FDA ADVISORY COMMITTEE BRIEFING MATERIALS

Epinephrine HFA MDI (E004) -- A Proposed Reformulation to Replace OTC Primatene® Mist CFC

NDA 205920

Joint Meeting of
the Nonprescription Drugs Advisory Committee and
the Pulmonary-Allergy Drugs Advisory Committee
Meeting Date: February 25, 2014

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Advisory Committee Briefing Materials: Available for Public Release

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Abbreviations

ADE	Adverse Drug Event
AERS	Adverse Event Reporting System
AUC	Area Under the Curve (pharmacokinetics)
BA	Bioavailability
CADE	Cardiovascular Adverse Drug Event
CBC	Complete Blood Count
CDM	Closest Data Model
CFC	Chlorofluorocarbon
CI	Confidence Interval
C_{max}	The Peak Plasma Concentration
CV	Coefficient of Variation (Statistics)
DBP	Diastolic Blood Pressure
DFL	Drug Fact Label
ECG	Electrocardiogram
FAERS	FDA Adverse Event Reporting System
FEV1	Forced Expiratory Volume in One (1) Second
F_{max}	Maximum Value of the Δ%FEV1Curve
HFA	Hydrofluoroalkanes
HR	Heart Rate
Inh	Inhalation
IR	Incidence Rate
ITT	Intent-To-Treat Population
LABA	Long-Acting Beta-Agonist
LC/MS/MS	Liquid Chromatography-Mass Spectrometry
LCS	Label Comprehension Study
MDH	Missing Data Handling
MDI	Metered-Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
PC	Primary Communication
PD	Pharmacodynamics
PK	Pharmacokinetics
PPP	Per-Protocol-Population
PR	Patient Rate

p-value	The probability of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true
PVC	Premature Ventricular Contraction
QID	Quarter in day (q.i.d.), a medical abbreviation meaning “four times each day”
QT, QTc	Measurement Used in Cardiology
SABA	Short-Acting beta-Agonist
SADE	Serious Adverse Drug Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Secondary Communication
SD	Standard Deviation

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1. EXECUTIVE SUMMARY

Epinephrine HFA MDI, 125 mcg/inh, (E004) is an epinephrine inhalation aerosol USP using a metered dose inhaler (MDI) with hydrofluoroalkane (HFA) as the propellant. It was reformulated to replace the over-the-counter (OTC) product Primatene® Mist, which was phased out in December 2011 due to the ban on the use of chlorofluorocarbons (CFCs) as the propellant.

Armstrong Pharmaceuticals, Inc. (Armstrong), a wholly owned subsidiary of Amphastar Pharmaceuticals, Inc. (Amphastar), submitted a new drug application (NDA 205920) to the FDA with data supporting E004 as a replacement for Primatene® Mist CFC.

Armstrong is seeking FDA approval for E004 as an OTC product for oral inhalation administration ***for temporary relief of mild symptoms of intermittent asthma*** in adults and children twelve (12) years of age and older.

Asthma is considered by the FDA as a condition that is self-recognizable and self-treatable after initial diagnosis by a physician. While E004 would be the first Epinephrine HFA MDI approved for the OTC market in the US, Epinephrine MDI (i.e., Primatene® Mist CFC) is a well-established OTC asthma medication that was used safely for over fifty (50) years by consumers.

Following FDA's recommendations, Armstrong/Amphastar conducted clinical trials for PK/PD, efficacy and safety evaluation of E004, as well as label comprehension and label behavioral human factors studies for evaluation of consumer understanding and actual use of the E004 MDI and Consumer Information Leaflet (Insert).

A key consideration in the OTC/approval for replacement formula E004 was to compare the consistency of E004 with Primatene® Mist CFC, which has a proven record of excellent safety and efficacy for over fifty (50) years of OTC use. In evaluating the appropriateness of E004 for OTC uses, including the label comprehension/behavioral studies, Armstrong/Amphastar conducted a comprehensive comparative review of E004 data with that of Primatene® Mist CFC.

This briefing report reviews the findings regarding efficacy and safety observed in E004 clinical studies, which have been reported in the NDA submissions. Further, the label comprehension and human behavioral study results are also summarized. The proposed OTC labeling for E004, DFL and Insert are provided in **Appendix 1** and **Appendix 2**, respectively.

1.1. UNMET MEDICAL NEED

It is well known that in the United States many patients lack regular access to adequate medical care that contributes to the medical under-treatment of some common diseases and conditions. In order to mitigate this well known public health problem, FDA promulgated the Nonprescription Safe Use Regulatory Expansion paradigm (NSURE Paradigm) on February 28, 2012 [1].

The NSURE Paradigm is aimed at identifying how, within the existing two-class system of prescription and nonprescription drugs, conditions of safe use might be developed and implemented as part of a comprehensive approach to drug regulation, thus ensuring that certain drugs will be safe and effective in the nonprescription setting.

By expanding the conditions of safe use, the goal of FDA under the NSURE Paradigm is to increase the number and kind of available OTC drugs. The desired outcome of the NSURE Paradigm is to conscientiously address the fact that under-treatment of common diseases and conditions have a large public health impact due to unnecessarily increased costs and patient suffering. FDA officials have informed the public that they are considering waiving prescription requirements for certain drugs used to treat ailments like diabetes, **asthma** and migraines, basing their decision on a true public healthcare need [1].

Asthma patients typically experience the following symptoms: wheezing, chest tightness, shortness of breath, and coughing. While we do not know what causes asthma, we do know that asthma symptoms are sometimes triggered by allergens (e.g., pollen, mold, animal dander, and dust mites), exercise, occupational hazards, tobacco smoke, air pollution, airway infections, change in weather conditions and emotional distress, while the triggers for some asthma episodes are unknown. Although there is no known cure for asthma, people with asthma can manage their disease with medical care and prevent episodic increased symptoms by avoiding triggers [2,3].

Asthma is a common and important public health issue. Asthma costs the United States $56 billion each year – Asthma is a serious health and economic concern in the United States [2]. The average yearly cost of care for a child with asthma was $1,039 in 2009. In 2008, asthma caused 10.5 million missed days of school and 14.2 million missed days of work. Further, in 2010, 18.7 million adults had asthma; that is equal to 1 in 12 adults and seven (7) million children had asthma; that is equal to 1 in 11 children. Asthma is also deadly: about 9 Americans die from asthma each day [2].

Asthma symptoms are inherently unpredictable. Even in stable chronic asthma patients, acute symptoms arise episodically triggered by infections, pollution, cold air, dusts, pet dander and other unanticipated triggers. These lead to episodic exacerbations, a characteristic of asthma, and are a major reason nearly all asthma patients require ready access to quick-relief bronchodilators. Quick-relief inhalers are generally utilized on an as needed basis and under the patient's own control.

As to how asthma disrupts daily life, it is well-known that asthma negatively impacts work and school attendance. Nearly 1 in 2 children miss at least 1 day of school each year because of their asthma. Nearly 1 in 3 adults miss at least 1 day of work each year because of their asthma. Asthma also interferes with daily activities. Nearly 3 in 5 people with asthma limit their usual activities because of their asthma [2].

Unfortunately, the number of individuals affected by asthma is growing. For example, in the United States, in the last decade alone, the proportion of people with asthma in the United States grew by nearly 15% [2,3]. Therefore, ease of access to effective asthma relief has become more important in recent years.

Epinephrine MDI is recognized to provide immediate, temporary relief of mild symptoms caused from intermittent asthma (i.e., a quick relief OTC medication for asthma). In reality, running out of medications or not having a current prescription when traveling are some of the causes for emergency doctor visits. Having an OTC Epinephrine MDI readily available would be beneficial in reducing the need for emergency care.

Primatene® Mist (CFC) was an FDA-approved NDA drug that has been proven to be safe and effective for over fifty (50) years. Before the sunset of Primatene® Mist (CFC) due to the Montreal Protocol, numerous patients could not afford and had difficulties seeking professional medical help, likely due to economic disadvantages, and therefore relied on Primatene® Mist (CFC) to relieve their symptoms caused from intermittent asthma. Getting "symptom control" for already diagnosed, economically disadvantaged asthma sufferers relieved the symptoms and improved the life quality of many Americans who experienced asthma episodic increased symptoms.

Further, Armstrong/Amphastar has received thousands of asthma sufferers' inquiries asking when a replacement for Primatene® Mist CFC would be available. Many of such inquiries

have indicated a preference for a readily available and lower cost quick-relief inhaler. Some have indicated that Albuterol and/or other prescription drugs for short-term relief of bronchospasm do not work or caused allergic reactions.

1.2. OVERVIEW OF PHARMACOLOGY PROFILE AND CLINICAL STUDIES

E004 (125 mcg per inhalation) and Primatene® Mist CFC (220 mcg per inhalation) share the same key elements: (i) the same active moiety --- epinephrine; (ii) the same administration route --- oral inhalation; (iii) the same delivery device --- pressurized MDI; and (iv) the same indication --- "for the temporary relief of mild symptoms of intermittent asthma." (Please refer to **Appendix 1**, DFL of E004).

With the use of the HFA propellant, several additional improvements have been made for E004. The major improvements of the E004 formulations from that of Primatene® Mist CFC are as follows:

- E004 eliminates the use of the CFC propellant, meeting the Montreal Protocol [5].
- The proposed nominal dose for E004 has been reduced by 43% while maintaining the same efficacy as that for Primatene® Mist CFC.
- The solution pH has been changed from acidic (Primatene® Mist CFC, pH= 3.5 – 4.5) to neutral (E004, pH ~ 7).
- The amount of alcohol in E004 has been reduced 34-fold, as compared to Primatene® Mist CFC, such that a false positive alcohol (breathalyzer) test after inhalation is minimized.
- The aluminum canister of E004 is stronger and safer than the glass bottle of Primatene® Mist CFC.
- The dose indicator of E004 functions to visually demonstrate adequate medication supply thereby contributing to patients' dosing safety and timely replacement.

The pharmacological class of E004 is adrenergic "Bronchodilator". Epinephrine (adrenaline) is a natural human hormone secreted by adrenal glands. It is a stimulant of both α and β adrenergic receptors, having particularly prominent effects on the heart and vascular when administered systemically and airway smooth muscles [6] when administered by oral inhalation.

It should be noted that E004 was formulated based on Amphastar/Armstrong's proprietary,

patented technology, which is covered under U.S. Patent No. 8,367,734 [15]. The "super high amount" of HFA has resulted in a more efficient delivery for E004 MDI via suspension, such that the inhalation dose of aerosolized epinephrine has been reduced from 220 mcg/inhalation for Primatene® Mist CFC to 125 mcg/inhalation for E004 (a 43% reduction)with comparable clinical efficacy and safety.

Armstrong/Amphastar conducted nine (9) randomized, controlled, blinded clinical studies in adult/adolescent subjects, ages 12 and older, for E004, in which:

- Five (5) were Phase I/II clinical studies of E004, including (i) two (2) single nominal dose, dose ranging efficacy and safety studies and three (3) studies of PK and safety at single high doses.

- Two (2) were Phase III studies, including a 12-week maximum dose, long-term efficacy and safety study, and an additional 3-month safety evaluation extension to a 6-month study.

  In total, 569 subjects were treated in all E004 clinical studies.

- Three (3) label comprehension studies and one (1) behavioral study were performed. In total 1,406 subjects participated in these OTC label comprehension and behavioral studies.

1.3. SUMMARY OF PHARMACOKINETICS (PK)

Since epinephrine exists naturally in the human body, Deuterium-labeled epinephrine was used. A single high dosage (10 × 125 mcg/inh) was used for PK evaluation. The PK study results indicate that:

- C_{max} in the blood system at a regular dose (i.e., 2 × 125 mcg/inhalation) is obtained by dose-normalization of high dose PK experimental data, as 0.18 ng/mL, which is approximately 20% of the normal human endogenous epinephrine level present during vigorous exercise, 5 nmol/L or 0.92 ng/mL [7, 8].
- The t_{max} is 2 minutes.
- The half life, t½, is 2.6 minutes (consistent with literature reporting 2 minutes [9] and 3.5 minutes [10])

The amount of epinephrine entering into the blood stream is only 0.9 mcg or 0.36% of total delivered regular dose (250 mcg). This is consistent with previous findings "*It has poor systemic bioavailability when delivered by a chlorofluorocarbon (CFC) MDI*" [11].

1.4. SUMMARY OF EFFICACY

The bronchodilatory effect of E004, placebo (control arm) and Primatene® Mist CFC arm was assessed by the change of "forced expiratory volume in 1 second" (FEV1) relative to the same day baseline. Since asthma obstructs airflow on expiration, the FEV1 is substantially reduced during acute and chronic asthma episodes, and is rapidly improved by quick reliever bronchodilators like E004.

The Δ%FEV1 is technically defined as:

$$\Delta\%FEV1(t) = \frac{FEV1(t) - FEV1(0)}{FEV1(0)} \times 100\%$$

where, FEV1(t) is the FEV1 at time t after dosing, and FEV1(0) is the baseline of FEV1 for the same day prior to dosing.

The primary efficacy endpoint studied was the area under the curve (AUC) of Δ%FEV1, which was reported in unit of %×hr.

The clinical results of two (2) single dose randomized, double-blinded, placebo and active-controlled crossover studies in adult asthma patients showed improvement in the primary endpoint, AUC of Δ%FEV1, with p-values of <0.0001, demonstrating statistically significant improvements with E004 compared to placebo.

The clinical results of the long-term randomized, double-blinded, placebo and active-controlled parallel efficacy and safety study for adult and adolescent patients up to twelve (12) weeks also showed p-values for the primary endpoint of <0.0001, demonstrating statistically significant improvements with E004 compared to placebo. Substantial adult/adolescent efficacy was demonstrated in the above studies.

Sixteen (16) secondary endpoints include several other measures of AUC in terms of liters× hours, maximal improvement in FEV1, in % and liters, time to maximal FEV1, and maximal

% change, time to onset of improvement of ≥12%, duration of improvement ≥12%, total time ≥12%, % of responders achieving ≥12% increase, and % improvement in FEV1 at each time point at 5 and 30 minutes, and 1, 2, 3, 4, and 6 hours post-dose.

For E004, the primary analysis of the 12 week, long-term study for all of the above secondary efficacy endpoints demonstrated significant efficacy for E004 (p-values < 0.05, most of them were <0.001), except Δ%FEV1 at 360 minutes. The results demonstrated statistically significant improvements with E004 compared to placebo.

The efficacy time trend of tachyphylaxis for primary and secondary endpoints was observed in long-term Study C. Notably, the bronchodilatory efficacy for endpoints based on Δ%FEV1 for both E004 and Primatene® Mist CFC consistently demonstrated a time trend, with the greatest efficacy observed on Day 1, along with a 20% to 40% reduction of bronchodilatory effect, but still showed a significant efficacy at Week 6. This was then maintained at about the same levels or even slightly higher levels of efficacy over the next 6 week period of time until the end of the study, i.e., Week 12. This pattern is likely due to partial tachyphylaxis at the beta-2 receptor.

It is also interesting to note that the bronchodilatory efficacy endpoints based on FEV1 for both E004 and Primatene® Mist CFC demonstrated a consistent and stable time trend.

1.5. SUMMARY OF SAFETY

The safety profile of E004 has been well established in clinical studies. In seven (7) E004 clinical studies, among the evaluated subjects, 373 were evaluated on the maximum recommended dose of 125 mcg/puff, two (2) puffs four (4) times daily, self-administered by study subjects for a period of three (3) months, and 207 were evaluated for a period of 6 months. In practice, patients are expected to utilize substantially lower doses.

The category of "major adverse events (ADEs)" observed in the E004 long-term clinical studies was defined as meeting all of the following three (3) criteria [12]: (i) "all ADEs (whether considered by the investigator as drug related or unrelated to drug)" (ii) "occurred at an incidence rate of at least 3.0%" in the E004 group, and (iii) occurred "more frequently" in the E004 group "than in the HFA-134a placebo inhaler group". Based on the definition of the major ADE above, the major ADEs for E004 observed in the long-term safety studies were: (i) Tremor (9.7%), (ii) Throat Irritation (5.2%), (iii) Cough (4.4%), (iv) Chest Discomfort (3.6%), and (v) Feeling Jittery (3.2%).

All of these reported ADEs were resolved without any residual effects.

"Serious ADEs" (SADEs) in the E004 clinical studies were defined as events reported by investigators to meet serious criteria including death, hospitalization, disability, congenital abnormality or other serious medical events, No deaths occurred in the E004 clinical trials. Two (2) SADEs (2/248 = 0.8%), one (1) episode of pregnancy and one (1) of breast cancer, from E004 treated population were reported in long-term adult/adolescent patients. Both were considered "definitely not related" to the treatment by the site investigators.

Adverse events of special interest (AESI) were identified based on cardiovascular ADEs, and the incidence rates of these are presented in **Table 1**. It was concluded that the long term E004 safety profile for these ADEs is very similar to that of Primatene® Mist CFC, which had demonstrated an excellent safety profile for more than 50 years.

Table 1 Cardiovascular ADEs Reported in E004 Clinical Studies (Up to 6 Month)

#	Category of Safety Data	ADE Incidence Rates in 6-month Clinical Studies (%)			Reference: FAERS Data # of ADEs per one million units*		
	Studied Products	E004 n=248	Placebo n=61	Primatene Mist n=64	Primatene Mist, x_1	Albuterol Inhaler, x_2	Ratio X_2/X_1
1	**Blood Pressure Increase**	**0.4%**	**0.0%**	**1.6%**	0.09	0.65	7.2
2	**Heart Rate Increase**	**0.4%**	**0.0%**	**0.0%**	0.23	0.89	3.9
3	**Hypertension**	**0.0%**	**1.6%**	**1.6%**	0.08	0.77	9.6
4	**Palpitations**	**1.2%**	**0.0%**	**1.6%**	0.09	0.89	9.9
5	**Tachycardia**	**0.4%**	**0.0%**	**0.0%**	0.09	0.87	9.7
6	**Myocardial Infarction**	**0.0%**	**0.0%**	**0.0%**	0.20	0.79	4.0
7	**Cardiac Arrest**	**0.0%**	**0.0%**	**0.0%**	0.08	0.47	5.9
8	**Hypotension**	**0.0%**	**0.0%**	**0.0%**	0.05	0.8	16
	Total	**2.4%**	**1.6%**	**4.7%**	0.89	6.13	6.9

* per FDA AERS data of Q4 1997- Q3 2012

Furthermore, evaluation of vital signs and ECGs, which includes more than 18,000 data points for vital signs (SBP, DBP & HR) and more than 17,000 data points for ECG (QT,

QTc, QTc-B and QTc-F) in Study C*, demonstrated that the profile for vital signs and ECG data for E004 was comparable with those for placebo and Primatene® Mist CFC. While there were transient increases in HR and SBP seen for E004 in the first 5-10 minutes after dose, as expected for this class of adrenergic bronchodilator, there were no increases compared to Primatene Mist CFC, and no other unexpected clinically significant cardiovascular issues in terms of frequency, severity or seriousness.

1.6. OVERVIEW OF THE OTC DEVELOPMENT PROGRAM

The program for E004 as a replacement for OTC Primatene® Mist CFC aimed to develop a label that consumers could understand, which would guide consumers' appropriate use of the medication without the need for a prescription to be written by a physician. The proposed OTC label for E004 was based on the label for Primatene® Mist CFC and the most up-to-date FDA Guidance for OTC bronchodilators [18], as well as formulation and dosage strength change information.

The proposed OTC labeling for E004 consists of two parts: the Drug Facts Label (DFL) and a Consumer Information Leaflet (insert). The DFL, which is mandated for all OTC medications, appears on the outer carton and on the immediate container of the product (i.e., the aluminum canister). Moreover, it communicates the indications, directions for use, and warnings, and its format is highly standardized and regulated under 21C.F.R. § 201.66. The insert contains supplemental information primarily focused on use and maintenance of the MDI inhalation unit, including its dose indicator. The insert is provided inside the proposed OTC unit package.

Prior to NDA submission, FDA advised Amphastar to specifically not test the DFL, but only evaluate the unique aspects of the E004 labeling, as compared to the Primatene® Mist CFC label. FDA requested a label comprehension study and a human factors study (i.e., behavioral demonstration study), in order to assess consumers' performance. Self-selection and actual consumer use studies were deemed not necessary in light of the experience with the previous Primatene® Mist CFC product and label, as well as the existence of FDA Guidance for OTC bronchodilators [18].

For the Label Comprehension Studies (LCS), multiple label comprehension studies were conducted to assess consumer understanding of the proposed insert for E004. Label

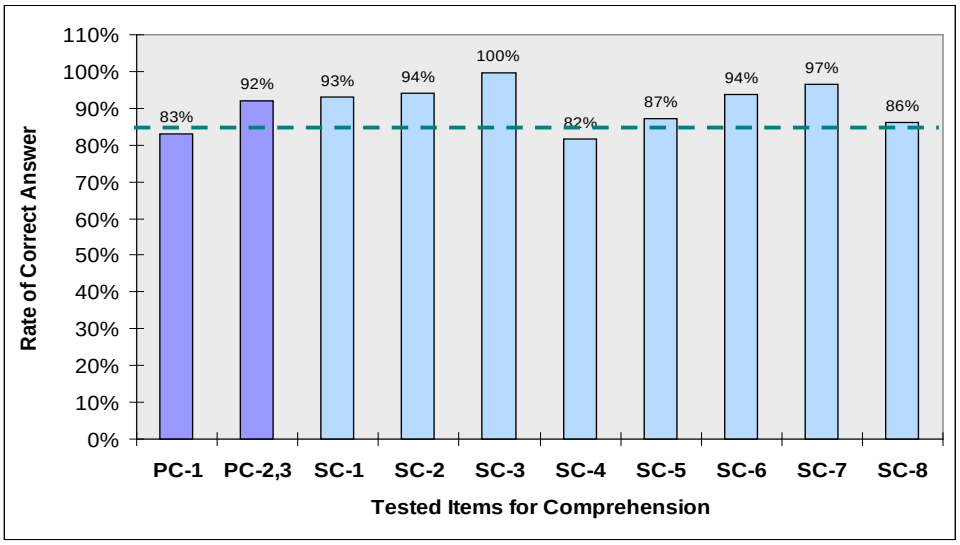
* In addition to these 35,000 vital sign/ECG data measured in Study C, more than 11,000 vital sign/ECG data were obtained in the other E004 studies. In total, there are 46,000 vital sign/ECG data for E004 clinical studies.

comprehension studies of E004 labeling were conducted in a general population sample recruited from 23 study sites across the US. The studies used an iterative process.

The primary objectives focused on comprehension of the labeling statements regarding the dose indicator use of E004, as this instruction was associated with a greater likelihood of consumer misunderstanding due to its uniqueness in OTC labeling. The target performance levels were set for comprehension of the primary end-points. The target level was set at 85%, reflecting the mitigated risk associated with overestimating the amount of medicine remaining in the inhaler. It required that the lower bound of the 2-sided 95% confidence interval must equal or exceed the target 85%. The E004 LCS assessment included two (2) primary communications (PC) and eight (8) secondary communications (SC).

The primary endpoints were related to the dose indicator. Secondary endpoints included priming/re-priming, cleaning the mouthpiece, taking an inhalation, and reliance on the dose indicator after dropping or damage. The results of E004 LCSs indicated that at Phase 3 of LCS and label improvement revisions, the important elements of the E004 insert were demonstrated to be well understood, with mean comprehension rates ranging from 82% – 100%, as shown in **Figure 1**. Please refer to Section 5 for detailed discussion of E004 OTC label studies.

Figure 1 Summary of Results of LCS Studies



As to E004 Human Factors (Behavioral Demonstration) Study, an observational human factors study of consumers' ability to (i) prime/reprime the inhaler, (ii) clean the inhaler, (iii)

reassemble the inhaler, (iv) correctly position, and (v) actually deliver a dose was conducted. A total of 61 subjects were enrolled. Participants reviewed the E004 insert and then were observed performing the tested steps with their performance scored by observers. Participants in this behavioral study demonstrated a very good ability to read and perform the steps of use and care of the E004 inhaler. In particular, participants performed remarkably well in the steps of actually delivering a dose.

In summary, E004 labeling provides effective directions for self-recognition and self-treatment in an OTC context. The E004 label is similar to Primatene® Mist CFC. Consumers are provided clear instructions from the E004 DFL and the illustrated insert. The LCS and human factor studies provide assurance that consumers correctly understand the directions for use for the E004 MDI.

1.7. BENEFIT RISK DISCUSSION

Asthma affects approximately seven (7) percent of the population of the United States. Quick reliever (adrenergic) bronchodilators are recommended for as needed use for intermittent and persistent asthma patients per NHLBI EPR3[19] and GINA[20] guidelines. Asthma continues to be a common and potentially debilitating disease and affects all ages from adolescents to the elderly. Asthma may be especially common in inner-city and some minority populations, and is worsened with exposures to triggers such as molds, rodent droppings, cockroaches, dust and pollution that may affect minorities. Symptoms flare unexpectedly with numerous daily variable triggers, including pollution, weather change, infections, allergen exposures, exercise, and at nighttime [4]. Asthma disrupts peoples' daily lives and costs the United States $56 billion each year. Asthma is a serious health and economic concern in the United States.

Medical Need for OTC Availability of Asthma Treatment

The most common symptom of asthma is expiratory wheezing and/or coughing reflecting bronchial constriction or obstruction. Other symptoms include: shortness of breath, chest tightness, and trouble sleeping due to coughing or wheezing. Consumers can self-recognize the symptoms of asthma and therefore, asthma is considered by the FDA as a condition that is self-recognizable and self-treatable following initial diagnosis by a physician.

There is no cure for asthma, but symptoms can be controlled with effective asthma treatment and management.

All available asthma medications have some limitation and side effects. It should be emphasized that there is currently no FDA approved OTC Asthma MDI medication available in the US market.

Concerns about Cardiovascular ADEs of Primatene® Mist CFC are mitigated by public health benefits, a reassuring drug safety profile and by careful labeling to direct consumers to see their physician for any persistent asthma symptoms or side effects.

OTC Epinephrine MDI CFC has been available since the 1960s for the relief of asthma symptoms. For more than 50 years, it is estimated some 207 million OTC Primatene® Mist CFC inhalers were sold. Approximately 2 – 3 million consumers per year utilized OTC Primatene® Mist CFC during these years [14]. However, there is a belief among some health care professionals that it is less effective and shorter acting and has more cardiovascular adverse effects than prescription β2-agonist MDIs [11]. In particular, the concerns have been focused on the cardiovascular adverse effects from the Epinephrine MDI CFC.

However, as pointed out for Primatene® Mist CFC, by Dr. Hendeles et al. in 2005, "***there is no basis for concerns about cardiovascular adverse effects from the epinephrine MDI***." [11]

The new reformulated E004 (Epinephrine HFA MDI) utilizes a lower dose, acts more rapidly and has been designed to be safer in multiple ways compared to the older Primatene® Mist CFC. Furthermore, the systematic controlled clinical studies conducted by Amphastar/Armstrong under the guidance of the FDA have confirmed the statement made by Dr. Hendeles *et al* and demonstrated a tolerable safety profile for E004.

The clinical study results showed a low frequency of 3-10% of typical side effects expected for this class of adrenergic agonist (tremor, jitteriness, etc.), and did not confirm any major or clinically significant cardiovascular issues in terms of frequency, severity or seriousness with E004, even after a long-term exposure (as long as six (6) months) or at an ultra-high dose (five (5) times that of the normal dose, i.e., ten (10) inhalations).

It should be noted, the vast majority of patients are expected to use lower doses, and use E004 only intermittently. The new Epinephrine HFA MDI (E004) has been improved and designed to have improved safety and resilience features compared to Primatene® Mist CFC. The new label will help patients utilize this quick reliever inhaler appropriately, and refer patients to see their physician for any persistent asthma symptoms, or any side effects encountered.

The results obtained from the randomized, controlled, blinded clinical studies of E004 conducted by Amphastar/Armstrong also demonstrate that **the amount of epinephrine entering into the blood system is only 0.9 mcg or 0.36% of delivered total dose (250 mcg)**. This very low bioavailability might well-explain why epinephrine MDI has no significant cardiovascular issues.

An OTC medication uniquely provides access to readily available treatment for millions with asthma. There appear to be gaps in the current asthma treatment available on the US market, primarily leaving the uninsured, financially underserved, and possibly elderly, inner city and rural populations at risk for lack of quick reliever inhalers when their asthma flares. As reported by consumers, many have difficulty accessing or affording asthma medications. Some do not experience sufficient relief with currently available asthma reliever treatment options. According to their experiences, epinephrine MDI CFC was the only product that worked for them. Many consumers simply stated that they could not afford or had limited access to the prescription drugs.

OTC status for E004 (Epinephrine HFA MDI) will address a number of these asthma treatment gaps. With OTC availability, consumers will have readily available access to this highly effective medication without the need for a prescription, an office visit, scheduling issues, and associated costs for that visit, including time off from school or work.

It should be noted that nearly all Americans with health insurance also commonly utilize OTC medicines. Use of OTC medications in no way precludes patients from seeing their primary and specialist physicians to help adjust and optimize their asthma care. OTC medications form a necessary adjunct to physician-provided healthcare that should be encouraged for all Americans.

E004 Overview, Efficacy and Safety

Epinephrine, the active ingredient in E004, is a well characterized chemical that has been included in numerous prescription and nonprescription products. It is well known that epinephrine, or adrenaline, is a naturally occurring hormone produced in the central nervous system and adrenal glands. Epinephrine's toxicities are well studied and well characterized due to the fact that it exists in our body.

The substantial efficacy of E004 for the treatment of mild to moderate asthma patients is

accompanied by expected side effects typical for adrenergic bronchodilators and by a generally reassuring and well characterized safety profile. It should be noted that the safety of E004 was supported by the analyses of up to 6-month long-term controlled clinical evaluation conducted in 34 clinical centers throughout the United States. The E004 product was developed in compliance with FDA recommendations for the approval of an Epinephrine HFA bronchodilator suitable to replace Primatene® Mist CFC for the OTC market.

As a therapy targeted to cause bronchodilation by β2 adrenergic stimulation for quick relief of asthma symptoms, the most common adverse events of E004 are classic effects common to other respiratory beta agonists. These occurred partially in the upper respiratory tract, including throat irritation and cough. Other beta adrenergic events, such as chest discomfort and jittery feeling were tolerated by patients of various ages 12 and up, with few discontinuations, and tended to be brief, decreasing within 10-15 minutes post-dose, also accompanied by a tenfold fall-off from peak in serum epinephrine levels by 12.5 minutes post-dose. These ADEs are a nominal risk compared to the public benefit of improving life quality by temporarily relieving the symptoms caused from asthma attacks.

It should be emphasized that no death or treatment related serious ADE were observed during the entire E004 clinical program.

E004 in the OTC Environment

An OTC label has been developed to update information from the OTC Primatene® Mist CFC label in language that is well understood by the consumer. Label comprehension studies support that consumers, even those with low health literacy, can understand the instructions in the proposed insert. The DFL includes specific sections for Purpose, Uses, Directions and Warnings following the FDA Guidance for OTC bronchodilators [18] and the most updated FDA guidance. The insert will be placed inside the E004 unit package and provide directions and illustrations for use and maintenance of the MDI unit. Language on the proposed DFL is similar to that of Primatene® Mist CFC, except where adaptations based on the specific new features of E004 MDI unit were needed. Label instructions, discussed by category below, help mitigate potential risks with use of E004 in the OTC consumer environment.

The directions for dosing of OTC E004 are straightforward, “one or two inhalations for each dose”, “start with one inhalation, wait at least 1 minute. If not relieved, use once more”, “wait at least 4 hours between doses”, and “do not use more than 8 inhalations in 24 hours”. It is well understood by consumers since it is based on FDA Guidance for OTC

bronchodilators [18] and is similar to the dosing instructions for Primatene® Mist CFC. This also represents the typical dosing pattern familiar to patients for their prescription quick-relief bronchodilators. It is important to note that there were few reports of misuse, abuse, or of taking excessive amounts of Primatene® Mist CFC.

E004 provides effective relief of the symptoms indicated in the DFL, wheezing, chest tightness, and shortness of breath, the typical asthma symptoms that sufferers find most bothersome. The efficacy and safety of the product has been characterized in controlled clinical studies. The proposed OTC labeling has been developed to ensure consumer understanding of the proper use of the product and to help mitigate potential safety risks.

In conclusion, the efficacy and safety for the use of E004 without physician's oversight would not be different or pose greater risks than those for OTC Primatene® Mist CFC, which demonstrated a favorable benefit-risk profile for over 50 years. Nor would it be different than when a physician prescribes albuterol MDI with multiple refills. The risks are mitigated by the strong safety profile demonstrated during the clinical evaluation of E004 and through the OTC labeling that follows the FDA requirements in format and content. Therefore, the benefits of broader access to an effective OTC treatment as a replacement formulation for OTC Primatene® Mist CFC, for temporary relief of mild symptoms of intermittent asthma, outweigh the risks.

Approval of E004 (Epinephrine HFA MDI) will add important public health benefits for asthma patients and form a beneficial supplement to other controller and reliever medications for asthma, none of which are currently available on the OTC market for consumers.

2. BACKGROUND INFORMATION

Epinephrine HFA MDI, 125 mcg/inh, (E004) is an epinephrine inhalation aerosol USP using a metered dose inhaler (MDI) with hydrofluoroalkane (HFA) as the propellant. It was reformulated to replace the over-the-counter (OTC) product Primatene® Mist (Epinephrine CFC MDI, 220 mcg/inh), which was phased out in December 2011 due to the ban on the use of chlorofluorocarbons (CFCs) as the propellant.

Armstrong Pharmaceuticals, Inc. (Armstrong), a wholly owned subsidiary of Amphastar Pharmaceuticals, Inc. (Amphastar), submitted a new drug application (NDA 205920) to the FDA with data supporting E004 as a replacement for Primatene® Mist

Armstrong is seeking FDA approval for E004 as an OTC product for oral inhalation administration ***for temporary relief of mild symptoms of intermittent asthma*** in adults and children twelve (12) years of age and older.

2.1 REGULATORY HISTORY AND EPINEPHRINE MDI MEDICATION

2.1.1 Regulatory History of Primatene® Mist CFC

Epinephrine CFC MDI (or Primatene® Mist CFC) was initially developed by Wyeth (NDA 016120) and formally approved by the FDA in 1967. It was distributed by Wyeth under the trade name Primatene® Mist (Primatene®). It was on the U.S. OTC Market for about fifty (50) years and had an excellent safety profile.

Epinephrine CFC MDI was a true solution of epinephrine chloride in CFC and 34% ethanol. It was supplied in glass bottles protected with externally coated plastic.

Armstrong, manufactured Primatene® Mist CFC for Wyeth as of 2006 and acquired the trademark of Primatene® in 2008. Primatene® Mist CFC was the only US OTC MDI medication that could provide quick relief symptoms for asthma patients, until it was phased out on December 31, 2011, as required by the Montreal Protocol, due to concerns of ozone depletion caused by CFC [5]. It should be emphasized that Primatene® Mist CFC was not withdrawn from the market for concerns related to consumer safety or efficacy.

There were approximately two to three million asthma sufferers per year who used

Primatene® Mist CFC for temporary relief of their mild asthma symptoms. A significant portion of these sufferers had no health insurance or prescription medication access prior to enactment of The Affordable Care Act. Many such asthma sufferers indicated that albuterol and/or other prescription drugs did not work for them or caused allergic reactions. Some asthma sufferers occasionally used Primatene® Mist CFC when their prescription drugs were not available to them, such as missing a refill, during travel, etc.

Primatene® Mist CFC was a well-established OTC asthma medication that was used safely for over 50 years by consumers. For Primatene® Mist CFC, 4.4 million units were sold per year before its sunset, which is equivalent to 1/12 of the Albuterol HFA MDI market. For more than 50 years, about 207 million units were sold [14], which corresponds to 41 billion inhalations.

The FDA AERS database further shows that the total ADE incidence rate of Primatene® Mist CFC was 17.8 per million units, compared to 228 per million units for Albuterol inhalers. The ADE incidence rate for Primatene® Mist CFC is 12.8 times lower than that for Albuterol inhalers.

2.1.2 Epinephrine HFA MDI (E004)

Before the sunset of Primatene® Mist CFC, a New York Times article reported in 2006:

> "*Wyeth said it had been unable so far, after years of effort, to develop an epinephrine inhaler that would be effective and acceptable to consumers but would use a propellant that does not harm the ozone layer*." [13]

Amphastar/Armstrong overcame the technical barriers and have developed Epinephrine HFA MDI, or E004, which is a suspension solution of epinephrine free base in HFA and 1% ethanol. E004 will be supplied in aluminum canisters.

E004 was formulated based on Amphastar/Armstrong's proprietary, patented technology, which is covered under U.S. Patent No. 8,367,734 [15]. The "super high amount" of HFA has resulted in a more efficient delivery for E004 MDI via suspension solution, such that the inhalation dose of aerosolized epinephrine has been reduced from 220 mcg/inhalation for Primatene® Mist CFC to 125 mcg/inhalation for E004, with comparable clinical efficacy and safety.

The recommended dosing for E004 is as follows:

> *In adults and adolescents (≥ 12 years), the recommended dose is 1 to 2 inhalations. Start with one (1) inhalation, wait at least 1 minute. If not relieved, use once more. Wait at least four (4) hours between doses. Do not use more than eight (8) inhalations in 24 hours.*

Mild asthma is considered by the FDA as a condition that is self-recognizable and self-treatable after initial diagnosis by a physician.

2.1.3 Primary and Proposed Proprietary Name

The primary and proposed proprietary name for E004 is "Primatene® Mist HFA". Before it is formally approved by the FDA, it is interchangeable with E004. **Figure 2** shows the proposed product package.

Figure 2 Proposed Product Package for E004

2.2 INTERACTION WITH THE AGENCY

In supporting E004 as a replacement for Primatene® Mist CFC as an over-the-counter (OTC) product, Armstrong/Amphastar had numerous interactions with the FDA to discuss the

overall development strategy, content of the submission, and clinical studies and consumer studies that would be required to support approval.

Based on the FDA requirements, two (2) single dose, randomized dose ranging, crossover studies were conducted and the results demonstrated the E004 efficacy profile in the dose range of 90 to 440 mcg. Based on the study results, the Agency advised to select the final dose of 125 x 2 = 250 mcg. E004 Phase III studies confirmed that 125 mcg/inh is the optimal strength of E004.

The FDA advised to have a long-term, twelve (12) week randomized efficacy and safety study and further extended to obtain up to six (6) months of safety data. These long-term clinical efficacy and safety studies were conducted at highest label dose, 2×125 mcg/inh, QID, i.e., 8 inhalations per day.

Furthermore, the FDA instructed Armstrong/Amphastar to perform label comprehension studies (LCS) and human factors consumer studies (behavioral study). The studies were instructed to focus on (i) changes of E004 labeling from the previous Primatene® Mist CFC labeling, or (ii) were defined in the up-to-date FDA guidance for OTC bronchodilators [18] that address the Drug Fact Label portion of the labeling (which by definition addresses the safe and effective use of OTC drug products).

2.3 MEDICAL NEED FOR OTC EPINEPHRINE MDI ASTHMA MEDICATION

OTC Epinephrine MDI CFC has been available since the 1960s for the relief of asthma symptoms. However, some health care professionals widely believe that it is less effective and has more cardiovascular system adverse drug effects (CADE) than prescription β_2-agonist MDIs [11]. In particular, the concerns have been focused on the CADE from an epinephrine MDI.

In fact, the FDA ADRS data from Q4 1997 to Q3 2012 demonstrated the CADE rate for Epinephrine MDI CFC is 0.91 CADE incidents per one million units of the medication. While the CADE rate for Albuterol inhaler is 9.62 CADE incidents per one million units of the medication. Thus, **the CADE rate for Albuterol inhaler is 10.6 times that for Epinephrine MDI CFC.**

The low bioavailability in the blood system for E004 also provides an indication that most of epinephrine seems to arrive at the site of action, the bronchus/lungs.

As early as 2005, Hendeles et al. pointed out the key reason for the low CADE of epinephrine MDI is that "***It [epinephrine] has poor systemic bioavailability when delivered by a chlorofluorocarbon (CFC) MDI***."[11]

The results obtained from the E004 clinical studies demonstrated that **the amount of epinephrine entering into the blood system is only 0.9 mcg or 0.36% of delivered total dose (250 mcg),** as discussed in **Section 2.4** of this Briefing. This extremely low systemic bioavailability (0.36%) clearly explains and justifies why epinephrine MDI has no significant CADE in terms of frequency, severity or seriousness.

Hendeles et al. also indicated that "*Given the poor systemic bioavailability of epinephrine when delivered by CFC-MDI, we hypothesized that the dose could be safely increased to achieve the same efficacy as albuterol*." [11]

Amphastar/Armstrong developed E004 based on proprietary, patented technology that is covered by U.S. Patent No. 8,367,734 [15]. The super high amount of HFA (> 98% w/w) has resulted in an effective delivery mode of E004 as an MDI, such that the inhalation dose of aerosolized epinephrine has been reduced from 220 mcg/inhalation for Primatene® Mist CFC to 125 mcg/inhalation for E004 with comparable clinical efficacy and safety.

Nocturnal asthma is complex but involves an increase in allergic inflammation during the night (especially the early morning hours). Several studies choose nocturnal asthma to test the efficacy of bronchodilators. Since airway obstruction on awakening from asthma is more severe than during the day, there is a greater capacity for bronchodilator response. Hendeles et al., for example, conducted a study entitled, "Response to nonprescription epinephrine inhaler during nocturnal asthma." [11] The results of this study concluded that "*Epinephrine was nearly as effective as albuterol in terminating an acute episode of airway obstruction but without cardiovascular effects in these otherwise healthy young adults*." [11] The authors further indicated that "nonprescription epinephrine CFC-MDI is more effective and safer than what many health care professionals believe." [11]

Hendeles et al., further compared asthma symptom improvement associated with the use of epinephrine and albuterol in a randomized cross-over study and reported, "*Severe airway obstruction was present on awakening from asthma, but FEV1 improved and symptoms resolved in a parallel manner, nearly as well with epinephrine as albuterol. These improvements are likely a result of bronchodilation and not just a function of time, since the*

maximum post-dose FEV1 values after both treatments were higher than their respective means on admission to the CRC [clinical research center] at 10 PM and on discharge at 7 AM." [11]

It is noteworthy that the clinical study conducted by Hendeles et al. used a higher dose than recommended in the labels of both Primatene® Mist CFC and Albuterol. Therefore, the authors concluded "***epinephrine was nearly as effective as albuterol in terminating an acute episode of airway obstruction but safer at higher doses***." [11]

Hendeles et al. hoped that a study with a larger number of patients could be conducted to eliminate people's concerns. The controlled clinical studies for E004 conducted by Amphastar/Armstrong under the FDA's guidance have fulfilled this mission, such that Epinephrine HFA MDI (E004) OTC asthma inhaler can fulfill the unmet medical need as discussed in **Section 1.1** of this briefing document.

2.4 PHARMACOLOGICAL PROFILE OF E004

Epinephrine is a sympathomimetic catecholamine. The actions of epinephrine resemble the effects of stimulation of adrenergic nerves [6, 7]. To a variable degree it acts on both alpha and beta receptor sites of sympathetic effector cells. Its most prominent effects are on the beta receptors of the heart and vascular when administered systemically and airway smooth muscles [6] when administered by oral inhalation. Epinephrine relaxes the smooth muscles of the bronchi and iris and is a physiologic antagonist of histamine.

Pharmacokinetic (PK) studies of E004 were conducted in healthy subjects with a high single dose of 5 times the regular dose (i.e., 5×2=10 inhalations). This study allows the plasma concentration of exogenous epinephrine-d3, a stable-isotope deuterium (^{2}H) labeled epinephrine, and epinephrine-h3, the endogenous epinephrine, to be quantifiably measured by the validated LC/MS/MS methodology under GLP compliance.

The peak concentration C_{max} (0.18 ng/mL at the regular dose) occurs at about 2 minutes. The elimination half life $t_{1/2}$ of 2.6 minutes was observed, which is consistent with previous reported 2 minutes [9] and 3.5 minutes [10]. The PK curves for both E004 and Primatene® Mist well match the one-compartment model with the first order input and first order output ("1,1,1-PK Model").

Figure 3 shows the plasma epinephrine concentration curves normalized to regular dose for

E004 (250 mcg) and Primatene Mist (440 mcg), as well as the curves from the 1,1,1-PK Model. **Figure 4** shows the data of C_{max} of the two products, E004 and Primatene® Mist CFC.

Figure 3 Plasma Epinephrine Concentrations for Regular Dose

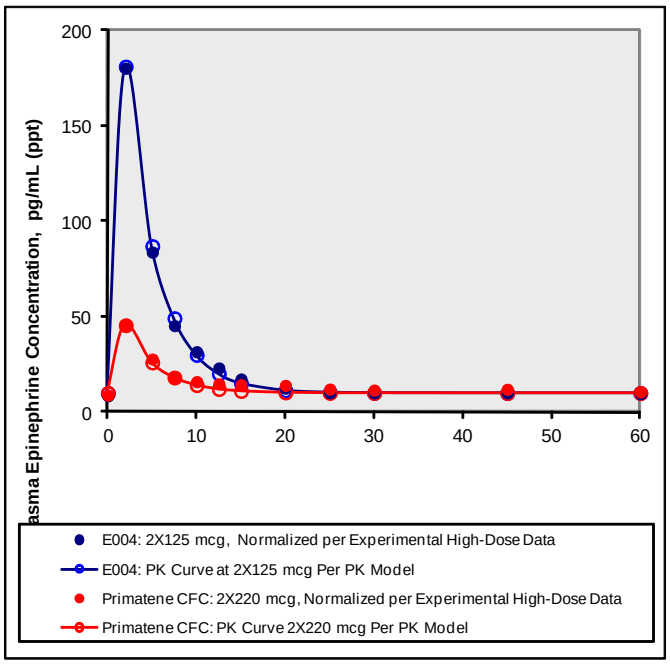
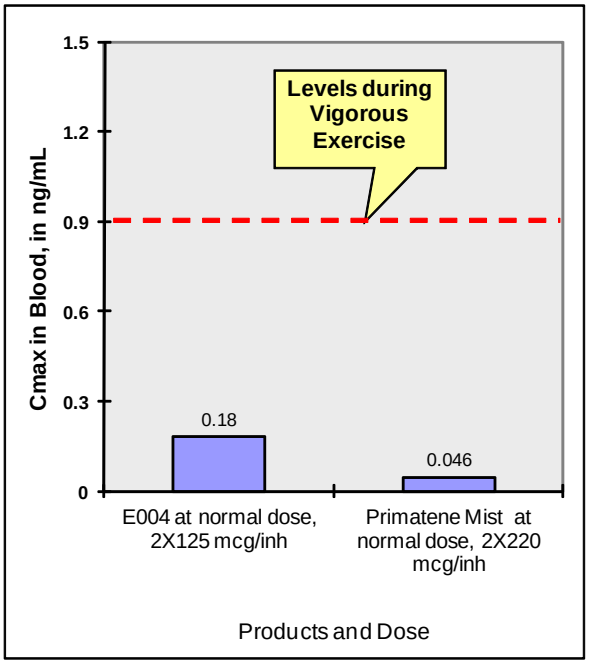


Figure 4: Data of Cmax of Epinephrine



The C_{max} of E004, 0.18 ng/mL (exogenous and endogenous), is approximately 20% of the normal human endogenous epinephrine levels presents during vigorous exercise, 5 nmol/L or 0.92 ng/mL[7,8] (**Figure 4**). Reference [8] defines the exercise level as 110% V_{O2max}, i.e., running 2 minutes at the speed of 9.7 km/hr for 323 meters, the epinephrine levels is in the range 3.6 to 8.7 nmol or 0.67 to 1.6 ng/mL.

Within 10 minutes following the t_{max} (=2.3 minutes), the plasma epinephrine level was reduced to less than one tenth of the C_{max} at 12.5 minutes post-dose showing an elimination half-life of 2.6 minutes. The exogenous epinephrine concentration in plasma declines to an undetectable level in the blood system after 60 minutes post-dose.

As to the Pharmacodynamic (PD) study, the FDA required two (2) single dose, dose ranging studies in order to demonstrate that the E004 efficacy profile in the dose range of 90 to 440 mcg. These studies showed that E004 efficacy

(i) rapidly increased from the lowest dose studied, 90 mcg;

(ii) became statistically significant for the dose of 125 mcg (p-value < 0.05);

(iii) reached a stable range with reliable efficacy near 250 mcg = 2×125 mcg/inh; and then
(iv) converged for higher doses up to the highest studied dose, 440 mcg.

Based on the study results, the FDA recommends a final dose of 125 x 2 = 250 mcg for E004. Phase III studies confirmed that 125 mcg/actuation is the optimal strength of E004.
The long-term efficacy/safety Study C demonstrated that:

(i) both E004 and Primatene® Mist CFC demonstrated long-term efficacy at the highest labeled dose (8 inhalations per day);
(ii) E004 has a very fast onset of action* , 12 to 18 minutes, which is slightly quicker than Primatene® Mist CFC (28 to 40 minutes) and
(iii) the mean efficacy durations of E004 (1.6 to 2.8 hours) and Primatene® Mist CFC (1.3 to 2.5 hours) are similar.

Formal drug-drug interaction studies have not been conducted. For all study arms (E004, Primatene® Mist CFC and Placebo) the concomitant drug usage profiles were similar. No drug-drug interactions have been identified with epinephrine from clinical trials.

As to the role of systemic absorption, only 0.9 mcg or 0.36% of epinephrine inhaled dose from E004 delivery (250 mcg) is distributed into the blood system at t_{max}, which is surprisingly low. This means that most of the epinephrine that reached patients' lungs after an inhalation, is rapidly inactivated in the lungs. This extremely low bioavailability may due to that lipophilicity of epinephrine free base in E004 makes the majority (>99%) of epinephrine remain in the local delivery site, bronchus and lung.

No serious ADEs that were reported were related to E004. Tremor was identified as one (1) of the Major ADEs and is discussed in more detail in the Safety section of this briefing document.

* The onset time is defined as the earliest moment when Δ%FEV1≥12%.

3. EFFICACY FROM CLINICAL STUDIES

3.1 OVERVIEW OF STUDY DESIGN SUPPORTING EFFICACY

E004 efficacy studies in adult/adolescent asthma patients consist of **Studies A, A2, and C**.

Table 2 provides a listing of the key characteristics of the three (3) randomized, placebo-controlled double- or evaluator-blinded studies that evaluates the efficacy of E004 in mild to moderate asthma patients.

Study A, a single dose crossover study in 26 adult asthma patients for (i) efficacy evaluation, (ii) dose optimization, and (iii) initial safety evaluation;
Study A2, a single dose crossover study in 30 adult asthma patients for (i) efficacy evaluation, (ii) dose optimization and (iii) safety evaluation; and
Study C, a multiple-dose and long-term (12 weeks) efficacy/safety parallel study in 373 adult/adolescent asthma patients.

One (1) multiple-dose and long-term (4 weeks) efficacy/safety parallel study (Study D) in 70 pediatric asthma patients was also conducted (for information only). An additional efficacy study in pediatric patients, aged 4-11 years, is in progress.

In the above studies, **Study C** was a pivotal Phase III study, designed as a randomized, double- and evaluator-blinded, active and placebo-controlled, three-arm, parallel, 12-week multiple-dose, multi-center (34 clinical sites) study and was conducted in 373 adult/adolescent subjects with intermittent, or mild-to-moderate asthma for at least 6 months, but who were otherwise generally healthy. This study included three (3) arms:

(i) Arm T, E004 250 mcg, 2 × 125 mcg/inh, QID, with 4-6 hr intervals;
(ii) Arm P, HFA Placebo, 2 × 0 mcg/inh, QID, with 4-6 hr intervals; and
(iii) Arm-A, Primatene® Mist CFC 440 mcg (active control), 2 × 220 mcg/inh, QID, with 4-6 hr intervals.

Table 2 Summary of Clinical Efficacy and Safety Studies in Adult/Adolescent Asthma Patients for E004

No.	Phase	Study Reference No.	Study Objectives	Number of Study Sites	Study Design, Control Type	Study Start Enrollment status Date Total Enroll./ Enroll. Goal	Duration & Diagnosis Inclusion Criteria	Primary Endpoint(s)	Arm	Treatment		# of Subject plan/ITT/ treated/ completed/ crossover	Treated Population		Crossover or Qualified Population	
										Drug	Dose, mcg		Gender (M/F)	Median Age (Range)	Gender (M/F)	Median Age (Range)
1	I	API-E004-CL-A, (Simplified as **E004-A**)	(1) Efficacy Evaluation; (2) Initial Safety Evaluation; (3). Identify the optimum dose	**4** sites in the US	Randomized, double-blinded or evaluator blinded, placebo- and active- controlled, five arm, crossover, single dose study in asthma patients	Started: 3/25/2010, Completed: 6/30/2010, 26/24	Single Dose adult patients with mild-to-moderate persistent asthma	AUC of Δ%FEV1, relative to the same day baseline	T1	E004	250	24/26/26/25/21	14/12	30.5 (18-55)	10/11	33.0 (20-55)
									T2	E004	320	24/26/25/22/20	14/12	31.0 (18-55)	10/10	32.0 (20-55)
									T3	E004	440	24/26/24/24/21	14/12	30.5 (18-55)	10/11	33.0 (20-55)
									P	Placebo	0	24/26/24/21/--	14/12	30.5 (18-55)	10/11	33.0 (20-55)
									A	Primatene®	440	24/26/25/24/21	14/12	31.0 (18-55)	10/11	33.0 (20-55)
2	II	API-E004-CL-A2, (Simplified as **E004-A2**)	(1) Efficacy Evaluation; (2) Initial Safety Evaluation; (3). Identify the optimum dose	**5** sites in the US	Randomized, double-blinded or evaluator blinded, placebo- and active- controlled, five arm, crossover, single dose study in asthma patients	Started: 11/22/2010, Completed: 2/10/2011, 30/24	Single Dose adult patients with mild-to-moderate persistent asthma	AUC of Δ%FEV1, relative to the same day baseline	T1	E004	90	24/30/29/29/25	17/13	31.0 (18-55)	13/12	31.0 (18-52)
									T2	E004	125	24/30/29/29/25	17/13	31.0 (18-55)	13/12	31.0 (18-52)
									T3	E004	180	24/30/29/28/25	17/13	31.0 (18-55)	13/12	30.5 (18-52)
									T4	E004	200	24/30/29/29/25	17/13	31.0 (18-55)	13/12	31.5 (18-52)
									T5	E004	250	24/30/29/28/24	17/13	31.0 (18-55)	12/12	31.5 (18-52)
									P	Placebo	0	24/30/30/26/--	17/13	30.5 (18-55)	14/12	30.5 (18-52)
									A1	Primatene®	220	24/30/30/29/25	17/13	30.0 (18-55)	13/12	30.0 (18-52)
									A2	Primatene®	440	24/30/29/28/24	17/13	31.0 (18-55)	12/12	31.5 (18-52)
3	III	API-E004-CL-C, (Simplified as **E004-C**)	(1) Efficacy (2) Safety Evaluation for adolescent & adult asthma patients	34 sites in the US	12-week, randomized, double- & evaluator-blinded, placebo- & active-controlled, parallel, multiple dose study in patients	Started: 5/5/2011, Completed: 11/16/2011, 373/300	12 weeks adolescent and adult patients with mild to moderate asthma	AUC of Δ%FEV1, relative to the same day baseline for Week-12	T	E004	250, QID	200/248/248/ 205/na	99/149	37.0 (12-75)	80/125	40.0 (12-75)
									P	Placebo	0, QID	50/61/61/52/na	21/40	38.0 (13-69)	19/33	38.5 (13-69)
									A	Primatene®	440, QID	50/64/64/53/na	29/35	40.0 (13-71)	23/30	40.0 (13-71)
4	III	API-E004-CL-C2, (Simplified as **E004-C2**)	(1) Safety Evaluation for adolescent & adult asthma patients	27 sites in the US	Additional 3-month extension safety study, randomized, double- & evaluator-blinded, placebo- & active-controlled, parallel, study in patients	Started: 11/9/2011, Completed: 4/5/2012, 207/180	additional 3 months, adolescent and adult patients with mild to moderate asthma	AUC of Δ%FEV1, relative to the same day baseline for Week-12	T	E004	250, QID	120/134/134/134/na	54/80	41.0 (12-65)	54/80	40.0 (12-69)
									P	Placebo	0, QID	30/38/38/38/na	13/25	36.0 (17-67)	13/25	37.5 (13-68)
									A	Primatene®	440, QID	30/35/35/35/na	16/19	35.5 (13-71)	16/19	40.0 (13-71)

3.2 PRIMARY AND SECONDARY ENDPOINTS FOR E004 EFFICACY STUDIES

The bronchodilatory effect of E004 and control arms was assessed by the change of "forced expiratory volume in one (1) second" (FEV1) relative to the same day baseline, denoted as Δ%FEV1 and is defined as:

$$\Delta\%FEV1(t) = \frac{FEV1(t) - FEV1(0)}{FEV1(0)} \times 100\%$$

where FEV1(t) is the FEV1 at time t after dosing, and FEV1(0) is the baseline of FEV1 for the same day prior to dosing.

The primary endpoint was the area under curve (AUC) of Δ%FEV1, which is reported in unit of %×hr.

Sixteen (16) secondary endpoints included

(i) AUC of ΔFEV1, in units of L×hr, which is defined as the difference between FEV1(t) and the same day baseline, FEV1(0);
(ii) AUC of FEV1;
(iii) F_{max}, in units of %, the maximum value of the curve Δ%FEV1 (t);
(iv) F_{max} of FEV1;
(v) t_{max} for Δ%FEV1, in hours, the time point of F_{max};
(vi) t_{max} for FEV1
(vii) onset time (t_{onset}), in minutes, the first moment t intersects with Δ%FEV1(t) ≥ 12%;
(viii) efficacy duration ($t_{duration}$), in hours, the total time intervals when Δ%FEV1(t) ≥ 12%;
(ix) % responders, in units of %, the percentage of treated subjects who met F_{max} ≥ 12%.

The other seven (7) secondary endpoints, items (x) to (xvi) are: Δ%FEV1(t), for t = 5', 30', 60', 120', 180', 240', and 360' post-dose respectively.

3.3 EFFICACY RESULTS

3.3.1 Long-term (12-Week) Adult/Adolescent Efficacy Studies

Study C was a randomized, double- and evaluator-blinded, active and placebo-controlled, three-arm, parallel, 12-week multiple-dose, multi-center (34 clinical sites)

study and was conducted in 373 adult/adolescent subjects with intermittent, or mild-to-moderate asthma for at least 6 months, but who were otherwise generally healthy. This study included three (3) arms: (i) Arm T, E004 250 mcg, 2 × 125 mcg/inh, QID, with 4-6 hr intervals; (ii) Arm P, HFA Placebo, 2 × 0 mcg/inh, QID, with 4-6 hr intervals; and (iii) Arm-A, Primatene® Mist CFC 440 mcg (active control), 2 × 220 mcg/inh, QID, with 4-6 hr intervals.

A total of 248, 61, and 64 subjects (in total 373) were randomized and treated for E004, placebo and Primatene® Mist CFC, respectively. Efficacy data was measured on Day-1 (Visit-1), at Week-6 (Visit-3) and Week-12 (Visit 5). The efficacy data at Week-12 (Visit-5) was used for the primary analysis of primary endpoint.

Three (3) imputation-based approach models were applied to the intent-to-treat (ITT) population for missing data handling (MDH). These methods included (i) a reasonable method, [Closest Data Model (CDM)]), (ii) a conservative method (Placebo Model), and (iii) the most conservative method (Baseline Model). The CDM was used for primary analysis. The Placebo Model was used for sensitivity analysis. The Baseline Model was used for sensitivity analysis and challenge. This primary analysis was performed on the ITT population with missing data handling by the closest data model. The statistical analysis was performed to examine whether E004, with a repeated maximum labeled dose for 12 weeks, has a significantly greater bronchodilatory effect compared to the Placebo-HFA control in terms of $AUC_{0\text{-}6hr}$ for Δ% FEV1.

Three hundred and eleven (311) patients completed the entire 12-week study (Visit-5) and have qualified efficacy data for the primary efficacy analysis, which are the per protocol population (PPP). Among them, 205, 53 and 53 were from E004, Placebo and Primatene® Mist CFC, respectively.

The subject age, gender, weight, height, race, regional distribution, and concomitant drug (including inhaled corticosteroid medications) usage profile were very similar among the three (3) arms.

The primary efficacy analysis was conducted with FEV1 data collected at Visit-5 (Week-12). Eight (8) FEV1 data time points were intended to be measured for each subject. The number of FEV1 data points collected at Visit-5 for the Treated Population (n=326) and PPP (n=311) were 2,503 and 2,466, respectively.

Primary Analysis of Efficacy Primary Endpoint Long-Term Study C

The primary analysis for primary efficacy demonstrates the following conclusions for long-term usage (Week-12, Visit-5) at the maximum dose of E004 (2×125 mcg QID).

The primary analysis of the primary endpoint was performed with a two-sided *t*-test for $AUC_{0\text{-}6hrs}$ of Δ%FEV1 for ITT population for Visit-5 (Week-12) data by using the closest data model for missing data handling (MDH), as listed in **Table 3**.

For purposes of sensitivity analysis, the primary analysis was conducted with the following four (4) models:

(i) ITT, with the closest data model (Model-A) for missing data handling (MDH);
(ii) ITT, with the placebo model (Model-B) for MDH;
(iii) ITT, with the baseline model (Model-C) for MDH; and
(iv) Per-Protocol Population for completed cases with interpolation method for MDH.

Table 3 Major Parameters for Primary Analysis of Study C

#	Items	Description
1	Population	ITT
2	Primary Endpoint	$AUC_{0\text{-}6hr}$ for Δ%FEV1
3	Dataset	All Data observed at Visit-5 (Week-12)
4	Missing Data Handling	Imputation-based Approach Closest Data Model
5	Type-1 error	α = 0.05
6	Statistical Method	two-sided t-test
7	Reference Arm	Placebo

Two-sided t-test analyses for secondary endpoints were conducted following the same principle as that for the primary endpoint, and the p-values were evaluated. For the secondary endpoint, responder rate, a χ^2-test was conducted.

The significance profile for the seventeen (17) tested items (1 primary endpoint and 16 secondary endpoints) for (i) Day-1, (ii) Week-6, and (iii) Week-12 is summarized in **Table 4** and mean Δ%FEV1 data over time is provided in **Figure 5**. In each visit, the

study starts in the mornings.

Table 4 Long-term Efficacy Significance Profile for Week-12 Study C for Various Populations and MDH Models

Studied Drugs	E004 (1-sided test)						Primatene Mist (1-sided test)					
Missing Data Handling	Day-1 (Visit-1)	Week-6 (Visit-3)	Week-12 (Visit-5) (Primary Analysis)				Day-1 (Visit-1)	Week-6 (Visit-3)	Week-12 (Visit-5) (Primary Analysis)			
Populations	PPP	PPP	ITT			PPP	PPP	PPP	ITT			PPP
Number of Patients, vs. Placebo	228 vs. 54	198 vs. 54	248 vs. 61			205 vs. 53	61 vs. 54	57 vs. 54	64 vs. 61			53 vs. 53
MDH Methods	-	-	Model A	Model B	Model C	-	-	-	Model A	Model B	Model C	-
Primary Endpoint: AUC of Δ%FEV1, %×hr	√	√	√	√	√	√	√	√	√	√	√	√
Secondary Endpoints												
1. $AUC_{0\text{-}6hr}$ of ΔFEV1, L×hr	√	√	√	√	√	√	√	X	√	√	√	√
2. F_{max} of Δ%FEV1, %	√	√	√	√	√	√	√	√	√	X	X	√
3. Duration, hrs	√	√	√	√	√	√	√	X	X	X	X	√
4. Time of onset, min	√	√	√	√	√	√	X	√	√	√	√	√
5. t_{max} of Δ%FEV1, hrs	√	√	√	√	√	√	√	√	√	X	√	√
6. Responder, %	√	√	√	√	√	√	√	√	√	√	√	√
7. Δ%FEV1 at 5 min, %	√	√	√	√	√	√	√	√	√	√	√	√
8. Δ%FEV1 at 30 min, %	√	√	√	√	√	√	√	√	√	√	√	√
9. Δ%FEV1 at 60 min, %	√	√	√	√	√	√	√	√	√	√	√	√
10. Δ%FEV1 at 120 min, %	√	√	√	√	√	√	√	√	√	√	√	√
11. Δ%FEV1 at 180 min, %	√	X	√	√	√	√	√	X	√	√	√	√
12. Δ%FEV1 at 240 min, %	√	X	√	√	√	√	√	X	√	X	X	√
13. Δ%FEV1 at 360 min, %	√	X	X	X	X	X	√	X	X	X	X	X
14. $AUC_{0\text{-}6hr}$ of FEV1, L×hr	√	√	√	√	√	√	X	X	√	X	X	X
15. F_{max} of FEV1, L	√	√	√	√	√	√	X	X	√	X	X	X
16. t_{max} of FEV1, hrs	√	√	√	√	√	√	√	√	√	√	√	√
The 16 Secondary Endpoints												
#, non-significance	0	3	1	1	1	1	3	7	2	7	6	3
#, Significant	**16**	**13**	**15**	**15**	**15**	**15**	**13**	**9**	**14**	**9**	**10**	**13**

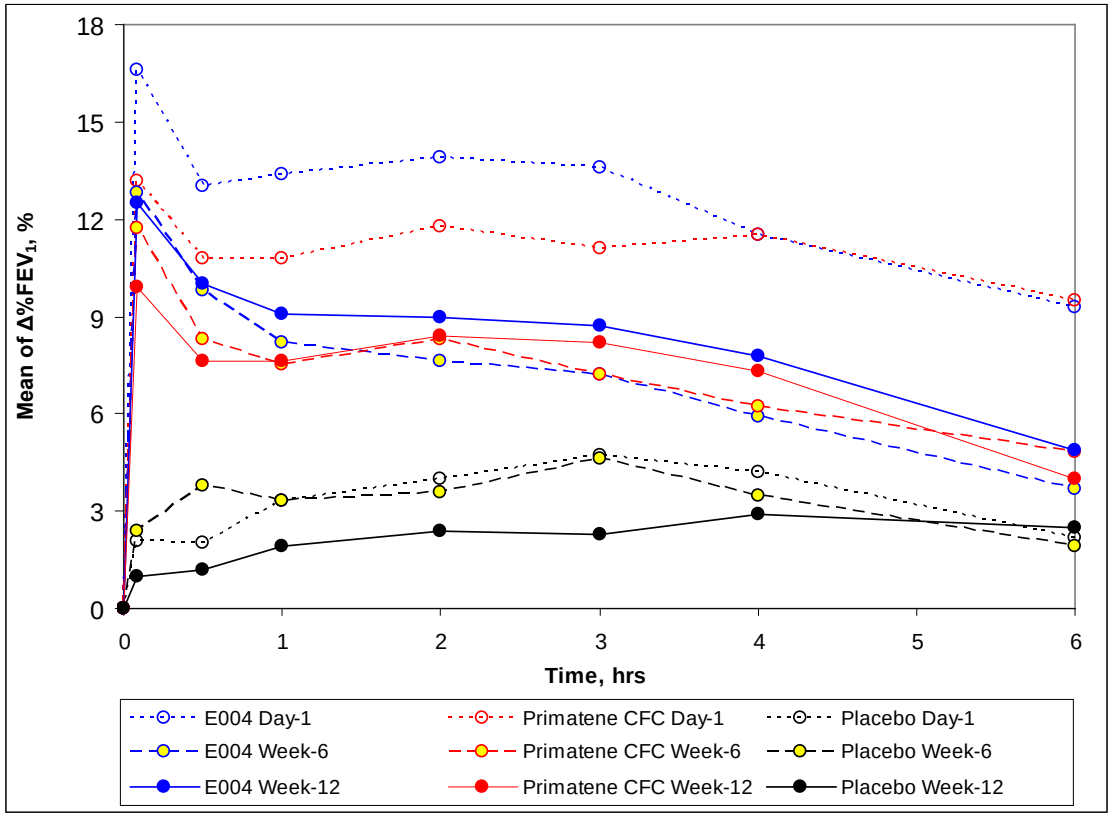
The "√" and "x" indicate "significant efficacy (p<0.05)" and "fail (p>0.05)", respectively, as far as efficacy is concerned.

The efficacy results provided in **Table 4** demonstrate the following conclusions for long-term usage (Week-12) at the maximum dose of E004 (2×125 mcg QID):

(i) <u>E004 Efficacy per the Primary Endpoint Analysis for Week-12 demonstrated the following:</u>

- E004 has significant efficacy per the primary analysis of the primary endpoint for ITT with the Closest Data Model (CDM) for missing data handling (MDH);
- E004 has significant efficacy per the primary endpoint tested (2-sided *t*-test) with all four (4) models of populations/MDH models; and
- Therefore, the conclusion of efficacy of E004 obtained in Study C per the primary endpoint is not sensitive to populations and the use of missing data handling models.

Figure 5 Efficacy Analysis of Mean Δ%FEV1 of Study C



(ii) Primatene® Mist CFC Efficacy per the Primary Endpoint Analysis for Week-12 demonstrated the following:

- Primatene® Mist CFC also has significant efficacy per the primary analysis of primary endpoint for ITT with CDM for MDH; and
- Primatene® Mist CFC has significant efficacy per the primary endpoint tested (2-sided *t*-test) with all four (4) models of populations/MDH

models.

(iii) E004 Efficacy per the Secondary Endpoint Analyses for Week-12 demonstrated:

- E004 has significant efficacy for 15 of the 16 secondary endpoints tested (2-sided *t*-test) for ITT with CDM for MDH; and
- E004 has significant efficacy for 15 of the 16 secondary endpoints tested (2-sided *t*-test) with all four (4) cases of populations/MDH models.

(iv) Primatene® Mist CFC Efficacy Per Secondary Endpoint Tests for Week-12

- Primatene® Mist CFC has significant efficacy for 12 of the 16 secondary endpoints tested (2-sided *t*-test) for ITT with CDM for MDH;
- Primatene® Mist CFC has significant efficacy for most (12, 8, 10, and 13 for the four models tested) of the 16 secondary endpoints tested (2-sided *t*-test) with all four (4) cases of populations/MDH models; and
- For 1-sided t-test, Primatene® Mist CFC has significant efficacy for most (14, 9, 10, and 13 for the four models tested) of the 16 secondary endpoints tested.

Long-term Efficacy Evaluation at Day-1, Week-6 and Week-12 of Study C

The efficacy of E004 was also evaluated throughout the entire study duration, at Day-1, Week-6 and Week-12.

Two-sided t-tests were conducted for the primary endpoint and 15 of the 16 secondary endpoints based on the FEV1 data measured at Day-1 (Visit-1), Week-6 (Visit-3), and Week-12 (Visit-5). For the secondary endpoint, responder rate (R%), a χ^2-test was conducted. The per-protocol population (PPP), i.e., the treated and qualified population for each visit was used for the above analysis. For reference purposes, the one-sided ^{t}-test was also performed for E004 versus placebo and Primatene® Mist CFC versus placebo.

The significance profile for E004 and Primatene® Mist CFC for Day-1, Week-6 and Week-12 are provided in **Table 4**, where a "√" mark is made for any efficacy item with p-value ≤ 0.05, or an "X" mark is placed with the actual p-value.

The significance profile in **Table 4** demonstrates the following observations and

conclusions:

(i) Efficacy of E004 versus Placebo:

- E004 showed significant efficacy (p-value ≤ 0.05) for bronchodilatory effect in asthma patients per the primary endpoint in all three (3) study visits, Visit 1indicating a positive response;
- At Day-1 (Visit-1), E004 showed significant efficacy for all (16/16) secondary endpoints for both 1-sided and 2-sided tests;
- At Week-6 (Visit-3), E004 showed significant efficacy for 12 of the 16 secondary endpoints for 2-sided tests. The four (4) secondary endpoints, which did not demonstrate significant efficacy for 2-sided tests were AUC of ΔFEV1 and the Δ%FEV1 for the time points at 3, 4 and 6 hours. However, for 1-sided test AUC of ΔFEV1 showed efficacy significance (p-value=0.026); and
- At Week-12 (Visit-5), E004 showed significant efficacy for 15 of the 16 secondary endpoints for both 1-sided and 2-sided tests. The one (1) secondary endpoint which did not demonstrate significant efficacy was Δ%FEV1 at 6 hours.

(ii) Efficacy of Primatene® Mist CFC versus Placebo

- Primatene® Mist CFC showed significant efficacy, (p-value ≤ 0.05) for bronchodilatory effect in asthma patients per the primary endpoint in Visit 1 (Day 1, n=61 vs. 54, p-value <0.0001), and Visit 5 (Week-12, n=53 vs. 53, p-value=0.0077) for both 1-sided and 2-sided tests;
- However, for Visit 3 (Week-6, n=57 vs. 54) Primatene® Mist CFC showed significant efficacy for the primary endpoint only for the 1-sided test (p-value=0.0358) and its p-value for the 2-sided t-test was 0.0715, which was greater than 0.05. This might have been due to a relatively smaller sample size for the Primatene® Mist CFC arm and the 2-sided test is a more conservative analysis;
- At Day-1 (Visit-1), Primatene® Mist CFC showed significant efficacy for 13 of the 16 secondary endpoints for both 1-sided and 2-sided tests. The one (1) secondary endpoint, which did not demonstrate significant efficacy was time of onset;
- At Week-6 (Visit-3), Primatene® Mist CFC showed significant efficacy for seven (7) of the 16 secondary endpoints for the 2-sided test and showed significant efficacy for nine (9) of the 16 secondary endpoints for

the 1-sided test. The secondary endpoints, which did not demonstrate significant efficacy were indicated with a marker "×" in **Table 4**; and

- At Week-12 (Visit-5), Primatene® Mist CFC showed significant efficacy for 13 of the 16 secondary endpoints. The three (3) secondary endpoint which did not demonstrate significant efficacy was Δ%FEV1 at 6 hours, $AUC_{0\text{-}6hr}$ of FEV1 and F_{max} of FEV1.

3.3.2 Discussion of Time Trend of Efficacy and Tachyphylaxis

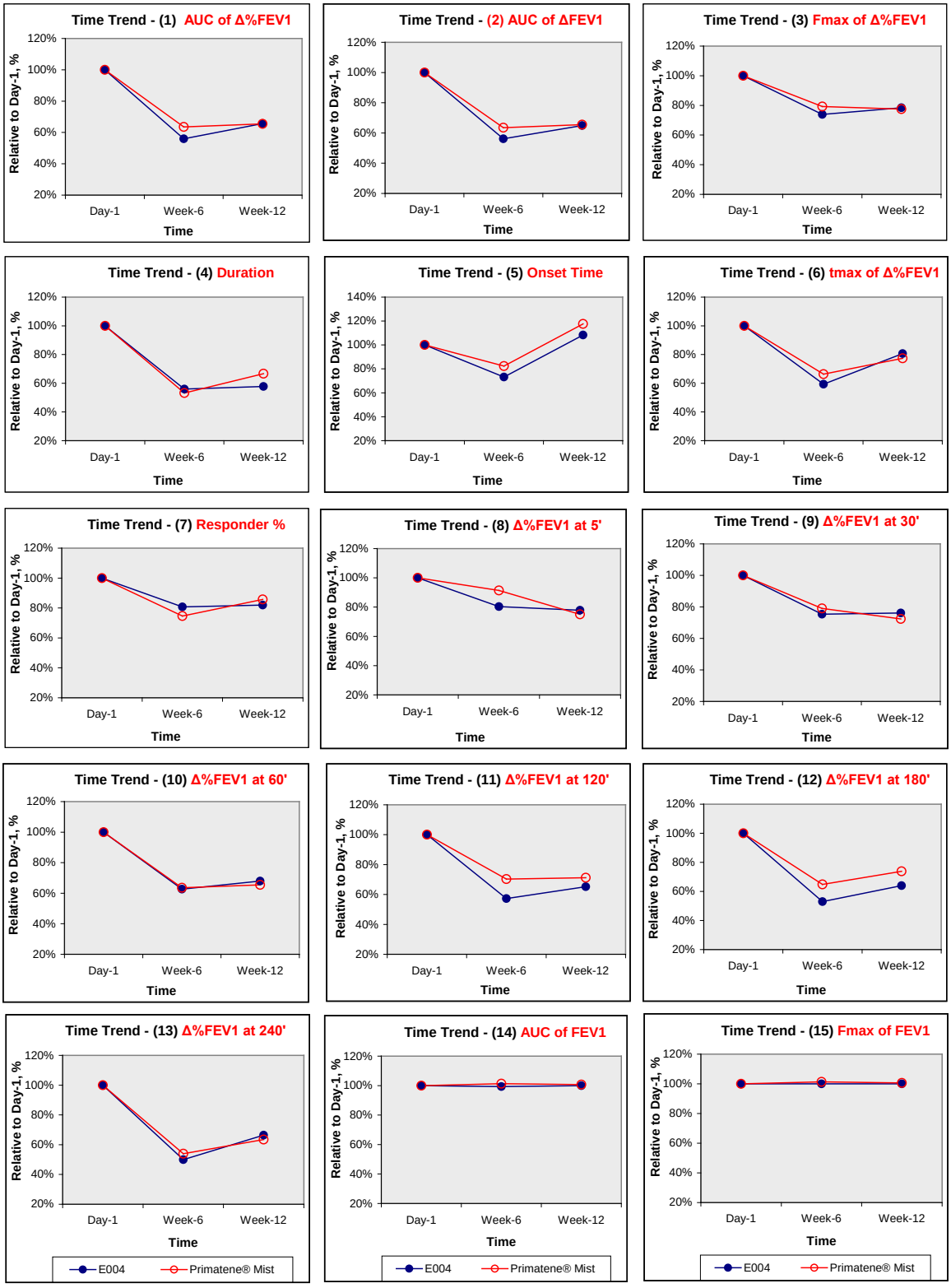
The efficacy time trend of tachyphylaxis effect for was observed in long-term Study C.

The time trend of E004 efficacy is studied as percentages relative to the corresponding efficacy data at Day-1 and demonstrated in **Figure 6** for fifteen (15) efficacy parameters, the primary endpoint and fourteen (14) secondary endpoints.

Notably, the bronchodilatory efficacy for Parameters (1) to (13) in **Figure 6** for both E004 and Primatene® Mist CFC consistently demonstrated a time trend, with the greatest efficacy observed on Day 1, along with a 20% to 40% reduction of bronchodilatory effect, but still showed a significant efficacy at Week 6. This was then maintained at about the same level or even slightly higher levels of efficacy over the next 6 week period of time until the end of the study, i.e., Week 12. This pattern is likely due to partial tachyphylaxis at the beta-2 receptor.

It is also interesting to note that the bronchodilatory efficacy for Parameters (14) and (15) in **Figure 6** for both E004 and Primatene® Mist CFC consistently demonstrated a stable time trend. Parameters (14) and (15) are AUC and F_{max} for direct FEV1. The other efficacy parameters are based on Δ%FEV1.

Figure 6 Time Trend of E004 Efficacy in 12-Week Study C



3.3.3 Inter-Trial Efficacy Comparison

The following four (4) efficacy studies were conducted at the same dose and similar conditions, i.e., single dose or initial use of 2×125 mcg, which is consistent with the proposed indication for E004, "the **temporary relief of mild symptoms** of intermittent asthma in adults and children 12 years of age and older":

- Phase I single dose crossover efficacy/safety Study A in adult asthma patients;
- Phase II single dose crossover efficacy/safety Study A2 in adult asthma patients;
- Phase III 12-week parallel Study C in adult/adolescent asthma patients at Day 1; and
- Phase III 4-week parallel Study D in pediatric asthma patients at Day 1.

Table 5 summarizes the efficacy results of the proposed E004 dose (2 × 125 mcg) and for Primatene® Mist CFC (2 × 220 mcg) for the above listed four (4) E004 clinical efficacy studies. As demonstrated in **Table 5**, based on the analysis of all efficacy parameters (primary and secondary), E004 (2×125 mcg) exhibited a comparable and/or greater bronchodilatory efficacy than the active control (Primatene® Mist CFC 2×220 mcg) although the administered doses for E004 is 43% lower than that for Primatene® Mist CFC.

The efficacy primary endpoint ($AUC_{0\text{-}6hrs}$ of Δ%FEV1) for E004, averaged from the four (4) related studies, is 79.2±9.1 %×hrs with a CV=12% (see **Table 5**), so that a consistency for E004 efficacy results is demonstrated among these four (4) trials. Meanwhile, the same efficacy primary endpoint for Primatene® Mist CFC, averaged among the related three (3) studies (**A, A2, and C**), is 62.5±13.8 %×hrs with a CV=22% (see **Table 5**), so that a consistency for efficacy results for Primatene® Mist CFC is also demonstrated among these three (3) adult/adolescent asthma patient trials.

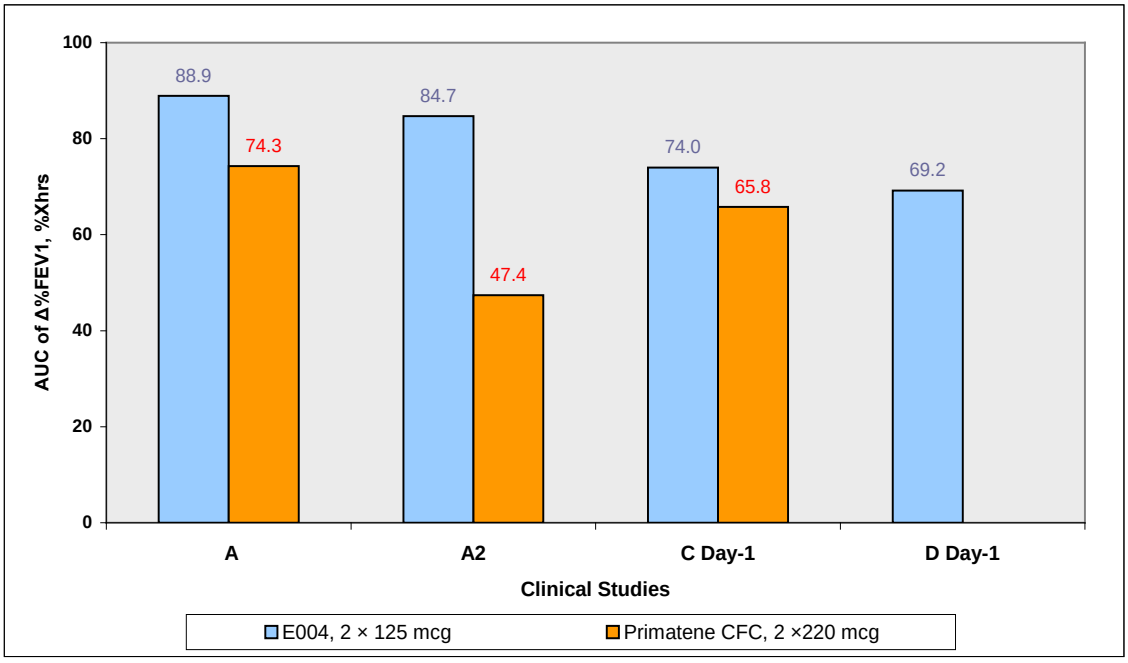
Figure 7 demonstrates the results for primary endpoints, $AUC_{0\text{-}6hrs}$ of Δ%FEV1, of E004 and Primatene® Mist CFC in all related trials.

Table 5 Inter-trial Efficacy Comparison for E004 and Primatene® Mist CFC

Studied Drugs		**E004, 2 × 125 mcg**						**Primatene® Mist, 2 ×220 mcg**					
Study Categories		Individual Studies				All 4 Efficacy Studies		**Individual Studies**			All 3 Efficacy Studies		
						Mean ± SD	CV				Mean ± SD		CV
Clinical Trials		**A**	**A2**	**C** Day-1	**D** Day-1	All		**A**	**A2**	**C** Day-1	All		
Clinical Phase		**I**	**II**	**III**	**III**	**I, II & III**		**I**	**II**	**III**	**I, II & III**		
Clinical Type		Cross-over	Cross-over	Parallel		-		Cross-over	Cross-over	Parallel	-		
# of Patients*		21	24	228	22	295		21	24	61	106		
Type of Patients		Adult	Adult	Adult	Pediatric	Adults & Pediatric		Adult	Adult	Adult	Adults		
1	AUC of Δ%FEV1, %×hr	88.9	84.7	74.0	**69.2**	**79.2** ± 9.1	12%	74.3	47.4	**65.8**	**62.5** ± 13.8		22%
2	AUC of ΔFEV1, L×hr	2.1	2.0	1.71	0.88	**1.7** ± 0.6	33%	1.7	1.2	1.48	**1.5** ± 0.3		17%
3	Fmax of Δ%FEV1, %	24	21	19.9	20.7	**21.3** ± 1.7	8%	20.4	17	17.8	**18.2** ± 2.0		11%
4	Duration, hrs	3.2	3.6	2.84	2.98	**3.2** ± 0.3	10%	3.2	2.1	2.52	**2.6** ± 0.6		22%
5	Time of onset, min	2.6	4.9	17	14.2	**9.6** ± 6.9	72%	22.4	3.1	34	**19.8** ± 15.6		79%
6	tmax, hr	1.1	1.7	1.5	1.84	**1.5** ± 0.3	22%	1.52	1.2	1.8	**1.5** ± 0.3		22%
7	Responder, %	81.0	70.8	72.3	68.2	**73.1** ± 5.5	8%	81.0	71	70.5	**74.1** ± 6.0		8%

* For Phase I/II all results are for "crossover population"; for Phase III, all results are for "per protocol population"

Figure 7 E004 Inter-trial Efficacy Comparison - Primary Endpoint, $AUC_{0\text{-}6\ hr}$ of Δ%FEV1



4. SAFETY

4.1 E004 SAFETY EVALUATION

E004 safety evaluations in adult/adolescent asthma patients included the following:

- Five (5) Phase I & II clinical studies of E004 consisting of single normal dose studies A and A2, and single high dose Studies B, B2 and B3; and

- Two (2) Phase III long-term clinical studies, (i) **Study C**: a 12-week (2×125 mcg, QID) study for adult/adolescent asthma patients; and (ii) **Study C2**: a 3-month extension of Study C as a parallel safety evaluation (2×125 mcg, QID) in adult/adolescent asthma patients

A 4-week long-term parallel efficacy and safety study (Study D) evaluating E004 (2×125 mcg, QID) and Placebo, in 4 – 11 year old pediatric patients with asthma was also conducted (for information only).

In the E004 safety studies, the following data was collected, documented and evaluated for all treatment groups: (i) drug exposure; (ii) adverse drug event (ADE) monitoring; (iii) safety parameters, including vital signs with systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), and 12-lead ECG; (iv) serum glucose and potassium, and clinical lab tests for CBC, blood chemistry panel and urinalysis; and (v) albuterol rescue medication usage and concomitant medications.

All ADEs for all subjects at all visits were recorded and assessed, as appropriate.

4.2 SAFETY EVALUATION RESULTS

4.2.1 E004 Drug Exposure

Drug Exposure for Long-term Adult/Adolescent Study C (12-week)

The average duration of drug exposure for subjects in the arms E004, placebo, and Primatene® Mist CFC were 79, 80 and 80 days (see **Figure 8**), respectively. The average total exposures for subjects in the arms E004, placebo, and Primatene® Mist

CFC were 557, 564 and 573 inhalations per patient (see **Figure 8**), respectively, during the 12 week study period.

Drug Exposure for Long-term Adult/Adolescent Study C2 (Up to 6 months)

The patients in the E004, Placebo, and Primatene® Mist CFC arms were treated for, on average, 97, 100 and 40 days (see **Table 6**), respectively. That the Primatene® Mist CFC arm was only treated for 40 days was due to the fact that the commercial distribution of Primatene® Mist CFC was subject to mandatory sunset as of December 31, 2011. The subjects in the Primatene® Mist CFC arm in Study C2 were subsequently withdrawn (Early Terminated) from the Study C2 at the subsequent visit after 12/31/2011.

The average total drug exposure for the E004, placebo, and Primatene® Mist CFC arms in Study C2 were 756, 770 and 299 inhalations per patient (see **Table 6**), respectively, during the additional three (3) month study period.

Study C2 is a continuation of Study C. Each subject in Study C2 was also a subject who had completed the 12-week Study C and remained in the same treatment arm for Study C2. Therefore, the accumulated drug exposure for patients of Study C2 was the total drug exposure received during both Study C and Study C2.

Table 6 Drug Exposure for Study C2

Arms & Studied Drugs	Arm-T: E004			Arm-P: Placebo			Arm-A: Primatene		
Description	Protocol Design	Study C2*	C + C2	Protocol Design	Study C2*	C + C2	Protocol Design	Study C2*	C + C2
# of Subjects, Treated	120	**134**		30	**38**		30	**35**	
# inhalations per Dosing	2	**2.0**		2	**2.0**		2	**1.9**	
Daily Drug Exposure									
# of dosing/day	4	**3.9**		4	**3.9**		4	**3.7**	
# of inhalations /day	8	**7.8**		8	**7.7**		8	**7.5**	
mg/day	1.00	**0.97**		0	**0.0**		1.76	**1.6**	
# of Days of Treatment, Days	98	**97**	**176**	98	**100**	**180**	98	**40**	**120**
Total Amount of Drug Exposure									
# of Inhalations/Subject	784	**756**	**1314**	784	**770**	**1334**	784	**299**	**872**
mg/Subject	98	**94**	**164**	0	**0.0**		172	**66**	**192**

* For more details see Table 5.3.5.1.4-9-2310, 2311

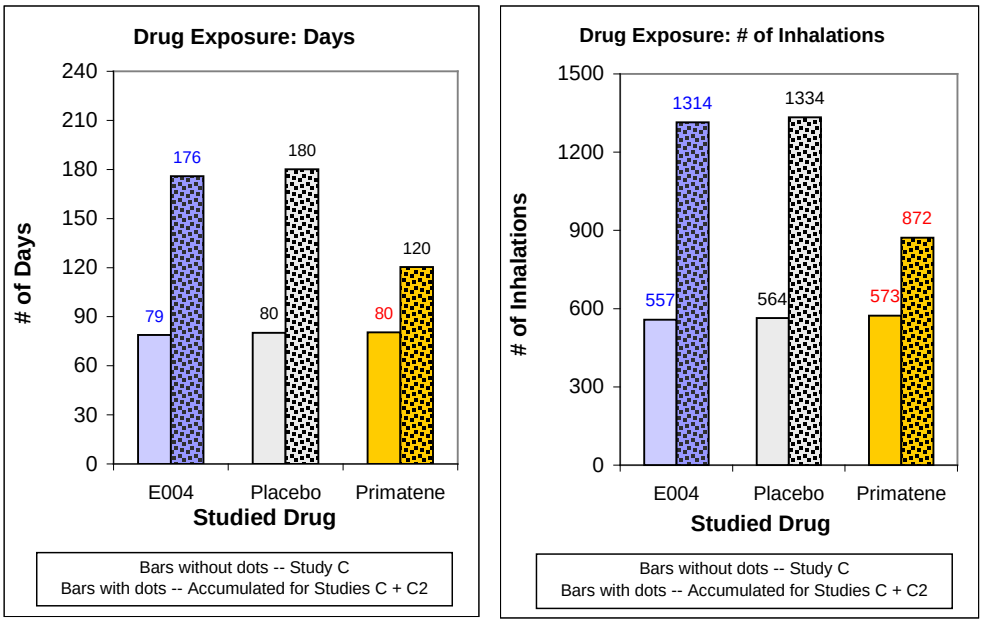
,

The subjects in the E004, Placebo, and Primatene® Mist CFC arms for Study C2 were treated, as an accumulation of both Studies C and C2, 176, 180 and 120 days,

respectively (**Figure 8**). Thus, Study C2 has provided safety information for six (6) months for E004.

The total drug exposure for the E004, Placebo, and Primatene® Mist CFC arms for Study C2 were, as an accumulation of both Studies C and C2, 1314, 1334, and 872 inhalations, respectively (**Figure 8**).

Figure 8 Drug Exposure for E004 Long-term (6-month) Studies C+C2



4.2.2 E004 ADE Evaluation

Global Profile of ADEs Observed in E004 Trials

In the eight (8) E004 clinical trials, there were, in total, 581 ADE incidences reported from 569 subjects. Among these 581 ADE incidences, 422, 83 and 76 were received from subjects who were treated with E004, Placebo and Primatene® Mist CFC, respectively.

Table 7 summarizes the global profile, including numbers of all ADEs received, numbers of ADEs possibly related to the studied drugs in the eight (8) E004 trials, in each of the three (3) studied arms (T – E004, P –Placebo, and A- active control Primatene® Mist CFC). Among these 581 ADE incidences, 202 were classified as the ADE incidences possibly related to the studied drugs.

Table 7 Global Profile of ADE Incidences Received in E004 Trials

Study Categories	Study Phase	Study Code	# of Subjects *				# of All ADE Received *, ††					# of ADE, Possibly Related to Drugs††			
			T	P	A	All	T	P	A	T+P+A	Before Treatment **	T*	P*	A*	T+P+A
Single Normal Dose	I/II	A	26	24	25	26	10	0	1	**11**	0	7	0	1	**8**
		A2	29	30	30	30	38	6	16	**60**	3	29	3	12	**44**
		Subtotal	*55*	*54*	*55*	*56*	*48*	*6*	*17*	***71***	*3*	*36*	*3*	*13*	***52***
Single High Dose	I/II	B	24	-	22	24	3	-	3	**6**	0	0	-	3	**3**
		B2	23	-	23	23	1	-	2	**3**	0	1	-	1	**2**
		B3	23	-	22	23	4	-	2	**6**	0	0	-	0	**0**
		Subtotal	*70*	*0*	*67*	*70*	*8*	*0*	*7*	***15***	*0*	*1*	*0*	*4*	***5***
Long-Term	III	C	248	61	64	373	204	35	32	**271**	12	89	5	12	**106**
		C2	134	38	35	207	148	28	20	**196**	16	34	0	3	**37**
		D	35	35	-	70	14	14	-	**28**	3	2	0	-	**2**
		Subtotal †	*283*	*96*	*64*	*443*	*366*	*77*	*52*	***495***	*31*	*125*	*5*	*15*	***145***
Total †			**408**	**150**	**186**	**569**	**422**	**83**	**76**	**581**	34	**162**	**8**	**32**	**202**

* T -- Arm-T, E004; P -- Arm-P, Placebo; A -- Arm-A, Primatene Mist.

** -- These ADEs were received before any treatment, and were tabulated in 5.3.5.1.X-9-2520a, 3511-3513 (X=1 to 5 for Studies A, A2, C, C2 and D, respectively) and 5.3.3.1.Y-9-2520a and 3511-3513 (Y=1 to 3, for Studies B, B2 and B3, respectively), and not included in these analysis.

† The number of subjects for Study C2 is not included in the total number since these patients are from Study C.

†† References: 5.3.5.1.X-9-2511 (X=1~5 for Studies A, A2, C, C2 & D); 5.3.3.1.Y-9-2511 (Y=1~3 for Studies B, B2 & B3).

ADE Incidences that Occurred in Long-term Adult/Adolescent Study C

A total of 271 ADE incidences for Study C occurred after the randomized treatments were given, which included: 204, 35, and 32 ADEs, respectively, reported from the E004 (Arm T), Placebo (Arm P), and Primatene® Mist CFC (Arm A). For all 271 ADE incidences that occurred in Study C, 15 were classified as "severe" ADEs by the investigators at study sites; only one (1) was classified as a "serious" ADE, which was in the Primatene® Mist CFC arm; no ADE incidence had "death" or "resolved with residual effects" outcome; the body systems, most frequently associated with the ADE incidences for the E004 arm, were the respiratory system (23%), the nervous system (17%) and the digestive system (15%).

Among the 271 ADE incidences that occurred in Study C, in total, 106 ADE incidences were classified as incidences possibly related to the studied drugs by the investigators at the clinical sites, which include (i) 89 from the E004 arm (Arm T); (ii) 5 from HFA placebo arm (Arm P); and (iii) 12 from Primatene® Mist CFC (Arm A).

Among these 106 ADE incidences possibly related to studied drugs in Study C, five (5) were classified as severe ADEs (4 for the E004 arm and 1 for the Primatene® Mist CFC arm); only one (1) was classified as a "serious" ADE by the site investigators, which occurred in the Primatene® Mist CFC arm; no ADE resulted in "death" or "resolved with residual effects" outcome; the body system, most frequently reported with these ADEs in Study C, was the nervous system (13%) for the E004 arm.

All 271 ADE incidences that occurred in Study C, were classified into ten (10) body systems and 114 symptoms, each of which was identified by the Medical Dictionary for Regulatory Activities code (MedDRA). The ADE incidences with the same MedDRA code are summarized together.

The ADE symptom with the highest incidence rate (IR) for all ADEs that occurred in Study C were;

- for the E004 arm (n=248), it was Tremor with an IR of 7.7%;
- for the Placebo arm (n=61), it was Asthma with an IR of 9.8%; and
- for the Primatene® Mist CFC arm (n=64) was also Asthma with an IR of 6.3%.

ADE Incidences that Occurred in Long-term Adult/Adolescent Study C2

In Study C2, a total of 196 post dose ADE incidences were reported. Among the 196 ADE incidences for Study C2, 148, 28 and 20 occurred in the E004, Placebo and Primatene® Mist CFC arms, respectively.

The incidence rates (IR) for all reported ADE incidences in Study C2 are 110%, 74%, and 57%, respectively for E004 (Arm T), Placebo (Arm P), and Primatene® Mist CFC (Arm A). The ADE incidence rate for Primatene® Mist CFC is lower, which might have been partially due to its reduced treatment time (40 days) which was significantly shorter than that for E004 (97 days) and Placebo (100 days).

For all 196 ADE incidences in Study C2: eight (8) ADE incidences were classified as "severe" ADEs by the investigators at the study sites, and 7, 1, and 0, respectively, were

from E004 (Arm-T), Placebo (Arm-P), and Primatene® Mist CFC (Arm-A); two (2) ADE incidences were identified as "serious" ADEs, which were from the E004 arm; no ADE has "death" or "resolved with residual effects" outcome; and the body systems, most frequently associated with the ADE incidences in Study C2, were the respiratory system (57%) and the digestive system (21%) for the E004 arm.

Among the 196 ADE incidences in Study C2, 37 incidences were classified as possibly related to the studied drugs by the site investigators. Among these 37 ADE incidences, 34, 0 and 3 were from Arms E004, Placebo and Primatene® Mist CFC, respectively.

The incidence rates (IR) for the ADEs possibly related to the studied drugs in Study C2 were 25%, 0%, and 9%, respectively for E004 (Arm T), Placebo (Arm P), and Primatene® Mist CFC (Arm A).

Among these 37 ADEs possibly related to the studied drugs in Study C2, none of them were classified as a "severe" ADE; none of them were classified as a "serious" ADE; none of them were classified as "resolved with residual effect"; and the body systems most frequently associated with ADEs possibly related to studied drugs in Study C2 were the digestive system (10%), the respiratory system (5%) and the nervous system (5%) for the E004 arm.

The 196 ADE incidences that occurred in Study C2 were classified into 10 body systems and 81 symptoms.

The ADE with the highest IR in Study C2 was "Nasopharyngitis": 11.2%, **15.8%,** and 2.9% for E004, Placebo and Primatene® Mist CFC arms, respectively. The placebo arm had the highest incidence rate (16%) for ADE "Nasopharyngitis". These results might have been related to the fact that the weather for most of the time during the additional three (3) months of Study C2 was during the cold season (November 2011 to February 2012). On the other hand, the Primatene® Mist CFC arm stopped on 12/31/2011 so that its treatment time was only 40 days, which was less than other arms (97 -100 days).

The ADE with the second highest IR in Study C2 was "Upper Respiratory Tract Infection": 8.2%, 13.2%, and 8.6% for E004, Placebo and Primatene® Mist CFC arms, respectively. These results might also have been related to the fact that most of the time during the 3-month Study C2 was during the cold season, November 2011 to February 2012.

The ADE "Tremor" (with IR 3.7% versus 0.0% for other arms) in Study C2 also occurred. It is consistent with the observation in Study C where E004 had a higher ADE IR for "Tremor" (7.7%).

4.2.3 Major ADE Incidences that Occurred in Long-term Phase III Studies

The category of "major ADEs" observed in the E004 long-term clinical studies were defined as meeting all of the following 3 criteria: [12] (i) "*all ADEs (whether considered by the investigator as drug related or unrelated to drug)*" (ii) "*occurred at an incidence rate of at least 3.0%*" in the E004 group, and (iii) *occurred "more frequently" in the E004 group "than in the HFA-134a placebo inhaler group"*. Based on the definition of the major ADE above, the major ADEs for E004 observed in the long-term safety studies in E004 Phase III, including Studies C and C2, are listed in **Table 8** below.

Table 8 Major ADEs Observed For E004 in Long-Term Studies (up to 6 Months)

#	Type of ADEs	All ADEs Reported			All Severe ADEs Reported			All Serious ADEs Reported		
	Studied Products	E004 n = 248	Placebo n = 61	Primatene n = 64	E004 n = 248	Placebo n = 61	Primatene n = 64	E004 n = 248	Placebo n = 61	Primatene n = 64
1	Tremor	9.7%	1.6%	1.6%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
2	Throat Irritation	5.2%	0.0%	1.6%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
3	Cough	4.4%	0.0%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
4	Chest Discomfort	3.6%	1.6%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
5	Feeling Jittery	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

The information in the above table indicates that the four (4) major ADE symptoms for E004 were: Tremor (9.7%), Throat Irritation (5.2%), Cough (4.4%), and Chest Discomfort (3.6%). The ADE "Tremor" was observed in both long-term clinical studies, Study C (7.7%) and C2 (3.7%).

It is notable that ADE incidence rates (IR) resulting from Phase III global analysis is always greater than the IR of any individual Phase III studies such as Study C. For example, IRs for Tremor are 7.7% and 3.7% in Studies C and C2, respectively. However, the IR for Tremor in Phase III analysis is 9.7%. This is due to the fact that Study C2 is a continuation of Study C and the subject population of Study C2 was not added again as part of the total population for Phase III analysis. Therefore, for numbers of ADE

incidences (numerator of IRs):

$$ADE_{Phase\ III} = ADE_{Study\ C} + ADE_{Study\ C2}$$

However, for number of subjects (denominator of IRs):

$$Population_{Phase\ III} = Population_{Study\ C}$$

This means the numerator (number of Tremor incidence) of IR is from 2 studies, but the denominator (number of treated patients) of IR is from 1 study, so that the IR for E004 Phase III analysis becomes larger than the IR for individual studies.

It is also notable that "7.7% of Tremor ADE in Study C" and "9.7% of Tremor ADE in E004 Phase III" have different meanings: the former (Study C) represents the safety profile for tremor in 3 months (12 weeks, 79 days); and the latter (Study C + Study C2) represents the safety profile for tremor in 6 months (176 days).

4.2.4 Severe ADEs that Occurred in E004 Phase III Studies

A total of 28 severe ADEs were reported during Phase I, II, and III studies. Among these 28 severe ADE incidences that occurred in the E004 clinical studies, five (5) were classified as possibly related to the studied drugs. Among these 5 ADE incidences, 4 (1.4%), 0 (0%), and 1 (1.6%) were from the E004, Placebo and Primatene® Mist CFC arms, respectively. All reported severe ADEs were resolved within 1 day without any residual effects.

4.2.5 Serious ADEs that Occurred in E004 Phase III Studies

A total of three (3) serious ADEs were reported through all E004 clinical studies. Two (2) were from E004 arms and one (1) was from Primatene® Mist CFC arm. For the two (2) in the E004 arm, breast cancer and pregnancy, both were considered "definitely not related" to the treatment by the investigators.

4.2.6 Inter-Trial Comparison of Tremor ADE Incidence Rate

The ADE Tremor/Shaky is the major ADE with the highest incidence rate for E004 observed in Phase III clinical studies. It is worthwhile to compare its rates among trials

conducted for this report with a related product (Albuterol HFA). **Table 9** lists related results for the ADE "Tremor". **Figure 9** demonstrates a comparison among these studies.

Table 9 Inter-trial Incidence Rates for ADE Tremor/Shaky

Clinical Studies	E004, Study C Epinephrine HFA **12 Weeks** Adolescent & Adults, n=248	E004, Study C2 Epinephrine HFA **Month-4 to Month-6** Adolescent & Adults, n=134	E004, Study D Epinephrine HFA **4 Weeks** Pediatrics, n=35	Proventil Albuterol HFA **12 Weeks** Adults, n=193 *
Incidence% of ADE Tremor/Shaky	**7.7**	**3.7**	**5.7**	**7**

* Data is cited from Proventil insert [14].

Figure 9 Inter-trial Incidence Rates for ADE Tremor

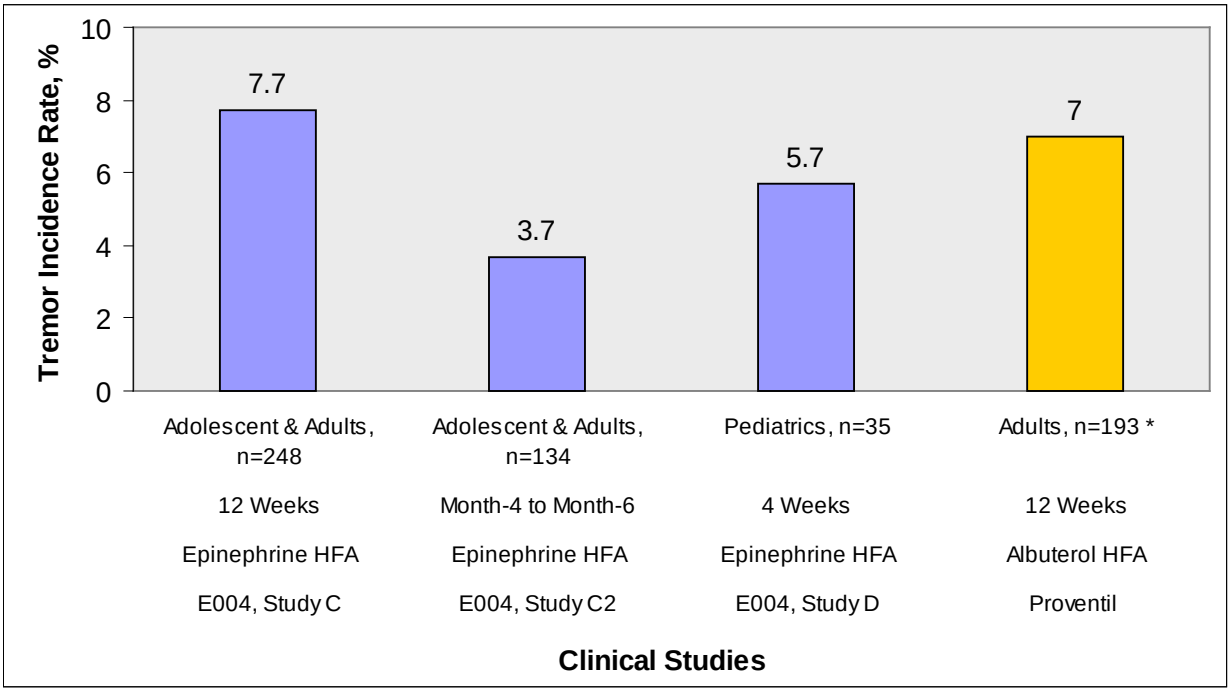


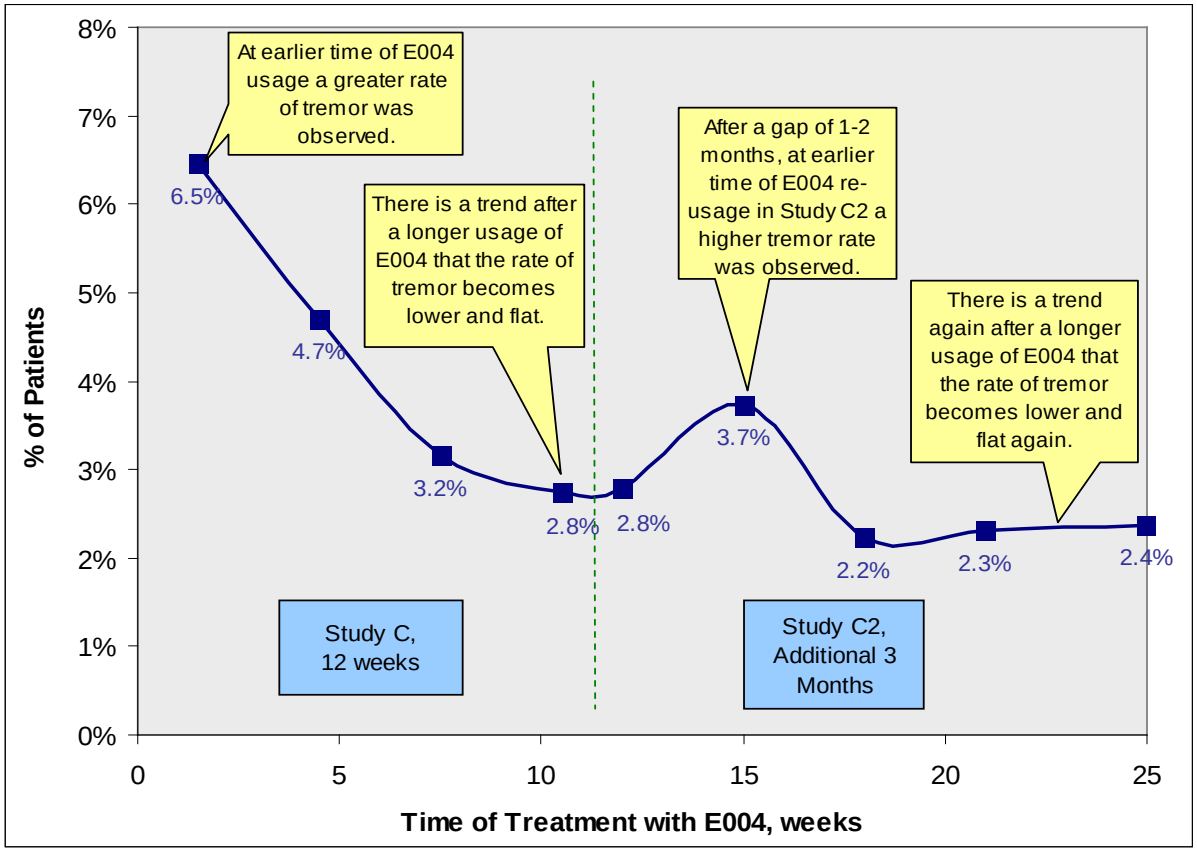
Figure 9 demonstrates that the incidence rates for ADE Tremor among E004 long-term trials (C and C2) are consistent. That Study C2 has a lower incidence rate for Tremor may reflect the time trend of ADE Tremor. Tachyphylaxis might develop for the tremorigenic side effects of beta-agonists over time.

Moreover, it is noteworthy that E004 has a similar incidence rate of ADE Tremor (7.7%) for the 12-week study with 248 patients compared to that of an albuterol HFA (Proventil®

HFA) study, which is reported as 7% through a long-term 12-week safety trial with 193 subjects.

The time trend of tremor ADEs, occurred in Studies C & C2 is illustrated in **Figure 10** below. The tremor ADE rate was reduced from the initial higher rate of 6.5% and finally became stable at the level of 2.2% to 2.4%. Again, the tremorigenic side effects of beta-agonists showed time trend of tachyphylaxis.

Figure 10 Time Trend of Tremor ADEs for E004 Long-term Use



4.2.7 Inter-Trial Comparison of ADE Incident Rate of HR Increase and Tachycardia

Rapid or increased heart rate is one (1) of the eight (8) expected ADE items listed in the label [1] for Primatene® Mist CFC. The ADE for heart rate (HR) increase or tachycardia potentially caused by epinephrine inhalation received specific attention as noted in *The*

Tan Sheet [16]. It is worthwhile to evaluate the ADEs for HR increase or tachycardia, although the IR for these two ADEs was very low in E004 clinical studies,

- One (1) ADE of Tachycardia was reported in Study C with IR of 0.4% (there were 18 HR data for this Subject, the highest HR after dosing is 70 bpm) and
- One (1) ADE of Heart Rate Increase was reported in Study C2 with IR of 0.7% (there were also 18 HR data for this subject, the largest ΔHR is 12 bpm, 6 hours after dosing.).

Table 10 lists related results for ADE IRs for Tachycardia or HR Increase that occurred in Studies C (12 weeks for adult/adolescent), C2 (additional 3 months for adult/adolescent) and D (4 weeks for pediatric) and a trial for a reference drug, Albuterol HFA (Proventil® HFA, 12 weeks for adults).

Table 10 Inter-trial Incidence Rates for ADE Tachycardia/HR Increase

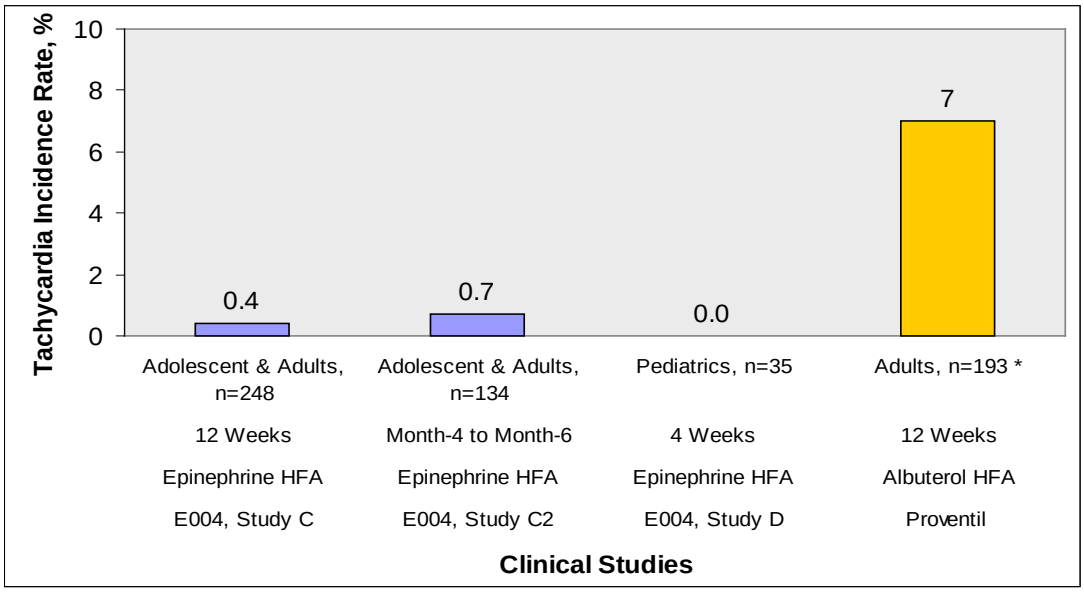
Clinical Studies	E004, Study C	E004, Study C2	E004, Study D	Proventil
Drug Substance	Epinephrine HFA	Epinephrine HFA	Epinephrine HFA	Albuterol HFA
Study Duration	12 Weeks	Month-4 to Month-6	4 Weeks	12 Weeks
Subject	Adolescent & Adults, n=248	Adolescent & Adults, n=134	Pediatrics, n=35	Adults, n=193 *
Incidence% of ADE Tachycardia or HR Increase	0.4	0.7	0.0	7

* Data is cited from Proventil insert [14].

Figure 11 demonstrates a comparison among these studies for IRs of the ADE Tachycardia/HR increase. **Figure 11** demonstrates that the IRs for ADE Tachycardia/HR Increase among E004 trials are consistent: they are very low in the range of 0.0% to 0.7%.

It is noteworthy that E004 demonstrates a lower incident rate of the ADE Tachycardia or HR Increase compared to that of Albuterol HFA (Proventil® HFA), which is reported as 7% through a long-term 12-week safety trial with 193 patients, which is very similar to Study C in terms of study duration (both are 12 weeks) and sample size (197 for Proventil® HFA and 248 for E004).

Figure 11 Inter-trial Comparison of IR for Tachycardia/HR Increase



4.2.8 Vital Signs and ECG Evaluation for E004

Statistical Analysis for Vital Signs and ECG Data Measured in Study C

In Study C, there are more than 35,000 data points for vital signs and ECG, which include more than 18,000 vital sign data points, and more than 17,000 ECG data points. The statistical analysis for vital sign and ECG observed in Study C indicates:

- the upper limit of the one-sided 95% confidence interval (CI) for ΔSBP relative to the same day baseline was 1.6, 2.6 and 4.5 mm Hg, respectively, for E004 (250 mcg QID), Placebo (QID) and Primatene® Mist CFC (440 mcg, QID), observed at 10' post-dosing in Study C;

- the upper limit of the one-sided 95% CI for ΔDBP relative to the same day baseline was 2.1, 1.7 and 1.4 mm Hg, respectively, for these three (3) arms observed at 10' post-dosing in Study C;

- the upper limit of the one-sided 95% confidence interval (CI) for ΔHR relative to the same day baseline (measured in vital sign) was 1.6, 1.4 and 1.5 bpm, respectively, for these 3 arms, observed at 2' post-dosing in Study C;

- the upper limit of the one-sided 95% CI for ΔHR relative to the same day baseline (measured in ECG) was 3.4, 1.4 and 2.2 bpm, respectively, for the three (3) arms observed, and also at 2' post-dosing in Study C;

- the upper limit of the one-sided 95% confidence interval (CI) for ΔQT relative to the same day baseline was 5.4, 11.3 and 9.2 ms, respectively, for E004, Placebo and Primatene® Mist CFC (440 mcg, QID), observed at 60' post-dosing in Study C;

- the upper limit of the one-sided 95% CI for ΔQTc relative to the same day baseline is 4.0 ms (at 10'), 4.2 ms (at 10') and 4.4 ms (at 20'), respectively, for E004, Placebo, and Primatene® Mist CFC. These results for the upper limit of the 95% confidence interval (CI) for ΔQTc, obtained in the long-term safety Study C, meet the FDA guidance regarding evaluation of QT/QTc [17]: " … *the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 ms."*;

- the upper limit of the one-sided 95% confidence interval (CI) for ΔQTc-B relative to the same day baseline (measured in vital sign) was 5.0, 5.3 and 3.3 ms, respectively, for E004, Placebo and Primatene® Mist CFC, observed at 10' post-dose in Study C; and

- the profile for ΔQTc-F is similar to the ΔQTc-B.

Therefore, based on the long-term use of E004 for adult/adolescent subjects at maximum label dose in Study C, statistically or on average, the impact of E004 on SBP, DBP, HR, QT, QTc, QTc-B, and QTc-F is very minimal, and is very similar to that of Placebo or Primatene® Mist CFC.

Individual Analysis for Vital Sign Data Measured in Study C

Individual data analysis for vital signs and ECG E004 showed that E004 had a slightly higher occurrence of >20 bpm ΔHR than Primatene® Mist CFC. The potential for clinically significant change by E004 is considered to be minimal. This is also supported

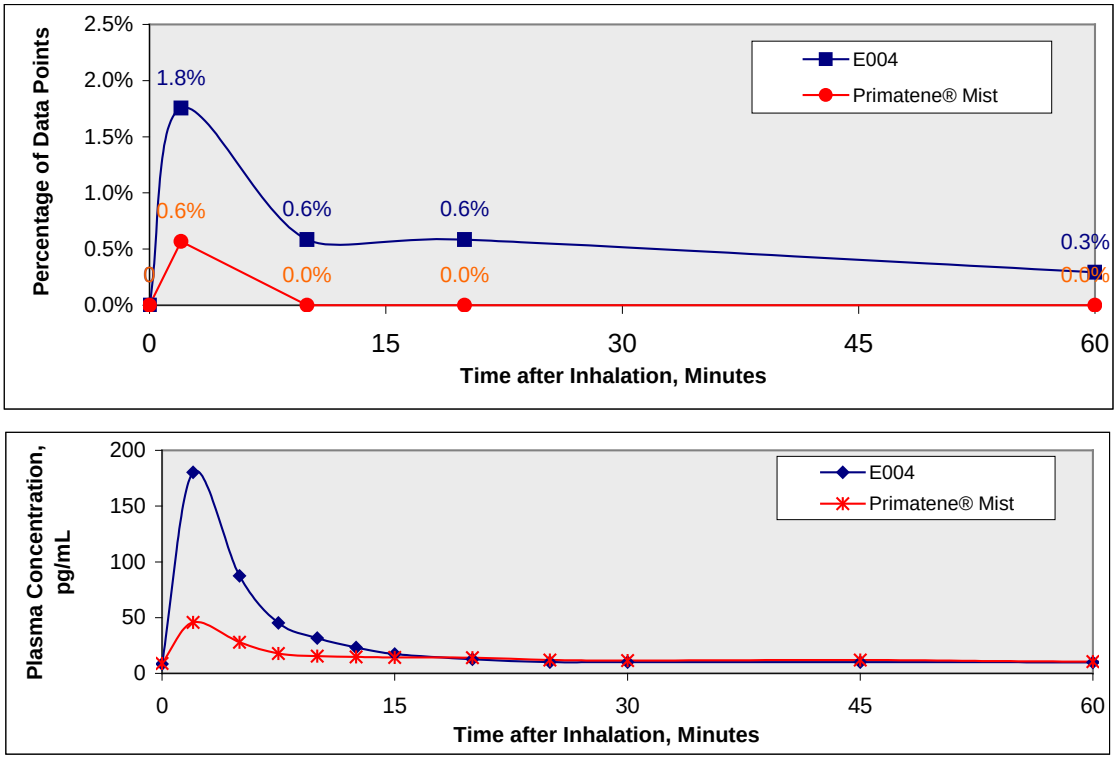
by the ADE profile of Study C: the IR of ADE Tachycardia is 0.4%, the IR of ADE HR Increase is 0.0%.

Figure 12 demonstrates that most of the incidences for ΔHR >20 bpm occurred at two (2) minutes post-dose (about the tmax of epinephrine blood concentration) for both the E004 and Primatene® Mist CFC arms with incident rates of 1.8% and 0.6%, respectively. Both time curves declined sharply afterward and by 10 minutes post-dose, the incident rate became comparable for E004 and Primatene® Mist CFC to a lower level.

This finding was in accord with the PK curves observed for E004 and Primatene® Mist CFC with a higher peak plasma concentration for E004 occurring at 2 minutes post-dose and lowered to comparable levels for both arms quickly.

Therefore, although E004 showed a slightly higher occurrence of >20 bpm ΔHR than Primatene® Mist CFC, the potential for clinically significant change by E004 is considered to be minimal. This is also supported by the ADE profile of Study C: the incident rate of tachycardia is 0.4%, as reported previously.

Figure 12 Relative # of Occurrences of ΔHR > 20 bpm in Study C



Individual Analysis for PVC in ECG Data Measured in Study C

In total, 13 PVC incidences were observed from 6 subjects during treatments in Study C. Among these 13 PVC incidences, 11, 1 and 1, respectively, were from the E004, Placebo and Primatene® Mist CFC arms. For the 11 PVC incidences for the E004 arm in Study C, four (4) were from the ECG reports taken at baseline, before the study drug treatment. (see **Table 11**)

The post-dosing IR for PVC in Study C were 0.4%, 0.2% and 0.2%, respectively, for the E004, Placebo and Primatene® Mist CFC arms in Study C. E004 has a slightly higher incident rate for PVC in Study C. However, the patient rate (PR) or patient percentages for those subjects who had PVC incidence are similar for the 3 products, E004 (1.4%), Placebo (1.0%) and Primatene® Mist CFC (1.6%).

Table 11 PVC Incidences of ECG Data for Study C

Time Points	# of ECG Data Sets			# of PVC Incidence				PVC Incidence Rate, %		
	T	P	A	T	P	A	All	T	P	A
Baseline	458	115	117	4	0	0	4	0.9%	0.0%	0.0%
2 min	462	117	119	1	0	0	1	0.2%	0.0%	0.0%
10 min	462	116	118	2	1	0	3	0.4%	0.9%	0.0%
20 min	463	117	118	1	0	0	1	0.2%	0.0%	0.0%
60 min	463	116	119	3	0	1	4	0.6%	0.0%	0.8%
Post-dosing (2, 10, 20 & 60')	1850	466	474	7	1	1	9	0.4%	0.2%	0.2%
Total	2308	581	591	11	1	1	13	0.5%	0.2%	0.2%

Reference: 5.3.5.1.3-9-2426

The 11 PVC incidences for the E004 arm in Study C were observed in ECG records from four (4) subjects:

- Seven (7) PVC incidences were from the same ONE subject, including two (2) PVC from ECG baseline, before E004 dosing; and
- Among other four (4) PVC incidences, two (2) were from ECG baseline.

5. THE OTC DEVELOPMENT PROGRAM

5.1 OVERVIEW OF OTC DEVELOPMENT PROGRAM

E004 was developed as a replacement of OTC Primatene® Mist CFC. One of the aims for the program for E004 was to develop a label that consumers could understand, such that the label could guide consumers' appropriate use of the medication without the intervention of a physician.

The proposed OTC label for E004 was based on the label for Primatene® Mist CFC, and the most up-to-date FDA Guidance, as well as formulation and dosage strength change information.

The proposed OTC labeling for E004 consists of two parts: the Drug Facts Label (DFL) and a Consumer Information Leaflet (insert). The DFL, which is mandated for all OTC medications, appears on the outer carton and on the immediate container of the product (i.e., the aluminum canister). It communicates the indication, directions for use, and warnings. Its format is highly standardized and regulated under 21C.F.R. 201.66. The insert contains supplementary information primarily focused on use and maintenance of the MDI inhalation unit, including its dose indicator. The insert is provided inside the proposed OTC unit package.

Prior to NDA submission, FDA has instructed that Armstrong evaluate only the unique aspects of the E004 label, compared to the Primatene® Mist CFC label. FDA requested a label comprehension study and a human factors (behavioral demonstration) study to assess consumers' performance. Self-selection and actual consumer use studies were deemed not necessary given the experience with previous Primatene® Mist CFC product and label as well as the existence of the FDA guidance.

For the Label Comprehension Studies (LCS), three (3) LCS were conducted to assess consumer understanding of the proposed insert for E004. In total, over 1,300 consumers participated in the label comprehension testing program.

LCS' of E004 labeling were conducted in a general population sample recruited from 23 study sites across the US. The studies used an iterative process.

An E004 Human Factors (Behavioral Demonstration) Study was also conducted. This entailed an observational human factors study of consumers' ability to carry out tasks related to use and maintenance of the MDI inhaler: (i) prime/reprime 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.

5.2 FINDINGS IN LABELING COMPREHENSION STUDIES

5.2.1 Summary of Findings

- The label comprehension studies of the E004 insert separately enrolled participants in two phases of study. The first phase led to modifications in the insert that were re-evaluated in Phase 2. Success in testing the primary communication objectives was pre-specified as a lower 95% CI of at least 85% comprehension.

- The primary communication objectives for the E004 insert were defined as understanding the instructions regarding the dose indicator of E004, as these instructions were associated with a greater likelihood of misunderstanding due to its uniqueness in OTC labeling and which were related to the possibility of consumers undercounting the number of doses used. There would be a potential safety risk in the event that the amount of medicine remaining in the inhaler is overestimated. In the study sample of 442 subjects, 92% (95%CI 89 – 94%) of subjects understood the communication regarding how to read the dose indicator, meeting the pre-specified definition for success.

- All secondary communication objectives for the insert were successfully communicated.

5.2.2 Study Design

Methodology

Study F (F1, F2 and F3) was conducted at multiple retail shopping malls across the United States to test key messages included in the INSERT regarding use of E004 inhaler and other communications. The study used an iterative study design in which initial testing in Phase 1 led to modifications to the INSERT. The modified statements were

tested in Phase 2. Changes were made to the questionnaire wording, where Phase 1 consumer responses indicated a question was unclear.

The primary objectives in testing the INSERT focused on consumer understanding of the following label directions:

- 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.
- The dose indicator will stop counting at "0" and the inhaler must be replaced.
- Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.

The study was conducted in accordance with FDA Guidance for Industry entitled "Label Comprehension Studies for Nonprescription Drug Products." That Guidance requires sponsors to pre-specify a target for the percentage of consumers who understand the label elements designated as primary end-points. The target comprehension level is expected to reflect the clinical consequences of failing to comprehend or follow the particular instruction. In these studies, understanding the instructions regarding dose indicator of E004 which were related to the risk of consumers undercounting the number of doses used was designated as the primary end-point for the INSERT.

The pre-specified success for the primary end-points was defined as at least an 85% comprehension by study participants across the entire sample. By protocol, the lower 95% confidence limit must equal or exceed 85% in the sample as a whole to define successful communication of the primary end-point.

Recruitment targets were set to ensure that:

- about half of the participants were male;
- about 25% of the sample had low health literacy (defined by REALM scores); and
- 16 to 85 year olds participated in the study.

Secondary communication objectives for E004 LCS studies tested the comprehension and concerned consumer understanding of the following directions:

- 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 Primatene® HFA inhaler soon.
- You must maintain (reprime) your inhaler under specific circumstances – not used for a week.
- You must maintain (reprime) your inhaler under specific circumstances – e.g., after cleaning and before it is dry
- The dose indicator starts beyond 160
- 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.

The retail sites (large shopping malls) at which participants were recruited were selected from diverse geographic areas of the United States. Recruiters from the research facility, who were themselves trained to use the screening instrument, approached and screened potential participants in a consumer traffic area of the shopping center immediately around the research facility.

One-on-one interviews were 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.

The participant was shown the package insert and asked to read it. Participants were given as much time to read the information as they needed. Participants were told they would be asked questions about the information they just read, and that they could refer to the insert to answer the questions. The insert remained in front of the participant during the questioning but after this instruction they were not directed to look at or refer to the label again. Prior to the first question, participants were told that they should answer all questions based on the information on the package insert and not on their own experience or opinions.

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. A score of 60 or less defined the low literacy group. Recruitment aimed to achieve a sample that included approximately 25% of participants classified as low literacy.

Exclusion Criteria

Participants were excluded if they met any of the following criteria:

- Younger than 16 years of age.
- Unable to speak or understand English.
- Could not see well enough to read information on the label (for example, need contact lenses or glasses to read but do not have them at the time of the interview).
- Consumer or someone else in the household reported working for a pharmaceutical, consumer research, or advertising company, as a healthcare professional, or as part of a health care practice (eliminated for reasons of confidentiality and increased awareness of drugs and their labels).
- Consumer or someone else in household reported that they were a current or former employee of PEGUS Research or Amphastar, or its subsidiaries.
- Participated in a consumer research study in the past six months.
- Once the target group size for normal literacy is reached, if necessary, an additional exclusion criterion was added to include only those consumers with REALM score ≤ 60 or REALM Teen ≤ 62 (low-literacy component).

Subject Recruitment and Qualification

Subjects participating in testing the insert were generally representative of the general population (**Tables 12a, 12b, and 12c for Studies F1, F2 and F3, respectively**). In total, 25.5%, 28.3% and 25.9% of Study F1, F2, and F3 subjects, respectively, were classified as low literacy.

Table 12a Demographic Characteristics of Participants in Study F1

Responses	All Combined (N = 432)	Normal Literacy (N = 322) [1]	Low Literacy (N = 110) [2]
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 (0.0%)
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%)	10 (3.1%)	3 (2.7%)
18 to 24	91 (21.1%)	60 (18.6%)	31 (28.2%)
25 to 34	71 (16.4%)	44 (13.7%)	27 (24.5%)
35 to 44	101 (23.4%)	83 (25.8%)	18 (16.4%)
45 to 54	73 (16.9%)	53 (16.5%)	20 (18.2%)
55 to 64	51 (11.8%)	45 (14.0%)	6 (5.5%)
65 to 74	25 (5.8%)	20 (6.2%)	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%)

[1] Scored at least 61 on the REALM test.

[2] Scored at most 60 on the REALM test.

Table 12b Demographic Characteristics of Participants in Study F2

Responses	All Combined (N = 442)	Normal Literacy (N = 317) [1]	Low Literacy (N = 125) [2]
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 (44.0%)
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 (0.0%)
Native Hawaiian or Other Pacific Islander	2 (0.5%)	2 (0.6%)	0 (0.0%)
American Indian or Alaska Native	5 (1.1%)	4 (1.3%)	1 (0.8%)
Refused	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 (17.0%)	54 (17.0%)	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%)

[1] Scored at least 61 on the REALM test.
[2] Scored at most 60 on the REALM test.

Table 12c Demographic Characteristics of Participants in Study F3

Responses	All Combined (N = 471) [1]	Normal Literacy (N = 348) [2]	Low Literacy (N = 122) [3]
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 (0.0%)	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 (18.0%)	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 (0.0%)
>=85	2 (0.4%)	2 (0.6%)	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%)

[1] Subject 1 did not take the REALM test.
[2] Scored at least 61 on the REALM test.
[3] Scored at most 60 on the REALM test.

5.2.3 Findings on E004 LCS

Comprehension Results of Primary Communication Objectives

Results of the comprehension questions used to test the primary communication objectives are summarized in **Table 13**. A communication message was considered to have met the *a priori* performance standard if the lower limit of the 2-sided 95% confidence interval for the rate of correct responses was greater than or equal to 85%. The study number below each question in this table indicates the study from which the results were obtained. Once adequate comprehension was demonstrated, that communication objective was not tested again in subsequent studies.

The first communication objective (what to do if the inhaler is dropped) was slightly short of the performance standard. There was a substantial difference between normal and low literacy participants (87.1% vs. 72.1%) and about a 10% difference between former Primatene® Mist CFC users and non-users (74.2%, 85.0% respectively).

The second and third objectives (tested by one question) exceeded the performance standard. The comprehension by low literacy participants was much closer to that of normal literacy participants (93.1%, 88.8% respectively) and there were no practical differences between former Primatene® Mist CFC users and non-users (90.0%, 92.4%, respectively).

Table 13 Comprehension Results for Primary Communication Objectives

Primary Communication Objective	Question	Normal Literacy	Low Literacy	Former Primatene® Mist Users	Non-Primatene® Mist Users	Total
1. If the inhaler is dropped, do not rely on the dose indicator. Keep track of the number of sprays.	**Question 4:** *What does the package insert say about the dose indicator if the inhaler is dropped?* [Study III]	87.1% N=348 95% CI= 83.1%, 90.4%	72.1% N=122 95% CI= 63.3%, 79.9%	74.2% N=62 95% CI= 61.5%, 84.5%	85.0% N=406 95% CI= 81.1%, 88.3%	83.0% N=471 95% CI= 79.3%, 86.3%
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?* [StudyII]	93.1% N=317 95% CI= 89.7%, 95.6%	88.8% N=125 95% CI= 81.9%, 93.7%	90% N=100 95% CI= 82.4%, 95.1%	92.4% N-342 95% CI= 89.1%, 95.0%	91.9% N=442 95% CI= 88.9%, 94.2%

Comprehension Results of Secondary Communication Objectives

Results of the secondary communication messages are summarized in **Table 14**. No *a priori* performance standards were set for these objectives. The study number below each question in this table indicates the study from which the results were obtained. Once adequate comprehension was demonstrated, that communication objective was not tested again in subsequent studies. Most of these communication objectives resulted in comprehension scores of greater than 90%. The performance of the Primatene® Mist CFC users and non-users differed very little. The comprehension rates for the following three communication objectives were lower, but still demonstrated satisfactory understanding.

- You must prime the inhaler if you need to use it while it is still wet (81.5%)
- You must prime the inhaler if you have not used it for 2 days or longer (87.0%)
- The number on the dose indicator counts down by 20 (86.0%)

Table 14 Comprehension Results for Secondary Communication Objectives

Secondary Communication Objective	Question	Normal Literacy	Low Literacy	Former Primatene Mist Users	Non-Primatene Mist Users	Total Group
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?* [Study II]	95.0% N=317 95% CI= 91.9%, 97.1%	88.8% N=125 95% CI= 81.9%, 93.7%	96% N=100 95% CI= 90.1%, 98.9%	92.4% N=342 95% CI= 89.1%, 95.0%	93.2% N=442 95% CI= 90.5%, 95.4%
2. The mouthpiece should be cleaned daily.	**Question 5:** *According to the package insert, how often should the mouthpiece be cleaned?* [Study III]	96.3% N=348 95% CI= 93.7%, 98.0%	88.5% N=122 95% CI= 81.5%, 93.6%	95.2% N=62 95% CI= 86.5%, 99.0%	94.6% N=406 95% CI= 91.9%, 96.6%	94.1% N=471 95% CI= 91.5%, 96.0%
3. Once the red zone appears and the display reads "20", you should buy a new Primatene HFA inhaler soon.	**Question 7:** *According to the package insert, what does it mean when the red zone appears on the dose indicator?* [Study II]	100% N=317 95% CI= 0.0%, 1.2%	98.4% N=125 95% CI= 94.3%, 99.8%	100% N=100 95% CI= 0.0%, 3.6%	99.4% N=342 95% CI= 97.9%, 99.9%	99.5% N=442 95% CI= 98.4%, 99.9%
2. You must prime your inhaler under the following circumstances: c. If you have not used it in more than 2 days d. 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?* [Study III]	83.9% N=348 95% CI= 79.6%, 87.6%	75.4% N=122 95% CI= 66.8%, 82.8%	75.8% N=62 95% CI= 63.3%, 85.8%	83.0% N=406 95% CI= 79.0%, 86.5%	81.5% N=471 95% CI= 77.7%, 84.9%
	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?* [Study III]	91.1% N=348 95% CI= 87.6%, 93.9%	76.2% N=122 95% CI= 67.7%, 83.5%	90.3% N=62 95% CI= 80.1%, 96.4%	87.2% N=406 95% CI= 83.5%, 90.3%	87.0% N=471 95% CI= 83.7%, 89.9%

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 the inhaler.	**Question 4:** *How do you tell if you have any sprays left in the container?* [Study II]	97.8% N=317 95% CI= 95.5%, 99.1%	84.0% N=125 95% CI= 76.4%, 89.9%	97% N=100 95% CI= 91.5%, 99.4%	93% N=342 95% CI= 89.7%, 95.5%	93.9% N=442 95% CI= 91.2%, 95.9%
	Question 5: *About how many sprays are there in a full container?* [Study II]	98.4% N=317 95% CI= 96.4%, 99.5%	92.0% N=125 95% CI= 85.8%, 96.1%	96.0% N=100 95% CI= 90.1%, 98.9%	96.8% N=342 95% CI= 94.3%, 98.4%	96.6% N=442 95% CI= 94.5%, 98.1%
	Question 9: *How many sprays does it take for the dose indicator number to change?* [Study II]	91.5% N=317 95% CI= 87.8%, 94.3%	72.0% N=125 95% CI= 63.3%, 79.7%	87% N=100 95% CI= 78.8%, 92.9%	85.7% N=342 95% CI= 81.5%, 89.2%	86.0% N=442 95% CI= 82.4%, 89.1%

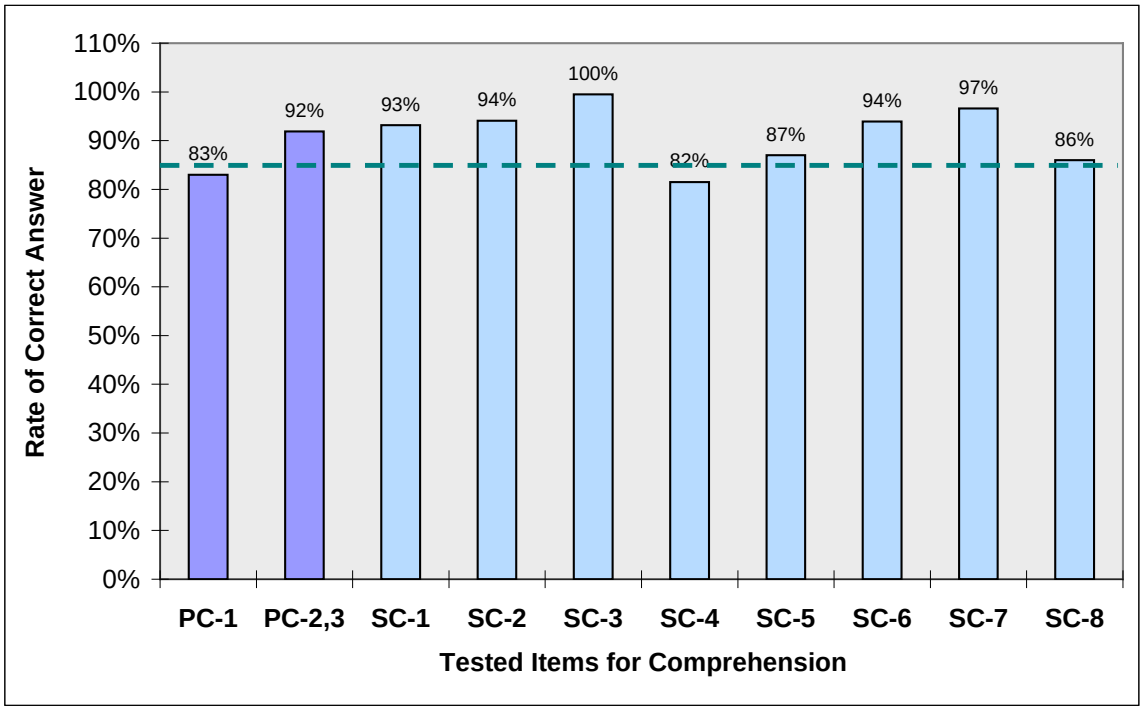
Summary and Conclusions

Overall, the important elements on the package insert were well understood. While one (1) of the three (3) primary communication messages (what to do if the inhaler is dropped) did not meet the performance standard, it was not excessively low. It is unlikely that a substantial health risk would be incurred, especially because many of the participants that missed this question suggested the inhaler should be replaced, or no longer used. Although they failed to comprehend this label message (by specifically stating that for future use they should keep track of the number of sprays used), the action of replacing the inhaler would ameliorate or mitigate the risk of continuing to use the inhaler and relying on the dose counter.

The likelihood of damage to the dispenser as a result of being dropped is minimal as the dose indicator has had rigorous in-vitro testing to determine device functionality and reliability. Moreover, the dose indicator is currently being marketed for an FDA regulated commercial product and no known events have taken place in which dose indicator undercounting has been determined to be the cause. There is also substantial mitigation of this risk through label messages on the Drug Facts Label. Users are reminded under the "Asthma Alert" and "Stop use and ask a doctor if" sections to see a doctor if you "are not getting better in 20 minutes", "get worse" or "your asthma is getting worse (see Asthma alert)".

In summary, LCS includes three (3) primary communication (PC) and eight (8) secondary communications (SC). The rates for these communications are summarized in **Figure 13**.

Figure 13 Summary of Acceptable Rates of E004 Label Comprehension Studies



5.3 FINDINGS IN HUMAN FACTORS (BEHAVIORAL) STUDY

5.3.1 Study Objectives

The objectives of this study were to evaluate the proposed E004 package insert and to test consumer ability to adequately follow the directions for care and use based on the directions in the insert. As this package information is nearly identical to the previously approved Primatene® Mist CFC product, this study did not test already approved sections and wording; rather, this study focused on assessing consumer comprehension of updated label elements on the proposed new package information.

Primary Objectives

The primary objectives of this study were to determine if participants are able to adequately demonstrate the following based on their understanding of the package insert directions:

- How to prime the inhaler.
- How to clean the mouthpiece.
- How to re-assemble the inhaler.
- How to correctly place finger on canister to actuate the inhaler.
- How to dose with the inhaler.

5.3.2 Study Design

This was a multi-center observational study to determine the ability of consumers to adequately demonstrate the inhaler use and care directions contained in the E004 package insert. Data were collected via in-person interviews using a standardized script.

5.3.3 Methods

Participants were recruited using online advertising and posters placed in local pharmacies. After calling a central scheduling number, participants were screened for minimal entry criteria and scheduled for an interview. Upon arrival, the REALM Test (participants 18 years and older) or REALM-Teen Test (participants 12 to 17 years old) was administered to classify participants as normal or low literacy. Participants were then asked to read the package insert, and to demonstrate proper use of the product during a structured, standardized one-on-one interview. Demographic information was collected.

5.3.4 Study Population

This study enrolled 61 participants where 10 participants were between 12 and 17 years old (16%) and 5 participants (8%) have been classified low literacy as defined by the Rapid Estimate of Adult Literacy in Medicine (REALM1) Test or the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen2) Test. 19 subjects (31%) of the study population were previously diagnosed with asthma. In addition, eight (8) subjects (13%) reported use of Primatene Mist CFC within the previous five (5) years.

5.3.5 Study Results and Findings

Participants in this behavioral demonstration study demonstrated a very good ability to read and perform the steps of use and care of the E004 inhaler. In particular, participants performed remarkably well in the steps of actually delivering a dose. Areas in which there was some room for improvement include shaking the device prior to priming or dosing (73.8% and 75.4% respectively), and cleaning the mouthpiece by washing through the opening and the top for 30 seconds each (77.0% and 63.9%). While participants underperformed in these areas, these are both areas that would be expected to improve with continued use and familiarity with the product. 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, and where they were only able to demonstrate portions of the behaviors and had to describe other portions).

The performance is summarized in **Table 15**.

Table 15 Performance of E004 Label Behavioral Study

1. Prime the inhaler.	Changed?	Safety Risk	Objective	Performance
Remove the cap	Y	None	For Information Only	93.4%
Shake the inhaler	Y	Significant	Primary	73.8%
Hold inhaler with dose indicator up	Y	Significant	Primary	93.4%
Spray into the air at least one time	Y	Significant	Primary	82.0%

2. Clean the Mouthpiece	Changed?	Safety Risk	Objective	Performance
Remove the cap	N	None	For Information Only	100%
Remove the container	N	Significant	Primary	93.4%
Wash the mouthpiece through the opening	Y	Significant	Primary	77.0%
for 30 seconds	Y	Significant	Primary	93.6%
Wash the mouthpiece through the top	Y	Significant	Primary	63.9%
Mention warm water should be used	N	Significant	Primary	96.7%
Shake off excess water	Y	Low	For Information Only	77.0%
Dry Completely (either by overnight or re-prime)	Y	Low	For Information Only	95.1%
Reassemble the inhaler	Y	None	For Information Only	63.9%

3. Put the Inhaler Back together	Changed?	Safety Risk	Objective	Performance
Attach removable cap to mouthpiece	Y	None	For Information Only	96.7%
Insert container in mouthpiece	Y	None	For Information Only	98.4%
4. Finger Placement	**Changed?**	**Safety Risk**	**Objective**	**Performance**
Place forefinger in the center of the dose indicator	Y	Significant	Primary	88.5%
5. Dosing	**Changed?**	**Safety Risk**	**Objective**	**Performance**
Take cap off mouthpiece	N	Low	For Information Only	98.4%
Shake the inhaler before inhalation	Y	Significant	Primary	75.4%
Place thumb on bottom and finger on top of container	N	Low	For Information Only	100%
Empty the lungs by exhaling	N	Moderate	Secondary	85.2%
Place mouthpiece in mouth	N	Moderate	Secondary	100%
Lips closed around the mouthpiece	N	Moderate	Secondary	98.4%
Inhale	N	Significant	Primary	100%
…while squeezing mouthpiece and container together,	N	Significant	Primary	98.4%
… pressing on the CENTER of the dose indicator	Y	Significant	Primary	98.4%
Continue the deep breath	N	Moderate	Secondary	98.4%
Hold breath	N	Moderate	Secondary	93.4%
Release (by releasing forefinger from the container)	N	None	For Information Only	100%
Remove inhaler from mouth	N	None	For Information Only	100%
Exhale slowly	N	Moderate	Secondary	90.2%
Keep lips nearly closed	N	Moderate	Secondary	96.7%
Replace cap	N	None	For Information Only	82.0%

5.3.6 Conclusions

Participants in this behavioral demonstration study demonstrated a very good ability to

read and perform the steps of use and care of the E004 inhaler. In particular, participants performed remarkably well in the steps of actually delivering a dose. Areas in which there was some room for improvement include shaking the device prior to priming or dosing (73.8% and 75.4%, respectively), and cleaning the mouthpiece by washing through the opening and the top for 30 seconds each (77.0% and 63.9%). While participants underperformed in these areas, these are both areas that would be expected to improve with continued use and familiarity with the product. It is also likely that the artificial nature of the testing environment (including handling an empty container) may 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 and where they were only able to demonstrate portions of the behaviors and had to describe other portions).

6. BENEFIT RISK ASSESSMENT OF OTC EPINEPHRINE HFA MDI

6.1 ASTHMA HAS BEEN RECOGNIZED AS A MAJOR PUBLIC HEALTH PROBLEM SINCE THE 1970S

Global rates of asthma have increased significantly as of the 1960s. Asthma has been recognized as a major public health problem since the 1970s.

The number of persons with asthma increased 2.9% each year, from 20.3 million persons in 2001 to 25.7 million persons in 2010. Of the 25.7 million, 7.0 million were children and 18.7 million were adults [3]. Asthma affects approximately 7% of the population of the United States.

Asthma symptoms are inherently unpredictable. Even in stable chronic asthma patients, acute symptoms arise episodically triggered by infections, pollution, cold air, dusts, pet dander and other unanticipated triggers. These lead to episodic exacerbations, a characteristics of asthma, and are a major reason nearly all asthma patients require ready access to quick-relief bronchodilators. Quick-relief inhalers are generally utilized on an as needed basis, and under the patient's own control of use.

Asthma disrupts peoples' daily life and costs the United States $56 billion each year – Asthma is a serious health and economic concern in the United States [2,3].

6.2 ASTHMA DIAGNOSIS AND TREATMENT

The most common symptom of asthma is wheezing. This is a scratchy or whistling sound when patient breathes. Other symptoms include:

- Shortness of breath
- Chest tightness or pain
- Chronic coughing
- Trouble sleeping due to coughing or wheezing

A physician diagnoses asthma by taking a thorough medical history and performing breathing tests to measure how well patients' lungs work. One of these tests is called spirometry. Patients are required to take a deep breath and blow into a sensor to measure the amount of air his/her lungs can hold and the speed of the air her/she inhales or exhales. This

test diagnoses asthma severity and measures how well treatment is working.

Asthma is considered by the FDA as a condition that is self-recognizable and self-treatable after initial diagnosis by a physician. Consumers can self-recognize the symptoms of asthma.

There is no cure for asthma, but symptoms can be controlled with effective asthma treatment and management. Controller medications are taken daily and include inhaled corticosteroids: fluticasone (Flovent Diskus, Flovent HFA), budesonide (Pulmicort Flexhaler), mometasone (Asmanex), ciclesonide (Alvesco), flunisolide (Aerobid), beclomethasone (Qvar) and others.

Combination inhalers contain an inhaled corticosteroid plus a long-acting beta-agonist (LABA).

Quick-relief medications are used to quickly relax and open the airways and relieve symptoms during an asthma flare-up, or are taken before exercising if prescribed. These medications include: short-acting beta-agonists. These inhaled bronchodilator medications include albuterol (ProAir HFA, Ventolin HFA, Proventil HFA), and levalbuterol (Xopenex HFA). Quick-relief medications do not take the place of controller medications.

Oral and intravenous corticosteroids may be required for acute asthma flare-ups or for severe symptoms. Examples include prednisone and methylprednisolone. All available asthma medications have some limitation and side effects.

There is currently no FDA approved OTC Asthma MDI medication available in the US market.

6.3 MEDICAL NEED FOR OTC AVAILABILITY OF EPINEPHRINE HFA MDI

OTC Epinephrine MDI CFC has been available in the United States since the 1960s for the relief of asthma symptoms. However, there is a belief among some health care professionals that it is less effective and shorter acting and has more cardiovascular adverse effects than prescription β2-agonist MDIs [11]. In particular, the concerns have been focused on the cardiovascular adverse effects from the epinephrine MDI CFC.

However, as pointed out by Dr. Hendeles et al. in 2005, "***there is no basis for concerns about cardiovascular adverse effects from the epinephrine MDI***." [11]

Furthermore, the systematic controlled clinical studies conducted by Amphastar/Armstrong under the guidance of the FDA have evidenced the validity of the statement made by Dr. Hendeles et al. The clinical study results have demonstrated that there are no significant cardiovascular issues in terms of frequency, severity or seriousness with E004, even after a long-term exposure (as long as 6 months) or under a ultra-high dose (5 times of the normal dose, i.e., 10 inhalations).

The results obtained from the randomized, controlled, blinded clinical studies of E004 conducted by Amphastar/Armstrong also demonstrated that **the amount of epinephrine entering into the blood system is only 0.9 mcg or 0.36% of delivered total dose (250 mcg). A** majority of the epinephrine inhaled does not get into blood system, it **likely arrives at the site of action, the bronchus/lungs**. This very low bioavailability might very well explain why epinephrine MDI has no significant cardiovascular issues.

An OTC medication could provide access to a readily available treatment for millions of people with asthma. There appear to be gaps in the current asthma treatment available on the market. As reported by consumers, many do not experience sufficient relief with currently available asthma treatment options. According to their experiences, epinephrine MDI CFC was the only product that worked for them. Some of the consumers simply stated that they could not afford the prescription drugs.

Thousands of inquiries from Primatene® Mist users were received by Armstrong after the sunset of Primatene® Mist:

- Consumer "Mark" wrote on 2/17/2012: Primatene® Mist "*saved my life several times, … I am now out of Primatene Mist.. Please do something to get your product available on the market again…*"
- Consumer ES wrote on 2/25/2012 "*Please give me an approximate date/month/whatever that your new HFA inhaler will be available. I'm (literally) dying over here. … The mist was the only medicine that worked.…*"
- Consumer VD wrote on 3/24/2012 "*I have been using the product since I was 16. I am now 61. Will an OTC replacement be coming soon?... We need help now! Please push to get your product to market ASAP. Some 3 million of us are waiting. Unfortunately, one in our group has died from an asthma attack. I don't want to be on the list*."

OTC status for E004 (Epinephrine HFA MDI) will address a number of these asthma treatment gaps. With OTC availability, consumers would have readily available access to this highly effective medication without the need for a prescription, an office visit, scheduling

issues, and associated costs for that visit, including time off from school or work.

It should be noted that nearly all Americans with health insurance also commonly utilize OTC medicines. Use of OTC medications in no way precludes patients from seeing their primary and specialist physicians to help adjust and optimize their asthma care. OTC medications form a necessary adjunct to physician-provided healthcare that should be encouraged for all Americans.

6.4 E004 OVERVIEW, EFFICACY AND SAFETY

Epinephrine, the active ingredient in E004, is a well characterized chemical that has been included in numerous prescription and nonprescription products. It is well known that epinephrine, or adrenaline, is produced in the central nervous system and adrenal glands. Epinephrine's toxicities are well studied and well characterized due to the fact that it exists in our body.

After inhalation, the exogenous epinephrine is detectable in the plasma. The observed risk for E004 is that it has higher C_{max} compared to Primatene® Mist CFC (0.18 ng/mL vs. 0.046 ng/mL). However, within 10 minutes (at 12.5 minutes post-dose) following the t_{max} (2.3 minutes), the plasma epinephrine level was reduced to less than one tenth of the C_{max}, showing an elimination half-life of 2.6 minutes. The exogenous epinephrine concentration in plasma declines to an undetectable level in the blood system after 60 minutes post-dose.

The clinical output correlated to the higher C_{max} for E004 is that E004 has higher occurrence rate for the ADE Tremor as compared to that for Primatene® Mist CFC. However, the tremor rate for E004 (7.7%, for 12 week study, n=248) is similar to that for Albuterol HFA (Proventil® HFA) (7% for 12 week study, n=193 [14]).

It is worthwhile to note that the bronchodilatory efficacy of both E004 and Primatene® Mist CFC consistently demonstrated a time trend – with the greatest efficacy observed on Day 1 and a reduced, but still significant efficacy observed at Week 6 when the maximum labeled dose was continuously used, then was maintained at about the same level of efficacy over the next 6 week period at the maximum labeled dose until the end of the study, Week 12.

The substantial efficacy of E004 for the treatment of mild to moderate asthma patients is accompanied by a favorable and well characterized safety profile. The safety of E004 is supported by the analyses of up to 6 months of long-term controlled clinical evaluation,

conducted in 34 clinical centers all over the United States.

As a therapy targeted to oral inhalation for quick relief of asthma symptoms, the most common adverse events of E004 are local, particularly in the upper respiratory tract, including throat irritation and cough. These events, along with events such as chest discomfort, jittery feeling, may also be associated with the underlying disease.

It should be emphasized that no death or treatment related serious ADE were observed during the entire E004 clinical program.

6.5 E004 IN THE OTC ENVIRONMENT

An OTC label has been developed to update information from the OTC Primatene® Mist CFC label in language that is well understood by the consumer. Label comprehension studies support that consumers, even those with low health literacy, can understand the instructions in the proposed insert. The DFL includes specific sections for Purpose, Uses, Directions and Warnings. The insert will be placed inside the E004 unit package and provides directions and illustrations for use and maintenance of the MDI unit. Language on the proposed DFL is similar to that of Primatene® Mist CFC except where adaptations based on the specific new features of E004 MDI unit were needed. Label instructions, discussed by category, help mitigate potential risks with use of E004 in the OTC consumer environment.

Purpose and Uses

The purpose for which E004 is used, "For temporary relief of MILD symptoms of INTERMITTENT asthma", has been well understood by consumers based on the history of Primatene® Mist CFC. The description of uses for the product, "For temporary relief of mild symptoms of intermittent asthma: wheezing, tightness of chest, shortness of breath" is based on language from the most up-to-date FDA guidance for OTC bronchodilators [18]. The Statement of Uses provides clear information for the consumer to identify what this OTC product can do for their asthma symptoms.

In the event a consumer chooses E004 for conditions other than asthma, the conditions would not worsen and the consumer would not be placed at additional risk since the initial diagnosis is required by physician as E004 DFL instructs "**Do not use unless a doctor said you have asthma**". The E004 DFL further instructs the following:

Warnings

- **Asthma alert: Because asthma may be life threatening, see a doctor if you**
  - are not better in 20 minutes
  - 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

Directions

The directions for dosing of OTC E004 are straightforward, "one or two inhalations for each dose", "start with one inhalation, wait at least 1 minute. If not relieved, use once more", "wait at least 4 hours between doses", and "do not use more than 8 inhalations in 24 hours". It was well understood by consumers since it is based on FDA guidance for OTC bronchodilators [18] and is similar to the dosing instructions of Primatene® Mist CFC. It is important to note that there were few reports of misuse, abuse, or of taking excessive amounts of Primatene® Mist CFC. The active ingredient in E004 is epinephrine, which is a natural human hormone. Further, the alcohol content is reduced 34-fold in E004 formulation compared to Primatene® Mist CFC. As an OTC product, E004 would have a lower potential for abuse.

Warnings

The warning statement of E004 DFL follows the most up-to-date FDA guidance for OTC bronchodilators [18], which was discussed above in "Purpose and Uses" section. Physician-patient relationship and doctor's guidance are highly emphasized in the proposed DFL of OTC E004 product and there is repeated emphasis on the doctor's role in diagnosis, treatment and management of asthma as follows:

-- "Do not use unless a doctor said you have asthma"
-- "Ask a doctor before use if you have …"
-- "If these symptoms persist or get worse, consult a doctor …"
-- "Asthma alert： because asthma can be life threatening, see a doctor if you …"

6.6 CONCLUSION

E004 provides effective relief of the asthma symptoms indicated in the DFL, namely, wheezing, chest tightness, and shortness of breath, all of which are the common symptoms that asthma sufferers find most bothersome. The efficacy and safety of the product has been

characterized in multiple controlled clinical studies. The proposed OTC labeling has been developed to ensure consumer understanding of the proper use of the product and to help mitigate potential safety risks. Studies have established and confirmed consumer understanding of the proposed label.

Accordingly, for all of the reasons discussed above, the efficacy and safety profile for the use of E004 without physician's oversight would not be different or pose greater risks than those for OTC Primatene® Mist CFC, which demonstrated a favorable benefit-risk profile for over fifty (50) years. Further, the risks clearly are mitigated by the strong safety profile demonstrated during the clinical evaluation of E004 and through OTC labeling that follows the FDA requirements in format and content. Therefore, the benefits (including prevention of death) of broader access to an effective OTC treatment as a replacement formulation for OTC Primatene® Mist CFC, for temporary relief of mild symptoms of intermittent asthma, clearly outweigh the risks associated with the minor ADEs observed in Armstrong's/Amphastar's clinical studies.

Approval of E004 (Epinephrine HFA MDI) inhalers will add important public health benefits for asthma patients and form a beneficial supplement to other controller and reliever medications for asthma, none of which are currently available on the OTC market for consumers.

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Appendix 1

Proposed Drug Fact Label
For
E004 (Epinephrine HFA MDI)

DRUG FACTS FONT SPECS
- DRUG FACTS HEADING FONT SIZE = HELVETICA 9 POINT
- BODY OF DRUG FACTS TEXT = HELVETICA 7 POINT

NON-VARNISH AREA

BARCODE TYPE C128
TO READ U5530B

U5530B

Primatene® Mist HFA

Epinephrine Inhalation Aerosol
Bronchodilator
0.125 mg per inhalation

Primatene® Mist HFA

Epinephrine Inhalation Aerosol
Bronchodilator
0.125 mg per inhalation

Total contents:
160 inhalations

For temporary relief of MILD symptoms of INTERMITTENT asthma

CONTAINS MOUTHPIECE AND CONTAINER WITH DOSE INDICATOR

UPC-A BARCODE
TO READ: 3 17270 55300 7

NON-VARNISH AREA

Drug Facts (continued)

Directions For Dosing:
- do not use more than directed
- adults and children 12 years of age and over
  - **1 to 2 inhalations** for each dose
  - Start with one inhalation, wait at least 1 minute. If not relieved, use once more
  - Wait at least **4 hours between doses**
  - Do not use more than **8 inhalations in 24 hours**
- children under 12 years of age: ask a doctor

Inhaler storage and other information
- store at room temperature, between 15-25˚C (59-77˚F)
- contains no sulfites
- see insert for mouthpiece use and care instructions

Inactive ingredients
dehydrated alcohol (1%), hydrofluoroalkane (HFA 134a), polysorbate 80, thymol

Questions or comments?
call **1-8 Primatene** or **1-877-462-8363**
Mon.- Fri. 7 am - 5 pm PST

Manufactured by:
Armstrong Pharmaceuticals, Inc.
Canton, MA 02021
© 2013 Made in USA
See www.armstrong-pharma.com

Drug Facts

Active Ingredient *(in each inhalation)* ***Purpose***
Epinephrine 0.125 mg.....Bronchodilator

Uses
For temporary relief of mild symptoms of intermittent asthma
- wheezing
- tightness of chest
- shortness of breath

Warnings
- **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
- For inhalation only

Do not use
- unless a doctor said you have asthma
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or a pharmacist before taking this product

Ask a doctor before use if you have
- ever been hospitalized for asthma
- heart disease
- high blood pressure
- diabetes
- trouble urinating due to an enlarged prostate gland
- thyroid disease
- seizures
- narrow angle glaucoma
- a psychiatric or emotional condition

Ask a doctor or pharmacist before use if you are
- taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
- taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

Open Here

U5530B

BARCODE TYPE C128
TO READ U5530B

NON-VARNISH AREA

Drug Facts (continued)

When using this product
- **your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death**
- **your risk of heart attack or stroke increases if you**
  - **have a history of high blood pressure or heart disease**
  - **take this product more frequently or take more than the recommended dose**
- avoid foods or beverages that contain caffeine
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect
- do not puncture or incinerate. Contents under pressure
- do not store near open flame or heat above 120˚F (49˚C). May cause bursting.

Intentional abuse of this product can be harmful or fatal.

If pregnant or breast-feeding, ask a health care professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Stop use and ask a doctor if
- your asthma is getting worse (see Asthma alert)
- you have difficulty sleeping
- you have a rapid heart beat
- you have tremors, nervousness, or seizures

U5530B

DESCRIPTION: Primatene Mist HFA
LABEL NO: U5530B
SIZE: 1.9375 X 1.3125 X 5.125
COLORS: PMS 4625, PMS 283, PMS 485, BLACK
BARCODES: CODE 128 TO READ: U5530B
UPC-A TO READ: 317270553007

Appendix 2

Proposed Insert (Consumer Information Leaflet)
For
E004 (Epinephrine HFA MDI)

Primatene® Mist HFA

Epinephrine Inhalation Aerosol Bronchodilator

For temporary relief of MILD symptoms of INTERMITTENT asthma

BENEFITS OF PRIMATENE® MIST HFA

This product is intended for use by individuals with **mild** symptoms of **intermittent** asthma.

When used according to directions, Primatene® Mist HFA provides an easy and effective way to obtain temporary relief of **mild** symptoms of **intermittent** asthma. Primatene® Mist HFA contains epinephrine, which is a dependable inhalation aerosol bronchodilator.

It is packaged in an aluminum container fitted with a specially designed valve, for use with the Primatene® Mist HFA mouthpiece only. The special valve is designed to deliver the same amount of medication with each spray. Primatene® Mist HFA can be used at any time of the day or night. Use only as directed.

Take Inhalation

The Primatene® Mist HFA mouthpiece, should be used for inhalation only with the Primatene® Mist HFA container.

1. Take cap off mouthpiece (See Figure 1).

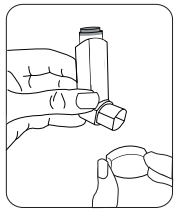


Figure 1

2. **SHAKE** the inhaler immediately before each inhalation (See Figure 2).

Figure 2

3. • Place thumb on bottom of mouthpiece.
   • Place finger on **center** of dose indicator (See Figure 3).

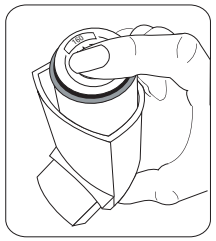


Figure 3

4. Empty the lungs as completely as possible by **exhaling**.

5. Place mouthpiece in mouth.
   • Lips closed around opening
   • Inhale deeply while squeezing mouthpiece and container together (See Figure 4).
   • Continue the deep breath, drawing medication into the lungs.
   • Hold breath as long as possible.

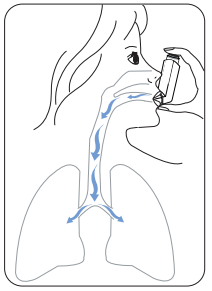


Figure 4

6. • Release and remove from mouth.
   • Exhale slowly keeping lips nearly closed (See Figure 5).
   • This helps distribute the medication in the lungs.

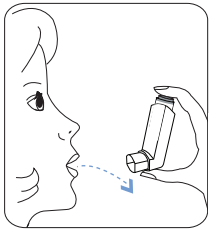


Figure 5

7. After the inhalations cover the mouthpiece opening with plastic cap for storage.

Manufactured by: Armstrong Pharmaceuticals, Inc., Canton, MA 02021 © 2013 Made in USA F5530B

CODE 128 BARCODE
TO READ F5530B

FRONT

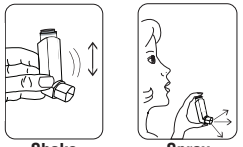
Priming

When to prime

Before 1ST use	4 times
Not used in more than 2 days	1 time
Still **wet** after cleaning	1 time
If **dropped**	1 time

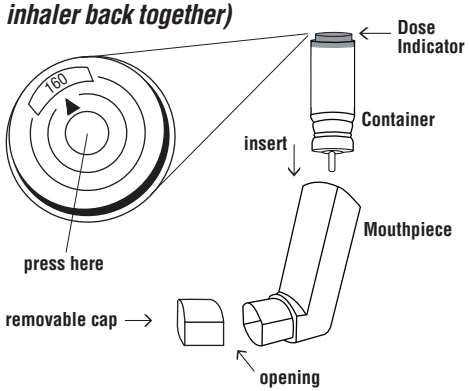
How to prime

1. Remove cap.
2. Shake.
3. Hold with dose indicator up and away from your face or others.
4. Place forefinger on **center** of dose indicator.
5. Immediately spray.



Before first use, prime four (4) times

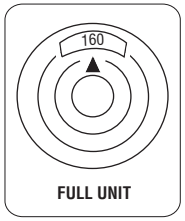
How to Assemble the Inhaler (How to put inhaler back together)



Dose Indicator- shows how many sprays you have left

A full container holds 160 sprays

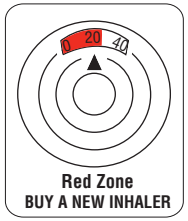
- The dose indicator **number** changes after you spray 20 times.
- The number **does not** change by one (1) each time you spray the inhaler.



Starts at 160:
160 sprays remaining

Red Zone

- Once the red zone appears and the display reads "20", buy a new Primatene® HFA inhaler soon.
- **The dose indicator will stop counting at "0" and the inhaler must not be used any longer.**
- When the dose indicator hits zero, the correct dose in each spray cannot be assured (even though there may be medication in the container).



Red Zone:
Buy a new Inhaler

CAUTION- Never try to change the numbers or take the dose indicator off the container.

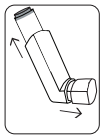
The dose indicator cannot be reset, it should remain permanently attached to the container.

If you **DROP** your inhaler:

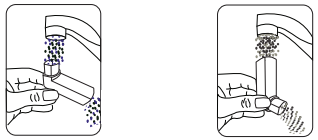
- DO NOT RELY ON DOSE INDICATOR
- Keep track of the number of sprays you take
- Prime one (1) time

Clean the Mouthpiece DAILY

1. Remove Cap
2. Remove Container

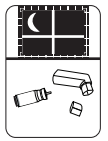


3. Wash **opening**
   - warm water
   - 30 seconds
4. Wash **top**
   - warm water
   - 30 seconds



5. Shake off excess water

6. Air Dry overnight



7. Assemble

Remember:

- Clean **DAILY**
- If **wet**, prime one (1) time before use
- It is normal to see some discoloration in the mouthpiece due to residual drug left on it after use.

BACK

DESCRIPTION: Primatene Mist HFA
LABEL NO: F5530B
SIZE: 5 1/4" X 8.8"
COLORS: PMS 485, PMS 659, PMS 430, BLACK
BARCODE: CODE 128 to read F5530B

Appendix 3

Drug Fact Label and Insert
For
Primatene® Mist CFC

Primatene® MIST

Epinephrine Inhalation Aerosol
Bronchodilator
For the Temporary Relief of
BRONCHIAL ASTHMA

Primatene® Mist (CFC) will not be available after December 31, 2011.
Talk to your doctor and/or pharmacist about other asthma medicines.

BENEFITS OF PRIMATENE® MIST

When used according to directions, Primatene® Mist provides an easy and effective way to obtain temporary relief of bronchial asthma. Primatene® Mist has been used safely by millions. Primatene® Mist contains epinephrine, which is a dependable inhalation aerosol bronchodilator.

It is packaged in a plastic-coated safety-glass bottle, fitted with a specially designed valve, for use with the Primatene® Mist mouthpiece only. The special valve is designed to deliver the same amount of medication with each spray. Primatene® Mist can be used at any time of the day or night. Use as directed.

Manufactured by: Armstrong Pharmaceuticals, Inc., West Roxbury, MA 02132 ©2009 Made in USA F5030J

CODE 128 BARCODE
TO READ F5030J

FRONT

Drug Facts

Active ingredient (in each inhalation) **Purpose**

Epinephrine 0.22 mg ..... Bronchodilator

Uses

- for temporary relief of occasional symptoms of mild asthma:
  - wheezing
  - tightness of chest
  - shortness of breath

Warnings

Asthma alert: Because asthma can be life threatening, see a doctor if you

- are not better in 20 minutes
- get worse
- need 12 inhalations in any day
- use more than 9 inhalations a day for more than 3 days a week
- have more than 2 asthma attacks in a week

For inhalation only

Do not use

- unless a doctor said you have asthma
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- ever been hospitalized for asthma
- heart disease
- high blood pressure
- diabetes
- thyroid disease
- seizures
- narrow angle glaucoma
- a psychiatric or emotional condition
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are

- taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
- taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

Drug Facts (continued)

When using this product

- **increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack and stroke. Your risk may increase if you take more frequently or more than the recommended dose.**
- nervousness, sleeplessness, rapid heart beat, tremor, and seizure may occur. If these symptoms persist or get worse, consult a doctor right away.
- avoid caffeine-containing foods or beverages.
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect.
- do not puncture or throw into incinerator. Contents under pressure.
- do not use or store near open flame or heat above 120°F (49°C). May cause bursting.

Contains CFC 12, 114, substances which harm public health and environment by destroying ozone in the upper atmosphere.

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not exceed dosage**
- supervise children using this product
- adults and children 4 years and over: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours.
- children under 4 years of age: ask a doctor

Other information

- store at room temperature, between 20-25°C (68-77°F)
- contains no sulfites
- see insert for mouthpiece use and care instructions

Inactive ingredients

ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water

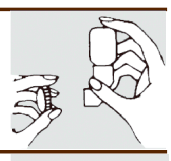
Questions or comments?

call **1-8 PRIMATENE or 1-877-462-8363**

Intentional abuse of this product can be harmful or fatal.

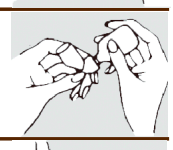
DIRECTIONS FOR USE OF MOUTHPIECE The Primatene® Mist mouthpiece, which is enclosed in the Primatene® Mist 15 mL size (not the refill size), should be used for inhalation only with Primatene® Mist.

1. Take plastic cap off mouthpiece. (For refills, use mouthpiece from previous purchase.)

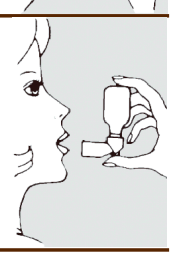


2. Take plastic mouthpiece off bottle.

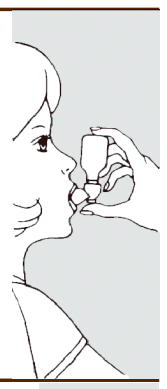
3. Place short end of mouthpiece on bottle.



4. Turn bottle upside down. Place thumb on bottom of mouthpiece and forefinger on top of vial. Empty the lungs as completely as possible by exhaling.

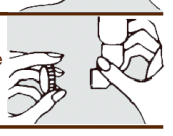


5. Place mouthpiece in mouth with lips closed around opening. Inhale deeply while squeezing mouthpiece and bottle together. Release immediately and remove unit from mouth, then complete taking the deep breath, drawing medication into your lungs, holding breath as long as comfortable.



6. Exhale slowly keeping lips nearly closed. This helps distribute the medication in the lungs.

7. For storage, place long end of mouthpiece back on bottle and cover with plastic cap.



CARE OF THE MOUTHPIECE The Primatene® Mist mouthpiece should be washed after each use with hot, soapy water, rinsed thoroughly, and dried with a clean, lint-free cloth.

If the unit becomes clogged and fails to spray, please write and send the clogged unit to:
Armstrong Pharmaceuticals, Inc., 423 La Grange Street, West Roxbury, MA 02132

BACK

NO COPY

DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	9 pt
• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

DESCRIPTION: Primatene Mist Insert
LABEL NO.: F5030J
SIZE: 9" x 4 3/4'
COLORS: PMS 4625, PMS 485
BARCODE: CODE 128 TO READ F5030J