

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208437Orig1s000**

**NON-CLINICAL REVIEW(S)**

## Pharmacology and Toxicology Secondary Review for NDA 208437

Date: May 18, 2017

To: **NDA 208437**  
Lonhala Magnair (Glycopyrrolate) inhalation solution for nebulization  
using the PARI eFlow nebulizer  
Sunovion Respiratory Development, Inc.

From: Carol M. Galvis, PhD  
Acting Pharmacology and Toxicology Team Leader  
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

### **Recommendation**

I concur with Dr. L. S. Leshin's review dated April 25, 2017 that recommended approval of NDA 208437 from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues.

### **Background**

Sunovion Respiratory Development, Inc. submitted a 505(b)(2) NDA 208437 on July 29, 2016, for Lonhala Magnair, a glycopyrrolate inhalation solution for oral inhalation via nebulization using the PARI eFlow Closed System (CS) nebulizer. The proposed indication is for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Sunovion is relying on the nonclinical safety information from previously approved glycopyrrolate products (Robinul Tablets under NDA 12-827, Robinul Injection under NDA 17-558, and Cuvposa Oral Solution under NDA 22-571). To support the inhalation route of administration, the applicant conducted inhalation toxicology studies in rats (1-month and 6-month studies) and dogs (1-month study). However, during development of this product, other glycopyrrolate products for inhalation were approved, including Seebri Neohaler (under NDA 207923), which is now owned by Sunovion. Therefore, the nonclinical information discussed below and used for NDA 208437 labeling purposes was obtained from the Seebri Neohaler approved label (October 2015).

### **Summary of Pharmacology and Toxicology Data**

Glycopyrrolate is a long-acting muscarinic antagonist which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M<sub>1</sub> to M<sub>5</sub>. In the airways, it exhibits pharmacological effects through inhibition of M<sub>3</sub> receptor at the smooth muscle leading to bronchodilation.

The applicant submitted inhalation toxicology studies in rats (1-month and 6-month studies) and dogs (1-month study). No new toxicities were identified in these studies. Because the proposed dose (25 mcg BID via nebulization - actually delivers approximately 56.8% of this dose, or approximately 14.2 mcg BID) is similar to the approved dose of Seebri Neohaler (15.6 mcg BID), it was not necessary to review these studies to support safety of this new product.

### **Labeling**

The nonclinical sections of the drug label (Section 8, Section 12.1, and Section 13) followed the approved label of Seebri Neohaler. For Section 8, the Pregnancy and Lactation Labeling Rule (PLLR) format was followed. The final language for the nonclinical sections of the label was discussed with the applicant during this review cycle. The Division and Sunovion reached agreement for these sections of the label.

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/s/  
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CAROL M GALVIS  
05/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208437

Supporting document/s: 2

Applicant's letter date: July 29, 2016

CDER stamp date: July 29, 2016

Product: SUN-101, Glycopyrrolate Inhalation Solution

Indication: Treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

Applicant: Sunovion Respiratory Development, Inc.

Review Division: DPARP

Reviewer: L.S. Leshin, D.V.M., Ph.D.

Acting Team Leader: Carol Galvis, Ph.D.

Division Director: Badrul A. Chowdhury, M.D., Ph.D.

Project Manager: Sadaf Nabavian

*Template Version: September 1, 2010*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208437 are owned by Sunovion Respiratory Development, Inc. or are data for which Sunovion Respiratory Development, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 208437 that Sunovion Respiratory Development, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208437.

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# 1 Executive Summary

## 1.1 Introduction

This NDA is for a drug and device combination product consisting of SUN-101 (glycopyrrolate) Inhalation Solution with a PARI eFlow Closed System (CS) nebulizer. It is indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. The tradename, Lonhala Magnair, was submitted to IND 110,663 on January 29, 2016 and accepted May 27, 2016. Lonhala refers to the drug product, glycopyrrolate, and Magnair refers to the PARI eFlow CS nebulizer system. The drug-device combination was developed under IND 110,663 by Elevation Pharmaceuticals Inc. (submitted on April 13, 2011). The company's name was later changed to Sunovion Respiratory Development Inc. (SD-20, September 5, 2012).

Glycopyrrolate is a long-acting, cholinergic muscarinic antagonist that is approved in liquid formulations for intravenous, intramuscular, and oral administration. Inhalation formulations of dry powder and aerosols are also approved. This would be the first nebulized glycopyrrolate product. The proposed dose is 25 mcg twice daily.

The Applicant is pursuing a 505(b)(2) NDA pathway, relying on nonclinical safety information from previous glycopyrrolate NDAs to support their application and labeling. The nonclinical information relies on previously demonstrated safety from approved products Robinul Injection (NDA 17-558), Robinul Tablets (NDA 12-827), and Cuvposa oral solution (NDA 22-571). The Applicant conducted additional inhalation toxicology studies to support the new inhalation route of administration. However, during development of SUN-101 Inhalation Solution, other inhalation glycopyrrolate products were approved, lessening the essential need for the Applicant's nonclinical inhalation studies. These products were formulated as a dry powder (Seebri Neohaler; NDA 207923), dry powder in combination with indacaterol (Utibron Neohaler; NDA 207930), and an aerosol in combination with formoterol fumarate (Bevespi Aerohaler NDA 208294). Furthermore, during the NDA review cycle, the Applicant notified the FDA on March 16, 2017 (SD-15) that they acquired ownership of Seebri Neohaler on January 27, 2017. Utibron Neohaler was also acquired, effective January 27, 2017. The Applicant now owns data that supported the approval of these two 505(b)(1) applications, but in the current NDA is requesting approval of a nebulizer, a different drug delivery device. However, as noted below, significant issues were found by the CDRH review of the device that will affect approval of this application.

## 1.2 Brief Discussion of Nonclinical Findings

Due to the reliance on previously approved glycopyrrolate products for safety through the 505(b)(2) NDA pathway, few nonclinical studies were submitted. The nonclinical program consisted of 1-month repeated-dosing inhalation studies in rats and dogs, followed by a 6-month repeated-dosing inhalation study in rats. The applicant acquired ownership of Seebri Neohaler on January 27, 2017 (during the application review period), and could rely solely on that data to support the safety of

glycopyrrolate for the inhalation route of administration. The Applicant's nonclinical inhalation toxicity studies, conducted prior to approval of any inhalation product for glycopyrrolate, produced results that were generally similar to those approved products.

The toxicities in the rat associated with inhaled glycopyrrolate in 1- and 6-month studies included reduced body weight and food intake; dilated pupils; increased red blood cell counts, hemoglobin, and hematocrit; increased lung weight associated with alveolar macrophages; laryngeal inflammation; and increased porphyrin secretion of the Harderian gland. The following findings were observed in the 1-month inhalation study in dogs: dilated pupils, dry mouth, reduced body weight and food consumption, emesis, and thymus atrophy with a reduction in thymus weights. All these effects were partly or completely reversible during a recovery phase. Two impurities of the drug substance,  $\alpha$ -cyclopentylmandalic acid (CPMA) and benzoic acid, were also assessed for safety. Neither of these compounds were detected in the drug substance (Batch 2017234) used in the 6-month inhalation study and these were not tested for their presence in the earlier drug substance (Batch GCP/013/2009-2010) used in the 1-month inhalation studies in rats and dogs.

CPMA is also a major human metabolite of glycopyrrolate formed upon hydrolysis of glycopyrrolate (corresponding to metabolite M9). CPMA lacks glycopyrrolate's pharmacological profile, but its potential pharmacology and toxicity is unknown. It is also present in the mouse, rat, rabbit, but there is no animal data concerning the quantitative levels or bioactivity. The safety of CPMA is confounded with the safety of glycopyrrolate due to CPMA's unavoidable presence as a metabolite in humans. Benzoic acid is a potential oxidative degradant that was formed in forced degradation studies. These two compounds lack mutagenic structural alerts and are negative in genotoxic tests. While the systemic safety of CPMA is established, the local safety from inhalation of CPMA has not been established and the specifications were reduced from those proposed by the Applicant to those requested by the CMC reviewer to NMT <sup>(b) (4)</sup> % for both compounds.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

The application may be approved from the nonclinical perspective.

#### **1.3.2 Additional Non Clinical Recommendations**

None

#### **1.3.3 Labeling**

The Applicant's proposed label sections containing or supported by nonclinical information are presented below. For each section, the Applicant's label is presented, followed by the Reviewer's recommended changes and explanation for the changes. During the review period, the applicant acquired Seebri Neohaler, an approved glycopyrrolate inhalation product. Therefore, the proposed label was modified to

resemble the label for Seebri Neohaler where possible. Additions to the Applicant's label are indicated by underlining, and deletions are indicated by strikeouts. An agreement was reached with the applicant during this review cycle for these labeling sections.

**FULL PRESCRIBING INFORMATION: CONTENTS\***

(b) (4)



(b) (4)



➤ Reviewer Recommended Changes (based on current labeling practices)

(b) (4)



(b) (4)



➤ [Applicant's Proposed Label](#)

### 12.1 Mechanism of Action

Glycopyrrolate is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine and acetylcholine induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

➤ [Reviewer Recommended Changes](#)

- No changes were recommended at this time, since this language resembles the Seebri Neohaler label, and this is considered appropriate.

## 13 NONCLINICAL TOXICOLOGY

➤ [Applicant's Proposed Label](#)

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)



(b) (4)





(b) (4)

## 2 Drug Information

### 2.1 Drug

CAS Registry Number	596-51-0
Generic Name	Glycopyrrolate Glycopyrronium Bromide
Code Name	SUN-101
Chemical Name	Pyrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-bromide, 3-Hydroxy-1,1-dimethylpyrrolidinium bromide $\alpha$

	cyclopentylmandelate
Molecular Formula / Molecular Weight	C <sub>19</sub> H <sub>28</sub> BrNO <sub>3</sub> 398.33 Salt free form known as glycopyrronium free base MW = 318.43 and is the active moiety.
Structure or Biochemical Description	<p>Glycopyrrolate contains two chiral centers and is a racemate of a 1:1 mixture of the R,S and S,R diastereomers (also known as threo diastereomers). <sup>(b) (4)</sup></p> <p><sup>(b) (4)</sup> The active moiety, glycopyrronium, is the free base form of glycopyrrolate, both R,S and S,R diastereomers are pharmacologically active.</p> <p style="text-align: center;">[2S, 3R]-stereoisomer                      [2R, 3S]-stereoisomer</p>
Pharmacologic Class	Muscarinic receptor antagonist (anticholinergic)

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

**IND 110663**, glycopyrrolate inhalation solution, Sunovion (formerly Elevation Pharmaceuticals Inc.), submitted April 13, 2011

**DMF** <sup>(b) (4)</sup>

**DMF**

**DMF**

### Glycopyrrolate-Containing Products (excluding ANDAs)

NDA #, Owner	Brand Name	Route	Indication	Approved
<b>Glycopyrrolate</b>				
<b>12827</b> (Casper Pharm)	<b>Robinul and Robinul Forte</b>	Oral tablets 1 mg/tablet (Robinul) and 2 mg/tablet (Robinul Forte)	Adjunctive therapy for treatment of peptic ulcers	1961
<b>14764</b> AH Robins Co. Discontinued marketing 1982	<b>Robinul</b>	0.2 mg/mL injection	Information unavailable	1967
<b>17558</b>	<b>Robinul</b>	IM or IV injection	<b>In Anesthesia</b>	1975

West Ward Pharms Int	<b>Injection</b>	Up to 8 mg/day(0.2 mg/mL)	<p>use preoperative:</p> <ul style="list-style-type: none"> <li>• to reduce salivary, tracheobronchial, and pharyngeal secretions</li> <li>• to reduce the volume and free acidity of gastric secretions</li> <li>• to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation</li> </ul> <p>used intraoperatively</p> <ul style="list-style-type: none"> <li>• to counteract surgically or drug-induced or vagal reflexes associated arrhythmias</li> <li>• protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants</li> </ul> <p><b>In Peptic Ulcer</b></p> <ul style="list-style-type: none"> <li>• adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated.</li> </ul>	
<b>22571</b> Shionogi Inc.	<b>Cuvposa</b>	Oral solution for ingestion, 3 mg glycopyrrolate, three times daily (9 mg per day), Daily administration over an indefinite period, resulting in chronic exposure	Treatment of severe drooling in secondary to cerebral palsy and other neurodevelopmental deficits	2010
<b>207923</b> Sunovion (previously Novartis)	<b>Seebri Neohaler</b> (NVA237)	Inhalation 15.6 mcg BID = 31.2 mcg/day	long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).including chronic bronchitis and/or emphysema	2015
<b>Combinations with glycopyrrolate for inhalation</b>				
<b>207930</b> Sunovion since Jan 27 2017 (previously Novartis)	<b>Utibron Neohaler</b> dry powder in combination with indacatrol	Inhalation	long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema	2015

<b>208294</b> AstraZeneca since April 11, 2017 (previously Pearl Therapeutics, Inc)	<b>Bevespi Aerohaler</b> aerosol in combination with formoterol fumarate	Oral Inhalation Aerosol metered 9 mcg/actuator Use 2 inhalations twice daily (36 mcg/day)	long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema	2016
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### 2.3 Drug Formulation

SUN-101 (glycopyrrolate) Inhalation Solution (SUN-101) is a sterile, non-preserved solution for oral inhalation. It is supplied in low-density polyethylene (LDPE) unit dose vials, each containing 1.0 mL of the drug solution consisting of 25 mcg/mL of glycopyrrolate, USP (glycopyrronium bromide) <sup>(b) (4)</sup> with pH adjusted to 4.0 for chemical stability. Two unit dose vials are overwrapped with <sup>(b) (4)</sup> foil as a sealed pouch. The mean delivered dose using the PARI eFlow CS nebulizer under *in-vitro* USP<1601> adult breathing pattern conditions was 14.2 mcg with a mean nebulization time of approximately 2 minutes.

**Table 1: Quantitative Composition of SUN-101**

Ingredient	Function	Amount per mL
Glycopyrrolate, USP	Active ingredient	25 mcg or 50 mcg
Citric Acid Monohydrate USP/Ph. Eur.	<sup>(b) (4)</sup>	
Sodium Chloride, USP/Ph. Eur.	<sup>(b) (4)</sup>	
Sodium Hydroxide, NF/Ph. Eur.	pH adjusting agent	Adjust to pH 4.0
Hydrochloric Acid, NF/Ph. Eur.	<sup>(b) (4)</sup>	
Water for Injection, Ph. Eur.	Diluent	q.s. to 1 mL

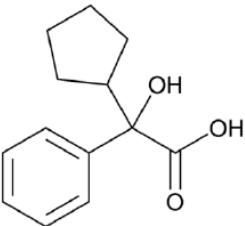
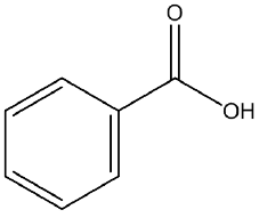
### 2.4 Comments on Novel Excipients

There are no novel excipients.

### 2.5 Comments on Impurities/Degradants of Concern

Two impurities of the drug substance,  $\alpha$ -cyclopentylmandalic acid (CPMA) and benzoic acid, were also assessed for safety. Both are degradation products. Neither of these compounds were detected in the drug substance (Batch 2017234) used in the 6-month inhalation study and were not tested for their presence in the drug substance (Batch GCP/013/2009-2010) used in the 1-month inhalation studies in rats and dogs (assay sensitivity unknown; both batches have specification limits of  $\leq$  <sup>(b) (4)</sup> % for these compounds; DMF <sup>(b) (4)</sup> ).

**Table 1: Glycopyrrolate Related Impurities (from Applicant's Table 12)**

Name/Other Designation	Structure	Origin/Classification
CPMA/ Cyclopentylmandelic acid/ USP Glycopyrrolate related substance C		Drug substance process impurity. Degradant resulting from hydrolysis of the drug substance and a recognized metabolite of glycopyrrolate in humans.
BA/ Benzoic Acid		Potential oxidative degradant

CPMA is also a major human metabolite of glycopyrrolate and if formed upon hydrolysis of glycopyrrolate (corresponding to metabolite M9). It was extensively studied for NDA 207923, but those reports were not reviewed for its approval. Briefly, CPMA lacks glycopyrrolate's pharmacological profile, but its potential pharmacology and toxicity has not been studied. It is present in the mouse, rat, rabbit, but there is no animal data concerning the quantitative tissue or blood levels, or its potential bioactivity. The safety of CPMA is confounded with the safety of glycopyrrolate due to CPMA's unavoidable presence as a metabolite in humans. Glycopyrrolate has not been used extensively as a continuous daily medication, and has only been marketed as an inhalation formulation since 2015. Given the above lack of data, local respiratory tract safety from inhalation of CPMA has not been established for CPMA.

The Applicant proposed CPMA specification limit of NMT (b) (4) % at release and NMT (b) (4) % for the shelf life. On January 11, 2017, in response to a December 23, 2016 Request for Information, the Applicant provided a revised release specification of (b) (4) % and a shelf-life specification for this impurity of NMT (b) (4) % as described in ICH Q3B(R2), due to the fact that the evidence to support a higher shelf life specification was applicable to systemic exposure, but lacked evidence for safety due to direct inhalation. CPMA was not measured in as a drug deposition compound in animal inhalation toxicity studies. This revised specification is considered acceptable.

Benzoic acid is a potential oxidative degradant that was formed in forced degradation studies. Specification limit for benzoic acid and individual unspecified impurity (NMT (b) (4) %) is the identification threshold recommended by ICH Q3B(R2) for drug product degradants.

Refer to the CMC Review for additional information concerning impurities.

### eFlow CS Nebulizer Drug Delivery Device

The drug/device combination product will be provided in two commercial configurations:

1. Starter Kit: SUN-101 drug product (30 day twice daily supply) with a complete nebulizer kit and nebulizer accessories.
2. Refill Kit: SUN-101 drug product (30 day twice daily supply) with a handset and handset components (including aerosol head).

The Starter Kit is intended for new patients with the Refill kit to be subsequently supplied every 30 days.

The device aerosol head, nebulizer chamber, blue inhalation valve, inside of the mouthpiece, inside of the top and bottom of the handset, and medication cap are permanent exposure, external communicating components (tissue, bone dentin). The outside of the mouthpiece is a permanent exposure, surface-mucosal membrane contact component. The mouthpiece is used in the FDA-cleared LC Sprint Nebulizer (510(k) K060399) and is used in the eFlow CS without modification and was therefore not further tested.

Biocompatibility testing was reviewed by CDRH and a number of concerns with the methods and results were identified. Ongoing communication between the Applicant and CDRH reviewer have not yet resolved the issues. The originally submitted conclusions identifying potential leachables and extractables and analysis of their potential toxicity is currently incomplete. Refer the CDRH reviews for additional information.

## **2.6 Proposed Clinical Population and Dosing Regimen**

Lonhala Magnair is indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The recommended dose is the inhalation of the contents of one Lonhala vial (25 mcg glycopyrrolate) twice-daily, once in the morning and once in the evening, using Magnair.

## **2.7 Regulatory Background**

The Applicant is pursuing a 505(b)(2) NDA pathway, relying on nonclinical safety information from previous glycopyrrolate NDAs to support their application and labeling. Lonhala Magnair drug-device combination was developed under IND 110,663, submitted on April 13, 2011. The original sponsor, Elevation Pharmaceuticals Inc, notified the Division on September 5, 2012 (SD-20) that the corporate name was changed to Sunovion.

At the Pre-IND meeting held on March 2, 2011, there was some discussion concerning appropriate study species and design for long term inhalation toxicity study to support the clinical program. Also discussed was the support needed to initiate clinical dose-response studies. The IND was submitted on April 13, 2011 and allowed to proceed. At the time of the IND submission, inhalation of glycopyrrolate was a new route of administration and clinical studies were supported for respiratory

tract safety by nonclinical inhalation toxicity studies in the rat and dog of 1-month duration. This was followed by a 6-month inhalation toxicity study in the rat.

The nonclinical support also relied on systemic and organ safety previously established for oral and intravenous routes of administration from approved products Robinul Injection (NDA 17-558), Robinul Tablets (NDA 12-827), and Cuvposa oral solution (NDA 22-571). However, during development of SUN-101 Inhalation Solution, other inhalation glycopyrrolate products were approved, lessening the need for the applicant's nonclinical inhalation studies. These products had various formulations, dry powder (Seebri Neohaler; NDA 207923), dry powder in combination with indacaterol (Utibron Neohaler; NDA 207930), and an aerosol in combination with formoterol fumarate (Bevespi Aerohaler NDA 208294). Toward the end of the review process, the Division was notified (SD-15, March 16, 2017) that the applicant acquired ownership of Seebri Neohaler effective January 27, 2017.

Due to the reliance on the safety of glycopyrrolate in these approved products for safety through the 505(b)(2) pathway, it was unnecessary to review additional nonclinical studies supporting Lonhala Magnair. The following sponsor's table indicates the sources of information supporting nonclinical safety of glycopyrrolate.

**Table 2: References Supporting the 505(b)(2) NDA**

<b>Source of Information</b>	<b>Information Provided</b>
<b>Listed Drugs</b>	
NDA 17-558 Robinul Injection	Clinical Metabolism and Excretion Secondary Pharmacodynamics Excretion Single-Dose Toxicity Reproductive and Developmental Toxicology Nonclinical Overview and Brief Summaries
NDA 12-827 Robinul Tablets	Nonclinical Overview and Brief Summaries
NDA 22-571 Cuvposa oral Solution	Repeat-Dose Toxicity Genotoxicity Nonclinical Overview and brief summaries
NDA 207923 Seebri Neohaler (EMA-european product)  Note: The applicant now owns the Seebri Neohaler data, a 505(b)(1)	Clinical Distribution SUN-101 Package Insert
<b>Published Literature</b>	
Casarosa 2009; Haddad 1999; Villetti 2006; Trifilieff	Primary pharmacodynamics

EMA/CHMP/508029/2012 (Seebri Breezhaler)  Note: The applicant now owns the Seebri Neohaler data, a 505(b)(1)	Secondary Pharmacodynamics Safety Pharmacology Absorption, Distribution, Metabolism, Excretion Repeat-Dose Toxicity Genotoxicity Carcinogenicity Reproductive and Developmental Toxicology Nonclinical Overview and Brief Summaries
PMDA Report on the Deliberation results for Seebri Inhalation Capsules 50 mcg (Seebri Breezhaler)  Note: The applicant now owns the Seebri Neohaler data, a 505(b)(1)	Absorption Metabolic Pathway Distribution Drug Interaction Nonclinical Overview and Brief Summaries
Proakis 1978	Distribution
Franko 1970	Single-dose toxicity Repeat-dose toxicity Reproductive and Developmental Toxicology Local Tolerance
Bartels 2013	Clinical Absorption

### 3 Studies Submitted

#### 3.1 Studies Reviewed

Report Number	Title	Previous Review
<b>General Toxicology</b>		
<b>Rat</b>		
101802A1	28-Day Inhalation Toxicity Study of EP-101 in Rats With a 14-Day Recovery Period	IND 110663, May 13, 2011
<b>Dog</b>		
101803A1	28-Day Inhalation Toxicity Study of EP-101 in Dogs with a 14-Day Recovery Period	IND 110663, May 13, 2011
<b>Impurities</b>		
101-805	Toxicological Qualification of a-Cyclopentylmandelic Acid to Support a Specification Limit in an Inhalation Drug Product	
101-806	Toxicological Assessment of Alkanes and Alkenes as Potential Leachables in Inhalation Drug Products	

#### 3.2 Studies Not Reviewed

Report Number	Title
101-500	The Method Validation and Stability Determination of a Liquid Chromatography-Mass Spectrometry



	Method for the Determination of Glycopyrrolate in Dog and Rat Plasma
<b>101-800</b>	Dose Escalation and 7-Day Inhalation Toxicity Study of EP-101 in Rats
<b>101-804</b>	6-Month Inhalation Toxicity and Toxicokinetic Study of EP-101 in Rats with a 3-Month Recovery Period
<b>101-801</b>	Dose Escalation and 7-Day Inhalation Toxicity Study of EP-101 in Dogs

### 3.3 Previous Reviews Referenced

These reviews are attached in the Appendix.

IND 110,663, Elevation Pharmaceuticals, Inc., May 13, 2011, Initial Safety Review by Dr. Kathleen Young

IND 110,663, Elevation Pharmaceuticals, Inc., June 14, 2011, Impurity consult for CPMA and benzoic acid by Dr. Kathleen Young

## 4 Pharmacology

The Applicant did not conduct pharmacology studies. The information below is from studies conducted for Seebri Neohaler (NDA 207923) for which the Applicant acquired ownership during the current review period.

Glycopyrrolate is a long-acting competitive cholinergic muscarinic receptor antagonist. It has similar affinity to muscarinic receptor subtypes M<sub>1</sub> to M<sub>5</sub>. It inhibits acetylcholine activity at sites innervated by postganglionic cholinergic nerves and on cholinergic sensitive smooth muscles. Acetylcholine from vagal nerve stimulation activates muscarinic receptors on smooth muscle cells, resulting in bronchoconstriction. In the airways, inhibition of these muscarinic receptors by glycopyrrolate results in bronchodilation. Its long duration of action for inducing bronchial dilation is due to its slow dissociation kinetics from the M<sub>3</sub> receptor, prevalent in the lower respiratory tract. At the human M<sub>3</sub> receptor, the [3S,2R] enantiomer has greater biological activity (~100 times) than [3R,2S] enantiomer. Glycopyrrolate also reduces the volume and free acidity of gastric secretions and secretions from the pharynx, trachea, and bronchi. Also affected by inhibition of muscarinic activity are cardiac muscles of the sinoatrial node and the atrioventricular node, exocrine glands and autonomic ganglia.

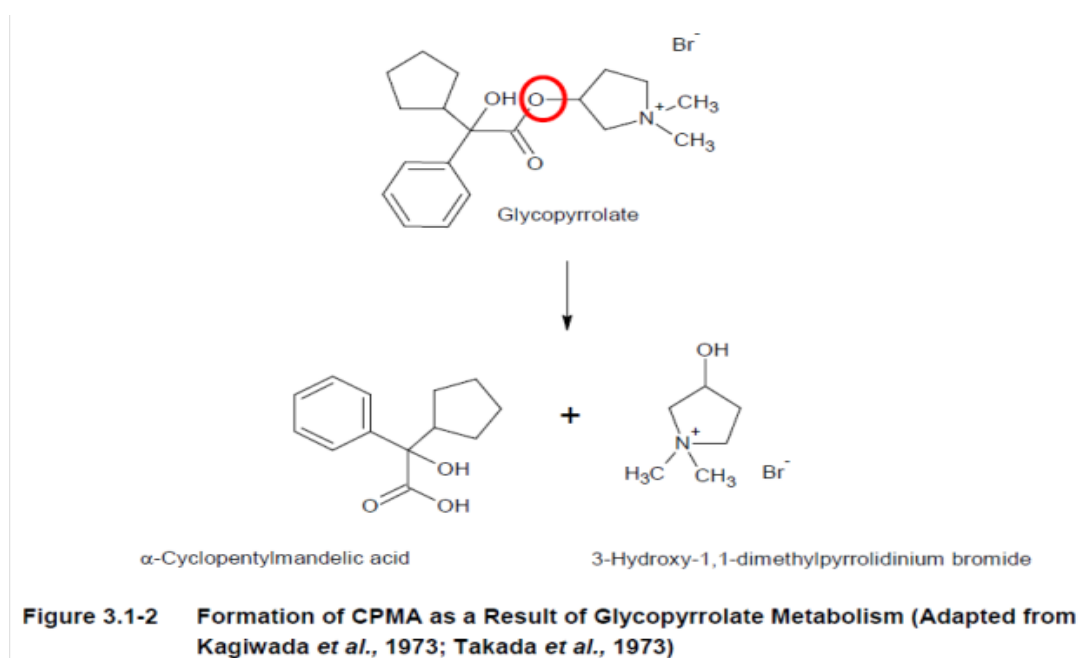
## 5 Pharmacokinetics/ADME/Toxicokinetics

The applicant did not conduct ADME Studies. Nonclinical toxicokinetics for glycopyrrolate were obtained for the 1-month inhalation toxicity studies in the rat and dog and the 6-month inhalation toxicity rat study.

Pertinent to the presence of the major metabolite of CPMA in human plasma are animal studies conducted for the approval of Seebri Neohaler (NDA 207923, currently owned by the Applicant) that were not previously reviewed. Major points of those studies are presented briefly below.

Glycopyrrolate is metabolized mainly in blood to CPMA by Phase 1 hydroxylations. Butyrylcholinesterases and acetylcholinesterases are involved in the ester hydrolysis. While there may be interconversion among the enantiomers, both are cleared at approximately similar rates. The metabolism of radiolabeled glycopyrrolate in human liver microsomes was very low and no metabolism was found in human lung microsomes. Liver microsomes of the mouse and rabbit, but not the rat, produced small amounts of CPMA.

**Figure 1: Metabolism of Glycopyrrolate**



In a 1-month inhalation toxicity study in rats, glycopyrrolate was spiked with 9.8% CPMA formulated as a powdered aerosol. Dose groups consisted of vehicle control, 0.13 mg/kg and 0.38 mg/kg spiked with CPMA, and 0.56 mg/kg glycopyrrolate only. Similar responses were seen across treatment groups, with the main histopathological finding of increased goblet cells in the nasal cavity and sinuses, and squamous metaplasia and epithelium hyperplasia in the larynx. There were no obvious local toxicological effects between inhaled glycopyrrolate with or without spiked CPMA. CPMA was negative in the Ames mutagenicity and chromosome aberration tests. The absence of a longer inhalation study, 3-months, with CPMA spiked dosing, hindered the acceptance of the Applicant's higher impurity specification (NMT<sup>(b) (4)</sup> %) for CPMA to extend shelf life.

Another inhalation study determined the toxicokinetics in blood and lung tissue of the rat after 1-month of daily inhalation of 0.1 mg/kg/day of glycopyrrolate. Concentrations of glycopyrrolate on day 1 and day 18 were 1800-fold and 3400-fold higher in the lung than in plasma, respectively. There was no accumulation in plasma over the 28 days, however lung accumulation varied from 1.7- to 2.8-fold over this period. Lung terminal clearance was 20 hours in males and 26 hours in females, plasma concentrations were not detectable 24 hours after the last dose.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

Escalating single-dose inhalation studies were conducted in rats and dogs to determine a maximal tolerated dose and were followed by a 7-day repeated-dose inhalation toxicity study. These studies were to determine doses for the 1-month repeated dose inhalation study. They were considered preliminary in nature and were not conducted under GLP. The studies and doses are listed in the Table below.

**Table 3: SUN-101 Toxicology Studies (from Applicant's Table 1, Module 2)**

**Table 1: Overview of SUN-101 Toxicology Studies**

Overview						Test Article: Glycopyrrolate	
Type of Study	Species (Strain)	Method of Administration	Duration of Dosing	Dose (mg/kg/day)	GLP Compliance	Testing Facility	Document Number
Single-Dose Toxicity	Rat (SD)	Inhalation (nose-only)	1-day	15, 45, 150	No	(b) (4)	101-800
	Dog (Beagle)	Inhalation (nose-only)	1-day	0.8, 2.4	No		101-801
Repeat-Dose Toxicity	Rat (SD)	Inhalation (nose-only)	7-days	0, 45	No		101-800
			28-days	0, 0.5, 5, 45	Yes		101-802
			6-months	0, 0.05, 0.5, 5	Yes		101-804
			7-days	0, 2.4	No		101-801
	Dog (Beagle)	Inhalation (nose-only)	28-days	0, 0.06, 0.6, 2.4	Yes		101-803

SD = Sprague-Dawley

### 6.2 Repeat-Dose Toxicity

Repeated-dose inhalation toxicity studies of 1-month duration were conducted in rats and dogs, and a 6-month inhalation toxicity study was conducted in rats. The 1-month studies were reviewed previously under IND 110,663; which can be found in the Appendix of this review. The 6-month study was not reviewed prior to submission of this NDA. Since the Applicant acquired the Seebri Neohalaer during the NDA review period (that consists of the same glycopyrrolate API drug substance), it was unnecessary to formally review the Applicant's 6-month toxicity study.

## 7 Genetic Toxicology

The Applicant did not conduct genetic toxicology studies.

## 8 Carcinogenicity

The Applicant did not conduct carcinogenicity toxicology studies.

## 8 Reproductive and Developmental Toxicology

The Applicant did not conduct reproductive and developmental toxicology studies.

## 10 Special Toxicology Studies

The Applicant did not conduct special toxicology studies.

## 11 Integrated Summary and Safety Evaluation

Due to the reliance on previously approved glycopyrrolate products for safety through the 505(b)(2) NDA pathway, few nonclinical studies were submitted. The nonclinical program consisted of 1-month repeated-dosing inhalation studies in rats and dogs, followed by a 6-month repeated-dosing inhalation study in rats. The applicant acquired ownership Seebri Neohaler during the application review period, and could rely solely on that data to support the safety of glycopyrrolate for the inhalation route of administration. The Applicant's own nonclinical inhalation toxicity studies, conducted prior to approval of any inhalation product for glycopyrrolate, produced results that were generally similar to those products that have since been approved (no new toxicities were identified).

The toxicities in the rat associated with inhaled glycopyrrolate in 1- and 6-month studies included reduced body weight and food intake; dilated pupils; increased red blood cell counts, hemoglobin, and hematocrit; increased lung weight associated with alveolar macrophages; laryngeal inflammation; and increased porphyrin secretion of the Harderian gland. In the 1-month inhalation study in dogs, the following findings were observed: dilated pupils, dry mouth, reduced body weight and food consumption, emesis, and thymus atrophy or a reduction in thymus weights. These findings were reversed after a recovery period. These findings were considered due to pharmacodynamic effects (mydriasis, dry mouth), species-specific effects due to differences in anatomy airway flow of particulate material (laryngeal metaplasia and inflammation in the rat), or indirect adverse changes (erythrocytosis, increased lung weight, Harderian gland porphyrin secretion, and thymic atrophy).

(b) (4)

and this section of the label was eliminated.

Studies of genotoxicity, carcinogenicity, reproductive and developmental toxicity, were not conducted by the applicant, but were referenced from other applications via the 505(b)(2) NDA pathway. Since similar studies across applications resulted in similar findings and since the Applicant now has ownership of the data used to support the approval of Seebri Neohaler (NDA 207923), an inhalation drug that also consists only of glycopyrrolate, safety margins in the label were based on nonclinical data from Seebri Neohaler as determined in the Table below.

**Table 4: Nonclinical Safety Margins for Lonhala Magnair**

Study	Species	Route	Dose	AUC	Exposure Margin <sup>2</sup>
Fertility	Rat	subcutaneous	NOAEL: 0.63 mg/kg/day,	M and F: 98 ng-h/mL	384X
			Adverse effect 1.88 mg/kg/day		M: 2035 F: 1136X

			<ul style="list-style-type: none"> <li>decreased implantation sites</li> <li>reduction of live fetuses</li> </ul>		
<b>EmbryoFetal Development</b>	Rat	inhalation	NOAEL: 3.8 mg/kg/day	388 ng-h/mL	1521X
	Rabbit	inhalation	NOAEL: 4.4 mg/kg/day	148 ng-h/mL	580X
<b>Pre-and Post-Natal Development</b>	Rat	subcutaneous	NOAEL: 1.88 mg/kg/day	290 ng- h/mL	1137X
<b>Carcinogenicity</b>	Rat: 2- year	inhalation	M and F: 0.56 mg/kg/day	36.45 ng-h/mL	143X
	Mouse: Tg.rasH2 6-month	oral gavage	M: 93.8 mg/kg/day, F: 125.1 mg/kg/day	M and F 16.8 ng-h/mL	66X
<p><sup>1</sup> Nonclinical studies used for the calculation of exposure margins were conducted to support Seebri Neohaler (NDA 207923, now owned by the Applicant).</p> <p><sup>2</sup> Exposure margins were calculated as animal dose/human dose (25 mcg, BID, or 50 mcg/day). The AUC<sub>0-24</sub> value for human therapeutic dosing was obtained from study SUN 101-201, in which an AUC<sub>0-12</sub> was 255 pg/hr/mL, for a single 50 mcg dose. For a 25 mcg, BID dose in a linear dose-AUC relationship, the AUC<sub>0-24</sub> was 255 pg-h/mL.</p>					

Two impurities of the drug substance,  $\alpha$ -cyclopentylmandalic acid (CPMA) and benzoic acid, were also assessed for safety. Neither of these compounds were detected in the drug substance (Batch 2017234) used in the 6-month inhalation study and these were not tested for their presence in the earlier drug substance (Batch GCP/013/2009-2010) used in the 1-month inhalation studies in rats and dogs.

CPMA is also a major human metabolite of glycopyrrolate and if formed upon hydrolysis of glycopyrrolate. CPMA lacks glycopyrrolate's pharmacological profile, but its potential pharmacology and toxicity is unknown. It is also present in the mouse, rat, rabbit, but there is no animal data concerning the quantitative levels or bioactivity. The safety of CPMA is confounded with the safety of glycopyrrolate due to CPMA's presence as a metabolite in humans. Benzoic acid is a potential oxidative degradant that was formed in forced degradation studies. Neither compound has mutagenic structural alerts. While the systemic safety of CPMA is established, the local safety from inhalation of CPMA has not been established and the specifications were reduced from those proposed by the Applicant to those requested by the CMC reviewer to NMT <sup>(b) (4)</sup> % for both compounds.

The drug deliver nebulizer device was subject to review by CDRH. There were a number of concerns with the methods and results obtained for biocompatibility testing that have not yet been adequately resolved, and these issues may result in a Complete Response action for this NDA. However, at this time there are no safety issues with the API, glycopyrrolate. Pending resolution of the biocompatibility testing

and absence of any related compounds that would affect safety, the application may be approved from the pharmacology and toxicology perspective.

## **12 Appendix/Attachments**

Two Pharmacology and Toxicology Reviews by Dr. Kathleen Young for the development of SUN-101 under IND 110,663 are included as Attachments. They are reviews dated May 13, 2011 and June 14, 2011.



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION**

**IND number:** 110663

**Sponsor:** Elevation Pharmaceuticals, Inc.

**Submission Type:** Initial IND Submission

**Supporting Doc Category/Subcategory:** SDN 000; SDN 002

**Submission Date/Receipt:** April 13, 2011/April 14, 2011; May 11, 2011

**Drug Substance:** Glycopyrrolate Inhalation Solution (GIS)

**Division name:** Division of Pulmonary, Allergy, and Rheumatology Products

**Review completion date:** May 8, 2011

**Reviewer name:** Kathleen Young, Ph.D.

**Pharmacology/Toxicology Supervisor:** Timothy W. Robison, Ph.D. for Molly E. Topper, Ph.D.

**Division Director:** Badrul Chowdhury, M.D., Ph.D.

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## 1 Executive Summary

### 1.1 Recommendations

**1.1.1** The proposed clinical inhalation study on GIS (# EP-101-03) is reasonably safe to proceed from a pharmacology and toxicology point of view.

**1.1.3 Additional Recommendations:** We have the following non-hold recommendations:

1. Please submit the final study reports for the 28-day inhalation toxicity studies in rats and dogs (N111001D and N111001E) within 120 days from the initial IND 110,663 submission.

### 1.2 Brief Discussion of Nonclinical Findings

Glycopyrrrolate is a muscarinic antagonist with potent bronchodilatory activity, proposed for long-term inhalation treatment of Chronic Obstructive Pulmonary Disease (COPD) using the newly modified Glycopyrrrolate Inhalation System (GIS) eFlow nebulizer (PARI)

Glycopyrrrolate has been used in the US for more than 30 years, and is approved in IM and IV systemic injection form (Robinul® Injection, IV, IM, NDA 17-558) as a preoperative antimuscarinic agent. Glycopyrrrolate is also approved in oral, tablet, and ophthalmic and oral solution (NDA 22-571, NDA 089170, NDA 089171, NDA 08410) forms as adjunctive therapy for the chronic treatment of drooling and peptic ulcer (Robinul® 1 and 2 mg oral tablet, NDA 12-827), with a maximum recommended dose (MRHD) of 8 mg/day PO.

The Sponsor is proposing to rely on Agency safety findings for the approved NDAs 17-558 (IV and IM injection) and NDA 12-827 (oral tablet) for the non-clinical systemic toxicity information to support the safety of the proposed clinical study on the inhalation product.

The Sponsor's nonclinical toxicology program is directed toward an assessment of local toxicity in the respiratory tract. The Sponsor submitted draft (unsigned GLP) reports of 28-day inhalation toxicology studies with rats and dogs in support of the proposed clinical trial.

A 28-day glycopyrrrolate inhalation toxicity study was conducted in Sprague-Dawley rats with a 14-day recovery period (b) (4) Study N111001D. The rats

(n=10/sex/group with 6/sex/group toxicokinetic evaluation and 5/sex/group recovery group rats) were administered glycopyrrolate by nose-only inhalation once daily for 28 days at doses of 0, 0.5, 5, and 45 mg/kg/day. There was one death with unknown relationship to treatment in a high dose male rat on Day 2, which was replaced immediately in the high dose group. The treatment-related effects included reversible decreased body weight gain during the 28-day dosing period, that was statistically significant at the high dose in the males (-66%) and females (-71%). Ophthalmoscopic examination showed primarily pharmacodynamic effects of glycopyrrolate, including papillary dilation at the mid- and high doses, which were reversible during the recovery period. Increased lung weights (absolute and relative to both body weights and brain weights) were shown at the mid- and high doses (percent differences from controls in the males were +33% and +30%, respectively, and +43% and +47% in the females, respectively). The increased lung weights might correlate with increased alveolar macrophages found in the microscopic examination. The target organs identified in the histopathology evaluation were the lungs, larynx and Harderian gland. There were reversible (during recovery) increased lung alveolar macrophages in terminal bronchioles and adjacent alveoli at all doses, with dose-related increases in incidence and severity with severity ratings of minimal with occasional mild. Furthermore, no inflammation or inflammatory cells were found. The Sponsor suggested that this was supportive of a particle removal function by the macrophages, representing normal lung function and not an inflammatory response. There were alterations of the epithelial lining in the larynx from pseudostratified flattened-to-low cuboidal "cobblestone" morphology to mucosal epithelium, that was consistent with stratified squamous type/squamous metaplasia. Laryngeal alterations were observed at all doses. These findings, commonly observed in inhalation toxicology studies with rats (Osimitz T, *et al.* 2007). Toxicologic significance of histologic change in the larynx of the rat following inhalation exposure: A critical review. *Toxicology and Applied Pharmacology* 225. 229-237), are attributed to an adaptive response to irritation and have no relevance to humans. Some (nonreversible at the highest dose) inflammation was also found in the laryngeal tissue, which included neutrophil and plasma cell macrophage infiltration of the submucosal glands and/or propria stroma with increased incidences for males and females in the high dose group. The NOAEL was 45 mg/kg/day (mean AUC male + female combined 7,255,000 pcg.h/ml) because increased lung alveolar macrophages observed at all doses were without evidence of inflammation and therefore likely performing an inhaled drug removal function, and epithelial lining changes in the larynx were without inflammation, reversible at the low dose, and commonly found in inhalation toxicity studies in rats.

The 28-day inhalation toxicity study on glycopyrrolate in dogs with 14-day recovery period (Study N111001E) used 3 dogs/sex/dose main study, and 2/sex/dose recovery evaluation animals. The dogs received glycopyrrolate at doses of 0, 0.06, 0.6 and 2.4 mg/kg/day by nose-only inhalation, once daily for approximately 32-53 minute exposures. There was no mortality during the study.

The clinical signs attributed to treatment included reversible dilated pupils (pharmacodynamic effect) persisting for up to 3 days during the recovery period, emesis in some control and low-dose dogs and all mid- and high dose dogs throughout the treatment period, and dry mouth (pharmacodynamic effect) at the mid and high doses during the first 10 dosing days. There was a decrease in body weights in the high dose males that was completely reversible by the end of the 14-day recovery period; the remaining groups showed body weight gains, although less than in the controls during treatment and decreased food consumption was found only in the high dose males. Thymus weight decreases in the mid dose (-60%) and high dose (-46%) females were reversible during recovery. The histopathology examination found no treatment-related effects, including any pulmonary changes. The incidence of thymic atrophy was increased in male treatment groups but was without dose-related increases in severity. In the female treatment groups, thymic atrophy incidence was also found although there was no dose-response relationship. A NOAEL can be considered to be the low dose of 0.06 mg/kg/day (AUC combined male and female 19450 pcg.h/ml), based on thymus weight reductions (females).

## 2 Drug Information

### 2.1 Drug Glycopyrrolate Inhalation System (GIS, EP-101)

**2.1.1 CAS Registry Number:** 596-51-0

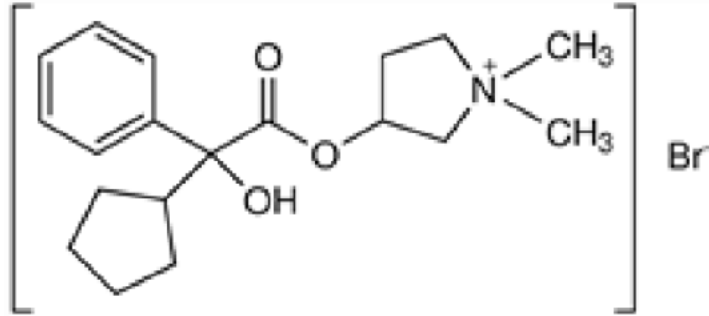
**2.1.2 Generic Name:** Glycopyrrolate Inhalation Solution

**2.1.3 Code Name:** EP 101

**2.1.4 Chemical Name:** 3-( $\alpha$ -Cyclopentylmandeloyloxy)-1-,1-dimethylpyrrolidinium bromide

**2.1.5 Molecular Formula/Molecular Weight:** C<sub>19</sub>H<sub>28</sub>BrNO<sub>3</sub> / 398.33

**2.1.6 Structure:**



**2.1.7 Pharmacologic class:** Synthetic Long-Acting Muscarinic Antagonist (LAMA)

**2.2 Relevant IND/s, NDA/s, and DMF/s:** DMF <sup>(b) (4)</sup>, DMF <sup>(b) (4)</sup>, DMF <sup>(b) (4)</sup>, NDA 17-588 (Robinul Injection), NDA 12-827 (Robinul oral tablet), and NDA

**2.3 Clinical Formulation:**

**Table 1: Components and Composition of EP-101**

Dose	Placebo	25 µg	50 µg	100 µg	200 µg
<sup>(b) (4)</sup>					

**Table 1: Composition of the Drug Product**

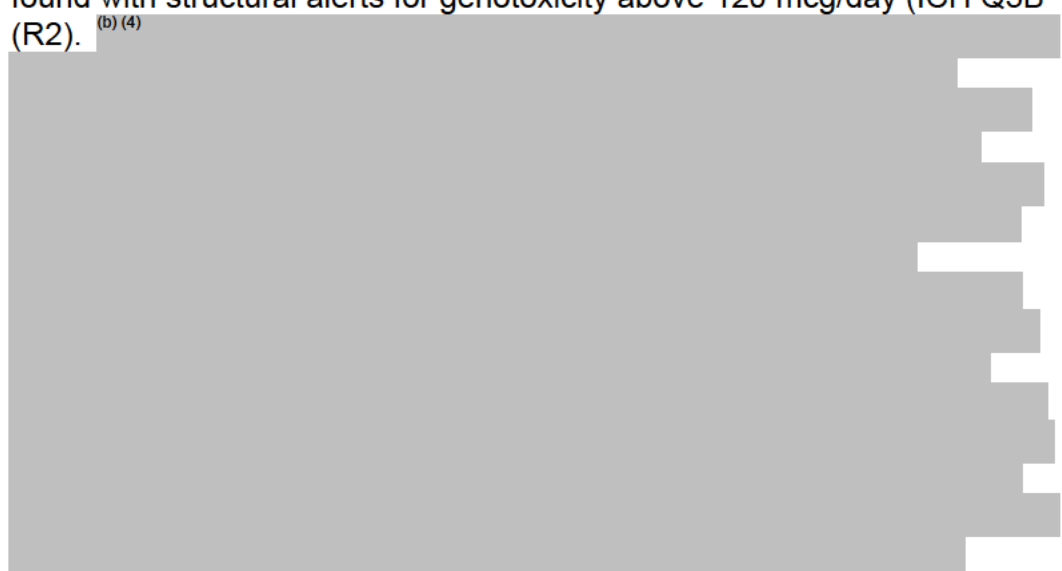
Ingredient	Function	Source	Quality Standard
<b>Active substance</b>			
Glycopyrrolate	Active ingredient	(b) (4)	USP
<b>Other excipients</b>			
Sodium Chloride	(b) (4)	(b) (4)	USP/EP/BP
Citric Acid (monohydrate)	(b) (4)		USP/EP/BP/JP
Sodium Hydroxide	pH adjustment		EP/BP/NF/JP
Hydrochloric Acid	(b) (4)		EP/NF
Water for injection	Diluent		EP

**Device:** (b) (4)



**2.3.2 Comments on Novel Excipients:** There are no new excipients, and the excipients are acceptable pending Final CMC review.

**2.3.3 Comments on Impurities/Degradants of Concern:** No impurities were found with structural alerts for genotoxicity above 120 mcg/day (ICH Q3B (R2)). (b) (4)



(b) (4)

**2.3.4 Proposed Clinical Population and Dosing Regimen:** GIS, a muscarinic antagonist with potent bronchodilatory activity is proposed for the chronic treatment of bronchoconstriction in Chronic Obstructive Pulmonary Disease (COPD) patients at doses of up to 200 mg/day by once daily inhalation. The 4-period crossover, steady state dose finding clinical study proposed in this submission (#EP-101-03) will include 133 subjects, ages ≥40 yo, who will be administered glycopyrrolate (0.25, 50, 100 and 200 mcg/ampule) once daily by inhalation for 14 days (with 7-day washout periods between treatments) with the eFlow nebulizer, vs. placebo and vs. the positive control articles tiotropium (18 g QD) and ipratropium (500 mcg t.i.d.).

**2.5 Regulatory Background:** The Sponsor is referencing DMF (b) (4), DMF (b) (4), and DMF (b) (4), and proposes to rely on Agency safety findings for the approved NDAs 17-558 (IV and IM injection) and NDA 12-827 (oral tablet) for the non-clinical systemic toxicity information to support the safety of the proposed clinical study on the inhalation product.

A pre-IND meeting for this submission was conducted with the Sponsor on March 11, 2011. The Agency recommended clarification of whether treatment in the proposed clinical study (EP-101-03) includes three 14-day periods, and revision of relative exposure ratios for the animal studies vs. clinical exposure to be based on 60 kg human weight and 0.25 rat weight for the safety margin calculations. The Agency further recommended that, based on lung findings in the 28-day rat study, the rat appears to be the most sensitive and relevant species for a 6-month nonclinical inhalation toxicity study to support chronic clinical GIS administration. The Agency advised the Sponsor that any neoplastic or preneoplastic changes observed in the 6-month repeat-dose study may require the conduct of an inhalation carcinogenicity study.

**2.5.1 Previous Clinical Experience:** Glycopyrrolate has been used in the US for more than 30 years, and is approved in IM and IV systemic injection form (Robinul® Injection, IV, IM, NDA 17-558) as a preoperative antimuscarinic agent to reduce salivation, tracheobronchial and pharyngeal secretions, and the volume and acidity of gastric secretion during surgery, and for blockade of cardiac vagal inhibitory reflexes during intubation. Glycopyrrolate is also approved in oral form as adjunctive therapy for the chronic treatment of drooling associated with neurological conditions such as cerebral palsy in patients ages 3-16 (NDA 22-

571), and for the chronic treatment of peptic ulcer (Robinul® 1 and 2 mg oral tablet, NDA 12-827), with a maximum recommended dose (MRHD) of 8 mg/day PO.

Two Phase 2 single dose studies in COPD patients using the proposed new inhalation route have been completed by the Sponsor in the United Kingdom. In Study EP-101, 12 subjects (ages 40-75) received GIS or placebo in a dose escalation paradigm using the eFlow device at doses of up to 200 mcg QD. Forty-two subjects (ages 40-75) were administered inhalation doses of 12.5-400 mcg QD vs. placebo in the 6-way crossover study EP-102. The effective dose for bronchodilation was found to be 25-400 mcg, although no additional benefit was found above 200 mcg.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

Report No. N111001D 28-Day Rat Inhalation Toxicity Study

Report No. N111001E 28-Day Dog Inhalation Toxicity Study

#### **3.2 Studies Not Reviewed**

Report No. N111001B Single Dose non-GLP Rat Inhalation Toxicity Study

Report No. N111001C Single Dose non-GLP Dog Inhalation Toxicity Study

Report N111001B 7-Day non-GLP Rat Inhalation Toxicity Study

Report N111001C 7-Day (non-GLP Dog Inhalation Toxicity Study

### **6. General Toxicology**

## **6.2 Repeat-Dose Toxicity**

Non-GLP 7-Day dose range-finding and maximum tolerated dose studies were conducted in rats and dogs for this submission. Rats (n=4-6/sex/dose) were administered control vehicle or 45 mg/kg/day (calculated dose 44-49 mg/kg/day) glycopyrrolate over 360 minutes each day for 7 days. The results showed no deaths. However, labored respiration was observed in 1 treated female on Day 1, reddened eyes in the males and females on Day 5 until the end of the study, persisting for less than 24 hours on Days 5-7. Body weights were reduced 6% and 8% in the males and females, respectively over the 7-day treatment period, but food consumption was reduced in the treated males only. There was a treatment-related increase in lung and larynx weights (both relative to body and brain weights) in the females. The histopathology examination identified target organs as the lungs and larynx in both the males and females given glycopyrrolate by inhalation. The findings included inflammation of the larynx with increased infiltrative neutrophils within the submucosa at the base of the epiglottis, likely due to irritation by the study drug. Also, there was an increase in alveolar macrophages in the lungs, which were enlarged and showed vacuolation of cytoplasm. The Day 1 AUC<sub>last</sub> values in that study were 6110 (males) and 7930 (females) ng.h/ml. The Day 1 AUC<sub>inf</sub> values were 6700 (males) and 9080 (females) ng.h/ml.

The non-GLP dose range-finding maximum tolerated dose (MTD) study was conducted for this submission in dogs administered 0 and 2.4 mg/kg/d glycopyrrolate by nose-only inhalation, once daily for 7 days. There were no deaths and no effects on clinical pathology, or macroscopic and microscopic findings. The clinical signs were primarily pharmacodynamic effects and included mydriasis, dry mouth, emesis and decreased body weights. The Day 7 AUC<sub>last</sub> values were 331 and 485 ng.h/ml in the males and females, respectively, and the AUC<sub>inf</sub> values were 380 in the males and 556 in the females at the 2.4 mg/kg/day dose.

### **Pivotal 28-Day Repeat-Dose Inhalation Toxicology Studies for Protocol Support**



**Study title: 28-Day Inhalation Toxicity Study of EF-101 in Rats with a 14-Day Recovery Period**

<b>Study no.:</b>	(b) (4) # N111001D
<b>Study report location:</b>	(b) (4)
<b>Conducting laboratory and location:</b>	(b) (4)
<b>Date of study initiation:</b>	August 4, 2010
<b>GLP compliance:</b>	Yes, however no signature
<b>QA statement:</b>	Yes, however no signature
<b>Drug, lot #, and % purity:</b>	EP-101, Lot GCP/013/2009-1010, 99.8% purity

**Key Study Findings:**

A 28-day glycopyrrolate inhalation toxicity study was conducted in Sprague-Dawley rats with a 14-day recovery period. The rats (n=10/sex/group with 6/sex/group toxicokinetic evaluation and 5/sex/group recovery group rats) were administered glycopyrrolate by nose-only inhalation once daily for 28 days at doses of 0, 0.5, 5, and 45 mg/kg/day.

The treatment-related effects included reversible decreased body weight gain during the entire 28-day dosing period, that was statistically significant at the high dose in the males (-66%) and females (-71%).

Ophthalmoscopic examination showed primarily pharmacodynamic effects of glycopyrrolate, including papillary dilation at the mid- and high doses, that was reversible during the recovery period.

Increased lung weights (absolute and relative to both body weights and brain weights) were shown at the mid- and high doses (percent differences from controls in the males were + 33% and +30%, respectively, and +43% and +47% in the females, respectively).

The target organs identified in the histopathology evaluation were the lungs, larynx and Harderian gland.

There were reversible (during recovery) increased lung alveolar macrophages in terminal bronchioles and adjacent alveoli at all doses, with dose-related increases in incidence and severity with severity ratings of minimal with occasional mild. Furthermore, no inflammation or inflammatory cells were found.

There were alterations of the epithelial lining in the larynx from pseudostratified flattened-to-low cuboidal "cobblestone" morphology to mucosal epithelium, that was consistent with stratified squamous type/squamous metaplasia. Laryngeal alterations were observed at all doses. Some (nonreversible at the highest dose) inflammation was also found in the laryngeal tissue that included neutrophil

and plasma cell macrophage infiltration of the submucosal glands and/or propria stroma with increased incidences for males and females in the high dose group..

The NOAEL was 45 mg/kg/day (mean AUC male + female combined 7,255,000 pcg.h/ml) because increased lung alveolar macrophages observed at all doses were without evidence of inflammation and therefore likely performing an inhaled drug removal function, and epithelial lining changes in the larynx were without inflammation, reversible at the low dose, and commonly found in inhalation toxicity studies in rats.

**Estimated Inhaled Dose:**

**Methods**

**Doses:** 0, 0.5, 5, & 45 mg/kg/day  
**Frequency of dosing:** Once daily for 28 days, using restraint in polycarbonate inhalation exposure tubes  
**Route of administration:** Nose-only inhalation  
**Dose volume:** Cannon-style rodent nose-only inhalation exposure system average air flow rate of 8.5 L/minute (total system flow rate of 25.5 L/minute) and test atmosphere flow rate of 0.46 L/minute/exposure port  
 Achieved aerosol concentration results:

Overall Estimated Achieved Aerosol Concentration Results						
Group	Solution Concentration (mg/mL)	Glycopyrrolate (EP-101) Aerosol Concentration				
		Target (µg/L)	Achieved			% Target
Males						
1	0	0	0	--	--	--
2	0.25	6.2	6.1	0.7	98	98
3	2.5	53	52	5	98	98
4	10	217	217	17	100	100
Females						
1	0	0	0	--	--	--
2	0.25	6.2	6.1	0.7	98	98
3	2.5	53	52	5	98	98
4	10	217	217	17	100	100

**Formulation/Vehicle:** Vehicle: citric acid, sodium chloride, sterile water for injection adjusted to pH 3.8. Formulations and stability analyzed (25-day storage) Particle size distribution (PSD) analysis showed

**Species/Strain:** Sprague-Dawley CD (SD) Rat

**Number/Sex/Group:** 10/sex/group

**Age:** 10-11 weeks at initiation of exposure

**Weight:** 207.8-407.8 g

**Satellite groups:** 6/sex/group TK, 5/sex/group 14-Day Recovery

**Unique study design:** Exposure durations adjusted to deliver target inhalation dose using predicted minute volume, (Bide’s formula), group mean aerosol concentration (sexes combined), and group mean body weights (combined sexes)

**Deviation from study protocol:** Staggered start of study, with Day 1 dosing in M beginning one day before Day 1 dosing in F.  
 Day 1: Control F observed for clinical observations 13 minutes early.  
 Day 29: Clinical observations recorded twice  
 HDM replacement on Day 2 due to death in 1 HDM had no Day BW, food consumption, or clinical observations until Day 3 and missed 2 days exposure

Overall Estimated Inhaled Dose by Sex					
Group	Solution Concentration (mg/mL)	Target Glycopyrrolate Inhaled Dose (mg/kg)	Sex	Estimated Glycopyrrolate Inhaled Dose (mg/kg)	% of Target Glycopyrrolate Inhaled Dose
1	0	0	M	0	NA
		0	F	0	NA
2	0.25	0.5	M	0.5	100
		0.5	F	0.5	100
3	2.5	5	M	5	100
		5	F	5	100
4	10	45	M	43	96
		45	F	47	104

NA = Not applicable.

**Particle Size Distribution:**

Overall Average PSD Results				
Group	Total Mass (Gravimetric)		Chemical Analysis	
	MMAD (µm)	GSD	MMAD (µm)	GSD
1	2.4	2.1	NS	NS
2	2.6	2.0	2.6	2.1
3	2.6	2.1	2.5	2.1
4	2.7	2.0	2.5	2.1

NS = Not submitted for chemical analysis.

**Animal study identification:**

Group	Core Male	Core Female	Recovery Male	Recovery Female	TK Male	TK Female
1-Vehicle	101-110	151-160	111-115	161-165	120-125	170-175
2-Low Dose	201-210	251-260	211-215	261-265	220-225	270-275
3-Mid Dose	301-310	351-360	311-315	361-365	320-325	370-375
4-High Dose	401-410 <sup>a</sup>	451-460	411-415	461-465	420-425	470-475

a. Study identification 409 was replaced with number 416.

## Observations and Results

**Mortality:** Death in 1 HDM Day 2: Animal replaced on Day 2. The relationship of the death to treatment was questionable.

### Clinical Signs

- No treatment-related clinical signs
- Incidental: alopecia in 1 MDF Day 4-29, 1 HDTKM eye opacity Day 7-29, 1 MDTKF eye abnormalities (clear discharge, red discharge, blood collection trauma)

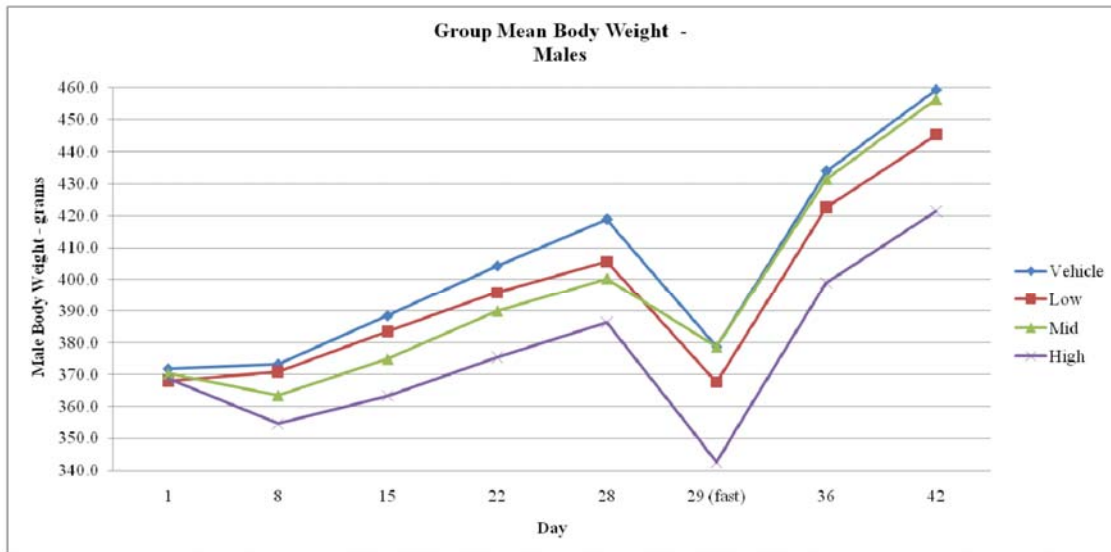
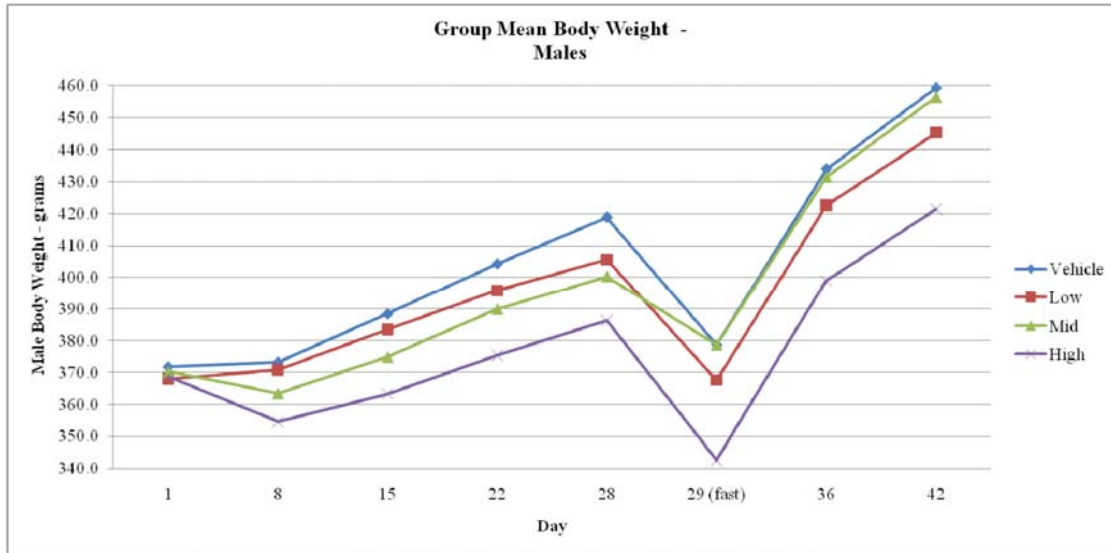
### Body Weights

- Body weight gains were decreased >10% for all male and female treatment groups. ↓ BWG treatment-related during 28-day dosing phase significant at the high dose in the males (-66%) and females (-71%).
- No differences from controls after 14-day recovery (reversible)
- The results of the BWG measurements are presented in the following table from the Sponsor:

Core and Recovery Group	Mean Body Weight (grams)			Mean Body Weight Gain (grams)	
	Day 1	Day 28	Day 42	Day 1 to Day 28	Day 28 to Day 42
<b>Males</b>					
1 - Vehicle	371.7	418.9	459.2	47.2	40.3
2 - Low Dose	368.0	405.6	445.2	37.6	39.6
3 - Mid Dose	370.3	400.3	456.3	30.0	56.0
4 - High Dose	368.8	386.4	421.4	17.6	35.0
<b>Females</b>					
1 - Vehicle	241.8	265.3	289.0	23.5	23.7
2 - Low Dose	243.0	253.0	275.8	10.0	22.8
3 - Mid Dose	243.7	252.0	270.4	8.3	18.4
4 - High Dose	239.5	246.4	268.9	6.9	22.5

- BWG from Day 1-28: -63% in the HDM and -71% in HDF vs. controls
- BWG from Day 28-42: -13% in HDM and -5% in HDF vs. controls
- BWG trends similar in TK rats, although statistically significant in M on Days 22 and 28 vs. controls

The group mean body weights are presented in the following graphs from the Sponsor:



### Food Consumption

- No statistically significant treatment-related effects

### Ophthalmoscopy

**Methods:** pupillary dilation via instillation of 1% Tropicamide Ophthalmic Solution prior to examination on Day 1 and after 14-day recover, but on Day 28 examination used only in control & vehicle rats, as the MD and HD rats' pupils were dilated by treatment

### Results:

- Pupillary dilation at MD and HD at Week 4 evaluation
- Reversible during recovery period
- Pharmacodynamic effect

**ECG:** Not conducted

## **Hematology**

Percent increases were as follows for the MD and HD male rats (vs. control M, statistically significant at the HD) in red blood cell parameters as follows:

RBC: +6% (MD and HD)

Hemoglobin: +5% (MD) and +9% (HD)

Hematocrit: + 5% (MD) and +8% (HD)

Percent increases were as follows for the MD and HD female rats (vs. control F, statistically significant at the HD):

RBC: +2% (MD) and +9% (HD)

Hemoglobin: +3% (MD) and + 9% (HD)

Hematocrit: + 3% (MD) and +10% (HD)

Hematology changes were reversible during the recovery period.

These changes were not regarded as dose-limiting.

The results of the treatment-related findings in the hematology evaluation are presented in the following tables from the Sponsor:

**Table 13. Group Mean Hematology Data – Males**

Group		Red Blood Cell Count (10 <sup>6</sup> /μL)		Hemoglobin (g/dL)		Hematocrit (%)		Mean Corpuscular Volume (fL)	
		Day		Day		Day		Day	
		29	43	29	43	29	43	29	43
Vehicle	Mean	8.69	8.13	15.0	14.6	46.6	45.2	53.7	55.6
	SD	0.40	0.49	0.6	0.9	2.2	2.7	1.9	0.7
	N	10	5	10	5	10	5	10	5
Low Dose	Mean	8.55	8.71	15.1	14.9	46.0	47.1	53.9	54.1
	SD	0.42	0.57	0.7	0.7	2.0	2.2	1.3	1.8
	N	10	5	10	5	10	5	10	5
Mid Dose	Mean	9.23*	8.37	15.7	14.8	49.1*	46.3	53.2	55.3
	SD	0.27	0.21	0.6	0.5	1.4	1.6	0.7	1.2
	N	9	5	9	5	9	5	9	5
High Dose	Mean	9.19*	8.51	16.3*	15.3	50.2*	47.4	54.7	55.7
	SD	0.59	0.34	0.8	0.4	2.6	1.8	1.6	0.8
	N	10	5	10	5	10	5	10	5

When N > 2, an asterisk (\*) indicates a statistically significant (p ≤ 0.05) difference from the comparison group (i.e., Vehicle).

**Table 14. Group Mean Hematology Data – Females**

Group		Red Blood Cell Count (10 <sup>6</sup> /μL)		Hemoglobin (g/dL)		Hematocrit (%)		Mean Corpuscular Volume (fL)	
		Day		Day		Day		Day	
		29	43	29	43	29	43	29	43
Vehicle	Mean	8.32	8.42	14.8	15.0	44.6	45.8	53.6	54.4
	SD	0.36	0.55	0.5	1.1	1.6	3.7	1.2	2.8
	N	10	5	10	5	10	5	10	5
Low Dose	Mean	8.43	8.24	14.6	15.0	44.3	45.0	52.6	54.6
	SD	0.47	0.29	0.9	0.9	2.5	2.0	1.6	0.9
	N	10	5	10	5	10	5	10	5
Mid Dose	Mean	8.50	8.38	15.2	14.7	45.8	45.0	53.9	53.7
	SD	0.38	0.34	0.9	0.7	1.9	1.9	1.1	1.3
	N	10	5	10	5	10	5	10	5
High Dose	Mean	9.11*	8.39	16.2*	15.1	48.9*	46.1	53.7	54.9
	SD	0.41	0.39	0.8	0.6	2.3	2.4	1.5	1.2
	N	10	5	10	5	10	5	10	5

When N > 2, an asterisk (\*) indicates a statistically significant (p ≤ 0.05) difference from the comparison group (i.e., Vehicle).

Clinical Chemistry & Coagulation:

Methods:

Serum chemistry parameters evaluated included those indicated below.

Alanine aminotransferase	Electrolytes
Albumin	Calcium
Albumin/globulin ratio (calculated)	Chloride
Alkaline phosphatase	Phosphorus
Aspartate aminotransferase	Potassium
Bilirubin, total	Sodium
Cholesterol	Globulin
Creatine kinase	Glucose
Creatinine	Lactate dehydrogenase
	Protein, total
	Triglycerides
	Urea nitrogen

Coagulation parameters evaluated included those indicated below.

Activated partial thromboplastin time	Prothrombin time
---------------------------------------	------------------

**Results:**

No treatment-related effects on coagulation

No effects deemed treatment-related, as differences were small in magnitude, in one sex only and/or not dose-related

Slight increases in globulin (2.3 g/dL vs. 2.0 in controls, +16.5%), cholesterol (116 mg/dL vs. 89 mg/dL in controls, + 30%) in main study HDF

**Urinalysis:** Not conducted. There were no histopathological findings in the kidneys. Further, the systemic toxicity of glycopyrrolate has been characterized by other routes that produced higher exposures.

**Gross Pathology:**

Methods: The following organs/tissues were examined on Days 29 (Main study) and 43 (Recovery):



Animal identification <sup>a</sup>	Ovaries (without oviduct)
Adrenal glands	Pancreas
Aorta	Pharynx
Bone with articular surface and marrow (femur)	Pituitary gland
Bone marrow smear (sternum) <sup>b</sup>	Prostate gland
Brain	Salivary glands (mandibular)
Epididymides	Sciatic nerve
Esophagus	Seminal vesicles
Eyes (with optic nerve)	Skeletal muscle (biceps femoris)
Gross lesions	Skin
Harderian glands	Spinal cord (thoracolumbar)
Heart	Spleen
Intestine, large (cecum, colon, rectum)	Stomach
Intestine, small (duodenum, ileum, jejunum)	Testes
Kidneys	Thymus
Larynx (three levels)	Thyroid gland (with parathyroid gland) <sup>c</sup>
Liver (median lobe and left lateral lobe)	Tongue
Lungs with bronchi	Trachea
Lymph node (mandibular, mesenteric, bronchial)	Urinary bladder
Mammary gland	Uterus (plus cervix)
Nasal turbinates (four levels)	Vagina

- a. Collected but not processed.
- b. Bone marrow smears were prepared for all animals at scheduled necropsy; evaluation was not warranted by changes in peripheral blood.
- c. Examined histopathologically when present in routine section.

**Results: No treatment-related findings**

**Organ Weights**

Adrenal glands	Pituitary gland <sup>a</sup>
Brain	Spleen
Heart	Testes (without epididymides)
Kidneys	Thymus
Liver	Thyroid/parathyroid gland <sup>a</sup>
Lung	Uterus
Ovaries (without oviduct)	

- a. Weighed post-fixation.

↑lung weights (absolute and relative to BW and brain weights) at MD and HD

Respective percent differences from controls were +33% to +44% and +30% to +42% in the MD and HD males, and +43% to +48% and +47% to +57% in the MD and HD females

There was no effect at 0.5 mg/kg/day

Day 29 Lung Weight (g) Evaluations

	Dose EP-101 (mg/kg/d INH)			
	0	0.5	5	45
Males (n=10)				
Absolute wt.	2.172	2.258	2.895*	2.821*
Relative to BW (%)	0.549	0.585	0.791*	0.780*
Relative to brain wt. (%)	107.49	111.13	140.77*	139.66*
Females (n=10)				
Absolute	1.669	1.786	2.390*	2.447*
Relative to BW (%)	0.693	0.767	1.023*	1.091*
Relative to brain wt. (%)	86.25	94.77	121.78*	129.75*

These changes might correlate with increased alveolar macrophages.

**Histopathology**

**Adequate Battery:** Yes: All tissues processed according to SOP for histopathology

**Peer Review:** Internal peer performed

**Target organs identified:** lungs, larynx, and Harderian gland

**↑ lung alveolar macrophages with terminal bronchioles and adjacent alveoli at all doses**

Incidence in controls, LD, MD, and HD, respectively:

1, 3, 6, 6, in M

2, 0, 1, 7 in F

3, 3, 7, 13 combined incidence (M+F)

Macrophages enlarged with finely vacuolated cytoplasm

Severity: minimal, with occasional mild, no increase in severity vs. 7-d study results

No inflammation/inflammatory cells found (Sponsor suggested this supports conclusion that macrophage presence represented normal lung function of particle removal and not inflammatory response)

Reversed during recovery

**Alteration of epithelial lining in larynx:**

From pseudostratified flattened-to-low cuboidal “cobblestone” morphology (normal) to mucosal epithelium

Incidence in controls, LD, MD, and HD, respectively:

0, 9, 10, and 10 in M

0, 2, 9, and 10 in F

Transformation consistent with stratified squamous type/squamous metaplasia) in all treated M & F groups

Some inflammation (neutrophil, plasma cell and macrophage infiltration of submucosal glands and/or propria stroma at HD (M & F)

Incidence in controls, LD, MD, HD, respectively:

1, 0, 0, and 4 in M

2, 0, 0, and 4 in F

Not reversed during recovery at HD

These findings in the larynx, commonly observed in inhalation toxicology studies with rats, are attributed to an adaptive response to irritation and have no relevance to humans.

The results of the laryngeal examinations are presented in the following table from the Sponsor:

Histopathological findings at the end of the treatment period

<b>Incidence and Average Severity of Treatment-Related Microscopic Findings -Interim (Day 29)</b>				
<b>Group (N =10)</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
<b>Sex</b>	<b>Males</b>			
<b>Tissue/Observation</b>	<b>Number observed per group</b>			
<b>Harderian Gland</b>				
Porphyrin Pigment, Increased (average severity <sup>a</sup> )	0 (0.0)	9 (1.1)	10 (2.9)	10 (2.8)
<b>Larynx</b>				
Epithelium Alteration (average severity <sup>a</sup> )	0 (0.0)	7 (0.7)	9 (0.9)	10 (2.4)
Inflammation (average severity <sup>a</sup> )	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.5)
<b>Lung</b>				
Alveolar Macrophages, Increased (average severity <sup>a</sup> )	1 (0.1)	3 (0.3)	6 (0.7)	6 (0.7)
<b>Sex</b>	<b>Females</b>			
<b>Harderian Gland</b>				
Porphyrin Pigment, Increased (average severity <sup>a</sup> )	0 (0.0)	6 (0.8)	10 (1.8)	10 (1.9)
<b>Larynx</b>				
Epithelium Alteration (average severity <sup>a</sup> )	0 (0.0)	2 (0.2)	9 (0.9)	10 (2.1)
Inflammation (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
<b>Lung</b>				
Alveolar Macrophages, Increased (average severity <sup>a</sup> )	2 (0.2)	0 (0.0)	1 (0.1)	7 (0.8)

a. Average severity was calculated by adding the severity grade of each microscopic finding and dividing by the number of animals per group.

Histopathological findings at the end of the recovery period

<b>Incidence and Average Severity of Treatment-Related Microscopic Findings –Final (Day 43)</b>				
<b>Group (N =5)</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
<b>Sex</b>				
<b>Males</b>				
<b>Tissue/Observation</b>	<b>Number observed per group</b>			
<b>Harderian Gland</b>				
Porphyrin Pigment, Increased (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	5 (1.4)	5 (1.6)
<b>Larynx</b>				
Epithelium Alteration (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)
Inflammation (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Lung</b>				
Alveolar Macrophages, Increased (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
<b>Sex</b>				
<b>Females</b>				
<b>Harderian Gland</b>				
Porphyrin Pigment, Increased (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	3 (0.8)	5 (1.0)
<b>Larynx</b>				
Epithelium Alteration (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)
Inflammation (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
<b>Lung</b>				
Alveolar Macrophages, Increased (average severity <sup>a</sup> )	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a. Average severity was calculated by adding the severity grade of each microscopic finding and dividing by the number of animals per group.

Excess porphyrin pigment secretion in Harderian gland in all treated M & F groups

Associated with glandular alveolar(?) dilatation

Not reversed at MD and HD in M & F

These findings are not relevant to humans.

**Toxicokinetics**

No sex-related differences except higher t1/2elim and decreased clearance in F on Day 28

T1/2 terminal long: 4.61-9.91 h on Day 1, 7.59-75.1 h on Day 28 vs. last sample collection time point at 18 h

Effect of repeated dosing (Day 28 vs. Day 1):

CI lower on Day 28

T<sub>1/2</sub> elim longer in all groups with the exception that effects in male treatment groups were relatively small compared to female treatment groups (4X longer or more)

↑ AUC<sub>inf</sub> (accumulation) in all groups

↑ AUC<sub>last</sub> at MD (M & F) but not at LD or HD

The results of the toxicokinetic evaluation are presented in the following table, from the Sponsor;

Day 1

Gender	Estimated Actual Dose (mg/kg/day)	Observed C <sub>max</sub> (pg/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	Terminal Elimination Rate Constant (hr <sup>-1</sup> )	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*pg/mL)	AUC <sub>∞</sub> (hr*pg/mL)
Male	0.50	20,400	0.250	8.66	0.0801	2710	33,800	137,000	185,000
	4.43	931,000	0.250	9.91	0.0700	3800	54,200	965,000	1,170,000
	43.3	3,390,000	0.250	8.34	0.0831	7120	85,700	5,020,000	6,080,000
Female	0.54	29,200	0.500	6.72	0.103	5030	48,800	93,100	107,000
	4.73	680,000	0.500	4.61	0.150	5420	36,100	831,000	873,000
	43.2	8,550,000	0.250	7.91	0.0876	3690	42,100	10,000,000	11,700,000

a. TK parameters were reported to three significant figures.

Day 28

Gender	Estimated Actual Dose (mg/kg/day)	Observed C <sub>max</sub> (pg/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	Terminal Elimination Rate Constant (hr <sup>-1</sup> )	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*pg/mL)	AUC <sub>∞</sub> (hr*pg/mL)
Male	0.43	62,300	0.500	11.7	0.0595	1040	17,400	269,000	415,000
	4.71	1,550,000	0.250	7.59	0.0913	1440	15,800	2,460,000	3,260,000
	44.9	1,730,000	0.500	10.8	0.0639	5920	92,700	5,360,000	7,580,000
Female	0.51	52,800	0.500	26.5	0.0262	1440	54,900	142,000	355,000
	5.09	1,110,000	0.250	75.1	0.00923	515	55,800	1,960,000	9,880,000
	46.6	4,650,000	0.250	30.6	0.0227	2000	88,200	9,150,000	23,300,000

a. TK parameters were reported to three significant figures.

Stability and Homogeneity:

Formulations found within 1.2% target solution concentrations

Stability analysis found formulations within 10% of respective target concentrations

**Study title: 29-Day Inhalation Toxicity Study of EF-101 in Dogs with a 14-Day Recovery Period**

<b>Study no.:</b>	(b) (4) Study no. N111001E)
<b>Study report location:</b>	(b) (4)
<b>Conducting laboratory and location:</b>	(b) (4)
<b>Date of study initiation:</b>	July 14, 2010
<b>GLP compliance:</b>	Yes: however no signature
<b>QA statement:</b>	Yes: however no signature
<b>Drug, lot #, and % purity:</b>	EP-101, Lot number GCP/013/2009/2010, 99.8% purity

**Key Study Findings**

- Dry mouth, mydriasis, emesis at  $\geq 0.06$  mg/kg/d
  - reversed during recovery period only at 0.06 mg/kg/d
  - Pharmacodynamic effects
- $\downarrow$ BW and food consumption at 0.06 mg/kg/d
- **Deceased thymus weights** in MD (0.6 mg/kg/d, -60%) and HD (2.4 mg/kg/d, -46%) F
- Thymic atrophy
  - Reversible
  - Incidence (at 0, 0.06, 0.6, and 2.4 mg/kg/d, respectively)
    - 1, 3, 3, and 3 in M
    - 0, 1, 2, and 1 in F
  - Severity:
    - 1.5, 2.7, 1.3, and 2.0 in M
    - 0, 0.3, 1.3, and 1.0 in F
- The NOAEL was 0.06 mg/kg/day

**Methods**

**Doses:**

Group	Target Glycopyrrolate Inhaled Dose (mg/kg/day)	Core		Recovery	
		Male	Female	Male	Female
1-Vehicle	0 <sup>a</sup>	3	3	2	2
2-Low Dose	0.06 <sup>b</sup>	3	3	2	2
3-Mid Dose	0.6 <sup>b</sup>	3	3	2	2
4-High Dose	2.4 <sup>b</sup>	3	3	2	2

- a. Exposure duration was the same as Group 4.  
b. Glycopyrrolate was the active pharmaceutical ingredient of EP-101. Target inhaled doses were based on target glycopyrrolate in vehicle (EP-101) formulation concentrations of 0.25, 2.5, and 10 mg/mL for Groups 2, 3, and 4, respectively (Amendment 1).

**Frequency of dosing:**

Once daily (32-53 minute exposures) for 28 consecutive days

**Route of administration:**

Nose only inhalation using mask with plenum exposure system providing fresh test atmosphere independent from other animals; dose adjusted using predicted minute volume (Bide's formula  $0.499 \times \text{combined sex group mean BW kg}^{0.089}$ ), group mean aerosol concentration (combined sexes), and actual group mean body weight (combined sexes)

**Dose volume:**

**Table 1. Overall Estimated Achieved Aerosol Concentration Results – Males**

Group	Solution Concentration (mg/mL)	Target (µg/L)	Estimated Glycopyrrolate (EP-101) Aerosol Concentration (µg/L)		
			Estimated Achieved		
			Average	SD	% Target
1	0	0	0		
2	0.25	5.7	5.8	0.6	101
3	2.5	44	44	5	99
4	10	156	146	15	94

**Table 2. Overall Estimated Achieved Aerosol Concentration Results – Females**

Group	Solution Concentration (mg/mL)	Target (µg/L)	Estimated Glycopyrrolate (EP-101) Aerosol Concentration (µg/L)		
			Estimated Achieved		
			Average	SD	% Target
1	0	0	0		
2	0.25	5.7	5.8	0.6	101
3	2.5	44	44	5	99
4	10	156	147	15	94

**Formulation/Vehicle:**

Citric acid, sodium chloride, sterile water for injection, pH adjusted to 3.8

**Species/Strain:**

Beagle dog

**Number/Sex/Group:**

3/sex/dose main study dogs

**Age:**

8-9 months

**Weight:**

9.3-11.5 kg

**Satellite groups:**

2/sex/dose for the 14-day recovery evaluation; All dogs underwent TK sampling on Days 1 and 28

**Unique study design:**

Dogs were restrained using inhalation restraint device and harness. Formulations analyzed and stability analysis conducted on 0.25 and 10 mg/ml formulations after 25 days storage at room temperature. Aerosol generation and exposure systems performed as intended, with aerosol concentrations stable over time. Gravimetric particle size distribution (PSD) appropriate for dog INH model at



1.9-2.5 µm mass median aerodynamic diameter (MMAD). Estimated INH dose/% target summarized below:

Group	Solution Concentration (mg/mL)	Target Glycopyrrolate Inhaled Dose (mg/kg)	Estimated Glycopyrrolate Inhaled Dose (mg/kg) (% of Target)	
			Male	Female
			1-Vehicle	0
2-Low Dose	0.25	0.06	0.06 (100%)	0.07 (117%)
3-Mid Dose	2.5	0.6	0.6 (102%)	0.6 (103%)
4-High Dose	10	2.4	2.3 (98%)	2.4 (100%)

NA = Not applicable.

**Deviation from study protocol:** -Ophthalmic examinations and clinical pathology assessments added during recovery period  
 -Additional deviations minor and did not affect the validity of the study (e.g. 1 MDM received clinical observation 4 minutes late, the first formulation was validated on same day as formulation analysis, actual time of blood collection for 1 MD dog not recorded on Day 28, etc)

## Observations and Results

**Mortality:** No mortality in any group

### Clinical Signs:

- Treatment-related dilated pupils persisting for up to 3 days during recovery period, reversible
- Emesis in some Control and LD dogs, and all MD and HD dogs every treatment Day
- Treatment-related dry mouth at MD and HD (1 LDF & M) first 10 treatment days
- These are PD effects
- The clinical signs (group summaries) are presented in the following tables from the Sponsor:

Males

Group	Observation	Animals Affected	Observed		
			First Day	Last Day	Total Number
Vehicle	Diarrhea	1	18	18	1
	Emesis	2	24	24	2
	Excessive Salivation	2	23	28	4
	Soft Feces	1	26	26	1
	Respiratory System, Laryngeal Spasm	1	25	25	1
Low Dose	Digestive System, Dry Mouth	1	2	2	1
	Emesis	2	2	26	3
	Soft Feces	3	1	26	4
	Respiratory System, Laryngeal Spasm	1	8	8	1
	Swelling, Foot	1	29	29	1
Mid Dose	Digestive System, Dry Mouth	5	1	6	10
	Emesis	5	3	23	24
	Excessive Salivation	3	9	11	4
	Eyes, Dilated	5	1	29	383
High Dose	Digestive System, Dry Mouth	5	1	10	38
	Emesis	5	2	27	32
	Excessive Salivation	2	3	15	9
	Eye Opacity	1	25	29	13
	Eyes, Dilated	5	1	29	418
	Yellow/Green Eye Discharge	1	25	29	13
	Respiratory System, Laryngeal Spasm	1	19	19	1

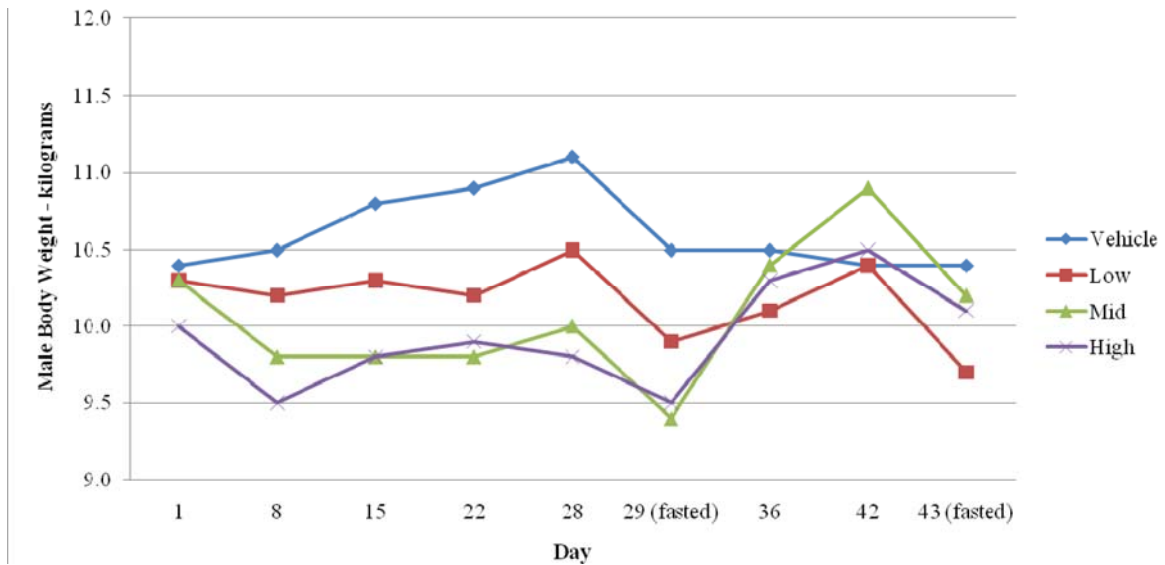
### Females

Group	Observation	Animals Affected	Observed		
			First Day	Last Day	Total Number
Vehicle	Emesis	3	7	27	8
	Soft Feces	1	18	18	1
	Red Vaginal Discharge	1	1	7	14
	Respiratory System, Laryngeal Spasm	1	11	11	1
Low Dose	Digestive System, Dry Mouth	1	1	3	2
	Emesis	5	2	29	10
	Soft Feces	4	6	29	5
	Eyes, Dilated	1	18	18	1
Mid Dose	Diarrhea	1	21	21	1
	Digestive System, Dry Mouth	1	2	2	1
	Emesis	5	4	25	30
	Excessive Salivation	2	3	19	7
	Reduced/Absent Feces	1	25	25	1
	Soft Feces	3	14	25	8
	Clear Eye Discharge	1	27	27	1
	Eyes, Dilated	5	1	29	398
	Yellow/Green Eye Discharge	2	15	29	19
	Red Vaginal Discharge	1	1	24	68
High Dose	Abrasion, Head	1	1	29	89
	Abrasion, Neck	1	18	29	33
	Diarrhea	3	20	28	6
	Digestive System, Dry Mouth	5	1	7	35
	Emesis	5	2	27	54
	Excessive Salivation	4	5	28	39
	Clear Eye Discharge	1	25	25	1
	Eyes, Dilated	5	1	29	416
	Yellow/Green Eye Discharge	1	25	29	6
	Red Vaginal Discharge	1	1	13	39

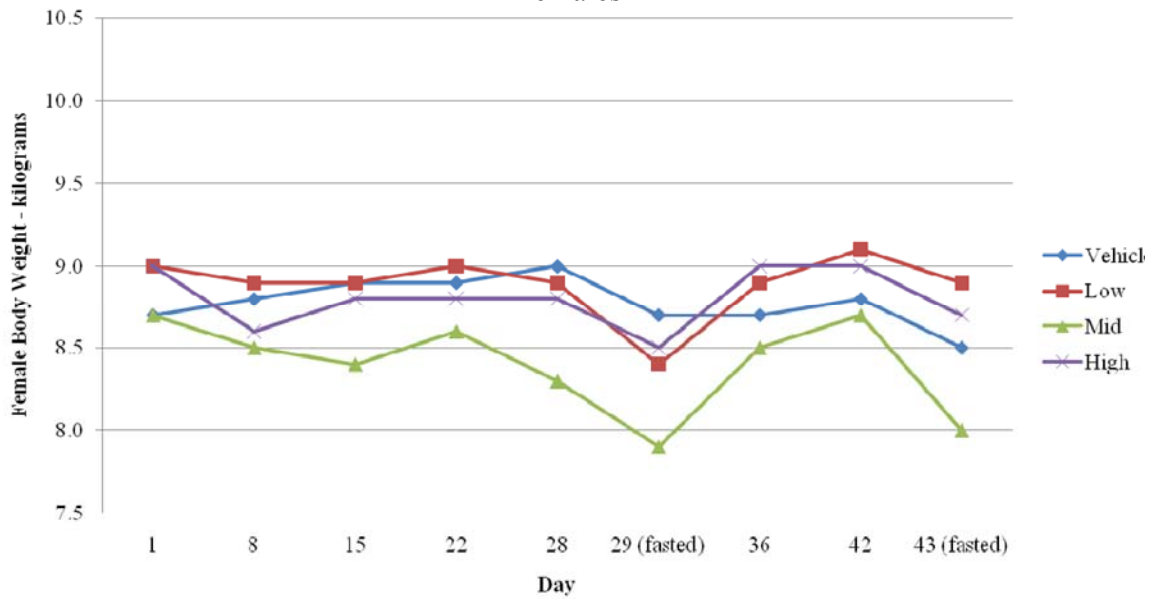
### Body Weights

- ↓BW in HD M (-12%) , completely reversible by end of 14-day recovery period
- Mean Body Weight Gains (Days 1 to 28) were 0.7, 0.2, -0.3, and -0.2 kg in the M, and 0.3, -0.1, -0.4, and -0.2 kg in the F at 0, LD, MD, HD, respectively
- The mean body weights are presented in the following graphs from the Sponsor:

### Males



### Females



### Feed Consumption

- ↓ particularly in HDM (approximately -65%) vs. controls during dosing Days 1-12

### Ophthalmoscopy

- Week 4 examination: papillary dilation at MD and HD M and F, not observed in recovery dogs after 14 days

**ECG:** Not performed. Information from the toxicology studies conducted in beagle dogs for the approved intravenous, intramuscular, and oral formulations will be referenced

### **Hematology**

- Slight ↑Mean WBC (+66%) , neutrophils (+70%), monocytes (+160%) and platelet (+35%) counts in HD F vs. control F (although also elevated at baseline, prior to treatment Day 1, not found in M, unlikely related to EP-101)
- ↑Monocytes in MDF (55%)

### **Clinical Chemistry**

Sporadic effects considered unlikely due to treatment, because differences were within variation, observed in one sex, were without clear dose response, and/or found in parameters without relationship to toxicity (e.g., ↓AST, creatine kinase)

**Urinalysis:** Not done. Information from the toxicology studies conducted in beagle dogs for the approved intravenous, intramuscular, and oral formulations will be referenced

**Gross Pathology:** No treatment-related findings

Results considered to be within background, and are without a dose-response relationship

**Organ Weights:** No treatment-related findings

↓Thymus weights in MD (-60%) and HD (-46%) F (reversible)

**Histopathology:** No treatment-related findings

**Adequate Battery:** yes

**Peer Review:** Internal peer

In comparison to the results of the histopathology examination in the 28-day study in rats, there were no treatment-related pulmonary changes

**Thymic atrophy** was found in the M and F in all groups, with higher incidence in the treated than in the control

The incidence of thymic atrophy was increased in male treatment groups, but was without dose-related increases in severity. In the female treatment groups, thymic atrophy was also found, although there was no dose-response relationship.

Reversible in all but 1MDF

**Thymic Atrophy (Incidence, with mean group severity scores in parentheses):**

	Dose Glycopyrrolate (mg/kg by inhalation)			
	0	0.06	0.6	2.4
Males	1 (1.5)	3 (2.7)	3 (1.3)	3 (2.0)
Females	0 (0)	1 (0.3)	2 (1.3)	1 (1.0)

**Toxicokinetics**

No gender or dose effects, and no effects of treatment duration (1 vs. 28 days) on TK parameters, including Tmax, elimination t1/2, elimination rate constant, Vd, AUCinf (no accumulation))

The results of the TK evaluation on Day 28 are presented in the following table:

TK Parameters for Day 28 <sup>a</sup> (Means)					
	Estimated Actual Inhaled Dose (mg/kg/day)	Observed C <sub>max</sub> (pg/mL)	Observed T <sub>max</sub> (hr)	Terminal Elimination Half-Life (hr)	Terminal Elimination Rate Constant (hr <sup>-1</sup> )
Sex	0.06	3870	0.250	16.4	0.0481
	0.54	31,000	0.250	11.3	0.0772
	2.25	95,100	0.250	8.47	0.0830
Female	0.05	4880	0.257	11.7	0.0645
	0.58	19,800	0.253	11.1	0.0630
	2.51	163,000	0.253	9.63	0.0760

	Estimated Actual Inhaled Dose (mg/kg/day)	Apparent Clearance (mL/hr/kg)	Apparent Volume of Distribution (mL/kg)	AUC <sub>last</sub> (hr*pg/mL)	AUC <sub>∞</sub> (hr*pg/mL)
Sex	0.06	3150	72,300	14,900	20,700
	0.54	4200	65,400	110,000	137,000
	2.25	7290	88,800	287,000	320,000
Female	0.05	2900	49,300	15,100	18,200
	0.58	8770	146,000	66,700	78,800
	2.51	7210	103,000	339,000	381,000

a. TK parameters were reported to three significant figures, doses reported to two decimal places.

### Stability and Homogeneity:

Analysis of formulations found test article solution concentrations within 1.2% target

Stability analysis showed both 0.25 and 10 mg/ml formulations within 10% target concentration range

## 11 Integrated Summary and Safety Evaluation

Glycopyrrrolate is a muscarinic antagonist with potent bronchodilatory activity. The Sponsor's Glycopyrrrolate Inhalation System (GIS), a newly modified drug delivery system, eFlow nebulizer (PARI) that delivers glycopyrrrolate by inhalation is proposed for the long-term treatment of Chronic Obstructive Pulmonary Disease (COPD).

Glycopyrrrolate has been used in the US for more than 30 years, and is approved in IM and IV systemic injection form (Robinul® Injection, IV, IM, NDA 17-558) as a preoperative antimuscarinic agent to reduce salivation, tracheobronchial and pharyngeal secretions, and the volume and acidity of gastric secretion during surgery, and for blockade of cardiac vagal inhibitory reflexes during intubation. Glycopyrrrolate is also approved in oral, tablet, and ophthalmic and oral solution

(NDA 089170, NDA 089171, NDA 08410, and others) forms as adjunctive therapy for the chronic treatment of drooling associated with neurological conditions such as cerebral palsy in patients ages 3-16 and for the chronic treatment of peptic ulcer (Robinul® 1 and 2 mg oral tablet, NDA 12-827), with a maximum recommended dose (MRHD) of 8 mg/day PO.

The Sponsor is referencing DMF<sup>(b) (4)</sup>, DMF<sup>(b) (4)</sup>, and DMF<sup>(b) (4)</sup>, and proposes to rely on Agency safety findings for the approved NDAs 17-558 (IV and IM injection) and NDA 12-827 (oral tablet) for the non-clinical systemic toxicity information to support the safety of the proposed clinical study on the inhalation product.

Supporting nonclinical studies: Nonclinical glycopyrrolate inhalation studies conducted by the Sponsor in support of the safety of the proposed clinical study included non-GLP 1-day (Studies N111001B and N111001C) and 7-day (Studies N111001B and N111001C) dose finding and MTD studies, and GLP 28-Day toxicity studies in rats (N111001D) and dogs (Study N111001E). Draft (unsigned GLP and Quality statements not signed) reports were submitted for the GLP 28-day toxicity studies in rats and dogs. For the remainder of the nonclinical information to support the safety of the proposed clinical study, the Sponsor submitted a summary of the safety pharmacology, pharmacokinetics, genetic toxicity, reproductive toxicity, and local (dermal irritation) toxicity findings in the nonclinical studies conducted for the approved drug products. Additional information from the published literature was summarized for this submission.

Pharmacology: A summary of the study results on primary and secondary pharmacology studies conducted for the original approved glycopyrrolate formulations was submitted. *In vivo* studies showed inhibition of gastric secretion in rat and dog, salivary secretion in dog and lacrimation in rat. Several *ex vivo* studies reported in the published literature (see Villetti et al) were conducted in guinea pig and human isolated trachea to demonstrate pharmacodynamic effects on respiratory system tissues by glycopyrrolate vs. tiotropium, a long-acting muscarinic antagonist, and vs. ipratropium, a muscarinic antagonist with a short duration of action. The results of these studies showed dose-dependent inhibition of isolated trachea and bronchus contractions induced by carbachol.

Secondary Pharmacology: In the secondary pharmacodynamics studies, parasympathetic inhibition by glycopyrrolate was demonstrated in mice (mydriatic, anti-tremorine [peripheral activity]), rats (inhibition of gastric secretion and blockade of lacrimation), and dogs (inhibition of gastric and salivary secretion and decreased intestinal tone/motility). The results of a study reported in the published literature (see Trifilieff A., et al. (2007). *The inhaled muscarinic receptor antagonist, glycopyrrolate, has a favorable side effect profile in brown*

*Norway rat lung function model when compared with tiotropium.* Chest 132(suppl): 530S) showed that glycopyrrolate dry powder and tiotropium inhibited methacholine-induced bronchoconstriction in rats and rabbits, with a duration of action allowing for once daily administration, The systemic toxicity findings for glycopyrrolate were below those for tiotropium bromide.

Safety Pharmacology: There were no treatment-related effects on CNS function in a study in mice conducted for the approved formulations. Studies on gastrointestinal safety, also conducted for the original NDA showed inhibition of gastric secretion in rats and dogs, and inhibition of salivary secretion and decreased intestinal tone/motility in dogs, all pharmacodynamic effects. A respiratory and cardiovascular safety pharmacology study in rats demonstrated up to 24-hour inhibition of methacholine-induced (30 mcg/kg) bronchoconstriction, salivation, hypotension and tachycardia by dry powder glycopyrrolate (NVA237) and tiotropium when given from 1-24 hours before the methacholine. The IV ED50 values for inhibition of methacholine effect for glycopyrrolate were 15.7, 10.1, 2.9, and 45.9 mcg/kg, (respectively). In the anesthetized rabbit, glycopyrrolate (20 mcg/kg) vs. tiotropium (3 mcg./kg) given prior to methacholine (10 mcg/kg IV for 70% max bronchoconstriction) inhibited bronchoconstriction for the 6h assessment period. Tiotropium inhibited bradycardia and hypotension by 95% and 85%, respectively. Glycopyrrolate had significantly less effect than tiotropium on cardiovascular parameters in that study.

ADME: The pharmacokinetics and ADME information was referenced from the Summary Basis of Approval for Robinul Injectable (NDA 17-558). No distribution or metabolism studies were conducted. Excretion is primarily as unchanged drug in feces; at 72 hours after oral administration in rat, 70%-90% drug was excreted in feces, and by 96 hours after dosing 99.36% radioactivity was recovered in feces (95.77%) and urine (3.59%).

Toxicology studies with glycopyrrolate administered by other routes: Intravenously administered glycopyrrolate showed 50X the potency of oral administration in mouse, and 80X potency vs. oral in rat. A single dose inhalation (nose only) MTD study in rats given 0, 15, 445, and 150 mg/kg over 360 minutes resulted in unscheduled termination in 3/6 rats at the highest dose of 150 mg/kg. The surviving rats showed labored breathing. A single inhalation dose escalation study in dog was terminated at the dose level of 2.4 due to excessive clinical signs, emesis and decreased food consumption, although there were no deaths in the dogs.

Studies on glycopyrrolate were conducted for NDA 17-558 and available in the published literature. By the dietary route, doses of 0, 250, 500, 1000, and 2000 ppm were administered for 6-7 weeks in rats. There were no treatment-related effects, including histopathologic changes, except for decreased body weights at the high dose. A second dietary study in rats at 0, 400, 1300, and 4000 ppm for 30 weeks, also showed no treatment-related effects except for decreased body



weights and food consumption at 1300 and 4000 ppm. Dogs were administered 0.4 and 2.0 mg/kg/day intravenous glycopyrrolate for 5 days each week for 4 weeks. There were no treatment-related toxicity findings, although pharmacodynamic effects were noted, and included mydriasis, cycloplegia, xerostomia, and occasional tachycardia. No treatment-related effect were found when glycopyrrolate was given orally (3, 9, and 27 mg/kg/day PO by capsule for 5 weeks, and 4, 16, and 64 mg/kg/day by gavage for 27 weeks) to dogs; as in the intravenous study in dogs, the observed effects were pharmacodynamic with occasional cycloplegia, xerostomia, mydriasis, and occasional lacrimation, emesis and, rhinorrhea. at the high dose of 64 mg/kg/day PO.

Genetic Toxicology: Glycopyrrolate was negative in a Standard Battery of studies conducted for the approved oral solution label (Ames Test, Human Lymphocyte Chromosome Aberration assay, Micronucleus assay).

Carcinogenicity: No studies have been conducted to evaluate potential carcinogenic effects by glycopyrrolate. During the Pre-IND meeting, the Agency advised the Sponsor that any neoplastic or preneoplastic changes observed in the 6-month repeat-dose study may require the conduct of an inhalation carcinogenicity study.

Reproductive Toxicology Studies: The results of the reproductive toxicity studies conducted for the approved product Robinul injectable (NDA 17-558) and found in the published literature showed a dose-related decrease in pregnancy rate and survival at weaning when given by the dietary route in rats at up to 65 mg/kg/day. Glycopyrrolate was negative for teratogenicity at up to 65 mg/kg/day dietary in rats and 0.05-0.5 mg/kg IM in rabbits, in the presence of maternal toxicity (decreased BWG). No studies were conducted to evaluate potential adverse effects on pre- and postnatal development.

Irritation Studies: Local irritation studies were conducted in support of the safety of the approved intramuscular and intravenous formulations. No irritation was found when glycopyrrolate was administered intramuscularly in rabbits at 0.1-25 mg/ml, vs. dimetane and robaxin injection. Topical exposure in abraded rabbit skin, at up to 2000 mg/kg was associated with edema at 632 mg/ml and above, and slight to minimal erythema at 200 mg/kg lasting 24 hours, and longer at 632 and 2000 mg/ml. Evidence of inflammation was found with some areas of extravasation of blood over 3 days, with subcutaneous administration of up to 2 mg/ml.

Nonclinical Inhalation Toxicology Studies: The sponsor's nonclinical toxicology program is directed toward an assessment of local toxicity in the respiratory tract. The sponsor submitted draft (unsigned GLP) reports of 28-day inhalation toxicology studies with rats and dogs in support of the proposed clinical trial.

A 28-day glycopyrrolate inhalation toxicity study was conducted in Sprague-Dawley rats with a 14-day recovery period ((b) (4) Study N111001D) for pivotal support for the safety of the proposed clinical study in this submission (Draft Study Report submitted). The rats (n=10/sex/group with 6/sex/group toxicokinetic evaluation and 5/sex/group recovery group rats) were administered glycopyrrolate by nose-only inhalation once daily for 28 days at doses of 0, 0.5, 5, and 45 mg/kg/day. There was one death in a high dose male rat on Day 2 although the relationship to treatment was unclear, the animal was replaced immediately. The treatment-related effects included reversible decreased body weight gain during the entire 28-day dosing period, that was statistically significant at the high dose in the males (-66%) and females (-71%). Ophthalmoscopic examination showed primarily pharmacodynamic effects of glycopyrrolate, including papillary dilation at the mid- and high doses, that was reversible during the recovery period. Increased lung weights (absolute and relative to both body weights and brain weights) were shown at the mid- and high doses (percent differences from controls in the males were +33% and +30%, respectively, and +43% and +47% in the females, respectively). The increased lung weights might correlate with increased alveolar macrophages found in the microscopic examination. The target organs identified in the histopathology evaluation were the lungs, larynx and Harderian gland. There were reversible (during recovery) increased lung alveolar macrophages in terminal bronchioles and adjacent alveoli at all doses, with dose-related increases in incidence and severity with severity ratings of minimal with occasional mild. Furthermore, no inflammation or inflammatory cells were found. The Sponsor suggested that this was supportive of a particle removal function by the macrophages representing normal lung function and not an inflammatory response. There were alterations of the epithelial lining in the larynx from pseudostratified flattened-to-low cuboidal "cobblestone" morphology to mucosal epithelium, that was consistent with stratified squamous type/squamous metaplasia. Laryngeal alterations were observed at all doses. These findings, commonly observed in inhalation toxicology studies with rats, are attributed to an adaptive response to irritation and have no relevance to humans. Some (nonreversible at the highest dose) inflammation was also found in the laryngeal tissue that included neutrophil and plasma cell macrophage infiltration of the submucosal glands and/or propria stroma with increased incidences for males and females in the high dose group. The NOAEL was 45 mg/kg/day (mean AUC male + female combined 7,255,000 pcg.h/ml) because increased lung alveolar macrophages observed at all doses were without evidence of inflammation and therefore likely performing an inhaled drug removal function, and epithelial lining changes in the larynx were without inflammation, reversible at the low dose, and commonly found in inhalation toxicity studies in rats.

The 28-day inhalation toxicity study on glycopyrrolate in dogs with 14-day recovery period (Study N111001E) used 3 dogs/sex/dose main study, and 2/sex/dose recovery evaluation animals. The dogs received glycopyrrolate at doses of 0, 0.06, 0.6 and 2.4 mg/kg/day by nose-only inhalation, once daily for

approximately 32-53 minute exposures. There was no mortality during the study. The clinical signs attributed to treatment included reversible dilated pupils (pharmacodynamic effect) persisting for up to 3 days during the recovery period, emesis in some control and low-dose dogs and all mid- and high dose dogs throughout the treatment period, and dry mouth (pharmacodynamic effect) at the mid and high doses during the first 10 dosing days. There was a decreased in body weights in the high dose males that was completely reversible by the end of the 14-day recovery period; the remaining groups showed body weight gains, although less than in the controls during treatment and decreased food consumption was found only in the high dose males. Thymus weight decreases in the mid dose (-60%) and high dose (-46%) females were reversible during recovery. The histopathology examination found no treatment-related effects, including any pulmonary changes. The incidence of thymic atrophy was increased in male treatment groups, but was without dose-related increases in severity. In the female treatment groups, thymic atrophy was also found although there was no dose-response relationship. A NOAEL can be considered to be the low dose of 0.06 mg/kg/day (AUC combined male and female 19450 pcg.h/ml), based on thymus weight reductions (females).

**Safety Margin Table:**

Safety margins for the highest proposed clinical dose (200 µg/day) relative to NOAELs identified in the 28-day inhalation toxicology studies with rats and dogs are shown in the table below. There are adequate safety margins for the highest proposed clinical dose.

Species/Study Inhaled Dose Concentration Achieved GIS concentration	NOAEL (mg/g lung weight) M/F	Safety Margin for 0.2 mg dose Based on AUC*	Safety Margin for HD Based on Inhaled Dose*
*60 kg Human: 7-day Starting Dose: 25 mcg (0.025 mg, 0.0004 mg/kg) Proposed HD: 200 mcg/d (0.2 mg, 0.0033 mg/kg) 0.0002 mcg/g lung weight	Reference	AUC0-time: 796 pcg.h/ml	(100% assumed)  Deposited dose: 0.0002 mg/g lung weight
Rat: 28-Day  0, 0.5, 5, and 45 mg/kg/d 0, 0.25, 2.5 and 10 mg/ml 0, 6.1, 52, 217 mcg/L	<b>45.0 mg/kg /d</b> (0.75 mg/g lung weight deposited at 10%)  AUC: 7,255,000 pcg/ml	9114X	Based on 10% delivered dose deposited in rat  3744X
Dog: 28-Day  0, 0.06, 0.6, 2.4 mg/kg/d 0, 0.25, 2.5, 10 mg/ml 0, 5.8, 44, 147 mcg/L	<b>0.06 mg/kg /d</b> (0.0014 mg/g lung weight deposited at 25%) AUC (M+F): 19450 pcg.h/ml	24X	Based on 25% delivered dose deposited 6.75 X

\*AUC in human: 796 pcg.hr/ml at 200 mg/day in a 60 kg human

\* Based on Pulmonary deposited dose (% achieved/delivered dose: 10% for rat, 25% for dog vs. 100% in a 60 kg human).

Based on adequate safety margins in the 28-day glycopyrrolate inhalation toxicity studies in rats and dogs, the abundant database on glycopyrrolate toxicity from nonclinical studies conducted using other routes of administration (systemic toxicity) including intravenous, intramuscular, subcutaneous and oral, and the extensive clinical experience of more than 30 years with glycopyrrolate for the approved and marketed (IV, IM, and oral tablet and solution forms) glycopyrrolate drug products as well as clinical experience using inhalation exposure in the two completed studies for this IND, the proposed clinical study is considered to be safe-to-proceed. Most of the treatment-related target organs identified in the 28-day nonclinical inhalation studies for this submission were reversible following discontinuation of dosing, and can be monitored during the proposed clinical study.

**Recommendations to the Sponsor:**

We have the following non-hold comments for future development of glycopyrrolate inhalation system:

1. Submit the final study reports for the 28-day inhalation toxicity studies in rats and dogs (N111001D and N111001E) within 120 days of the initial IND 110,663 submission.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN A YOUNG  
05/13/2011

TIMOTHY W ROBISON  
05/13/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**PHARMACOLOGY/TOXICOLOGY MEMO TO FILE**

**IND number:** 110663

**Sponsor:** Elevation Pharmaceuticals, Inc.

**Submission Type:** Initial IND Submission

**Supporting Doc Category/Subcategory:** SDN 000; SDN 002

**Submission Date/Receipt:** April 13, 2011/April 14, 2011; May 11, 2011

**Drug Substance:** Glycopyrrolate Inhalation Solution (GIS)

**Division name:** Division of Pulmonary, Allergy, and Rheumatology Products

**Review completion date:** June 14, 2011

**Reviewer name:** Kathleen Young, Ph.D.

**Pharmacology/Toxicology Supervisor:** Molly E. Topper, Ph.D.

**Division Director:** Badrul Chowdhury, M.D., Ph.D.

**MEMO TO FILE**

**RE:** The original IND for glycopyrrolate inhalation system (GIS) for the treatment of chronic obstructive pulmonary disease (COPD) was submitted on April 13, 2011. The chemistry reviewer submitted an Information Request (IR) to the Sponsor on May 4, 2011 during the 30-day safety review period requesting clarification of the acceptance criteria for drug product related substances and for the assay and impurity profile of the drug product before and after nebulization to show stability. The Sponsor responded on May 11, 2011. The CMC reviewer requested toxicological review and evaluation of the sponsor's response on May 16, 2011. The following memo is an analysis of these data. From the nonclinical perspective, the Sponsor's impurity specification of NMT  $\frac{(b)}{(4)}$  % is considered acceptable for impurities that lack a structural alert for genotoxicity ( $\alpha$ -cyclopentyl mandelic acid (CPMA)). For the initial clinical trial of 14-day treatment, the impurity specification of NMT  $\frac{(b)}{(4)}$  % is acceptable for the known genotoxin benzoic acid for the maximum proposed clinical dose of 200 mcg/day GIS giving 2.0 mcg/day of benzoic acid exposure. To support an NDA, the levels of benzoic acid should be below  $\frac{(b)}{(4)}$  mcg/day.

The Chemistry, Manufacturing and Controls (CMC) reviewer, Dr. Xiaobin Shen indicated concern regarding drug stability pre-and post-nebulization, particularly for the genotoxic impurity benzoic acid and the impurity  $\alpha$ -cyclopentyl mandelic acid (CPMA) (see CMC Review of 5/25/2011). The proposed drug substance specifications in the original IND submission of April 13, 2011 were for NMT  $\frac{(b)}{(4)}$  % for each of these impurities (see Table, below), providing

for up to a maximum exposure of <sup>(b) (4)</sup> mcg/day each impurity at the highest proposed clinical dose of 200 mcg/day GIS.

(b) (4)





(b) (4)



(b) (4)



(b) (4)

In conclusion, the results of the impurity analyses showed levels of CPMA and benzoic acid impurities detected in the clinical Lots to be considerably lower than the specified levels. The levels of CPMA and benzoic acid detected were below those specified in ICH (Q3B(R2) Guidance for Industry of NMT <sup>(b)</sup><sub>(4)</sub> % and CDER Guidance for Industry of 120 mcg/day for a potential genotoxin, respectively.

**Recommendations:** No additional nonclinical studies are needed for impurity qualification at the specifications presented in this submission for the proposed 14-day Phase 2 clinical study # EP-101-03. To support an NDA or clinical studies >12 months, benzoic acid levels should be below <sup>(b)</sup><sub>(4)</sub> mcg/day.

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/s/  
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KATHLEEN A YOUNG  
06/14/2011

MOLLY E TOPPER  
06/14/2011  
I concur.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LAWRENCE S LESHIN  
04/25/2017

CAROL M GALVIS  
04/25/2017  
I concur.