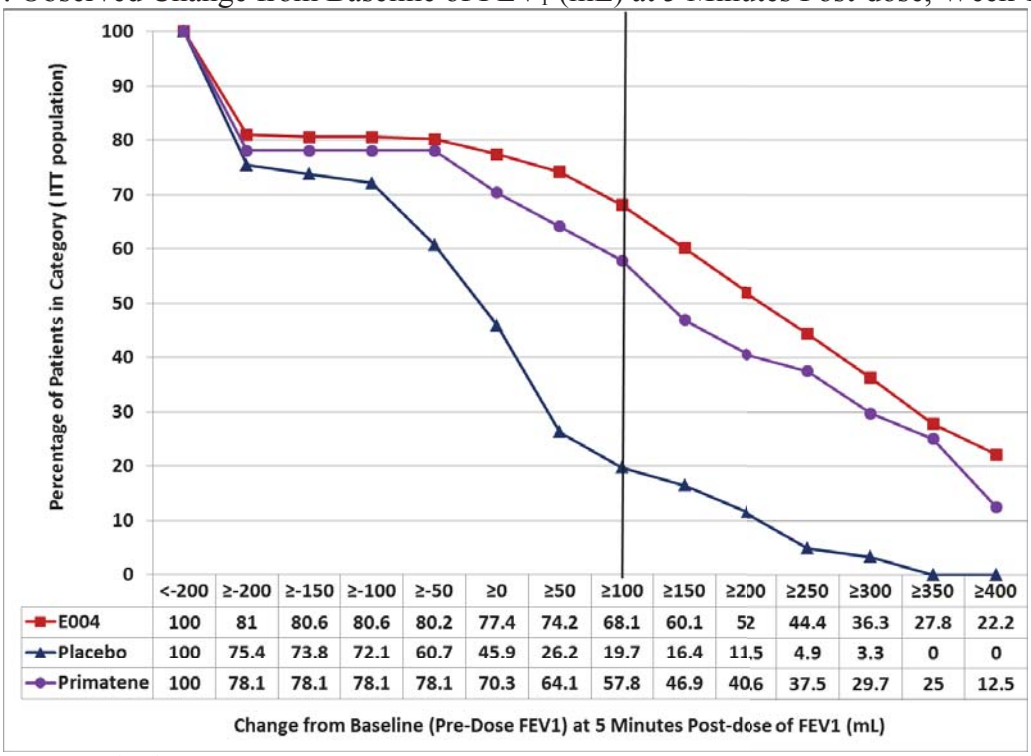
[Source: seq_fev_study_c.xlsx]

The continuous responder plot by treatment arms is presented on Figure 7. This presentation is developed as follows. Each patient is classified as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the change from baseline in FEV_1 at 5 minutes post-dose at week 12. This dichotomization of the change from baseline in FEV_1 is repeated across a range of possible thresholds, in this case from -200 to +400 mL. In the continuous responder plot, the x-axis displays the thresholds. The y-axis represents

the proportion of ITT patients who achieved the corresponding threshold. The proportion of E004 patients achieving each threshold is represented by the red line, proportion of placebo patients by the blue, and proportion of Primatene by the purple.

There is an initial dramatic drop from 100% to approximately 80% in the y-axis, corresponding to the proportion of patients who dropped out since patients with missing data were classified as unsuccessfully treated for all thresholds. Dropouts were similar between the three treatment groups. A higher proportion of patients treated with E004 achieved the change from baseline FEV_1 thresholds compared to placebo since E004 generally lies above placebo in the figure. This supports the primary analysis findings.

Figure 7: Observed Change from Baseline of FEV_1 (mL) at 5 Minutes Post-dose, Week 12 (ITT)



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
E004	100	81	80.6	80.6	80.2	77.4	74.2	68.1	60.1	52	44.4	36.3	27.8	22.2
Placebo	100	75.4	73.8	72.1	60.7	45.9	26.2	19.7	16.4	11.5	4.9	3.3	0	0
Primatene	100	78.1	78.1	78.1	78.1	70.3	64.1	57.8	46.9	40.6	37.5	29.7	25	12.5

[Source: responder.xlsx]

3.2.3 Phase 3 Pediatric Study

Study D was a phase 3 randomized, multicenter, double-blinded/evaluator-blinded, placebo- and active-controlled, 4-week trial to assess the bronchodilator efficacy of E004 250 mcg four times daily (QID), as compared with placebo in patients aged 4 – 11 years with moderate to severe asthma.

A total of 70 patients were randomized to Arm T (E004 2×125 mcg/inh) and Arm P (Placebo) in a 1:1 ratio stratified by age (i.e., 4 to 8 versus 9 to 11). This study consisted of a screening visit, 7– 14 days run-in period, and three visits scheduled at 2-week intervals, as Visit-1 (Day 1), Visit-2 (week 2), and Visit-3 (week 4). During the run-in period, patients were allowed to remain

taking their inhaled short-acting β-agonist and all log-acting β-agonists. Study drug was self-administered via oral inhalation, two inhalations/dose, QID for the 4-week study period. Dosing time was recommended to be before the 3 meals and before bedtime, approximately every 4 – 6 hours. The bronchodilatory efficacy of E004 was assessed by preforming serial FEV1 measurements with the first AM randomized study drug dosing on Day 1 (Visit 1) and Week 4 (Visit 3, end of the study). All primary and secondary endpoints, the statistical analysis methods, missing data handling were the same as for the adult study (Study C).

Patient Disposition

Eight sites participated in this study. Of 111 screened patients, only 70 patients were randomized to either E004 (35) and Placebo (35). All of 70 patients were treated with at least one dose of study drug. Sixty-three (90%) patients completed the entire 4-weeek study (visit-3) and patients in placebo arm had the most completion rate (91%) compared to E004 arm (Table 8). For those 7 patients who prematurely discontinued treatment, the reasons were mainly due to adverse event (6%). Eighteen patients treated in Visit 3 were excluded Treated population (TP) due to disqualify FEV_1 measurements. The applicant's primary analysis was based on the PP population.

Table 8: Patient Disposition, N (%) ITT Population

			E004 250 mcg	***Placebo***	***Total***
Population	Randomized		35	35	70
	ITT [a]		35	35	70
	TP [b]	Visit 1	35	35	70
		Visit 3	31 (89)	32 (91)	63 (90)
	Per-protocol (PP) [c]	Visit 1	22 (63)	22 (63)	44 (63)
		Visit 3	23 (66)	22 (63)	45 (64)
	Disqualified in TP [c]	Visit 1	13 (37)	13 (37)	26 (37)
		Visit 3	8 (26)	10 (31)	18 (29)
	Completed study		31 (89)	32 (91)	63 (90)
	Discontinued study treatment		4 (11)	3 (9)	7 (10)
Reasons for early Discontinuation From study	Due to AEs		2 (6)	2 (6)	4 (6)
	Consent withdrawn (not due to AE)		0	1 (3)	1 (1)
	Protocol violation		2 (6)	0	2 (3)

Percentages are based on the ITT population.

a. ITT – ITT population included all randomized patients who have passed enrollment confirmation evaluation at Study Visit 1.

b. TP - The Treated Population included all randomized patients who had taken at least one dose of the randomized treatment.

c. The Per Protocol population comprises all randomized patients with baseline and post treatment data and at least one drug intake without any relevant protocol violations.

Demographic and Baseline Characteristics

Study D consisted of slightly more male patients than female patients, with an average age of 8 years (range 4 to 11). Forty percent of patients were Caucasian, 30% were African American, and 20% Hispanic. Patients in each treatment arms represented a broad range of disease severity with baseline FEV_1 values ranging from 0.63L to 2.63L (Table 9).

Table 9: Demographic and Baseline Characteristics of ITT Patients, N (%)

Demographic Parameter		***E004 250 mcg (N=35)***	***Placebo (N=35)***
Age at Randomization (yrs)	Mean ± SD (range)	8.6±2.2 (4,11)	8.2±1.8 (4,11)
Age Group, N (%)	<9	15 (43)	20 (57)
	9-11	20 (57)	15 (43)
Sex, N (%)	Male	20 (57)	24 (69)
	Female	15 (43)	11 (31)
Race, N (%)	Caucasian	15 (43)	14 (40)

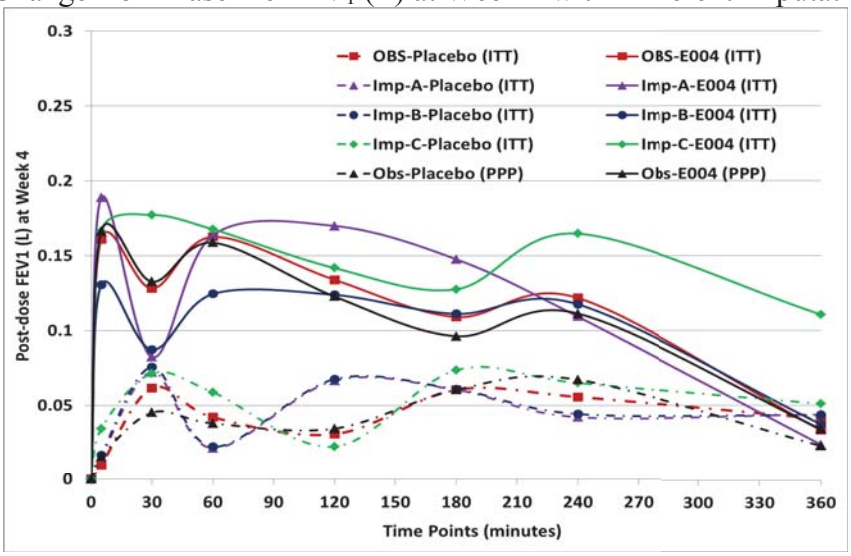
	African-American	11 (31)	11 (31)
	Hispanic/Latino	8 (23)	9 (26)
	Others	1 (3)	1 (3)
Height (cm)	Mean ± SD (range)	135±16 (103, 163)	132±13 (106, 158)
Weight (kg)	Mean ± SD (range)	37±18 (17, 97)	35±15 (15, 85)
Baseline FEV_1 (L)[1]	Mean ± SD (range)	1.48±0.47 (0.63, 2.63)	1.42±0.42 (0.86, 2.31)

Note: Baseline FEV_1 = Pre-dose FEV_1 at visit 1. Data source: dm01.xpt, ds.xpt, arm.xpt, demo.xpt, FEV.xpt.

Efficacy Results and Conclusions

The primary efficacy analysis was conducted with FEV_1 data collected in Visit 3 (Week 4). Eight (8) FEV_1 data were expected to be measured for each patient. There were 11% and 9% patients missing all FEV_1 measurements at visit 3 for E004 and placebo, respectively. The main reason for the treatment discontinuation and missing data was due to adverse event (Table 8). Post-discontinuation FEV_1 data were not collected. The applicant's primary analysis was based on the PP population (Table 19 Appendix). The applicant also provided the results using the intent-to-treat population in which the Division considers the more appropriate analysis population (refer to section 2.1.2 of the review, meeting comments #2). Per Division's request, the applicant applied the same strategies to impute missing data. Figure 8 displays the sequence FEV_1 data with observed data, imputed data with three imputation models for ITT population, and observed data for PP population. There is no clear separation between the three imputation models. I To be consistent with the analysis results in Study C, the efficacy results based on the model C imputed data is presented.

Figure 8: Change from Baseline FEV_1 (L) at Week 4 with Different Imputation Models



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Efficacy results

The applicant's pre-specified primary analysis was based on the PP population. Although the results showed numerical benefit of E004 over placebo in $AUC_{0\text{-}6hr}$ of $\Delta\%FEV_1$ at Visit 3, the difference was not statistically significant with a two-sided p-value of 0.124 (Table 10). This finding is supported by the result from the analysis using the ITT population. This finding is also

supported by the results from the three sensitivity analyses based on ITT population (Table 20 in Appendix). Since the primary endpoint failed, the results from the analyses of the secondary endpoints were considered exploratory (Table 19 in Appendix). A few secondary endpoints showed some numerical benefit of E004 over placebo. For example, 5 minutes after dosing at week 4, the E004 treated patients had a 0.17L FEV_1 improvement compared to 0.03L for placebo group (Table 10).

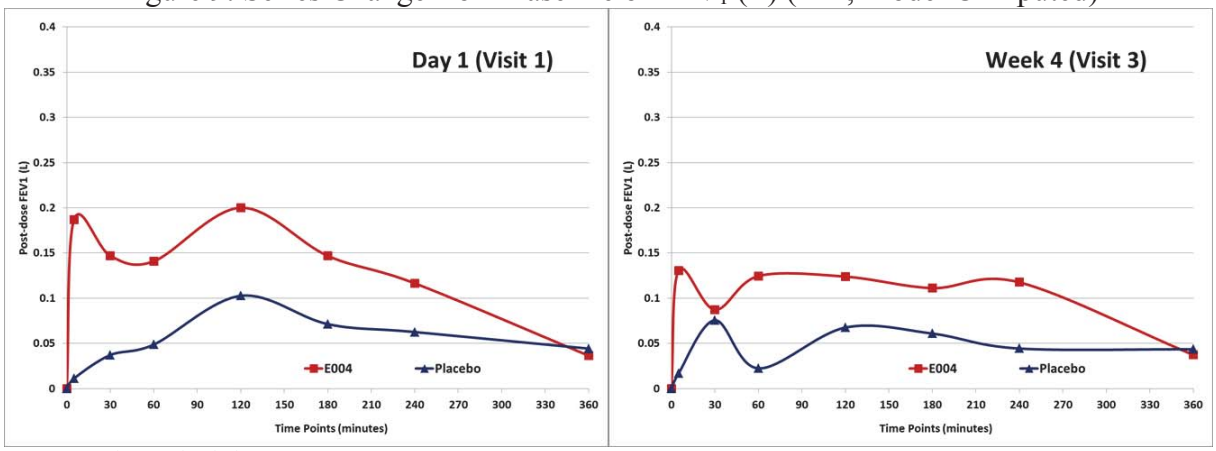
Serial FEV_1 profile curves between 0 to 6 hours at day 1 and week 4 by treatment arms (i.e., E004 (red), placebo (blue)) based on PP population are presented in Figure 9. The curve for E004 is above the curve for placebo which suggests a greater bonchodilatory effect. The magnitude of effect in FEV_1 during 6 hours post-dose is slightly larger in patients treated with E004 at Day 1 compared to at week 4, which suggests that the efficacy of E004 may decrease over time.

Table 10: Analyses Results on Selected Endpoints for Study D

	E004 (N=35) Mean (SD)	***Placebo (N=35) Mean (SD)***	***Mean Difference (E004 - Placebo) 95%CI, p-value***
Based on PP population observed data			
N	23	22	
$AUC_{0\text{-}6hrs}$ of Δ%FEV_1 (%*hr)	**47.62 (68.65)**	**21.20 (41.47)**	**26.42 (-7.69, 60.52), p=0.125**
$AUC_{0\text{-}3hrs}$ of Δ%FEV1 (%*hr)	27.10 (37.50)	9.90 (20.24)	17.21 (-0.94, 35.36), p=0.062
$AUC_{0\text{-}6hrs}$ of FEV1 (L*hr)	10.92 (3.21)	9.03 (2.38)	1.89 (0.20, 3.59), p=0.030
ΔFEV_1 at 5 min. post-dose (L)	0.17 (0.15)	0.02 (0.09)	0.15 (0.07, 0.23), p<0.001
Fmax of FEV1 (L)	1.94 (0.55)	1.61 (0.41)	0.33 (0.04, 0.62), p=0.028
Tmax (hr)	1.36 (1.67)	2.65 (2.30)	-1.29 (-2.61, -0.08), p=0.038
Based on ITT population with Model C imputed data			
N	35	35	
$AUC_{0\text{-}6hrs}$ of Δ%FEV_1 (%*hr)	**34.15 (60.29)**	**15.79 (34.63)**	**18.36 (-5.20, 41.92), p=0.124**
$AUC_{0\text{-}3hrs}$ of Δ%FEV1 (%*hr)	19.51 (33.17)	7.91 (17.03)	11.60 (-1.05, 24.26), p=0.072
$AUC_{0\text{-}6hrs}$ of FEV1 (L*hr)	8.60 (5.09)	7.79 (3.76)	0.81 (-1.33, 2.95), p=0.453
ΔFEV_1 at 5 min. post-dose (L)	0.17 (0.32)	0.03 (0.17)	0.13 (0.00, 0.26), p=0.043
Fmax of FEV1 (L)	1.57 (0.85)	1.40 (0.66)	0.17 (-0.20, 0.53), p=0.361
Tmax (hr)	1.28 (1.75)	2.21 (2.19)	-0.93 (-1.88, 0.01), p=0.053

Note 1: p-value <0.05. ΔFEV_1= Change from baseline (pre-dose) FEV_1
The mean, standard deviations, 95% confidence interval, and p−value are based on two-sided t-test analyses.

Figure 9: Series Change from Baseline of FEV_1 (L) (ITT, Model C imputed)



[Source: seq_fev_study_d.xlsx]

3.3 Evaluation of Safety

There is no need for a safety review for this supplement since there are no new additional safety signals detected at this time.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The Primatene® Mist (epinephrine chlorofluorocarbon (CFC)-MDI) was approved for patients aged 4 years and older. In Study D, there is not enough evidence to support the efficacy of E004 in asthma patients aged 4 to 11 years old. In this section, I evaluated the following subgroups: age (12 to 17 years and 18 years and older), gender, race and asthma severity.

There were only 5% to 7% patients between the ages 12 and 18. There is no apparent treatment by age interaction. For patients between the ages 12 and 18, the primary analysis results based on the imputation model C showed that E004 has a significant improvement in the $AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ compared to placebo at week 12 (Table 11), consistent with the overall population.. Figure 10 demonstrates the curves for serial FEV_1 by age group, as a function of time for E004 (red), placebo (blue), and Primatene (purple) at visit 5, respectively, based on ITT population imputed by model C. All curves for E004 and Primatene are clearly above the curves for placebo which demonstrates a greater bronchodilatory effect. There is less variability in the serial FEV_1 measurements in the older patients compared to the younger patients (Figure 10).

While no treatment-by gender, and treatment by race interactions are observed, there is some numerical difference in treatment effects by gender in favor of the female group. There is no notable difference between the race groups (Figure 11 and Figure 12).

There were only 20% of patients with FEV_1%predicted ≥80% at screening. While treatment difference in this subgroup appears to be smaller compared to patients with FEV_1%predicted <80% at screening, there was no apparent treatment by severity interaction (Table 11, Figure 13).

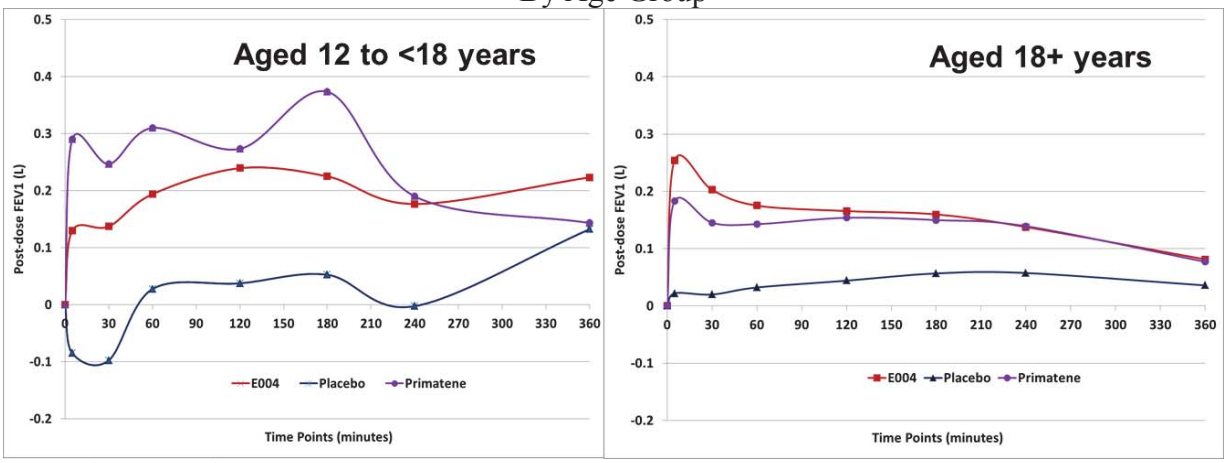
Table 11: Subgroup Analysis for the AUC0-6hrs of Δ%FEV1 (%*hr) (ITT, Model C Imputed)

	E004 (n=248) Mean (SD)	***Placebo (n=61) Mean (SD)***	***Primatene (n=64) Mean (SD)***	***Mean Difference (E004 - Placebo) 95%CI***
Age Group				
Aged 12 - < 18 years	N=18	N=4	N=3	
	58.06 (87.95)	7.24 (24.54)	66.98 (43.70)	50.82 (0.26, 101.4) [1]
Aged 18 years and older	N=230	N=57	N=61	
	39.22 (52.85)	13.14 (57.43)	34.13 (45.58)	26.08 (9.43, 42.73) [1]
Gender				
Female	N=149	N=40	N=35	
	45.51 (64.28)	11.61 (47.01)	34.48 (44.00)	33.90 (15.78, 52.02) [1]
Male	N=99	N=21	N=29	
	33.18 (39.85)	14.94 (70.81)	37.10 (48.42)	18.25 (-14.80, 51.29)
Race				
Caucasian	N=177	N=40	N=49	
	41.50 (56.53)	11.08 (59.79)	31.92 (37.44)	30.42 (9.65, 51.18) [1]
African American	N=39	N=14	N=9	

	46.24 (53.13)	20.86 (52.79)	39.52 (74.03)	25.39 (-8.69, 59.46)
Hispanic/Latino	N=23	N=4	N=5	
	31.67 (65.33)	-4.76 (44.50)	64.04 (62.31)	36.44 (-28.63, 101.5)
Others*	N=9	N=3	N=1	
	21.06 (29.16)	20.64 (35.96)	42.61 (--)	0.42 (-73.43, 74.27)
Asthma Severity				
FEV_1%predicted <80%	N=213	N=52	N=52	
	39.88 (57.52)	10.58 (53.53)	29.06 (41.47)	29.31 (12.59, 46.03) [1]
FEV_1%predicted ≥80%	N=35	N=9	N=12	
	44.90 (46.88)	25.35 (69.64)	64.33 (53.7)	19.55 (-35.15, 74.24)

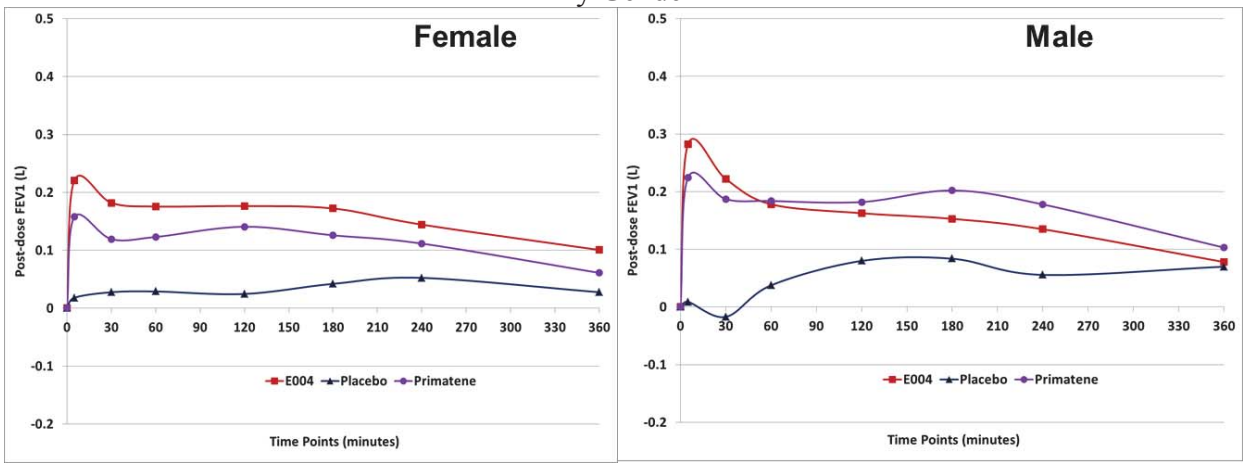
Note 1: p-value <0.05. ΔFEV_1= Change from baseline (pre-dose) FEV_1
The mean, standard deviations, 95% confidence interval, and p−value are based on two-sided t-test analyses.
*: Other race group included: Asian/Asian American, Hispanic/Latino Black, and others.

Figure 10: Series Change from Baseline of FEV_1 (L) at Week 12, Study C (Model C imputed) By Age Group



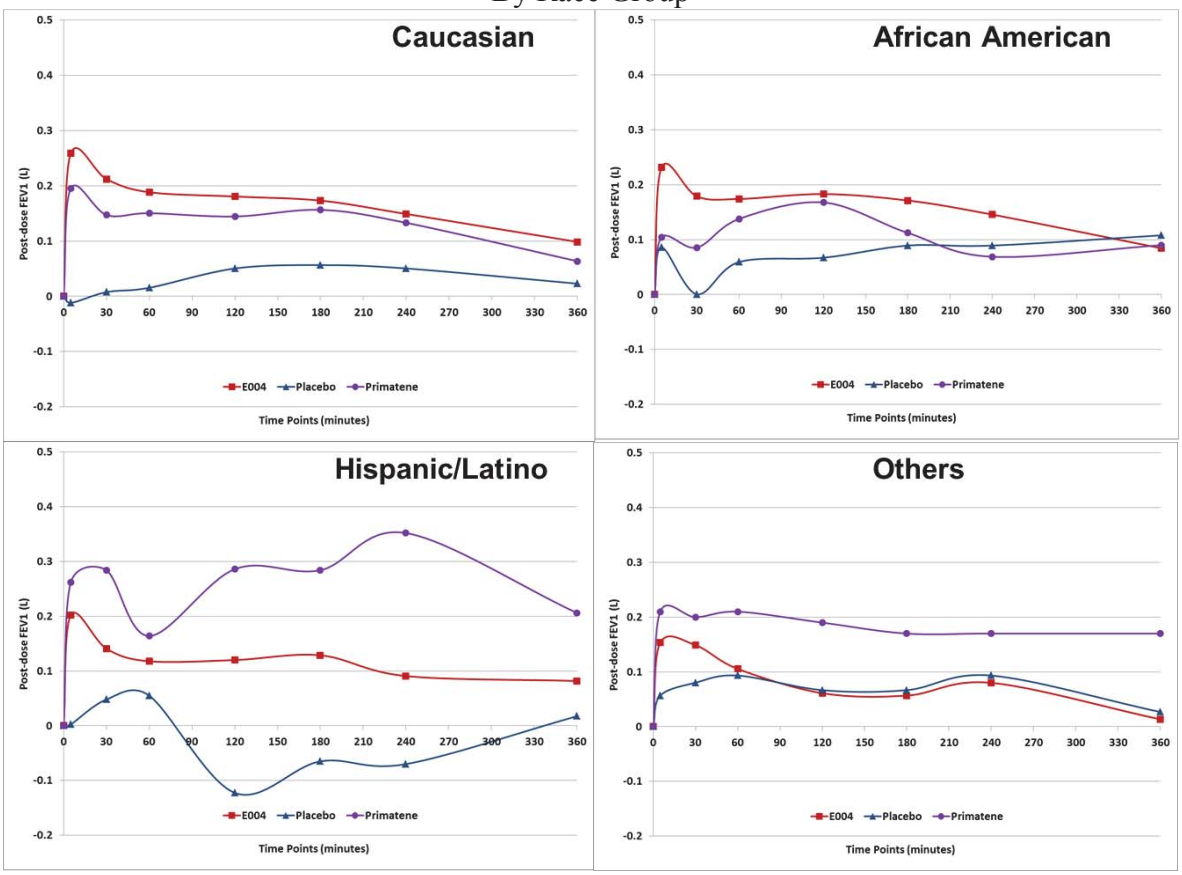
[Source: study_c_agegrp.xlsx]

Figure 11: Series Change from Baseline of FEV_1 (L) at Week 12, Study C (Model C imputed) By Gender



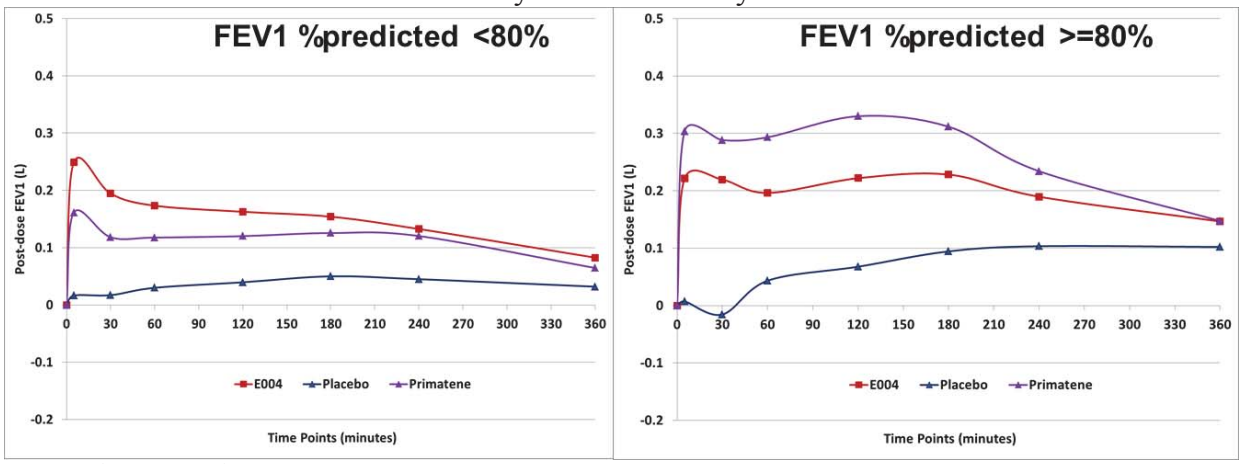
[Source: study_c_agegrp.xlsx]

Figure 12: Series Change from Baseline of FEV_1 (L) at Week 12, Study C (Model C imputed) By Race Group



[Source: study_c_agegrp.xlsx]

Figure 13: Series Change from Baseline of FEV_1 (L) at Week 12, Study C (Model C imputed) By Asthma Severity



[Source: study_c_agegrp.xlsx]

5 SUMMARY AND CONCLUSIONS

5.1 Collective Evidence

The following are the efficacy findings from 4 studies reviewed.

1. Study C was a 12-week study designed to evaluate the long-term efficacy and safety of E004 250 mcg QID HFA inhaler in 373 patients 12 years and older. Patients treated with E004 demonstrated a significant improvement in lung function over 12 weeks when compared to patients treated with placebo. Difference in $AUC_{0\text{-}6hrs}$ of $\Delta\%FEV_1$ between E004 and placebo was statistically significant across all timepoints studied (i.e., Day 1, Week 6, and week 12) regardless of the imputation strategies used to handle missing data. Treatment difference was 28 (%*L) over a period of 12 weeks using placebo imputation approach (imputation model C) with 95% confidence interval of (12.0, 43.7) (%*L) (Section 3.2.2.3).

   This estimated treatment difference is supported by the results from the analyses of secondary endpoints. E004 treated patients had a significant higher mean $AUC_{0\text{-}6hrs}$ of FEV_1 of 15.8 (Lxhr) compared placebo group of 14.4 (Lxhr). At 5 minutes after dosing, the E004 treated patients had a 0.25L FEV_1 improvement compared to 0.02L for placebo group. The E004 treated patients reached the maximum FEV_1 in an hour compared to 2 hours in the placebo group. These findings demonstrated E004's bronchodilator effect. The treatment effect observed in the Primatene arm was numerically smaller compared to E004.

   There was no treatment by age interaction. The results from subgroup analysis by age showed a consistent effect on lung function in the patients aged 12 to 17 years and in patients aged 18 years and older.

2. Study D was the pediatric study designed for evaluating the E004 250 mcg in children aged 4 to 11 years old. Although the results showed numerical benefit of E004 over placebo in $AUC_{0\text{-}6hr}$ of $\Delta\%FEV_1$ at Visit 3, the difference was not statistically significant. While some secondary endpoints showed numerical benefit of E004 over placebo, this is not adequate to demonstrate the bronchodilator effect of E004 in this younger population.

5.2 Conclusions

In summary, there is statistical evidence of a difference between E004 and placebo in asthma patients aged 12 years and older based on Study C and supported by the two dose-finding studies (studies A and A2). In Study C, the estimated treatment difference in $AUC_{0\text{-}6hrs}$ of $\%\Delta$ FEV_1 at week 12 was about 28 (%xL) (95% CI of (12, 44) (%xL)) applying the applicant's model C to impute missing data. Of note, there is about a 15% reduction in the treatment effect when model C was applied instead of model A. This finding is supported by the results from the analyses of the secondary endpoints. E004 treated patients had a higher mean $AUC_{0\text{-}6hrs}$ of FEV_1 of 15.8 (Lxhr) compared placebo group of 14.4 (Lxhr). At 5 minutes after dosing, the E004 treated

patients had a 0.25L FEV_1 improvement compared to 0.02L for placebo group. The E004 treated patients reached the maximum FEV_1 in an hour compared to 2 hours in the placebo group. These findings demonstrated E004's bronchodilator effect. The treatment effect observed in the Primatene arm was numerically smaller compared to E004.

In Study D, there is not enough evidence to support the efficacy of E004 in asthma patients aged 4 to 11 years old. The applicant is not seeking the approval for this age group in this current application.

6 APPENDIX

Table 12: Patients' Demographic and Baseline Characteristics, Study A1 (Treated Population)

Items	E004			Placebo	Active Control (Primatene®)
	250 mcg n=26	320 mcg n=25	440 mcg n=24	0 mcg n=24	440 mcg n=25
Age (Years)					
Mean ± SD	34.7 ± 12.0	34.8 ± 12.2	34.2 ± 12.0	34.2 ± 12.0	34.8 ± 12.2
Range	18 - 55	18 - 55	18 - 55	18 - 55	18 - 55
Groups					
< 18	0	0	0	0	0
18 - 40	17 (65%)	16 (64%)	16 (67%)	16 (67%)	16 (64%)
41 - 64	9 (35%)	9 (36%)	8 (33%)	8 (33%)	9 (36%)
65 - 75	0	0	0	0	0
> 75	0	0	0	0	0
Gender					
Female	14 (53.8%)	13 (52.0%)	13 (54.2%)	13 (54.2%)	13 (52.0%)
Male	12 (46.2%)	12 (48.0%)	11 (45.8%)	11 (45.8%)	12 (48.0%)
Weight & Height					
Weight, kg	79.2 ± 20.3	79.5 ± 20.7	79.8 ± 21.1	79.8 ± 21.1	79.5 ± 20.7
Hieght	172.2 ± 9.9	172.1 ± 10.1	172.3 ± 10.2	172.3 ± 10.2	172.1 ± 10.1
Race					
Asian	1 (3.8%)	1 (4.0%)	1 (4.2%)	1 (4.2%)	1 (4.0%)
African-American	4 (15.4%)	4 (16.0%)	4 (16.7%)	4 (16.7%)	4 (16.0%)
Caucasian	19 (73.1%)	18 (72.0%)	17 (70.8%)	17 (70.8%)	18 (72.0%)
Hispanic or Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Others	2 (7.7%)	2 (8.0%)	2 (8.3%)	2 (8.3%)	2 (8.0%)

[Source: Table 7-2 in report-study-a.pdf]

Table 13: Patients' Demographic and Baseline Characteristics, Study A2 (safety population)

Items	E004					Placebo	Active Control (Primatene®)	
	90 mcg n=29	125 mcg n=29	180 mcg n=29	200 mcg n=29	250 mcg n=29	0 mcg n=30	220 mcg n=30	440 mcg n=29
Age (Years)								
Mean ± SD	35.7±11.0	35.7±11.0	35.7±11.0	35.7±11.0	35.7±11.0	35.3±11.0	35.3±11.0	35.7±11.0
Range	18 - 55	18 - 55	18 - 55	18 - 55	18 - 55	18 - 55	18 - 55	18 - 55
Groups								
< 18	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 - 40	17 (58.6%)	17 (58.6%)	17 (58.6%)	17 (58.6%)	17 (58.6%)	18 (60%)	18 (60%)	17 (58.6%)
41 - 64	12 (41.4%)	12 (41.4%)	12 (41.4%)	12 (41.4%)	12 (41.4%)	12 (40%)	12 (40%)	12 (41.4%)
65 - 75	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
> 75	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender								
Female	16 (55.2%)	16 (55.2%)	16 (55.2%)	16 (55.2%)	16 (55.2%)	17 (56.7%)	17 (56.7%)	16 (55.2%)
Male	13 (44.8%)	13 (44.8%)	13 (44.8%)	13 (44.8%)	13 (44.8%)	13 (43.3%)	13 (43.3%)	13 (44.8%)
Weight & Height								
Weight, Kg	78.0 ± 16.0	78.0 ± 16.0	78.0 ± 16.0	78.0 ± 16.0	78.0 ± 16.0	77.7 ± 15.8	77.7 ± 15.8	78.0 ± 16.0
Height, cm	169.8 ± 10.5	169.8 ± 10.5	169.8 ± 10.5	169.8 ± 10.5	169.8 ± 10.5	169.8 ±10.3	169.8 ± 10.3	169.8 ± 10.5
Race								
Caucasian	24 (82.8%)	24 (82.8%)	24 (82.8%)	24 (82.8%)	24 (82.8%)	24 (80%)	24 (80%)	24 (82.8%)
African-American	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	3 (10.0%)	3 (10.0%)	2 (6.9%)
Hispanic/Latino	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.3%)	1 (3.3%)	1 (3.4%)
Asian	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.7%)	2 (6.7%)	2 (6.9%)
Others	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[Source: Table 7-2 in report-study-a2.pdf]

Table 14: Applicant's Efficacy Evaluation for Study A (PP population)

Arms	Arm-T1	Arm-T2	Arm-T3	Arm-P*	Arm-A
Product Information					
Studied Drugs	E004	E004	E004	Placebo	Primatene®
API	Epinephrine	Epinephrine	Epinephrine	Epinephrine	Epinephrine
Dosage Form	HFA MDI	HFA MDI	HFA MDI	HFA MDI	CFC MDI
Strength, mcg/inh	125	160	220	0	220
# of inhalation	2	2	2	2	2
Dose, mcg	250	320	440	0	440
Dose reduction relative to Primatene, %	-43%	-27%	0%	-	-
Subject Information					
# of Subjects (M, F)	21 (10, 11)	20 (10, 10)	21 (10, 11)	21 (10, 11)	21 (10, 11)
Age, yr	36 ± 12	35 ± 11	36 ± 12	36 ± 12	36 ± 12
Weight, kg	76 ± 14	76 ± 14	76 ± 14	76 ± 14	76 ± 14
Height, cm	172 ± 11	172 ± 10	172 ± 11	172 ± 11	172 ± 11
Primary Efficacy Endpoint					
AUC_{0-t} for Δ%FEV1, %×hr	88.9 ± 70	63 ± 62	76 ± 49	22 ± 41	74 ± 56
Secondary Efficacy Endpoint					
AUC_{0-t} for ΔFEV1, L×hr	2.1 ± 1.7	1.5 ± 1.8	1.9 ± 1.3	0.6 ± 1.1	1.7 ± 1.4
F_{max} for Δ%FEV1, %	24 ± 12	19 ± 9	21 ± 9	10 ± 8	20 ± 10
Duration, hr	3.2 ± 2.7	3.2 ± 2.3	3.4 ± 2.5	1.1 ± 1.7	3.2 ± 2.4
Onset time, minutes	2.6 ± 1.0	3.0 ± 0.9	6.3 ± 11	74 ± 71	22 ± 78
t_{max} for Δ%FEV1, hr	1.1 ± 1.7	1.6 ± 2.0	1.3 ± 1.6	3.4 ± 1.8	1.5 ± 1.9
Responder, %	81.0	75	81	33	81

[Source: Table 7-4 in report-study-a.pdf]. * The data of Arm P is for all data available population

Table 15: Applicant's Efficacy Evaluation for Study A2 (PP population)

Studied Drugs	E004					Placebo	Primatene® Mist	
Arms	Arm-T1	Arm-T2	Arm-T3	Arm-T4	Arm-T5	Arm-P*	Arm-A1	Arm-A2
Product Information								
Strength, mcg/inh	90	125	90	100	125	0	220	220
# of inhalations	1	1	2	2	2	2	1	2
Dose, mcg	90	125	180	200	250	0	220	440
Dose reduction relative to Primatene, %	-80%	-72%	-59%	-55%	-43%	-	-50%	-
Subject Information								
# of Subjects (M, F)	25 (13, 12)	25 (13, 12)	25 (13, 12)	25 (13, 12)	24 (12, 12)	26 (14, 12)	25 (13, 12)	24 (12, 12)
Age, yr	35 ± 10	35 ± 10	35 ± 10	35 ± 10	36 ± 11	35 ± 10	35 ± 11	36 ± 11
Weight, kg	76 ± 16	76 ± 16	76 ± 16	76 ± 16	76 ± 16	76 ± 15	76 ± 16	76 ± 16
Height, cm	168 ± 9	168 ± 9	168 ± 9	168 ± 9	168 ± 9	169 ± 9	168 ± 9	168 ± 9
Primary Endpoint								
$AUC_{0\text{-}t}$ for Δ%FEV1, %×hr	37.1 ± 50.0	72.5 ± 62.3	98.2 ± 58.6	76.1 ± 57.7	84.7 ± 62.9	24.1 ± 55.8	63.0 ± 56.7	47.4 ± 43.8
Secondary Endpoint								
$AUC_{0\text{-}t}$ for ΔFEV1, L×hr	0.9 ± 1.2	1.7 ± 1.4	2.2 ± 1.2	1.8 ± 1.3	2.0 ± 1.4	0.6 ± 1.1	1.5 ± 1.3	1.2 ± 1.1
F_{max} for Δ%FEV1, %	14 ± 8	20 ± 10	24 ± 10	21 ± 10	21 ± 11	10 ± 10	18 ± 9	17 ± 7
Duration, hr	1.6 ± 2.0	3.1 ± 2.6	4.2 ± 2.2	3.1 ± 2.8	3.6 ± 2.6	0.6 ± 1.3	2.7 ± 2.6	2.1 ± 2.4
Onset time, minutes	3.2 ± 0.6	8.8 ± 17	2.6 ± 1.0	2.9 ± 1.0	4.9 ± 9.6	16 ± 18	4.2 ± 5.1	3.1 ± 0.8
t_{max} for Δ%FEV1, hr	1.3 ± 2.0	1.5 ± 1.7	1.6 ± 1.7	1.6 ± 1.7	1.7 ± 1.9	2.6 ± 1.9	2.1 ± 2.1	1.2 ± 1.6
Responder, %	64	76	88	80	71	31	68	71

[Source: Table 7-4 in report-study-a2.pdf]. * The data of Arm P is for all data available population

The calculation of efficacy endpoints:

The primary variable was calculated as follow and shown in Figure 14:

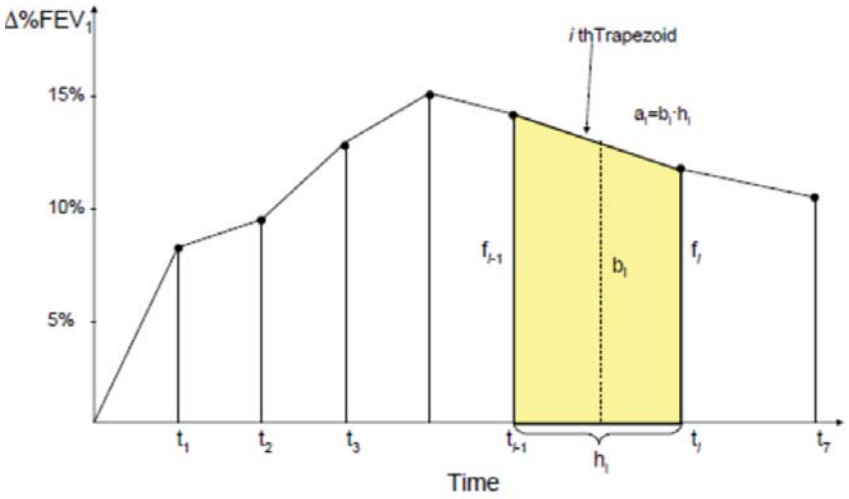
$$\Delta\%FEV1_i = \frac{FEV1_i - FEV1_0}{FEV1_0} \times 100\%$$, which be represented in unit of %

$$AUC_{0-t}(\Delta\%FEV1) = \sum_{i=0}^{n-1} \frac{\Delta\%FEV1_i + \Delta\%FEV1_{i+1}}{2}(t_{i+1} - t_i)$$

The primary endpoint $AUC_{0\text{-}t}$ of $\Delta\%FEV_1$ will be represented in units of %*hour for statistical analysis. $AUC_{0\text{-}t}$ of $\Delta\%FEV_1$ is disqualified if any of the following four cases is true:

i) FEV_1 at baseline (t=0) is unavailable; ii) $t_1 > 30$; iii) $n \leq 4$; iv) $t_n < 360$.

Figure 14: Trapezoidal Method to Calculate AUC of $\Delta\%FEV_1$



$\Delta FEV1_i = FEV1_i - FEV1_0$, which be represented in unite of liter

$$AUC_{0-t}(\Delta FEV1) = \sum_{i=0}^{n-1} \frac{\Delta FEV1_i + \Delta FEV1_{i+1}}{2}(t_{i+1} - t_i)$$, which be represented in unit of liter*hour

$$t_{onset} = t_s - \frac{\Delta\%FEV1_s - 12\%}{\Delta\%FEV1_s - \Delta\%FEV1_{s-1}} \times (t_s - t_{s-1})$$, which be represented in unit of minutes and where Δ% $FEV_{1\ s-1}$ <12% and Δ% $FEV_{1\ s}$ ≥12%; s, and s-1 are the two continuous post-dose FEV_1 measurement time points.

$$F_{\max} = \max(\Delta\%\text{FEV1}_1 \cdots \Delta\%\text{FEV1}_i \cdots \Delta\%\text{FEV1}_n) \quad i = 1,2,3 \cdots n$$, which be represented in unit of %.

The meaning of Fmax is demonstrated in Figure 15. Tmax is the time to peak FEV_1 effect (Fmax). Duration of effect, defined as the sum of all intervals when post-dose FEV_1 Δ% reaches and stays ≥12% above the $FEV_{1(0)}$ (baseline FEV_1).

$$Duration = \sum_{i=0}^{n} f_i(t_i - t_{i-1}) Duration = t_1 + t_2$$

$$f_i = \begin{cases} 0 & F_{\geq} < 12\% \\ 1 & F_{\leq} \geq 12\% \\ \dfrac{F_{\geq} - 12\%}{\Delta\%FEV1_i - \Delta\%FEV1_{i-1}} & F_{\leq} < 12\% \leq F_{\geq} \end{cases}$$

$$where \begin{array}{l} F_{\geq} = \max(\Delta\%FEV1_{i-1}, \Delta\%FEV1_i) \\ F_{\leq} = \min(\Delta\%FEV1_{i-1}, \Delta\%FEV1_i) \end{array}$$

Bronchodilator response rate is defined as the percentage of responders who demonstrate Fmax≥12%:

$$R\% = \frac{\sum_{j=1}^{N} \delta_j}{N}, \ \delta_j = \begin{cases} 0 & F_{\max,j} < 12\% \\ 1 & F_{\max,j} \geq 12\% \end{cases}$$

Figure 15: Definitions of Fmax, Tmax, Tonset, and Duration

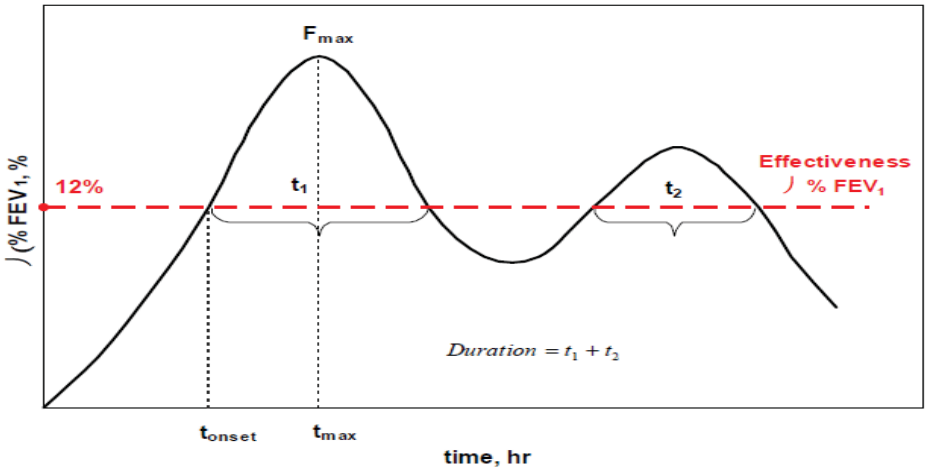


Table 16: The Applicant's Primary Efficacy Endpoint Results at Week 12 (Visit 5)

#	Efficacy Parameters and Statistical Test Method	Products	Items	Populations				Reference to Original Output of Statistical Analysis Reports
				ITT at Missing Data Handling Models			PPP (Complete-case Analysis)	
				Model-A (Closest Data Model)	Model-B (Placebo Model)	Model-C (Baseline Model)		
	# of Patients	E004		248	248	248	205	
		Primatene Mist		64	64	64	53	
		Placebo		61	61	61	53	
1	**$AUC_{0\text{-}6hr}$ of Δ%FEV1** (%×hr),	E004	Mean ± S.D.	47.3 ± 54.2	42.3 ± 55.7	40.6 ± 56.1	48.6 ± 58.4	5.3.5.1.3-9 2211
			p-value, 1-sided	<0.0001	0.0003	0.0004	0.0002	
			p-value, 2-sided	<0.0001	0.0007	0.0007	0.0004	
		Primatene Mist	Mean ± S.D.	41.0 ± 43.4	37.6 ± 44.3	35.7 ± 45.7	43.1 ± 47.0	
			p-value, 1-sided	0.0019	0.0054	0.0068	0.0038	
			p-value, 2-sided	0.0038	0.0108	0.014	0.0077	
		Placebo	Mean ± S.D.	14.6 ± 55.6	14.3 ± 55.6	12.8 ± 55.8	14.7 ± 59.7	
2	**$AUC_{0\text{-}6hr}$ of ΔFEV1** (L×hr)	E004	Mean ± S.D.	1.08 ± 1.15	0.96 ± 1.19	0.92 ± 1.20	1.11 ± 1.24	5.3.5.1.3-9 2212
			p-value, 1-sided	<0.0001	0.0003	0.0003	0.0001	
			p-value, 2-sided	<0.0001	0.0005	0.0005	0.0003	
		Primatene Mist	Mean ± S.D.	0.97 ± 1.08	0.89 ± 1.11	0.84 ± 1.14	1.02 ± 1.18	
			p-value, 1-sided	0.0012	0.0036	0.0045	0.0026	
			p-value, 2-sided	0.0024	0.0071	0.009	0.005	
		Placebo	Mean ± S.D.	0.30 ± 1.31	0.29 ± 1.31	0.26 ± 1.32	0.30 ± 1.41	
3	**F_{max} of Δ%FEV1 (%)**	E004	Mean ± S.D.	15.4 ± 11.4	13.9 ± 11.8	13.2± 11.4	15.6 ± 10.9	5.3.5.1.3-9 2213
			p-value, 1-sided	<0.0001	0.0003	0.0008	0.0002	
			p-value, 2-sided	<0.0001	0.0007	0.0016	0.0004	
		Primatene Mist	Mean ± S.D.	13.0 ± 8.1	11.9 ± 8.9	11.5 ± 9.4	13.8 ± 8.6	
			p-value, 1-sided	0.006	0.033	0.044	0.014	
			p-value, 2-sided	0.012	0.066	0.088	0.027	
		Placebo	Mean ± S.D.	8.9 ± 9.8	8.8 ± 9.8	8.5± 10.1	9.7 ± 10.2	
4	**Efficacy Duration (hours)**	E004	Mean ± S.D.	1.44 ± 2.08	1.39 ± 2.09	1.37± 2.08	1.64 ± 2.19	5.3.5.1.3-9 2214
			p-value, 1-sided	0.0046	0.0081	0.009	0.005	
			p-value, 2-sided	0.0092	0.016	0.018	0.01	
		Primatene Mist	Mean ± S.D.	1.40 ± 2.08	1.39 ± 2.09	1.39± 2.09	1.68 ± 2.19	
			p-value, 1-sided	0.033	0.036	0.036	0.0227	
			p-value, 2-sided	0.066	0.073	0.073	0.0454	
		Placebo	Mean ± S.D.	0.78 ± 1.62	0.78 ± 1.62	0.78 ± 1.62	0.90 ± 1.71	
5	**Onset Time (minutes)**	E004	Mean ± S.D.	16.0 ± 46.1	18.2 ± 50.7	18.2 ± 50.7	18.2 ± 51.4	5.3.5.1.3-9 2215
			p-value, 1-sided	0.0019	0.0023	0.0023	0.0023	
			p-value, 2-sided	0.0038	0.0047	0.0047	0.0047	
		Primatene Mist	Mean ± S.D.	42.3 ± 68.0	40.1 ± 66.2	40.1 ± 66.2	40.1 ± 66.2	
			p-value, 1-sided	0.023	0.020	0.020	0.020	
			p-value, 2-sided	0.047	0.040	0.040	0.040	
		Placebo	Mean ± S.D.	99.1± 100.9	99.1 ± 100.9	99.1 ± 100.9	99.1± 100.9	
6	**t_{max} of Δ%FEV1 (hour)**	E004	Mean ± S.D.	1.17 ± 1.57	1.66 ± 1.73	1.02± 1.43	1.21 ± 1.48	5.3.5.1.3-9 2216
			p-value, 1-sided	<0.0001	0.0027	0.0009	0.007	
			p-value, 2-sided	<0.0001	0.0054	0.0018	0.0013	
		Primatene Mist	Mean ± S.D.	1.38 ± 1.74	1.87± 1.88	1.18 ± 1.70	1.42 ± 1.77	
			p-value, 1-sided	0.0010	0.044	0.013	0.016	
			p-value, 2-sided	0.0020	0.087	0.027	0.033	
		Placebo	Mean ± S.D.	2.46 ± 2.06	2.48 ± 2.07	1.95 ± 2.12	2.25 ± 2.13	
7	**Responder Rate, %**	E004	Mean	64.5	51.2	51.2	60.0	5.3.5.1.3-9 2217
			p-value, 1-sided	<0.0001	0.0005	0.0005	0.0001	
			p-value, 2-sided	<0.0001	0.0011	0.0011	0.0003	
		Primatene Mist	Mean	54.7	50.0	50.0	60.4	
			p-value, 1-sided	0.0012	0.0056	0.0056	0.0017	
			p-value, 2-sided	0.0024	0.011	0.011	0.0035	
		Placebo	Mean	27.9	27.9	27.9	32.1	

[Source: Table 7.4-2 of study report api-e004-cl-c.pdf]

Table 17: The Applicant's Additional Efficacy Endpoint Results at Week 12 (Visit 5)

#	Efficacy Parameters and Statistical Test Method	Products	Items	Populations/MDH Models for Visit-5 (Week-12)				Reference to Original Output of Statistical Analysis Reports
				ITT at MDH Models			PPP (Complete-case Analysis)	
				Model-A (Closest Data Model)	Model-B (Placebo Model)	Model-C (Baseline Model)		
	# of Patients	E004		248	248	248	205	
		Primatene Mist		64	64	64	53	
		Placebo		61	61	61	53	
16	$AUC_{0\text{-}6hr}$ of FEV1 (L×hr),	E004	Mean ± S.D.	15.8 ± 3.9	15.6 ± 3.9	15.6 ± 4.0	15.9 ± 4.2	5.3.5.1.3-9 2228
			p-value, 1-sided	0.0041	0.0109	0.0109	0.0085	
			p-value, 2-sided	0.0082	0.0217	0.0217	0.017	
		Primatene Mist	Mean ± S.D.	15.7 ± 4.2	15.4 ± 4.0	15.4 ±4.0	15.7 ± 4.3	
			p-value, 1-sided	0.0328	0.0617	0.0641	0.0573	
			p-value, 2-sided	0.0656	0.1235	0.1282	0.1147	
		Placebo	Mean ± S.D.	14.4 ± 3.6	14.4 ± 3.6	14.4 ± 3.6	14.4 ± 3.8	
17	F_{max} of FEV1 (L)	E004	Mean ± S.D.	2.8 ± 0.7	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	5.3.5.1.3-9 2229
			p-value, 1-sided	0.0014	0.0066	0.0081	0.0058	
			p-value, 2-sided	0.0028	0.0132	0.0161	0.0116	
		Primatene Mist	Mean ± S.D.	2.8 ± 0.7	2.7 ± 0.7	2.7 ± 0.7	2.8 ± 0.8	
			p-value, 1-sided	0.0325	0.0753	0.0795	0.0626	
			p-value, 2-sided	0.0649	0.1505	0.1589	0.1252	
		Placebo	Mean ± S.D.	2.5 ± 0.6	2.5 ± 0.6	2.5 ± 0.6	2.6 ± 0.6	
18	t_{max} of FEV1 (hrs)	E004	Mean ± S.D.	1.2 ± 1.6	1.7 ± 1.7	1.0 ± 1.4	1.4 ± 1.8	5.3.5.1.3-9 2230
			p-value, 1-sided	<0.0001	0.0027	0.0009	0.0007	
			p-value, 2-sided	<0.0001	0.0054	0.0018	0.0013	
		Primatene Mist	Mean ± S.D.	1.4 ± 1.7	1.9 ± 1.9	1.2 ± 1.7	1.4 ± 1.8	
			p-value, 1-sided	0.001	0.0437	0.0134	0.0163	
			p-value, 2-sided	0.002	0.0874	0.0268	0.0327	
		Placebo	Mean ± S.D.	2.5 ± 2.1	2.5 ± 2.1	2.0 ± 2.1	2.2 ± 2.1	

[Source: Table 7.4-2S, cover-letter.pdf in submission S005 dated Nov. 6, 2013]

Table 18: Analyses Results on FEV_1 on Day 1/ Week 12 Based on the Imputation Model C (ITT)

	E004 (n=248) Mean (SD)	*Placebo (n=61) Mean (SD)*	*Primatene (n=64) Mean (SD)*	*Mean Diff. (E004 - Placebo) 95%CI*
ΔFEV_1 at 5 min. post-dose (L)				
Day 1	0.360 (0.272)	0.021 (0.157)	0.296 (0.258)	0.338 (0.284, 0.392) [1]
Week 12	0.245 (0.238)	0.015 (0.139)	0.188 (0.226)	0.230 (0.184, 0.276) [1]
ΔFEV_1 at 360 min. post-dose (L)				
Day 1	0.215 (0.282)	0.050 (0.345)	0.215 (0.238)	0.165 (0.065, 0.266) [1]
Week 12	0.092 (0.216)	0.042 (0.272)	0.080 (0.183)	0.049 (-0.025, 0.124)

Note 1: p-value <0.05. ΔFEV_1= Change from baseline (pre-dose) FEV_1
The mean, standard deviations, 95% confidence interval, and p−value are based on two-sided t-test analyses.

Table 19: The Applicant's Pediatric Efficacy Data of Study D

#	Studied Drugs	E004 (PPP)		Placebo (PPP)		p-values, 1-sided	
	Evaluation Time	Day-1	Week-4	Day-1	Week-4	Day-1	Week-4
	# of Pediatric Patients	22	23	22	22	22 vs. 22	23 vs.22
1	**$AUC_{0\text{-}6hr}$ of Δ%FEV1, %×hr**	**69.2 ± 65.3**	**47.6 ± 68.6**	**34.5 ± 61.2**	**21.2 ± 41.5**	**0.0382**	**0.0625**
2	$AUC_{0\text{-}3hr}$ of Δ%FEV1, %×hr	40.9 ± 34	27.1 ± 37.5	17.6 ± 32.2	9.9 ± 20.2	0.0124	0.0312
3	$AUC_{0\text{-}6hr}$ of ΔFEV1, L×hr	0.88 ± 0.8	0.65 ± 0.83	0.41 ± 0.74	0.28 ± 0.57	0.0263	0.0434
4	Fmax of Δ%FEV1, %	20.7 ± 12.9	15.2 ± 12.7	13.3 ± 12.4	10.8 ± 7.9	0.0307	0.0861
5	Duration, hrs	2.98 ± 2.59	1.56 ± 2.29	1.56 ± 2.15	0.96 ± 1.64	0.0266	0.1601
6	Time of onset, min	14.2 ± 26.8	11.0 ± 13.6	30.3 ± 21.1	125 ± 95	0.0597	0.0021
7	tmax, hr	1.84 ± 1.8	1.36 ± 1.67	2.28 ± 1.94	2.65 ± 2.3	0.2205	0.0190
8	Responder, %	68.2	39.1	40.9	45.5	0.0346	0.3338
9	Δ%FEV1 at 5 min, %	14.1 ± 12.3	10.2 ± 11.4	3.6 ± 7.0	1.4 ± 8.0	0.0015	0.0032
10	Δ%FEV1 at 30 min, %	13.1 ± 16.5	8.1 ± 11.8	3.6 ± 8.5	3.6 ± 8.1	0.0232	0.0710
11	Δ%FEV1 at 60 min, %	12.3 ± 12.6	10.9 ± 13.4	6.2 ± 12.2	3.4 ± 8.6	0.0609	0.0177
12	Δ%FEV1 at 120 min, %	15.8 ± 13.1	8.8 ± 14.9	8.1 ± 14.2	2.2 ± 8.8	0.0383	0.0436
13	Δ%FEV1 at 180 min, %	13.1 ± 12.6	7.3 ± 12.1	7.3 ± 14.0	5.0 ± 9.8	0.0893	0.2521
14	Δ%FEV1 at 240 min, %	10.1 ± 11.8	9.1 ± 13.7	5.8 ± 12.5	4.6 ± 8.0	0.1371	0.0996
15	Δ%FEV1 at 360 min, %	6.1 ± 14.8	2.8 ± 8.4	4.0 ± 10.3	1.5 ± 10.4	0.2965	0.3228
# of Efficacy Parameters Did Not Show Significance						6	8
# of Efficacy Parameters Showed Significance						9	7

Table 20: The Applicant's Primary Efficacy Endpoint Results at Week 4, Study D

#	Efficacy Parameters and Statistical Test Method	Products	Items	Populations/MDH Models for Visit-3 (Week-4)				PPP of Visit-1 (Day-1)	Reference to Original Output of Statistical Analysis Reports
				ITT at MDH Imputation Models			PPP (Complete-case Analysis)		
				Model-A (Closest Data Model)	Model-B (Placebo Model)	Model-C (Baseline Model)			
	# of Patients	E004		35	35	35	23	22	
		Placebo		35	35	35	22	22	
1	**$AUC_{0\text{-}6hr}$ of Δ%FEV1** (%×hr),	E004	Mean ± S.D.	63.6 ± 126.9	53.6 ± 97.5	34.2 ± 60.3	47.6 ± 68.6	69.2 ± 65.30	5.3.5.1.5-9 2211
			p-value, 1-sided	0.1294	0.1905	0.0620	0.0625	0.0382	
		Placebo	Mean ± S.D.	32.6 ± 98.5	33.0 ± 98.5	15.8 ± 34.6	21.2 ± 41.5	34.5 ± 61.2	
2	**$AUC_{0\text{-}3hr}$ of Δ%FEV1** (%×hr),	E004	Mean ± S.D.	37.1 ± 60.8	27.9 ± 47.3	19.5 ± 33.2	27.1 ± 37.5	40.9 ± 34.0	5.3.5.1.5-9 2219
			p-value, 1-sided	0.0554	0.1526	0.0358	0.0312	0.0124	
		Placebo	Mean ± S.D.	16.3 ± 45.7	16.5 ± 45.6	7.9 ± 17.0	9.9 ± 20.2	17.6 ± 32.2	
3	**$AUC_{0\text{-}6hr}$ of ΔFEV1** (L×hr)	E004	Mean ± S.D.	0.71 ± 1.23	0.62 ± 1.11	0.88 ± 1.87	0.65 ± 0.83	0.88 ± 0.80	5.3.5.1.5-9 2212
			p-value, 1-sided	0.0660	0.1101	0.0620	0.0434	0.0263	
		Placebo	Mean ± S.D.	0.29 ± 1.08	0.30 ± 1.08	0.33 ± 0.86	0.28 ± 0.57	0.41 ± 0.74	
4	**F_{max} of Δ%FEV1 (%)**	E004	Mean ± S.D.	21.5 ± 28.2	17.3 ± 19.7	10.9 ± 12.4	15.2 ± 12.7	20.7 ± 12.9	5.3.5.1.5-9 2213
			p-value, 1-sided	0.1495	0.3474	0.3560	0.0861	0.0307	
		Placebo	Mean ± S.D.	15.4 ± 19.8	15.4 ± 19.8	10.0 ± 9.0	10.8 ± 7.9	13.3 ± 12.4	
5	**Efficacy Duration (hours)**	E004	Mean ± S.D.	1.64 ± 2.25	1.61 ± 2.35	1.15 ± 2.06	1.56 ± 2.29	2.98 ± 2.59	5.3.5.1.5-9 2214
			p-value, 1-sided	0.2167	0.2405	0.1525	0.1601	0.0266	
		Placebo	Mean ± S.D.	1.23 ± 2.07	1.23 ± 2.07	0.72 ± 1.37	0.96 ± 1.64	1.56 ± 2.15	
6	**Onset Time (minutes)**	E004	Mean ± S.D.	12.0 ± 16.9	14.9 ± 19.6	12.2 ± 13.4	11.0 ± 13.6	14.2 ± 26.8	5.3.5.1.5-9 2215
			p-value, 1-sided	0.0045	0.0057	0.0003	0.0021	0.0597	
		Placebo	Mean ± S.D.	91.4 ± 96.3	91.4 ± 96.3	116.6 ± 87.9	125.0 ± 94.7	30.3 ± 21.1	
7	**t_{max} of Δ%FEV1 (hour)**	E004	Mean ± S.D.	1.11 ± 1.47	1.89 ± 1.81	0.98 ± 1.49	1.36 ± 1.67	1.84 ± 1.84	5.3.5.1.5-9 2216
			p-value, 1-sided	<0.0001	0.0197	0.0044	0.0190	0.2205	
		Placebo	Mean ± S.D.	2.81 ± 2.05	2.86 ± 2.05	2.20 ± 2.20	2.65 ± 2.30	2.28 ± 1.94	
8	**Responder Rate, %**	E004	Mean	48.6	37.1	28.6	39.1	68.2	5.3.5.1.5-9 2217
			p-value, 1-sided	0.2352	0.4030	0.1569	0.3338	0.0346	
		Placebo	Mean	40	40	40	45.5	40.9	
9	**Δ%FEV1 at 5 minutes (%)**	E004	Mean ± S.D.	13.5 ± 21.1	9.0 ± 14.7	9.0 ± 10.9	10.2 ± 11.4	14.1 ± 12.3	5.3.5.1.5-9 2221
			p-value, 1-sided	0.0091	0.0414	0.0010	0.0032	0.0015	
		Placebo	Mean ± S.D.	2.1 ± 16.8	2.2 ± 16.7	0.6 ± 7.3	1.4 ± 8.0	3.6 ± 7.0	
10	**Δ%FEV1 at 30 minutes (%)**	E004	Mean ± S.D.	5.4 ± 15.1	5.6 ± 13.3	7.4 ± 11.4	8.1 ± 11.8	13.1 ± 16.5	5.3.5.1.5-9 2222
			p-value, 1-sided	0.2910	0.2773	0.1004	0.0710	0.0232	
		Placebo	Mean ± S.D.	8.1 ± 23.4	8.3 ± 23.4	3.9 ± 9.0	3.6 ± 8.1	3.6 ± 8.5	
11	**Δ%FEV1 at 60 minutes (%)**	E004	Mean ± S.D.	12.8 ± 20.6	9.6 ± 16.5	10.2 ± 12.8	10.9 ± 13.4	12.3 ± 12.6	5.3.5.1.5-9 2223
			p-value, 1-sided	0.0318	0.0860	0.0121	0.0177	0.0609	
		Placebo	Mean ± S.D.	3.8 ± 18.1	3.8 ± 17.8	3.4 ± 8.0	3.4 ± 8.6	6.2 ± 12.2	
12	**Δ%FEV1 at 120 minutes (%)**	E004	Mean ± S.D.	15.2 ± 29.9	10.8 ± 21.7	8.3 ± 14.2	8.8 ± 14.9	15.8 ± 13.1	5.3.5.1.5-9 2224
			p-value, 1-sided	0.0653	0.1639	0.0246	0.0436	0.0383	
		Placebo	Mean ± S.D.	6.1 ± 17.1	6.1 ± 17.0	1.8 ± 7.9	2.2 ± 8.8	8.1 ± 14.2	
13	**Δ%FEV1 at 180 minutes (%)**	E004	Mean ± S.D.	13.6 ± 29.3	10.2 ± 21.1	6.9 ± 11.7	7.3 ± 12.1	13.1 ± 12.6	5.3.5.1.5-9 2225
			p-value, 1-sided	0.1045	0.1942	0.2475	0.2521	0.0893	
		Placebo	Mean ± S.D.	6.1 ± 17.0	6.1 ± 17.0	4.9 ± 9.9	5.0 ± 9.8	7.3 ± 14.0	
14	**Δ%FEV1 at 240 minutes (%)**	E004	Mean ± S.D.	11.3 ± 29.3	11.2 ± 23.1	8.4 ± 13.1	9.1 ± 13.7	10.1 ± 11.8	5.3.5.1.5-9 2226
			p-value, 1-sided	0.1568	0.1294	0.0324	0.0996	0.1371	
		Placebo	Mean ± S.D.	5.0 ± 21.1	5.1 ± 21.1	2.7 ± 8.3	4.6 ± 8.0	5.8 ± 12.5	
15	**Δ%FEV1 at 360 minutes (%)**	E004	Mean	2.8 ± 18.2	3.6 ± 13.5	2.4 ± 7.8	2.8 ± 8.4	6.1 ± 14.8	5.3.5.1.5-9 2227
			p-value, 1-sided	0.2884	0.3382	0.4701	0.3228	0.2965	
		Placebo	Mean	5.6 ± 23.8	5.5 ± 23.8	2.2 ± 10.3	1.5 ± 10.4	4.0 ± 10.3	
16	**$AUC_{0\text{-}6hr}$ of FEV1** (L×hr),	E004	Mean ± S.D.	10.39 ± 2.94	10.34 ± 2.80	8.60 ± 5.09	10.92 ± 3.21	9.89 ± 2.93	5.3.5.1.5-9 2228
			p-value, 1-sided	0.0106	0.0133	0.2266	0.0148	0.0929	
		Placebo	Mean ± S.D.	8.95 ± 2.09	9.01 ± 2.08	7.79 ± 3.76	9.03 ± 2.38	8.82 ± 2.31	
17	**F_{max} FEV1 (L)**	E004	Mean ± S.D.	1.88 ± 0.50	1.85 ± 0.49	1.57 ± 0.85	1.94 ± 0.55	1.77 ± 0.48	5.3.5.1.5-9 2229
			p-value, 1-sided	0.0087	0.0215	0.1805	0.0141	0.0646	
		Placebo	Mean ± S.D.	1.63 ± 0.37	1.64 ± 0.37	1.40 ± 0.66	1.61 ± 0.41	1.57 ± 0.38	
18	**t_{max} of FEV1 (hour)**	E004	Mean ± S.D.	1.11 ± 1.47	1.89 ± 1.81	1.28 ± 1.75	1.36 ± 1.67	1.84 ± 1.84	5.3.5.1.5-9 2230
			p-value, 1-sided	<0.0001	0.0197	0.0267	0.0190	0.2205	
		Placebo	Mean ± S.D.	2.81 ± 2.05	2.86 ± 2.05	2.21 ± 2.19	2.65 ± 2.30	2.28 ± 1.94	

[Source: Table 7-8U, cover-letter.pdf in submission S005 dated Nov. 6, 2013]

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/s/

FENG ZHOU
03/03/2014

RUTHANNA C DAVI
03/04/2014
Joan Bueconsejo completed secondary review of this document. Ruthanna Davi is signing for her in her absence.

THOMAS J PERMUTT
03/06/2014
I concur.